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Editorial

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Guest Editor: B. List

During the past 12 years or so, hardly any other field has impacted the art and science of chemical synthesis more profoundly than organocatalysis. The growth, both in academic research and in industrial use, has been breathtaking. Judging by the development of its impact factor, the *Beilstein Journal of Organic Chemistry* is currently attempting to achieve the same impact within chemistry publishing. A Beilstein Thematic Series on Organocatalysis therefore appeared to be quite logical. A brilliant opportunity arose in the context of a priority program sponsored by the Deutsche Forschungsgemeinschaft (DFG), which has in the meanwhile supported the organocatalysis research of over thirty groups in Germany between 2004 and 2010. The series in hand serves as the final report of this highly productive and successful “DFG Organokatalyse Schwerpunktprogramm, SPP 1179”. In addition, it captures the latest research activities in organocatalysis from many of the leading groups from all over the world.

Organocatalysis describes catalysis with low-molecular-weight organic compounds, in which a metal is not part of the active principle. Organocatalysts donate or remove electrons or protons as their activation mode, hence defining four distinct subareas: Lewis base and Lewis acid catalysis on the one hand, and Brønsted base and Brønsted acid catalysis on the other hand. There are additional aspects that belong to the field and that are being actively researched, including supported catalysts, organocatalysis in unusual reaction media, and applications in polymerizations, in total synthesis and drug-discovery, as well as in drug manufacturing, among many others. Potential advantages of organocatalysis have been emphasized on various occasions and will not be repeated here as such statements are becoming more and more inaccurate generalizations in light of the diversification and growth of the field. Suffice to say here that organocatalysis has plentiful and complementary reactivity to offer. Indeed, certain things that cannot be done with enzymes or metals may well be feasible with organic catalysts.

The present Thematic Series serves to showcase the current state of the art of organocatalysis and covers many of the aspects mentioned above. The productivity and creativity of the researchers in the field as such, and of the authors publishing here specifically, is truly amazing. I am highly grateful to all of the many contributors.

Ben List

Mülheim, August 2012

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Stereoselective, nitro-Mannich/lactamisation cascades for the direct synthesis of heavily decorated 5-nitropiperidin-2-ones and related heterocycles

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Full Research Paper

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Abstract

A versatile nitro-Mannich/lactamisation cascade for the direct stereoselective synthesis of heavily decorated 5-nitropiperidin-2-ones and related heterocycles has been developed. A highly enantioenriched substituted 5-nitropiperidin-2-one was synthesised in a four component one-pot reaction combining an enantioselective organocatalytic Michael addition with the diastereoselective nitro-Mannich/lactamisation cascade. Protodenitration and chemoselective reductive manipulation of the heterocycles was used to install contiguous and fully substituted stereocentres in the synthesis of substituted piperidines.

Introduction

The piperidine ring is a common motif found in many biologically active natural products and drugs. The structures of these compounds range from the architecturally complex polycyclic ring systems, such as those found in the alkaloids haliclonacyclamine F [1], manzamine A [2-6], and reserpine [7,8] (Figure 1), to relatively simple piperidines found in pharmaceutical compounds, such as paroxetine [9,10] and alvimopan [11].

The abundance of this motif in desirable targets has led to considerable interest from the synthetic community [12-19]. Common synthetic approaches to incorporate this motif include nucleophilic additions to pyridine rings and further manipulation [20-25], intramolecular iminium ion cyclisation [26-29], reduction of unsaturated heterocycles [30-32], ring closure via intramolecular nucleophilic substitution [33-37], cascade reactions of enamines/imines and aldehydes [38-41], and ring-

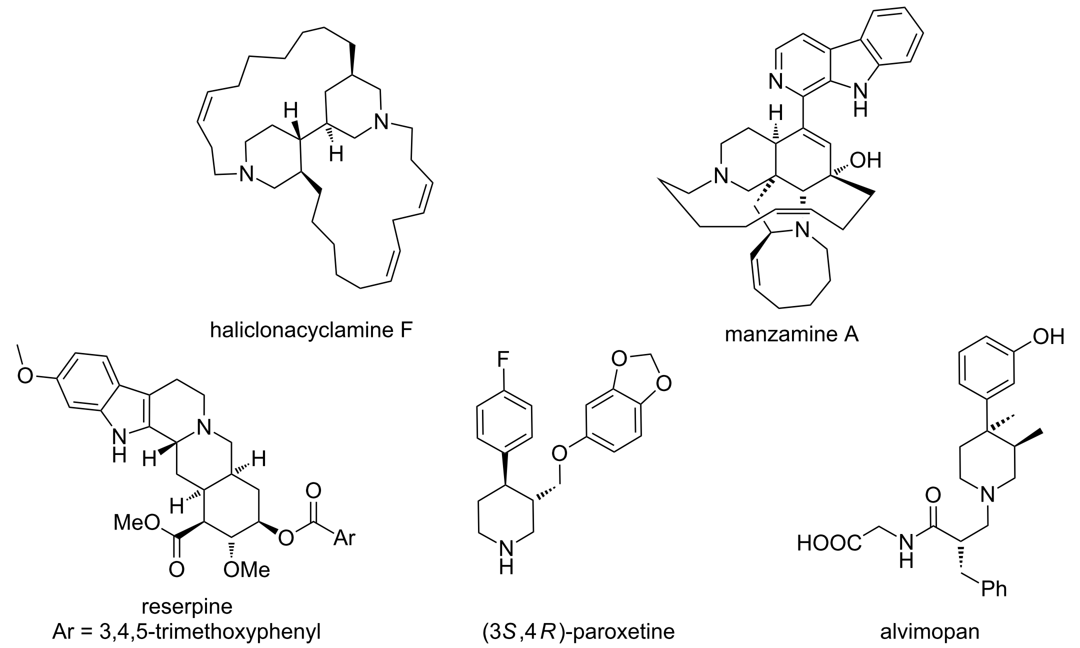
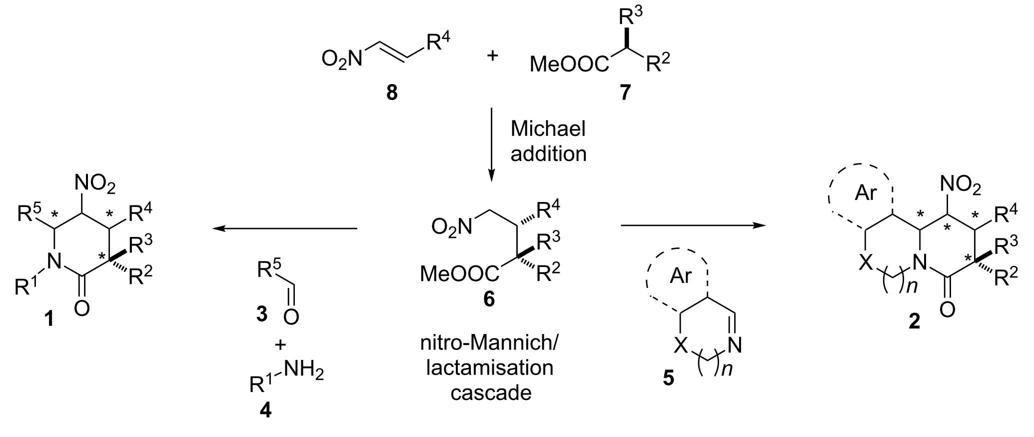


Figure 1: Biologically active natural products and drugs containing the piperidine ring.

closing metathesis followed by hydrogenation [42-48]. Arguably the most general route employs cycloadditions and subsequent manipulation of the partially unsaturated ring system [49-53]. We believed a powerful entry to piperidine rings and related heterocyclic structures could employ a nitro-Mannich/lactamisation cascade of γ-nitro ester starting materials with imines (cyclic or acyclic, preformed or formed in situ) as a key step. Not only could this approach allow the rapid generation of structural complexity, but the products would be amenable to further synthetic transformations. Furthermore, the γ-nitro ester starting materials are accessible in an enantioenriched form by using an organocatalytic Michael addition methodology, which was developed by our group and others [54-59]. In pursuit of this we have successfully harnessed the power of the nitro-Mannich/lactamisation cascade in a formal synthesis of (3*S*,4*R*)-paroxetine [60], in the construction of architecturally complex polycyclic alkaloid structures [61] and more recently as a key complexity building step in the total synthesis of nakadomarin A [62-65]. Herein we wish to report our full findings in this synthetically powerful cyclisation cascade.

The first example of a simple nitro-Mannich/lactamisation cascade was reported independently by Mühlstädt and Jain in the mid-1970s [66,67]. The condensation of methyl 4-nitrobutanoate **6** (Scheme 1; $R^2 = R^3 = R^4 = H$) with aromatic aldehydes **3** (R^5 = Ar) and ammonium acetate provided access



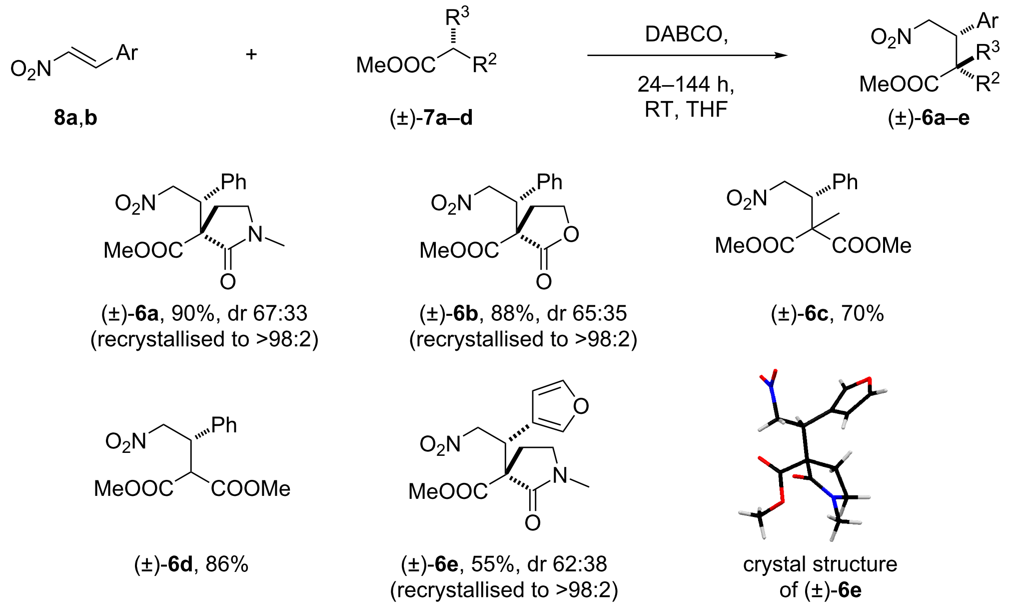
Scheme 1: A general strategy to 5-nitropiperidin-2-ones and related heterocycles.

to simple 6-aryl-substituted 5-nitropiperidin-2-ones **1** ($R^1 = R^2 = R^3 = R^4 = H$, $R^5 = Ar$). The power of this transformation was not immediately recognised and only in the last two decades has the cascade been successfully applied to the synthesis of simple biologically active compounds and their precursors, such as (±)-CP-99,994 [68,69], inhibitors of farnesyltransferase [70,71], selective dipeptidyl peptidase IV inhibitors [72,73], and functionalised bispidines [74]. Very recently, a related cascade inspired by the original work of Jain incorporating C–C bond formation was accomplished through a nitro-Mannich reaction [75-80] of nitro carbonyl compounds with imines, followed by ring-closure condensation [81-83]. Despite improvements of, and developments to, the nitro-Mannich/lactamisation cascade during the last few decades, we recognised, that further enhancement of the method was necessary to transform it into a general synthetic tool of use in both medicinal chemistry and natural-product synthesis.

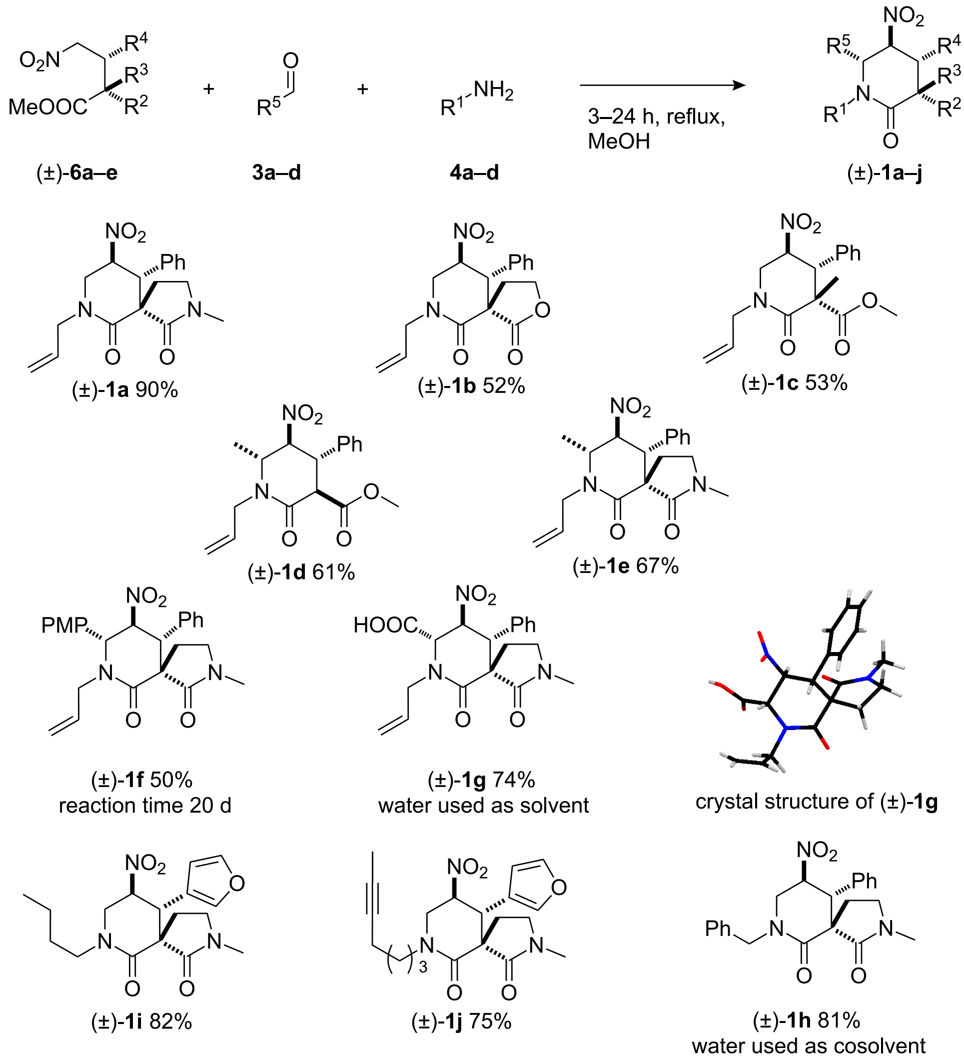
Results and Discussion

To allow us to further explore the nitro-Mannich/lactamisation cascade, a range of Michael adducts **6a–e** were synthesised on a gram scale by the reaction of active methylene or methine carbon acids with nitro olefins in the presence of DABCO (20–30 mol %) in THF (Scheme 2). Where diastereoisomers were created in the Michael addition step and stereocontrol was poor, the diastereomeric mixtures were recrystallised to afford single diastereomers **6a**, **b**, **e**. The relative stereochemistry of the major diastereomer **6e** was assigned unambiguously by single-crystal X-ray analysis.

With a range of suitable test substrates in hand, formaldehyde-derived imines were then investigated in the nitro-Mannich/lactamisation reaction. Aqueous formaldehyde (**3a**) and allylamine (**4a**) were added to a methanol solution of lactam **6a** and the mixture heated under reflux for 4 hours until judged to be complete by TLC. Pleasingly, the desired δ-lactam product **1a** was isolated in 90% yield as a *single diasteromer* (Scheme 3) [84]. Under identical reaction conditions the other Michael adducts, lactone **6b** and ester **6c**, provided moderate yields of the desired δ-lactams **1b** and **1c** as single diastereoisomers in both cases. The diastereoselectivity in the latter case is notable, as the quaternary stereogenic centre is created in the lactamisation step. The relative stereochemical configurations of **1a–c** were established by ^{1}H NMR spectroscopic analysis. For more details on the elucidation of the relative configuration see [61] and Supporting Information File 1. To incorporate substituents at the 6 position of the piperidine ring in **1**, imines derived from aldehydes other than formaldehyde were required in the reaction. Thus acetaldehyde (**3b**), anisaldehyde (**3c**) and glyoxylic acid (**3d**) were chosen as representative aliphatic, aromatic and functionalised aldehydes, respectively, and reacted with Michael adducts **6a** and **6d** under the conditions described above with allylamine. High diastereoselectivities were observed in each case and the reaction products **1d–g** were obtained in moderate to good yields (50–74%). The relative stereochemistry of **1g** was assigned unambiguously by single-crystal X-ray analysis. Similarly, variation at position 1 required the use of an alternative amine for in situ imine formation. Thus replacement of allylamine (**4a**) with benzylamine (**4b**) in the



Scheme 2: The synthesis of Michael adduct model substrates for the nitro-Mannich/lactamisation cascade.



Scheme 3: Nitro-Mannich/lactamisation cascade with in situ formed imines.

reaction afforded the desired product **1h** in good yield and as a single diastereoisomer (Scheme 3).

The use of substrate **6e** allowed us to investigate further variations at positions 1 and 4; piperidin-2-ones **1i** and **1j** were formed as single diastereoisomers in good yields (82% and 75%) when nitro-Mannich/lactamisation cascades were carried out with formaldehyde (**3a**) and butylamine (**4c**) or hept-5-yn-1-amine (**4d**), respectively. To extend the cascade methodology to the potential construction of architecturally complex piperidine-ring-containing polycyclic natural products, the successful employment of preformed cyclic imines was required.

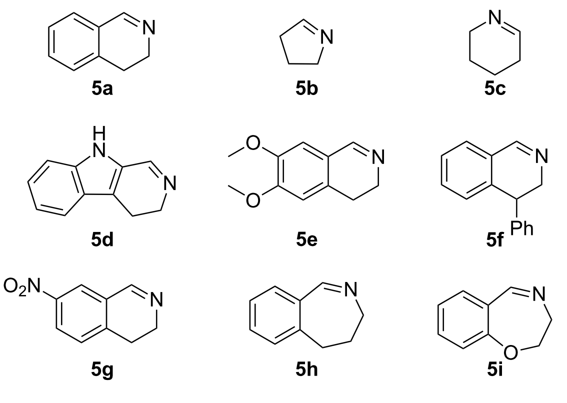
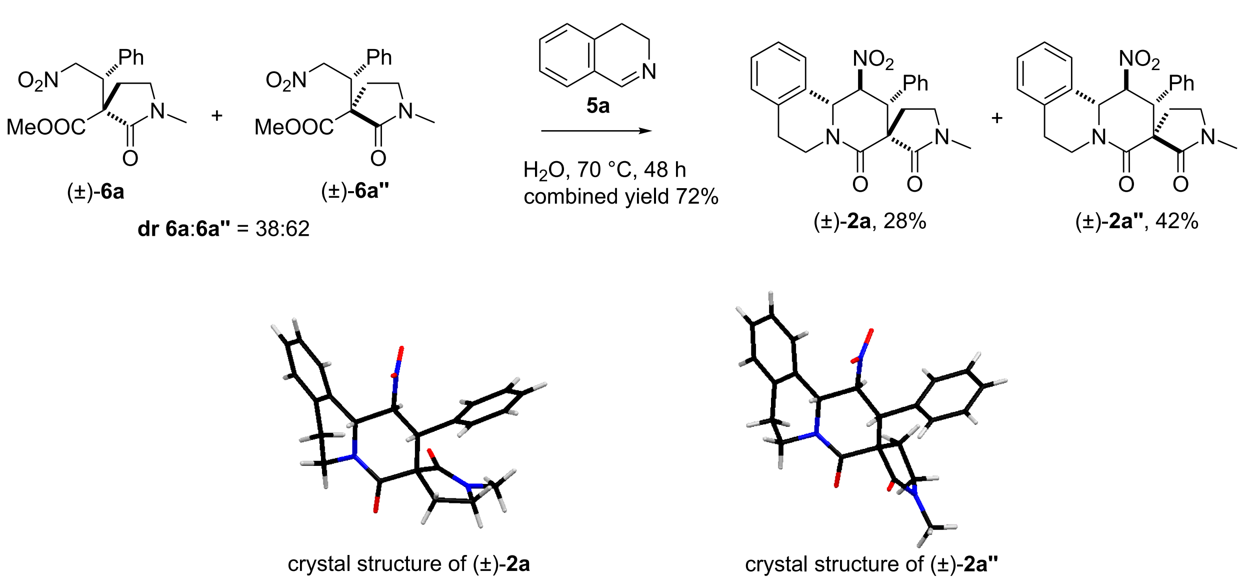


Figure 2: Cyclic imines employed in nitro-Mannich/lactamisation cascade.

Accordingly, the imine **5a** (Figure 2) was synthesised from commercially available 2-phenylethylamine [85] and reacted with the chromatographically inseparable mixture of diastereo-



crystal structure of (±)-**2a**

crystal structure of (±)-**2a''**

Scheme 4: Nitro-Mannich/lactamisation cascade of diastereomeric Michael adducts **6a**, **6a''** with cyclic imine **5a**.

meric Michael adducts **6a** and **6a''**, under slightly modified conditions (water was used instead of MeOH as the solvent). Pleasingly the reaction proceeded smoothly and only two, **2a** and **2a''**, of the possible eight diastereoisomeric tetracyclic compounds were obtained in good combined yield (70%, Scheme 4). Chromatographic separation followed by single-crystal X-ray diffraction studies of both isomers allowed unambiguous determination of the relative stereochemical configurations in each case. For more details of the elucidation of the relative configuration see Supporting Information File 1. The products were epimeric *only* at the quaternary centre and therefore both new stereogenic centres were created with high stereocontrol in each case.

Imines **5a**–**5i** [61,86-94], chosen so as to afford common target motifs in the products [95-102], were synthesised and reacted with diastereomerically pure Michael adduct **6a** and Michael adduct **6d** following the conditions described above. Employing the optimal reaction conditions, products **2a**–**2l**, which possess 4,5-trans relative stereochemistry, were formed in moderate to good yields and with high diastereoselectivities as described in our previous work (Scheme 5) [61].

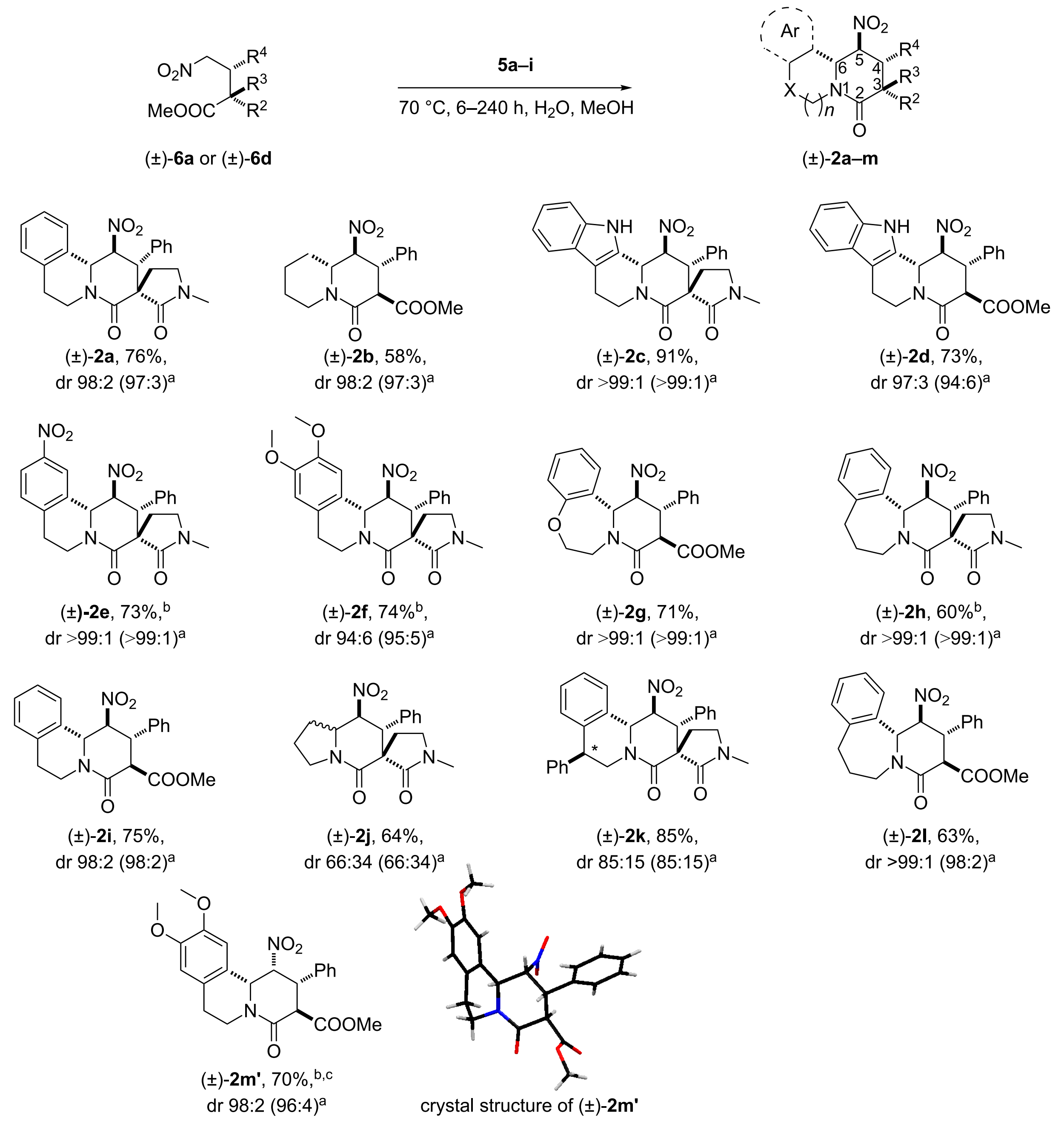
Interestingly, however, when diastereomerically pure Michael adduct **6d** was reacted with imine **5e**, the nitropiperidinone **2m'**, possessing 4,5-cis relative stereochemistry [103], was isolated in 70% yield as a single diastereomer (Scheme 5). This one exceptional case together with the generally high diastereocontrol in the formation of piperidinones **1a**–**j** and **2a**–**l** is interesting and worthy of further commentary. With the knowledge that the retro-Michael reaction does not occur under standard reaction conditions (Scheme 4) and assuming that the final step of the cascade (the δ-lactam ring formation) is irreversible, there are at least three possible explanations for the high diastereocontrol in the formation of **1a**–**j** and **2a**–**l**:

- The first is that the nitro-Mannich step is highly diastereoselective and lactamisation occurs subsequently without any effect on the stereochemical outcome of the cascade.

- The second is that the nitro-Mannich reaction [78-80] is fast and reversible (but not necessarily stereoselective), and only one of the diastereomeric nitro-Mannich products preferentially cyclises in the irreversible lactamisation step to the (likely) most thermodynamically stable product (Scheme 6, Path A).

- The third is similar to the second, but the two direct nitro-Mannich products A and B with the observed configurations at the 6 position preferentially lactamise, and there is a postcyclisation epimerisation at the stereogenic carbon bearing the nitro group allowing equilibration to the (likely) most thermodynamically stable product (thermodynamic control, Path B) or a crystallisation-induced diastereoselectivity to give products **2** or **2'** with the nitro group occupying an axial or equatorial position, respectively [104-108] (Scheme 6, Path B/B').

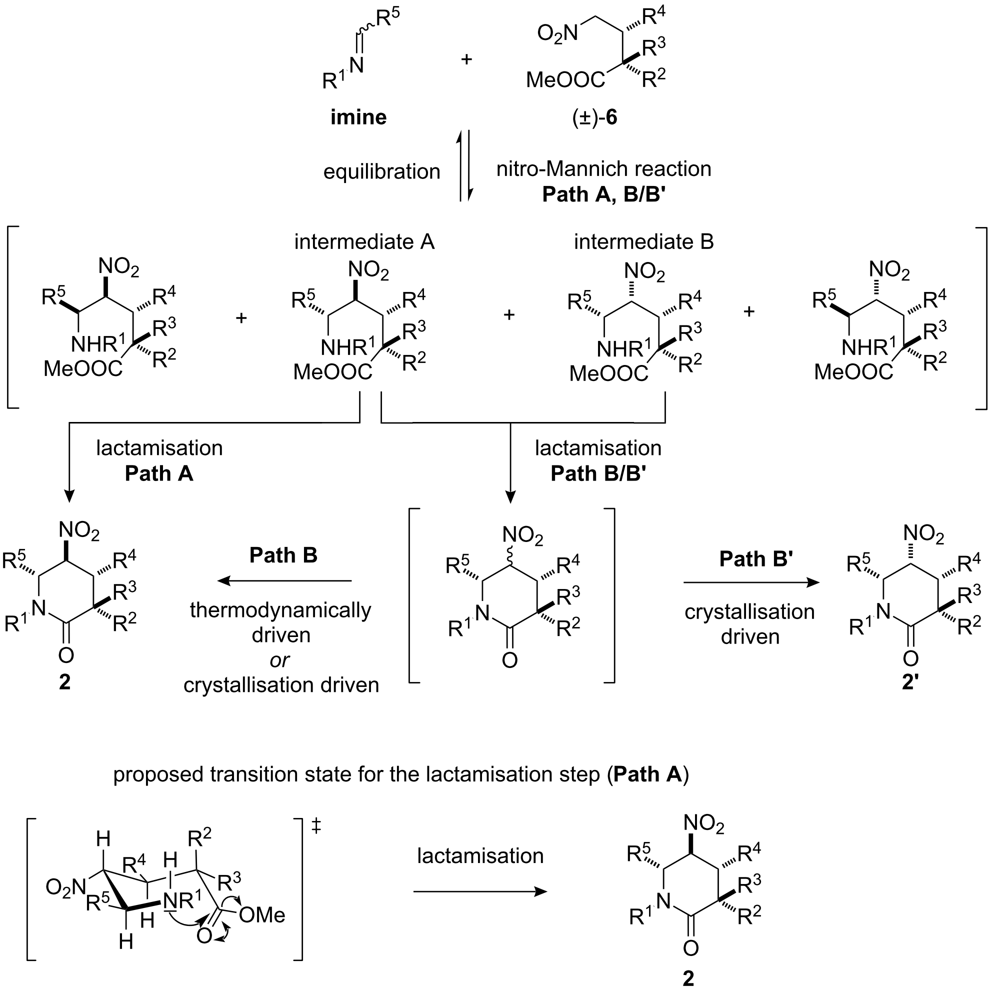
A further scrutiny of each hypothesis was, unfortunately, hampered by our failure to isolate or identify in situ the direct nitro-Mannich products from the reaction mixtures or to prepare them separately using standard procedures for a nitro-Mannich



Scheme 5: Nitro-Mannich/lactamisation cascade with cyclic imines. [a]Diastereomeric ratio in a crude reaction mixture, [b]H_2O/MeOH 1:1 mixture used as a solvent, [c]minor diastereomer **2m** isolated in 5% yield.

reaction with imines [109]. The first hypothesis, however, was not supported by the low diastereoselectivity in the formation of **2j**, in which presumably the relatively fast irreversible cyclisation outcompetes the equilibration processes. Considering the relatively broad range of imines and Michael adducts involved in the stereoselective cascade, we believe that the second or third explanations are the most plausible and that the observed diastereoselectivities in the formation of products **1a–j**, **2a–l** can be explained by following either Path A or B (Scheme 6).

The formation of product **2m'** with its exceptional 4,5-*cis* relative stereochemistry, can be explained by following path B' (Scheme 6). In this case the observed diastereoselectivity is believed to be driven by preferential crystallisation of the 4,5-*cis*-configured diastereoisomer in the reaction flask rather than thermodynamic equilibration. As such, this reaction represents an example of a crystallisation-induced diastereomeric transformation (CIDT) [104-108]. This is supported by the observation that **2m** and **2m'**, when exposed separately to simulated

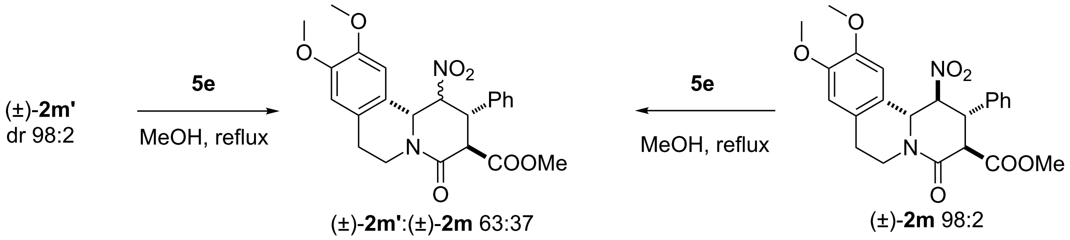


Scheme 6: Possible explanations for the observed high stereoselectivities in the nitro-Mannich/lactamisation cascade.

reaction conditions, epimerised at C5 to afford an identical 63:37 thermodynamic mixture of **2m**/**2m’**(Scheme 7; Figure 3) [110].

With all of the necessary variations to the nitro-Mannich/lactamisation cascade having been tested, optimised and scoped, we looked at the possibility of combining it with a catalytic asymmetric synthesis of a particular Michael adduct, so as to construct a one-pot enantio- and diastereoselective four-component coupling reaction (Scheme 8).

As described in our previous communication [61], the employment of bifunctional catalyst **9** [54,55] in a highly stereoselective two-stage one-pot cascade led to the formation of enan-



Scheme 7: Thermodynamically-driven epimerisation of 5-nitropiperidin-2-ones **2m** and **2m’**.

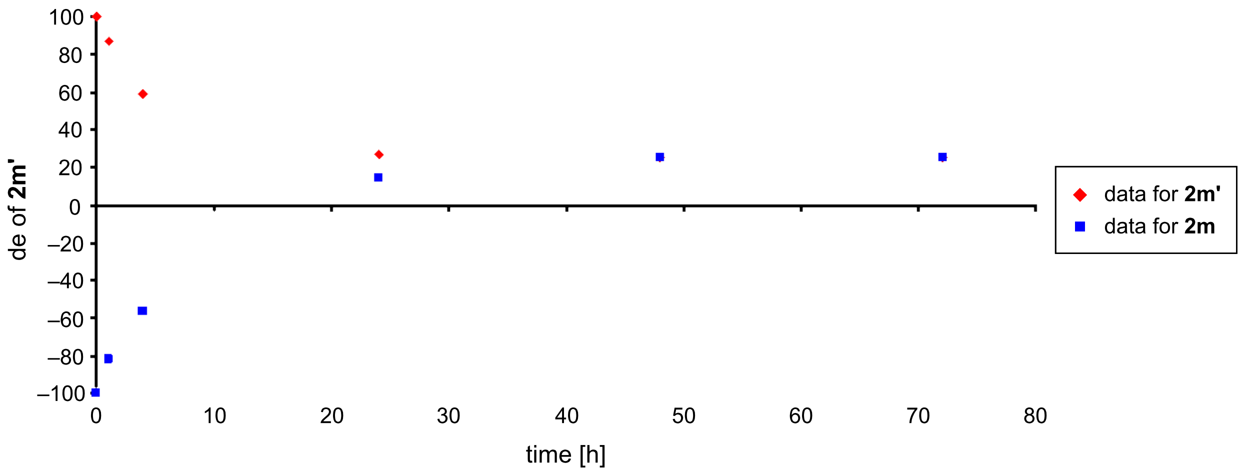
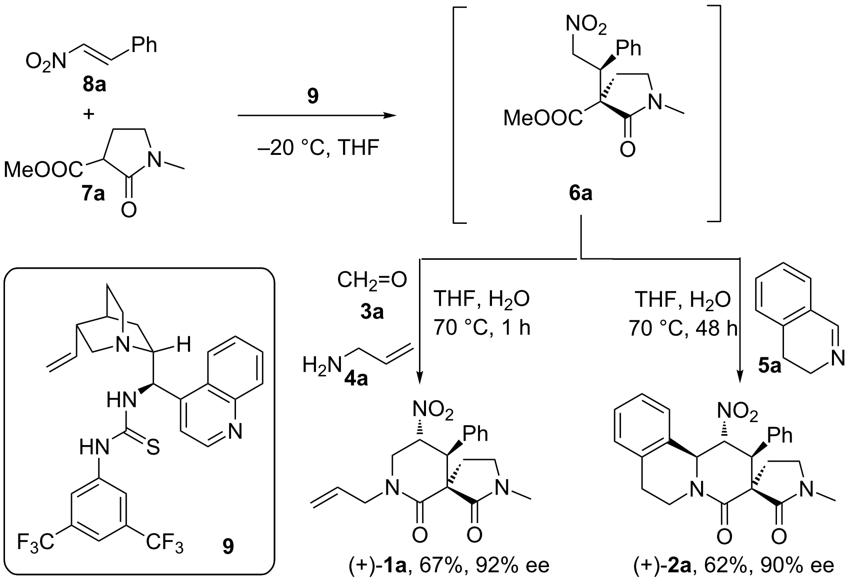


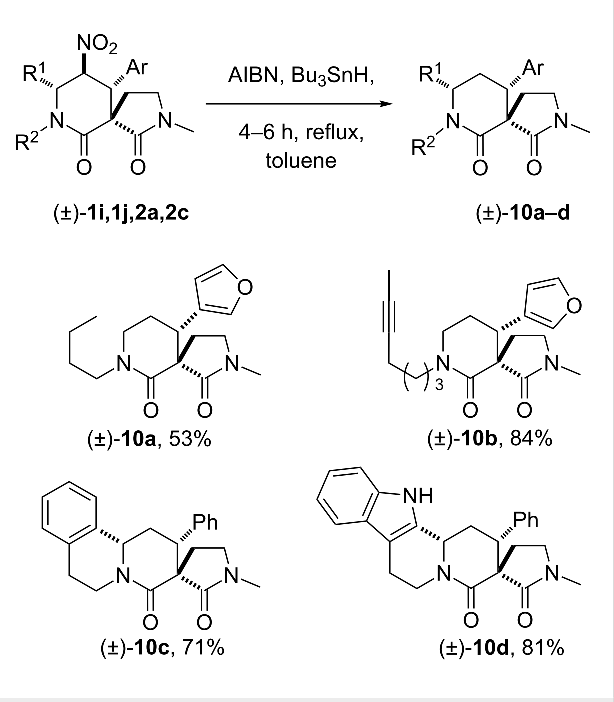
Figure 3: Thermodynamically driven epimerisation of 5-nitropiperidin-2-ones **2m** and **2m'**; identical diastereomeric excess measured for both diastereomers after 48 h and 72 h.



Scheme 8: One-pot three/four-component enantioselective Michael addition/nitro-Mannich/lactamisation cascade.

tiomerically highly enriched spirocycle (+)-**1a** (Scheme 8). In a repeat of the process but with the intention of targeting a piperidin-2-one ring-containing polycyclic scaffold, cyclic imine **5a** was added at the second stage. Tetracyclic spirolactam **2a** was isolated in high enantiomeric purity (90% ee) in good chemical yield (62%, Scheme 8) [111,112].

For the products of the nitro-Mannich/lactamisation cascade to be of use in alkaloid natural-product synthesis (or even simple stereoselective piperidine synthesis), controlled, reductive manipulation of both the nitro group and the lactam carbonyl were required. Although Nef-type oxidation followed by exhaustive reduction of the resulting carbonyl group was considered, Ono's radical procedure [113-116] was initially investigated. With some modification and optimisation, this was found to be compatible with the piperidin-2-one scaffold. Thus treatment of **2a** and **2c** with tributyltin hydride and AIBN in toluene under reflux smoothly afforded the protodenitrated products **10c** and **10d** in good yield (average 76% yield, Scheme 9). Other examples of successful nitro-group removal were also achieved when substrates **1i** and **1j**, lacking additional rings but bearing sensitive moieties (triple bond and furan

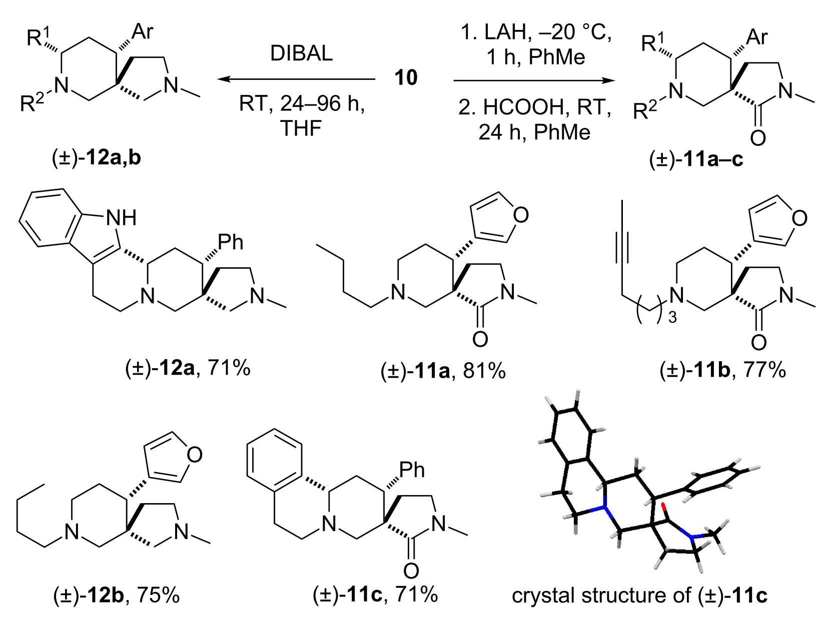


Scheme 9: Protodenitration of 5-nitropiperidin-2-ones.

moiety), were exposed to identical reaction conditions. The piperidin-2-ones **10a** and **10b** were obtained in 53% and 84%, respectively. The reduction of both piperidin-2-one and pyrrolidin-2-one heterocycles to piperidine or pyrrolidine rings by using a range of reagents is well-documented in the literature [117,118]. However, we believed that a controlled, chemoselective reduction would offer more options in any synthesis, and thus several commercially available reducing agents were screened in order to achieve selective reduction of only one lactam carbonyl. A notable find was that, by short exposure of denitrated heterocycle **10a–c** to $LiAlH_4$ in THF followed by quenching and treatment with HCOOH, spirocycles **11a–c** were obtained in good yields. The chemoselectivity of the reduction was unambiguously confirmed by single-crystal X-ray diffraction studies of **11c**. Furthermore, the use of an excess of DIBAL at room temperature smoothly afforded the diamines **12a** and **12b** (Scheme 10).

Conclusion

In summary, a versatile nitro-Mannich/lactamisation cascade for the direct synthesis of heavily decorated 5-nitropiperidin-2-ones and related heterocycles has been developed. A highly enantioenriched substituted 5-nitropiperidin-2-one was synthesised in a four-component one-pot cascade combining an enantioselective Michael addition with the diastereoselective nitro-Mannich/lactamisation cascade. Protodenitration and chemoselective reductive manipulation of the heterocycles could be used to install contiguous and fully substituted stereocentres in the synthesis of architecturally complex multicyclic alkaloid structures. The first applications of the developed methodology were disclosed recently as the total syntheses of paroxetine [60] and nakadomarin A [61-65] were successfully finished by employing the strategy as a fundamental synthetic tool. Further development is ongoing in our laboratory and the results will be disclosed in due course.



Scheme 10: Various reductions of denitrated heterocycles.

Supporting Information

Supporting Information File 1

General experimental, copies of ^{1}H and ^{13}C NMR spectra for all new compounds (**1a–j, 2a, 2a’’, 2m, 2m’, 6b–e, 10a–d, 11a–c, 12a,b**).
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-64-S1.pdf]

Supporting Information File 2

X-ray crystal structure of compound **2m’**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-64-S2.cif]

Supporting Information File 3

X-ray crystal structures of compounds **1g**, **2**, **2a’’**, **6e** and **11c**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-64-S3.cif]

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Facile isomerization of silyl enol ethers catalyzed by triflic imide and its application to one-pot isomerization–(2 + 2) cycloaddition

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Letter

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Abstract

A triflic imide (Tf_2NH) catalyzed isomerization of kinetically favourable silyl enol ethers into thermodynamically stable ones was developed. We also demonstrated a one-pot catalytic reaction consisting of (2 + 2) cycloaddition and isomerization. In the reaction sequence, Tf_2NH catalyzes both of the reactions.

Introduction

Silyl enol ethers, which are isolable equivalents of metal enolates, are useful and important intermediates in synthetic chemistry [1-3]. They react as a good nucleophile for the introduction of a carbon skeleton or a functional group at the α-position of a carbonyl group under appropriate conditions. Although silyl enol ethers are easily prepared from the corresponding ketones, the regiochemical issue would arise in the case of asymmetric ketones. Treatment with a strong base such as lithium diisopropylamide (LDA), followed by silyl chloride, under cryogenic conditions selectively affords kinetically favourable silyl enol ethers. On the other hand, thermodynamically stable ones can be predominantly obtained by the reaction with a silylating agent in the presence of a weak base, such as triethylamine, under equilibration conditions. Although the preparation of silyl enol ethers has been extensively studied, there have only been a limited number of studies on their isomerization [4-7]. Deyine reported that a catalytic amount of triethylammonium chloride promotes the isomerization to give thermodynamically favourable ones in moderate yield [5]. However, harsh conditions (reaction temperature: ca. 100 to 200 °C) were required for the complete equilibration. Yamamoto and co-workers reported that a $SnCl_4$–(BINOL monomethyl ether) complex (5–10 mol %) catalyzes the isomerization of silyl enol ethers at −78 °C [6]. By using this catalyst, they remarkably achieved the kinetic resolution of racemic silyl enol ethers. To make this isomerization synthetically useful and valuable, the development of more-reactive catalysts and a facile procedure would be required. In this communication, we describe isomerization of silyl enol ethers by an organocatalyst under mild conditions and its application to a one-pot catalytic reaction involving isomerization of silyl enol ethers and (2 + 2) cycloaddition.

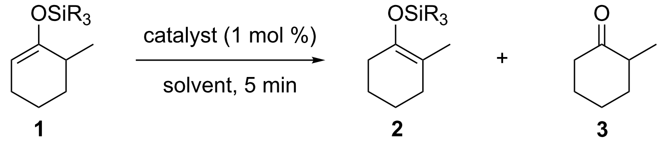
Results and Discussion

During our research on triflic imide (Tf_2NH)-catalyzed reactions [8], we accidentally found that the isomerization of kinetically favourable silyl enol ethers into thermodynamically stable ones occurs smoothly in the presence of Tf_2NH. When the TBS enol ether **1a** was treated with a catalytic amount of Tf_2NH (1.0 mol %) in CH_2Cl_2 at ambient temperature, isomerization resulted in the thermodynamically stable **2a** in 92% yield along with the recovered **1a** and ketone **3** (Table 1, entry 1). Equilibrium was reached within 5 min. The reaction using 20 mol % of Tf_2NH resulted in an increase of decomposition into **3** (entry 2). When the reaction was performed at −10 °C, the chemical yield of **2** was slightly improved (entry 3). In contrast, no isomerization was observed at −78 °C even after 1 h (entry 4). The catalytic isomerization reaction also proceeded in toluene (entry 5), but no (or almost no) isomerization occurred in CH_3CN (entry 6). When 10-camphorsulfonic acid (5 mol %) was used as a catalyst for 1 h, the isomerization was incomplete (entry 7). Enol ethers bearing typical silyl groups were also isomerized (entries 8–12). The decomposition of TMS enol ether **1b** into **3b** slightly increased at ambient temperature compared to that at −10 °C (entries 8 and 9). In the reaction of TIPS enol ether **1d**, the reaction rate decreased and more catalyst (5 mol %) was necessary to achieve equilibrium within 5 min (entry 12).

Several silyl enol ethers were explored for catalytic isomerization under the optimized conditions (1 mol % of Tf_2NH, −10 °C, CH_2Cl_2). The results are summarized in Table 2. All the kinetically favourable silyl enol ethers **1** were smoothly isomerized to the thermodynamically stable **2** in the presence of Tf_2NH.

A plausible mechanism for the catalytic isomerization is shown in Scheme 1. Silyl enol ether **1** is rapidly protonated by a catalytic amount of Tf_2NH to give the corresponding siloxonium cation **4**, and, then, another molecule of silyl enol ether **1** deprotonates the α-position of **4**. Equilibration results in the selective production of the thermodynamically more stable **2**. As a side reaction, the counter anion, Tf_2N^-, could attack the silicon atom of **2** to produce silyl triflic imide (R_3SiNTf_2) [8-12] and the corresponding ketone **3**. Therefore, the use of a large amount of Tf_2NH causes decomposition into **3** (Table 1, entry 2).

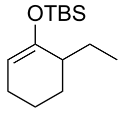
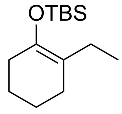
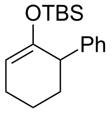
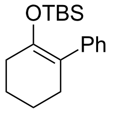
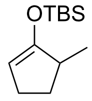
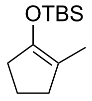
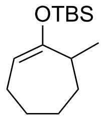
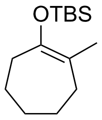
Table 1: Tf_2NH-catalyzed isomerization of silyl enol ethers.[a,b]



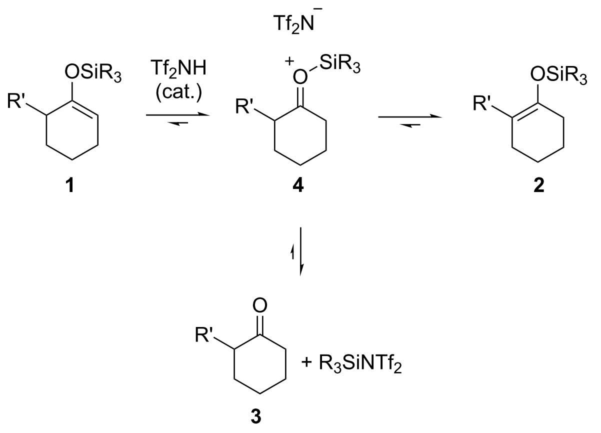
entry	**1** (SiR_3)	solvent	temp. (°C)	% yield		
				2	**1** (recovd.)	**3**
1	**1a** (TBS)	CH_2Cl_2	rt	92	6	2
2[c]	**1a**	CH_2Cl_2	rt	71	4	25
3	**1a**	CH_2Cl_2	−10	93	4	3
4[d]	**1a**	CH_2Cl_2	−78	1	97	2
5	**1a**	toluene	−10	92	5	2
6	**1a**	CH_3CN	−10	2	96	2
7[d,e,f]	**1a**	CH_2Cl_2	−10	25	64	11
8	**1b** (TMS)	CH_2Cl_2	rt	85	6	9
9	**1b**	CH_2Cl_2	−10	91	4	5
10	**1b**	CH_2Cl_2	−78	0	95	5
11	**1c** (TES)	CH_2Cl_2	−10	78	5	17
12[e]	**1d** (TIPS)	CH_2Cl_2	−10	92	3	5

[a]Yields were determined by GC–MS. [b]Regioisomer **1** (>99% purity) was used as a substrate. [c]20 mol % of catalyst was used. [d]Reactions were carried out for 1 h. [e]5 mol % of catalyst was used. [f]10-Camphorsulfonic acid was used as a catalyst.

Table 2: Substrate scope for Tf_2NH-catalyzed isomerization.[a,b]

entry	substrate	product	% yield of **2**	recovd. **1** (%)
1[c]	 **1e**	 **2e**	83	7
2[d]	 **1f**	 **2f**	89	11
3[e]	 **1g**	 **2g**	95	3
4[f,g]	 **1h**	 **2h**	99	1

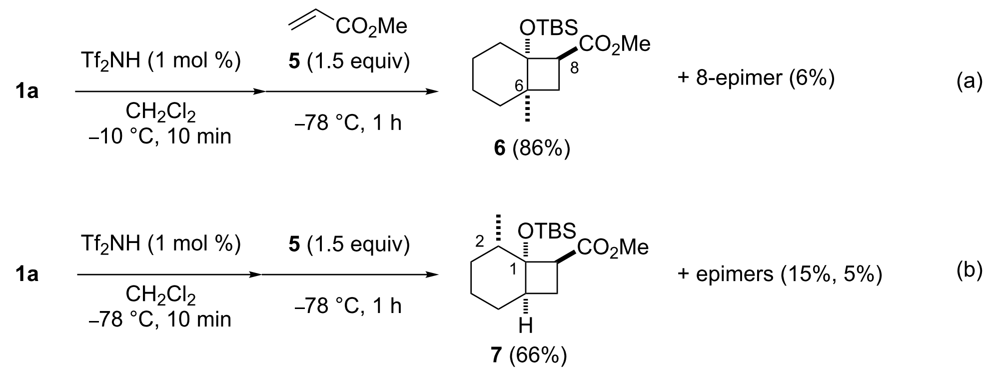
[a] Reactions were performed under the same conditions as given in Table 1, entry 3. [b] Yields were determined by GC–MS. [c] Purity of **1e** is 99% (including isomer **2e** (1%)). [d] Purity of **1f** is 100% (no isomer **2f**). [e] Purity of **1g** is 95% (including isomer **2g** (5%)). [f] Purity of **1h** is 93% (including isomer **2h** (7%)). [g] 5 mol % of Tf_2NH was used.



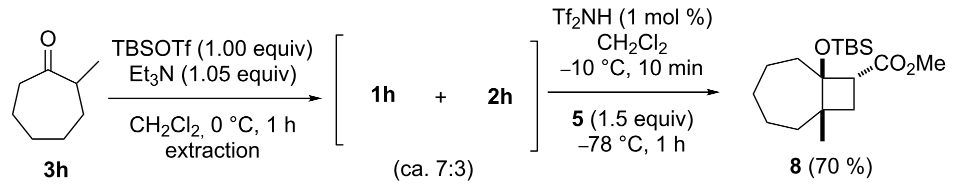
Scheme 1: Plausible mechanism for Tf_2NH-catalyzed isomerization of silyl enol ethers.

We have previously reported the Tf_2NH catalyzed (2 + 2) cycloaddition of silyl enol ethers with acrylates generating substituted cyclobutanes [10]. We are intrigued that the isomerization of silyl enol ethers and successive (2 + 2) cycloaddition could be promoted by Tf_2NH in a one-pot reaction. When **1a** was treated with Tf_2NH (1 mol %) under the isomerization conditions (−10 °C), followed by the addition of methyl acrylate (**5**) at −78 °C, 6-methylbicyclo[4.2.0]octane **6** and its diastereomer were obtained in 86% and 6%, respectively (Scheme 2a). No formation of their regioisomers was observed. The obtained compound **6** is identical to the product in the reaction of **2a** with **5** [10,13]. It is noteworthy that two different reactions, isomerization and (2 + 2) cycloaddition, are catalyzed by Tf_2NH [14-18]. By contrast, when **1a** reacted with **5** in the presence of Tf_2NH at −78 °C, (2 + 2) cycloaddition directly proceeded to give 2-methylbicyclo[4.2.0]octane **7** in 66% yield along with the formation of two diastereomers (Scheme 2b). Obviously, at this temperature, no isomerization of **1a** occurred.

The above finding can be applied to (2 + 2) cycloaddition, even if a mixture of regioisomeric silyl enol ethers is used as a substrate (Scheme 3). Thus, the reaction of ketone **3h** with TBSOTf in the presence of NEt_3 afforded a regioisomeric mixture of silyl enol ethers **1h** and **2h** (ca. 7:3). After extraction to remove the amine reagent, the crude regioisomeric mixture was subjected to Tf_2NH at −10 °C and subsequently reacted with acrylate **5** to afford (2 + 2) cycloadduct **8** in 70% yield. This result indicates that the Tf_2NH catalyzed reaction can save not



Scheme 2: Regioselective formation of bicyclo[4.2.0]octanes from the same substrates by the isomerization–(2 + 2) cycloaddition procedure.



Scheme 3: Formation of bicyclo[5.2.0]octane from the regioisomeric mixture of silyl enol ethers.

only the separation to remove the corresponding kinetically favourable regioisomer, but also loss of the undesired regioisomer.

Conclusion

In summary, we have developed a new catalytic isomerization reaction of silyl enol ethers. Kinetically favourable silyl enol ethers were smoothly converted into thermodynamically stable ones by treatment with a catalytic amount of Tf$_2$NH under mild conditions. Moreover, we demonstrated that the one-pot reaction involves two different catalytic reactions, an isomerization and a (2 + 2) cycloaddition.

Supporting Information

Supporting Information File 1

Experimental details and spectral data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-73-S1.pdf]

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Enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes catalyzed by binaphthyl-derived organocatalysts

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Letter

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Abstract

The highly enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes, promoted by binaphthyl-modified chiral bifunctional organocatalysts is described. This reaction afforded the chiral functionalized naphthoquinones in high yields (81–95%) and excellent enantioselectivities (91–98% ee) under low catalyst loading (1 mol %).

Introduction

Quinone and naphthoquinone structures exist in a large number of natural products and biologically active molecules [1-4]. Many of these naturally occurring naphthoquinones and their synthetic analogues are important precursors for the synthesis of natural products and pharmaceuticals [5-9]. The stereoselective formation of C–C bonds is of great importance for the synthesis of enantiomerically pure, biologically active organic compounds [10,11]. It is widely recognized that the Michael addition is one of the most versatile and general methods for C–C bond formation in organic synthesis [12], and intensive research efforts have been directed toward the development of enantioselective catalytic protocols for this reaction [13-15]. The organocatalyst-mediated enantioselective conjugate addition reactions, which are both powerful and environmentally friendly, have been subjected to rigorous investigation in recent years [16-22]. The asymmetric Michael addition of various nucleophiles to nitroalkenes is of great interest, because the products obtained are versatile intermediates in organic synthesis [23-26]. Extensive studies have been devoted to the development of asymmetric conjugate additions of 1,3-dicarbonyl compounds to various Michael acceptors [27-33]. Recently, the groups of Du and Zhou reported a highly enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinones to nitroalkenes catalyzed by chiral, bifunctional tertiary-amine thioureas, thiophosphorodiamides, and squaramide-based organocatalysts [34-36].

Findings

In the framework of our research program for the development of synthetic methods for the enantioselective construction of stereogenic carbon centers [37-42], we recently reported the enantioselective Michael addition of active methines to nitroalkenes [43,44]. Herein, we describe the direct enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone with nitroalkenes, catalyzed by bifunctional organocatalysts (Figure 1) that bear both central and axial chiral elements [45-47].

We initially investigated the reaction system with 2-hydroxy-1,4-naphthoquinone (**1**) and nitrostyrene **2a** in the presence of 10 mol % of Takemoto's catalyst **I** in acetonitrile at room temperature, to determine the optimum reaction conditions for the catalytic, enantioselective Michael addition. This reaction exhibited good yield and high enantioselectivity (89% ee, Table 1, entry 1). In order to enhance the enantioselectivity, other bifunctional organocatalysts **II**–**VIII** were evaluated in the model reaction (Table 1, entries 2–8). The quinine-derived thiourea catalyst **II** was less effective (Table 1, entries 1 and 2),

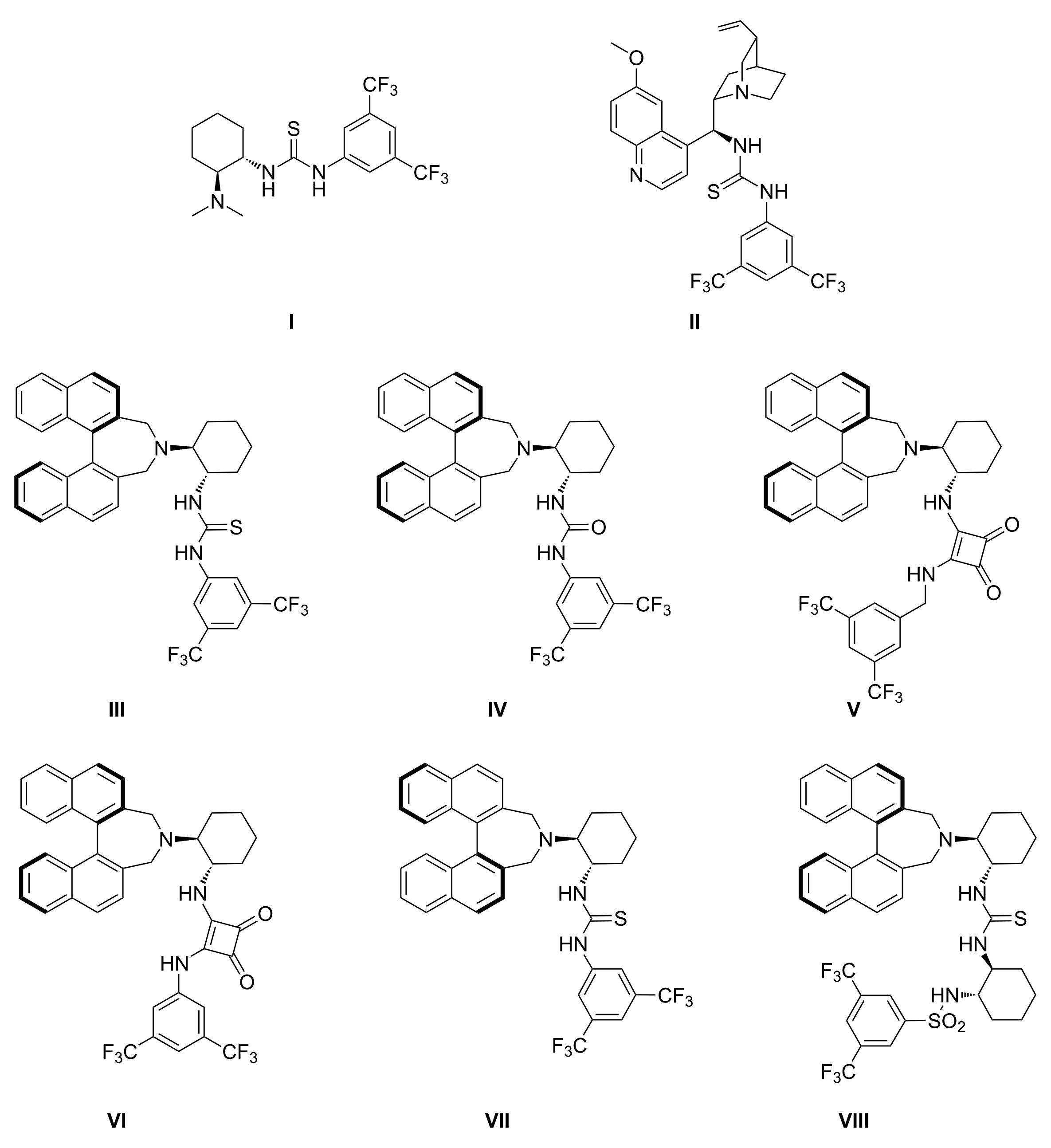


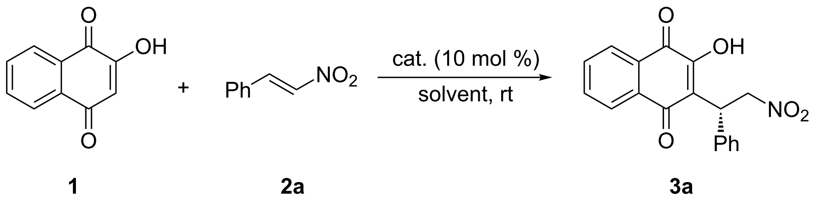
Figure 1: Structures of chiral organocatalysts.

whereas the binaphthyl-modified, chiral, bifunctional organocatalysts **III–VIII**, bearing both central and axial chiral elements, effectively promoted the addition reaction in high yield, with high enantioselectivity (78–97% ee, Table 1, entries 3–8). Catalyst **III** gave the desired product **3a** with high enantioselectivity (97%, Table 1, entry 3), whereas the diastereomeric catalyst **VII** afforded product **3a** in lower enantioselectivity (78% ee, Table 1, entry 7). These results demonstrate that the central and axial chiral elements in the chiral amine-thiourea catalyst **III** are matched, thus enhancing the stereochemical control, whereas in the diastereomeric catalyst **VII** this is not the case.

Different solvents were then tested in the presence of 10 mol % of catalyst **III** together with 2-hydroxy-1,4-naphthoquinone (**1**) and nitrostyrene **2a** in order to further improve the selectivity of the reaction. Aprotic solvents, such as acetonitrile, toluene, dichloromethane, THF, diethyl ether, were well tolerated in this conjugate addition without a significant decrease of enantioselectivities (89–99% ee, Table 1, entries 3 and 9–12). Remarkably, water and brine also afforded products in good yields; however, the selectivity dropped significantly (Table 1, entries 13 and 14). Among the solvents probed, the best results (92% yield and 99% ee) were achieved when the reaction was conducted in THF (Table 1, entry 11). The present catalytic system tolerates catalyst loading down to 5, 2.5, and 1 mol % without compromising the yield or enantioselectivity (Table 1, entries 11 and 15–17).

With the optimized reaction conditions in hand, the scope of the methodology was investigated in reactions with 2-hydroxy-1,4-naphthoquinone (**1**) and various nitroalkenes **2a–l** in the presence of 1 mol % of catalyst **III** in THF at room temperature (Table 2). A range of electron-donating and electron-withdrawing substitutions on the β-aryl ring of the nitrostyrenes **2b–h** provided reaction products in high yields and excellent enantioselectivities. Heteroaryl- and naphthyl-substituted nitroalkenes **2i** and **2j** provided products with high selectivity

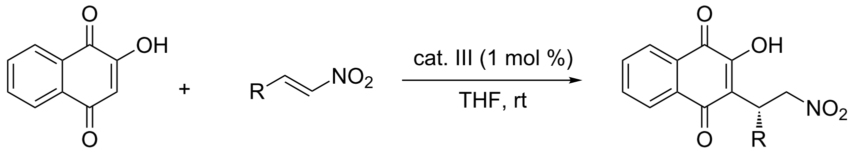
Table 1: Optimization of the reaction conditions.



entry	cat.	solvent	time (h)	yield (%)[a]	ee (%)[b]
1	**I**	CH_3CN	2	84	89
2	**II**	CH_3CN	2	87	77
3	**III**	CH_3CN	2	96	97
4	**IV**	CH_3CN	2	95	87
5	**V**	CH_3CN	2	93	81
6	**VI**	CH_3CN	2	90	93
7	**VII**	CH_3CN	2	85	78
8	**VIII**	CH_3CN	2	88	93
9	**III**	toluene	4	75	95
10	**III**	DCM	4	93	89
11	**III**	THF	2	92	99
12	**III**	Et_2O	3	81	91
13	**III**	H_2O	17	89	19
14	**III**	brine	17	86	37
15[c]	**III**	THF	2	90	98
16[d]	**III**	THF	2	90	99
17[e]	**III**	THF	2	89	99

[a] Isolated yield.
[b] Enantiopurity was determined by HPLC analysis using chiralcel OJ-H column.
[c] Reaction was carried out in the presence of 5 mol % catalyst.
[d] Reaction was carried out in the presence of 2.5 mol % catalyst.
[e] Reaction was carried out in the presence of 1 mol % catalyst.

Table 2: Catalytic asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone **1** to nitroalkenes **2**.



1 **2** **3**

entry	**2**, R	time (h)	yield (%)[a]	ee (%)[b]
1	**2a**, Ph	2	**3a**, 89	99
2	**2b**, *p*-MeC_6H_4	2	**3b**, 93	95
3	**2c**, *p*-$MeOC_6H_4$	4	**3c**, 81	99
4	**2d**, *p*-FC_6H_4	3	**3d**, 95	95
5	**2e**, *p*-ClC_6H_4	3	**3e**, 90	91
6	**2f**, *p*-BrC_6H_4	3	**3f**, 95	95
7	**2g**, *o*-FC_6H_4	4	**3g**, 95	95
8	**2h**, *o*-BrC_6H_4	4	**3h**, 95	95
9	**2i**, 2-thienyl	5	**3i**, 93	93
10	**2j**, 2-naphthyl	5	**3j**, 93	99
11	**2k**, isobutyl	5	**3k**, 90	97

[a] Isolated yield.
[b] Enantiopurity was determined by HPLC analysis using chiralcel OJ-H (**3a**–**j**) and chiralpak AD-H (for **3k**) columns.

(93–99% ee, Table 2, entries 9 and 10). The β-alkyl-substituted nitroalkene, 4-methyl-1-nitropent-1-ene (**2k**), was also an acceptable starting material and provided the corresponding Michael adducts in high yield and excellent enantioeselectivity (97% ee, Table 2, entry 11).

In conclusion, we have developed a highly efficient catalytic, enantioselective Michael addition of 2-hydroxy-1,4-naphthoquinone to nitroalkenes using a binaphthyl-derived tertiary amine-thiourea organocatalyst. The various types of nitroalkylated naphthoquinone derivatives were obtained in good to high yields with excellent enantioselectivities (91–99% ee) for all the substrates examined in this work. We believe that this method should provide a practical entry for the preparation of chiral nitroalkylated naphthoquinone derivatives. Further details and application of this asymmetric Michael addition of 2-hydroxy-1,4-naphthoquinone nucleophiles will be presented in due course.

Experimental

General procedure for the Michael addition of 2-hydroxy-1,4-naphthoquinone (1) with nitroalkenes 2: A mixture of 2-hydroxy-1,4-naphthoquinones (**1**, 34.8 mg, 0.2 mmol) and catalyst **III** (1.3 mg, 0.002 mmol) in THF (0.4 mL) was stirred at room temperature for 5 min. A solution of nitroalkene **2** (0.2 mmol) was added. The reaction mixture was stirred for 2–5 h at room temperature. After completion of the reaction, the resulting solution was concentrated in vacuo and the obtained residue was purified by flash chromatography (EtOAc–hexane) to afford the corresponding Michael adducts **3**. Products **3** are known compounds, and their data were identical to those reported in the literature [34-36].

Supporting Information

Supporting Information File 1

Characterization data of products **3**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-78-S1.pdf]

Acknowledgements

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Chiral multifunctional thiourea-phosphine catalyzed asymmetric [3 + 2] annulation of Morita–Baylis–Hillman carbonates with maleimides

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Letter

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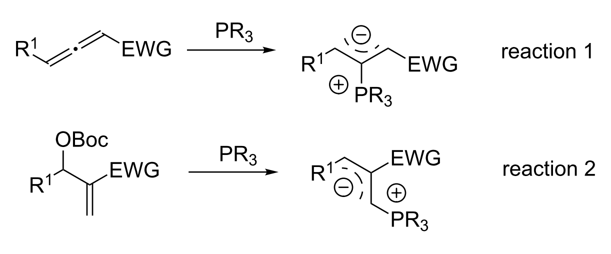
Abstract

We have developed a multifunctional thiourea-phosphine catalyzed asymmetric [3 + 2] annulation of Morita–Baylis–Hillman (MBH) carbonates with maleimides, which can efficiently construct functionalized cyclopentenes bearing three contiguous stereocenters in moderate to excellent yields and excellent diastereo- and enantioselectivities. A plausible mechanism has been also proposed on the basis of control experiments and previous literature.

Introduction

Highly functionalized cyclopentene derivatives are important subunits in a variety of biologically active molecules and have attracted the broad attention of synthetic and pharmaceutical chemists [1,2]. Among numerous synthetic approaches, phosphine-mediated [3 + 2] annulation of electron-deficient olefins is an efficient method to construct this interesting structural motif [3-10]. According to the pioneering work of Lu [11-20], all phosphine-mediated [3 + 2] annulations proceeded through an important intermediate "1,3-dipolar synthon". The formation of a 1,3-dipolar synthon by using a catalytic amount of phosphines have been directed toward the following two paths: phosphines attack the middle carbon atom of allenes to produce the 1,3-dipolar synthon (Scheme 1, reaction 1), and phosphines add to the β-position of MBH carbonate to remove carbon dioxide and *tert*-butanol, affording the 1,3-dipolar synthon (Scheme 1, reaction 2). Concerning the asymmetric [3 + 2] annulation catalyzed by chiral phosphines, Zhang and co-workers first reported the asymmetric [3 + 2] annulation of allenoates with acrylates catalyzed by a bicyclic chiral phosphine in 1997 [21]. Moreover, Fu [22-24], Marinetti [25-28], Lu [29-31] and other researchers [32-36] have also developed asymmetric [3 + 2] annulations of allenoates to give the corresponding cyclopentene derivatives in good yields with excellent enantioselectivities [37].



Scheme 1: Paths to the formation of 1,3-dipolar synthons by using a catalytic amount of phosphines.

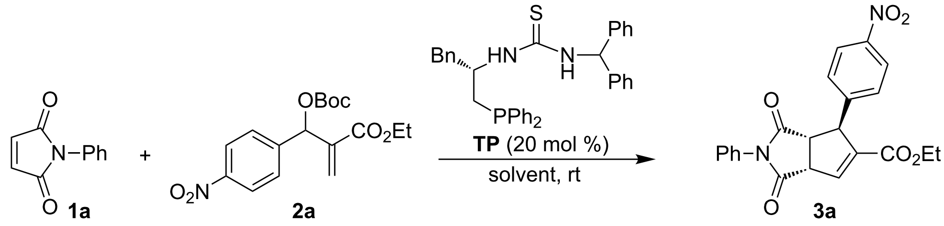
On the other hand, some examples of phosphine-catalyzed [3 + 2] annulation of MBH carbonates with electron-deficient alkenes have been reported in the literature recently. Lu and co-workers first disclosed the formation of 1,3-dipoles through phosphine-catalyzed MBH carbonates under mild conditions, which can efficiently react with various electron-deficient olefins to afford the desired cyclic products in good yields along with high regioselectivities, through intra- and intermolecular [3 + *n*] annulations [38-47]. To the best of our knowledge, there is little in the literature regarding the asymmetric version of this reaction. In 2010, Tang and co-workers reported the first example of asymmetric intramolecular [3 + 2] annulations of MBH carbonates tethered with another electron-deficient olefin in the presence of spirobiindane-based chiral phosphines, giving the corresponding cycloadducts in good yields along with high ee values [48]. Barbas and co-workers first reported asymmetric intermolecular [3 + 2] cycloaddition of MBH carbonates with methyleneindolinones to afford the corresponding spirocyclopentaneoxindoles in good yields and high ee values in 2011 [49]. Moreover, Lu and co-workers have recently explored a series of thiourea-phosphine catalysts derived from L-threonine, which are effective catalysts in the [3 + 2] annulation of MBH carbonates with isatylidene malononitriles to give the desired products in high yields with high enantioselectivities [50]. Furthermore, our group recently also synthesized a series of L-phenylalanine-derived multifunctional thiourea-phosphine catalysts and used them in the [3 + 2] annulation of MBH carbonates with trifluoroethylidenemalonates to give the cycloadducts in high yields along with excellent diastereo- and enantioselectivities [51]. Herein we wish to report the development of a multifunctional thiourea-phosphine catalyzed asymmetric [3 + 2] annulation of MBH carbonates with maleimides, which can efficiently construct functionalized cyclopentene derivatives bearing three contiguous stereocenters in moderate to excellent yields along with excellent diastereo- and enantioselectivities.

Results and Discussion

In our previous work, it was shown that chiral multifunctional thiourea-phosphines were excellent catalysts for the asymmetric aza-MBH reaction, asymmetric allylic substitution of MBH adducts, and asymmetric [3 + 2] annulation of MBH carbonates with electron-deficient olefins [52-56]. Hence, we initially used multifunctional thiourea-phosphine (TP), which could be easily prepared from L-phenylalanine in four steps [57], as a catalyst to investigate the asymmetric [3 + 2] annulation of *N*-phenylmaleimide (**1a**) with MBH carbonate **2a** in toluene at room temperature. We were pleased to find that the corresponding highly functionalized cyclopentene **3a** was obtained in 54% yield with 96% ee after 24 h (Table 1, entry 1). The examination of solvent effects revealed that toluene is the best solvent (Table 1, entries 2–4). Increasing the ratio of **1a**/**2a** from 1:1.3 to 2:1 afforded **3a** in 74% yield and 96% ee, while continuously increasing the ratio of **1a**/**2a** to 4:1 gave **3a** in lower yield (Table 1, entries 5 and 6).

Having identified the optimal reaction conditions, we next set out to examine the scope and limitations of this asymmetric [3 + 2] annulation of maleimides with MBH carbonates, and the results are summarized in Table 2. All of the reactions proceeded smoothly under the optimal conditions, providing annulation products with good to excellent diastereo- and enantioselectivities. Using MBH carbonate **2a** as a substrate, we examined its reaction with maleimides **1b**–**1e** and found that the reactions proceeded smoothly to give the corresponding products **3b**–**3e** in excellent yields along with excellent ee values (Table 2, entries 2–5). Taking *N*-benzhydrylmaleimide (**1d**) as a substrate, we found that substrates with an electron-withdrawing substituent on the aromatic ring of MBH carbonates **2** produced **3f** and **3g** in good yields and excellent ee values (Table 2, entries 6 and 7), and MBH carbonate **2d** gave the corresponding annulation product **3h** in 3:1 dr value with 74% yield of major isomer and 97% ee (Table 2, entry 8). A variety of MBH carbonates **2** having either electron-donating or -withdrawing groups as substituents at the *para*- and *meta*-position of the benzene ring and *N*-methylmaleimide (**1b**) underwent this asymmetric [3 + 2] annulation smoothly, affording the corresponding products **3** in moderate to excellent yields with excellent ee values upon lengthening of the reaction time (Table 2, entries 9–11, 13–15). Substrate **2k**, incorporating a heteroaromatic group, could also react with **1b** under the same reaction conditions, giving the corresponding cyclopentene **3p** in 69% yield with 96% ee, and substrates **2l** and **2m** derived from

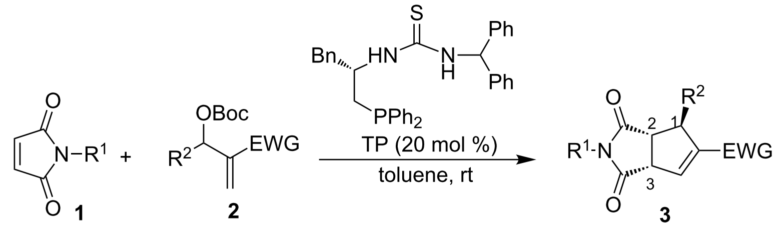
Table 1: Optimization of the reaction conditions for asymmetric [3 + 2] annulation of MBH carbonates and maleimides.



entry[a]	**1a**/**2a**	solvent	yield (%)[b]	ee (%)[c]
1	1/1.3	toluene	54	96
2	1/1.3	$CHCl_3$	54	96
3	1/1.3	THF	25	90
4	1/1.3	CH_3CN	12	43
5[d]	2/1	toluene	74	96
6[e]	4/1	toluene	62	96

[a]Reactions were performed with **1a** (0.1 mmol) and **2a** (0.13 mmol) in toluene (1.0 mL) at room temperature for 24 h. [b]Isolated yield of major isomer. [c]Determined by chiral HPLC. [d]Reaction was performed with **1a** (0.2 mmol) and **2a** (0.1 mmol) in toluene (1.0 mL) at room temperature for 24 h. [e]Reaction was performed with **1a** (0.4 mmol) and **2a** (0.1 mmol) in toluene (1.0 mL) at room temperature for 24 h.

Table 2: Substrate scope of asymmetric [3 + 2] annulation.



entry[a]	R^1	R^2	EWG	yield (%)[b]	ee (%)[c]
1	**1a**, Ph	**2a**, 4-$NO_2C_6H_4$	CO_2Et	**3a**, 74	96
2	**1b**, Me	**2a**, 4-$NO_2C_6H_4$	CO_2Et	**3b**, 99	98
3	**1c**, Bn	**2a**, 4-$NO_2C_6H_4$	CO_2Et	**3c**, 86	94
4	**1d**, benzhydryl	**2a**, 4-$NO_2C_6H_4$	CO_2Et	**3d**, >99	98
5	**1e**, 1-methylnaphthyl	**2a**, 4-$NO_2C_6H_4$	CO_2Et	**3e**, 91	96
6	**1d**, benzhydryl	**2b**, 3-$NO_2C_6H_4$	CO_2Et	**3f**, 87	94
7	**1d**, benzhydryl	**2c**, 4-CNC_6H_4	CO_2Et	**3g**, 84	96
8[d,e]	**1d**, benzhydryl	**2d**, 4-BrC_6H_4	CO_2Et	**3h**, 74	97
9[e]	**1b**, Me	**2d**, 4-BrC_6H_4	CO_2Et	**3i**, 79	95
10[e]	**1b**, Me	**2e**, 4-ClC_6H_4	CO_2Et	**3j**, 90	96
11[e]	**1b**, Me	**2f**, 3-ClC_6H_4	CO_2Et	**3k**, 81	97
12[f]	**1b**, Me	**2g**, 2-ClC_6H_4	CO_2Et	**3l**, 39	73
13[f]	**1b**, Me	**2h**, C_6H_5	CO_2Et	**3m**, 74	94
14[f]	**1b**, Me	**2i**, 4-MeC_6H_4	CO_2Et	**3n**, 64	96
15[f]	**1b**, Me	**2j**, 4-$MeOC_6H_4$	CO_2Et	**3o**, 55	98
16[f]	**1b**, Me	**2k**, 2-furyl	CO_2Et	**3p**, 69	96
17	**1b**, Me	**2l**, 4-$NO_2C_6H_4$	COMe	**3q**, >99	97
18	**1b**, Me	**2m**, 4-$NO_2C_6H_4$	COMe	**3r**, 92	98
19[f]	**1b**, Me	**2n**, $(CH_3)_2CH$	CO_2Et	–	–

[a]Reactions were performed with **1** (0.2 mmol), **2** (0.1 mmol) in toluene (1.0 mL) at room temperature for 24 h. [b]Isolated yield of major isomer. [c]Determined by chiral HPLC. [d]dr = 3:1. [e]Reaction was performed for 36 h. [f]Reaction was performed for 48 h.

methyl vinyl ketone (MVK) afforded the corresponding annulation products **3q** and **3r** in excellent yields and ee values under the standard conditions (Table 2, entries 16–18). The absolute configuration of the major product **3r** was determined as (1*S*,2*R*,3*S*) by X-ray crystal structure. Its ORTEP plot is shown in Figure 1 and the corresponding CIF data are presented in the Supporting Information File 2 [58]. As for MBH carbonate **2g**, having a chlorine substituent at the *ortho*-position of the aromatic ring, this produced **3l** in lower yield and ee value, perhaps due to the steric effect; reaction of MBH carbonate **2n** derived from isobutyraldehyde did not occur (entries 12 and 19). When we utilized dimethyl maleate or dimethyl fumarate instead of maleimides, it was found that the reactions could not be performed either.

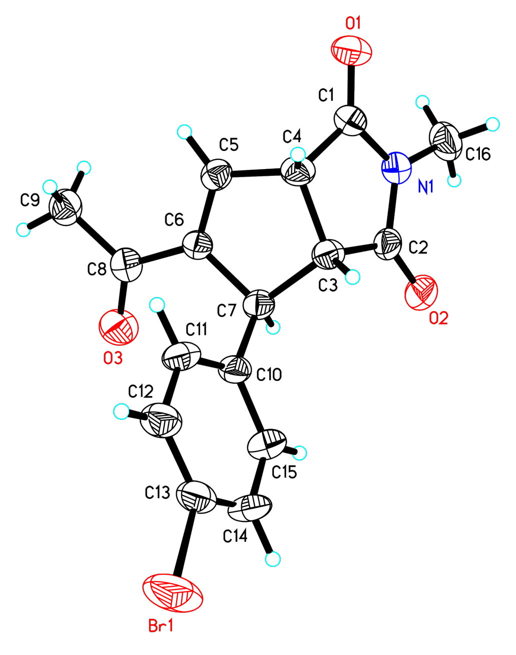


Figure 1: The ORTEP plot of compound **3r**.

As aforementioned, increasing the ratio of **1a**/**2a** from 1:1.3 to 2:1 obtained the highest yield. In order to explain this finding, three control experiments were performed in $CDCl_3$ and the results were studied by using ^{31}P NMR spectroscopy (Figure 2, also see Figure SI-1 in the Supporting Information File 1). The NMR studies revealed that catalyst TP seems to react with *N*-phenylmaleimide (**1a**) to form a new species (Figure 2, spectra b), which costs some maleimide **1a**. Thus, the excess **1a** has to be added in order to make the reaction complete. This is why increasing the ratio of **1a**/**2a** raised the yield of product **3a** (Table 1, entry 5). On the other hand, if too much maleimide **1a** is used in this reaction, it will waste some of the catalyst TP, leading to a decrease in the yield of product **3a** (Table 1, entry 6). The allylic phosphorus ylide species can be recognized in spectra c from the combination of **2d** and TP (1:1) (Figure 2, also see Figure SI-1 in the Supporting Information File 1) [59].

As reported before [15,51], TP attacks MBH carbonate to afford allylic phosphorus ylide **I**, which attacked the maleimide to produce intermediate **II** (Scheme 2). Since there is a steric effect between the phenyl group and the benzyl group in inter-

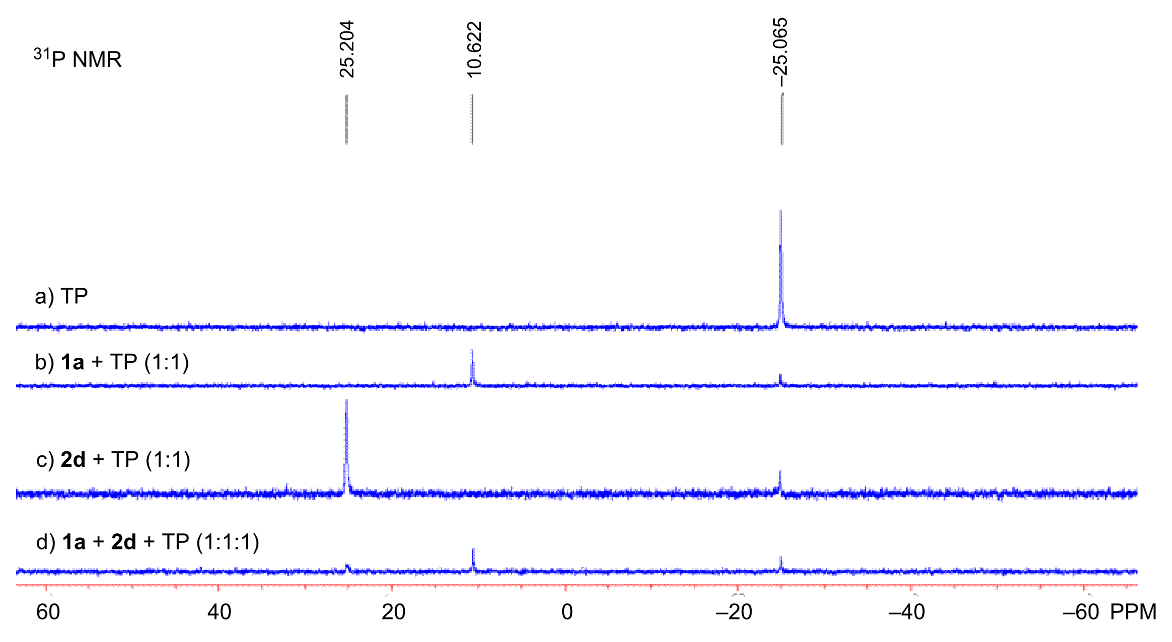
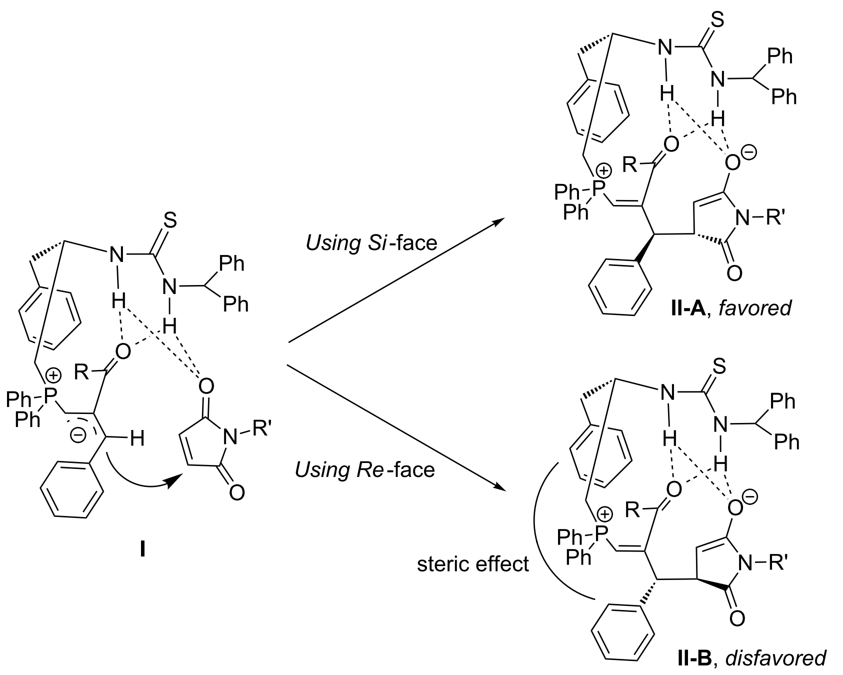


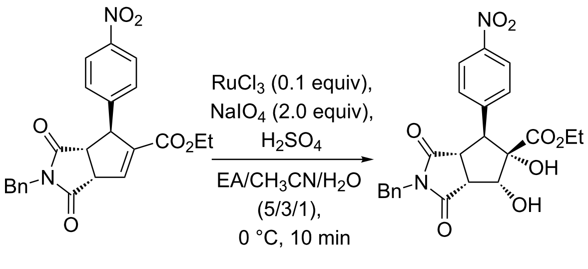
Figure 2: ^{31}P NMR spectra (161.9 MHz, $CDCl_3$) of control experiments.



Scheme 2: Proposed transition models.

mediate **II-B**, allylic phosphorus ylide **I** using its *Si*-face to attack maleimide is favored (intermediate **II-A**). Undergoing Michael addition and elimination of catalyst along with the double-bond formation, intermediate **I** affords the corresponding highly functionalized cyclopentene product and completes the catalytic cycle. The control experiments demonstrated that catalyst TP can react with maleimide, affording an unidentified complex and partially wasting maleimide and catalyst (spectra d in Figure 2). Hypothetically, the activity of the in situ generated allylic phosphorous ylide **I** is crucial for the yield of product. If the activity of phosphorous ylide is not high enough, it may deprotonate the NH proton in TP, which will cause the catalyst to lose activity (See Table 2, entries 12–16). In addition, if the phosphorous ylide is not active enough to react with maleimide, maleimide can directly react with the catalyst to form the other unidentified species as indicated in the ^{31}P NMR spectroscopy (spectra b in Figure 2), which may retard the desired catalytic cycle.

To illustrate the synthetic utility of these products **3** obtained from the above asymmetric [3 + 2] annulation, the further transformation of **3c** was performed in the presence of $RuCl_3$ and $NaIO_4$ under mild conditions (Scheme 3) [22,60]. Upon dihydroxylation of **3c**, the corresponding product **4c** containing five stereocenters was produced in 69% yield and good diastereoselectivity on the basis of NMR spectroscopic data (dr = 20:1, see Supporting Information File 1).



Scheme 3: Dihydroxylation of **3c**.

Conclusion

In conclusion, we have developed a novel multifunctional thiourea-phosphine catalyzed asymmetric [3 + 2] annulation of MBH carbonates with maleimides, which can efficiently construct functionalized cyclopentenes bearing three contiguous stereocenters in moderate to excellent yields and excellent diastereo- and enantioselectivities, and the product can be efficiently transformed into a cyclopentane containing five stereocenters under mild conditions, which was difficult to construct by other synthetic methodologies. Current efforts are in progress to apply this new methodology to synthesize biologically active products.

Experimental

General procedure for asymmetric [3 + 2] annulation

Under an argon atmosphere, a mixture of maleimide **1** (0.2 mmol), MBH carbonate **2** (0.2 mmol) and catalyst TP (0.02 mmol, 11 mg) in toluene (1.0 mL) was stirred at room temperature for 24–48 h. Then the solvent was removed under reduced pressure, and the residue was chromatographed on silica gel (elution with petroleum ether/EtOAc 10:1–4:1) to provide compound **3**.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization data of compounds given in this article.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-121-S1.pdf]

Supporting Information File 2

Crystal structure data of compound **3r**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-121-S2.pdf]

Supporting Information File 3

cif data of **3r**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-121-S3.cif]

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Asymmetric total synthesis of smyrindiol employing an organocatalytic aldol key step

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Full Research Paper

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Abstract

The first organocatalytic asymmetric synthesis of smyrindiol, by using an (*S*)-proline catalyzed enantioselective intramolecular aldol reaction as the key step, is described. Smyrindiol was synthesized from commercially available 2,4-dihydroxybenzaldehyde in 15 steps, with excellent stereoselectivity (de = 99%, ee = 99%). In the course of this total synthesis a new and mild coumarin assembly was developed.

Introduction

Furocoumarins are a group of compounds that are structurally derived from psoralen or angelicin (Figure 1) [1]. Naturally occurring furocoumarins are mainly found in plants of the Apiaceae and Rutaceae families [2] and are used in the treatment of vitiligo, psoriasis and other skin diseases [3]. Some furocoumarins exhibit vasodilatory, antifungal and antibacterial activity [4,5].

Smyrindiol (**1**), also called (+)-(2’*S*,3’*R*)-3-hydroxymarmesin [7], is a linear dihydrofurocoumarin, which was isolated from the roots of Smyrniopsis aucheri by Dzhafarov et al. in 1992 [6] and from the roots of Brosimum gaudichaudii by Vilegas et al.

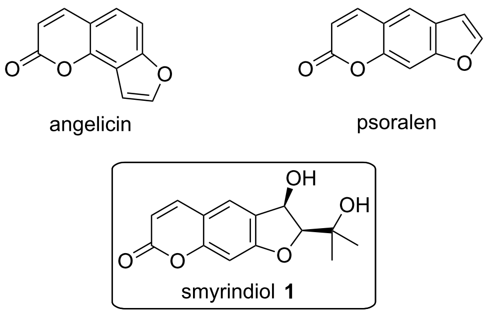
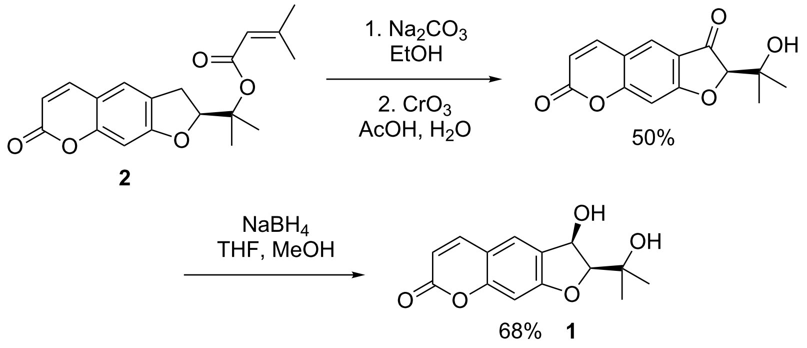
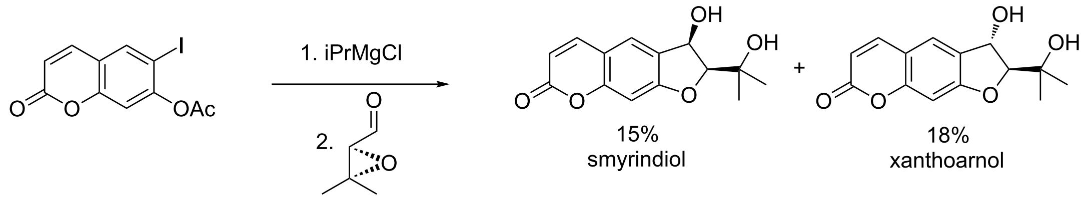


Figure 1: Furocoumarins.



Scheme 1: Synthesis of smyrindiol (**1**) by Grande et al.



Scheme 2: Synthesis of smyrindiol by Snider et al.

in 1993 [7]. Its 1'-*O*-glucoside was isolated in 1982 by Lemmich et al. from the roots of Angelica archangelica [4]. Smyrindiol has shown antifungal and antibacterial effects [5].

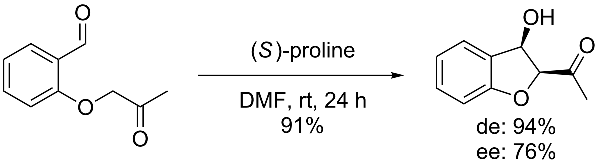
The first synthesis of smyrindiol was described by the group of Grande [8]. Starting with the naturally occurring dihydrofurocoumarin (−)-prantschimgin (**2**), the hydroxy group in 3-position was introduced by a Cr(VI)-mediated benzylic oxidation, followed by a diastereoselective sodium borohydride reduction (Scheme 1).

A few years later Snider et al. described the, up to now, sole total synthesis of smyrindiol using an enantiomerically pure epoxy aldehyde [9]. The two possible diastereoisomers resulting from the addition of the epoxy aldehyde to the coumaryl Grignard intermediate, occurred with low diastereoselectivity, with a slight preference (18% versus 15%) towards the *anti*-isomer xanthoarnol (Scheme 2).We now wish to present the first diastereo- and enantioselective, organocatalytic, asymmetric synthesis of smyrindiol.

Results and Discussion

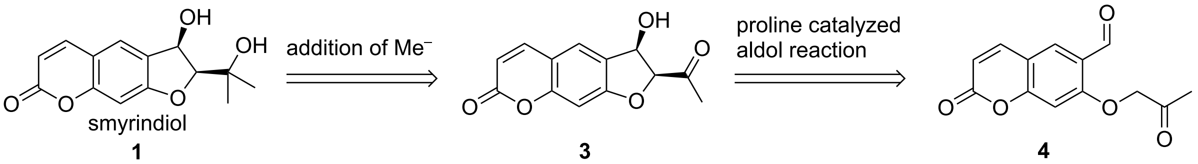
Retrosynthetic analysis

Previously the proline-catalyzed intramolecular aldol reaction of *O*-acetonyl-salicylaldehydes was described by our research group (Scheme 3) [10].

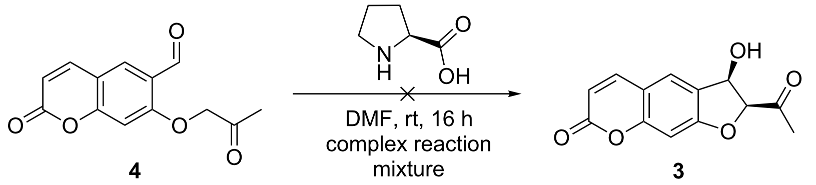


Scheme 3: Proline-catalyzed intramolecular aldol reaction of *O*-acetonyl-salicylaldehydes.

We envisaged that this 5-*enolexo* aldolization could be utilized to construct the 1,3-diol moiety of smyrindiol, if a coumarin derivative of the *O*-acetonyl-salicylaldehyde were to be used. The addition of a methyl group to the carbonyl of the aldol product would yield smyrindiol (Scheme 4).



Scheme 4: First retrosynthetic analysis.

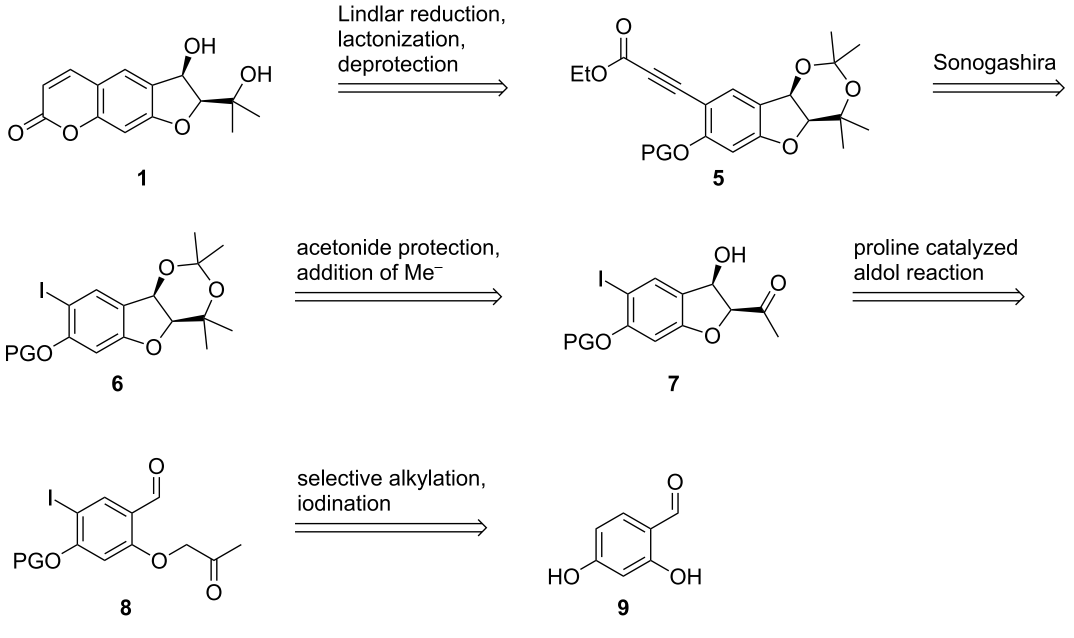


Scheme 5: Attempted proline catalyzed aldol reaction.

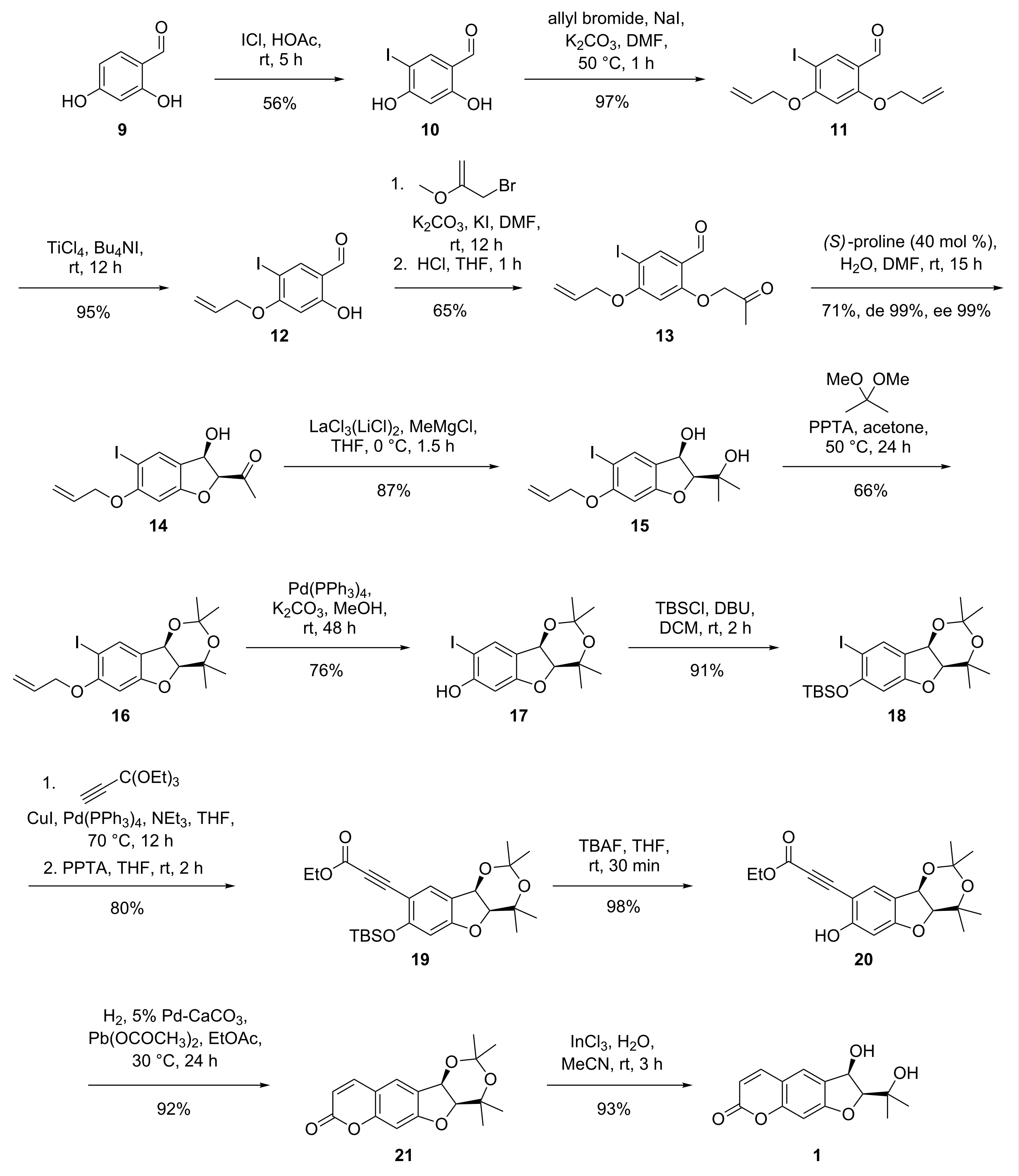
Unfortunately, all attempts to conduct the intramolecular aldol reaction with the ketoaldehyde **4** failed (Scheme 5). Instead of the expected hydroxy ketone **3**, we obtained a complex reaction mixture. This was probably the result of unwanted intermolecular side reactions of the keto group of one molecule on the coumarin system of another molecule, as an NMR analysis of the reaction mixture showed that an aldehyde signal was still present after the reaction and had, thus, not taken part in the aldol reaction. For this reason, we decided to construct the coumarin system *after* the proline catalyzed aldol reaction had taken place.

We envisaged that the preparation of the coumarin system of smyrindiol (**1**) could be achieved by Lindlar reduction of the propiolate ester **5**, in which the 1,3-diol would be protected as an acetonide, whereupon lactonization would take place simultaneously. Alkyne **5** could be synthesized through a Sonogashira coupling with iodide **6**. This acetonide could be formed by addition of a methyl anion equivalent to the carbonyl group of the aldol product **7** with subsequent protection of the 1,3-diol. The substrate for the aldol key step **8** could be prepared starting with commercially available 2,4-dihydroxybenzaldehyde (**9**) by a selective iodination of the 5-position of the aromatic ring, protection of the hydroxy group in the 4-position, and 2-*O*-acetonylation of the selectively protected salicylaldehyde (Scheme 6).

The total synthesis of smyrindiol is depicted in Scheme 7. Firstly, the *O*-acetonyl-salicylaldehyde **13**, as the substrate for the aldol reaction, was synthesized in five steps. Iodination of commercially available 2,4-dihydroxybenzaldehyde (**9**) with iodine monochloride in acetic acid [11] furnished a mixture of different iodination products. After the addition of water to the reaction mixture, only the 5-iodo derivative **10** precipitated from the solution and could be separated from the other isomers by filtration in 56% yield. We decided to protect the 4-hydroxy group as an allyl ether, as we found that other protecting groups were either not compatible with the reaction conditions towards



Scheme 6: Second retrosynthetic analysis.



Scheme 7: Asymmetric total synthesis of smyrindiol (**1**).

acetonide **15** or were found to be impossible to cleave afterwards while leaving the rest of the molecule intact.

Since we were unable to conduct a selective mono-allylation of the hydroxy group in the 4-position, both hydroxy groups were allylated, followed by a selective, titanium tetrachloride/tetra-*n*-butylammonium iodide mediated deprotection of the salicylic hydroxy group. The selectivity of this deprotection is caused by the chelating effect of the carbonyl oxygen towards titanium [12], directing the Lewis acidic species to the oxygen in the 2-position. In spite of this circuitous protection–deprotection procedure, the yield is excellent (92% over two steps) and the procedure is straightforward. The mono-allylated phenol must then be converted to the *O*-acetonylaldehyde **13**.

The alkylation of the monoprotected salicylaldehyde **12** with 1-bromo- or chloroacetone under basic conditions led to side products due to a subsequent base-catalyzed aldol reaction. For this reason, the alkylation was conducted under basic conditions with 2-methoxyallyl bromide as a masked acetonylating reagent. Hydrolysis of the methyl vinyl ether with dilute acid liberated the ketone derivative **13**. The synthesis of this starting material for the envisaged intramolecular aldol reaction could be conducted on a multigram scale without the need for column chromatography.

Similar to the previously reported aldol reaction (Scheme 3), the (*S*)-proline catalyzed 5-*enolexo* aldol key step of this synthesis could be performed in good yield (71%). To our delight, we found in this case an exceedingly high diastereo- (99%) and enantioselectivity (99%) for the aldol reaction, furnishing the aldol product **14** as a single stereoisomer.

The introduction of the methyl group by using the Imamoto protocol [13] employing cerium(III) chloride and methyllithium at −78 °C, was unreliable with highly varying yields of the 1,3-diol. This irreproducibility is probably due to the heterogeneous nature of the reaction mixture. Fortunately, the use of Knochel's published modification [14] of this reaction using a lanthanum(III) chloride bis(lithium chloride) complex solution and a methyl Grignard reagent proved to be robust and produced the desired 1,3-diol **15** in high yields (87%). The 1,3-diol was found to be sensitive towards condensation to the benzofuran system; thus, for further modifications it was protected as acetonide **16** in a moderate yield (66%) using 2,2-dimethoxypropane under PPTA catalysis.

As we turned towards the Sonogashira reaction of the iodide **16** with a propiolic acid derivative, we found that the allyl protecting group was cleaved readily by the palladium present in the reaction mixture. Since the Sonogashira reaction did not occur with the unprotected *ortho*-iodophenol **17**, we decided to reprotect the phenol as a *tert*-butyldimethylsilyl (TBS) ether, using TBS chloride and DBU. Reprotection was necessary, since employing the TBS protected ketoaldehyde **8** (PG = TBS) in the proline catalyzed aldol reaction led to complete condensation to the corresponding benzofuran.

Propiolic acid esters are known to be problematic substrates for Sonogashira reactions, due to side reactions [15]. For this reason, we used an orthoester, which coupled smoothly with iodide **18** and could be transformed into the aryl alkynoate **19** under mild acidic conditions, leaving the acetonide unscathed. The TBS group could now be cleaved by the addition of tetrabutylammonium fluoride in THF. When subjected to Lindlar catalyst and 1 atm of hydrogen, the resulting ethyl (2-hydroxyphenyl)propiolate **20** could be reduced to the corresponding *ortho*-hydroxy-(*Z*)-cinnamate, which ring closed immediately to coumarin **21**. Deprotection of the acetonide under acidic conditions proved to be difficult due to the acid labile nature of the 1,3-diol. However, indium(III) catalysis in acetonitril in the presence of water was found to cleave the acetonide selectively, yielding smyrindiol (**1**), whose spectroscopic data were identical to those published in the literature [9].

Conclusion

In summary, we have developed the first asymmetric organocatalytic total synthesis of smyrindiol, using an (*S*)-proline catalyzed 5-*enolexo* aldol reaction as the key step. The diastereo- and enantioselectivity is virtually complete (de 99%, ee 99%), and the title compound was obtained in 15 steps in an overall yield of 6.3%. All steps were performed under mild conditions with short reaction times. Our novel total synthesis should allow the synthesis of larger quantities of the natural compound without having to rely on natural sources. Needless to mention, the unnatural enantiomer could be synthesized if (*R*)-proline were to be used as the organocatalyst. In addition, the Sonogashira/Lindlar reduction/lactonization sequence opens a new efficient and flexible entry to the coumarin core of other natural products.

Supporting Information

Supporting Information File 1

Experimental procedures and characterization of compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-123-S1.pdf]

Supporting Information File 2

NMR-spectra and chromatograms.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-123-S2.pdf]

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Combined bead polymerization and *Cinchona* organocatalyst immobilization by thiol–ene addition

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Letter

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Abstract

In this work, we report an unusually concise immobilization of *Cinchona* organocatalysts using thiol–ene chemistry, in which catalyst immobilization and bead polymerization is combined in a single step. A solution of azo initiator, polyfunctional thiol, polyfunctional alkene and an unmodified *Cinchona*-derived organocatalyst in a solvent is suspended in water and copolymerized on heating by thiol–ene additions. The resultant spherical and gel-type polymer beads have been evaluated as organocatalysts in catalytic asymmetric transformations.

Introduction

Polymer-supported chiral organocatalysts have emerged as a rapidly expanding field of research in recent years [1], in part due to the traditionally emphasized advantages of polymeric immobilization (facilitated separation and recovery procedures, recycling etc.), but perhaps even more due to the enhanced activity and selectivity sometimes exhibited by such organocatalysts, especially under aqueous conditions [2]. Recently, the use of polymer-supported organocatalysts in continuous-flow systems has also surfaced in the literature, and their development is quickly gaining momentum [3-5]. Regrettably, cost issues linger over the field as a whole, due to the lengthy and laborious syntheses involved in the preparation of these polymer-supported entities, hampering the more widespread utilization of polymer-supported reagents or catalysts as part of conventional chemical synthesis.

Consequently, we have been engaged in the development of scalable and expedient syntheses of polymer-supported organocatalysts for some time now [6,7]. In our bottom-up approach for the preparation of polymer-supported organocatalysts, the catalyst immobilization and the preparation of the polymer scaffold are closely connected, to facilitate the synthesis of larger quantities of supported catalyst [6,7]. Acrylic derivatives of established organocatalysts are prepared on a gram scale by using nonchromatographic procedures and copolymerized with suitable comonomers to give cross-linked and microporous beads. Such polymer beads have provided good to excellent results as organocatalysts in various asymmetric transformations [6,7].

Cinchona derivatives are used in several types of organocatalysts, and they are all equipped with a pendant vinylic functionality susceptible to activation by chemical transformations based on radical intermediates [1]. As a result, polymeric immobilization of *Cinchona* derivatives by using thiol–ene addition has a substantial history, founded on procedures developed already in the early 1970s [1]. *Cinchona* derivatives are either copolymerized with certain comonomers, such as acrylonitrile, directly in a bottom-up fashion to give linear copolymers [1,8], or anchored to prefabricated cross-linked and thiol-funtionalized resins in a traditional post-modification approach [1,9]. However, for the preparation of the preferred beaded and cross-linked polymer resins, so easily handled and separated from reaction mixtures by filtration, this necessitates several steps, as the cross-linked resin must be prepared first by copolymerization, then equipped with thiol functionalities, and finally joined with the *Cinchona* derivative through thiol–ene coupling.

The thiol–ene addition was described by Theodor Posner already in 1905 [10], and it has been in more or less continuous use since then. The thiol–ene addition can readily be adapted for polymerization, by using polyfunctional alkenes in combination with polyfunctional thiols [11-13]. We envisaged that polymerization into a cross-linked and beaded resin could be combined with immobilization of a *Cinchona* derivative in a single step under suitable conditions. Such a procedure would enable us to prepare polymer-supported *Cinchona* organocatalysts directly in a single step and on a large scale, using unmodified *Cinchona* organocatalyst precursors.

Results and Discussion

Building blocks for the preparation of cross-linked thiol–ene resins

Research oriented towards thiol–ene chemistry has experienced near explosive growth in the past few years, perhaps due to its efficiency and functional tolerance, but possibly even more due to its recent conceptualization as a “click” reaction [13]. In order to prepare different polymer beads with varying degrees of swelling characteristics, we assembled a small collection of useful thiol and alkene building blocks (Figure 1).

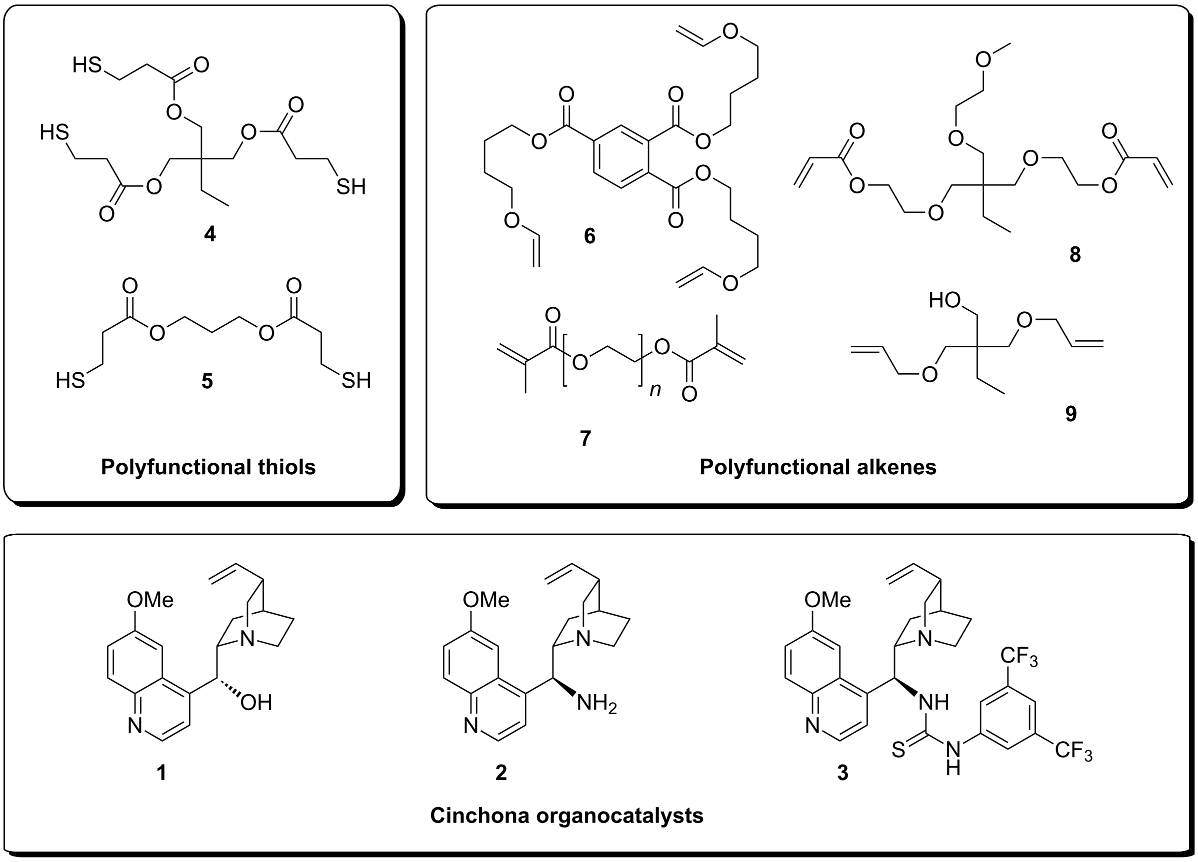


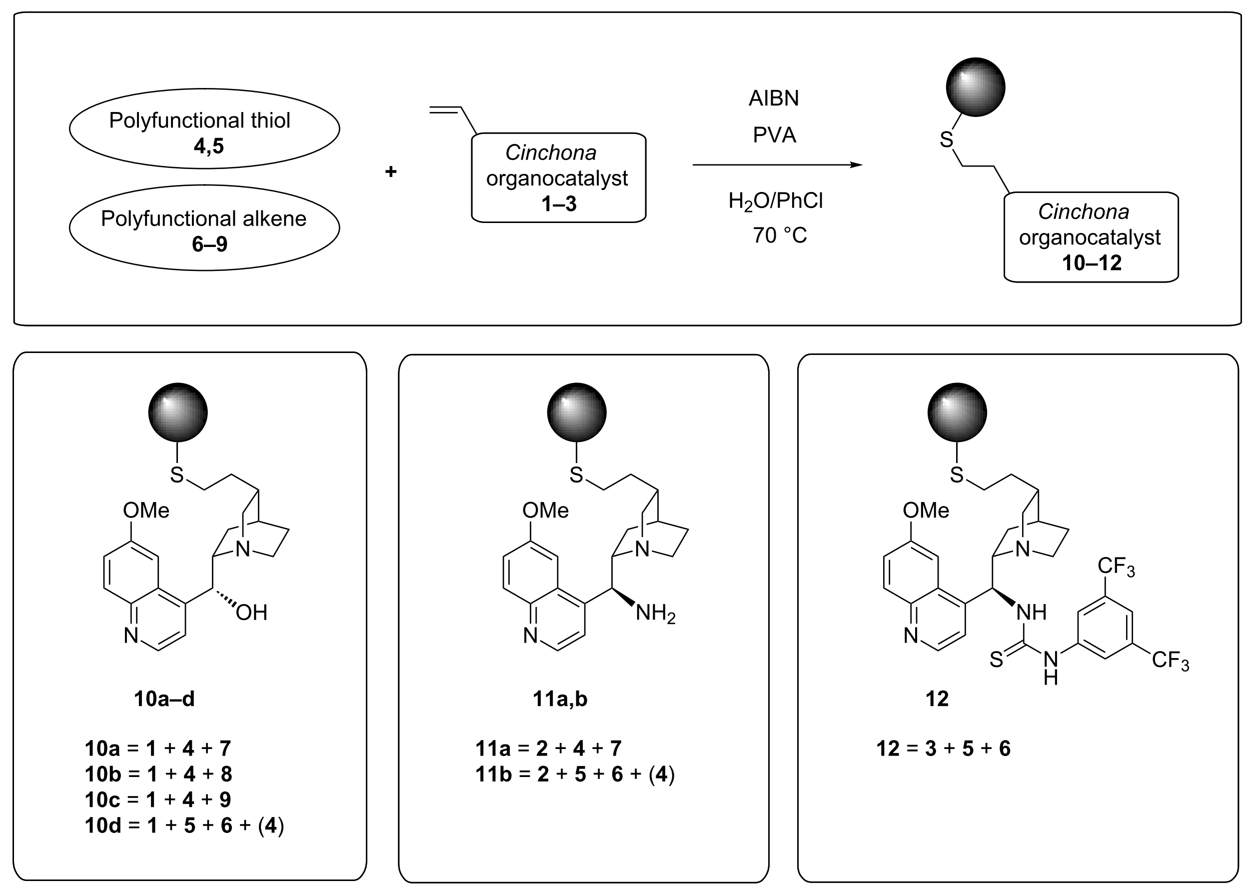
Figure 1: Thiol, alkene and organocatalyst building blocks for combined bead polymerization and *Cinchona* organocatalyst immobilization.

Trithiol **4** is a readily available commercial product, whereas dithiol **5** was easily obtained from esterification of 3-mercaptopropionic acid and propane-1,3-diol [14]. Trivinyl ether **6**, polyethylene glycol (PEG) dimethacrylate **7**, diacrylate **8** and diallyl ether **9** are all commercially available compounds. For thiol–ene additions via the radical pathway, the order of reactivity of unsaturated compounds **6**–**9** towards the thiols is generally so: vinyl ether **6** > allyl ether **9** > acrylate **8** > methacrylate **7** [11]. Thiol–ene additions according to the anionic (Michael-type) mechanism have not been investigated in this work. As a minimum for obtaining cross-linked polymeric networks, either trithiol **4** has to be copolymerized with dialkenes **7**–**9**, or dithiol **5** has to be copolymerized with trivinyl ether **6**. These two main approaches can then be modified or finely tuned to match suitable swelling characteristics by incorporation of smaller amounts of any of the other constituents **4**–**9**, thereby adjusting the degree of cross-linking.

As for the *Cinchona* organocatalysts, we wanted to incorporate either unmodified quinine (**1**), the primary amine organocatalyst **2**, or thiourea organocatalyst **3** into the thiol–ene network (Figure 1). While quinine is available directly, primary amine organocatalyst **2** was prepared from quinine, via the azide, in a two-step sequence by using the Bose–Mitsunobu reaction followed by Staudinger reduction, as described by others [15]. Thiourea *Cinchona* organocatalyst **3** was easily obtained from catalyst **2** by reaction with the appropriate aromatic isothiocyanate [15].

Single step thiol–ene polymerization and *Cinchona* organocatalyst immobilization

With the assortment of building blocks depicted in Figure 1 available, we could now obtain immobilized versions (**10**–**12**) of unmodified *Cinchona* catalysts **1**–**3** directly by oil-in-water type thiol–ene suspension copolymerization. A solution of polyfunctional thiol, polyfunctional alkene and *Cinchona* organocatalyst in a water immiscible solvent, such as chlorobenzene or toluene, containing a small amount of azo radical initiator (AIBN), was suspended in dilute aqueous polyvinyl alcohol (PVA) and heated under vigorous agitation. The suspended and stabilized droplets then converted to spherical and gel-type polymer beads. An overview of the immobilized *Cinchona* organocatalysts, and their constituents, is provided in Scheme 1.



Scheme 1: Combined bead polymerization and *Cinchona* organocatalyst immobilization by thiol–ene addition.

After polymerization, the polymer beads were filtered and purified by Soxhlet extraction, and their organocatalyst loadings were determined on the basis of CHN analysis, as only the organocatalytic moiety contains nitrogen. Generally, the yield of polymer beads, calculated on the basis of recovered material versus the combined mass of starting materials, varied between ca. 60–80%. Only an azo initiator, such as AIBN, could be utilized, because peroxide initiators, such as dibenzoyl peroxide, oxidise thiols.

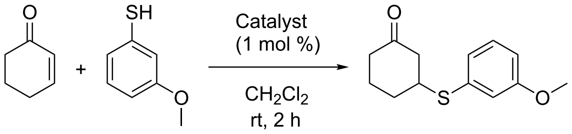
The thiol-ene polymer beads **10**–**12** had a distinctively soft and gel-like appearance, but were easily handled like conventional microporous beads. They had favourable swelling characteristics in several organic solvents, particularly in THF and CH_2Cl_2, despite their significant degree of cross-linking. As such, they have much in common with the CLEAR (cross-linked ethoxylate acrylate resin) resins, a type of polymer support with all the characteristics of a microporous polymer that also has an unusually high degree of cross-linking [16]. Unlike vinyl ether **6** and allyl ether **9**, acrylic building blocks such as **7** and **8** may undergo some degree of acrylic homopolymerization during network formation, although the thiol–ene addition is usually more rapid than the polymerization.

The ratio of thiol and alkene functionalities was adjusted to be close to unity, and the thiol–ene reaction usually has a high degree of conversion; however, the presence of free thiol groups is probably unavoidable. We were, nevertheless, curious to investigate how these supported organocatalysts would function in asymmetric transformations when compared to the unsupported catalysts.

Asymmetric organocatalytic transformations using immobilized *Cinchona* organocatalysts

With supported *Cinchona* organocatalysts **10**–**12** available, numerous organocatalytic transformations were potentially available for benchmarking. As a rough indication of activity, we started out by investigating quinine (**1**) and supported catalyst **10a**–**d** in the Michael addition of 3-methoxythiophenol and cyclohex-2-enone (Table 1) [17]. Although the performance of quinine in this reaction is poor with regards to selectivity (providing only 23% ee), and probably not very useful for benchmarking, the supported catalysts **10a**–**d** were obviously catalytically active, albeit modestly selective compared to the free catalyst, giving quantitative yields and a selectivity of 11–14% ee.

Table 1: Polymer-supported quinines in asymmetric Michael addition.

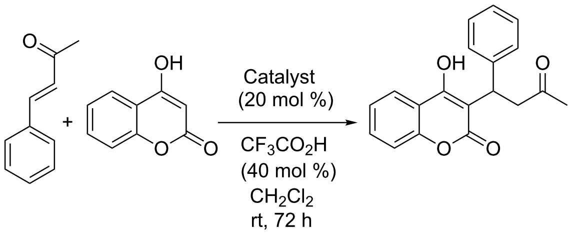


Catalyst	Yield [%][a]	ee [%][b]
1	>95	23
10a	>95	14
10b	>95	11
10c	92	14
10d	>95	12

[a]Isolated yield. [b]Determined by HPLC analysis.

Of greater interest was the performance of the primary amine organocatalysts **11**. Polymer-supported catalysts **11a**,**b** were tried out in the asymmetric preparation of the anticoagulant warfarin from benzylideneacetone and 4-hydroxycoumarin, a transformation that we have investigated in our group as part of developmental work in primary amine organocatalysis on a previous occasion (Table 2) [18]. Compared to the free catalyst **2**, the yields obtained by using supported catalysts **11a**,**b** are inferior, but this is most probably due to the lack of solubility of the hydroxycoumarin, a very insoluble compound, in the reaction medium (CH_2Cl_2) and probably not so much a lack of inherent activity. Interestingly, catalyst **11b**, made by using dithiol **5** and trivinyl ether **6** (in addition to a few mol % of trithiol **4** to increase cross-linking slightly, giving beads of better quality), exhibited markedly improved selectivity compared to catalyst **11a**, even matching that of the free catalyst **2**. This may be connected to the fact that the *Cinchona* moiety becomes bound to the polymer network through the

Table 2: Polymer-supported primary amine *Cinchona* organocatalysts in asymmetric preparation of warfarin.



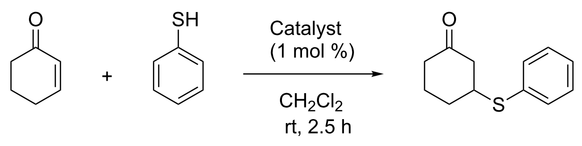
Catalyst	Yield [%][a]	ee [%][b]
2	75	92
11a	15	77
11b[c]	25	94
11b[d]	15	84
11b[e]	—	—

[a]Isolated yield. [b]Determined by HPLC analysis. [c]First cycle. [d]Second cycle. [e]Third cycle.

thiol, and use of a difunctional thiol then improves the mobility of this catalytic unit as it is now positioned at the end of a linker of greater length. This effect does not seem to have played out for catalyst **10d** though. Catalysts **10a**–**d** all seemed to behave much the same. Catalyst **11b** could be recycled, but both yield and selectivity quickly eroded (Table 2).

Having confidence in the overall validity of our approach to polymer-supported *Cinchona* organocatalysts, we tested the supported thiourea catalyst **12** in the Michael addition of thiophenol and cyclohex-2-enone [17], a transformation known to be very efficiently catalysed by the free thiourea catalyst **3** (Table 3) [19,20]. The immobilized catalyst **12** proved highly active (the uncatalysed reaction is very slow), rapidly giving quantitative yield, but somewhat reduced selectivity of the addition product compared to the free thiourea catalyst **3**. To investigate the extent to which free thiol groups could influence the reaction by catalyzing a racemic pathway, we also tested polymer beads without any *Cinchona* moiety present in this transformation. Undeniably, polymer beads prepared without any *Cinchona* organocatalyst present did also catalyze the reaction. However, we found that several other polymer resins, such as unmodified Merrifield resin (chloromethylated and cross-linked polystyrene), influence the reaction in the same manner. Consequently, we do not believe this to be an intrinsic property of our thiol–ene polymer beads, connected to the effect of free thiol groups. In addition, capping free thiol groups on beforehand by treatment with excess methyl acrylate did not affect the performance in this transformation.

Table 3: Polymer-supported thiourea *Cinchona* organocatalyst in the asymmetric Michael addition.

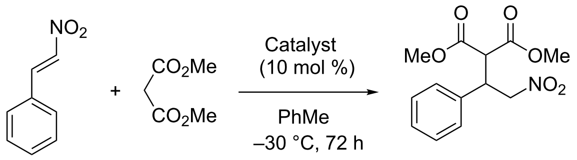


Catalyst	Yield [%][a]	ee [%][b]
3	>95	83
12	>95	69

[a]Isolated yield. [b]Determined by HPLC analysis.

Catalyst **12** was also tested in the Michael addition of methyl malonate to *trans*-β-nitrostyrene (Table 4) [21]. The catalyst gave quantitative yield and excellent enantioselectivity after 3–4 days reaction time. However, the catalyst exhibited poor recycling properties as yields fell sharply after the second reaction cycle; but selectivity remained largely untouched. At this point, we suspected that loss of the catalytic entities from the polymer resin may explain this, and indeed, CHN analysis of polymer resins after recycling verified that a loss of nitrogen content, meaning leaching of the active species, had occurred.

Table 4: Polymer-supported thiourea *Cinchona* organocatalyst in the asymmetric Michael addition.



Catalyst	Conversion [%][a]	ee [%][b]
12[c]	>95	92
12[d]	>95	92
12[e]	34	92
12[f]	trace	—

[a]Determined by ^{1}H NMR analysis of crude reaction mixture. [b]Determined by HPLC analysis. [c]First cycle, 3 d reaction time. [d]Second cycle, 4 d reaction time. [e]Third cycle, 4 d reaction time. [f]Fourth cycle, 4 d reaction time.

Conclusion

We have developed an unusually concise immobilization of *Cinchona* organocatalysts by thiol–ene suspension copolymerization of polyfunctional thiols and alkenes together with unmodified *Cinchona* organocatalyst precursors. As such, bead polymerization and catalyst immobilization is combined in a single step. Vinyl ethers, allyl ethers, acrylates and methacrylates can all be effectively incorporated as part of such thiol–ene networks. The supported organocatalysts have been tried out successfully in several asymmetric transformations, but catalyst recycling so far is relatively poor. Hopefully, this expedient method for immobilization of *Cinchona* derivatives can be further developed in the future to improve activity and selectivity, and also be widened to include other useful *Cinchona*-derived species.

Experimental

General: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker AV 600 (600/150 MHz), Bruker Advance DRX 500 (500/125 MHz), Bruker DPX 300 (300/75 MHz) or Bruker DPX 200 (200/50 MHz) spectrometer. Dry THF was obtained from a solvent purification system (MB SPS-800 from MBraun). All other reagents and solvents were used as received. CHN analyses were carried out in the School of Chemistry, at the University of Birmingham, UK. For flash chromatography, silica gel from SdS (60 A, 40–63 µm, 550 m^2/g, pH 7) and Merck (silica gel 60, 0.40–0.63 mm, 480–540 m^2/g, pH 6.5–7.5) were used, either manually or with an automated system (Isco Inc. CombiFlash Companion with PeakTrak software), with EtOAc/hexanes of technical quality. Enantiomeric excess was determined by HPLC analysis using analytical columns (Chiralpak AS-H or AD-H from Daicel Chemical Industries).

The *Cinchona* organocatalysts **2** and **3** were prepared from quinine (**1**) as described in the literature [15]. Dithiol **5** was prepared as described in the literature [14], and this compound was kept refrigerated and protected from light in order to avoid deterioration on storage.

Preparation of polymer-supported quinines 10a–d: Quinine (**1**, 2.10 mmol for **10a** or 2.00 mmol for **10b**/**10c** or 1.50 mmol for **10d**), trithiol **4** (6.20 mmol for **10a**/**10c** or 6.00 mmol for **10b** or 0.18 mmol for **10d**), dithiol **5** (4.00 mmol for **10d**), dimethacrylate **7** (8.90 mmol for **10a**), diacrylate **8** (8.10 mmol for **10b**), diallyl ether **9** (8.10 mmol for **10c**), trivinyl ether **6** (2.43 mmol for **10d**) and AIBN (5 wt % relative to monomers) were dissolved in a monomer diluent (13 mL PhCl for **10a** or 15 mL PhCl for **10b**/**10c** or 5 mL PhCl for **10d**). Aqueous PVA (100 mL for **10a** or 70 mL for **10b**/**10c** or 39 mL for **10d**, 0.5% Mowiol 40-88) was added under stirring to give an oil-in-water type emulsion. The system was flushed with argon for 5 min. The suspension was heated to 70 °C and kept at this temperature for 3 h under stirring, allowed to cool to room temperature, and poured into a beaker containing MeOH (250 mL). The suspension was stirred for 15 min, and the polymer beads were allowed to settle by gravity for 10 min. The supernatant was removed by decantation and the process was repeated until the supernatant was transparent (1–2 repetitions). CH_2Cl_2 (50 mL) was added, the suspension was filtered by vacuum, and the polymer beads were washed with water (1000 mL), THF–H_2O (200 mL, 1:1), MeOH (200 mL) and CH_2Cl_2 (50 mL). The polymer beads were then transferred to a cellulose paper thimble and purified by Soxhlet extraction with CH_2Cl_2 (70 mL) for 12 h, and then the purified beads were left to dry at room temperature for 24 h (67% yield for **10a**, 67% yield for **10b**, 63% yield for **10c**, 64% yield for **10d**). Catalyst loadings were determined by CHN analysis.

Preparation of polymer-supported primary amine *Cinchona* organocatalysts 11a,**b**: *Cinchona* derivative **2** (2.00 mmol for **11a** or 1.20 mmol for **11b**), trithiol **4** (5.00 mmol for **11a** or 0.16 mmol for **11b**), dithiol **5** (4.20 mmol for **11b**), dimethacrylate **7** (6.24 mmol for **11a**), trivinyl ether **6** (2.51 mmol for **11b**) and AIBN (5 wt % relative to monomers) were dissolved in a monomer diluent (12 mL PhCl for **11a** or 6 mL PhMe for **11b**). Aqueous PVA (70 mL for **11a** or 40 mL for **11b**, 0.5% Mowiol 40-88) and potassium iodide (to inhibit polymerization in the aqueous phase, 23 mg for **11b**) was added under stirring to give an oil-in-water type emulsion. The system was flushed with argon for 5 min. The suspension was heated to 70 °C and kept at this temperature for 3 h under stirring, allowed to cool to room temperature, and then poured into a beaker containing MeOH (250 mL). The suspension was stirred for 15 min, and the polymer beads were allowed to settle by gravity for 10 min. The supernatant was removed by decantation, and the process was repeated until the supernatant was transparent (1–2 repetitions). CH_2Cl_2 (50 mL) was added, the suspension was filtered by vacuum, and the polymer beads washed with water (1000 mL), THF–H_2O (200 mL, 1:1), MeOH (200 mL) and CH_2Cl_2 (50 mL). The polymer beads were then transferred to a cellulose paper thimble and purified by Soxhlet extraction with CH_2Cl_2 (70 mL) for 12 h, and then the purified beads were left to dry at room temperature for 24 h (75% yield for **11a**, 85% yield for **11b**). Catalyst loadings were determined by CHN analysis.

Preparation of polymer-supported thiourea *Cinchona* organocatalyst 12: *Cinchona* derivative **3** (0.538 mmol), trithiol **4** (0.17 mmol), dithiol **5** (3.48 mmol), trivinyl ether **6** (2.32 mmol) and AIBN (15 wt % relative to monomers) were dissolved in PhMe (7 mL). Aqueous PVA (50 mL, 0.5% Mowiol 40-88) and potassium iodide (to inhibit polymerization in the aqueous phase, 20 mg) was added under stirring to give an oil-in-water type emulsion. The system was flushed with argon for 5 min. The suspension was heated to 70 °C and kept at this temperature for 1 h under stirring, allowed to cool to room temperature, and poured into a beaker containing MeOH (250 mL). The suspension was stirred for 15 min, and the polymer beads were allowed to settle by gravity for 10 min. The supernatant was removed by decantation, and the process was repeated until the supernatant was transparent (1–2 repetitions). CH_2Cl_2 (50 mL) was added, the suspension was filtered by vacuum, and the polymer beads washed with water (1000 mL), THF–H_2O (200 mL, 1:1), MeOH (200 mL) and CH_2Cl_2 (50 mL). The polymer beads were then transferred to a cellulose paper thimble and purified by Soxhlet extraction with CH_2Cl_2 (70 mL) for 12 h, and the purified beads were left to dry at room temperature for 24 h (62% yield). Catalyst loadings were determined by CHN analysis.

General procedure for asymmetric Michael addition of 3-methoxythiophenol to cyclohex-2-enone: 3-Methoxythiophenol (0.30 mL, 3.10 mmol), and catalyst (1 mol %) were dissolved in CH_2Cl_2 (6 mL). Cyclohex-2-enone (0.50 mL, 4.03 mmol) was then added in one portion, and the resulting mixture was stirred at room temperature for 2 h. The crude reaction mixture was filtered, and the polymer beads were washed with CH_2Cl_2 (50 mL). The combined organic phase was evaporated in vacuo, and the crude product was purified by flash chromatography on silica gel (10% EtOAc in hexanes) to give the product as a colorless oil. This is a known compound [17]. Enantiomeric excess was determined by HPLC analysis (Chiralpak AS-H, 50% iPrOH in isohexane, 0.3 mL/min): t_R = 25.2 min and 38.2 min.

General procedure for asymmetric Michael addition of 4-hydroxycoumarin to benzylideneacetone: To a vial containing 4-hydroxycumarin (0.35 g, 2.17 mmol), benzylideneacetone (0.56 g, 3.82 mmol) and catalyst (20 mol %), was added CH_2Cl_2 (18 mL) and CF_3CO_2H (60 µL, 40 mol %). The reaction mixture was stirred at room temperature for 72 h, diluted with CH_2Cl_2 and filtered. The polymer beads were washed with CH_2Cl_2 (70 mL). The combined organic phase was evaporated in vacuo, and the crude product was purified by flash chromatography on silica gel (10% EtOAc in hexanes and then 25% EtOAc in hexanes) to give the product as a colorless solid. This is a known compound [18]. Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H, 20% iPrOH in isohexane, 1.0 mL/min): t_R = 7.3 min and 14.7 min.

General procedure for asymmetric Michael addition of thiophenol to cyclohex-2-enone: Thiophenol (0.20 mL, 1.95 mmol) and catalyst (1 mol %) were dissolved in CH_2Cl_2 (1.7 mL). Cyclohex-2-enone (0.15 g, 1.52 mmol) was added in one portion, and the resulting reaction mixture was stirred at room temperature for 2.5 h. The crude reaction mixture was diluted with CH_2Cl_2 and filtered, and the polymer beads were washed with CH_2Cl_2 (70 mL). The combined organic phase was evaporated in vacuo, and the crude product was purified by flash chromatography on silica gel (5% EtOAc in hexanes) to give the product as a colorless oil. This is a known compound [17]. Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H, 2% iPrOH in isohexane, 1.0 mL/min): t_R = 19.2 min and 26.2 min.

General procedure for asymmetric Michael addition of methyl malonate to *trans*-β-nitrostyrene: *trans*-β-Nitrostyrene (83.4 mg, 0.56 mmol) and methyl malonate (0.23 g, 1.78 mmol) were dissolved in toluene (1 mL). Catalyst **12** (10 mol %) was added, and the reaction mixture was left at −30 °C for 72 h. The crude reaction mixture was diluted with CH_2Cl_2 and filtered, and the polymer beads were washed with CH_2Cl_2 (50 mL). The combined organic phase was evaporated in vacuo, and the crude product was purified by flash chromatography on silica gel (Gradient: 5–40% EtOAc in hexanes). This is a known compound [21]. The conversion of starting material was determined by ^1H NMR analysis of the crude product. Enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H, 30% iPrOH in isohexane, 1.0 mL/min): t_R = 7.3 min and 9.3 min.

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Recyclable fluorous cinchona alkaloid ester as a chiral promoter for asymmetric fluorination of β-ketoesters

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Full Research Paper

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Abstract

A fluorous cinchona alkaloid ester has been developed as a chiral promoter for the asymmetric fluorination of β-ketoesters. It has comparable reactivity and selectivity to the nonfluorous versions of cinchona alkaloids and can be easily recovered from the reaction mixture by simple fluorous solid-phase extraction (F-SPE) and used for the next round of reaction without further purification.

Introduction

Fluorinated organic compounds have unique properties because fluorine forms a strong carbon–fluorine bond with a small covalent radius and high electronegativity. Other than fluorinated polymers in materials science, organofluorine compounds have gained increasing popularity in medical chemistry and agricultural chemistry. Introducing one or a few fluorine atoms to biologically interesting molecules can significantly change the physical, chemical and biological properties [1,2]. The significant amount of publications on fluorinated small molecules, amino acids, carbohydrates, steroids and nucleosides indicates that organofluorine chemistry plays an important role in the life sciences [3,4].

A fluorine atom has been introduced to the α-position of some biologically interesting β-ketoesters, such as erythromycin and sesquiterpenic drimane (Figure 1) [5,6]. The achiral fluorination of β-ketoesters can be achieved by electrophilic reaction with Selectfluor (F-TEDA-BF_4, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)), as developed by Bank [7-9]. The Cahard [10-12] and Shibata [13,14] groups combined cinchona alkaloids and Selectfluor for asymmetric fluorination of substrates such as imido-protected phenylglycines (up to 94% ee), indanones and tetralones (up to 91% ee), ethyl α-cyanotolyl acetates (up to 87% ee), and cyclic β-ketoesters (up to 80% ee) [15]. A catalytic approach for the cinchona alkaloids and Selectfluor combinations has also been developed [16]. The Togni group employed chiral titanium Lewis acid $TiCl_2$(TADDOLate) for the asymmetric fluorination of β-ketoesters (up to 96% ee) [17-20]. Most Selectfluor-promoted asymmetric fluorinations require a stoichiometric amount of chiral promoters to suppress the competitively direct achiral fluorination. Different supported cinchona alkaloids have been developed as recyclable chiral promoters or organocatalysts. Among them, the Cahard group developed soluble polymer- and ionic-liquid-supported cinchona alkaloids for electrophilic fluorination [21,22]. The Fache and Soós groups developed fluorous tag-attached cinchona alkaloids for catalytic Diels–Alder reactions [23,24]. Introduced in this paper is a new fluorous cinchona alkaloid ester for flourination of β-ketoesters. It is part of our recent effort on the development of recyclable fluorous reagents and organocatalysts for asymmetric synthesis [25-27].

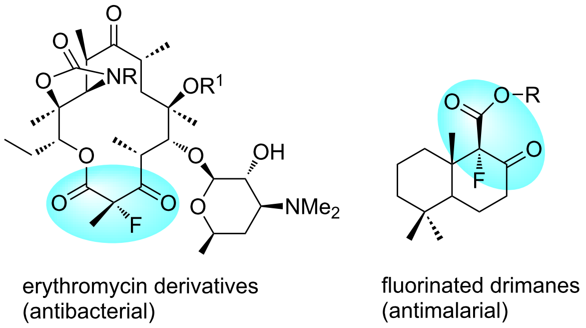


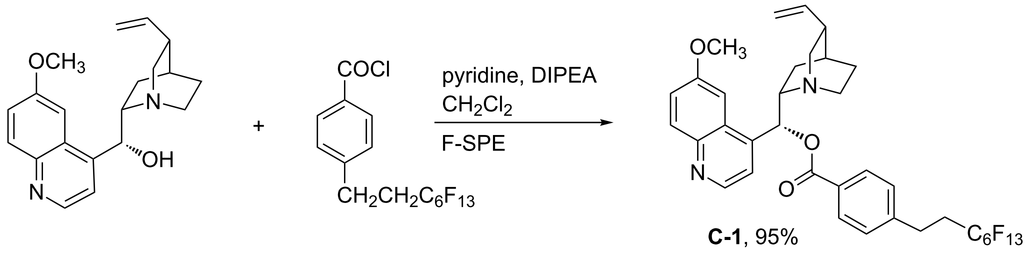
Figure 1: Biologically interesting α-fluorinated β-ketoesters.

Results and Discussion

Cinchona alkaloids and their derivatives have been well-explored in asymmetric synthesis [28]. We envisioned that the introduction of a fluorous tag could facilitate the recycling of cinchona alkaloids. The synthesis of fluorous quinine ester **C-1** was accomplished by the reaction of quinine with a fluorous acid chloride (Scheme 1). This compound was easily purified by fluorous-solid phase extraction (F-SPE) with a cartridge charged with fluorous silica gels [29,30]. It is stable in air and soluble in solvents such as CH_2Cl_2, CH_3OH, and CH_3CN.

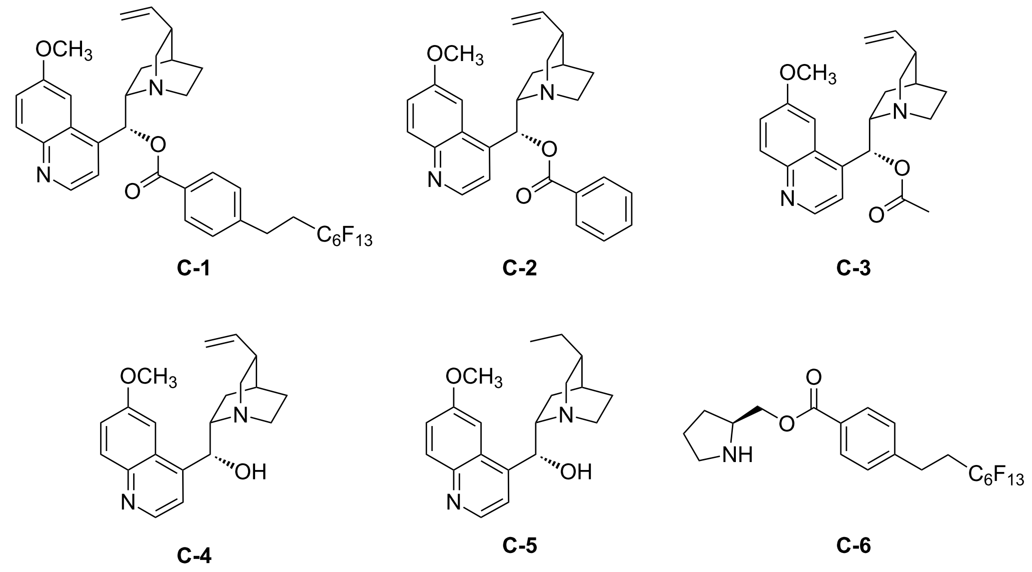
With the fluorous quinine ester **C-1** in hand, we explored the fluorination reaction using ethyl 2-methyl-3-oxo-3-phenylpropanoate (**1a**) as a model compound. Nonfluorous quinine esters, such as **C-2** and **C-3**, cinchona alkaloids **C-4** and **C-5**, and fluorous pyrrolidine ester **C-6**, were also evaluated (Figure 2). The results of the fluorination of β-ketoester **1a** with Selectfluor and different promoters are listed in Table 1. It was found that using MeCN as a solvent with 1 equiv of **C-1** gave fluorinated product **2a** in 49% yield and 65% ee (Table 1, entry 1). Compared to other promoters (Table 1, entries 2–5), **C-1** gave fluorinated products in a slightly low yield but better enantioselectivity. This may be attributed to the stereo and the electronic effect of the fluorous tag. Fluorous pyrrolidine **C-6** (Table 1, entry 6) gave the lowest product yield and ee among all six promoters. Reducing the amount of **C-1** from 1 equiv to 0.5 and 0.2 equiv significantly reduced the ee of the product (Table 1, entries 7 and 8). A control reaction without **C-1** gave **2a** in 35% yield as a racemic product (Table 1, entry 9). The results suggest that a stoichiometric amount of **C-1** is required to minimize the formation of achiral fluorination product by direct fluorination. Solvent screening indicated that using 1:1 CH_3CN/CH_2Cl_2 gave product **2a** in 51% yield and 70% ee (Table 1, entry 15), which is better than using CH_3CN alone. Other single or binary solvent systems containing toluene, THF, H_2O, and $CF_3C_6H_5$ did not afford better results (Table 1, entries 10–14). It was also found that lowering of the reaction temperature from 25 to 10 or 0 °C did not necessarily improve the enantioselectivity of the fluorination (Table 1, entries 16 and 17).

Recycling of promoter **C-1** is an important part of this project. In our previous work we have demonstrated that fluorous organocatalysts and reagents can be readily recovered by F-SPE



C-1, 95%

Scheme 1: Preparation of quinine ester **C-1**.

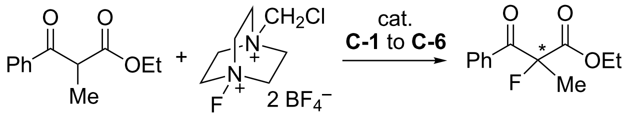


C-1 **C-2** **C-3**

C-4 **C-5** **C-6**

Figure 2: Promoters for asymmetric fluorination.

Table 1: Asymmetric fluorination of **1a**.[a]

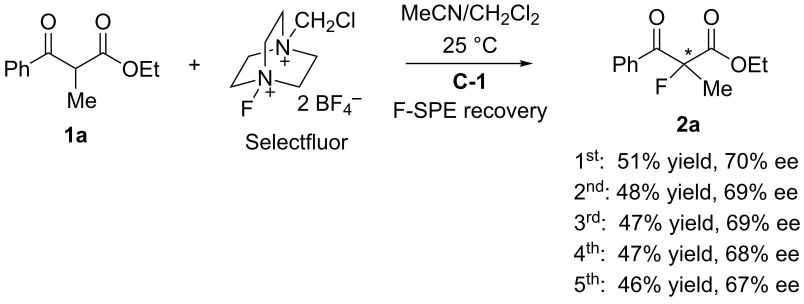


1a Selectfluor **2a**

Entry	Cat. (equiv)	Solvent	*t* (h)	Yield (%)	ee (%)
1	**C-1** (1.0)	MeCN	72	49	65
2	**C-2** (1.0)	MeCN	72	52	56
3	**C-3** (1.0)	MeCN	72	54	51
4	**C-4** (1.0)	MeCN	72	62	46
5	**C-5** (1.0)	MeCN	72	65	48
6	**C-6** (1.0)	MeCN	96	41	18
7	**C-1** (0.5)	MeCN	60	51	26
8	**C-1** (0.2)	MeCN	60	41	<5
9	–	MeCN	96	35	0
10	**C-1** (1.0)	Toluene	72	16	23
11	**C-1** (1.0)	THF	72	32	41
12	**C-1** (1.0)	H_2O	96	–	–
13	**C-1** (1.0)	MeCN/THF	60	38	45
14	**C-1** (1.0)	MeCN/$CF_3C_6H_5$	60	43	59
15	**C-1** (1.0)	MeCN/CH_2Cl_2	60	51	70
16[b]	**C-1** (1.0)	MeCN/CH_2Cl_2	72	46	69
17[c]	**C-1** (1.0)	MeCN/CH_2Cl_2	72	39	71

[a]Reaction temperature 25 °C unless otherwise indicated. [b]Reaction temperature 10 °C. [c]Reaction temperature 0 °C.

[19,20]. In the current work, upon completion of the fluorination reaction, a base such as aqueous NaOH or KOH was added to the reaction mixture to convert the cinchona alkaloid/Selectfluor complex to free cinchona alkaloid. The organic phase was loaded onto a fluorous silica gel cartridge for F-SPE. Promoter **C-1** was recovered in high yield (94%) and excellent purity (98%). It was used for five rounds without significant change of product yield and ee (Scheme 2).



Scheme 2: Preparation of **2a** by using recycled quinine ester **C-1**.

The scope of fluorous quinine ester **C-1**-mediated fluorination was evaluated by carrying out the reactions with a number of α-substituted ethyl benzoylacetates **1a–e** and **1g–i** as well as ethyl 2-cyclohexanonecarboxylate (**1f**). Results summarized in Figure 3 indicate that benzoylacetates bearing R^2 such as Me, $PhCH_2$, Cl, and Br gave fluorination products **2a–d** in 43–71% yields and 60–70% ee. The nonsubstituted benzoylacetate **1e** gave product **2e** in good yield 69% but low ee (31%). Ethyl 2-cyclohexanonecarboxylate (**1f**) afforded product **2f** in 73% yield and 63% ee. Reactions of ethyl benzoylacetates with bigger substitution groups, such as phenylsulfonyl and maleimide derivatives, were also attempted and gave products **2g–i** in 74–83% yields and 78–81% ee.

Conclusion

A fluorous cinchona alkaloid-ester has been introduced as a promoter for Selectfluor-based asymmetric fluorination of β-ketoesters. The fluorous promoter has slightly lower reactivity but better enantioselectivity than the nonfluorous cinchona alkaloids. It can be easily recovered by simple fluorous solid-phase extraction for reuse.

Experimental

General

Chemicals and solvents were purchased from commercial suppliers and used as received. ^1H and ^{13}C NMR spectra were recorded on a 300 MHz Varian NMR spectrometer. Chemical

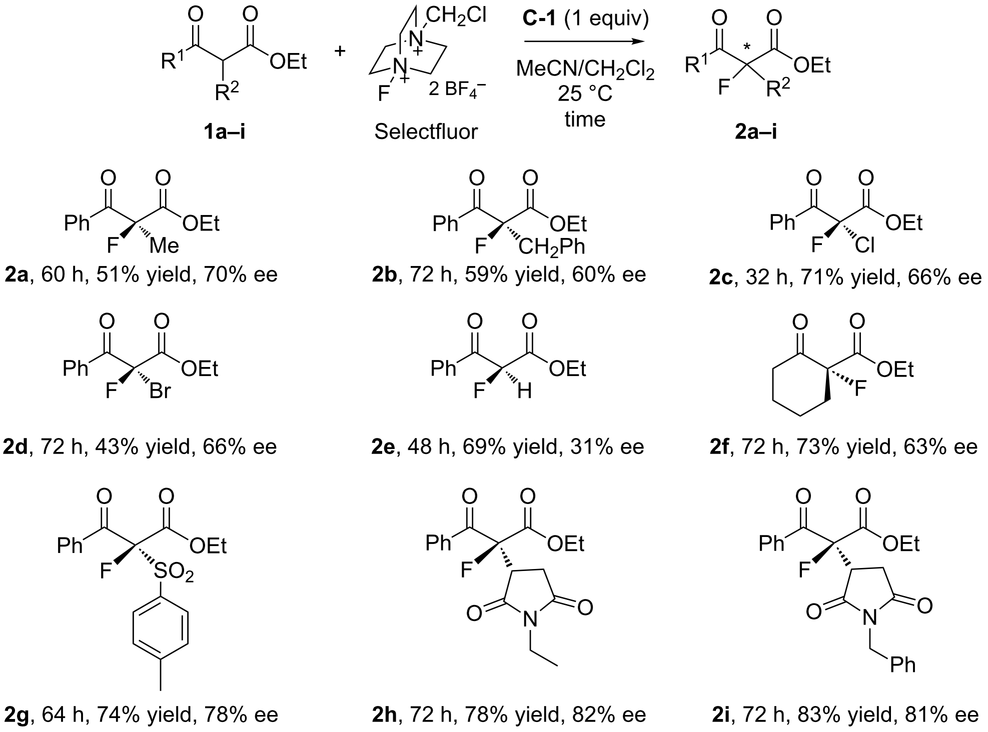


Figure 3: The asymmetric fluorination of various β-ketoesters.

shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference, i.e., proton (chloroform δ 7.26), carbon (chloroform δ 77.0). Multiplicity was indicated as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), br s (broad singlet). Coupling constants were reported in hertz (Hz). LC–MS were performed on an Agilent 2100 system. A C18 column (5.0 µm, 6.0 × 50 mm) was used for the separation. The mobile phases were methanol and water, both containing 0.05% trifluoroacetic acid. A linear gradient was used to increase from 25:75 v/v methanol/water to 100% methanol over 7.0 min at a flow rate of 0.7 mL/min. UV detections were conducted at 210, 254 and 365 nm. Low-resolution mass spectra were recorded in APCI (atmospheric pressure chemical ionization). The high-resolution mass spectra were obtained on a Finnigan/MAT 95XL-T spectrometer. Sorbent silica gel XHL TLC plates (130815) were used for the thin-layer chromatography (TLC). Flash chromatography separations were performed on YAMAZEN AI-580 flash column system with Agela silica gel columns (230–400 µm mesh). The enantiomeric excesses of products were determined by chiral phase HPLC analysis on an SHIMADZU LC-20AD system.

Synthesis of fluorous quinine ester **C-1**

Thionyl chloride (1.19 g, 10 mmol) was added to a mixture of (1*H*,1*H*,2*H*,2*H*-perfluorooctyl)benzoic acid (0.468 g, 1 mmol) and pyridine (75 mg, 1 mmol). After stirring of the mixture for 4 h at 50 °C, the reaction container was flushed with nitrogen gas to remove unreacted thionyl chloride. Quinine (0.275 g, 0.85 mmol) and *N*,*N*-diisopropylethylamine (129 mg, 1 mmol) in CH_2Cl_2 (3 mL) was added, and the solution was stirred for 24 h under reflux. After the reaction had been quenched with H_2O (2 mL) for 1 h, aqueous K_2CO_3 (2 M, 10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 layer was washed with aqueous HCl (ca. 2 M, 10 mL) and H_2O (20 mL). The combined extracts were dried over K_2CO_3 and evaporated. The slightly yellow residue was purified by a fluorous silica gel cartridge (5 g). It was first eluted with 80:20 MeOH/H_2O (20 mL) and then with 100% MeOH. The MeOH fraction was concentrated to give **C-1** as a yellowish solid (0.625 g, 95%). Mp 175–177 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.51–2.05 (m, 6H), 2.30–2.42 (m, 3H), 2.65–2.70 (m, 2H), 2.97–3.18 (m, 4H), 3.50 (q, *J* = 6.9 Hz, 1H), 3.98 (s, 3H), 5.02 (m, 2H), 5.83 (m, 1H), 6.72 (d, *J* = 6.9 Hz, 1H), 7.32–7.51 (m, 5H), 8.01–8.07 (m, 3H), 8.72–8.73 (d, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.2, 26.5, 27.6, 27.9, 32.4, 39.7, 42.6, 55.6, 56.7, 59.4, 74.5, 101.3, 114.6, 117.3, 118.6, 121.9, 126.9, 128.3, 128.63, 130.2, 131.9, 141.7, 143.6, 144.8, 145.0, 147.5, 156.0, 165.3; APCIMS *m/z*: 775.1 (M^+ + 1); HRMS–ESI (*m/z*): $[M + H]^+$ calcd. for $C_{35}H_{32}F_{13}N_2O_3$, 775.2205; found, 775.2214.

Synthesis of quinine benzoate catalyst **C-2**

Benzoyl chloride (28 mg, 0.2 mmol) was added to a mixture of quinine (65 mg, 0.2 mmol) in CH_2Cl_2 (0.5 mL). After stirring at rt for 4 h, aqueous K_2CO_3 (2 M, 1 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (2 × 3 mL). The CH_2Cl_2 layer was washed with aqueous HCl (2 M, 2 mL) and H_2O (3 mL). The combined organic extracts were dried (K_2CO_3) and evaporated. The white residue was purified by flash column chromatography (18:1 CH_2Cl_2/MeOH) to give quinine benzoate **C-2** (77 mg, 90%) as a colorless solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.69–2.00 (m, 5H), 2.42 (m, 1H), 2.82 (m, 2H), 3.19–3.40 (m, 2H), 3.49–3.56 (q, *J* = 7.2 Hz, 1H), 4.00 (s, 3H), 5.04 (m, 2H), 5.82 (m, 1H), 6.97 (d, *J* = 7.2, 1H), 7.40–7.65 (m, 6H), 8.01–8.13 (m, 3H), 8.73 (d, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 23.1, 27.2, 27.5, 39.0, 42.5, 56.0, 56.1, 59.0, 73.5, 101.2, 115.2, 117.2, 122.3, 126.6, 127.9, 128.7, 129.6, 129.6, 131.6, 131.8, 133.6, 140.6, 144.7, 147.2, 158.3, 165.1, 200.2; APCIMS *m/z*: 429.2 (M^+ + 1).

Synthesis of quinine acetate **C-3**

Acetic anhydride (30 mg, 0.3 mmol) was added to a mixture of quinine (65 mg, 0.2 mmol) in CH_2Cl_2 (0.5 mL). After stirring at rt for 8 h, aqueous K_2CO_3 (2 M, 1 mL) was added, and the mixture was extracted with CH_2Cl_2 (2 × 3 mL). The CH_2Cl_2 layer was washed with aqueous HCl (2 M, 2 mL) and H_2O (3 mL). The combined organic extracts were dried (K_2CO_3) and evaporated. The white residue was purified by flash column chromatography (18:1 CH_2Cl_2/MeOH) to give quinine acetate **C-3** (67 mg, 92%) as a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.26–1.89 (m, 5H), 2.42 (m, 1H), 2.12 (s, 3H), 2.23–2.36 (m, 2H), 2.37–2.70 (m, 2H), 3.00–3.16 (m, 2H), 3.34–3.42 (q, *J* = 7.2 Hz, 1H), 3.96 (s, 3H), 5.03 (m, 2H), 5.86 (m, 1H), 6.50 (d, *J* = 7.2 Hz, 1H), 7.35–7.44 (m, 3H), 8.02 (d, *J* = 9.0 Hz, 3H), 8.74 (d, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.1, 24.3, 27.5, 27.7, 39.6, 42.4, 55.6, 56.5, 59.0, 73.7, 101.4, 114.5, 118.9, 121.8, 127.0, 131.8, 141.7, 143.5, 144.8, 147.4, 149.6, 157.9, 170.0, 199.5, 200.2; ACPIMS *m/z*: 367.2 (M^+ + 1).

Synthesis of fluorous pyrrolidine ester **C-6**

N,*N*'-Dicyclohexylcarbodiimide (DCC) (0.206 g, 1 mmol) was added to a mixture of (1*H*,1*H*,2*H*,2*H*-perfluorooctyl)benzoic acid (0.468 g, 1 mmol), *N*-Boc-L-prolinol (0.221 g, 1.1 mmol), 4-dimethylaminopyridine (DMAP) (0.122 g, 1 mmol) in THF. After being stirred for 24 h at rt, the mixture was directly loaded onto a fluorous silica-gel cartridge (5 g; eluted by 100% methanol) to give the *N*-Boc-L-prolinyl (1*H*,1*H*,2*H*,2*H*-perfluorooctyl)benzoate (0.618 g, 95%). The *N*-Boc ester was then added to a mixture of TFA in CH_2Cl_2. After being stirred for 12 h at 0 °C, the reaction mixture was loaded onto a fluorous silica-gel cartridge (5 g) again to give the title compound L-prolinyl (1*H*,1*H*,2*H*,2*H*-perfluorooctyl)benzoate (0.496 g, 90%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.62–1.89 (m, 3H), 2.16–2.21 (m, 1H), 2.29–2.47 (m, 2H), 2.92–2.98 (m, 2H), 3.48–3.54 (m, 2H), 3.71–3.84 (m, 2H), 4.38–4.42 (m, 1H), 4.95–4.97 (m, 2H), 7.27–7.31 (d, 2H), 7.48–7.50 (d, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.0, 26.2, 26.3, 26.3, 28.5, 32.2, 32.6, 51.1, 61.6, 67.2, 127.3, 127.6, 128.3, 128.3, 128.4, 130.1, 135.1, 141.4, 171.9; APCIMS *m/z*: 552.1 ($M^+ + 1$).

General procedure for fluorination reaction

A mixture of Selectfluor (0.057 g, 0.16 mmol) and fluorous quinine ester **C-1** (0.124 g, 0.16 mmol) in CH_3CN and CH_2Cl_2 was stirred at rt for 1 h. Ethyl 2-methyl-3-oxo-3-phenylpropanoate (**1a**) (0.033 g, 0.16 mmol) was added. After stirring of the mixture at rt for 32 h, the reaction was quenched with H_2O. After F-SPE, the mixture was extracted with EtOAc. The organic layer was washed with aqueous HCl (2 M, 5 mL) and H_2O (5 mL), and then dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash column chromatography (8:1 hexane/EtOAc) to give (*S*)-ethyl 2-methyl-2-fluoro-3-oxo-3-phenylpropanoate (**2a**) as a colorless oil.

(*S*)-Ethyl 2-methyl-2-fluoro-3-oxo-3-phenylpropanoate (**2a**)

51% yield, 70% ee. The enantiomeric excess was determined by HPLC on (R,R)-WHELK-O1 with hexane/iPrOH (92:8) as the eluent. Flow rate: 0.6 mL/min, λ = 254 nm; t_{minor} = 20.132 min, t_{major} = 17.924 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.00 (t, *J* = 7.2 Hz, 3H), 1.93 (s, 1H), 4.11 (q, *J* = 7.2 Hz, 2H), 7.33–7.38 (m, 2H), 7.46 (m, 1H), 7.90–7.92 (m, 2H); APCIMS *m/z*: 225.2 ($M^+ + 1$).

(*S*)-Ethyl 2-benzyl-2-fluoro-3-oxo-3-phenylpropanoate (**2b**)

59% yield, 60% ee. The enantiomeric excess was determined by HPLC on Regis Chiral 5 Micron with hexane/iPrOH (90:10) as the eluent. Flow rate: 0.8 mL/min, λ = 254 nm; t_{minor} = 8.732 min, t_{major} = 10.352 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, *J* = 7.2 Hz, 3H), 3.48 (d, *J* = 14.1 Hz, 1H), 3.67 (d, *J* = 14.1 Hz, 1H), 4.01 (q, *J* = 7.2 Hz, 2H), 7.14–7.23 (m, 5H), 7.26 (m, 2H), 7.36 (m, 1H), 7.91 (d, 2H); APCIMS *m/z*: 301.1 ($M^+ + 1$).

(*R*)-Ethyl 2-chloro-2-fluoro-3-oxo-3-phenylpropanoate (**2c**)

71% yield, 66% ee. The enantiomeric excess was determined by HPLC on Regis Chiral 5 Micron with hexane/iPrOH (90:10) as the eluent. Flow rate: 0.8 mL/min, λ = 254 nm; t_{minor} = 12.220 min, t_{major} = 14.492 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, *J* = 7.2 Hz, 3H), 4.32 (q, *J* = 7.2 Hz, 2H), 7.47–7.49 (m, 2H), 7.60 (m, 1H), 8.02–8.05 (m, 2H); APCIMS *m/z*: 245.0 ($M^+ + 1$).

(*R*)-Ethyl 2-bromo-2-fluoro-3-oxo-3-phenylpropanoate (**2d**)

43% yield, 66% ee. The enantiomeric excess was determined by HPLC on Regis Chiral 5 Micron with hexane/iPrOH (90:10) as the eluent. Flow rate: 1.2 mL/min, λ = 254 nm; t_{minor} = 5.912 min, t_{major} = 7.004 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.28 (t, *J* = 7.2 Hz, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 7.48–7.53 (m, 2H), 7.64 (m, 1H), 8.06–8.10 (m, 2H); APCIMS *m/z*: 289.0 ($M^+ + 1$).

(*S*)-Ethyl 2-fluoro-3-oxo-3-phenylpropanoate (**2e**)

69% yield, 31% ee. The enantiomeric excess was determined by HPLC on (R,R)-WHELK-O1with hexane/iPrOH (95:5) as the eluent. Flow rate: 1.0 mL/min, λ = 254 nm; t_{minor} = 5.904 min, t_{major} = 5.380 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, *J* = 7.2 Hz, 3H), 4.23 (q, *J* = 7.2 Hz, 2H), 5.70–5.87 (s, *J* = 48.9 Hz, 1H), 7.18–7.45 (m, 2H), 7.53 (m, 1H), 7.94–7.98 (m, 2H); APCIMS *m/z*: 211.1 ($M^+ + 1$).

(*R*)-Ethyl 2-fluoro-2-cyclohexanonecarboxylate (**2f**)

73% yield, 63% ee. The enantiomeric excess was determined by HPLC on (R,R)-WHELK-O1 with hexane/iPrOH (90:10) as the eluent. Flow rate: 0.8 mL/min, λ = 210 nm; t_{minor} = 10.848 min, t_{major} = 12.440 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.32 (t, *J* = 7.2 Hz, 3H), 1.61–1.89 (m, 2H), 2.06–2.10 (m, 1H), 2.51–2.73 (m, 3H), 4.30 (q, *J* = 7.2 Hz, 2H).

(*S*)-Ethyl 2-(4'-methylbenzenesulfonyl)-2-fluoro-3-oxo-3-phenylpropanoate (**2g**)

74% yield, 78% ee. The enantiomeric excess was determined by HPLC on Venusil Chiral OD-H with hexane/iPrOH (92:8) as the eluent. Flow rate: 0.3 mL/min, λ = 254 nm; t_{minor} = 27.176 min, t_{major} = 24.288 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.41 (t, *J* = 7.2 Hz, 3H), 2.36 (s, 3H), 4.38 (q, *J* = 7.2 Hz, 2H), 7.09–7.18 (m, 4H), 7.20–7.35 (m, 3H), 7.54 (s, 2H); APCIMS *m/z*: 365.1 ($M^+ + 1$).

(*S*)-Ethyl 2-(*N*-ethylmaleimide)-2-fluoro-3-oxo-3-phenylpropanoate (**2h**)

78% yield, 82% ee. The enantiomeric excess was determined by HPLC on Venusil Chiral OD-H with hexane/iPrOH (94:6) as the eluent. Flow rate: 0.5 mL/min, λ = 254 nm; t_{minor} = 13.832 min, t_{major} = 12.432 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.16 (t, *J* = 7.2 Hz, 3H), 1.28 (t, *J* = 7.2 Hz, 3H), 2.58 (dd, *J* = 18.3 Hz, 1H), 3.05 (dd, *J* = 18.3 Hz, 1H), 3.61 (q, *J* = 7.2 Hz, 2H), 4.14 (m, 1H), 4.42 (m, *J* = 7.2 Hz, 2H), 7.46–7.51 (m, 2H), 7.62 (m, 1H), 8.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.9, 13.8, 30.8, 34.1, 44.9, 63.5, 128.5, 128.8, 130.1, 130.2, 134.8, 168.5, 174.8; APCIMS *m/z*: 336.1 ($M^+ + 1$).

(*S*)-Ethyl 2-(*N*-benzylmaleimide)-2-fluoro-3-oxo-3-phenylpropanoate (**2i**)

83% yield, 81% ee. The enantiomeric excess was determined by HPLC on Venusil Chiral OD-H with hexane/iPrOH (92:8) as the eluent. Flow rate: 0.3 mL/min, λ = 254 nm: t_{minor} = 27.176 min, t_{major} = 24.288 min; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, J = 7.2 Hz, 3H), 2.58 (dd, J = 18.3 Hz, 1H), 3.05 (dd, J = 18.3 Hz, 1H), 4.14 (m, 1H), 4.42 (m, J = 7.2 Hz, 2H), 7.67 (q, J = 15 Hz, 2H), 7.25–7.37 (m, 5H), 7.46–7.51 (m, 2H), 7.62 (m, 1H), 8.12 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 13.8, 30.8, 42.7, 45.0, 45.3, 63.5, 128.0, 128.6, 128.7, 128.8, 130.1, 130.2, 134.9, 174.6; APCIMS *m*/*z*: 398.1 (M^+ + 1).

Synthesis of racemic samples

The mixture of Selectfluor (0.057 g, 0.16 mmol) and ethyl benzoylacetate (0.031 g, 0.16 mmol) in CH_3CN (1 mL) was stirred at 90 °C under microwave irradiation for 40 min. The reaction was quenched by water. The mixture was extracted with ethyl acetate (3 mL). The organic layer was washed with aqueous HCl (2 M, 5 mL) and water (5 mL), and dried over Na_2SO_4. After evaporation of the solvent, the residue was purified by flash column chromatography (8:1 hexane/EtOAc) to give ethyl 2-methyl-2-fluoro-3-oxo-3-phenylpropanoate (0.032 g, 94%) as a colorless oil.

General procedure for recycling of **C-1**

The reaction mixture was loaded onto a fluorous silica-gel cartridge (5 g) and eluted by 80:20 $MeOH/H_2O$ to collect nonfluorous components, including the fluorinated product. The cartridge was eluted with MeOH to collect **C-1**. After concentration of the MeOH fraction and drying at 60 °C for 8 h, the recovered promoter was ready for the next round of reactions.

Supporting Information

Supporting Information File 1

Chiral HPLC chromatograms for fluorination products **2a–i**. LC–MS, NMR spectra for fluorination products **2a–i** and cinchona alkaloid derivatives **C-1**, **C-2**, **C-3** and **C-6.** LC–MS spectra for **2h** and HRMS spectra for **C-1**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-138-S1.pdf]

Acknowledgements

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Organocatalytic asymmetric allylic amination of Morita–Baylis–Hillman carbonates of isatins

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Letter

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Abstract

The investigation of a Lewis base catalyzed asymmetric allylic amination of Morita–Baylis–Hillman carbonates derived from isatins afforded an electrophilic pathway to access multifunctional oxindoles bearing a C3-quaternary stereocenter, provided with good to excellent enantioselectivity (up to 94% ee) and in high yields (up to 97%).

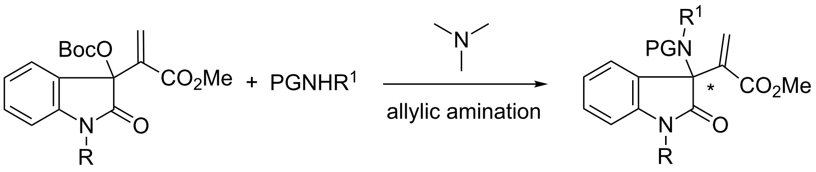
Introduction

Chiral 3-amino-2-oxindoles are versatile and useful units for the preparation of natural products and drug candidates, such as the vasopressin VIb receptor antagonist SSR-149415 [1,2], the potent gastrin/CCK-B receptor antagonist AG-041R [3], chartelline C [4,5] and psychotrimine [6]. Therefore, the development of asymmetric protocols to construct such chiral scaffolds has provoked wide interest. The application of 3-substituted oxindoles as nucleophiles in the reactions with azodicarboxylates or nitrosobenzene provides a very simple and direct approach for the synthesis of optically active 3-amino-2-oxindole derivatives [7], either by the catalysis of chiral metal complexes [8-10] or organic catalysts [11-15]. On the other hand, the asymmetric addition to electrophilic imines of isatins is also an attractive pathway, and a variety of examples have been presented [16-21].

Recently, we have developed the asymmetric allylic alkylation reactions [22] with Morita–Baylis–Hillman (MBH) carbonates of isatins to obtain 2-oxindoles bearing a C3-quaternary chiral center, by the catalysis of chiral tertiary amines, β-isocupreidine (β-ICD) or its derivatives [23,24]. We envisaged that such a catalytic strategy should be applicable to the allylic amination of the corresponding MBH carbonates [25-28], as outlined in Scheme 1. Thus, multifunctional chiral 3-amino-2-oxindoles could be obtained in a straightforward manner.

Results and Discussion

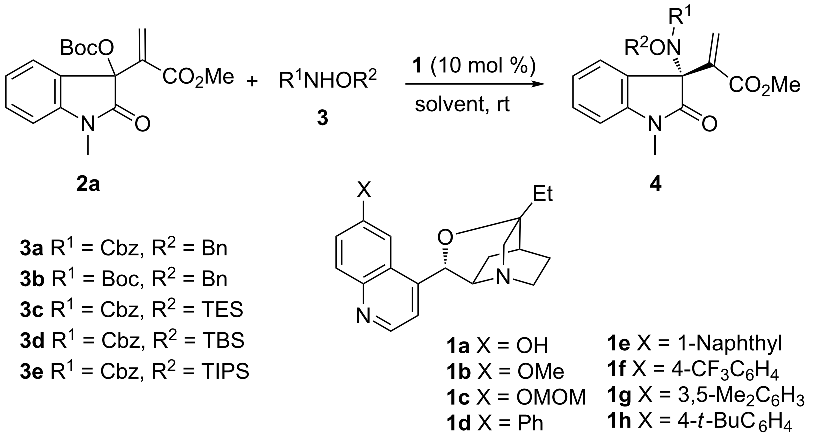
Based on the above considerations, we initially investigated the reaction of MBH carbonate **2a** and a diversity of nucleophilic nitrogen sources by the catalysis of DABCO. No desired reaction occurred for phthalimide [25] or *N*-allyl *p*-toluenesulfon-



Scheme 1: Allylic amination of MBH carbonates of isatins to access 3-amino-2-oxindoles.

amide [27], which has been successfully applied in the asymmetric amination of MBH carbonates derived from aryl aldehydes. Pleasingly, the reaction took place smoothly to afford product **4a** when hydroxylamine **3a** with *N*-benzyloxycarbonyl and *O*-benzyl groups [29] was applied in diethyl ether (Table 1, entry 1). Subsequently, an array of tertiary amines derived from quinidine was explored to introduce chirality into the product. While poor enantioselectivity was obtained when β-iso-

Table 1: Screening studies of asymmetric allylic amination of MBH carbonate of isatin.[a]



3a R^1 = Cbz, R^2 = Bn
3b R^1 = Boc, R^2 = Bn
3c R^1 = Cbz, R^2 = TES
3d R^1 = Cbz, R^2 = TBS
3e R^1 = Cbz, R^2 = TIPS

1a X = OH
1b X = OMe
1c X = OMOM
1d X = Ph
1e X = 1-Naphthyl
1f X = 4-$CF_3C_6H_4$
1g X = 3,5-$Me_2C_6H_3$
1h X = 4-*t*-BuC_6H_4

entry	1	3	solvent	*t* (h)	yield[b] (%)	ee[c] (%)
1	DABCO	**3a**	Et_2O	12	**4a**, 86	–
2	**1a**	**3a**	Et_2O	12	**4a**, 83	17
3	**1b**	**3a**	Et_2O	12	**4a**, 80	37
4	**1c**	**3a**	Et_2O	12	**4a**, 85	52
5	**1d**	**3a**	Et_2O	12	**4a**, 85	58
6	**1d**	**3b**	Et_2O	12	**4b**, <10	–
7	**1d**	**3c**	Et_2O	12	**4c**, 80	72
8	**1d**	**3d**	Et_2O	24	**4d**, 85	83
9	**1d**	**3e**	Et_2O	12	**4e**, 53	72
10	**1e**	**3d**	Et_2O	24	**4d**, 88	77
11	**1f**	**3d**	Et_2O	24	**4d**, 78	72
12	**1g**	**3d**	Et_2O	24	**4d**, 90	74
13	**1h**	**3d**	Et_2O	24	**4d**, 88	85
14	**1d**	**3d**	DCE	18	**4d**, 74	74
15	**1d**	**3d**	$PhCF_3$	12	**4d**, 93	86
16	**1d**	**3d**	*m*-xylene	12	**4d**, 97	82
17	**1d**	**3d**	PhF	12	**4d**, 83	85
18	**1d**	**3d**	PhCl	12	**4d**, 93	88
19[d]	**1h**	**3d**	**PhCl**	**24**	**4d, 92**	**91**

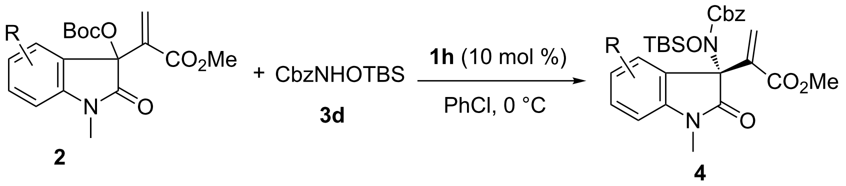
[a]Unless otherwise noted, reactions were performed with 0.12 mmol of **2a**, 0.1 mmol of **3**, and 0.01 mmol **1** of in 0.5 mL solvent at room temperature. [b]Isolated yield. [c]Based on chiral HPLC analysis. [d]At 0 °C.

cupreidine **1a** (β-ICD) or β-isoquinidine **1b** was used (Table 1, entries 2 and 3), a moderate ee value was attained in the presence of *O*-MOM isocupreidine **1c** (Table 1, entry 4) [30]. Moreover, even a slightly higher enantiocontrol was observed for a phenyl-substituted amine **1d** (Table 1, entry 5) [31]. Consequently, we paid attention to the structural modifications on the nitrogen source. Very poor conversion was observed when *N*-Boc protected hydroxylamine **3b** was applied in the catalysis by **1d** (Table 1, entry 6). To our gratification, dramatically improved enantioselectivity was obtained for **3c** bearing an *O*-TES group (Table 1, entry 7), and an even higher ee value was gained for **3d** with a bulkier *O*-TBS group, although it exhibited lower reactivity (Table 1, entry 8). Nevertheless, inferior results were afforded for **3e** with an *O*-TIPS group (Table 1, entry 9). Furthermore, we prepared more isocupreidines with diverse aryl-substitutions and tested their catalytic efficacy in the reaction of MBH carbonate **2a** and **3d**. Diminished enantioselectivity was delivered in the presence of catalysts **1e**–**1g** (Table 1, entries 10–12), but a slightly higher ee value could be obtained upon catalysis by **1h** with a 4-*tert*-butylphenyl group (Table 1, entry 13). In addition, a number of solvents were investigated in the catalysis by **1d** (Table 1, entries 14–18), and chlorobenzene was found to be the optimal selection (Table 1, entry 18). Finally, it was found that the reaction still proceeded smoothly at 0 °C, and a high ee value could be obtained in the catalysis by amine **1h**, although a longer reaction time was required to give a better yield (Table 1, entry 19). It should be noted that the reaction became sluggish when (*S*)-BINOL [32] was added, and even no reaction happened in the presence of other additives such as $LiClO_4$ or $Ti(OiPr)_4$ [33].

With the optimized conditions in hand, we explored a diversity of MBH carbonates derived from isatins in the reactions with protected hydroxylamine **3d** by the catalysis of chiral amine **1h** in chlorobenzene at 0 °C. The results are summarized in Table 2. A series of MBH carbonates **2** bearing either electron-donating or -withdrawing substituents on the aromatic moiety of 2-oxindoles were well tolerated. A higher reactivity was generally observed for MBH carbonates with electron-donating substitutions, and excellent yields and enantioselectivity were obtained (Table 2, entries 2–4). On the other hand, MBH carbonates with electron-withdrawing groups exhibited a slower reaction rate, but both good yields and ee values were still obtained (Table 2, entries 5–10).

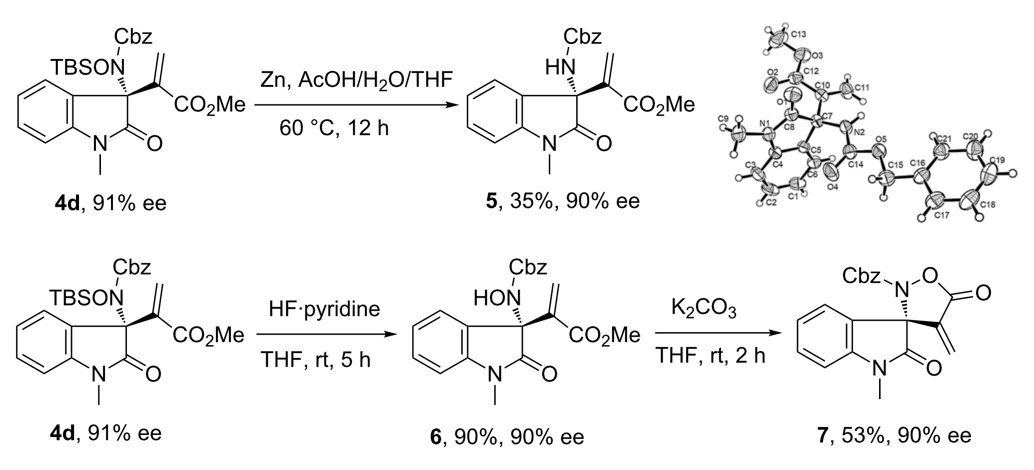
As outlined in Scheme 2, some synthetic transformations were conducted with the multifunctional allylic amination product **4d**. The N–O bond cleavage of **4d** could be realized with Zn powder in acetic acid to produce compound **5**, albeit in modest yield [34,35], whose absolute configuration has been determined by X-ray analysis [36]. The removal of the *O*-TBS unit proceeded efficiently in the presence of hydrofluoric acid, and an intramolecular transesterification process of intermediate **6** happened to afford a spirocyclic oxindole **7** without loss of enantiopurity [37].

Table 2: Substrate scope and limitations.[a]



entry	R	*t* (h)	yield[b] (%)	ee[c] (%)
1	H (**2a**)	24	**4d**, 92	91
2	5-Me (**2b**)	24	**4f**, 93	91
3	5-MeO (**2c**)	26	**4g**, 97	94
4	5,7-Me_2 (**2d**)	40	**4h**, 93	90
5	5-F (**2e**)	36	**4i**, 86	90
6	5-Cl (**2f**)	30	**4j**, 88	89
7	5-Br (**2g**)	36	**4k**, 81	88
8	5-I (**2h**)	36	**4l**, 85	86
9	5-CF_3O (**2i**)	36	**4m**, 71	85
10	7-F (**2j**)	36	**4n**, 85	90

[a] Reactions were performed with 0.12 mmol of **2**, 0.1 mmol of **3d**, and 0.01 mmol of **1h** in 0.5 mL of chlorobenzene at 0 °C. [b] Isolated yield. [c] Based on chiral HPLC analysis.



Scheme 2: Synthetic transformations of multifunctional product **4d**.

Conclusion

We have developed a highly enantioselective allylic amination of Morita–Baylis–Hillman carbonates of isatins with *N*-silyloxycarbamates by the catalysis of a modified β-ICD derivative, which provides an electrophilic process to 3-amino-2-oxindoles with a C3-quaternary chiral center. A range of products with high molecular complexity were obtained with good to excellent enantioselectivity (up to 94% ee) and high yields (up to 97%). Currently, more studies on the catalytic asymmetric transformations of MBH carbonates of isatins are under way in our laboratory.

Supporting Information

General experimental procedures, copies of ^{1}H, ^{13}C NMR spectra and HPLC chromatograms for all new compounds, crystal data and structure refinement for enantiopure **5**.

Supporting Information File 1

General procedures and analytical data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-139-S1.pdf]

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Asymmetric organocatalytic decarboxylative Mannich reaction using β-keto acids: A new protocol for the synthesis of chiral β-amino ketones

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Letter

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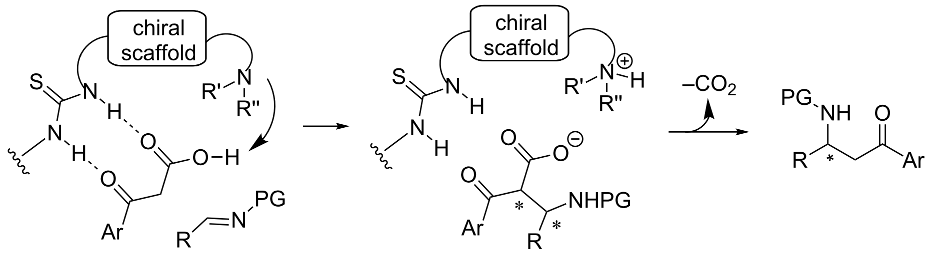
Abstract

The first decarboxylative Mannich reaction employing β-keto acids, catalyzed by cinchonine-derived bifunctional thiourea catalyst has been described. The desired β-amino ketones were obtained in excellent yields and with moderate to good enantioselectivities.

Introduction

Chiral β-amino ketones are an important class of building blocks for the synthesis of 1,3-amino alcohols [1,2], 1,3-amino acids [3] and other bioactive nature products [4-6]. Given their synthetic significance, methods for the asymmetric synthesis of β-amino ketones have been extensively investigated over the past few decades [7]. Among them, the Mukaiyama–Mannich reaction performed with silyl enol ethers and sulfonyl aldimines, catalyzed by a chiral Lewis acid complex, is one of the most important synthetic methods [8-13]. Apparently, direct use of inactivated ketones as a donor would be of great practical value. Indeed, direct approaches such as asymmetric enamine catalysis [14-17] and Brønsted acid catalysis [18] have been reported, through the activation of ketones or aryl imines [19]. However, substrates for the enamine activation are limited to only acetone and cyclic alkyl ketones. Application of aryl methyl ketones in the asymmetric Mannich reaction by enamine catalysis remains elusive. On the other hand, the only chiral Brønsted acid catalytic system based on BINOL-phosphates was reported by Rueping et al. Unfortunately, the yields of the reported reactions were unsatisfactory and the enantioselectivities were modest [20].

In recent years, inspired by the enzymatic synthesis of polyketides and fatty acids in biological systems, the enantioselective decarboxylative reactions of malonic acid half thioesters (MAHTs) have received much attention. In this regard, various electrophiles, including aldehydes, ketones, imines, activated alkenes and azodicarboxylates, have been employed as elec-



Scheme 1: Working hypothesis: Decarboxylative Mannich reaction.

trophiles in the presence of metal [21-25] or organocatalysts [26-36].

To provide a practical solution to the low reactivity associated with aryl methyl ketones, we wondered whether β-keto acids could serve as an enolate equivalent to aryl methyl ketones upon decarboxylation (Scheme 1). The proposed addition–decarboxylation sequence is consistent with current mechanistic understanding [31,35,37,38]. However, we cannot exclude an alternative decarboxylation–addition pathway at this stage. In fact, in sharp contrast to the popular use of malonic acid half thioesters (MAHTs) as an ester enolate equivalent in enantioselective decarboxylative additions [39], the employment of β-keto acids as a reaction partner in decarboxylative processes has rarely been explored [37]. Herein, we reported the first decarboxylative Mannich reaction between the β-keto acids and sulfonylimines, affording chiral β-amino ketones in excellent yields and good enantioselectivities.

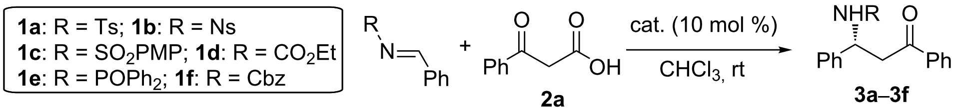
Findings

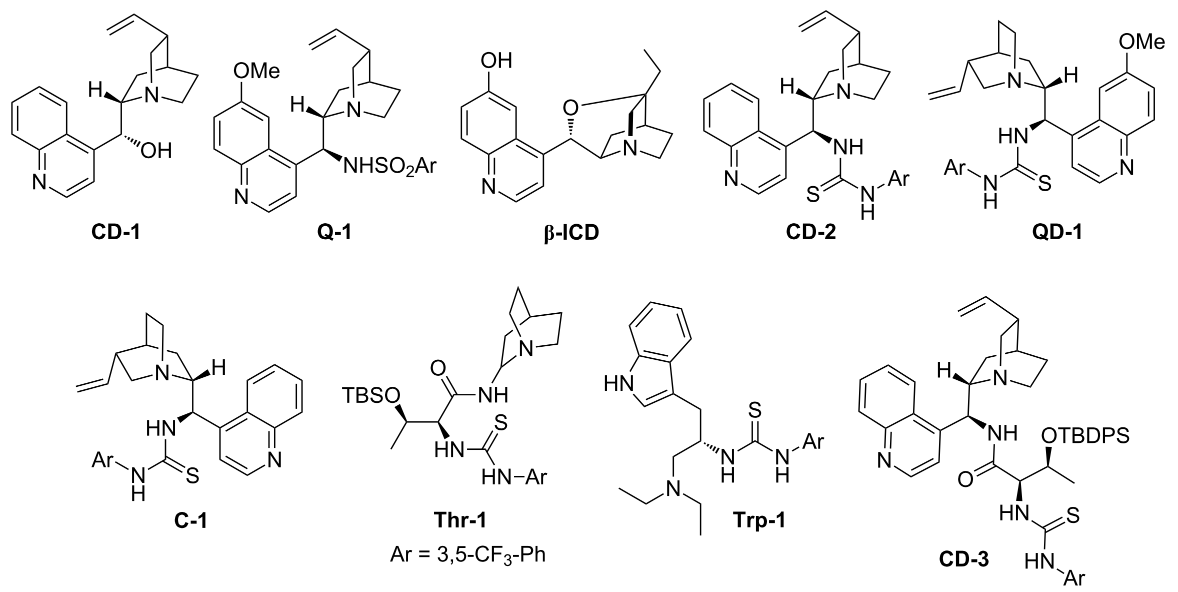
In our initial screening, we examined the model reaction between tosylimine **1a** and β-keto acid **2a** in the presence of a range of bifunctional catalysts (Table 1). We first evaluated the catalytic effects of several cinchona alkaloid derivatives. Commercially available cinchonidine (**CD-1**) led to the formation of the product with disappointing enantioselectivity (Table 1, entry 1). Quinine-derived sulfonamide [40], β-isocupreidine **(β-ICD)** [41,42] and biscinchona alkaloid $(DHQ)_2AQN$ were all found to be poor catalysts (Table 1, entries 2–4). On the other hand, cinchona alkaloid derived bifunctional thiourea tertiary amine catalysts afforded much improved results (Table 1, entries 5–7). Among them, the cinchonine based thiourea **C-1** turned out to be the best catalyst, and the Mannich product was isolated with 58% ee (Table 1, entry 7). In addition, we also examined several other bifunctional catalysts based on amino acids [43,44], including threonine derived **Thr-1** [45], and tryptophan based **Trp-1** [46], as well as threonine incorporated multifunctional catalyst **CD-3** [47]. However, no further improvement could be achieved (Table 1, entries 8–10). The influence of different imines on the reaction was subsequently explored, and it was found that the electronic nature of the sulfonyl protective groups affected the enantioselectivity. While the employment of nosylimine **1b** led to decreased enantioselectivity (Table 1, entry 11), replacement of tosylimine **1a** with *N*-(*p*-methoxybenzenesulfonyl)imine **1c** resulted in further improvement, and the product was obtained in 65% ee (Table 1, entry 12). However, when ethoxycarbonylimine **1d** was used, nearly racemic products were obtained, suggesting the importance of the sulfonyl group in the asymmetric induction (Table 1, entry 13). Less reactive imines, such as diphenylphosphinoylimine **1e** and Cbz-imine **1f**, proved to be unsuitable for the reaction (Table 1, entries 14 and 15).

A screening of the solvent effect was then followed, and the results are summarized in Table 2. In general, the reaction proceeded very well in common aprotic solvents, and excellent yields were consistently obtained (Table 2, entries 1–9). Enantioselectivity of the reaction varied, and diethyl ether was found to be the best solvent, furnishing the desired product with 72% ee. Employment of other etheric solvents, including methyl *tert*-butyl ether and dioxane, and lowering reaction temperature did not offer further improvement (Table 2, entries 10–12).

To establish the substrate scope, a number of sulfonylimines derived from aromatic aldehydes were employed as acceptors, and the results are summarized in Table 3. In general, the reaction worked well for imines with various substituents at different positions of the phenyl ring, including electron-withdrawing groups, electron-donating groups and halogen atoms, and excellent yields and moderate ee values were obtained (Table 3, entries 1–10). Heterocycles were well-tolerated, and good enantioselectivities were obtained with 2-furyl and thiophen-2-yl containing substrates (Table 3, entries 11 and 12). The aryl groups of β-keto acids could also be varied, and the reaction was applicable to β-keto acids with different aromatic substituents (Table 3, entries 13–17). Furthermore, the reaction

Table 1: Exploration of the decarboxylative addition of β-ketoacids to imines.





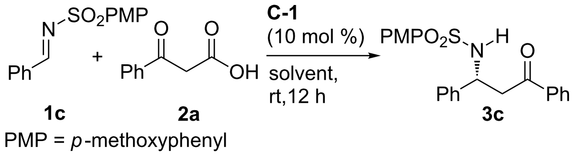
Entry[a]	**1**	cat	Yield (%)[b]	ee (%)[c]
1	**1a**	**CD-1**	86	17
2	**1a**	**Q-1**	54	13
3	**1a**	$(DHQ)_2AQN$	90	2
4	**1a**	**β-ICD**	93	27
5	**1a**	**CD-2**	97	44
6	**1a**	**QD-1**	93	54
7	**1a**	**C-1**	95	58
8	**1a**	**Thr-1**	88	12
9	**1a**	**Trp-1**	95	21
10	**1a**	**CD-3**	92	13
11	**1b**	**C-1**	95	49
12	**1c**	**C-1**	96	65
13	**1d**	**C-1**	91	5
14	**1e**	**C-1**	trace	–
15	**1f**	**C-1**	trace	–

[a]Reactions were performed with **1** (0.05 mmol), **2a** (0.075 mmol) and the catalyst (0.005 mmol) in $CHCl_3$ (0.5 mL). [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase.

was also applicable to alkyl β-keto acids, and comparable chemical yields and enantioselectivities were attainable (Table 3, entries 18–19). The absolute configurations of the products were assigned by comparing the optical rotation of **3a** with the value reported in the literature [48] (see the Supporting Information File 1 for details).

In conclusion, we have developed the first organocatalytic decarboxylative Mannich reaction employing β-keto acids as the donor. The reaction was effectively catalyzed by cinchonine-based bifunctional catalyst **C-1**, and the synthetically useful β-amino ketones were prepared in excellent yields and with moderate to good enantioselectivities. The method reported

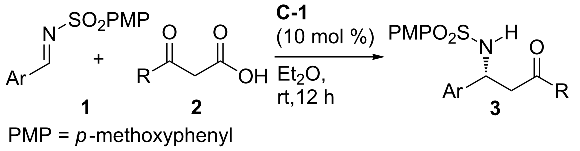
Table 2: Solvent screening.



Entry[a]	Solvent	Yield (%)[b]	ee (%)[c]
1	$CHCl_3$	96	65
2	THF	93	64
3	DCM	92	66
4	toluene	90	63
5	**diethyl ether**	**93**	**72**
6	ethyl acetate	92	66
7	benzene	90	67
8	DCE	91	66
9	acetone	92	52
10	methyl *tert*-butyl ether	92	62
11	dioxane	94	65
12[d]	diethyl ether	67	65

[a]Reactions were performed with **1c** (0.05 mmol), **2a** (0.075 mmol) and **C-1** (0.005 mmol) in the solvent specified (0.5 mL). [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]Reaction was performed at 0 °C.

Table 3: Substrate scope.



Entry[a]	Ar	R	3	Yield (%)[b]	ee (%)[c]
1	Ph	Ph	**3c**	93	72
2	4-Me-C_6H_4	Ph	**3g**	90	64
3	4-Br-C_6H_4	Ph	**3h**	88	61
4	4-CF_3-C_6H_4	Ph	**3i**	85	55
5	4-OMe-C_6H_4	Ph	**3j**	97	62
6	2-F-C_6H_4	Ph	**3k**	89	65
7	2-Me-C_6H_4	Ph	**3l**	92	65
8	2-Br-C_6H_4	Ph	**3m**	87	59
9	3-Me-C_6H_4	Ph	**3n**	97	65
10	3-Br-C_6H_4	Ph	**3o**	96	61
11	2-furyl	Ph	**3p**	94	83
12	thiophen-2-yl	Ph	**3q**	87	77
13	Ph	4-F-C_6H_4	**3r**	95	64
14[d]	Ph	3-Cl-C_6H_4	**3s**	62	70
15	Ph	2-naphthyl	**3t**	62	69
16	Ph	4-Me-C_6H_4	**3u**	93	67
17	Ph	2-OMe-C_6H_4	**3v**	88	60
18	Ph	*n*-Pr	**3w**	92	54
19	Ph	*t*-Bu	**3x**	75	73

Table 3: Substrate scope. (continued)

[a]Reactions were performed with **1** (0.05 mmol), **2** (0.075 mmol) and **C-1** (0.005 mmol) in Et_2O (0.5 mL). [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase. [d]The catalyst loading was 20 mol %.

represents a new protocol for the asymmetric construction of β-amino ketones.

Experimental

General procedure for the decarboxylative Mannich reaction of β-keto acids and aldimines

To a solution of imine **1c** (13.8 mg, 0.05 mmol) and **C-1** (2.8 mg, 0.005 mmol) in ether (0.5 mL) at room temperature, was added β-keto acid **2a** (12.3 mg, 0.075 mmol). The reaction mixture was stirred for 12 h. The solvent was then removed under reduced pressure, and the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 5:1 to 3:1) to afford **3c** as a white solid (18.4 mg, 93% yield).

Supporting Information

Supporting Information File 1

Characterization data and spectra of synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-144-S1.pdf]

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Asymmetric one-pot sequential Friedel–Crafts-type alkylation and α-oxyamination catalyzed by a peptide and an enzyme

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Letter

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Friedel–Crafts-type alkylation; laccase; one-pot reaction; organocatalysis; α-oxyamination; resin-supported peptide catalyst

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Abstract

In the presence of a peptide catalyst and the oxidative enzyme laccase, a one-pot sequential reaction including a Friedel–Crafts-type alkylation of α,β-unsaturated aldehydes followed by an α-oxyamination was realized. The reaction in aqueous solvent to promote the enzymatic oxidation, and the use of a peptide catalyst compatible with such conditions, were essential. The present sequential reaction afforded oxygen-functionalized indole or pyrrole derivatives in a highly enantioselective manner.

Findings

Indole derivatives represent a class of biologically active compounds [1-3], and they often have chiral carbon chains attached to indole rings. A Friedel–Crafts-type asymmetric alkylation (FCAA) to indoles is a versatile method for synthesizing such chiral indole derivatives. To date, a number of FCAA reactions by either metal catalysts or organocatalysts have been reported [4-11]. Especially because organocatalysts have been demonstrated to possess a high feasibility for sequential reactions [12-16], it is expected that a sequential reaction including an organocatalytic FCAA step could provide highly functionalized indole compounds [17-20].

Indoles with an oxygenated stereogenic carbon at the β-position of the ring, such as indolmycin [21,22] and diolmycin [23], are known as antibiotics (Figure 1). The framework of these compounds could be constructed though the conjugate addition of an indole to α,β-unsaturated aldehydes followed by oxygenation at the α-position of the carbonyl group. If such a sequence can be realized in a one-pot reaction, it would be a powerful method for the synthesis of oxy-functionalized indole derivatives with operational simplicity. To date, there has been no report on the FCAA reaction combined with an α-oxygenation of aldehydes [24-29] in a one-pot sequential reaction.

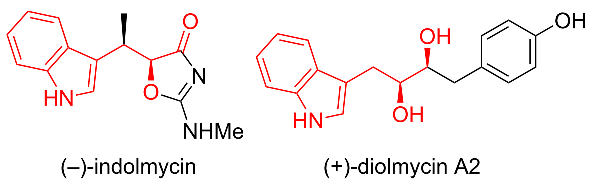


Figure 1: Oxygen-functionalized indole compounds.

Meanwhile, our group has developed resin-supported peptide catalysts (Figure 2) for several organic reactions in aqueous media [30-37]. Since these catalysts can be applicable for the FCAA reaction toward α,β-unsaturated aldehydes through iminium intermediates [32,37], and an asymmetric α-oxyamination of aldehydes via enamines [33], they are expected to be suitable for a one-pot sequential reaction to make the chiral indoles mentioned above. Herein, we report on an enantioselective synthesis of oxygenated indole compounds through a one-pot sequential FCAA/α-oxyamination catalyzed by the resin-supported peptide.

Pro-D-Pro-Aib-Trp-Trp–$(AA)_n$–●

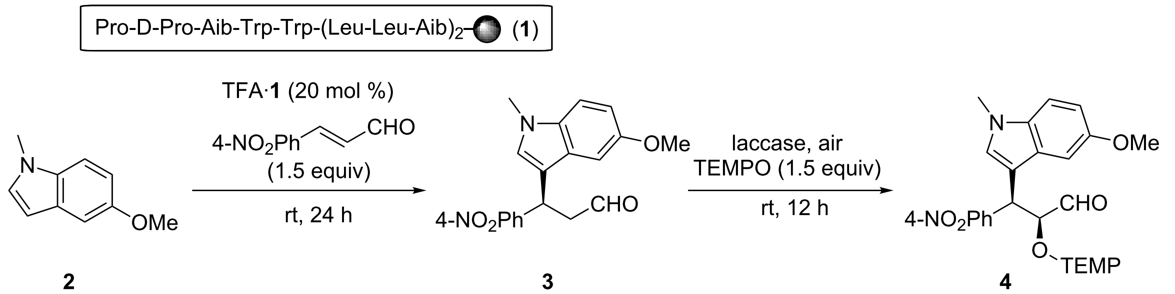
$(AA)_n = \begin{cases} (Leu)_{25.4} \\ (Leu\text{-}Leu\text{-}Aib)_2 \end{cases}$

–● = amphiphilic resin

Figure 2: Resin-supported peptide catalyst.

In a one-pot sequential reaction, the compatibility of reaction conditions in each step is important. Previously, we have reported a reaction system for the asymmetric α-oxyamination of aldehydes catalyzed by a peptide and an oxidizing enzyme, laccase [36,38]. Because the reaction conditions for that system are mild without employing a strong oxidant, we envisaged that the sequential FCAA/α-oxygenation could be attained by adopting the peptide-and-laccase-cocatalyzed oxyamination, even though indoles are generally prone to be oxidized [39,40]. By considering that enzymes promote reactions efficiently under aqueous conditions, we thought it necessary to conduct the one-pot reaction in aqueous media. Therefore, the reaction sequence shown in Table 1 was first examined in water. After the FCAA by peptide catalyst **1**, the α-oxyamination was successively performed by adding 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) and laccase directly to the reaction mixture. The desired two-step reaction product **4** was obtained with syn/anti ratio of 75:25, and the ee value of the syn diastereomer was 96% (Table 1, entry 1). It is noteworthy that the ee of the major diastereomer was higher than that of each single reaction [33,37]. Such enantio-enrichment is generally caused in consecutive catalytic asymmetric reactions through the formation of diastereomeric pairs [17,41]. From the viewpoint of reaction efficiency, the conversion in each step was low, presumably because of poor solubility of the substrates in water. Thus, use of the organic cosolvent THF was examined (Table 1, entries 2 to 5). As a result, the solvent system H_2O/THF 2:1 was regarded as the optimum (Table 1, entry 4). When the reaction was performed under conditions with a higher content of THF,

Table 1: One-pot sequential Friedel–Crafts-type alkylation/α-oxyamination.



entry	solvent	**2**:**3**:**4**[a]	syn/anti of **4**[a]	ee [%][b] of syn-isomer (anti-isomer)
1	H_2O	67:14:19	75:25	96 (64)
2	H_2O/THF 9:1	32:17:51	73:27	96 (62)
3	H_2O/THF 5:1	44:10:46	76:24	97 (57)
4	H_2O/THF 2:1	17:5:78	75:25	98 (56)
5	H_2O/THF 1:1	15:85:0	–	–

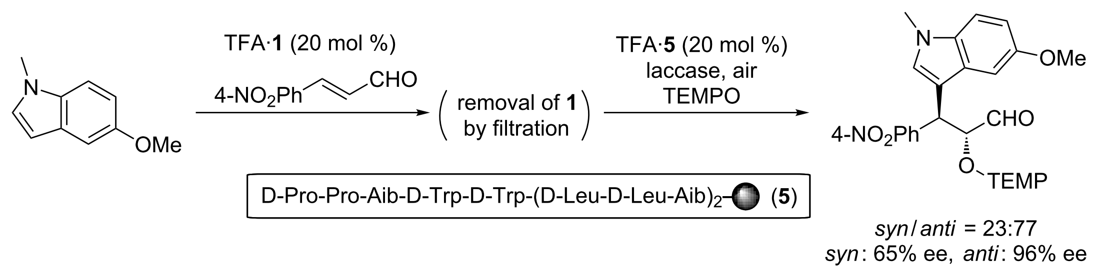
[a]Determined by ^1H NMR spectroscopy of crude mixture. [b]Determined by HPLC analysis after being reduced to the corresponding alcohol.

such as in the case of H_2O/THF 1:1, the peptide/laccase-catalyzed oxidation did not proceed at all, due to inactivation of laccase (Table 1, entry 5). This indicates the importance of water as a solvent for realization of the present sequential reaction.

To elucidate the origin of the stereocontrol in the present sequential reaction, the following control experiment was conducted. After the first FCAA reaction, peptide catalyst **1** was removed by filtration and another peptide catalyst **5**, which is the enantiomer of **1**, was added to promote the α-oxyamination (Scheme 1). In this case, the anti-isomer was obtained as a major diastereomer, and the ee value of the anti-product was high. The reversal of the diastereoselectivity along with the high ee of the major diastereomer demonstrates that the stereochemical course of the second-step α-oxyamination was determined mainly by the stereostructure of the peptide catalyst rather than by the chirality of the intermediate **3**.

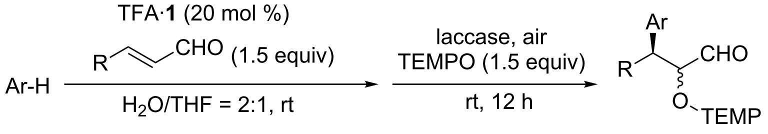
Finally, other substrates were tested in the present one-pot sequential reaction system (Table 2). Several substituted indoles gave the products with high enantioselectivity (Table 2, entries 1 to 3). As an α,β-unsaturated aldehyde, 3-nitrocinnamaldehyde was also applicable (Table 2, entry 4). Other than indoles, a pyrrole compound could be employed as a starting nucleophile in the sequential FCAA/α-oxyamination (Table 2, entry 5).

In conclusion, the FCAA followed by the asymmetric α-oxyamination was realized in a one-pot reaction, by using a peptide catalyst and laccase. This sequential reaction afforded the



Scheme 1: Effect of the stereostructure of the peptide catalyst.

Table 2: Examples of the one-pot synthesis of oxygenated heteroaromatic compounds.



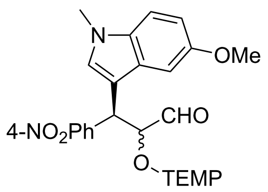
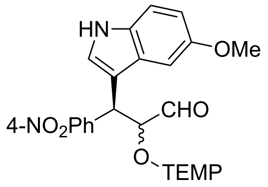
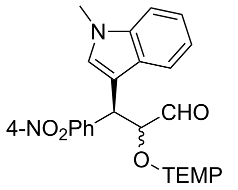
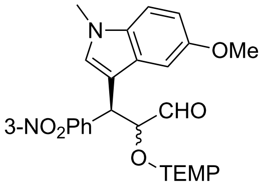
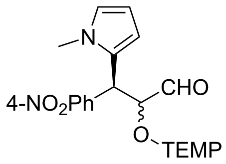
entry	product	time (h) of first step	yield [%][a]	syn/anti[b]	ee [%][c] of syn-isomer (anti-isomer)
1	 **4**	24	59	75:25	98 (56)
2	 **6**	24	70	79:21	98 (73)

Table 2: Examples of the one-pot synthesis of oxygenated heteroaromatic compounds. (continued)

3	 **7**	72	57	75:25	98 (55)
4	 **8**	36	55	72:28	98 (61)
5	 **9**	48	51	70:30	91 (30)

[a]Isolated yield. [b]Determined by ^{1}H NMR spectroscopy. [c]Determined by HPLC analysis after being reduced to the corresponding alcohol.

oxygen-functionalized indole derivatives with high optical purity. By utilizing the wide applicability of peptide catalysts in aqueous media, and mild reaction conditions for enzymatic reactions, various types of new sequential reactions can be expected for producing highly functionalized compounds.

Supporting Information

Supporting Information File 1

Typical experimental procedure, spectroscopic data for products, determination of stereochemistry, ^{1}H and ^{13}C NMR spectra and HPLC charts.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-152-S1.pdf]

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Organocatalytic asymmetric Michael addition of unprotected 3-substituted oxindoles to 1,4-naphthoquinone

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Letter

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Abstract

We reported the first example of organocatalytic Michael addition of unprotected 3-prochiral oxindoles **1** to 1,4-naphthoquinone. Quinidine derivative $(DHQD)_2PYR$ was found to be able to catalyze this reaction in up to 83% ee, with moderate to excellent yields. This method could be used for the synthesis of enantioenriched 3,3-diaryloxindoles, and the catalytic synthesis of which was unprecedented.

Introduction

The catalytic asymmetric synthesis of 3,3-disubstituted oxindoles has recently received great attention because of the wide occurrence of this structural motif in natural products and pharmaceutically active compounds [1-3]. In addition, structure–activity relationship studies have revealed that the absolute configuration and the substituent of the C3 position of oxindole greatly influenced the biological activities [4]. Accordingly, the development of efficient synthetic methods to enable the synthesis of 3,3-disubstituted oxindoles in great structural diversity is of current interest, and much progress had been made in the catalytic enantioselective synthesis of 3-hydroxyoxindoles [5-10], 3-aminooxindoles [11-15] and 3-quaternary oxindoles [16-20]. Despite achievements, the catalytic asymmetric synthesis of 3,3-diaryloxindoles has not been reported. This is possibly due to the challenge in the construction of such congested quaternary stereogenic centers. Only Sammakia tried the S_NAr reaction of unprotected 3-phenyloxindole with chiral electron-deficient 5-halooxazoles, promoted by 1.0 equiv of Cs_2CO_3 [21], with ca. 1:1 diastereoselectivity obtained.

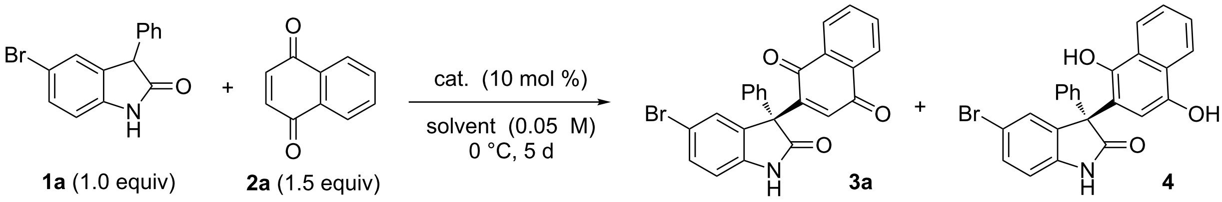
In this context, we are interested in the catalytic economical asymmetric diverse synthesis of 3,3-disubstituted oxindoles, using cheap and easily available starting materials and simple chiral catalysts to facilitate biological evaluation. We have developed the catalytic asymmetric addition of acrolein, allyltrimethylsilane or difluoroenoxysilanes to isatins to furnish differently substituted enantioenriched 3-hydroxyoxindoles [22-24]. For the synthesis of chiral 3-aminooxindoles, we developed the first example of catalytic asymmetric addition of nucleophiles to isatin-derived ketoimines using TMSCN [25] and the amination of unprotected 3-prochiral oxindoles using di-*tert*-butyl azodicarboxylate [26,27]. To construct the C3 quaternary stereogenic carbon center, we have designed a novel cinchona alkaloid-based phosphoramide bifunctional catalyst to realize a highly enantioselective Michael addition of both unprotected 3-alkyl- and 3-aryloxindoles to nitroolefins [28]. Based on these results, together with our efforts in the synthesis of unsymmetric 3,3-diaryloxindoles [29], we try to develop a catalytic asymmetric method to enantioenriched 3,3-diaryloxindoles.

In 2007, Jørgensen and coworkers pioneered the organocatalytic asymmetric addition reactions to quinones [30,31] which turned out to be a powerful strategy for the α-arylation of β-ketoesters and aldehydes. Inspired by their work, we anticipated that the catalytic asymmetric addition of 3-aryloxindoles to quinones would possibly install a hydroquinone moiety at the C3 position of oxindole to furnish the desired chiral 3,3-diaryloxindoles. It also came to our attention that, while the addition of 3-prochiral oxindole to a variety of Michael acceptors had been studied [32-46], the use of quinones as the Michael acceptor had not been realized. Therefore, in this letter we are going to report our initial results about the catalytic asymmetric Michael addition of unprotected 3-prochiral oxindoles to 1,4-naphthoquinone.

Results and Discussion

We began the reaction development by the evaluation of different chiral catalysts derived from cinchona alkaloids in the reaction of 3-phenyloxindole **1a** and 1,4-naphthoquinone (**2a**), with ethyl acetate (EtOAc) as the solvent at 0 °C (Table 1, Figure 1). A variety of bifunctional cinchona alkaloid-derived

Table 1: Condition optimization for the reaction of **1a** and **2a**.



1a (1.0 equiv) **2a** (1.5 equiv) **3a** **4**

Entry[a]	Cat.	Solvent	Additive	Yield of **3a** (%)[b]	ee (%)[c]
1	**5**	EtOAc	–	52	43[d]
2	**6**	EtOAc	–	61	59
3	**7**	EtOAc	–	40	14
4	**8**	EtOAc	–	34	4
5	**9**	EtOAc	–	14	15
6	**10**	EtOAc	–	60	64[d]
7	**11**	EtOAc	–	64	73[d]
8	**12**	EtOAc	–	51	77
9	**12**	THF	–	50	64
10	**12**	Acetone	–	61	64
11	**12**	CH_3CN	–	32	47
12	**12**	DCM	–	21	36
13	**12**	Toluene	–	31	73
14	**12**	EtOAc	MS 4Å	43	80
15	**12**	EtOAc	MS 5Å	29	70
16	**12**	EtOAc	H_2O (5.0 equiv)	50	78
17	**12**	EtOAc	H_2O (10.0 equiv)	50	78
18	**12**	EtOAc	$PhCO_2H$[e]	33	76
19	**12**	EtOAc	(*S*)-BINOL[e]	36	40
20	**12**	EtOAc	(*R*)-BINOL[e]	43	77
21	**12**	EtOAc	LiCl[e]	65	4

[a]Reactions were run on a 0.10 mmol scale. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Opposite enantiomer. [e]10 mol % used.

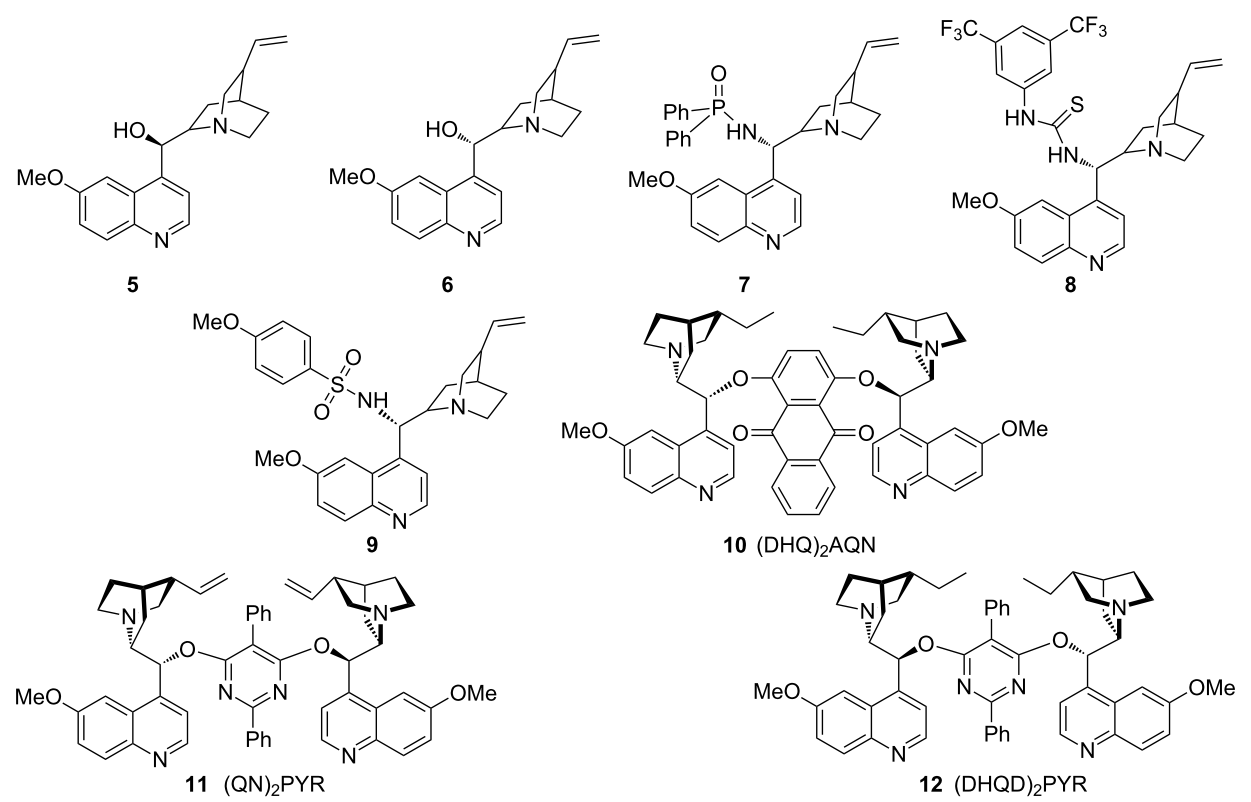


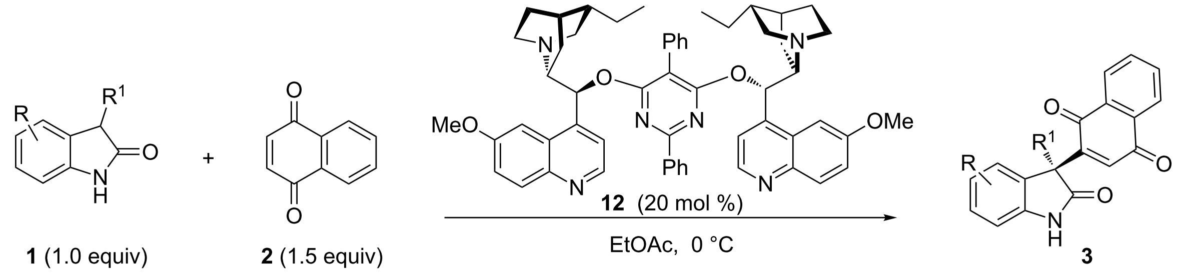
Figure 1: Cinchona alkaloid-derived catalysts screened for condition optimization (Table 1).

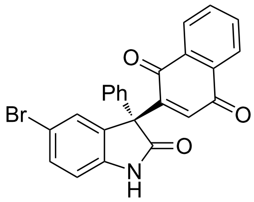
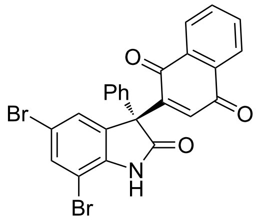
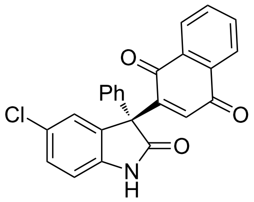
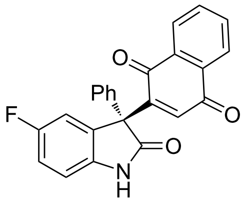
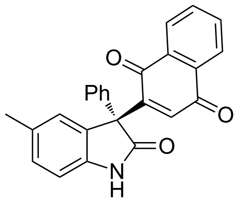
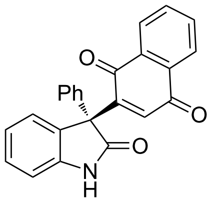
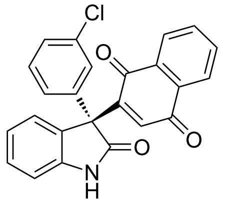
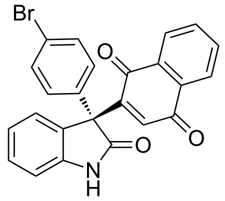
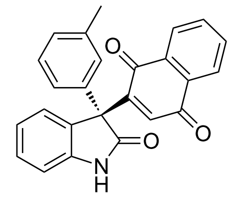
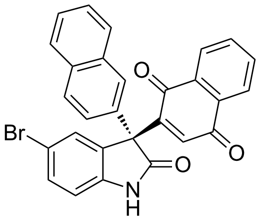
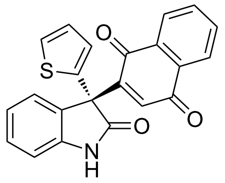
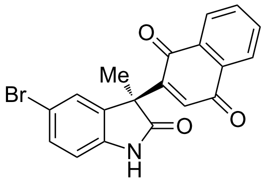
catalysts **5**–**9** were first tried, aiming to facilitate the reaction by the dual activation of both reaction partners, with H-bonding donor moiety of the catalyst to activate quinone **2a** and the tertiary amine to deprotonatively activate oxindole **1**. The reaction generally proceeded slowly, and only the oxidation product, 1,4-naphthoquinone derivative **3a**, was obtained in moderate yield after five days. No hydroquinone product **4** was detected by TLC and NMR analysis of the crude reaction mixture. While the simple quinine and quinidine as catalysts could deliver product **3a** in 59% ee (Table 1, entry 2), all other bifunctional catalysts turned out to be much less enantioselective (Table 1, entries 3–5). However, the dinuclear Brønsted base catalysts **10**–**12** could achieve higher ee for the desired product **3a** with comparable yields (Table 1, entries 6–8). When the hydrogenated catalyst **12** was used, 77% ee for product **3a** was obtained with 51% yield (Table 1, entry 8). In light of this, we used catalyst **12** for the following screenings.

We further examined the solvent effects, and found that EtOAc turned out to be the most suitable solvent which afforded product **3a** in highest ee (Table 1, entries 8–13). Since the reactivity was unsatisfactory, we further tried the use of some additives to improve the reaction rate. The use of MS 4Å could improve the enantioselectivity to 80%, but decreased the yield from 51% to 43% (Table 1, entry 8 versus 14). The use of MS 5Å had a negative effect on both the reactivity and the enantioselectivity (Table 1, entry 15). Water had no obvious effect on the reaction outcome (Table 1, entries 16 and 17). The addition of acids led to diminished yield and enantioselectivity (Table 1, entries 18–20).

Based on these screenings, we determined to examine the substrate scope by running the reaction at 0 °C in EtOAc, with 20 mol % of (DHQD)$_2$PYR **12** to improve the reactivity. Different substituted 3-prochiral oxindoles were first examined and the results are shown in Table 2. An electron-withdrawing substituent at the C5 position of the oxindole had a positive effect on the reactivity and enantioselectivity of the reaction. The corresponding products **3a**–**d** could be obtained in good to excellent yields with up to 81% ee. Without an electron-withdrawing group, products **3e** and **3f** were obtained in diminished yields and enantioselectivities. Different aryl substituents at the C3 position were also investigated, the corresponding products **3g**–**k** were obtained in acceptable yields and up to 83% ee. We also tried if this method could be extended to 3-alkyloxindoles but had to find out that product **3l** was obtained in only moderate enantioselectivity and yield. The absolute configuration of product **3f** was determined to be (*S*) by chemical trans-

Table 2: Substrate scope of unprotected 3-prochiral oxindoles[a–c].



Product, yield, enantioselectivity and reaction time			
 **3a** 70% yield, 79% ee, 5 d	 **3b** 97% yield, 80% ee, 6 d	 **3c** 74% yield, 81% ee, 6 d	 **3d** 71% yield, 79% ee, 8 d
 **3e** 46% yield, 69% ee, 9 d	 **3f** 51% yield, 70% ee, 9 d	 **3g** 76% yield, 81% ee, 6 d	 **3h** 45% yield, 54% ee, 8 d
 **3i** 55% yield, 83% ee, 6 d	 **3j** 68% yield, 77% ee, 6 d	 **3k** 53% yield, 65% ee, 6 d	 **3l** 58% yield, 19% ee, 8 d

[a]Run on a 0.25 mmol scale. [b]Isolated yield. [c]Determined by chiral HPLC analysis.

formation to the corresponding known compound [47]; all other products were tentatively assigned in analogy (for details, see Supporting Information File 1).

Other quinones such as 2,6-dichloro-1,4-benzoquinone and 1,4-benzoquinone were also examined, however, none of them could react with 3-phenyloxindole **1a** to give the desired product.

While the oxidation product **3** was obtained as the only product from the Michael addition, it could be hydrogenated to the corresponding hydroquinone product **4.** The free hydroxy groups were protected to prevent re-oxidation. For example, product **3i** was reduced and converted to the desired 3,3-diaryloxindole **13** in 57% yield without the loss of ee. We further checked if this protocol could be operated as a "one-pot" sequential reaction. After the reaction of **1i** and **2** was run at 0 °C for five days a small amount of oxindole **1i** still remained. Then, the reaction was warmed to room temperature, followed by the addition of Pd/C and ammonium formate. When TLC analysis revealed that the hydrogenation of product **3i** was completed, acetyl chloride and triethylamine were added. The desired product **13** was obtained in 50% yield with 75% ee (Scheme 1). The diminished enantioselectivity was due to the fact that the remaining oxindole **1i** continued to react with **2** at room temperature during the following steps. Even if there is much potential for further improvement in the ee, this sequential reaction represented the first example of catalytic asymmetric synthesis of 3,3-diaryl oxindoles.

Conclusion

In summary, we have developed the first example of organocatalytic Michael addition of unprotected 3-prochiral oxindoles to 1,4-naphthoquinone [48] with good to high yields and enantioselectivities. This method could be used for the synthesis of enantioenriched 3,3-diaryloxindoles and the catalytic synthesis of which was unprecedented. The development of new chiral catalysts to improve both the reactivity and enantioselectivity of this reaction is now in progress in our lab.

Supporting Information

Supporting Information File 1

General experimental procedures and compound characterization.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-157-S1.pdf]

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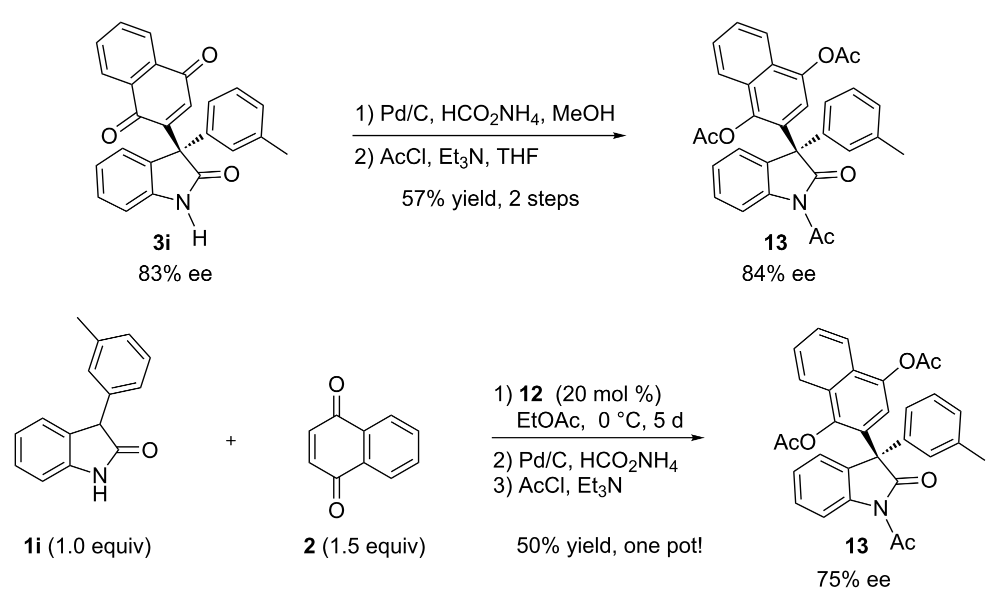

Scheme 1: A one-pot synthesis of enantioenriched 3,3-diaryloxindoles.

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    During publication of our manuscript, Wang and coworkers reported the Michael addition of N-protected 3-substituted oxindoles to 1,4-naphthoquinone.
48. The unprotected 3-substituted oxindoles are less reactive but easier to access than *N*-Boc protected 3-substituted oxindoles (for discuss, see [28]). While we focused on the use of unprotected 3-prochiral oxindoles for reaction development [26-28], we tried the reaction of *N*-Boc 3-phenyloxindole and 1,4-naphthoquinone, as suggested by the referee. At the standard reaction condition, the corresponding product was obtained in 47% yield with 67% ee.

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Organocatalytic C–H activation reactions

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Review

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Abstract

Organocatalytic C–H activation reactions have recently been developed besides the traditional metal-catalysed C–H activation reactions. The recent non-asymmetric and asymmetric C–H activation reactions mediated by organocatalysts are discussed in this review.

Introduction

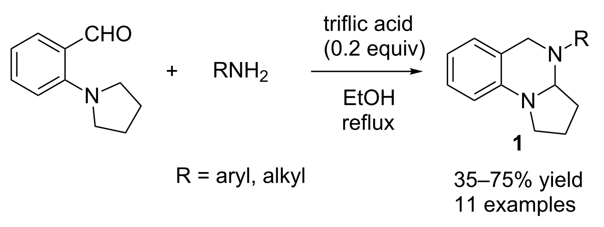
C–H activation reactions have recently been found to be a powerful method for the formation of C–C and C–X bonds [1-3]. The advantage of this method is that it does not require the functional group of the carbon atom, as in the conventional approach. Transition-metal-catalysed C–H bond functionalization reactions have been well-studied and different site-selective (regioselective and chemoselective) reactions have been reported [1-3]. However, one drawback of this approach is the requirement of the removal of the metal impurity from the products. An organocatalytic approach is attractive in this sense as it is metal-free, cost-effective, and favoured by the pharmaceutical industry for being one of the "key green chemistry research areas" [4-6]. This review describes the current "state of the art" in organocatalyzed C–H activation reactions and highlights recent advances in sp^2 and sp^3 C–H bond functionalization. For simplicity, iodide or hypervalent iodine-mediated metal-free C–H transformations will not be covered in this review.

Review

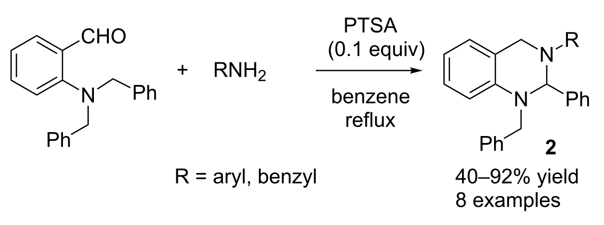
Organocatalytic sp^3 C–H bond activation reactions

Non-asymmetric variants

tert-Amino effect: The "*tert*-amino effect" refers to the ring-closure reactions that proceed by redox processes for C–C and C–X bond formation within conjugated systems [7-9]. One well-known example of the "*tert*-amino effect" is the cyclization of *N*,*N*-dialkyl-substituted anilines with imines to generate cyclic aminals. The groups of Seidel and Akiyama independently reported mild organocatalytic approaches to cyclic aminals involving aminobenzaldehydes and primary amines [10,11]. Previously, only preformed imines were used for this purpose, and the reactions were mostly thermally controlled [12-15]. Seidel and co-workers found that the combination of triflic acid and ethanol provided an effective system for the formation of cyclic aminals (Scheme 1), whereas the combination



Scheme 1: Triflic acid-catalysed synthesis of cyclic aminals.



Scheme 2: PTSA-catalysed synthesis of cyclic aminals.

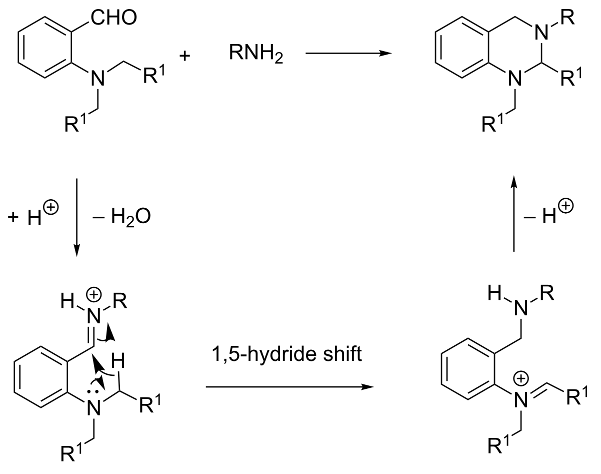
of *para*-toluenesulfonic acid (PTSA) and benzene was the optimum system for Akiyama and co-workers (Scheme 2).

After evaluating different Lewis and Brønsted acids with their equivalents as well as different solvents, Seidel and co-workers found that 0.2 equivalents of triflic acid in ethanol under reflux provided the maximum yield of the desired product **1**. The reaction was examined with different amines and moderate to good yields (35–75%) were obtained (Scheme 1) [10]. In certain cases, a stoichiometric amount of triflic acid was required to obtain acceptable yields of the desired products.

Akiyama and co-workers screened different Brønsted acid catalysts for their reaction, with PTSA emerging as the most effective catalyst [11]. Employing an optimized set of conditions, the reaction was conducted with different amines, and good to excellent yields (40–92%) were obtained (Scheme 2). A plausible mechanism for these reactions is depicted in Scheme 3.

After initial imine formation, a Brønsted acid promoted 1,5-hydride shift occurs yielding an imino-amine intermediate. Cyclization of the newly formed amine affords the desired aminal product.

In 2011, Seidel and co-workers reported an indole-annulation cascade reaction with *N*,*N*-(dialkylamino)benzaldehydes, a process in which a 1,5-hydride shift occurs followed by larger ring formation [16]. After the evaluation of different Brønsted acid catalysts, diphenylphosphate (20 mol %) was identified as a suitable catalyst for the reaction. Toluene again was the solvent of choice, and microwave irradiation was used for a



Scheme 3: Plausible mechanism for cyclic aminal synthesis.

shorter reaction time. The scope of the reactions was broad allowing different indoles and a variety of *N*,*N*-(dialkylamino)benzaldehydes to be employed, and the products **3** were obtained in good to excellent yields (Scheme 4) [16].

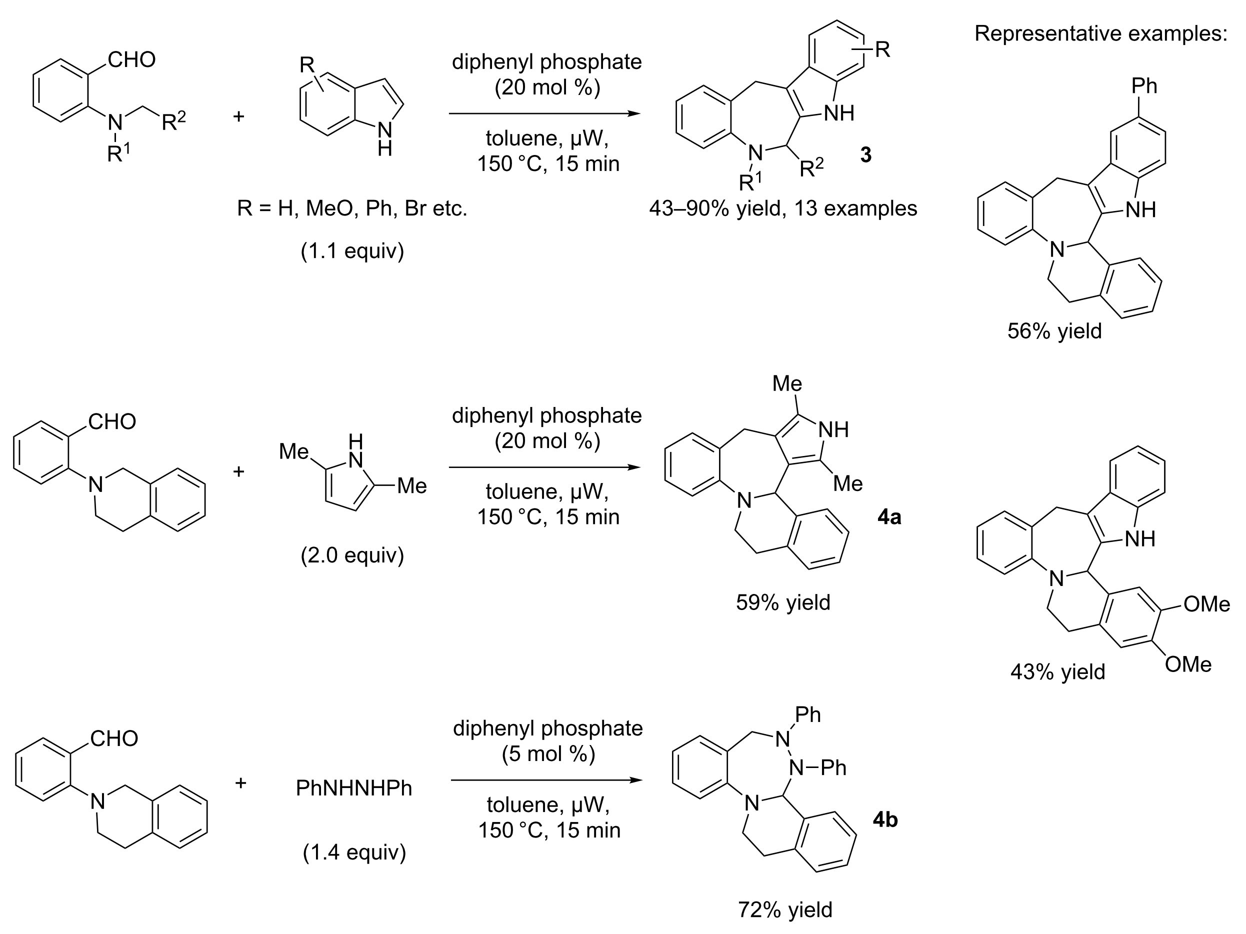
For some substrates, 50 mol % of the catalyst was required to obtain reasonable yields of the products. The authors also successfully extended this methodology to other double nucleophiles, i.e., 2,5-dimethylpyrroles and *N*,*N*'-diphenylhydrazine, and the products **4a** and **4b** were isolated in good yields (Scheme 4). A plausible mechanism was suggested by the authors and is shown in Scheme 5.

Initially, the vinylogous iminium (azafulvenium) ion **5** is formed from the acid-catalyzed dehydration reaction of tertiary aminobenzaldehyde and indole (Scheme 5). Subsequently, **5** undergoes a 1,5-hydride shift to generate iminium ion **6**. Finally, ring closure and proton loss provides the formation of the product **3**.

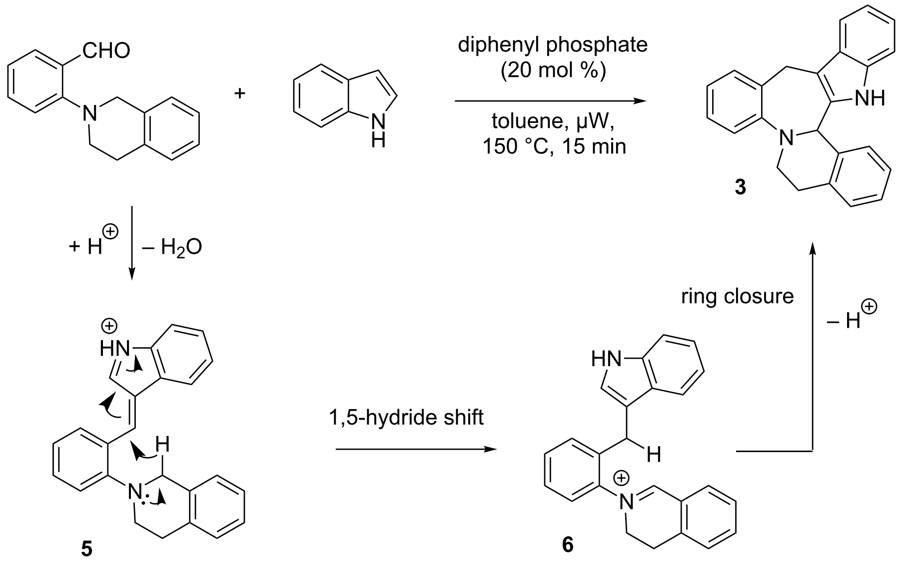
Redox alkylation

In 2009, Tunge and co-workers demonstrated the synthesis of *N*-alkyl-pyrroles by redox isomerisation from the reaction of 3-pyrroline and aldehydes or ketones (Scheme 6) [17].

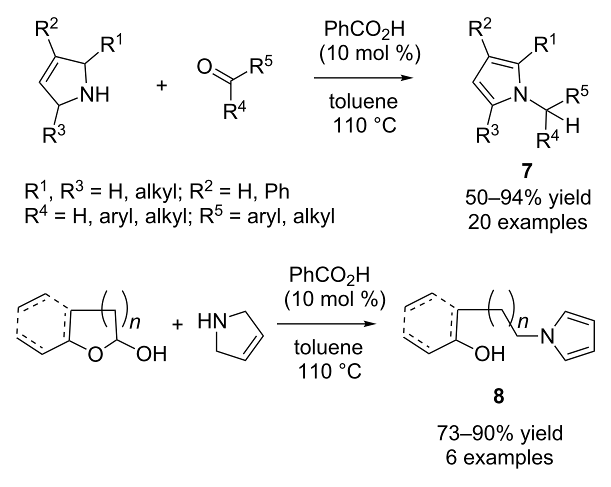
A series of Brønsted acids as catalysts was screened for this reaction, and the best reaction efficiency in terms of yield and reaction time was achieved with benzoic acid (10 mol %). The scope of the reaction was investigated and was found to tolerate a wide variety of functional groups including nitro, nitriles, ether and acetals delivering the products **7** in good to excellent yields (50–94%). The reaction was also compatible with different ketones although extended reaction times were required to obtain good yields of the desired products. Interest-



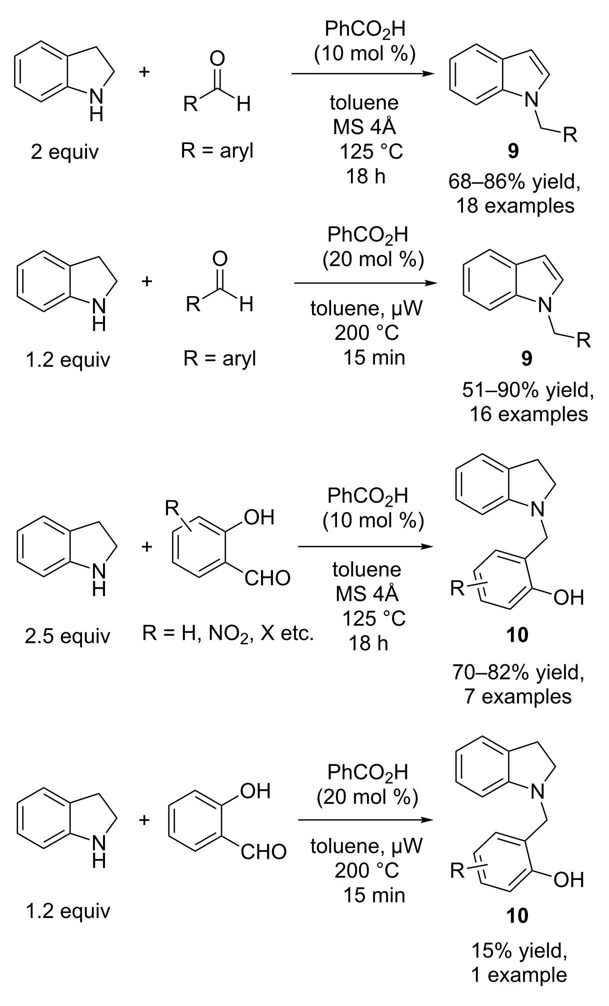
Scheme 4: Annulation cascade reaction with double nucleophiles.



Scheme 5: Mechanism for the indole-annulation cascade reaction.



Scheme 6: Synthesis of *N*-alkylpyrroles and δ-hydroxypyrroles.



Scheme 7: Synthesis of *N*-alkylindoles **9** and *N*-alkylindolines **10**.

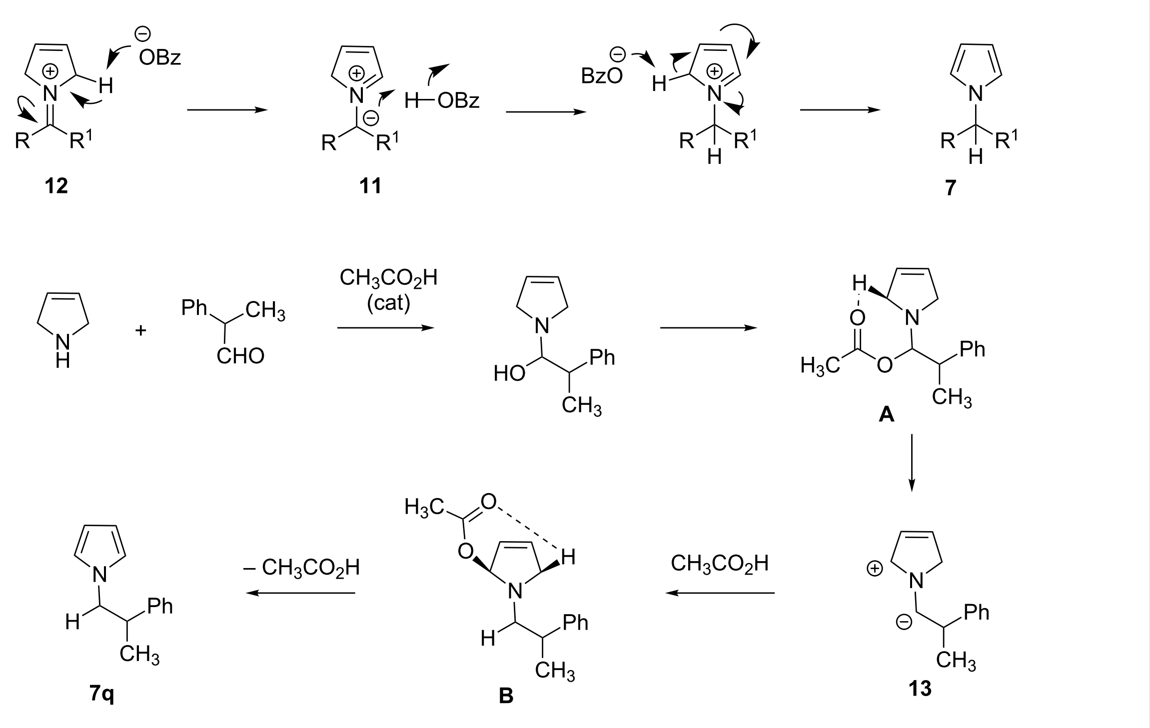
ingly, when the substrates were extended to five and six-membered lactols, δ-hydroxypyrroles **8** were achieved as the products in good yields (Scheme 6).

Later, Pan and Seidel independently extended this methodology to indolines using benzoic acid as the catalyst, conducting the reaction under reflux and microwave irradiation conditions, respectively, to generate indole **9** (Scheme 7) [18,19].

Only aryl aldehydes are able to perform the reaction, but the yields as reported by both groups are very good. Besides the usual reaction between indolines and aldehydes, both groups also found that intermolecular hydride transfer occurred when salicylaldehyde was employed as the substrate, and the *N*-alkylindoline product **10** was obtained in good yields (70–82%) mainly by the method of the Pan group (Scheme 7). In this case, another molecule of indoline acts as the hydride donor and is converted to indole.

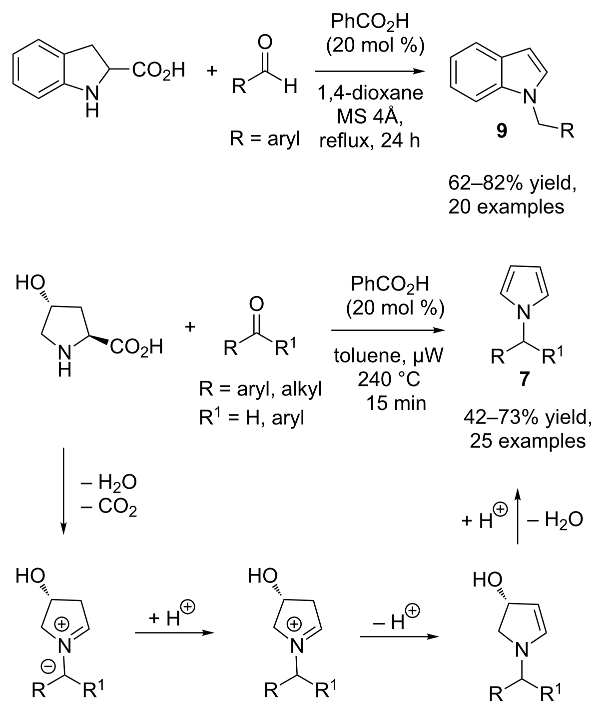
Both Tunge and Pan suggested redox isomerization in the formation of their products, but did not provide a detailed mechanism. 1,3-Hydride shift could be the most direct pathway for the formation of the redox isomerization products. However, Seidel pointed out that a 1,3-hydride shift will occur antarafacially and is geometry-forbidden. An alternative explanation is the formation of azomethine ylide intermediate **11** (Scheme 8) [19,20].

The carbanion of ylide **11** is then protonated by benzoic acid, and the resulting benzoate anion supports the aromatization process. In fact, Seidel and co-workers provided the experimental evidence for the existence of azomethine ylide intermediates in the Tunge pyrrole formation and in the formation of *N*-alkylindoles from indoline [19]. These reactions are considered C–H activation reactions, as during the azomethine ylide formation, the C–H bond that is cleaved is not activated by electron-withdrawing (such as ester) groups. Recently, Xue, Cheng and co-workers carried out detailed DFT and MP2 computational studies for the reaction of 3-pyrroline and 2-phenylpropanal using acetic acid as the catalyst [21]. Interestingly, the authors could not find the existence of free iminium ion **12** in the rearrangement. They indicated that the formation of acetic acid assisted azomethine ylide **13** is the most plausible pathway for the rearrangement process [21]. The first step is the nucleophilic addition of an amine to the carbonyl group to generate a carbinolamine intermediate (Scheme 8). It then becomes *O*-acetylated by acetic acid to form intermediate **A**. Azomethine ylide **13** is then produced by extrusion of acetic acid from intermediate **A**. Protonation of **13** generates another *O*-acetyl intermediate **B**, and finally, regeneration of acetic acid and aromatization provides the pyrrole product **7q**. Pan and Seidel also independently disclosed examples of Brønsted acid catalysed decarboxylative redox-amination reactions. 2-Carboxyindoline and *trans*-4-hydroxyproline were used as the substrates, respective-



Scheme 8: Mechanistic study for the *N*-alkylpyrrole formation.

ly [22,23]. Benzoic acid as catalyst and 1,4-dioxane as solvent was identified by the Pan group as the best system for the reaction (Scheme 9) [22].



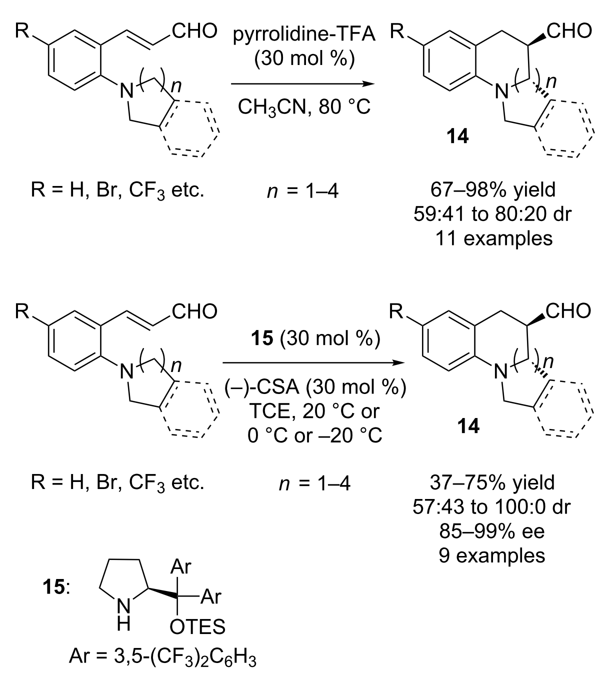
Scheme 9: Benzoic acid catalysed decarboxylative redox amination.

Different aromatic and heteroaromatic aldehydes were screened and *N*-alkylindole products **9** were isolated in moderate to good yields (62–82%). One current limitation of this method is its restriction to non-enolisable aldehydes. In contrast, Seidel and co-workers successfully applied both aromatic and enolisable aldehydes and ketones to their reaction and the desired *N*-alkylpyrrole products **7** were formed in moderate to good yields (42–73%) under microwave irradiation [23]. Both groups suggested azomethine ylide as the intermediate in their reactions (Scheme 9).

Asymmetric variants

The first organocatalytic asymmetric C–H activation reaction was disclosed by Kim and co-workers for the synthesis of chiral tetrahydroquinolines **14** (Scheme 10) [24].

ortho-(Dialkylamino)cinnamaldehydes were employed as the substrates for this aminocatalytic intramolecular redox reaction. The authors first demonstrated a non-asymmetric version of the reaction using pyrrolidine-TFA as catalyst in acetonitrile. High yields (67–98%) and moderate to good diastereoselectivities (59:41 to 80:20) were obtained for amine donors of different ring size [24]. After successfully performing the non-asymmetric synthesis of tetrahydroquinolines by C–H activation, the authors embarked on the asymmetric transformation utilizing chiral secondary amine catalysis. After the screening of different chiral amine catalysts, solvents, and acid additives, as



Scheme 10: Organocatalytic redox reaction of *ortho*-(dialkylamino)cinnamaldehydes.

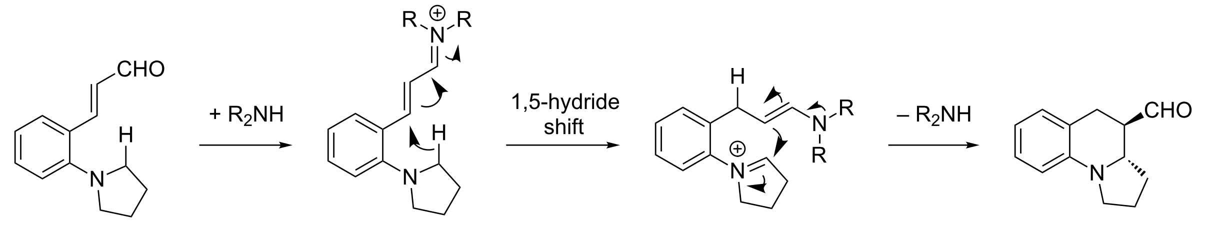
well as temperatures, chiral pyrrolidine catalyst **15** in combination with (−)-camphorsulfonic acid (CSA) in 1,1,2-trichloroethane (TCE) at 20 °C provided the desired product in highest enantioselectivity (89% ee). Under the optimized conditions, a range of *ortho*-(dialkylamino)cinnamaldehydes were employed and chiral tetrahydroquinoline products **14** were obtained in moderate to good yields (37–75%), moderate to excellent diastereoselectivities (57:43 to 100:0 dr) and high to excellent enantioselectivities (85–99% ee) (Scheme 10) [24]. For some substrates, the reaction temperature was lowered to 0 or −20 °C in order to attain high enantioselectivities. A possible mechanism for the transformation is shown in Scheme 11.

At first, the secondary amine catalyst reacts with the α,β-unsaturated aldehyde to generate an iminium ion. Subsequent 1,5-hydride shift generates the corresponding enamine. Finally, Mannich-type cyclization provides the product **14**, and the secondary amine catalyst is regenerated (Scheme 11).

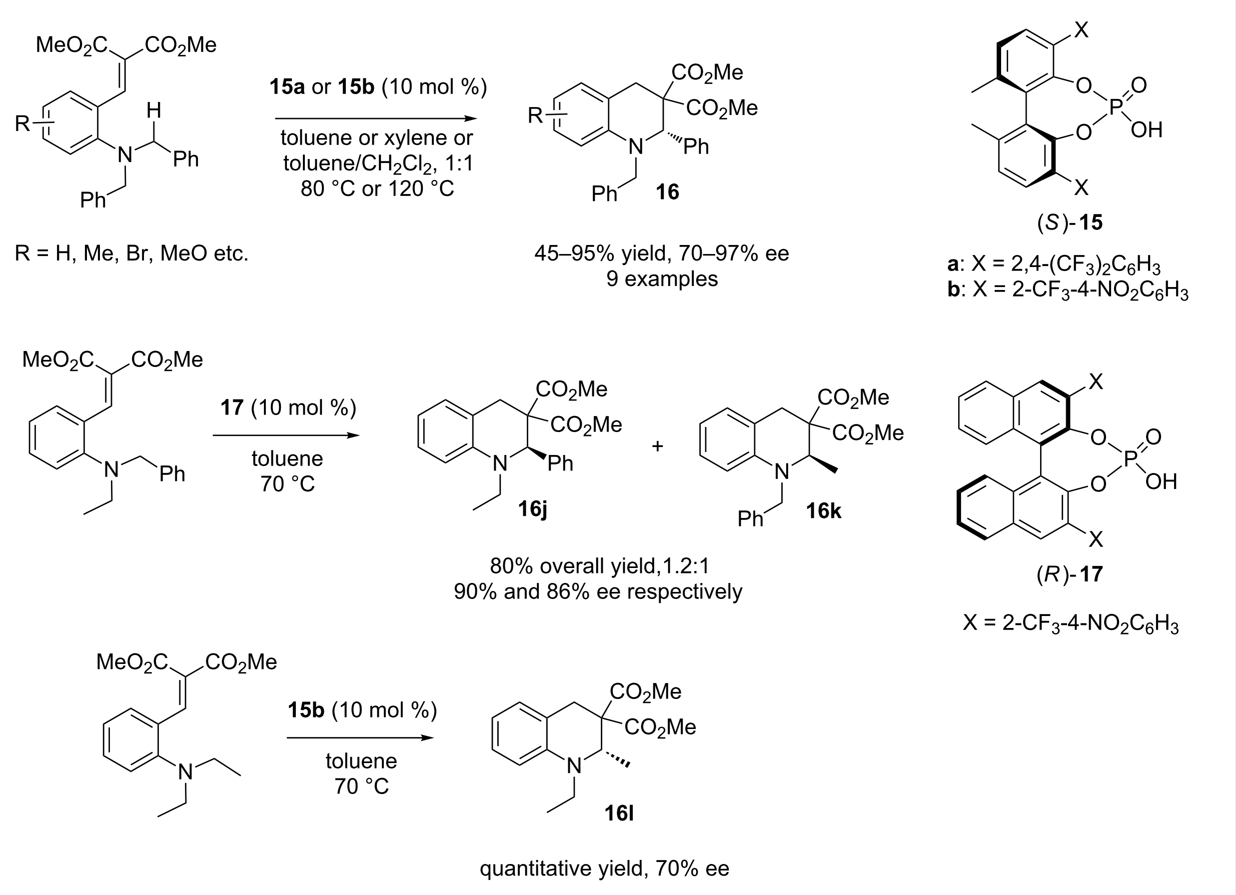
The following year, Akiyama and co-workers reported another organocatalytic asymmetric synthesis of tetrahydroquinolines using chiral phosphoric acid as the catalyst [25]. In this instance, benzylidene malonates were used as the hydride acceptor. Another important feature of this report by the Akiyama group is the predominant use of *N,N*-dibenzylamine as the amine donor in their reaction instead of cyclic tertiary amines as used by the Kim group. The present authors employed biphenyl-based chiral phosphoric acid catalysts **15a** and **15b** and moderate to high yields (45–95%) and excellent enantioselectivities (70–97% ee, mostly above 90% ee) were achieved for different tetrahydroquinoline products **16** having *gem*-methyl ester groups (Scheme 12).

For substrates containing one *N*-benzyl group and one *N*-ethyl group, binaphthol-based catalyst **17** was used; however, no chemoselectivity (**16j**:**16k** = 1.2:1) was observed (Scheme 12). Also, catalyst **15b** was used for the substrate having a *N,N*-diethyl group and product **16l** was obtained with lower enantioselectivity (70% ee). The authors carried out a series of model experiments with chiral substrates (*R*)-**18** and (*S*)-**18** to gain insight into the mechanism of their reaction (Scheme 13) [25].

In the presence of catalyst **15a**, (*S*)-**18** underwent a smooth reaction to provide product **19** with 90% ee in favour of the (*S*)-isomer. In contrast, when (*R*)-**18** was employed, the reaction was sluggish (10% yield) and only 68% ee of product **19** was observed in favour of the (*R*)-isomer. Even when achiral catalyst Yb(OTf)$_3$ was used for the reaction with (*S*)-**18**, product **19** was obtained with 85% ee with the (*S*)-enantiomer as the major product. This clearly demonstrates that the chiral information in **18** did not disappear during the reaction and was retained as helical chirality in cationic intermediate **C** (Scheme 13). Nucleophilic attack then occurred from the same side of the



Scheme 11: Mechanism for aminocatalytic redox reaction of *ortho*-(dialkylamino)cinnamaldehydes.



Scheme 12: Asymmetric synthesis of tetrahydroquinolines having *gem*-methyl ester groups.

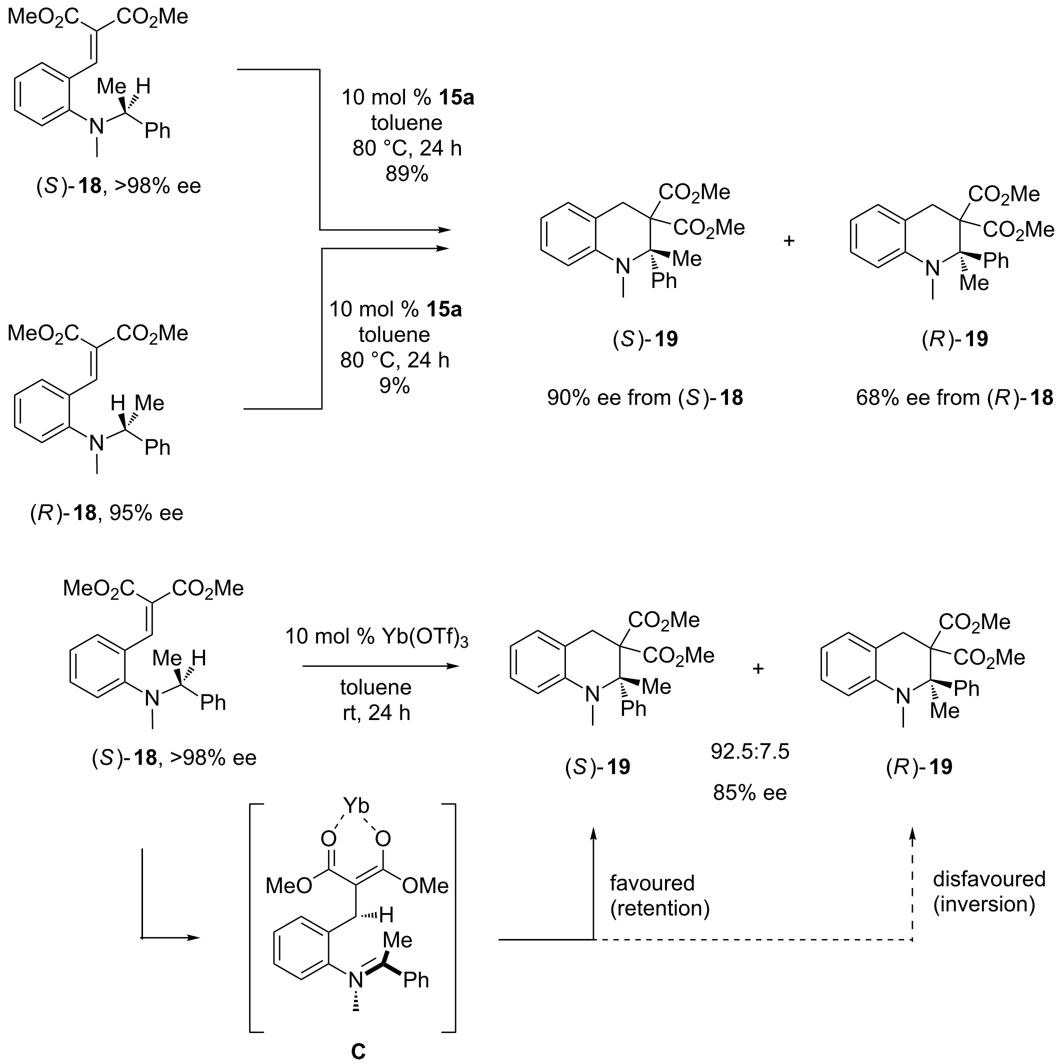
transferred hydrogen to provide (*S*)-**19**. The authors concluded that selective activation of one of the enantiotopic hydrogen atoms by chiral phosphoric acid is the main reason for obtaining enantioselectivity for their reaction [25].

Organocatalytic sp^2 C–H bond activation reactions

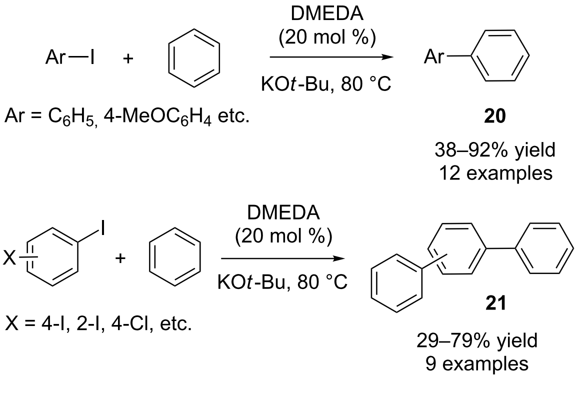
The catalytic cross-coupling of arenes and aryl halides to construct biaryl compounds is an important area in synthetic organic chemistry. Transition-metal-catalyzed biaryl synthesis from unactivated arenes by C–H activation is well-known in the literature [26-30]. Stoichiometric amounts of a radical source, such as tributyltin hydride and tris(trimethylsilyl)silicon hydride [31], or irradiation [32] were also utilized for biaryl synthesis from unactivated arenes. However, organocatalysts have not been studied for this class of transformation. In 2010, three research groups independently reported organocatalytic biaryl synthesis from unactivated arenes and aryl halides [33-35]. Since these reactions follow a homolytic radical aromatic substitution mechanism (HAS) as pointed out by Studer and Curran [36], they are better termed as “organocatalytic direct arylations of arenes” rather than “C–H activation reactions”. Kwong, Lei and co-workers initially carried out the reaction between 4-iodotoluene and benzene with different bases and catalysts at 80 °C [33]. After varying bases and catalysts, potassium *tert*-butoxide (1.0 equiv) and DMEDA (*N*,*N*’-dimethylethane-1,2-diamine) were found to be the best base and catalyst, respectively, providing the desired product **20** in 84% yield (Scheme 14).

It is remarkable that *cis*-cyclohexane-1,2-diol is also a good catalyst for this reaction (81% yield). Under the optimized conditions, different aryl iodides were tested and good to excellent yields (38–92%) were obtained [33]. Dihalobenzenes were also employed as substrates, and poor to good yields (29–79%) for the products **21** were observed (Scheme 14). However, the reaction failed with anisole and toluene under the same reaction conditions.

Shi and co-workers reported a similar reaction with 1,10-phenanthroline as catalyst at 100 °C employing aryl iodides and aryl bromides as the substrates [34]. Whereas 40 mol % of the catalyst and 3.0 equivalents of potassium *tert*-butoxide as base were needed for the reaction with bromides, 20 mol % of the



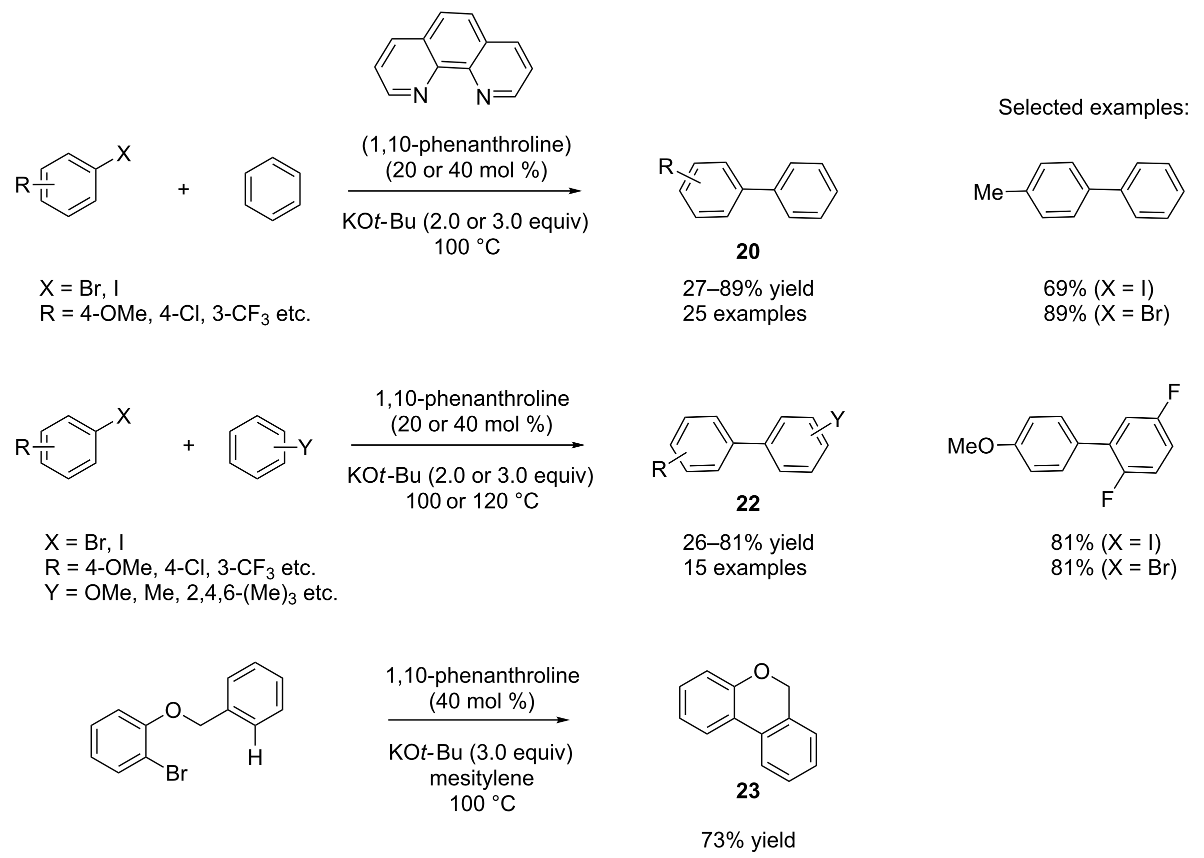
Scheme 13: Asymmetric synthesis of tetrahydroquinolines from chiral substrates **18**.



Scheme 14: Organocatalytic biaryl synthesis by Kwong, Lei and co-workers.

catalyst and 2.0 equivalents of potassium *tert*-butoxide were required for the reaction with iodides. Under these optimized conditions, different aryl bromides and aryl iodides were screened, and poor to good yields (27–89%) for the products **20** were observed (Scheme 15) [34].

It is interesting that different arenes were also explored under the reaction conditions, and poor to good yields (26–81%) were attained for the desired products **22**. The authors found a decreased reactivity with increased electron density in the arenes; however, better conversion was obtained after long reaction time (2 days) at higher temperature (120 °C). The authors also discovered an intramolecular version of their reaction employing 1-(benzyloxy)-2-bromobenzene as the substrate in mesitylene as solvent, and 73% yield of the cyclized product **23** was obtained (Scheme 15).



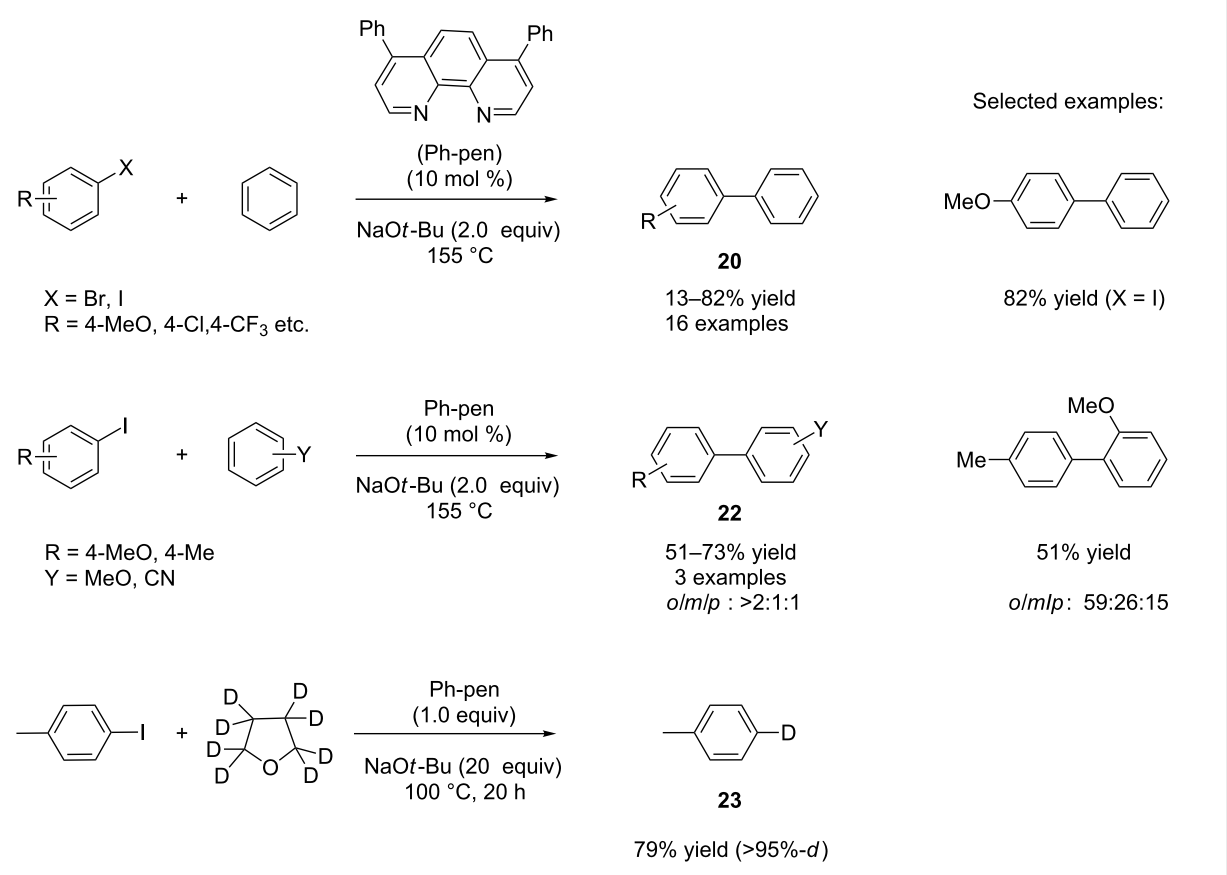
Scheme 15: Organocatalytic biaryl synthesis by Shi and co-workers.

The third report of organocatalytic biaryl synthesis came from the group of Hayashi [35]. The combination of 4,7-diphenylphenanthroline (Ph-phen) as catalyst and sodium *tert*-butoxide as base at 155 °C was identified as the best system for their reaction. The authors applied their arylation method to different aryl and heteroaryl iodides as well as bromides, and poor to good yields (13–82%) for products **20** were obtained (Scheme 16) [35].

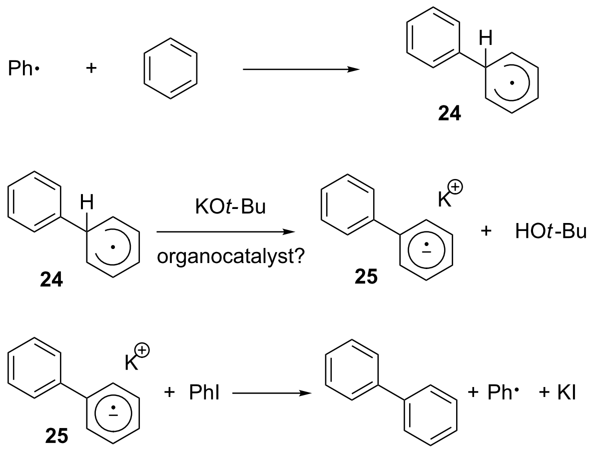
A variety of electron-donating and -withdrawing substituents were incorporated on the arene part and high *ortho*-selectivities were observed for the products **22**. The authors also investigated the reaction mechanism by performing a model reaction between 4-iodotoluene and THF-d_8 with 20 equivalents of sodium *tert*-butoxide and Ph-phen (1 equiv) at 100 °C (Scheme 16). The formation of 4-deuterotoluene (**23**) implied the generation of a tolyl radical in the reaction, which finally abstracts a deuterium radical from THF-d_8 to provide **23**. The authors found a low conversion (2%) for **23** in the absence of Ph-phen indicating the involvement of Ph-phen in the radical generation. The authors explained that Ph-phen can act as a single-electron-transfer (SET) mediator because it has a low lying LUMO and thus accepts an electron to generate a radical anion, and then passes the electron to aryl halide [35].

A general mechanism for the organocatalytic cross-coupling reactions was proposed by Studer and Curran [36], which suggests a “base-promoted homolytic aromatic substitution” mechanism. In the first step, a phenyl radical generated from iodobenzene reacts with benzene to afford phenylcyclohexadienyl radical (**24)** (Scheme 17).

Radical **24** is then deprotonated by potassium *tert*-butoxide to generate the biphenyl radical anion (**25**), potentially promoted by an organocatalyst. In the last step, radical anion **25**, a strong reducing agent, transfers one electron to starting iodobenzene and results in the formation of biphenyl, potassium iodide and phenyl radical (Scheme 17). However, the role of the organocatalyst is still not fully understood at this point and detailed mechanistic studies are ongoing.



Scheme 16: Organocatalytic biaryl synthesis by Hayashi and co-workers.



Scheme 17: Proposed mechanism for organocatalytic biaryl synthesis.

Conclusion

In summary, this review highlights the recent developments of organocatalytic C–H activation reactions. Organocatalysts have been involved in 1,5-hydride shift and decarboxylative/non-decarboxylative redox-amination processes. Asymmetric organocatalytic C–H activation reactions have also been developed for the synthesis of chiral tetrahydroquinolines. Additionally, organocatalytic direct biaryl synthesis has been discovered; however, these are not considered to be “true” C–H activation reactions. It will be interesting to see true organocatalytic sp^2 C–H activations in future, and more organocatalytic non-asymmetric and asymmetric sp^3 C–H activation processes are expected [37].

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Highly enantioselective access to cannabinoid-type tricyles by organocatalytic Diels–Alder reactions

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Full Research Paper

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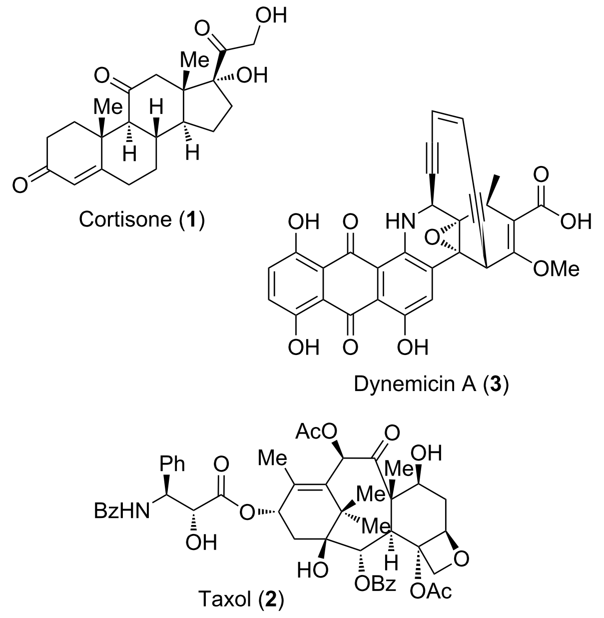
Abstract

After prosperous domino reactions towards benzopyrans, the products were used as the starting material in Lewis acid catalyzed and organocatalytic Diels–Alder reactions to build up a tricyclic system. Herein, an asymmetric induction up to 96% enantiomeric excess was obtained by the use of imidazolidinone catalysts. This approach can be utilized to construct the tricyclic system in numerous natural products, in particular the scaffold of tetrahydrocannabinol (THC) being the most representative one. Compared with other published methods, condensation with a preexisting cyclohexane moiety in the precursor is needed to gain the heterogenic tricycle systems, whereas we present a novel strategy towards cannabinoid derivatives based on a flexible modular synthesis.

Introduction

The Diels–Alder reaction is one of the most important processes for carbon–carbon-bond formation in organic chemistry [1,2]. Especially in the synthesis of natural products it is a widely used method [3-7]. Some examples are shown in Figure 1. The first application was the total synthesis of the steroid Cortisone (**1**) in 1952 by Woodward et al. [8]. Another example, indicating the importance of the well-known [4 + 2] cycloaddition in natural-product synthesis, is the first published total synthesis of Taxol (**2**) by Nicolaou. Two different [4 + 2]-cycloaddition reactions were applied to set up each of the two six-membered rings of the target molecule [9,10]. As a final example, Dynemicin A (**3**) should be mentioned, which is an enediyne consisting of a complex heterocyclic skeleton and a network of sensitive functional groups, exhibiting antitumor and antibiotic activity [11]. Three independent research groups (Schreiber, Myers and Danishefsky) successfully applied [4 + 2]-cycloaddition reactions in elegant and divergent strategies to reach the target molecule [12-14].



Cortisone (**1**)

Dynemicin A (**3**)

Taxol (**2**)

Figure 1: An assortment of natural products synthesized by Diels–Alder reactions.

Given the importance of the Diels–Alder reaction, considerable efforts have been directed towards increasing the reaction rate and enantioselectivity. In the past century, catalysts that were employed for the enantioselective synthesis of organic compounds, such as pharmaceuticals, agrochemicals, or fine chemicals, were either transition-metal complexes or enzymes. In the past few years, however, organocatalysis has emerged as an alternative approach for the catalytic production of enantiomerically pure organic compounds [15,16]. These organocatalysts have several important advantages. They are metal-free, usually nontoxic, stable, moisture-insensitive, and often easy to obtain. Because of their inertness towards oxygen and moisture, the use of absolute solvents, inert atmosphere, low temperature, etc., is, in many instances, not required. Furthermore, due to the absence of transition metals, organocatalytic methods are especially attractive for the preparation of compounds that do not tolerate metal contamination, e.g., active pharmaceutical ingredients.

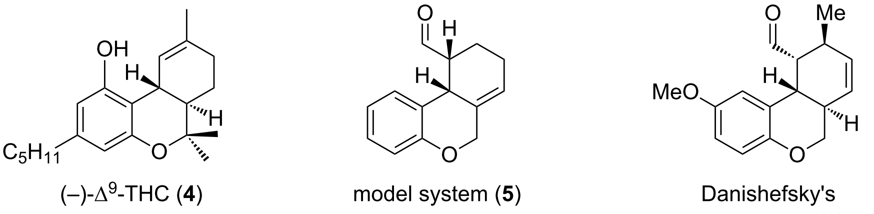
MacMillan's imidazolidinone-based organocatalysts are general catalysts for a variety of asymmetric transformations. The first highly enantioselective organocatalytic Diels–Alder reaction was reported by MacMillan in his pioneering work in 2000 [17]. The activated iminium ion, formed through condensation of imidazolidinone and an α,β-unsaturated aldehyde, underwent reactions with various dienes to yield [4 + 2]-cycloadducts in excellent yields and enantioselectivities.

Results and Discussion

On our way towards a metal-free total synthesis of (−)-Δ^9-tetrahydrocannabinol (**4**, Figure 2) we developed a convenient organocatalytic Diels–Alder route to generate the desired tricycle **5** of a model-system that also represents an alternative approach to key-intermediate **6** in Danishefsky's total synthesis of Dynemicin A (**3**) [14].

Our strategy, using the [4 + 2]-cycloaddition to obtain the cannabinoid tricycle system, is able to employ a variety of dienophiles and, hence, provides a versatile entry to this significant group of naturally occurring compounds [18], whereas the achieved Diels–Alder products can be further modified to gain a variety of heterocycles. Most published strategies are based on the use of a preexisting cyclohexane moiety in the starting material to form the heterogenic tricycle [19-28].

In former experiments of our group [29-31] it became apparent that without a catalyst no conversion towards the desired product occurred. Only the homodimer of the diene **10** could be isolated. Metal-based Lewis acids (e.g., catechol boronates) proved to be inefficient or too reactive. Due to the fact that other groups have used thiourea-derivatives as successful catalysts [32], we decided to test, on a model system, whether these catalysts could increase the reaction rate based on specific hydrogen bonds. In our initial screening we used the proven Schreiner catalyst 1,3-bis(3,5-bis(trifluoromethyl)phenyl)thiourea, which gave a satisfying 60% yield. In order to optimize the yield and to introduce chiral elements, we screened a number of analogues. These thiourea catalysts **9a**–**l** were easy to obtain from the corresponding isothiocyanates **7a**,**b** and chiral



(−)-Δ^9-THC (**4**)

model system (**5**)

Danishefsky's intermediate (**6**)

Figure 2: Intermediates towards the total synthesis of (−)-Δ^9-tetrahydrocannabinol (**4**).

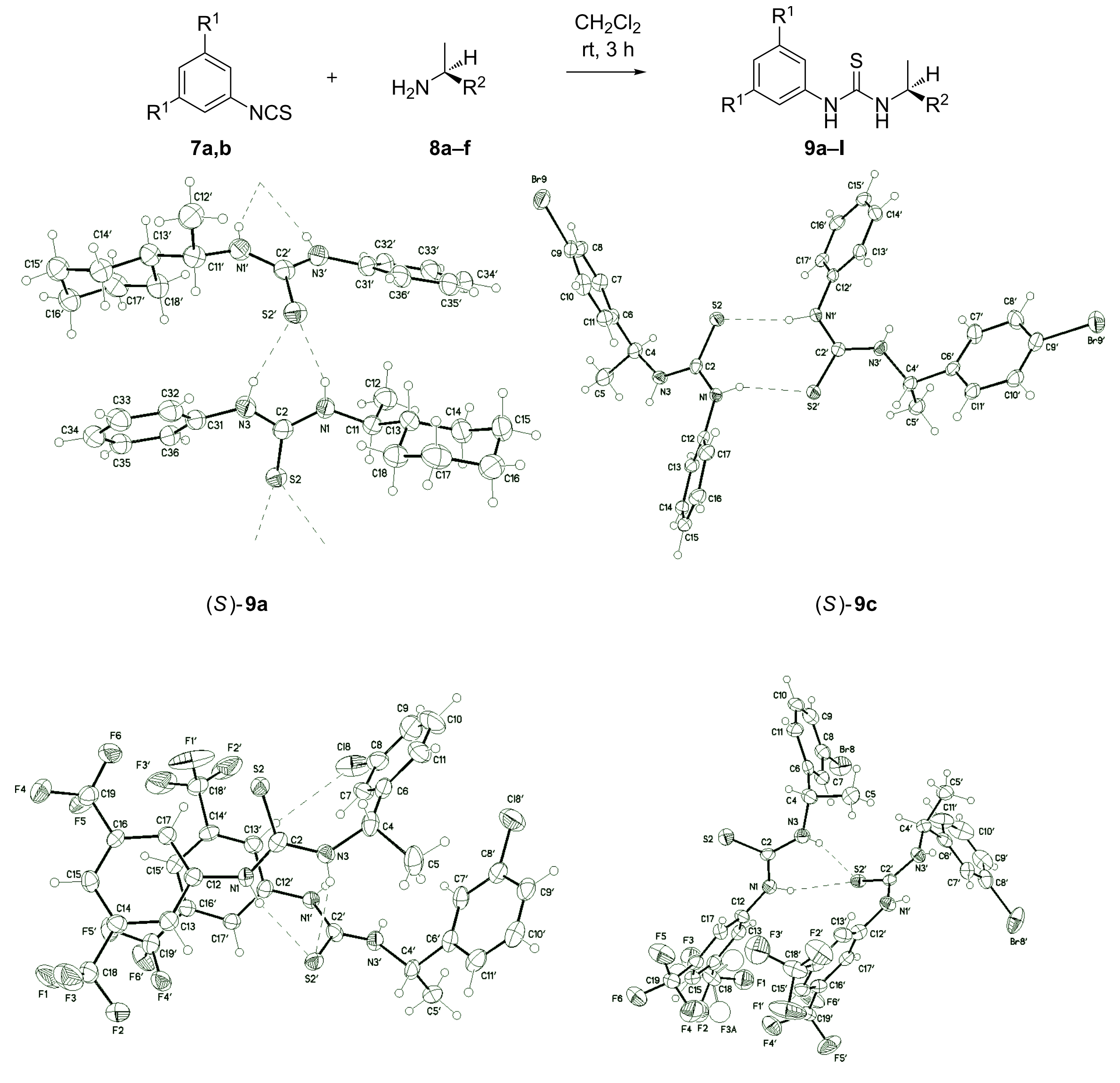
amines **8a**–**f** in a one-step synthesis (Scheme 1) [33]. The yields were good to excellent in all procedures (Table 1).

These thioureas were used in an intermolecular Diels–Alder reaction of diene **10** [36] with acrolein (**11**) to obtain cannabinoid tricycle **5** shown in Scheme 2.

In all cases we only achieved one *cis*-diastereomer and the carbonyl function was always in the 10-position. The reaction was carried out at low temperature and high dilution to avoid the dimer formation of diene **10**. An increase of the temperature to 40 °C resulted in a higher conversion but unfortunately no enantioselectivity was observed. We obtained good to excellent yields from 68% to 99% depending on the substitution of the thiourea-catalyst **9a**–**l** (Table 2).

When the substitution of the various thioureas **9a**–**l** is further compared with the obtained yields in the Diels–Alder reaction (Table 2), the following tendencies are also observed. A noticeable fact is that, in contrast to the thioureas with a cyclopropyl- and *m*-halophenyl-moiety (Table 2, entries 7–9), the corresponding bis(trifluoromethyl)thioureas (Table 2, entries 16–18) provide a higher conversion.

Next to the previously described thiourea catalysts, we also analyzed iminium-ion catalysts according to MacMillan on



7a,b **8a–f** **9a–l**

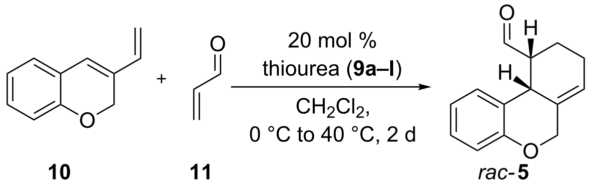
(*S*)-**9a** (*S*)-**9c**

(*S*)-**9k** (*S*)-**9l**

Scheme 1: Synthesis of thiourea catalysts **9a–l**.

Table 1: Yields of thiourea syntheses.

Entry	R^1	R^2	Product	Yield [%]
1	H	Cy	(*R*)-**9a** [34]	99
2	H	Cy	(*S*)-**9a** [34]	95
3	H	Ph	(*R*)-**9b**	99
4	H	Ph	(*S*)-**9b** [34]	99
5	H	*p*-BrC_6H_4	(*R*)-**9c**	99
6	H	*p*-BrC_6H_4	(*S*)-**9c**	99
7	H	cyclopropyl	(*R*)-**9d**	99
8	H	*m*-ClC_6H_4	(*S*)-**9e**	99
9	H	*m*-BrC_6H_4	(*S*)-**9f**	99
10	CF_3	Cy	(*R*)-**9g**	69
11	CF_3	Cy	(*S*)-**9g**	62
12	CF_3	Ph	(*R*)-**9h**	89
13	CF_3	Ph	(*S*)-**9h** [35]	99
14	CF_3	*p*-BrC_6H_4	(*R*)-**9i**	99
15	CF_3	*p*-BrC_6H_4	(*S*)-**9i**	99
16	CF_3	cyclopropyl	(*R*)-**9j**	91
17	CF_3	*m*-ClC_6H_4	(*S*)-**9k**	99
18	CF_3	*m*-BrC_6H_4	(*S*)-**9l**	76



Scheme 2: Organocatalytic Diels–Alder reaction with thiourea-catalysis.

various model systems (Figure 3) [37]. The effect of these catalysts is based on the formation of iminium ions by condensation of the dienophile bearing a carbonyl group, with the sterically hindered imidazole catalyst. In this way, one side is shielded and only the other side can be attacked by the diene. Hence, reaction rate and asymmetric induction are increased.

The synthesis of imidazolidinone catalysts [38] is the premise for the construction of the demanding amide **13**, which was afforded by the reaction of (*S*)-phenylalanine methyl ester hydrochloride (**12**) with methylamine (Scheme 3). In the second step of the synthesis, amide **13** was cyclized with different aldehydes **14** and addition of catalytic amounts of $FeCl_3$ at high temperatures into (2*S*,5*S*)- or (2*R*,5*S*)-imidazolidinone **15** [39,40].

To gain electron-poor catalysts for the degradation of the dienophilic LUMO in the Diels–Alder reaction and to consequently increase the reaction rate, we used aldehydes with elec-

Table 2: Summarized results of the Diels–Alder reaction.

Entry	Catalyst	Yield [%][a]
1	(*R*)-**9a**	97
2	(*S*)-**9a**	91
3	(*R*)-**9b**	99
4	(*S*)-**9b**	85
5	(*R*)-**9c**	93
6	(*S*)-**9c**	92
7	(*R*)-**9d**	74
8	(*S*)-**9e**	82
9	(*S*)-**9f**	77
10	(*R*)-**9g**	68
11	(*S*)-**9g**	78
12	(*R*)-**9h**	73
13	(*S*)-**9h**	88
14	(*R*)-**9i**	76
15	(*S*)-**9i**	85
16	(*R*)-**9j**	87
17	(*S*)-**9k**	93
18	(*S*)-**9l**	83

[a] The conversion is quantitative with respect to **10**, the byproduct is the uncatalyzed dimer of compound **10**.

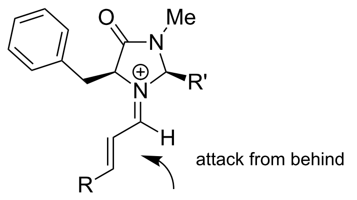
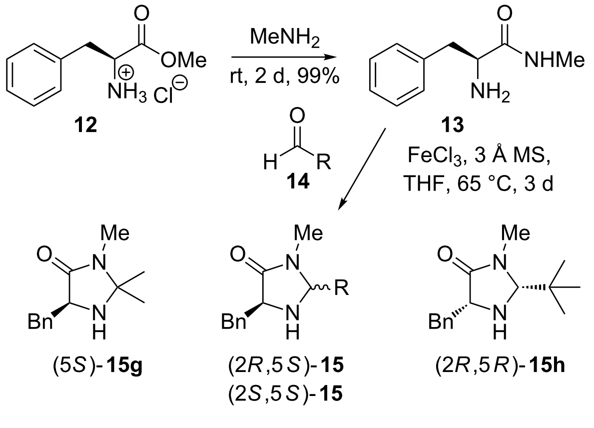


Figure 3: Formation of the iminium-ion.

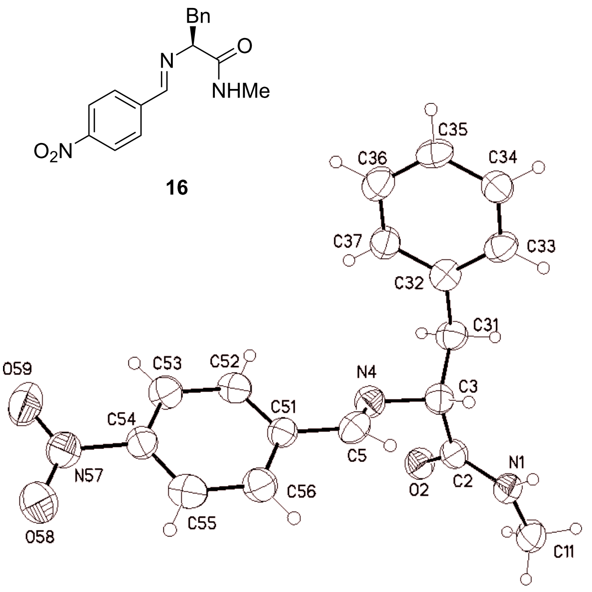


Scheme 3: Synthesis of electron poor imidazolidinone catalysts.

tron-withdrawing groups in *ortho*-, *meta*- and *para*-positions (Scheme 3, Table 3). Reaction with *p*-nitrobenzaldehyde gave compound **16** in 66% yield (Figure 4).

Table 3: Results of the conversion of various aldehydes **14** with amide **13**.

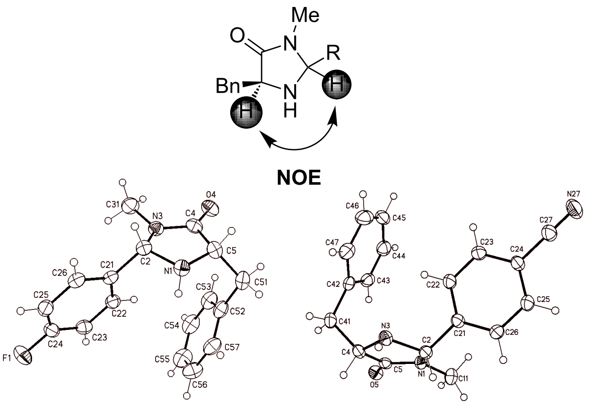
Entry	(Aldehyde **14**) R =	Catalyst **15**	Yield [%]
1	*t*-Bu	(2*R*,5*S*)-**15a**	35 [41]
2		(2*S*,5*S*)-**15a**	25 [40]
3	*o*-NO_2-C_6H_4	(2*R*,5*S*)-**15b**	42
4		(2*S*,5*S*)-**15b**	52
5	*m*-F-C_6H_4	(2*R*,5*S*)-**15c**	28
6		(2*S*,5*S*)-**15c**	39
7	*p*-F-C_6H_4	(2*R*,5*S*)-**15d**	32
8		(2*S*,5*S*)-**15d**	43
9	*p*-Br-C_6H_4	(2*R*,5*S*)-**15e**	39
10		(2*S*,5*S*)-**15e**	45
11	*p*-CN-C_6H_4	(2*R*,5*S*)-**15f**	38
12		(2*S*,5*S*)-**15f**	46



16

Figure 4: Crystal structure of the side product from the reaction of **13**.

The organocatalytic species **15** were synthesized in moderate yields. A conspicuous feature is that the yields of the (2*S*,5*S*)-derivatives, with the exception of the *tert*-butyl substituted catalyst **15a** (Table 3, entries 1–2), are always higher than those of the corresponding (2*R*,5*S*)-components (Table 3, entries 3–12). The configuration of the afforded imidazolidinone catalysts **15** could be confirmed by NOESY experiments and from their X-ray structures (Figure 5).

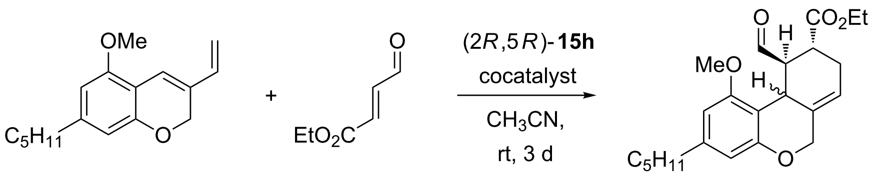


15d **15f**

Figure 5: Confirmation of the relative configuration with NOESY experiments and X-ray crystal structures of two imidazolidinones **15d** and **15f**.

Before testing the catalysts in the Diels–Alder reaction, we analyzed a few co-catalysts with the commercially available imidazolidinone catalyst **15h**. A pentyl-substituted tricycle was used as a model system (model system II) **19** (Scheme 4, Table 4).

Hydrochloric acid has been proven to be the best co-catalyst (Table 4, entry 1), providing *cis*-**19** in good yield and with an enantiomeric excess of 96%. Even perchloric acid and trifluoroacetic acid gave high enantiomeric excesses but in much poorer yields (Table 4, entries 2 and 3). Using *para*-toluenesulfonic acid also afforded *cis*-**19** in good yield, but its enantiomeric excess could not be determined (Table 4, entry 4). Trifluoro-



17 **18**

model system II
19

Scheme 4: Co-catalyst screening.

Table 4: Summary of the screening of co-catalysts.

Entry	Co-catalyst	*cis*-**19** Yield [%]	*cis*-**19** ee [%]	*trans*-**19** Yield [%]	*trans*-**19** ee [%]
1	HCl (1 M)	51	96	12	91
2	$HClO_4$ (60%)	6	95	10	n.d.
3	TFA	31	96	9	77
4	*p*-TSA·H_2O	50	n.d.	15	90
5	TfOH	—	—	—	—

n.d.: not determined.

methanesulfonic acid as co-catalyst only led to decomposition (Table 4, entry 5).

Under these optimized reaction conditions, we performed a catalyst screening with the previously synthesized imidazolidinone catalysts **15** to study their asymmetric induction (Scheme 5). As starting material we used compound **17** with the THC-typical pentyl side chain. The results are summarized in Table 5.

Table 5: Catalyst screening towards model system II **19**.

Entry	Catalyst **15** R =		*cis*-**19** Yield [%]	*cis*-**19** *ee* [%]
1	*t-Bu*	(2*R*,5*R*)-**15h**	51	96
2	*t*-Bu	(2*R*,5*S*)-**15a**	47	−24
3		(2*S*,5*S*)-**15a**	66	−98
4	*o*-NO_2-C_6H_4	(2*R*,5*S*)-**15b**	43	−89
5		(2*S*,5*S*)-**15b**	50	−29
6	*m*-F-C_6H_4	(2*R*,5*S*)-**15c**	47	−78
7		(2*S*,5*S*)-**15c**	55	−38
8	*p*-F-C_6H_4	(2*R*,5*S*)-**15d**	48	−79
9		(2*S*,5*S*)-**15d**	54	−37
10	*p*-CN-C_6H_4	(2*R*,5*S*)-**15f**	52	−83
11		(2*S*,5*S*)-**15f**	54	−43

The used organocatalysts, having a (*S*)-configured stereocenter in the 5-position, should prefer the formation of opposite enantiomers, compared to the commercially available (2*R*,5*R*)-**15h**. This is indicated by negative enantiomeric excess (Table 5). Due to low yields of diastereomer *trans*-**19** and the less successful determination of their enantiomeric excess, Table 5 only contains results for *cis*-**19**. Except for in the case of **15a**, we observe tendencies such as the achievement of higher yields through the use of (2*S*,5*S*)-configurated imidazolidinones **15** compared to the yields afforded by (2*R*,5*S*)-configurated catalysts **15**. There is an opposite trend for the enantiomeric excess, which is also related to the steric hindrance of the phenyl substituent, i.e., the smaller the substituent, the lower the enantiomeric excess. Application of the known *tert*-butylimidazolidinone catalyst **15a** provides the highest yield (66%) and enantiomeric excess (98% ee) with its (2*S*,5*S*)-derivate (Table 5, entry 3).

Conclusion

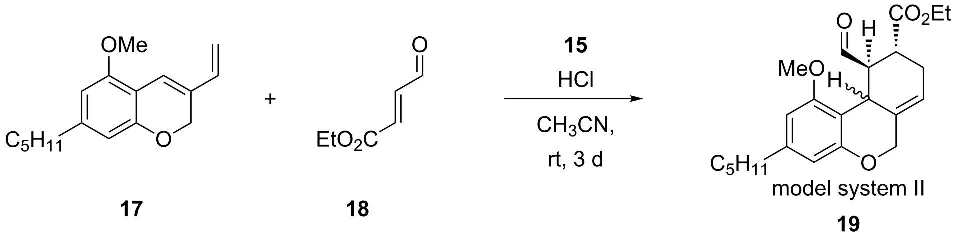
In conclusion, we have demonstrated that the Diels–Alder reaction of 3-vinyl-2*H*-chromene with acrolein can be accelerated with different thioureas, obtained in a one-step synthesis (in some cases with quantitative conversion). Application of imidazolidinone catalysts, inspired by the work of MacMillan, achieved good yields up to 66% and enantiomeric excesses up to 98%.

Experimental

Crystal structure determinations

The single-crystal X-ray diffraction study was carried out on a Nonius Kappa-CCD (**9a**, **16**) or Bruker-Nonius APEXII diffractometer (**9c**, **9k**, **9l**, **15d**, **15f**) at 123(2) K, by using Mo Kα radiation (λ = 0.71073 Å). Direct methods (SHELXS-97) [42] were used for structure solution, and refinement was carried out with SHELXL-97 [42] (full-matrix least-squares on F^2). Hydrogen atoms were localized by difference electron density determination and refined by using a riding model (H(N) free). The absolute configurations of **9a**, **9c**, **9k**, **9l** were determined by refinement of Flack's x-parameter [43] and by using Bayesian statistics on Bijvoet differences (Hooft's y-parameter) [44].

The absolute configuration of **15d** and **15f** could not be determined reliably by refinement of Flack's x-parameter [43], nor by using Bayesian statistics on Bijvoet differences (Hooft's y-parameter) [44]. The enantiomer was assigned by reference to an unchanging chiral center in the synthetic procedure.



Scheme 5: Screening of imidazolidinone catalysts **15**.

Semi-empirical absorption corrections were applied for **9c** and **9l**. In **9l** one CF_3-group is disordered.

9a: colorless, $C_{15}H_{22}N_2S$, M = 262.41, crystal size 0.30 × 0.10 × 0.05 mm, monoclinic, space group $P2_1$ (no. 4): a = 8.5864(5) Å, b = 22.2641(17) Å, c = 8.6811(6) Å, β = 117.350(4)°, V = 1474.04(17) Å^3, Z = 4, ρ(calc) = 1.182 Mg m^{-3}, F(000) = 568, μ = 0.206 mm^{-1}, 8575 reflections ($2\theta_{max}$ = 50°), 4687 unique [R_{int} = 0.057], 337 parameters, 5 restraints, $R1$ ($I > 2\sigma(I)$) = 0.048, $wR2$ (all data) = 0.119, GOOF = 1.09, largest diff. peak and hole 0.235/−0.290 e Å^{-3}, x = −0.01(8), y = −0.05(5).

9c: colorless, $C_{15}H_{15}BrN_2S$, M = 335.26, crystal size 0.25 × 0.10 × 0.05 mm, monoclinic, space group $P2_1$ (no. 4): a = 16.2276(4) Å, b = 5.5562(2) Å, c = 17.3953(6) Å, β = 108.894(2)°, V = 1483.92(8) Å^3, Z = 4, ρ(calc) = 1.501 Mg m^{-3}, F(000) = 680, μ = 2.899 mm^{-1}, 11045 reflections ($2\theta_{max}$ = 50°), 4958 unique [R_{int} = 0.037], 355 parameters, 5 restraints, $R1$ ($I > 2\sigma(I)$) = 0.030, $wR2$ (all data) = 0.072, GOOF = 1.06, largest diff. peak and hole 0.387/−0.504 e Å^{-3}, x = −0.018(7), y = −0.012(2).

9k: colorless, $C_{17}H_{13}ClF_6N_2S$, M = 426.80, crystal size 0.20 × 0.10 × 0.05 mm, monoclinic, space group $P2_1$ (no. 4): a = 8.1359(6) Å, b =16.2464(13) Å, c = 13.9980(7) Å, β = 92.246(4)°, V = 1848.8(2) Å^3, Z = 4, ρ(calc) = 1.533 Mg m^{-3}, F(000) = 864, μ = 0.381 mm^{-1}, 9231 reflections ($2\theta_{max}$ = 50°), 5469 unique [R_{int} = 0.039], 499 parameters, 5 restraints, $R1$ ($I > 2\sigma(I)$) = 0.055, $wR2$ (all data) = 0.116, GOOF = 1.16, largest diff. peak and hole 0.388/−0.252 e Å^{-3}, x = 0.07(9), y = 0.07(4).

9l: colorless, $C_{17}H_{13}BrF_6N_2S$, M = 471.26, crystal size 0.35 × 0.20 × 0.10 mm, monoclinic, space group $P2_1$ (no. 4): a = 8.2910(7) Å, b = 16.1565(8) Å, c = 14.0204(10) Å, β = 92.073(3)°, V = 1876.9(2) Å^3, Z = 4, ρ(calc) = 1.668 Mg m^{-3}, F(000) = 936, μ = 2.362 mm^{-1}, 10315 reflections ($2\theta_{max}$ = 50°), 5936 unique [R_{int} = 0.046], 494 parameters, 320 restraints, $R1$ ($I > 2\sigma(I)$) = 0.056, $wR2$ (all data) = 0.125, GOOF = 1.09, largest diff. peak and hole 1.033/−0.634 e Å^{-3}, x = −0.014(11), y = −0.009(6).

15d: colorless, $C_{17}H_{17}FN_2O$, M = 284.33, crystal size 0.45 × 0.25 × 0.10 mm, orthorhombic, space group $P2_12_12_1$ (no. 19): a = 8.4559(3) Å, b = 10.5000(4) Å, c = 16.6177(5) Å, V = 1475.43(9) Å^3, Z = 4, ρ(calc) = 1.280 Mg m^{-3}, F(000) = 600, μ = 0.089 mm^{-1}, 11771 reflections ($2\theta_{max}$ = 50°), 2602 unique [R_{int} = 0.045], 194 parameters, 1 restraint, $R1$ ($I > 2\sigma(I)$) = 0.038, $wR2$ (all data) = 0.084, GOOF = 1.11, largest diff. peak and hole 0.135/−0.173 e Å^{-3}, x = −0.8(10), y = 0.3(5).

15f: colorless, $C_{18}H_{17}N_3O$, M = 291.35, crystal size 0.50 × 0.40 × 0.30 mm, monoclinic, space group $P2_1$ (no. 4): a = 6.0140(1) Å, b =15.7002(4) Å, c = 8.5232(2) Å, β = 95.211(2)°, V = 801.44(3) Å^3, Z = 2, ρ(calc) = 1.207 Mg m^{-3}, F(000) = 308, μ = 0.077 mm^{-1}, 13805 reflections ($2\theta_{max}$ = 55°), 3628 unique [R_{int} = 0.027], 203 parameters, 2 restraints, $R1$ ($I > 2\sigma(I)$) = 0.033, $wR2$ (all data) = 0.077, GOOF = 1.08, largest diff. peak and hole 0.181/−0.152 e Å^{-3}, x = −0.2(11), y = 0.8(5).

16: colorless, $C_{17}H_{17}N_3O_3$, M = 311.34, crystal size 0.30 × 0.05 × 0.05 mm, monoclinic, space group $P2_1$/c (no. 14): a = 18.265(5) Å, b =10.935(2) Å, c = 7.857(2) Å, β = 101.60(1)°, V = 1537.2(6) Å^3, Z = 4, ρ(calc) = 1.345 Mg m^{-3}, F(000) = 656, μ = 0.094 mm^{-1}, 4930 reflections ($2\theta_{max}$ = 50°), 2685 unique [R_{int} = 0.128], 212 parameters, 1 restraint, $R1$ ($I > 2\sigma(I)$) = 0.071, $wR2$ (all data) = 0.185, GOOF = 0.99, largest diff. peak and hole 0.227/−0.247 e Å^{-3}.

Crystallographic data (excluding structure factors) for the structures reported in this work have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications no.'s CCDC-865479 (**9a**), CCDC-865480 (**9c**), CCDC-865481 (**9k**), CCDC-865482 (**9l**), CCDC-965483 (**15d**), CCDC-865484 (**15f**), and CCDC-865485 (**16**). Copies of the data can be obtained free of charge on application to The Director, CCDC, 12 Union Road, Cambridge DB2 1EZ, UK (Fax: int. code +(1223)336-033; email: deposit@ccdc.cam.ac.uk).

Supporting Information

Supporting Information File:

Supporting Information File 1

Experimental data for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-160-S1.pdf]

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Cation affinity numbers of Lewis bases

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Full Research Paper

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Abstract

Using selected theoretical methods the affinity of a large range of Lewis bases towards model cations has been quantified. The range of model cations includes the methyl cation as the smallest carbon-centered electrophile, the benzhydryl and trityl cations as models for electrophilic substrates encountered in Lewis base-catalyzed synthetic procedures, and the acetyl cation as a substrate model for acyl-transfer reactions. Affinities towards these cationic electrophiles are complemented by data for Lewis-base addition to Michael acceptors as prototypical neutral electrophiles.

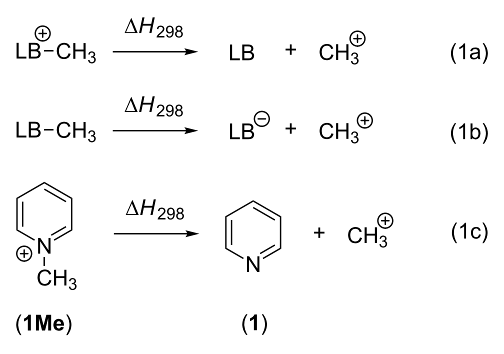
Introduction

Cation affinity values are important guidelines for the reactivity of Lewis and Brønstedt bases [1-3]. While proton affinity numbers (either as gas phase proton affinities or as solution phase pK_a values) have been used for a long time in quantitative approaches to describe base-induced or base-catalyzed processes, affinity data towards carbon electrophiles have only recently been adopted as tools for the assessment of Lewis base reactivity [4]. This is mainly due to the scarcity of accurate experimentally measured or theoretically calculated data. The performance of various theoretical methods to provide accurate affinity data has recently been analyzed and a number of cost-efficient methods for the determination of accurate gas phase values have been identified [5,6]. Using these methods we now present a broad overview over the cation affinities of N- and P-based nucleophiles.

Results and Discussion

Methyl cation affinities (MCA)

The methyl cation (CH_3^+) is the smallest carbocation which is useful as a chemical probe for Lewis bases. The respective methyl cation affinity of a given Lewis base (LB) is obtained as the reaction enthalpy at 298.15 K and 1 bar pressure for the reaction shown in equation 1a for a neutral Lewis base and in equation 1b for an anionic base (Scheme 1). This definition is in analogy to that for proton affinities (PA) and implies large positive energies for most of the P- and N-based Lewis bases used in catalytic processes. Using pyridine (**1**) as an example for a weak Lewis base, the methyl cation affinity corresponds to the enthalpy of the reaction in equation 1c and amounts to MCA(**1**) = +519.2 kJ/mol at the G3 level of theory [5].



Scheme 1: Reactions for the methyl cation affinity (MCA) of a neutral Lewis base (1a), an anionic Lewis base (1b) and pyridine (1c).

A recent analysis of theoretical methods found that calculations at the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level of theory (in short: "MP2-5") reproduce results obtained at the G3 level within 4.0 kJ/mol for selected small and medium-sized organocatalysts [5]. For pyridine (**1**) the MCA value obtained with this model amounts to MCA(**1**) = +518.7 kJ/mol, which is only 0.5 kJ/mol lower than the G3 value. The following discussion will thus be based on results obtained with the MP2-5 model, if not noted otherwise. Methyl cation affinity values obtained for N-centered Lewis bases using this approach are collected in Table 1. For organocatalytic processes especially the Lewis bases **12**, **14**, **18**, **24**, **44**, **45** and **52-65** are of note.

Pyridine is a comparatively weak nucleophile as already mentioned above. This also applies to imidazole (**12**), pyrrolidine (**18**) and a number of trialkylamines, all of which have MCA values below 550 kJ/mol. In the case of pyridine it is possible to increase the Lewis basicity by introducing electron-

Table 1: MCA values for N-centered Lewis bases, ordered by increasing MCA values.

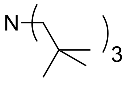
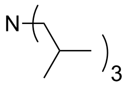
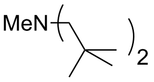
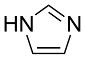
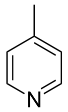
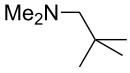
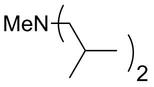
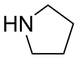
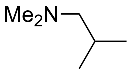
system	MCA [kJ/mol]	system	MCA [kJ/mol]
NH_3 (**2**)	+436.5	NH_2Me (**3**)	+488.7
$NMePh_2$ (**4**)	+514.4	pyridine (**1**)	+518.7
N*c*-Pr_3 (**5**)	+521.2	 (**6**)	+521.4
$NHMe_2$ (**7**)	+523.1	NMe*c*-Pr_2 (**8**)	+523.7
NMe_2Ph (**9**)	+527.7	 (**10**)	+529.4
 (**11**)	+531.1	 (**12**)	+531.7[a]
NMe_2*c*-Pr (**13**)	+532.0	 (**14**)	+532.8
 (**15**)	+535.9	N(iPr)$_3$ (**16**)	+536.0
 (**17**)	+538.2	 (**18**)	+539.8
 (**19**)	+541.5	NMe_3 (**20**)	+543.5

Table 1: MCA values for N-centered Lewis bases, ordered by increasing MCA values. (continued)

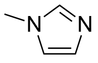
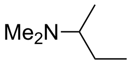
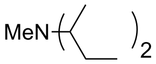
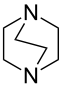
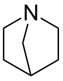
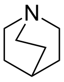
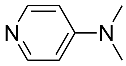
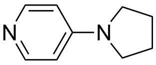
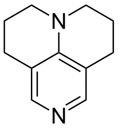
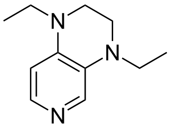
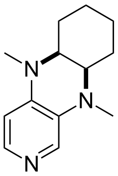
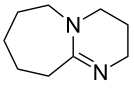
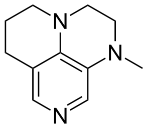
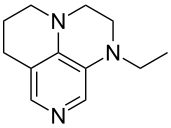
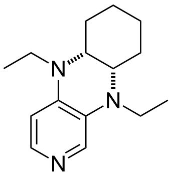
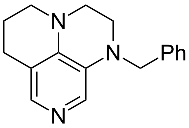
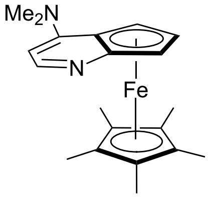
N*t*-Bu$_3$ (**21**)	+545.5	NMe$_2$Et (**22**)	+548.6
NMe*t*-Bu$_2$ (**23**)	+549.4	 (**24**)	+550.0
NMe$_2$*c*-Bu (**25**)	+551.2	NMe$_2$(iPr) (**26**)	+551.7
NMe$_2$*n*-Pr (**27**)	+552.1	 (**28**)	+552.5
NMe$_2$*t*-Bu (**29**)	+552.6	NMe$_2$*n*-Bu (**30**)	+553.8
NMe$_2$*c*-Pen (**31**)	+554.3	NMe$_2$*n*-Pen (**32**)	+554.5
NMe$_2$*c*-Oct (**33**)	+554.6	 (**34**)	+555.2
NMeEt$_2$ (**35**)	+555.3	NMe$_2$*n*-Hex (**36**)	+555.4
NMe$_2$*n*-Hep (**37**)	+555.7	N*c*-Hex$_3$ (**38**)	+556.9
NMe(iPr)$_2$ (**39**)	+557.3	NMe$_2$*c*-Hep (**40**)	+560.3
NMe*c*-Bu$_2$ (**41**)	+560.4	NMe$_2$*c*-Hex (**42**)	+561.1
NMe*n*-Pr$_2$ (**43**)	+561.7	 (**44**)	+562.2
NEt$_3$ (**45**)	+562.3	NMe*n*-Bu$_2$ (**46**)	+564.1
N*n*-Pr$_3$ (**47**)	+567.5	N*c*-Pen$_3$ (**48**)	+568.3
NMe*c*-Pen$_2$ (**49**)	+570.6	N*c*-Bu$_3$ (**50**)	+570.9
NMe*c*-Hex$_2$ (**51**)	+572.0	 (**52**)	+576.0
 (**53**)	+580.6	 (**54**)	+581.2^b
NPh$_3$ (**55**)	+583.5	 (**56**)	+590.1^b
 (**57**)	+602.7	 (**58**)	+609.0
 (**59**)	+609.1	 (**60**)	+609.6^c
 (**61**)	+611.0	 (**62**)	+613.3

Table 1: MCA values for N-centered Lewis bases, ordered by increasing MCA values. (continued)

 (**63**)	+616.0	 (**64**)	+620.8
 (**65**)	+624.1[b,d]		

[a]N3; [b]pyridine nitrogen; [c]N(sp²); [d]see [7].

donating groups in *para*-position. The dialkylamino groups in 4-*N*,*N*-dimethylaminopyridine (DMAP, **54**) or in 4-pyrrolidinopyridine (PPY, **56**) increase the MCA values dramatically. This is in accordance with the much higher catalytic efficiency of **54** and **56** for e.g., acylation reactions [3,8-12]. The currently highest MCA value has been obtained for ferrocenyl DMAP-derivative **65** with MCA(**65**) = +624.1 kJ/mol [7]. This is approximately 40 kJ/mol more than the value for DMAP with MCA(**54**) = +581.2 kJ/mol and may be the reason for the outstanding catalytic potential of **65**. For the chiral Lewis bases **59**, **63**, and **65** only one enantiomer is listed in Table 1. Affinity values towards achiral electrophiles such as the MCA values collected in Table 1 are, of course, exactly identical for both enantiomers, and therefore we will in the following report affinity values for only one of the enantiomers of a given chiral Lewis base.

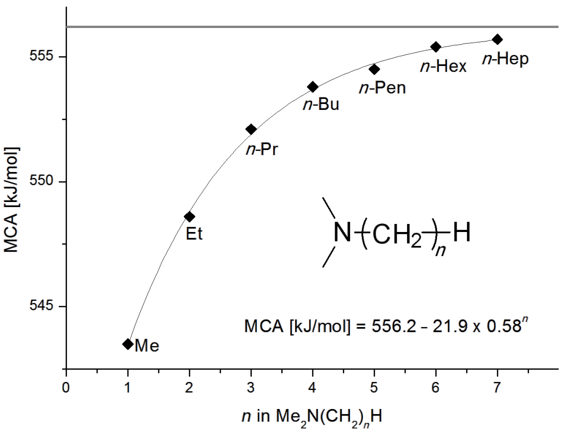


Figure 1: MCA values of monosubstituted amines of general formula Me$_2$N(CH$_2$)$_n$H (*n* = 1–7, in kJ/mol).

The MCA values of trialkylamines depend in a systematic manner on the number and structure of the attached alkyl groups. The influence of the length of linear alkyl groups has been explored using alkyldimethylamines. As can be seen in Figure 1 the MCA values of these bases depend in an exponential manner on the length of the alkyl group. This systematic dependence can be expressed quantitatively by the equation given in Scheme 2.

$$\mathrm{MCA(Me_2N(CH_2)}_n\mathrm{H)} = 556.2 - 21.9 \cdot 0.58^n \text{ kJ/mol} \qquad (2)$$

Scheme 2: Systematic dependence of MCA.

This relationship predicts a limiting MCA value of 556.2 kJ/mol for alkyldimethylamines with an alkyl substituent of infinite length. This is an increase of 12.7 kJ/mol compared to trimethylamine. In amines with three identical substituents – such as N*n*-Pr$_3$ (**47**) with MCA(**47**) = 567.5 kJ/mol – the electron-donation effects induced by the alkyl groups are close to additive for linear alkyl chains, thus leading to systematically higher affinity values as compared to the respective mono-substituted amine (e.g., NMe$_2$*n*-Pr (**27**) with MCA(**27**) = 552.1 kJ/mol). However, even in systems with linear alkyl substituents unfavorable steric effects appear to exist between the alkyl substituents, and confining the alkyl groups to a bicyclic cage structure as in quinuclidine (**53**) thus raises the MCA value considerably to MCA(**53**) = +580.6 kJ/mol. For amines with branched or cyclic substituents a further erosion of MCA values can be observed due to increasing steric effects in the methyl cation adducts. The following trends in amine MCA values can therefore be observed for a variety of systems (Scheme 3).

MCA(NMe_2R) < MCA(NR_3) R = acyclic substituents (3a)

MCA(NMe_2R) > MCA(NR_3) R = cyclic/branched substituents (3b)

Scheme 3: Trends in amine MCA values.

For branched and cyclic substituents additional unfavorable steric interactions come into play, for the cationic methyl-adducts more than for the parent amines. In order to illustrate these effects a closer look at the best conformations of the simple most branched amines $Me_2N(iPr)$ (**26**, MCA = 551.7 kJ/mol), $MeN(iPr)_2$ (**39**, MCA = 557.3 kJ/mol) and $N(iPr)_3$ (**16**, MCA = 536.0 kJ/mol) is helpful. In the absence of steric effects a systematic increase in the MCA value is expected on replacing methyl by isopropyl substituents. However, the number of gauche interactions increases more rapidly for the methyl cation adducts than for the parent amines; this leads to an increase which is smaller than expected. For amine **26** ($Me_2N(iPr)$) there are two gauche interactions in the neutral parent and four such interactions in the respective methyl cation adduct. For amine **39** ($MeN(iPr)_2$) the number of unfavorable interactions increases to five in the neutral parent and to eight in the methyl cation adduct. The unexpectedly low MCA value for amine **16** ($N(iPr)_3$) is a consequence of additional, more strongly repulsive *syn*-pentane interactions, whose magnitude is larger in the methyl cation adduct than in the neutral amine. Figure 2 shows the projection through the C–N bond of one of the isopropyl-groups in **16Me**.

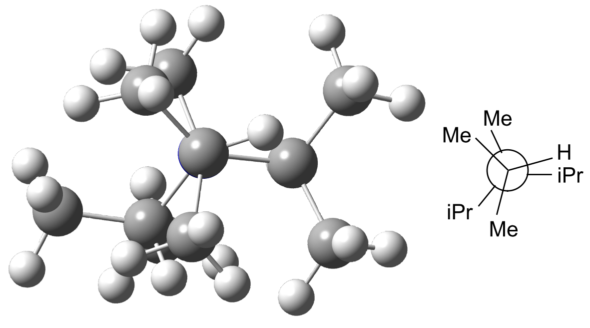


Figure 2: Eclipsing interactions in the best conformation of $N^+Me(iPr)_3$ (**16Me**) (left), and the corresponding Newman projection through the C–N bond (right).

Trialkyl- and triarylphosphanes are equally potent nucleophiles, whose use in catalytic processes is, however, often limited due to their oxygen sensitivity. Table 2 lists MCA values for a large number of trialkylphosphanes and alkyldiphenylphosphanes. For organocatalytic processes especially the phosphanes **89**, **98**, **117**, **120**–**124** are of note.

Table 2: MCA values of saturated trialkylphosphanes without heteroatoms, PPh_3, PH_3, PH_2Me and $PHMe_2$, ordered by increasing MCA values.

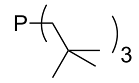
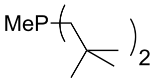
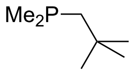
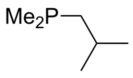
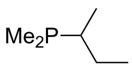
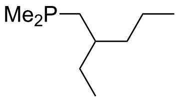
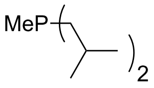
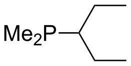
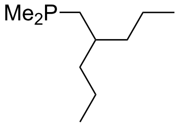
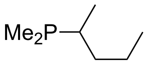
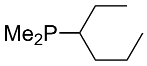
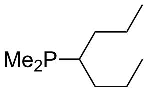
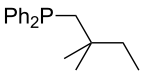
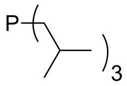
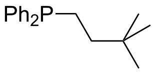
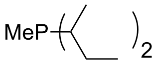
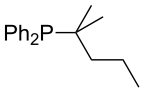
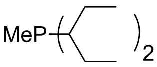
system	MCA [kJ/mol]	system	MCA [kJ/mol]
PH_3 (**66**)	+448.4	PH_2Me (**67**)	+513.0
$PHMe_2$ (**68**)	+564.2	 P ( )$_3$ (**69**)	+603.3
PMe_3 (**70**)	+604.2	 MeP ( )$_2$ (**71**)	+606.9
Me_2c-Pr (**72**)	+607.2	 Me_2P (**73**)	+607.9
PMe_2Et (**74**)	+610.5	Me*c*-Pr_2 (**75**)	+611.8
 Me_2P (**76**)	+611.9	$PMe_2(iPr)$ (**77**)	+613.5
PMe_2n-Pr (**78**)	+614.3	$PMeEt_2$ (**79**)	+616.1
PMe_2n-Bu (**80**)	+616.3	PMe_2c-Bu (**81**)	+616.7
PMe_2n-Pen (**82**)	+617.3	 Me_2P (**83**)	+617.3

Table 2: MCA values of saturated trialkylphosphanes without heteroatoms, PPh$_3$, PH$_3$, PH$_2$Me and PHMe$_2$, ordered by increasing MCA values. (continued)

PMe$_2$*n*-Hex (**84**)	+617.7	PMe$_2$*n*-Hep (**85**)	+617.9
PMe$_2$*n*-Oct (**86**)	+618.1	 (**87**)	+618.2.
 (**88**)	+618.5	PPh$_3$ (**89**)	+618.7
 (**90**)	+618.8	PMe$_2$*t*-Bu (**91**)	+619.4
 (**92**)	+619.5	 (**93**)	+619.6
PMe$_2$*c*-Pen (**94**)	+620.4	 (**95**)	+620.8
P*c*-Pr$_3$ (**96**)	+621.1	PMe$_2$*c*-Hex (**97**)	+621.9
PEt$_3$ (**98**)	+622.5	 (**99**)	+623.3
PMe*n*-Pr$_2$ (**100**)	+624.1	 (**101**)	+624.5
PPh$_2$*n*-Bu (**102**)	+624.6	PMe(iPr)$_2$ (**103**)	+624.8
PMe$_2$*c*-Hep (**104**)	+624.9	 (**105**)	+625.7
PMe$_2$*c*-Oct (**106**)	+626.1	PMe$_2$*c*-Non (**107**)	+627.5
 (**108**)	+627.7	PMe*n*-Bu$_2$ (**109**)	+627.8
PMe*c*-Bu$_2$ (**110**)	+628.7	PMe$_2$*c*-Dec (**111**)	+628.9
 (**112**)	+630.5	 (**113**)	+631.7
 (**114**)	+631.8	P*n*-Pr$_3$ (**115**)	+633.6
PMe*t*-Bu$_2$ (**116**)	+635.1	P(iPr)$_3$ (**117**)	+635.4
PMe*c*-Pen$_2$ (**118**)	+637.1	P*c*-Bu$_3$ (**119**)	+638.5
P*n*-Bu$_3$ (**120**)	+639.5	PMe*c*-Hex$_2$ (**121**)	+641.0
P*t*-Bu$_3$ (**122**)	+648.3	P*c*-Pen$_3$ (**123**)	+650.8
P*c*-Hex$_3$ (**124**)	+655.7		

Analysis of the results for unbranched trialkylphosphanes indicates that longer alkyl chains increase the MCA values in a systematic manner. This was also found for trialkylamines and reflects inductive electron donation through alkyl substituents with variable length [13]. The results obtained for dimethylalkylphosphanes of general structure $Me_2P(CH_2)_nH$ with n = 1–8 lead to a general expression for the chain-length dependence of the MCA values that can again be derived as given in equation 4 (Scheme 4). This is shown together with the respective data points in Figure 3.

$$MCA(Me_2P(CH_2)_nH) = 618.3 - 26.5 \cdot 0.54^n \text{ kJ/mol} \quad (4)$$

Scheme 4: General expression for the chain-length dependence of MCA values.

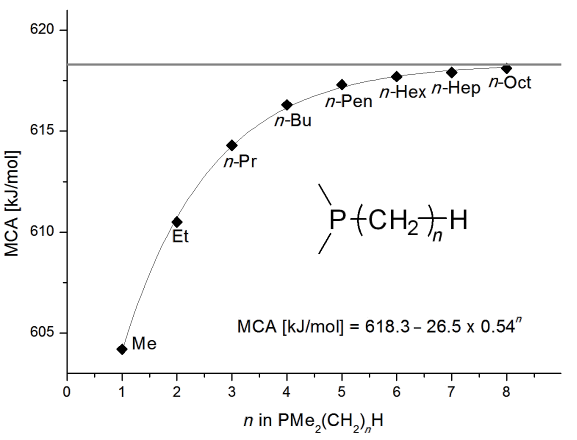


Figure 3: MCA values of monosubstituted phosphanes of general formula $Me_2P(CH_2)_nH$ (n = 1–8, in kJ/mol).

On the basis of equation 4 it is possible to predict the MCA value for a phosphane Me_2PR with one infinitively long alkyl substituent (MCA = 618.3 kJ/mol) and for a phosphane PR_3 with three infinitively long alkyl substituents (MCA = 646.5 kJ/mol). Phosphanes with branched alkyl substituents show systematically larger MCA values as compared to unbranched systems of otherwise comparable structure. An α-branched substituent leads to a higher MCA value than a β-branched substituent; this can be illustrated with the phosphanes **76** and **83**. Both phosphanes are dimethyl(methylpropyl)phosphanes, but one in α-position (**83**, MCA = 617.3 kJ/mol) and one in β-position (**76**, MCA = 611.9 kJ/mol). Deviations from the regular behavior of the MCA values are due to steric interactions, mostly 1,5-*syn*-pentane interactions. The MCA values obtained for phosphanes with cycloalkyl substituents show similar trends as already observed for acyclic systems in that larger rings lead to higher MCA values. However, as shown in Figure 4 for phosphanes carrying one cyclic substituent, the correlation between ring size and MCA value is not quite as good as found for phosphanes with acyclic substituents.

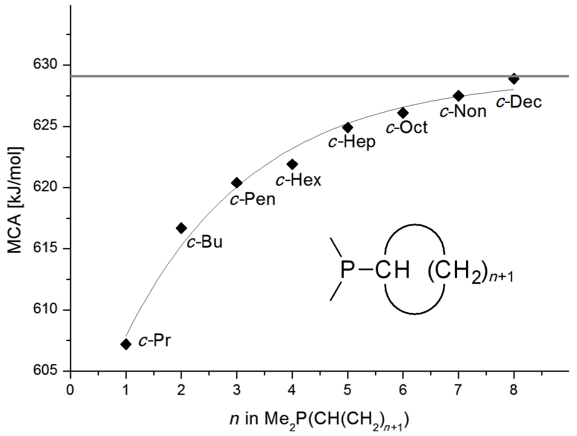


Figure 4: MCA values of monosubstituted phosphanes of general formula $PMe_2(CH(CH_2)_{n+1})$ (n = 1–8, in kJ/mol).

A similar analysis applies to phosphanes combining one alkyl and two phenyl substituents with the general formula PPh_2R. The results of phosphanes **101**, **102**, **108**, **113** are particularly interesting, because they contain an *n*-butyl substituent decorated with additional methyl groups in varying positions (Figure 5). With two methyl groups in α-position the MCA value is increased by 7 kJ/mol compared to the phosphane without methyl groups. In contrast, the positive inductive influence of two methyl groups in β-position is balanced by disfavorable steric interactions, which are similar to 1,5-*syn*-pentane interactions. But the methyl groups in γ-position lead again to a

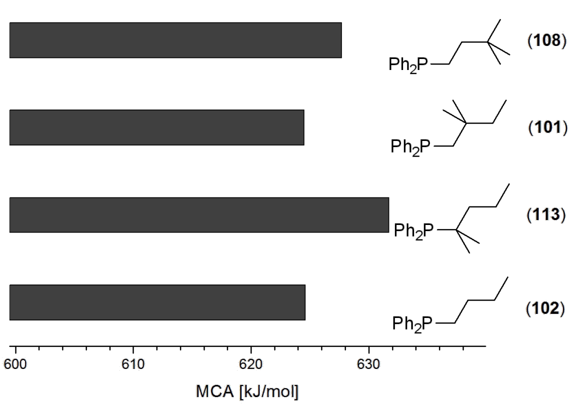


Figure 5: The MCA values of *n*-butyldiphenylphosphane (**102**) and its (αα-/ββ-/γγ-) dimethylated analogues.

slight rise of the MCA value. The latter increase is just about 3 kJ/mol, because the γ-position is quite far away from the reaction center. Therefore, it can be summarized that branched phosphanes are most sensitive for disfavorable steric interactions when branching occurs in β-position.

Large MCA values can be expected for phosphanes and amines which carry substituents that are able to act as lone pair donors. This was explored for phosphanes which possess a nitrogen-containing moiety. Table 3 lists results for phosphanes containing a direct phosphorus–nitrogen bond. In the case of phosphanes with a second nucleophilic position (e.g., nitrogen atom) all MCA values are calculated for the reaction at the phosphorus atom, if not mentioned otherwise.

The largest increase in MCA value compared to the reference of trimethylphosphane (**70**) is obtained through the introduction of the pyrrolidino substituent present in phosphanes **148**, **154** and **157**. Introduction of the first pyrrolidino group as in phosphane **148** leads to MCA(**148**) = +634.2 kJ/mol, an increase of 30.0 kJ/mol compared to the reference systems PMe$_3$ (**70**). Despite the fact that the MCA value increases somewhat more slowly on introduction of the second and third pyrrolidino substituent, the tris(pyrrolidino)phosphane **157** counts among the most Lewis-basic systems studied here with MCA(**157**) = +686.6 kJ/mol except the bicyclic, unusual phosphane **158**. For systems of general formula PMe$_2$NRR’ the unsaturated substituents (pyrrole (**133**), imidazol (**131**), triazol (**129**)) show MCA values below 570 kJ/mol, whereas the saturated

Table 3: MCA values of phosphanes containing one to three P–N bonds, ordered by increasing MCA values.

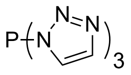
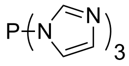
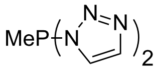
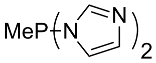
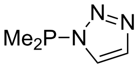
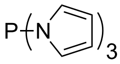
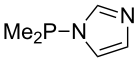
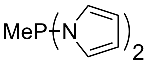
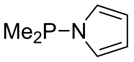
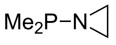
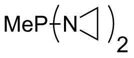
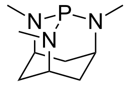
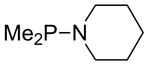
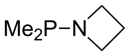
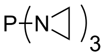
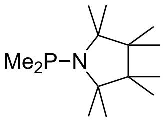
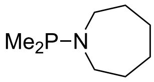
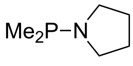
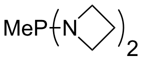
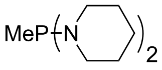
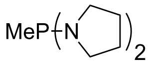
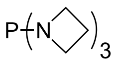
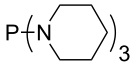
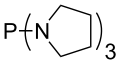
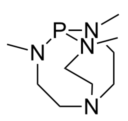
system	MCA [kJ/mol]	system	MCA [kJ/mol]
 (**125**)	+418.4	 (**126**)	+451.3
 (**127**)	+466.1	 (**128**)	+487.0
 (**129**)	+523.3	 (**130**)	+524.6
 (**131**)	+535.5	 (**132**)	+541.2
 (**133**)	+563.8	 (**134**)	+605.4
 (**135**)	+611.9	Me$_2$P–NMe$_2$ (**136**)	+615.5
 (**137**)	+620.0	Me$_2$P–NMeEt (**138**)	+620.6
 (**139**)	+624.7	 (**140**)	+624.8
 (**141**)	+626.8	Me$_2$P–NEt$_2$ (**142**)	+626.8
 (**143**)	+626.9	Me$_2$P–NEtPr (**144**)	+627.7

Table 3: MCA values of phosphanes containing one to three P–N bonds, ordered by increasing MCA values. (continued)

 (**145**)	+629.6	$Me_2P–NPr_2$ (**146**)	+629.8
$MeP(NMe_2)_2$ (**147**)	+631.8	 (**148**)	+634.2
$P(NMe_2)_3$ (**149**)	+642.3	 (**150**)	+642.7
MeP(NMeEt)$_2$ (**151**)	+642.7	 (**152**)	+648.7
$MeP(NEt_2)_2$ (**153**)	+653.2	 (**154**)	+661.6
 (**155**)	+666.4	 (**156**)	+666.5
 (**157**)	+686.6	 (**158**)	+701.1

substituents show MCA values above 600 kJ/mol. In the case of saturated, acyclic substituents the trend ‘longer alkyl chains – higher MCA values’ is again observed (Figure 6). For saturated, cyclic substituents, however, the MCA values increase from aziridine (**134**) to azetidine (**140**) and pyrrolidine (**148**), but then decrease again for piperidine (**139**) and azepane (**145**).

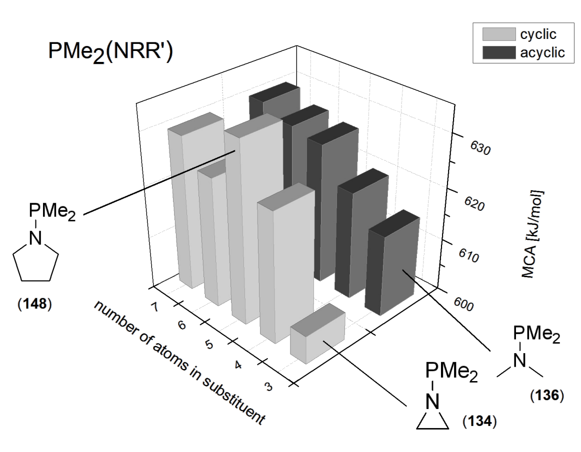


Figure 6: MCA values of phosphanes $Me_2P–NR_2$ with cyclic and acyclic amine substituents.

Aside from phosphanes with a direct phosphorus–nitrogen bond, a variety of phosphanes with nitrogen-containing substituents can be envisioned in which P- and N-centers are separated by at least one carbon atom. Results for these phosphanes are listed in Table 4. All MCA values are calculated for reaction at the phosphorus atom, if not mentioned otherwise.

For saturated substituents a general trend of higher MCA values with larger cyclic substituents can be observed. It is also visible that the β-connectivity usually leads to higher MCA values than the α-connectivity (Figure 7).

Most of the unsaturated substituents as 1-methyltriazoles (**160**, **162**, **164**, **174**, **175**, **177**) and 2-/5-(1-methylimidazoles) (**165**, **168**, **170**, **172**, **173**, **176**) lead to lower MCA values compared to the reference system PMe_3 (**70**) due to their electron withdrawing character. The 4-(1-methylimidazole) substituents present in phosphanes **194**, **207**, and **208** are, however, electron donating. The most effective electron-donating effects are in this group found for methylated pyrrole substituents (**201**, **203**, **205**, **209**–**214**), particularly in systems connecting the phosphorous atom to the C3 position of the pyrrole ring. In these cases, the trisubstituted phosphanes reach MCA values above 720 kJ/mol. This is an extraordinary MCA value for neutral Lewis bases.

Table 4: MCA values of phosphanes with nitrogen-containing substituents lacking direct phosphorous–nitrogen bonds.

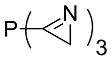
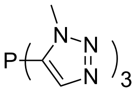
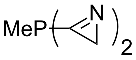
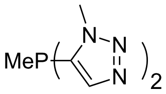
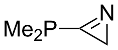
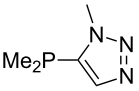
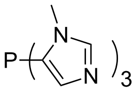
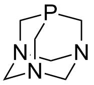
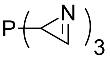
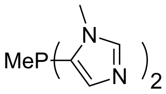
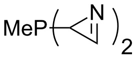
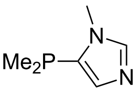
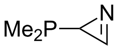
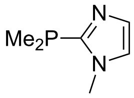
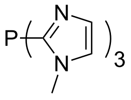
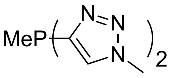
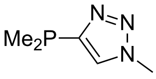
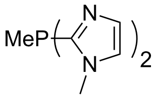
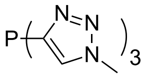
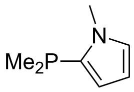
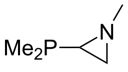
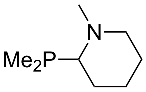
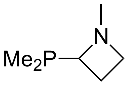
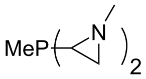
system	MCA [kJ/mol]	system	MCA [kJ/mol]
 (**159**)	+431.3	 (**160**)	+470.2
 (**161**)	+480.1	 (**162**)	+510.5
 (**163**)	+539.2	 (**164**)	+548.8
 (**165**)	+556.6	 (**166**)	+559.5
 (**167**)	+565.1	 (**168**)	+571.0
 (**169**)	+571.7	 (**170**)	+582.0
 (171)	+588.4	 (**172**)	+591.4
 (**173**)	+594.4	 (**174**)	+596.1
 (**175**)	+596.7	 (**176**)	+601.1
 (**177**)	+603.5	 (**178**)	+605.6
 (**179**)	+610.7	 (**180**)	+614.9
 (**181**)	+615.1	 (**182**)	+616.2

Table 4: MCA values of phosphanes with nitrogen-containing substituents lacking direct phosphorous–nitrogen bonds. (continued)

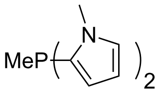
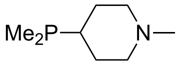
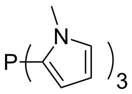
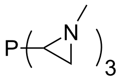
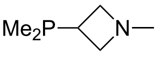
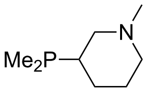
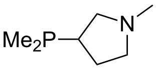
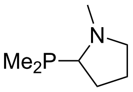
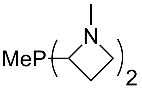
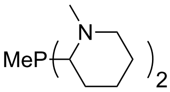
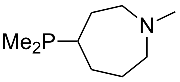
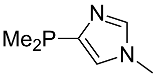
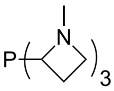
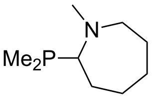
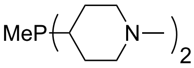
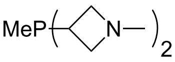
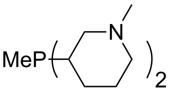
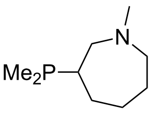
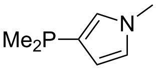
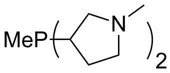
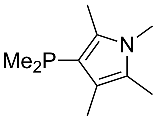
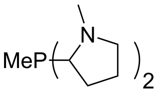
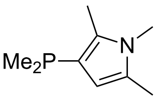
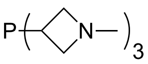
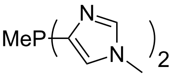
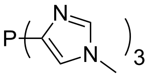
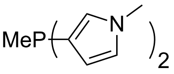
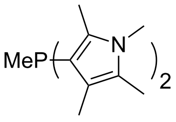
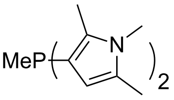
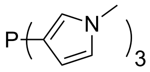
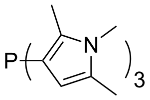
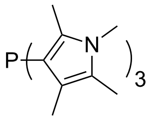
 (**183**)	+618.1	 (**184**)	+619.2
 (**185**)	+620.2	 (**186**)	+621.1
 (**187**)	+622.4	 (**188**)	+623.9
 (**189**)	+625.9	 (**190**)	+626.0
 (**191**)	+626.1	 (**192**)	+627.2
 (**193**)	+627.8	 (**194**)	+628.7
 (**195**)	+632.0	 (**196**)	+633.0
 (**197**)	+634.7	 (**198**)	+635.7
 (**199**)	+636.1	 (**200**)	+636.7
 (**201**)	+638.2	 (**202**)	+644.4
 (**203**)	+645.3	 (**204**)	+645.8
 (**205**)	+646.4	 (**206**)	+650.0
 (**207**)	+656.1	 (**208**)	+672.4

Table 4: MCA values of phosphanes with nitrogen-containing substituents lacking direct phosphorous–nitrogen bonds. (continued)

 (**209**)	+673.5	 (**210**)	+688.8
 (**211**)	+694.3	 (**212**)	+702.9
 (**213**)	+722.3	 (**214**)	+726.8

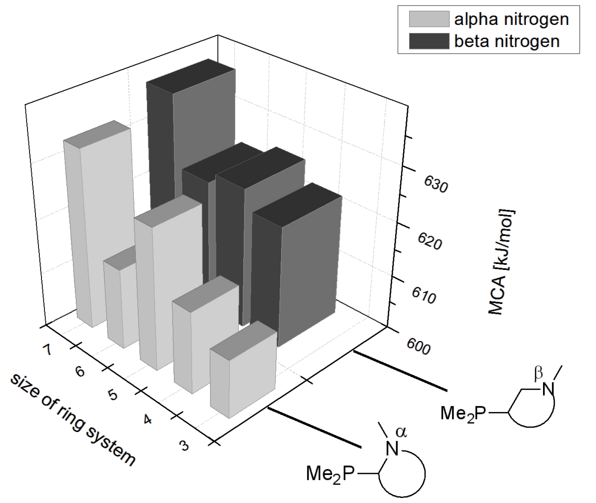


Figure 7: MCA values of phosphanes PMe$_2$R connected to α,α- and β,β-position of nitrogen containing cyclic substituents.

Phosphanes with cyclic substituents containing heteroatoms such as oxygen or sulfur are not quite as Lewis basic as the nitrogen-containing analogs (Table 5). All MCA values refer to reaction at the phosphorus atom, if not mentioned otherwise.

Surveying the MCA values obtained for phosphanes with furane (**218**, **219**, **222**, **224**, **227**, **228**), thiophene (**223**, **225**, **226**, **231**, **233**, **237**), cyclopentadiene (**232**, **234**–**236**, **238**, **241**, **242**, **244**, **245**), thiazole (**217**, **221**, **230**), and thiazine (**229**, **240**) substituents clearly illustrates that these substitution patterns lead to low or moderate MCA values.

Phosphanes with aromatic substituents are expected to display largely different MCA values depending on the functionalization pattern of these substituents. Results for this group of phosphanes are presented in Table 6 in which most of the phosphanes are interesting for organocatalysis. Again, all MCA values are calculated for reaction at the phosphorus atom if not mentioned otherwise.

Table 5: MCA values of phosphanes with oxygen- and sulfur-containing cyclic substituents.

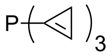
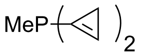
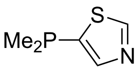
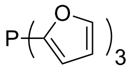
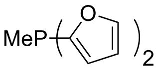
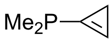
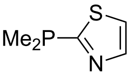
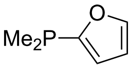
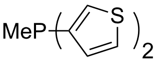
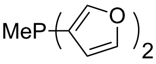
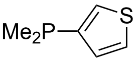
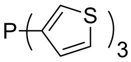
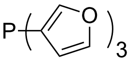
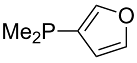
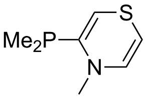
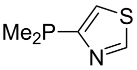
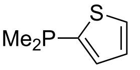
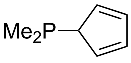
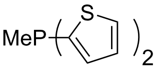
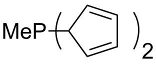
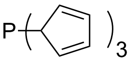
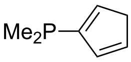
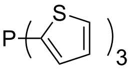
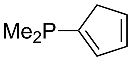
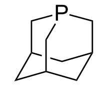
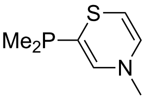
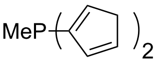
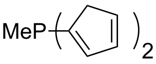
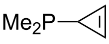
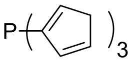
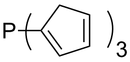
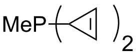
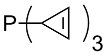
system	MCA [kJ/mol]	system	MCA [kJ/mol]
 (**215**)	+559.4	 (**216**)	+570.5
 (**217**)	+572.1	 (**218**)	+576.6
 (**219**)	+578.2	 (**220**)	+585.8

Table 5: MCA values of phosphanes with oxygen- and sulfur-containing cyclic substituents. (continued)

 (**221**)	+586.4	 (**222**)	+588.2
 (**223**)	+595.1	 (**224**)	+595.3
 (**225**)	+596.0	 (**226**)	+596.2
 (**227**)	+596.7	 (**228**)	+596.8
 (**229**)	+598.1	 (**230**)	+598.5
 (**231**)	+606.0	 (**232**)	+607.8
 (**233**)	+608.5	 (**234**)	+610.1
 (**235**)	+611.0	 (**236**)	+611.5
 (**237**)	+612.9	 (**238**)	+613.9
 (**239**)	+613.9	 (**240**)	+614.1
 (**241**)	+617.1	 (**242**)	+618.7
 (**243**)	+619.4	 (**244**)	+626.3
 (**245**)	+633.9	 (**246**)	+634.5
 (**247**)	+647.3		

In order to discuss inductive and mesomeric electron-donating effects the tri-*para*-substituted triphenylphosphanes (**295**, **298**, **300**) were chosen. The methyl group as the simplest example for an electron-donating substituent raises the MCA value by about 6 kJ/mol per group. The mesomeric effects of the methoxy- and dimethylamino-groups are significantly larger at about 11 and 25 kJ/mol per substituent. Beside the strong neutral dimethylamino group as electronic donating group also

Table 6: MCA values of aryl-substituted phosphanes.

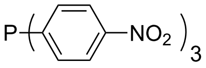
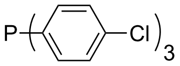
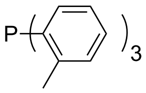
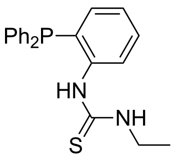
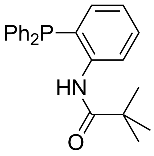
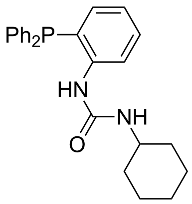
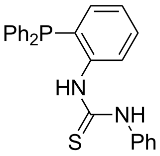
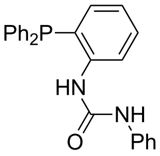
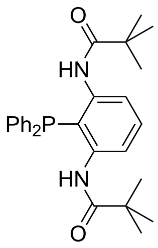
system	MCA [kJ/mol]	system	MCA [kJ/mol]
PMe_3O (**248**)	+463.5[a]	$P(C_6F_5)_3$ (**249**)	+494.1
 (**250**)	+526.6	$Ph_2P–NEt_2$ (**251**)	+545.5[b]
$P(OPh)_3$ (**252**)	+575.7	PPh_2H (**253**)	+577.2
 (**254**)	+586.5	$P(OEt)_3$ (**255**)	+599.9
$PPhMe_2$ (**256**)	+608.5	 (**257**)	+610.7
 (**258**)	+612.3	PPh_2Me (**259**)	+614.1
 (**260**)	+616.6	$PPhEt_2$ (**261**)	+617.8
PPh_3 (**89**)	+618.7	 (**262**)	+619.7
 (**263**)	+619.8	PPh_2Et (**264**)	+620.0
 (**265**)	+620.6	 (**266**)	+621.3
PPh_2c-Pr (**267**)	+622.4	$PPh_2(iPr)$ (**268**)	+623.0
$PPhn$-Pr_2 (**269**)	+623.5	PPh_2n-Pr (**270**)	+623.6

Table 6: MCA values of aryl-substituted phosphanes. (continued)

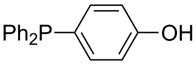
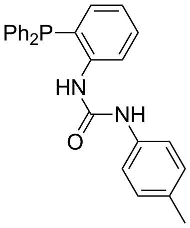
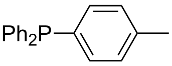
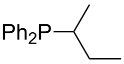
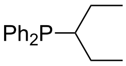
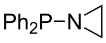
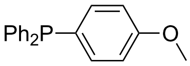
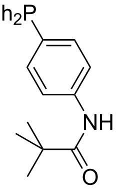
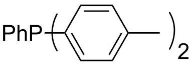
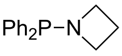
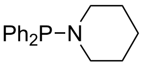
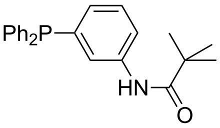
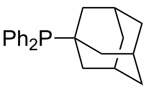
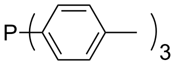
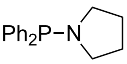
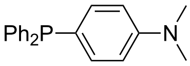
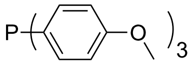
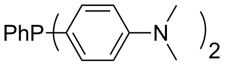
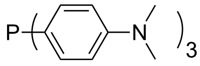
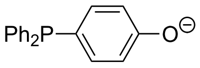
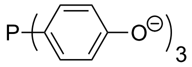
 (**271**)	+624.2	 (**272**)	+624.2
 (**273**)	+624.9	Ph$_2$P–NMe$_2$ (**274**)	+624.9
PPh$_2$*n*-Pen (**275**)	+625.3	 (**276**)	+625.8
 (**277**)	+625.8	PPh$_2$*c*-Bu (**278**)	+626.1
PPh(iPr)$_2$ (**279**)	+627.0	PPh*n*-Bu$_2$ (**280**)	+627.7
PPh$_2$*t*-Bu (**281**)	+628.5	 (**282**)	+628.6
Ph$_2$P–NMeEt (**283**)	+629.0	 (**284**)	+629.8
PPh$_2$*c*-Hex (**285**)	+630.2	PPh$_2$*c*-Pen (**286**)	+630.5
 (**287**)	+630.6	 (**288**)	+630.8
PPh$_2$*c*-Hep (**289**)	+631.8	 (**290**)	+632.3
 (**291**)	+632.3	PPh$_2$*c*-Oct (**292**)	+633.1
Ph$_2$P–NEt$_2$ (**252**)	+634.3^{c}	 (**293**)	+634.4
 (**294**)	+636.4	 (**295**)	+636.9
 (**296**)	+638.6	 (**297**)	+646.7

Table 6: MCA values of aryl-substituted phosphanes. (continued)

 (**298**)	+651.0	 (**299**)	+673.1
 (**300**)	+694.9	 (**301**)	+923.4
 (**302**)	+1490.5		

[a]MCA value at oxygen; [b]MCA value at nitrogen; [c]MCA value at phosphorus.

anionic substituents could be worthwhile. Phosphanes **301** and **302** have the highest MCA values of all Lewis bases considered here. One phenolate instead of a phenyl substituent increases the MCA value by approx. 300 kJ/mol.

Triarylphosphanes can be of interest for organocatalysis if at least one substituent in *ortho*-position of a phenyl group enables hydrogen bonds to the substrate as is, for example, the case in phosphanes **260**, **287,** and **293**. These latter three compounds differ only in the position of the pivaloylamido group (α, β, γ). The resulting MCA values vary by about 18 kJ/mol. Besides these amide-containing phosphanes (thio-)urea-containing phosphanes were also investigated. They possess lower MCA values than the previously discussed ones. In general, the ‘thiourea-phosphanes’ (**258**, **263**) show even lower MCA values than the ‘urea-phosphanes’ (**262**, **265**, **272**).

Can MCA values be increased through integration of the P-atom into a ring system? With respect to the results obtained for a small set of cyclic phosphanes (Table 7) it appears that there is at least no general trend for cyclic and acyclic phosphanes of otherwise comparable substitution pattern. The combination of phosphanes with unusually strained cyclic substituents such as diamandoids or cyclophanes also

Table 7: MCA values of miscellaneous phosphanes, ordered by increasing MCA values.

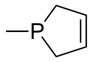
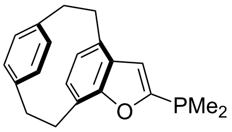
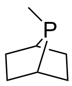
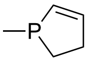
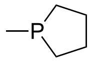
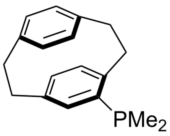
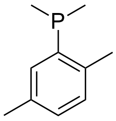
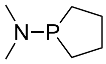
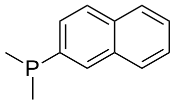
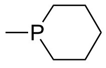
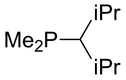
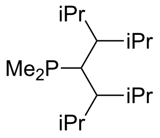
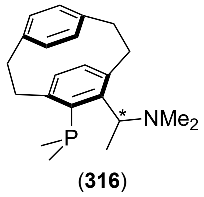
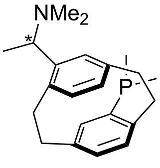
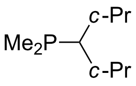
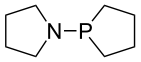
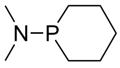
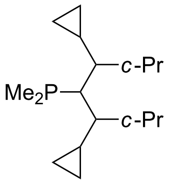
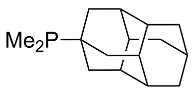
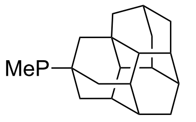
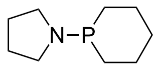
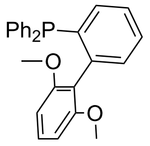
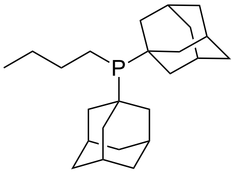
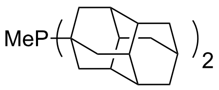
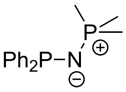
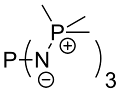
system	MCA [kJ/mol]	system	MCA [kJ/mol]
PF_3 (**303**)	+356.0	 (**304**)	+584.0
 (**305**)	+591.3	 (**306**)	+598.5
 (**307**)	+599.6	 (**308**)	+602.0
 (**309**)	+614.0	 (**310**)	+614.3
 (**311**)	+616.3	 (**312**)	+616.4

Table 7: MCA values of miscellaneous phosphanes, ordered by increasing MCA values. (continued)

 (**313**)	+616.8	 (**314**)	617.1
 (**315**)	+620.2	 (**316**)	+620.8[a] +642.0[b] +586.0[c]
 (**317**)	+621.3[a] +619.7[b] +586.6[c]	 (**318**)	+627.3
 (**319**)	+629.9	 (**320**)	+631.2
 (**321**)	+631.6	 (**322**)	+634.8
 (**323**)	+637.3	 (**324**)	+644.8
 (**325**)	+647.6	 (**326**)	+662.2
 (**327**)	+663.2	 (**328**)	+702.3
 (**329**)	+848.1		

[a](*S*)-configuration, phosphorus; [b](*R*)-configuration, phosphorus; [c](*S*)-configuration, nitrogen.

appears to have no particularly unusual effects. Phosphanes with strongly electron-withdrawing substituents such as PF_3 (**303**) have the expected low MCA values, while exceedingly high cation affinties are found for phosphoranylideneamines. In the case of phosphanes with a second nucleophilic position (e.g., oxygen atoms) all MCA values are calculated for the phosphorus atom if not mentioned otherwise.

The chiral phosphanes **316** and **317** show that the (*R*)- and the (*S*)-enantiomer do not have to have the same affinity values. For the phosphane **317** the difference is below 2 kJ/mol, but for phosphane **316** the difference is 21 kJ/mol.

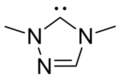
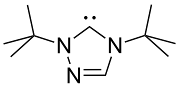
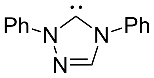
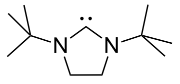
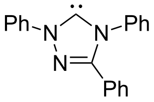
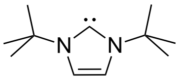
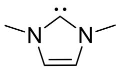
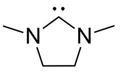
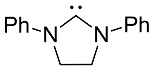
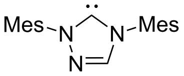
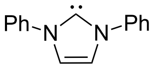
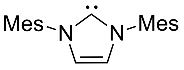
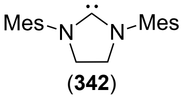
A last group of nucleophiles employed in Lewis-base catalysis concerns nucleophilic carbenes (Table 8) [14-17].

MCA values obtained for NHC-carbenes are significantly larger than those obtained for nitrogen- and phosphorus-based nucleophiles and depend on both the structure of the heterocyclic ring system as well as the substituents attached to the respective 2- and 5-positions. With respect to the dimethyl substituted carbenes, the lowest MCA value is found for the triazolyl carbene **330**, followed by imidazolyl carbene **336** and imidazolidinyl carbene **337**. It should be added that the MCA values for the latter two systems are closely similar (MCA(**336**) = +718.0 kJ/mol vs. MCA(**337**) = +719.3 kJ/mol, indicating a negligible influence of ring aromaticity. The influence of the ring substituents on MCA values is less systematic and depends on the ring system at hand. For all systems, however, the largest MCA values are obtained for mesityl substituents. Mayr and co-workers have determined nucleophilicity parameters *N* and slope parameters *s* of NHC-carbenes **334**, **341** and **342** in THF [18-20]. The slowest reactions were found for triazolyl carbene **334** with *N* = 14.07 (*s* = 0.84). The imidazolyl carbene **341** (*N* = 21.75, *s* = 0.45) and the imidazolidinyl carbene **342** (*N* = 23.35, *s* = 0.40) are, in contrast, 10^8 to 10^9 times more nucleophilic. This is in agreement with the MCA values for **341** and **342**, which are approx. 50 kJ/mol higher compared to the value of **334**. However, including other typical organocatalysts such as PPh_3 (**89**), DMAP (**54**), and DBU (**60**) in the comparison of MCA- and N-values, Mayr et al. note that no general correlation appears to exist between reaction rates and reaction energies for the addition of these nucleophiles to cationic electrophiles. This has been interpreted as a reflection of much larger Marcus intrinsic barriers for carbene nucleophiles as compared to those of phosphanes or N-nucleophiles [21].

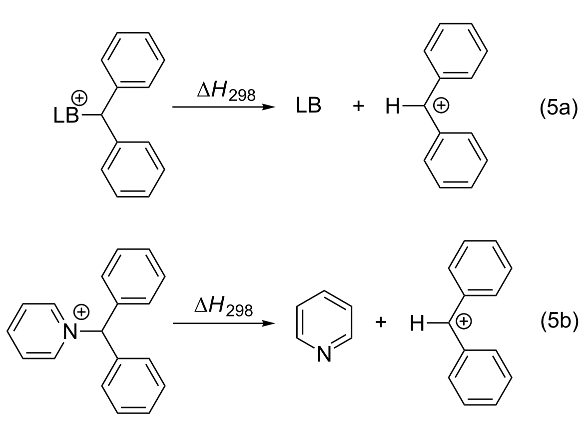
Benzhydryl cation affinities (BHCA)

The carbon electrophiles involved in Lewis base-catalyzed reactions are typically much larger than the methyl cation. The substituents present in these systems do not only add, in part considerable, steric bulk to the systems, but also stabilize the

Table 8: MCA values of carbenes, ordered by increasing MCA values [18].

system	MCA [kJ/mol]	system	MCA [kJ/mol]
 (**330**)	+674.4	 (**331**)	+676.8
 (**332**)	+694.4	 (**333**)	+699.4
 (**334**)	+712.2	 (**335**)	+714.3
 (**336**)	+718.0	 (**337**)	+719.3
 (**338**)	+722.9	 (**339**)	+728.4
 (**340**)	+742.4	 (**341**)	+767.2
 (**342**)	+768.9		

cation through charge delocalization [22]. Affinity numbers obtained for larger carbocations such as the benzhydryl cation may thus more closely mimic the steric and electronic properties of synthetically used carbon electrophiles. The corresponding benzhydryl cation affinity (BHCA) of a neutral Lewis base (LB) is defined as the reaction enthalpy for the dissociation process shown in equation 5 in Scheme 5. For pyridine as the Lewis base the benzhydryl cation affinity (BHCA) amounts to BHCA(**1**) = 160.0 kJ/mol.



Scheme 5: Reactions for the benzhydryl cation affinity (BHCA) of a Lewis base (5a) and pyridine (5b).

BHCA values of Lewis bases commonly used in organocatalysis and of selected phospanes have been collected in Table 9.

The benzhydryl cation affinities (BHCA) of weak nucleophiles like ammonia (**344**) and phosphane (**343**) are less than 100 kJ/mol and thus much smaller than the respective MCA values. In contrast, often used organocatalysts like 4-dimethylaminopyridine (**54**), PPY (**56**), and PPh_3 (**89**) possess BHCA values above 200 kJ/mol. The strongest nucleophiles, the tris-*para*-methoxy- and tris-*para*-dimethylamino-substituted triphenylphosphanes (**298** and **300**) reach BHCA values of 267 and 306 kJ/mol, respectively. BHCA values of selected pyridine and phosphane bases correlate in a linear fashion with experimentally measured nucleophilicity parameters *N* of these systems (Figure 8) [23,24].

Table 9: BHCA values of Lewis base, ordered by increasing BHCA values.

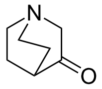
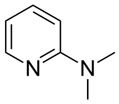
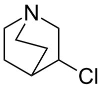
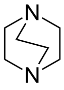
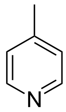
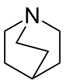
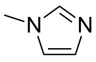
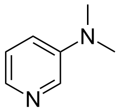
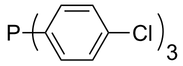
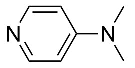
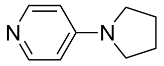
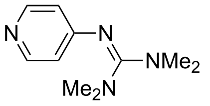
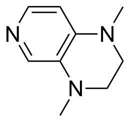
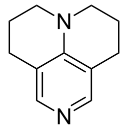
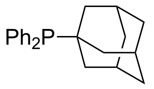
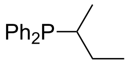
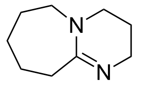
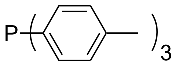
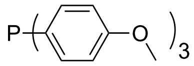
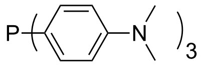
system	BHCA [kJ/mol]	system	BHCA [kJ/mol]
PH_3 (**343**)	+77.8	NH_3 (**344**)	+84.3
$Ph_2P–NEt_2$ (**251**)	+137.7[a]	 (**345**)	+148.1[b]
NEt_3 (**45**)	+150.7	NMe_3 (**20**)	+153.0
 (**346**)	+157.8[b]	pyridine (**1**)	+160.0
 (**347**)	+164.4[b]	 (**44**)	+167.8
 (**14**)	+171.7	 (**53**)	+184.6
 (**24**)	+186.4[c]	$P(OPh)_3$ (**252**)	+193.0
 (**348**)	+200.5[b]	 (**254**)	+207.7

Table 9: BHCA values of Lewis base, ordered by increasing BHCA values. (continued)

P(OEt)$_3$ (**255**)	+208.1	 (**54**)	+213.0[b]
PMe$_3$ (**70**)	+215.5	 (**56**)	+221.4[b]
P(iPr)$_3$ (**117**)	+224.8	 (**349**)	+225.8[b]
PPhMe$_2$ (**256**)	+230.1	PPh(iPr)$_2$ (**279**)	+230.4
PEt$_3$ (**98**)	+230.6	PPh$_2$*t*-Bu (**281**)	+232.7
 (**350**)	+233.3[b]	 (**57**)	+233.3[b]
PPh$_3$ (**89**)	+235.0	PPh$_2$Me (**259**)	+236.0
PPhEt$_2$ (**261**)	+237.6	PPh$_2$Et (**264**)	+241.1
PPh$_2$*c*-Pr (**267**)	+241.9	 (**294**)	+242.1
PPh$_2$*n*-Bu (**102**)	+243.2	PPh*n*-Pr$_2$ (**269**)	+244.0
PPh$_2$*n*-Pr (**270**)	+245.8	Ph$_2$P–NEt$_2$ (**251**)	+245.8[d]
 (**276**)	+246.0	PPh*n*-Bu$_2$ (**280**)	+248.0
PPh$_2$*c*-Bu (**278**)	+248.3	PPh$_2$(iPr) (**268**)	+248.3
P*c*-Hex$_3$ (**124**)	+249.8	PPh$_2$*c*-Hex (**285**)	+250.5
 (**60**)	+250.6[e]	PPh$_2$*c*-Pen (**286**)	+251.3
 (**295**)	+252.4	PPh$_2$*c*-Hep (**289**)	+254.5
 (**298**)	+266.5	 (**300**)	+306.2

[a]BHCA value on nitrogen; [b]pyridine nitrogen; [c]N3; [d]BHCA value on phosphorus; [e]N(sp^2).

While correlation within each of the catalyst families is very good, it is also apparent that the pyridines and phosphanes form clearly separate correlation lines. This is commonly understood as a reflection of systematically different Marcus intrinsic barriers [21] for these two classes of nucleophiles.

Trityl cation affinities (TCA)

The benzhydrylium cation is attacked by the nucleophile on a secondary carbon atom. In order to cover also electrophiles with tertiary carbon atoms as the center of attack we chose the trityl cation ($^+CPh_3$) as the third reference electrophile. In this case the steric bulkiness is increased even more than in the benzhydrylium cation. The corresponding trityl cation affinity (TCA) of a neutral Lewis base (LB) is defined as the reaction enthalpy for the dissociation process shown in equation 6 in Scheme 6. For pyridine as the Lewis base the benzhydryl cation affinity (TCA) amounts to TCA(**1**) = 82.9 kJ/mol at the MP2-5 level of theory.

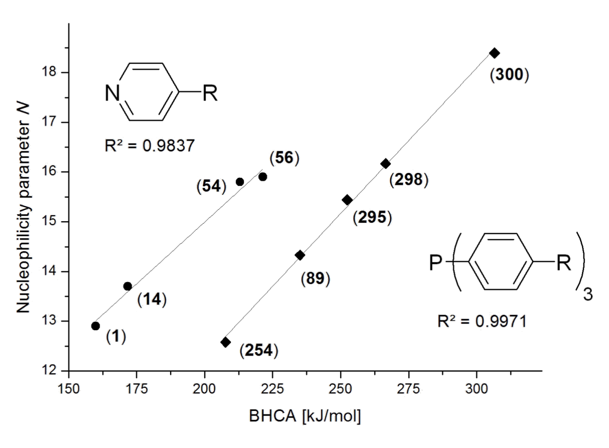
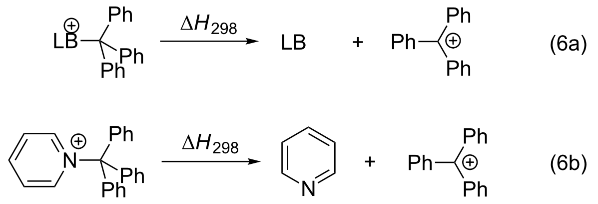


Figure 8: Comparison of BHCA values (kJ/mol) and nucleophilicity parameters *N* for sterically unbiased pyridines and phosphanes.

The TCA values of some Lewis bases commonly used in organocatalysis as well as various phosphanes and phosphites are shown in Table 10.

In general, TCA values are about 70 to 80 kJ/mol smaller than the respective BHCA values (e.g., for pyridine (**1**) or triphenylphosphane (**89**)). Moreover, some of the weakest Lewis bases considered here such as DABCO (**44**) are not sufficently basic to form covalently bound adducts with trityl cations. The TCA values calculated for these systems thus represent the reaction enthalpies for the formation of ion-dipole complexes. Aside from DABCO this is the case for **345**, **45**, and **347**. The C–N bond distances of the energetically best conformations of these complexes range from 2.8 Å to 4.0 Å. As a reference bond length the C–N distance in pyridine-trityl adduct (**1TT**), which amounts to 1.57 Å, can be used. A slightly increased C–N bond length can be found for the TCA-adduct of quinuclidine **53** (1.76 Å), which is in distinct contrast to the structurally similar DABCO. It should be added that all other electrophiles considered here form covalent adducts even with weak Lewis bases, and that the formation of ion-dipole complexes between the



Scheme 6: Reactions for the trityl cation affinity (THCA) of a Lewis base (6a) and pyridine (6b).

Table 10: TCA values of Lewis bases, ordered by increasing TCA values.

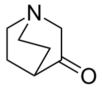
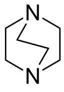
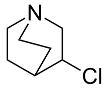
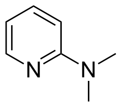
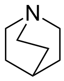
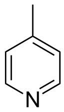
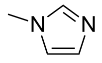
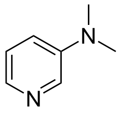
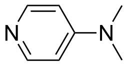
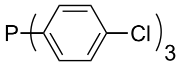
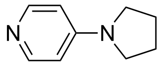
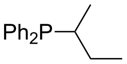
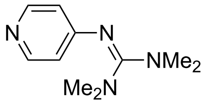
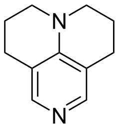
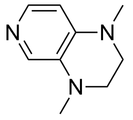
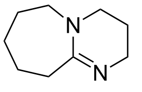
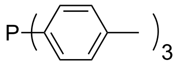
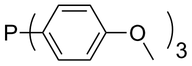
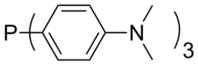
system	TCA [kJ/mol]	system	TCA [kJ/mol]
PH_3 (**343**)	+18.2	 (**345**)	+28.0
NEt_3 (**45**)	+31.6	 (**44**)	+34.1
 (**347**)	+34.9[a]	 (**346**)	+54.1[a]
$P(iPr)_3$ (**117**)	+66.6	 (**53**)	+70.8
pyridine (**1**)	+82.9	 (**14**)	+94.4
$PPh(iPr)_2$ (**279**)	+106.5	 (**24**)	+113.4[b]

Table 10: TCA values of Lewis bases, ordered by increasing TCA values. (continued)

PPh$_2$*t*-Bu (**281**)	+115.3	 (**348**)	+121.4[a]
P(OPh)$_3$ (**252**)	+121.5	P*c*-Hex$_3$ (**124**)	+129.5
PMe$_3$ (**70**)	+131.3	PEt$_3$ (**98**)	+134.2
P(OEt)$_3$ (**255**)	+134.3	 (**54**)	+134.7[a]
 (**254**)	+135.5	PPh$_2$(iPr) (**268**)	+137.5
PPhMe$_2$ (**256**)	+141.9	 (**56**)	+142.6[a]
 (**276**)	+142.8	 (**349**)	+145.9[a]
PPh$_2$*c*-Hex (**285**)	+147.4	PPh*n*-Bu$_2$ (**280**)	+148.5
PPh$_2$Et (**264**)	+149.6	PPh$_2$*n*-Bu (**102**)	+150.4
PPh$_2$Me (**259**)	+150.6	PPh$_2$*c*-Pen (**286**)	+152.5
PPh$_2$*n*-Pr (**270**)	+154.2	 (**57**)	+154.8[a]
 (**350**)	+155.6[a]	PPh$_3$ (**89**)	+158.8
 (**60**)	+160.0[c]	 (**295**)	+176.1
 (**298**)	+189.9	 (**300**)	+229.7

[a]Pyridine nitrogen; [b]N3; [c]N(sp^2).

trityl cation and weak nucleophiles are therefore true exceptions.

General comparison

The affinity data for cationic electrophiles of varying stability presented in the previous section for a large range of different Lewis bases provides the basis for a more general analysis of Lewis base affinity data. Perusal of the results obtained for pyridine (**1**) with MCA(**1**) = +518.7 kJ/mol, BHCA(**1**) = +160.0 kJ/mol, and TCA(**1**) = +82.9 kJ/mol already indicates that cation affinity values towards different carbocations span an extraordinarily large energy range. In order to find out, whether different nucleophiles respond to changes in the electrophile in a systematically comparable manner, we have selected a small group of nucleophiles of different type for a direct comparison of affinity data (Figure 9).

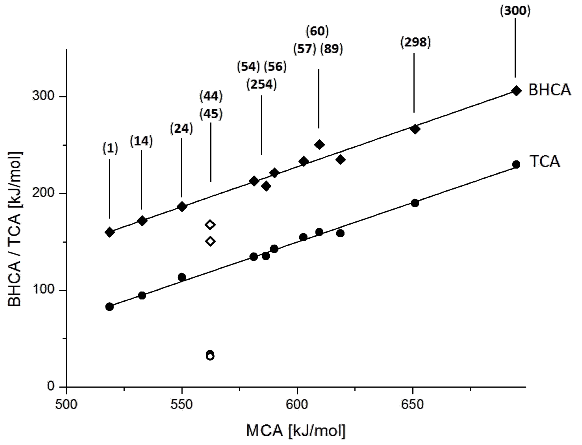


Figure 9: Comparison of MCA, BHCA, and TCA values of selected Lewis bases.

From Figure 9 it can be seen that most Lewis bases respond to the change from methyl cation (MCA) to benzhydryl cation (BHCA) and trityl cation (TCA) affinities in the same way, that is, with a large reduction of cation affinity. This is also reflected in the correlations of BHCA/TCA values with the respective MCA data for sterically unbiased systems (excluding DABCO (**44**) and triethylamine (**45**)), which can quantitatively be expressed by equations 7a and 7b given in Scheme 7.

$$\text{BHCA [kJ/mol]} = 0.826 \cdot \text{MCA} - 268.0 \quad (R^2 = 0.9757) \qquad (7a)$$

$$\text{TCA [kJ/mol]} = 0.815 \cdot \text{MCA} - 339.0 \quad (R^2 = 0.9941) \qquad (7b)$$

Scheme 7: Correlations of BHCA/TCA values with the respective MCA data for sterically unbiased systems (excluding DABCO (**44**) and triethylamine (**45**)).

The rather similar slope of both correlation lines (0.826 vs. 0.815) implies that the offset between both datasets of 268.0 − 339.0 = −71 kJ/mol is a reflection of the stability difference between the triphenylmethyl and the benzhydryl cation. This stability difference is slightly larger than that derived from theoretically calculated gas phase hydride ion affinities (63 kJ/mol) [25], or from experimentally determined hydride ion affinities in DMSO solution (38 kJ/mol) [26]. The only deviations from the general correlations in Figure 9 can be seen for bases unable to form covalently bound adducts, and for the sterically more demanding bases, which show much smaller BHCA values than should be expected on the basis of their MCA values. The much smaller Lewis basicity of DABCO (**44**) compared to that of DMAP (**54**) has also been cited in experimental studies as the prime reason for the different catalytic profile of these two catalysts [27]. The fact that no covalent adduct could be identified between the trityl cation and DABCO (**44**) also illustrates that this (kinetically very competent) nucleophile may not be able to form stable adducts with sterically demanding electrophilic substrates, thus limiting its catalytic potency for these types of substrates. This implies that for very strong Lewis bases any of the cation affinity scales can be used as a measure of Lewis basicity. For weak and sterically biased Lewis bases the reference cation has to be selected with the electrophilic substrate of the Lewis base-catalyzed process in mind.

In order to identify further differences between reactions of amines and phosphanes the pyramidalization angle *d(RNRR/RPRR)* (Figure 10), the HOMO–LUMO gap ($\Delta_{\text{HOMO–LUMO}}$), and the s/p composition of the lone pair from NBO analysis has been compiled in Table 11 for selected systems.

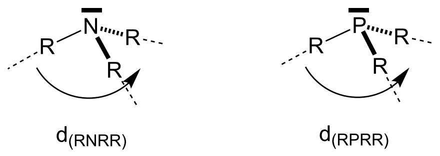


Figure 10: Scheme for the angle *d(RXRR)* measurements.

Table 11: RXRR angle, $\Delta_{\text{HOMO-LUMO}}$ and character of the lone pair of Lewis bases.

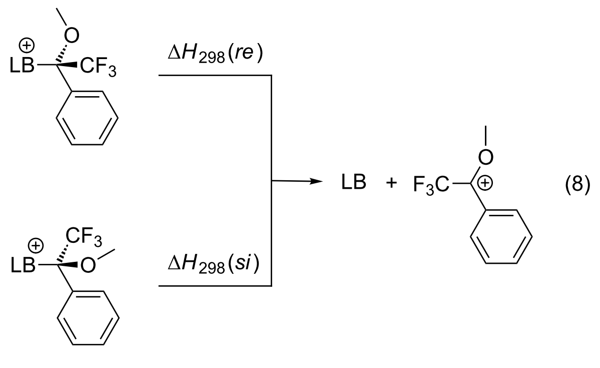
system	angle (RXRR)[a]	$\Delta_{\text{HOMO–LUMO}}$ [a.u.]	lone pair character
NH_3	112.1°	0.3463	25.3% s 75.6% p
PH_3	93.8°	0.3154	54.2% s 45.8% p
NMe_3	124.8°	0.3027	15.9% s 84.1% p
PMe_3	101.2°	0.2914	53.5% s 46.5% p
NPh_3	179.2°	0.1756	0.0% s 100.0% p
PPh_3	106.1°	0.1976	48.9% s 51.1% p

[a] X = N or P; R = C or H.

From the data above it can easily be seen that the RXRR angle in phosphanes is systematically smaller than the one in amines. This implies that phosphanes have a more pyramidal structure than amines with a comparable substitution pattern. The least pyramidal structure is found here for triphenylamine, which is almost perfectly planar at the nitrogen atom. The degree of planarity correlates well with the character of the lone pair orbital. In amines the contribution of the s orbital is decreasing with increasing size of the substituents. This is different for phosphanes, where the lone pair orbital has a systematically larger s-character, which depends only marginally on the substitution pattern. The HOMO–LUMO gap, in contrast, shows no significant correlation with the degree of pyramidalization but depends largely on the substitution pattern.

Mosher’s cation affinities (MOSCA)

For the multitude of stereoselective organocatalytic transformations the affinity of chiral Lewis bases towards chiral or prochiral carbon electrophiles may constitute part of the overall stereodifferentiating process. The potential of differentiating the faces of a prochiral electrophile can be quantified for Lewis bases through affinity numbers to a prochiral reference cation. The potential of this approach has been explored using the 1-methoxy-1-trifluoromethylbenzyl cation shown in equation 8 (Scheme 8), whose substitution pattern resembles that of Mosher's acid [28] and has thus been named "Mosher's cation" [29]. The respective "Mosher's cation affinity" values (MOSCA) for the *re* and *si* face adducts of chiral Lewis bases will not be identical, but differ depending on how much of the chiral information is relayed to the reaction center (Scheme 8).



Scheme 8: Reactions for the Mosher's cation affinity (MOSCA) of a Lewis base.

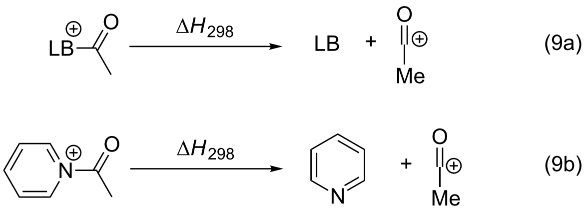
The results for selected systems relevant as Lewis base catalysts are shown in Table 12. In absolute terms it can readily be seen that MOSCA values are of similar magnitude like BHCA values.

It was recently shown that 3,4-diaminopyridines are catalytically active in a variety of group transfer reactions [9,10,30]. Chiral 3,4-diaminopyridines thus have the potential to act as catalysts in stereoselective transformations. In how far the chiral information present in Lewis bases **63**, **351**–**355** has the potential to reach the reaction center has therefore been elucidated through calculation of the respective MOSCA values. The very small difference between *re* and *si* face attack calculated for **351** indicates that stereoselectiove transformations may be difficult to achieve with this catalyst design.

In contrast, substantial *re*/*si* face differences have been obtained for Lewis bases **352** and **354**, indicating that these compounds may be useful catalysts for stereoselective transformations. This property is already well established for quinine (**356**) and quinidine (**357**), whose $\Delta\text{MOSCA}_{re\text{-}si}$ values imply the clear potential of stereoselective Lewis base-catalyzed reactions [31-40].

Acetyl cation affinities (ACA)

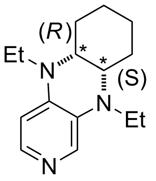
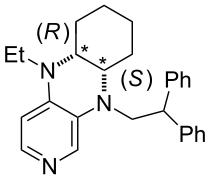
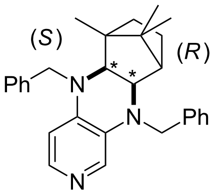
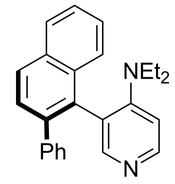
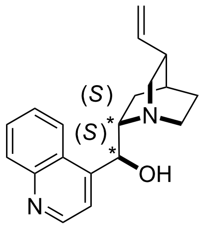
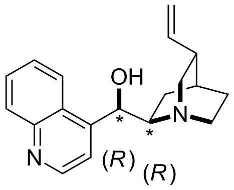
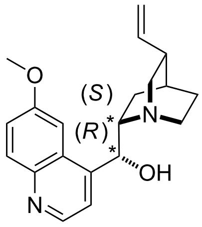
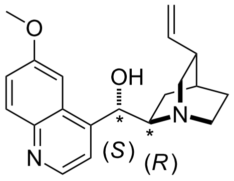
Reactions between carbon electrophiles and Lewis bases may also lead to the formation of a new common π-system. This is, for example, the case in all acyl transfer reactions catalyzed by pyridine bases which involve acetylpyridinium cations as intermediates of the catalytic cycle [7,41-46]. The acetyl cation may be considered to be a representative cationic probe for this type of situation and the corresponding acetyl cation affinities (ACA) of neutral Lewis bases thus reflect the enthalpies for the reaction shown in equation 9 in Scheme 9. Using pyridine again as a typical example, the acetyl cation affinity amounts to ACA(**1**) = +156.1 kJ/mol. Additional ACA values can be found in Table 13.



Scheme 9: Reactions for the acetyl cation affinity (ACA) of a Lewis base (9a) and pyridine (9b).

For *N,N*-dialkyl-4-aminopyridines (**54**, **369**, **370**, **373**–**377**) it is interesting to see how elongation of the alkyl substituents leads to a rapid convergence of the ACA values. The two methyl groups in **54** lead to an ACA value just 7 kJ/mol or 3% below the two octyl groups (**377**). The group of pyridines derived from the tricyclic moiety (**57**) can just slightly be modified towards higher affinity to acetyl cation (**381**, **382**). Inclusion of too many methyl groups as in **379** leads to disfavorable interactions and therefore to a decrease of the ACA value. The 2,2’-paracyclophanes (**368**, **371**, **372**, **380**) are derived from DMAP (**54**) and PPY (**56**). In the first case (**368**) the paracyclophane substituent leads to a lower affinity towards the acetyl cation. The two Lewis bases **371** and **372** show almost no influence of the paracyclophane moiety on the ACA values. Inclusion of an amide substituent as in pyridine **380** leads to a surprisingly large increase in the ACA value. This is due to the formation of close

Table 12: MOSCA values of chiral Lewis bases, ordered by increasing MCA values.

system	MOSCA [kJ/mol]	system	MOSCA [kJ/mol]
 (**63**)	255.7(*si*) 257.5(*re*) 1.8^{a}	 (**351**)	264.3(*si*) 264.2(*re*) −0.1^{a}
 (**352**)	255.5(*si*) 248.8(*re*) −6.7^{a}	 (**353**)	233.7(*si*) 235.6(*re*) 1.9^{a}
 (**354**)	188.4(*si*)^{b} 197.6(*re*)^{b} 9.2^{a}	 (**355**)	180.0(*si*)^{b} 183.7(*re*)^{b} 3.7^{a}
 (**356**)	233.7(*si*)^{b} 227.3(*re*)^{b} −6.4^{a}	 (**357**)	223.3(*si*)^{b} 231.2(*re*)^{b} 7.9^{a}

^{a}ΔMOSCA$_{re\text{-}si}$; ^{b}without PCM calculation.

Table 13: ACA values of pyridines and 4-aminopyridines, ordered by increasing ACA values.

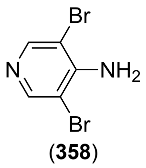
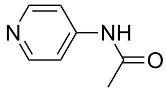
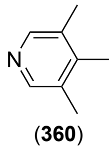
system	ACA [kJ/mol]	system	ACA [kJ/mol]
pyridine (**1**)	+156.1	 (**358**)	+164.7
 (**359**)	+175.0	 (**360**)	+182.4

Table 13: ACA values of pyridines and 4-aminopyridines, ordered by increasing ACA values. (continued)

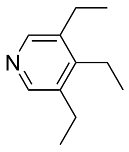
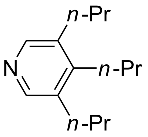
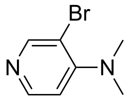
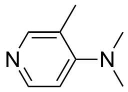
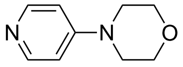
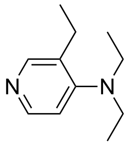
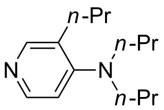
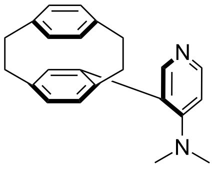
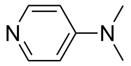
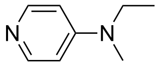
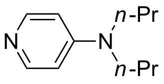
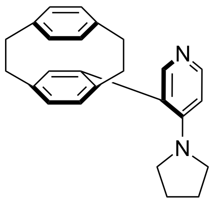
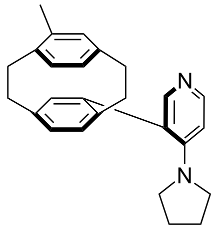
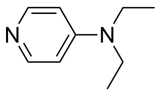
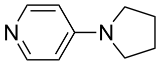
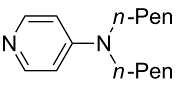
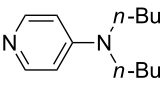
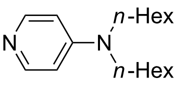
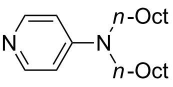
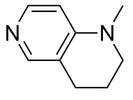
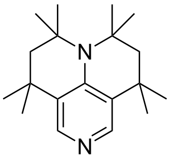
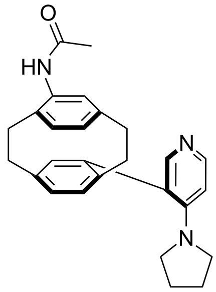
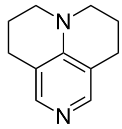
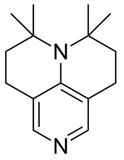
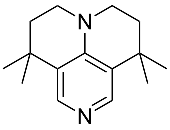
 (**361**)	+183.8	 (**362**)	+183.5
 (**363**)	+184.1	 (**364**)	+206.4
 (**365**)	+207.2	 (**366**)	+210.7
 (**367**)	+211.4	 (**368**)	+211.5
 (**54**)	+217.3	 (**369**)	+219.4
 (**370**)	+222.2	 (**371**)	+222.8
 (**372**)	+223.0	 (**373**)	+223.2
 (**56**)	+223.7	 (**374**)	+223.9^a
 (**375**)	+224.0^a	 (**376**)	+224.2^a
 (**377**)	+224.6^a	 (**378**)	+227.8

Table 13: ACA values of pyridines and 4-aminopyridines, ordered by increasing ACA values. (continued)

 (**379**)	+230.0	 (**380**)	+236.6
 (**57**)	+238.3	 (**381**)	+238.5
 (**382**)	+239.1		

[a]The conformational space used is based on the minima found for system **370** and elongation of alkyl groups using all-*trans* conformations.

contacts between the amide substituent and the acetylpyridinium moiety in the acetylated catalysts (Figure 11).

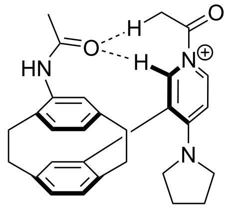


Figure 11: Structure of the acetylated pyridine **380** (**380Ac**).

3,4-Diaminopyridines have been shown to be particularly effective as acyl transfer catalysts. This is also visible in the respective ACA values (Table 14).

Most of the 3,4-diaminopyridines (**58**, **59**, **63**, **399**–**408**) show ACA values which are roughly between 235 and 243 kJ/mol. However, the introduction of a (thio)urea moiety as in **383**–**387**, **389**–**394**, and **397** lowers the ACA value by 10 to 25 kJ/mol. Annelation of an additional six-membered ring to bicyclic 3,4-diaminopyridines leads to tricyclic diaminopyridines **407**, **408**, and **410** and is accompanied by an increase in acetyl cation affinities above 240 kJ/mol. Annelation of a carbocyclic ring thus has a comparabel effect as already observed for DMAP (**54**) and its ring-extended forms **378** and **57**. This is in remarkable contrast to DMAP derivatives such as **364** carrying non-annelated alkyl substituents in 3- and/or 5-position with clearly lower ACA values. Comparison of pyridines **63** and **388** furthermore shows that alkyl groups directly attached to the amine substituents in 3- and 5-position are significantly more effective than aryl substituents in stabilizing the pyridinium ions formed through acetyl cation addition.

Photo-switchable 3,4-diaminopyridines including a diazo moiety are potentially useful as special-purpose catalysts. The azobenzene substituent itself is electron-withdrawing in nature and the calculation of ACA values can thus be used to optimize the design of these Lewis bases (Table 15).

In terms of their overall architecture the pyridine bases presented in Table 15 fall into two different categories: The first of these attaches the diazo bridge to the C8-position of the pyridoquinoxaline framework and leads to a significant drop in ACA values (e.g., in compounds **411**/**412**). In the second category, the diazo bridge connects to the 3,4-diaminopyridine amino nitrogen atoms through a phenyl spacer unit and leads to significantly larger ACA values as is best seen for compounds **418** and **426**. This latter system also displays a significant difference in ACA values for the *cis*- and *trans*-diazo isomers, indicating the potential for a photoswitchable Lewis base.

Table 14: ACA values of 3,4-diaminopyridines, ordered by increasing ACA values.

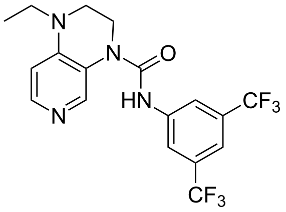
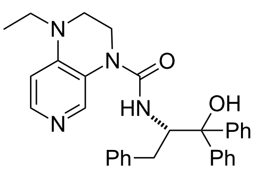
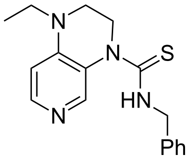
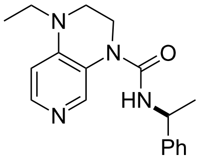
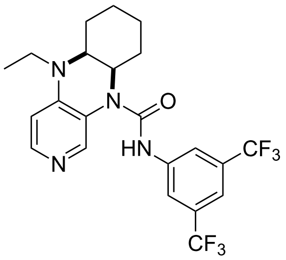
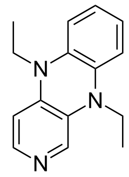
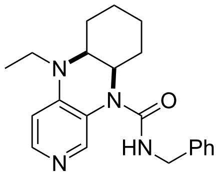
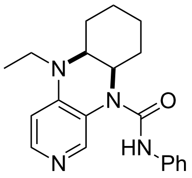
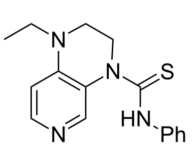
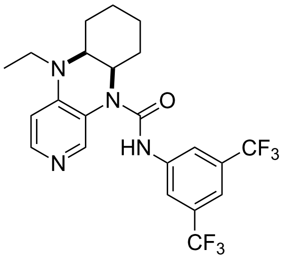
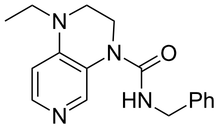
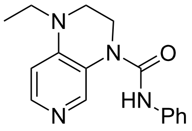
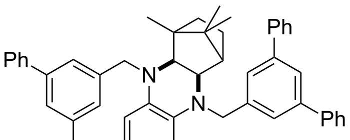
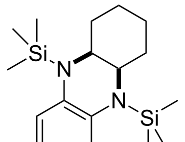
system	ACA [kJ/mol]	system	ACA [kJ/mol]
 (**383**)	+207.3	 (**384**)	+211.1
 (**385**)	+214.0	 (**386**)	+215.2
 (**387**)	+215.6	 (**388**)	+216.2
 (**389**)	+217.3	 (**390**)	+219.1
 (**391**)	+219.3	 (**392**)	+219.8
 (**393**)	+220.4	 (**394**)	+220.4
 (**395**)	+225.4	 (**396**)	+225.9

Table 14: ACA values of 3,4-diaminopyridines, ordered by increasing ACA values. (continued)

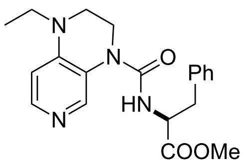
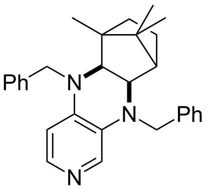
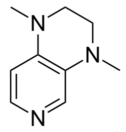
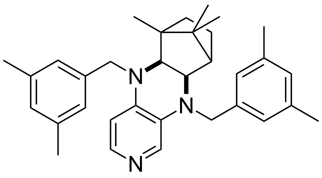
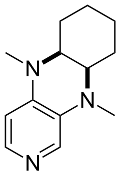
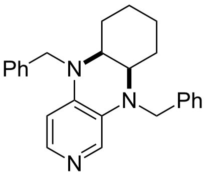
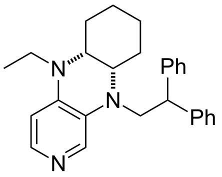
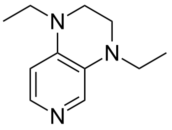
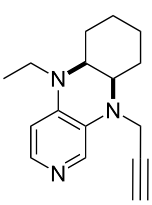
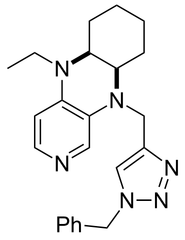
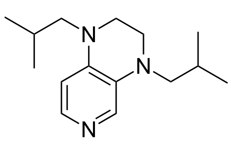
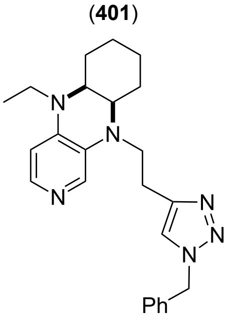
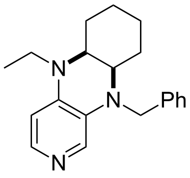
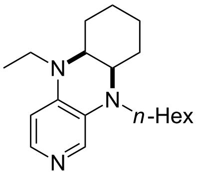
 (**397**)	+226.7	 (**352**)	+231.5
 (**350**)	+233.8	 (**398**)	+233.9
 (**59**)	+235.5	 (**399**)	+236.0
 (**351**)	+236.2	 (**58**)	+237.5
 (**400**)	+237.9	 (**401**)	+238.2
 (**402**)	+238.8	 (**403**)	+239.3
 (**404**)	+240.2	 (**405**)	+240.9

Table 14: ACA values of 3,4-diaminopyridines, ordered by increasing ACA values. (continued)

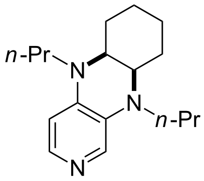
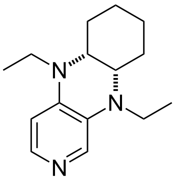
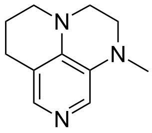
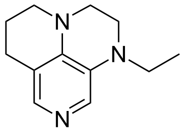
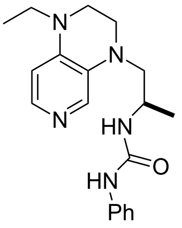
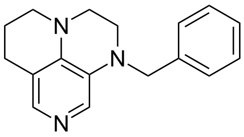
 (**406**)	+241.2	 (**63**)	+241.3
 (**407**)	+242.9	 (**408**)	+243.6
 (**409**)	+245.0	 (**410**)	+246.3

Table 15: ACA values of 3,4-diaminopyridines with diazo moiety, ordered by increasing ACA values.

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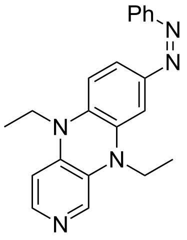
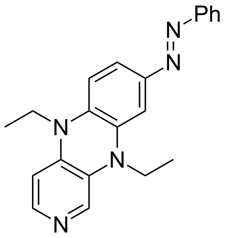
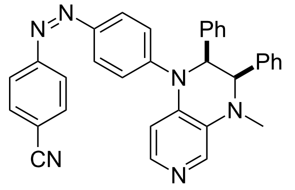
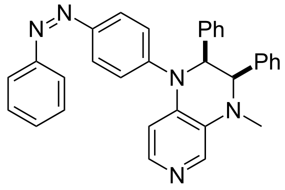
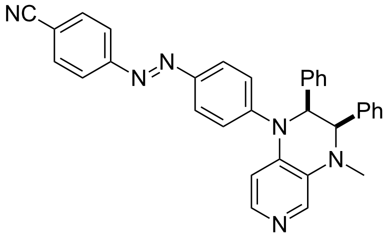
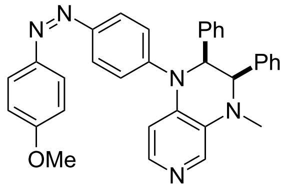
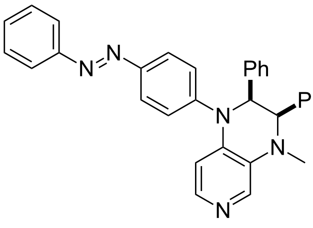
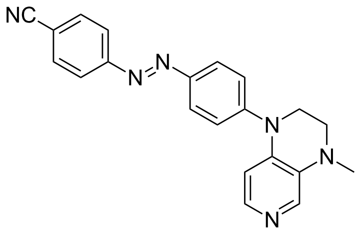
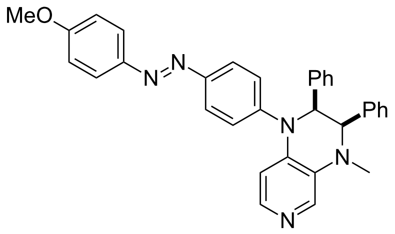
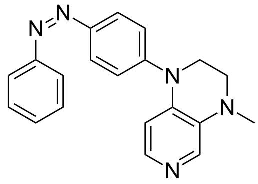
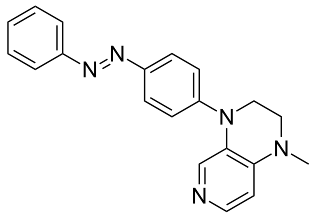
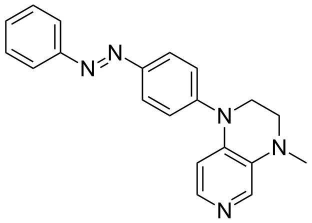
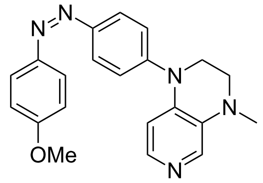
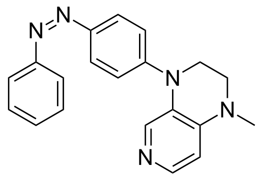
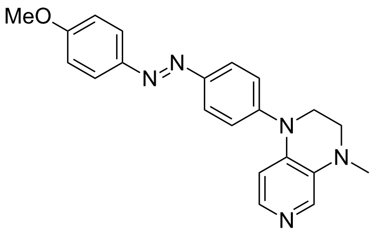
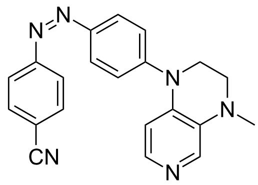
 (**411**)	+205.2	 (**412**)	+209.0
 (**413**)	+214.3	 (**414**)	+217.0
 (**415**)	+217.2	 (**416**)	+218.0

Table 15: ACA values of 3,4-diaminopyridines with diazo moiety, ordered by increasing ACA values. (continued)

 (**417**)	+219.1	 (**418**)	+220.1
 (**419**)	+221.2	 (**420**)	+223.1
 (**421**)	+223.2	 (**422**)	+223.7
 (**423**)	+223.7	 (**424**)	+225.5
 (**425**)	+225.6	 (**426**)	+225.9

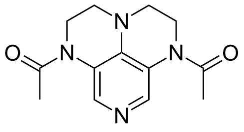
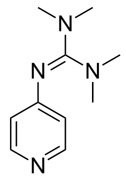
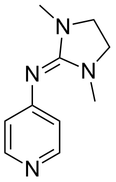
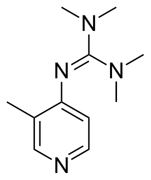
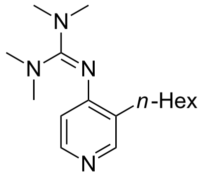
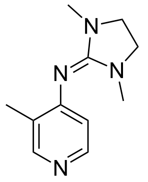
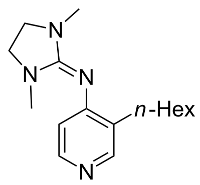
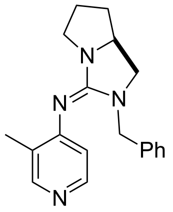
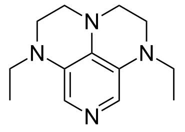
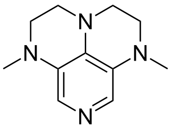
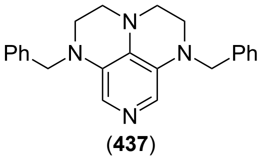
Pyridine-bases including a larger number of electron-donating substituents are highly interesting as Lewis base catalysts. ACA values for this class of compounds have been collected in Table 16.

The 3,4,5-triaminopyridines (**435**–**437**) show the highest ACA values of all examined neutral Lewis bases with affinity values ranging from 244 to 255 kJ/mol. These values parallel the impressivley high nucleophilicity parameters *N* measured recently for these compounds and indicate that carbon basicities parallel the kinetics of base addition to carbocations for this class of compounds [47]. Guanidinyl pyridines such as **433** have, in contrast, surprisingly low ACA values around 230 kJ/mol. Structural changes in the guanidine motif have only a moderate influence on the affinity to the acetyl cation.

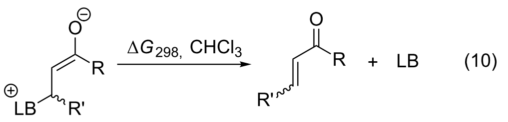
Michael-acceptor affinities (MAA)

A large number of reactions induced or catalyzed by Lewis bases involve initial or rate-limiting reaction with neutral electrophiles such as alkyl halides (substitution) or Michael accep-

Table 16: ACA values of 3,4,5-triaminopyridines and guanidines, ordered by increasing ACA values.

system	ACA [kJ/mol]	system	ACA [kJ/mol]
 (**427**)	+204.3	 (**428**)	+223.6
 (**429**)	+226.2	 (**430**)	+229.1
 (**431**)	+229.9	 (**432**)	+231.5
 (**433**)	+231.6	 (**434**)	+232.8
 (**435**)	+243.9	 (**436**)	+245.3
 (**437**)	+254.4		

tors (addition). Taking the (aza-)Morita–Baylis–Hillman reaction as an example the first step of the catalytic cycle involves the attack of N- or P-centered nucleophiles to a Michael acceptor (equation 10, Scheme 10). In contrast to the Lewis base additions to cationic electrophiles discussed above, in which a cationic substrate reacts to yield a cationic adduct, the reaction now leads from two neutral reactants to a zwitterionic adduct. Solvation energies for this latter type of species are typically significantly larger than for the neutral reactants, indicating a much larger role of solvent effects on this type of



Scheme 10: Reaction for the Michael-acceptor affinity (MAA) of a Lewis base.

process than for the cation addition reactions considered initially. The use of this type of affinity data as the guiding principle in quantitative reactivity studies will thus be restricted to the comparison of structurally and electronically similar systems.

For ethyl acrylate, methyl vinly ketone (MVK) and cyclohexenone as representative examples for synthetically useful Michael acceptors, the reaction with pyridine **63** and triphenylphosphane (**89**) is found to be significantly endergonic (Figure 12) [30].

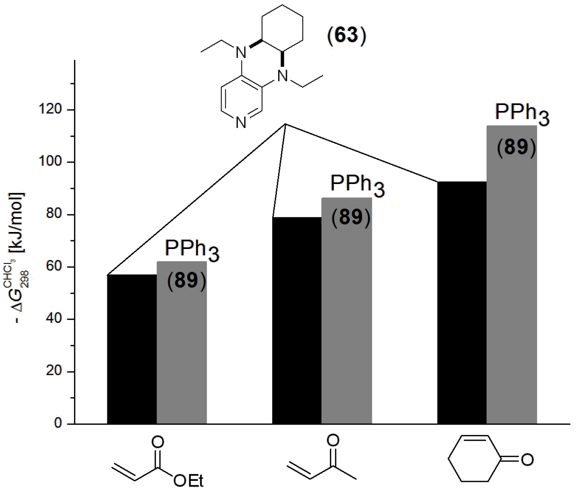


Figure 12: Inverted reaction free energies for the addition of N- and P-based Lewis bases to three different Michael acceptors.

In turn this implies that the free energy for dissociation of the zwitterionic adduct as defined in equation 10 is exergonic, which is in remarkable contrast to the energetics calculated for all cationic electrophiles above. Zwitterionic adducts formed by pyridine **63** are somewhat more stable than those formed by triphenylphosphane (**89**). These energetics parallel results obtained in azaMBH reactions of these three substrates with aromatic imines [30]. Matching the affinity data for Michael acceptors with MCA values we also find an inversion of Lewis basicity in that phosphane **89** has a larger MCA value but a lower binding affinity to the prototypical Michael acceptors selected here. The discussed results are depicted in Figure 13.

Technical aspects

It was shown recently that MCA values can be calculated with high accuracy with methods like G2, G3 or W1 [5]. Beside these expensive methods some MP2 calculations can also afford, slightly less, accurate results. For the MP2 calculations different combinations of polarization functions and diffuse functions were tested. In contrast, DFT methods such as B3LYP seem to be unsuitable for predicting MCA values in an adequate manner. A good compromise between computational effort and predictive value was found for the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) level of theory. Therefore, all results described in this publication have been obtained using this approach.

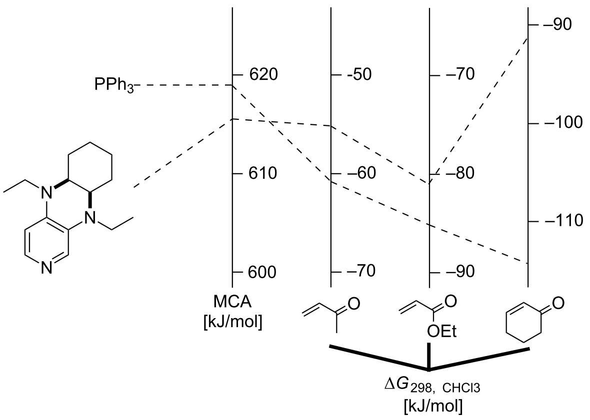
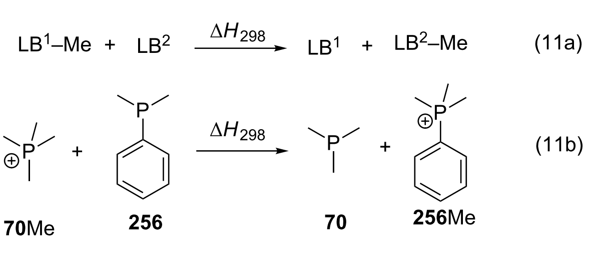


Figure 13: Correlation between MCA values and affinity values towards three different Michael acceptors.

Despite the fact that all affinity definitions in equations 1, 5, 6, 8–10 use the separate reactants as the thermochemical reference state, for most applications in synthesis and catalysis it is absolutely sufficient to consider differences in cation affinities between two different Lewis bases. These differences can most easily be expressed as cation transfer reactions between two Lewis bases as described by equation 11a (Scheme 11). Taking the methyl cation affinities of trimethylphosphane (**70**) with MCA(**70**) = 604.7 kJ/mol and dimethylphenylphosphane (**256**) with MCA(**256**) = 611.3 kJ/mol as an example we note that the latter is larger by 6.6 kJ/mol at the G3 level of theory (equation 11b, Scheme 11). A slightly lower value of 4.3 kJ/mol is obtained with the MP2-5 method used throughout this manuscript (Table 2 and Table 6).



Scheme 11: (a) General definition for a methyl cation transfer reaction between Lewis bases LB^1 and LB^2, and (b) methyl cation exchange between trimethylphosphane (**70**) and dimethylphenylphosphane (**256**).

The enthalpy for the methyl cation transfer reaction between these two species as expressed in equation 11b amounts to −6.6 kJ/mol, the negative sign indicating that the MCA of phosphane **256** is larger than that of phosphane **70**. Under the condition that the two Lewis bases involved in cation exchange are as similar as the two phosphanes **70** and **256**, the overall transformation represents an isodesmic reaction, in which the numbers of bonds of particular type are identical (at least formally) on both sides. The calculation of thermochemical data for isodesmic reactions is usually more accurate than for other defining equations due to the cancellation of numerous errors. Additional practical challenges in calculating accurate affinity numbers concern the often large conformational space of Lewis bases and their cationic adducts. This can easily be demonstrated for P*n*-Bu$_3$ (**120**) and its methylated form P$^+$Me(*n*-Bu)$_3$ (**120**Me). Depending on the strategy and the programs used for conformational searches, both species will have hundreds of conformations. Using systematic searches in combination with specifically selected force fields leads to 665 (**120**) and 601 (**120**Me) conformations. Some of these conformations are eliminated on geometry optimizations at DFT level, but the final low-energy window of 10 kJ/mol for "good" structures still contains 139 (**120**) and 94 (**120**Me) structures (after the elimination of mirror-image conformers). A reliable calculation of Boltzmann-averaged thermochemical data and the identification of the best conformers thus requires frequency calculations and MP2 single point calculations for all of these structures. It should be added that the energetically best structure varies on moving from E_{tot}(DFT) to H_{298}(DFT) to H_{298}(MP2). At this last level of theory two close-lying all-*trans* conformations can be found for P*n*-Bu$_3$ (**120**) as depicted in Figure 14.

For the sake of clarity only the seven best conformations are shown in Figure 15.

The eventually best conformation **120**_1 is less favorable by 3 kJ/mol as compared to conformation **120**_2 when using total energies (E_{tot}) or enthalpies at 298 K (H_{298}) obtained at B98/6-31G(d) level of theory. Moving to the MP2(FC)/6-31+G(2d,p)//B98/6-31G(d) energies or enthalpies the difference shrinks to 0.3 kJ/mol, now with **120**_1 as the more stable structure. The reduction of energy differences on moving from DFT to MP2

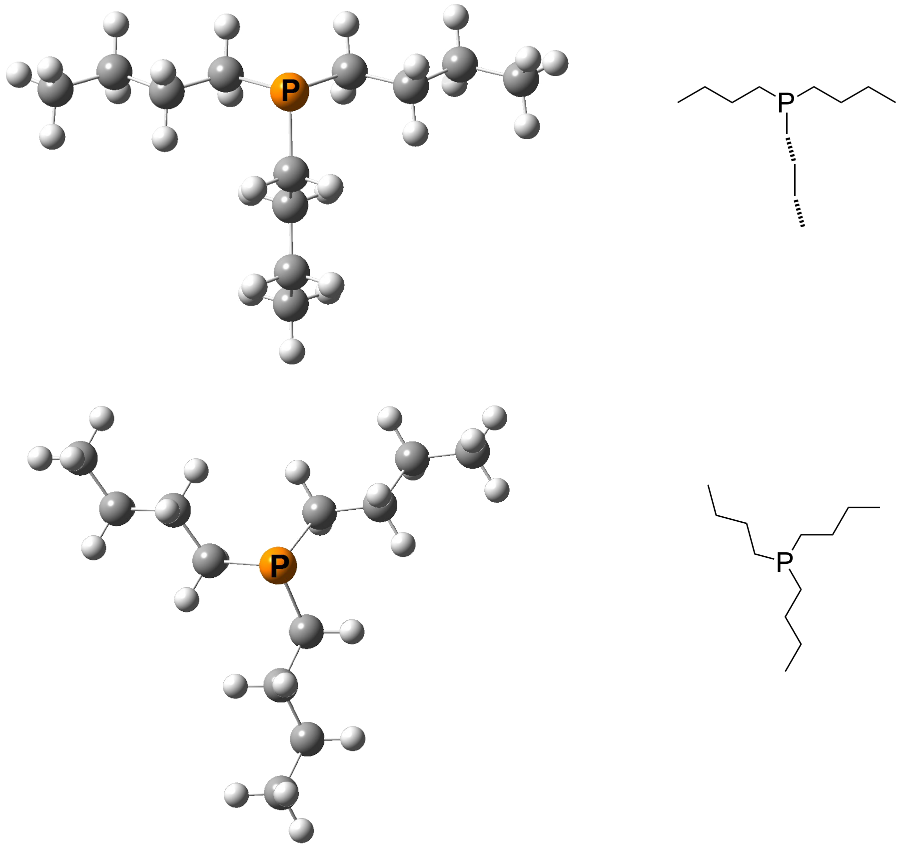


Figure 14: The energetically best conformations of P*n*-Bu$_3$ (**120**_1, top) and (**120**_2, bottom).

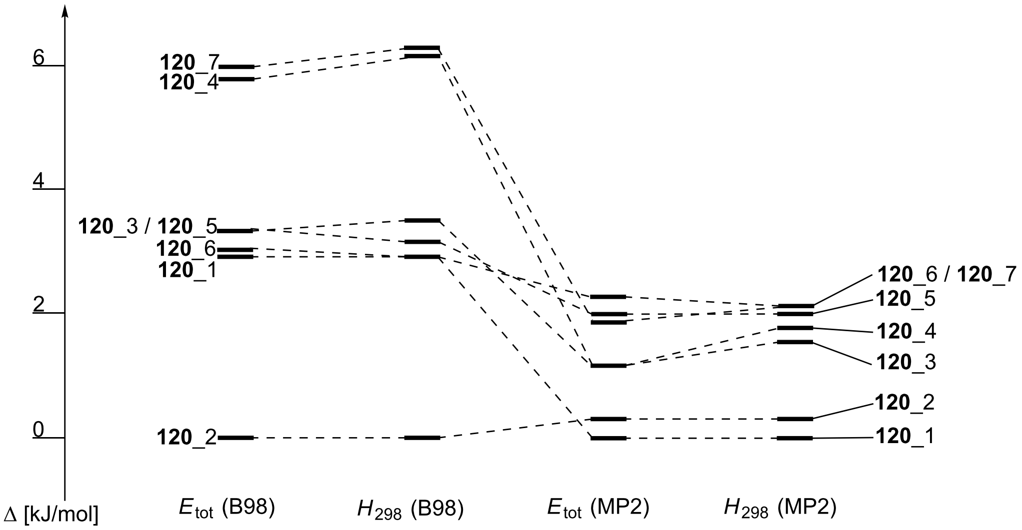


Figure 15: Relative order of the conformations **120**_1 to **120**_7 depending on the level of theory.

single point energies is a rather general phenomenon observed in these studies. This implies that the definition of, for example, an energy window of 10 kJ/mol for conformational selection has different implications at these different levels of theory. Conformational preferences can, of course, also be quite different for the neutral Lewis base and its methyl cation adduct. For phosphane **120** we find that conformation **120**Me_1 (Figure 16) has the lowest E_{tot} on both levels of theory as well as the lowest H_{298}.

All calculated MCA values employ Boltzmann-averaging over all available conformations within a 15 kJ/mol (10 kJ/mol for P*n*-Bu$_3$ (**120**)) energy window. The Boltzmann-averaged MCA value of P*n*-Bu$_3$ (**120**) thus amounts to +639.5 kJ/mol. Taking only the energetically best conformations in each case (**120** and **120**Me) into account, the MCA value amounts to +639.2 kJ/mol. For this particular system the Boltzmann averaging procedure thus offers no notable benefit for the calculation of MCA values, but this can change depending on the systems under study. The most relevant role of extensive conformational searches is therefore that of the identification of the best conformation of the Lewis base as well as the cationic adduct (LB$^+$-methyl, LB$^+$-benzhydryl, LB$^+$-trityl, LB$^+$-MOSCA, LB$^+$-acetyl). Unfortunately, the actual conformational rank depends on the used level of theory, especially if dispersion interactions play an important role. This problem will gain more relevance when the steric demand is large. In the present study it can be neglected due to the use of MP2 single point calculations and the fact that, even in the case of TCA (trityl cation affinity) values as the sterically most demanding electrophile, the important minima could be found at the B98 level of theory.

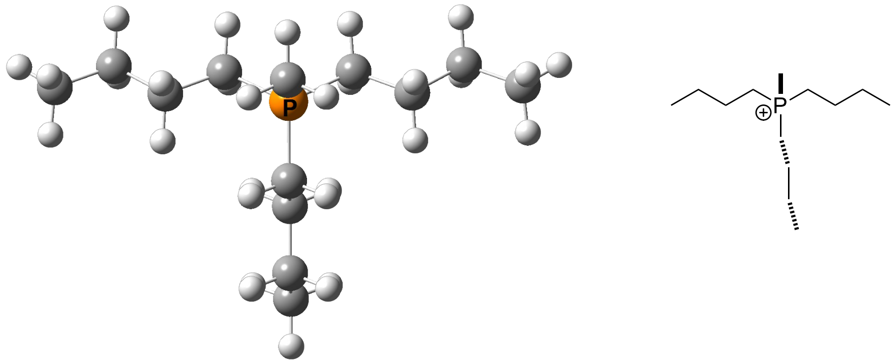


Figure 16: The structure of the energetically best conformations of **120**Me.

Conclusion

Affinity data towards selected electrophiles provide the means to quantify Lewis bases with respect to their carbon basicity. This complements the limited amount of experimental affinity data and provides a quantitative guideline in catalyst development projects in which the addition of Lewis bases to carbon electrophiles represents the key step of the catalytic cycle.

Supporting Information

Supporting Information File 1

File Typ: PDF.
Energies, enthalpies and geometries for all Lewis bases and their respective adducts with various electrophiles.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-163-S1.pdf]

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Synthesis of chiral sulfoximine-based thioureas and their application in asymmetric organocatalysis

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Full Research Paper

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Abstract

For the first time, chiral sulfoximine derivatives have been applied as asymmetric organocatalysts. In combination with a thiourea-type backbone the sulfonimidoyl moiety leads to organocatalysts showing good reactivity in the catalytic desymmetrization of a cyclic *meso*-anhydride and moderate enantioselectivity in the catalytic asymmetric Biginelli reaction. Straightforward synthetic routes provide the newly designed thiourea-sulfoximine catalysts in high overall yields without affecting the stereohomogeneity of the sulfur-containing core fragment.

Introduction

Since their discovery in the middle of the last century, sulfoximines **1** (Figure 1) represent an important compound class among the comprehensive group of organosulfur reagents [1-4].

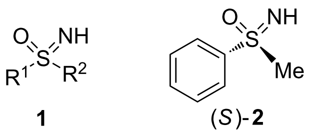


Figure 1: General structure of sulfoximines **1** and one of the enantiomers of *S*-methyl-*S*-phenylsulfoximine ((*S*)-**2**) used in this study.

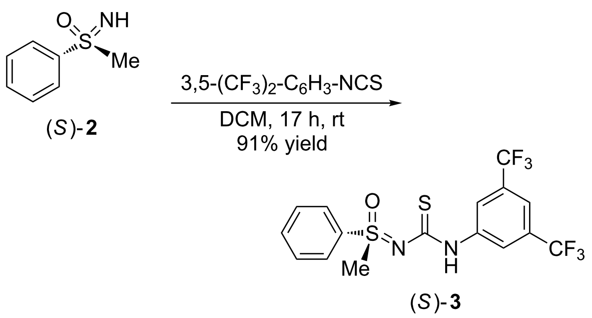
Being monoaza analogs of sulfones, sulfoximines have fascinated researchers from both academia and industry. Because of their interesting chemical properties and the biological activities found for several derivatives, the use of sulfoximines has been explored in numerous applications. For instance, in agricultural chemistry it was discovered that sulfoximines can improve plant growth or act as insecticides in crop protection [5-9]. Further exemplary contributions come from medicinal chemistry where sulfoximines show potential as enzyme inhibitors [10-14], and from materials science where they were evaluated as functional building blocks [15]. In addition, sulfoximines are most present in synthetic organic chemistry for various reasons and recent findings include their use as fluoromethylation reagents, as fluorophores or as directing groups [16-19]. Two quality characteristics make them particularly attractive for asymmetric synthesis: 1) The stereogenic sulfur atom which is stable towards many reaction conditions, and 2) the ease of functionalization at the adjacent nitrogen and carbon atoms which allows a great structural diversity of the sulfoximine motif. Hence, optically active compounds based on **2** have been utilized in the synthesis of pseudopeptides [20-24], and they have found widespread application in auxiliary-assisted diastereoselective transformations or as chiral ligands in enantioselective metal catalysis [25-33]. With respect to the latter field we have recently demonstrated that various ligands bearing a sulfonimidoyl moiety lead to excellent stereoselectivities in transition metal-catalyzed hydrogenations and carbon–carbon bond formations [34-36].

During the past decade, asymmetric organocatalysis had a tremendous impact on synthetic organic chemistry [37-41]. Yet, this field of research continues to grow, and the quest for new organic molecules which efficiently catalyze reactions in a highly enantioselective manner has no end in sight. In this context, thiourea-based organocatalysts have caught significant attention due to their ability to activate substrates through hydrogen-bonding [42-47]. Usually, these chiral thioureas are classified into several categories, for example, being mono- or bis-thioureas. Furthermore, they can be mono- or bifunctional with variably weak amine (primary, secondary, tertiary) or amide groups attached. Figure 2 illustrates a few selected examples of the aforementioned chiral thioureas which have successfully been applied in organic transformations with hydrogen bond accepting substrates.

Recently, we reported the enantioselective ring opening of cyclic *meso*-anhydrides and asymmetric Michael additions of 1,3-dicarbonyl compounds to nitroalkenes with thiourea-based organocatalysts [48,49]. Based on those studies and in the light of our long-standing interest in utilizing chiral sulfoximines in stereoselective catalytic reactions, we wondered about a molecular combination of the two successfully applied entities, thioureas and sulfoximines. To the best of our knowledge, such compounds have never been reported and thiourea(-like) catalysts with S-stereogenic sulfonimidoyl substituents are unknown. Herein, we present our first results concerning synthetic approaches towards such molecules and describe preliminary studies of two applications in asymmetric organocatalysis.

Results and Discussion

Our investigations began with a very straightforward approach: Enantiopure (*S*)-*S*-methyl-*S*-phenylsulfoximine [(*S*)-**2**] was added to 3,5-bis(trifluoromethyl)phenyl isothiocyanate to provide product (*S*)-**3** (Scheme 1).



Scheme 1: Synthesis of compound (*S*)-**3**.

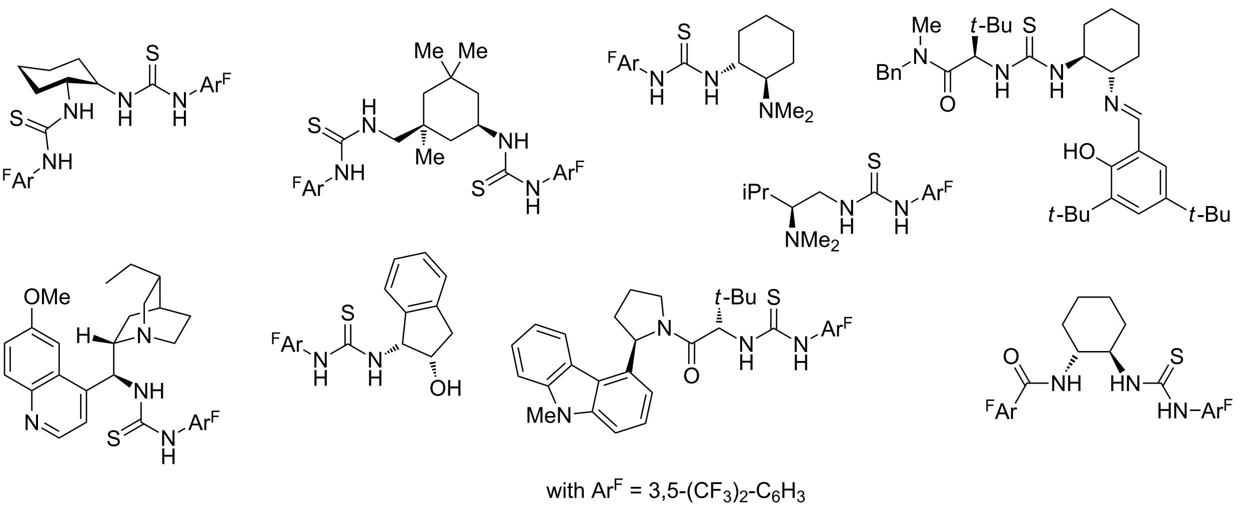


Figure 2: Structures of chiral mono- and bifunctional (bis-)thioureas that have been used as organocatalysts.

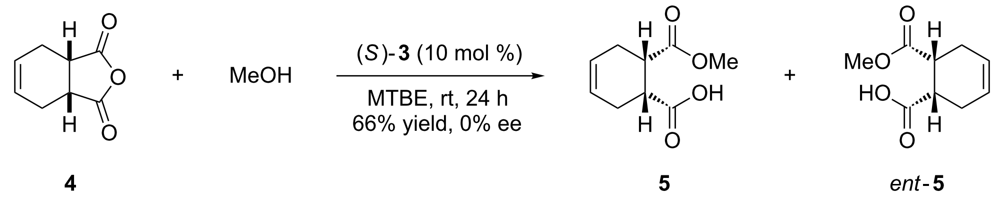
This kind of addition was first described by Wehr in 1965 who allowed a number of isothiocyanates to react with dimethylsulfoximine [50]. The chemistry of the resulting thiourea-like compounds, however, has remained rather unexplored until now. Only two patents from Dow Agrosciences report syntheses of related structures, their use as intermediate products, and their insecticidal activity [51,52]. Furthermore, only achiral or racemic sulfoximines have been applied, and the reactions were performed at elevated temperatures, such as 80 °C, or in a steam bath. The protocol introduced here is most simple: After addition of the isothiocyanate to a solution of sulfoximine (*S*)-**2** in dichloromomethane (DCM) the mixture was stirred at room temperature, and after a few hours, (*S*)-**3** started to precipitate. Removal of the solvent and washing of the product with *n*-pentane gave analytically pure (*S*)-**3** in 91% yield.

Although not capable of double hydrogen bonding [53], we wondered about the possible catalytic activity of (*S*)-**3**. Because it was known for chiral bifunctional amine-based sulfonamides that two hydrogen bond donors were not strictly required in the enantioselective organocatalytic ring opening of *meso*-anhydrides [48,54], this particular transformation was chosen as initial test reaction. Cyclic anhydride **4** served as starting material for a methanolysis in the presence of a catalytic amount of enantiopure (*S*)-**3** (Scheme 2). To our delight, the use of a combination of 10 equiv of methanol and 10 mol % of (*S*)-**3** in methyl *tert*-butyl ether (MTBE) at room temperature furnished the desired products, hemiesters **5** and *ent*-**5**, in good yield (66%) within 24 h. Disappointingly, however, the product was racemic.

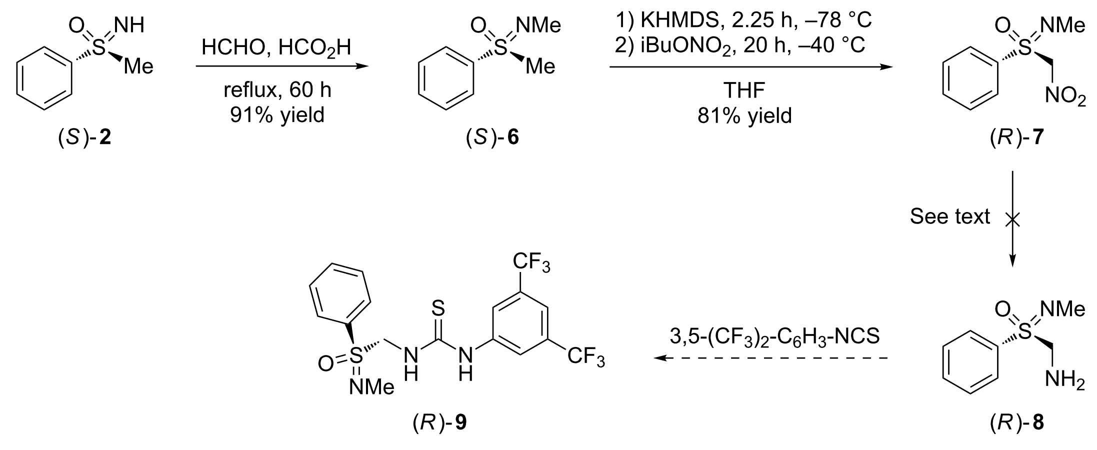
In general, two concomitant events are discussed for bifunctional organocatalysts such as amino group-containing sulfonamides or thioureas: One is the activation of the anhydride carbonyl group by hydrogen bonding to the thiourea or sulfonamide unit, and the second relates to the activation of the alcohol by the basic nitrogen of the amine. Which effect dominates in the case of (*S*)-**3** – a carbonyl activation by a single hydrogen bond or an enhancement of the alcohol activity by the weakly basic sulfoximine nitrogen – remains to be elucidated. An organocatalytic activity of thiourea(-like) (*S*)-**3**, however, was clearly demonstrated.

Next, our attention was focused on sulfoximine-based thioureas with the potential of double hydrogen bond donation. Two structural alternatives were envisaged as represented by compounds (*R*)-**9** and (*S*)-**12**. In the first, the stereogenic sulfur of the sulfonimidoyl moiety was linked to the thiourea core by a methylene group, which originated from the methyl substituent of (*S*)-**2**. In the second, a linker connected the thiourea backbone with the sulfonimidoyl nitrogen. Preference was given to the first strategy, because in structures such as (*R*)-**9** the stereogenic center was rather close to the thiourea hydrogen bridge binding site. Scheme 3 summarizes our intended preparative approach towards (*R*)-**9** via *N*-methyl-α-aminosulfoximine (*R*)-**8**, which unfortunately, remained unsuccessful.

Heating of (*S*)-**2** with 2 equiv of formaldehyde in formic acid under Eschweiler–Clarke conditions led to *N*-methylated sulfoximine (*S*)-**6** in 91% yield [55,56]. The α-nitro group was introduced under conditions reported by Wade [57]. Thus, deprotonation of (*S*)-**6** in tetrahydrofuran (THF) with potassium bis(trimethylsilyl)amide (KHMDS) at −78 °C and trapping the resulting carbanion with isobutyl nitrate at −40 °C afforded nitrosulfoximine (*R*)-**7** in 81% yield. The product proved rather stable at low temperature and could be stored in the fridge without decomposition for several months. All attempts, however, to reduce the α-nitro group of (*R*)-**7** to the corresponding amino substituent (as in (*R*)-**8**) failed [58]. None of the reductive conditions, which included (1) hydrogenation over palladium/charcoal, (2) applying samarium diiodide with methanol as proton source, and (3) using a combination of zinc powder with hydrochloric acid or calcium chloride in aqueous ethanol allowed the isolation of α-aminosulfoximine (*R*)-**8**. In all cases the starting material was fully consumed and degraded. As decomposition products *N*-methylbenzenesulfinamide and diphenyl disulfide were identified and isolated. Hence, α-aminosulfoximine (*R*)-**8** could not be obtained, and the synthesis of the sulfoximine-based thiourea (*R*)-**9** had to remain uncompleted.



Scheme 2: Organocatalytic desymmetrization of the cyclic anhydride **4** with (*S*)-**3**.



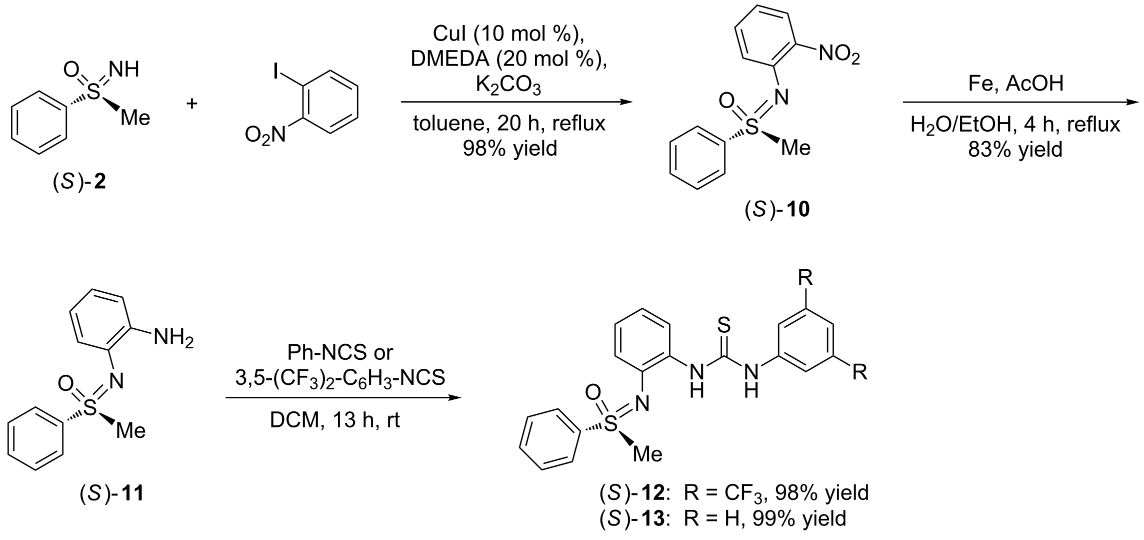
Scheme 3: Attempted synthesis of sulfonimidoyl-substituted thiourea (*R*)-**9**.

Next, the second strategy was approached, and thiourea/sulfoximine derivatives (*S*)-**9** and (*S*)-**13** became synthetic targets (Scheme 4). In both the stereogenic fragments are linked to the thiourea core via the sulfonimidoyl nitrogen. They differ in their aryl substitution pattern.

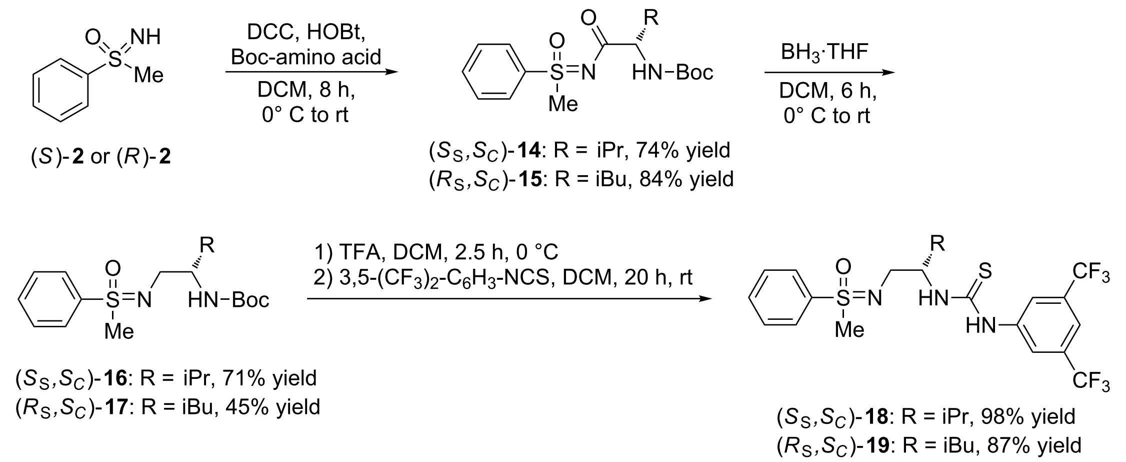
Copper-catalyzed arylation of (*S*)-**2** with 2-iodonitrobenzene gave rise to coupling product (*S*)-**10** in excellent yield (98%). After subsequent reduction of the aromatic nitro group to give aniline (*S*)-**11** in 83% yield [35,59,60], two isothiocyanates, namely phenyl isothiocyanate and 3,5-bis(trifluoromethyl)phenyl isothiocyanate, were added. Both thiourea formations went very well, and the desired products (*S*)-**12** and (*S*)-**13** were obtained in almost quantitative yields (98% and 99%, respectively).

In (*S*)-**12** and (*S*)-**13** the 1,2-benzene linker connects both functional groups – the stereogenic sulfonimidoyl group and the thiourea core – in a rather rigid manner. In order to allow a higher degree of conformational flexibility and with the goal to determine the effects of structural rigidity and the presence of additional stereogenic centers, alternative molecules with substituted ethylene linkers ((S_S,S_C)-**18** and (R_S,S_C)-**19**) were designed. Their syntheses are outlined in Scheme 5, which also underlines the value of the highly modular preparative approach towards such compounds leading to a variety of molecules by using closely related synthetic protocols.

In the syntheses of (S_S,S_C)-**18** and (R_S,S_C)-**19** we benefited from our expertise in preparing sulfoximine-based pseudopeptides [20,21]. Hence, the reaction of (*S*)-**2** with *N*-Boc protected



Scheme 4: Synthesis of the sulfonimidoyl-containing thioureas (*S*)-**12** and (*S*)-**13**.



Scheme 5: Syntheses of ethylene-linked sulfonimidoyl-containing thioureas (*S*$_S$,*S*$_C$)-**18** and (*R*$_S$,*S*$_C$)-**19**.

L-valine, *N*,*N*'-dicyclohexylcarbodiimide (DCC) and hydroxybenzotriazole (HOBt) provided (homochiral) (*S*$_S$,*S*$_C$)-**14** in good yield (74%). Already at this early stage we wondered, which of the two stereogenic centers in the resulting thioureas – the one at the sulfur atom or the one stemming from the amino acid – would determine the absolute configuration of the catalysis products. For this reason, a heterochiral product was prepared by coupling (*R*)-**2** (the mirror image of the previously applied sulfoximine) with *N*-Boc protected L-leucine to give (*R*$_S$,*S*$_C$)-**15** (84% yield). Reduction of the two *N*-acylated sulfoxmines (*S*$_S$,*S*$_C$)-**14** and (*R*$_S$,*S*$_C$)-**15** with borane-THF complex led to removal of the carbonyl groups and established the desired substituted ethylene bridges in (*S*$_S$,*S*$_C$)-**16** and (*R*$_S$,*S*$_C$)-**17** (71% and 45% yield, respectively). Subsequently, the *N*-Boc groups were smoothly cleaved upon treatment with trifluoroacetic acid (TFA), and for both substrates full conversion was observed after 2.5 h. An aqueous work-up followed by the addition of 3,5-bis(trifluoromethyl)phenyl isothiocyanate to each crude primary amine completed the syntheses of ethylene-linked sulfonimidoyl-containing thioureas (*S*$_S$,*S*$_C$)-**18** and (*R*$_S$,*S*$_C$)-**19** providing them in very good yields (98% and 87%, respectively) over two steps.

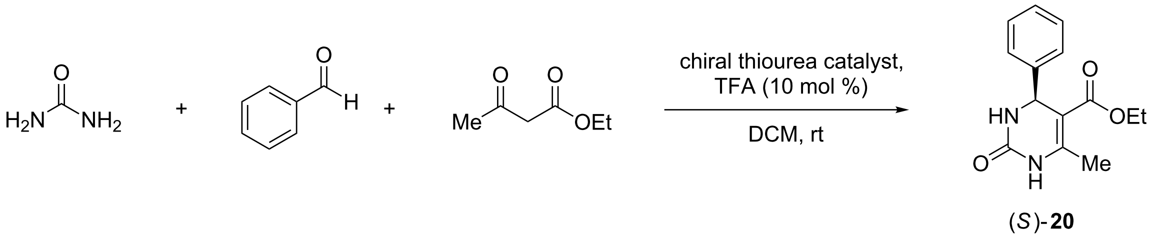
One representative of each class was briefly tested in the desymmetrization of anhydride **4**. Under the conditions described above for organocatalyst (*S*)-**3** two catalyses were performed with (*S*)-**12** (10 mol %) and (*R*$_S$,*S*$_C$)-**19** (5 mol %). Whereas benzene-bridged sulfonimidoyl-containing thiourea (*S*)-**12** provided the product (**5**/*ent*-**5**) in a comparable yield (67%) as (*S*)-**3**, the reactivity of (*R*$_S$,*S*$_C$)-**19** was remarkably higher. Even though in the reaction with (*R*$_S$,*S*$_C$)-**19** the catalyst loading was lower, the product was isolated in a better yield (81%) under identical conditions. Unfortunately, both catalyses led to racemic hemiesters (**5**/*ent*-**5**). Apparently, both thioureas proved inappropriate for this reaction, and no further efforts were made to improve the anhydride desymmetrization with these types of organocatalysts.

Next, the catalysis screening was focused on Biginelli reactions, which provide access to dihydropyrimidines by three-component condensations of aldehydes, urea-type substrates and enolisable carbonyl compounds. Because of the pharmacological relevance of the products, considerable research has been directed towards asymmetric approaches of these inherently chiral heterocycles [61-63]. Until recently, enantioenriched dihydropyrimidines could only be obtained by special resolution methods which were not generally applicable. The search for a truly catalytic asymmetric Biginelli reaction with high enantiocontrol has proven very challenging for a long time and useful protocols have just recently been developed. They involve both metal catalysis [64,65] as well as organocatalysis. In the latter field, chiral phosphoric acids [66,67], bicyclic diamines [68], bifunctional thioureas [69], proline ester salts [70], pyrrolidinyl tetrazoles [71], and a quinine-derived amine [72] were reported to catalyze the condensation reaction in an asymmetric fashion.

Using a slightly modified procedure of the thiourea-catalyzed Biginelli reaction developed by Miao and Chen [69], we chose the condensation between urea, benzaldehyde (1.5 equiv), and ethyl acetoacetate (3 equiv) to give dihydropyrimidine **20** (Table 1) as test reaction. As catalysts, substoichiometric quantities of the sulfonimidoyl-containing thioureas in combination with 10 mol % of trifluoroacetic acid (TFA) were applied. The results are summarized in Table 1.

The experiment with 10 mol % of chiral organocatalyst (*S*)-**3** served as starting point (Table 1, entry 1). The low product

Table 1: Evaluation of the sulfonimidoyl-containing thiourea organocatalysts in the asymmetric Biginelli reaction to afford scalemic dihydropyrimidinone (*S*)-**20**.



entry	chiral thiourea	catalyst loading (mol %)/ concentration (mol/L)	time (d)	substrate concentration (mol/L)[a]	yield (%)	er (%)[b]
1	(*S*)-**3**	10/0.025	3	0.25	28	50:50
2	(S_S,S_C)-**18**	10/0.025	3	0.25	32	50:50
3	(R_S,S_C)-**19**	10/0.025	3	0.25	30	50:50
4	(*S*)-**12**	10/0.025	3	0.25	42	58:42
5	(*S*)-**13**	10/0.025	3	0.25	21	57:43
6	(*S*)-**12**	10/0.025	5	0.25	89	58:42
7	(*S*)-**13**	10/0.025	5	0.25	40	57:43
8	(*S*)-**12**	20/0.05	5	0.25	90	59:41
9	(*S*)-**13**	20/0.05	5	0.25	42	57:43
10	(*S*)-**12**	10/0.0025	5	0.025	92	72:28
11	(*S*)-**12**	1/0.0025	5	0.25	53	51:49

[a]With respect to urea. [b]Determined by HPLC analysis with a chiral stationary phase.

yield (28%) even after a long reaction time (3 days) revealed the insufficient catalytic activity of this thiourea derivative. Furthermore, product **20** was racemic. Analogous results were observed with the two ethylene-bridged sulfonimidoyl-containing thioureas (S_S,S_C)-**18** and (R_S,S_C)-**19** when the catalyses were conducted under identical conditions (Table 1, entries 2 and 3). Racemic dihydropyrimidinone **20** was obtained in 32% and 30% yields, respectively. Next, we focused on the application of thioureas (*S*)-**12** and (*S*)-**13** having a more rigid benzene linker (Table 1, entries 4 and 5). Although the yields were only moderate (42% and 21%, respectively), we delightfully noted that product **20** was enantioenriched for the first time (with the *S*-enantiomer being formed in preference). With enantiomer ratios of 58:42 and 57:43 the enantioselectivities were still low, but we envisaged that improvements were possible by catalyst structure optimizations and reaction condition adjustments. Apparently, the substituents at the 3,5-positions of the phenyl rings at the thiourea moieties (CF_3 versus H) had only a marginal effect on the stereoselectivity of the Biginelli reaction. However, they affected the catalyst activity as indicated by the doubled yield in the catalysis with (*S*)-**12** compared to the one with (*S*)-**13** (42% versus 21%). This increase in yield might have been because of a higher acidity of (*S*)-**12** due to the presence of the two CF_3 substituents on the thiourea aryl [73]. Prolonging the reaction time from 3 to 5 days raised the yields (Table 1, entries 6 and 7), and now, for example, the catalysis with (*S*)-**12** gave the product in 89% yield (Table 1, entry 6). The enantiomer ratios remained unaffected. Increasing the catalyst loading from 10 to 20 mol % had essentially no effect on both yield and enantioselectivity (Table 1, entries 8 and 9).

In previous studies it was found that the enantioselectivity in some thiourea-catalyzed reactions was dependent on the concentration of the substrates and that in several cases the enantiomeric excess could significantly be improved by dilution [48,74-76]. This effect was attributed to the formation of less active aggregates by thioureas self-association at high concentrations resulting in lower enantioselectivities [77]. Interestingly, a dilution effect was also observed in our study. Thus, changing the molar substrate (urea) concentration from 0.25 mol/L to 0.025 mol/L caused a distinct improvement of the enantiomeric excess and the enantiomer ratio of the product **20** raised from 58:42 to 72:28 (Table 1, entry 6 vs entry 10). In addition, product **20** was isolated in a slightly better yield (92%). The attempt to reduce the catalyst loading from 10 mol % to 1 mol % (while retaining its concentration at 0.0025 mol/L; Table 1, entry 10 vs entry 11) remained unsuccessful resulting in 53% of **20** with an er of only 51:49. Probably, the reaction path was affected by the 10-fold higher substrate concentration, which led to this unsatisfying enantioselectivity.

These results allow drawing a few preliminary conclusions related to the structural requirements of the chiral sulfonimidoyl-containing thioureas for achieving enantiocontrol in subsequent asymmetric catalysis studies. For example, it is noteworthy that compared to most other organocatalysts of the thiourea-type, which commonly have the stereogenic center directly attached to one of the NH groups of the thiourea moiety (Figure 2), the nearest stereogenic center in (*S*)-**12**, (*S*)-**13**, (S_S,S_C)-**18** and (R_S,S_C)-**19** is relatively remote from the thiourea core, which most likely serves as binding site for the substrate. Nevertheless, a remarkable enantiomeric ratio of 78:22 has already been achieved in the Biginelli reaction, which is known to be difficult to control. Thus, bringing the sulfonimidoyl group into closer proximity to the thiourea core might be beneficial for achieving a higher enantiocontrol, but it does not appear to be essential. Another point should be emphasized here as well. Compounds such as (*S*)-**12** and (*S*)-**13** are some of the very rare examples of chiral organocatalysts, whose only stereocontrolling element is not an asymmetrically substituted carbon but rather a stereogenic sulfur center [78-80].

With respect to the properties of the linker between the sulfonimidoyl group bearing the stereogenic sulfur atom and the thiourea unit (aryl vs substituted ethylene as is **12** and **13** vs **18** and **19**) it became clear that conformational rigidity is beneficially leading to higher enantioselectivities. Perhaps, substituted arene backbones could be used for inducing enhanced positive effects on both units through electronic fine-tuning.

The additional stereogenic centers in the ethylene linker as in (S_S,S_C)-**18** and (R_S,S_C)-**19** had none or at best only a minor impact on the stereochemistry-determining path despite the fact that they were relatively close to the thiourea substrate binding site. Thus, reducing molecular flexibility by incorporation of plain arenes as linkers appears to be more important than conformational fixation through additional stereogenic centers in the catalyst backbone.

Overall, promising results have been achieved, which shall be taken as stimulus for further investigations of structurally related sulfonimidoyl-containing thioureas. In that catalyst design, the aforementioned aspects related to structure, activity and stereoselectivity must then be considered and serve as guideline.

Conclusion

In summary, we introduced enantiopure sulfoximines to the field of organocatalysis. The present work demonstrates that the addition of phenyl isothiocyanates to suitable amino-functionalized sulfoximines or to the sulfoximine nitrogen itself proceeds in high yields to give sulfonimidoyl-containing thiourea-type structures. While these compounds show good catalytic activity but no enantiocontrol in the ring opening of a cyclic *meso*-anhydride, low to moderate enantioselectivities have been achieved in the catalytic asymmetric Biginelli reaction leading to a dihydropyrimidinone. In the future we aim to expand the scope of the chiral sulfonimidoyl-containing thiourea framework and hope to find more applications of these interesting molecules in asymmetric organocatalysis.

Supporting Information

Supporting Information File 1

Experimental section and full characterization data of all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-164-S1.pdf]

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Organocatalytic asymmetric addition of malonates to unsaturated 1,4-diketones

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Abstract

The organocatalytic Michael addition of malonates to symmetric unsaturated 1,4-diketones catalyzed by thiourea and squaramide derivatives with *Cinchona* alkaloids afforded the formation of a new C–C bond in high yields (up to 98%) and enantiomeric purities (up to 93%). The absolute configuration of the product was suggested from comparison of the experimental and calculated VCD spectra of the reaction product **3a**.

Introduction

The asymmetric 1,4-conjugated addition (Michael reaction) of C-nucleophiles to enones is a powerful tool for obtaining a significant variety of enantioenriched products through a carbon–carbon bond formation [1-5]. Recently, unsaturated 1,4-dicarbonyl compounds, such as 1,4-ketoesters [6-8], 1,4-diketones [9], 1,4-ketoamides [9,10] and dialkylfumarates [11], have been the substrates for this reaction. The reaction products can undergo further chemical transformations, allowing the possibility of cascade reactions, making the method attractive for the synthesis of several valuable compounds, such as drugs and natural products. Tan et al. performed the addition of 1,3-alkylthiomalonates to 1,4-dicarbonylbut-2-enes, catalyzed by chiral bicyclic guanidines [7,9,12]. Xiao et al. reported the addition of nitroalkanes to 4-oxo-enoates, using chiral urea derivatives [7]. Miura et al. achieved an asymmetric addition of α,α-disubstituted aldehydes to maleimides catalyzed by primary amine thiourea organocatalyst [13]. Wang et al. reported the addition of dialkylmalonates and nitromethane to 4-oxo-4-arylbutenoates catalyzed by *N,N′*-dioxide-Sc(OTf)$_3$ complexes [8]. Despite these and other successful experimental results, the asymmetric addition of malonates to symmetric aromatic unsaturated 1,4-diketones has not been systematically studied. Products of that reaction can be used as precursors of biologically active compounds. Padmaja et al. have reported that racemic heterocyclic compounds derived from the Michael addition of malonates and malononitrile to unsaturated 1,4-diketones possess antimicrobial and antifungal properties [14,15]. Therefore, new asymmetric additions of C-nucleophiles to unsaturated 1,4-diketones are highly in demand.

The asymmetric desymmetrization of symmetric unsaturated 1,4-diketones is a very challenging target. *si*-Attack on one carbon atom of the double bond and *re*-attack on the other leads to the same enantiomer. From the synthetic point of view, the conjugate addition of the nucleophile is, at the same time, a formal umpolung reaction with respect to the other carbonyl group (Figure 1).

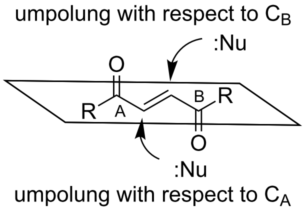


Figure 1: The conjugated addition to unsaturated 1,4-diketone **1**.

Results and Discussion

Catalyst screening

As a part of our ongoing studies in organocatalysis [16-19] we investigated the organocatalytic approach to the asymmetric desymmetrization of the title compounds with malonates. Three types of organocatalysts providing noncovalent interactions were used for this purpose: *Cinchona* alkaloids (**I**–**V**), thiourea derivatives (**VI**, **VII**) and squaramide derivatives (**VIII**, **IX**) (Figure 2). All of these screened catalysts are bifunctional compounds possessing hydrogen-bonding donor and acceptor moieties. Catalysts based on thiourea and squaramide differ from each other in their possible hydrogen-bond angles, rigidity of conformation, and pK_a values [20]. Although the two squaramide based catalysts **VIII** and **IX** are structurally similar, they have quite different properties. Catalyst **IX** is a self-association-free compound [21], while catalyst **VIII** forms associates, and the stereoselectivity of the reaction in its presence depends on the catalyst concentration [22].

The catalysts were screened in the reaction of phenyl disubstituted unsaturated 1,4-diketone **1a** with diethyl malonate (**2a**, Table 1). The reaction was run in DCE at room temperature in the presence of 10 mol % of catalyst with a five-fold excess of malonate. In all cases, the yields of the products were very high. *Cinchona* alkaloids (Table 1, entries 1–4) catalyzed the reaction with low stereoselectivity. There was a remarkable difference in their reaction rates. Quinine (**II**) and quinidine (**IV**, Table 1, entries 2 and 4) were more efficient than cinchonine (**I**) and cinchonidine (**III**, Table 1, entries 1 and 3). The reduction of the vinyl group in quinine afforded dihydroquinine **V**. Unfortunately, no changes in the stereoselectivity of the model reaction were observed (Table 1, entry 5). Both thiourea catalysts derived from *Cinchona* alkaloids (**VI**, **VII**) gave high yields with good selectivities (Table 1, entries 6 and 7). Squaramide

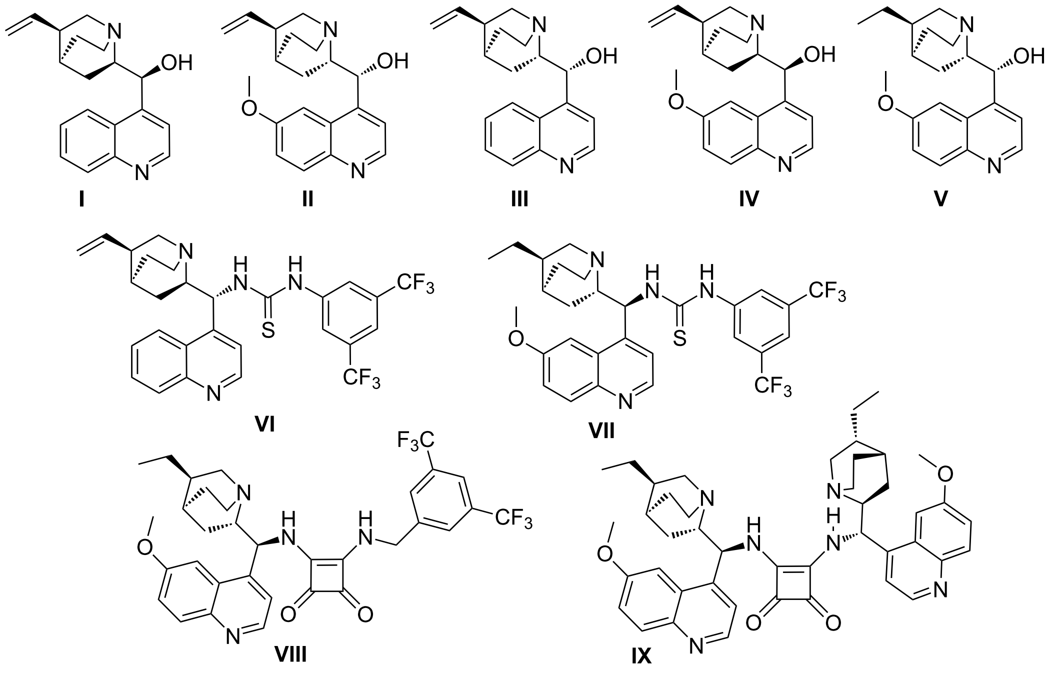
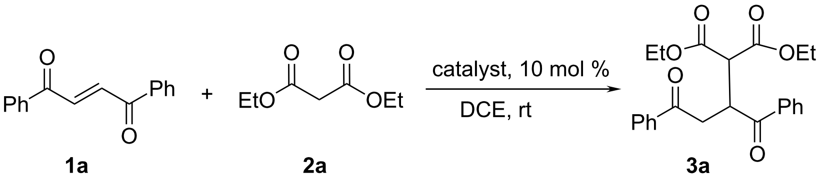


Figure 2: Organocatalysts screened.

Table 1: Screening of the catalysts for the asymmetric conjugated-addition reaction.



entry	catalyst	time (h)	yield^a (%)	ee^b (%)	abs. conf.^{c}
1	**I**	120	97	13	R
2	**II**	28	98	27	R
3	**III**	168	88	10	R
4	**IV**	24	>98	19	S
5	**V**	20	>98	18	R
6	**VI**	24	>98	74	S
7	**VII**	19	98	74	R
8	**VIII**	15	96	60	R
9	**IX**	96	96	39	R

^{a}Isolated yield; ^{b}determined by chiral HPLC; ^{c}determined by a comparison of the experimental and calculated VCD spectra (see the following).

VIII and C_2-symmetric squaramide **IX** gave good yields but slightly lower selectivities (Table 1, entries 8 and 9). The catalyst **VII** was selected for further studies as being the most efficient. Also, considering the partially aromatic character of the cyclobutenedione system, which may possibly allow additional interactions with the aromatic substrates **1**, the catalyst **IX** was also chosen.

Scope of the reaction

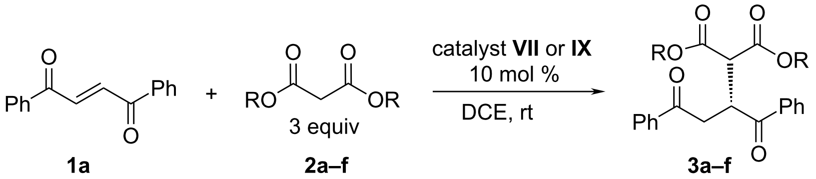
Next, we studied the effect of the malonate structure on the stereoselectivity of the reaction (Table 2). Although, the ester moiety can be replaced by other functional groups in the course of further synthetic transformations its main role is to provide the addition products with high ee value. The conditions for the reaction remained the same as they were in the catalyst screening experiments, except that a smaller excess of malonate (3 equiv, unless stated otherwise) was used. This did not influence the reaction time or the enantioselectivity, but afforded easier purification of the crude product.

1,4-Diketone **1a** reacted smoothly with a variety of malonates **2a**–**2f**, affording the products **3a**–**3f** in high yields and with moderate to high stereoselectivities. In the case of the catalyst **VII**, the increase of steric hindrance of the malonate (Table 2, entries 1, 3, 5 and 7) led to a gradual drop in selectivity. Sterically more demanding malonates with branched alkyl or aryl groups (**2c**–**e**) gave products in much lower enantioselectivity (ee 37–69%) than the simple alkyl malonates (**2a, b**) (ee 73–74%). There was no clearly observed similar dependence with squaramide catalyst **IX**. Almost equally high ee values were obtained with methyl, phenyl or benzyl malonates (Table 2, entries 4, 10 and 12). A possible reason for the high selectivity with the phenyl-ring-containing esters could be the aromatic nature of the squaramide functional group in catalyst **IX**, allowing additional π–π-interactions.

The properties of the enone double bond of the substrate depend on the nature of the substituents in the phenyl ring. Therefore, the electronic effect of the *para*-substituent of unsaturated 1,4-diketone **1** on the reaction was investigated (Table 3). Electron-withdrawing groups, such as bromo and nitro, (Table 3, entries 10 and 13) as well as the electron-donating methoxy group (Table 3, entry 7) led to an increase in stereoselectivity, but the reaction time was also increased and the yields were lower with catalyst **VII**. A methyl substituent slightly decreased the enantioselectivity (Table 3, entry 4). This means that these dependencies cannot be clearly rationalized by the use of the electronic effects of the substituents in the phenyl ring. In the case of squaramide catalyst **IX**, all of the reactions became sluggish at room temperature (Table 3, entries 5, 8, 11 and 14). The reaction times were unreasonably long and the yields remained low. However, in the case of reactions with electron-withdrawing groups, the enantiomeric purity of the products was higher (Table 3, entries 11 and 14).

Increasing the temperature had a drastic positive effect on the reactions performed in the presence of catalyst **IX**. It was found that by raising the temperature to 80 °C it was possible to

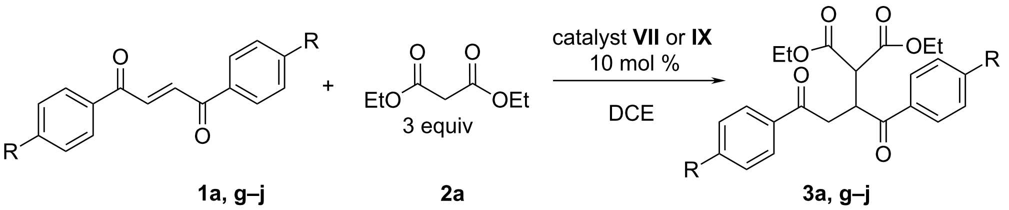
Table 2: Enantioselective addition of malonates **2a**-**2f** to unsaturated 1,4-diketone **1a**.



entry	R	catalyst	time (h)	yield[c] (%)	ee[d] (%)
1	**a:** Et	**VII**	19	99	74
2	**a:** Et	**IX**	96	96	39
3	**b:** Me	**VII**	15	92	73
4	**b:** Me	**IX**	30	95	87
5	**c:** iPr	**VII**	36	96	69
6	**c:** iPr	**IX**	96	96	60
7[a]	**d:** *t*-Bu	**VII**	75	70	59
8[a]	**d:** *t*-Bu	**IX**	33	95	70
9[b]	**e:** Ph	**VII**	3	44	37
10[b]	**e:** Ph	**IX**	2	41	81
11	**f:** Bn	**VII**	6	95	68
12	**f:** Bn	**IX**	6	92	84

[a]Reaction at 80 °C, malonate/dione 2:1; [b]malonate/dione 1:1; [c]yields of isolated products; [d]determined by chiral HPLC.

Table 3: Enantioselective addition of diethylmalonate **2a** to substituted 1,4-diketones **1a, g–j**.



entry	R	catalyst	temp. (°C)	time (h)	yield[b] (%)	ee[c] (%)
1	**a**: H	**VII**	rt	19	99	74
2	**a**: H	**IX**	rt	96	97	39
3	**a**: H	**IX**	80	10	97	82
4	**g**: Me	**VII**	rt	18	96	69
5	**g**: Me	**IX**	rt	213	25	18
6	**g**: Me	**IX**	80	22	76	66
7	**h**: MeO	**VII**	rt	88	90	79
8	**h**: MeO	**IX**	rt	48	—	—
9	**h**: MeO	**IX**	80	22	90	83
10[a]	**i**: Br	**VII**	rt	48	83	81
11[a]	**i**: Br	**IX**	rt	123	20	93
12[a]	**i**: Br	**IX**	80	6	86	91
13	**j**: NO_2	**VII**	rt	54	66	81
14	**j**: NO_2	**IX**	rt	94	44	89
15	**j**: NO_2	**IX**	80	6	98	89

[a]Dione/malonate 1.2:1; [b]yields of isolated products; [c]determined by chiral HPLC.

significantly decrease the reaction time and increase yields up to 98% with almost no negative effect on the stereoselectivity (ee 66–89%, Table 3, entries 6, 9, 12 and 15). Moreover, the compounds **3a** and **3g** were obtained in much higher enantioselectivities, and the reaction with the unsaturated 1,4-diketone containing the electron-donating substituent **1h**, which did not react at room temperature, also afforded the product in good yield and selectivity (Table 3, entry 9). As the squaramide-type catalyst **IX** is known to be self-association-free [21], the increase in enantioselectivity at higher temperatures can be attributed to the thermodynamic control of the conjugate addition. At the same time, the increase in temperature resulted in a small drop in stereoselectivity for the model reaction with catalyst **VII**.

The mechanism of the reaction is believed to be similar to that previously reported for 1,3-dicarbonyl compounds and acyl phosphonates [23]. Squaramide **IX** is a bifunctional catalyst that simultaneously coordinates electrophilic unsaturated 1,4-diketone via hydrogen bonding and activates the nucleophilic malonate via the tertiary amine of the quinuclidine moiety. Due to the symmetry of the substrate, there is no regioselectivity problem. A face selection is determined by the different access of the nucleophile to the tertiary amino group between the side chains of the catalysts. The *re*-face of the Michael acceptor is shielded by the flat quinoline unit and the *si*-attack of the malonate is preferred, affording *R*-selectivity (Figure 3).

Determination of the absolute configuration

The absolute configuration of the product **3a** was determined by a comparison of the experimental and calculated vibrational circular dichroism (VCD) spectra. DFT calculations (method B3PW91/6-311G**) of a series of conformers of compound **3a** with *R*-configuration were performed. Calculations of harmonic vibrational frequencies were carried out for all favored conformers to verify their stability. The Boltzmann distribution of the Gibbs energy showed that one conformation out of six is dominant (84%). The experimental and calculated IR spectra match well in the range 1500–1800 cm^{-1} (both experimental and calculated spectra are normalized to 100% by using the highest peak from that range, Figure 4A).

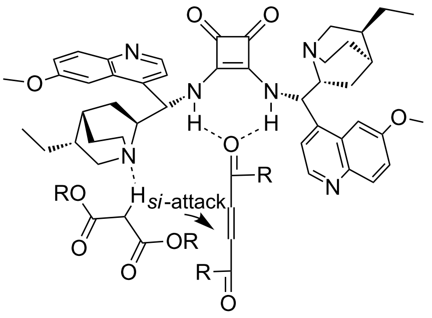


Figure 3: Proposed transition state.

The most characteristic peaks of VCD spectra are in the same region (Figure 4B). The good agreement between calculated and experimental spectra directly allows for the assignment of the absolute configuration of **3a** as the *R*-enantiomer.

Conclusion

We have developed a highly enantioselective method for the desymmetrization of aromatic unsaturated 1,4-diketones through organocatalytic reactions with malonates. The reaction is catalyzed by thiourea and squaramide derivatives with *Cinchona* alkaloids and affords products in very high yields (up to 99%) and in high enantioselectivities (up to 93%). This enantioselective 1,4-addition to unsaturated 1,4-diketones affords valuable intermediates for further synthetic transformations.

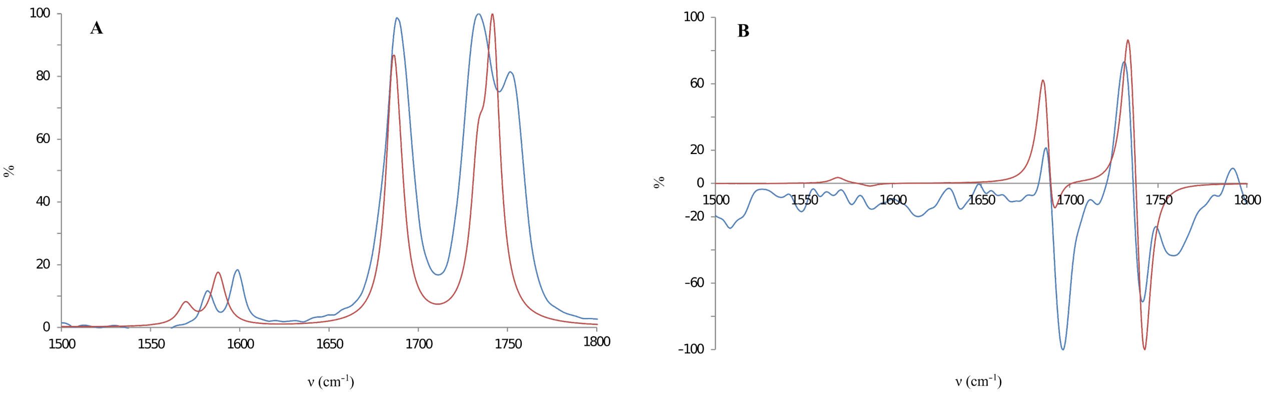


Figure 4: Calculated (red) and experimental (blue) IR (A) and VCD spectrum (B) of compound (*R*)-**3a**.

Supporting Information

Supporting Information File 1

Experimental procedures, compound characterization and computational data.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-165-S1.pdf]

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A quantitative approach to nucleophilic organocatalysis

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Review

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Abstract

The key steps in most organocatalytic cyclizations are the reactions of electrophiles with nucleophiles. Their rates can be calculated by the linear free-energy relationship $\log k(20\ °\text{C}) = s_\text{N}(E + N)$, where electrophiles are characterized by one parameter (E) and nucleophiles are characterized by the solvent-dependent nucleophilicity (N) and sensitivity (s_N) parameters.

Electrophilicity parameters in the range $-10 < E < -5$ were determined for iminium ions derived from cinnamaldehyde and common organocatalysts, such as pyrrolidines and imidazolidinones, by studying the rates of their reactions with reference nucleophiles. Iminium activated reactions of α,β-unsaturated aldehydes can, therefore, be expected to proceed with nucleophiles of $2 < N < 14$, because such nucleophiles are strong enough to react with iminium ions but weak enough not to react with their precursor aldehydes. With the N parameters of enamines derived from phenylacetaldehyde and MacMillan's imidazolidinones one can rationalize why only strong electrophiles, such as stabilized carbenium ions ($-8 < E < -2$) or hexachlorocyclohexadienone ($E = -6.75$), are suitable electrophiles for enamine activated reactions with imidazolidinones. Several mechanistic controversies concerning iminium and enamine activated reactions could thus be settled by studying the reactivities of independently synthesized intermediates.

Kinetic investigations of the reactions of N-heterocyclic carbenes (NHCs) with benzhydrylium ions showed that they have similar nucleophilicities to common organocatalysts (e.g., PPh_3, DMAP, DABCO) but are much stronger (100–200 kJ mol^{-1}) Lewis bases. While structurally analogous imidazolylidenes and imidazolidinylidenes have comparable nucleophilicities and Lewis basicities, the corresponding deoxy Breslow intermediates differ dramatically in reactivity. The thousand-fold higher nucleophilicity of 2-benzylidene-imidazoline relative to 2-benzylidene-imidazolidine is explained by the gain of aromaticity during electrophilic additions to the imidazoline derivatives. O-Methylated Breslow intermediates are a hundred-fold less nucleophilic than deoxy Breslow intermediates.

Review

Introduction

The most comprehensive nucleophilicity and electrophilicity scales presently available, are based on Equation 1, in which electrophiles are characterized by one solvent-independent parameter *E,* and nucleophiles are characterized by two solvent-dependent parameters, the nucleophilicity parameter *N* and the sensitivity parameter s_N [1-3].

$$\log k(20\ °\mathrm{C}) = s_\mathrm{N}(E + N) \qquad (1)$$

By defining benzhydrylium ions, structurally related quinone methides, and arylidenemalonates as reference electrophiles, which cover a reactivity range of 32 orders of magnitude corresponding to relative reaction times from nanoseconds to 10^{15} years, we have been able to compare nucleophiles of widely differing structure and reactivity [4]. As illustrated by Figure 1, this method allows us to characterize strong nucleophiles, such as carbanions and ylides, by their reactivities toward weak electrophiles, and to characterize weak nucleophiles, such as nonactivated alkenes, by their reactivities toward strong electrophiles. Recently we have explicitly outlined the reasons why we prefer Equation 1, a nonconventional version of a linear free-energy relationship, which defines nucleophilicities as the negative intercepts on the abscissa, over the conventional (mathematically equivalent) linear free-energy relationship depicted in the red frame at the top of Figure 1 [5].

The reactivity scales, developed on this basis, have not only be employed for designing organic syntheses [6-18], but were also helpful for rigorous examinations of general concepts of organic reactivity, such as the “Reactivity Selectivity Principle” [19], the “HSAB Treatment of Ambident Reactivity” [20] and the changes of mechanisms in nucleophilic aliphatic substitutions [21,22]. In this essay, we will illustrate applications of Equation 1 in nucleophilic organocatalysis.

Iminium activated reactions

A key step of the commonly accepted catalytic cycle for iminium activated reactions (Figure 2) is the attack of a nucleophile **4** on the intermediate iminium ion (**3**), which can be treated by Equation 1 as indicated in the bottom right of Figure 2 [23-28].

In order to predict which nucleophiles **4** are suitable reagents for such transformations because they are strong enough to react with iminium ions **3**, but weak enough not to react with

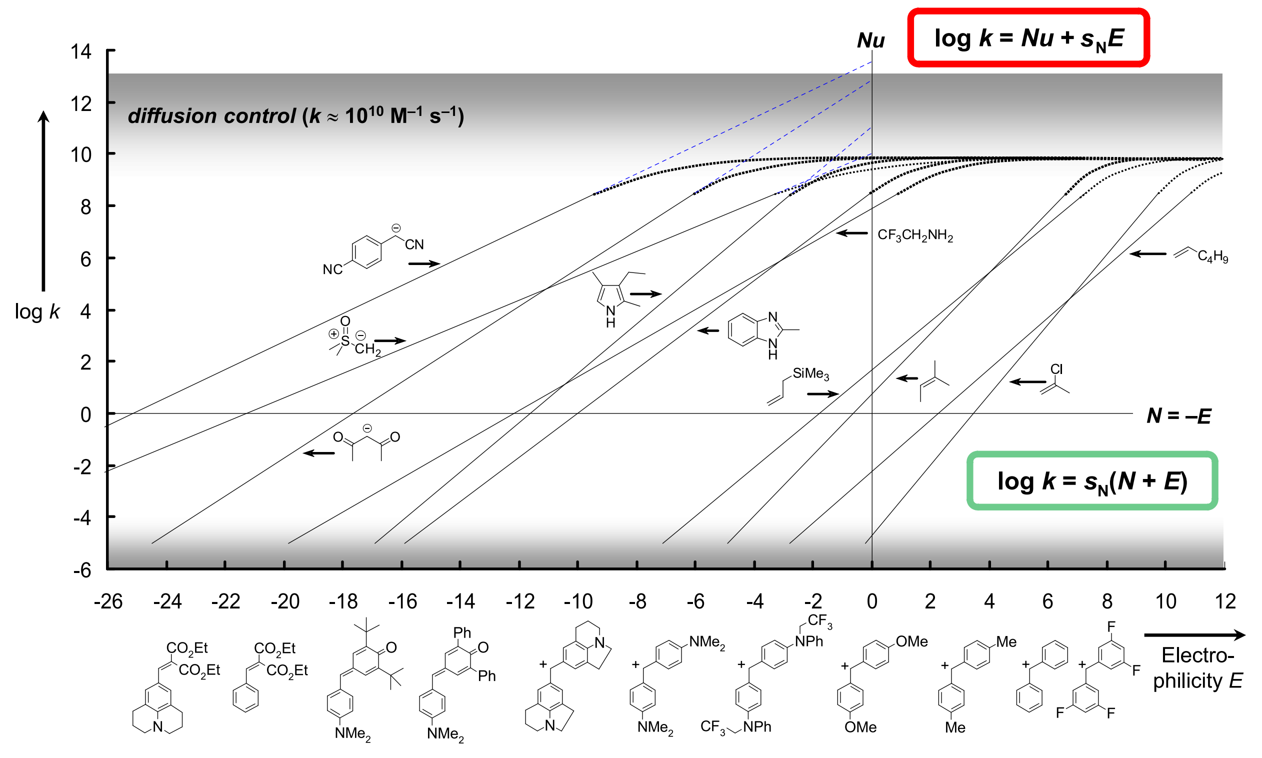


Figure 1: Second-order rate constants for reactions of electrophiles with nucleophiles.

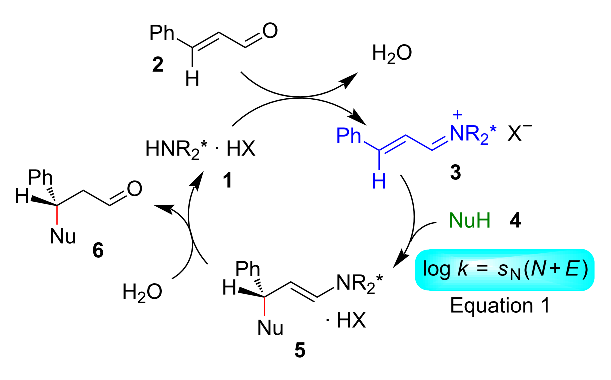


Figure 2: Mechanism of amine-catalyzed conjugate additions of nucleophiles [23-28].

the precursor carbonyl compounds (e.g., **2**), it was necessary to determine the reactivity parameters *N* and s_N of potential nucleophilic substrates **4** and the electrophilicity parameters *E* of iminium ions **3**.

Iminium triflates, tetrafluoroborates, or hexafluorophosphates were synthesized as stable salts according to literature procedures [29-35]. Cinnamaldehyde-derived iminium ions **3** are particularly suitable for kinetic investigations because their reactions with nucleophiles can easily be followed photometrically by monitoring the decay of their absorbance at 370 nm (as exemplified in Figure 3a,b). By using the nucleophiles (for example **7a**) in large excess, pseudo-first-order kinetics were achieved, and the first-order rate constants k_{obs} (s^{-1}) were derived from the exponential decays of the iminium ions **3** (Figure 3c). Plots of k_{obs} versus the concentrations of the nucleophiles (Figure 3d) were linear, with their slopes giving the second-order rate constants k_2 (M^{-1} s^{-1}) [35,36].

For the investigations of reactions of the iminium ions on the micro- and nanosecond time scale, laser flash spectroscopy was employed [37]. As tertiary phosphines PR_3 (**10**) are known to be excellent photonucleofuges [38-41], the stable iminium salts **3**-PF_6 were treated with tertiary phosphines **10** at room temperature to give the enamino-phosphonium ions **11** instantaneously (Figure 4a). Their irradiation with 7 ns laser pulses (266 nm) regenerated the iminium ions, the decay of which was monitored photometrically in the presence of variable concentrations of nucleophiles (Figure 4b).

As above, the second-order rate constants for the reactions of the iminium ions with nucleophiles were obtained as the slopes

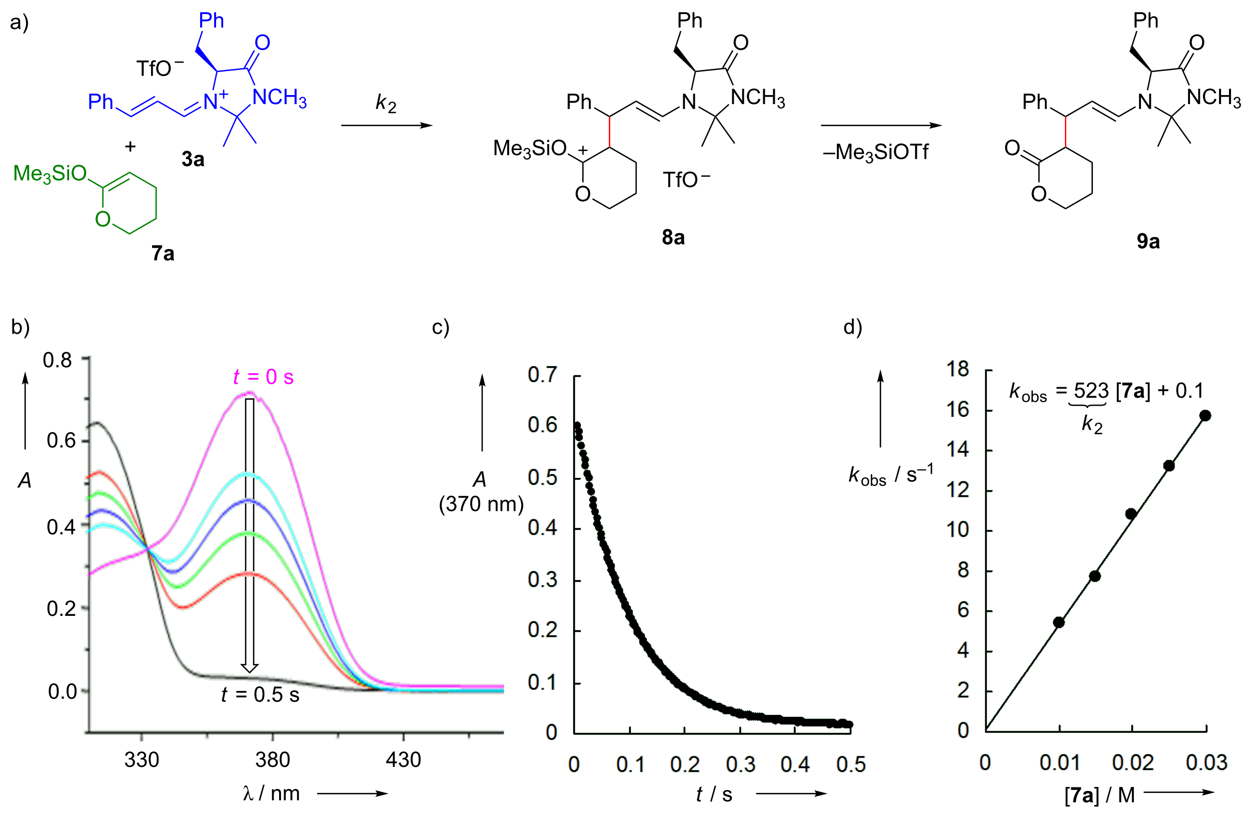


Figure 3: Kinetics of the reactions of the iminium ion **3a** with the silylated ketene acetal **7a** [35].

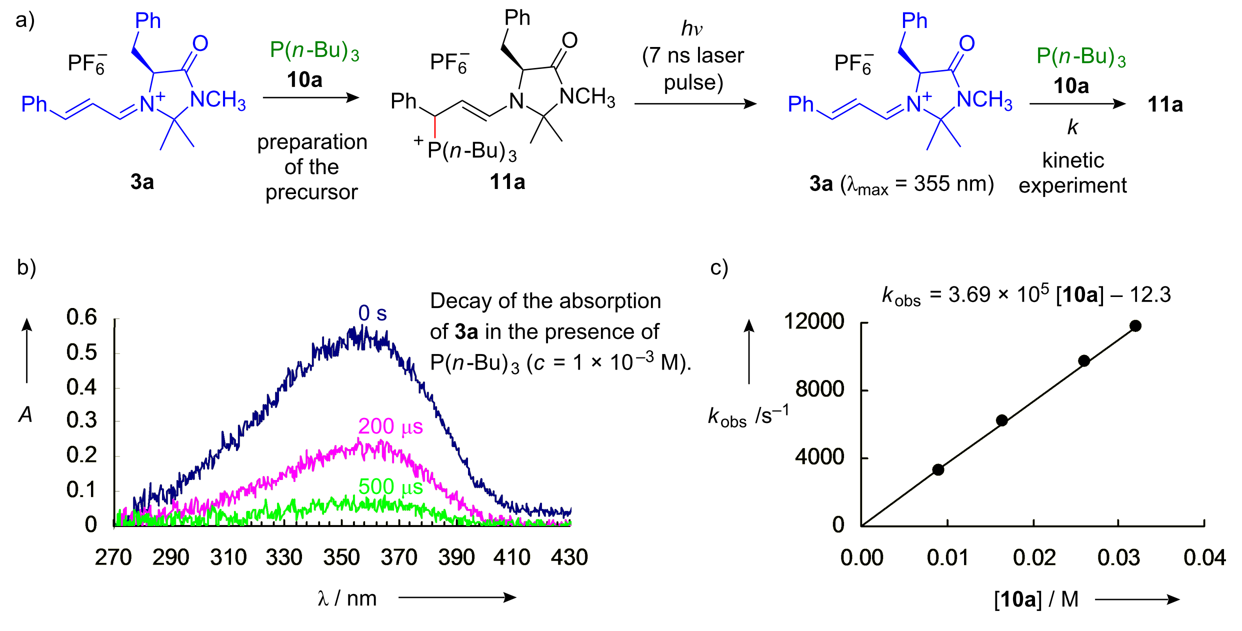


Figure 4: Laser flash photolytic generation of iminium ions **3a**.

of the plots of the first-order rate constants k_{obs} versus the concentrations of the corresponding nucleophiles (Figure 4c).

The fair correlations of (log k_2)/s_N versus the nucleophilicity parameters N with slopes of unity in Figure 5 indicate the applicability of Equation 1, and is a further evidence that the reactivity parameters N and s_N, which are derived from reactions with benzhydrylium ions, also hold for reactions with iminium ions **3**.

Analogous experiments showed that the cinnamaldehyde-derived iminium ions **3a–i** cover a reactivity range of five orders of magnitude; the iminium ion **3b**, derived from MacMillan's generation II catalyst, turned out to be by far the most reactive one of this series (Figure 6) [37,42,43].

When comparing the N parameters of substrates previously employed in iminium activated reactions (Figure 7) [35,42,44-52], one can see that they are characterized by nucleophilicity parameters in the range $2 < N < 14$. As Equation 1 describes only one step of the catalytic cycle in Figure 2, we do not claim that N parameters in the indicated range represent a sufficient criterion for the selection of potential substrates in iminium activated reactions. It will be difficult, however, to find suitable nucleophilic substrates outside this range, as stronger nucleophiles will either react with the carbonyl compounds directly or inhibit the formation of the iminium ions due to their high basicity. Weaker nucleophiles, on the other hand, will not be able to attack iminium ions **3**; exceptions may be expected for

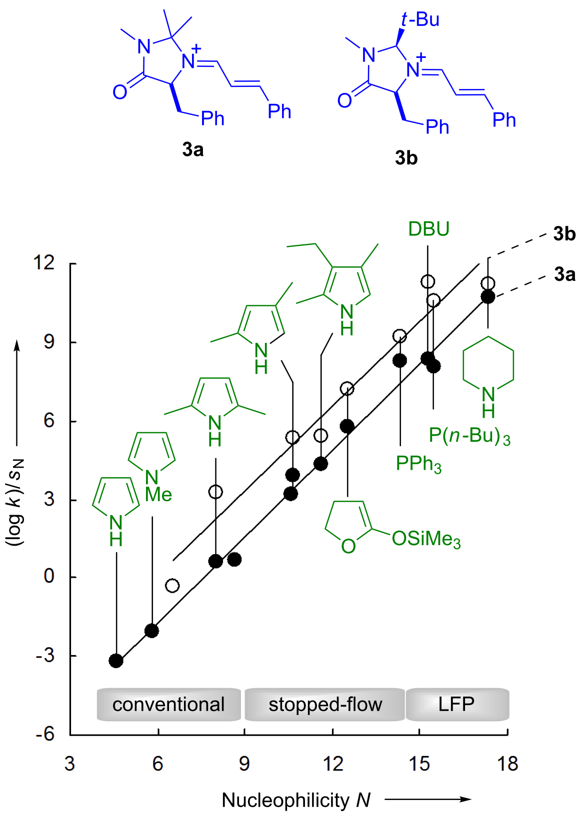


Figure 5: Correlations of the reactivities of the iminium ions **3a** and **3b** toward nucleophiles with the corresponding N parameters – LFP = laser flash photolysis.

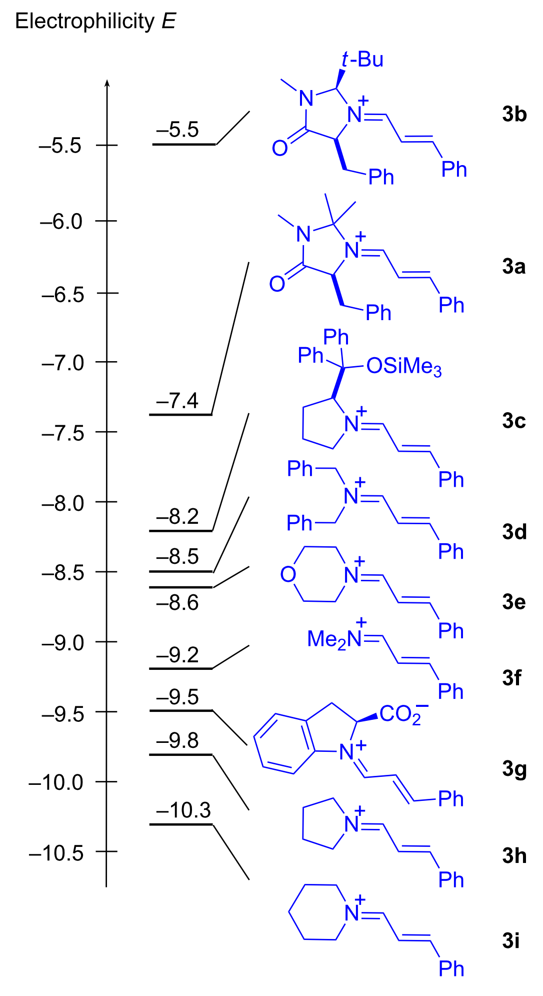


Figure 6: Comparison of the electrophilicities of cinnamaldehyde-derived iminium ions **3a**–**3i**.

substrates which undergo concerted pericyclic reactions with the iminium ions and therefore do not follow Equation 1 [53].

Let us now consider the role of counterions, as the imidazolidinone catalyzed reactions of cinnamaldehyde with pyrrole were reported to proceed with high yields and enantioselectivities, when using trifluoroacetic acid as cocatalyst, while yields and enantioselectivities are low with strong acids, such as CF_3SO_3H, TsOH, or HCl, as cocatalysts [46,54,55].

Figure 8 shows that the rates of the reactions of **3a**-X with 2-(trimethylsiloxy)-4,5-dihydrofuran (**7b**) were only slightly affected by the nature of the counterions X^- ($X^- = PF_6^-$, BF_4^-, TfO^-, Br^-, $CF_3CO_2^-$) [56].

In contrast, the reaction of **3a**-X with 3-ethyl-2,4-dimethylpyrrole (kryptopyrrole, **12a**) was considerably faster when $CF_3CO_2^-$ was present than when less basic counterions were employed. The acceleration of the reaction by increasing the concentration of $CF_3CO_2^-$ demonstrated that $CF_3CO_2^-$ acted as a general base to deprotonate the Wheland intermediate $\mathbf{13a}^+$ and thus suppresses its retroaddition with regeneration of the pyrrole **12a** and the iminium ion **3a**. Rate constants observed at variable concentrations of $CF_3CO_2^-$ allowed us to calculate the second-order rate constants k_2 for the attack of the iminium ion **3a** at the pyrroles **12a**–**12f**, and Figure 9 shows that the observed rate constants agree, within a factor of five, with those calculated by using Equation 1.

We consider this agreement remarkable, as the E parameter for **3a** has been derived from rate constants with a large variety of nucleophiles [37] and the N and s_N parameters of the pyrroles **12a**–**12f** have been derived from their reactivities toward benzhydrylium ions [57]. As Equation 1 is employed for calculating absolute rate constants k_2 in a reactivity range of 40 orders of magnitude with only three parameters, N, s_N, and E, one generally has to tolerate deviations up to factors of 10 to 100 [2,3,5].

However, an even better agreement between calculated and experimental values was observed for the reactions of **3a** with imidazoles **15** (Figure 10) [58].

These additions are highly reversible, however, and the adducts could only be isolated when the reaction mixtures containing **16** (for $R^2 = H$) were worked up with dry K_2CO_3. Aqueous workup led to regeneration of the reactants. Vicario's report that imidazoles, in contrast to triazoles and tetrazoles, do not readily undergo iminium activated additions to α,β-unsaturated aldehydes can thus be explained by the low acidity of imidazolium ions [59]. Unlike triazolium and tetrazolium ions, imidazolium ions are unable to transfer a proton to the enamine unit in **16** (corresponding to **5** in the general Figure 2), which is necessary to close the catalytic cycle shown in Figure 2 [60].

General base catalysis appeared also to be essential for iminium activated reactions of α,β-unsaturated aldehydes with enamides **17**. By studying the kinetics of the reactions of enamides **17** with benzhydrylium ions **18** (Figure 11) we determined the reactivity parameters N and s_N for these π-nucleophiles, which are listed in Figure 12 [61].

Figure 12 shows that the nucleophilicities N of the enamides **17** are comparable to those of silylated enol ethers, in between those of allylsilanes and enamines. Accordingly, we expected them to react readily with the iminium ions **3** at room temperature.

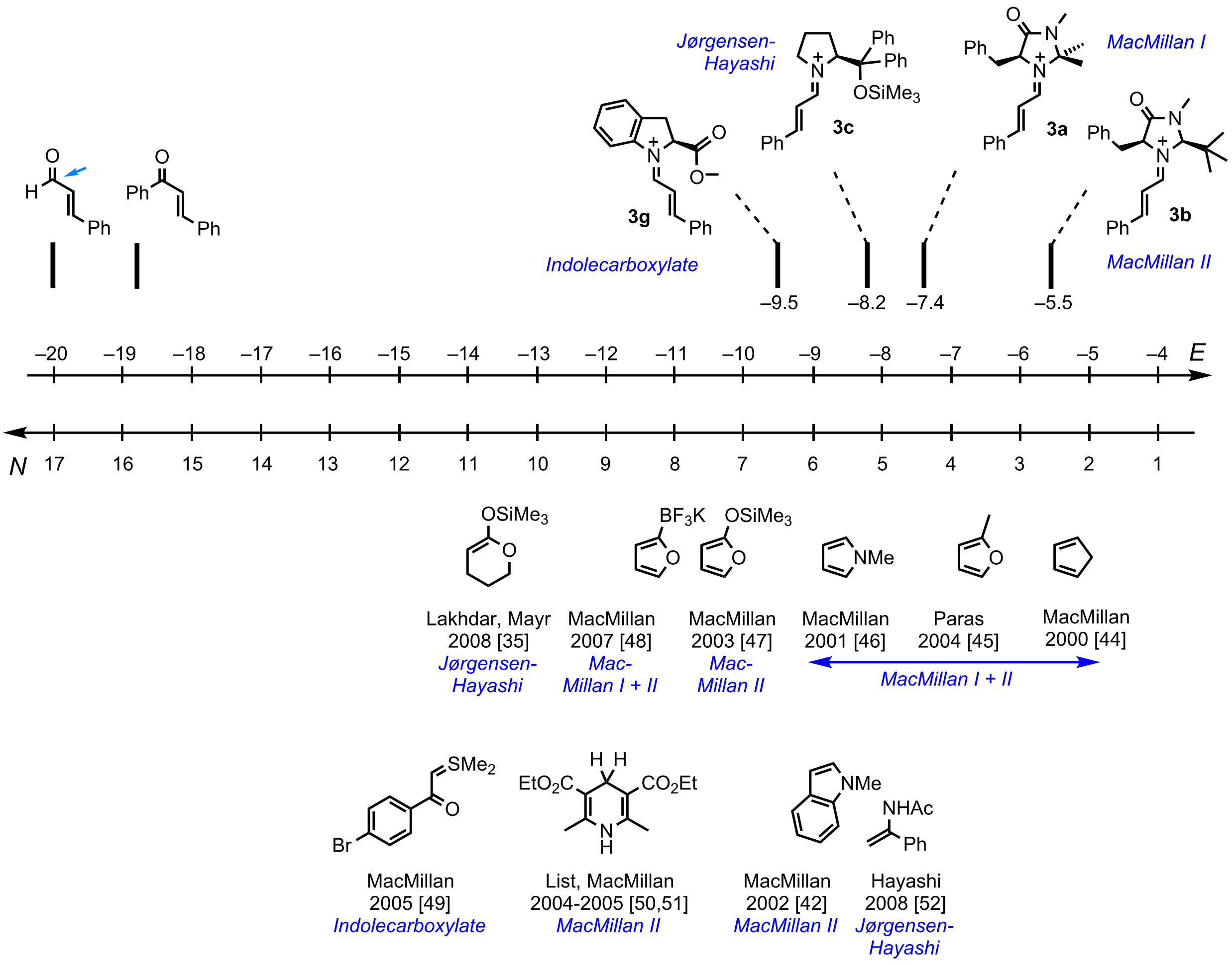


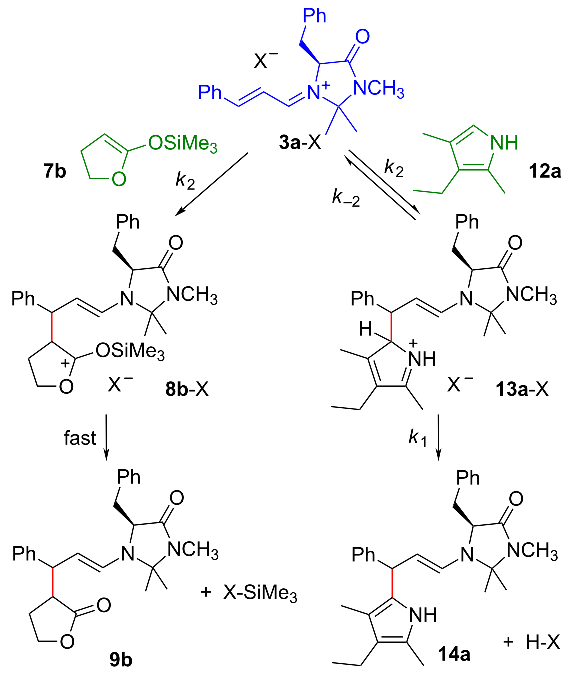
Figure 7: Nucleophiles used in iminium activated reactions [35,42,44-52].

However, when the iminium triflates or hexafluorophosphates **3a** and **3b** (~ 5 × 10^{-5} M) were combined with 25 equivalents of the enamides **17b** and **17g** in CH_2Cl_2 or CH_3CN, no consumption of the iminium ions was observed [61]. These reactions took place in the presence of 2,6-lutidine, however, indicating the need of general base assistance. By studying the kinetics of these reactions in the presence of variable concentrations of 2,6-lutidine, we were able to determine k_2, the rate constant for the attack of the iminium ions **3** at the enamides **17**. As shown in Figure 13, the rate constants thus determined, agree within a factor of 3 with those calculated by Equation 1 using the N and s_N parameters of enamides **17**, which have been derived from their reactions with the benzhydrylium ions **18** (Figure 11 and Figure 12) [61].

These observations explain why strong acids, such as *p*-TsOH, proved not to be suitable cocatalysts for iminium activated reactions of α,β-unsaturated aldehydes with enamides [62]. The demonstration of general base catalysis for these reactions furthermore rules out Hayashi's proposal of a concerted ene reaction for the formation of tetrahydropyridines by the diphenylprolinol-catalyzed reaction of α,β-unsaturated aldehydes with enamides [52] and is in line with Wang's stepwise mechanism with initial formation of **19** [62].

In view of the high nucleophilicities of sulfur ylides [63], we were surprised by MacMillan's statement that iminium ions derived from the imidazolidinones **1a** and **1b** (for structures, see Figure 16) were inert to the ylide **21** [49]. When we combined the pregenerated iminium salts **3a**–**e** with the sulfur ylide **21**, the expected cyclopropanes **23** were indeed formed in good yield, although with low diastereo- and enantioselectivity (Figure 14) [64].

Even the rate constants calculated by Equation 1 agreed, within the general tolerance, with the experimental values; with one exception. The iminium intermediate derived from indole-2-carboxylic acid (**3g**) reacted at least 10^5 times faster with the



X^-	k_{rel} (**3a**-X + **7b**)	k_{rel} (**3a**-X + **12a**)
PF_6^-	1.0	1.0
Br^-	0.37	1.0
TfO^-	0.84	0.38
BF_4^-	1.0	0.89
$CF_3CO_2^-$	0.59	**9.5**

Figure 8: Counterion effects in electrophilic reactions of iminium ions **3a**-X (at 20 °C, silyl ketene acetal **7b** in dichloromethane with c(**3a**-CF_3CO_2) = (1.7–2.5) × 10^{-5} M, kryptopyrrole **12a** in acetonitrile with c(**3a**-CF_3CO_2) = 5.0 × 10^{-5} M).

sulfur ylide **21** than calculated by Equation 1, which can be explained by electrostatic activation as initially proposed by MacMillan (Figure 15) [49].

Thus, the failure of the imidazolidinones **1a** and **1b** to catalyze cyclopropanations with the sulfur ylide **21** is not due to the low reactivities of sulfur ylides toward iminium ions, but is due to the high Brønsted basicity of the sulfur ylides **24**, which leads to deprotonation of the imidazolidinium ions **1**-H^+ and inhibition of the formation of the iminium ions **3** (Figure 16) [64].

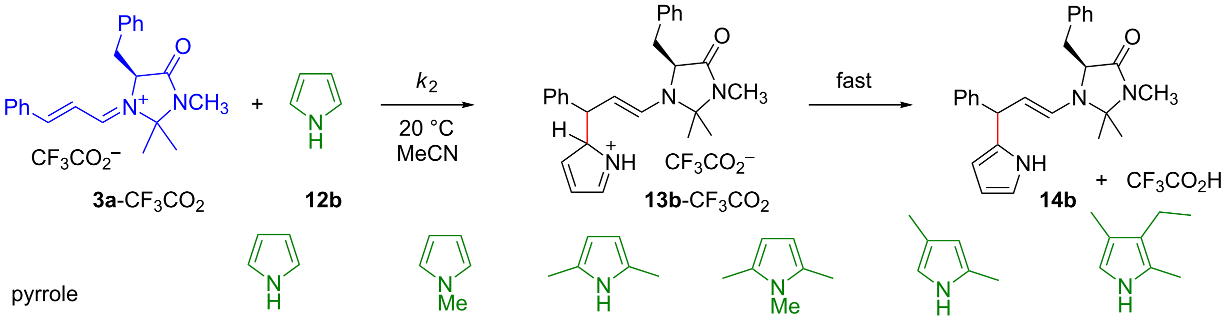
Enamine activated reactions

When proline catalysis and related amino-acid catalyzed reactions are excluded, the catalytic cycle depicted in Figure 17 represents the generally accepted mechanism for enamine activated reactions [65-71]. A key-step, not necessarily the rate-determining step, is the attack of an electrophile **29** at the enamine **28**, at the bottom of Figure 17 [72].

In order to calculate the rate constant for this step by Equation 1 one needs the reactivity parameters N and s_N for the enamines **28** and the electrophilicity parameter E for the electrophiles **29**.

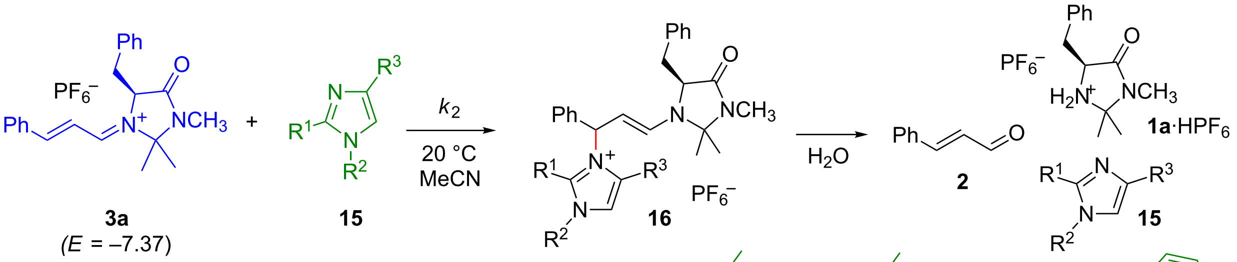
The electrophilicity parameters for the Michael acceptors, stabilized carbenium ions, and azodicarboxylates shown in Figure 18 have been derived from the kinetics of their reactions with C-nucleophiles, mostly stabilized carbanions [4,73-80].

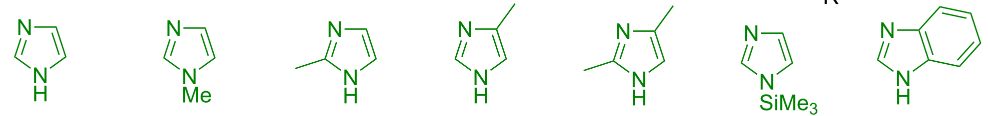
As illustrated in Figure 19, the benzhydrylium methodology was again employed for the determination of the nucleophilicities of enamines. Whereas the enamine **32b**, which is



pyrrole	**12b**	**12c**	**12d**	**12e**	**12f**	**12a**
N, s_N	4.63, 1.00	5.85, 1.03	8.01, 0.96	8.69, 1.01	10.67, 0.91	11.63, 0.95
k^{calcd} (M^{-1} s^{-1})	1.8 × 10^{-3}	2.7 × 10^{-2}	4.1	22	1.0 × 10^{3}	1.1 × 10^{4}
k^{exptl} (M^{-1} s^{-1})	6.8 × 10^{-4}	7.2 × 10^{-3}	3.6	5.3	3.5 × 10^{3}	1.3 × 10^{4}
k^{calcd}/k^{exptl}	2.6	3.7	1.1	4.2	0.28	0.85

Figure 9: Comparison of calculated and experimental rate constants of electrophilic aromatic substitutions with iminium ions [56].





imidazole	**15a**	**15b**	**15c**	**15d**	**15e**	**15f**	**15g**
N, s_N	11.5, 0.79	11.9, 0.73	11.7, 0.76	11.8, 0.77	11.5, 0.84	11.4, 0.79	10.5, 0.79 in DMSO
k^{calcd} (M^{-1} s^{-1})	1.7×10^3	2.0×10^3	2.1×10^3	2.5×10^3	3.0×10^3	1.6×10^3	3.0×10^2
k^{exptl} (M^{-1} s^{-1})	3.0×10^3	4.2×10^3	2.8×10^3	4.6×10^3	3.0×10^3	2.9×10^3	2.8×10^2
k^{exptl}/k^{calcd}	1.7	2.0	1.4	1.8	1.0	1.8	0.93

Figure 10: Aza-Michael additions of the imidazoles **15** with the iminium ion **3a** [58].

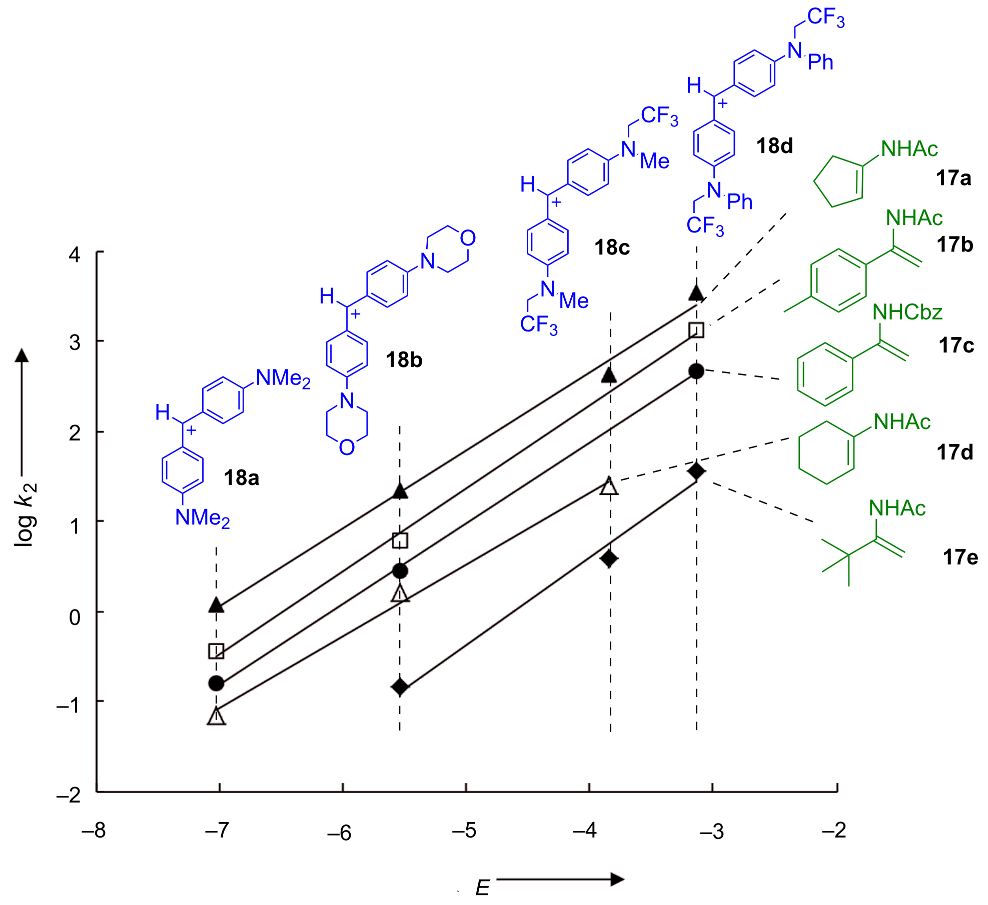


Figure 11: Plots of log k_2 for the reactions of enamides **17a–17e** with the benzhydrylium ions **18a–d** in CH_3CN at 20 °C versus the electrophilicity parameters (E).

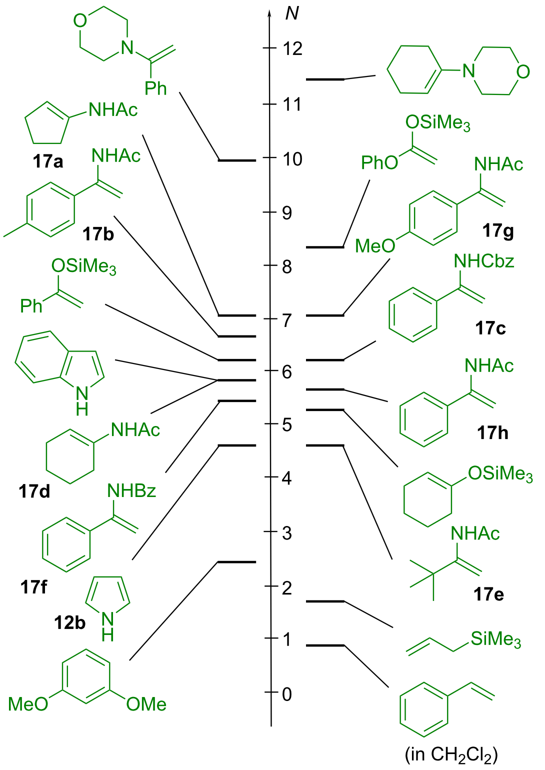
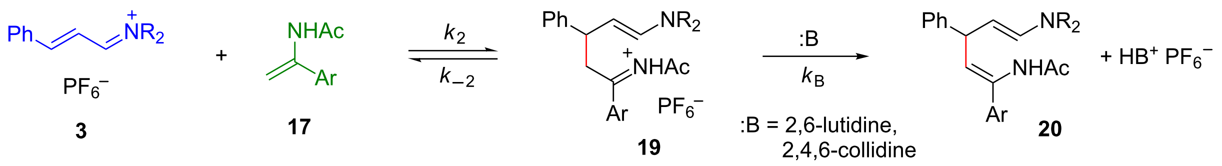


Figure 12: Comparison of the nucleophilicities of enamides **17** with those of several other C nucleophiles (solvent is CH_3CN unless otherwise mentioned, *N* values taken from [4,61]).

derived from the diphenylprolinol silyl ether [81], had previously been synthesized and characterized (X-ray structure) by Seebach et al. [30], neat samples of the imidazolidinone-derived enamines **32c**–**32e** became only recently available by TsOH-catalyzed condensation of phenylacetaldehyde with the corresponding imidazolidinones and column chromatography on silica gel. The presence of triethylamine (5%) in the eluent (ethyl acetate/*n*-pentane) turned out to be crucial to avoid decomposition of these enamines on the column [82,83].

Kinetic studies of their reactions with benzhydrylium ions **18** of suitable electrophilicity showed that introduction of the $(Me_3SiO)Ph_2C$-group in the 2-position of the pyrrolidine ring of *N*-(β-styryl)pyrrolidine caused a reduction of reactivity by a factor of 30 to 60 (**32a** versus **32b**). A reduction of nucleophilicity by three to five orders of magnitude is encountered for the enamines **32c**–**32e** (Figure 19). The low nucleophilicities of the imidazolidinone derived enamines, which are in line with the larger ^{13}C NMR chemical shifts of C-2 in **32d** (101.9 ppm) and **32e** (102.9 ppm) compared to that of C-2 in **32a** (97.4 ppm), are not only due to the electron-withdrawing effect of the additional heteroatoms in the heterocyclic rings [83]. An additional factor is shown in Figure 19: While the enamine nitrogen is almost planar in **32b**, it becomes pyramidalized in the enamines **32c** and **32e** and thus has a weaker electron-donating effect because of the reduced overlap between the nitrogen lone-pair and the π_{C-C}-bond.



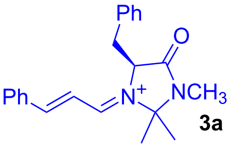
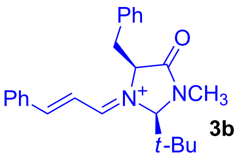
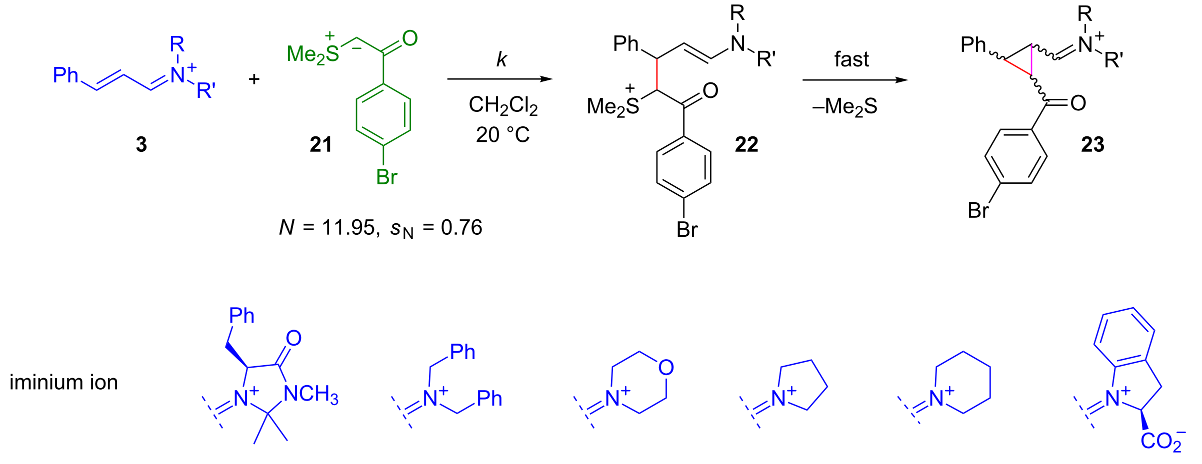
iminium ion				
enamide	**17b** (Ar = 4-Me-C_6H_4-)	**17g** (Ar = 4-OMe-C_6H_4-)	**17b** (Ar = 4-Me-C_6H_4-)	**17g** (Ar = 4-OMe-C_6H_4-)
N, s_N	6.57, 0.91	7.06, 0.85	6.57, 0.91	7.06, 0.85
k^{calcd} (M^{-1} s^{-1})	0.19	0.55	9.0	20
k^{exptl} (M^{-1} s^{-1})	0.26	0.73	3.3	7.1
k^{exptl}/k^{calcd}	1.4	1.3	0.36	0.35

Figure 13: Experimental and calculated rate constants k_2 for the reactions of **17b** and **17g** with **3a** and **3b** in the presence of 2,6-lutidine in CH_2Cl_2 at 20 °C [61].



iminium ion	3a	3d	3e	3h	3i	3g
E	–7.37	–8.5	–8.6	–9.8	–10.3	–9.5
k^{calcd} (M^{-1} s^{-1})	4.1×10^3	4.2×10^2	3.5×10^2	4.3×10^1	1.8×10^1	7.1×10^1
k^{exptl} (M^{-1} s^{-1})	1.31×10^5	1.08×10^4	4.01×10^3	1.19×10^2	1.22×10^2	**$> 10^7$**
$k^{\text{exptl}}/k^{\text{calcd}}$	32	26	11	2.8	6.8	**$> 10^5$**

Figure 14: Comparison between experimental and calculated (Equation 1) cyclopropanation rate constants [64].

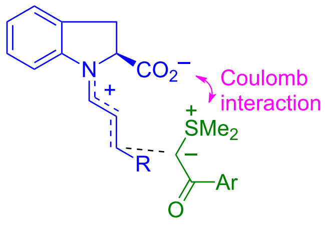


Figure 15: Electrostatic activation of iminium activated cyclopropanations with sulfur ylides.

Combination of the data in Figure 18 and Figure 19 now explains why the Jørgensen-Hayashi diphenylprolinol trimethylsilyl ether [81], the precursor of **32b**, and structurally related pyrrolidines have previously been employed for catalyzing the reactions of aldehydes and ketones with weak electrophiles, such as β-nitrostyrene (E = –13.9) [85] or di-*tert*-butyl azodicarboxylate (E = –12.2) [86]. The less basic imidazolidinones, which yield the less nucleophilic enamines **32d** and **32e**, are suitable catalysts for reactions with stronger electrophiles, such as the chlorinating agent 2,3,4,5,6,6-hexachlorocyclohexan-2,4-dien-1-one (E = –6.75) [87] and, in particular, stabilized carbocations, which are generated in situ from the corresponding alcohols under weakly acidic conditions [14,88,89]. Suggestions for further promising electrophilic reaction partners in enamine activated reactions [90] can be derived from the electrophilicity scales in [4].

When proline or structurally related bifunctional catalysts are employed, the mechanism depicted in Figure 17 has to be modified. List and Houk explained the high enantioselectivity of proline catalyzed reactions of aldehydes or ketones with electrophiles by the transition state **TS-A** in Figure 20, in which the electrophile is activated by the proton of the carboxy group [71]. The formation of oxazolidinones, the only observable intermediates of this reaction cascade, was considered to be an unproductive dead end [70]. On the other hand, Seebach and Eschenmoser raised the question of whether oxazolidinones, rather than being “parasitic species”, may also play a decisive role in determining the stereochemical course of proline-catalyzed reactions. In order to account for the observed stereoselectivities, it was suggested that **TS-B** is favored over the stereoelectronically preferred **TS-C**, because it yields the more stable oxazolidinone [91].

Figure 21 shows that the enaminocarboxylate **33**$^-$ reacts 50 to 60 times faster with benzhydrylium ions than pyrrolidinocyclohexene **36** and even 800 to 900 times faster than the methyl ester **37** [92].

We consider the high rates of the reactions of **33**$^-$ with benzhydrylium ions **18** as evidence for anchimeric assistance by the carboxylate group. As only part of the accelerating effect of the CO_2^- group can be due to Coulomb attraction, the formation of the C–O bond of the oxazolidone **34** is concluded to

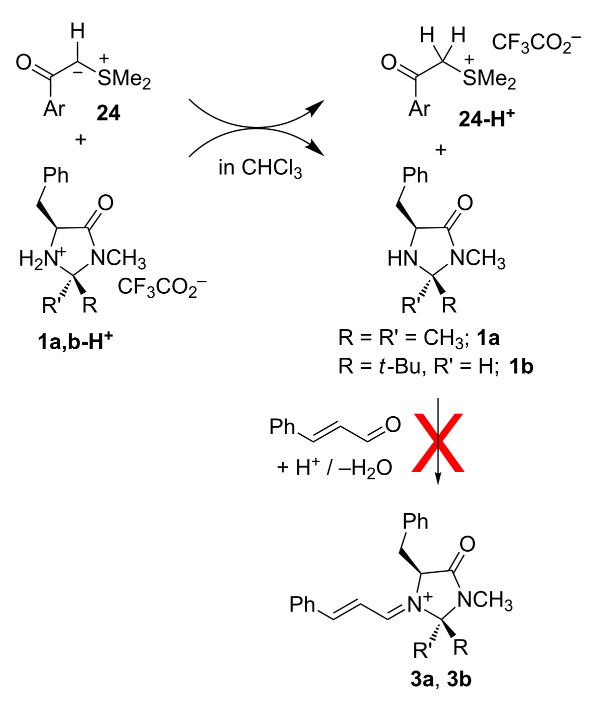


Figure 16: Sulfur ylides inhibit the formation of iminium ions.

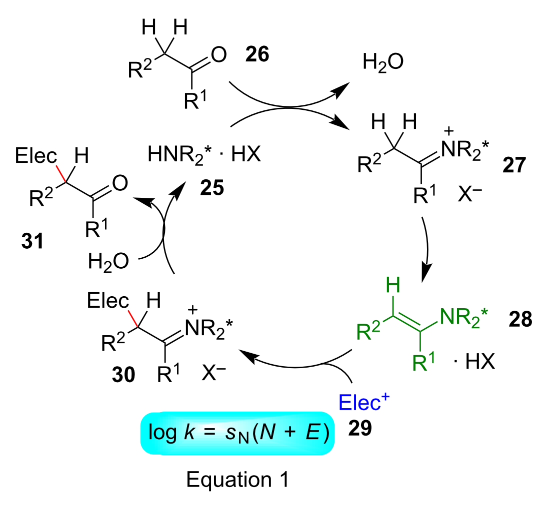


Figure 17: Enamine activation [65].

occur concomitantly with the formation of the C–C bond. The observation that β-nitrostyrene, a neutral electrophile, also reacts 10^2 times faster with **33**$^-$ than with **36** also excludes Coulomb attraction to be the major factor for the high reactivity of **33**$^-$. On the other hand, di-*tert*-butyl azodicarboxylate

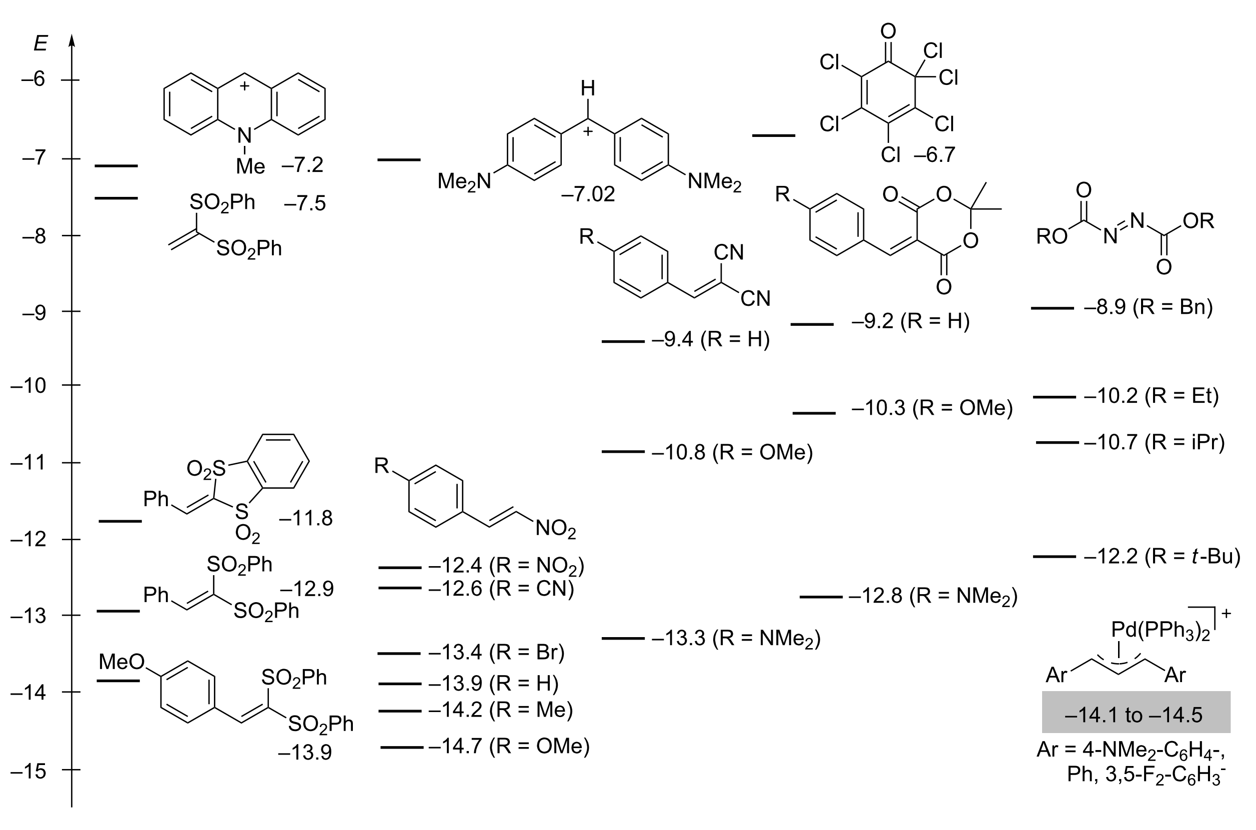


Figure 18: Electrophilicity parameters *E* for classes of compounds that have been used as electrophilic substrates in enamine activated reactions [4,73-80].

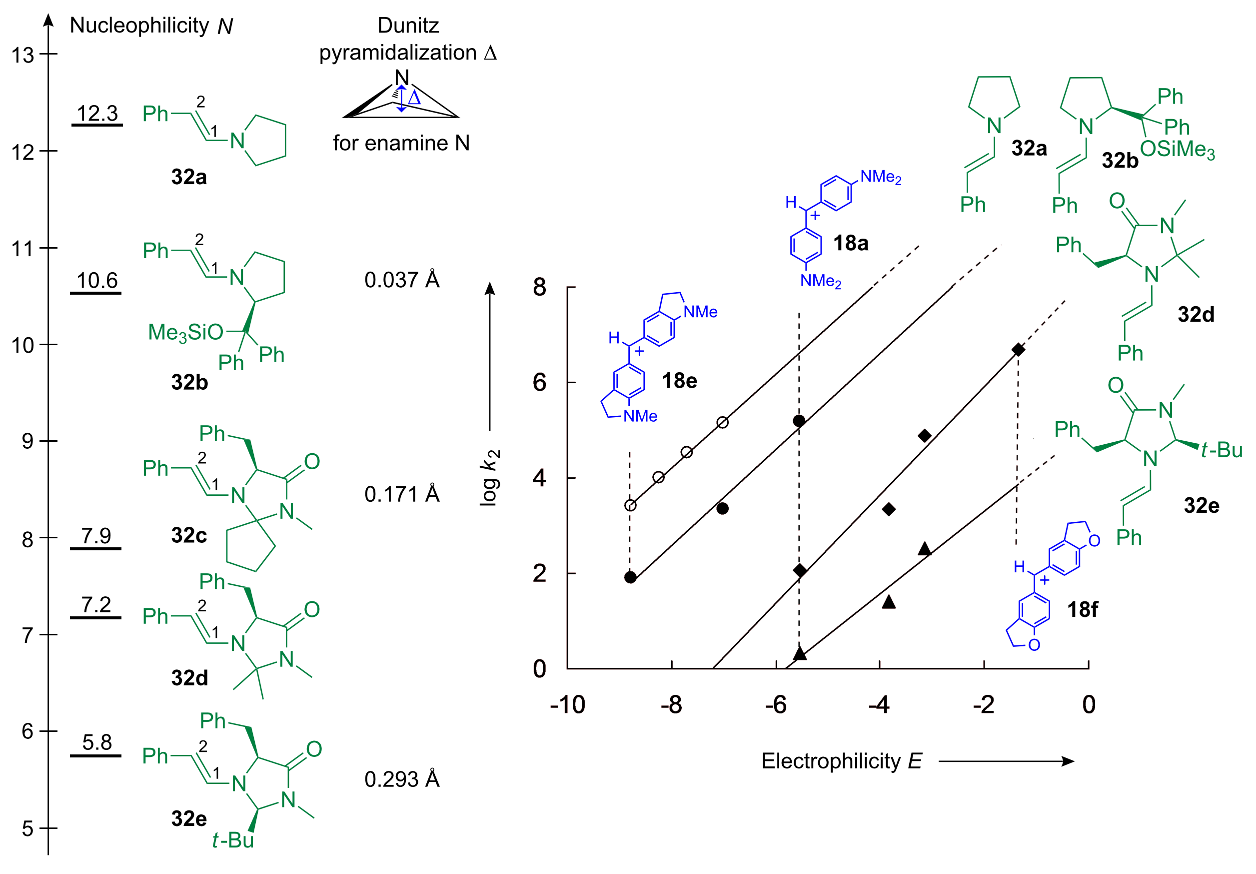


Figure 19: Quantification of the nucleophilic reactivities of the enamines **32a–e** in acetonitrile (20 °C) [83]; a definition of the Dunitz pyramidalization Δ is given in [84].

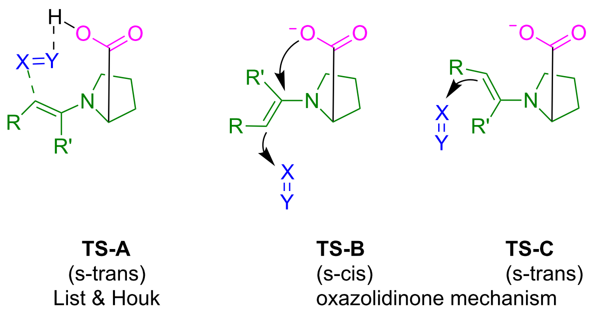


Figure 20: Proposed transition states for the stereogenic step in proline-catalyzed reactions.

reacts only six times faster with **33**$^-$ than with **36**, showing that the magnitude of the anchimeric assistance depends largely on the nature of the electrophile.

The data in Figure 21 thus suggest that the oxazolidinones **34** are formed in the stereodifferentiating step when enaminecarboxylate anions are the effective nucleophiles. However, our observations do not affect the rationalization of the stereoselectivities of proline-catalyzed reactions by **TS-A** when the electrophilic attack occurs at an enaminocarboxylic acid. Blackmond's observation of a change of enantioselectivity by added bases is in line with our interpretations [93].

Quantitative aspects of N-heterocyclic carbene (NHC) catalysis

As the following discussion will focus on the difference between the kinetic term "nucleophilicity" and the thermodynamic term "Lewis basicity", let us first illustrate this aspect by comparing the behavior of two well-known organocatalysts, 1,4-diazabicyclo[2.2.2]octane (DABCO, **38**) and (4-dimethylamino)pyridine (DMAP, **39**). As shown in Figure 22, DABCO (**38**) reacts approximately 10^3 times faster with benzhydrylium ions than DMAP (**39**), i.e., DABCO (**38**) is considerably more nucleophilic than DMAP (**39**) [94].

On the other hand, the equilibrium constant for the formation of the Lewis acid–Lewis base adduct with **18g** is 160 times smaller for DABCO (**38**) than for DMAP (**39**), i.e., DABCO (**38**) is a significantly weaker Lewis base than DMAP (**39**). We have previously discussed that it is the higher reorganization energy

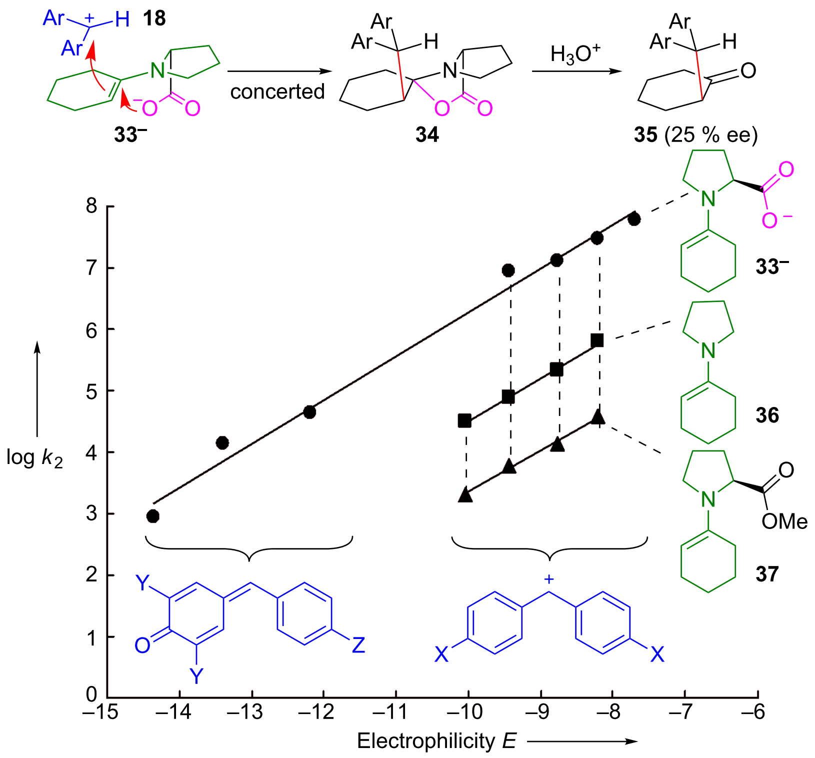
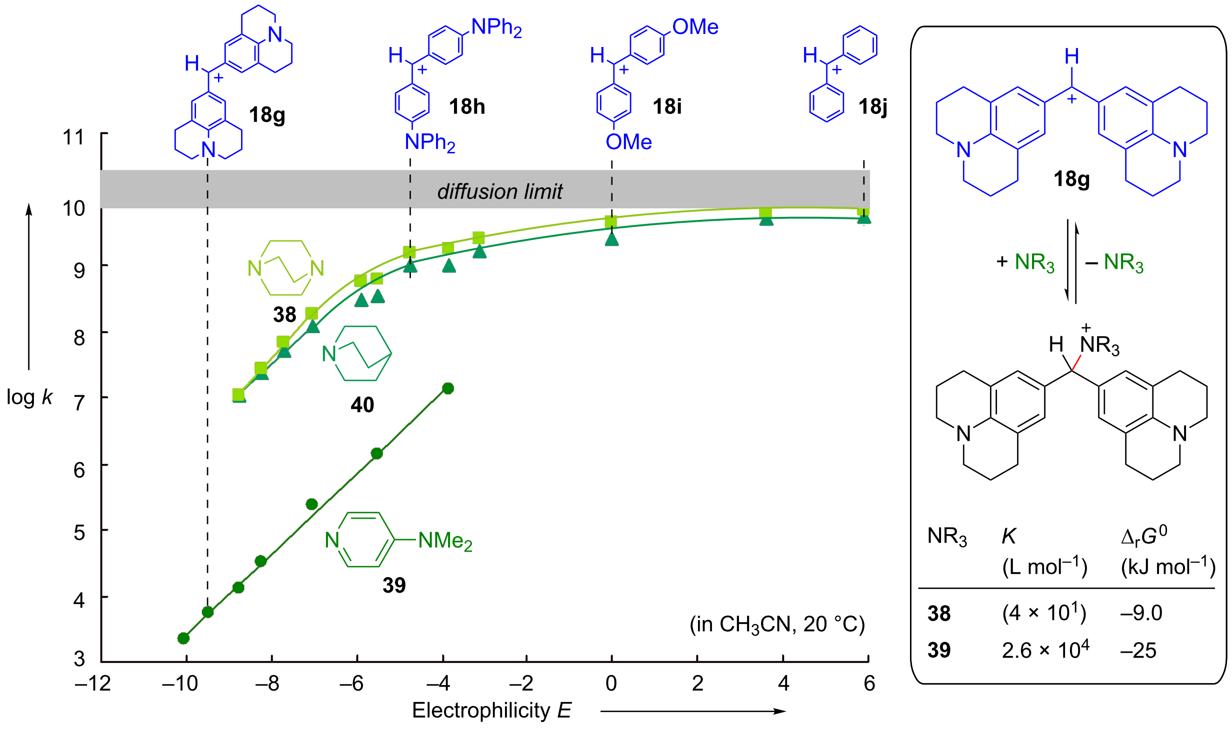


Figure 21: Kinetic evidence for the anchimeric assistance of the electrophilic attack by the carboxylate group. The hydrolysis product (*R*)-**35** was obtained with 25% ee from the reaction of **33⁻** (counterion: protonated DBU) with **18a**-BF_4^- (Ar = 4-Me_2N-C_6H_4) in MeCN after aqueous workup [92].



NR_3	*K* (L mol⁻¹)	Δ_rG^0 (kJ mol⁻¹)
38	(4 × 10^1)	–9.0
39	2.6 × 10^4	–25

Figure 22: Differentiation of nucleophilicity and Lewis basicity (in acetonitrile at 20 °C): Rate (left) and equilibrium constants (right) for the reactions of amines with benzhydrylium ions [94,95].

for the reaction of DMAP (**39**) that is responsible for the higher intrinsic barrier and subsequently the lower nucleophilicity of DMAP (**39**) [94].

The upper part of Figure 23 compares the relative rates for the reactions of various organocatalysts (in THF) with the benzhydrylium ion **18e** and the structurally related quinone methide **18k**. This comparison reveals that the nucleophilicities of the NHCs **41**–**43** do not differ fundamentally from those of other organocatalysts, e.g., triphenylphosphine (**10b**), DMAP (**39**), and DABCO (**38**) [96].

The considerably lower nucleophilicity of the triazolylidene **43** compared with the imidazolylidene **42** can be explained by the inductive electron withdrawal of the extra nitrogen in the triazol derivative **43**. The similar nucleophilicities of the imidazole- and imidazolidine-derived carbenes **42** and **41** are, at first glance, surprising and will be discussed below. The lower part of Figure 23 illustrates that all three NHCs, **41**, **42**, and **43**, react quantitatively with the quinone methide **18k**, while none of the other Lewis bases, despite their similar nucleophilicities, gives an adduct. The resulting conclusion, that all NHCs are significantly stronger Lewis bases than PPh_3 (**10b**), DMAP (**39**), and DABCO (**38**), is confirmed by quantum chemical calculations: The methyl cation affinities (MCAs) of the three carbenes **41**–**43** are 100–200 kJ mol^{-1} higher than those of the other Lewis bases in Figure 23 [96].

As the carbenes **41** and **42** have almost identical nucleophilicities and Lewis basicities, the question arose as to why imidazolidine-2-ylidenes (for example, **41**) have rarely been used as organocatalysts, while unsaturated NHCs (for example, **42**) have been reported to catalyze a large variety of reactions [97-104]. Can the difference be explained by the properties of the Breslow intermediates [105]? To address this question, the deoxy Breslow intermediates **45** [106-108] were synthesized by

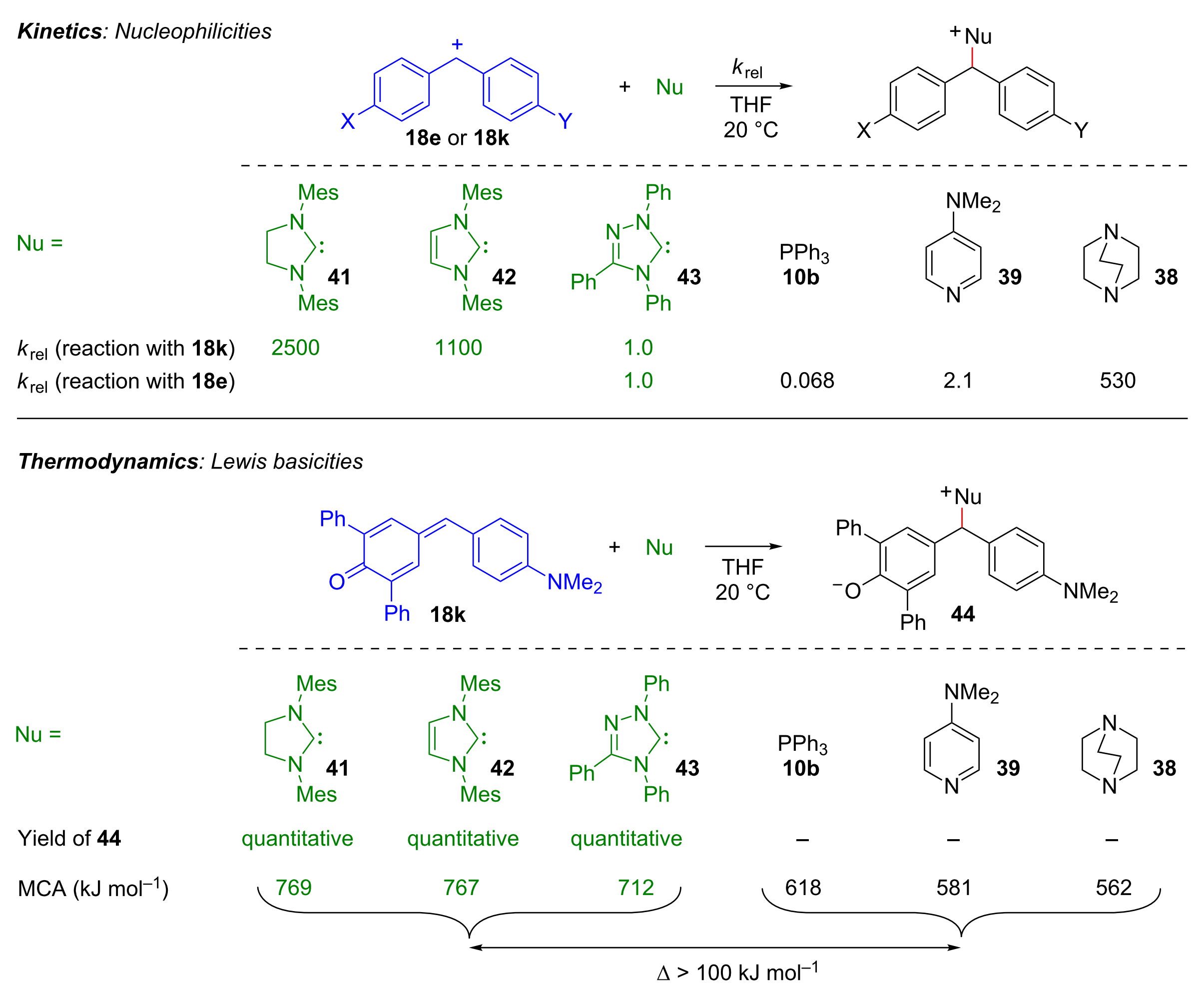


Figure 23: NHCs **41**, **42**, and **43** are moderately active nucleophiles and exceptionally strong Lewis bases (methyl cation affinity, MCA, was calculated for the reaction $CH_3^+ + Nu \rightarrow CH_3\text{–}Nu^+$ on MP2/6-31+G(d,p)//B98/6-31G(d) level of theory) [96].

reactions of the NHCs **41**–**43** with benzyl bromides and subsequent deprotonation of the resulting amidinium ions.

The linear correlations in Figure 24 show that the nucleophilic reactivities of the so-called deoxy Breslow intermediates **45a**–**f** can be described by Equation 1 [107]. In contrast to the situation described for the NHCs in Figure 23, the benzylidene-imidazolines **45a**,**d** are now 10^3 times more nucleophilic than the corresponding benzylidene-imidazolidines **45c**,**f** (Figure 24 and Figure 25a).

The different behavior was analyzed by quantum chemical calculations (Figure 25b). In the same way that the nucleophilicity order of the carbenes (**41** ≈ **42** > **43**, Figure 23) parallels the order of the Lewis basicities (methyl cation affinities) of the model compounds (**49c** ≈ **49a** > **49b**, Figure 25b bottom), the nucleophilicity order of the deoxy Breslow intermediates (**45a** > **45b** > **45c**, Figure 25a) also mirrors the order of the proton affinities of the model compounds (**47a** > **47b** > **47c**, Figure 25b, top) [107].

A rationalization for the different sequence in the two series can be derived from the nucleus-independent chemical shifts (NICS) [109-111], which are considered to be a measure of aromaticity. In agreement with the almost equal lengths of the exocyclic C–C bonds in **45a** (136.1 pm) and **45c** (135.4 pm), as determined by X-ray crystallography, none of the two heterocyclic rings in **47a** and **47c** shows aromatic character (NICS(1)). However, while the electrophilic addition to the exocyclic double bond of **47a** yields the cyclic conjugated 6π system in **48a**, the analogous electrophilic addition to **47c** yields the nonaromatic amidinium ion **48c**. The high nucleophilicity of **45a**, which is mirrored by the high proton affinity of **47a**, can thus be explained by the gain of aromaticity during electrophilic attack. The same line of arguments can be used to rationalize the higher nucleophilicities and basicities of the triazoline derivatives **45b** and **47b**, respectively [107].

As the unsaturated carbenes **49a** and **49b** have already a similar aromatic character as the azolium ions **48a** and **48b** generated

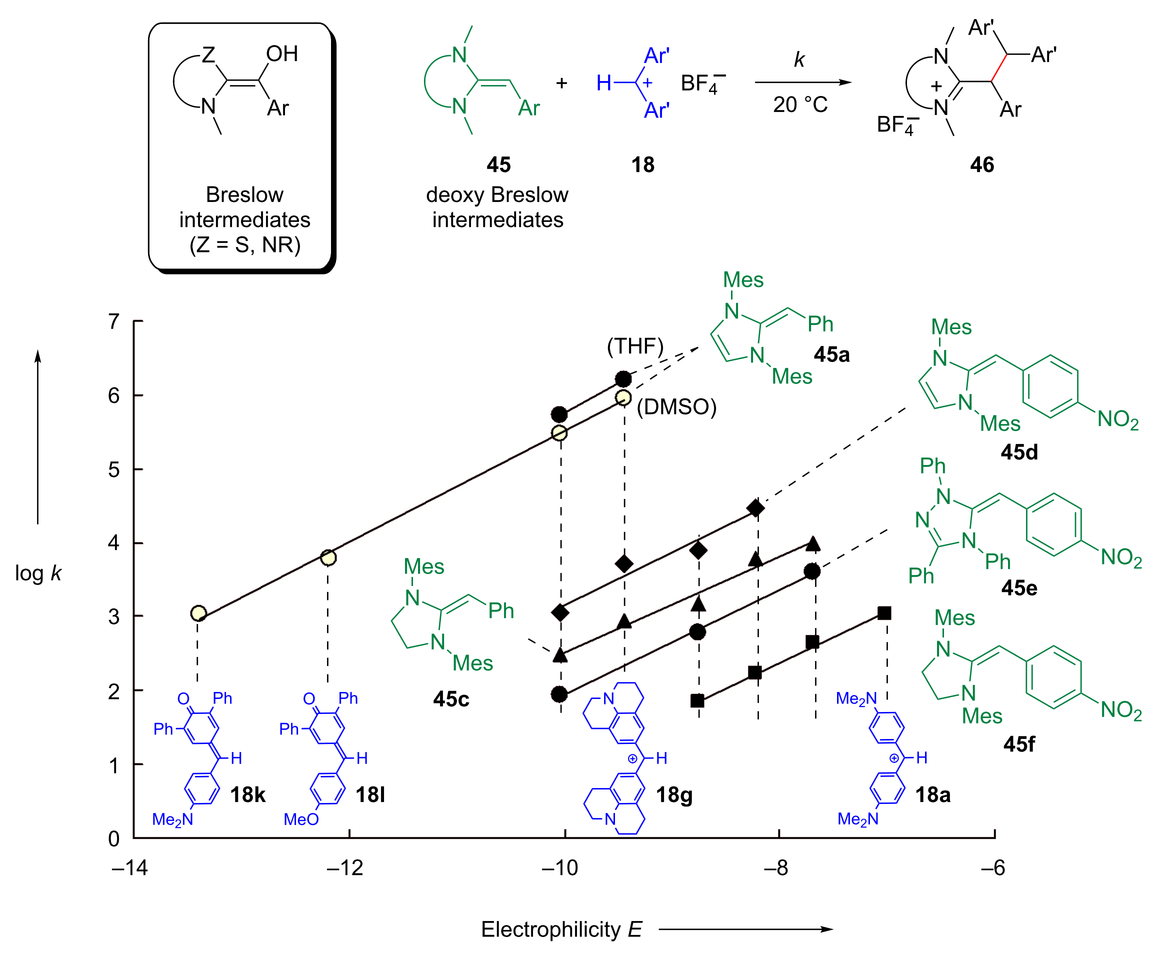


Figure 24: Nucleophilic reactivities of the deoxy Breslow intermediates **45** in THF at 20 °C [107].

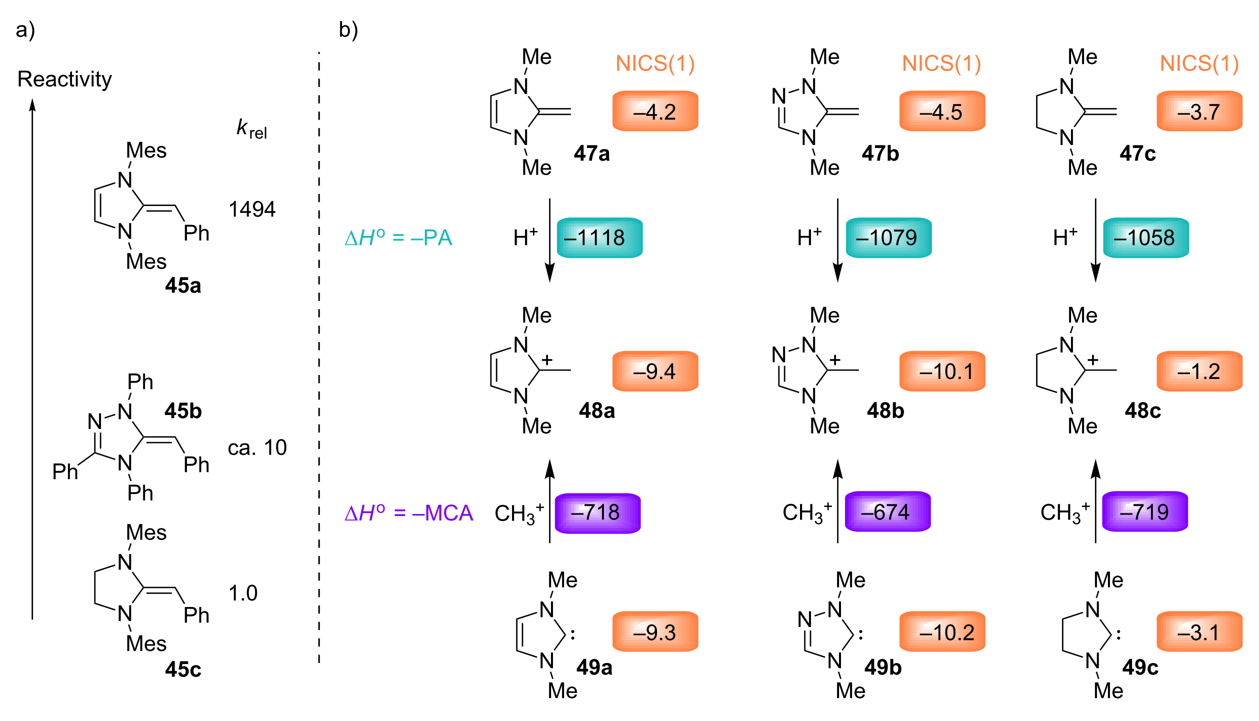


Figure 25: Comparison of the proton affinities (PA, from [107]) of the diaminoethylenes **47a–c** with the methyl cation affinities (MCA, from [96]) of the corresponding carbenes **49a**–**c** (in kJ mol^{-1}, MP2/6-31+G(2d,p)//B98/6-31G(d)), and the NICS(1) values of **47**–**49** (B3LYP/6-311+G(d)) (from [107]).

by protonation, unsaturated carbenes neither show higher basicity nor higher nucleophilicity than their saturated analogues [107].

Are the properties of the deoxy Breslow intermediates also representative for the real Breslow intermediates? As shown by Berkessel and co-workers [112], Breslow intermediates generally exist as the keto tautomers **51**, and attempts to generate their O-silylated derivatives **52** have failed (Figure 26).

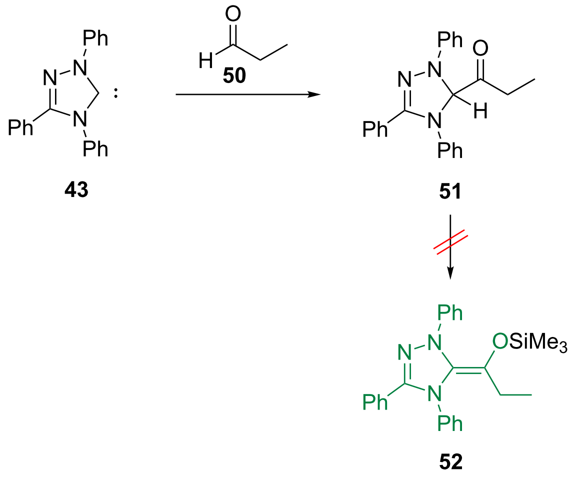


Figure 26: Berkessel’s synthesis of a Breslow intermediate (**51**, keto tautomer) from carbene **43** [112].

In order to get closer to the actual Breslow intermediates than in Rovis’ aza-Breslow intermediates [113], we synthesized and isolated the O-methylated Breslow intermediates **55a**–**c**, **57**, and **59** as described in Figure 27 [114]. Some of them were characterized by single-crystal X-ray crystallography.

Kinetic studies of their reactions with benzhydrylium ions provided their reactivity parameters N and s_N [114], and Figure 28 compares the relative reactivities of O-methylated and deoxy-Breslow intermediates toward the bis-pyrrolidino-substituted benzhydrylium ion **18l**. Comparison of the left and the central column shows that the O-methylated Breslow intermediates **55b** and **59** are 10^2 times less reactive than their deoxy analogues **61** and **45b**, respectively. Obviously, the transition state is more affected by the destabilization of the cationic adduct due to the inductive electron-withdrawing effect than by the +M-effect of the methoxy group, which raises the HOMO of the reactants. Replacement of the sulfur atom in the benzothiazole by a NCH_3 group (**55b** → **55c**) shows that imidazole derivatives are approximately four orders of magnitude more reactive than structurally analogous thiazole derivatives, which can, again, be assigned to the different electronegativities of sulfur and nitrogen.

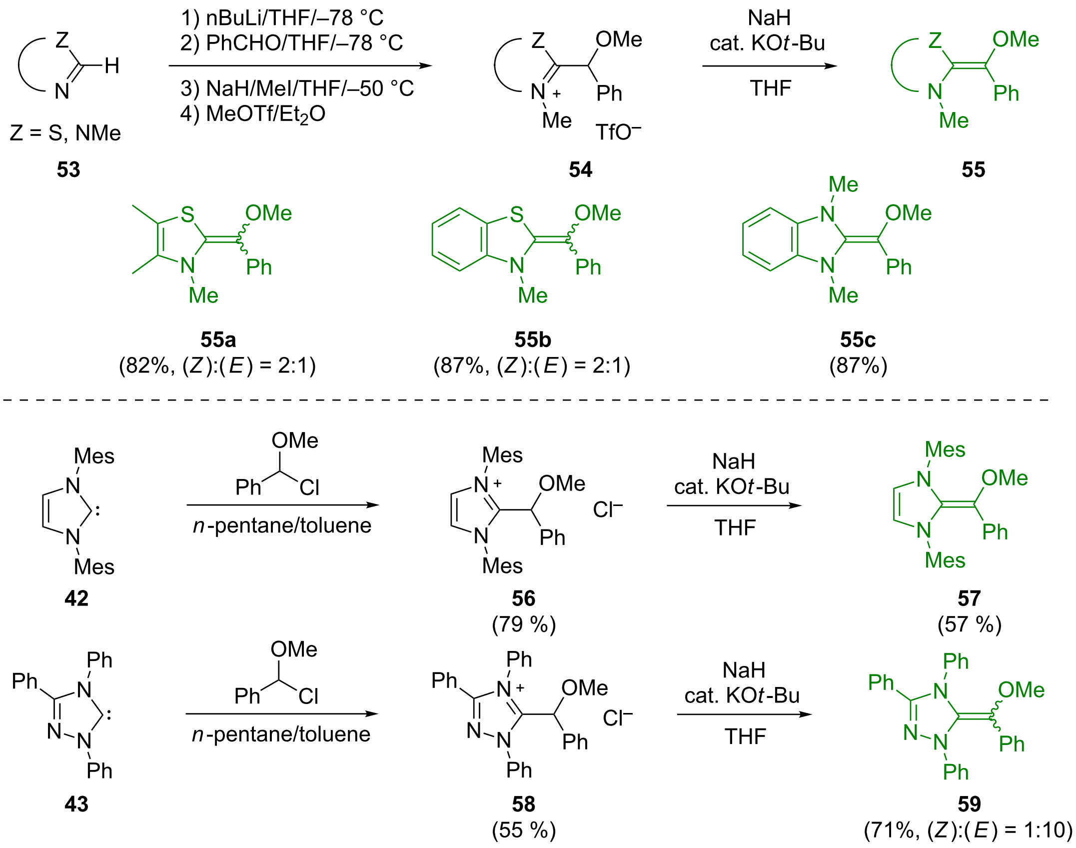


Figure 27: Synthesis of O-methylated Breslow intermediates [114].

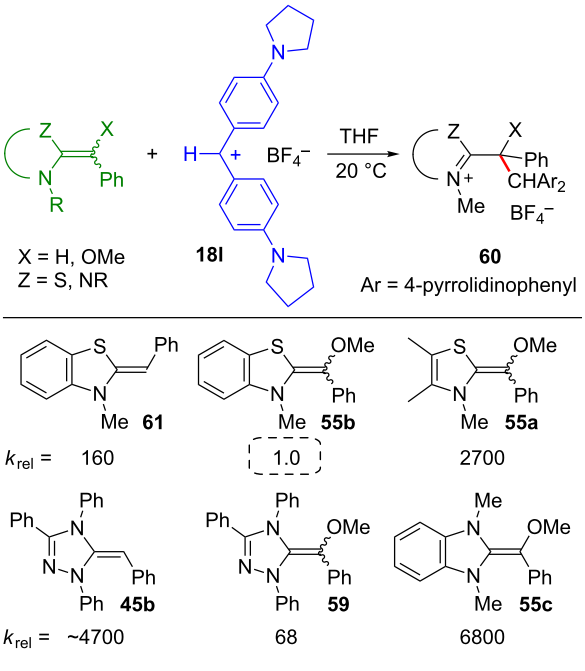


Figure 28: Relative reactivities of deoxy- and O-methylated Breslow intermediates [114].

Conclusion

Organocatalytic reactions are complex multicomponent reactions, and a detailed description of the kinetics of the complete catalytic cycles is not yet possible. We have demonstrated, however, that important information can be obtained by specifically synthesizing relevant intermediates and studying the kinetics of their reactions with nucleophiles or electrophiles. By including them in our comprehensive electrophilicity and nucleophilicity scales (Figure 29), it has become possible to settle mechanistic controversies and to explore the scope of substrates suitable for iminium as well as for enamine activated reactions.

Rate and equilibrium studies of the reactions of N-heterocyclic carbenes and the corresponding deoxy Breslow intermediates showed that N-heterocyclic carbenes have similar nucleophilicities as other frequently employed organocatalysts, but are much stronger Lewis bases. The 10^3 times higher nucleophilicities of benzylidene-imidazolines compared with benzylidene-imidazolidines explain why imidazol-2-ylidenes but not imidazolidine-2-ylidenes are commonly used organocatalysts.

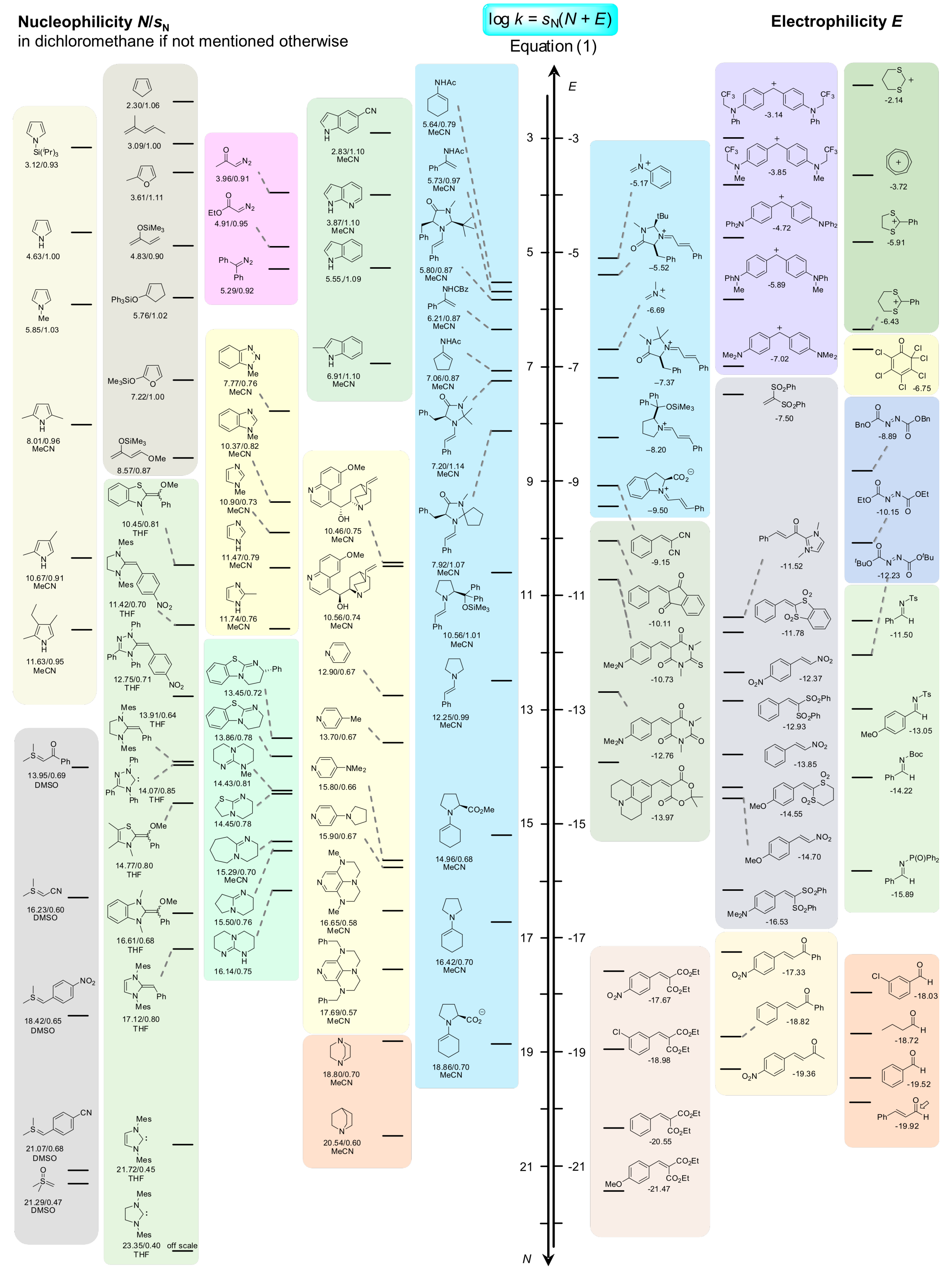


Figure 29: Reactivity scales for electrophiles and nucleophiles relevant for organocatalytic reactions (references and further reactivity parameters: [4]).

Acknowledgements

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Synthesis and evaluation of new guanidine-thiourea organocatalyst for the nitro-Michael reaction: Theoretical studies on mechanism and enantioselectivity

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Full Research Paper

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Abstract

A new guanidine-thiourea organocatalyst has been developed and applied as bifunctional organocatalyst in the Michael addition reaction of diethyl malonate to *trans*-β-nitrostyrene. Extensive DFT calculations, including solvent effects and dispersion corrections, as well as ab initio calculations provide a plausible description of the reaction mechanism.

Introduction

In recent years bifunctional compounds have found frequent applications as organocatalysts in modern synthetic organic chemistry [1-8]. Over the past decade, different catalytic methodologies have been reported that use chiral thiourea-based bifunctional molecules [9-13]. In particular, remarkable progress has been made in the development of secondary and tertiary amine-thiourea bifunctional organocatalysts for a great number of useful transformations [14-35].

Recently, the Tsogoeva group and that of Jacobsen reported the first successful application of primary amine-thiourea organocatalysts with the synchronous dual activation of a nucleophile and an electrophile in nitro-Michael addition reactions [36-42]. Bifunctional organocatalysts that contain both a thiourea moiety and an imidazole group [43,44] on a chiral scaffold, as asymmetric catalysts in the addition of acetone to *trans*-β-nitrostyrene, have also been reported [44-47].

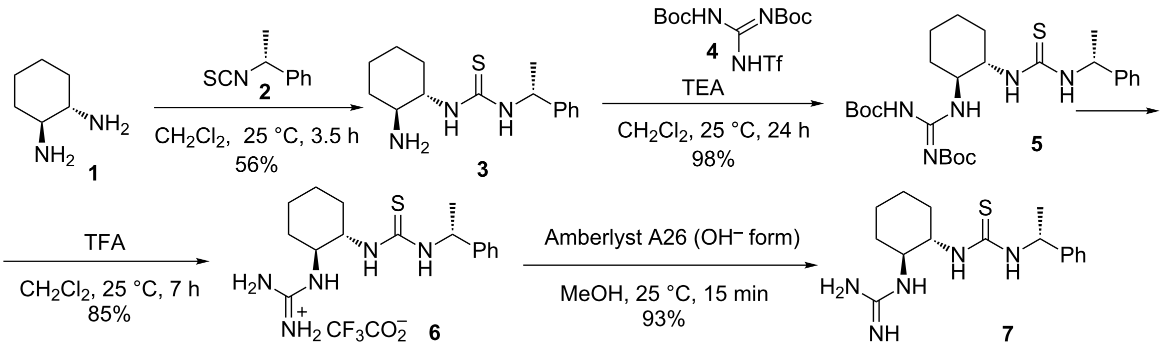
Since guanidines [48] are stronger bases than amines and/or imidazole, we were interested in exploring whether guanidine-thiourea organocatalysts would perform as well as or even better than amine-thioureas and imidazole-thioureas. Generally, guanidines are well-known basic catalysts in organic synthesis, but only scattered examples of chiral guanidines as organocatalysts are known [49]. Indeed, only one guanidine-thiourea organocatalyst has been published up until now [50-53]. This encouraged us to synthesize and investigate the potential of new guanidine-thiourea **7** as organocatalyst for the nitro-Michael addition reactions. Here we report the first results of our investigations, accompanied by quantum-chemical calculations on the mechanism and the observed stereoselectivity.

Results and Discussion

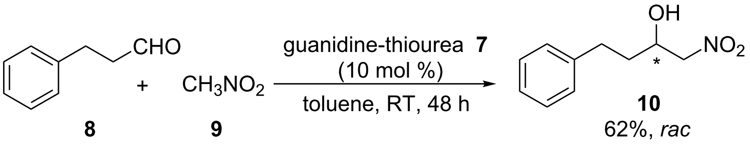
Synthesis and application of new guanidine-thiourea catalyst 7

The syntheses of new guanidine-thiourea compound **7** was accomplished by known methods [36,38,40,54-56] as summarised in Scheme 1. (*S*,*S*)-1,2-Diaminocyclohexane (**1**) and (*R*)-1-phenylethyl isothiocyanate (**2**) were employed for the synthesis of primary amine-thiourea **3** [36,38,40,54]. Subsequent treatment of **3** with a guanidinylation reagent, *N*,*N'*-di-Boc-*N''*-triflylguanidine (**4**) [54,55], gave the intermediate **5** in 98% yield. The next step involved cleavage of the *tert*-butyl groups with trifluoroacetic acid (TFA) to give the corresponding salt **6** in 85% yield. Finally, guanidinium salt neutralisation with Amberlyst A26 (OH⁻ form) [56], filtration and evaporation afforded the guanidine-thiourea **7** in high yield and purity. This compound was then examined for its ability to mediate the enantioselective C–C bond-formation reactions. As an initial model transformation we studied the Henry reaction of 3-phenylpropionaldehyde (**8**) with nitromethane (**9**) in the presence of 10 mol % of **7**, with the reaction proceeding for 48 h at room temperature in toluene. However, guanidine-thiourea **7** gave the product **10** only in racemic form and in moderate yield (62%, Scheme 2).

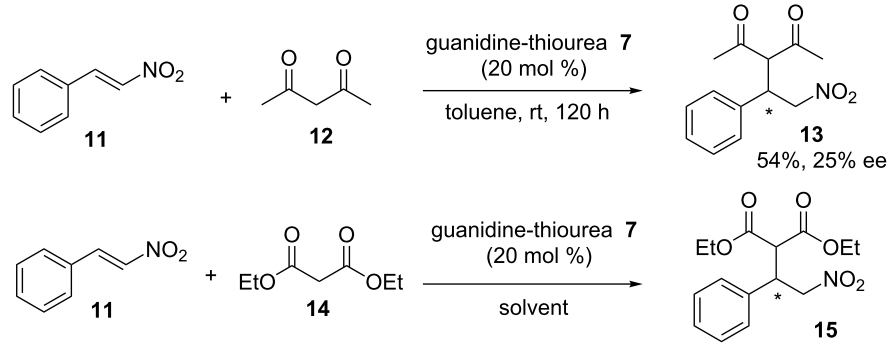
The Michael additions of 2,4-pentanedione and diethylmalonate to *trans*-β-nitrostyrene were further explored (Scheme 3). The use of guanidine-thiourea **7** at 20 mol % in toluene at room temperature resulted in the formation of the corresponding products **13** and **15** in moderate yields and low enantioselectivities, i.e., 54%, 25% ee for **13** (Scheme 3) and 66%, 5% ee for **15** (Scheme 3, Table 1, entry 1). Interestingly, while catalyst **7** provides the product **13** in 54% yield after 120 h, the same catalyst produces the Michael product **15** with 66% yield in only 2 h. We therefore decided to study the solvent effects on the reaction outcome in the nitro-Michael reaction of diethylmalonate with *trans*-β-nitrostyrene further. The results are shown in Table 1. Whereas Michael reactions performed in dichloromethane and ethyl acetate showed better results in terms of yields, compared to the results obtained in toluene (Table 1, entries 2 and 3 versus entry 1), reactions in ether and ethanol gave the adduct with lower yields (Table 1, entries 4 and 5). Notably, the highest yield (96%, Table 1, entry 6) was observed in THF. However, the Michael product was nearly racemic in all runs, indicating that the influence of chirality of



Scheme 1: Synthesis of guanidine-thiourea organocatalyst **7**.



Scheme 2: Henry reaction of 3-phenylpropionaldehyde (**8**) with nitromethane (**9**).



Scheme 3: Michael addition of (**12**) and (**14**) to *trans*-β-nitrostyrene (**11**).

the catalyst was minimal in all of the solvents screened. We expected that the resulting ee value would be higher at a lower temperature. However, carrying out the reaction for 24 h in THF at −78 °C gave again the racemic product in 78% yield. Hence, yield rather than ee value is influenced here by the reaction temperature. In order to explain the enantioselectivities observed, as well as to refine the catalyst design, or possibly get ideas that can be transferred to other systems, we decided to carry out a computational investigation of this guanidine-thiourea catalysed nitro-Michael reaction employing density functional calculations.

Table 1: Screening of solvents for the guanidine-thiourea **7** catalysed *nitro*-Michael addition of diethylmalonate (**14**) to *trans*-β-nitrostyrene (**11**) (Scheme 3).

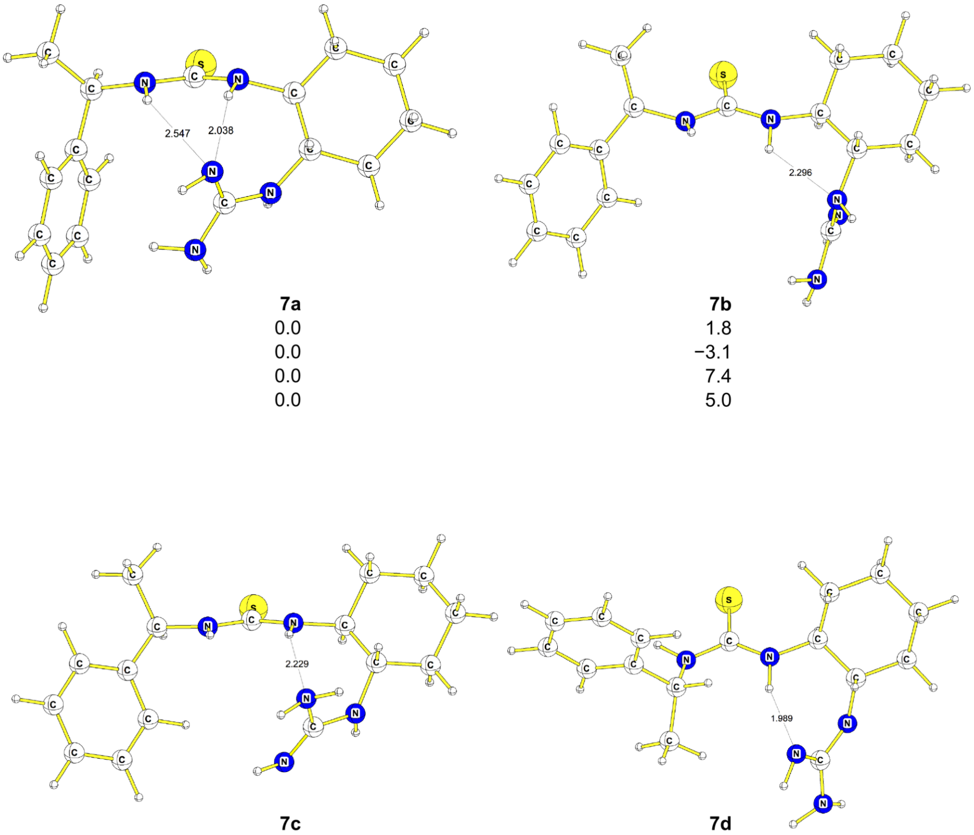
entry	temperature	solvent	reaction time [h]	yield [%]^a
1	rt	toluene	2	66
2	rt	CH_2Cl_2	2	81
3	rt	EtOAc	2	83
4	rt	Et_2O	2	42
5	rt	EtOH	2	56
6	**rt**	**THF**	**2**	**96**
7	−78 °C	THF	24	78

^{a}Yield of isolated product after column chromatography on SiO_2.

Theoretical studies: DFT calculations

The main goal of our calculations was to gain insight into the mechanism of the nitro-Michael addition of diethyl malonate (**14**) to nitrostyrene (**11**) and to find a plausible explanation as to why the enantioselectivity of this reaction is low. As a first step, we explored the conformational flexibility of the catalyst **7** itself. Pápai and co-workers [57] studied a similar dimethylaminothiourea catalyst and found that their system cannot be treated as conformationally rigid. Thus, a full conformational search of **7** was performed at the AM1 level by using the TORQUE algorithm within the VAMP program [58]. Based on the clustered semiempirical results, the four most stable structures were selected for the further optimization at the B3PW91/6–31G(d) level. Conformer **7a** is the only one with two hydrogen bonds between a nitrogen atom in the guanidine moiety and hydrogen atoms from the thiourea fragment. While inclusion of the solvent effect (DFT-PCM) gives a preference of 3.1 kcal·mol^{-1} for **7b** over **7a** (Figure 1), gas-phase DFT, MP2 and DFT-D with van der Waals correction predict **7a** to be more stable than **7b** by between 1.8 and 7.4 kcal·mol^{-1} (Figure 1). The MP2 and DFT-D energies agree very well. The two other conformers, **7c** and **7d**, are less stable than **7a**/**7b** at all levels employed and were therefore not considered for the further studies.

A similar Michael reaction of 1,3-dicarbonyl compounds with nitroolefins has been studied in some detail before [57,59]. It is generally proposed that the reaction proceeds first by deprotonation of the acidic proton of malonate **14** followed by formation of a complex between **7** and **14**. Formation of **Complex1** between catalyst **7** and malonate **14** is exothermic (−6.5, −15.0 and −16.6 kcal·mol^{-1} B3PW91/6–31G(d), MP2 and DFT-D, respectively, Scheme 4). Two energetically almost equivalent complexes **Complex1** and **Complex2** are connected by the H-abstraction transition state with a rather low activation barrier of 4.4 kcal·mol^{-1} at the B3PW91/6–31G(d) level. Inclusion of PCM, MP2 and DFT-D corrections increases the activation barrier to 12.2, 9.4 and 8.0 kcal·mol^{-1}, in the DFT-PCM, MP2 and DFT-D results, respectively. We were also able to find a second complex **Complex2a**, which is less stable than **Complex2** by up to 22.9 kcal·mol^{-1} (MP2, Scheme 4). Again, gas-phase DFT, MP and DFT-D results follow the same trend, while inclusion of the solvent effect makes **Complex2a** 0.4 kcal·mol^{-1} more stable than **Complex2** (Scheme 4). In this complex, malonate **14** is coordinated only to the guanidine moiety.



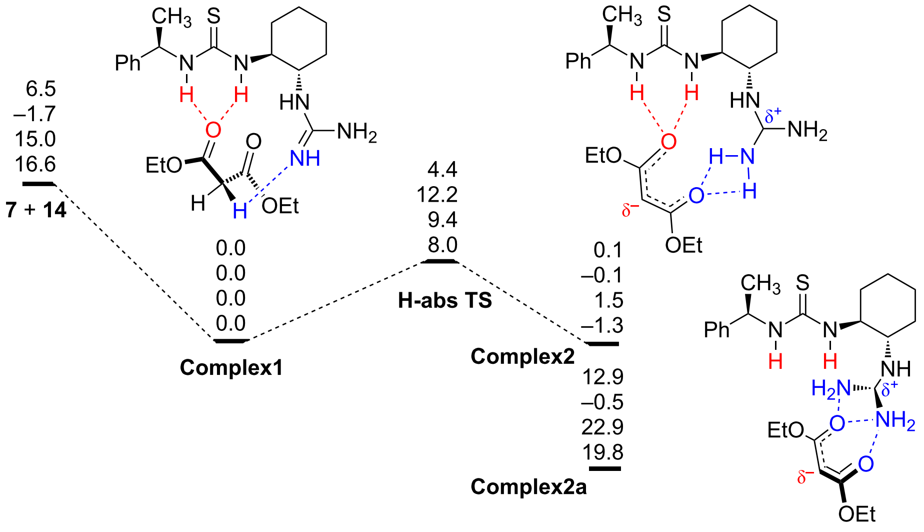
7a
0.0
0.0
0.0
0.0

7b
1.8
−3.1
7.4
5.0

7c
5.4
1.8
9.3
7.6

7d
8.5
3.9
13.1
12.0

Figure 1: Optimized geometries of four conformers of catalyst **7**. Energies are in kcal·mol^{-1}, B3PW91/6–31G(d) (first entry), DFT-PCM (second entry), MP2/6–311++G(d,p)// B3PW91/6–31G(d) (third entry), DFT-D (fourth entry). Bond lengths are in Å.



Scheme 4: Energy profile for the first step of the reaction between catalyst **7** and malonate **14**. Energies are in kcal·mol^{-1}, B3PW91/6–31G(d) (first entry), DFT-PCM (second entry), MP2/6–311++G(d,p)//B3PW91/6–31G(d) (third entry), DFT-D (fourth entry).

Since catalyst **7** has a certain degree of conformational flexibility, one can expect various complexes between the catalyst **7** and nitrostyrene (**11**) to exist. We were able to locate five complexes (Figure 2) that differ in energy by up to 10.3 kcal·mol^{-1} {5.0 kcal·mol^{-1} (DFT–PCM), 22.6 kcal·mol^{-1}, (MP2), 18.5 kcal·mol^{-1}, (DFT-D)}.

It is interesting to note that nitrostyrene can coordinate not only to the thiourea moiety, as originally suggested by Takemoto and co-workers [22], but also to the amino group (as pointed out by Pápai and co-workers [57]) or both. The ternary complex **Init10** between catalyst **7**, malonate **14** and nitrostyrene (**11**) can be formed via two routes (Scheme 5): Formation of **Complex1**, activation of catalyst and H-transfer followed by addition of nitrostyrene (**11**) to **Complex2** or addition of malonate **14** to the complex **CatN1** followed by catalyst activation and H-transfer. The thermodynamics of both routes are comparable at all levels. Once ternary complex **Init10** is formed, there are few C–C bond-forming pathways.

Based on the extensive conformational search, we were able to find eleven competing transition states (Figure 3 and Figure 4), six of which lead to *R* products (**TS1**, **TS3**, **TS7**, **TS9**, **TS11, TS12**), and five of which (**TS2**, **TS5**, **TS6**, **TS8**, **TS10**) lead to *S* products; the corresponding initial and final complexes were also located. All but one (**TS6 *S***) transition state for the *S* enantiomer were found to lay lower on the potential-energy surface (PES), at all levels employed, compared to the corresponding transition states that lead to the *R* product. The activation barriers vary between +7.3 kcal·mol^{-1} (+7.5 kcal·mol^{-1} DFT-PCM, **TS8 *S***) and +14.1 kcal·mol^{-1} (+14.5 kcal·mol^{-1} DFT-PCM, **TS7 *R***). DFT-D and MP2/6–311++G(d,p)//6–31G(d) results support the same trend, although the absolute values of the activation energies are much lower and in some cases even

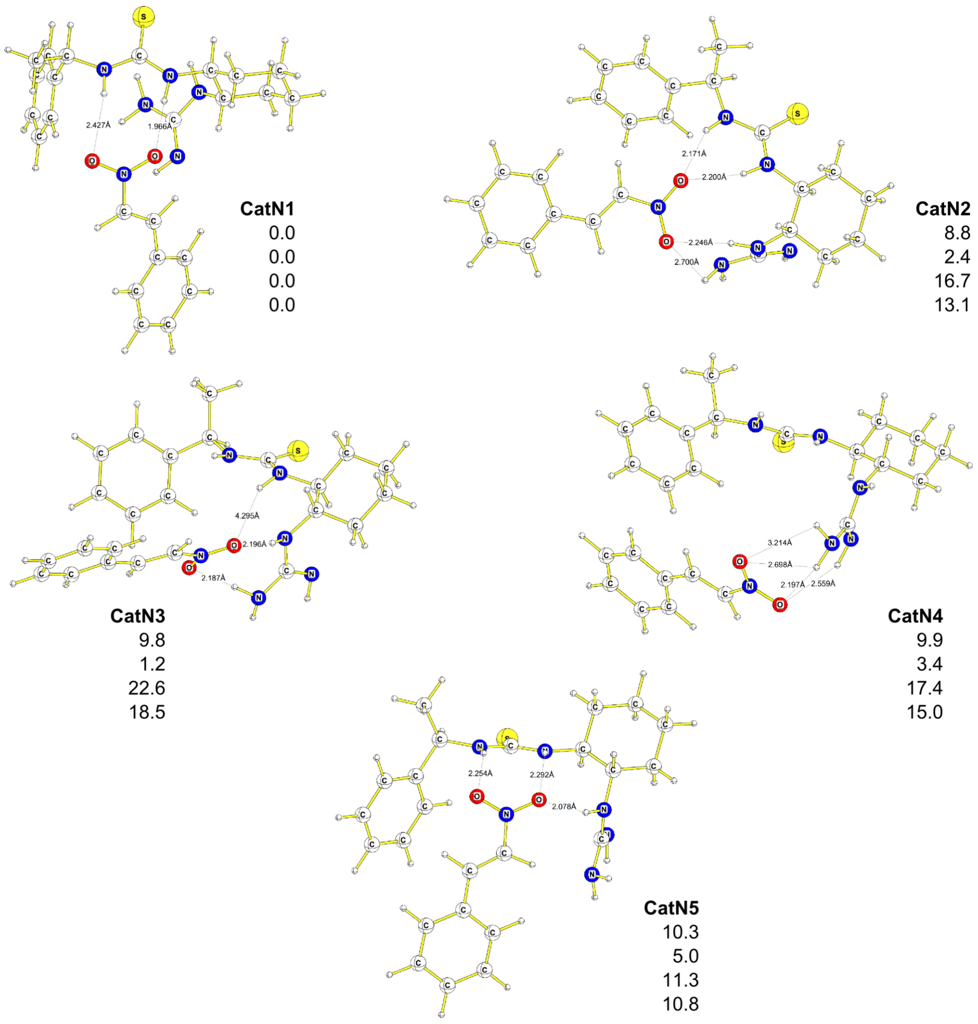
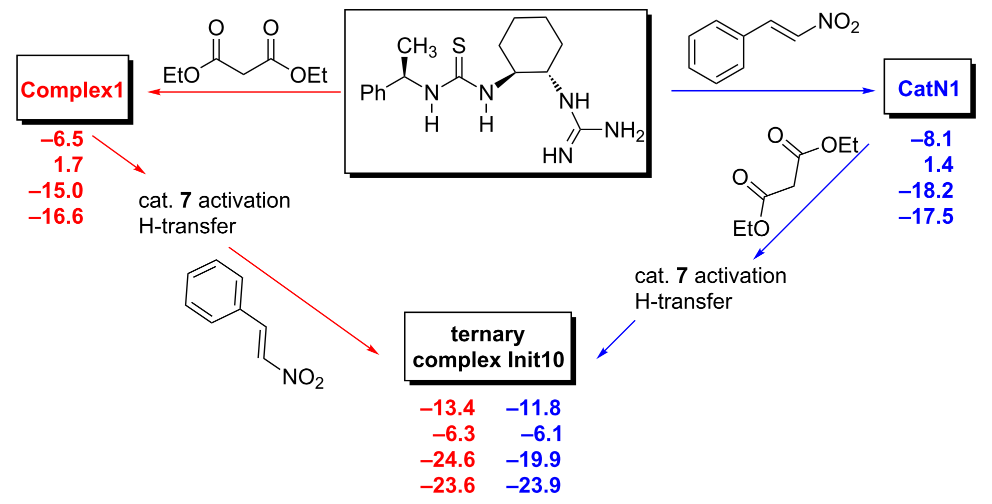


Figure 2: Complexes (**CatN1**–**CatN5**) between catalyst **7** and nitrostyrene **11**. Energies are in kcal·mol^{-1}, B3PW91/6–31G(d) (first entry), DFT-PCM (second entry), MP2/6–311++G(d,p)// B3PW91/6–31G(d) (third entry), DFT-D (fourth entry). Bond lengths are in Å.



Scheme 5: Two possible routes for ternary complex formation. Energies are in kcal·mol^{-1}, B3PW91/6–31G(d) (first entry), DFT-PCM (second entry), MP2/6–311++G(d,p)//B3PW91/6–31G(d) (third entry), DFT-D (fourth entry).

negative activation barriers were found (Figure 3 and Figure 4, Table 2). Relatively low activation barriers could explain the poor selectivity observed experimentally for this reaction, i.e., catalyst **7** is too active. The computed ee based on the theory of the activated complex (see Supporting Information File 1) give values between 43% and 99%, significantly higher than those observed experimentally. Also, at least six initial complexes (**INIT7–INIT12**) can interconvert, as the energy difference between them ranges from 0.7 kcal·mol^{-1} to 4.3 kcal·mol^{-1} (B3PW91/6–31G(d), Table 2).

In such a case (i.e., low barriers that result in thermodynamic control of the reaction products), the course of the reaction will be determined by the stability of the final *R* and *S* products. The most stable conformations of the final *R* and *S* complexes are essentially equally stable (Table 2). Thus, the experimentally observed low ee can be explained by the high catalytic activity of **7**. To lower its activity and to increase the selectivity of the reaction one can modify catalyst **7**, either by modifying a substituent, e.g., by introducing the bulky groups (*t*-Bu) into the phenyl ring, or by modifying the guanidine moiety. Preliminary

Table 2: Computed energy difference between initial and final complexes and activation barriers with respect to the **Init10** complex. Energies are in kcal·mol^{-1}, B3PW91/6–31G(d), (DFT-PCM), {MP2/6–311++G(d,p)//B3PW91/6–31G(d)} and [DFT-D].

	INIT	TS	FIN
1 *R*	10.7 (10.9) {8.8} [10.4]	12.2 (13.1) {7.9} [10.5]	1.7 (−1.0) {−10.6} [−2.5]
5 *S*	8.9 (7.3) {9.7} [10.1]	10.3 (9.5) {7.2} [8.3]	−0.2 (−2.9) {−12.8} [−4.9]
2 *S*	8.5 (8.7) {7.8} [10.5]	13.8 (13.3) {8.9} [11.6]	3.0 (1.6) {−9.0} [−3.3]
3 *R*	7.0 (5.6) {9.5} [10.8]	10.0 (10.1) {5.6} [8.7]	1.8 (−0.7) {−11.2} [−3.7]
6 *S*	7.5 (6.4) {8.4} [9.5]	10.2 (10.3) {5.9} [9.3]	1.9 (0.1) {−12.2} [−5.0]
7 *R*	4.3 (4.9) {3.9} [4.7]	14.1 (14.5) {3.0} [8.0]	5.4 (3.9) {−11.9} [−4.6]
8 *S*	1.0 (1.5) {−0.4} [0.7]	7.4 (8.1) {−1.6} [1.1]	−5.7 (−6.8) {−21.3} [−13.8]
9 *R*	1.1 (0.9) {0.5} [1.6]	8.1 (8.7) {3.0} [4.8]	−5.9 (−6.6) {−20.5} [−13.2]
10 *S*	0.0 (0.0) {0.0} [0.0]	8.1 (8.4) {−0.8} [2.7]	−4.5 (−5.2) {−14.1} [−8.7]
11 *R*	0.7 (1.4) {0.4} [1.4]	9.0 (9.7) {1.0} [4.1]	−1.4 (−3.4) {−16.8} [−9.4]
12 *R*	1.3 (1.0) {−0.2} [1.2]	7.3 (7.5) {−3.2} [0.6]	−5.9 (−6.6) {−20.5} [−13.2]

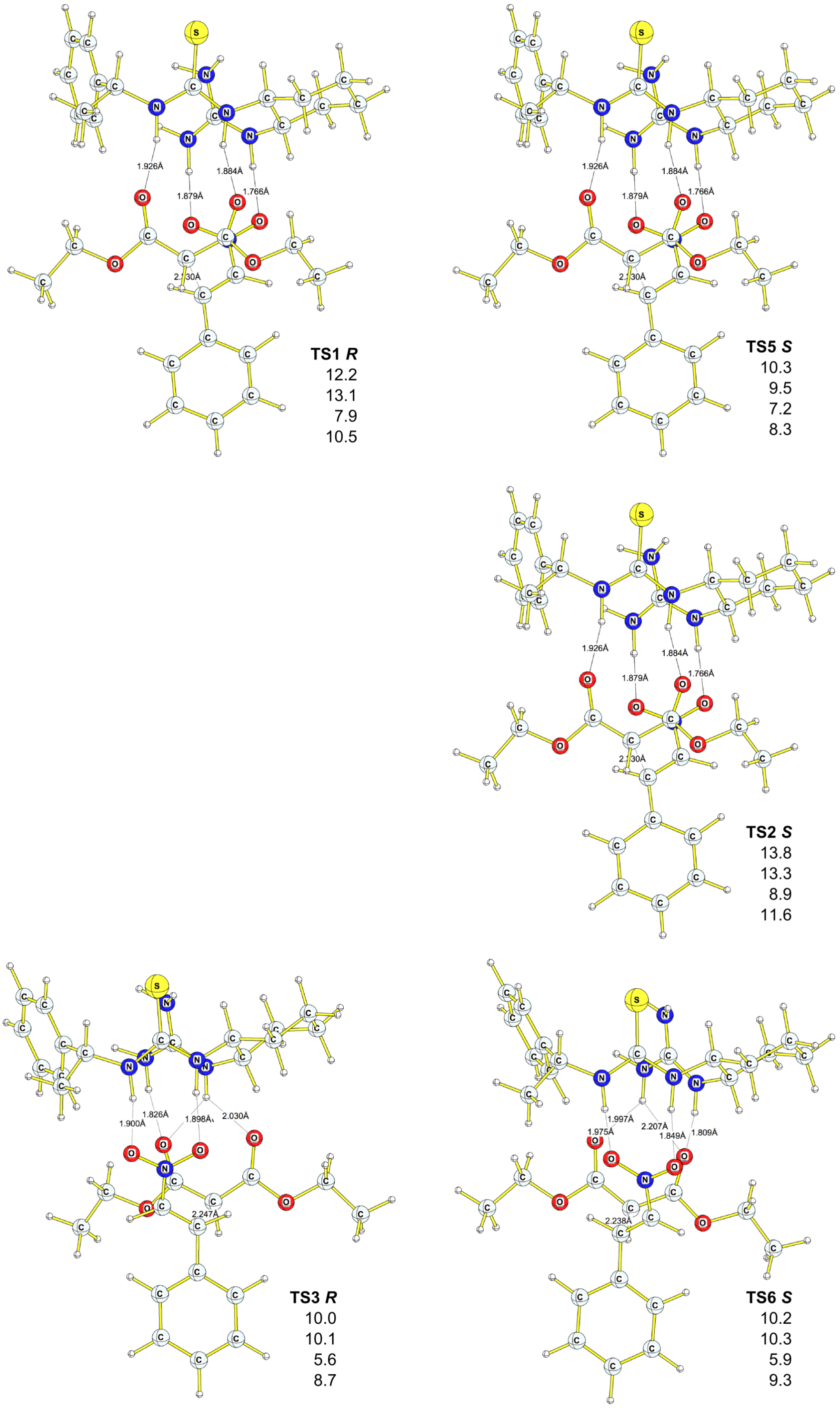


Figure 3: Geometries of transition states for *R* and *S* products. Relative energies (with respect to **Init10**) are in kcal·mol^{-1}, B3PW91/6–31G(d) (first entry), DFT-PCM (second entry), MP2/6–311++ G(d,p)//B3PW91/6–31G(d) (third entry), DFT-D (fourth entry). Bond lengths are in Å.

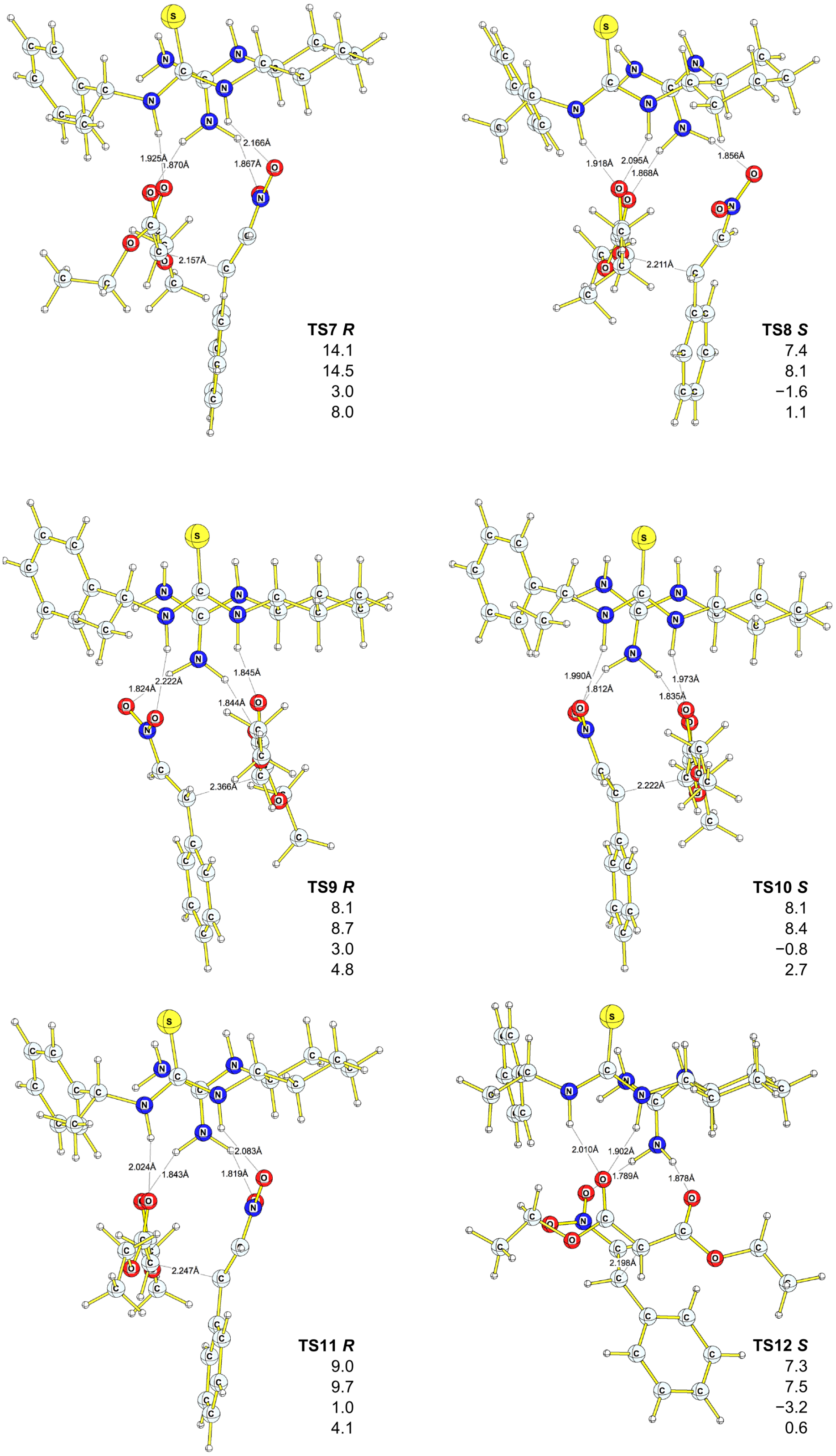
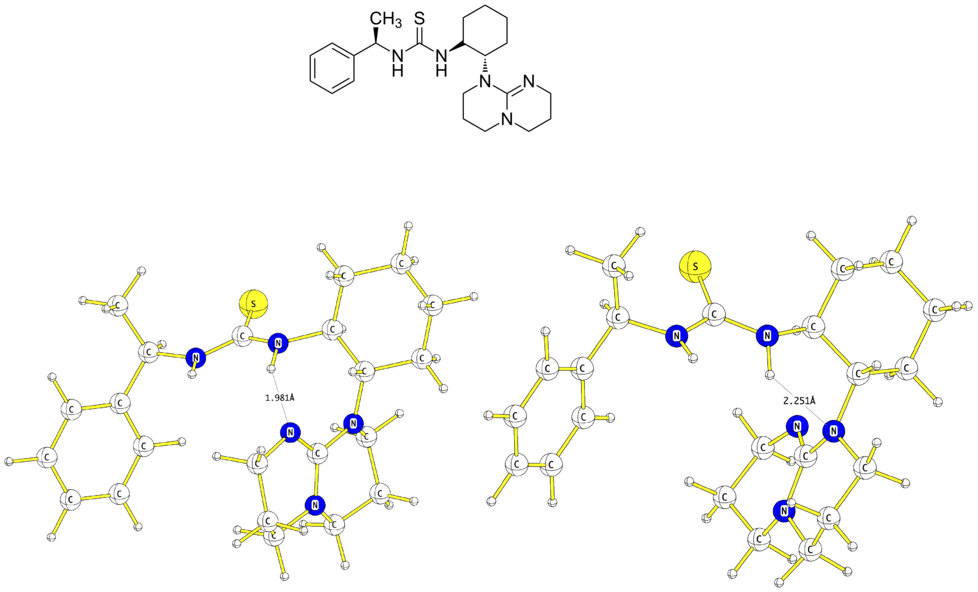


Figure 4: Geometries of transition states for *R* and *S* products. Relative energies (with respect to **Init10**) are in kcal·mol^{-1}, B3PW91/6–31G(d) (first entry), DFT-PCM (second entry), MP2/6–311++ G(d,p)//B3PW91/6–31G(d) (third entry), DFT-D (fourth entry). Bond lengths are in Å.



7-TABDa	7-TABDb
0.0	7.7
0.0	6.1
0.0	7.8
0.0	8.0

Figure 5: B3PW91/6–31G(d) (first entry), DFT-PCM (second entry), MP2/6–31G(d)//B3PW91/6–31G(d) (third entry) and DFT-D (fourth entry) optimized geometries of modified **7-TABD** catalyst. Energies are in kcal·mol^{-1}, bond lengths are in Å.

Table 3: Computed energy differences between initial and final complexes and activation barriers with respect to the **Init13** complex. Energies are in kcal·mol^{-1}, B3PW91/6–31G(d), (DFT-PCM), {MP2/6–31G(d)//B3PW91/6–31G(d)} and [DFT-D].

	INIT	TS	FIN
13 *R*	0.0 (0.0) {0.0} [0.0]	12.4 (12.8) {7.4} [6.8]	−2.4 (−2.6) {−13.2} [−8.5]
14 *S*	5.8 (4.6) {7.2} [6.9]	9.8 (10.4) {5.6} [5.4]	−3.4 (−7.0) {−9.4} [−3.3]
15 *R*	7.7 (8.0) {7.2} [6.5]	8.2 (8.8) {4.7} [5.5]	−2.4 (−2.7) {−12.5} [−7.5]
16 *R*	2.9 (1.6) {5.2} [5.6]	14.7 (14.4) {11.8} [12.7]	−2.2 (−4.2) {−11.4} [−6.6]

semiempirical calculations suggest that the introduction of two *t*-Bu-groups into the 1,3- aryl positions would not improve the performance of the catalyst; the system remains too flexible. On the other hand, modification of the guanidine moiety by introducing a rigid aza-heterocycle (1,5,7-triazabicyclo[4.4.0]dec-5-ene (TABD)) gave promising results.

For the modified **7-TABD** catalyst, we found only two conformers that differ by ca. 6–8 kcal·mol^{-1} (Figure 5). Assuming that the first part of the reaction pathway (coordination of either malonate or nitrostyrene to the catalyst, followed by addition of the third molecule) proceeds similarly to the pathway described above for the catalyst **7**/nitrostyrene/malonate system (Scheme 5), we focused our attention on the second part of the reaction, the C–C bond formation. We found four transition states, three of which lead to the *R* product and only one to the *S* equivalent (Figure 6).

Compared to the initial complexes **INIT1**–**INIT12**, the energy difference between the initial complexes **INIT13**–**INIT16** is much higher (between 4.6 and 8.0 kcal·mol^{-1}, Table 3). Thus, in the case of the **7-TABD** catalyst, interconversion between the initial complexes is less probable. Again, as in the case of catalyst **7**, the activation barriers seem to be overestimated at the gas-phase DFT and DFT-PCM levels, and underestimated with MP2/6–31G(d) and DFT-D corrections. Nevertheless,

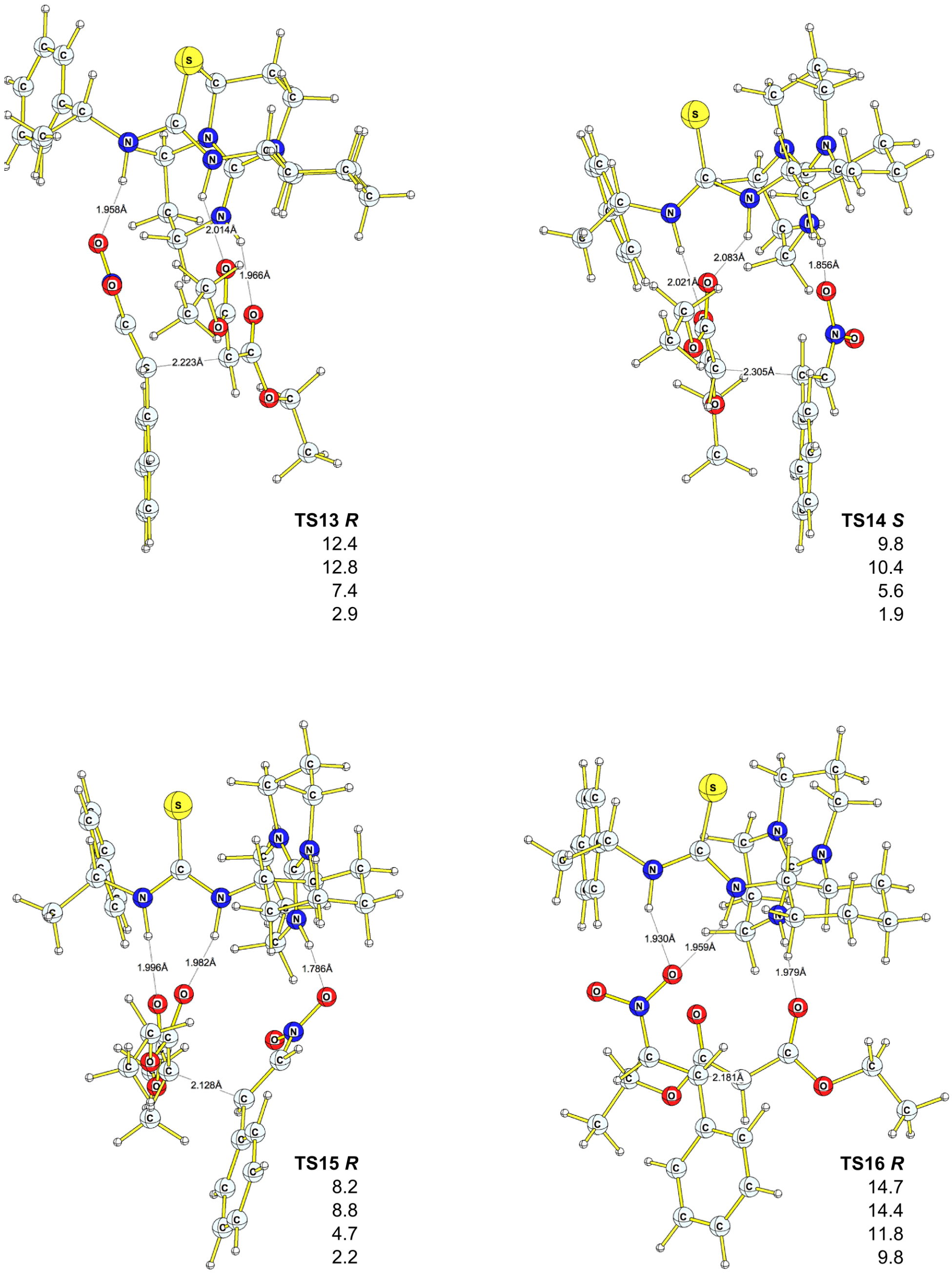


Figure 6: Geometries of transition states for *R* and *S* products with **7-TABD** catalyst. Relative energies (to **Init13**) are in kcal·mol^{-1}, B3PW91/6–31G(d) (first entry), DFT-PCM (second entry), MP2/6–31G(d)//B3PW91/6–31G(d) (third entry), DFT-D (fourth entry). Bond lengths are in Å.

compared to catalyst **7**, the presence of the cyclic tri-aza moiety in **7-TABD** increases the activation barriers. The reaction is calculated to favour the *R* product, as both the initial complex and the TS leading to the *R* product were found to be lower in energy than the *S* equivalents.

Conclusion

In summary, we have demonstrated that the new guanidine derived chiral thiourea **7** can catalyse the asymmetric nitro-Michael addition of diethyl malonate with trans-β-nitrostyrene, giving high yields (up to 96%) but low enantioselectivities. Based on extensive computational studies, the low observed enantioselectivity of this nitro-Michael reaction can be explained in terms of the high activity and high conformational flexibility of the guanidine-thiourea catalyst, which lead to thermodynamic control of the reaction products. For further experimental studies, a modified more conformationally rigid catalyst is proposed.

We would like to stress here that studies on systems of this size are influenced quite strongly by dispersion contributions [60-66] and that standard DFT calculations should be supplemented by at least single-point MP2 energy corrections with an extensive, large basis set. The DFT-D method agrees very well with the MP2 results.

Experimental

General: Reagents obtained from commercial sources were used without further purification. Dichloromethane was dried by heating under reflux over P_2O_5 and by distillation. Diethylether was dried by heating under reflux over sodium/benzophenone and by distillation prior to use. Solvents for chromatography were distilled prior to use. TLC chromatography was performed on precoated aluminium silica gel ALUGRAM SIL G/UV254 plates (Macherey-Nagel GmbH & Co.). Flash chromatography was performed on silica gel 60 Å (Acros particle size: 0.035–0.070 mm). NMR spectra were recorded on a Bruker Avance 300. FAB mass spectra were measured with a Micromass: ZabSpec. The enantiomeric excess of products was determined by chiral HPLC analysis in comparison with authentic racemic material. HPLC measurements were performed using Agilent 1200 Series equipment: vacuum degasser G1322-90010, quaternary pump G1311-90010, thermostated column compartment G1316-90010, diode array and multiple-wavelength detector SL G1315-90012, standard and preparative autosampler G1329-90020, and Agilent Chemstation for LC software.

(*R*)-(−)-α-Methylbenzyl isothiocyanate (2): To a solution of (*R*)-1-phenylethylamine (3.000 g, 3.151 mL, 24.76 mmol, 1.0 equiv) in anhydrous diethyl ether (20 mL), cooled to 0 °C and under a nitrogen atmosphere, carbon disulfide (12.065 g, 158.46 mmol, 9.6 mL, 6.4 equiv) and *N*,*N*′-dicyclohexylcarbodiimide (5.109 g, 24.76 mmol, 1.0 equiv) were added. The reaction mixture was stirred overnight and allowed to warm to ambient temperature during this time. The precipitated *N*,*N*″-dicyclohexylthiourea was filtered off, washed three times with diethyl ether and discarded. After evaporation of the filtrate, the residue was subjected to flash chromatography over silica gel (petrol ether/ethyl acetate 8:1) to yield **2** (3.909 g, 23.94 mmol, 97%) as a colourless oil. $[\alpha]_D^{25}$ −4.3 (*c* 1.0, acetone); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.68 (d, *J* = 6.7 Hz, 3H), 4.92 (q, *J* = 6.7 Hz, 1H), 7.27–7.50 (m, 5H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$) δ 24.96, 57.00, 125.39, 128.18, 128.88, 140.11 ppm.

Primary amine-thiourea 3: To a solution of (*S*,*S*)-1,2-diaminocyclohexane (**1**) (1.273 g, 11.15 mmol, 1.0 equiv) in anhydrous dichloromethane (100 mL), at ambient temperature and under a nitrogen atmosphere, a solution of **2** (1.820 g, 11.15 mmol, 1.0 equiv) in anhydrous dichloromethane (60 mL) was added dropwise over 7 h. The solvent was evaporated and flash chromatography on silica gel (first with ethyl acetate to elute impurities, then with ethyl acetate/ethanol 8:1) gave **3** (1.731 g, 6.24 mmol, 56%) as a colourless solid. $[\alpha]_D^{25}$ −85 (*c* 1.0, chloroform); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.90–1.30 (m, 4H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.49–1.67 (m, 2H), 1.72–1.84 (m, 1H), 1.88–2.02 (m, 1H), 2.40–2.46 (m, 1H), 5.34–5.52 (m, 1H), 7.14–7.42 (m, 5H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 22.81, 24.71, 24.84, 31.82, 34.69, 52.63, 54.53, 59.73, 126.42, 126.95, 128.59, 144.85, 182.03 ppm; MS–FAB (*m*/*z*): 181, 262, 278 $[M + H]^+$, 289, 391.

Compound 5: A solution of **3** (0.100 g, 0.36 mmol, 1.0 equiv), 1,3-bis(*tert*-butoxycarbonyl)-2-(trifluoromethylsulfonyl)-guanidine (0.141 g, 0.36 mmol, 1.0 equiv) and triethylamine (0.036 g, 0.049 mL, 0.36 mmol, 1.0 equiv) in dichloromethane (5 mL) was stirred for 24 h at ambient temperature and evaporated. The residue was purified by flash chromatography over silica gel (petrol ether/ethyl acetate 6:1) to obtain **5** (0.182 g, 0.35 mmol, 98%) as a colourless solid. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.17–1.36 (m, 4H) 1.41 (s, 3H), 1.45 (s, 9H), 1.47 (s, 9H), 1.51–1.60 (m, 2H), 1.63–1.79 (m, 1H), 1.89–2.07 (m, 1H), 2.60–2.68 (m, 1H), 3.83–3.98 (m, 1H), 4.15–4.32 (m, 1H), 7.16–7.39 (m, 5H), 7.77 (m, 1H), 8.33 (d, *J* = 7.7 Hz, 1H), 9.02 (m, 1H), 11.56 (m, 1H) ppm; MS–FAB (*m*/*z*): 193, 199, 205, 225, 260, 287, 320 $[M - 2Boc + H]^+$, 420 $[M - Boc + H]^+$, 521 $[M + H]^+$.

Compound 6: A solution of **5** (0.160 g, 0.31 mmol, 1.0 equiv) in dichloromethane (3 mL) was treated with trifluoroacetic acid (1.535 g, 1.0 mL, 13.46 mmol, 43.4 equiv) at ambient temperature for 7 h. The solvents were evaporated and the residue was purified by column chromatography over silica gel (dichloromethane/methanol 95:5) to yield **6** (0.112 g, 0.26 mmol, 85%) as a colourless, hygroscopic solid. $[\alpha]_D^{25}$ −13.62 (*c* 0.1, ethanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.05–1.35 (m, 4H), 1.41 (d, *J* = 6.2 Hz, 3H), 1.51–1.74 (m, 2H), 1.79–1.93 (m, 1H), 1.93–2.19 (m, 1H), 2.56–2.68 (m, 1H), 3.37–3.47 (m, 1H), 4.11 (d, *J* = 6.2 Hz, 1H), 6.65–6.97 (m, 2H), 7.12–7.58 (m, 9H), 7.91–8.06 (m, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6) δ 14.15, 20.72, 22.39, 23.54, 30.92, 31.45, 53.55, 59.72, 115.64, 118.76, 125.52, 126.03, 126.23, 128.33, 144.46, 156.41, 158.44, 170.34 ppm. MS–FAB (*m*/*z*): 107, 120, 124, 136, 154, 199, 286, 289, 307, 320 $[M - CF_3COO^-]^+$, 376, 391; Anal. calcd: C, 49.87; H, 6.05; N, 16.16; S, 7.40; found: C, 47.41; H, 5.37; N, 13.98; S, 7.26.

Guanidine-thiourea 7: Compound **6** (0.115 g, 0.27 mmol, 1.0 equiv) was treated with Amberlyst A26 (OH^- form) (1.885 g) in methanol (20 mL) for 15 min. The ion exchanger was filtered off over Celite and the filtrate was evaporated to yield **7**

(0.081 g, 0.25 mmol, 93 %) as a white solid. $[\alpha]_D^{25}$ +19.92 (*c* 0.1, methanol); ^{1}H NMR (300 MHz, DMSO-d_6) δ 0.97–1.44 (m, 4H), 1.44–1.58 (m, 3H), 1.58–1.80 (m, 2H), 1.81–1.94 (m, 1H), 1.94–2.37 (m, 1H), 2.48–2.57 (m, 1H), 3.44–3.58 (m, 1H), 3.71–3.98 (m, 1H), 4.60 (br s, 4H), 7.22–7.50 (m, 5H) ppm; MS–FAB (*m*/*z*): 107, 120, 136, 154, 176, 199, 286, 307, 320 $[M + H]^+$, 376, 391.

Henry reaction of 3-phenylpropionaldehyde (8) and nitromethane (9), mediated by 7: 4-Phenyl-1-nitro-2-butanol (10): A solution of **7** (0.1 equiv), 3-phenylpropionaldehyde (1.0 equiv) and nitromethane (3.0 equiv) in toluene ([aldehyde] = 0.11 M) was stirred for the appropriate time and at the corresponding temperature. The organic phase was diluted with toluene, washed with saturated aqueous ammonium chloride solution, and dried over magnesium sulfate. Product **10** was isolated by preparative thin-layer chromatography over silica gel. ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.58–1.83 (m, 2H), 2.55–2.82 (m, 2H), 4.05–4.17 (m, 1H), 4.39 (dd, *J* = 9.3 Hz, *J* = 12.2 Hz, 1H), 4.71 (dd, *J* = 3.0 Hz, *J* = 12.2 Hz, 1H), 5.48 (d, *J* = 6.4 Hz, 1H), 7.10–7.36 (m, 5H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ 30.62, 35.36, 67.21, 81.34, 125.56, 128.09, 141.33 ppm; MS–FAB (*m*/*z*): 107, 120, 124, 137, 149 $[M - NO_2^-]^+$, 154, 167, 289, 307, 391.

Michael addition of 2,4-pentanedione (12) and *trans*-β-nitrostyrene (11), mediated by 7: 3-(2-Nitro-1-phenylethyl)-pentane-2,4-dione (13): A solution of **7** (8.99 mg, 28.14 µmol, 0.2 equiv) and acetylacetone (140.87 mg, 1407.00 µmol, 10.0 equiv) was stirred for 5 min at ambient temperature. *trans*-β-Nitrostyrene was added and the mixture was stirred for 5 d at ambient temperature. The solution is diluted with ethyl acetate (10 mL), washed with aqueous 20% potassium hydrogen sulfate solution (3 mL) and brine (3 mL). After drying over magnesium sulfate, the organic phase was evaporated and purified by column chromatography over silica gel (petrol ether/ethyl acetate 2:1) to yield **13** (19.00 mg, 76.23 µmol, 54%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 1.87 (s, 3H), 2.21 (s, 3H), 4.12–4.23 (m, 1H), 4.30 (d, *J* = 10.7 Hz, 1H), 4.48–4.64 (m, 2H), 7.07–7.33 (m, 5H) ppm; ^{13}C NMR (75 MHz, CDCl$_3$) δ 29.54, 30.38, 42.74, 70.62, 78.11, 127.90, 128.48, 129.27, 135.97, 200.98, 201.70 ppm.

Michael addition of diethylmalonate (14) and *trans*-β-nitrostyrene (11), mediated by 7: Diethyl 2-(2-nitro-1-phenylethyl)malonate (15): A solution of *trans*-β-nitrostyrene (1.0 equiv), diethyl malonate (5.0 equiv) and **7** (0.2 equiv) in the desired solvent ([*trans*-β-nitro-styrene] = 0.1 M) is stirred at a certain temperature and for the appropriate time. The reaction is quenched with concentrated aqueous hydrochloric acid/methanol 1:10, and subjected to flash chromatography over silica gel (petrol ether/ethyl acetate 6:1). ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.98 (2t, *J* = 7.2 Hz, 3H), 1.20 (2t, *J* = 7.2 Hz, 3H), 3.76 (2d, *J* = 9.4 Hz, 1H), 3.94 (2q, *J* = 7.2 Hz, 2H), 4.10–4.24 (m, 3H), 4.73–4.92 (m, 2H), 7.11–7.33 (m, 5H) ppm; ^{13}C NMR (150.8 MHz, CDCl$_3$) δ 13.66, 13.90, 42.89, 54.88, 61.82, 62.10, 77.59, 127.96, 128.28, 128.86, 136.14, 166.76, 167.40 ppm.

Computational methods

Geometries of all structures were fully optimized at the B3PW91 [67-69] level of theory by using the 6–31G(d) [70-80] basis set within the Gaussian 03 program package [81]. Stationary points were confirmed to be minima or transition states by calculating the normal vibrations within the harmonic approximation. The reaction pathways along both directions from the transition structures were followed by the IRC method [82,83]. DFT-computed energies were corrected for zero-point vibrational energies (ZPVE). Single-point self-consistent reaction field (SCRF) [84] calculations were used to calculate the solvation energies in tetrahydrofuran within the PCM model (denoted as DFT-PCM). Single-point MP2 [66] energies with DZ and TZ basis sets were computed at the B3PW91 optimized geometries (denoted as MP2/6–31G(d)//B3PW91/6–31G(d) and MP2/6–311+G(d,p)//B3PW91/6–31G(d), respectively). Single-point DFT calculations with empirical van der Waals corrections [63] were performed with the ORCA program [85].

Supporting Information

The Supporting Information File features data from DFT computations (computed absolute energies (Hartree) and zero-point vibrational energies (ZPVE, kcal·mol^{-1}) at different levels of theory) as well as the respective GAUSSIAN archive entries.

Supporting Information File 1

Detailed information about the DFT calculations
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-168-S1.pdf]

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N-Heterocyclic carbene-catalyzed direct cross-aza-benzoin reaction: Efficient synthesis of α-amino-β-keto esters

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Letter

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Abstract

An efficient catalytic synthesis of α-amino-β-keto esters has been newly developed. Cross-coupling of various aldehydes with α-imino ester, catalyzed by *N*-heterocyclic carbene, leads chemoselectively to α-amino-β-keto esters in moderate to good yields with high atom efficiency. The reaction mechanism is discussed, and it is proposed that the α-amino-β-keto esters are formed under thermodynamic control.

Introduction

α-Amino-β-keto ester derivatives are one of the fundamental structural subunits in natural products such as miuraenamides [1], and important building blocks for the synthesis of a variety of heterocyclic compounds [2] and pharmaceutically active products [3-5]. In addition, they are valuable intermediates for chiral α-amino acids [6,7], including β-hydroxy-α-amino acids [8-14]. Consequently, significant efforts have been devoted to synthesizing the privileged structure (Figure 1), and two main distinct approaches based on the bond-forming position have been developed. One approach utilizes C_α–C_β bond formations, such as (a) acylation of Schiff bases or α-isocyano esters with acyl halides [4,15-17], and (b) intramolecular N–C acyl migration of the *N*-acyl glycine derivatives [18]. The other consists of C–N bond-forming reactions, such as (c) a rhodium-catalyzed N–H insertion reaction with α-diazo-β-keto esters [19-21], and (d) α-oxidation of β-keto esters to the corresponding oximes and the subsequent hydrogenation [22]. However, the former methods require a stoichiometric amount of strong bases, and the latter employ inaccessible substrates or multistep protocols. Recently, Zhang and co-workers reported $Zn(ClO_4)_2 \cdot 6H_2O$-catalyzed, mild and direct α-amination of β-keto esters with $TsNH_2$, but in this case, a stoichiometric amount of PhI=O is needed as the oxidant (Figure 1, (e)) [23]. Therefore, mild, efficient and environmentally friendly strategies for the synthesis of

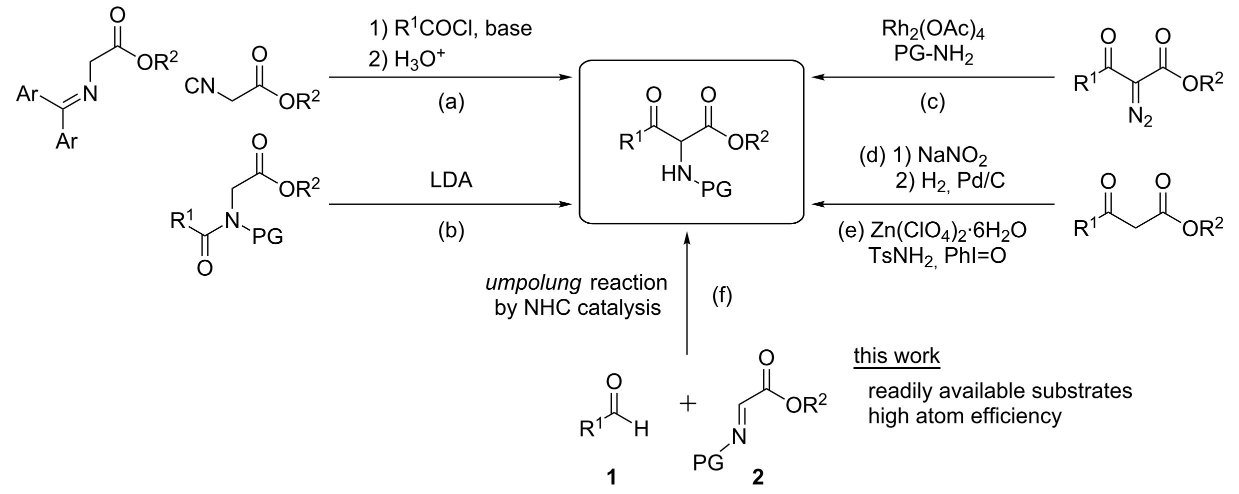


Figure 1: Synthetic methods for α-amino-β-keto esters.

these esters are still needed. We envisioned that highly atom-efficient synthesis of α-amino-β-keto esters could be achieved by a novel umpolung approach including C–C bond construction, that is, formal addition of acyl anion equivalents generated from aldehydes **1** with NHCs, to α-imino esters **2** (Figure 1, (f)).

Although a large number of NHC-catalyzed umpolung reactions, such as the benzoin reaction and Stetter reaction, have been developed [24-34], the related reactions of aldehydes with imines, i.e., the cross-aza-benzoin reactions, have been much less studied, in spite of the pharmaceutical and biological importance of providing α-amino ketones [35-43]. In particular, a reaction employing the imines directly has rarely been developed [40,42], due to the unproductive reaction of NHCs with the imines. Therefore, in situ generation of imines or iminium ions from their precursors is generally required to control their reactivity. We anticipated that the introduction of appropriate protecting groups of the nitrogen atom of α-imino esters **2**, which have been known to be excellent electrophiles, would suppress an unexpected reaction of **2** with NHCs, enabling the direct use of **2** as acyl anion acceptors in the cross-aza-benzoin reaction. In this communication, we describe a new, efficient, and atom-economical synthesis of the α-amino-β-keto esters by NHC-catalyzed cross-aza-benzoin reaction of aldehydes with α-imino esters under mild basic conditions.

Results and Discussion

First we initiated the cross-aza-benzoin reaction of benzaldehyde (**1a**) by employing 20 mol % of commercially available precatalyst **3a** (Figure 2) and K_2CO_3. Gratifyingly, when ethyl *N*-PMP-2-iminoacetate (**4**) was used as acyl anion acceptor [44], the reaction proceeded smoothly in THF at room temperature to generate the desired product **5a** in 58% yield (Table 1, entry 1). Surprisingly, no benzoin **6** arising from homo-coupling of **1a** was obtained. Encouraged by this result, we then attempted the other precatalysts **3b–e** depicted in Figure 2. Imidazolium salt **3b** and simple triazolium salt **3c** gave no coupled product **5a** (Table 1, entries 2 and 3). Further screening revealed that bicyclic triazolium salt **3d** could catalyze the reaction to give **5a** in 42% yield (Table 1, entry 4). We reasoned that the acidity of the NHC precursor was important to promote the reaction under mild basic conditions (Table 1, entry 3 versus entry 4), and therefore we next investigated the substituent on the nitrogen atom of NHC. As envisaged, *N*-pentafluorophenyl-substituted precatalyst **3e** [45-49], whose C-2 proton is more

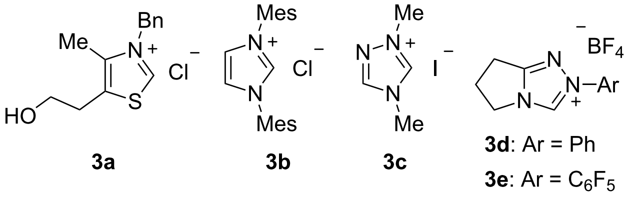
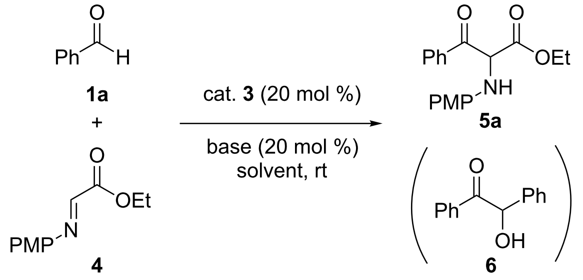


Figure 2: Structures of several NHC precatalysts.

acidic than **3d**, furnished the coupled product **5a** in good yield (Table 1, entry 5). Subsequently, we attempted several bases to find that cesium carbonate gave slightly lower yield (Table 1, entry 6), whereas an amine base and a stronger base were not effective, due to the competitive decomposition of **4** under these conditions (Table 1, entries 7 and 8). Different solvents, such as CH_2Cl_2, toluene, and MeCN, have been tested in this reaction, and THF was found to be optimal in terms of chemical yield (Table 1, entries 9–11).

Table 1: Reaction optimization.^{a}

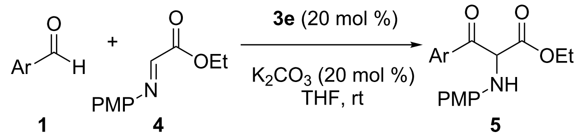


Entry	Cat. **3**	Base	Solvent	Yield (%)^b
1	**3a**	K_2CO_3	THF	58
2	**3b**	K_2CO_3	THF	<5
3	**3c**	K_2CO_3	THF	<5
4	**3d**	K_2CO_3	THF	42
5	**3e**	K_2CO_3	THF	70
6	**3e**	Cs_2CO_3	THF	66
7	**3e**	NEt_3	THF	56
8	**3e**	KO*t*-Bu	THF	37
9	**3e**	K_2CO_3	CH_2Cl_2	61
10	**3e**	K_2CO_3	toluene	56
11	**3e**	K_2CO_3	MeCN	40

^{a}Reactions conducted with **1a** (0.3 mmol) and **4** (1.3 equiv) in THF (0.5 M). ^{b}Isolated yields.

With the efficient catalytic system in hand (20 mol % of **3e** and K_2CO_3 in THF at room temperature), we next evaluated the substrate generality with a variety of aromatic aldehydes **1** bearing a diverse range of functionality (Table 2). Chloro-, nitro-, cyano-, and methoxycarbonyl-substituted aromatic aldehydes were compatible with the reaction conditions (Table 2, entries 1–6). In all cases, the reaction led to the desired products in moderate to good yields. In addition, *ortho*-substituted aldehyde, which is considered to be a poor acyl donor in benzoin reactions [46], was also smoothly converted to the expected product **5d** in 61% yield (Table 2, entry 3). It is noteworthy that chloro-substituted aldehydes were tolerated, because the corresponding products **5b**–**d** could in principle undergo further functionalization by palladium-catalyzed cross-coupling reactions. Additionally, electron-rich aromatic aldehydes, which are often known to be less reactive in NHC-catalyzed reactions, could be coupled with **4** to provide **5h** and **5i** in 66% and 68% yields, respectively (Table 2, entries 7 and 8). Notably, heteroaromatic aldehydes, such as 3-thiophenecarboxaldehyde and furfural, were also successful in yielding the expected products **5j** and **5k** in 72% and 49% yield, respectively (Table 2, entries 9 and 10).

Table 2: Substrate scope.^{a}

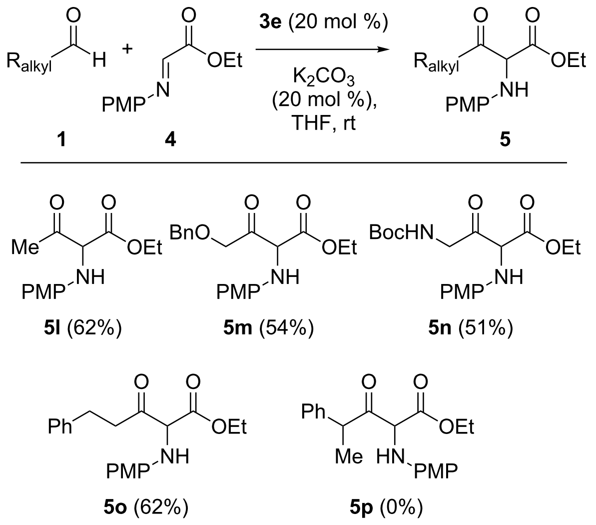


Entry	Ar	**5**	Yield (%)^b
1	4-ClC_6H_4	**5b**	69
2	3-ClC_6H_4	**5c**	59
3	2-ClC_6H_4	**5d**	61
4	4-$NO_2C_6H_4$	**5e**	45
5	4-CNC_6H_4	**5f**	39
6	4-$MeOCOC_6H_4$	**5g**	73
7	4-MeC_6H_4	**5h**	66
8	4-$MeOC_6H_4$	**5i**	68
9	thiophen-3-yl	**5j**	72
10	furan-2-yl	**5k**	49

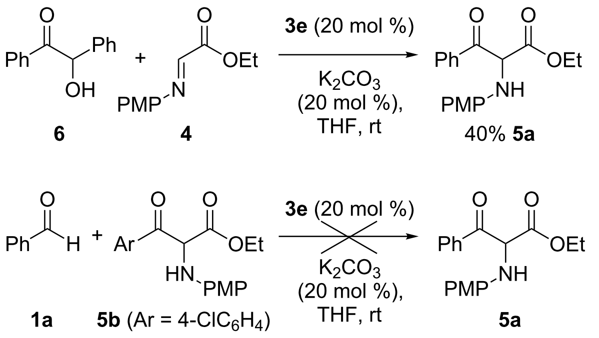
^{a}Reactions performed with **1** (0.3 mmol) and **4** (1.3 equiv) in THF (0.5 M). ^{b}Isolated yields.

We next investigated the reaction with several aliphatic aldehydes (Scheme 1). Generally, unactivated aliphatic aldehydes are unsuccessful for the NHC-catalyzed reactions, because of their low electrophilicity relative to aromatic aldehydes [40,46,47,50]. To our delight, this methodology was found to be also suitable for the enolizable aliphatic aldehydes. Under the optimal reaction conditions (Table 1, entry 5), acetaldehyde and other primary alkyl aldehydes bearing functional groups such as ether, carbamate, and phenyl groups, were converted into the corresponding products **5l**–**o** in good yields. The α-branched aldehyde, however, failed to give the desired product **5p**, presumably due to the increased steric hindrance along with the inherently low electrophilicity.

In order to elucidate the reaction mechanism, a 0.5 equiv of benzoin (**6**) was used instead of aldehyde **1a** under standard conditions, affording the cross-coupled product **5a** in 40% yield (Scheme 2). In addition, when the reaction was conducted with α-amino-β-keto ester **5b** in place of α-imino ester **4**, the crossover product **5a** was not detected. These findings indicate that the formation of benzoin is reversible via the Breslow intermediate, whereas the retro-benzoin reaction of cross-coupled



Scheme 1: Scope of aliphatic aldehydes.



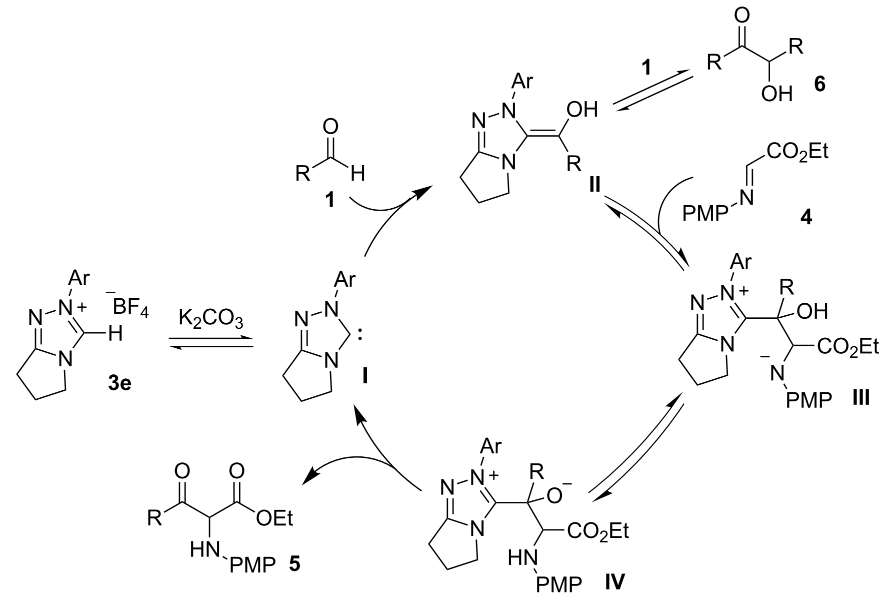
Scheme 2: Cross-over experiments.

product **5** does not occur under the present reaction conditions, and that the product **5** is formed under thermodynamic control.

A plausible mechanism for the cross-aza-benzoin reaction is shown in Scheme 3. Carbene **I** is generated by deprotonation of triazolium salt **3e** in the presence of K_2CO_3. The carbene **I** reacts with aldehyde **1** to afford Breslow intermediate **II**, which could lead to benzoin (**6**), or tetrahedral intermediate **III** when treated with α-imino ester **4**. Intermolecular proton transfer from **III** gives intermediate **IV**, which could release the product **5** and the carbene **I** to complete the catalytic system. We speculated that the desired product **5** is thermodynamically more stable than **6** and the formation of **5** is the irreversible step, from the finding that cross-coupled product **5** is predominantly obtained under the reaction conditions.

Conclusion

In conclusion, we have developed a direct, atom-efficient synthesis of α-amino-β-keto esters by an umpolung reaction. We found that the NHC-catalyzed cross-aza-benzoin reaction of aldehydes with *N*-PMP-imino ester proceeds chemoselectively under very mild conditions. Therefore, the reaction is tolerant of a range of functional groups and substituents, including aliphatic aldehydes, and thus this method would be an attractive approach for deriving various α-amino-β-keto ester derivatives, which are useful synthetic blocks and valuable pharmaceutical intermediates.



Scheme 3: Proposed reaction mechanism.

Supporting Information

Supporting Information File 1

Experimental details and characterization of the synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-169-S1.pdf]

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Cyclization of *ortho*-hydroxycinnamates to coumarins under mild conditions: A nucleophilic organocatalysis approach

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Full Research Paper

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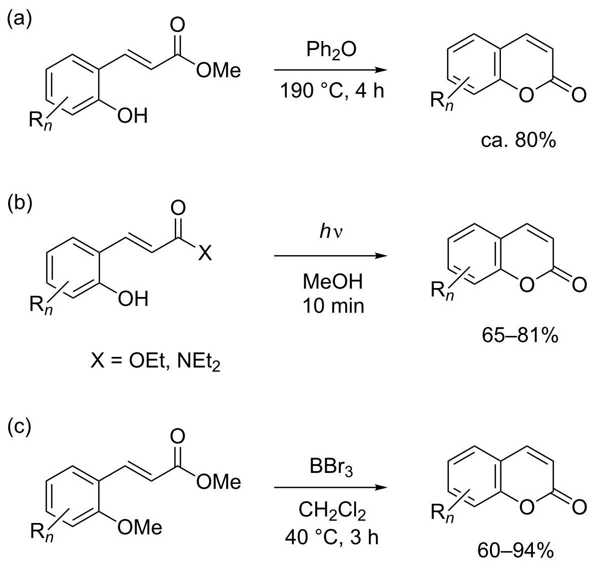
Abstract

(*E*)-Alkyl *ortho*-hydroxycinnamates cyclize to coumarins at elevated temperatures of 140–250 °C. We find that the use of tri-*n*-butylphosphane (20 mol %) as a nucleophilic organocatalyst in MeOH solution allows cyclization to take place under much milder conditions (60–70 °C). Several coumarins were prepared, starting from *ortho*-hydroxyarylaldehydes, by Wittig reaction with $Ph_3P{=}CHCO_2Me$ to (*E*)-methyl *ortho*-hydroxycinnamates, followed by the phosphane catalyzed cyclization.

Introduction

Coumarins are important structural motifs in natural products and bioactive compounds, in which they exhibit broad biological activity, e.g., as anticoagulants, antifungal agents, antioxidants, or as anthelmintic, hypnotic and cytotoxic agents [1-4]. Due to their fluorescent properties, coumarins are also widely used as agrochemicals, additives in cosmetics and food, optical brighteners, and dispersed fluorescent and tunable laser-dye optical agents [5,6]. Classical synthetic approaches for coumarins are based on the Perkin reaction or von Pechmann condensation, i.e., reactions under harsh conditions and at elevated temperatures [1]. Recent new methodologies based on CH-activation reactions still use acidic reaction media and show, in part, a lack of regioselectivity [7-10]. Such problems may be circumvented by using ring-closing metathesis [11,12] or other approaches [13-15]. In selective synthetic schemes, the generation of coumarins is typically realized by the cyclization of *ortho*-hydroxycinnamates (Scheme 1).

This reaction requires high temperatures (140–250 °C, Scheme 1a) [16,19-29] or photochemical double-bond isomerization (Scheme 1b) [15,17,30,31]. An alternative boron tribromide induced lactonization proceeds at a lower temperature (Scheme 1c), but is not compatible with acid-sensitive functionality [18,32]. It follows that synthetic methods converting

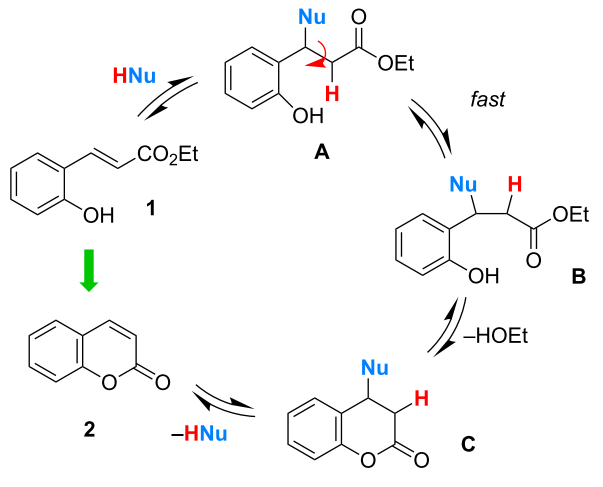


Scheme 1: Conditions for the cyclization of 2'-hydroxycinnamate and related precursors to coumarins. (a) Thermal cyclization [16]. (b) Photochemical isomerization/cyclization [17]. (c) Lewis acid induced demethylation/cyclization [18].

hydroxycinnamates to coumarins in the absence of acid under mild conditions are very desirable, particularly for labile starting materials, as often found in the late stages of multistep natural-product syntheses.

The difficulty of cyclizing (*E*)-2'-hydroxycinnamates to coumarins can be traced to the (*E*)-configuration of the starting material, which places the ester carbonyl group out of reach of the phenolic nucleophile [33-35]. The starting material must first be isomerized to a (*Z*)-configured intermediate, before cyclization can occur in a geometrically favored manner, but there is a considerable kinetic and energetic barrier against this isomerization process, provoking the observed high reaction temperatures. We wondered whether this problem could be circumvented by adding a nucleophile (HNu) to the reaction mixture containing **1**, which is capable of undergoing a reversible conjugate addition to form an intermediate **A** devoid of an alkene functionality (Scheme 2).

Rotation around the single bond to give **B** should be a fast process, and cyclization to a 2-chromanone **C** is then entropically favored. Eventually, the elimination to coumarin (**2**) could be driven by aromatic stabilization (Scheme 2). In fact, a related stoichiometric two-step protocol has been proposed [36]. It appeared to us that the practical problem of developing a mild and convenient catalytic conversion of *ortho*-hydroxycinnamates to the corresponding coumarins could be an ideal test case to show the utility of using organocatalytic rationales for solving a synthetic problem.



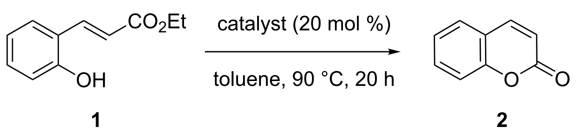
Scheme 2: Hypothetical catalytic cycle: Nucleophile-assisted cyclization of (*E*)-ethyl 2'-hydroxycinnamate (**1**) to coumarin (**2**).

Results and Discussion

The reaction of (*E*)-ethyl 2'-hydroxycinnamate (**1**) to coumarin (**2**) was chosen as the assay to find catalytic activity under mild conditions (Table 1).

It was initially thought that hydro-heteroatomic nucleophiles such as thiols, which are known to easily undergo hetero-Michael additions [38], could be suitable candidates for the screen. However, coumarin was not formed in the presence of thiols (Table 1, entry 1). We turned our attention to nucleophiles that are established catalysts in Morita–Baylis–Hillman type reactions, where they add to conjugated acceptor systems

Table 1: Screening of catalysts for nucleophilic double-bond isomerization.[a]



Entry	Catalyst	Yield (%)[b]
1	PhSH	–
2	DABCO	–
3	cinchonine	–
4	DBU	–
5	DMAP	–
6	IMes[c]	<1
7	PPh_3	–
8	*n*-Bu_3P	89

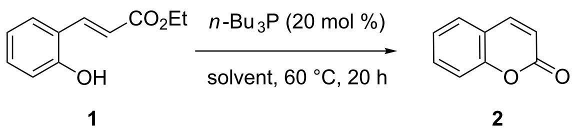
[a]Reactions were performed on 0.5 mmol scale in 1 mL of solvent; reaction time 20–23 h. [b]Screening yields were determined by GC and/or HPLC analysis with *N*-pivaloylaniline as internal standard. [c]IMes was generated in situ from IMes·HCl [37] and DBU.

[39]. Tests with either nitrogen bases (Table 1, entries 2–5) or N-heterocyclic carbenes (Table 1, entry 6) were not rewarded with success. Finally, phosphanes were tested, and while triphenylphosphane was not active (Table 1, entry 7), a change to the smaller and more nucleophilic tri-*n*-butylphosphane, a widely used nucleophilic catalyst [39-42], produced coumarin in rather high yields. Concentrating on *n*-Bu_3P as a very successful catalyst, a solvent screen was performed at the lower temperature of 60 °C (Table 2).

Conversion to the product in toluene was now considerably reduced (Table 2, entry 1). The broad solvent screening implied that some protic solvents, in particular methanol (Table 2, entry 7), were superior to toluene or polar aprotic solvents. The alternative phosphane PCy_3 was also briefly tested in that solvent, but the reduced activity implied that there was a negative steric influence with this catalyst (Table 2, entry 8).The scope and utility of the optimal catalyst system *n*-Bu_3P in MeOH was next studied in preparative reactions with a range of substituted 2'-hydroxycinnamic esters **3**, which were readily obtained by reaction of substituted salicylaldehydes with methyl triphenylphosphoranylidene acetate ($Ph_3P{=}CHCO_2Me$) [16,28]. They were cyclized to the corresponding substituted coumarins **4** under the optimized conditions, involving 20 mol % of *n*-Bu_3P as the catalyst in methanol solution at 70 °C (Table 3).

In these preparative experiments, the reaction mixtures were quenched by the addition of a cocatalytic amount of 1,2-dibro-

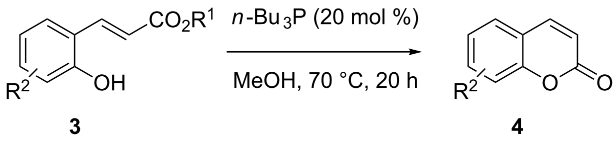
Table 2: Screening of solvents in catalyzed coumarin synthesis.[a]



Entry	Solvent	Time (h)	Yield (%)[b]
1	toluene	28	26
2	isopropanol	28	19
4	EtCN	28	8
5	dioxane	28	2
5	hexane	20	7
6	$CHCl_3$	28	21
7	MeOH	22	77
8	MeOH	22	47[c]
9	glycol	22	3
10	glycerol	16	27
11	$MeOH/H_2O$ (1:1)	16	30
12	CF_3CH_2OH	16	43
13	MeCN	16	6
14	DMSO	16	–
15	*tert*-butanol	23	36

[a]Reactions were performed on a 0.5 mmol scale in 1 mL of solvent. [b]Screening yields were determined by GC and/or HPLC analysis with *N*-pivaloylaniline as the internal standard. [c]PCy_3 was used as the catalyst instead of *n*-Bu_3P.

Table 3: Substrate scope of the phosphane catalyzed coumarin synthesis.[a]



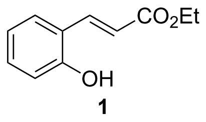
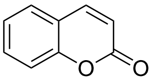
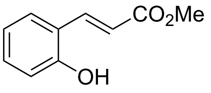
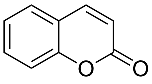
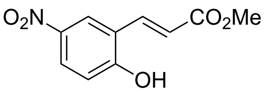
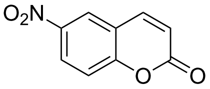
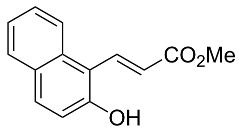
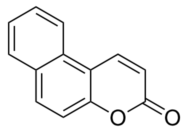
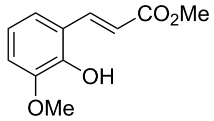
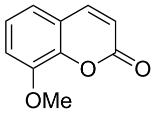
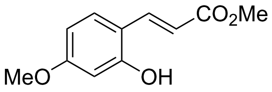
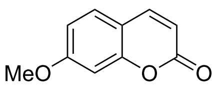
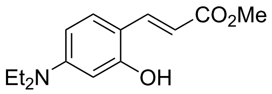
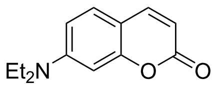
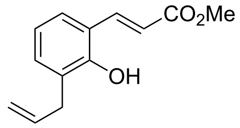
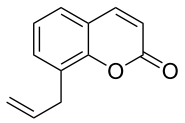
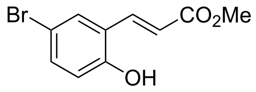
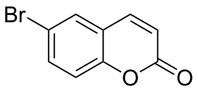
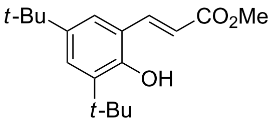
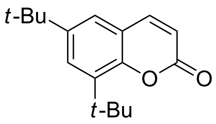
Entry	Substrate	Product	Yield (%)[b]
1	 **1**	 **2**	82
2	 **3a**	 **2**	80
3	 **3b**	 **4b**	–[c]

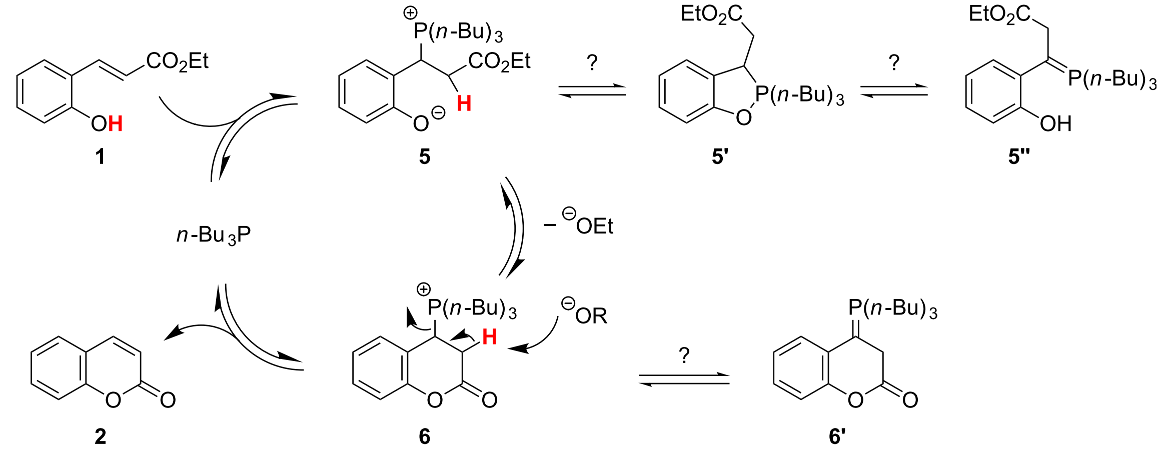
Table 3: Substrate scope of the phosphane catalyzed coumarin synthesis.[a] (continued)

4	 **3c**	 **4c**	96
5	 **3d**	 **4d**	88[d]
6	 **3e**	 **4e**	83
7	 **3f**	 **4f**	96
8	 **3g**	 **4g**	96
9	 **3h**	 **4h**	75
10	 **3i**	 **4i**	99

[a]Reactions were performed on a 1 mmol scale in 1 mL of methanol at 70 °C for 20 h. 15 min prior to workup, the mixture was quenched by addition of 1,2-dibromoethane (20 µL, 0.23 equiv). [b]Yields of pure isolated material. [c]No reaction to coumarin observed; starting material (60%) was reisolated. [d]Reaction performed at 90 °C in a closed vessel.

moethane prior to work-up, as described below (see the experimental section). The coumarins were generally obtained in good to excellent yields under the satisfactorily mild conditions of this catalysis. An exception was methyl 4'-nitro-2'-hydroxycinnamate, which did not cyclize to coumarin under the present conditions (Table 3, entry 3). Several of the products in Table 3, including the *N*,*N*-diethylamino- (Table 3, entry 7), and methoxy-derivatives (Table 3, entries 5 and 6) show strong fluorescence.

The cyclization of (*E*)-2'-hydroxycinnamates **1** and **3** to coumarins **2** and **4** is slow because it requires prior inversion of the double-bond geometry, a process that calls for harsh conditions such as high temperatures (140–250 °C). We have considered a strategy to perform a fast catalytic conjugate addition of a heteronucleophile to the starting material in order to speed up the overall cyclization reaction. Initial experiments with neutral thiols as nucleophiles were not successful. On the other hand, addition of a nucleophilic trialkylphosphane to (*E*)-ethyl 2'-hydroxycinnamate (**1**) in methanol solution, immediately produced a yellow color indicative of the generation of a phenolate anion. When this experiment was carried out in an NMR tube in [D_4]-methanol, ^{31}P NMR spectroscopy indicated that n-Bu$_3$P ($\delta = -30$ ppm) was indeed consumed by a conjugate addition to **1**, with generation of a tributylphosphonium salt ($\delta = +37$ ppm) of the probable zwitterionic structure **5** (Scheme 3;



Scheme 3: Proposed catalytic cycle, based on ^{31}P NMR spectroscopic and color evidence.

for the ^{31}P NMR spectrum see the Supporting Information File 1).

Similar phosphonium phenolates are known to exist either as the zwitterionic (analogue to **5**) or neutral phosphorane structure (analogue to **5'**) [43,44]. Under the conditions of the catalytic reaction, phosphonium (+37 ppm) was the only species of importance and thus represents the resting state of the catalytic reaction, which could be either **5** or **6**. We did not observe a ^{31}P NMR signal for *n*-Bu$_3$P, or a signal for the phosphorane structure **5'**, which is not favored in the highly polar solvent methanol [43]. Interestingly, we noted that quenching of the catalytic reaction mixtures with a cocatalytic amount of 1,2-dibromoethane prior to work-up had a favorable effect on product yield and purity: First, any of the catalyst *n*-Bu$_3$P present will be converted to a water-soluble phosphonium salt, which is easier to separate from the coumarin product than the neutral phosphane is. Second, the yields of coumarins were higher when the quenching procedure was used. This implies that part of the coumarin product may remain associated with the catalyst after full conversion of the starting material, for example in the form of **6** or **6'**. Addition of 1,2-dibromoethane will assist in shifting the equilibrium away from **6**/**6'** to release product **2** and *n*-Bu$_3$P, since the latter should react irreversibly with the alkylating reagent.

Conclusion

In conclusion, we have developed a new catalytic cyclization of (*E*)-alkyl 2'-hydroxycinnamates to coumarins with the aid of a nucleophilic alkyl phosphane catalyst, which allows this conversion to be carried out under much milder conditions compared to established procedures [16,19-29]. The reaction should be of particular utility in the generation of coumarin derivatives in the late stages of multi-step syntheses of sensitive targets. This work also illustrates the utility of using organocatalytic rationales (mechanistic predictions) for developing new solutions to synthetic problems.

Experimental

General procedure for coumarin synthesis

The starting hydroxycinnamate ester (1 mmol) was inserted in a headspace vial containing a magnetic stirring bar. The vial was flushed with argon and capped. Methanol (1 mL, degassed with argon) was added by syringe through the cap. After addition of tri-*n*-butylphosphane (50 µL, 0.20 mmol; 20 mol %) with a microliter syringe, the solution turned bright yellow. The reaction mixture was heated to 70 °C and stirred for 20 h. The reaction was quenched by the addition of 1,2-dibromoethane (20 µL, 0.23 mmol, 0.23 equiv) and cooled to room temperature. After evaporation, the crude mixture was purified by column chromatography.

Reaction example: 7-(*N*,*N*-Diethylamino)coumarin (**4f**)

Prepared according to the general procedure from (*E*)-methyl 3-(2-hydroxy-4-*N*,*N*-diethylaminophenyl)propenoate (**3f**, 249 mg, 1 mmol) with *n*-Bu$_3$P (50 µL, 0.20 mmol, 20 mol %) in MeOH (1 mL). After work-up and column chromatography (EtOAc/hexanes 1:5 + 5% NEt$_3$), the product was obtained as a yellow crystalline solid (209 mg, 96%). CAS-Nr. 20571-42-0; mp 90 °C; R_f = 0.32 (Hex/EtOAc 5:1 + 5% NEt$_3$); ^{1}H NMR (360 MHz, CDCl$_3$) δ 7.54 (d, *J* = 9.4 Hz, 1H), 7.25 (d, *J* = 8.5 Hz, 1H), 6.60 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.51 (d, *J* = 2.6 Hz, 1H), 6.04 (d, *J* = 9.3 Hz, 1H), 3.42 (q, *J* = 7.1 Hz, 4H), 1.21 (t, *J* = 7.1 Hz, 1H) ppm; ^{13}C NMR (90 MHz, CDCl$_3$) δ 162.2 (C=O), 156.7 (C), 150.5 (C), 143.7 (CH), 128.7 (CH), 109.3 (CH), 108.9 (CH), 108.5 (C), 97.7 (CH), 45.0 (2 × CH$_2$), 12.4 (2 × CH$_3$) ppm.

See Supporting Information File 1 for experimental details and NMR spectra of coumarins and the precursor 2'-hydroxycinnamates.

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data and copies of NMR spectra.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-186-S1.pdf]

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Organocatalytic cascade aza-Michael/hemiacetal reaction between disubstituted hydrazines and α,β-unsaturated aldehydes: Highly diastereo- and enantioselective synthesis of pyrazolidine derivatives

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Abstract

The catalytic synthesis of nitrogen-containing heterocycles is of great importance to medicinal and synthetic chemists, and also a challenge for modern chemical methodology. In this paper, we report the synthesis of pyrazolidine derivatives through a domino aza-Michael/hemiacetal sequence with chiral or achiral secondary amines as organocatalysts. Thus, a series of achiral pyrazolidine derivatives were obtained with good yields (up to 90%) and high diastereoselectivities (>20:1) with pyrrolidine as an organocatalyst, and enantioenriched pyrazolidines are also achieved with good results (up to 86% yield, >10/1 regioselectivity, >20:1 dr, 99% ee) in the presence of (*S*)-diphenylprolinol trimethylsilyl ether catalyst.

Introduction

Pyrazolidines are privileged and valuable heterocyclic compounds, which are of great importance in biological and medicinal chemistry (Figure 1) [1-5]. Besides, pyrazolidines are also important synthetic intermediates in organic chemistry. For instance, the N–N bond of pyrazolidines can be cleaved under reductive conditions to afford useful 1,3-diamines [6,7], and moreover, pyrazolidines can also be oxidized to afford pyrazolines [8-12] and pyrazoles [13-15]. The pyrazolidine structural unit is commonly constructed by [3 + 2] cycloaddition reactions using hydrazones [16-23] or azomethine amines [24-27] as dipoles. Recently, the Ma group and Toste et al. have reported efficient methods for the synthesis of pyrazolidine derivatives

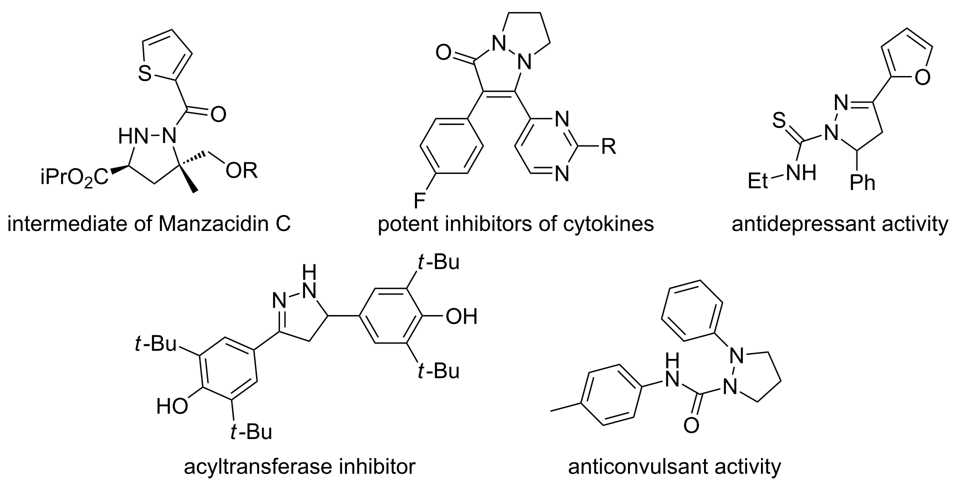


Figure 1: Important heterocycles containing pyrazolidine or pyrazoline structures.

by metal-catalyzed aminations of allenes [28-32]. Meanwhile, Lewis acid catalyzed carboamination reactions have also been reported as efficient methods for the synthesis of pyrazolidine derivatives by Wolfe et al. [33].

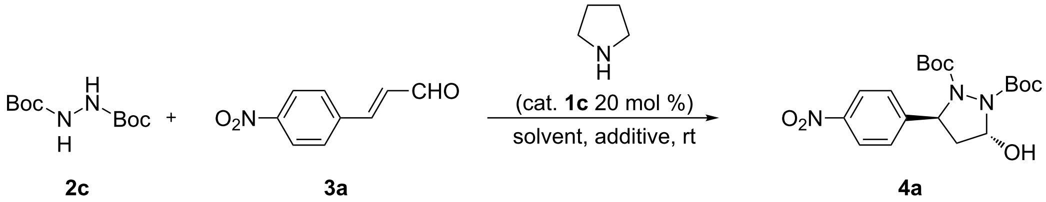
In the past decade, the research area of organocatalysis has grown rapidly and become a third brand of catalysis besides the well-established biocatalysis and metal catalysis [34-44]. Particularly, organocatalytic domino/cascade reactions have come into focus and become a powerful synthetic approach that allows the construction of structurally diverse and complex molecules, minimizes the number of manual operations, and saves time, effort, and production costs [45-47]. Thus, many nitrogen-containing heterocyclic compounds have been efficiently generated by means of organocatalytic domino reactions [48-69].

In 2009 and 2010, List et al. and the Brière group both reported, separately, the enantioselective synthesis of 2-pyrazolines starting from α,β-unsaturated ketones and phenylhydrazine or *N*-*tert*-butyloxycarbonylhydrazine in the presence of a chiral Brønsted acid or a phase-transfer catalyst [70,71]. Compared with monosubstituted hydrazines in organocatalytic asymmetric synthesis, disubstituted hydrazines were also explored by several groups [72,73]. In 2007, Jørgensen et al. reported that the organocatalyzed asymmetric aza-Michael addition of hydrazones to cyclic enones had been achieved in good yield and stereoselectivity [74]. In 2011, the Deng group developed a highly enantioselective organocatalytic synthesis of 2-pyrazolines using disubstituted hydrazines through an asymmetric conjugate addition followed by a deprotection–cyclization sequence [75]. Due to the importance of pyrazolidine derivatives in both organic and medicinal chemistry, we have become interested in developing an efficient stereoselective cascade reaction for the synthesis of the pyrazolidine compounds through organocatalysis. In this paper, we present a convenient access to racemic and enantioenriched 5-hydroxypyrazolidines through a domino aza-Michael/hemiacetal organocatalytic sequence of disubstituted hydrazines to α,β-unsaturated aldehydes. While proceeding with the submission of our results, we noticed that a related excellent work has been reported by Vicario and co-workers [76]. When comparing Vicario's work with this manuscript, both works are complementary in scope since Vicario's work makes use of unsaturated aldehydes containing only linear alkyl chains, whereas our work provides better results when unsaturated aldehydes bearing an aromatic moiety are employed.

Results and Discussion

First, the cascade aza-Michael/hemiacetal reactions between disubstituted hydrazines **2a**–**c** and 4-nitrocinnamaldehyde (**3a**) were investigated in the presence of several common secondary amines **1a**–**f** as organocatalysts in chloroform. Pyrrolidine (**1c**) turned out to be an effective catalyst and di-*tert*-butyl hydrazine-1,2-dicarboxylate (**2c**) was a potent donor (see Table S1 in the Supporting Information File 1). When di-*tert*-butyl hydrazine-1,2-dicarboxylate (**2c**) was used as the donor and 20 mol % pyrrolidine (**1c**) as the catalyst, 5-hydroxypyrazolidine **4a** could be obtained in 68% yield with over 20:1 dr after five days (Table 1, entry 1). Thus, the tandem aza-Michael/hemiacetal reaction between di-*tert*-butyl hydrazine-1,2-dicarboxylate (**2c**) and 4-nitrocinnamaldehyde (**3a**) was chosen as the model reaction to further optimize the reaction conditions. The catalytic results were summarized in Table 1. In order to improve the yield, a variety of common solvents were screened (Table 1, entries 2–6). Dichloromethane was finally found to be

Table 1: Secondary amine catalyzed cascade aza-Michael/hemiacetal reaction.



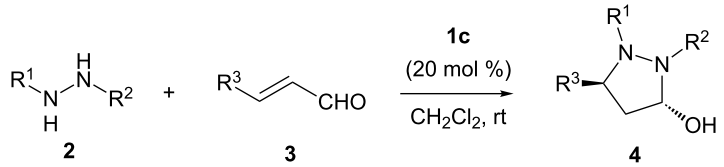
Entry[a]	Solvent	Additive	dr[b]	Yield (%)[c]
1	$CHCl_3$	–	>20:1	68
2	CH_2Cl_2	–	>20:1	74
3	MeOH	–	–	48
4	DMF	–	–	51
5	PhMe	–	–	42
6	THF	–	–	37
7	CH_2Cl_2	NaOAc	>20:1	68
8	CH_2Cl_2	$NaHCO_3$	>20:1	63
9	CH_2Cl_2	Na_2CO_3	–	38
10	CH_2Cl_2	LiOAc	>20:1	56
11	CH_2Cl_2	Et_3N	>20:1	42
12	CH_2Cl_2	DMAP	>20:1	50
13	CH_2Cl_2	benzoic acid (**5a**)	>20:1	77
14	CH_2Cl_2	4-nitrobenzoic acid (**5b**)	>20:1	67
15	CH_2Cl_2	3,5-dinitrobenzoic acid (**5c**)	–	56
16[d]	CH_2Cl_2	–	>20:1	81

[a]The reaction was run with **2c** (0.3 mmol), **3a** (0.25 mmol), **1c** (0.05 mmol) and the specified additive (0.05 mmol) in the given solvent (0.5 mL) at room temperature for 5 d. [b]Determined by ^{1}H NMR. [c]Isolated yield. [d]The molar ratio of **2c**/**3a** is 2.0:1.

the best medium for this reaction (74% yield with excellent diastereoselectivity was achieved, Table 1, entry 2). Subsequently, the effects of some basic/and acidic additives were examined. Inorganic bases seemed to be ineffective for the further improvement of the yields (Table 1, entries 7–10). Soluble organic bases were also tested and failed to increase the yields (Table 1, entries 11 and 12). When benzoic acid (**5a**) was used as an additive, the yield was slightly improved to 77% (Table 1, entry 13). With the increase of the acidity, the yield was noticeably decreased (Table 1, entry 13 versus entries 14 and 15). Finally, when increasing the amount of di-*tert*-butyl hydrazine-1,2-dicarboxylate (**2c**) to 2 equiv, the desired product **4a** was obtained in 81% yield without any additive (Table 1, entry 16).

Having established the optimized reaction conditions, we investigated the scope of substrates for the cascade aza-Michael/hemiacetal reaction with pyrrolidine (**1c**, 20 mol %) as the catalyst, without any additives, in methylene chloride (Table 2). We found that the nature of the substituents on the phenyl group of α,β-unsaturated aldehydes dramatically affected the reactivity. For example, with disubstituted hydrazine **2c** as the donor, the presence of a stronger electron-deficient substituent (-NO_2, -CN) on the phenyl ring of the α,β-unsaturated aldehydes **3a**, **3b** and **3c** promoted the cascade aza-Michael/hemiacetal reaction readily to provide the desired products in good yields (75–81%, Table 2, entries 1–3). The presence of less-electron-deficient substituents (-Cl and -Br) on the phenyl ring of the α,β-unsaturated aldehydes, such as 4-chloro- or 4-bromocinnamaldehyde derivatives **3d** and **3e**, afforded the corresponding products in moderate yields (64 and 74%) even when 5 equiv of disubstituted hydrazine **2c** was used (Table 2, entries 4 and 5). When cinnamaldehyde derivatives **3f** and **3g**, bearing electron-donating substituents (-Me, -OMe) on phenyl rings, were used as the substrate, the reactions became very sluggish (Table 2, entries 6 and 7). On the other hand, more symmetric and asymmetric hydrazine derivatives **2d**–**h** were synthesized and investigated for the tandem aza-Michael/hemiacetal reaction. Generally, all the reactions between **2d**–**h** and α,β-unsaturated aldehydes **3a** and **3b** proceeded smoothly with sequential catalytic actions of **1c**, affording the corresponding desired products **4h**–**o** in moderate to good yields (Table 2, entries 8–11 and 13–16). Notably, the reaction between **2e** and 4-methoxycinnamaldehyde (**3f**) afforded the desired product in 52% yield (Table 2, entry 12). For the asymmetric disubstituted

Table 2: Substrate scope for the cascade aza-Michael/hemiacetal reactions between **2** and α,β-unsaturated aldehydes **3**.



2c: $R^1 = R^2$ = Boc; **2d**: $R^1 = R^2$ = COOiPr
2e: $R^1 = R^2$ = Cbz; **2f**: $R^1 = R^2$ = COOEt
2g: R^1 = Boc, R^2 = Ph; **2h**: R^1 = Boc, R^2 = *p*-ClPh

Entry[a]	Donor	R^3	dr[b]	Yield (%)[c]
1	**2c**	4-$NO_2C_6H_4$ (**3a**)[d]	>20:1	**4a**/81
2	**2c**	3-$NO_2C_6H_4$ (**3b**)[d]	>20:1	**4b**/78
3	**2c**	4-CNC_6H_4 (**3c**)[d]	>20:1	**4c**/75
4	**2c**	4-ClC_6H_4 (**3d**)[e]	>20:1	**4d**/64
5	**2c**	4-BrC_6H_4 (**3e**)[e]	>20:1	**4e**/74
6	**2c**	4-$MeOC_6H_4$ (**3f**)[d]	–	**4f**/<5
7	**2c**	4-MeC_6H_4 (**3g**)[d]	–	**4g**/<5
8	**2d**	4-$NO_2C_6H_4$ (**3a**)[d]	>20:1	**4h**/86
9	**2d**	3-$NO_2C_6H_4$ (**3b**)[d]	>20:1	**4i**/82
10	**2e**	4-$NO_2C_6H_4$ (**3a**)[d]	>20:1	**4j**/90
11	**2e**	3-$NO_2C_6H_4$ (**3b**)[d]	>20:1	**4k**/76
12	**2e**	4-$MeOC_6H_4$ (**3f**)[d]	>20:1	**4l**/52
13	**2f**	4-$NO_2C_6H_4$ (**3a**)[d]	>20:1	**4m**/77
14	**2g**	4-$NO_2C_6H_4$ (**3a**)[f]	>20:1	**4n**/20 (43)
15	**2g**	4-$NO_2C_6H_4$ (**3a**)[f,g]	>20:1	**4n**/72 (<5)
16	**2h**	3-$NO_2C_6H_4$ (**3b**)[f,g]	>20:1	**4o**/66 (<5)

[a]Reaction was conducted on 0.25 mmol scale in solvents (0.5 mL) at room temperature for five days. [b]Determined by ^{1}H NMR. [c]Isolated yield (the data in parentheses is related to the isolated yield of the regioselective product). [d]The ratio of **2**/**3** is 2.0:1. [e]The ratio of **2**/**3** is 5.0:1. [f]The ratio of **2**/**3** is 1.2:1. [g]100 mol % of pyrrolidine was used at rt for 12 h.

hydrazines **2g** and **2h** as substrates, regioselective results could be observed (Table 2, entry 14). However, with increasing catalyst loading from catalytic to stoichiometric amounts, the corresponding cascade reactions could provide the major products in 72 and 66% yields (Table 2, entries 15 and 16). In all the reactions, high diastereoselectivity could be obtained (>20:1 dr). Finally, we were able to obtain single crystals of compounds **4a** and **4n**, which allowed for an unambiguous assignment of the *trans* configuration of C3 and C5 by X-ray crystallographic analysis (Figure 2 and Figure 3).

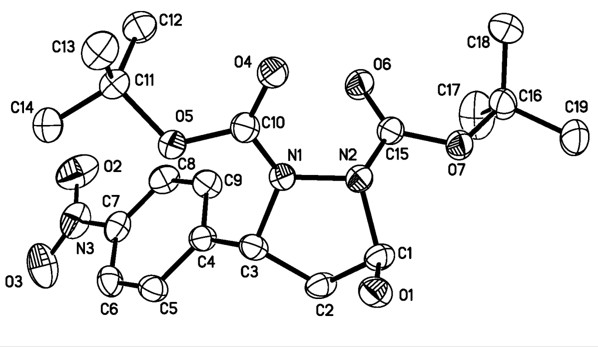


Figure 2: X-ray crystal structure of racemic **4a** (25% thermal ellipsoids).

Then, we turned our attention to the development of the asymmetric version of the cascade aza-Michael/hemiacetal reaction. Initially, a series of readily available chiral organocatalysts **1g–o** were chosen and investigated for the domino aza-Michael/hemiacetal reaction of disubstituted hydrazine **2c** and 4-nitrocinnamaldehyde (**3a**) under catalytic loading of 20 mol % in CH_2Cl_2 at room temperature. The screening results are summarized in Table 3. (*S*)-Proline derivatives **1g–h**, **1k**, **1l** were found to be ineffective for the reaction, because they afford only trace products after one day (Table 3, entries 1, 2, 5 and 6). Although a moderate yield was obtained with organocatalyst **1i** bearing a sulfone functional group, the stereochemical induction was very poor (Table 3, entry 3). MacMillan's cata-

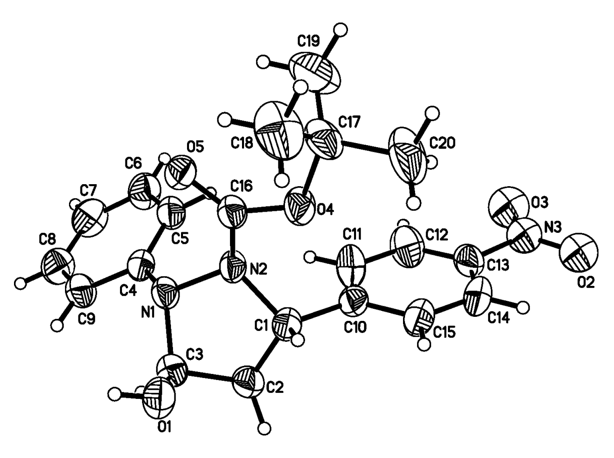
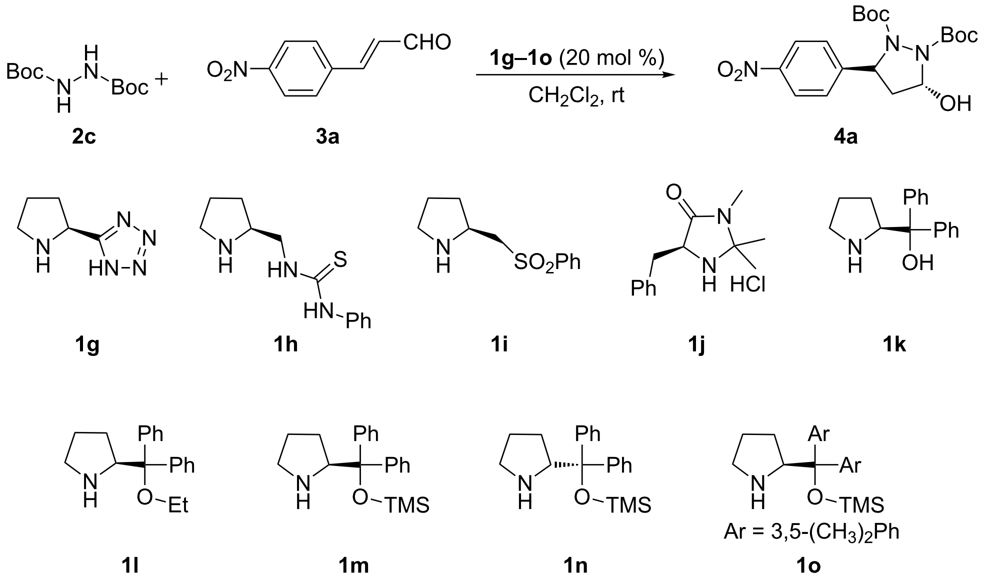


Figure 3: X-ray crystal structure of racemic **4n** (25% thermal ellipsoids).

lyst **1j** was proven to be inefficient for this transformation as only 13% ee was obtained (Table 3, entry 4). Subsequently, three diarylprolinol silyl ether catalysts **1m–o** were investigated for this tandem reaction [77-79]. Gratifyingly, 82% ee was achieved when **1m** was used as the catalyst. For catalysts **1n** and **1o**, slightly higher yields could be obtained, but the enantioselectivities became lower (Table 3, entry 7 versus entries 8 and 9). Relatively speaking, (*S*)-diphenylprolinol trimethylsilyl ether **1m** turned out to be the optimal catalyst in terms of both enantioselectivity and reactivity.

Having identified the readily available catalyst **1m** as the optimal catalyst for the tandem aza-Michael/hemiacetal reaction of **2c** and **3a**, we summarize the results for the optimization of the other reaction parameters, including reaction solvents and additives, in Table 4. When the reaction was carried out in a protonic solvent, i.e., methanol, at room temperature for two days, the desired product was furnished in

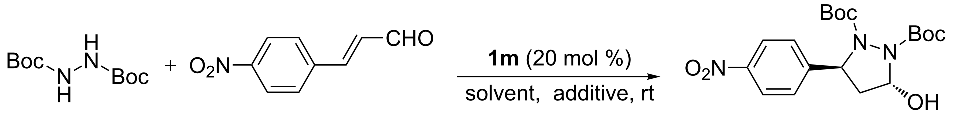
Table 3: Chiral-amine-catalyzed cascade aza-Michael/hemiacetal reaction of **2c** with **3a**.



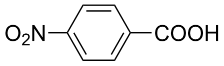
Entry[a]	R	Time (d)	Yield (%)[b]	ee (%)[c]
1	**1g**	1	<10	n.d.
2	**1h**	1	<5	n.d.
3	**1i**	1	48	5
4	**1j**	1	21	13
5	**1k**	1	<10	n.d.
6	**1l**	1	<5	n.d.
7	**1m**	1	86	82
8	**1n**	1	89	(−)79[d]
9	**1o**	1	87	76

[a]The reaction was run with **2c** (0.5 mmol), **3a** (0.25 mmol), and **1** (0.05 mmol) in CH_2Cl_2 (0.5 mL) at room temperature. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase (Chiralcel OD-H), >20:1 dr. [d]Opposite enantiomer of the product formed. n.d. = not determined.

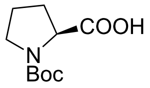
Table 4: Optimization of the reaction of **2c** and **3a** catalyzed by chiral amine **1m**.



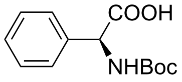
2c **3a** **4a**



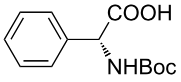
5b



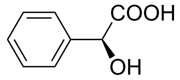
5d



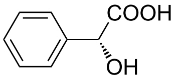
5e



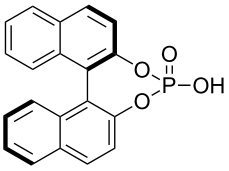
5f



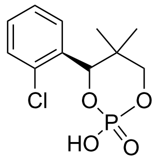
5g



5h



5i



5j

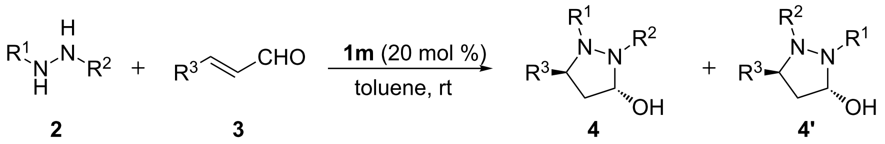
Entry[a]	Additive	Solvent	Time (d)	Yield (%)[b]	ee (%)[c]
1	–	MeOH	2	56	22
2	–	$CHCl_3$	1	84	75
3	–	$CHCl_2$	1	86	82
4	–	THF	2	51	92
5	–	PhMe	2	72	92
6	–	PhMe	4	80	92
7	**5b**	PhMe	4	27	93
8	**5d**	PhMe	4	56	94
9	**5e**	PhMe	4	48	92
10	**5f**	PhMe	4	45	92
11	**5g**	PhMe	4	51	94
12	**5h**	PhMe	4	20	94
13	**5i**	PhMe	4	38	94
14	**5j**	PhMe	4	53	95
15	LiOAc	PhMe	4	79	93
16	DMAP	PhMe	4	83	87
17	DABCO	PhMe	4	79	89
18	Et_3N	PhMe	4	83	87
19	TMEDA	PhMe	4	81	88
20	DBU	PhMe	4	58	11

[a]The reaction was run with **2c** (0.5 mmol), **3a** (0.25 mmol), **1m** (0.05 mmol) and the specified additive (0.05 mmol) in the given solvent (0.5 mL) at room temperature. [b]Isolated yield. [c]Determined by HPLC analysis on a chiral stationary phase (Chiralcel OD-H), >20:1 dr.

56% yield with only 22% ee (Table 4, entry 1). After screening several aprotic solvents for this reaction, we were pleased to find that the enantioselectivity of the desired product was improved to 92% ee with toluene or THF as solvent after two days (Table 4, entries 4 and 5). Considering both yield and enantioselectivity, toluene was the optimal reaction medium (Table 4, entry 5). When the time was prolonged to four days, the yield of the product was increased to 80% and the enantioselectivity was retained (Table 4, entry 6). Thereafter, several Brønsted acids **5b**, **5d**–**j** were tested as additives for this transformation. Although enantioselectivity was somewhat improved from 92 to 95% ee, the reactivity dramatically decreased as evidenced by the prolonged reaction time and lower yields (Table 4, entry 6 versus entries 7–14). It seemed that the present catalytic system could be inhibited by acidic additives. Therefore, we considered whether the reaction could be accelerated by basic additives without loss of enantioselectivity and reactivity. Subsequently, several common inorganic and organic bases were investigated [80-83]. Unfortunately, the catalytic results showed that with LiOAc, DMAP, DABCO, Et_3N, TMEDA as additives, the yield and enantioselectivity were only marginally influenced (Table 4, entries 15–19). When DBU was used as an additive, only 11% ee was obtained with moderate yield (Table 4, entry 20). Thus, **1m** (20 mol %) as the catalyst and toluene as the reaction medium without any additive at room temperature proved to be the optimal reaction conditions for the asymmetric cascade aza-Michael/hemiacetal reaction.

With the optimized reaction conditions in hand, the substrate scope of the organocatalyzed asymmetric domino aza-Michael/hemiacetal sequence was subsequently explored. Firstly, with symmetric di-*tert*-butyl hydrazine-1,2-dicarboxylate (**2c**) as nucleophilic reagent, aromatic α,β-unsaturated aldehydes **3a**–**g** were examined to study the effects of electronic properties and steric hindrance on both enantioselectivity and reactivity. For the substrates **3a**, **3b** and **3c**, bearing substituents of -NO_2 and -CN at the *para*- or *meta*-position of the phenyl group, the reactions proceeded smoothly and led to the desired products **4a**, **4b** and **4c** in 80–86% yields with 89–92% ee's (Table 5, entries 1–3). With **3d** and **3e** bearing -Cl or -Br substituents at the *para*-position of the phenyl group as substrates, the desired products **4d** and **4e** were obtained in 61 and 62% yields with 74 and 77% ee, respectively (Table 5, entries 4 and 5). For substrates **3f** and **3g** bearing electron-donating groups (-Me, -OMe) on the phenyl rings, only a trace amount of the desired products could be observed under otherwise identical reaction conditions (Table 5, entries 6 and 7). These experimental results indicated that chemical yields and enantioselectivities were

Table 5: Substrate scope of **2** and **3** catalyzed by chiral amine **1m**.



2c: $R^1 = R^2$ = Boc; **2d**: $R^1 = R^2$ = COOiPr
2g: R^1 = Boc, R^2 = Ph; **2h**: R^1 = Boc, R^2 = *p*-ClPh
2i: R^1 = Boc, R^2 = *p*-BrPh; **2j**: R^1 = Boc, R^2 = *p*-MeOPh

Entry[a]	Donor	R^3	Time (d)	Yield (%)[b]	Ratio[c]	ee (%)[d]
1	**2c**	4-$NO_2C_6H_4$ (**3a**)	4	**4a**/80	–	92
2	**2c**	3-$NO_2C_6H_4$ (**3b**)	2	**4b**/83	–	91
3	**2c**	4-CNC_6H_4 (**3c**)	4	**4c**/86	–	89
4	**2c**	4-ClC_6H_4 (**3d**)	4	**4d**/61	–	74
5	**2c**	4-BrC_6H_4 (**3e**)	4	**4e**/62	–	77
6	**2c**	4-$MeOC_6H_4$ (**3f**)	4	**4f**/<5	–	–
7	**2c**	4-MeC_6H_4 (**3g**)	4	**4g**/<5	–	–
8	**2d**	4-$NO_2C_6H_4$ (**3a**)	2	**4h**/60	–	72
9	**2g**[e]	4-$NO_2C_6H_4$ (**3a**)	4	**4n**/58 (**4n'**/32)	1.8:1	88/55
10	**2h**[e]	3-$NO_2C_6H_4$ (**3b**)	4	**4o**/60	3.2:1	88
11	**2h**[e]	4-$NO_2C_6H_4$ (**3a**)	4	**4p**/72	4.5:1	99
12	**2h**[e]	4-CNC_6H_4 (**3c**)	4	**4q**/65	4.7:1	93
13	**2h**[e]	3-$CF_3C_6H_4$ (**3h**)	4	**4r**/53	–[g]	81
14	**2i**[e]	4-$NO_2C_6H_4$ (**3a**)	4	**4s**/74	6.4:1	99
15	**2i**[e]	4-CNC_6H_4 (**3c**)	4	**4t**/72	4.0:1	90
16	**2j**[e]	4-$NO_2C_6H_4$ (**3a**)	4	**4u'**/75	1:9.0	–/11
17	**2h**[f]	Me (**3i**)	2	**4v**/78	>10:1	72
18	**2i**[f]	Me (**3i**)	2	**4w**/83	>10:1	74
19	**2h**[f]	Et (**3j**)	3	**4x**/<10	–	–

[a] Unless noted, the reaction was run with **2** (0.5 mmol), **3** (0.25 mmol), and **1m** (0.05 mmol) in toluene (0.5 mL) at room temperature. [b] Isolated yield of pure isomer **4** (the data in parentheses is related to the isolated yield of the **4'**). [c] The ratio based on isolated yield of pure **4** and **4'**. [d] Determined by HPLC analysis on a chiral stationary phase (Chiralcel OD-H, AD-H or AS-H), >20:1 dr. [e] The ratio of **2**/**3** is 1.2:1. [f] The reaction was run with **2** (0.25 mmol), **3** (0.38 mmol), and **1m** (0.05 mmol) in toluene (0.5 mL) at room temperature. [g] Due to the difficulty of separation of the product **4r'** from starting material **2h**.

dramatically affected by the electronic properties and steric hindrance of the aryl group on the α,β-unsaturated aldehydes. High yield and good enantioselectivity could be obtained with strong electron-withdrawing substituents on the phenyl ring of cinnamaldehydes. When diisopropyl hydrazine-1,2-dicarboxylate (**2d**) as nucleophilic reagent reacted with 4-nitro cinnamaldehyde (**3a**), the product **4h** was obtained in 60% yield and 72% ee (Table 5, entry 8). The result showed that the small-sized substituent on hydrazines was unfavorable on the reaction (Table 5, entry 8 versus entry 1). Subsequently, asymmetric disubstituted hydrazines **2g**–**j** were investigated for the domino aza-Michael/hemiacetal sequence. Due to nucleophilic competition of the two nitrogens in the asymmetric disubstituted hydrazines, regioselective results were observed for these reactions. For asymmetric disubstituted hydrazines **2g**, the reaction gave the 1.8:1 molar ratio of the regioselective products **4n** to **4n'**. The major product **4n** was obtained in 58% yield and 88% ee. The enantioselectivity of the minor product **4n'** was 55% (Table 5, entry 9). For asymmetric disubstituted hydrazines **2h**–**i**, the molar ratios of the regioselective products ranged from 3.2:1 to 6.4:1. The major products were obtained in moderate to good yields and good enantioselectivities (Table 5, entries 10–15). When disubstituted hydrazine **2j** with an electron-donating group on the aromatic ring was used as the nucleophilic donor, the major, reversely regioselective product **4u'** was obtained in 75% yield, but with very low enantioselectivity (11% ee, Table 5, entry 16). To our delight, (*E*)-but-2-enal (**3i**) was a suitable substrate for this transformation. The reactions of asymmetric disubstituted hydrazines **2h** and **2i** with (*E*)-but-2-enal (**3i**) proceeded smoothly and provided the desired products in 78 and 83% yields with 72 and 74% ee, respectively (Table 5, entries 17 and 18). However, when the cascade aza-Michael/hemiacetal reaction of (*E*)-pent-2-enal (**3j**) and **2h** was carried out, only a trace amount of the expected products could be detected (Table 5, entry 19). Fortunately, single crystals of compound **4s** were obtained by recrystallization from petroleum ether/acetyl acetate, and the absolute configuration was determined by X-ray analyses (Figure 4) [84].

Conclusion

In summary, we have developed an organocatalytic approach for the synthesis of pyrazolidine derivatives through the cascade aza-Michael/hemiacetal reaction between disubstituted hydrazines and α,β-unsaturated aldehydes. The asymmetric version of this one-pot cascade reaction has also been realized with (*S*)-diphenylprolinol trimethylsilyl ether **1m** as a secondary amine organocatalyst, and a series of enantiomerically enriched pyrazolidine derivatives were obtained in moderate to good chemical yields with moderate to excellent enantioselectivities. The application of the products and further investigation of the reaction are ongoing in our laboratory.

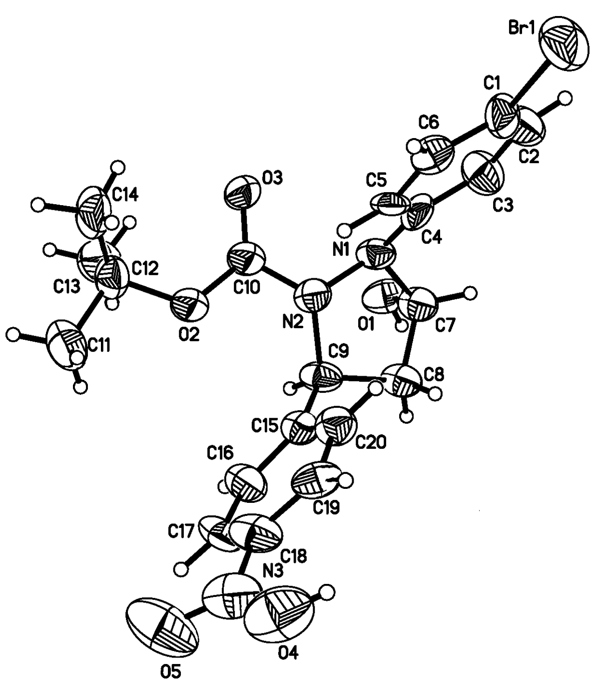


Figure 4: The X-ray crystal structure of chiral compound **4s** (40% thermal ellipsoids).

Experimental

Representative experimental procedure for the cascade aza-Michael/hemiacetal reaction of disubstituted hydrazines with α,β-unsaturated aldehydes

To a stirred solution of catalyst **1c** or **1m** (20 mol %) in CH_2Cl_2 or toluene (0.5 mL) was added α,β-unsaturated aldehyde **3** (1.0 equiv, 0.25 mmol) and di-substituted hydrazine **2** (1.2 equiv or 2.0 or 5.0 equiv and 0.3 mmol or 0.5 mmol or 1.25 mmol) at rt. The reaction was vigorously stirred for 2–5 days. Then, the reaction mixture was directly subjected to flash column chromatography on silica gel (petroleum ether/ethyl acetate) to afford the corresponding products **4**.

(−)-Di-*tert*-butyl 3-hydroxy-5-(4-nitrophenyl)pyrazolidine-1,2-dicarboxylate (4a): 80% yield, >20/1 dr, 92% ee. The enantiomeric ratio was determined by HPLC on Chiralpak OD-H column (10% 2-propanol/hexane, 1 mL/min), t_{major} = 7.219 min, t_{minor} = 6.013 min; $[\alpha]_D^{26}$ −11.8 (*c* 0.38, acetone); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, *J* = 8.6 Hz, 2H), 7.55 (d, *J* = 8.6 Hz, 2H), 5.92 (d, *J* = 4.7 Hz, 1H), 5.52–5.39 (m, 1H), 3.40 (s, 1H), 2.71 (dd, *J* = 13.2, 8.4 Hz, 1H), 2.13–2.03 (m, 1H), 1.53 (s, 9H), 1.43 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.27, 149.72, 147.21, 126.75, 124.01, 82.62, 82.56, 82.19, 61.66, 43.43, 28.33, 28.19; IR (KBr) ν_{max}: 3354.8, 2980.4, 2934.2, 2854.2, 1728.7, 1705.9, 1600.2, 1518.9, 1456.0, 1367.7, 1345.9, 1311.6, 1243.1, 1145.0, 990.9, 853.5, 758.4 cm^{-1}; HRMS–ESI (*m*/*z*): $[Na]^+$ calcd for $C_{19}H_{27}N_3O_7$, 432.1741; found, 432.1724.

Supporting Information

Supporting Information File 1

General experimental procedures, ^1H, ^{13}C NMR spectra and HPLC chromatograms for all new compounds, crystal data and structure refinement for enantiopure **4**.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-195-S1.pdf]

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Synthesis and ring openings of cinnamate-derived N-unfunctionalised aziridines

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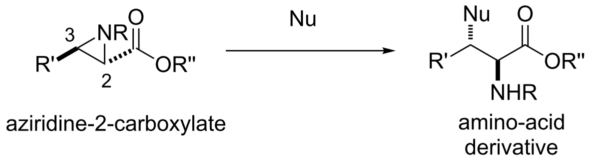
Abstract

tert-Butyl cinnamates are aziridinated with high trans-selectivity by an N–N ylide generated in situ from *N*-methylmorpholine and *O*-diphenylphosphinyl hydroxylamine. The resulting N-unfunctionalised aziridines are shown to be versatile synthetic building blocks that undergo highly selective ring-opening reactions with a wide range of nucleophiles.

Introduction

Amino acids are the fundamental building blocks of life on earth, and consequently their molecular structure is ubiquitous in natural and synthetic chemistry [1]. An attractive method of installing the amino-acid functionality is through the regioselective ring opening of an aziridine-2-carboxylate (Scheme 1) [2,3].



Scheme 1: Regioselective ring opening of an aziridine-2-carboxylate.

Such a methodology has been developed for N-functionalised aziridines [4-9], as N-functionality offers both activation of the aziridine to ring opening [10], and protection of the nitrogen. However, an extra synthetic step may be required to remove the N-functionality, which is often difficult and low yielding [11-15]. Ring opening of N-unfunctionalised (*NH*-) aziridines allows direct access to amino-acid derivatives, yet the published methodology is currently limited for this transformation [16-20]. In literature examples where ring-opening protocols have been developed, synthesis of the starting *NH*-aziridine-2-carboxylates is multistep and low-yielding. Synthetic routes include Gabriel–Cromwell addition of ammonia to an enoate [16,17]; epoxide opening with azide, followed by ring closure [19]; and a sequence of olefin dihydroxylation, conversion to a cyclic sulfate, ring opening with azide, and finally ring closure to afford the *NH*-aziridine [18].

We recently reported [21,22] a nucleophilic aziridination methodology [23-30] that allows access to *NH*-aziridines in a single step from α,β-unsaturated carbonyl compounds. Our method produces *trans-NH*-aziridines from α,β-unsaturated carbonyl compounds in good to excellent yield with high diastereoselectivity (Figure 1) [21]. An N–N ylide (aminimine) is the presumed active intermediate, formed from the reaction of a tertiary amine promoter and an aminating agent. Conjugate addition of the ylide, followed by a ring-closure step affords the *NH*-aziridine. More recently, the methodology has been extended to α,β,γ,δ-unsaturated carbonyl compounds, with excellent regio- and diastereoselectivity [31].

Herein, we report the optimisation of our nucleophilic aziridination methodology to access *NH*-aziridine-2-carboxylates in a single step from enoates. To the best of our knowledge, there exist only three examples of this transformation. Furukawa used diphenyl sulfilimine to form *NH*-aziridines from fumarate esters [32], and *O*-mesitylenesulfonylhydroxylamine (MSH) was used to aziridinate electron-poor alkenes by Hamelin [33]. We described the aziridination of two *tert*-butyl enoate substrates in our initial disclosure, but arguably the more synthetically useful of these, *tert*-butyl cinnamate, gave a modest yield of 32% [21]. We also report here our studies into the ring opening of aziridine **1a**, derived from *tert*-butyl cinnamate. As a result, a diverse array of amino-acid derivatives is generated in three steps from commercially available starting materials.

Results and Discussion

The aziridination of *tert*-butyl cinnamate was the starting point chosen for our optimisation. A control reaction in the absence of NMM gave no aziridine product. Despite the low conversion in the reported procedure [21], the only compounds apparent in the ^{1}H NMR spectrum of the crude reaction mixture were the starting cinnamate and the aziridine. A time delay of 20 minutes between the addition of NaOH and the cinnamate to the reaction mixture led to increased conversion (Table 1, entry 1 versus entry 2), with longer times leading to lower conversions (Table 1, entry 3 and entry 4). Using 4 equiv of NaOH increased the conversion to 50% (Table 1, entry 5), although a large excess (20 equiv) did not increase the conversion any further (Table 1, entry 5 versus entry 6). Increasing the concentration of the reaction mixture was found to have the most significant effect; performing the reaction at a concentration of 0.24 M provided a 63% conversion to aziridine (Table 1, entry 8). Problems with mechanical stirring were observed at

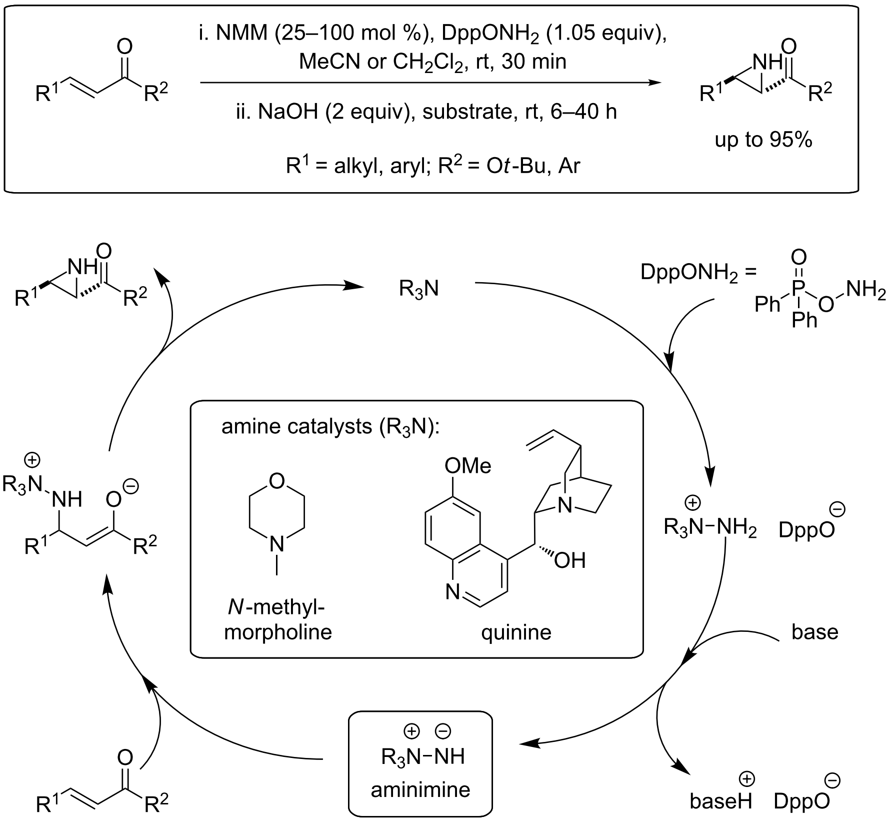


Figure 1: Amine-promoted alkene aziridination.

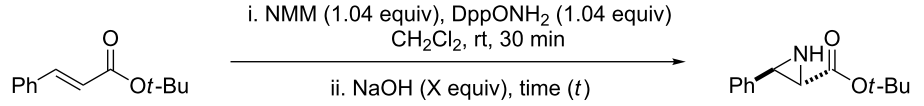
concentrations above 0.24 M, due to the heterogeneous nature of the reaction mixture. The isolated yield of this reaction (51%) was slightly lower than the conversion, but was reproducible on a 12 mmol scale (Table 1, entry 9). Use of an increased number of equiv of the aminating agent, tertiary amine and NaOH provided the aziridine in 65% isolated yield on a 3 mmol scale (Table 1, entry 10). The increased equiv of the heterogeneous reagents meant that the concentration of the reaction was reduced to 0.12 M for these conditions. The reaction was found to be specific for *tert*-butyl esters, with γ- and δ-benzylidene lactones, methyl, ethyl, phenyl, and benzyl cinnamates all suffering from degradation, presumably via hydrolysis pathways. β-Alkyl-substituted enoates were not explored, and will be the subject of future investigation. A preliminary screen of alternative solvents, tertiary amines and bases showed that NMM and NaOH in CH_2Cl_2 was the optimum reagent combination for the aziridination.

Having optimised our aziridination protocol for *tert*-butyl cinnamate, our attention then turned to examining the scope for aromatic substitution in the aziridination. A range of *ortho-, meta-* and *para*-substituted cinnamates were synthesised via Wittig, Heck or esterification routes (for details, see Supporting Information File 1). Each substrate was subjected to two sets of aziridination conditions, with the optimum yields reported.

Electron-rich substrates and the *ortho*-chloro cinnamate favoured conditions (B), in which increased equiv of reagents were used (Table 2, entries 2, 3, 7, 9). Electron-poor substrates and *para*-halo-substituted cinnamates provided optimum yields when subjected to conditions (A), using fewer equiv of reagents (Table 2, entries 4–6, 8, 10). Poor isolated yields were observed when conditions (B) were used on electron-poor substrates; this was attributed to the increased susceptibility to hydrolysis of the aziridine products. The increased steric demand posed by *ortho* substitution was found to have a detrimental effect on the aziridination (Table 2, entry 6 versus entry 8). A 5-chloro-furyl-substituted enoate was also subjected to the aziridination (Table 2, entry 10); a shorter reaction time of 20 h under the moderate set of aminating conditions (A) was optimal for this substrate. In all cases, only starting material and product were observed in the ^1H NMR spectrum of the crude reaction mixture. However, a loss in mass recovery was often observed during the isolation/purification process (see Table 2, isolated yield and recovered starting material columns), meaning that many of the isolated yields of aziridine are moderate. Nonetheless, it is worth noting that this single-step transformation provides *NH*-aziridine-2-carboxylates in competitive or superior yields to alternative multistep methodologies.

Having explored the scope of the aziridination, we were keen to investigate the susceptibility of our unactivated *NH*-aziridines to ring-opening chemistry. To the best of our knowledge, only four papers exist detailing the regioselective ring opening of *NH*-aziridine-2-carboxylates to provide amino-acid derivatives [16-19]. The substrate scope has been limited to *NH*-aziridine-2-carboxylates derived from isopropyl [16], menthyl [17], benzyl [18], and methyl [19] cinnamates. Nucleophiles are

Table 1: Enoate aziridination optimisation.[a]

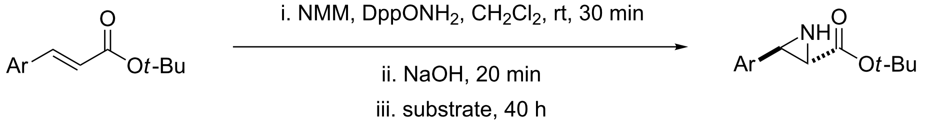


1a

Entry	NaOH (equiv)	Concentration[b] (M)	Time for step ii (min)	Conversion (%)[c,d]
1	2	0.06	0	32 (30)
2	2	0.06	20	47
3	2	0.06	30	41
4	2	0.06	160	23
5	4	0.06	20	50
6	20	0.06	20	47
7	4	0.12	20	58
8	4	0.24	20	63 (51)
9[e]	4	0.24	20	63 (50)
10[f]	11	0.12	20	(65)

[a]All reactions performed on 0.11 mmol scale unless stated otherwise. [b]With respect to *tert*-butyl cinnamate. [c] Estimated by ^1H NMR: relative integration of *tert*-butyl peaks in starting material and product. [d]Isolated yield in parentheses. [e]12 mmol scale. [f]NMM (3 equiv), $DppONH_2$ (3 equiv), 3 mmol scale.

Table 2: Substrate scope of enoate aziridination.



Entry		Ar	Conditions[a]	Isolated yield (%)	R.S.M[b] (%)
1[c]	**1a**	Ph	B	65	6
2	**1b**	(4-OMe)C$_6$H$_4$	B	39	34
3	**1c**	(4-Me)C$_6$H$_4$	B	36	12
4[d]	**1d**	(4-I)C$_6$H$_4$	A	33	40
5[e]	**1e**	(4-Cl)C$_6$H$_4$	A	53	12
6	**1f**	(4-NO$_2$)C$_6$H$_4$	A	76	6
7	**1g**	(2-Cl)C$_6$H$_4$	B	47	5
8	**1h**	(2-NO$_2$)C$_6$H$_4$	A	40	24
9	**1i**	(3-OMe)C$_6$H$_4$	B	32	14
10	**1j**	(5-Cl)furyl	A[f]	35	44

[a] Conditions A: NMM (1.04 equiv), DppONH$_2$ (1.04 equiv), NaOH (4 equiv), 0.24 M; Conditions B: NMM (3 equiv), DppONH$_2$ (3 equiv), NaOH (11 equiv), 0.12 M. All reactions performed on 0.20–0.23 mmol scale. [b] Recovered starting material (cinnamate ester) following purification. [c] 2.90 mmol scale. [d] 0.15 mmol scale at 0.08 M. [e] Reaction performed at 0.06 M. [f] 20 h reaction.

limited to thiophenols [17-19], fluoride [16], indole [18,19] and acetic acid [18,19] and a hydrogenation protocol also exists [18]. We were keen to test these nucleophiles in the ring opening of our *NH*-aziridines, in order to provide products with alternative ester functionality in the form of a *tert*-butyl group. Additionally, we wanted to expand the range of ring-opening nucleophiles, to provide access to a wider variety of amino-acid derivatives.

Aziridine **1a** was selected for initial investigations. Pleasingly, aziridine **1a** was found to undergo ring opening under Lewis and Brønsted acid catalysed conditions with a range of nucleophiles to provide amino-acid derivatives in good to excellent yield (Figure 2). The ring openings proved to be completely regioselective for the C3-benzylic position of aziridine **1a**. This regioselectivity was confirmed through atom correlations observed in 2D NMR experiments and by comparison with literature compounds, including C2-substituted analogues.

Indole was the first nucleophile investigated, as regioselective ring opening of the analogous benzyl [18] and methyl [19] ester protected *NH*-aziridines with indole in the presence of BF$_3$·OEt$_2$ had previously been reported, in 48 and 53% yields, respectively. On subjecting the orthogonally protected aziridine **1a** to the reported conditions, only a 7% isolated yield of ring-opened product was observed. Pleasingly, the use of BF$_3$·THF resulted in a considerably cleaner reaction. Separation of a major and minor product was achieved, with the major product identified as the tryptophan derivative **2a**, isolated in 63% yield.

The regiochemistry of **2a** was established through correlation spectroscopy. A ^2J correlation between the *ipso*-carbons of both aromatic systems and the C3 proton was observed by HMBC NMR. Comparison of the ^{1}H NMR chemical shifts of the minor product with **2a** and literature compounds led to the tentative assignment of the minor product as the C3 ring-opened diastereomer of **2a**. This reaction provides an attractive example of how our ring-opening chemistry can be used to form new carbon–carbon bonds.

Hruby reported the hydrogenation of the benzyl ester analogue of aziridine **1a**, resulting in the concomitant removal of the benzyl group to provide free phenylalanine [18]. Pleasingly, treatment of aziridine **1a** with H$_2$ in the presence of Pd/C provides phenylalanine *tert*-butyl ester (**2b**) in an excellent yield of 95%, without the need for purification. The orthogonal protection provided by the *tert*-butyl ester yields a product that is easier to handle than the free amino acid.

The ring opening of *NH*-aziridine-2-carboxylates with alcoholic nucleophiles is almost unexplored. To the best of our knowledge, only one literature example exists, in which the *NH*-aziridine derived from dimethyl fumarate is subjected to ring opening with MeOH in 50% yield [20]. We report that the ring opening of aziridine **1a** with alcohols in the presence of camphorsulfonic acid (CSA), provides a facile synthesis of 1,2-aminoalcohols. The alcohol nucleophiles were used as solvents, as stoichiometric quantities resulted in decreased conversions. Single ring-opened products were observed in the ^{1}H NMR

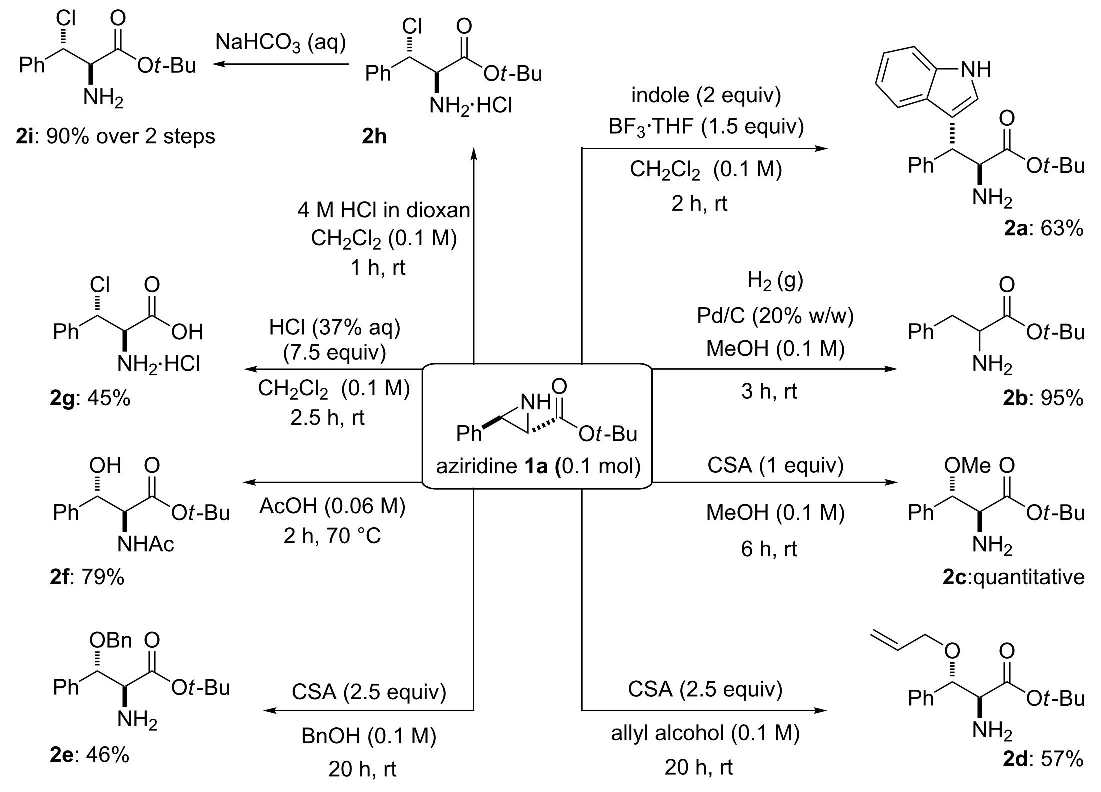


Figure 2: Ring-opened products of aziridine **1a**.

spectra of the crude products in all cases. In MeOH, amino-acid derivative **2c** was obtained in quantitative yield, without the need for purification. This represents the first regioselective example of the ring opening of an *NH*-aziridine-2-carboxylate with methanol. Allyl alcohol gave access to amino-acid derivative **2d** (57%). The terminal olefin provides a useful handle for further functionalisation of this substrate. Reaction of benzyl alcohol yielded the β-benzyloxy amino-acid derivative **2e** in 46%. The orthogonal benzyl protection could allow the free alcohol to be accessed selectively by hydrogenation protocols, leaving the *tert*-butyl ester intact. Products **2d** and **2e** are the first examples of the ring opening of *NH*-aziridine-2-carboxylates with alcoholic nucleophiles other than MeOH.

Acetic acid has previously been used as a nucleophile to achieve ring opening of benzyl [18] and methyl-ester [19] substituted *NH*-aziridines in 88% and 69% yields, respectively, with *O*- to *N*-acetate transfer observed. Ring opening of **1a** in acetic acid at 70 °C provides pure product **2f** (79%), with orthogonal *tert*-butyl ester protection in contrast to the reported examples. As detailed in the literature, the acetate protecting group was found to transfer to the nitrogen of the ring-opened aziridine. Product **2f** can be considered complementary to **2e**; O- or N-protected amino-acid derivatives can be accessed easily, depending on the choice of conditions.

Finally, β-chlorophenylalanine derivatives were accessed in three different forms, depending on the choice of HCl source and work-up conditions employed. Treatment of aziridine **1a** with HCl (35% aq) in dichloromethane led to isolation of **2g**, i.e., the HCl salt of β-chlorophenylalanine, in 45% yield. It is notable that this is the only one of our examples in which the *tert*-butyl ester is cleaved to provide the amino-acid motif. Altering the HCl source to 4 M HCl in dioxane provided product **2h** as the HCl salt, with the *tert*-butyl ester intact. Treatment with aqueous $NaHCO_3$ provided pure β-chloroamine **2i** in 90% yield over two steps. The chlorine atom provides a useful handle for further functionalisation, via substitution or coupling reactions, for example [34,35]. This is the first reported regio- and diastereoselective synthesis of *NH*-β-chlorophenylalanine derivatives from *NH*-aziridine-2-carboxylates.

Conclusion

In summary, we have reported the synthesis of a range of amino-acid derivatives from the ring opening of an *NH*-aziridine in excellent regio- and diastereoselectivity. *NH*-aziridines were synthesised in a single step from *tert*-butyl cinnamates, following optimisation of our nucleophilic aziridination methodology. This allows access to amino-acid derivatives in three steps from commercially available starting materials. Efforts are currently underway to develop an enantioselective version of the aziridination that is applicable to *tert*-butyl enoates.

Supporting Information

Supporting Information File 1

Experimental procedures and characterisation data for all new *NH*-aziridines, including ^{1}H and ^{13}C NMR spectra for all new compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-199-S1.pdf]

Acknowledgements

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Asymmetric desymmetrization of *meso*-diols by C_2-symmetric chiral 4-pyrrolidinopyridines

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Abstract

In this work we developed C_2-symmetric chiral nucleophilic catalysts which possess a pyrrolidinopyridine framework as a catalytic site. Some of these organocatalysts effectively promoted asymmetric desymmetrization of *meso*-diols via enantioselective acylation.

Introduction

Since the pioneering discovery of a catalyst for enantioselective acylation by Vedejs [1], numerous efforts have been devoted to the development of catalysts for enantioselective acylation [2,3]. We have focused on the development of chiral nucleophilic catalysts possessing a pyrrolidinopyridine (PPY) framework as a catalytic site because PPY has been known to be one of the most powerful catalysts for the acylation of alcohols [4-7]. The salient feature of our catalyst design is to introduce chiral elements far from the catalytically active pyridine nitrogen as shown in Figure 1 [8-18]. These catalysts are expected to show high catalytic activity because the introduction of substituents close to the pyridine nitrogen has been known to result in the significant decrease of the catalytic activity [19]. Catalyst **1** was demonstrated to be effective for the kinetic resolution of racemic diols (*s*: up to 12) [8] and amino alcohol derivatives (*s*: up to 54) [9]. Catalyst **2**, readily prepared from L-proline, could be employed for the kinetic resolution of amino alcohol derivatives (*s*: up to 11) [10]. Chiral PPY catalysts with dual functional side chains at C(2) and C(4) of the pyrrolidine ring such as **3** were prepared from *trans*-4-hydroxy-L-proline. These catalysts were found to be moderately effective for the asymmetric desymmetrization of *meso*-diols [11]. C_2-Symmetric PPY-catalyst **4** was found to be effective for the chemo- and regioselective acylation of carbohydrates [12,14,16] and the chemoselective monoacylation of linear diols [17]. Here, we report the asymmetric desymmtrization of *meso*-diols

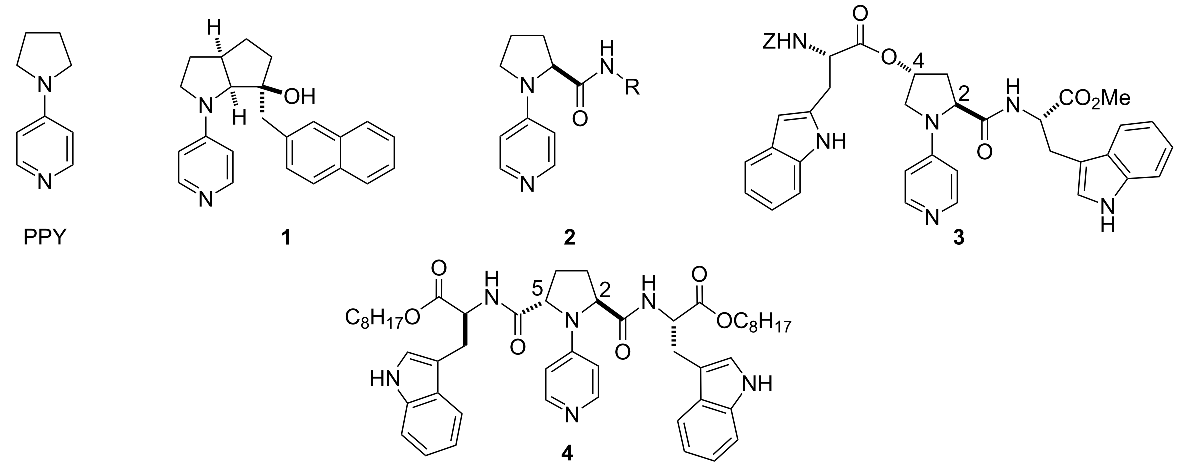


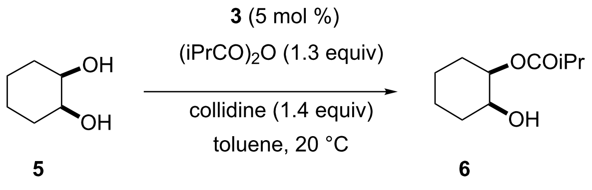
Figure 1: Chiral PPY catalysts.

by C_2-symmetric PPY catalysts [20]. The effects of the functional side chains at C(2) and C(5) on the efficiency of the asymmetric desymmetrization are discussed. Some of the results shown here have already been appeared in the patent JP2005132746.

Results and Discussion

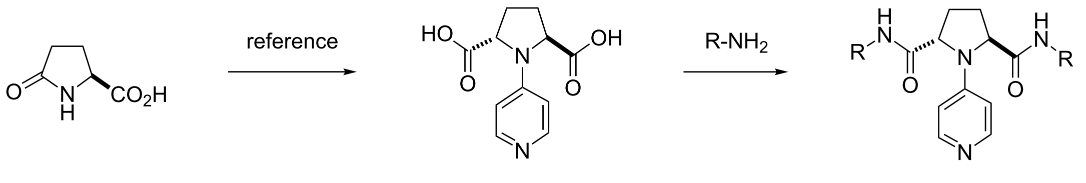
Asymmetric desymmetrization of *meso*-1,2-cyclohexanediol

The asymmetric desymmetrization of *meso*-diols via organocatalytic enantioselective acylation has been extensively studied [1,21-38]. We have reported the asymmetric desymmetrization of *meso*-1,2-cyclohexanediol (**5**) by catalytic enantioselective acylation with catalyst **3** (Scheme 1) [11]. Among various chiral PPY catalysts with dual functional side chains at C(2) and C(4) of the pyrrolidine ring, catalyst **3** was found to be most effective for the asymmetric desymmetrization (Scheme 1). However, the enantioselectivity of the asymmetric desymmetrization was far from being sufficient. Molecular modeling of the related catalysts indicated that a C_2-symmetric PPY catalyst with functional side chains at C(2) and C(5) might be better suited for this purpose [12,13]. Based on these background, we have prepared various C_2-symmetric chiral PPY-catalysts according to Scheme 2 [12] and employed them for asymmetric desymmetrization of *meso*-1,2-cyclohexanediol (**5**) [20].



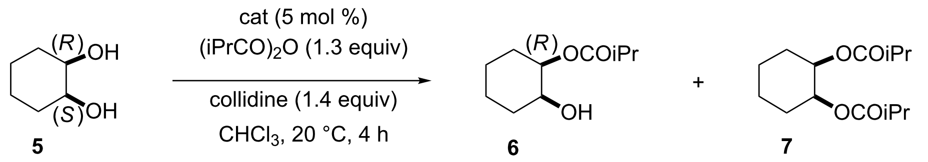
Scheme 1: Asymmetric desymmetrization of **5** with catalyst **3**.

We first examined chiral PPY catalyst **8a** with an L-tryptophan side chain, which was disclosed to be an excellent catalyst for the regioselective acylation of glycopyranoses [12]. Reaction of **5** with isobutyric anhydride (1.3 equiv) in the presence of 5 mol % of **8a** in chloroform at 20 °C gave monoacylate **6** in 73% ee and 85% yield with concomitant formation of 15% of diacylate **7** (Table 1, entry 1). Catalyst **8b** with a D-tryptophan side chain gave a lower enantioselectivity (54% ee, Table 1, entry 2). The hydroxy group at the (*R*)-chiral center was preferentially acylated in both cases. Since both catalysts **8a** with an L-tryptophan side chain and **8b** with a D-tryptophan side chain gave (1*R*,2*S*)-**6** [8] by asymmetric desymmetrization of **5**, catalysts with achiral side chains were then examined. The acylation of **5** with catalyst **9** which possesses a tryptamine moiety



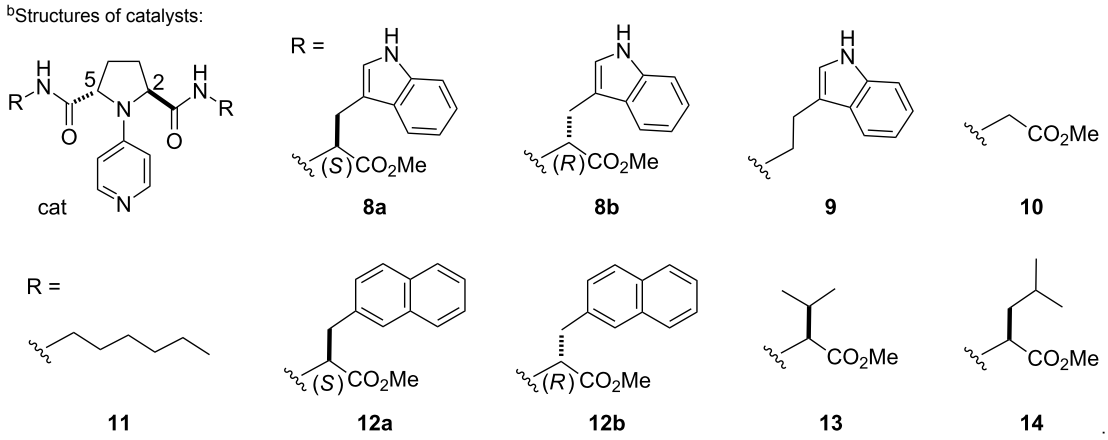
Scheme 2: Preparation of a small library of chiral C_2-symmetric PPY catalysts (reference, see [12]).

Table 1: Effects of the catalysts' side chains on the asymmetric desymmetrization of *meso*-1,2-cyclohexanediol (**5**).[a]



Entry	Catalyst[b]	**6**:**7**:Recovery of **5** (%)[c]	ee of **6** (%)[d,e]
1	**8a**	85:15:0	73
2	**8b**	70:18:12	54
3	**9**	74:16:10	72
4	**10**	72:19:9	71
5	**11**	75:23:3	87
6	**12a**	70:25:5	74
7	**12b**	77:14:9	83
8	**13**	76:18:6	54
9	**14**	75:20:5	81

[a]Reactions were run at a substrate concentration of 0.2 M.
[b]Structures of catalysts:

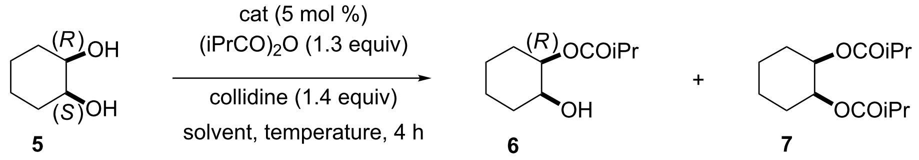


[c]Yields determined by ^{1}H NMR with dibenzyl ether as an internal standard. [d]Determined by GC analysis with a chiral stationary phase, beta-DEX 225. [e](1*R*,2*S*)-Isomer was obtained in each case.

gave **6** in 72% ee and 74% yield (Table 1, entry 3). Catalyst **10** with a glycine moiety gave **6** in 71% ee and 72% yield on treatment of **5** (Table 1, entry 4). Monoacylate **6** was also obtained in 87% ee and 75% yield by acylation of **5** with catalyst **11** which possesses a simple *n*-hexyl side chain (Table 1, entry 5). Catalysts with chiral side chains, **12a**, **12b**, **13**, and **14**, possessing L-β-phenylalanine, D-β-phenylalanine, L-valine, or L-leucine moiety, respectively, also gave **6** in 54–83% ee and 70–77% yields via acylative asymmetric desymmetrization of **5** with isobutyric anhydride (Table 1, entries 6–9). In each case, (1*R*,2*S*)-**6** was preferentially obtained. These results indicate that the functionality and chirality of catalyst side chains do not affect the absolute configuration of the monoacylate obtained by the asymmetric desymmetrization while they influence the extent of the enantioselectivity. Accordingly, the configuration of the stereocenters in C(2) and C(5) position bearing the amide substituents appears to have decisive effects on the stereochemical course of the asymmetric desymmetrization.

Since catalyst **12b** showed relatively high enantioselectivity (83% ee) and mono/diacylation ratio (77:14), we next investigated the solvent effects of the asymmetric desymmetrization of **5** with isobutyric anhydride in the presence of catalyst **12b** (Table 2, entries 1–5). A clear relationship between the enantioselectivity and the solvent polarity was observed: The lower the polarity of the solvent, the higher the enantioselectivity. This suggests that the hydrogen-bonding interaction between the catalyst and the substrate may be involved in the transition state of the enantioselective acylation (Figure 2 and Figure 3). The temperature effects (lower temperature) of the asymmetric desymmetrization employing catalysts **14** and **11** were examined because both of the catalysts show high solubility in chlo-

Table 2: Effects of solvents and temperature on the asymmetric desymmetrization of **5**.[a]



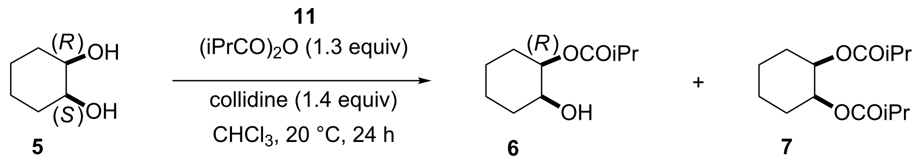
Entry	Catalyst	Solvent	Temp. (°C)	**6**:**7**:recovery of **5** (%)[b]	ee of **6** (%)[c,d]
1	**12b**	CCl_4	20 °C	75:20:5	93
2	**12b**	toluene	20 °C	75:19:6	91
3	**12b**	$CHCl_3$	20 °C	77:14:9	83
4	**12b**	THF	20 °C	57:28:15	51
5	**12b**	CH_3CN	20 °C	69:23:8	34
6	**14**	$CHCl_3$	20 °C	75:20:5	81
7[e]	**14**	$CHCl_3$	−40 °C	85:6:9	87
8	**11**	$CHCl_3$	20 °C	75:23:2	87
9[e]	**11**	$CHCl_3$	−40 °C	92:5:3	88

[a]Reactions were run at a substrate concentration of 0.2 M. [b]Yields determined by ^1H NMR with dibenzyl ether as an internal standard. [c]Determined by GC analysis with a chiral stationary phase, beta-DEX 225. [d](1*R*,2*S*)-Isomer was obtained in each case. [e]Run for 24 h.

roform at low temperatures (Table 2, entries 6–9). Both enantioselectivity (87% ee) and mono/diacylation ratio (85:6) of the acylation of **5** catalyzed by **14** at −40 °C were improved compared with those in the corresponding reaction at 20 °C (Table 2, entry 6 vs entry 7). Similarly, the efficiency of the asymmetric desymmetrization of **5** catalyzed by **11** was improved by conducting the reaction at −40 °C (Table 2, entry 8 vs entry 9). Monoacylate **6** was obtained in 88% ee and 92% yield by treatment of **5** with isobutyric anhydride in the presence of 5 mol % of **11** at −40 °C.

Further optimization of the asymmetric desymmetrization of **5** with catalyst **11** was examined at 20 °C (Table 3). The use of only 0.5 mol % of catalyst was found to be still effective in the asymmetric desymmetrization of **5** to give **6** in 90% ee and 76% yield (Table 3, entry 2) [20]. Further decrease in the amount of the catalyst to 0.05 mol % resulted in a lower enantioselectivity (74% ee) and in lower yield (66%) (Table 3, entry 3). The use of a less amount (1.0 equiv) of the anhydride in the presence of 5 mol % of **11** improved the mono/diacylation ratio (84:7), while the enantioselectivity was decreased (81% ee, Table 3,

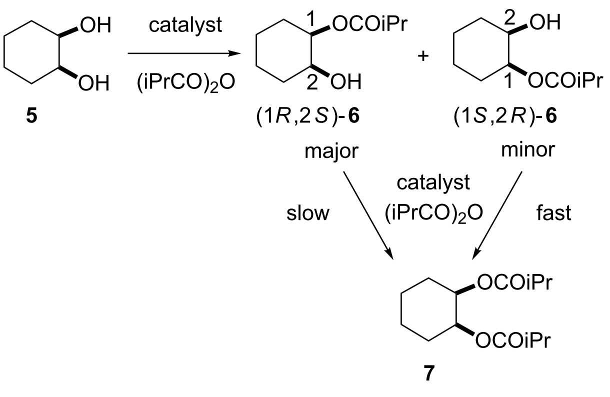
Table 3: Optimization of the asymmetric desymmetrization of **5** with catalyst **11**.[a]



Entry	Mol % of **11**	Equiv of $(iPrCO)_2O$	**6**:**7**:Recovery of **5** (%)[b]	ee of **6** (%)[c,d]
1	5	1.3	75:23:2	87
2[e]	0.5	1.3	76:20:3	90
3	0.05	1.3	66:10:24	74
4	5	1.0	84: 7:4	81
5[e,f]	5	1.6	59:41:0	98

[a]Reactions were run at a substrate concentration of 0.2 M. [b]Yields determined by ^1H NMR with dibenzyl ether as an internal standard. [c]Determined by GC analysis with a chiral stationary phase, beta-DEX 225. [d](1*R*,2*S*)-Isomer was obtained in each case. [e]Data quoted from reference [20].
[f]1.7 Equiv of collidine were used.

entry 1 vs entry 4). On the other hand, the use of an excess amount (1.6 equiv) of the anhydride resulted in the highest enantioselectivity (98% ee) in compensation for the low yield (59%) for monoacylation (Table 3, entry 5) [20]. The increase in the amount of diacylate **7** is associated with the higher ee of monoacylate **6** (Table 3, entries 1, 4 and 5). This suggests that the ee of monoacylate **6** would be amplified by the second acylation step, i.e., acylative kinetic resolution of enantioenriched monoacylate **6** produced by the asymmetric desymmetrization of the *meso*-substrate (Scheme 3).



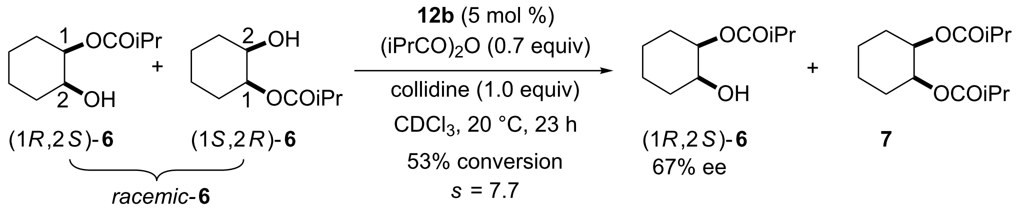
Scheme 3: Amplification of enantiomeric purity of the major enantiomer produced at the step of asymmetric desymmetrization of the *meso*-substrate by the following kinetic resolution with the same catalyst.

To confirm this issue, kinetic resolution of *racemic*-**6** was performed with catalyst **12b** because **12b** is almost as effective as **11** in the asymmetric desymmetrization of **5** (Table 1, entry 5 and entry 7). Treatment of *rac*-**6** with 0.7 equiv of isobutyric anhydride in the presence of 5 mol % of **12b** gave (1*R*,2*S*)-**6** in 67% ee at 53% conversion (Scheme 4). This clearly indicates that the (1*S*,2*R*)-isomer reacts faster than the (1*R*,2*S*)-isomer in the acylation catalyzed by **12b**.

The results in Table 1 suggest that the amide carbonyl groups at C(2) and C(5) of the pyrrolidine ring of the catalysts **8**–**14** would play the key role in asymmetric acylation. This is due to the fact that the amide carbonyl group is the common structural subunit among these chiral PPY catalysts. We chose catalyst **11**, which possesses the simplest *n*-hexyl amide side chain, and examined the effect of the secondary amide linkage by comparing the performance of the asymmetric desymmetrization with that shown by the analogous catalysts possessing the corresponding tertiary amide- or ester linkage, **15** or **16**, respectively (Table 4, entries 1–3). Much diminished enantioselectivity (13% ee) was observed in the asymmetric desymmetrization of **5** with isobutyric anhydride in the presence of catalyst **15** with the tertiary amide linkage (Table 4, entry 2). Similarly, catalyst **16** with the ester linkage was found to be far less effective (13% ee) than **11** (Table 4, entry 3) in the asymmetric acylation. These results indicate that the secondary amide linkage in **11** is essential for the high efficiency of the asymmetric acylation. The superior property of **11** compared to **16** as an asymmetric acylation catalyst could be ascribed to the stronger Lewis basicity of the amide carbonyl group than that of the ester carbonyl group (donor number of amides > donor number of esters). However, the reasons for the poorer efficiency of catalyst **15** with a tertiary amide linkage compared with catalyst **11** with a secondary amide linkage are unclear (see also Figure 3). We then examined the effects of the C_2-symmetric structure of catalysts **11** and **12a** by comparing the corresponding mono-functionalized chiral PPY catalysts **17** and **18** [10], respectively (Table 4, entry 4 and entry 5). Catalyst **17** was found to be slightly less effective than **11** in the asymmetric desymmetrization of **5** to give the monoacylate in 76% ee (Table 4, entry 4). Catalyst **18** gave monoacylate **6** in diminished ee (41% ee) in the acylative desymmetrization of **5** (Table 4, entry 5 vs entry 6). The corresponding (1*R*,2*S*)-**6** was obtained in each case. These results imply that a C_2-symmetric structure in catalysts is responsible for the higher efficiency in the asymmetric acylation.

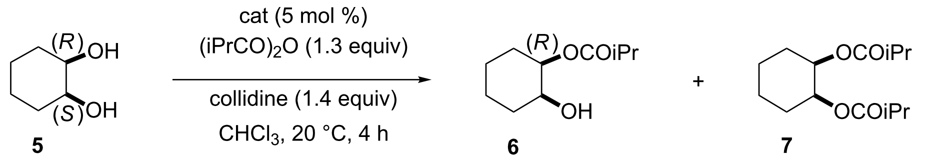
Asymmetric desymmetrization of *meso*-1,3-cyclohexanediol

We have reported that catalyst **3** promoted the acylative asymmetric desymmetrization of *meso*-1,3-cyclohexanediol (**19**) to give **20** in 52% ee and 48% yield [11]. Here, C_2-symmetric chiral PPY catalysts were examined for this asymmetric transformation (Table 5). Treatment of **19** with isobutyric anhydride



Scheme 4: Acylative kinetic resolution of *racemic*-**6** with catalyst **12b**.

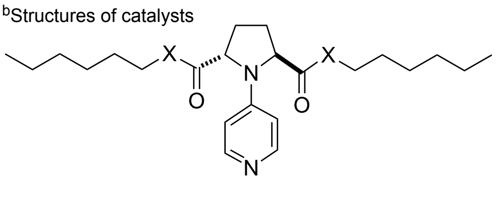
Table 4: Effects of side chain linkage and C_2-symmetric structure of catalysts on the asymmetric desymmetrization of **5**.[a]



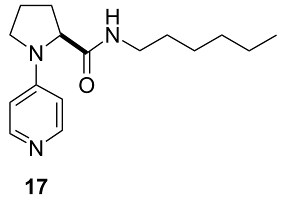
Entry	Catalyst[b]	**6**:**7**:Recovery of **5**[c] (%)	ee of **6** (%)[d,e]
1	**11**	75:23:3	87
2	**15**	79:15:6	13
3	**16**	65:24:11	13
4	**17**	70:26:4	76
5	**18**	61:34:5	41
6	**12a**	70:25:5	74

[a] Reactions were run at a substrate concentration of 0.2 M.

[b] Structures of catalysts



11 : X = NH
15 : X = NMe
16 : X = O



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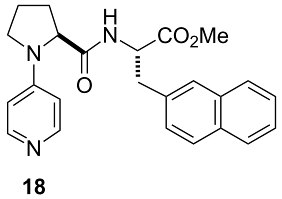

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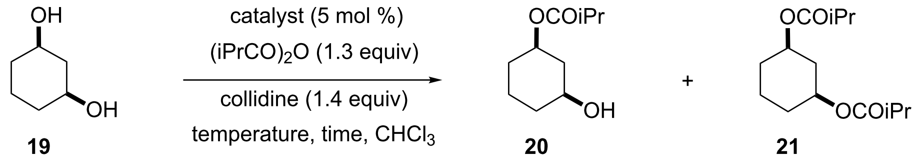
[c] Yields determined by ^{1}H NMR with dibenzyl ether as an internal standard. [d] Determined by GC analysis with a chiral stationary phase, beta-DEX 225. [e] (1*R*,2*S*)-Isomer was obtained in each case.

in the presence of catalyst **4** at 0 °C gave monoacylate **20** in 48% ee and 66% yield (Table 5, entry 1). The corresponding reaction at −40 °C did not improve the enantioselectivity (Table 5, entry 2). The attempted asymmetric desymmetrization of **19** at 20 °C promoted by catalysts **11**, **12a**, **12b**, and **14** resulted in the formation of the monoacylate in 19–31% ee and 48–69% yield (Table 5, entries 3, 5–7). Lowering the temperature of acylation of **19** in the presence of **11** did not improve the enantioselectivity (Table 5, entry 3 vs entry 4). The lack of temperature effects may indicate that the hydrogen-bonding

Table 5: The asymmetric desymmetrization of *meso*-1,3-cyclohexanediol (**19**) with C_2-symmetric chiral PPY catalysts.[a]



Entry	Catalyst	Temp. (°C)	Time (h)	**20**:**21**:Recovery of **19** (%)[b]	ee of **20** (%)[c,d]
1	**4**	0	12	66:15:17	48
2	**4**	–40	48	26: 2:72	50
3	**11**	20	4	69:24:7	31
4	**11**	–40	48	44:10:44	25
5	**12a**	20	4	48:43:9	27
6	**12b**	20	4	49:30:21	20
7	**14**	20	4	62:33:6	19

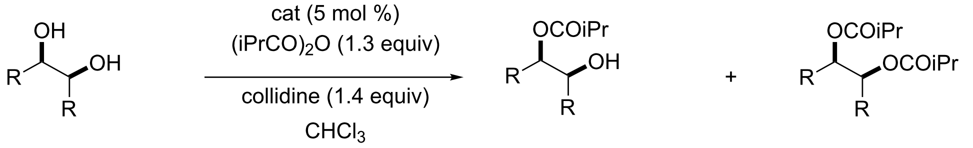
[a] Reactions were run at a substrate concentration of 0.2 M. [b] Yields determined by ^{1}H NMR with dibenzyl ether as an internal standard. [c] Determined by GC analysis with a chiral stationary phase, beta-DEX 225. [d] The absolute configuration of **20** was not determined.

interaction between the catalyst and the substrate may not significantly be involved in the process of enantioselective acylation of **19** in the presence of catalysts **4** and **11**.

Asymmetric desymmetrization of *meso*-2,3-butanediol and *meso*-hydrobenzoin

The asymmetric desymmetrization of *meso*-2,3-butanediol (**22a**) and *meso*-hydrobenzoin (**22b**) were examined (Table 6). Treatment of **22a** with isobutyric anhydride in the presence of 5 mol % of catalyst **8a** at 20 °C for 4 h gave monoacylate **23a** in 53% ee and 78% yield (Table 6, entry 1). Catalysts **10**, **11**, **12b**, and **14** were also examined for asymmetric desymmetrization of **22a** (Table 6, entries 2–8). These catalysts are almost equally effective in the asymmetric desymmetrization of **22a** at 20 °C to give monoacylate **23a** in 57–66% ee and 72–78% yield (Table 6, entries 2, 3, 5, and 6). As observed in the asymmetric desymmetrization of **5**, the acylation of **22a** at a lower temperature gave better selectivity. The catalytic enantioselective acylation of **22a** with isobutyric anhydride in the presence of **11** or **14** at −60 to −65 °C gave monoacylate **23a** in 87% ee (72% yield) or 92% ee (61% yield), respectively (Table 6, entries 4 and 8) [20] . The higher enantioselectivity was found to be associated with the higher mono/diacylation ratio in the asymmetric acylation of **22a** promoted by **14** (Table 6, entries 6–8). (Notice: Enantioenriched **23a** gradually undergoes partial racemization when it is kept as a $CHCl_3$ solution probably via intramolecular

Table 6: The asymmetric desymmetrization of *meso*-2,3-butanediol (**22a**), *meso*-hydrobenzoin (**22b**) and *meso*-1,2-cyclopentanediol (**22c**).[a]



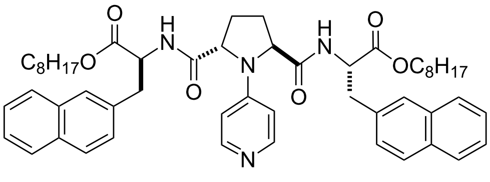
22a: R = Me
22b: R = Ph
22c: R, R = –(CH$_2$)$_3$–

23a: R = Me
23b: R = Ph
23c: R, R = –(CH$_2$)$_3$–

24a: R = Me
24b: R = Ph
24c: R, R = –(CH$_2$)$_3$–

Entry	Substrate	Catalyst[b]	Temp. (°C)	Time (h)	**23**:**24**:Recovery of **22** (%)[c]	ee of **23** (%)
1	**22a**	**8a**	20	4	78:11:11	53[d,e]
2	**22a**	**10**	20	4	77:16:7	62[d,e]
3	**22a**	**11**	20	4	78:13:9	66[d,e]
4[f]	**22a**	**11**	−60	24	72:7:21	87[d,e]
5	**22a**	**12b**	20	4	72:6:22	61[d,e]
6	**22a**	**14**	20	24	73:18:9	57[d,e]
7	**22a**	**14**	−40	24	82:4:14	85[d,e]
8[f]	**22a**	**14**	−65	24	61:<1:39	92[d,e]
9	**22b**	**8a**	20	4	64:25:11	40[g,h]
10	**22b**	**8b**	20	4	63:22:15	23[g,h]
11	**22b**	**12b**	20	4	54:25:21	19[g,h]
12	**22c**	**4**	−20	6	85:12:3	~0[i]
13	**22c**	**25**	−20	4	73:27:0	~0[i]
14[j]	**22c**	**25**	−20	4	67:33:0	~0[i]

[a] Reactions were run at a substrate concentration of 0.2 M.
[b] Structure of catalyst **25**:



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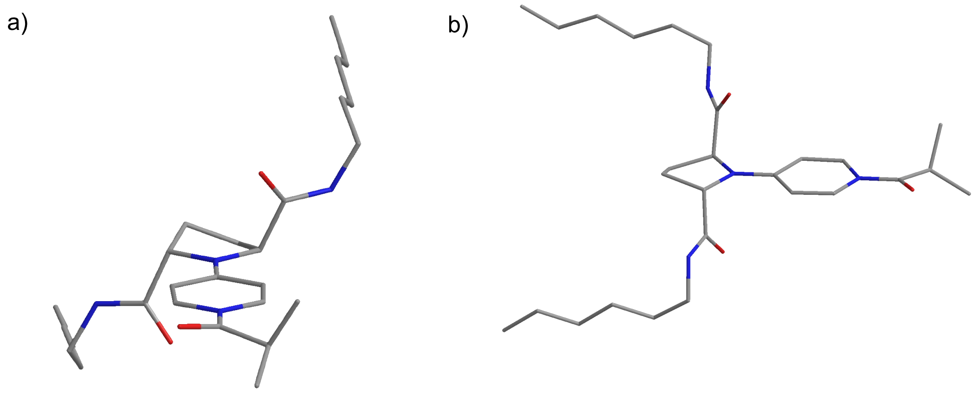
[c] Yields determined by ^1H NMR with dibenzyl ether as an internal standard. [d] Ee was determined by GC analysis with a chiral stationary phase, beta-DEX 225. [e] (2*R*,3*S*)-Isomer was obtained. [f] Data quoted from reference [20]. [g] Ee was determined by HPLC analysis with a chiral stationary phase, Chiralcel OJ (iPrOH:hexane = 5:95, flow 0.5 mL min^{-1}, t_R = 35, 51 min). [h] The absolute configuration was not determined. [i] Ee of the corresponding benzoate, which was determined by HPLC analysis with a chiral stationary phase, Chiralcel AS (iPrOH/hexane 1:99, flow 0.2 mL min^{-1}, t_R = 43, 49 min). [j] Run in toluene.

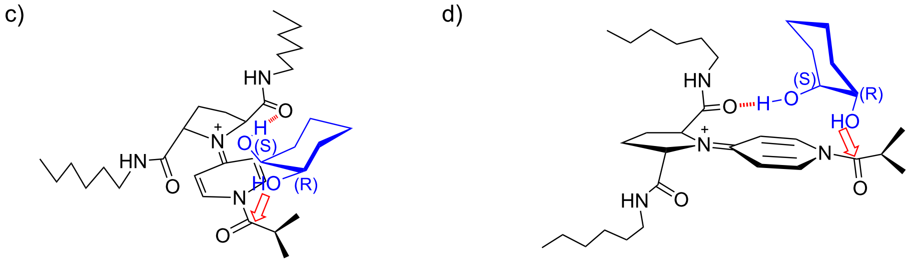
acyl migration: e.g., from 88% ee to 71% ee after 168 h.) The asymmetric desymmetrization of *meso*-hydrobenzoin (**22b**) was examined. Treatment of **22b** with isobutyric anhydride in the presence of catalysts **8a**, **8b**, and **12b** at 20 °C gave **23b** in 19–40% ee in 54–64% yield (Table 6, entries 9–11). Significant amounts of the diacylate were also formed (22–25% yield) together with the recovery of the unreacted material (11–21%). In these transformations, the low enantioselectivity is associated with the low mono/diacylation ratio, which was also observed in the asymmetric desymmetrization of *meso*-1,3-cyclohexanediol (**19**, Table 5). The asymmetric desymmetrization of *meso*-1,2-cyclopentanediol (**22c**) was also examined using catalysts **4** and **25** [18], the corresponding octyl ester analogues of **8a** and **12a**, respectively (Table 6, entries 12–14). The acylation of **22c** with isobutyric anhydride in the presence of **4** in chloroform at −20 °C gave monoacylate **23c** as a racemate in 85% yield (Table 6, entry 12). Similarly, racemic **23c** was obtained by the reaction of **22c** with isobutyric anhydride in the presence of **25**, either in chloroform or in toluene (Table 6, entries 13 and 14).

Mechanistic implication

Several characteristic phenomena were observed in the asymmetric desymmetrization of *meso*-diols promoted by C_2-symmetric chiral PPY catalysts. (1) Substrate specificity: *Meso*-1,2-cyclohexanediol (**5**) and *meso*-2,3-butanediol (**22a**) (matched substrates) gave high enantioselectivity, while *meso*-1,3-cyclohexanediol (**19**), *meso*-hydrobenzoin (**22b**), and *meso*-1,2-cyclopentanediol (**22c**) (mismatched substrates) gave poor enantioselectivity in the asymmetric desymmetrization. (2) A higher enantioselectivity was observed in the reactions of matched substrate **5** in the solvents of the lower polarity (Table 2, entries 1–5). (3) A higher enantioselectivity and a higher mono/diacylation ratio were observed in the acylation of the matched substrates at the lower temperatures (Table 2, entries 6–9; Table 6, entries 3, 4, 6–8). These phenomena suggest that the enantioselective acylation of the matched substrates proceeds in an accelerative manner via hydrogen-bonding interaction between the catalyst and the substrate. A possible model for the transition state assembly for the enantioselective acylation of *meso*-1,2-cyclohexanediol (**5**) catalyzed by **11** is shown in Figure 2. A chiral acylpyridinium ion generated from **11** and isobutyric anhydride is expected to be the reactive intermediate which is responsible for the asymmetric acylation. The most stable conformer **A** of the acylpyridinium ion was generated by a molecular modeling search (AMBER* force field with the GB/SA solvation model for chloroform using MacroModel V 9.0 (50,000 steps MCMM)) and shown in Figure 2a and Figure 2b. Since the amide carbonyl groups at C(2) and C(5) seem to play the key role in the asymmetric



A (front view)   A (side view)



substrate approach to **A** (front view)   substrate approach to **A** (side view)

Figure 2: A hypothetical model for the transition-state assembly of the asymmetric acylation of **5** promoted by catalyst **11**. Front view a) and side view b) of the calculated structure of acylpyridinium ion **A**. Front view c) and side view d) of the possible modes for the substrate approach to **A**.

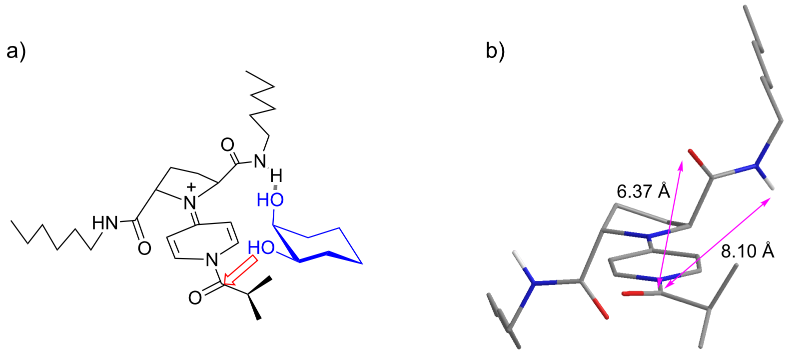


Figure 3: An alternative model for the transition state assembly of the asymmetric acylation of **5** promoted by catalyst **11**. a) A possible mode of the substrate approach to acylpyridinium ion **A**, and b) the calculated structure of **A**.

desymmetrization of **5** to give (1*R*,2*S*)-**6** (Table 1 and Table 4), we assume that the amide carbonyl group would serve as a hydrogen-bond acceptor and the non-reacting OH of **5** as a hydrogen-bond donor. A possible approach of substrate **5** to **A** is shown in Figure 2c and Figure 2d. In the case where a hydrogen bond between the amide carbonyl group and an axial-OH at the (*S*)-chiral center of **5** is formed, an equatorial-OH at the (*R*)-chiral center locates in the close proximity to the reactive carbonyl group without any unfavorable steric interaction, resulting in the selective acylation of the hydroxy group at the (*R*)-chiral center to give (1*R*,2*S*)-**6**. On the other hand, there may be other possible modes of the approach of **5** to **A**. They involve hydrogen-bonding interaction between the amide carbonyl group of **A** and (1) an equatorial-OH at the (*S*)-chiral center of **5**, (2) an axial-OH at the (*R*)-chiral center of **5**, or (3) an equatorial-OH at the (*R*)-chiral center of **5**. The first one would give (1*R*,2*S*)-**6**, while the latter two would give (1*S*,2*R*)-**6**. In these cases, however, unfavorable steric interaction is expected based on our molecular modeling study. It is also anticipated that an axial-OH may be the better hydrogen-bond donor than an equatorial-OH, according to the reported higher acidity of the axial hydroxy groups of cyclohexane derivatives [39]. An alternative model for the transition-state assembly is shown in Figure 3 where the amide NH group of **A** serves as a hydrogen-bond donor and the non-reacting OH of substrate **5** as a hydrogen-bond acceptor. This model could explain the difference between effective catalyst **11** and ineffective catalysts **15** and **16** (Table 4, entry 1 vs entries 2 and 3). However, the calculated distance between the amide NH group and the reactive amide carbonyl group of **A** seems too long (8.10 Å) for the accommodation of the 1,2-diol substructure (calculated distance between two oxygen atoms of the hydroxy groups: 2.66 Å). It is also difficult to find the reasons for the preferable acylation of the hydroxy group at the (*R*)-chiral center of **5** from this model. We prefer the model shown in Figure 2, however, the model in Figure 3 cannot be eliminated.

Conclusion

We have developed an organocatalytic method for the acylative asymmetric desymmetrization of *meso*-diols. Highly enantioselective desymmetrization of *meso*-1,2-cyclohexanediol and *meso*-2,3-butanediol (matched substrates) was achieved while low to moderate enantioselectivity was observed in the asymmetric desymmetrization of *meso*-1,3-cyclohexanediol, *meso*-hydrobenzoin, and *meso*-1,2-cyclopentanediol (mismatched substrates). Organocatalytic enantioselective acylation of the matched substrates was proposed to proceed via hydrogen-bonding interaction between the catalyst and the substrate.

Supporting Information

Supporting Information File 1

Experimental details and characterization data of new compounds, copies of ^{1}H NMR and ^{13}C NMR.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-203-S1.pdf]

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Imidazolinium and amidinium salts as Lewis acid organocatalysts

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Full Research Paper

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Abstract

The application of imidazolinium and amidinium salts as soft Lewis acid organocatalysts is described. These salts were suitable catalysts for the activation of unsaturated thioesters in a Diels–Alder reaction and in the ring opening of thiiranes and epoxides. The products were isolated in good yields. The mild catalysts did not cause desulfurization of the products containing a thiol or thiocarbonyl group.

Introduction

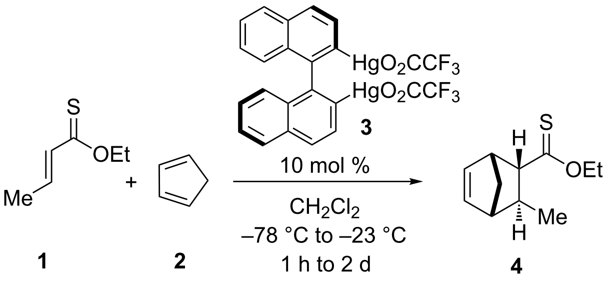
Salts with melting points below 100 °C are known as ionic liquids and are often used as novel solvents for reactions and electrochemical processes [1]. Several of these solvents can contribute to the research field of "green chemistry" [2]. The most common used ionic liquids are based on imidazolium cations. Next to their application in catalytic reactions [3-6], they are also capable of catalyzing reactions themselves, either in substoichiometric amounts or as reaction medium due to hydrogen-bond activation of the protons of the imidazolium cation [7-10] and other variables, such as π-orbital and charge–charge interactions [8-10].

Recently, we applied saturated imidazolium salts with an aryl substituent at the C(2) position as catalysts for the aza-Diels–Alder reaction [11,12]. These catalysts do not activate the substrate through hydrogen bonding, but instead, like other carbon-cation based catalysts, through their positive center [8-10,13-15], and belong also to the field of organocatalysis [10,16,17].

Taking the soft Lewis acidic character of imidazolinium salts into consideration, we were interested to apply these salts in a Diels–Alder reaction with ethyl crotonthioate as dienophile.

Due to the low electronegativity of sulfur it would be difficult to catalyze this reaction with hydrogen-bond activation catalysts [18]. The utilization of the soft Lewis basic sulfur groups in this reaction is rare. Often mercury Lewis acids are applied [19-22] to activate the sulfur group and there is also the risk of desulfurization [23].

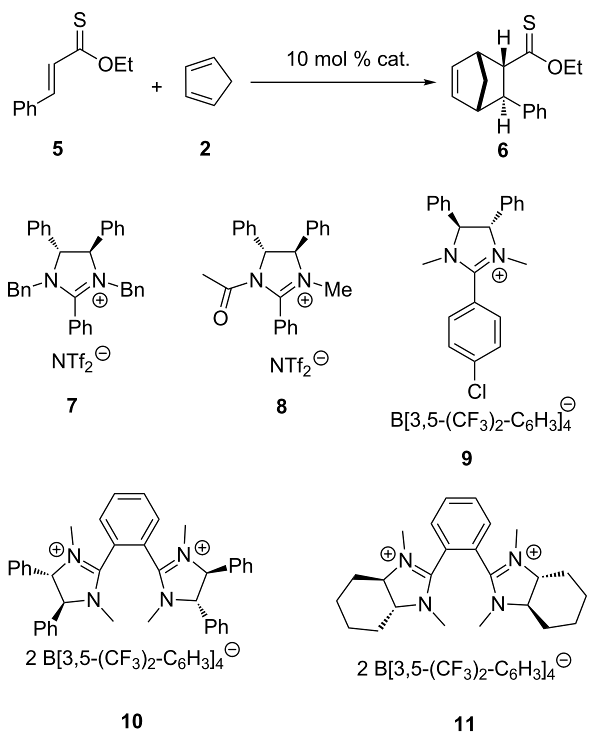
The only known asymmetric Diels–Alder reaction with ethyl crotonthioate (**1**) and cyclopentadiene (**2**) in the presence of optically pure 2,2'-dimercurio-1,1'-binaphthyl compound **3** gave the product **4** in 44% yield with 58% ee (Scheme 1) [20].



Scheme 1: Diels–Alder reaction with ethyl crotonthioate (**1**) and cyclopentadiene (**2**).

Results and Discussion

Since product **4** has a low boiling point and proved difficult to purify on a small scale, the model reaction shown in Scheme 2 was evaluated. The α,β-unsaturated thioester **5** was prepared from ethyl cinnamate and 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiadiphosphetane-2,4-disulfide (Lawesson's reagent) [22]. The cycloaddition of ethyl thionocinnamate (**5**) with 1.5 equiv of cyclopentadiene (**2**) was performed in different solvents, at varied temperatures, by using a broad range of catalysts, which are summarized in Table 1.



Scheme 2: Diels–Alder reaction catalysed with imidazolinium salts.

First a few metal-based Lewis acids were applied in the reaction. $BF_3•Et_2O$ is known to activate also sulfur carbonyl groups [24] and gave the product in 90% yield, while TMSOTf gave the product in 55% yield. In both cases the *endo* product was the major product. The reaction was followed by TLC and the temperature was gradually increased from –10 to 45 °C over 4 days in ca. 10 °C steps.

Next, imidazolinium salt **7** [25] was used in the reaction. The formation of the product was observed at 45 °C; however, the

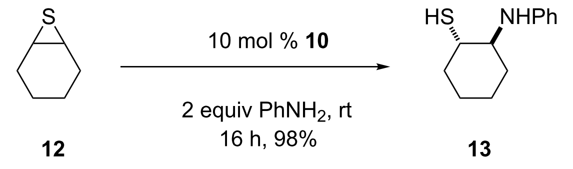
Table 1: Diels–Alder reaction with 10 mol % catalyst according to Scheme 2. Reactions with CH_2Cl_2 were carried out in a pressure vessel.

entry	solvent	catalyst	temp [°C]	time [d]	yield %^{a} (*endo*:*exo*)
1	CH_2Cl_2	$Hg(OAc)_2$	−10–45	4	0
2	CH_2Cl_2	$BF_3{\cdot}Et_2O$	−10–45	4	90 (99:1)
3	CH_2Cl_2	TMSOTf	−10–45	4	55 (99:1)
4	CH_2Cl_2	**7**	25–45	4	8 (13:1)
5	toluene	**7**	25–110	4	0
6	dioxane	**7**	25–110	4	6 (3:1)
7	CH_2Cl_2	**8**	25–45	4	5 (9:1)
8	CH_2Cl_2	**9**	0–45	4	12 (14:1)
9	CH_2Cl_2	**10**	−10–45	4	69 (99:1)
10	CH_2Cl_2	**11**	0–45	3	66 (99:1)

^{a}Isolated yields.

product was isolated only in a low yield of 8%. In toluene no reaction was observed even under reflux. In dioxane under reflux a low yield of 6% was obtained with a low *endo*/*exo* ratio of (3:1). Salt **8** [25] and **9** [25] gave similar poor results as salt **7** [25]. Finally, the bis-imidazolinium salt **10** [12] gave the product in 69% yield with an *endo*/*exo* ratio comparable to $BF_3 \cdot Et_2O$. The reaction started slowly at 10 °C. In addition, the similar salt **11** [12] gave the product in a comparable yield of 66%. Although in all cases the product was racemic, the results show that bis-imidazolinium salts can be applied as Lewis acid organocatalysts to activate a thiocarbonyl group.

Next, the behavior of these salts in the ring opening of a thiirane was explored. No activity was observed with salt **9** in the ring opening with aniline. Therefore, the more active bis-imidazolinium salt **10** was applied with thiirane **12** and aniline in CH_2Cl_2. A yield of 18% was obtained. However, in the absence of a solvent the yield increased to 98% after 16 h (Scheme 3). In the absence of a catalyst a yield of 12% was obtained under neat conditions. Product **13** was obtained in all reactions as racemate in the error range of the HPLC measurements.

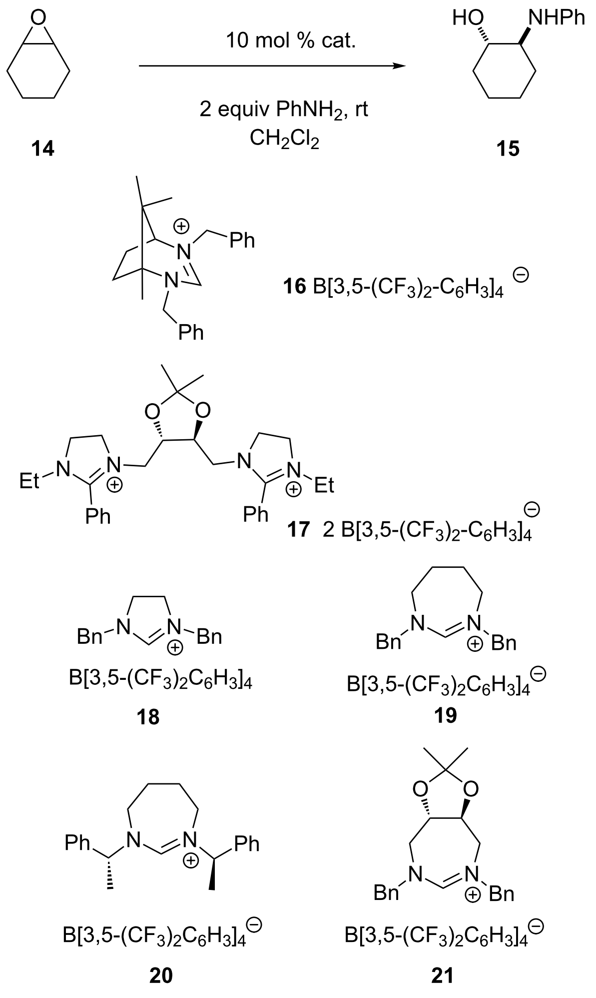


Scheme 3: Ring opening of thiirane **12**.

Next, several salts were explored in the ring opening of cyclohexene epoxide with aniline (Scheme 4, Table 2). A reaction in CH_2Cl_2 in the absence of the catalyst gave a yield of 10% after 24 h (Table 2, entry 1).

The camphor based salt **16** gave a yield of 24%, while bis-imidazolinium salt **17** resulted in a yield of 60% (Table 2, entries 2 and 3). The bis-imidazolinium salts **10** and **11** gave lower yields compared to **17**. However, when the reaction was carried out in the absence of a solvent, the yield increased with salts **10** and **11** to 98 and 96%, respectively (Table 2, entries 6 and 7).

Compared to sulfur, oxygen is a good hydrogen-bond acceptor. Hence, also imidazolinium salts with a C(2)H unit were applied in the reaction. Here, an activation of the epoxide can be also possible through hydrogen bonding next to the direct interaction with the positively charged NCN center. While salt **18** displayed very low catalytic activity, salt **19** gave the product in 78% yield (Table 2, entry 10). This phenomenon may be

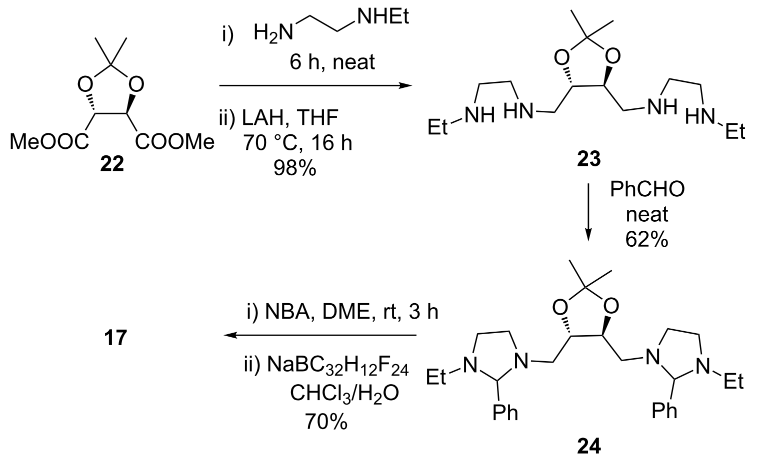


Scheme 4: Ring opening of epoxide **14**.

Table 2: Ring opening of epoxide **15** with aniline and 10 mol % salt.

entry	solvent	catalyst	time	yield %[a]
1	CH_2Cl_2	–	24 h	10
2	CH_2Cl_2	**16**	24 h	24
3	CH_2Cl_2	**17**	48 h	60
4	CH_2Cl_2	**10**	48 h	34
5	CH_2Cl_2	**11**	48 h	48
6	neat	**10**	24 h	98
7	neat	**11**	24 h	96
8	neat	**–**	24 h	0
9	CH_2Cl_2	**18**	48 h	12
10	CH_2Cl_2	**19**	24 h	78
11	CH_2Cl_2	**20**	24 h	38
12	CH_2Cl_2	**21**	6 h	99
13	toluene	**–**	2 h	0
14	toluene	**21**	2 h	89

[a] Isolated yields.

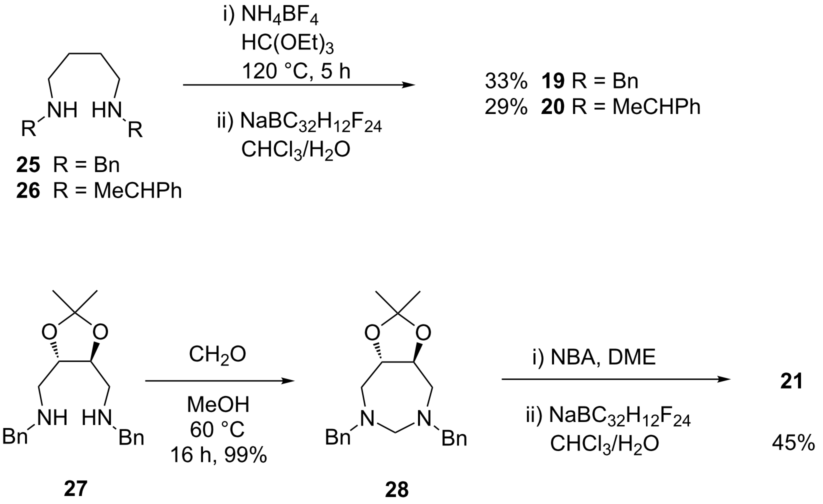


Scheme 5: Synthesis of bis-imidazolium salt **17**.

explained by the better delocalization of the positive charge in the planar sp^2-centered imidazoline scaffold in salt **18**. Meanwhile the special geometry of 7-membered 1,3-diazepinium cations such as **19** does not allow the planar conformation to be kept, thus the positive charge is less delocalized over the NCN atoms (Scheme 4) [26-29]. Salt **16**, incorporating a six-membered ring as the smallest ring, displayed a catalytic activity between salt **18** and **19**. Salt **20**, with a larger steric environment around the amidinium unit next to the nitrogen atoms, gave a yield of only 38% (Table 2, entry 11). On the other hand salt **21** gave the product in 99% yield after 6 h (Table 2, entry 12). By changing the solvent from dichloromethane to toluene the reaction time was even further reduced with salt **21**, and the product was isolated in 89% yield (Table 2, entry 14). In all cases product **15** was racemic in the error range of the HPLC measurements.

Salt **17** was prepared according to Scheme 5. The synthetic route involved a tetraamine formation via amidation under neat conditions and reduction with LAH, furnishing the product in 98% yield over two steps. Next, the aminal formation under neat conditions was performed. The aminal was further oxidized to a bromide salt by *N*-bromoacetamide in dimethoxyethane. The bromide counter anion was further efficiently replaced by a tetrakis(3,5-bis(trifluoromethyl)phenyl)borate anion providing the salt **17** by anion metathesis.

The 7-membered 1,3-diazepinium salts were prepared according to Scheme 6. Salts **19** and **20** were prepared in a standard way by treatment with triethyl orthoformate in the presence of ammonium tetrafluoroborate followed by anion metathesis in 33 and 29% yield, respectively.



Scheme 6: Synthesis of amidinium salt **21**.

Due to the low yield, salt **21** was prepared through a different route. First amine **27** [30] was transformed with formaldehyde to the aminal **28**. The latter could be oxidized to the corresponding bromide salt, which was transformed directly by anion metathesis to the salt **21**.

Conclusion

It was possible to prepare new metal-free Lewis acids containing bis-imidazolinium cations and investigate the salts as organocatalysts. Although with enantiopure chiral salts no enantiomeric excess was observed, it was shown for the first time that these salts can interact with thiocarbonyl groups and thiiranes in order to activate these substrates. In addition, it was found that 7-membered 1,3-diazepinium cations are good catalysts for the ring opening of epoxides and that these salts are more reactive than imidazolinium salts.

Supporting Information

Supporting Information File 1

Experimental part.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-205-S1.pdf]

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Asymmetric Brønsted acid-catalyzed aza-Diels–Alder reaction of cyclic *C*-acylimines with cyclopentadiene

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Full Research Paper

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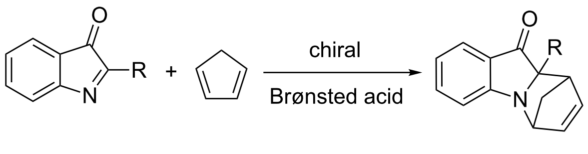
Abstract

A new chiral Brønsted acid-catalyzed aza-Diels–Alder reaction of cyclic *C*-acylimines with cyclopentadiene has been developed. The reaction provides optically active aza-tetracycles in good yields with high diastereo- and enantioselectivities under mild reaction conditions.

Introduction

The enantioselective aza-Diels–Alder reaction is an important method for the construction of optically active, nitrogen-containing, six-membered rings, such as tetrahydroquinolines and piperidines. N-heterocycles are found in a wide range of natural products and many biologically active compounds [1-4]. To date, most aza-asymmetric Diels–Alder reactions have been catalyzed by chiral Lewis acids [5-16]. Recently, chiral Brønsted acids have attracted interest as effective catalysts for a variety of asymmetric transformations involving imine electrophiles [17-23]. Among others, the aza-Diels–Alder reaction of imino-dienophiles has been investigated and it was shown that the reaction between arylimines and dienes, catalyzed by chiral Brønsted acids, proceeds with high levels of enantioselectivity. However, these reactions are limited to electron-rich dienes including Brassard's and Danishefsky dienes [24-32]. To the best of our knowledge the enantioselective Brønsted acid catalyzed aza-Diels–Alder reaction of imines with less-electron-rich dienes has not been reported. Thus, we decided to examine the unprecedented Brønsted acid catalyzed aza-Diels–Alder reaction of cyclic *C*-acylimines with cyclopentadiene providing optically active nitrogen-containing heterocycles (Scheme 1).

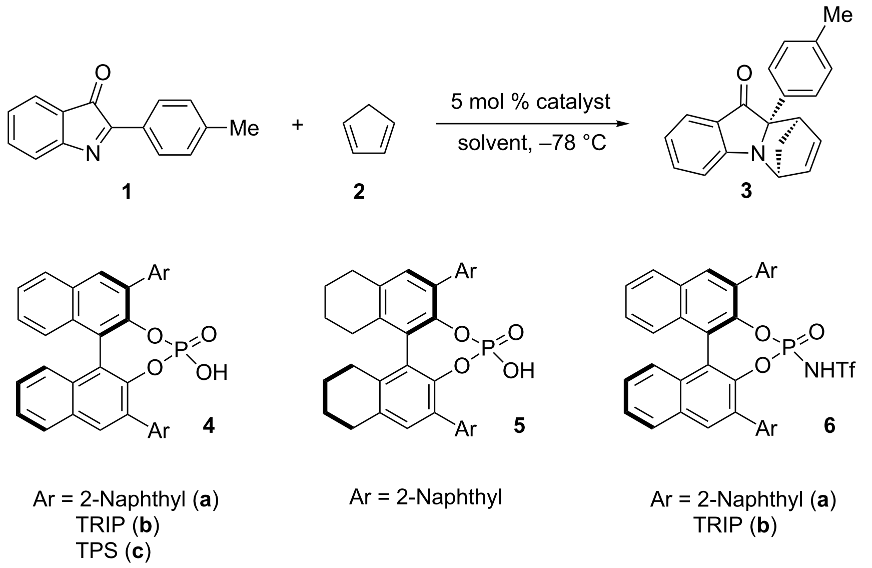


Scheme 1: Brønsted acid catalyzed aza-Diels–Alder reaction of cyclic *C*-acylimines with cyclopentadiene.

Results and Discussion

Our initial study began with the examination of the the aza-Diels–Alder reaction of cyclic *C*-acylimine **1** with cyclopentadiene (**2**) in the presence of BINOL-derived phosphoric acid diesters and *N*-triflylphosphoramides **4–6** (Table 1) [33-51] as the catalysts. We were delighted to see that the reaction proceeded smoothly at different temperatures and that the product could be obtained with an enantiomeric excess of 8% ee when the reaction was performed in toluene at −60 °C in the presence of catalyst **4a** (Table 1, entry 1). A slight increase in enantioselectivity was observed when the reaction was conducted at −78 °C (Table 1, entry 2). Subsequently, different catalysts were applied in the Brønsted acid catalyzed hetero-Diels–Alder reaction. From the different catalysts tested, phosphoric acid diester **4b**, with the 2,4,6-triisopropylphenyl substituent in the 3,3’-position of the BINOL backbone, proved

Table 1: Optimization of reaction conditions[a].



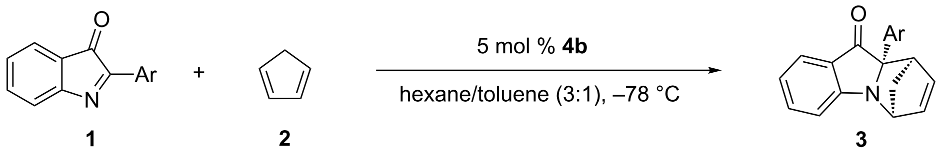
entry	catalyst	x mol %	solvent	*t* [min]	ee [%][b, c]
1[d]	**4a**	5	toluene	2	8
2	**4a**	5	toluene	15	16
3	**4b**	5	toluene	20	74
4	**4c**	5	toluene	8h	40
5	**5**	5	toluene	90	16
6	**6a**	5	toluene	40	20
7	**6b**	5	toluene	20	60
8	**4b**	2	toluene	60	60
9	**4b**	1	toluene	60	43
10	**4b**	5	toluene:$CHCl_3$ 1:1	40	13
11	**4b**	5	toluene:CH_2Cl_2 1:1	10	20
12	**4b**	5	toluene:hexane 1:1	5 h	74
13	**4b**	5	toluene:hexane 1:2	6 h	90
14	**4b**	5	toluene:hexane 1:3	8 h	94
15	**4b**	5	toluene:hexane 1:4	16 h	94

[a]Reaction conditions: Imine **1**, cyclopentadiene (2.0 equiv) and catalyst. [b]Enantiomeric excess was determined by HPLC on a chiral phase. [c]Only one diastereomer is formed. [d]The reaction was carried out at −60 °C.

to be the best catalyst, and the product was obtained with an encouraging enantiomeric excess of 74% (Table 1, entry 3). To optimize the reaction conditions further we evaluated the catalyst loading and solvent. However, the reduction of catalyst loading from 5 to 1 mol % resulted in a significant decrease in enantioselectivity (Table 1, entries 8 and 9).

In our previous studies in asymmetric Brønsted acid catalysis, we noticed that solvent mixtures can strongly influence both the reactivity and selectivity. Thus, we evaluated different solvent mixtures. When a 1:1 mixture of toluene and $CHCl_3$ was used the enantioselectivity dropped considerably. The same effect was observed when a mixture of toluene and CH_2Cl_2 was used (Table 1, entries 10 and 11). Hence, the chlorinated solvents were replaced by hexane. Interestingly, use of a 1:1 mixture of toluene and hexane afforded the corresponding product without loss of selectivity, but, as anticipated, the reaction time was longer (Table 1, entry 12). Pleasingly, when the reaction was carried out in a 2:1 mixture of hexane/toluene the product exhibited excellent enantioselectivity (Table 1, entry 13). Further improvement of selectivity was obtained by increasing the hexane/toluene ratio to 3:1, which delivered the product with an excellent enantiomeric excess of 94% (Table 1, entry 14). With the optimal reaction conditions in hand, the substrate scope of the aza-Diels–Alder reaction was examined (Table 2). Various substituted cyclic *C*-acylimines **1a–i** with electron-donating and electron-withdrawing groups, as well as different substitutions patterns, were applied. In all cases the corresponding tetracyclic products were obtained in high yields and with excellent diastereo- and enantioselectivities. However, the

Table 2: Scope of the aza-Diels–Alder reaction[a].



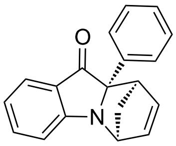
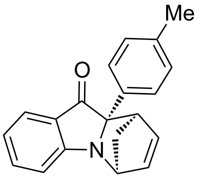
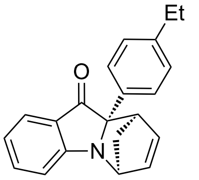
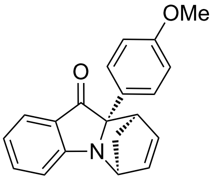
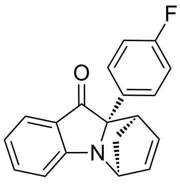
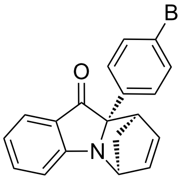
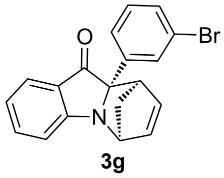
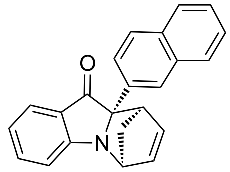
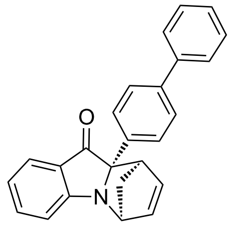
entry	product	*t* [h]	yield [%][b]	ee [%][c, d]
1	 **3a**	3	92	89
2	 **3b**	8	86	94
3	 **3c**	2	83	86
4	 **3d**	4	79	90

Table 2: Scope of the aza-Diels–Alder reaction[a]. (continued)

5	 **3e**	8	73	91
6	 **3f**	3	94	82
7	 **3g**	48	83	84
8	 **3h**	96	79	91
9	 **3i**	96	83	86

[a]Reaction conditions: Imine **1**, cyclopentadiene (2.0 equiv) and 5 mol % **4b**. [b]Yield of the isolated product after column chromatography. [c]The enantiomeric excess was determined by HPLC on a chiral phase. [d]Only one diastereomer is formed.

use of less reactive dienes including cyclohexadiene or linear 1,3-pentadienes resulted in reduced product formation or provided the desired products with low enantioselectivities [52-55].

Conclusion

In conclusion, we have developed an enantioselective Brønsted acid catalyzed aza-Diels–Alder reaction of *C*-acylimines with cyclopentadiene. The corresponding aza-tetracycles were obtained in high yields and with excellent enantio- and diastereoselectivities under mild reaction conditions. The results reported not only show that chiral BINOL derived phosphoric acid diesters can be efficient catalysts for [4 + 2] cycloadditions involving less-electron-rich dienes but additionally demonstrate the high potential of these acidic Brønsted acids in asymmetric catalysis.

Experimental

The starting materials **1a–i** were synthesized according to a known literature procedure [56].

General procedure for the aza-Diels–Alder reaction: In a typical experiment the imine and cyclopentadiene were suspended in a mixture of hexane/toluene (3:1) in a screw-capped test tube and stirred at −78 °C for 10 min. The catalyst (5 mol %) was added to the solution and the mixture was stirred until consumption of the imine. The crude reaction mixture was directly charged on silica gel and purified by column chromatography (hexane/ethyl acetate as eluent) to afford the desired products.

Supporting Information

Supporting Information File 1

Experimental details and characterization of the synthesized compounds.
[http://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-8-208-S1.pdf]

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Mechanochemistry assisted asymmetric organocatalysis: A sustainable approach

Pankaj Chauhan and Swapandeep Singh Chimni*

Review

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Abstract

Ball-milling and pestle and mortar grinding have emerged as powerful methods for the development of environmentally benign chemical transformations. Recently, the use of these mechanochemical techniques in asymmetric organocatalysis has increased. This review highlights the progress in asymmetric organocatalytic reactions assisted by mechanochemical techniques.

Introduction

Green chemistry involves innovation in chemical research and engineering that encourages the design of processes to minimize the use and production of hazardous materials and also reduce the use of energy [1-4]. These requirements are fulfilled by preventing or minimizing the use of volatile and toxic solvents and reagents, minimizing chemical wastage, development of atom-economical processes and recyclable supported catalyst that are less toxic, biodegradable and can be used at low loading.

To address many of these issues mechanochemical methods such as ball-milling and grinding with pestle and mortar have emerged as powerful techniques [5-12]. The mechanical energy generated by grinding two solids or one solid and one liquid substance results in the formation of new surfaces and cracks by breaking the order of the crystalline structure, and this results in the formation of products [8].

Grinding and ball-milling are widely applied to pulverize minerals into fine particles, in the preparation and modification of inorganic solids. Recently, their use in synthetic organic chemistry has increased considerably, due to the need for development of sustainable methodologies, and has been widely used in solvent-free non-asymmetric transformations.

On the other hand, demands for the development of stereoselective synthesis of organic molecules have noticeably amplified in recent times. In this regard, catalytic asymmetric synthesis involving the use of chiral organocatalysts has emerged as a powerful tool from the infancy to the maturity of asymmetric organocatalysis [13-26]. The use of organocatalysts for catalysing asymmetric reactions may allow several advantages, such as lower toxicity compared to metal analogues, robustness, no requirement of an inert atmosphere, provision of high stereoselectivity, and the ability to be used for the synthesis of opposite enantiomers by using enantiomeric catalysts. Organocatalyts also provide an insight into biological catalytic processes, as a number of these catalysts work by the phenomenon of enzyme mimicry. These advantages of chiral organocatalysts also meet many of the requirements of green chemistry [27].

Recently developed, organocatalytic asymmetric transformations assisted by mechanochemical techniques proved to be an excellent alternative to atom-economical stereoselective transformations under solvent-free reaction conditions. This review gives an overview of the solvent-free asymmetric organocatalytic transformation assisted by mechanochemical techniques, viz. ball-milling and grinding with pestle and mortar.

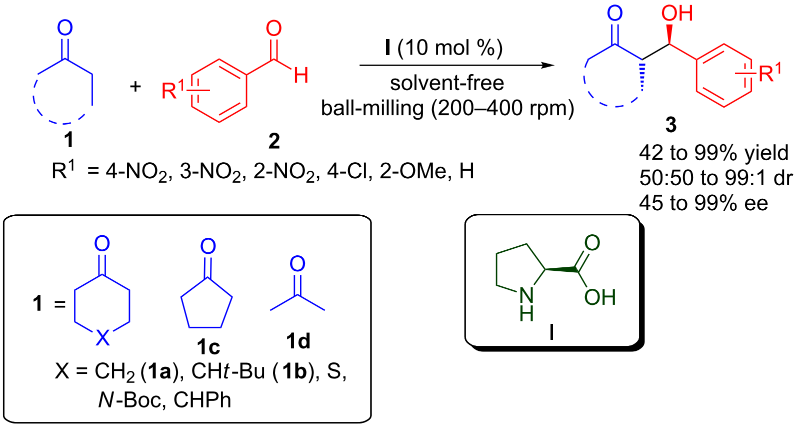
Review

Aldol reaction

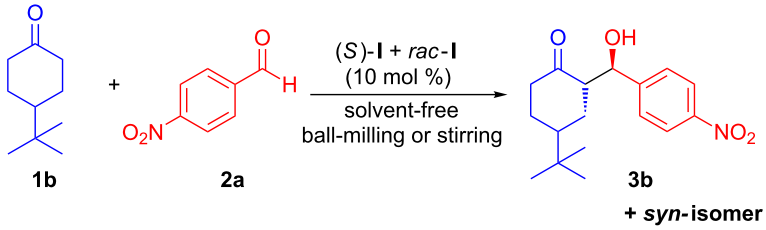
Since the origin of organocatalysis, the asymmetric aldol reaction has been one of the most intensely studied reactions, providing an easy access to chiral β-hydroxycarbonyl compounds, which are important building blocks for various bioactive molecules [28]. Among different organocatalysts used for asymmetric aldol reactions, proline and its derivatives emerged as powerful catalysts for the enamine activation of donor aldehyde or ketone. Bolm's group reported a solvent-free asymmetric organocatalytic aldol reaction under ball-milling conditions using L-proline (**I**) as catalyst (Scheme 1) [29,30]. Various five and six-membered cyclic ketones **1** were reacted with aromatic aldehydes **2** to provide *anti*-aldol products **3** in good to excellent yield (42–99%) and poor to high diastereoselectivity (50:50 to 99:1 dr) and moderate to excellent enantioselectivity (45 to >99% ee). Cyclohexanone derivatives resulted in high stereoselectivity of *anti*-aldol products; however, in the case of cyclopentanone poor diastereoselectivity was observed. The advantages of ball-milling technique over traditional stirring in the proline-catalysed aldol reaction can be highlighted as follows: (1) faster reaction rate, which leads to high yield of aldol products with excellent stereoselectivity; (2) clean reactions providing predominantly crystalline solids, which can be easily isolated; and (3) uneconomical and impractical use of a large excess of ketone could be avoided, as almost equimolar amounts of the starting materials were employed. Further, the entirety of the starting materials was consumed, which facilitated the isolation of the product from the reaction mixture.

The phase behaviour study of the proline-catalysed aldol reactions between solid substrates (**1b** and **2a**) under solvent-free ball-milling reveals a significant nonlinear relationship between the enantioselectivity of the proline and that of the aldol product **3b** (Scheme 2) [31]. This nonlinear behaviour was thought to originate from the ternary phase behaviour of scalemic proline. Neither a phase change nor the product formation was observed upon stirring of mixtures of solids **1b**, **2a** and proline at room temperature. However, heating the reaction mixture to 42 °C resulted in the completion of reaction in 72 hours, and a linear relationship between the enantioselectivity of proline and that of the aldol product was observed.

Subsequently, Bolm and co-workers also reported an enantioenrichment of a scalemic aldol product **3b** by iterative *retro*-aldol/aldol reactions of *anti*-aldol product in the presence of an achiral or racemic catalyst, i.e., pyrrolidine, by magnetically stirring a solution of the *anti*-aldol product (800 rpm) in DMSO, with ZrO_2 beads as the grinding medium [32]. The enantio-



Scheme 1: Proline-catalysed aldol reaction in a ball-mill.

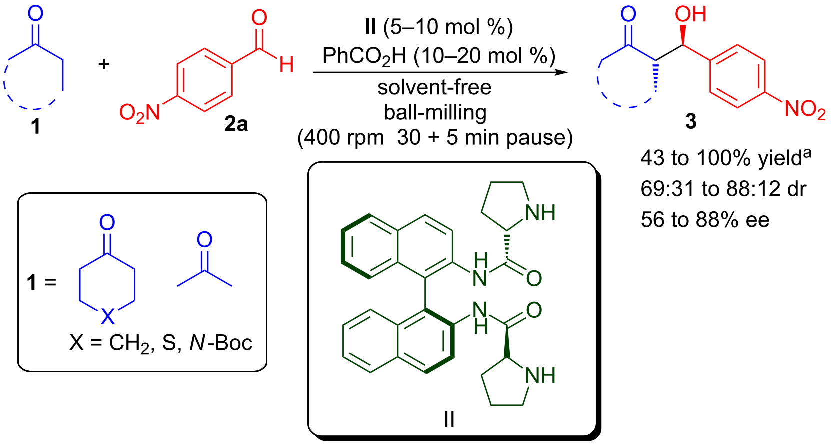


Scheme 2: Proline-catalysed aldol reaction between solid substrates (**1b** and **2a**).

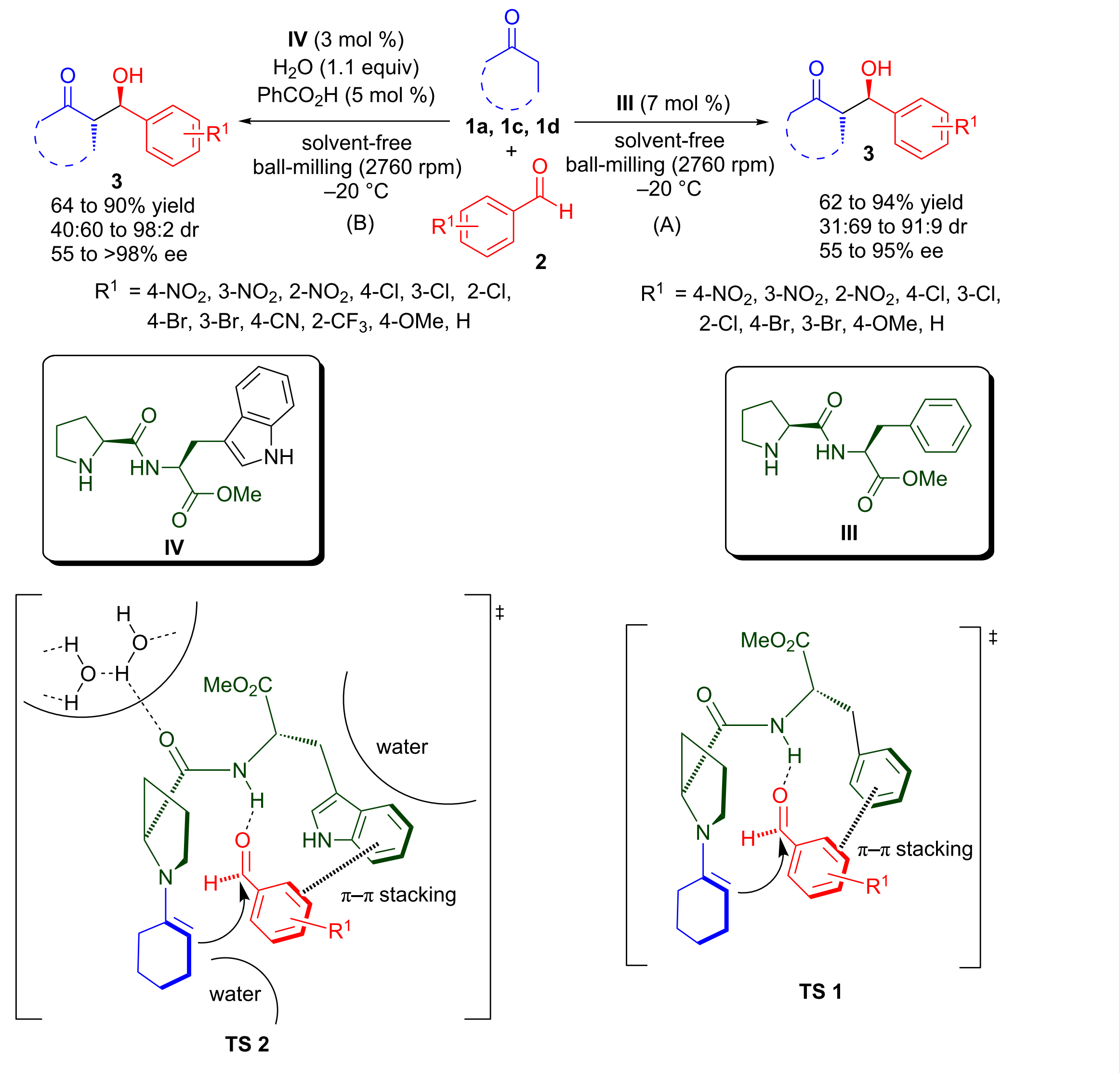
selectivity of the aldol product increases from an initial 70% ee to 92% ee after one day. Subsequently, after two and eleven days, a slow enantio-enrichment (95% ee and 96% ee, respectively) was observed.

The ball-milling approach was applied to the (*S*)-BINAM-L-prolinamide (**II**) catalysed direct aldol reaction between ketones and aldehydes under solvent-free conditions by Najera and co-workers (Scheme 3) [33,34]. Using 5–10 mol % of **II** and 10–20 mol % of benzoic acid as additive, the aldol reaction of ketones **1** and 4-nitrobenzaldehyde (**2a**) proceeded well and the corresponding aldol products **3** were obtained in moderate to excellent yield (43–100%), low to good diastereoselectivity (69:31 to 88:12 dr), and moderate to good enantioselectivity (56–88% ee). However, no real advantage of ball-milling over traditional stirring in terms of reaction rate, product yield, and stereoselectivity was observed.

In 2011, Hernández and Juaristi utilized the catalytic potential of α,α-dipeptide, i.e., methyl ester of (*S*)-proline-(*S*)-phenylalanine (**III**) for organocatalytic asymmetric aldol reaction of cyclohexanone, cyclopentanone and acetone with various aromatic aldehydes **2** under solvent-free reaction conditions with the high-speed ball-milling (HSBM) technique (Scheme 4) [35]. Using 7 mol % of **III** the *anti*-aldol products (in the case of cyclohexanone) and *syn*-aldol product (in the case of cyclopentanone) were obtained in good to high yield (62–94%), moderate to high diastereoselectivity (31:69 to 91:9 dr, *anti*/*syn*) and moderate to high enantioselectivity (55–95% ee). Under HSBM conditions, **III** also catalyses the aldol reaction of acetone with **2a** to provide the corresponding aldol product in 82% yield and 69% ee. In the previous studies by Szöllösi's group on the dipeptide **III** catalysed asymmetric aldol reactions between acetone and 2-ethylbutanal in the presence of an excess of acetone (68:1) under traditional stirring affords (*R*)-β-hydroxyketone in moderate yield and 86% ee after 24 hours [36]. The proposed transition state (**TS 1**) involves enamine formation between the pyrrolidine unit of the catalyst with the ketone and synergic activation of the aldehyde by hydrogen bonding between carbonyl oxygen and amidic NH of the catalyst. Higher stereoselectivity under solvent-free reaction conditions in comparison to reactions carried out in solvent could be attributed to lower molecular motion due to increased hydrogen bonding between aldehyde and amidic NH, and more effective π–π-stacking interaction between the phenyl ring of the catalyst and aldehyde.



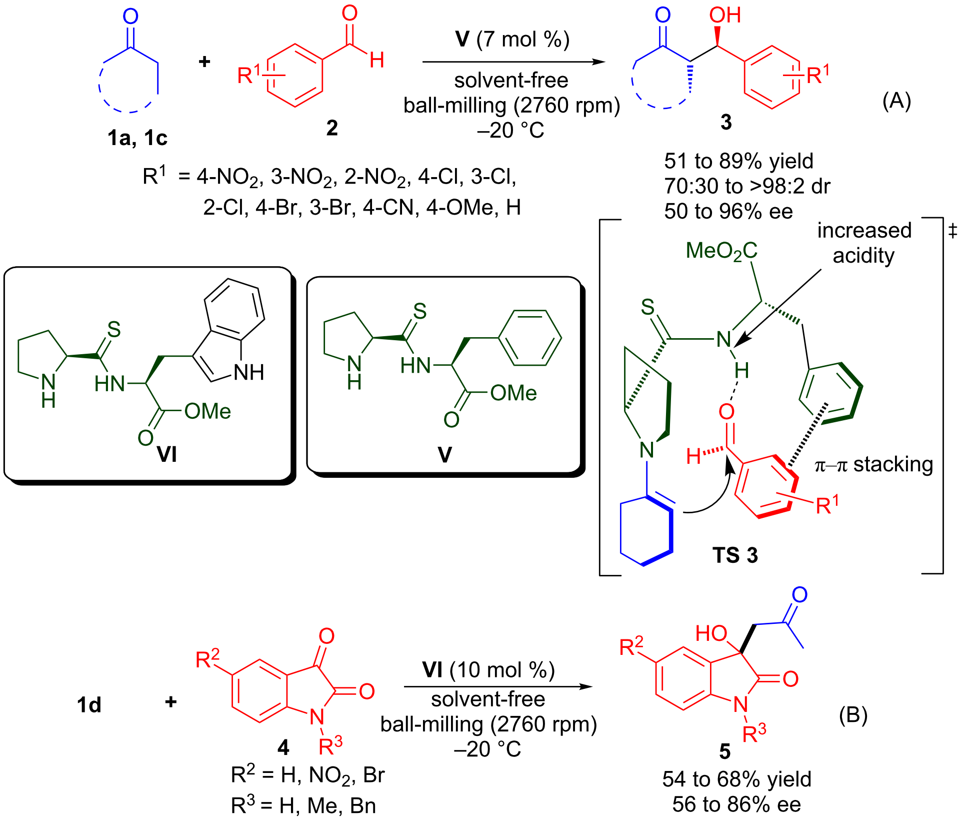
Scheme 3: (*S*)-Binam-L-prolinamide catalysed asymmetric aldol reaction by using a ball-mill. [a]Conversion.



Scheme 4: Asymmetric aldol reaction assisted by ball-milling catalysed by dipeptides (A) with **III** and (B) with **IV**.

The methyl ester of (*S*)-proline-(*S*)-tryptophan (**IV**) was shown to be an efficient organocatalyst for asymmetric aldol reactions of ketones with aromatic aldehydes in the presence of water by using HSBM (Scheme 4) [37]. The corresponding aldol products **3** were obtained in good yield (64–90%), low to high diastereoselectivity (40:60 to 98:2 dr, *anti*/*syn*) and moderate to excellent enantioselectivity (55 to >98% ee) by using only 3 mol % of **IV**. A similar transition state (**TS 2**) to that of **III** could be proposed, which involves the formation of enamine and simultaneous hydrogen bonding activation of the aldehyde by amidic NH of the catalyst. The large surface area of the lipophilic residue of the tryptophan, reinforced by the hydrophobic environment created by the addition of water, appears to be responsible for the improvement in diastereoselectivity. These factors also enhance the π–π stacking between the catalyst and aldehyde to form a more rigid transition state, which induces higher stereoselectivity. In addition, the acidity of the amidic N–H bond is increased by the formation of a hydrogen bond between water molecules and amidic carbonyl, thus providing a stronger hydrogen-bonding interaction with the aldehyde.

Recently, Juaristi and co-workers reported a highly efficient asymmetric aldol reaction of cyclic ketones with various aromatic aldehydes catalysed by a new series of (*S*)-proline containing thiodipeptides under solvent-free HSBM conditions (Scheme 5) [38]. The thiodipeptide **V** catalyses the stereoselective formation of aldol products in 51–89% yield and moderate to high stereoselectivity (70:30 to >98:2 dr, *anti*/*syn* and 50–96% ee). It was proposed that the thiodipeptide catalyst possesses increased acidity of the thioamidic N–H compared to the amide analogue, which results in a stronger hydrogen-bonding

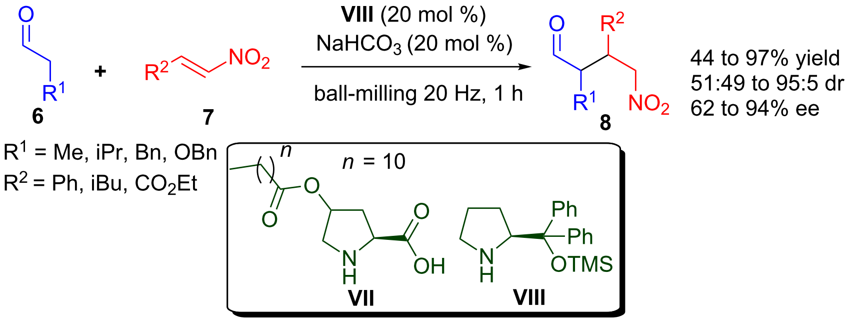


Scheme 5: Thiodipeptide-catalysed asymmetric aldol reaction of (A) ketones with aldehydes and (B) acetone with isatin derivatives.

interaction with the aldehyde carbonyl in the transition state (**TS 3**). Under ball-milling conditions, thiodipeptide **VI** catalyses the enantioselective aldol reaction of acetone (**1d**) with isatin derivatives **4** to provide 3-substituted-3-hydroxyoxindole derivatives **5** in moderate yield (54–68%) and moderate to good enantioselectivity (56–86% ee). The reactions carried out under HSBM afford (*S*)-3-hydroxyindole with higher enantioselectivity, relative to the reaction performed under traditional stirring in solvent.

Michael reaction

The asymmetric organocatalytic Michael addition to various unsaturated acceptors is one of the most highly studied and important reactions for the synthesis of valuable chiral molecules [39-44]. Recently, Sebesta and co-workers compared the enantioselective organocatalytic Michael addition of aldehydes to nitroalkenes in aqueous solution with the reaction performed under solvent-free ball-milling conditions catalysed by pyrrolidine-derived organocatalysts (Scheme 6) [45]. Both the pro-

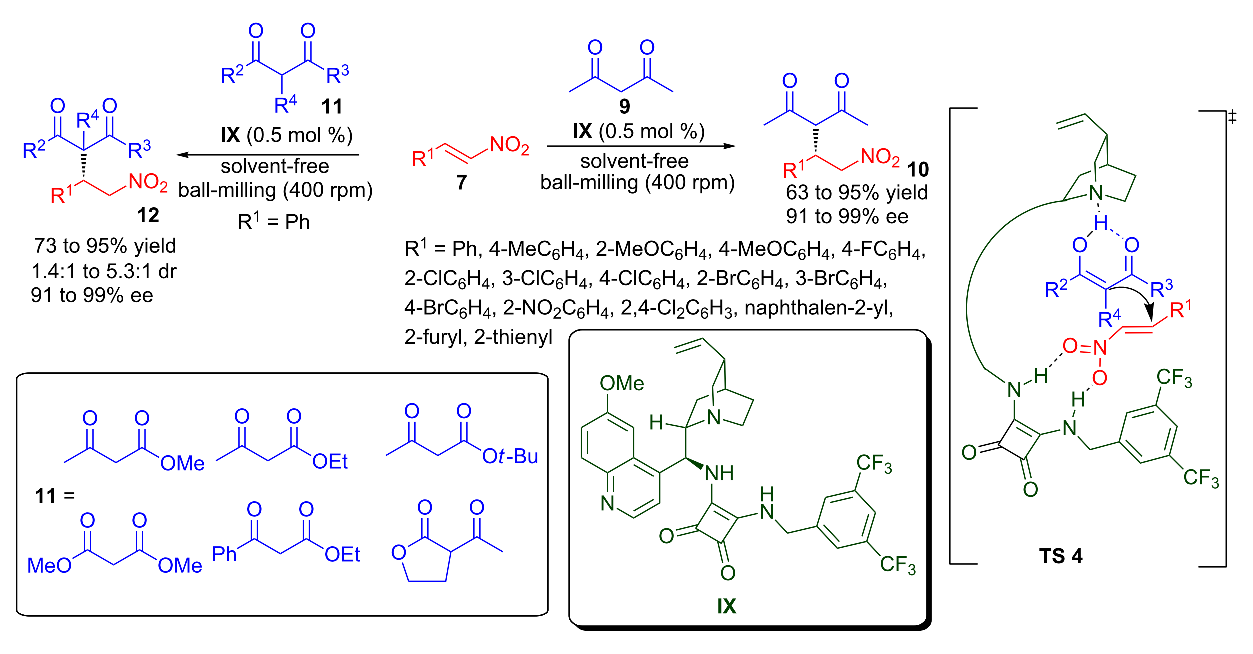


Scheme 6: Enantioselective Michael reaction of aldehydes with nitroalkenes catalysed by pyrrolidine-derived organocatalysts.

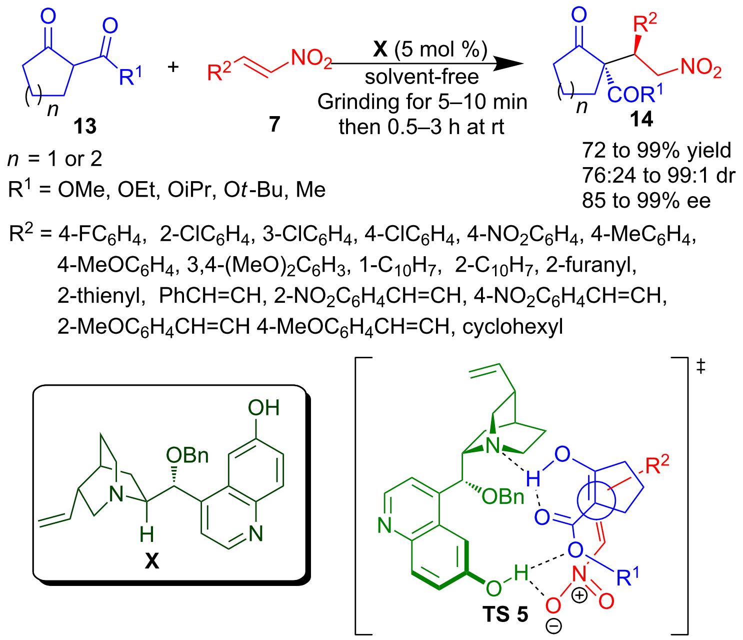
cedures provided the product in good yield, poor to high diastereoselectivity, and moderate to high enantioselectivity. Two different organocatalysts were identified for aqueous and solvent-free ball-milling conditions. *O*-Lauroyl-*trans*-4-hydroxyproline (**VII**) was identified as the best catalyst in aqueous media, whilst α,α-diphenylprolinol trimethylsilyl ether (**VIII**) turned out to be the best catalyst under ball-milling conditions. Michael reaction of aliphatic aldehydes **6** with nitroalkenes **7** proceeded rapidly in the presence of 20 mol % of **VIII** under solvent-free ball-milling conditions to provide the desired Michael adducts **8** in 44–97 % yield, 51:49 to 95:5 dr and 62–94% ee. It was also observed that the combination of an organocatalyst with solvent-free ball-milling was more efficient than with conventional stirring, because when the reaction was carried out by conventional stirring, the product yield and stereoselectivity deteriorated significantly.

Xu and co-workers reported a highly enantioselective organocatalytic Michael reaction of 1,2-carbonyl compounds to nitro-olefins under solvent-free conditions by using a planetary ball mill (Scheme 7) [46]. Cinchona-derived chiral squaramide **IX**, at low catalyst loading of 0.5 mol %, efficiently catalyses the solvent-free Michael reaction of acetylacetone (**9**) with various substituted nitroalkenes **7** in a short reaction time (5–30 minutes) under ball-milling (400 rpm) to provide an easy access to Michael adducts **10** in good to high yield (63–95%) and excellent enantioselectivity (91–99% ee). The chiral squaramide **IX** also catalyses the Michael reaction of β-ketoesters **11** with nitrostyrene to provide Michael adducts **12** in 73–95% yield, 1.4:1 to 5.3:1 dr and 91–99% ee. The solvent-free ball-milling of dimethyl malonate with nitrostyrene in the presence of **IX** provides the corresponding Michael adduct in 80% yield and 91% ee. However, chiral squaramide catalysed Michael addition of dicarbonyl compounds to nitroalkenes in dichloromethane by traditional stirring proceeds at a slower reaction rate as compared to ball-milling [47]. The transition state (**TS 4**) for this transformation involves a hydrogen-bonded ternary complex of catalyst and substrates in which two NH groups of the squaramide moiety activate the nitroalkene and the quinuclidine nitrogen activates and orients the dicarbonyl compounds to provide the Michael adduct in high enantioselectivity.

Application of grinding with pestle and mortar for highly stereoselective Michael addition of trisubstituted β-ketoesters to nitroalkene derivatives was reported by Chimni's group (Scheme 8) [48]. Grinding an equimolar quantity of six/five-membered cyclic β-ketoesters **13** and various nitroalkenes **7**, including nitrodienes, in the presence of 5 mol % of cupreine-derived organocatalyst **X** provided Michael adducts **14** in good to high yield (72–99%) and good to excellent stereoselectivity (85–99% ee and 76:24 to 99:1 dr). It was observed that the reaction proceeds much faster under grinding conditions, when compared with the reaction carried out under traditional stirring in toluene as solvent or under neat conditions. This was attributed to the fact that grinding facilitates the proper mixing of the catalyst and substrates and also provides additional mechanical pressure. The proposed transition state (**TS 5**) involves a



Scheme 7: Chiral squaramide catalysed asymmetric Michael reaction assisted by ball-milling.

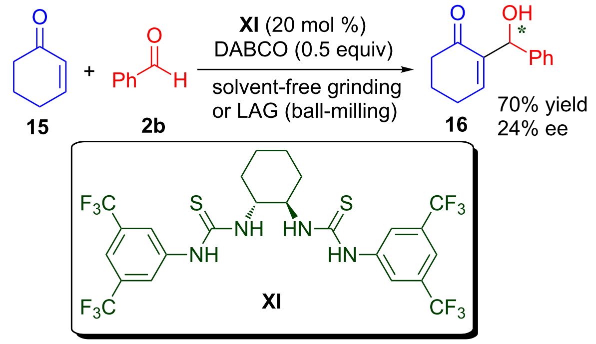


Scheme 8: Asymmetric organocatalytic Michael reaction assisted by pestle and mortar grinding.

hydrogen-bonded ternary complex of substrates and catalyst, in which the aromatic hydroxy group activates the nitro group of nitroalkene while the tertiary amine of the catalyst activates and orients the β-ketoester.

Morita–Baylis–Hillman (MBH) reaction

The Morita–Baylis–Hillman (MBH) reaction provides a very useful and interesting method for the synthesis of β-hydroxycarbonyl compounds with an α-alkylidene group [49-53]. Mechanochemical methods of neat grinding and liquid-assisted grinding (LAG) have been applied to the synthesis of mono- and bis(thiourea)s in quantitative yield by using the click coupling of aromatic or aliphatic diamines with aromatic isothiocyanates (Scheme 9) [54]. The mechanochemically prepared chiral molecules were applied as organocatalysts in an enantioselective MBH reaction and as cyanide ion sensors in organic solvents. Chiral bis-thiourea **XI** catalyses the MBH reaction of benzaldehyde (**2b**) and 2-cyclohexen-1-one (**15**) to provide MBH adduct **16** in 70% yield and 24% ee under neat grinding and LAG.



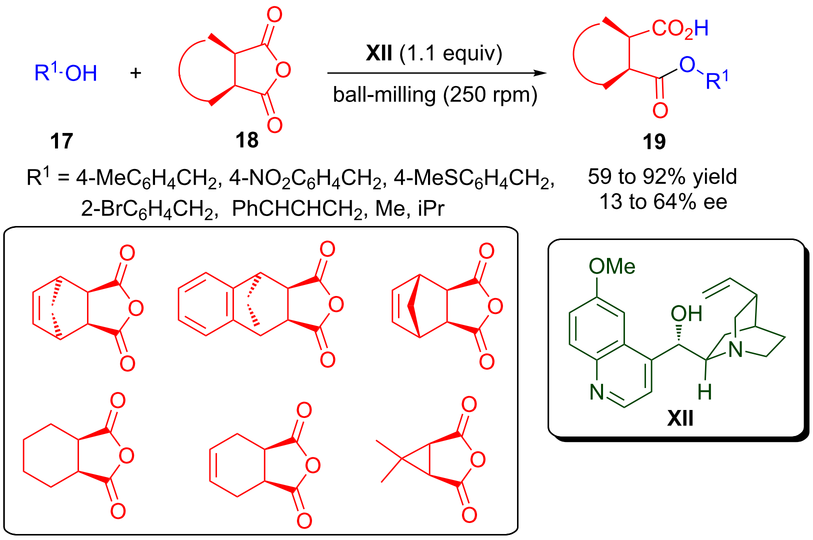
Scheme 9: *C*-2 symmetric thiourea catalysed enantioselective MBH reaction.

Anhydride ring opening

The stereoselective *meso*-anhydride ring opening represents an important approach for providing multiple stereogenic centres in the target molecule [55-57]. In this feat the Cinchona alkaloids have emerged as powerful organocatalysts. A ball-milling-assisted highly efficient asymmetric ring opening of *meso*-anhydride with alcohols catalysed by quinine (**XII**) was developed by Bolm's group (Scheme 10) [58]. A variety of *meso*-anhydrides **18** were opened with a variety of alcohols **17** under solvent-free conditions to provide optically active dicarboxylic acid monoesters **19** in good to high yield (59–92%) and low to moderate enantioselectivity (13–64% ee). This methodology have several advantages such as solvent-free reaction conditions, a simple work-up procedure, no column chromatography, use of an almost equimolar substrate, wide substrate scope, and the fact that even two solid substrates react efficiently.

Alkylation of imine

Alkylation of glycine imine by using a chiral phase-transfer catalyst emerged as a very good strategy for the asymmetric

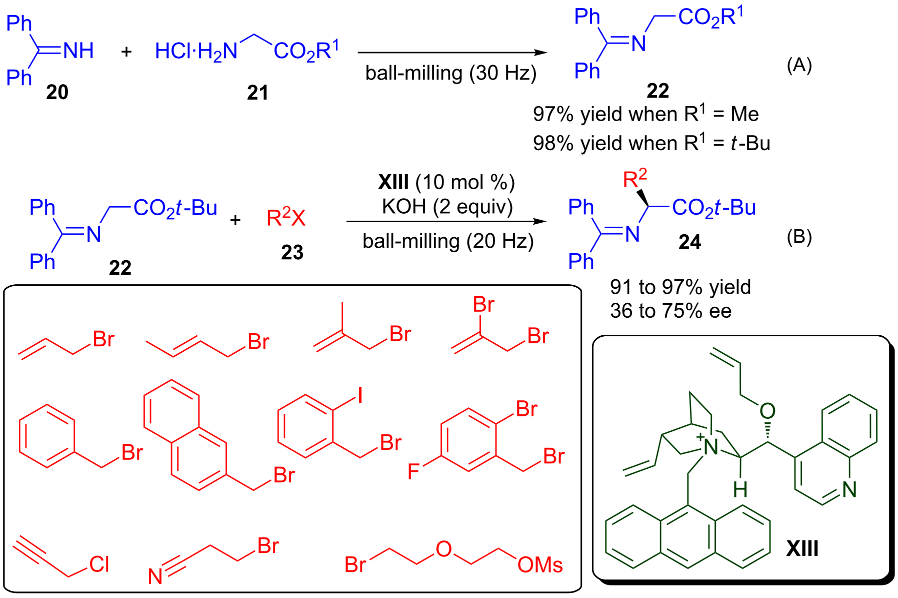


Scheme 10: Quinine-catalysed ring opening of *meso*-anhydride by ball-milling.

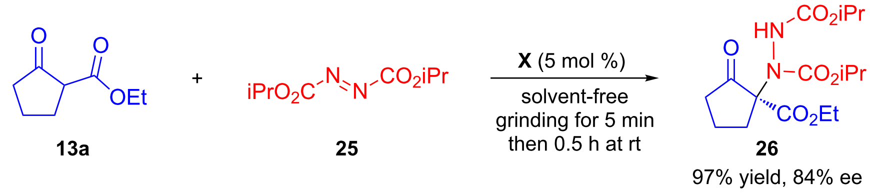
synthesis of amino-acid derivatives [59-61]. Lamaty and co-workers prepared a series of glycine Schiff bases **22** in excellent yield (97–98%) in short reaction time by milling protected glycine hydrochloride **21** and diphenylmethanimine (**20**), under solvent-free conditions (Scheme 11) [62]. The asymmetric alkylation of glycine imine **22** was carried out by using a phase-transfer catalyst under basic conditions in a ball-mill. The Schiff base reacted rapidly with various halogenated derivatives **23** in a ball-mill in the presence of KOH and the chiral ammonium salt derived from cinchonidine (**XIII**) as phase-transfer catalyst, to provide excellent yield (91–97%) and good enantioselectivity (35–75% ee) of the corresponding amino esters **24**. Purification of the product was greatly simplified, as equimolar amounts of starting materials were used.

Asymmetric amination reaction

Enantioselective organocatalytic amination of trisubstituted β-ketoesters provides an access to quaternary amino stereogenic centres [63-66]. Chimni and Chauhan extended the application of the solvent-free organocatalytic pestle and mortar



Scheme 11: Ball-milling-assisted (A) synthesis of glycine schiff bases and (B) their organocatalytic asymmetric alkylation.



Scheme 12: Enantioselective amination of β-ketoester by using pestle and mortar.

grinding methodology for the enantioselective amination of β-ketoester **13a** with di-isopropylazodicarboxylate (**25**) (Scheme 12) [48]. Using 5 mol % of **X** the chiral adduct **26** bearing an amino group at a quaternary stereocentre was obtained in 97% yield and 84% ee in short reaction time.

Conclusion

All the above reports represent a very significant contribution to the development of sustainable asymmetric syntheses. The mechanochemical techniques provide an alternate source of energy, which has been successfully applied in asymmetric organocatalytic reactions. It is very clear that the mechanochemical techniques have an edge over the conventional stirring in terms of higher reaction rate and improved yield. In addition to this, these techniques avoid the use of organic solvents and also facilitate the use of equimolar amounts of reactants, which helps in the easy isolation of products.

Besides the significant progress in the application of mechanochemical techniques in asymmetric organocatalysis, there exists a lot of scope for other asymmetric reactions ranging from simple carbon–carbon, and carbon–heteroatom bond formation to more complex cascade, tandem and multicomponent reactions. However, the stereochemical outcome of many reactions involving chiral organocatalysts is dependent on the reaction conditions and mainly on the nature of the solvents. Thus, it is highly desirable to develop some new organocatalysts whose catalytic efficiency is not dependent on the solvents. Furthermore, the efficiency of some other organocatalytic transformations that were carried out in neat conditions can be increased by performing these reactions with mechanochemical techniques.

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