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New advances in asymmetric organocatalysis

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BEILSTEIN JOURNAL OF ORGANIC CHEMISTRY

New advances in asymmetric organocatalysis

Radovan Šebesta

Editorial

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Address:
Department of Organic Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava, Mlynská dolina, Ilkovičova 6, 842 15 Bratislava, Slovakia

Email:
Radovan Šebesta - radovan.sebesta@uniba.sk

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Asymmetric catalysis is undoubtedly the most efficient way to prepare chiral compounds that our society requires as medicines, materials, or crop protecting agents. Traditionally, enzymes and metal complexes with chiral ligands served as the main type of enantioselective catalysts. Even though small chiral organic compounds have been recognized as chiral organocatalysts as early as 1912, the concept was at the periphery of the attention of synthetic organic chemists. An initial flash of interest appeared in the 1970s when proline was shown to catalyze the Robinson annulation [1,2], but this seminal work seemed to come too early to stimulate greater developments. Things started to change in the late 1990s when short-chain peptides [3], carbohydrate-based ketones [4,5], and thioureas [6] were shown to catalyze enantioselective transformations. The real breakthrough came in the year 2000 when two teams independently disclosed important discoveries with proline and imidazolidinones as ample chiral catalysts for aldol [7,8], Diels–Alder [9], dipolar cycloaddition [10], and Mannich reactions [11]. The organic chemistry community this time took a tremendous interest in this concept, which led to many valuable developments [12]. The recent culmination of the rapid advent of organocatalysis was the Nobel prize in 2021, which was awarded to Benjamin List and David MacMillan for their pioneering discoveries. Organocatalysis outgrew its initial inspiration by enzymatic catalysis, but the analogy with nature can be seen within the area. Organocatalytic reactions are highly suitable components of cascade transformations as exemplified by the seminal work of Enders [13]. Besides traditional enamine and iminium activation of carbonyl compounds other activation modes were uncovered which significantly broadened the repertoire of chemical transformations that are amenable to organocatalysis [14]. Within the realm of covalent activation, chiral carbenes and phosphines are diverse and structurally rich groups of catalysts. The synthetic scope was greatly expanded by noncovalent activation via a range of proton-mediated transformations using chiral Brønsted acids, Brønsted base, and hydrogen bond donors. Recently noncovalent activation continues to expand into other types of weak attractive interactions such as halogen and chalcogen bonds. Not surprisingly, all activation modes allow further expansion and diversification via a combination of activation modes in bifunctional or multifunctional catalysis. Important is also a “green” aspect of organocatalysis as well as its fruitful overlap with many sustainability ideas [15].

In 2012, there has been a thematic issue of the *Beilstein Journal of Organic Chemistry* devoted to asymmetric organocatalysis edited by one of the pioneers Benjamin List. After another decade, this thematic issue likes to survey new advances in this field. Three review articles and nine research papers showcase the diversity and breadth into which asymmetric organocatalysis has grown since then.

The suitability of asymmetric organocatalytic methods to assemble biologically relevant compounds is highlighted by a review article devoted to the syntheses of coumarin derivatives [16]. Conjugated additions of stabilized nucleophiles are the cornerstone of organocatalytic methodology. Recent advances in this area are covered by a review article devoted to aza-Michael reactions of amines and amides [17]. The evolution of the understanding of noncovalent activation modes led to the realization that anion-binding is a critical feature in many transformations. Halide anions are highly relevant and widely occurring within many reactions and a variety of organocatalysts can engage with them [18].

Nine excellent research articles within this special issue demonstrate the current state of the art in asymmetric organocatalysis. Chiral isothioureas became useful Lewis base catalysts for various transformations. Weinzierl and Waser employed an isothiourea catalyst for esterification-mediated kinetic resolution of paracyclophane derivatives with planar chirality [19]. Parida and Pan showed that a Michael reaction coupled with an acyl transfer reaction between α-nitroketones and 4-arylidenepyrrolidine-2,3-diones can produce a variety of enantioenriched 1,5-dihydro-2*H*-pyrrol-2-ones [20]. The development of any area is critically dependent on the understanding of underlying features and relationships. Slugovc and co-workers provide such mechanistic investigation of phosphine-catalyzed Michael additions [21]. Chiral cyclopropenimines exemplify Brønsted base organocatalysts that are useful for diverse reactions not easily accessible by other means. Here, Lambert and co-workers employed this type of catalyst in the formation of pyroglutamates via enantioselective Michael addition of amino ester imines [22]. Phase-transfer catalysis relies on the deprotonation of one of the substrates, but basic conditions may limit the applicability of this methodology. A unique base-free variant of chiral phase-transfer catalytic alkylation of 2-oxindoles was developed by Connon and co-workers [23]. Pentacarboxycyclopentadienes are a unique type of Brønsted acid catalyst that expanded the range of available acidities as well as molecular arrangements in acid-catalyzed reactions. Veselý and co-workers demonstrated that these catalysts are effective in the enantioselective aminalization of aldehydes with anthranilamides [24]. To explore new possibilities in combination of covalent and noncovalent activation, our group designed and synthesized *N*-sulfinylpyrrolidine-containing ureas and thioureas and applied them in Michael additions of aldehydes to heterocycle containing nitroalkenes [25]. Dubey and Chowdhury showed that 1,4-conjugate additions of nitromethane to β-silyl α,β-unsaturated carbonyl compounds catalyzed by bifunctional squaramide catalysts are effective under solvent-free conditions [26]. Zhai and Du demonstrated that asymmetric [3 + 2] annulation reactions of 2-isothiocyanato-1-indanones with barbiturate-based olefins are efficiently catalyzed by cinchona-based thiourea catalysts [27].

As guest editor of this thematic issue, I am grateful to all authors for their excellent contributions. I thank the referees for providing their expertise and time, and the whole team at the *Beilstein Journal of Organic Chemistry* for their great level of professionalism and support.

Radovan Šebesta

Bratislava, February 2022

ORCID® iDs

Radovan Šebesta - https://orcid.org/0000-0002-7975-3608

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Chiral isothiourea-catalyzed kinetic resolution of 4-hydroxy[2.2]paracyclophane

David Weinzierl and Mario Waser*

Letter

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Address:
Institute of Organic Chemistry, Johannes Kepler University Linz, Altenbergerstrasse 69, 4040 Linz, Austria

Email:
Mario Waser* - mario.waser@jku.at

* Corresponding author

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This article is part of the thematic issue "New advances in asymmetric organocatalysis" and is dedicated to Prof. Dr. Norbert Müller, who has been a supportive mentor and good friend over all the years, on the occasion of his 65th birthday.

Guest Editor: R. Šebesta

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Abstract

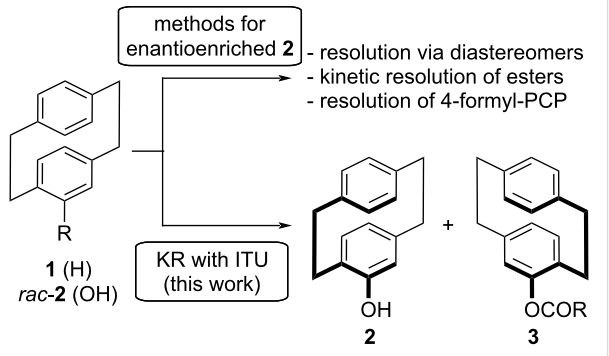
We herein report a method for the kinetic resolution of racemic 4-hydroxy[2.2]paracyclophane by means of a chiral isothiourea-catalyzed acylation with isobutyric anhydride. This protocol allows for a reasonable synthetically useful *s*-factor of 20 and provides a novel entry to obtain this interesting planar chiral motive in an enantioenriched manner.

Introduction

Substituted [2.2]paracyclophanes are fascinating planar chiral molecules [1-12] which have been systematically investigated since Brown and Farthing discovered the formation of the unsubstituted and achiral parent [2.2]paracyclophane (**1**) via gas phase pyrolysis of *para*-xylene in 1949 [5]. Over the years, these compounds established themselves as a unique class of "bent and battered" [6] strained molecules with remarkable chemical and physical properties [1-4,7-9]. Besides their potential applications in material and polymer chemistry [1,2,7-9], these planar chiral molecules have been very successfully used in asymmetric catalysis [3,4,10-12]. Accordingly, the development of methods for the asymmetric synthesis of enantiomerically pure, or at least enantiomerically enriched, derivatives that can be utilized as building blocks for more demanding ligands and catalysts became a task of high importance. Thus, several strategies to access enantioenriched [2.2]paracyclophanes have been reported, either relying on classical resolution approaches or, more recently, making use of asymmetric catalysis to carry out kinetic resolutions of easily accessed racemic precursors [3,4,13-15]. 4-Hydroxy[2.2]paracyclophane (**2**) is one of the commonly used building blocks, which is easily accessible in a racemic manner starting from **1** according to nowadays well-established procedures [16-18]. Over the last decades, it was shown that enantioenriched **2** may serve as a valuable building

block to access more advanced chiral cyclophane ligands and catalysts [3,4,19-22] and therefore its asymmetric synthesis became an important task [3,4,18-27]. Several strategies to access **2** in an enantioenriched fashion have been developed. One commonly used method relies on the resolution of 4-formyl[2.2]paracyclophane via formation of a chiral Schiff base first, followed by a subsequent Dakin-type oxidation to alcohol **2** [18]. Alternatively, the direct resolution of *rac*-**2** via transformation into diastereomers by esterification with chiral acid chlorides [19,20] as well as the kinetic resolution (KR) of racemic esters of **2** via an enzymatic hydrolysis [25-27] were very successfully used to access enantioenriched **2**. Recently, Akiyama and co-workers reported the kinetic resolution of *rac*-PHANOL (4,12-dihydroxy[2.2]paracyclophane) by means of a chiral phosphoric acid-catalyzed esterification with achiral anhydrides [28]. This method allowed for high *s*-factors but was unfortunately not satisfyingly applicable to *rac*-4-hydroxy[2.2]paracyclophane (*rac*-**2**) [28].

Considering the interest in compound **2**, we thus thought about developing an alternative organocatalytic kinetic resolution protocol to control the esterification of *rac*-**2**. Chiral isothioureas (ITUs) emerged as easily available and powerful catalysts for numerous applications [29-32] and have been very successfully used for the kinetic resolution of different racemic alcohols [33-37]. Inspired by this unique catalysis potential, we therefore became interested in testing those chiral catalysts for the, to the best of our knowledge, so far not investigated acylative kinetic resolution of 4-hydroxy[2.2]paracyclophane (**2**, Scheme 1).



Scheme 1: Overview about established methods to access enantioenriched **2** and the herein investigated kinetic resolution (KR) with chiral isothiourea (ITU) catalysts.

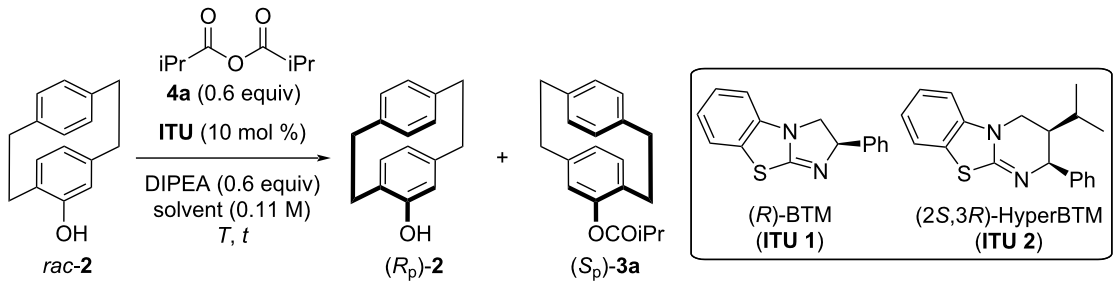
Results and Discussion

BTM (**ITU 1** [33]) and HyperBTM (**ITU 2** [38]) are amongst the most commonly used chiral ITUs and these nowadays commercially available catalysts were used to optimize the resolution of *rac*-**2** with isobutyric anhydride (**4a**) (Table 1 gives an overview of the most significant results obtained in this screening). Anhydride **4a** was chosen in a first instance as it proved successful in previous acylative resolutions reported by others [28,33,34,36,37] but we later on also tested other anhydrides and acid chlorides (vide infra, Scheme 2). First experiments with 10 mol % BTM (**ITU 1**) carried out in $CHCl_3$ or toluene at room temperature (Table 1, entries 1 and 2) proved the general feasibility of this concept, resulting in *s*-factors around 6. When lowering the temperature, a slight improvement could be achieved at −15 °C (Table 1, entry 3) but unfortunately **ITU 1** performed less selective at −78 °C (Table 1, entry 4). Instead, (2*S*,3*R*)-HyperBTM (**ITU 2**) resulted in an enhanced selectivity with s = 14.5 at −78 °C but conversion was relatively slow (Table 1, entry 5). Gratefully however, the obtained *s*-factor was almost the same at −40 °C and a reasonable conversion of around 30% could be observed after 4 h reaction time (Table 1, entry 6). Varying solvent and concentration at −40 °C next showed that toluene allows for higher selectivities than $CHCl_3$ (compare Table 1, entries 6 and 7), while the use of other solvents like CH_2Cl_2 and THF resulted in almost no product formation and no reasonable selectivities (not mentioned in Table 1). In addition, higher concentrations lead to notably lower selectivities (Table 1, entry 9), while more diluted conditions did not allow for a significant improvement of the *s*-factor anymore (Table 1, entry 8). Lowering the catalyst loading from 10 to 5 mol % allowed for a similar conversion, but resulted in a slightly reduced selectivity (Table 1, entry 10).

At this point, we decided to screen other anhydrides and acid chlorides **4**, but, as outlined in Scheme 2, the initially used isobutyric anhydride **4a** clearly outperformed its analogous acid chloride **4b**, as well as the other derivatives **4c**–**f**.

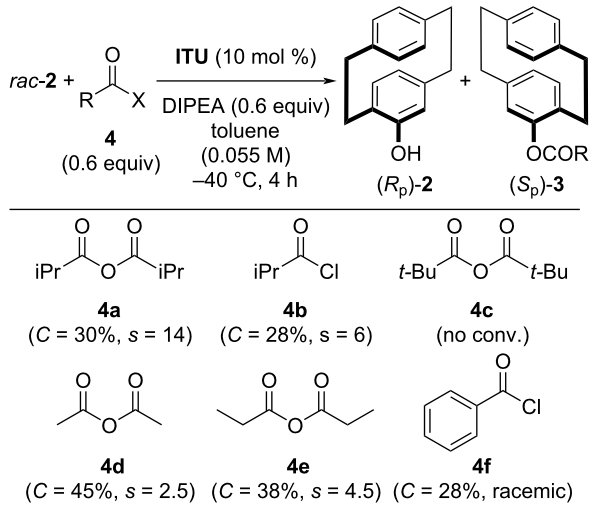
Finally, the resolution of *rac*-**2** was run for 22 h in the presence of 10 mol % HyperBTM (**ITU 2**) with 1.1 equivalents of anhydride **4a** (instead of the previously used 0.6 equiv; Table 1, entry 11). Under these conditions it was possible to achieve a conversion of slightly above 50% combined with good enantioselectivities for both, the recovered alcohol **2** and the ester **3a** (s = 20). With these optimum conditions the resolution was also successfully carried out on 1 mmol scale, resulting in an identical conversion and *s*-factor (s = 20; C = 57%) and allowing for the isolation of (R_p)-**2** in 39% yield (94% ee) and (S_p)-**3a** in 53% yield (71% ee) (Table 1, entry 11). Mechanistically, this resolution process should proceed via the well-understood formation of a chiral acyl-transfer species between the isothiourea catalyst **ITU 2** and the anhydride **4a** [33-37], which then allows for the resolution of the enantiomers of alcohol **2**. Unfortunately, however, the true nature of this enantiodiscriminating step has not yet been elucidated and will require detailed computational studies.

Table 1: Identification of the optimum catalyst and best conditions for the resolution of *rac*-**2** with anhydride **4a**[a].



Entry	ITU	Solvent	*T* [°C]	*t* [h]	Conv. (*C*) [%][b]	ee (**2**) [%][c,d]	ee (**3a**) [%][c]	*s*[e]
1	**ITU 1**	$CHCl_3$	25	1	41	42	60	6
2	**ITU 1**	toluene	25	1	38	39	64	6.5
3	**ITU 1**	toluene	–15	1	34	38	74	10
4	**ITU 1**	toluene	–78	1	15	13	74	7.5
5	**ITU 2**	toluene	–78	1	16	16	85	14.5
6	**ITU 2**	toluene	–40	4	33	40	81	14
7	**ITU 2**	$CHCl_3$	–40	4	45	55	67	9
8	**ITU 2**	toluene (0.055 M)	–40	4	30	35	82	14.5
9	**ITU 2**	toluene (0.22 M)	–40	4	36	32	75	9.5
10[f]	**ITU 2**	toluene	–40	4	30	34	79	12
11[g]	**ITU 2**	toluene	–40	22	57	94 (39%)[h]	71 (53%)[h]	20

[a]All reactions were carried out using 0.1 mmol *rac*-**2** and 0.06 mmol **4a** in the presence of 0.06 mmol Hünig's base (diisopropylethylamine, DIPEA) and 10 mol % ITU in the indicated solvent (0.11 M with respect to **2**) unless otherwise stated; [b]determined by ^{1}H NMR of the crude product; isolated yields of **2** and **3** were almost quantitative in all cases; [c]determined by HPLC using a chiral stationary phase; [d]absolute configuration of recovered **2** was assigned to be (R_p) by comparison of its (+)-optical rotation with previous reports [20,26,39]; [e]the *s*-factor was calculated from the ee of recovered **2** and/or the ee of ester **3** [40-43]; [f]using 5 mol % **ITU 2**; [g]using 1.1 equiv of **4a**; [h]isolated yield when carried out on 1 mmol *rac*-**2** scale.



Scheme 2: Use of alternative acylating agents **4** for the kinetic resolution of *rac*-**2**.

Conclusion

In conclusion, we identified conditions that allow for the kinetic resolution of racemic 4-hydroxy[2.2]paracyclophane (**2**) by means of an acylation with isobutyric anhydride (**4a**) in the presence of the chiral isothiourea catalyst HyperBTM (**ITU 2**). The reaction can be carried out with an *s*-factor around 20 and allows for the isolation of recovered (R_p)-**2** and ester (S_p)-**3a** with reasonable enantiomeric excesses around 90%, depending on the conversion. These two compounds can easily be separated by silica gel column chromatography in almost quantitative yields, thus providing a novel entry to obtain these interesting planar chiral motives in an enantioenriched manner.

Experimental

General details

^{1}H- and ^{13}C NMR spectra were recorded on a Bruker Avance III 300 MHz spectrometer with a broad band observe probe and a sample changer for 16 samples. NMR spectra were referenced on the solvent peak and chemical shifts are given in ppm.

High-resolution mass spectra were obtained using a Thermo Fisher Scientific LTQ Orbitrap XL with an Ion Max API Source. Analyses were made in the positive ionization mode if not otherwise stated. HPLC was performed using a Thermo Scientific Dionex Ultimate 3000 system with diode array

detector with a CHIRAL ART Cellulose-SB stationary phase. Optical rotations were recorded on a Schmidt + Haensch Polarimeter Model UniPol L1000 at 589 nm.

All chemicals were purchased from commercial suppliers and used without further purification unless otherwise stated. *rac*-**2** was prepared from **1** according to a previously published procedure [16].

Optimized procedure for the KR of *rac*-**2**

Racemic 4-hydroxy[2.2]paracyclophane (*rac*-**2**; 250 mg; 1.115 mmol) and HyperBTM (**ITU 2;** 35 mg; 10 mol %) were dissolved in dry toluene (10 mL) in a Schlenk flask (Ar atmosphere), followed by the addition of Hünig's base (DIPEA; 118 µL; 0.67 mmol; 0.6 equiv). The solution was then cooled to −40 °C and isobutyric anhydride (**4a**; 208 µL; 1.226 mmol; 1.1 equiv) was added and the mixture was stirred at −40 °C for 22 h. The reaction was quenched by addition of MeOH. The crude product was filtered over Na_2SO_4 and the solvent removed in vacuum. Recovered alcohol **2** and ester **3a** were separated by silica gel column chromatography (heptanes/ethyl acetate 10:1), yielding (S_p)-**3a** in 53% (175 mg) and (R_p)-**2** in 43% (98 mg) (39%).

(R_p)-**2a**: Analytical data match those reported in literature [18-20,26,28,39]. TLC (heptanes/ethyl acetate 10:1; R_f = 0.11). $[\alpha]_D^{24}$ 14.1 (*c* 1, CH_2Cl_2, 92% ee) and 12.1 (*c* 1, $CHCl_3$, 92% ee); ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ/ppm 7.00 (dd, *J* = 8, 1.8 Hz, 1H), 6.55 (dd, *J* = 8, 1.8 Hz, 1H), 6.45 (dd, *J* = 8, 1.8 Hz, 1H), 6.41–6.37 (m, 2H), 6.26 (dd, *J* = 8, 1.8 Hz, 1H), 5.54 (d, *J* = 1.6 Hz, 1H), 4.42 (s, 1H), 3.37–3.29 (m, 1H), 3.14–3.02 (m, 4H), 2.98–2.85 (m, 2H), 2.71–2.60 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ/ppm 153.8 (1C, CAr), 142.1 (1C, CAr), 139.8 (1C, CAr), 139.0 (1C, CAr), 135.6 (1C, CAr), 133.8 (1C, CAr), 132.9 (1C, CAr), 132.0 (1C, CAr), 128.1 (1C, CAr), 125.6 (1C, CAr), 125.2 (1C, CAr), 122.7 (1C, CAr), 35.4 (1C, -CH_2), 34.9 (1C, -CH_2), 34.0 (1C, -CH_2), 32.2 (1C, -CH_2); HRMS (ESI) *m*/*z*: calcd for $[C_{16}H_{16}O + H]^+$, 225.1274; found, 225.1280, HPLC: YMC Chiral ART Cellulose-SB, *n*-hexane/iPrOH 3:1, 1 mL/min, 10 °C; t_R = 6.4 min [S_p; minor], 7.2 min [R_p; major].

(S_p)-**3a**: Analytical data match those reported in literature [28]. TLC (heptanes/ethyl acetate 10:1; R_f = 0.33). $[\alpha]_D^{24}$ 27.5 (*c* 1.0, $CHCl_3$, 82% ee); mp 80–82 °C; ^{1}H NMR (300 MHz, $CDCl_3$, 298.0 K) δ/ppm 6.91 (dd, *J* = 7.8, 1.8 Hz, 1H), 6.56–6.43 (m, 5H), 6.00 (d, *J* = 1.7 Hz, 1H), 3.17–2.94 (m, 7H), 2.93–2.79 (m, 1H), 2.73–2.64 (m, 1H), 1.42 (d, *J* = 7 Hz, 3H), 1.38 (d, *J* = 7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$, 298.0 K) δ/ppm 174.8 (1C, C=O), 149.1 (1C, CAr), 141.7 (1C, CAr), 139.6 (1C, CAr), 139.3 (1C, CAr), 135.4 (1C, CAr), 133.5 (1C, CAr), 133.1 (1C, CAr), 132.3 (1C, CAr), 131.1 (1C, CAr), 130.1 (1C, CAr), 129.6 (1C, CAr), 128.2 (1C, CAr), 35.4 (1C, -CH_2), 35.0 (1C, -CH_2), 34.4 (2C, -CH, -CH_2), 31.8 (1C, -CH_2), 19.4 (1C, -CH_3), 19.1 (1C, -CH_3); HRMS (ESI) *m*/*z*: calcd for $[C_{20}H_{22}O_2 + NH_4]^+$, 312.1958; found, 312.1958, HPLC: YMC Chiral ART Cellulose-SB, *n*-hexane/iPrOH 3:1, 1 mL/min, 10 °C; t_R = 7.3 min [R_p; minor], 8.4 min [S_p; major].

Supporting Information

Supporting Information File 1

Copies of NMR spectra and HPLC chromatograms as well as analytical data of esters **3** obtained with the alternative acyl-transfer reagents **4**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-68-S1.pdf]

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ORCID® iDs

Mario Waser - https://orcid.org/0000-0002-8421-8642

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42. Calculation from recovered **2**: s = ln[(1 − C)(1 − ee(**2**))] / ln[(1 − C)(1 + ee(**2**))].
43. Calculation from isolated **3**: s = ln[1 − C(1 + ee(**3**))] / ln[1 − C(1 − ee(**3**))].

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Organocatalytic asymmetric Michael/acyl transfer reaction between α-nitroketones and 4-arylidenepyrrolidine-2,3-diones

Chandrakanta Parida and Subhas Chandra Pan*

Full Research Paper

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Address:
Department of Chemistry, Indian Institute of Technology Guwahati, North Guwahati, Assam, 781039, India

Email:
Subhas Chandra Pan* - span@iitg.ernet.in

* Corresponding author

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Abstract

An organocatalytic asymmetric Michael/acyl transfer reaction between α-nitroketones and 4-arylidenepyrrolidine-2,3-diones is reported. A bifunctional thiourea catalyst was found to be effective for this reaction. With 10 mol % of the catalyst, good results were attained for a variety of 1,5-dihydro-2*H*-pyrrol-2-ones under mild reaction conditions.

Introduction

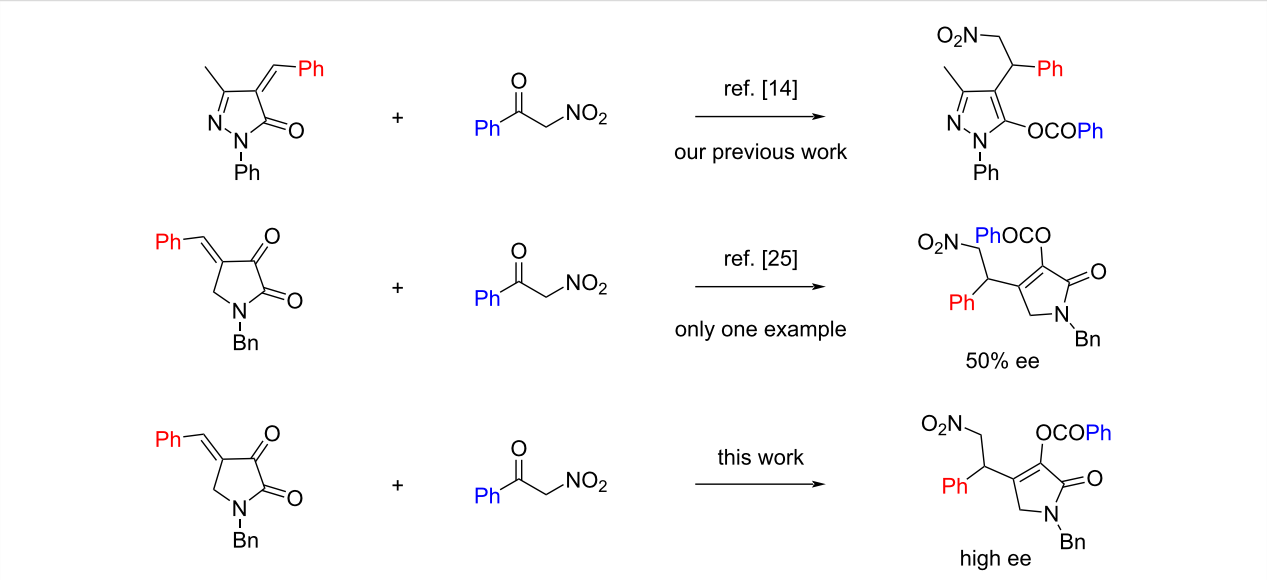
The Michael reaction is a powerful reaction that has been so far applied for the formation of carbon–carbon and carbon–heteroatom bonds in organic synthesis [1,2]. After the renaissance of organocatalysis in the year 2000, this field has been applied tremendously for the development of catalytic asymmetric conjugate addition reactions [3-5]. In particular, the conjugate addition of nitroalkanes and their derivatives to enones has drawn the attention of organic chemists as the corresponding products can be chemoselectively converted to a variety of useful structures [6]. Thus a variety of methods has been developed with a range of different catalysts [7-9]. One of the challenges is to employ highly substituted enones in the reaction. Indeed, additional substituents, especially at the α-position of enones/activated olefins, decreases the reactivity significantly because of unfavorable steric interactions. To overcome this problem, reactive Michael donors must be used to achieve a good conversion in the reaction. In recent years, α-nitroketones have emerged as active nucleophiles in Michael reactions and a range of substrates have been explored [10]. Also, α-nitroketones have been found to be a popular nucleophilic acyl transfer reagent. In 2011, three research groups namely Wang, Yan and Kwong independently revealed the organocatalytic asymmetric conjugate addition of α-nitroketones to β,γ-unsaturated α-keto esters with the concomitant acyl transfer reaction to the keto group [11-13]. Consequently, our group developed an organocatalytic asymmetric Michael–acyl transfer reaction of α-nitroketones with unsaturated pyrazolones, 2-hydroxycinnamaldehydes, γ/δ-hydroxyenones, *o*-quinone methides, etc. [14-18]. Other groups also contributed contemporarily [19-21].

In recent years 4-arylidenepyrrolidine-2,3-diones have been explored mainly for the preparation of bicyclic dihydropyran derivatives through the catalytic inverse-electron-demand hetero-Diels–Alder reaction [22-24]. We postulated that 4-arylidenepyrrolidine-2,3-diones could also be suitable reaction partners of α-nitroketones. However, during the progress of our work, Bonne, Bugaut and co-workers have shown one example for the reaction of 2-nitroacetophenone with 4-benzylidenepyrrolidine-2,3-dione and only moderate enantioselectivity (50% ee) was achieved (Scheme 1) [25]. Herein, we report a better enantioselective version of the reaction between α-nitroketones and 4-arylidenepyrrolidine-2,3-diones (Scheme 1).

Results and Discussion

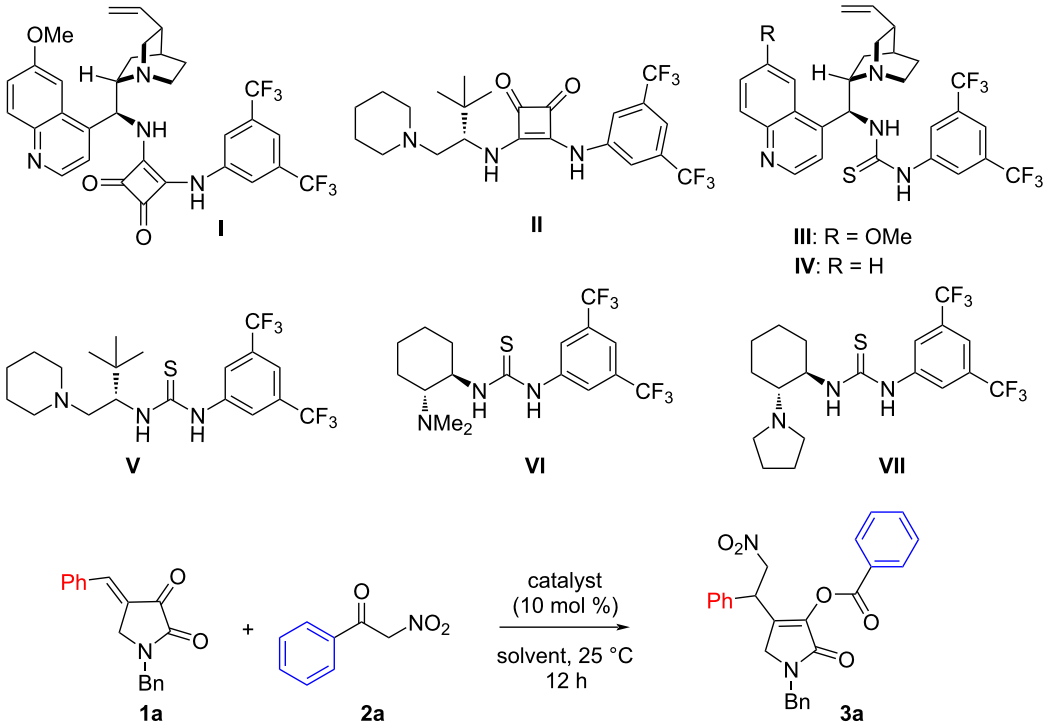
Initially a model reaction was examined between *N*-benzyl-4-benzylidenepyrrolidine-2,3-dione (**1a**) and 2-nitro-1-phenylethanone (**2a**) in the presence of the quinine-derived bifunctional squaramide catalyst **I** in dichloromethane at room temperature (Table 1). Delightfully, after stirring for 12 hours, a product was isolated in 70% yield that was characterized as compound **3a** and was supposed to be formed through conjugate addition followed by benzoyl-transfer reaction. However, only 20% enantiomeric excess was achieved. Then, the *tert*-leucine-derived squaramide catalyst **II** was employed and here both yield and ee slightly improved. Next, we turned our attention to bifunctional thiourea catalysts [26,27] that proved to be fruitful. Thus, the quinine and cinchonidine-derived bifunctional thiourea catalysts **III** and **IV** were employed in the reaction and moderate enantiomeric excesses were achieved. The yield and enantioselectivity further improved when using the *tert*-leucine-derived thiourea catalyst **V**. Also, Takemoto's catalyst **VI** [28] was suitable for the reaction though a moderate enantiomeric excess was detected. Finally, the best catalyst turned out to be the pyrrolidine-containing bifunctional thiourea catalyst **VII** and the desired product was isolated in 80% yield with 80% ee. Then, solvent optimization was carried out to obtain better enantioselectivities. A similar enantioselectivity was attained in α,α,α-trifluorotoluene and tetrahydrofuran as the solvent, whereas in chloroform a slightly improved enantioselectivity of 86% ee was observed. Finally, the best solvent was found to be 1,2-dichloroethane and the product **3a** was obtained in 82% yield with 90% ee.

After having identified the optimized conditions we ventured in the scope and generality of the reaction. Initially a variety of α-nitroketones **1** having different aryl substituents were tested (Table 2). In fact, different *ortho*-, *meta*-, and *para*-substitutions on the phenyl group were compatible with the reaction conditions and satisfactory results were obtained (Table 2, entries 2–11). For example, *p*-tolyl-containing nitroketone **2b** delivered the product **3b** in 80% yield with 88% ee (Table 2, entry 2). A similar enantioselectivity was obtained for product **3c** with a *p*-anisyl group (Table 2, entry 3). Interestingly, the enantioselectivity dropped slightly when replacing a *p*-methoxy substituent with a *p*-ethoxy group and product **3d** was isolated in 78% yield with 80% ee (Table 2, entry 4). Also, a biphenyl group was tolerated and a good result was achieved (Table 2, entry 5). Then, 4-fluoro and 4-bromo-containing nitroketones **2f** and **2g** were employed in the reaction and gratifyingly the same 90% ee were obtained for both products **3f** and **3g** (Table 2, entries 6 and 7). *meta*-Substitutions were also tolerated in the



Scheme 1: Reactions of α-nitroketones with unsaturated pyrazolone and with 4-benzylidenepyrrolidine-2,3-dione.

Table 1: Catalyst screening and optimization of the reaction conditions.



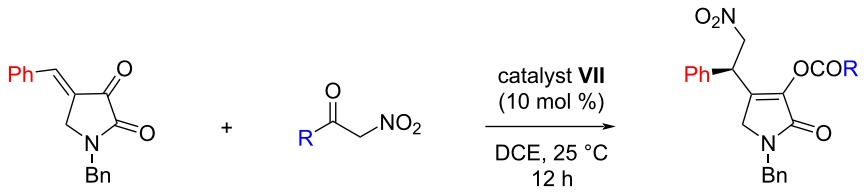
entry[a]	catalyst	solvent	yield[b]	ee[c]
1	**I**	CH_2Cl_2	70	20
2	**II**	CH_2Cl_2	73	34
3	**III**	CH_2Cl_2	76	55
4	**IV**	CH_2Cl_2	78	52
5	**V**	CH_2Cl_2	80	74
6	**VI**	CH_2Cl_2	75	50
7	**VII**	CH_2Cl_2	80	80
8	**VII**	$PhCF_3$	78	78
9	**VII**	THF	80	80
10	**VII**	$CHCl_3$	80	86
11	**VII**	$(CH_2Cl)_2$	82	90

[a]Reactions were carried out with 0.1 mmol of **1a** and 0.1 mmol of **2a** in 0.6 mL solvent at 25 °C for 12 hours; [b]isolated yield after silica gel column chromatography; [c]determined by chiral HPLC.

reaction although decreased enantioselectivities were detected for the products **3h** and **3i**, respectively (Table 2, entries 8 and 9). Then, *o*-methyl- *and o*-methoxyphenyl-substituted nitroketones **2j** and **2k** were employed in the reaction. Here also, the reactions progressed well to provide products **3j** and **3k** in moderate yields and enantioselectivities (Table 2, entries 10 and 11). The 2-naphthyl-substituted nitroketone **2l** also participated in the reaction to deliver **3l** in 80% ee (Table 2, entry 12). Moreover, the hydrocinnamyl group containing nitroketone **2m** also took part in the reaction and the corresponding product **3m** was isolated in 65% yield with 64% ee (Table 2, entry 13). Finally, nitroketone **2n** with a cyclohexyl group was engaged in the reaction and a moderate enantioselectivity was detected for product **3n** (Table 2, entry 14).

In the next step, we investigated the scope of the reaction of substrate **2a** with a variety of pyrrolidine-2,3-diones **1** having different benzylidene substituents under the optimized conditions (Table 3). It turned out that a range of substitutions was tolerated and good results were attained. Initially, different *para*-substituted arylidene substrates were screened that smoothly afforded products **3o–s** (Table 3, entries 1–5). For example, the pyrrolidine-2,3-dione **1b** with a 4-methylbenzylidene-substituent provided the product **3o** in 83% yield and

Table 2: Scope of α-nitroketones **2** in the reaction with **1a**.

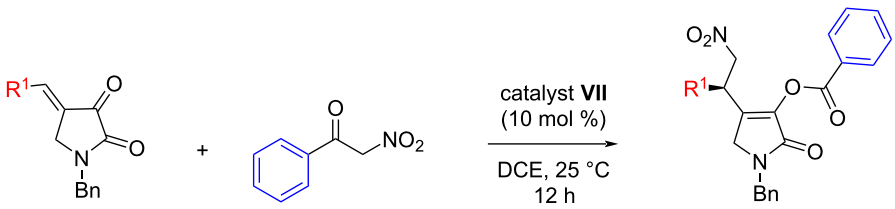


1a **2** **3a–n**

entry[a]	R	3	yield[b]	ee[c]
1	Ph	**3a**	80	90
2	4-MeC_6H_4	**3b**	80	88
3	4-$MeOC_6H_4$	**3c**	82	88
4	4-$EtOC_6H_4$	**3d**	78	80
5	4-PhC_6H_4	**3e**	82	82
6	4-FC_6H_4	**3f**	79	90
7	4-BrC_6H_4	**3g**	78	90
8	3-MeC_6H_4	**3h**	70	72
9	3-$MeOC_6H_4$	**3i**	72	66
10	2-MeC_6H_4	**3j**	65	68
11	2-$MeOC_6H_4$	**3k**	68	70
12	2-naphthyl	**3l**	75	80
13	$PhCH_2CH_2$	**3m**	65	64
14	cyclohexyl	**3n**	70	72

[a]The reactions were carried out with 0.1 mmol of **1a** and 0.1 mmol of **2** in 0.6 mL 1,2-dichloroethane at 25 °C for 12 hours; [b]isolated yield after silica gel column chromatography; [c]determined by chiral HPLC.

Table 3: Scope of pyrrolidine-2,3-diones **1** in the reaction with **2a**.



1 **2a** **3o–w**

entry[a]	R^1	1	3	yield[b]	ee[c]
1	4-MeC_6H_4	**1b**	**3o**	83	72
2	4-*t*-BuC_6H_4	**1c**	**3p**	80	72
3	4-FC_6H_4	**1d**	**3q**	80	84
4	4-ClC_6H_4	**1e**	**3r**	79	70
5	4-BrC_6H_4	**1f**	**3s**	82	76
6	2-FC_6H_4	**1g**	**3t**	79	86
7	2,4-$F_2C_6H_3$	**1h**	**3u**	78	72
8	3,5-$(MeO)_2C_6H_3$	**1i**	**3v**	80	72
9	2-thienyl	**1j**	**3w**	81	82

[a]Reactions were carried out with 0.1 mmol of **1** and 0.1 mmol of **2a** in 0.6 mL 1,2-dichloroethane at 25 °C for 12 hours; [b]isolated yield after silica gel column chromatography; [c]determined by chiral HPLC.

72% ee (Table 3, entry 1). A similar enantioselectivity was obtained with the 4-*tert*-butylenzylidene-substituted pyrrolidine-2,3-dione **1c** (Table 3, entry 2). Then, different 4-halobenzylidene-substituted pyrrolidine-2,3-diones **1d–f** were employed in the reaction and mixed results were obtained. Although product **3q** having a 4-fluorophenyl-substitution was isolated in 80% yield and 84% ee, slightly decreased enantioselectivities were obtained for the corresponding 4-chloro- (**3r**, 70% ee) and 4-bromophenyl (**3s**, 76% ee) derivatives (Table 3, entries 3–5). These products could be particularly useful for further transformations via cross-coupling reactions. The *ortho*-fluoroarylidene-substituted pyrrolidine-2,3-dione **1g** also participated in the reaction to deliver product **3t** in 86% ee (Table 3, entry 6). 2,4-Disubstitution at the aromatic ring was also tolerated in the reaction and a moderate enantioselectivity was observed for the 2,4-difluorophenyl-substituted product **3u** (Table 3, entry 7). The 3,5-dimethoxybenzylidene-containing pyrrolidine-2,3-dione **1i** was prepared and also engaged in the reaction. Here also, a smooth conversion was detected and the product **3v** was isolated in 80% yield with 72% ee (Table 3, entry 8). Finally, pyrrolidine-2,3-dione **1j** containing a heteroaromatic group was also screened and an acceptable enantioselectivity for the 2-thienyl-substituted product **3w** was witnessed (Table 3, entry 9).

To further expand the scope of the reaction, 4-benzylidenedihydrofuran-2,3-dione (**4**) was prepared and reacted with nitroketones **2b** and **2c**, respectively. To our delight, the reactions proceeded smoothly at room temperature providing the desired products **5a** and **5b** in good yields and enantioselectivities (Scheme 2).

Conclusion

In summary, in this paper we reported an organocatalytic asymmetric Michael/acyl transfer reaction between α-nitroketones and 4-arylidenepyrrolidine-2,3-diones/4-benzylidenedihydrofuran-2,3-dione. The products were obtained in good yields with moderate to high enantioselectivities. An easily available bifunctional thiourea catalyst was employed in the methodology.

Supporting Information

Supporting Information File 1

Experimental part.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-100-S1.pdf]

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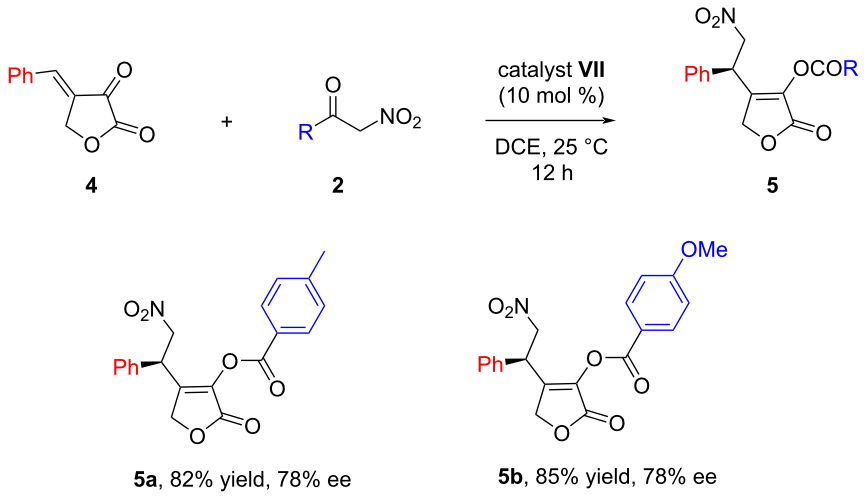
Chandrakanta Parida - https://orcid.org/0000-0003-4258-8239
Subhas Chandra Pan - https://orcid.org/0000-0002-7581-1831

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Scheme 2: Reaction of 4-benzylidenedihydrofuran-2,3-dione (**4**) with α-nitroketones **2b**,**c**. Reaction conditions: furan **4** (0.1 mmol), α-nitroketone **2** (0.1 mmol), 10 mol % **VII** in 0.6 mL 1,2-dichloroethane were reacted at 25 °C for 12 hours. Yields correspond to isolated yields after silica gel column chromatography and ees were determined by chiral HPLC.

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Electron-rich triarylphosphines as nucleophilic catalysts for oxa-Michael reactions

Susanne M. Fischer[1,2], Simon Renner[1], A. Daniel Boese[3] and Christian Slugovc[*1,2]

Full Research Paper

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Address:
[1]Institute for Chemistry and Technology of Materials, Graz University of Technology, Stremayrgasse 9, 8010 Graz, Austria, [2]Christian Doppler Laboratory for Organocatalysis in Polymerization, Stremayrgasse 9, 8010 Graz, Austria, and [3]Physical and Theoretical Chemistry, Institute of Chemistry, University of Graz, Heinrichstrasse 28/IV, 8010 Graz, Austria

Email:
Christian Slugovc[*] - slugovc@tugraz.at

* Corresponding author

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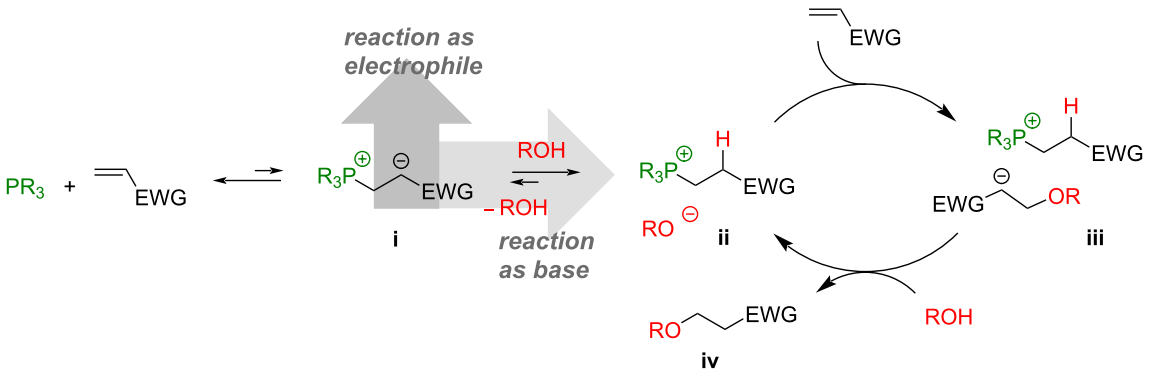
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Abstract

Electron-rich triarylphosphines, namely 4-(methoxyphenyl)diphenylphosphine (MMTPP) and tris(4-trimethoxyphenyl)phosphine (TMTPP), outperform commonly used triphenylphosphine (TPP) in catalyzing oxa-Michael additions. A matrix consisting of three differently strong Michael acceptors and four alcohols of varying acidity was used to assess the activity of the three catalysts. All test reactions were performed with 1 mol % catalyst loading, under solvent-free conditions and at room temperature. The results reveal a decisive superiority of TMTPP for converting poor and intermediate Michael acceptors such as acrylamide and acrylonitrile and for converting less acidic alcohols like isopropanol. With stronger Michael acceptors and more acidic alcohols, the impact of the more electron-rich catalysts is less pronounced. The experimental activity trend was rationalized by calculating the Michael acceptor affinities of all phosphine–Michael acceptor combinations. Besides this parameter, the acidity of the alcohol has a strong impact on the reaction speed. The oxidation stability of the phosphines was also evaluated and the most electron-rich TMTPP was found to be only slightly more sensitive to oxidation than TPP. Finally, the catalysts were employed in the oxa-Michael polymerization of 2-hydroxyethyl acrylate. With TMTPP polymers characterized by number average molar masses of about 1200 g/mol at room temperature are accessible. Polymerizations carried out at 80 °C resulted in macromolecules containing a considerable share of Rauhut–Currier-type repeat units and consequently lower molar masses were obtained.

Introduction

Phosphines are potent nucleophiles that are used as catalysts in many reactions, like Rauhut–Currier, Morita–Baylis–Hillman or Michael reactions [1-3]. The first step of these reactions is a conjugate addition of the phosphine to an activated electrophile, e.g., an electron-deficient olefin, generating a zwitterion (**i**, Scheme 1). In further course, the zwitterion acts as a nucleo-



Scheme 1: Mechanism for the phosphine-initiated oxa-Michael addition.

phile or as a base [1]. The efficiency of the formation of this β-phosphonium α-carbanionic species depends on the nucleophilicity of the phosphine which is usually stronger in trialkylphosphines and decreases with aryl substitution [4,5]. Consequently, the first phosphine-catalyzed reactions have been described with trialkylphosphines [6-10]. However, trialkylphosphines are characterized by a pronounced oxidation sensitivity demanding the exclusion of oxygen. This issue can be mitigated by using triarylphosphines that are by far less prone to oxidation. Both, the rate of oxidation and the reactivity in nucleophilic additions correlate with the electron density residing on the phosphorous center [11-13]. Accordingly, triarylphosphines are generally less reactive in conjugate additions than trialkylphosphines and often high catalyst loadings of up to 20 mol % and elevated temperatures are necessary to obtain satisfactory conversions [5,14,15]. The low reactivity of arylphosphines can be enhanced by introducing electron-donating groups (e.g., -CH_3, -OMe, -NMe_2) at the aryl moieties. In this way, the electron density on the phosphorous and thus the nucleophilicity is increased. This strategy has for example been exploited in the reaction of ethyl acrylate with 4-nitrobenzaldehyde [16], in aza-Morita–Baylis–Hillman reactions [17], or in umpolung [3 + 2] annulations [18]. In all these cases, the reactions were performed without protective gas indicating that electronically modified arylphosphines tolerate the presence of oxygen.

Herein we wish to report the scope of three different triarylphosphine catalysts in the oxa-Michael addition. Triphenylphosphine (TPP), (4-methoxyphenyl)diphenylphosphine (MMTPP) and tris(4-trimethoxyphenyl)phosphine (TMTPP). The catalysts were investigated in the reaction of four different Michael acceptors with four different alcohols. In the oxa-Michael addition, the zwitterion **i**, initially formed by the conjugate addition of the phosphine to the Michael acceptor, is believed to be protonated by the alcohol forming the actual catalytically active species namely ion pair **ii**, consisting of a phosphonium cation and an alkoxide. The alkoxide in **ii** then reacts with another electrophile generating the ion pair **iii**. In the final step, the α-carbanionic species in **iii** gets protonated by an alcohol generating the oxa-Michael addition product (**iv**) and regenerating **ii** (Scheme 1). Additionally, the ion par **ii** might directly react via a nucleophilic substitution of the phosphonium group by the alkoxide to yield the product **iv** and the phosphine. Our results disclosed in the following contribute to the rational selection of proper (pre-)catalysts for this and similar reactions also considering the oxygen sensitivity of the nucleophiles.

Results and Discussion

To compare the activity of the triarylphosphines TPP, MMTPP and TMTPP as catalysts for the oxa-Michael reaction three varyingly strong Michael acceptors, namely acrylonitrile (**1**), acrylamide (**2**) and divinyl sulfone (**3**) were reacted with four different alcohols of similar molecular mass but different acidity (Figure 1). The stoichiometry of Michael acceptor to alcohol was set to 1 to 2 and no additional solvent was used. The reaction was carried out at room temperature with 1 mol % catalyst (with respect to the Michael acceptor). The reaction progress was monitored after 1 h and 24 h using ^{1}H NMR spectroscopy. The set-up of the study aims to show the scope and the limitations of the different catalysts. An optimization of the reaction conditions in terms of obtaining full conversion in the shortest time possible with the lowest reasonable achievable catalyst loading was not undertaken. The results are shown in Figure 1. The benchmark catalyst TPP is unable to promote the oxa-Michael reaction of the good Michael acceptor **1** (electrophilicity parameter E of −19.05 [19]) with the least acidic alcohol 2-propanol (**a**) as virtually no conversion was observed after 24 h. Using MMTPP leads to a minor improvement and a 3% conversion towards **1a** was found after 24 h. TMTPP, however, gives already 4% conversion after 1 h and 38% conver-

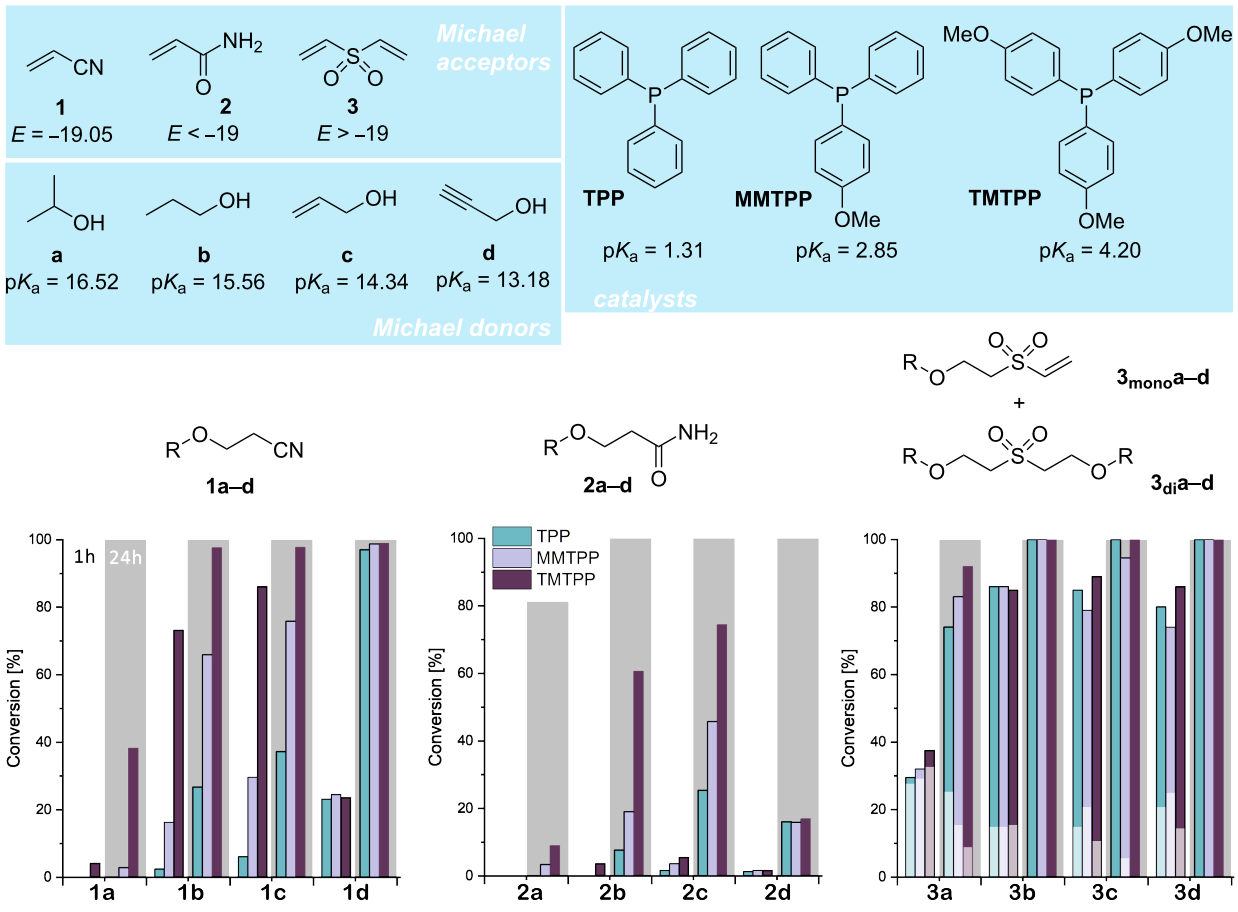


Figure 1: Above: Michael acceptors, Michael donors and catalysts used in this study; pK_a (respectively pK_a of the conjugated acid in case of phosphines) calculated using the pK_a prediction platform (neural network result for solvent H_2O) available at pka.luo-group.com [20]; below: Conversion of the oxa-Michael reaction of acrylonitrile (left), acrylamide (middle), and divinyl sulfone (right; double bond conversion is given; light sections of the bar represent the share of $\mathbf{3_{mono}a–d}$, dark sections represent the share of $\mathbf{3_{di}a–d}$) with the alcohols propan-2-ol (**a**), propan-1-ol (**b**), prop-2-en-1-ol (**c**), and prop-2-yn-1-ol (**d**) catalyzed by triphenylphosphine (TPP), (4-methoxyphenyl)diphenylphosphine (MMTPP), and tris(4-methoxyphenyl)phosphine (TMTPP). Reaction conditions: 1 equiv Michael acceptor, 2 equiv alcohol (in case of **3**, 3 equiv alcohol), 1 mol % catalyst (with respect to the Michael acceptor), 1 h and 24 h (bars above grey boxes) at room temperature (23 °C); no solvent used.

sion after 24 h. The more acidic 1-propanol (**b**) readily reacts in the presence of TPP (27% conversion after 24 h). MMTPP already provides a considerable improvement since a conversion of 66% is obtained after 24 h but TMTPP is again a distinctly better catalyst providing 73% conversion after 1 h and almost full conversion (98%) after 24 h. Allyl alcohol (**c**) is more reactive than 1-propanol as conversions with all catalysts at all conditions are slightly higher. Most importantly, the TMTPP-catalyzed reaction shows already 86% conversion after 1 h. In sharp contrast, propargyl alcohol (**d**), the most acidic one, gave only about 24% conversion after 1 h irrespective of which catalyst had been used. After 24 h almost full conversion (97% TPP or 99% MMTPP and TMTPP) was found for all three catalysts. Accordingly, in this case, the activity of the catalyst is not rate determining. This observation is rationalized by the occurrence of a non-productive acid–base equilibrium involving the de- and re-protonation of the considerably acidic alkyne proton in **d** (pK_a = 15.61 [20]) [21]. The reaction conditions disclosed here are an improvement compared to the state of the art. For example, addition product **1c** has been obtained in 93% conversion before using 10 mol % TPP, 3 equiv **c** and heating the reaction mixture for 8 h under refluxing conditions [14]. However, with base catalysis (KO*t*-Bu) even better results than those presented here can be achieved [22,23].

Switching to the weaker Michael acceptor acrylamide (E = −23.54 for *N*,*N*-dimethylacrylamide) [19], no useful conversions on any account were obtained. However, TMTPP performs best, giving 61 and 74% conversions with 1-propanol (**b**) and allyl alcohol (**c**) after 24 h. To illustrate that the reaction does not stop after 24 h the conversions were re-checked after 21 d. After this time with TMTPP as the catalyst, conversions of 44% (**3a**), 92% (**3b**), 98% (**3c**), and 91% (**3d**) are ob-

tained. No indications for aza-Michael reactions potentially leading to polyamide 3 like structures were observed [24]. A more efficient transformation of acrylamide can be obtained with base catalysis. Using activated potassium carbonate, a reaction temperature of 40 °C, and 4 h reaction time give typically better conversions than those reported herein with nucleophiles [25].

Next, the difunctional divinyl sulfone was tested as the strongest Michael acceptor (E = −18.36, for phenyl vinyl sulfone [19]) under investigation. In distinction from the experiments described above, three equivalents of the alcohol were used. In general, the different catalysts perform very similar in this reaction giving high double-bond conversions of about 80% after already 1 h [26]. A mixture of mono- ($\mathbf{3}_{mono}$**a**–**d**) and di-adducts ($\mathbf{3}_{di}$**a**–**d**) are observed and only in case of 2-propanol also divinyl sulfone is still present. With 2-propanol a slight but significant influence of the catalyst choice on the conversion is observed (Figure 1). With all other (more acidic) alcohols, the conversion is reaching completeness after 24 h. Why MMTPP is performing slightly worse than TPP as indicated by the double-bond conversion and by the higher share of the mono-adduct $\mathbf{3}_{mono}$**a**–**d** after 1 h reaction time is not clear. The reaction of **3** with 3 equiv **a** or **c** catalyzed with 10 mol % TPP at 40 °C using dichloromethane ([DVS] = 0.55 M) as solvent has been described. The product **3a** was obtained as a 76:13 mixture of $\mathbf{3}_{mono}$**a** and $\mathbf{3}_{di}$**a** and **3c** as a 11:89 mixture of $\mathbf{3}_{mono}$**c** and $\mathbf{3}_{di}$**c** [21]. The herein disclosed results highlight that solvent-free conditions are particularly effective and allow for reducing the catalyst loading by the factor of 10, thereby obtaining a higher share of $\mathbf{3}_{di}$**a** and full conversion towards $\mathbf{3}_{di}$**c**. Interestingly, the catalytic activity of TPP in reactions with **3** as the Michael acceptor is only slightly lower than the activity of the methoxy-substituted congeners.

As an example for acrylates as Michael acceptors, the performance of the catalysts in the oxa-Michael addition polymerization of 2-hydroxyethyl acrylate (HEA, **4**) was investigated [27-29]. The catalyst loading was increased to 5 mol %, because 1 mol % was not sufficient to obtain satisfying conversions. The reaction mixture consisting of **4** and the catalyst was either stirred at room temperature or put in a drying chamber operated at 80 °C. Aliquots of the reaction mixture were sampled after 1 and 24 h and analyzed by ^{1}H NMR spectroscopy and size exclusion chromatography (SEC). The results are shown in Figure 2.

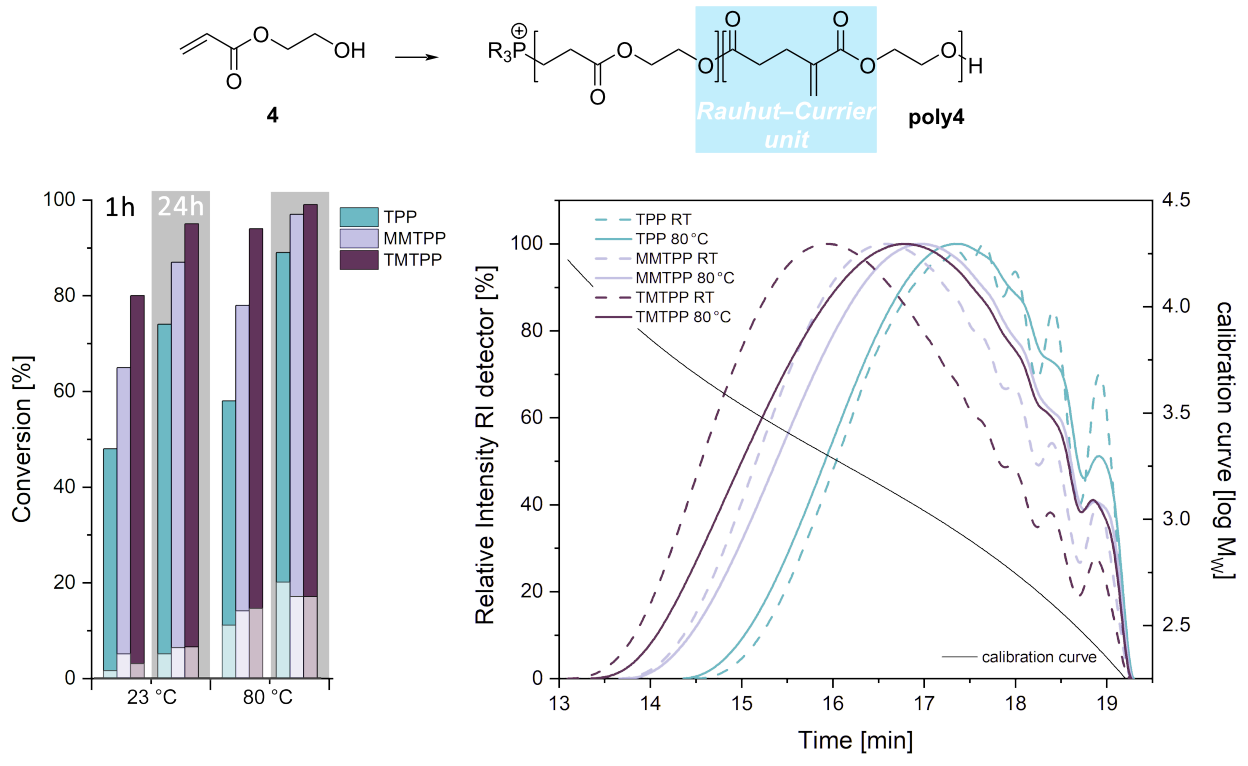


Figure 2: Left: double-bond conversion of the polymerization of **4** initiated by 5 mol % TPP, MMTPP or TMTPP after 1 h at room temperature (23 °C) and at 80 °C as well as after 24 h at 23 °C and at 80 °C; light sections of the bars represent the share of Rauhut–Currier repeat units; right: size exclusion chromatograms (in THF, relative to poly(styrene) standards) of **poly4** prepared with 5 mol % TPP, MMTPP or TMTPP using a reaction time of 24 h and a reaction temperature of 23 °C (dashed lines) or 80 °C (full lines).

After 1 h at room temperature, an impact of the catalysts on the double bond conversion is evident. TPP gave a double bond conversion of 48%, while MMTPP and TMTPP performed better with 67 and 80%, respectively. After 24 h at room temperature conversions increased to 74% (TPP), 85% (MMTPP), and 90% (TMTPP). Performing the reaction at 80 °C leads to higher double-bond conversions than reactions run at room temperature. After 1 h reaction time conversions of 58% (TPP), 78% (MMTPP), and 94% (TMTPP) were obtained. Prolonging the reaction time to 24 h led to high double-bond conversion of 89% in case of TPP and 97% and 99% in the cases of MMTPP and TMTPP. Molar mass distributions of the polymers prepared with a reaction time of 24 h were determined by SEC. First, the polymerizations conducted at room temperature are discussed. As expected from the trend in double-bond conversion, the number average molar mass (M_n) of **poly4** increases according to the activity of the initiator. The M_n values nearly doubled when going from TPP (660 g/mol, dispersity $Đ$ = 1.5) to TMTPP (1160 g/mol, $Đ$ = 1.8) with MMTPP (910 g/mol, $Đ$ = 1.7) lying in about the middle of these two values. Turning to the results obtained for the polymerization conducted at 80 °C it is revealed that **poly4** prepared with TPP is characterized by only a slightly higher M_n value of 680 g/mol than **poly4** from the room temperature reaction. MMTPP and TMTPP derived **poly4** exhibiting even lower M_n values (820 and 890 g/mol, $Đ$ = 1.7 and 1.8) than those obtained in the room temperature reaction. Considering the distinctly higher double-bond conversions at 80 °C, these findings point to another double-bond consuming reaction beside the oxa-Michael reaction. The evaluation of the NMR spectra indicate, among repeating units from oxa-Michael and transesterification reactions [30,31], the presence of Rauhut–Currier-derived linkages [32-34]. This repeat unit is characterized by peaks at 6.22 and 5.64 ppm in the ^{1}H NMR spectrum and at 126.6, 33.0, 27.3 ppm in the ^{13}C NMR spectrum of **poly4** (see Supporting Information File 1) and its share is with approximately 17–20% higher in polymers prepared at 80 °C (Figure 2). The formation of this repeat unit consumes two equivalents of acrylates and thus, disproportionally decreases the quantity of acrylate groups in relation to alcohol groups. Consequently, the originally ideal stoichiometry of Michael acceptors and Michael donors is changed in favor of alcohols. This eventually results in lower molecular mass distributions in cases in which more Rauhut–Currier repeat units are formed. In comparison, **poly4** has been prepared with nucleophilic catalysis using 10 mol % N-heterocyclic carbenes such as 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene or 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene. The polymerization was carried out at room temperature for 24 h and no solvent was used. The resulting reaction mixture was dissolved in dichloromethane and precipitated from diethyl ether resulting in about 50% polymer yield featuring M_n values of 1500–1800 g/mol [30].

Next, the oxidation stability of the catalysts was tested. For this purpose, the three different phosphines were exposed to air for 14 d in dark conditions. Four different conditions were chosen. Undissolved solid samples and samples dissolved in chloroform or in 1-hexanol were kept at room temperature and solutions in 1-hexanol were also heated at 80 °C. The reaction mixture was then investigated via ^{31}P NMR spectroscopy. Under all conditions, the formation of the corresponding phosphine oxide derivative as the only decomposition product was observed. The results, shown in Figure 3, reveal that the oxidation stability is decreasing in the order TPP > MMTPP > TMTPP, which is in line with electrochemical studies showing a decrease of the oxidation potential from 1.400 V (TPP) to 1.050 V (TMTPP) [35].

Furthermore, the share of phosphine oxide is dependent on the oxygen solubility in the solvent, as indicated by the experiments in chloroform and 1-hexanol exhibiting the higher oxygen solubility [36]. To obtain further insight, the SOMO energies of the radical cations of the phosphines under investigation were calculated by density functional theory (DFT), namely B3LYP-def2-TZVPPD. According to criterion introduced by Stewart et al. postulating air stability of phosphines when the SOMO energy is higher than −10 eV, the three derivatives should be air stable [13]. However, the SOMO energies decrease within the series from −9.60 eV (TPP, −9.50 according to [13]) to −9.18 (MMTPP) and −8.59 (TMTPP) suggesting TMTPP to exhibit the highest oxidation stability within the series; the opposite what was observed experimentally. Therefore, the oxidation stability of the phosphines discussed here cannot be described by evaluating their SOMO energies as suggested previously. Overall, the experiments demonstrate that the oxidation stability of all phosphines under investigation can be considered sufficient for running reactions (under typically employed reaction conditions, i.e., reaction temperatures and times not exceeding 80 °C and 24 h) without the unconditional need to exclude oxygen.

A first hint for rationalizing the different reactivity of the different phosphines can be retrieved from the pK_a value of their conjugated acids. Substitution of the aromatic rings with methoxy groups increases the pK_a value from 1.31 (TPP) to 4.20 (TMTPP) (Figure 1). Methyl cation affinities (MCA) which can be used as descriptors for the nucleophilicity of a compound were calculated by Lindner et al. who suggested TMTPP (651.0 kJ/mol) to be a stronger Lewis base than TPP (618.7 kJ/mol) [37]. However, for PMe_3, discussed as a model for aliphatic phosphines, a distinctly lower MCA of 604.2 kJ/mol was calculated. This is in contrast to experimental

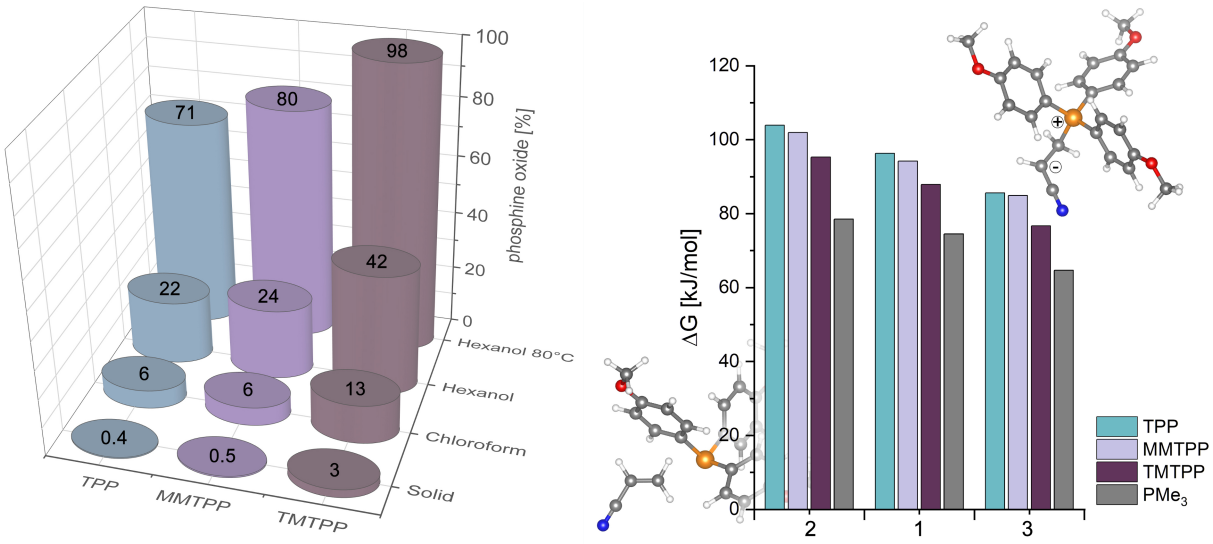


Figure 3: Left: Oxidation stability of the phosphines. Phosphine oxide content in % as determined by ^{31}P NMR spectroscopy after a 14 d exposure to air under the following conditions: sample stored as a solid at room temperature, samples dissolved in chloroform and 1-hexanol (stored at room temperature in the dark), and in 1-hexanol (stored at 80 °C in the dark). Right: Relative stabilities of the zwitterions formed upon reaction of Michael acceptors **1**–**3** with the phosphines (the cartoon shows the structures of the educts acrylonitrile and TMTPP (left, behind the chart) and the corresponding zwitterion (right, above), optimized at the B3LYP/def2-TZVPPD level of theory).

data as PMe_3 is known as a more active catalyst for oxa-Michael additions than arylphosphines [8,14]. Apparently, the MCA is not correlating with the phosphines' activities in conjugate addition reactions. Another approach for assessing the nucleophilicity of the phosphines is to compare their HOMO energy. The nucleophilicity should decrease with increasing s character of the orbital containing the lone pair, which should also be the HOMO of the molecule. A higher s character of the HOMO, going in hand with a lower energy level of the HOMO, is thus indicative for a lower nucleophilicity [38,39]. Accordingly, the HOMO energies have been calculated and increase from −5.91 eV (TPP) to −5.73 eV (MMTPP) and −5.42 eV (TMTPP). A comparison of the orbital distributions of the arylphosphines reveals that the HOMO of all phosphines under investigation has a significant phosphorous character (visual representations are provided in Supporting Information File 1). However, considering the HOMO energy of PMe_3 which is calculated to be as low as −6.10 eV, it is obvious that also this approach fails in sufficiently describing the activity of phosphines in catalyzing oxa-Michael reactions. To resolve this issue, the Gibbs free energy (ΔG) of the reaction of TPP, MMTPP, TMTPP, and PMe_3 with acrylonitrile leading to zwitterion formation (Figure 3, right) was calculated in chloroform. The Michael acceptor affinity (MAA) of the nucleophiles is then given by the Gibbs free energy of the back reaction [37]. The respective energy differences calculated at the B3LYP/def2-TZVPPD level of theory are −96.3 kJ/mol (TPP), −94.2 kJ/mol (MMTPP), −87.9 kJ/mol (TMTPP), and −74.5 kJ/mol (PMe_3) in favor of the educts acrylonitrile and phosphine. Accordingly, the zwitterion formed from PMe_3 is in relation the most stable and the zwitterion formed from TPP the most unstable one within the series. The stability trend of the zwitterions based on acrylamide and divinyl sulfone is the same (Figure 3, right). The different reactivity of the three Michael acceptors is apparent from the relative stabilities of the zwitterion. Acrylamide gives the least stable (MAA with TPP is −103.9 kJ/mol) and DVS the most stable zwitterion (MAA with TPP: −85.6 kJ/mol). Consequently, such calculated Michael acceptor affinities correlate with the experimental results and are suited to reflect the actual activity of the phosphines under investigation. This is reasonable because the position of the thermodynamic equilibrium of the unreacted Michael acceptor and -donor and the corresponding zwitterion **i** is believed to be decisive for the efficacy of the subsequent reaction, protonation of **i** by the alcohol resulting in the formation of ion pair **ii** (Scheme 1) [40]. In turn, the pK_a value of the alcohol is another important parameter for the speed of the overall reaction. The alcohol's acidity is determining how efficiently **i** is transformed into the ion pair **ii** (Scheme 1) being the actual entry point into the catalytic cycle of the oxa-Michael reaction. Accordingly, the reactivity trend observed for the different alcohols under investigation is rationalized. Note that although a two-step process is

discussed herein, it is also conceivable that the reaction towards **ii** proceeds via a single transition state involving the Michael acceptor, the Michael donor, and the alcohol. Furthermore, the different nucleophilicity of the generated alkoxides might play an additional role. However, it has been shown, that the nucleophilicity of alkoxides differs only moderately [41]. Therefore, this effect is considered to be less important for the explanation of the relative characteristics of the reactions than the factors discussed above.

Conclusion

The activity of differently substituted triarylphosphines in the oxa-Michael addition of alcohols to electron-deficient olefins was investigated. In general, the activity increases with increasing methoxy-substitution in the order TPP < MMTPP < TMTPP. The activity order was rationalized based on DFT calculations by an increasing stationary concentration of the primary reaction product, the corresponding β-phosphonium α-carbanionic zwitterion, when using arylphosphines with more electron-donating substituents. Besides the catalyst, the second decisive factor for the speed of the reaction is the acidity of the alcohol as the efficacy of the secondary reaction, where the zwitterion reacts with the alcohol, increases when more acidic alcohols are used. Moreover, concentrated conditions or the omission of solvents is beneficial for this reaction. In summary, the better catalyst TMTPP is particularly useful for reacting weak Michael acceptors and/or less acidic alcohols. Phosphine loadings of only 1 mol % with respect to the Michael acceptor are in many cases sufficient to provide a full conversion within 24 h at room temperature. With good Michael acceptors and/or acidic alcohols the catalytic activity of TPP becomes competitive to the one of the more expensive TMTPP. Furthermore, TMTPP is somewhat more sensitive to oxidation in air than TPP. Nevertheless, exclusion of air is, in contrast to trialkylphosphines, not mandatory. Oxidation under typical reaction conditions (reaction time not longer than 24 h and reaction temperature below 80 °C) is slow and can be considered as unproblematic.

Experimental

General information

All experiments were performed under ambient conditions. Chemicals were purchased from Sigma-Aldrich, Carl Roth, Merck, or TCI and were used as received. The catalysts TPP and TMTPP were purchased from Sigma-Aldrich. MMTPP was prepared according to literature [42]. Stabilizers present in the Michael acceptors were not removed. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 300 MHz spectrometer at 25 °C (^{1}H: 300.36 MHz; ^{13}C: 75.53 MHz). Chemical shifts δ are given in ppm relative to the residual protons and carbons of the deuterated solvent. ($CHCl_3$: 7.26 ppm and 77.16 ppm, DMSO: 2.50 and 39.52 for ^{1}H and ^{13}C, respectively). ^{31}P NMR measurements were performed on a Varian Inova 500 MHz instrument operating at 202.547 MHz. Chemical shifts are reported in ppm relative to an external standard (85% H_3PO_4). Spectra are ^{1}H-decoupled and as delay time (d1) 25 s was set. Deuterated solvents were obtained from Cambridge Isotope Laboratories Inc. Size exclusion chromatography (SEC) was performed on a system provided by Shimadzu (equipped with two separating columns from MZ-Gel SD plus, 500 A and 100 A, linear 5 µ; UV detector (SPD-20A) and RI detector (RID-20A)) using THF as eluent. Poly(styrene) standards in the range of 350 to 17800 g/mol purchased from Polymer Standard Service were used for calibration.

Computational details

All calculations were run with the TURBOMOLE program (version 7.4.1) [43]. Geometries were pre-optimized using the PBE [44] functional, the def2-SVPD [45,46] basis set and D3 [47] dispersion correction. All structures were then re-optimized using the hybrid functional B3LYP [48-51] D3 with the def2-TZVPPD basis set. For gas-phase calculations, temperature effects (298 K) and zero-point energies have been approximated by the rigid-rotor-harmonic oscillator (RRHO) approximation. The zero-point energies have been scaled by a factor of 1.0030 (B3LYP/def2-TZVPPD) and 1.0302 (PBE/def2-SVPD) to account for anharmonic effects [52]. Solvent effects of chloroform have been considered for calculation of the Gibbs free energy (ΔG) of zwitterion formation and were calculated by the conductor-like screening model (COSMO) [53,54] with a dielectric constant of 4.8 and a radius of 3.17. Our best estimate for the calculation of zwitterion energies resulted in using B3LYP-D3 /TZVPPD + Δsolv (B3LYP-D3) + ZPE,temp (PBE-D3/def2-SVPD).

General procedure for oxa-Michael additions

The alcohol (2.0 equiv for mono-functionalized Michael acceptors, 3.0 equiv for **3**) and the catalyst (0.01 equiv) were added to a 4 mL-sealed tube. Then, the Michael acceptor was added, and the reaction mixture was stirred at room temperature or at 80 °C. The reaction progress was monitored by ^{1}H NMR spectroscopy after 1 and 24 h. All experiments were performed at least three times.

Oxa-Michael addition polymerization of 2-hydroxyethyl acrylate (**4**)

A 4 mL-glass tube was charged with phosphine (0.05 equiv) and **4** (1.0 equiv, 0.1 g, 0.861 mmol) and sealed. The reaction mixture was stirred at room temperature or at 80 °C. Samples taken after either 1 h or 24 h were evaluated by ^{1}H NMR spectroscopy and SEC. All experiments were performed at least three times.

Supporting Information

Supporting Information File 1

Experimental details, data in tabular form, NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-117-S1.pdf]

Supporting Information File 2

xyz Files of the calculated structures.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-117-S2.zip]

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ORCID® iDs

Susanne M. Fischer - https://orcid.org/0000-0002-8187-1902
Christian Slugovc - https://orcid.org/0000-0003-1873-5200

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Asymmetric organocatalyzed synthesis of coumarin derivatives

Natália M. Moreira‡, Lorena S. R. Martelli‡ and Arlene G. Corrêa*

Review

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Address:
Centre of Excellence for Research in Sustainable Chemistry, Department of Chemistry, Federal University of São Carlos, 13565-905 São Carlos, SP – Brazil

Email:
Arlene G. Corrêa* - agcorrea@ufscar.br

* Corresponding author ‡ Equal contributors

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Abstract

Coumarin derivatives are essential scaffolds in medicinal and synthetic chemistry. Compounds of this class have shown important activities, such as anticancer and antiparasitic, besides the commercially available drugs. These properties led to the development of efficient and greener synthetic methods to achieve the 2*H*-chromen-2-one core. In this context, the advances in asymmetric organocatalyzed synthesis of coumarin derivatives are discussed in this review, according to the mode of activation of the catalyst.

Introduction

Coumarins are important naturally occurring plant constituents and display a wide range of pharmacological and biological activities, such as anticancer [1], antibacterial [2], and antifungal [3]. Moreover, coumarin derivatives have shown activity against neglected diseases as leishmaniasis [4], tuberculosis [5,6] and Chagas' disease [7]. Examples of coumarin-derived drugs are: methoxsalen, used to treat psoriasis, eczema, vitiligo, and some cutaneous lymphomas; warfarin, an anticoagulant, used to treat blood clots such as deep vein thrombosis and pulmonary embolism, and to prevent stroke; and tioclomarol, also an anticoagulant, that is a long-acting vitamin K antagonist (Figure 1) [8].

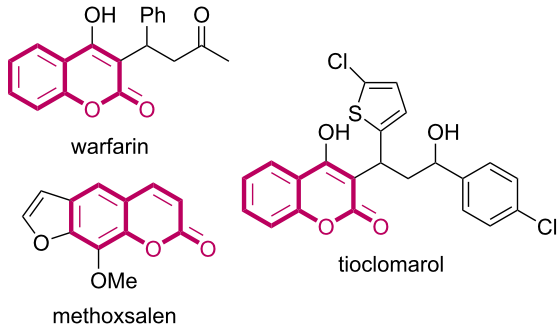


Figure 1: Coumarin-derived commercially available drugs.

This scaffold has also been reported as anti-Alzheimer's disease [9], such as the natural product decursinol, isolated from *Angelica gigas* [10]. In this sense, our research group has synthesized and evaluated a library of coumarin derivatives as acetylcholinesterase inhibitors [11-13], being LSPN223 the most potent compound (Figure 2).

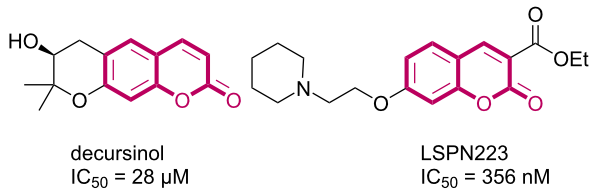


Figure 2: Inhibition of acetylcholinesterase by coumarin derivatives.

Furthermore, coumarin derivatives have been used as fluorescent probes, laser dyes, fluorescent chemosensors, light absorbers for solar cells, optical brighteners, and organic light emitting diodes (OLEDs) [14,15].

From a synthetic perspective, coumarin derivatives have received much attention due to their pivotal role in organic synthesis [16-18]. The development of efficient synthetic processes with eco-friendliness and sustainability that avoid the extensive use of toxic and hazardous reagents and solvents, as well as harsh reaction conditions, has become paramount in the field of organic synthesis in recent years [19]. In this sense, Molnar et al. published a review on green chemistry approaches to the synthesis of coumarin derivatives [20] and Chandrakar et al. reviewed the developments of multicomponent synthesis of biologically relevant coumarins in aqueous medium [21].

Catalysis is one of the fundamental pillars of green chemistry [22], and the transition-metal-catalyzed synthesis of coumarins has been reviewed by Sharma et al. [23]. More recently, Kanchana et al. published an account on the palladium-catalyzed cross-coupling reactions of coumarin derivatives [24].

Coumarins are a promising scaffold for design and development of bioactive agents, however it possesses a flat system [25]. One of the attractive benefits of introducing chirality in a drug candidate is that it leads to increased complexity to a specific target, i.e., it gives access to a greater diversity of compounds to be explored [26]. In this work, a compilation of the enantioselective synthesis of coumarin derivatives using asymmetric organocatalysis is presented, highlighting the proposed mechanism pathways for the formation of the stereogenic centers.

Review

A plethora of highly effective small-molecule organocatalysts have enriched the field of organic synthesis [27], including chiral proline derivatives, *N*-heterocyclic carbenes, chiral thioureas and Brønsted acids as well as phase-transfer catalysts (PTC), such as the quaternary ammonium salts derived from cinchona alkaloids [28]. Therefore, the asymmetric synthesis of coumarin derivatives is herein presented according to the activation mode, i.e., via covalent or non-covalent bonding. Furthermore, the use of bifunctional catalysts and multicatalysis are discussed as well.

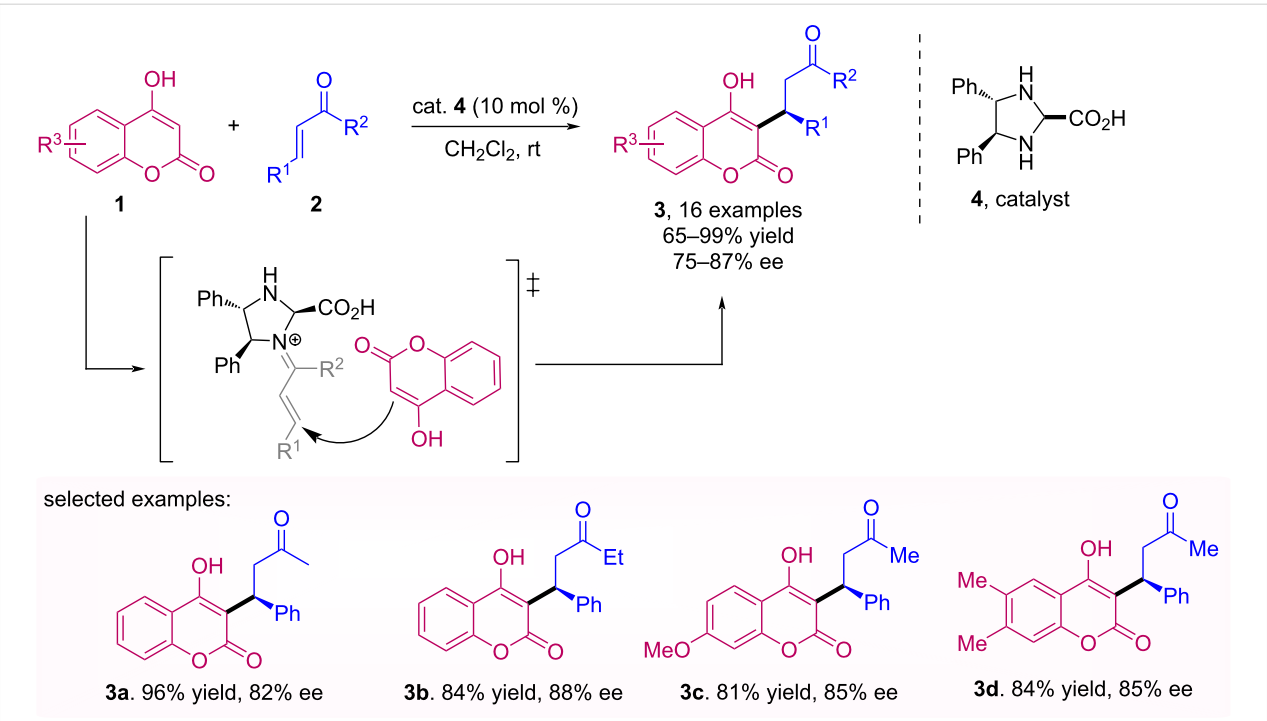
Catalysis via covalent bonding

Organocatalysts made from chiral secondary amines have been widely used in the last years. According to Jørgensen, in general, the carbonyl functionalization employing amine catalysts can be separated in four different types [29]. When aldehydes are employed, both electrophilic and nucleophilic α-functionalizations are possible, whereas with the use of α,β-unsaturated aldehydes the β-position is functionalized with nucleophiles and the γ-position with electrophiles.

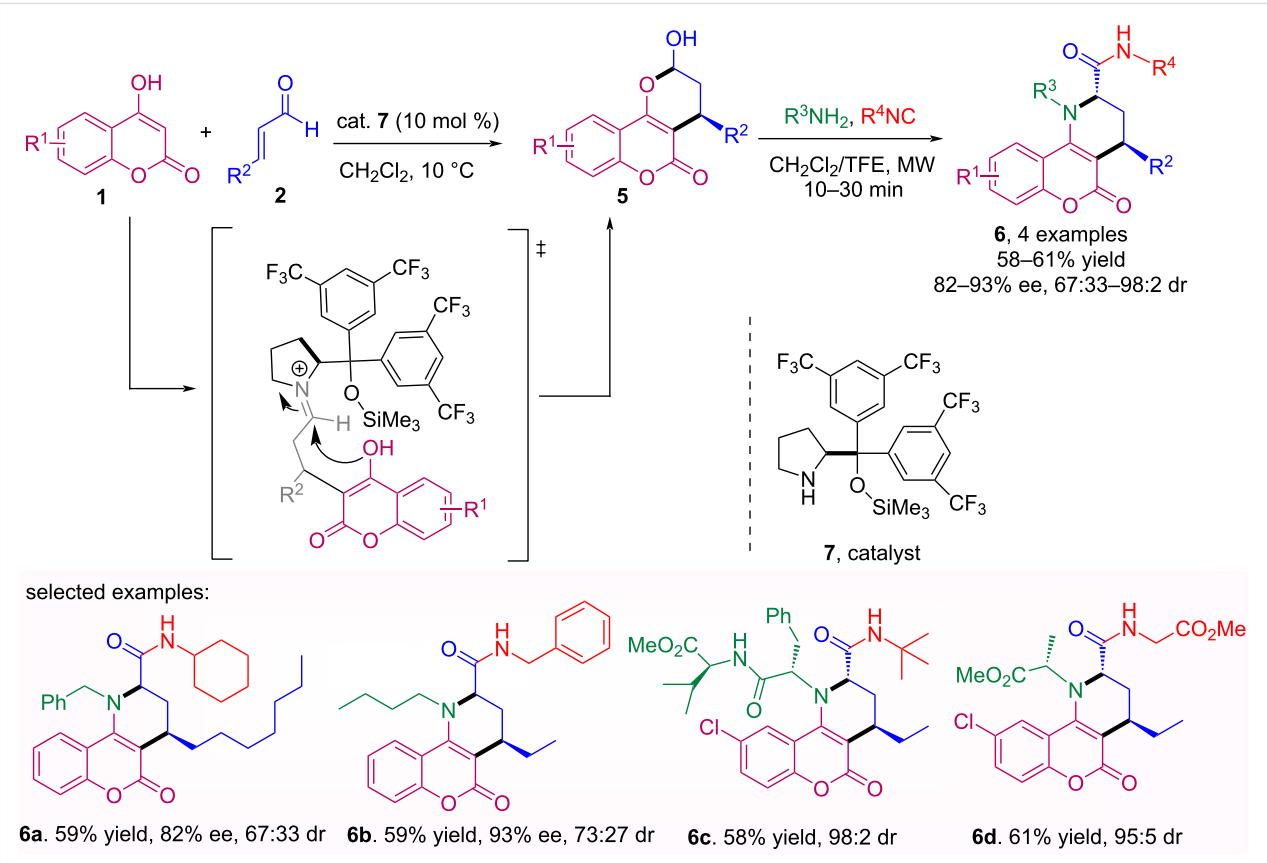
In this sense, Jørgensen and colleagues have developed the first organocatalytic asymmetric Michael addition of cyclic 1,3-dicarbonyl compounds, including 4-hydroxycoumarins **1**, to α,β-unsaturated enones **2** (Scheme 1). This versatile Michael reaction afforded (*S*)-warfarin (**3a**) and other Michael adducts **3** in high yields and good enantiomeric excess (ee), using (4*S*,5*S*)-4,5-diphenylimidazolidine-2-carboxylic acid (**4**) as catalyst [30].

Based on this pioneer work, our research group described an efficient, highly stereoselective, one-pot process comprising an organocatalytic conjugate addition of dimedone or 4-hydroxycoumarin **1** to α,β-unsaturated aldehydes **2** followed by an intramolecular isocyanide-based multicomponent reaction (IMCR) [31]. The enantioenriched hemiacetals **5** were obtained using the Jørgensen catalyst **7** as previously described by Rueping et al. [32]. This approach enables the rapid assembly of complex natural product hybrids **6** including up to four different molecular fragments, such as hydroquinolinone, chromene, piperidine, peptide, lipid, and glycoside moieties (Scheme 2).

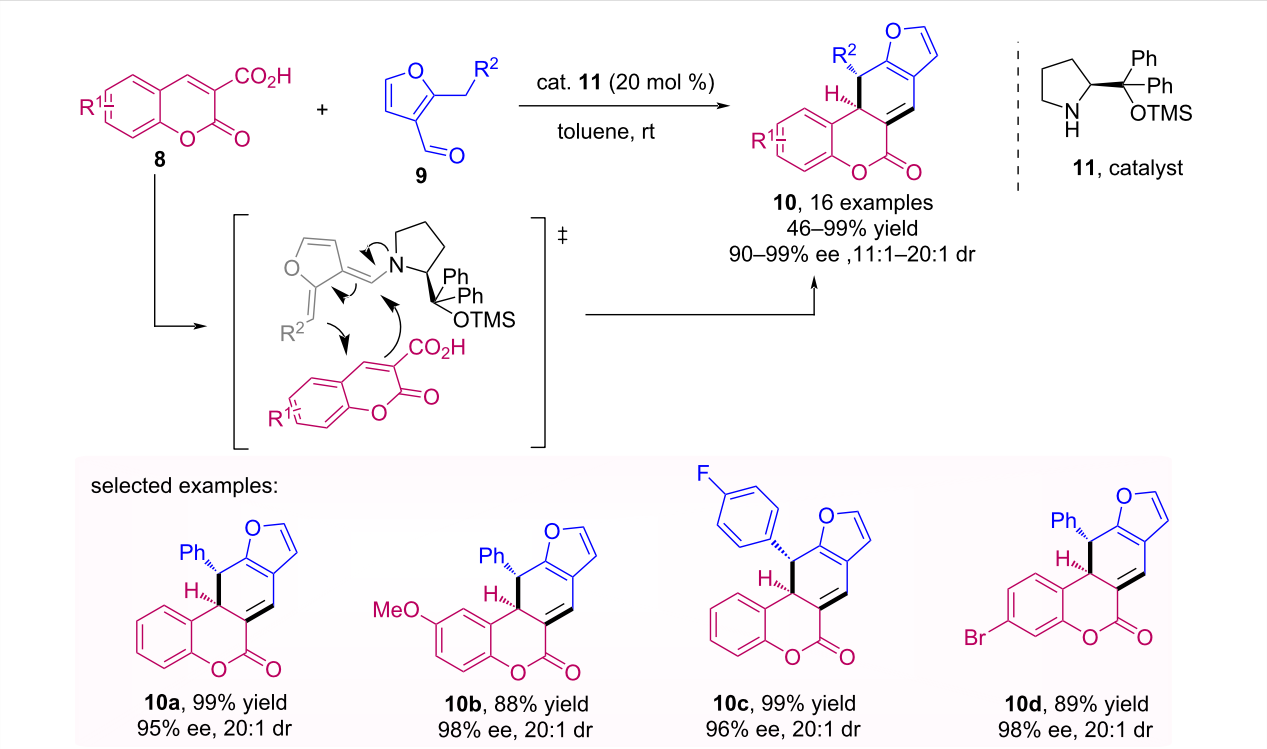
Bojanowski and co-workers developed a methodology to synthetize 3,4-dihydrocoumarins **10** through a decarboxylative and dearomatizative cascade reaction [33]. This reaction was carried out using coumarin-3-carboxylic acids **8**, 2-alkyl-3-furfural derivatives **9** and diphenylprolinol trimethylsilyl ether **11** as catalyst, and it was possible to obtain 3,4-dihydrocoumarin derivatives with excellent yields, ee and dr (Scheme 3).



Scheme 1: Michael addition of 4-hydroxycoumarins **1** to α,β-unsaturated enones **2**.

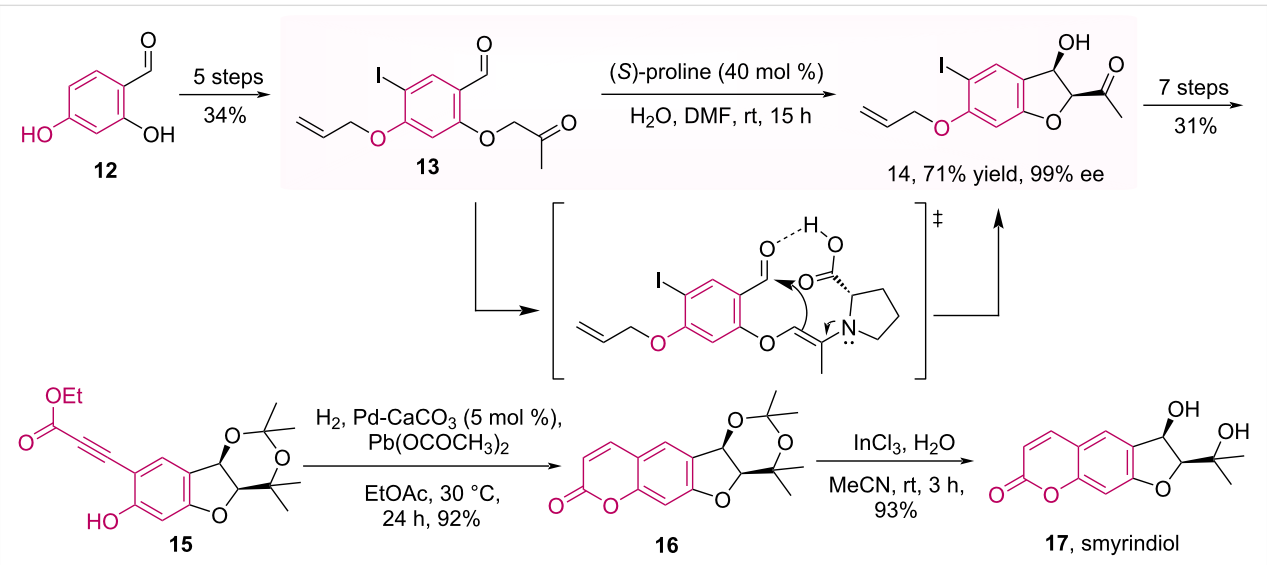


Scheme 2: Organocatalytic conjugate addition of 4-hydroxycoumarin **1** to α,β-unsaturated aldehydes **2** followed by an IMCR.



Scheme 3: Synthesis of 3,4-dihydrocoumarin derivatives **10** through decarboxylative and dearomatizative cascade reaction.

Using a completely different strategy from the above discussed, in which the coumarin core was the starting material in the asymmetric organocatalyzed reaction, the Enders group described the use of (*S*)-proline as catalyst in an intramolecular aldol reaction, enabling a new strategy to obtain coumarin natural products [34]. As for example, the total synthesis of (+)-smyrindiol (**17**), a linear dihydrofuranocoumarin isolated from the roots of *Smyrniopsis aucheri*, was developed [35]. The 5-enolexo aldol key step of this synthesis was performed using 40 mol % of (*S*)-proline and the desired product **14** was obtained in good yield (71%), and high diastereo- and enantioselectivities (Scheme 4). Moreover, the natural product **17** was obtained in 15 steps with 6% overall yield.

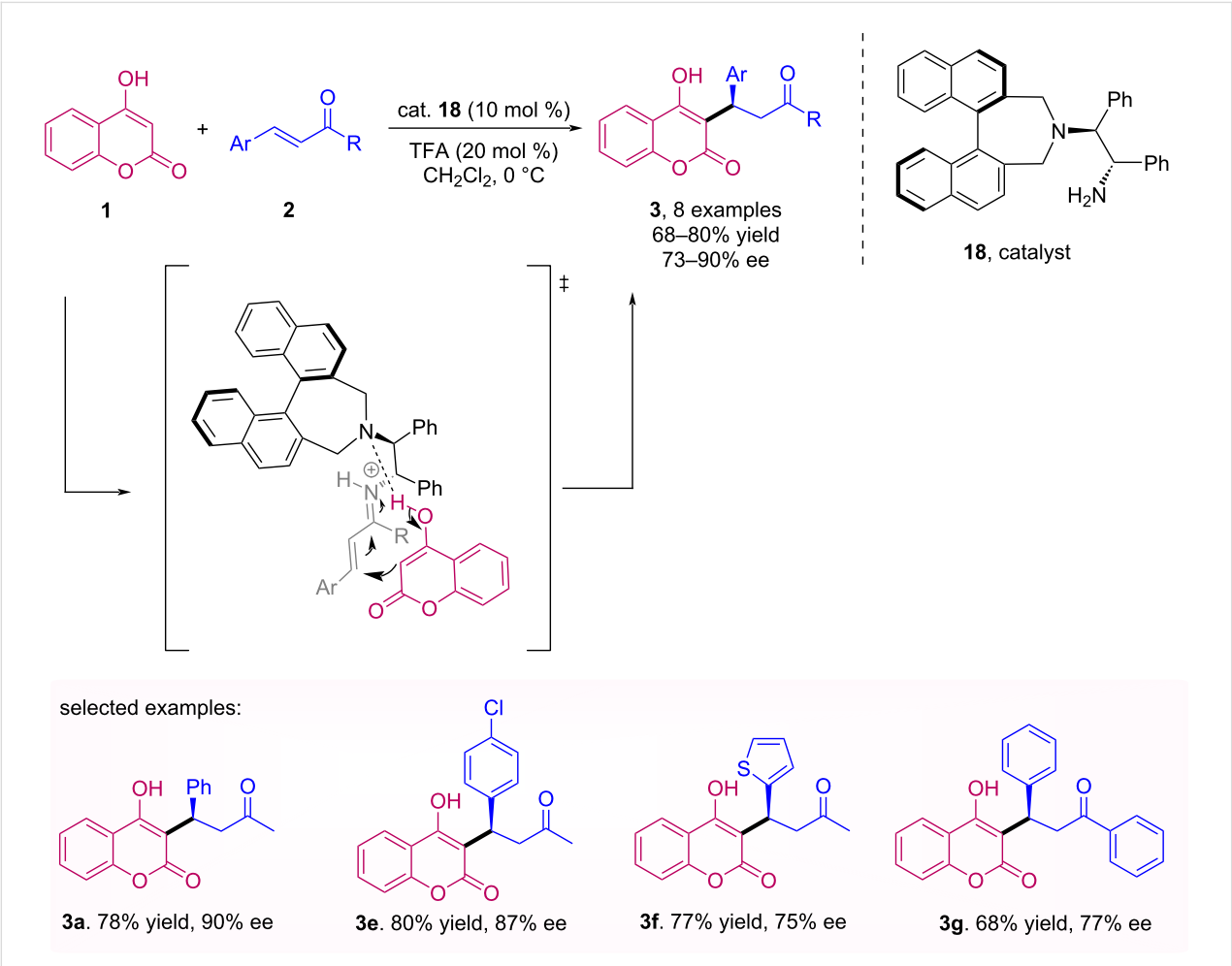


Scheme 4: Total synthesis of (+)-smyrindiol (**17**).

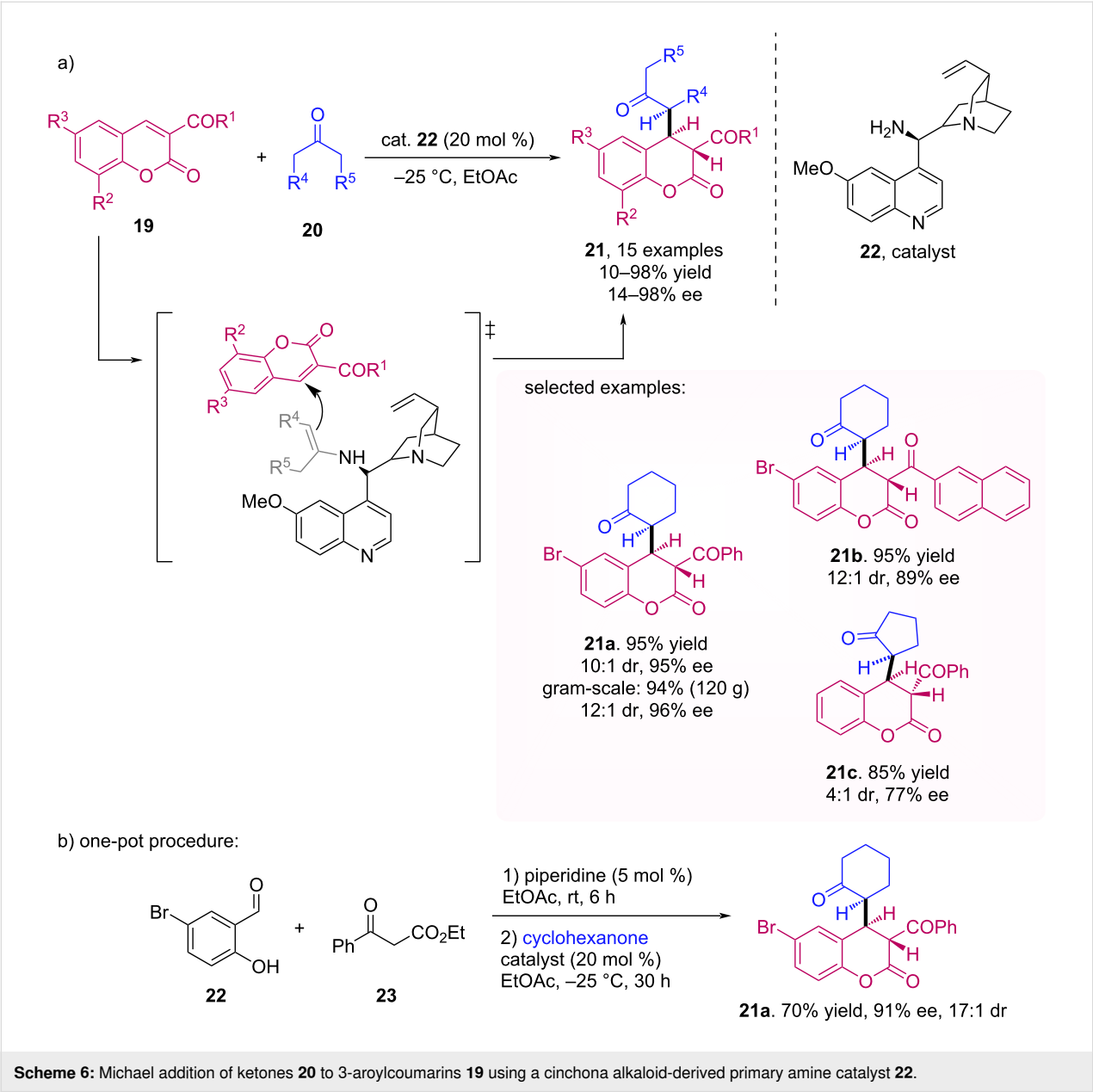
Although chiral secondary amines have proved to be particularly useful catalysts, primary amines as organocatalysts in asymmetric synthesis have also played a significant role [36]. For instance, Kim et al. described the enantioselective Michael addition of 4-hydroxycoumarin (**1**) by the *Re* face of the enones **2** through a bifunctional modified binaphthyl organocatalyst **18** with primary amine [37]. The reaction occurs through the activation of the enone substrate by formation of an iminium ion intermediate and, in the presence of an acid additive, provides coumarin derivatives **3** with good to excellent yields and moderate to good enantiomeric excesses (Scheme 5). The authors highlighted that the employed organocatalyst **18** is an alternative to those of squaramide and thiourea commonly used with coumarins.

In 2013, Lee et al. reported the enantioselective Michael addition of ketones **20** to 3-aroylcoumarins **19** [38]. For this transformation, the authors used a cinchona alkaloid-derived primary amine catalyst **22** (Scheme 6a). The study was performed with cyclic and acyclic ketones **20** and various 3-aroylcoumarins **19** and the desired products **21** were obtained with good to excellent yields and enantiomeric excesses. Besides, the one-pot synthesis of coumarins followed by the Michael addition step was proven to be a good alternative, affording the desired product with excellent yield and ee. The applicability of the methodology was also demonstrated by a gram-scale experiment, affording the desired product **21a** with excellent yield and ee (Scheme 6b).

Ren et al. reported an enantioselective reaction of cyclopent-2-enone-derived Morita–Baylis–Hillman (MBH) alcohols **24** with 4-hydroxycoumarins **1** catalyzed by a chiral primary amine derived from dihydrocinchonine **26** in combination with trifluoracetic acid (TFA) as Brønsted acid [39]. The reaction provides pyranocoumarins **25** with three vicinal stereogenic centers in high regio-, diastereo- and enantioselectivities through a tandem allylic alkylation/intramolecular oxa-Michael addition (Scheme 7).



Scheme 5: Michael addition of 4-hydroxycoumarin (**1**) to enones **2** through a bifunctional modified binaphthyl organocatalyst **18**.

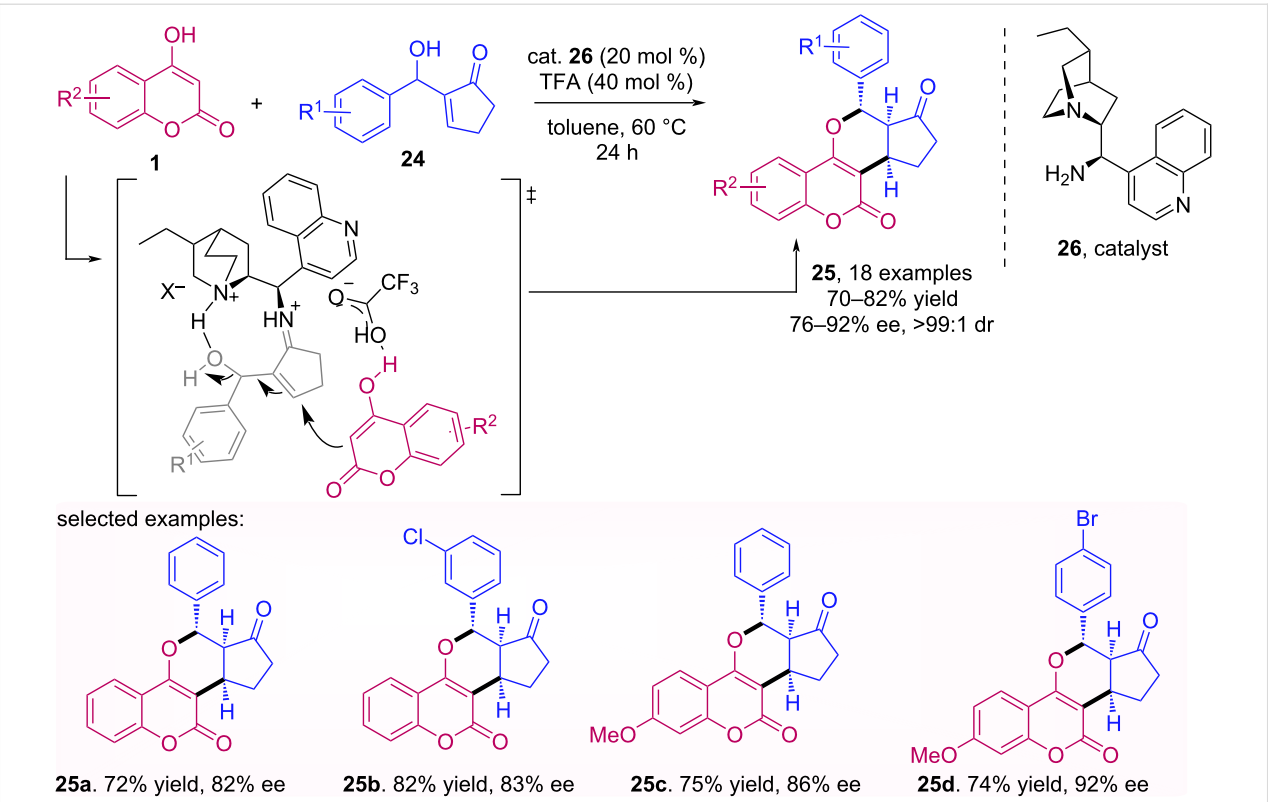


Scheme 6: Michael addition of ketones **20** to 3-aroylcoumarins **19** using a cinchona alkaloid-derived primary amine catalyst **22**.

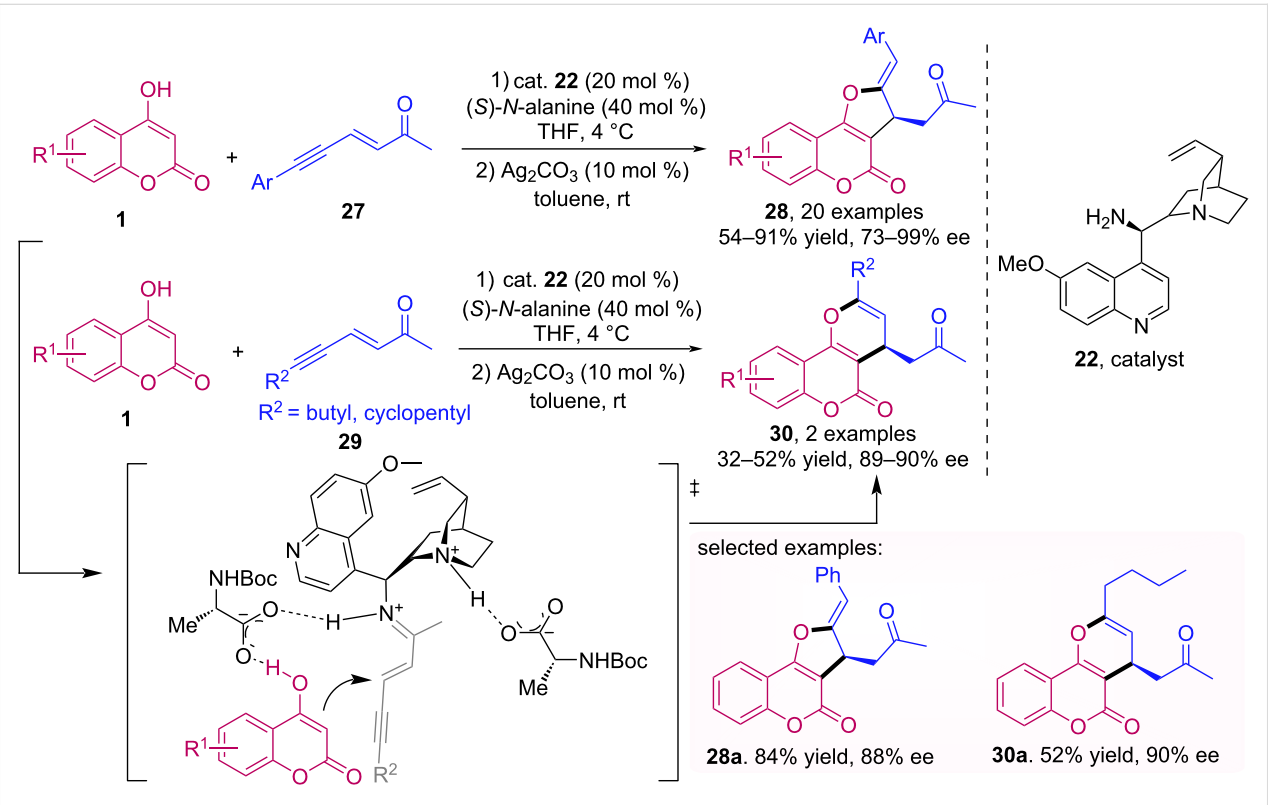
A stereoselective one-pot procedure for the synthesis of five-membered annulated coumarins **28** was described by the group of Enders [40]. Using dual catalysis, with a cinchona primary amine derivative **22** and silver carbonate, a series of functionalized coumarin derivatives **28** were obtained in good yields (up to 91%) and good to excellent enantioselectivities (up to 99% ee) via a Michael addition/hydroalkoxylation reaction (Scheme 8). Interestingly, when alkyl substituted substrates **29** were employed, the corresponding six-membered annulated coumarins **30** were obtained.

The synthesis of (*R*)-warfarin (**3a**) was described by Herrera et al. for the first time using primary aromatic diamines **31** as organocatalysts. The application of this class of catalysts for the Michael asymmetric addition of 4-hydroxycoumarins **1** to enones **2** is interesting from the point of view of organocatalysis, since the presence of two primary amines enables both the formation of an imine ion with the enone and activation of the hydroxycoumarin by hydrogen bonding [41]. Despite the long reaction time (3 days), the desired products **3** were obtained with good to excellent yields and moderate enantiomeric excesses (Scheme 9).

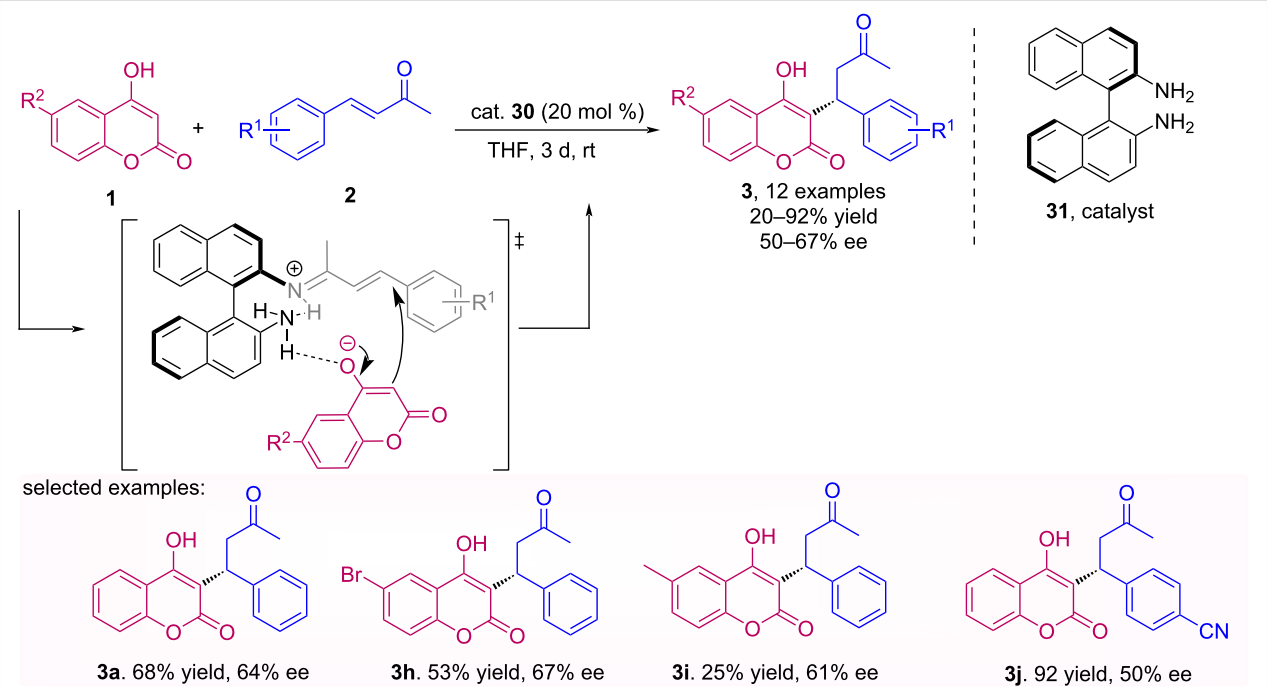
A new organocatalyst was synthesized by Kumagai et al. and applied in the Michael addition of 4-hydroxycoumarin **1** with α,β-unsaturated ketones **2** [42]. This chiral primary amino



Scheme 7: Enantioselective reaction of cyclopent-2-enone-derived MBH alcohols **24** with 4-hydroxycoumarins **1**.



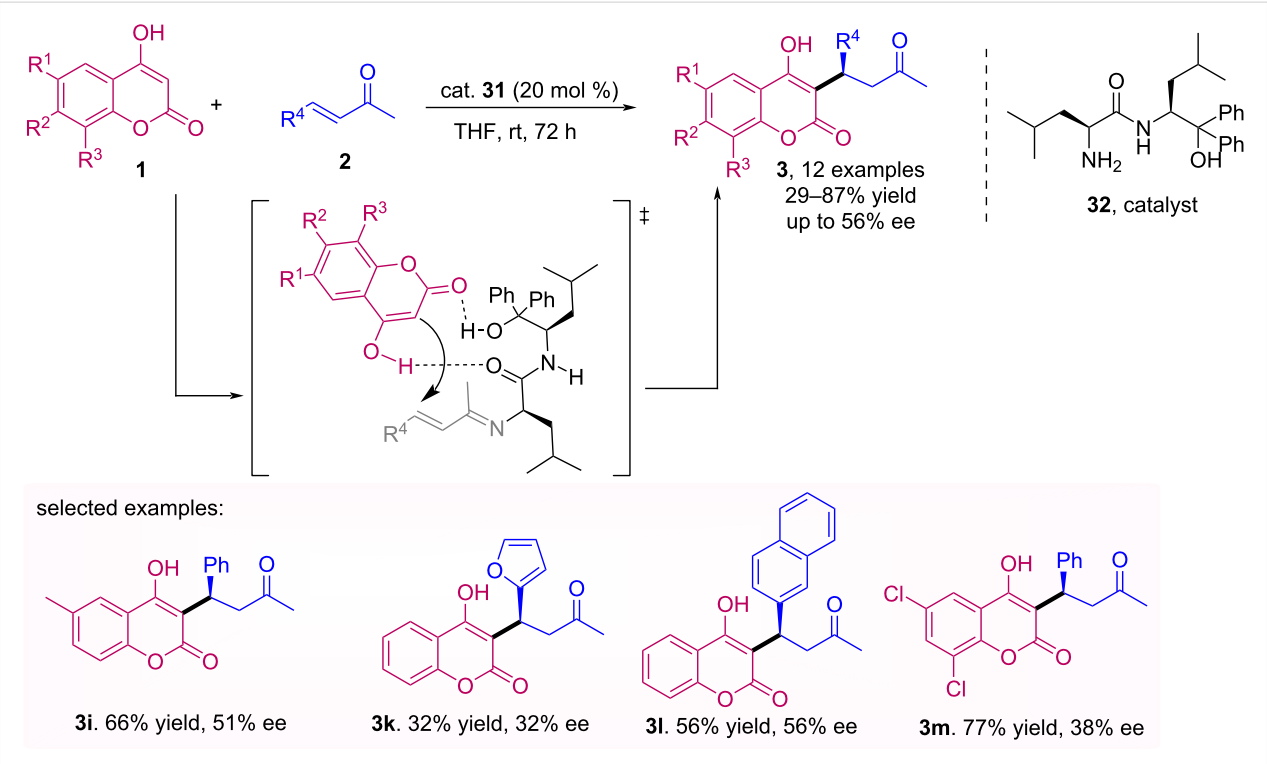
Scheme 8: Sequential Michael addition/hydroalkoxylation one-pot approach to annulated coumarins **28** and **30**.



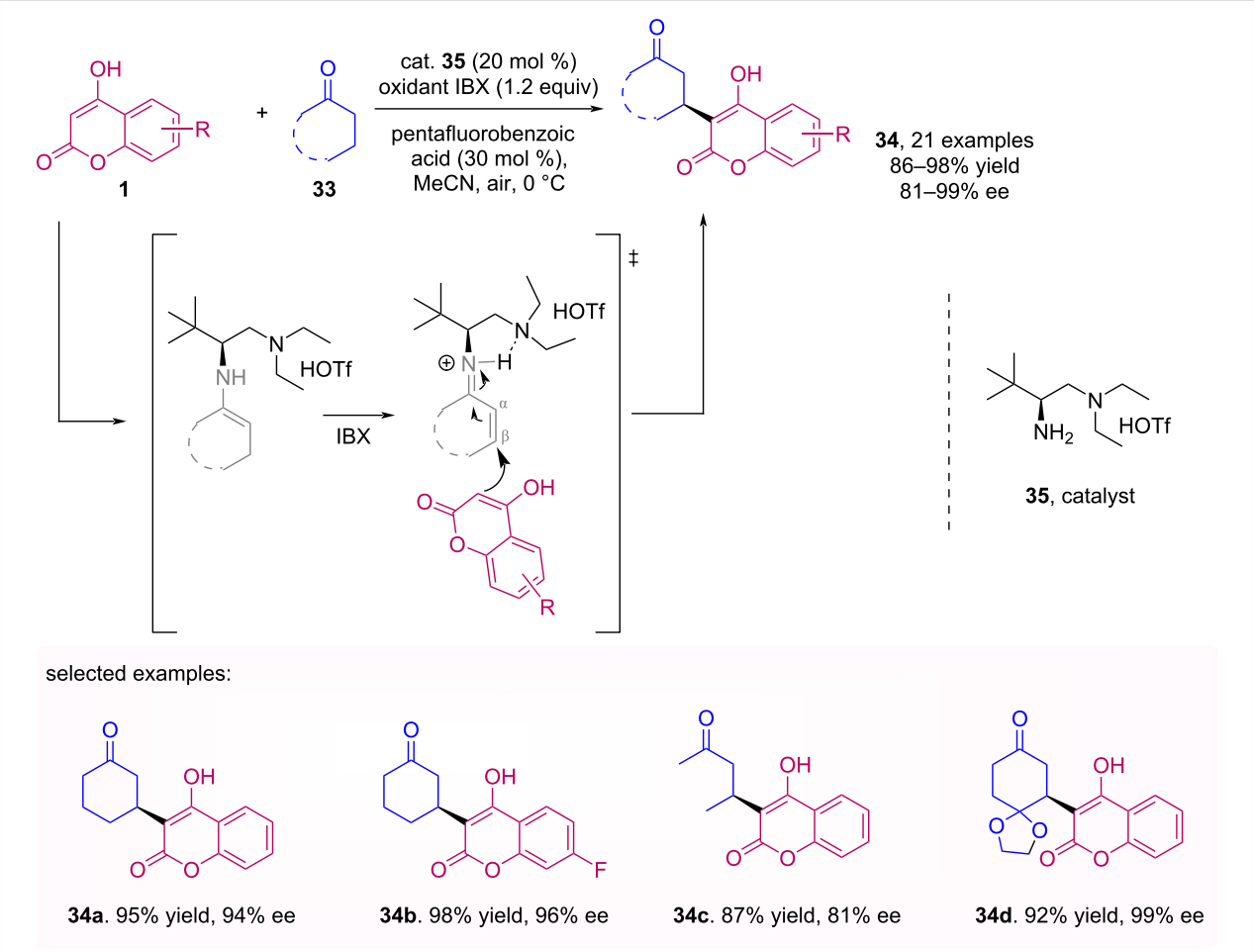
Scheme 9: Michael addition of 4-hydroxycoumarins **1** to enones **2** using a binaphthyl diamine catalyst **31**.

amide organocatalyst **32** afforded the desired products **3**, including warfarin (**3a**) in 86% yield, although in moderate enantioselectivity (up to 56% ee) (Scheme 10).

A catalytic asymmetric β-C–H functionalization of ketones **33** with 4-hydroxycoumarins **1** was developed by Zhu et al. [43]. The enamine, formed via reaction of the aminocatalyst **35** with



Scheme 10: Asymmetric Michael addition of 4-hydroxycoumarin **1** with α,β-unsaturated ketones **2** catalyzed by a chiral primary amino amide **32**.



Scheme 11: Catalytic asymmetric β-C–H functionalization of ketones via enamine oxidation.

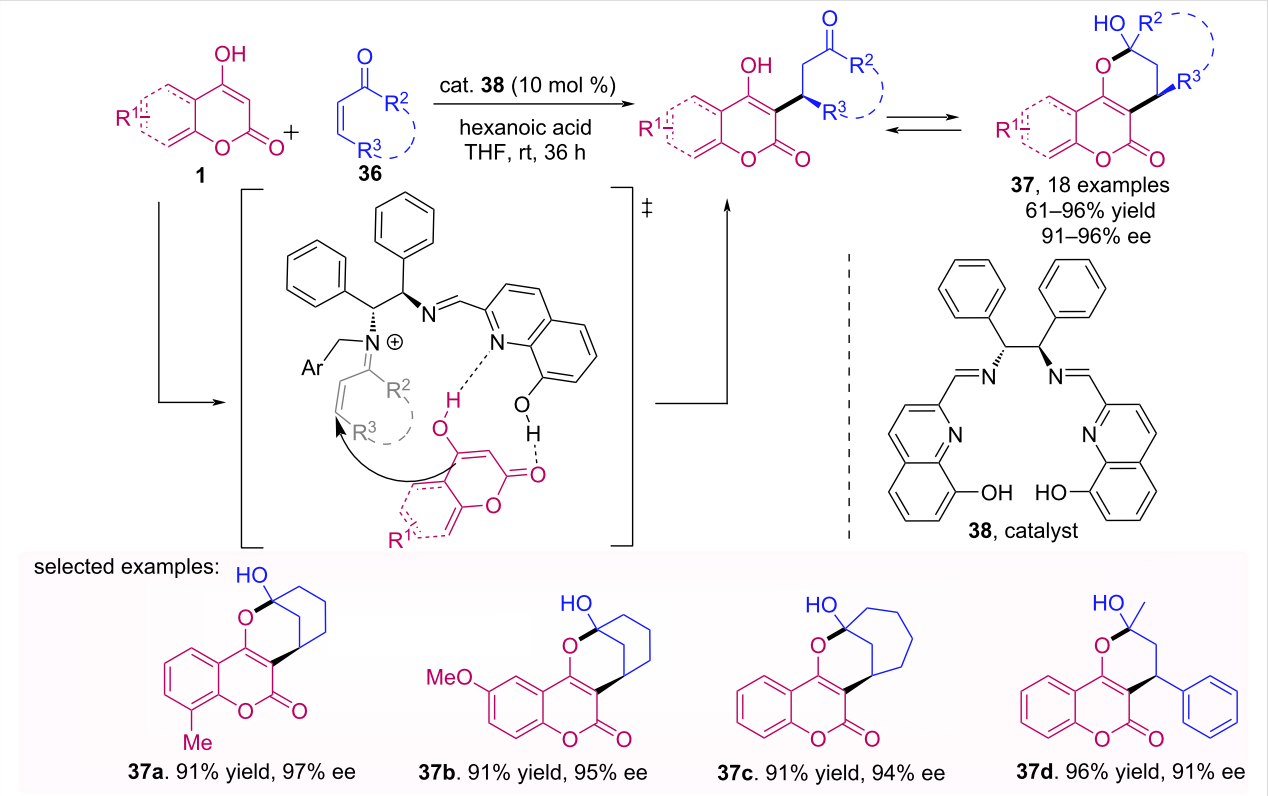
the ketone, is oxidased by IBX resulting in the electrophilic imine, which in turn undergoes a nucleophilic addition of the hydroxycoumarin. The procedure allowed obtaining products **34** with excellent yields and enantiomeric excesses (Scheme 11).

Zhu et al. described the asymmetric Michael addition of substituted 4-hydroxycoumarins (**1**) to cyclic enones **36**, using an in situ formed organocatalyst [44]. The proposed transition state includes activations of the enone via an iminium ion and the coumarin by hydrogen bonding. A series of optically active polycyclic pyranocoumarin derivatives **37** was obtained in high yields with excellent enantioselectivities (up to 97% ee) (Scheme 12).

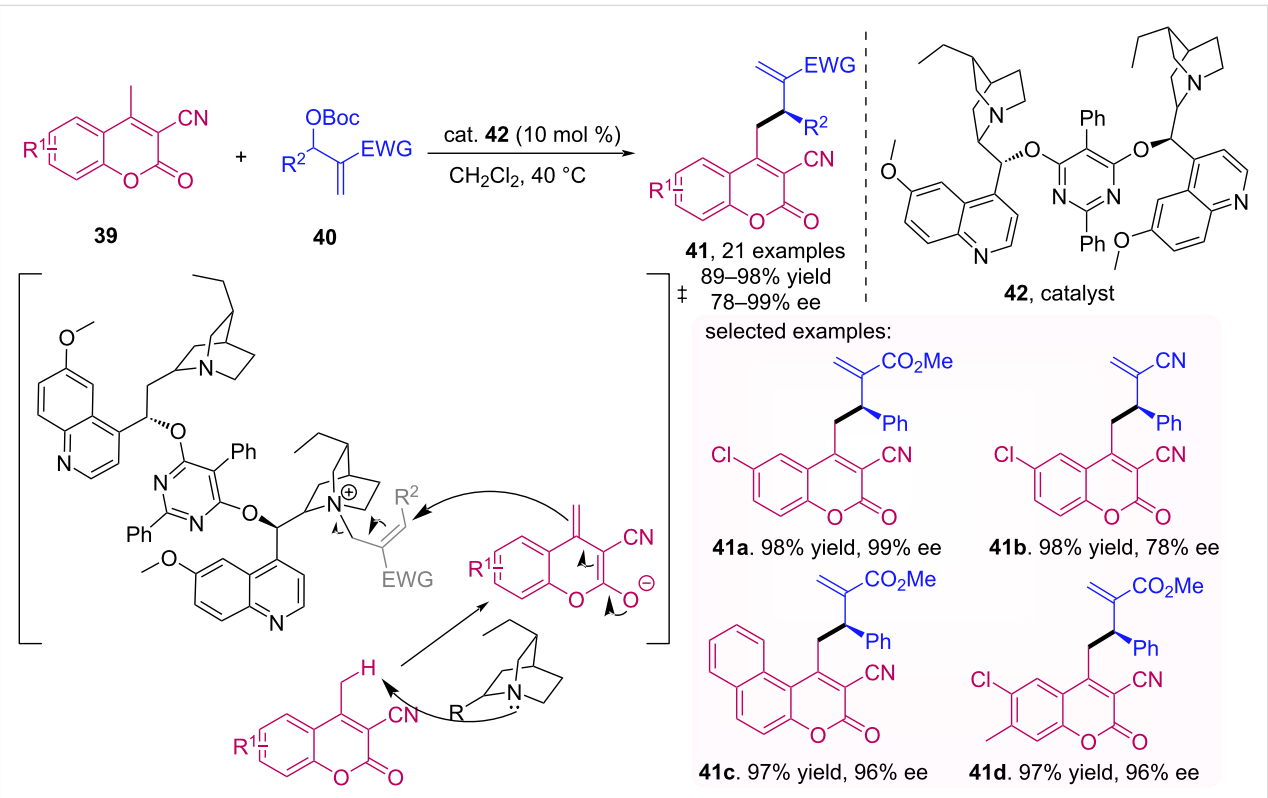
Kowalczyk and Albrecht described an allylic alkylation reaction between 3-cyano-4-methylcoumarins **39** and Morita–Baylis–Hillman (MBH) carbonates **40** [45]. In this case, the catalyst $(DHQ)_2PYR$ **42** activates the MBH substrate and generates the dienolate in the vinylogous coumarin moiety, acting as a base. After the nucleophilic substitution reaction between the coumarin and the activated MBH substrate, it is possible to obtain functionalized coumarins **41** (Scheme 13). Furthermore, the absolute configuration of the stereogenic center was determined by X-ray crystallography.

The enantioselective synthesis of cyclopropa[*c*]coumarins **45** was described by Sun et al. [46]. In this method, the catalyst $(DHQ)_2PYR$ **42** reacts with *tert*-butyl 2-bromoacetate, and then an ylide is formed by the base Cs_2CO_3. After a conjugated addition of this intermediate to the coumarin **43** followed by nucleophilic substitution, the corresponding cyclopropa[*c*]coumarins are formed with good to excellent yields and enantioselectivities (Scheme 14).

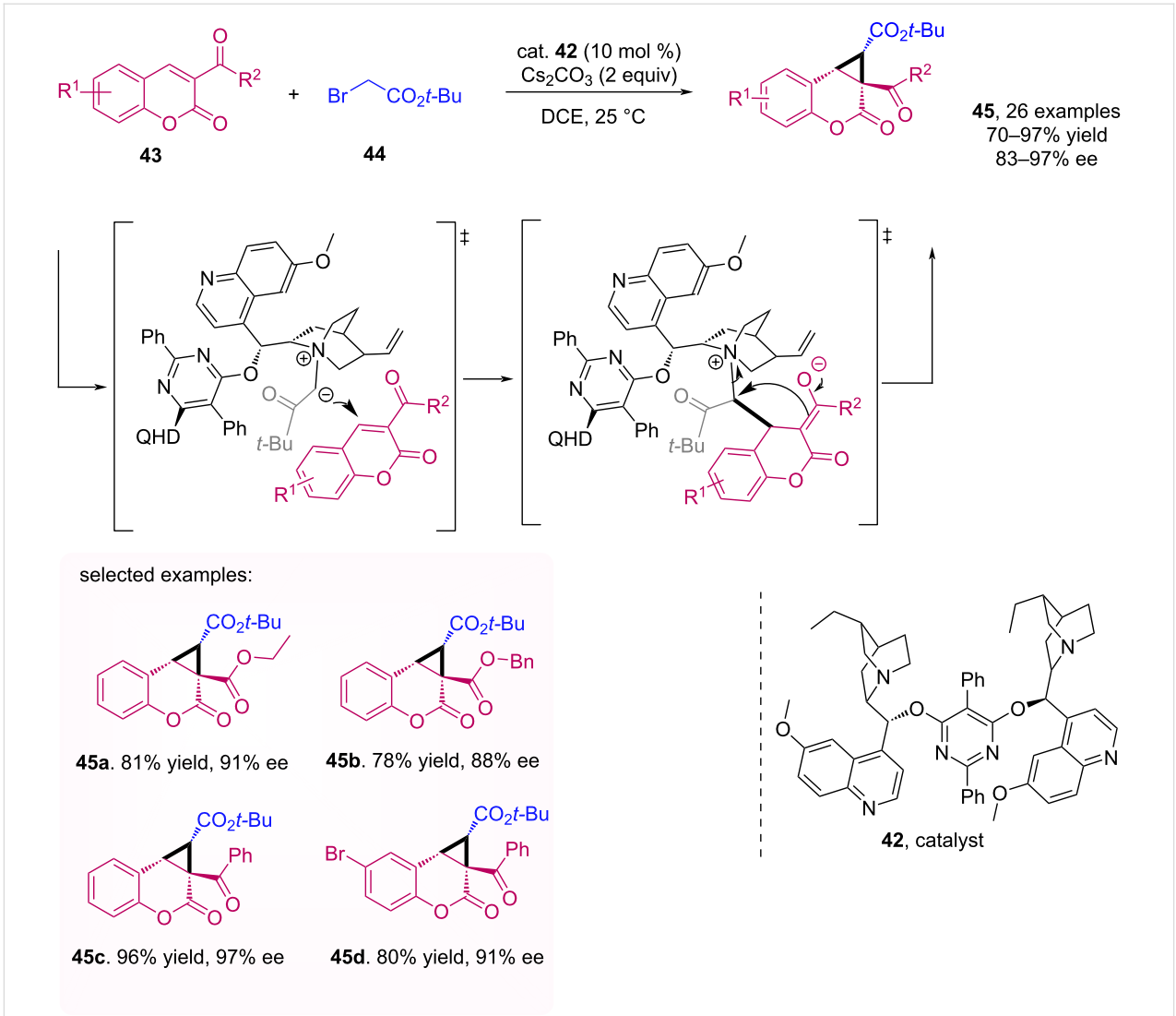
N-heterocyclic carbenes (NHC) have also been successfully used as organocatalysts, in particular, to obtain coumarin derivatives [47]. In this context, Yetra et al. reported a NHC catalyzed reaction of 2-bromoenals **46** with various heterocyclic C–H acids, resulting in the synthesis of coumarin/quinolinone



Scheme 12: Enantioselective synthesis of polycyclic coumarin derivatives **37** catalyzed by an primary amine-imine catalyst **38**.



Scheme 13: Allylic alkylation reaction between 3-cyano-4-methylcoumarins **39** and MBH carbonates **40**.



Scheme 14: Enantioselective synthesis of cyclopropa[*c*]coumarins **45**.

fused dihydropyranones and dihydropyridinones **47**. The reaction optimization and the scope and limitations study were carried out using an achiral NHC, but the enantioselective version was also performed using 4-hydroxycoumarin (**1**) with the chiral catalyst **48**, as shown in Scheme 15 [48].

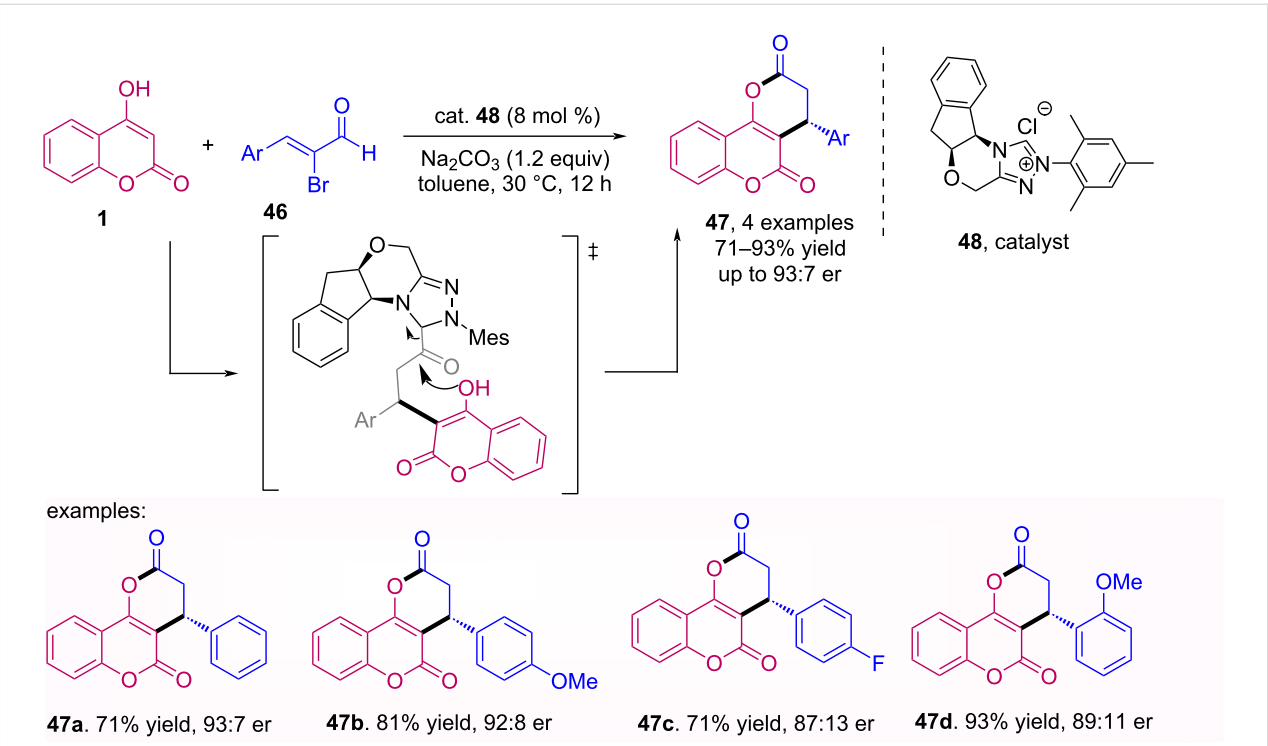
The enantioselective synthesis of dihydrocoumarins **51** from an inverse demand [4 + 2] cycloaddition of ketenes **50** with *o*-quinone methides **49** using carbene catalyst (NHC) **52** was described by Ye and co-workers [49].This transformation resulted in products with moderate to excellent yields and enantiomeric excesses as shown in Scheme 16.

Enders et al. developed the enantioselective synthesis of cyclopenta[*c*]-fused chromenones **54** starting from hydroxylated malonate **53** with enals **2** [50]. The reaction stands out for its good to excellent yields and enantioselectivities when subjected to four sequential reactions mediated by a cooperative catalysis of a NHC organocatalyst with LiCl in the presence of DPQ as an oxidant, as shown in Scheme 17.

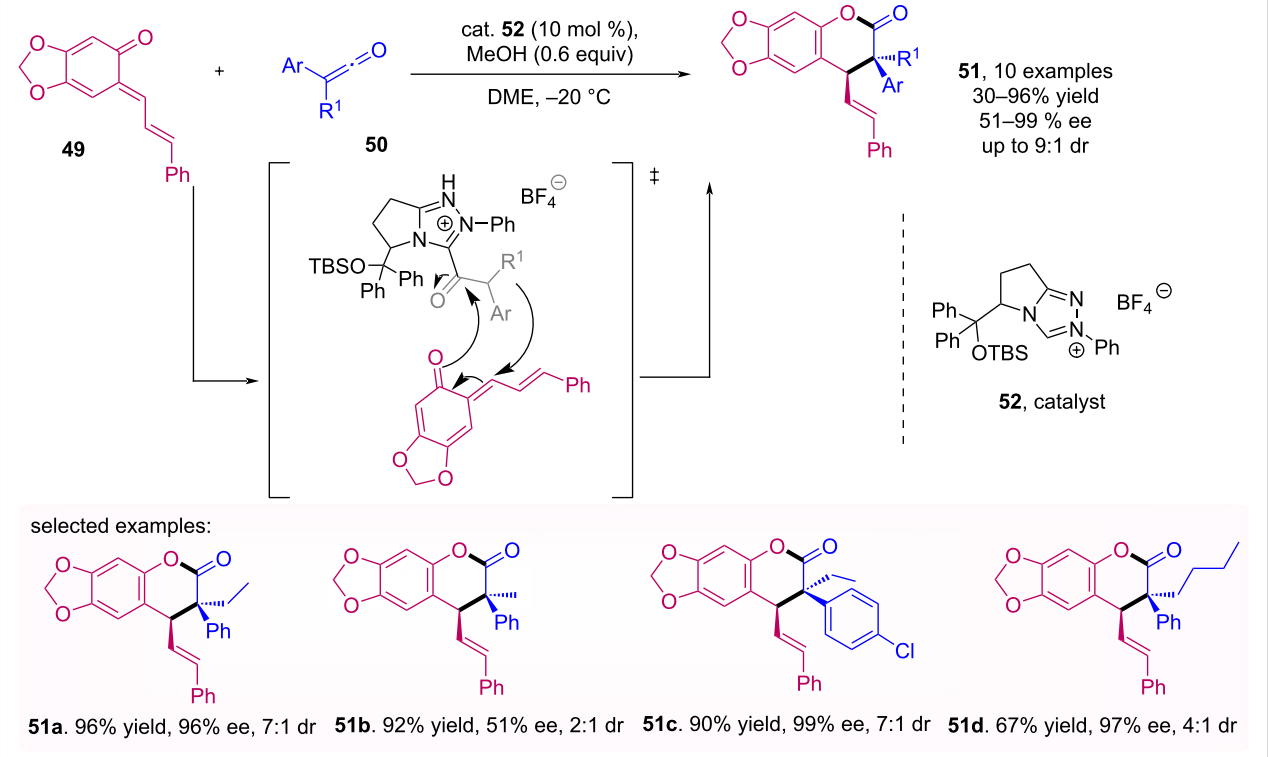
Recently, Chen et al. used a NHC catalyst **59** in γ,δ-difunctionalization of coumarins **56** through an oxidative [4 + 2] cycloaddition with unsaturated aldehydes **57** [51]. The methodology draws attention for the wide variety of products **58** obtained with moderate to excellent yields and enantiomeric excesses (Scheme 18).

Activation via noncovalent bonding

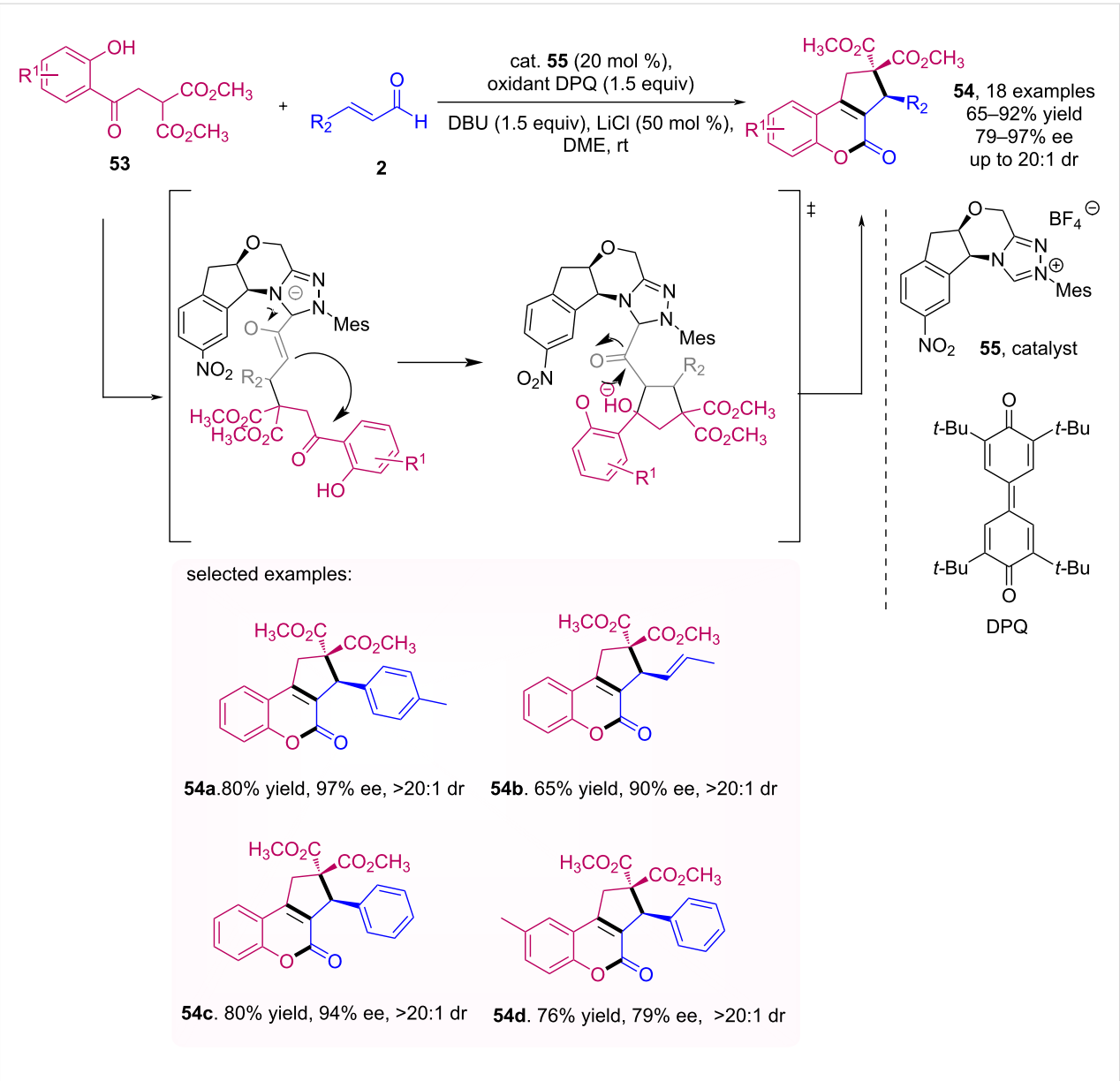
Besides the activation mode via a covalent bond, as discussed above, the organocatalysts may also proceed by noncovalent activation, in which a hydrogen bond or an ion pair is formed. A



Scheme 15: NHC-catalyzed lactonization of 2-bromoenals **46** with 4-hydroxycoumarin (**1**).



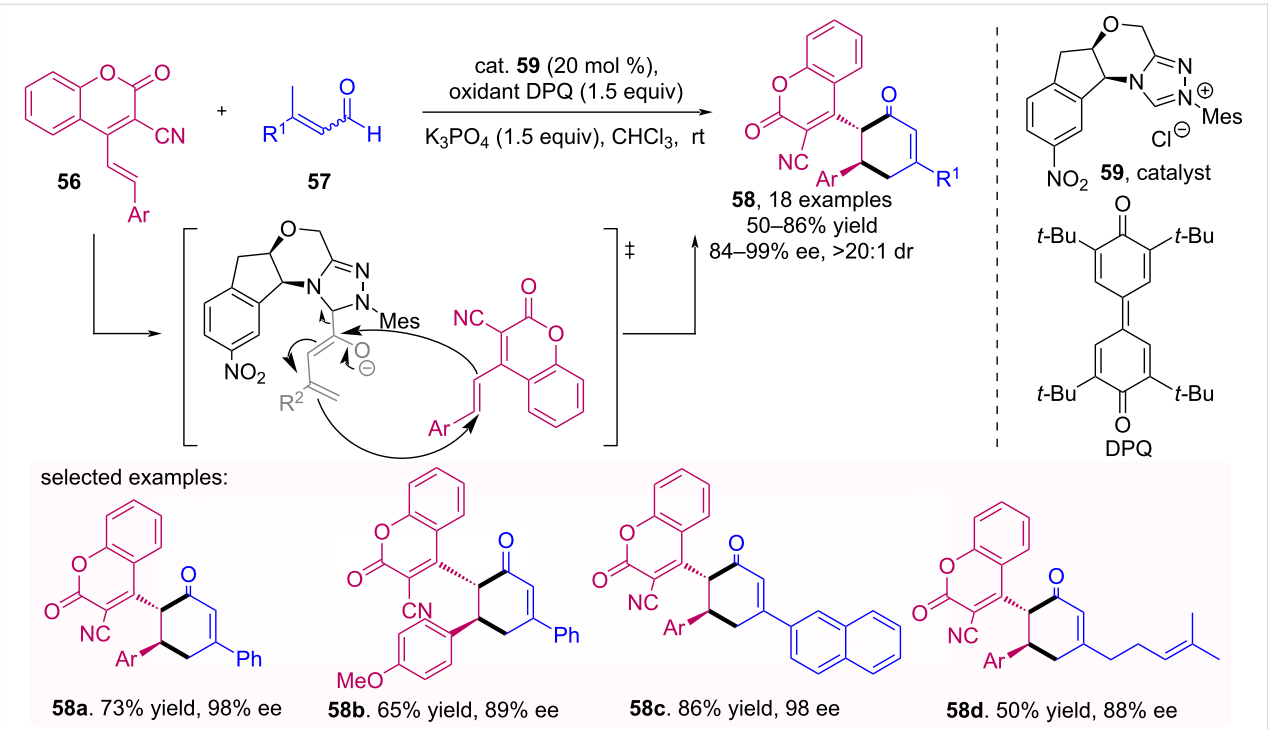
Scheme 16: NHC-catalyzed enantioselective synthesis of dihydrocoumarins **51**.



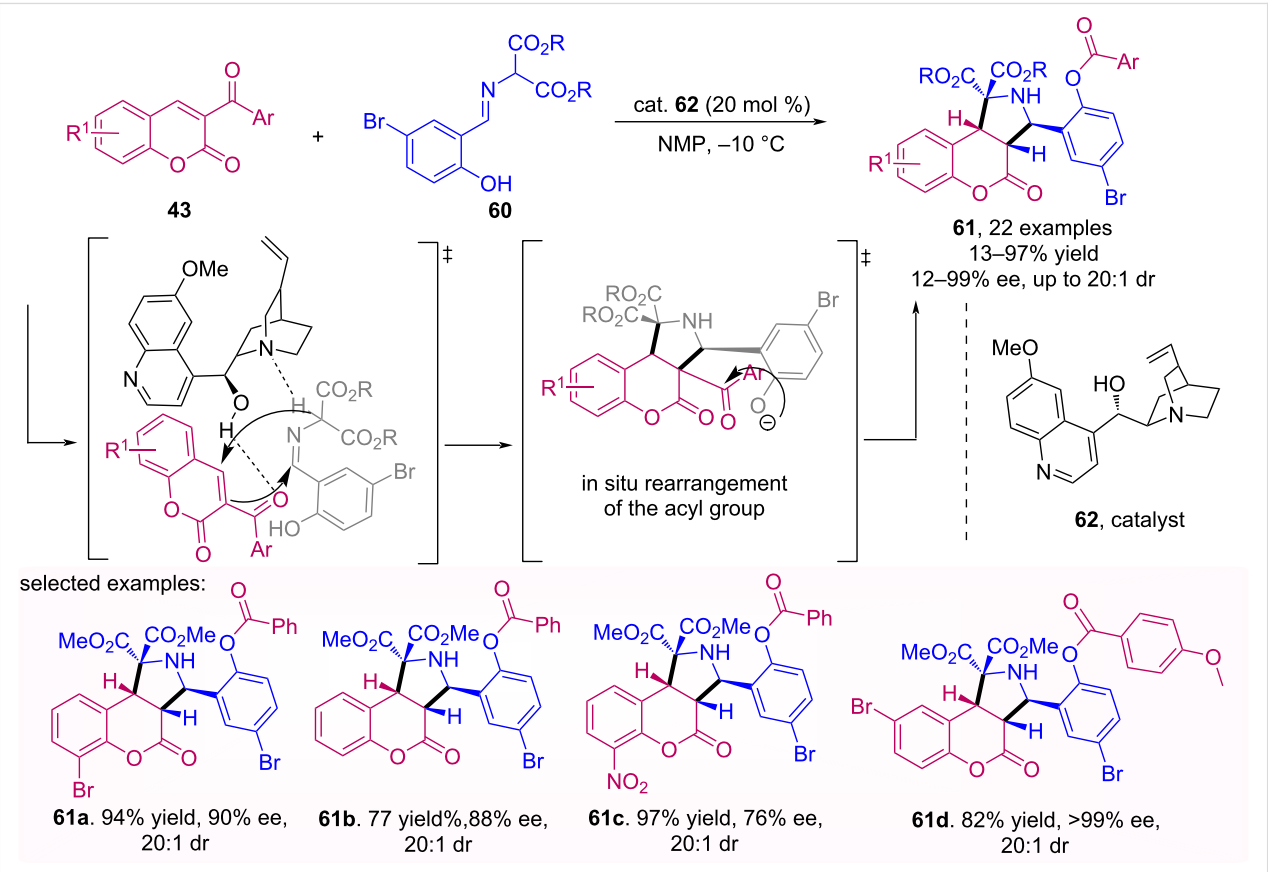
Scheme 17: Domino reaction of enals **2** with hydroxylated malonate **53** catalyzed by NHC **55**.

broad variety of mono- and bifunctional chiral hydrogen-bonding organocatalysts has been developed, in special using cinchona alkaloid derivatives [52]. In this sense, Lin and colleagues proposed an asymmetric [3 + 2] cycloaddition employing a coumarin dipolarophile **43** with azomethine ylides **60** organocatalyzed by quinidine (**62**) for the formation of fused pyrrolidine compounds through activation of the coumarin substrate by hydrogen bonding [53]. The methodology enabled a high diastereoisomeric control and in most cases with good enantioselectivity of the products. It becomes even more attractive, since it allows an in situ rearrangement of the acyl group that can be used in other functionalization methodologies. However, it presents a limitation relative to the presence of a carbonyl group in the coumarin, since it makes a hydrogen bond with the organocatalyst and when it is replaced by other electron-withdrawing groups, the hydrogen bond formation is blocked, consequently there is no product formation (Scheme 19).

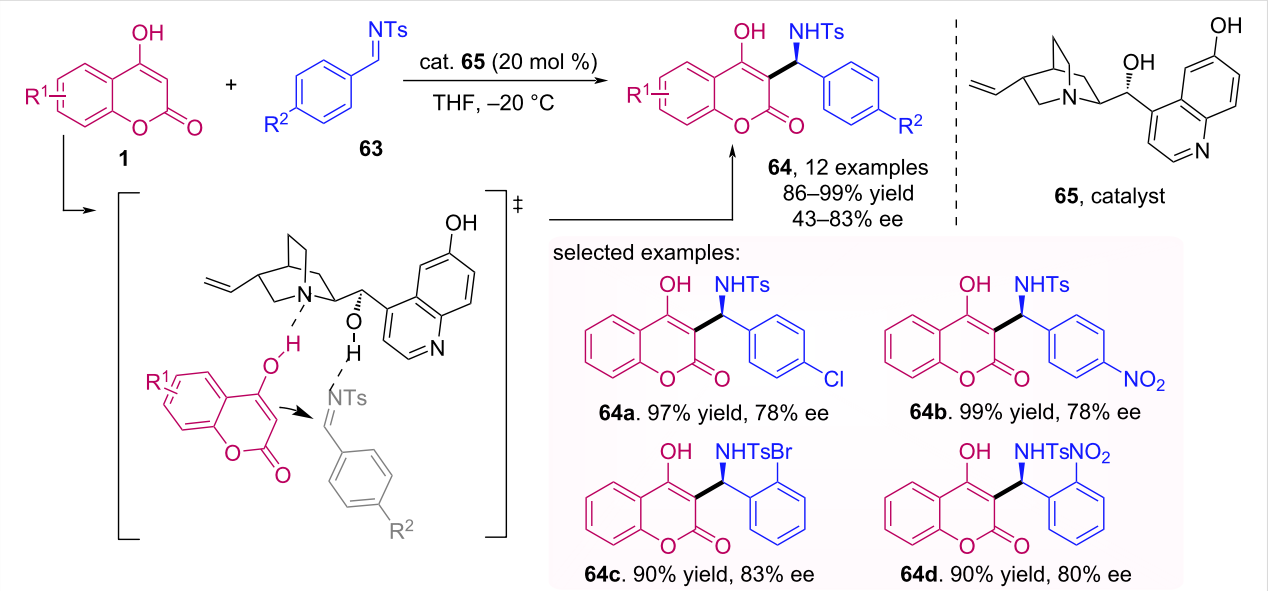
Lin et al. described an organocatalyzed Mannich reaction between 4-hydroxycoumarins **1** and aromatic imines **63** for the synthesis of α-benzylaminocoumarins **64** [54]. Among the cinchona alkaloid derivatives evaluated in this reaction, cupreine (**65**) was found to be the best option in terms of yields and enantioselectivities (Scheme 20). Both electron-withdrawing and electron-donating substituents were well tolerated in either coumarin or imine portion, and electron-withdrawing



Scheme 18: Oxidative [4 + 2] cycloaddition of enals **57** to coumarins **56** catalyzed by NHC **59**.



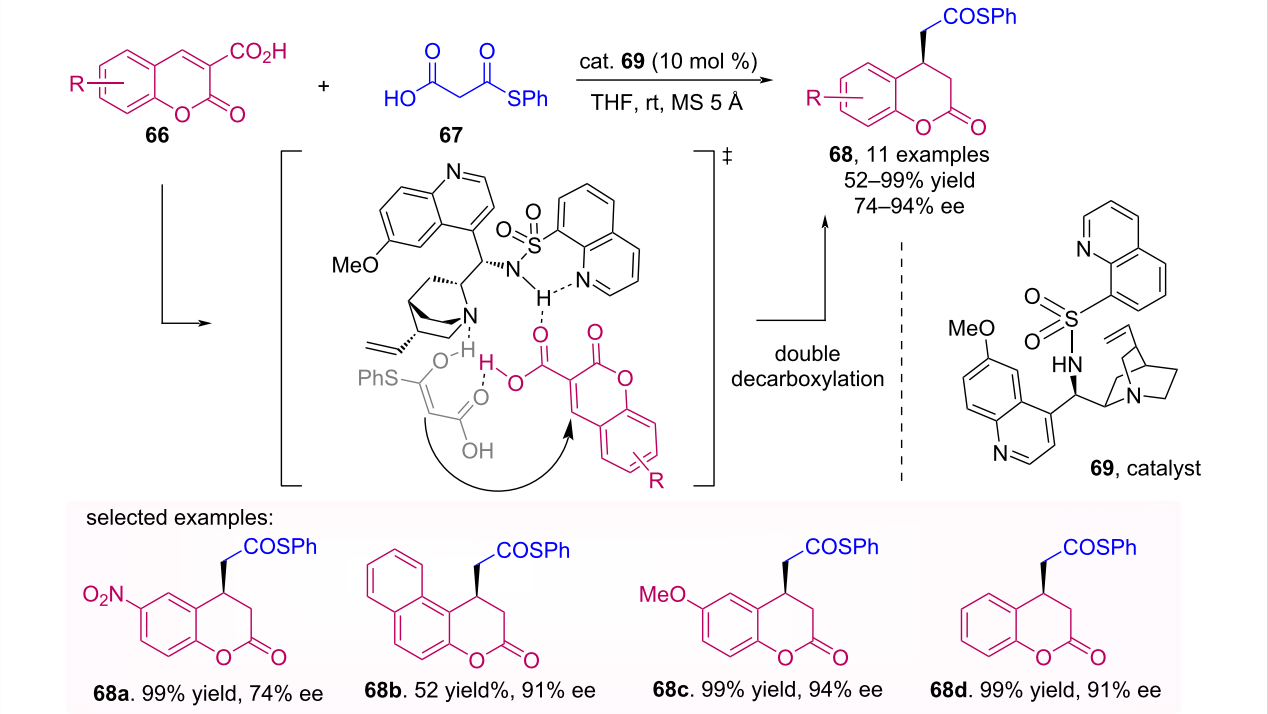
Scheme 19: Asymmetric [3 + 2] cycloaddition of coumarins **43** to azomethine ylides **60** organocatalyzed by quinidine **62**.



Scheme 20: Synthesis of α-benzylaminocoumarins **64** through Mannich reaction between 4-hydroxycoumarins (**1**) and aromatic imines **63** promoted by cupreine (**65**).

substituents at *ortho*-position of the imine phenyl ring afforded the corresponding products with excellent yields and moderated to good ee.

The asymmetric addition of malonic acid half-thioesters **67** to coumarins **66** using a sulphonamide organocatalyst **69** was reported by Nakamura et al. [55]. The hydrogen bond between the secondary amine and the coumarin carboxyl provides a nucleophilic addition on the *Re* face, and therefore resulting in products **68** with *R* absolute configuration, with moderate to excellent enantioselectivity followed by two decarboxylations (Scheme 21).

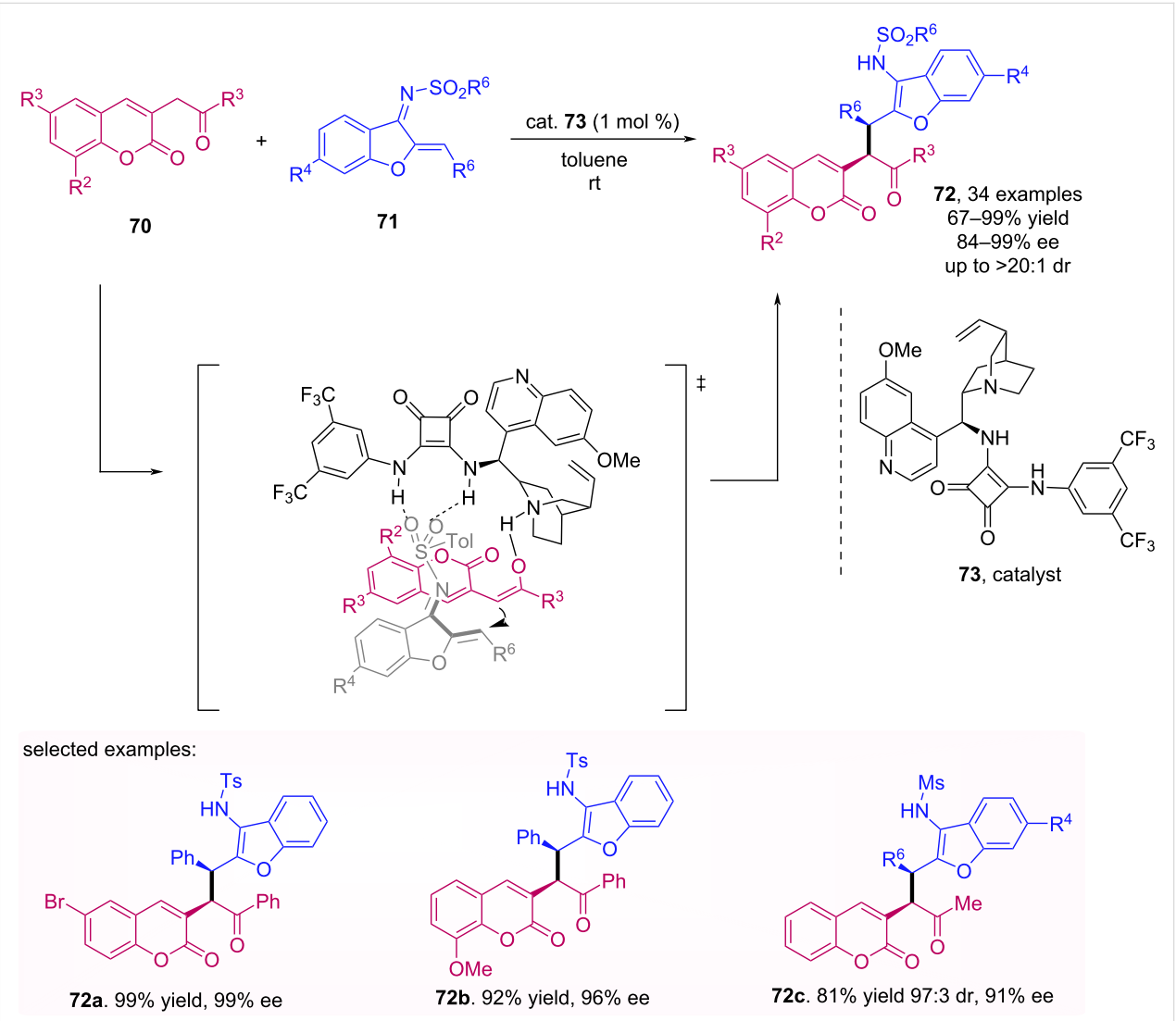


Scheme 21: Asymmetric addition of malonic acid half-thioesters **67** to coumarins **66** using the sulphonamide organocatalyst **69**.

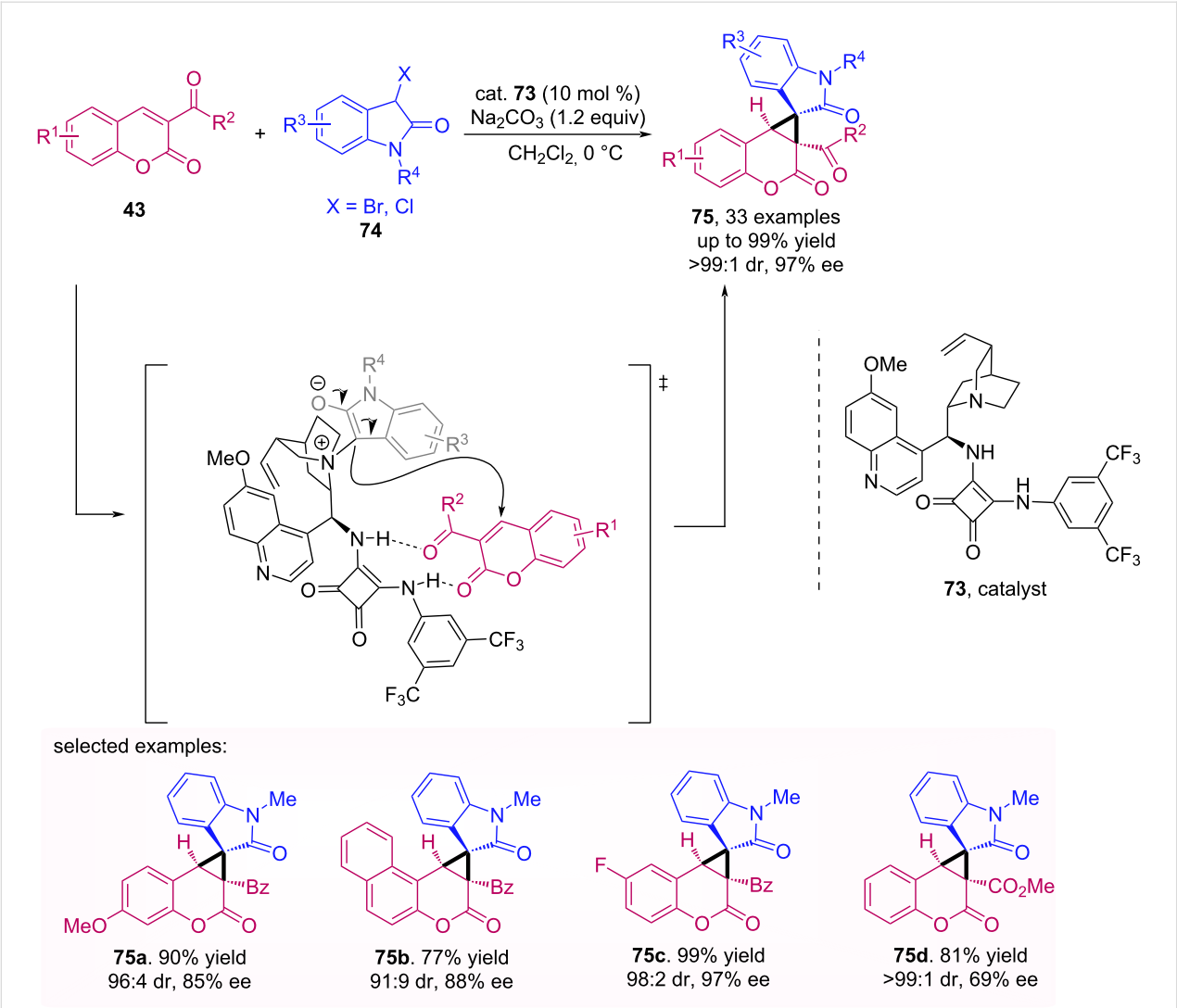
Huang's group has used azadienes to perform an enantioselective 1,4-addition to afford benzofuran-fused six-membered heterocycles with a squaramide catalyst [56]. Based on their previous work, the authors reported an enantioselective 1,4-addition of azadienes **71** to 3-homoacyl coumarins **70** to achieve benzofuran coumarin derivatives **72** [57]. It was possible to obtain good to excellent diastereo- and enantioselectivities by using a low amount of the catalyst, besides the high yield of the reaction. The best results were obtained using a squaramide cinchona alkaloid catalyst **73** in only 1 mol % loading. In addition, the reaction was also very efficient in a gram-scale experiment, which demonstrates the applicability of the method (Scheme 22).

More recently, Yuan et al. developed a methodology for the synthesis of spiroonxindole-cyclopropa[*c*]coumarins **75** through the cyclopropanation of 3-acylcoumarins **43** and 3-halooxindoles **74** [58]. The authors chose a quinine-derived squaramide catalyst **73** to perform the [2 + 1] cycloaddition. This catalyst reacts with 3-halooxindole, generating an ammonium salt which is deprotonated by a base, affording an ammonium ylide/enolate. Meanwhile, the *Re*-face attack is favored after interaction of squaramide portion of the catalyst with coumarin. Then, a Michael addition followed by intramolecular cyclization affords the desired product **75**, as shown in Scheme 23.

An enantioselective cascade synthesis of hydrocoumarin **78** mediated by squaramide catalyst with 9-amino-9-deoxy-epiquinine moiety **73** was reported by Albrecht et al. [59]. In this transformation, the authors developed a Michael addition of azlactones to 2-hydroxychalcones **76** followed by the opening of the azlactone **77** ring to form the product of interest, which



Scheme 22: Enantioselective 1,4-addition of azadienes **71** to 3-homoacyl coumarins **70**.



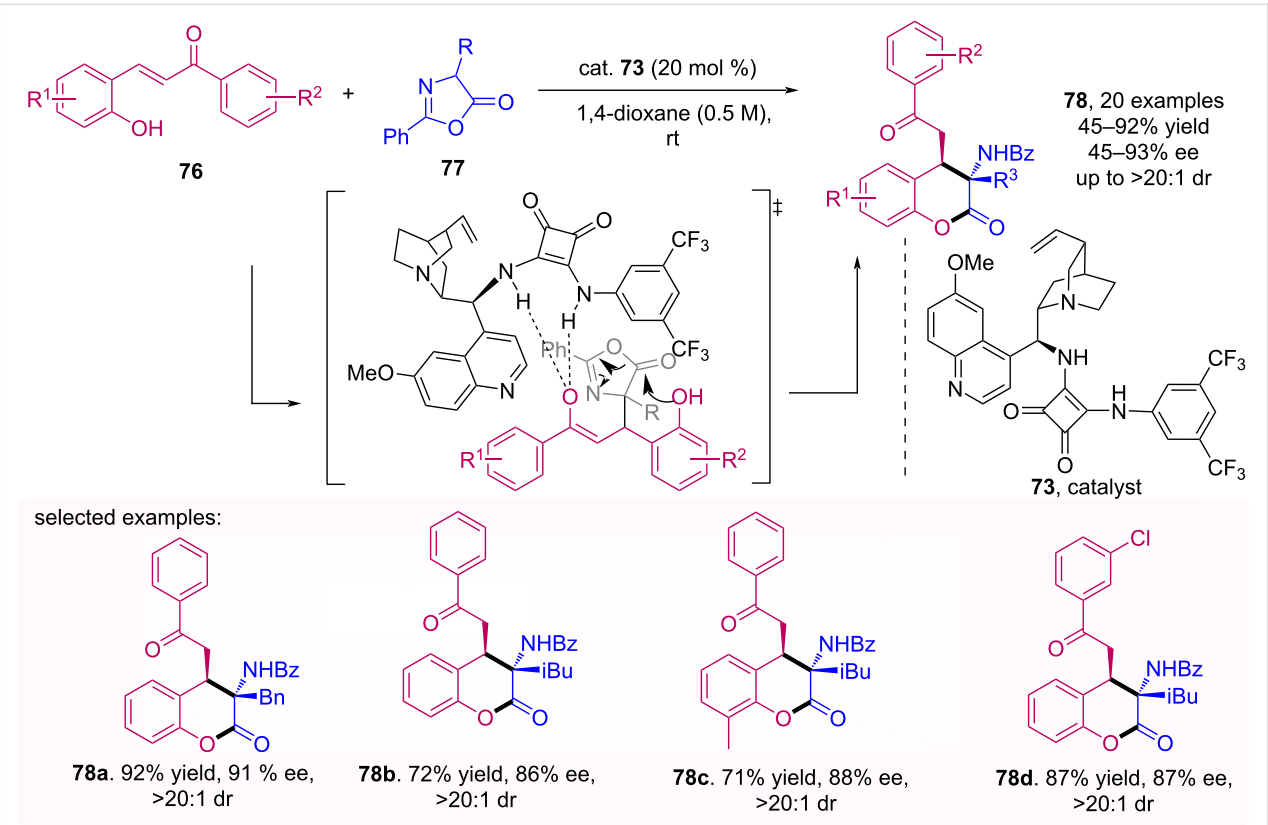
Scheme 23: Michael addition/intramolecular cyclization of 3-acylcoumarins **43** to 3-halooxindoles **74**.

could be obtained with moderate to excellent yields and enantioselectivities. The protocol used allowed obtaining hydrocoumarins with a wide structural variety and with a diastereoselective control, as shown in Scheme 24.

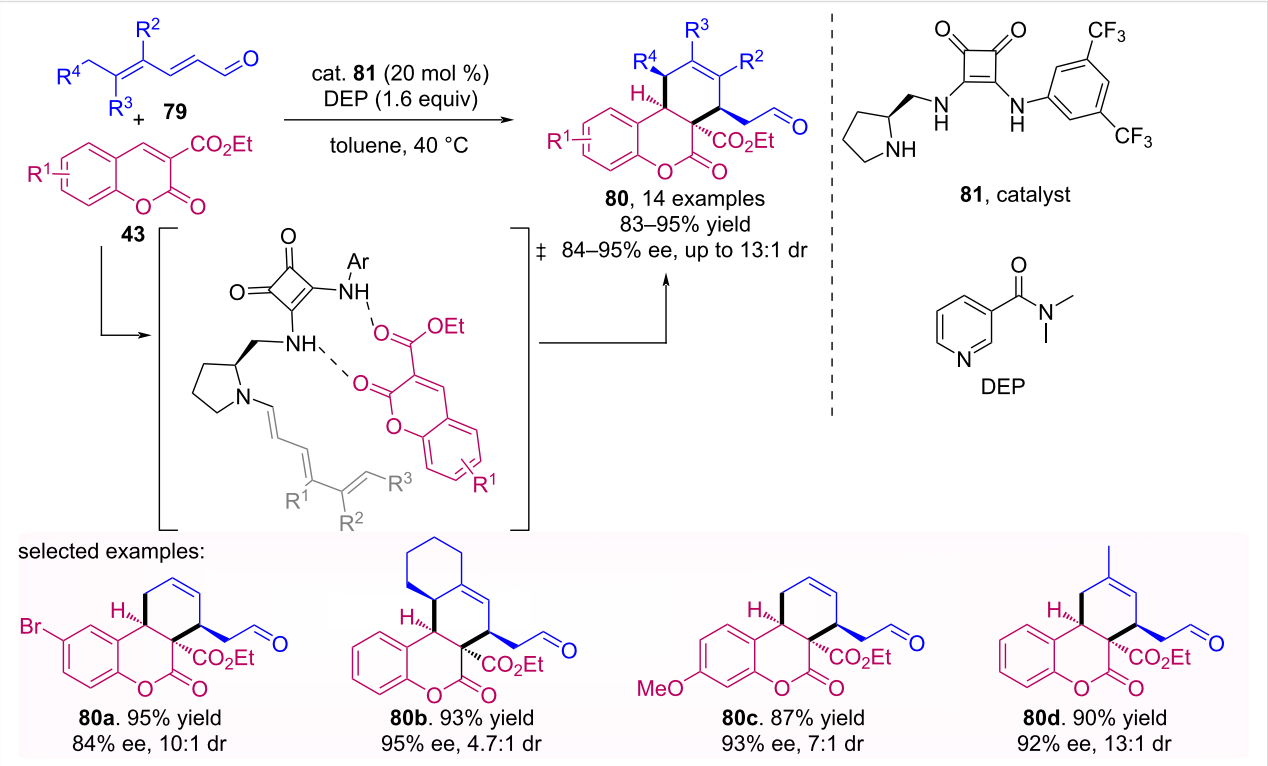
In 2016, Albrecht et al. [60] published the synthesis of 3,4-dihydrocoumarins **80** bearing a cyclohexene ring, through [4 + 2] cycloaddition between 2,4-dienals **79** and 3-coumarincarboxylates **43**. This stereoselective transformation was performed using a squaramide **81** derivative catalyst, which activates the aldehyde with the formation of an enamine intermediate and the coumarin through hydrogen bonding, as shown in Scheme 25.

An enantioselective one-pot synthesis of spiro[dihydrofurocoumarin/pyrazolone] **83** mediated by quinine and squaramide catalyst **84** was reported by Xu et al. [61]. The work draws attention for the wide range of compounds obtained with high diastereo- and enantioselectivity and moderate to excellent yields. The authors highlighted that the catalyst also contributes to cyclization, since subjecting the isolated Michael adduct to the second conditions with iodine and K_2CO_3 there is a decrease in yield and enantiomeric excess when compared to the one-pot procedure. The obtained products possess a (*R*)-configuration, determined by X-ray crystallography (Scheme 26).

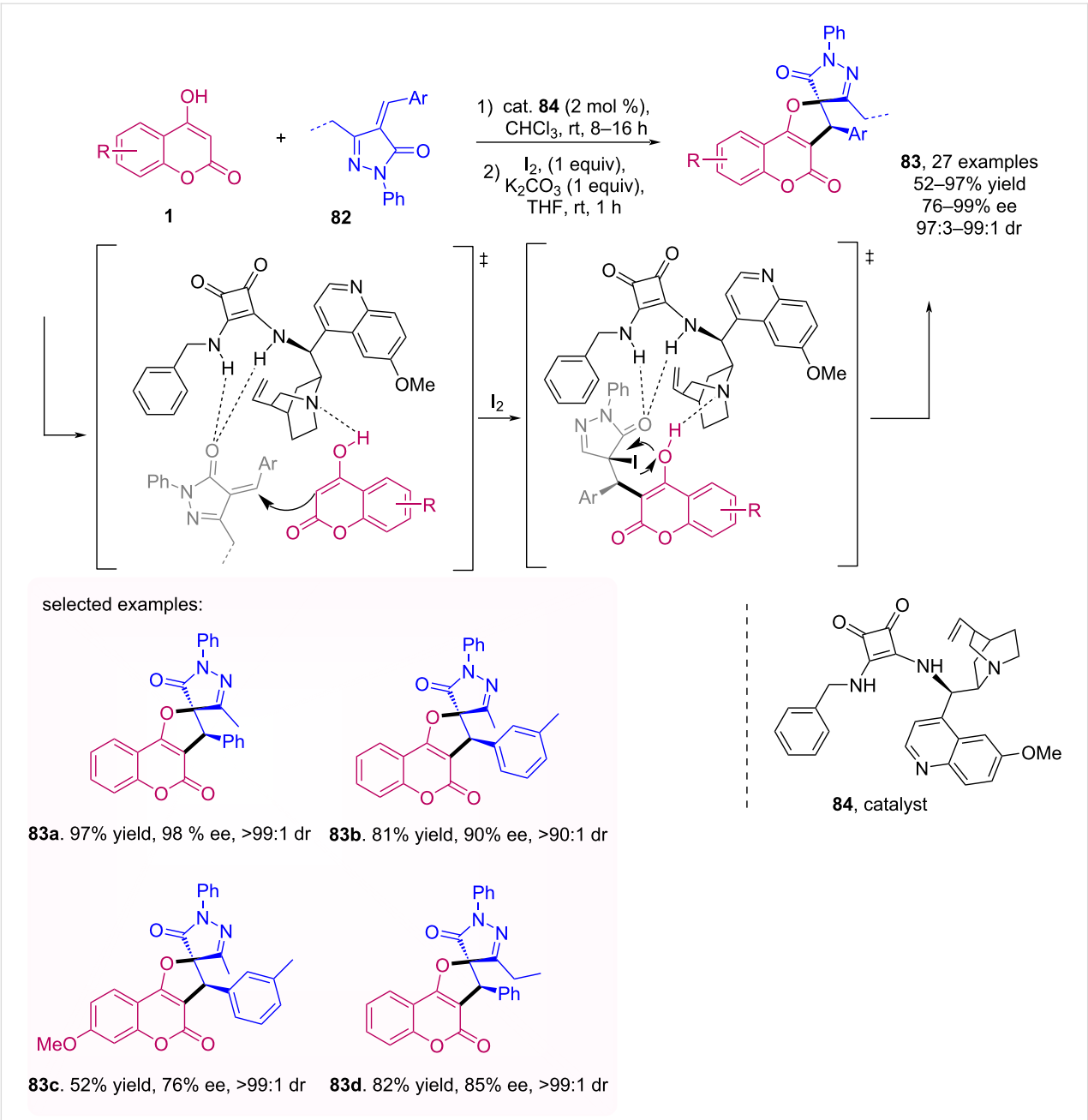
Sebesta and colleagues described an enantioselective Michael/hemiketalization addition of hydroxycoumarins **1** to enones **2** and ketoesters **86** using squaramide **85** [62]. The methodology developed made it possible to obtain a mixture of open and closed forms of (*R*)-warfarin (**3a**) from a bifunctional catalyst of squaramide by the formation of an iminium ion intermediate with enone and hydrogen bonding with hydroxycoumarin



Scheme 24: Enantioselective synthesis of 3,4-dihydrocoumarins **78** catalyzed by squaramide **73**.



Scheme 25: Organocatalyzed [4 + 2] cycloaddition between 2,4-dienals **79** and 3-coumarincarboxylates **43**.

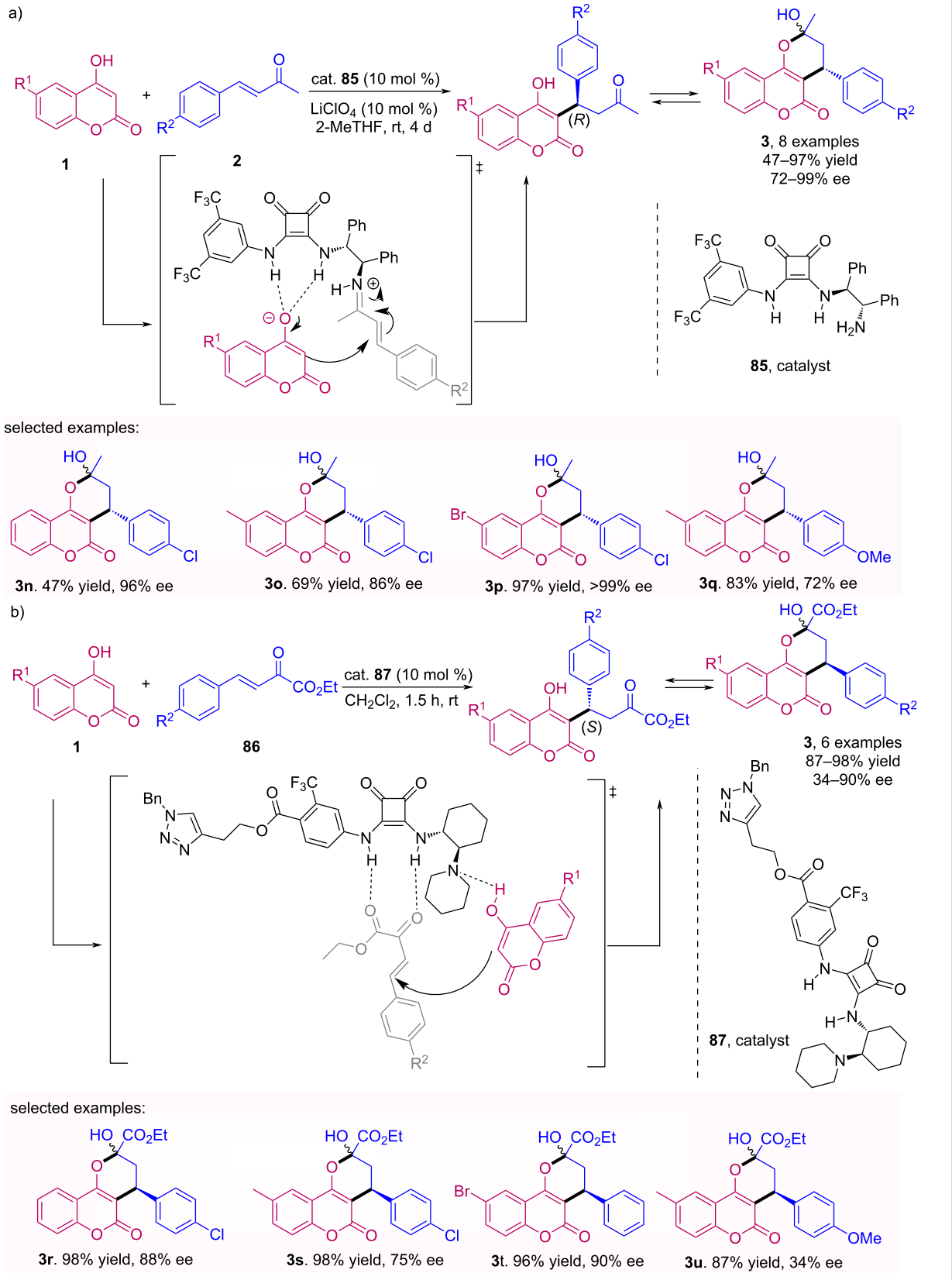


Scheme 26: Enantioselective one-pot Michael addition/intramolecular cyclization for the synthesis of spiro[dihydrofurocoumarin/pyrazolone] **83**.

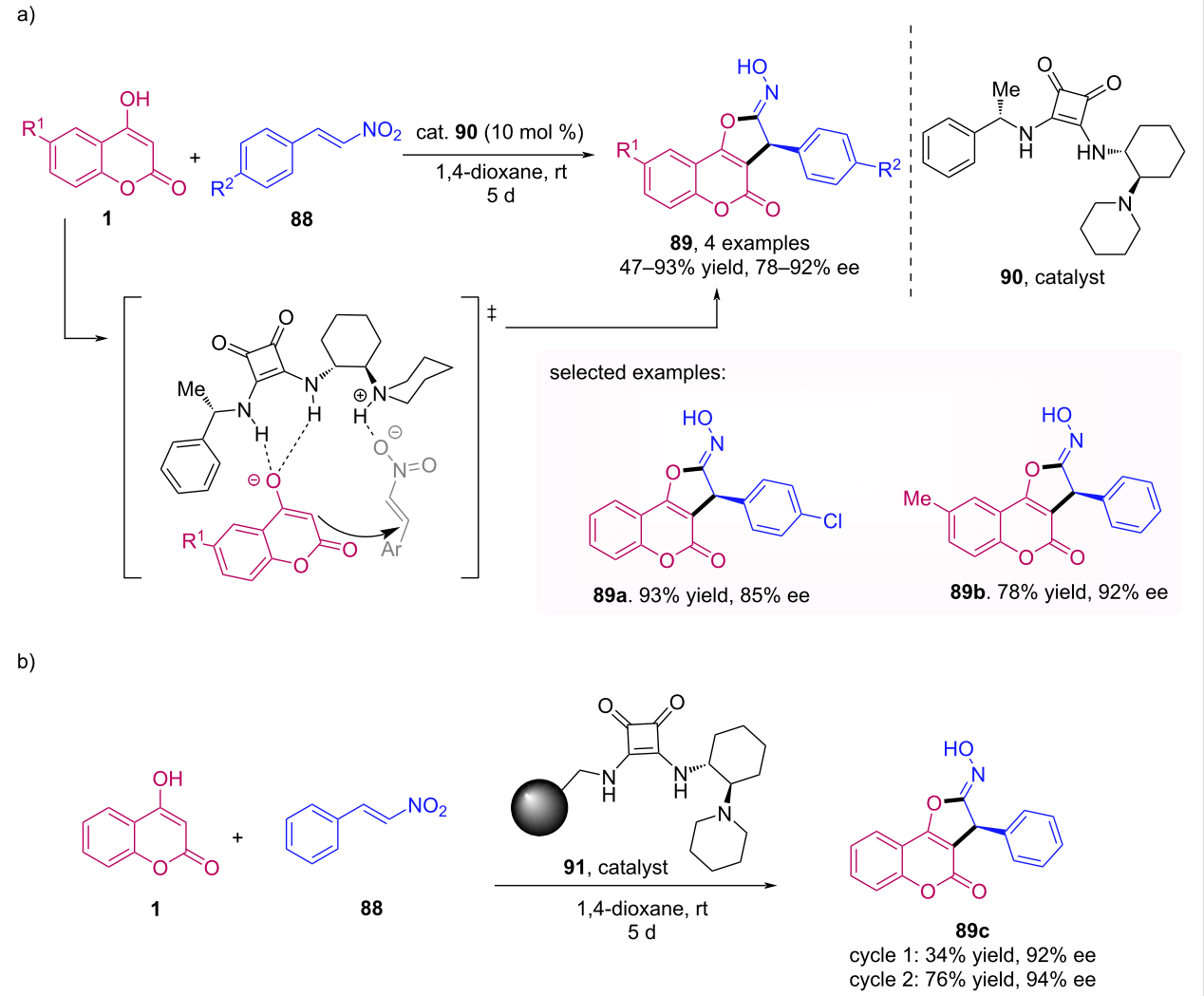
(Scheme 27a). By using the squaramide catalyst with tertiary amine (*S*)-warfarin analogues **3** could be obtained with moderate to excellent enantiomeric excesses (Scheme 27b).

In 2018, Modrocká et al. described the synthesis of 2,3-dihydrofurocoumarins **89** through an enantioselective Michael addition of 4-hydroxycoumarins **1** to β-nitrostyrenes **88**, followed by an intramolecular cyclization [63]. For this transformation, the authors use a squaramide catalyst **90** to perform the enantioselective Michael addition in 1,4-dioxane at room temperature, as shown in Scheme 28a. Moreover, the group tried a reusable immobilised squaramide catalyst **91**, which gave the desired product with high ee in the two first cycles, although the yield of the product in the first cycle was lower (Scheme 28b). Finally, the absolute configuration of the products was determined by ECD analysis.

Zheng et al. described an asymmetric organocatalyzed domino reaction between 4-hydroxycoumarins **1** and substituted methylene malononitriles **92**, affording a variety of pyrano[3,2-



Scheme 27: Michael/hemiketalization addition enantioselective of hydroxycoumarins (**1**) to: (a) enones **2** and (b) α-ketoesters **86**.



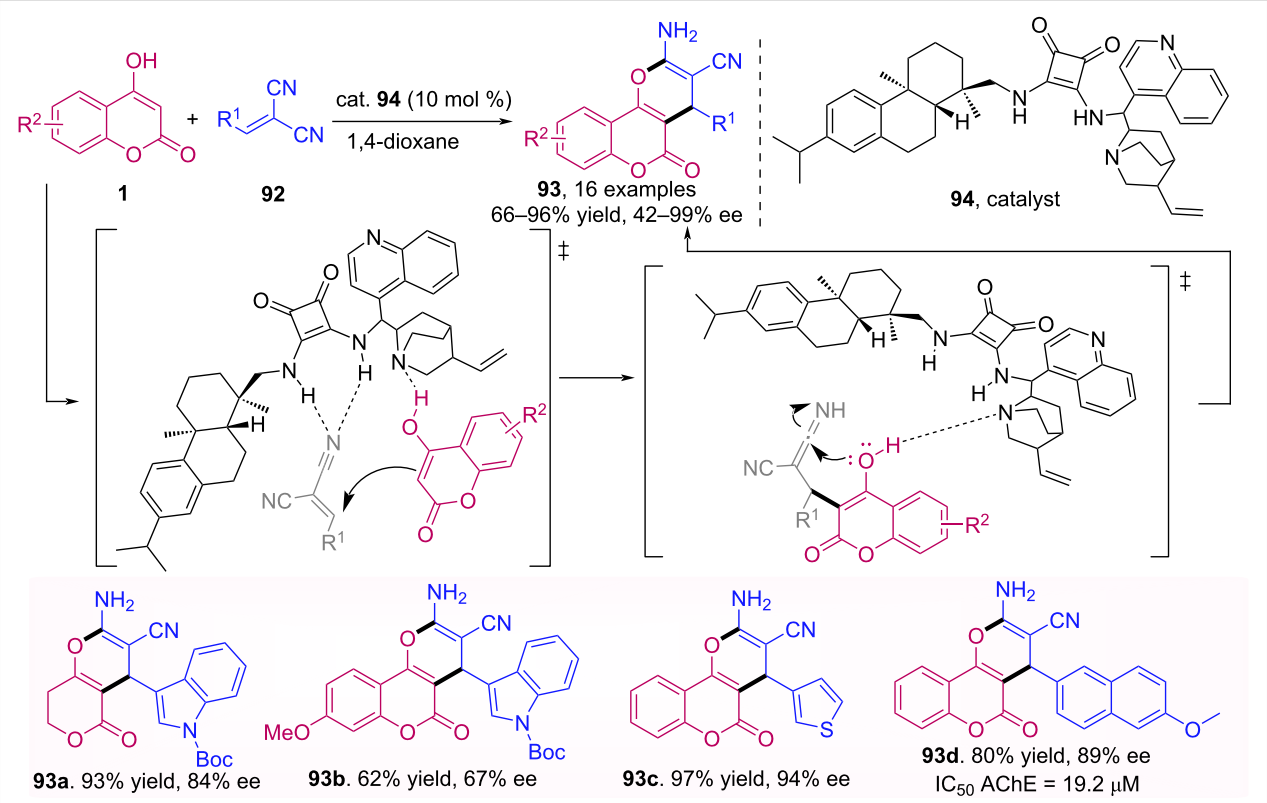
Scheme 28: Synthesis of 2,3-dihydrofurocoumarins **89** through Michael addition of 4-hydroxycoumarins **1** to β-nitrostyrenes **88**.

c]chromene derivatives **93** (Scheme 29) [64]. The catalyst used in this reaction was the dehydroabietylamine-cinchone-squaramide derivative **94**. The products were obtained with good to excellent yields and enantioselectivities with both electron-donating and electron-withdrawing substituents. Additionally, the products were evaluated as acetylcholinesterase (AChE) inhibitors and compound **93d** showed a promising activity.

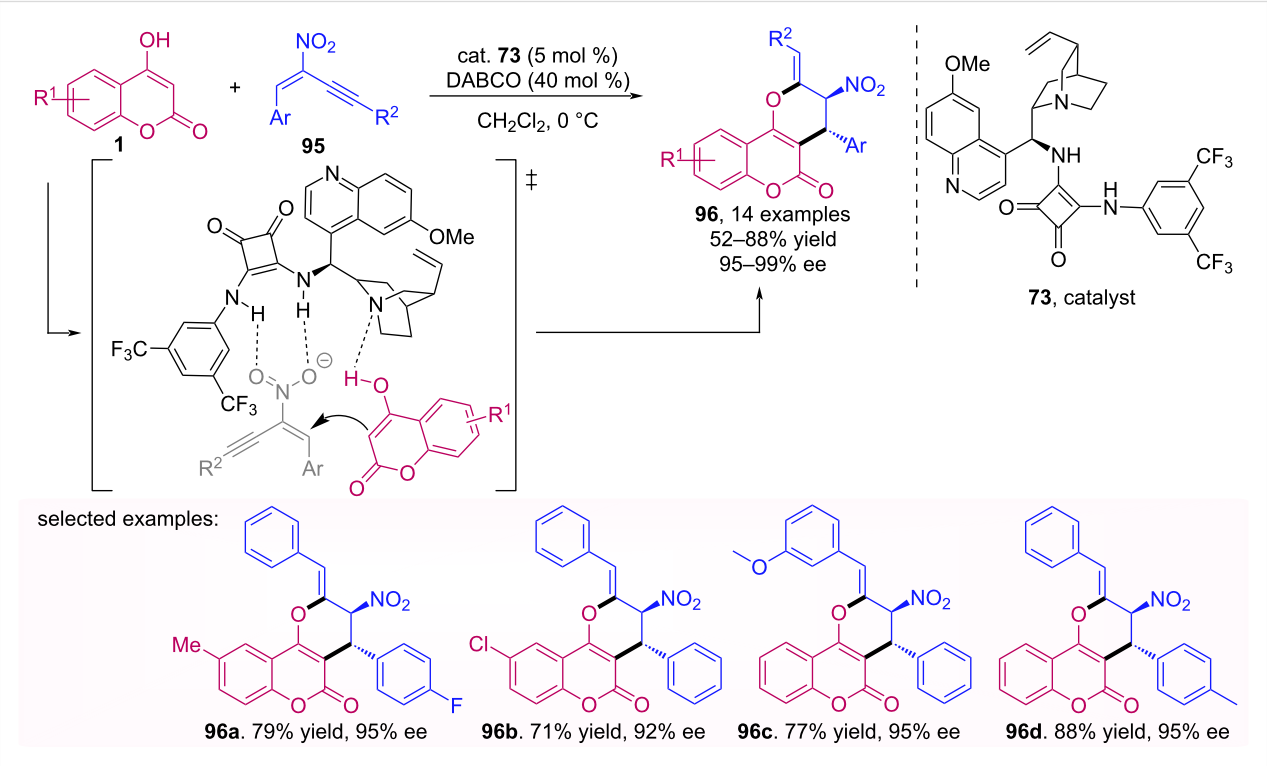
Gurubrahaman et al. developed a method for the synthesis of (*Z*)-2-methylenepyrans **96** through a conjugated addition of 4-hydroxycoumarins **1** [65]. This reaction was catalyzed by a bifunctional squaramide **73** and initially both (*Z*)- and (*E*)-isomers were observed, besides the isomer **96** as the major product. After the addition of DABCO, the (*Z*)-isomer became the major product with good to excellent yields and excellent ee, as shown in Scheme 30.

An asymmetric Michael addition of 4-hydroxycoumarin (**1**) to α,β-unsaturated ketones **2** promoted by chiral primary amine thiourea bifunctional catalyst **97** was reported by Mei et al. [66]. Using the optimized conditions, a series of Michael adducts **3** were obtained in excellent yields (up to 97%) and enantioselectivities (up to 95% ee) (Scheme 31). As a highlight, optically pure (*S*)-warfarin (**3a**) was obtained in 99% ee after simple and single recrystallization.

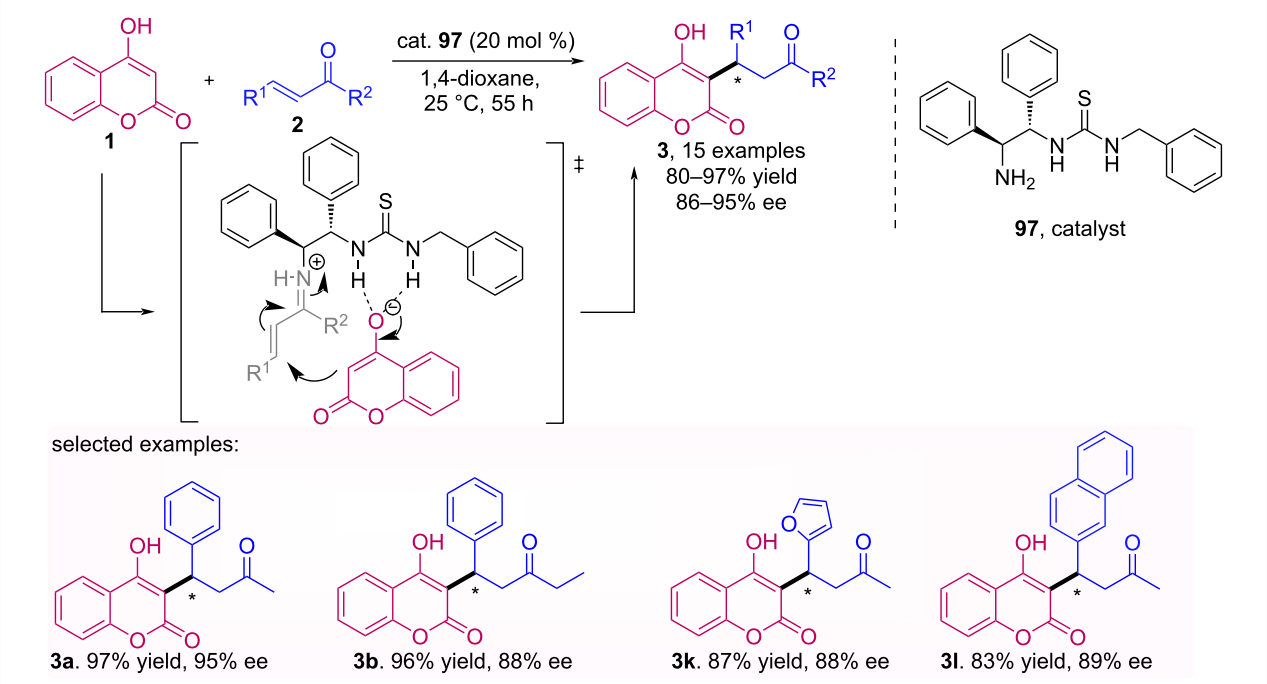
Wang's group developed a bifunctional thiourea and abietic acid catalyst for enantioselective synthesis. In this context, they applied this catalyst in a domino reaction of pyranocoumarins **99** [67]. The procedure proved to be efficient for obtaining products with good to excellent yields and enantiomeric excesses, and in some cases starting from three components in a one-pot procedure (Scheme 32). The chiral catalyst **100** allows the addition in the least hindered *Re* face, consequently result-



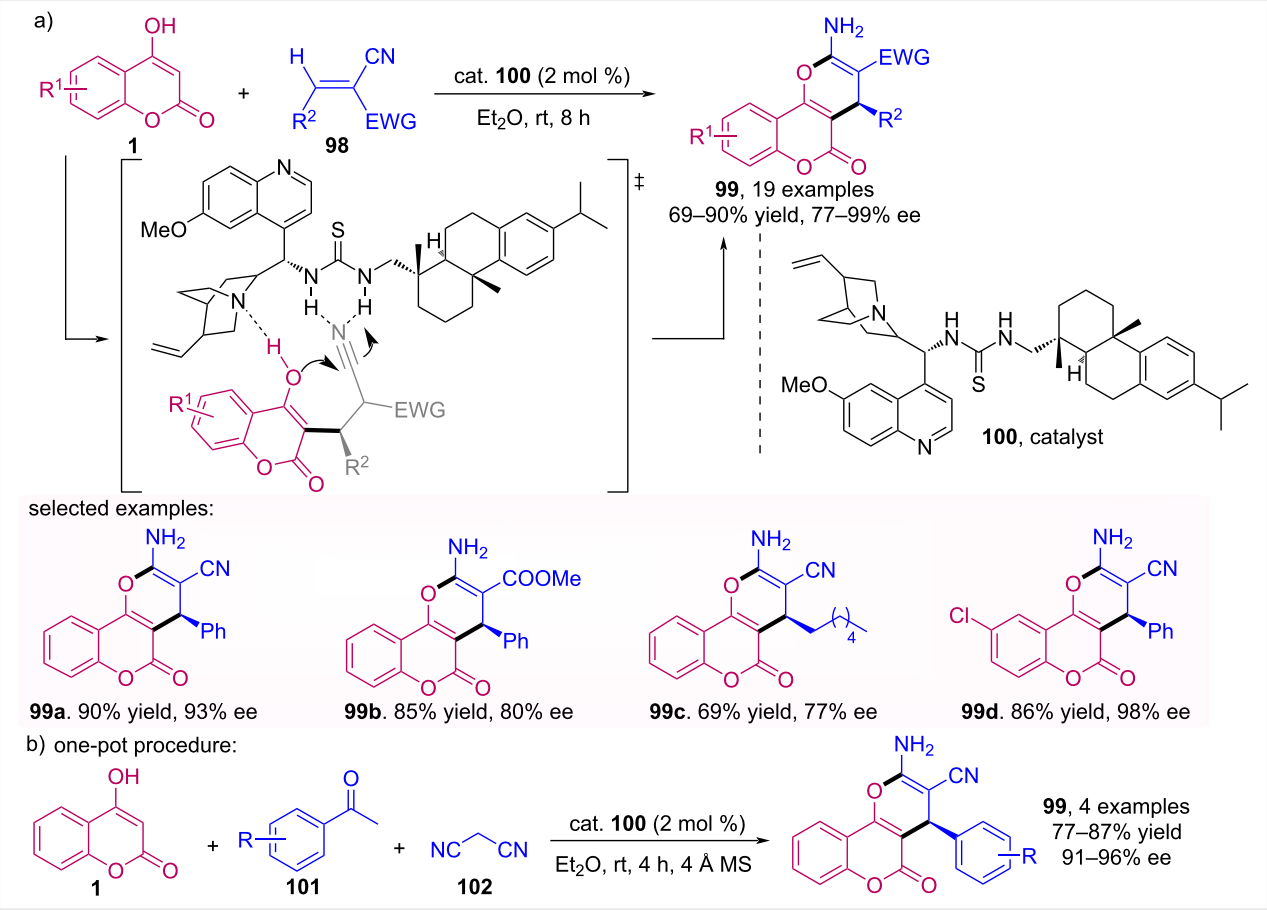
Scheme 29: Synthesis of pyrano[3,2-*c*]chromene derivatives **93** via domino reaction between 4-hydroxycoumarins (**1**) and substituted methylene malononitriles **92**.



Scheme 30: Conjugated addition of 4-hydroxycoumarins **1** to nitroolefins **95**.



Scheme 31: Michael addition of 4-hydroxycoumarin **1** to α,β-unsaturated ketones **2** promoted by primary amine thiourea bifunctional catalyst **97**.



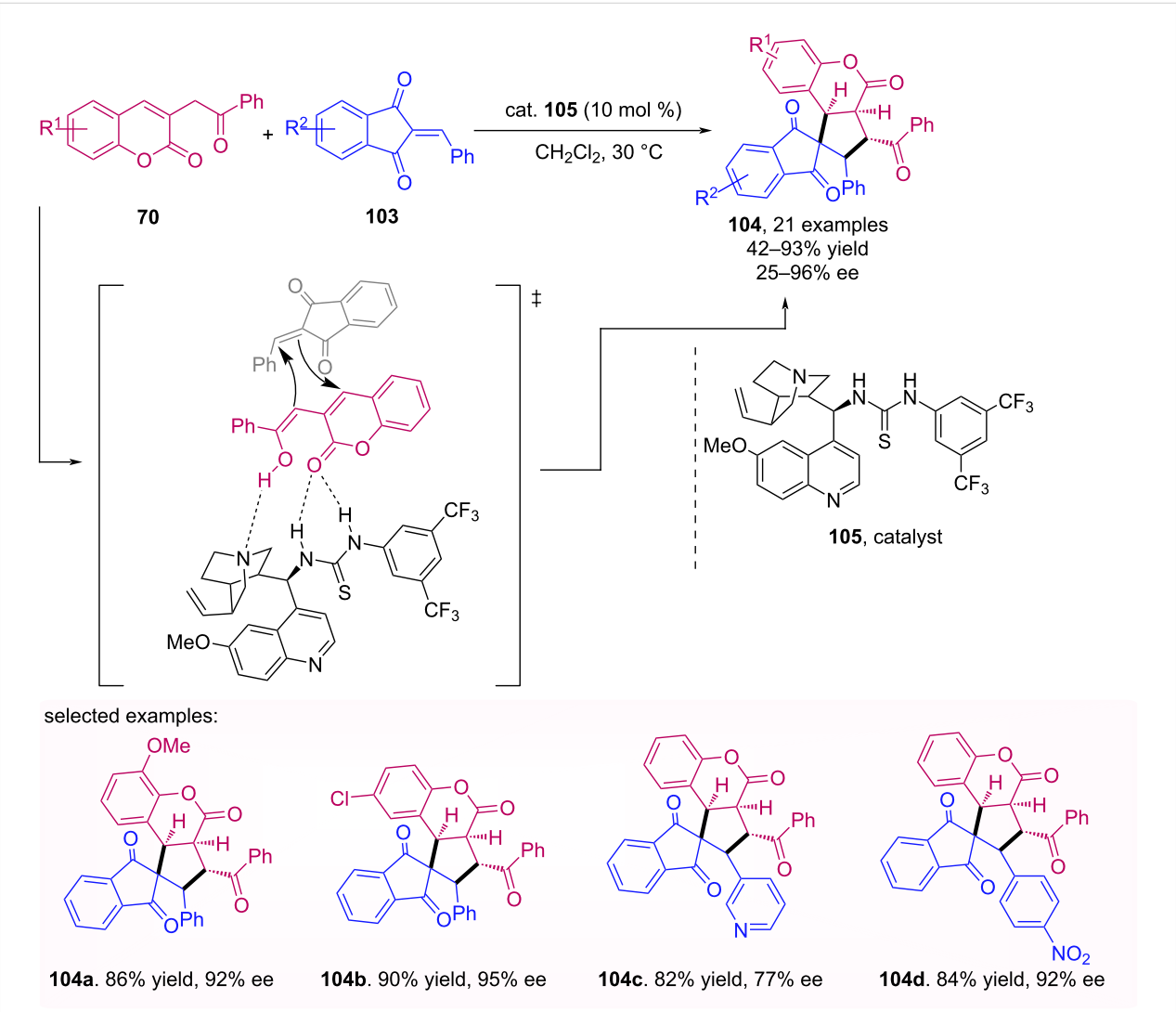
Scheme 32: Enantioselective synthesis of functionalized pyranocoumarins **99**.

ing in products of (*R*)-configurations, which were determined via X-ray crystallography.

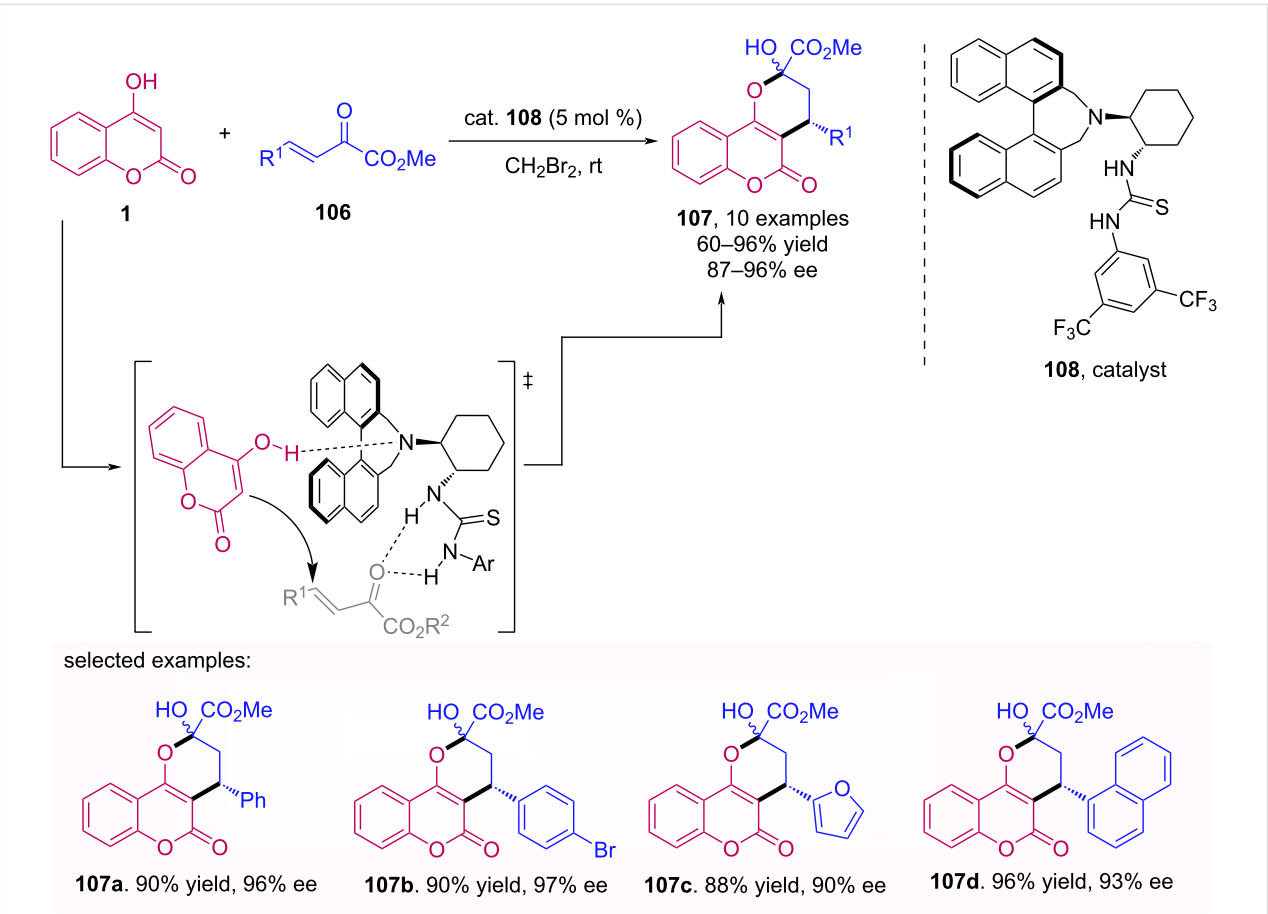
A stereoselective [3 + 2] cycloaddition with indandione alkylidenes **103** and 3-homoacylcoumarin **70** as the 1,3-dipole precursor, to generate a series of coumarin/indandione-fused spirocyclopentanes **104** bearing four contiguous stereogenic centers, was described by Chen et al. [68]. This transformation was catalyzed by a cinchona-thiourea derivative **105** furnishing the spiro compounds with good to high yield and enantioselectivity (Scheme 33). In this method two mechanisms occur in parallel, which results in the formation of the Michael adduct as a by-product and the desired spirocyclopentanes **104**. It is noteworthy that the mechanistic studies showed that the product is formed through a concerted mechanism and therefore is not part of an intermediate adduct.

A conjugate addition of 4-hydroxycoumarin (**1**) to β,γ-unsaturated α-ketoesters **106** was reported the Kim's group [69]. In this case, a bifunctional binaphthyl-modified thiourea organocatalyst **108** was used, and among the solvents probed (such as CH_2Cl_2, CH_3CN and toluene), the best results were achieved when the reaction was conducted in dibromomethane at room temperature. The use of only 5 mol % of the catalyst afforded the desired products with excellent yields and enantioselectivities (Scheme 34).

The use of multicatalytic systems have become a useful strategy for the case where it is not possible to achieve the desired transformation by using only one catalyst [70]. In this sense, an efficient asymmetric organocatalytic reaction was reported by Zhang et al. for the synthesis of 2,8-dioxabicyclo[3.3.1]nonanes [71]. A combination of catalysts **7** and **110**, involving iminium



Scheme 33: 3-Homoacylcoumarin **70** as 1,3-dipole for enantioselective concerted [3 + 2] cycloaddition.



Scheme 34: Synthesis of warfarin derivatives **107** through addition of 4-hydroxycoumarins **1** to β,γ-unsaturated α-ketoesters **106**.

and anion-binding catalysis, respectively, has proved to be the most effective for the promotion of the conjugate addition of 4-hydroxycoumarins **1** to 2-hydroxycinnamaldehydes **109**, leading to chiral bridged bicyclic acetal products **110** with high ee (Scheme 35). The mechanistic study performed showed that possibly the phenolic hydroxy group of 2-hydroxycinnamaldehydes is important for the success of the employed catalytic system.

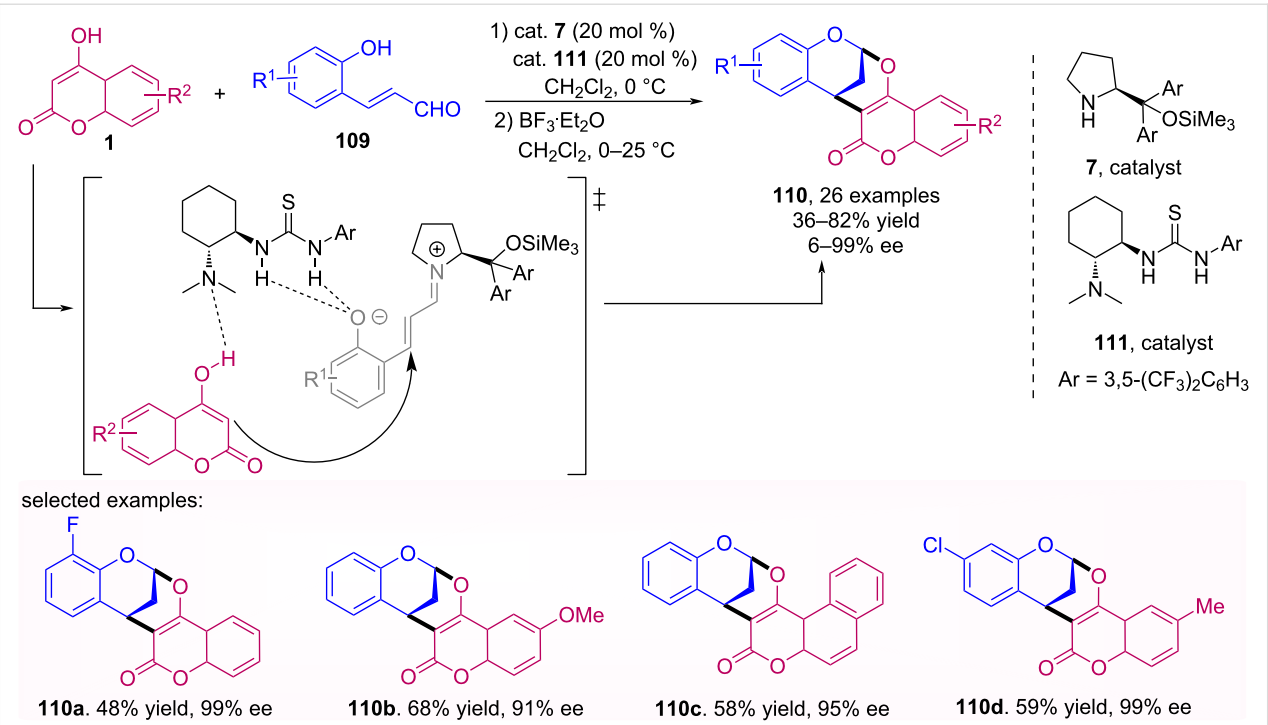
Finally, but not least, the phase-transfer chiral organocatalysts have also been highly explored [72,73]. Most of the PTCs are based on the skeletons of cinchona alkaloids and chiral binaphthyls, though, more recently, the strategy via introducing secondary interactions for the design of the bifunctional catalysts achieved wide application in asymmetric reactions [74].

Wu et al. described a Mannich asymmetric addition of cyanocoumarins **39** to isatin imines **112** catalyzed by an amide-phosphonium salt **114**. This catalyst provides the formation of an ionic pair with coumarin enolate and activation of the imine by hydrogen bonding with the secondary amine, resulting in products **113** with excellent yields and high enantioselectivity [75]. This transformation draws attention because it uses only 0.1 mol % of catalyst, tolerates electron-donating and -withdrawing groups and maintains its performance in gram scale (Scheme 36).

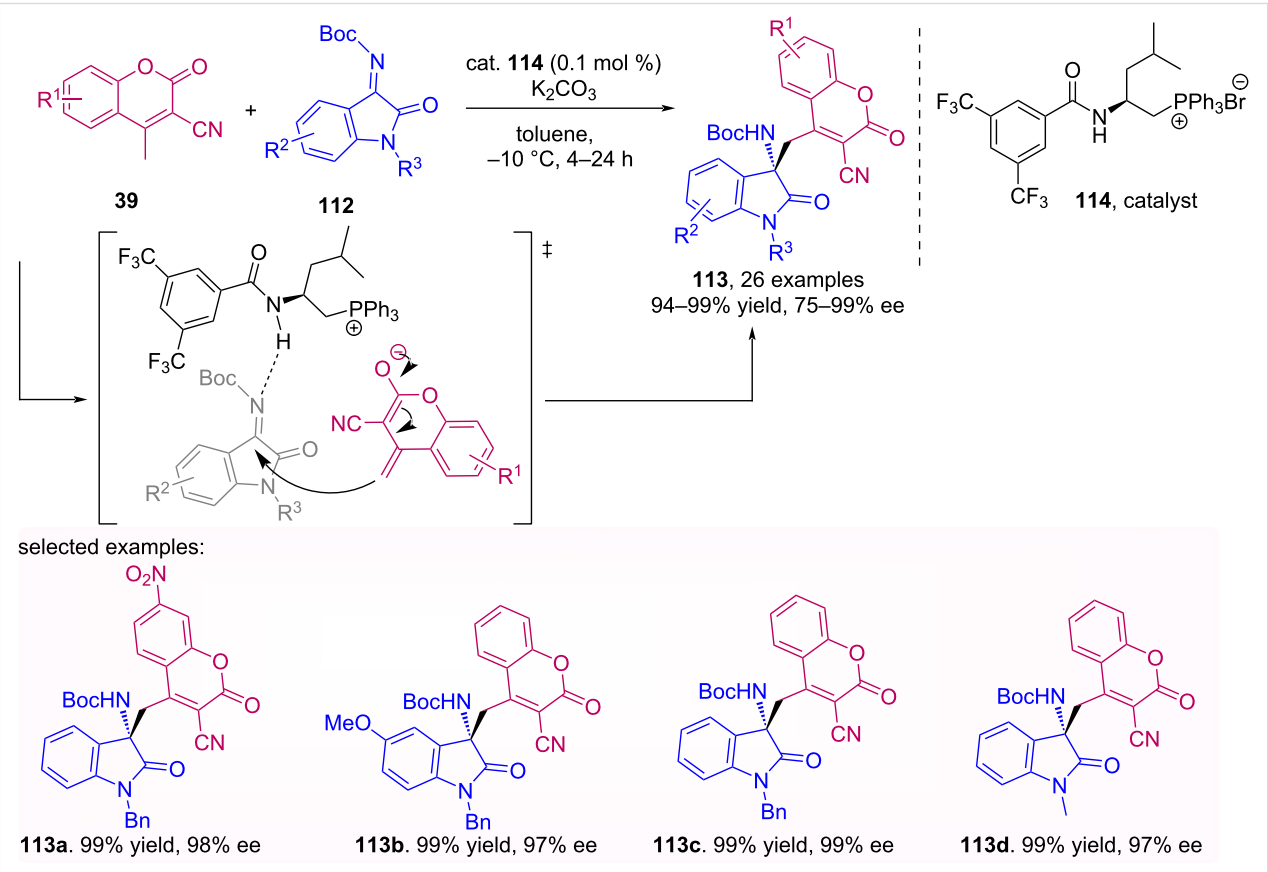
Page et al. developed a total synthesis of the natural product (+)-scuteflorin A (**119**), being the key step an asymmetric epoxidation of xanthyletin (**115**) employing biphenylazepinium **120** as PTC together with tetraphenylphosphonium monoperoxysulfate (TPPP) as the stoichiometric oxidant [76]. The authors mentioned that this epoxidation had been previously reported using Jacoben's (*S*,*S*)-(+)-salen-Mn(III) catalyst with 78–83% yield and 95% ee, and via organocatalysis they obtained 98% yield and ≥99% ee (Scheme 37). Furthermore, the natural product was synthesized in seven steps with 14% overall yield.

Conclusion

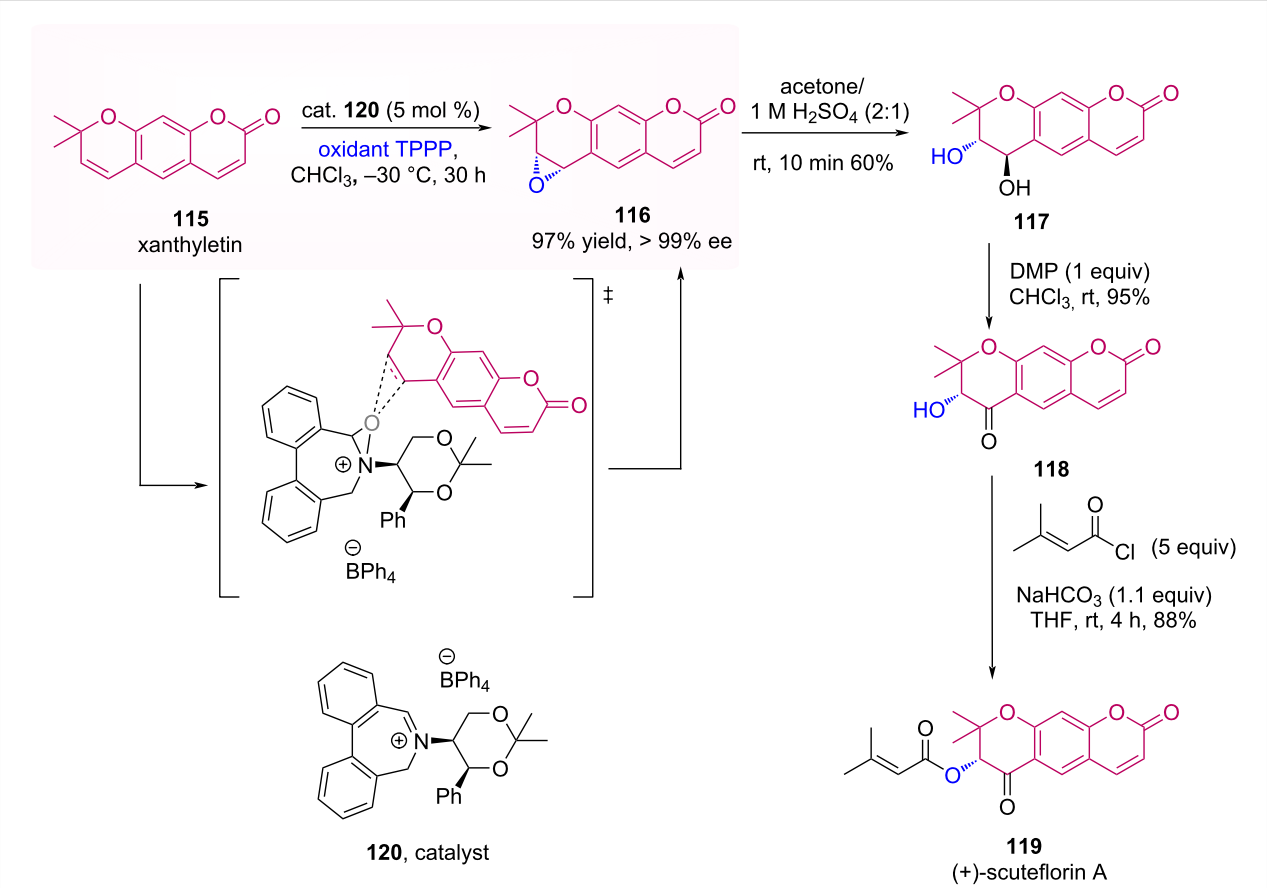
Coumarin derivatives are important scaffolds for synthetic and medicinal chemistry. These structures have an interesting reactivity and can be used in diverse organic reactions, for example



Scheme 35: Asymmetric multicatalytic reaction sequence of 2-hydroxycinnamaldehydes **109** with 4-hydroxycoumarins **1**.



Scheme 36: Mannich asymmetric addition of cyanocoumarins **39** to isatin imines **112** catalyzed by the amide-phosphonium salt **114**.



Scheme 37: Enantioselective total synthesis of (+)-scuteflorin A (**119**).

enantioselective organocatalyzed reactions, as presented in this review. Furthermore, coumarin derivatives are known for their wide variety of biological activities.

As can be noticed in this literature review, a wide variety of new catalysts were applied in the synthesis of coumarin derivatives and the methodologies were found to be good choices to achieve functionalized coumarins, such as the use of immobilized squaramide catalyst, which allowed the catalyst to be recycled twice with high ee. Moreover, the squaramide catalyst could also be used with low catalyst loading (1–2 mol %) providing excellent results, besides the use of only 0.1 mol % of amide-phosphonium salt for the synthesis of coumarin derivatives. Some methodologies have also proven to be highly efficient in one-pot and gram-scale procedures, which turns to be more environmentally benign.

Nevertheless, studies are still needed to accomplish procedures that allow recycling and lower catalyst loading, intertwined with the use of green solvents, in order to provide efficient and sustainable synthesis of these important pharmacologically active compounds.

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ORCID® iDs

Natália M. Moreira - https://orcid.org/0000-0001-7996-2859
Lorena S. R. Martelli - https://orcid.org/0000-0001-5939-8672
Arlene G. Corrêa - https://orcid.org/0000-0003-4247-2228

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Enantioenriched α-substituted glutamates/pyroglutamates via enantioselective cyclopropenimine-catalyzed Michael addition of amino ester imines

Zara M. Seibel[1,§], Jeffrey S. Bandar[1,¶] and Tristan H. Lambert[*1,2]

Letter

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Address:
[1]Department of Chemistry, Columbia University, New York, New York 10027, USA and [2]Department of Chemistry and Chemical Biology, Cornell University, Ithaca, New York 14853, USA

Email:
Tristan H. Lambert[*] - thl36@cornell.edu

* Corresponding author
§ present address: Codexis, Inc. Redwood City, CA 94063, USA
¶ present address: Department of Chemistry, Colorado State University, Fort Collins, CO 80523, USA

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Abstract

A procedure for the enantioselective synthesis of α-substituted glutamates and pyroglutamates via a cyclopropenimine-catalyzed Michael addition of amino ester imines is described. Enantioselectivities of up to 94% have been achieved, and a variety of functional groups were found to be compatible. The impact of the catalyst structure and imine substitution is discussed. Compared to other methods, this protocol allows for a broader and more enantioselective access to pyroglutamate derivatives.

Introduction

α-Substituted glutamates have value as synthetic building blocks and as a common substructure in a number of biologically active molecules [1-5]. In addition, the lactamized derivatives of these compounds, pyroglutamates, occur in a number of well-known biologically active natural products including dysibetaine [6-12], salinosporamide A [13-18], and lactacystin [19-22] (Figure 1). Accordingly, efficient procedures to access α-substituted glutamates and pyroglutamates in enantioenriched form have been the target of numerous reports [23-27].

One of the most straightforward approaches to α-substituted glutamate derivatives is via the Michael addition of α-amino ester enolates to acrylate acceptors. These products can also be easily converted to pyroglutamates by lactamization [28-30]. Although the use of substituted amino ester derivatives for the enantioselective α-alkylation has been achieved [31], Michael reactions with these nucleophiles have met with limited success [32-39]. In terms of enantioselective catalytic strategies, Kobayashi has reported the conjugate addition of azlactones to acrylates using a calcium pybox complex, but with enantiose-

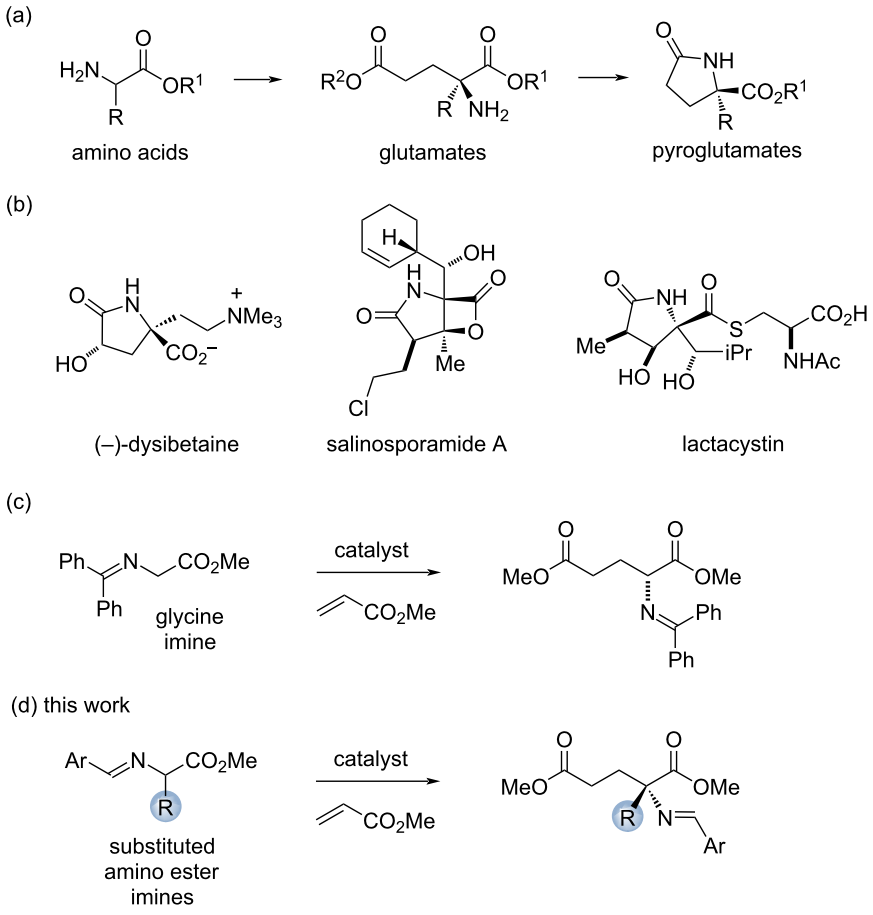


Figure 1: Strategy for the synthesis of glutamate and pyroglutamate derivatives and several natural products with pyroglutamate substructures.

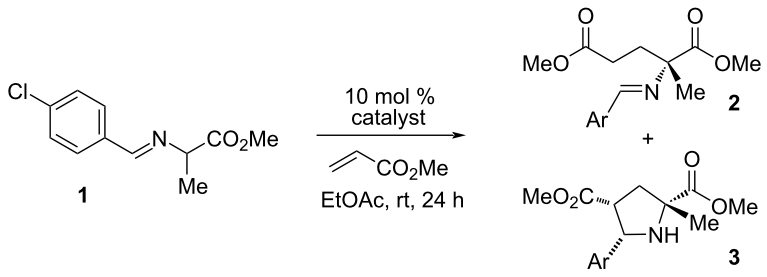
lectivities only up to 84% ee [36]. Phase-transfer catalysis has been employed for the enantioselective addition of an alanine imine derivative, although the selectivity achieved in this case was only 64% ee [37]. In a related work, enantioselectivities of up to 90% ee were realized, but the procedure required an unusual di-*tert*-butylmethyl ester moiety and was limited solely to the alanine derivative [38]. Finally, a Baylis–Hillman-type approach has been employed to realize enantioselective reactions, albeit with a limited scope of substituents at the quaternary carbon [39]. Thus, the development of a general strategy for the enanantioselective conjugate addition of amino acid derivatives for this reaction remains an unmet goal.

Our group previously described a chiral cyclopropenimine catalyst that displayed outstanding reactivity for addition reactions of glycine imines [40,41]. We hypothesized that this reactivity might be sufficient to overcome the reactivity limitations of pronucleophiles derived from other α-amino esters [42]. In this paper, we describe the use of cyclopropenimine catalysis for the enantioselective catalytic Michael reaction of α-substituted amino ester imines.

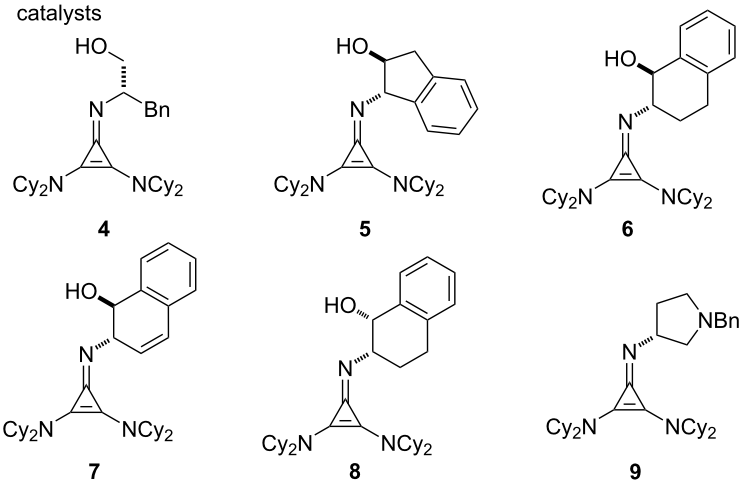
Results and Discussion

To optimize this process, we selected the addition of alanine imine **1** to methyl acrylate as our test reaction (Table 1). We found that the previously reported cyclopropenimine **4** catalyzed this transformation with 90% conversion and 84% ee in 24 hours at ambient temperature (Table 1, entry 1). The desired Michael adduct **2** was generated in a 4:1 ratio along with the cycloadduct **3** [43], which we had not observed in our previous study of glycinate imine substrates. The aminoindanol-derived catalyst **5** was more reactive and resulted in improved enantioselectivity (89% ee), but afforded the same 4:1 ratio of the Michael adduct to cycloaddition product (Table 1, entry 2). Interestingly, the larger ring-containing catalyst **6** improved this ratio somewhat to 6:1 while retaining the enantiomeric ratio, albeit at the expense of reactivity (Table 1, entry 3). Incorporation of additional unsaturation (catalyst **7**) improved the reactivity somewhat but was detrimental to enantioselectivity (Table 1, entry 4), while changing the relative stereochemistry of the hydroxy substituent resulted in an inactive catalyst (**8**, entry 5 in Table 1). Likewise, catalysts such as **9** lacking a hydrogen-bonding substituent were not active (Table 1, entry 6).

Table 1: Optimization of the cyclopropenimine-catalyzed addition of alanine imine **1** to methyl acrylate.



entry	catalyst	solvent	conc. (M)	conv (%)[a]	% ee[b]	**2**:**3**[c]
1	**4**	EtOAc	0.25	90	84	4:1
2	**5**	EtOAc	0.25	>95	89	4:1
3	**6**	EtOAc	0.25	62	89	6:1
4	**7**	EtOAc	0.25	75	70	6:1
5	**8**	EtOAc	0.25	<5	–	–
6	**9**	EtOAc	0.25	<5	–	–
7	**5**	PhMe	0.25	>95	92	3:1
8	**5**	TBME	0.25	>95	91	3:1
9	**5**	dioxane	0.25	34	86	3:1
10	**5**	toluene	0.25	>95	92	2.5:1
11	**5**	ether	0.25	>95	93	4:1
12	**5**	ether	0.35	>95[d]	91	4:1



[a]Determined by ^{1}H NMR versus Bn_2O as an internal standard. [b]Determined by HPLC. [c]Determined by ^{1}H NMR on crude reaction mixtures. The minor products **3** were isolated as single diastereomers, but the % ee was not determined. [d]Reaction time 7 h.

With the identification of cyclopropenimine **5** as our optimal catalyst [44], we examined the effect of the reaction medium. Solvents such as benzene (Table 1, entry 7), TBME (Table 1, entry 8), and toluene (Table 1, entry 10) produced reactivities on par with ethyl acetate and approximately equal enantioselectivities but resulted in slightly worse ratios of **2** and **3**. 1,4-Dioxane was notably detrimental to the reactivity and selectivity (Table 1, entry 9). On the other hand, the use of diethyl ether as solvent resulted in a high reactivity, enantioselectivity of 93%, and no erosion of the Michael product to cycloadduct ratio (Table 1, entry 11). Finally, increasing the concentration of the reaction shortened the reaction time without significant detriment to selectivity (Table 1, entry 12).

We also examined the impact of the imine aryl substituent on the reaction efficiency, stereoselectivity, and selectivity for the

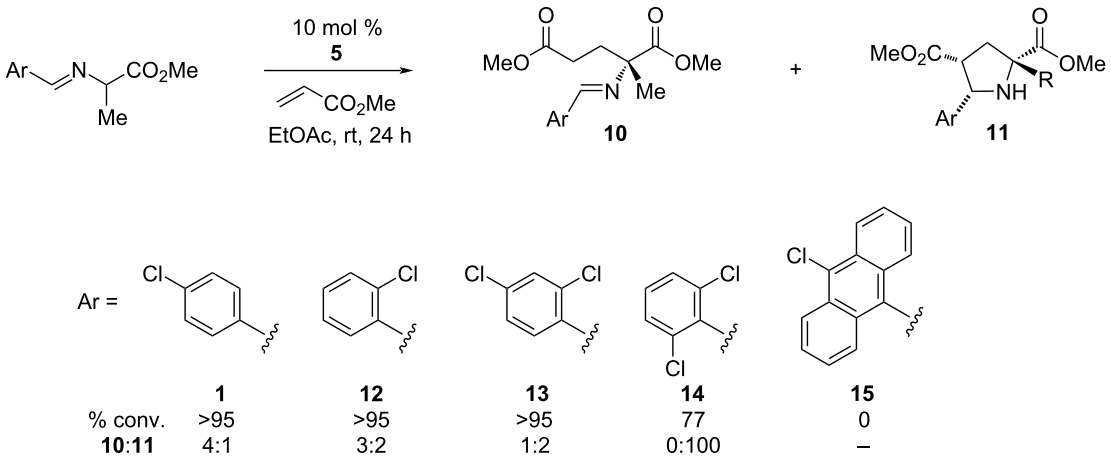
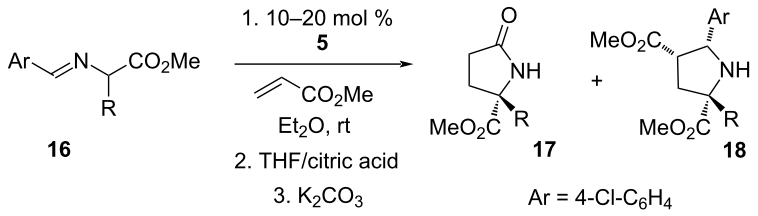


Figure 2: Effect of the aryl substituent on reaction efficiency and selectivity.

Michael addition versus cycloaddition (Figure 2). The optimal substituent in this regard proved to be *p*-chlorophenyl **1**, which resulted in the yield and selectivities using catalyst **5** as already discussed in Table 1. The *o*-chlorophenyl imine **12** was equally reactive, but led to a greater production of the cycloadduct. Interestingly, the 2,4-dichlorophenyl imine **13** resulted in a 2:1 ratio in favor of the cycloadduct, which suggests that this selectivity has a significant electronic sensitivity. On the other hand, the 2,6-dichlorophenyl imine **14** led to exclusive formation of the cycloadduct. Other, more elaborate aryl imines such as chloroanthracenyl **15** proved to be unproductive.

With the optimized conditions in hand, we proceeded to examine the substrate scope of this protocol (Table 2). Remarkably, changing the substituent on the amino ester imine substrate from methyl (Table 2, entry 1) to ethyl (Table 2, entry 2) resulted in a significant increase of reaction time and reduction of yield and enantioselectivity. Indeed, 20 mol % of the catalyst were required to realize a 48 h reaction time in the latter case. This hindrance of reaction efficiency was exacerbated by further extension of the alkyl substituent to *n*-propyl, *n*-butyl, or *n*-hexyl (Table 2, entries 3–5). Underscoring the sensitivity of this reaction to steric encumbrance with this substituent, we

Table 2: Substrate scope of amino ester imine additions to methyl acrylate.



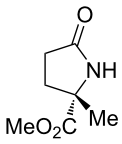
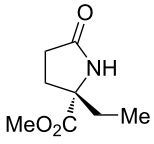
entry	product	**5** (mol %)	time (h)	**17** yield (%)[a]	**17** % ee[b]	**18** yield (%)[a]
1	 **17a**	10	16	73	93	19
2	 **17b**	20	48	70	87	11

Table 2: Substrate scope of amino ester imine additions to methyl acrylate. (continued)

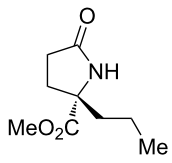
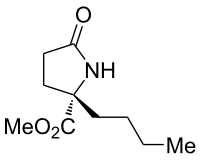
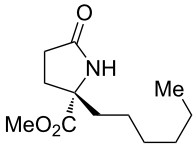
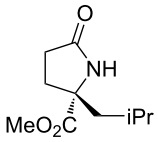
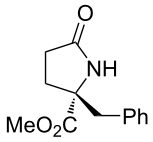
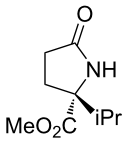
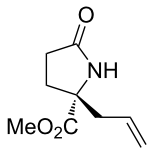
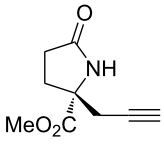
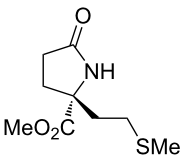
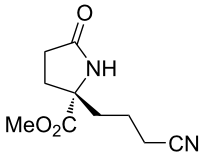
3	 **17c**	20	48	67	82	13
4	 **17d**	20	48	54	82	11
5	 **17e**	20	48	46	80	9
6	 **17f**	20	48	62	77	10
7	 **17g**	15	48	77	75	21
8	 **17h**	20	48	0	–	0
9	 **17i**	10	48	69	94	23
10	 **17j**	10	16	64	88	20
11	 **17k**	10	16	76	84	19

Table 2: Substrate scope of amino ester imine additions to methyl acrylate. (continued)

12	 **17l**	10	16	75	16	16

[a]Calculated based on isolated and purified material. The minor products **18** were isolated as single diastereomers, but the % ee was not determined.
[b]Determined by HPLC or by ^{1}H NMR using Eu(hfc)$_3$ as a chiral shift reagent.

found that isobutyl or benzyl (Table 2, entries 6 and 7) further reduced the enantioselectivity and an isopropyl completely suppressed reactivity (Table 2, entry 8). On the other hand, allyl (Table 2, entry 9) and propargyl (Table 2, entry 10) groups proved to viable substituents, leading to the products in good yield and high enantioselectivities. Of course, these two functional groups provide convenient handles for derivatization and so represent important achievements for this method. In terms of additional functionality, we found that a thioether substrate could be engaged with reasonably good efficiency and enantioselectivity (Table 2, entry 11). On the other hand, while a nitrile was compatible with the reaction (Table 2, entry 12), the incorporation of this substituent led to a nearly total loss in selectivity.

Although we have not examined this specific reaction computationally, it is reasonable to expect that it shares many similarities to the corresponding glycine imine addition we previously reported [45], for which a detailed transition state model was developed. In that study, it was determined that the reaction proceeds via several competing low-energy transition states involving both O–H and N–H enolate binding modes, *E* and *Z* enolate isomers, and a range of H-bonding and other noncovalent organizational interactions. This complexity makes the detailed prediction of the transition state organization for the current process very challenging. However, we propose that the general structure **19** shown in Figure 3 is a reasonable representation of one of the likely pathways (the major ambiguities being enolate geometry and N–H vs O–H binding). From this transition state, addition of the enolate to the acrylate followed by rapid proton transfer would lead to the glutamate derivative **10** (path a, red dashed line). A competing pathway involving bond formation between the acrylate α-carbon and the imine carbon, either in a concerted fashion or via subsequent addition of a putative acrylate enolate intermediate, would lead to the cycloaddition byproduct **11** (path b, red and blue dashed lines). It should be noted that cyclopropenimine catalysts do not promote the cyclization of **10** to **11**. From this model, it is understandable that increasing the electron deficiency of the aryl (Ar) substituent would increase the level of cycloadduct, while greater steric encumbrance from this substituent would bolster the Michael addition pathway, as illustrated by the data from Figure 2.

Conclusion

In conclusion, we have developed an improved method for the synthesis of enantioenriched α-substituted glutamates and pyroglutamates using cyclopropenimine catalysis. This protocol offers significantly faster reaction rates, increased enantioselectivities, and broader substrate scope than previous efforts. However, this chemistry remains quite sensitive to structural modifications, and thus there remains significant room for further de-

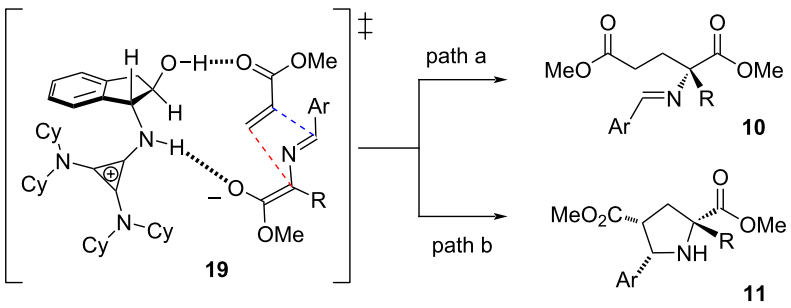


Figure 3: Proposed transition state model.

velopment. Nevertheless, this work provides a convenient means to access a variety of these important structural motifs.

Supporting Information

Supporting Information File 1

Experimental details, characterization data, spectra, and HPLC traces.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-134-S1.pdf]

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Halides as versatile anions in asymmetric anion-binding organocatalysis

Lukas Schifferer, Martin Stinglhamer, Kirandeep Kaur and Olga García Macheño*

Review

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Address:
Organic Chemistry Institute, Westfälische-Wilhelms University Münster, Correnstraße 36, 48149 Münster, Germany

Email:
Olga García Macheño* - olga.garcia@uni-muenster.de

* Corresponding author

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Abstract

This review intends to provide an overview on the role of halide anions in the development of the research area of asymmetric anion-binding organocatalysis. Key early elucidation studies with chloride as counter-anion confirmed this type of alternative activation, which was then exploited in several processes and contributed to the advance and consolidation of anion-binding catalysis as a field. Thus, the use of the halide in the catalyst–anion complex as both a mere counter-anion spectator or an active nucleophile has been depicted, along with the new trends toward additional noncovalent contacts within the HB-donor catalyst and supramolecular interactions to both the anion and the cationic reactive species.

Introduction

Halogens and the respective anionic halides occupy an essential role in natural and chemical processes [1-4]. While in chemical syntheses halogens are often regarded as surrogates for further functionalization, their role in natural and physiological processes is much more diverse. One of these processes is the ability of large complex molecules and enzymes to recognize halide anions via hydrogen bonds in aqueous media [5]. Amongst others, the regulation of membrane potentials is one of such applications, in which the transport of chloride anions is facilitated by noncovalent hydrogen bonding interactions (Figure 1a) [6]. Noncovalent interactions are in fact one of the essential factors for the molecular recognition in enzymatic reactions, especially anionic species [7]. Even though initial reports of nonenzymatic halide recognition date back to the 1960s [8], strategies to exploit this ability for synthetic or catalytic purposes were vastly disregarded in the following decades [9]. This relies on the fact that it is highly challenging to design small molecule catalysts that resemble anion-binding properties of enzymes. Hence, a major challenge of small organic receptors to mimic nature's capability of binding to the targeted anions resides in the supramolecular properties of enzymes and co-factors to form exact matching binding cavities. In this context, halides offer an advantage over various other anionic species because their spherical topology reduces the number of

possible isomers or complexes upon interaction with the receptor. As a consequence, predictable cavity sizes based on the employed halide allows for easier targeting of the small receptor molecule and, thus, reducing the need for complexity compared to enzymes or co-factors. Conversely, a multitude of geometries may need to be considered for anions with linear, coplanar, trigonal or tetrahedral topologies (Figure 1b) [5,10].

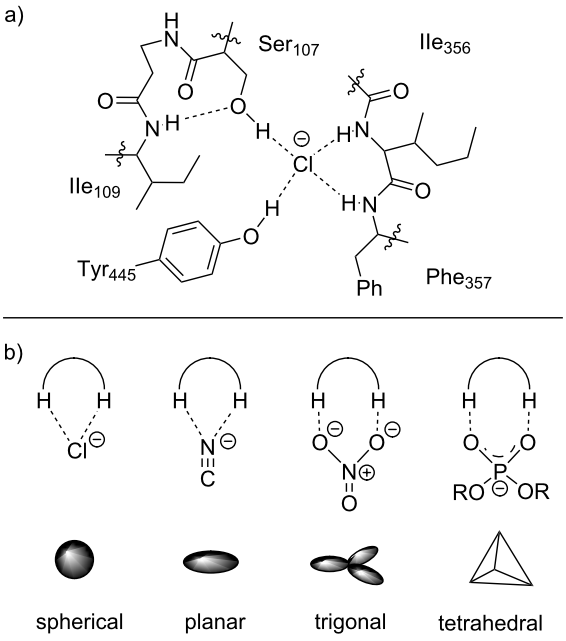


Figure 1: a) Binding interactions in the chloride channel of *E. coli.* and b) examples of chloride, cyanide, nitrate and phosphate anions with their respective topology.

However, following the advances in anion coordination and supramolecular chemistry [7-11], this field of research has attracted more attention within the past two decades. Immense efforts were made to identify small molecules that are able to productively bind anions via noncovalent hydrogen bonding, from which cationic receptors have often proven more efficient [9,12]. A breakthrough in the field of anion binding towards its application in catalysis was achieved with the findings that neutral (thio)urea derivatives are potent anion receptors due to their ability to bind anions of various topologies, including the spherical halides [10]. The key to hydrogen bonding of the halide anion resides in the polarized N–H bonds of these (thio)urea units, which have since served as a benchmark in the design and development of anion receptor catalysts [12-14]. Consequently, other synthetic anion receptors have been developed in the past decades, all based on polarized hydrogen bond motifs. While commonly based on N–H bonds [15-18], also polarized O–H [19,20] and even C–H [21,22] bond-based systems have been realized. As a consequence of the importance and increasing attention of this field, there are already a few reviews on anion-binding catalysis implying different types of anions [10,15,23-29]. However, in this review, we aim at providing an overview of the evolution of anion-binding catalysis by focusing on the key role of halides as decisive anions for the development of the concepts and implementation of natural principles of anion recognition by small molecule catalysts.

Review

Hydrogen bonding to neutral substrates or anion binding?

In the early stages of anion-binding-catalysis development, some reactions might have potentially been mistaken to be hydrogen-bond catalyzed [15,23]. While both catalyses are closely related by making use of hydrogen-bond interactions as the directing noncovalent force, they can be distinguished by the type of substrate that is bound to and activated by the catalyst (Figure 2a). In H-bond catalysis, neutral substrates such as carbonyl compounds are coordinated to the H-bond catalyst, whereas anion-binding catalysis relies on the formation of an ion pair by binding to the counter-anion of an ionic substrate. The ionization of the corresponding substrate can either occur before the coordination to the anion or the catalyst itself directly participates in the ionization step by an anion abstraction-type

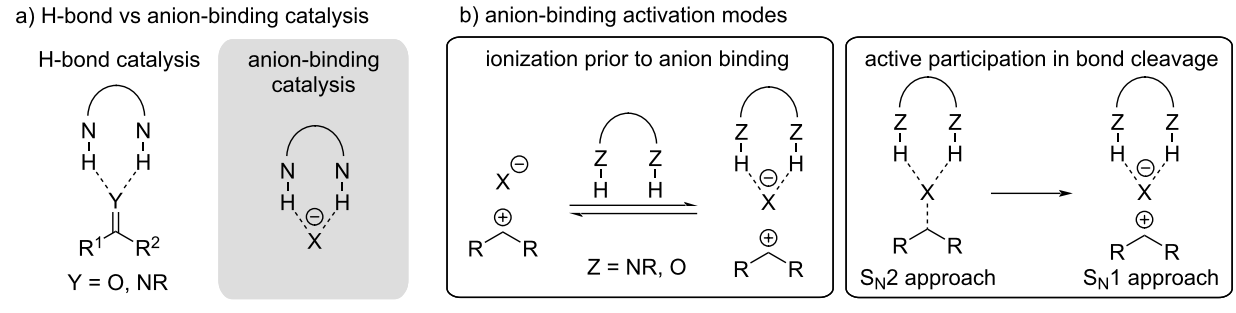
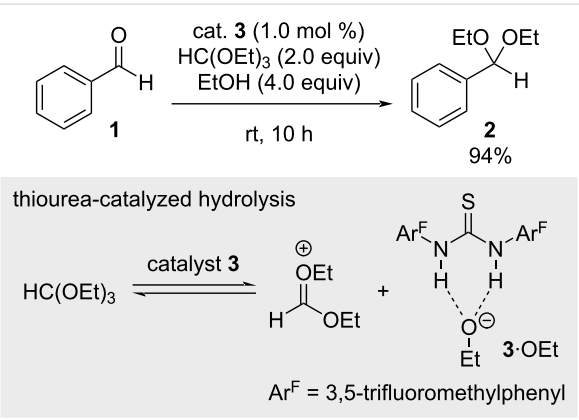


Figure 2: a) H-bond vs anion-binding catalysis and b) activation modes in anion-binding catalysis.

process (Figure 2b). In the latter approach, the C–X bond cleavage can then either follow a S_N1 or S_N2 pathway.

For enantioselective purposes, solvation of the ion pair is crucial for obtaining high stereoinduction. While more polar solvents give solvent-separated or solvent-shared ion pairs – in which the components have their own solvent shells –, nonpolar solvents are more likely to lead to contact-ion pairs. As such, the cation and anion are in closer proximity as one solvent shell is shared. If a chiral catalyst binds then to the anion, a chiral contact-ion pair can be formed, which is necessary for the transfer of the chiral information to the product. As a consequence, most of the reported methods embracing enantioselective anion-binding catalysis rely on the use of nonpolar solvents such as ethers or aromatic compounds.

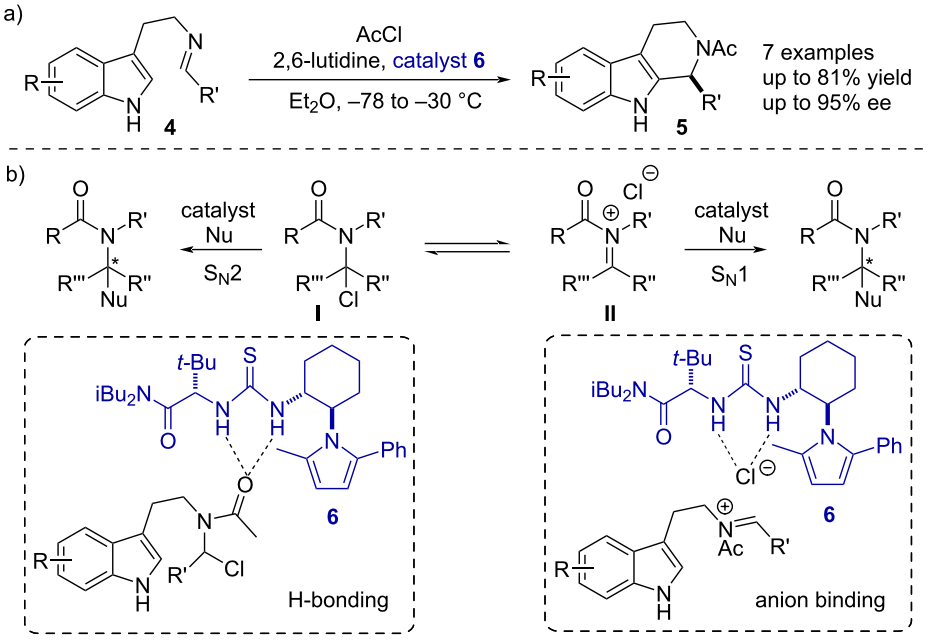


Scheme 1: First proposed anion-binding mechanism in the thiourea-catalyzed acetalization of benzaldehyde.

Pioneering work

The concept of anion-binding catalysis was first penned by Schreiner et al. in 2006, who realized the acetalization of benzaldehyde (**1**) with a thiourea catalyst (**3**, Scheme 1) [30,31]. They proposed the reaction to proceed via thiourea-catalyzed orthoester hydrolysis, leading to the formation of a catalyst-bound alkoxide species (**3**·OEt) that is then able to attack the benzaldehyde for product **2** formation.

However, it took some time until the scientific community started considering and taken cognizance of the potential of this type of activation mode in catalysis. In this regard, Jacobsen and co-workers reported in 2004 an asymmetric Pictet–Spengler reaction of tryptamine-derived imines **4** in the presence of acetyl chloride and 2,6-lutidine, where the chiral thiourea catalyst **6** was employed to enable good yields and enantioselectivities (Scheme 2a) [32]. The initial motivation of their first studies revolved around hydrogen bond donor catalysts and their application in *N*-acyliminium ion reactions. At this point, the mechanistic proposal, albeit speculative, was based on the hypothesis that neutral chloroamide structures **I** were the reactive intermediates in the reaction. Under this premise, H-bonding to the carbonyl group was proposed as the binding mode of the catalyst and the reaction to proceed via a S_N2-type mecha-



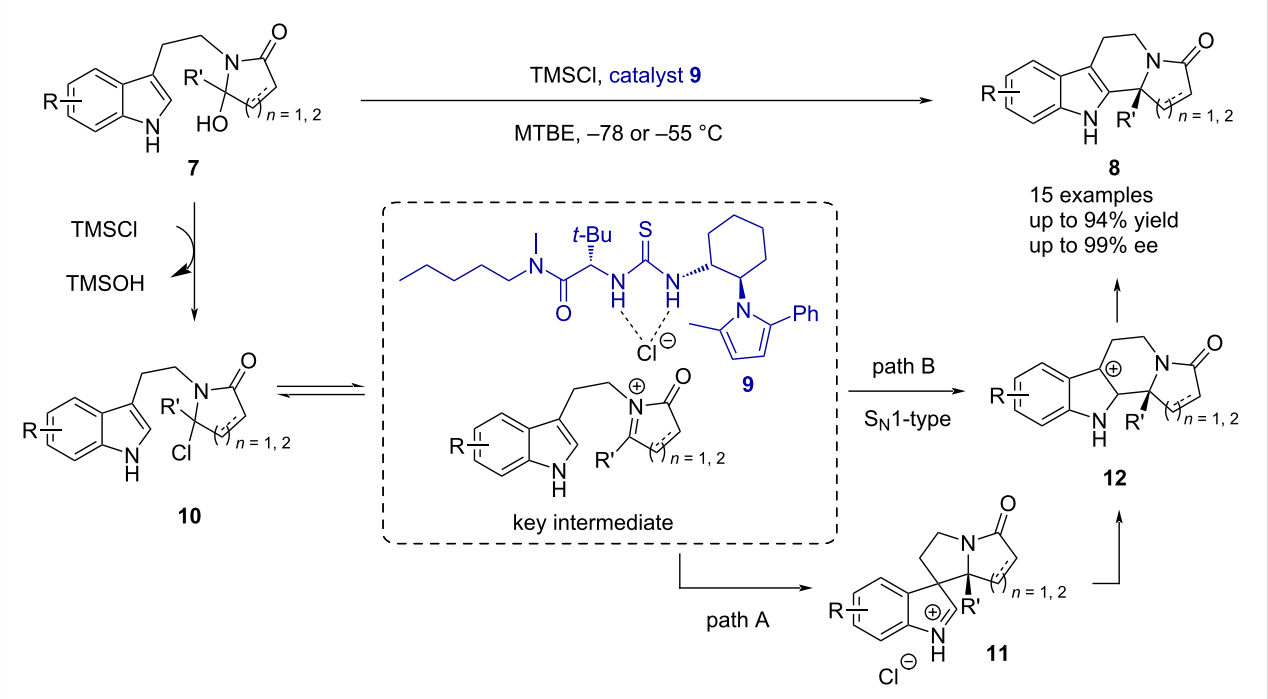
Scheme 2: a) Thiourea-catalyzed enantioselective acyl-Pictet–Spengler reaction of tryptamine-derived imines **4**. b) Equilibrium between the ionic (S_N1-type mechanism) and neutral form (S_N2-type reaction). The key intermediates for the respective binding modes are displayed in the boxes.

nism (Scheme 2b, left). Not considered at that time was the anion-binding pathway through the iminium chloride salt **II**, which would proceed via a S_N1-type mechanism (Scheme 2b, right).

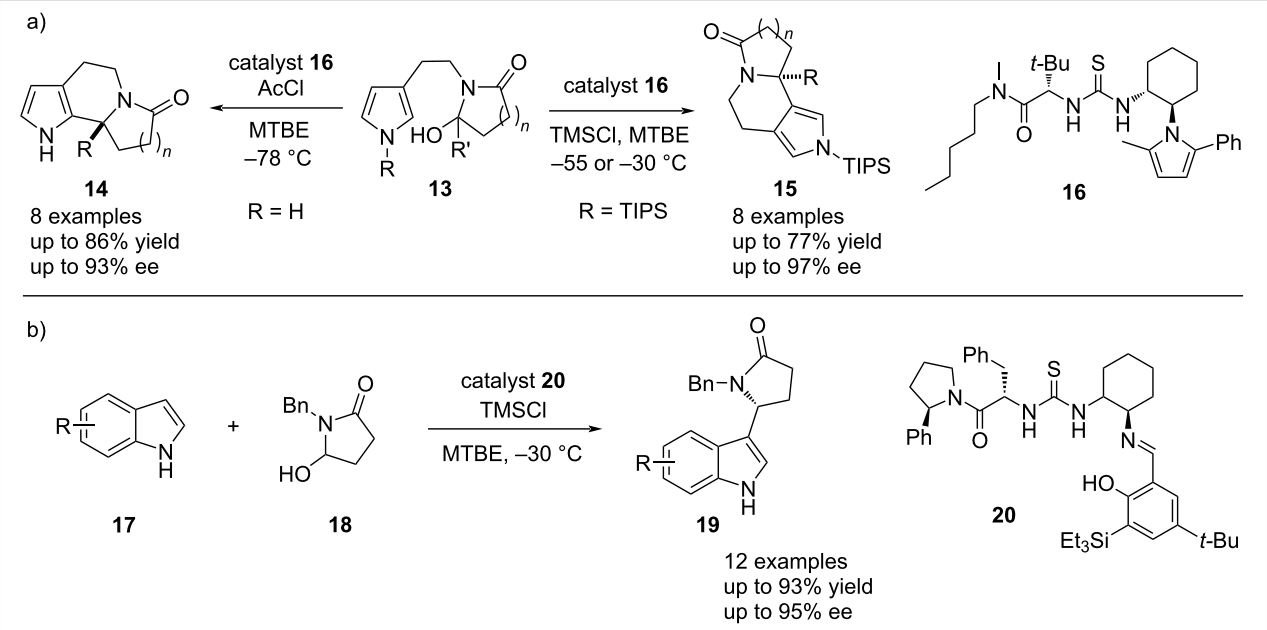
However, based on the freshly coined concept of anion-binding activation [30,31] and as the exact interaction mode of the catalyst remained elusive, Jacobsen's group focused their attention towards mechanistic studies of thiourea-catalyzed reactions. In 2007, they reported a Pictet–Spengler cyclization reaction of succinimide and glutarimide-derived hydroxylactams **7** (Scheme 3) [33]. This system was designed in a way that key experimental observations could be made to analyze whether a S_N1 or S_N2-type mechanism takes place. A strong dependence of the enantioselectivity on the counterion and solvent was observed and, therefore, a S_N1-type mechanism was concluded. Furthermore, their studies proved that an ion pair is required for the reaction to proceed and, most importantly, that the thiourea catalyst **9** interacts with the chloride of the *N*-acyliminium ion as opposed to the carbonyl group.

Based on this concept, the applicability of *N*-acyliminium chlorides in thiourea-catalyzed anion-binding reactions was further explored. In 2008, an intramolecular asymmetric Pictet–Spengler-type cyclization reaction with pyrrole derivatives **13** was reported. The authors were not only able to control the enantioselectivity, but this system also allowed the control over regioselectivity (C2 vs C4 cyclization) through alteration of the *N*-substituent of the pyrrole substrate and the acylating reagent (Scheme 4a) [34]. This example showcases that next to the counterion, the acylating group can have a major influence on these types of reactions. The first thiourea-catalyzed asymmetric intermolecular reaction with *N*-acyliminium chlorides was then also realized by the same group in 2009. Therein, nucleophilic addition of indoles **17** to the *N*-acyliminium chlorides was achieved with excellent enantiomeric excess (Scheme 4b) [35].

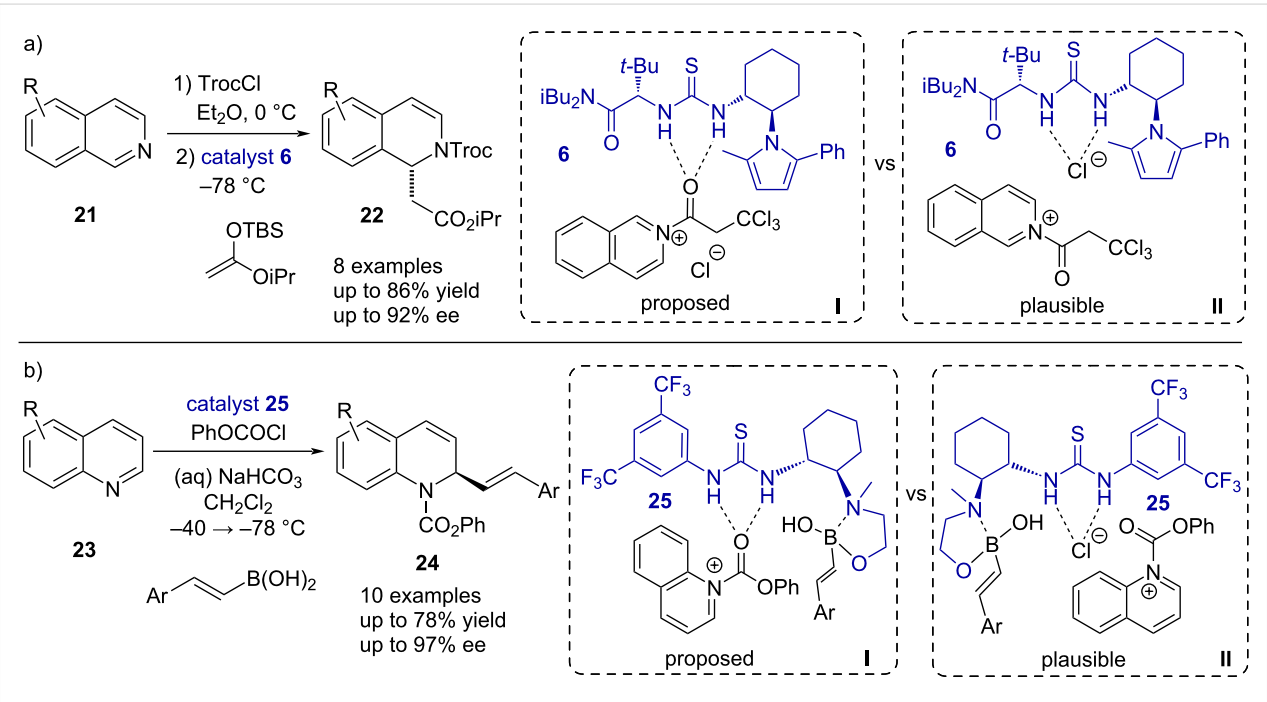
During this early period, the group of Jacobsen also reported an asymmetric thiourea-catalyzed Reissert reaction of isoquinolines **21** (Scheme 5a) [36]. The mechanism proceeds by initial activation of the isoquinoline via *N*-acylation and subsequent dearomatization by a nucleophilic attack in the C1 position. Analogously to the Pictet–Spengler cyclization, the group initially speculated that the thiourea catalyst **6** interacts with the carbonyl function of the amide intermediate **I** and, thus, a S_N2-type mechanism via hydrogen bonding catalysis was proposed. A similar bidentate carbonyl activation proposal was later on reported from the Takemoto group in 2007, where the less reactive quinoline derivatives **23** were employed in a thiourea-catalyzed Reissert reaction (Scheme 5b) [37]. In both cases, however, the binding mode of the catalyst can rather be described by the formation of a close ion pair with the chloride of the *N*-acyl(iso)quinolinium intermediate **II**. Hence, the reaction



Scheme 3: Proposed mechanism of the thiourea-catalyzed enantioselective Pictet–Spengler reaction of hydroxylactams **7**. First provided evidence of anion binding instead of carbonyl hydrogen bonding.



Scheme 4: a) Thiourea-catalyzed intramolecular Pictet–Spengler-type cyclization of hydroxylactam-derived *N*-acyliminium chlorides and b) thiourea-catalyzed intermolecular hydroxy lactam-derived *N*-acyliminium chlorides with indoles.



Scheme 5: Enantioselective Reissert-type reactions of a) (iso)quinolines with silyl ketene acetals, and b) vinylboronic acids.

would follow a S_N1-type mechanism via anion-binding catalysis. In Jacobsen's report, the acylating agent 2,2,2-trichloroethyl chloroformate (TrocCl) and nucleophilic silyl ketene acetals were employed to obtain the dihydroisoquinolines **22** in good yields and enantioselectivities up to 92% ee. The Takemoto group with their system also achieved yields up to 78% and enantioselectivities up to 97% ee, using phenyl chloroformate as the acylating reagent and vinylboronic acids as the nucleophiles in the presence of sodium bicarbonate.

The key finding of anion-binding activation opened up a whole new field for asymmetric transformations. Thus, many asym-

metric transformations relying on this type of activation mode were subsequently developed [15,23-29]. It is worthy to be mentioned, that Reissert dearomatizations of *N*-heteroarenes, especially of isoquinolines [36], and nucleophilic addition to 1-chloroisochromanes [38] have become benchmark reactions in the context of anion-binding catalysis. Besides reports of thiourea-catalyzed reactions with different nucleophiles [39,40], the focus has also been turned to the development of other catalyst systems that are not based on N–H bonds, such as the chiral silanediol catalysts first reported by Mattson and co-workers in 2013 [19,20]. Furthermore, it is worthy to mention that in parallel to the investigations towards new chiral catalysts and asymmetric methodologies, a few innovative nonchiral alternative H-donor or halide-binding organocatalysts, like, e.g., tridentate phosphoramides [41], onium salts [42] such as Berkessel's pyridinium systems [43], or Huber's bis-iodo imidazolium [44] and neutral bridged 2,6-diiodo-3,4,5-trifluorophenyl-type catalysts [45]. Additionally, the first asymmetric systems involving purely halogen bond donor catalysis have recently been developed by the groups of Huber [46] and García Mancheño [47]. Moreover, though chloride as halide counter-anion still being particularly prominent, the application of anion-binding catalysis has been successfully demonstrated for other halogens, and different types of substrates such as the benzhydryl cation [48-51].

Halides as counter-anions vs nucleophiles

The latest advances in anion-binding catalysis not only allowed for excellent translation of stereochemical information, but also delivered an insight into the mechanism of the anion-binding process. However, the counter-anion involved, and more precisely the halide anion itself, has remained a mere spectator in the developed catalyses (Figure 3a). Nevertheless, recent reports showed that the bound halide anions can also engage as the nucleophile, which has been exploited in ring opening and related reactions (Figure 3b).

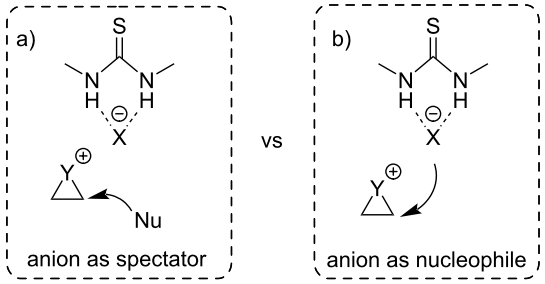
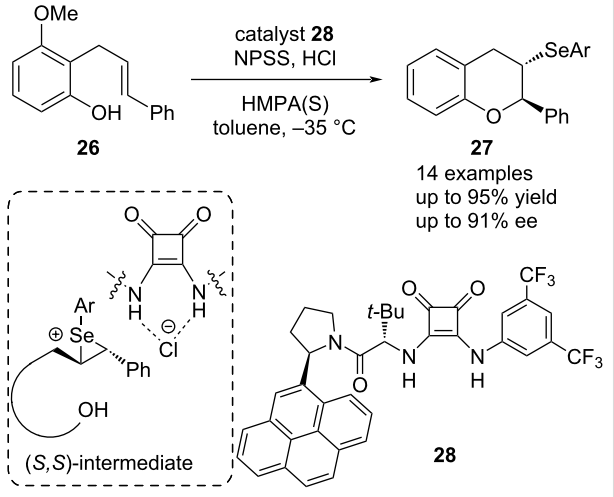


Figure 3: Role of the counter-anion: a) Anion acting as a spectator and b) anion participating directly as the nucleophile.

In general, the idea of enantioselective ring opening produces two fixed stereocenters during one synthetic operation, increasing the complexity of the product significantly. This makes asymmetric ring-opening reactions a powerful tool for the synthesis of highly complex target molecules. With this concept in mind, anion-binding catalysis has successfully been employed for asymmetric ring-opening reactions, implying halide anions as both mere counter-anions in the ion-pair complex or active nucleophiles.

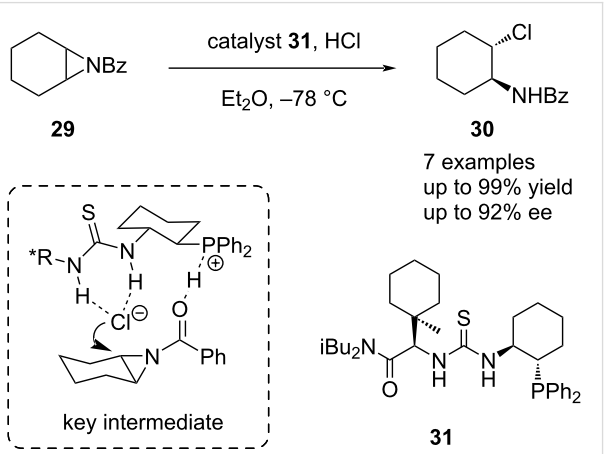
In 2014, Jacobsen et al. developed a highly enantioselective selenocyclization reaction of olefins **26**, using the chiral squaramide **28** as a dual hydrogen bond donor (Scheme 6) [16]. Although early-stage enantio-enrichment during the introduction of selenium is hard to maintain due to the conformational lability of the seleniranium ion [52-54], this initial problem can be exploited through the addition of an anion-binding catalyst. In this way, the configurational scrambling is used for a dynamic kinetic resolution during the intramolecular nucleophilic opening of the seleniranium ring. Through favorable cation–π interactions with the catalyst, the (*S*,*S*)-intermediate reacts faster than its opposing enantiomer, allowing for excellent yields up to 95% and high enantioselectivities up to 91% ee.



Scheme 6: Enantioselective selenocyclization catalyzed by squaramide **28**.

In contrast to the previous example, in which the chloride anion was only a spectator linking the substrate and catalyst in the presence of an external nucleophile, halides can also be tuned to participate as the nucleophile in certain reactions. In theory, the close association of the catalyst and the anionic nucleophile might allow for better stereocontrol. An early example utilizing this strategy was provided by Jacobsen and co-workers for the desymmetrization of *meso*-aziridines **29**. In their work, the bifunctional phosphinothiourea catalyst **31** promoted the C–N

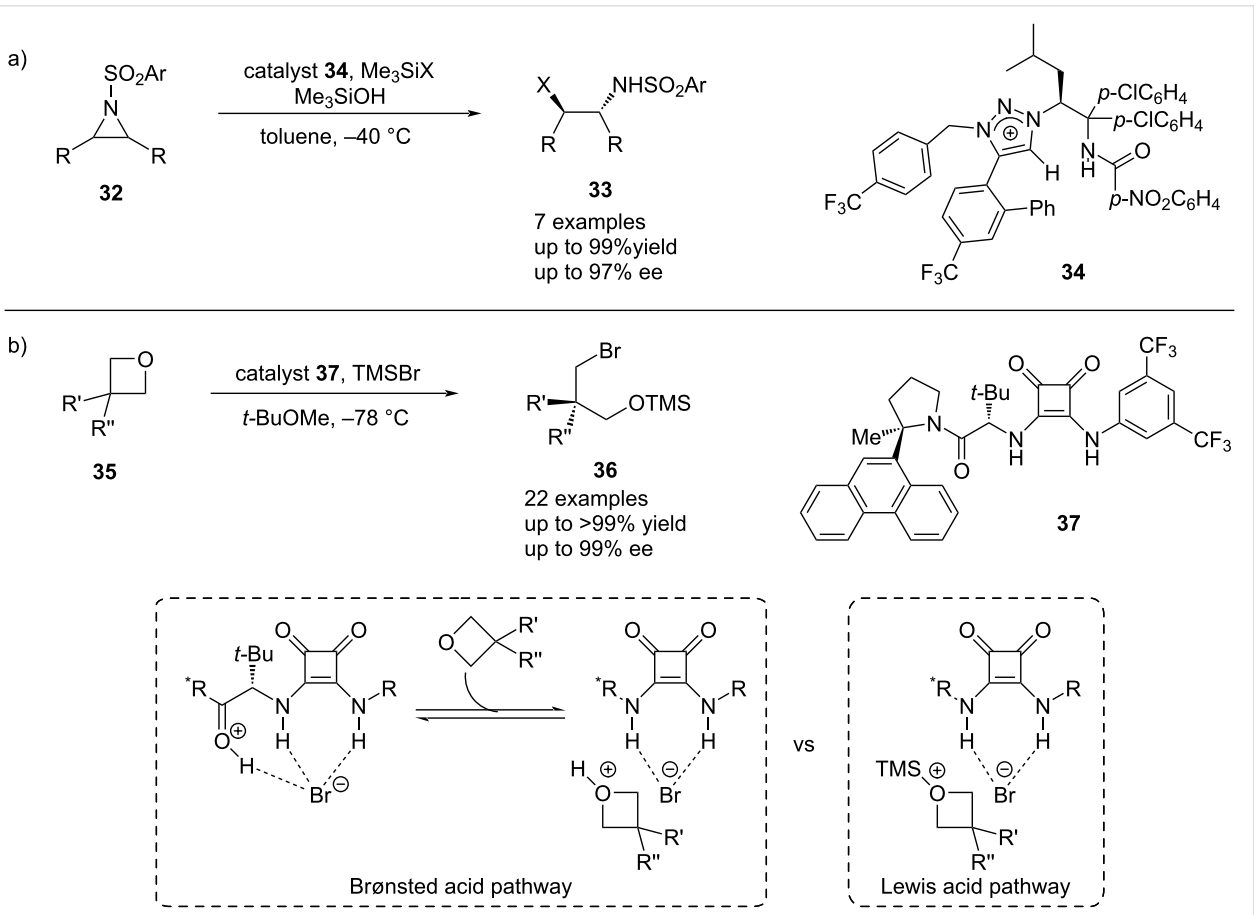
bond cleavage by hydrochloric acid upon initial protonation (Scheme 7) [55]. Subsequently, the catalyst-bound chloride anion performs a S_N2-type attack on the coordinated benzoyl-protected aziridine, which leads to a formal addition of HCl.



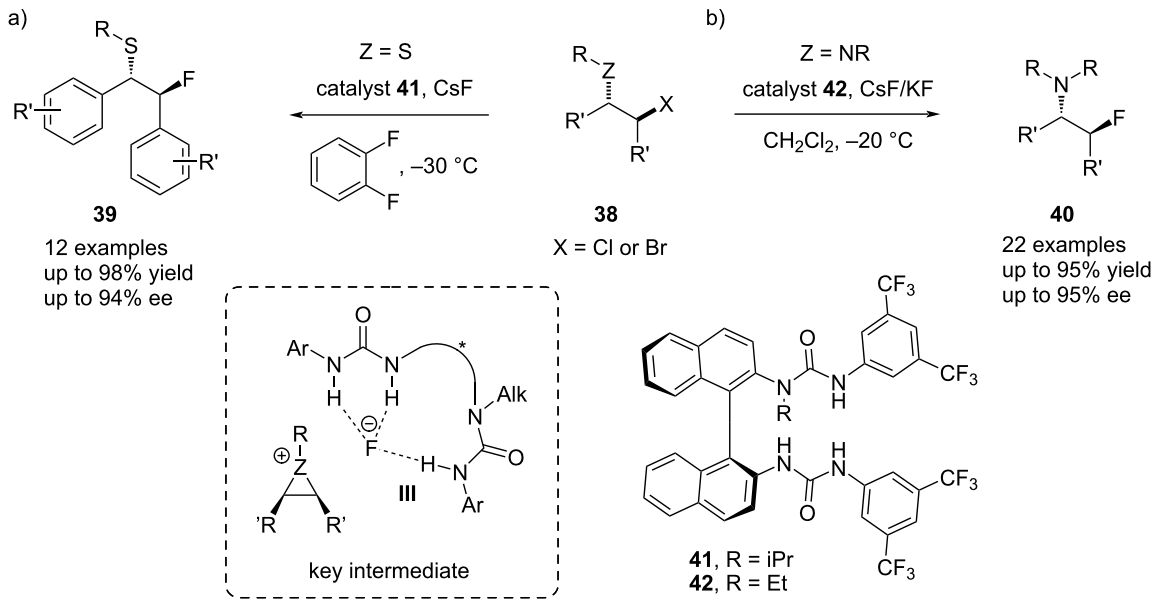
Scheme 7: Desymmetrization of *meso*-aziridines catalyzed by bifunctional thiourea catalyst **31**.

This concept was further developed and successfully employed by Ooi in the desymmetrization of *meso*-aziridines **32** with TMSX as chloride and bromide with similar performances as nucleophile precursors using a triazolium-amide chiral catalyst **34** [21] (Scheme 8a), as well as by Jacobsen in the desymmetrization of oxetanes **35** using TMSBr and squaramide **37** as catalyst [56] (Scheme 8b). For the latter, a more detailed mechanistic study was recently provided [57]. The existence of two competing Brønsted acid and Lewis acid mechanistic pathways leading to the same product with high enantioselectivity was then uncovered. Jacobsen et al. reasoned that the key for this highly selective transformation lies in attractive cation–π and cation–dipole secondary interactions between the catalyst and the substrate, which exclusively stabilize the transition state that forms the major enantiomer.

Furthermore, Gouverneur and co-workers established an enantioselective nucleophilic fluorination protocol using a chiral bis-urea catalyst **41** and CsF as an inorganic fluoride source (Scheme 9a) [18]. By employing in situ-generated *meso*-episulfonium ions, they were able to synthesize β-fluorosulfides **39** in



Scheme 8: Anion-binding-catalyzed desymmetrization of a) *meso*-aziridines catalyzed by chiral triazolium catalyst **34** by Ooi et al., and b) oxetans catalyzed by chiral squaramide **37** by Jacobsen et al.



Scheme 9: Bis-urea-catalyzed enantioselective fluorination of a) β-bromosulfides and b) β-haloamines by Gouverneur et al.

high yields up to 98% and enantioselectivities up to 94% ee. The key step in this transformation is the formation of the noncovalent catalyst–fluoride complex **III** during the phase-transfer step. This provides low amounts of reactive, nucleophilic fluoride in the nonpolar solution, circumventing thereby selectivity and reactivity issues owing to the high basicity of alkali metal fluorides [58-62]. By modifying the reaction conditions, the same group was also able to substitute CsF with KF, making their protocol more cost-effective and widening the scope of the reaction to include β-chloroamines and β-bromoamines as aziridinium precursors **38** (Scheme 9b). In this way, medicinal interesting β-fluoroamines **40** were obtained in good yields and high enantioselectivity up to 95% ee [63].

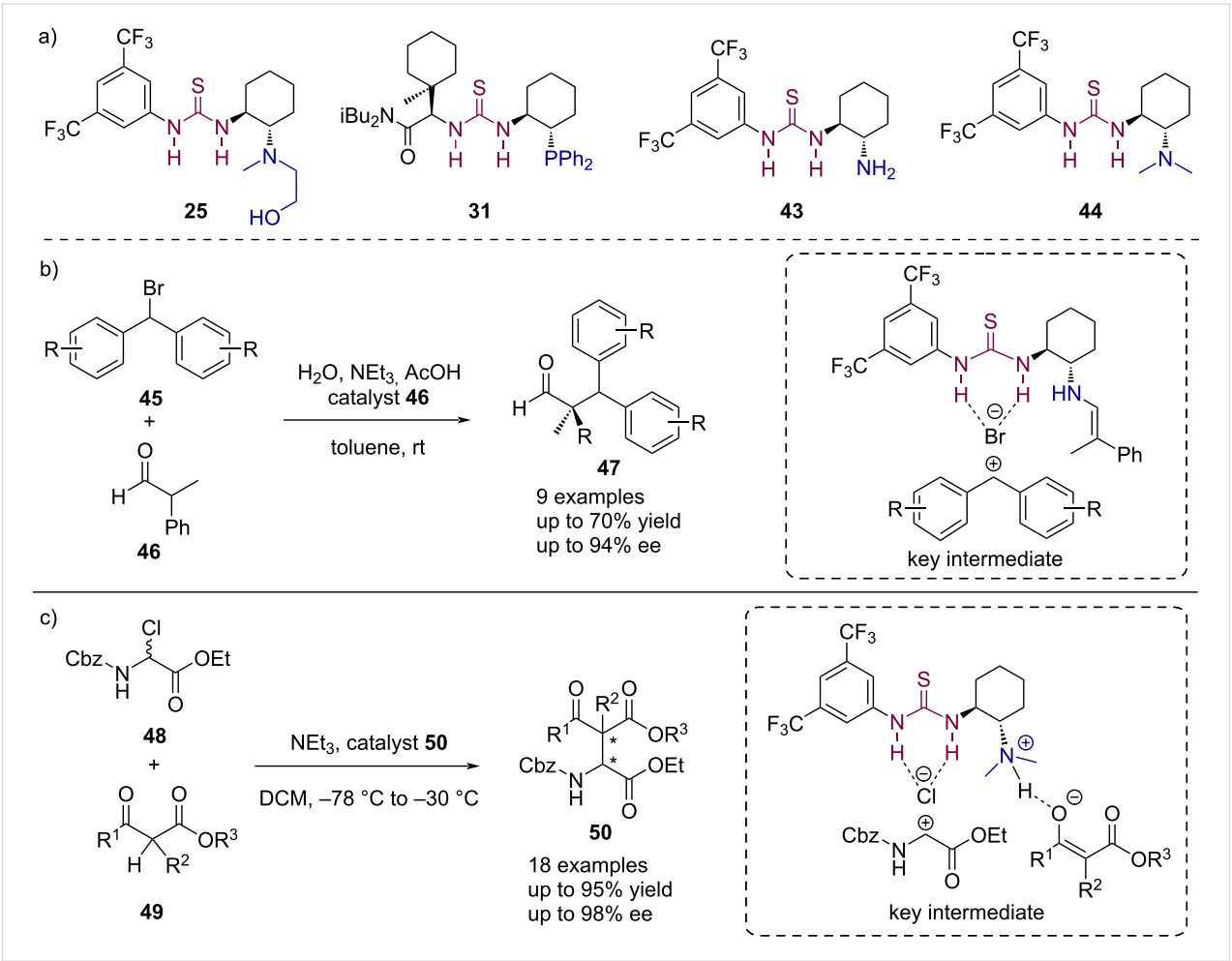
Evolution of catalyst designs: from bidentate to supramolecular multidentate anion-binding catalysts

Despite the evident potential that anion-binding catalysis showed in the pioneering publications – especially in regard to exerting high stereocontrol –, the strategy was still faced with typical limiting factors of hydrogen bond donor catalysis, ranging from high catalyst loadings to high dilution, long reaction times and, in some cases, insufficient chirality transfer into the products. As a consequence, many efforts have been spent to overcome those limitations. Some of them rely on the design of more efficient H-donor catalyst structures, offering additional noncovalent interactions in order to provide extra coordination points with the anion, substrate and/or reagent. The most important approaches in this direction used to date are presented in the following.

(Thio)urea and squaramide catalysts' designs

Basic/nucleophilic – H-donor bifunctional catalysts: Over the past decades, chiral bifunctional catalysts bearing a thiourea as HB-donor and a basic or nucleophilic group such as an amine have emerged as a powerful tool in organocatalysis by assisting to enhance the catalyst performance and fixation of both reaction partners [64-66]. This strategy has also been used in the field of anion-binding catalysis, by designing hydrogen bond donor catalysts with the appropriate additional functionalities in their chiral backbone (Scheme 10a). Some examples have been already presented in the previous sections. For example, catalyst **25** bearing a nucleophilic aminoalcohol functionality interacts with the boronic acid reagent in the Reissert-type reaction with acylated quinolines (Scheme 5b) [36], while the phosphine moiety in the bifunctional phosphinothiourea catalyst **31** allows for heterolytic cleavage of HCl as displayed in Scheme 7 [55].

Moreover, other catalysts with amine functional groups were found more efficient in the enantioselective α-alkylation of aldehydes (Scheme 10b) [48] or in the asymmetric Mannich synthesis of α-amino esters using Takemoto's bifunctional catalyst **44** [67] (Scheme 10c) described by Jacobsen and co-workers in 2010 and 2014, respectively [50]. In the one hand, while the thiourea unit in catalyst **43** abstracts the bromide in **45** and forms an electrophilic benzhydryl cation, the



Scheme 10: a) Bifunctional thiourea anion-binding – basic/nucleophilic catalysts. Selected applications in b) enantioselective α-alkylation of aldehydes, and c) asymmetric Mannich synthesis of α-amino esters.

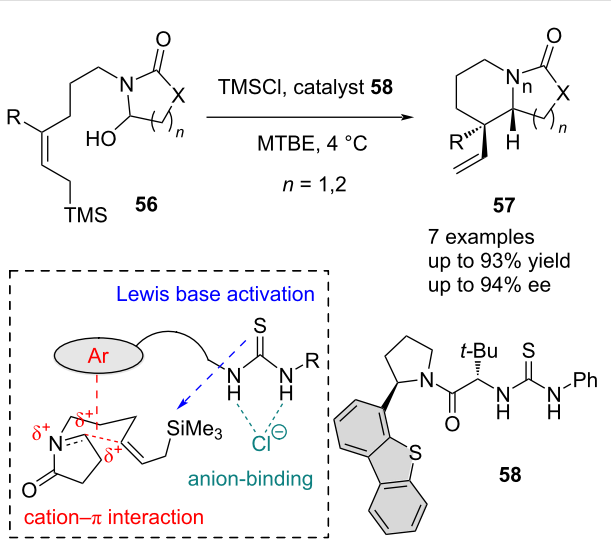
free amine group activates the aldehyde substrate **46**. The resulting enamine can then serve as the nucleophile as displayed in the key intermediate shown in Scheme 10b. As a result, yields up to 70% and excellent enantioselectivities up to 94% ee could be achieved at room temperature. On the other hand, the secondary amine group in Takemoto's catalyst **44** acts as a base, abstracting the proton of the enolizable β-ketoester **49** and thus activating the nucleophilic species. This enolate then adds to the cationic substrate from in situ upon halide abstraction of α-chloro amino acid derivatives **48** by the thiourea moiety of the bifunctional catalyst (Scheme 10c, key intermediate), leading to excellent yields and enantioselectivities up to 95% and 98% ee, respectively.

Cation–π interaction: expanding the functionality of hydrogen bond donor catalysts: The development of hydrogen bond donor anion-binding catalysts mainly focuses on the interaction and binding properties towards the anionic species. However, the cationic counterpart can have important effects on the kinetics of the systems. This hypothesis has evidently been identified in enzymatic reactions [68]. Mechanistic studies have shown that in such processes, cationic species are stabilized through various attractive interactions with aromatic residues of the enzymes. In fact, these additional stabilizing effects can be exploited in the design of more effective noncovalent catalytic structures for anion-binding catalysis. In this regard, cation–π interactions have been used to develop several types of anion binding-catalyzed transformations such as cyclizations or nucleophilic additions.

Inspired by cationic terpene-type cyclization cascades, Jacobsen's group turned their attention to the structure and properties of the chiral part of thiourea catalysts by introducing extended π-groups. A series of thiourea catalysts **53**–**55** with varying aromatic residues were synthesized to elucidate if interactions with the anionic and cationic species could simultaneously be achieved. Hence, in 2010, they successfully showed that such rather small catalysts can mimic nature's principle of

cation–π interactions, allowing for a highly enantioselective polycylization reaction of **51** (Scheme 11) [69]. Modification of the aromatic ring system on the chiral side of the thiourea catalyst proved to be crucial, as both the reactivity and the enantioselectivity were significantly influenced by the stabilization of the cationic substrate and not by interactions with the anion. Specifically, extension of the aromatic system from the simple phenyl (**53**) over the 1-naphthyl (**54**) to the 4-pyrenyl (**55**) substituent led to improved yields from 12% to 72% and enantioselectivities from 25% to 94% ee.

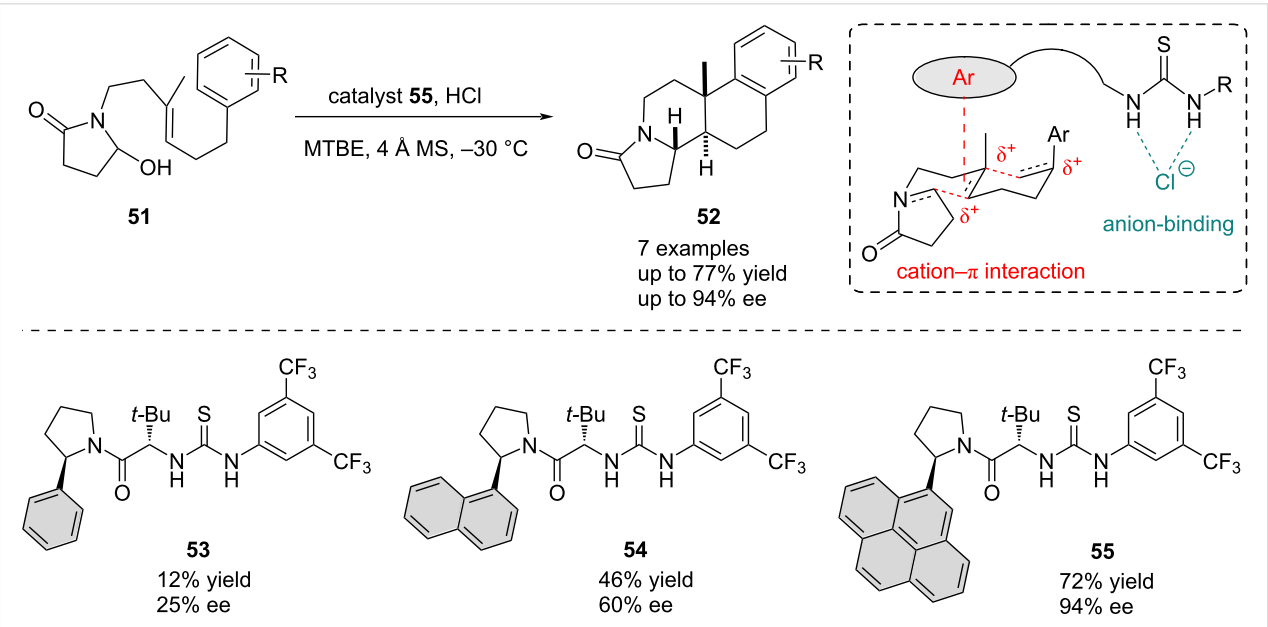
In 2016, this cation–π strategy was further employed for the development of an enantioselective aza-Sakurai cyclization (Scheme 12) [70]. In this transformation, a chiral thiourea catalyst **58** with a dibenzothiophene functionality serves as a dual H-bond donor and Lewis base to facilitate the cyclization of hydroxylactams **56**. Thus, indolizine and quinolidizine frameworks **57** were accessed in excellent yields up to 93% and enantioselectivities up to 94% ee. Increased aromaticity proved again to be essential for achieving high enantioselectivities. Additionally, Lewis base activation of the allylsilane substrates through the thiourea sulfur atom is proposed to be crucial, while the urea analog of the catalysts proved less efficient and led to diminished reactivity and stereoselectivity. Further mechanistic studies corroborated this hypothesis as more electron-rich allylsilane derivatives were consumed slower despite being inherently more nucleophilic.



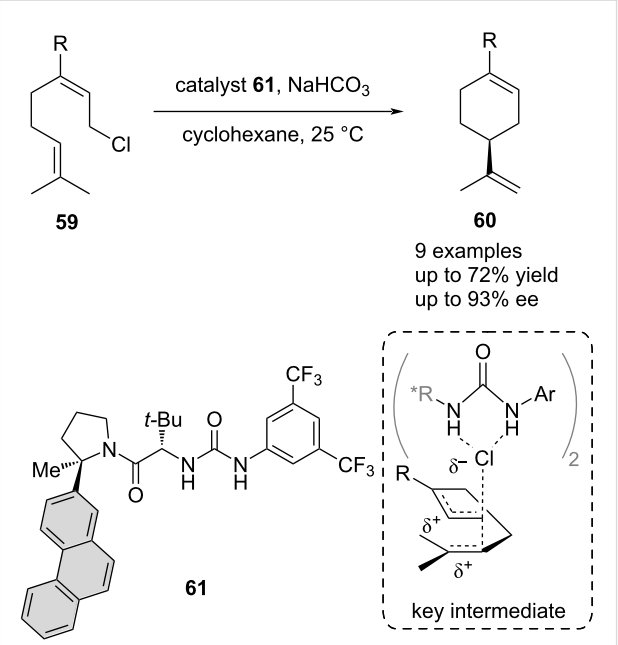
Scheme 12: Enantioselective aza-Sakurai cyclization of hydroxylactams **56** implicating additional cation–π and Lewis base activation.

Another example highlighting the importance of sidechain catalyst design was given by Jacobsen et al. in the tail-to-head cyclization of neryl chloride and derivatives **59** (Scheme 13) [17]. Mechanistic studies and DFT calculations revealed that an extended π-system in the sidechain of the bidentate urea catalyst **61** was required to form the key aggregate involving two catalyst molecules and the substrate. This complex is the one involved in the rate and enantio-determining ionization step, allowing to furnish the desired products **60** in up to 93% ee.

Finally, similar examples utilizing cation–π interactions have been provided by the group of Jacobsen in the nucleophilic ad-



Scheme 11: Thiourea-catalyzed enantioselective polycyclization reaction of hydroxylactams **51** through cation–π interaction.



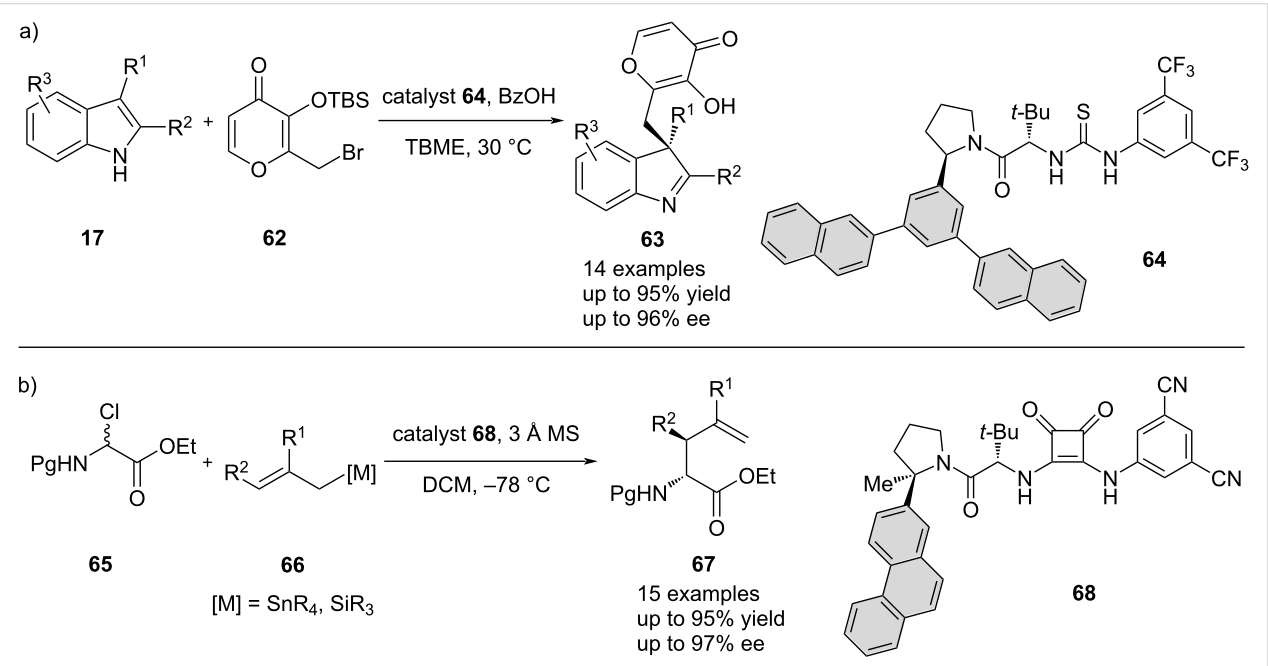
Scheme 13: Enantioselective tail-to-head cyclization of neryl chloride derivatives.

dition of indoles **17** to pyranones **62** (Scheme 14a) [71], as well as in the enantioselective synthesis of α-allyl amino esters **67** by the reaction of α-chloro amino acid derivatives **65** with allyltin and allylsilane **66** nucleophiles [72] (Scheme 14b). In both cases, an extended π-system on the side chain of the chiral thiourea catalysts is able to interact with the reactant and was required to achieve high enantioinductions, providing the corresponding products in excellent yields up to 95% and enantioselectivities up to 96% and 97% ee, respectively.

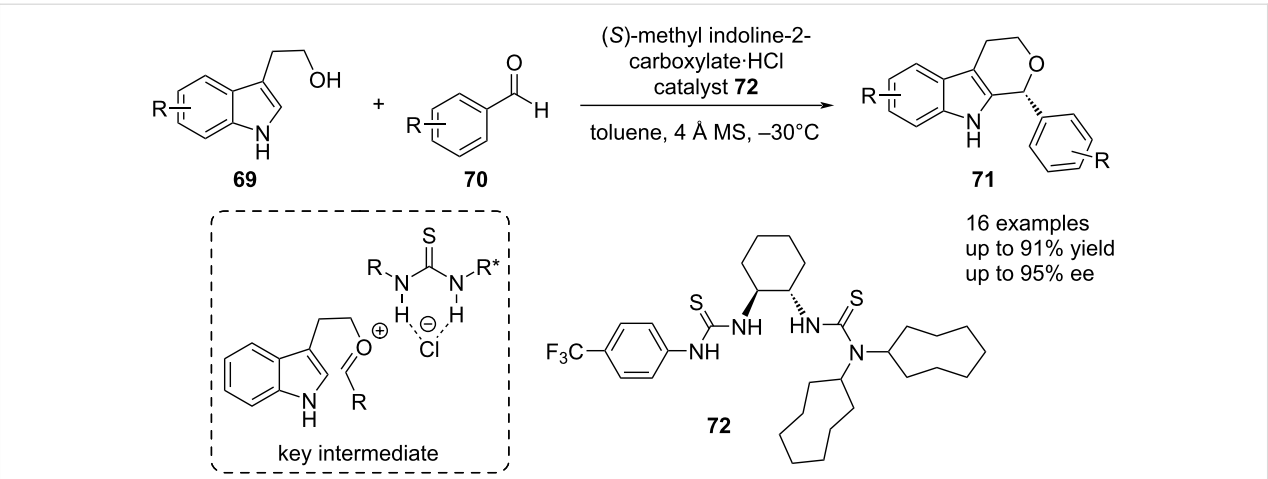
Bis- and macrocyclic thiourea catalysts

Besides the introduction of cation–π interactions in anion-binding catalyst design, bisthiourea catalysts have been applied with the aim of accelerating certain catalytic reactions. In this regard, the group of Seidel reported in 2016 an enantioselective HCl co-catalyzed oxa-Pictet–Spengler reaction employing bisthiourea catalyst **72** bearing two aliphatic groups at one of the nitrogen atoms of one thiourea (Scheme 15) [51]. The key intermediate in this reaction system is the contact ion pair of the thiourea catalyst with the in situ-generated oxycarbenium ion, which enables high enantioselectivities up to 95% ee and yields up to 91%. Furthermore, an investigation of the involved halide counter-anion revealed that chloride was the most potent one in regards of both yield and enantioinduction. Bromine and iodine on the other hand, afforded the final product **71** in lower yields (71% and 90%) and also a detriment in enantioinduction was observed with 76% and 46% ee, respectively.

Alternatively, Jacobsen´s group carried out a series of studies to elucidate whether the targeted design of a catalyst can increase its efficiency for a given reaction [73-76]. For this purpose, based on their initial findings in 2008 [38], the enantioselective addition of silyl ketene acetals to racemic 1-chloroisochromane

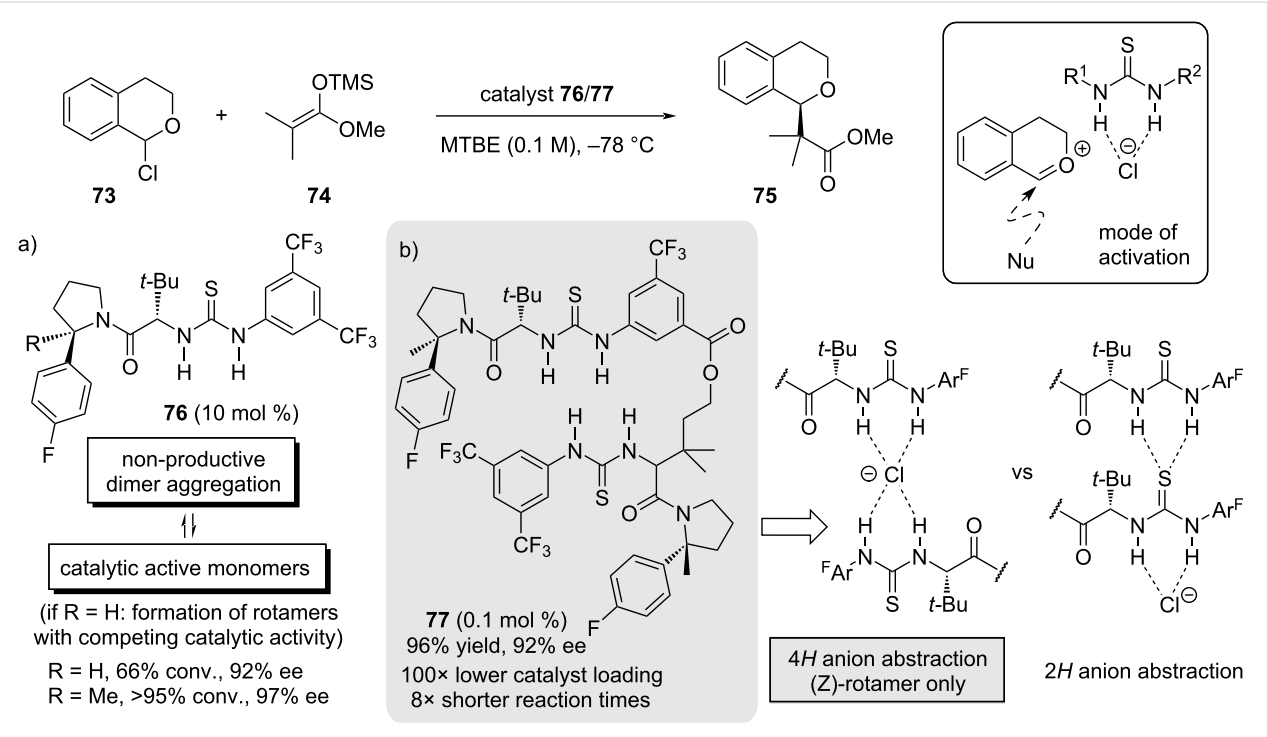


Scheme 14: Cation–π interactions in anion binding-catalyzed asymmetric addition reactions: a) addition of indoles to pyrones and b) allylation of α-chloro glycinates.



Scheme 15: Bisthiourea catalyzed oxa-Pictet–Spengler reaction of indole-based alcohols and aromatic aldehydes under weakly acidic conditions.

(**73**) was more closely examined (Scheme 16) [73-76]. In this type of reaction, thiourea catalyst **76** actively engages in the ionization step by chloride abstraction that leads to the formation of an oxocarbenium intermediate, which then undergoes the stereoselective addition of the nucleophile. Mechanistic insights revealed that two thiourea molecules are, in fact, needed and cooperatively participate in the activation of **73**. However, nonproductive dimeric aggregates form under standard reaction conditions. These dimers exist in different combinations of the thiourea rotamers and lead to competing catalytic pathways (Scheme 16a). Moreover, anion abstraction was calculated to proceed either through a 4*H* abstraction mechanism of two thioureas binding simultaneously to the chloride or through a cooperative 2*H* abstraction mechanism. These findings proved to be decisive in the development of new and more efficient anion-binding catalysts. By introducing a methyl group (R = Me) into the pyrrolidine moiety of the initial catalyst design, the amide is conformationally constricted to the (*Z*)-



Scheme 16: Anion-binding catalyst development in the enantioselective addition of silyl ketene acetals to 1-chloroisochromane (**73**). Limiting factors and influences on catalyst activation and anion abstraction.

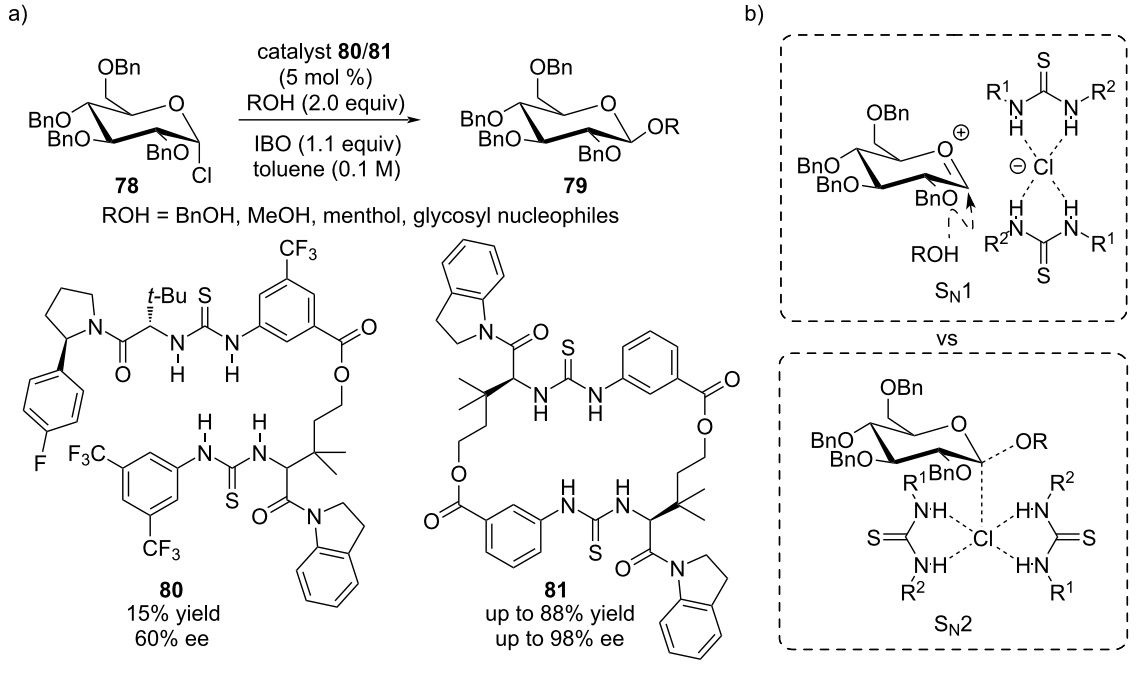
rotamer [75]. Consequently, improved enantioselectivity and catalytic efficiency could be observed (>95% conv., 97% ee). This design was then further refined by covalently linking two thiourea molecules together to give bis-thiourea catalyst **77** (Scheme 16b) [76]. Due to the linkage of the two molecules, the participating hydrogen bonds are aligned such that a 4*H*-abstraction mode is achieved, which is more likely to ensure higher catalyst activity in the activation step than the competing 2*H*-abstraction pathway. Indeed, with multidentate bis-thiourea catalyst **77**, the catalyst loading could be decreased from 10 to only 0.1 mol % without significant loss of enantioselectivity (96% yield, 92% ee). Ultimately, this work gave a tremendous insight and a myriad of applications of such bis-thiourea catalysts with halogen counter-anions and phosphates [73-78].

Nevertheless, the activation of α-chloro ethers via anion abstraction continued to be a foundation for anion-binding catalyst evolution. In fact, Jacobsen's group further refined the design of their tetradentate N–H-bond donor catalyst **80** by covalently linking it into the more rigid macrocycle **81** (Scheme 17a) [78]. Compared to bis-thiourea **80**, the higher rigidity in the macrocycle **81** not only enforces halide abstraction significantly, but also allowed for a better control of the stereoselectivity in the glycosylation of glycosyl halides **78** with a variety of coupling partners. In this way, the corresponding β-glycosides **79** were almost exclusively obtained (up to 88% yield, up to 98% ee). The reaction was found to proceed stereospecifically with inversion of the anomeric configuration and, therefore, being dependent on the configuration of the electrophilic partner **78**. With this observation, the reaction was concluded to proceed via a S_N2 mechanism. However, mechanistic investigations revealed the existence of a competing S_N1 pathway featuring an oxocarbenium cation, which explains the formation of the minor diastereoisomer (Scheme 17b).

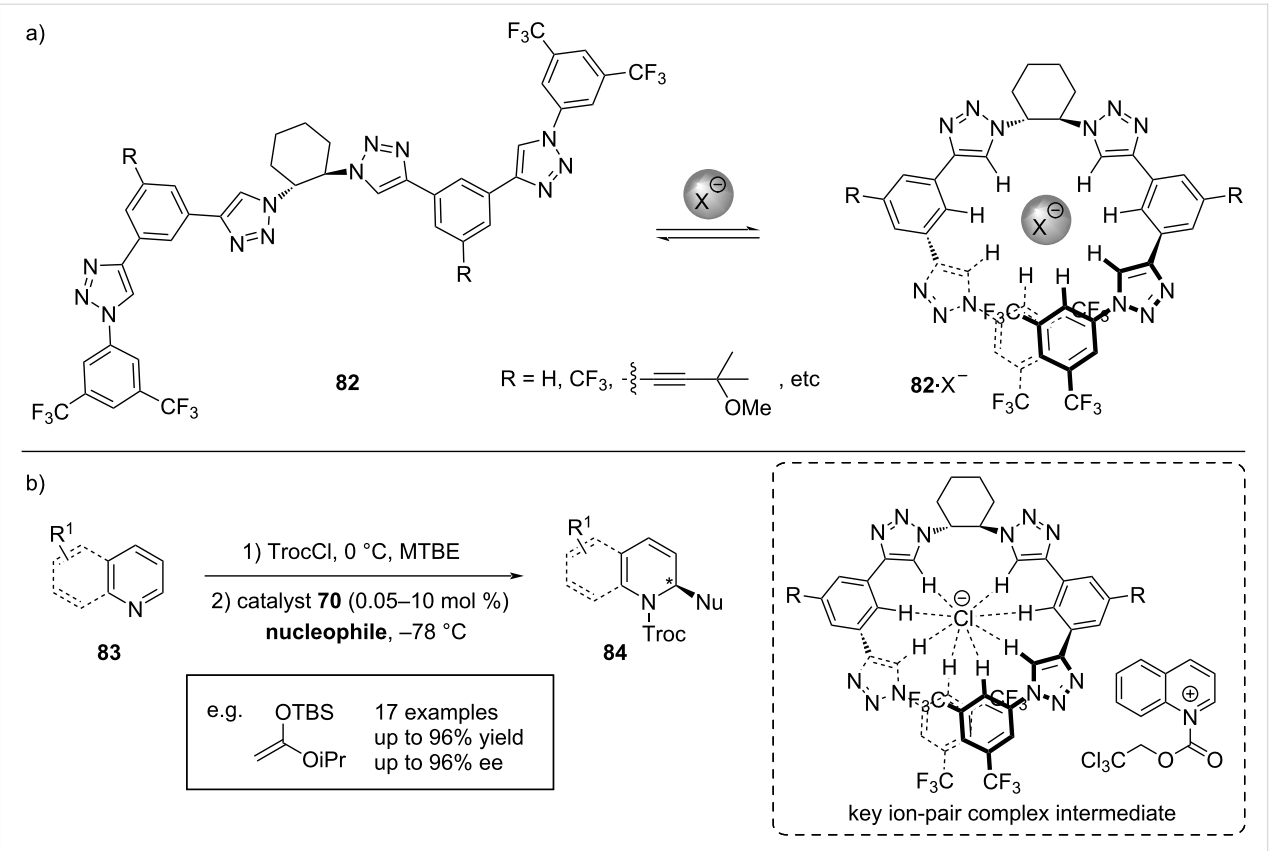
Non-thiourea-based supramolecular catalysts

The combination of anion-binding catalysis and supramolecular chemistry is a fairly new arisen field, with a set number of notable examples [79-83]. Next to thioureas, investigations in this area of anion binding were also conducted for other catalytic systems. In 2014, the García group reported a family of chiral helical tetratriazoles **82** as a new class of anion-binding catalysts, which can be considered as supramolecular anion-binding catalysts (Scheme 18) [22]. Not only is the increased H-bonding network in multidentate **82** beneficial for giving a firm control over both regio- and enantioselectivity, but the catalyst itself accommodates the anion by adopting a helical conformation upon complexation (Scheme 18a) [84-86]. Initial studies proved these systems highly effective for the enantioselective Reissert reaction of quinolines with silyl ketene acetals [22], which could be later extended to other *N*- and *O*-heteroarenes and various nucleophiles (Scheme 18b) [87-91].

Computational studies on the helical tetrakistriazole catalyst were additionally carried out, aiming at gaining insight into its interactions with the anion and cationic counterpart of the ionic



Scheme 17: a) Macrocyclic bis-thiourea catalyst in a diastereoselective glycosylation reaction. b) Competing S_N1 vs S_N2 reactivity.



Scheme 18: a) Folding mechanism of oligotriazoles upon anion recognition. b) Representative tetratriazole **82** catalyzed enantioselective Reissert-type reaction of quinolines and pyridines with various nucleophiles.

substrate [86]. Besides the contact to the chloride anion, investigations with tetrabutylammonium chloride (TBACl) and pyridinium chloride salt as model compounds found evidence for productive interactions between the catalyst and the cations. However, these interactions may not solely be attributed to cation–π, but also to cation–H or π–π interactions.

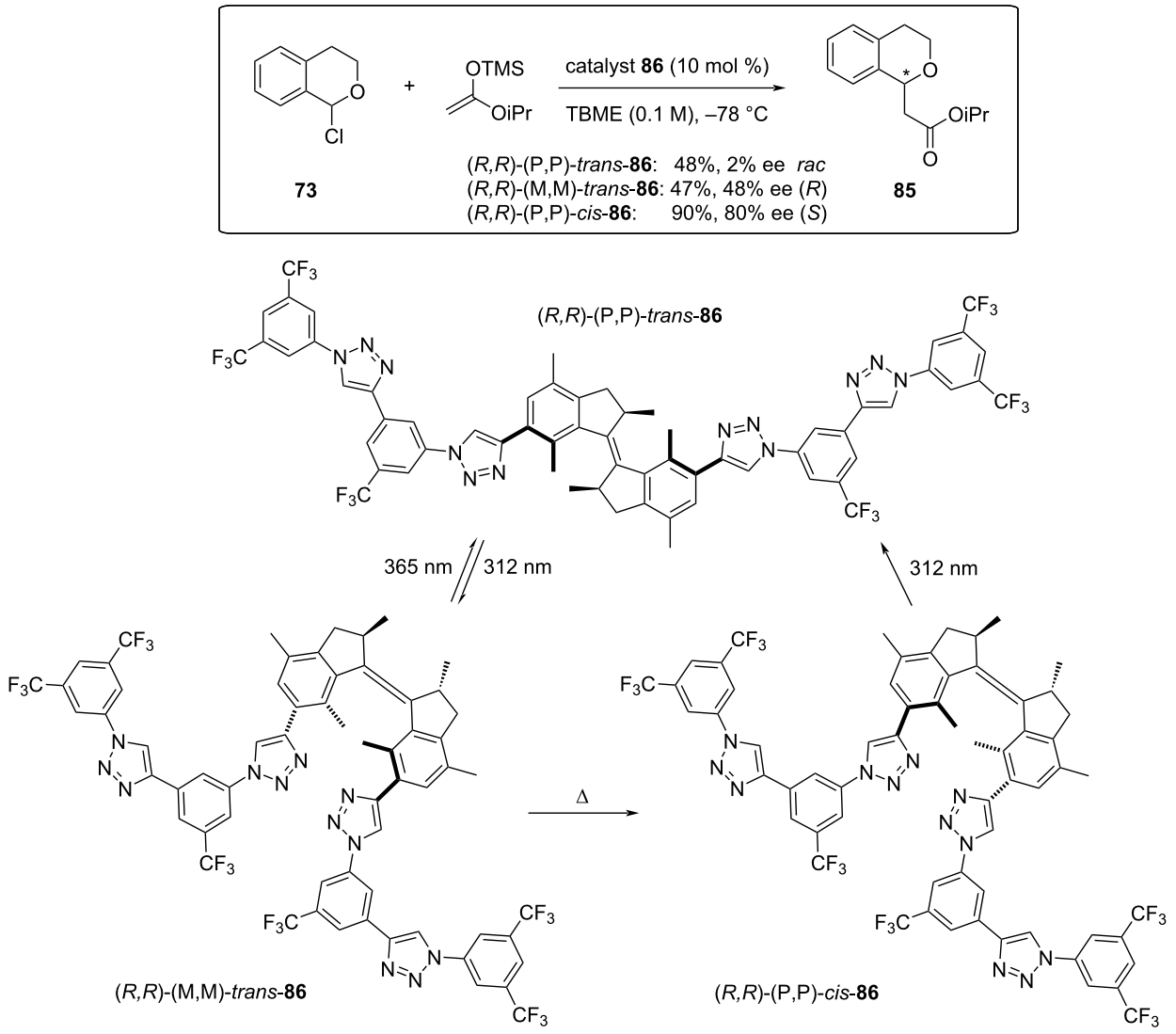
Some of the advantages of multidentate, supramolecular anion-binding catalysis were recently exploited by the Feringa group, who designed an anion-binding catalyst **86** that fuses the known triazole binding properties with a light-switchable molecular motor. In this way, they were not only able to control the folding of the triazole units through successive irradiation and thermal excitation, but they could also selectively control the stereochemical outcome of the benchmark reaction of 1-chloroisochromane (**73**) with silylketene acetals (Scheme 19) [92].

Such examples, and the advance of anion-binding-catalyzed strategies involving more complex H-bonding networks clearly highlight that it is indeed possible to mimic enzyme-like structures with small-molecule catalysts for asymmetric synthesis.

Conclusion

In the past two decades, tremendous advances in the field of anion-binding catalysis have been made, evolving as a valuable addition to the synthetic toolbox.

In this review, we have presented the essential role that halide anions, especially chloride, have played in the development of this area of research in the past decades. From the initial endeavors, in which differentiation between classical H-bonding to neutral substrates and the binding to anionic species was delineated, anion-binding interactions became more prominent and started being considered in the design of new syntheses and catalytic approaches. In this context, the emphasis was to display the role of the halide anions and how the predictability of binding properties towards these anions led to the development of a multitude of catalytic concepts and (supramolecular) catalyst systems. Hence, the possibility of employing the catalyst-bound halide anions in the key ion pair complexes as active nucleophiles were also featured. Though less explored so far than their use as simple, inert counter-anions to build the ion pair, this approach provides new possibilities and substantially broadens the synthetic applicability of anion-binding catalysis. Finally, the evolution from simple H-bonding to complex halide



Scheme 19: Switchable chiral tetratriazole catalyst **86** in the enantioselective addition of silyl ketene acetals to 1-chloroisochromane.

anion-binding catalyst designs has been outlined. Recent reports show that synthetic and computational research become more intertwined, and a trend towards multiple noncovalent interactions, as well as supramolecular chemistry, might be in-bound soon.

Based on the tremendous developments in this field thus far, important advances in the understanding of complex anion-binding processes, the design of more potent, efficient catalysts, and the development of innovative activations and reactions can be certainly envisioned to be further evolved in the near future.

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ORCID® iDs

Lukas Schifferer - https://orcid.org/0000-0001-6183-8948
Olga García Macheño - https://orcid.org/0000-0002-7578-5418

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Base-free enantioselective S_N2 alkylation of 2-oxindoles via bifunctional phase-transfer catalysis

Mili Litvajova, Emiliano Sorrentino, Brendan Twamley and Stephen J. Connon*

Letter

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Address:
School of Chemistry, Trinity Biomedical Sciences Institute, Trinity College Dublin, 152-160 Pearse Street, Dublin 2, Ireland

Email:
Stephen J. Connon* - connons@tcd.ie

* Corresponding author

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Abstract

N-Protected oxindole derivatives of unprecedented malleability bearing ester moieties at C-3 have been shown to participate in enantioselective phase-transfer-catalysed alkylations promoted by ad-hoc designed quaternary ammonium salts derived from quinine bearing hydrogen-bond donating substituents. For the first time in such phase-transfer-catalysed enolate alkylations, the reactions were carried out under base-free conditions. It was found that urea-based catalysts outperformed squaramide derivatives, and that the installation of a chlorine atom adjacent to the catalyst's quinoline moiety aided in avoiding selectivity-reducing complications related to the production of HBr in these processes. The influence of steric and electronic factors from both the perspective of the nucleophile and electrophile were investigated and levels of enantiocontrol up to 90% ee obtained. The synthetic utility of the methodology was demonstrated via the concise enantioselective synthesis of a potent CRTH2 receptor antagonist.

Introduction

The 2-oxindole scaffold is an important motif present in a myriad of natural products. Among 2-oxidole derivatives, 3,3'-disubstituted-2-oxindoles are particularly widespread and can also be found in a diverse array of pharmaceutical agents (Figure 1A) [1-4].

In addition, their facile transformation into pyrroloindoline and spirooxindole derivatives as well as more structurally complex molecules renders them potentially highly valuable synthetic building blocks [5-12].

Both pyrroloindolines **1** and spirooxindoles **2** are conceivably available from key 3,3-disubstituted intermediates **3**, which could be prepared via an enantioselective S_N2 alkylation involving enolate **3a** (Figure 1B). The versatility of this approach is significantly enhanced when both the substituents at the 3-po-

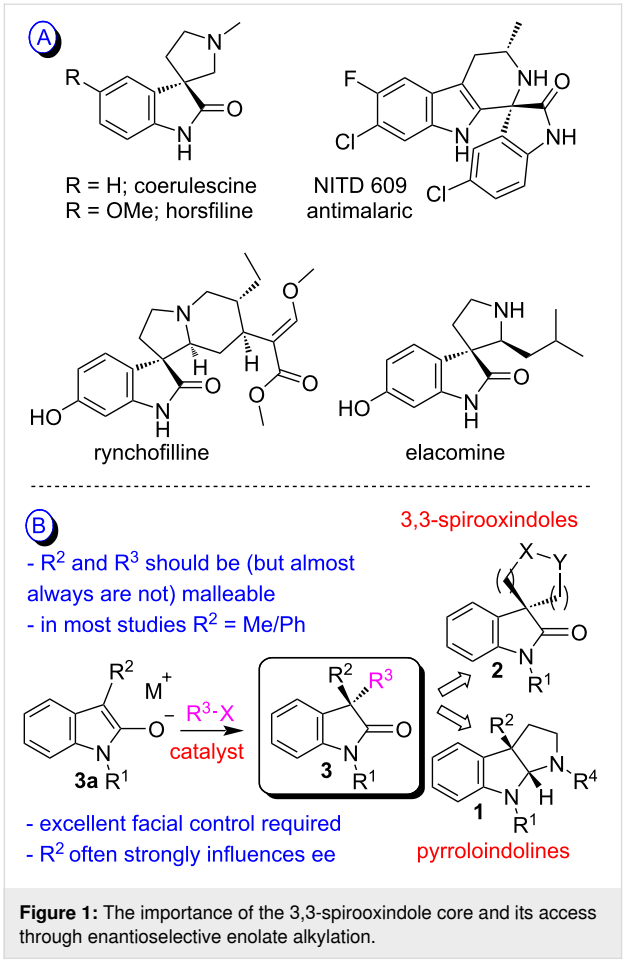


Figure 1: The importance of the 3,3-spirooxindole core and its access through enantioselective enolate alkylation.

sition are modifiable as much as possible to facilitate further transformations.

In this context, we realised that phase-transfer catalysis, due to its operational simplicity and utility in mediating reactions involving charged intermediates, could be an excellent methodology for the enantioselective S_N2 alkylation of enolates derived from the 2-oxindole core [13-23]. In recent years, several examples regarding the alkylation of 3-subsituted-2-oxindoles, via asymmetric phase-transfer catalysis, have been reported [24-30].

However, despite the excellent levels of enantiocontrol often achieved, in the majority of these studies the 2-oxindole subjected to enantioselective alkylation lacks the structural architecture necessary for further modifications (Scheme 1A), presenting instead a fixed – not easily modifiable – group which is not ideal for a modular approach to the construction of more complex molecules such as those shown in Figure 1A. Recently, we partially overcame this challenge by developing a highly enantioselective phase-transfer-catalysed methodology for the S_N2 alkylation of methylene ester-substituted 2-oxindole **4** [31]. The utility of this methodology has been demonstrated through the total synthesis of (−)-debromoflustramine B (Scheme 1B). In an attempt to devise variants of this reaction of greater versatility and synthetic utility; we sought to employ the intriguing substrate **5**.

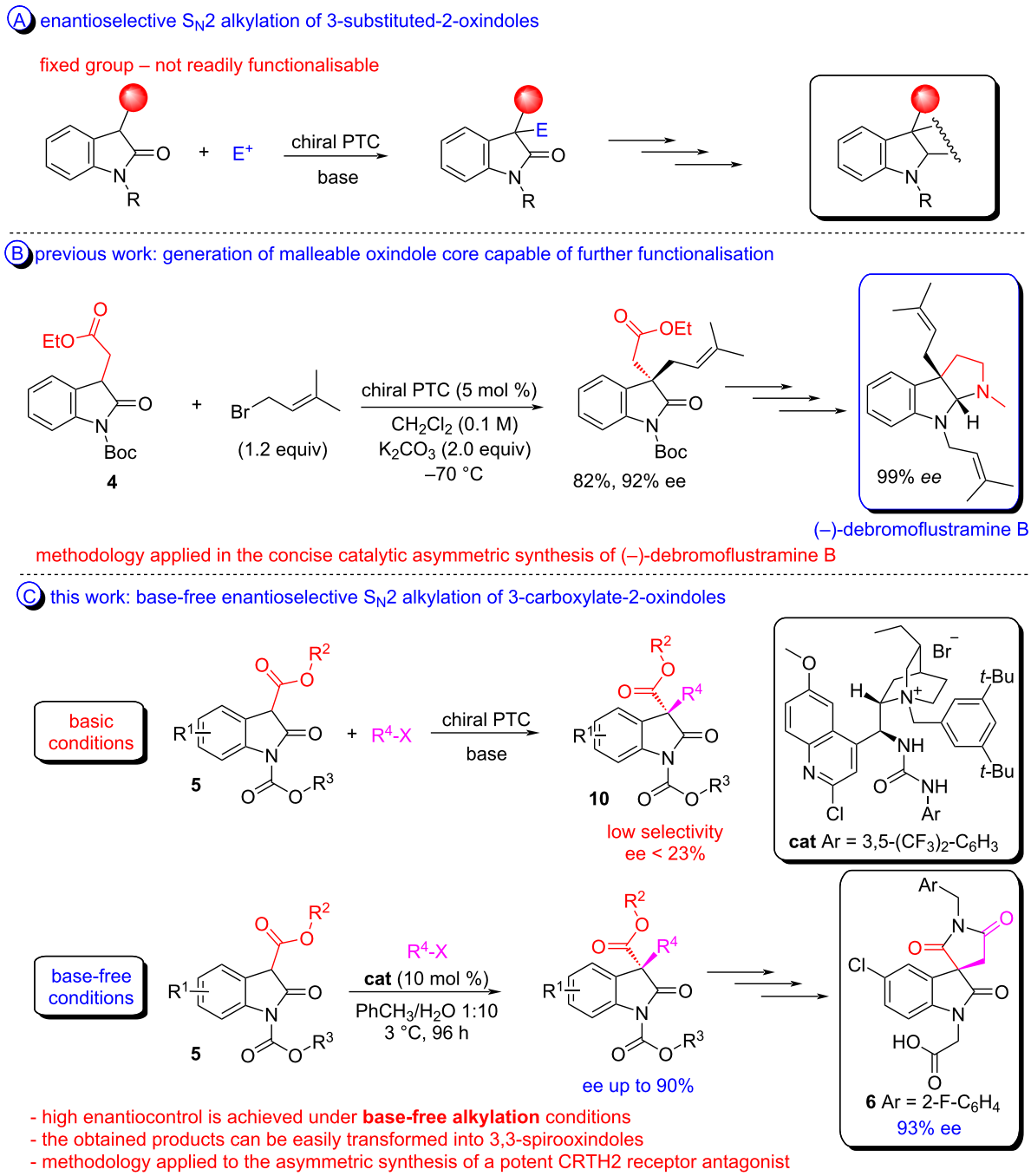
In comparison with 2-oxindole **4**, compound **5** possesses ester functionality directly attached to the 2-oxindole ring – which would provide a functional handle at this position of considerably greater plasticity than anything previously evaluated in the literature. On the other hand, such electron-withdrawing groups, α to the reactive centre, dramatically changes the acidity of the substrate (and thus the reactivity of the enolate conjugate base) and as consequence its reactivity which can drastically impact the enantioselectivity in S_N2 alkylation processes. In this report we disclose the outcome of an investigation into the design of an efficient catalytic asymmetric system capable of manipulating this substrate and its application to the enantioselective synthesis of the potent CRTH2 receptor antagonist **6** [32] (Scheme 1C).

Results and Discussion

We began our investigation by evaluating, as a model alkylation, the phase-transfer-catalysed benzylation of substrate **5** under 'classical' basic reaction conditions using cinchona alkaloid-based catalysts capable of hydrogen-bonding as a control element [33-40]. As expected, the ester group α to the reactive centre dramatically increases the acidity at this position and, in preliminary studies, we found that under biphasic basic conditions 2-oxindole **5** was undergoing alkylation also in the absence of a phase-transfer catalyst (not ideal when designing a catalytic enantioselective process).

Despite investigating the effects of different solvents, bases and buffer systems, in preliminary experiments we were not able to prevent the non-catalysed benzylation of substrate **5**; nevertheless, the enantioselective alkylation of **5** with benzyl bromide in the presence of a phase-transfer catalyst was attempted. This catalytic reaction exhibited poor enantioselectivity and none of the catalysts employed were able to promote the reaction with product ee higher than 22% (Scheme 1C – for more details see Supporting Information File 1).

Over the last decade, Maruoka and co-workers discovered that phase-transfer-catalysed reactions can be occasionally performed even in absence of base under water-enriched/organic biphasic conditions [41-47]. Taking inspiration from these studies, it was envisaged that by employing base-free neutral reaction conditions – given the likely acidity of substrate **5** – that it could be possible to develop an effective catalytic asymmetric protocol.



Scheme 1: A) S_N2 alkylation of 3-subtituted-2-oxindoles not readily functionalisable; B) Previous work: enantioselective synthesis of a malleable 2-oxindole capable of further manipulations; C) This work: base-free enantioselective alkylation of 2-oxindoles **5**.

To the best of our knowledge such base-free catalytic systems have never been applied to processes such as the alkylation of enolates generated in situ. These reactions would produce stoichiometric amounts of acid, which can inhibit the formation of the reactive enolate by driving the enol/enolate equilibrium toward the enol form.

While these considerations seemed discouraging, we were able to define a set of base-free/water-rich reaction conditions suitable for our catalytic system where the formation of the alkylated product was not observed in the absence of a phase-transfer catalyst after a prolonged reaction time of 504 hours (see Supporting Information File 1).

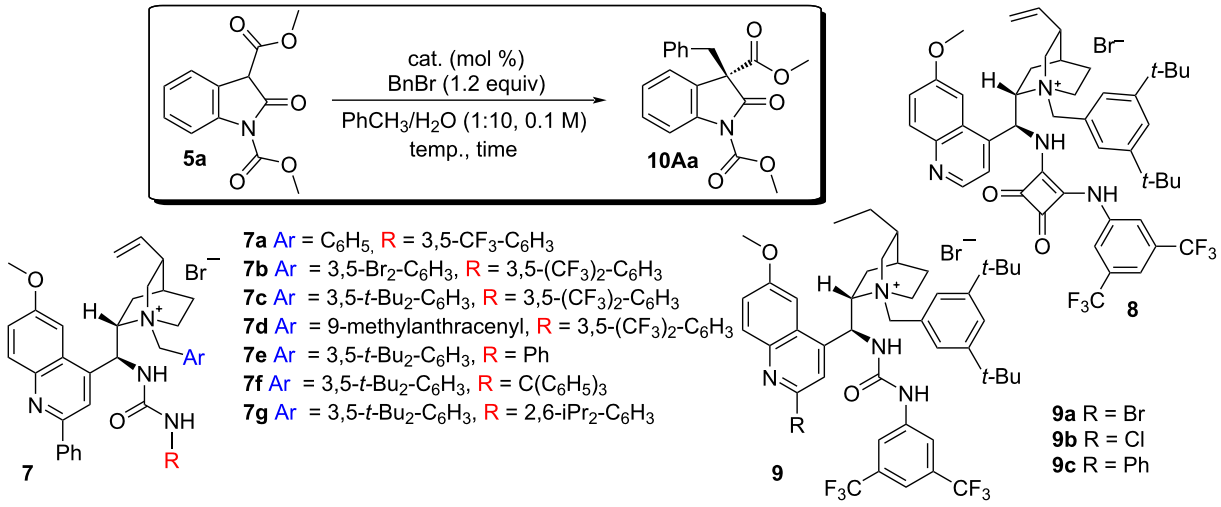
With this new set of conditions in hand, a rational catalyst design process commenced, aimed at improving the selectivity of the base-free S_N2 alkylation process.

In preliminary studies, we observed that a substituent at the catalyst C-2' position was enhancing the enantioselectivity of the reaction. Initial attention was therefore focused on the influence the other catalyst subunits (i.e., catalysts **7–9**, Table 1) exerted over both reactivity and selectivity.

Attention first turned to the catalyst's *N*-substituent. Catalyst **7a**, bearing a benzyl group, was able to promote the transformation of **5a** in moderate enantioselectivity (Table 1, entry 1). Modification of the *N*-benzyl unit to incorporate either electron-withdrawing or bulky substituents did not lead to appreciable variations, with the latter leading to a marginal improvement (Table 1, entries 2 and 3). As observed in earlier studies [31], the employment of a *N*-9-methylantracenyl-substituted catalyst (i.e., **7d**) caused a dramatic loss of enantiocontrol (Table 1, entry 4).

Modifications to the hydrogen bond-donating functionality – while keeping the *N*-3,5-di-*tert*-butylbenzyl unit unchanged – were then introduced. Removing the two electron-withdrawing -CF_3 groups from the ureaphenyl moiety resulted in diminished enantioselectivity (Table 1, entry 5), whereas increasing the steric demand in this region of the catalyst led to racemic products (Table 1, entries 6 and 7). Employing a different hydrogen bond-donating motif such as the squaramide (catalyst **8**, Table 1, entry 8) resulted in a substantial drop of the enantio-

Table 1: Catalyst evaluation.



entry	catalyst	loading (mol %)	temp (°C)	time (h)	conv (%)[a]	ee (%)[b]
1	**7a**	5	rt	90	>99	50
2	**7b**	5	rt	114	90	49
3	**7c**	5	rt	45	>99	52
4	**7d**	5	rt	168	54	7
5	**7e**	5	rt	48	>99	34
6	**7f**	5	rt	114	97	2
7	**7g**	5	rt	114	>99	0
8	**8**	5	rt	161	46	5
9	**9a**	5	rt	60	>99	56
10	**9b**	5	rt	48	>99	55
11	**9c**	5	rt	45	>99	53
12	**7c**	10	3	144	>99	59
13	**9b**	10	3	144	>99	62
14	**9a**	10	3	144	>99	58
15	**9c**	10	3	144	>99	58

[a]Determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as internal standard. [b]Determined by CSP-HPLC.

control as well as in the reduction of the reaction rate [29,31] – probably due to the ability of squaramides to bind anionic species more strongly than ureas.

The moderate enantiocontrol observed thus far prompted us to posit that the nitrogen atom on the quinoline moiety of the catalyst could participate to the deprotonation of **5a**, therefore, leading to less selective alkylation.

In order to test this hypothesis, we designed novel dihydroquinine-derived catalysts of general type **9** bearing an electron-withdrawing substituent at the C-2' position with the intent of lowering the basicity of the quinoline ring. In addition, we prepared a C-2'-phenyl-substituted dihydroquinine-derived catalyst (**9c**) for comparison. Rather disappointingly, the improvement was marginal (Table 1, entries 9–11) with **9a** affording product **10Aa** in 56% ee. Therefore, we decided to evaluate the most promising catalysts at lower temperature (3 °C) using 10 mol % catalyst loading. Under these reaction conditions, the chloro derivative **9b** proved to be the most efficient catalyst – mediating the formation of product **10Aa** in 62% ee after full conversion (Table 1, entries 12–15).

Attention then turned to the 2-oxindole structure. Due to solubility issues chlorobenzene was chosen as the preferred solvent (Figure 2).

Introduction of a bromo substituent in proximity to the reaction centre led to the formation of product **10Ba** in 72% yield with an augmented 83% ee. Disappointingly, 2-oxindoles incorporating similar substituents at different locations, such as the 5-position, afforded products only in moderate ee, with lower enantiocontrol associated with groups possessing greater electron-withdrawing character (i.e., **10Da**, **10Ca**, **10Ea**). Finally, modifications on both the substrate ester and carbamate-moieties did not afford remarkably different outcomes (i.e., **10Fa**, **10Ga**).

We continued our studies by investigating the behaviour of different alkylating agents (Table 2).

Reactions with alkylating agents with increased steric demand provided products in higher ee (compare Table 2, entries 1, 2 and 3); with 3,5-bis(*tert*-butyl)benzyl bromide allowing the isolation of oxindole **10Ac** in 92% yield and 84% ee. The employment of benzyl bromides bearing electron-withdrawing groups led to products with moderate ee in the cases of *para*-substituted analogues (Table 2, entries 4 and 5) while an increase in enantioselectivity, up to 79% ee, was observed using *meta*-substituted variants (Table 2, entries 6 and 7).

To our delight, relatively electron-rich benzyl bromides were able to afford products in high yields and with improved

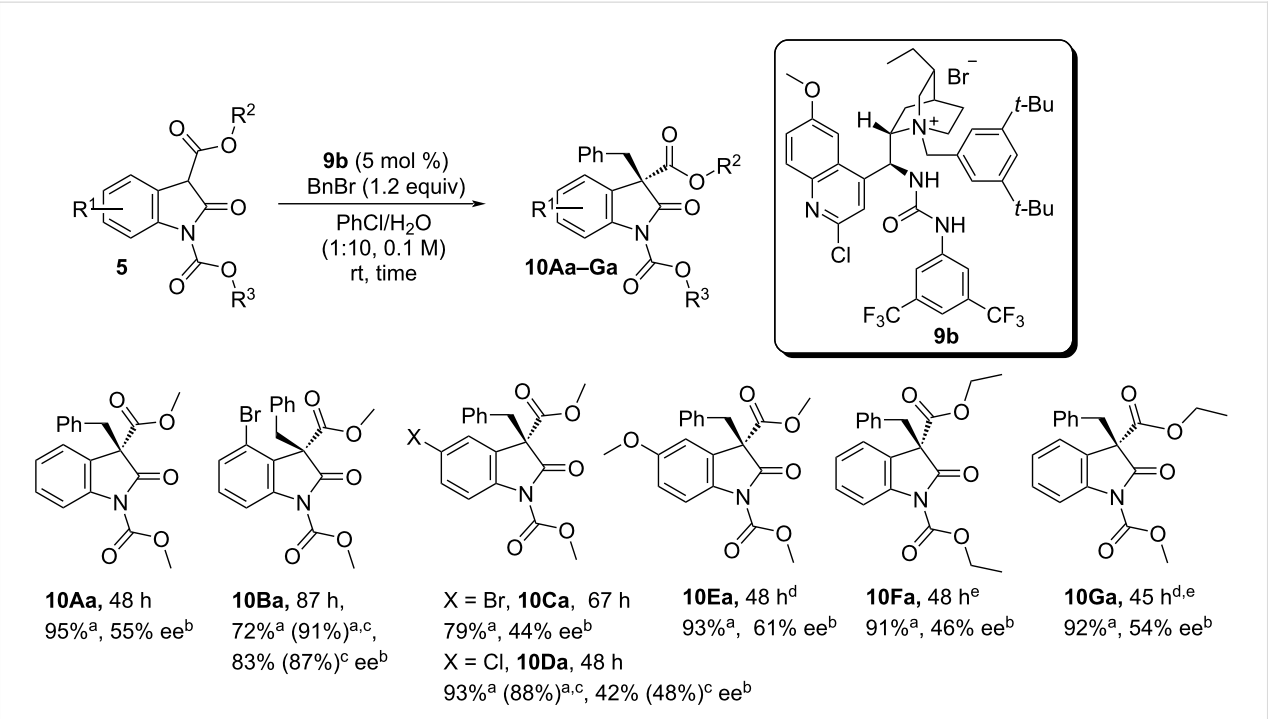
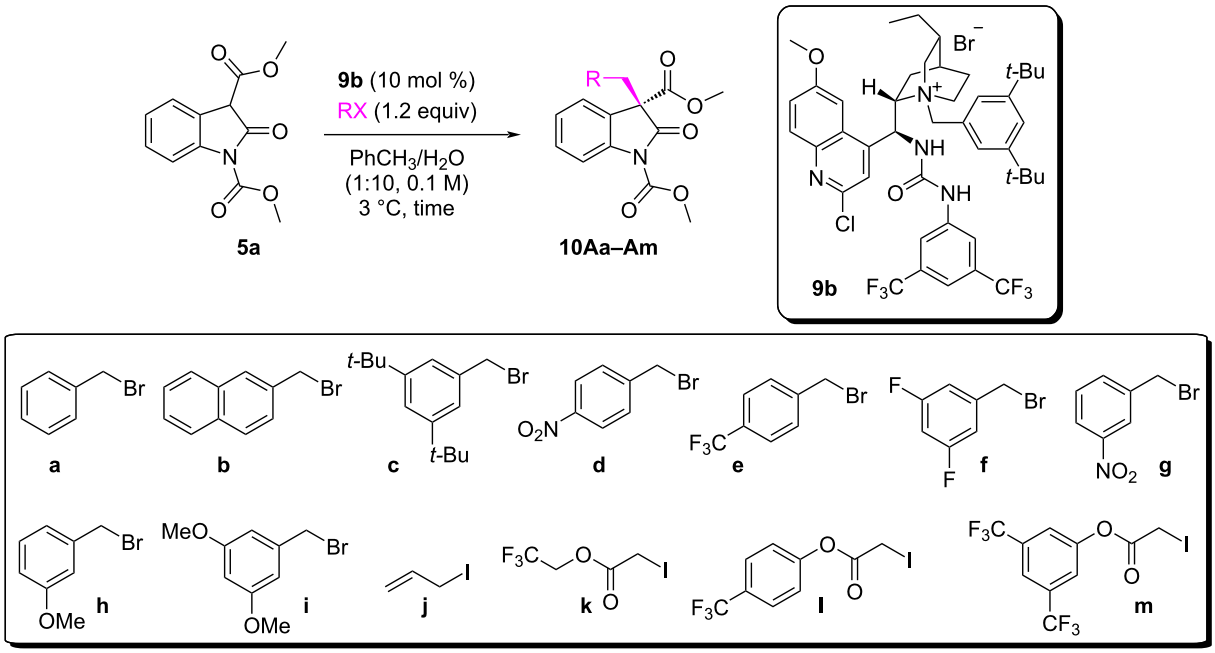


Figure 2: Substrate scope. [a]Isolated yield. [b]Determined by CSP-HPLC. [c]Value in brackets refers to reaction conducted at 3 °C, using 10 mol % of catalyst. [d]Performed in $PhCH_3$. [e]Performed using **7c** as the catalyst.

Table 2: Electrophile scope.



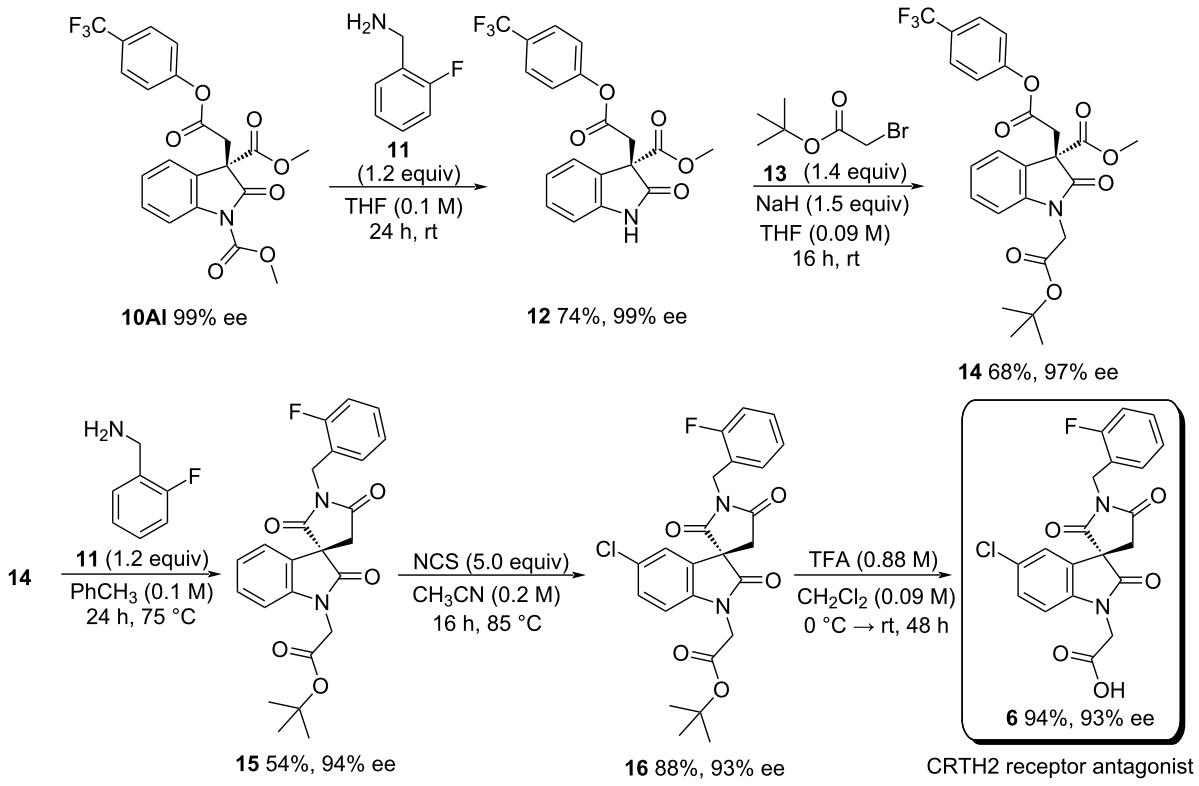
entry	electrophile	product	time (h)	yields (%)	ee (%)[a]
1	**a**	**10Aa**	144	94	62
2	**b**	**10Ab**	144	94	72
3	**c**	**10Ac**	120	92	84
4	**d**	**10Ad**	144	96	66
5[b]	**e**	**10Ae**	24	94	68
6	**f**	**10Af**	144	96	74
7	**g**	**10Ag**	144	97	79
8	**h**	**10Ah**	120	89	80
9	**i**	**10Ai**	144	90	90
10[b]	**j**	**10Aj**	48	99[c]	51
11[b]	**k**	**10Ak**	24	99[c]	54
12	**l**	**10Al**	96	98	76
13	**m**	**10Am**	96	90	70

[a]Determined by CSP-HPLC. [b]At rt. [c]Determined by ^{1}H NMR spectroscopic analysis using 4-iodoanisole as internal standard.

product ee – up to 90% (Table 2, entries 8 and 9). Attention then switched to non-benzyl bromide-based electrophiles – however, use of allyl iodide was able to furnish product **10Aj** with only 51% ee (Table 2, entry 10). Consistent with the goal of developing a protocol of the best possible synthetic utility; alkylating agents which would be easily modified after installation on the oxindole core – such as α-iodoesters – were also evaluated (Table 2, entries 10–12). Although, alkyl esters participated in less enantioselective chemistry (Table 2, entry 11); it was possible to achieve moderate enantiocontrol by employing aromatic ester derivatives, with product **10Al** obtained in 98% yield and 76% ee (Table 2, entry 12).

The potential utility of this newly developed methodology was demonstrated through the enantioselective synthesis of the (*S*)-antipode potent CRTH2 receptor antagonist **6** [48] (Scheme 2).

Compound **10Al**, isolated in 76% ee, was recrystallised in *n*-hexane to obtain optically pure **10Al**. This material was deprotected with benzylamine **11** to afford oxindole **12,** which was subsequently *N*-alkylated with bromo ester **13**. The formed product (i.e., **14**) was first amidated and then cyclised using benzylamine **11** to generate spirooxindole **15** in 54% yield and 94% ee. Chlorination with NCS, followed by *tert*-butyl ester cleavage in TFA/CH_2Cl_2 provided the final bioactive compound **6** in 93% ee.



Scheme 2: Enantioselective synthesis of a CRTH2 receptor antagonist.

Conclusion

In conclusion, we have described a base-free protocol for the asymmetric phase-transfer-catalysed S_N2 alkylation of densely functionalised 2-oxindole derivatives, employing a biphasic water-rich solvent system. To the best of our knowledge, these base-free neutral reaction conditions have never previously been applied to phase-transfer-catalysed S_N2 enolate alkylation reactions and represents an effective process for the generation of carbonaceous quaternary stereocentres.

The process generates malleable di-ester and mono-ester benzylated oxindole substrates which can easily give access to products of biological interest, as evidenced by the facile preparation of the (*S*)-enantiomer of a potent CRTH2 receptor antagonist.

Supporting Information

Supporting Information File 1

Experimental part.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-146-S1.pdf]

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ORCID® iDs

Mili Litvajova - https://orcid.org/0000-0002-5641-3088
Stephen J. Connon - https://orcid.org/0000-0003-2984-9246

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48. We identified **6** as the *S* enantiomer. The absolute configuration was assigned by analogy to the absolute configuration of **10Al**, which was determined using XRD analysis (structure submitted to the CCDC No. 2089007).

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Enantioselective PCCP Brønsted acid-catalyzed aminalization of aldehydes

Martin Kamlar[1], Robert Reiberger[1], Martin Nigríni[1], Ivana Císařová[2] and Jan Veselý[*1]

Full Research Paper

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Address:
[1]Department of Organic Chemistry Charles Univerzity, Hlavova 2030/8, Prague 2, 12800, Czech Republic and [2]Department of Inorganic Chemistry, Charles Univerzity, Hlavova 2030/8, Prague 2, 12800, Czech Republic

Email:
Jan Veselý[*] - jxvesely@natur.cuni.cz

* Corresponding author

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Abstract

Here we present an enantioselective aminalization of aldehydes catalyzed by Brønsted acids based on pentacarboxycyclopentadienes (PCCPs). The cyclization reaction using readily available anthranilamides as building blocks provides access to valuable 2,3-dihydroquinazolinones containing one stereogenic carbon center with good enantioselectivity (ee up to 80%) and excellent yields (up to 97%).

Introduction

Nitrogen-containing heterocyclic compounds are commonly occurring in nature and constitute the core structures of many biologically important compounds. An important example of such heterocycles are 2,3-dihydroquinazolinones which scaffold can be found in various compounds exhibiting pharmacological properties [1-6]. Some of them are currently used to treat numerous diseases, such as the diuretic drug fenquizone used for the treatment of hypertension [7,8], or evodiamine, a stimulant used in fat reduction or inflammation [9-11]. Moreover, it was reported that both enantiomers of 2,3-dihydroquinazolinones exhibit different bioactivities [12,13]. Thus, the development of enantioselective synthetic strategies towards 2,3-dihydroquinazolinone derivatives has drawn the attention of organic chemists for a long time [14-18], even though the aminal stereocenter is sensitive to racemization [12].

The well-established and straightforward approach in the asymmetric organocatalytic synthesis of molecules with this moiety uses the reaction between aldehydes and anthranilamide building blocks. The advantage of this methodology lies in the fact that both starting materials are readily available, and the enantioselectivity of such cyclization reactions can be controlled by chiral Brønsted acids. In the scope of Brønsted acid catalysis, chiral phosphoric acids (CPA) are dominating as potent cata-

lysts in various asymmetric transformations [19-23], although the synthesis of these catalysts is expensive and laborious [24]. One of the most frequent examples of CPAs is the binaphthol (BINOL)-derived phosphoric acid class of catalysts, firstly reported by Akiyama [25] and Terada [26]. Soon after, BINOL-derived phosphoric acids were employed in the enantioselective synthesis of 2,3-dihydroquinazolinones. The initial report in this area was made by List and co-workers, using an (*S*)-TRIP derivative as the chiral catalyst (Figure 1) [14]. Soon after, Rueping et al. developed a similar methodology catalyzed by other chiral BINOL-phosphoric acids [15]. However, the reaction suffered from limited scope to aromatic aldehydes without an *ortho*-substitution; the corresponding dihydroquinazolinones were obtained in high yields and with good enantiomeric purities. In 2013, Lin and co-workers published the application of a chiral SPINOL-phosphoric acid in the asymmetric aminalization reaction [27]. Tian´s research group developed the synthesis of dihydroquinazolinones from preformed imines instead of aldehydes catalyzed by BINOL-phosphoric acid [17]. The corresponding aminals were prepared with a wide range of substitutions using aromatic, α,β-unsaturated, or aliphatic imines. Apart from chiral phosphoric acids, chiral quaternary ammonium salts were successfully employed as catalysts in asymmetric dihydroquinazolinone synthesis [18]. Regarding the above-mentioned strategies involving chiral Brønsted acids, we envisioned that chiral pentacarboxycyclopentadiene (PCCP) derivatives could be used in the enantioselective aminalization of aldehydes with anthranilamide derivatives. PCCPs were firstly reported by Otto Diels [28,29], but recently, Lambert and co-workers introduced a new generation, chiral PCCPs (Figure 1) [30]. Due to the high stability of the aromatic cyclopentadienyl anion, PCCPs exhibit a low pK_a value comparable to that of phosphoric acids. Contrary to chiral phosphoric acids, PCCPs offer less laborious and inexpensive prepa-

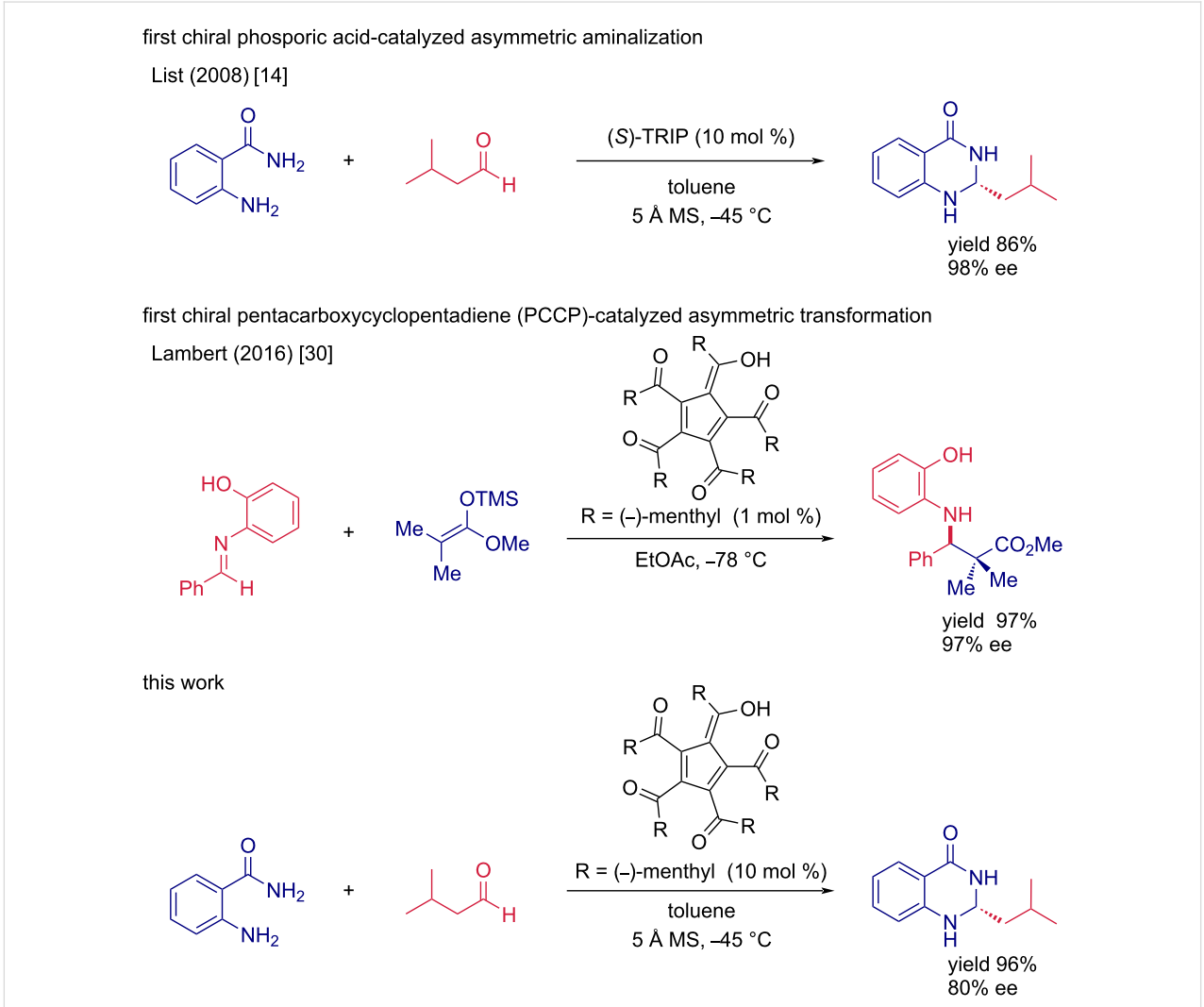


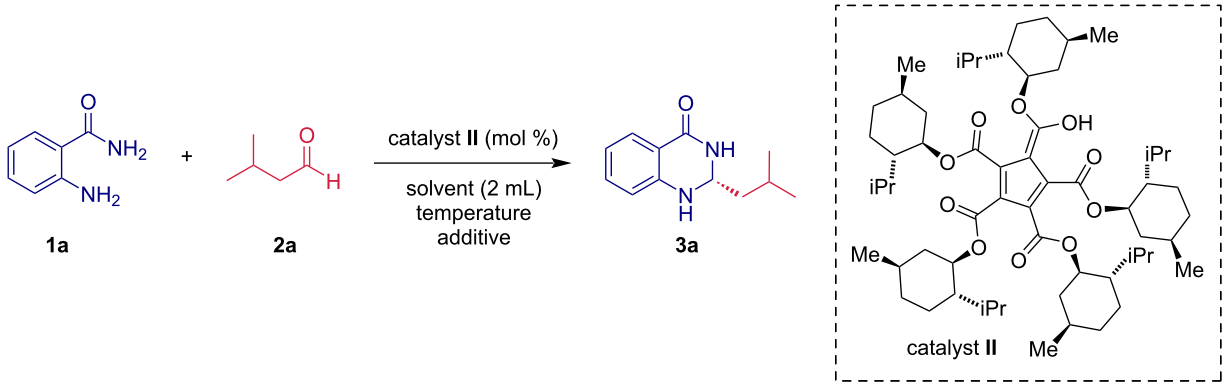
Figure 1: Synthetic strategies employing chiral Brønsted acid catalysis.

ration protocols [31,32], which makes them an interesting alternative for chiral Brønsted acid-catalyzed transformations [30-35].

Results and Discussion

Herein, we describe our findings regarding the aminalization of aldehydes using PCCP catalysis. Our investigation commenced with the screening of the reaction between anthranilamide (**1a**) and isovaleraldehyde (**2a**) in the presence of 10 mol % of catalyst **II** (Table 1). First, we turned our attention to the solvent and temperature effect concerning the yield and the enantioselectivity of the aminalization reaction. While most solvents tested showed to be effective at room temperature, the enantiomeric purity of the corresponding aminal **3a** was low in all cases (Table 1, entries 1–5). On the other hand, the yield of **3a** was satisfactory in all reactions. In particular, when the reaction between **1a** and **2a** was performed in toluene, the isolated yield of **3a** was almost quantitative (97%, entry 1 in Table 1). In our pursuit of better enantioselectivity, we continued with the reaction proceeded in toluene at lower temperatures. We found a temperature of −45 °C as optimal for the enantiocontrol of the model reaction, affording the product **3a** in 90% yield with an enantiomeric purity of 66% ee (Table 1, entry 7). Additionally, the effect of molecular sieves on the course of the reaction was investigated and the obtained results demonstrated that molecular sieves dramatically improved the enantioselectivity (Table 1, entries 9–11). In particular, when the aminalization reaction between **1a** and **2a** was carried out in the presence of 5 Å molecular sieves, the corresponding product **3a** was delivered in high yield (96%) and with enantiomeric purity 80% ee (Table 1, entry 11). In addition, the effect of the catalyst loading on the course of the reaction was examined. Our data clearly show that reducing the catalyst loading of **II** caused a significant decrease in the enantioselectivity (Table 1, entries 12 and 13). It is worth mentioning that no differences in the enantioselectivity were observed after a prolonged exposure of compound **3a** to the chiral PCCP catalyst **II** indicating a relatively high stability of the new chiral carbon center in product **3a**.

Table 1: Optimization of reaction conditions for the aminalization reaction between **1a** and **2a**.



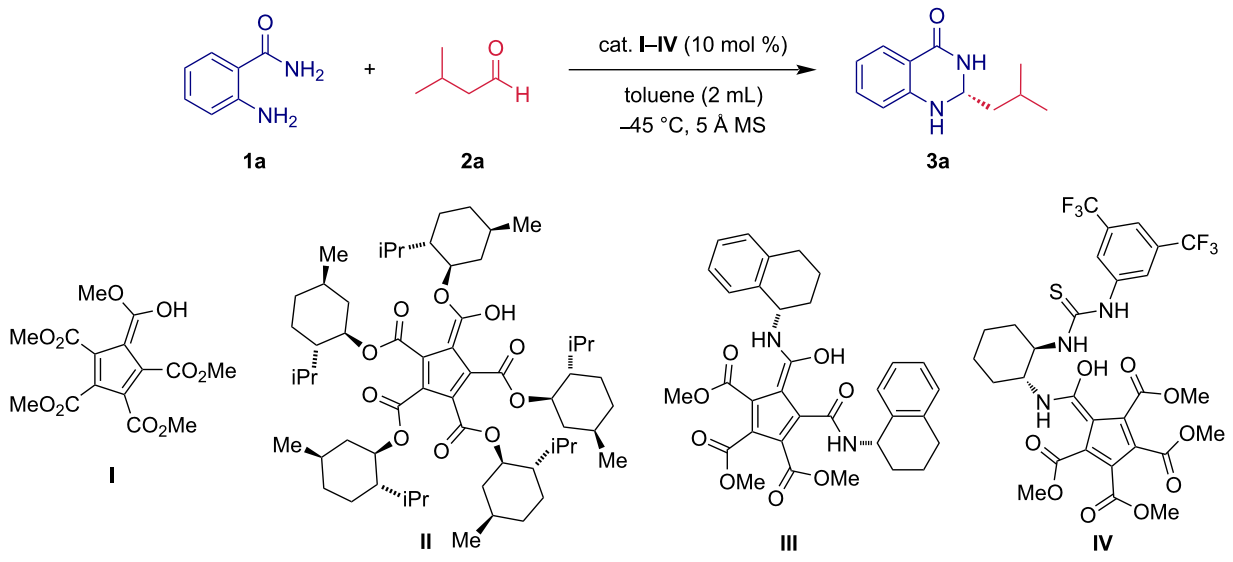
entry	solvent	temperature [°C]	cat. loading [mol %]	additive	time [h]	yield [%][a]	ee [%][b]
1	toluene	25	10	–	0.5	97	50
2	THF	25	10	–	1	72	50
3	MTBE	25	10	–	1	50	40
4	DCM	25	10	–	1	93	45
5	EtOAc	25	10	–	1	86	44
6	toluene	0	10	–	12	96	58
7	toluene	−45	10	–	20	90	66
8	toluene	−65	10	–	48	65	60
9	toluene	−45	10	3 Å MS	20	81	71
10	toluene	−45	10	4 Å MS	21	73	73
11	toluene	−45	10	5 Å MS	21	96	80
12	toluene	−45	5	5 Å MS	18	91	74
13	toluene	−45	2	5 Å MS	16	86	74

[a]Isolated yield; [b]determined by chiral HPLC.

Next, a small set of functionalized derivatives of cyclopentadienes as organocatalysts was surveyed in the model reaction (Table 2). Apart from model catalyst **II**, equipped with five (−)-menthol units, also the sterically less demanding amide-type catalyst **III** and the thiourea derivative **IV** were tested (Table 2). First, the diamide-type catalyst **III** was examined (Table 2, entry 4). Although complete conversion of **1a** and **2a** was achieved after a significantly prolonged time (7 days), the aminal **3a** was isolated in a good yield of 60%. Unfortunately, the reaction proceeded nearly in a racemic fashion. An inefficient catalyst showed up to be the PCCP catalyst derivatized with thiourea functional units (**IV**); a formation of **3a** was not observed even after prolonged reaction time (Table 2, entry 5). It is also worth mentioning that the non-catalyzed reaction did not deliver the corresponding product **3a** even after 40 hours (Table 2, entry 1). Based on the results summarized in Table 2, the chiral PCCP catalyst **II** was selected as the optimal catalyst.

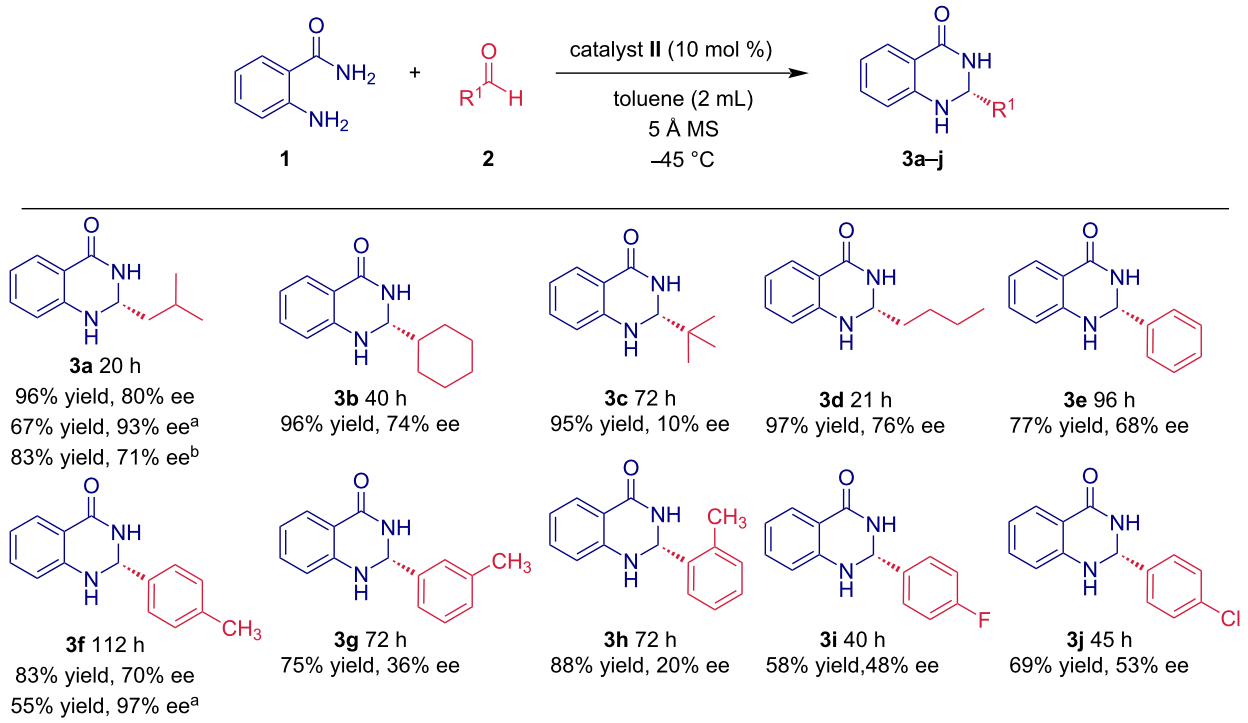
With the optimized reaction conditions in our hands, we continued investigating the scope of the reaction. First, we focused on the reactivity of anthranilamide (**1a**) with various aldehydes **2a–j** (Scheme 1). Generally, aliphatic aldehydes delivered the cyclic aminals **3a–d** in excellent yields between 95–97% and enantiomeric purities between 74–80% ee. However, the sterically demanding pivalaldehyde (**2c**) needed a prolonged reaction time to reach the complete conversion. In addition, a significant drop in the enantioselectivity (10% ee) of **3c** was observed. Also, benzaldehyde derivatives were successfully tested in the aminalization reaction. However, a decrease in reactivity and enantioselectivity was observed when compared to aliphatic aldehydes. The corresponding products **3e–j** were isolated in lower yields (58–83%) with enantiomeric purities ranging from 20 to 70% ee. For example, when benzaldehydes substituted with fluorine or chlorine in the *para*-position were employed in catalytic reaction with anthranilamide (**1a**), the corresponding derivatives **3i,j** were isolated in 58 and 69% yield, respectively. The rates of enantioselectivity for both reactions were lower and averaged only around 50%. In addition, the role of an electron-donating methyl group on the aromatic ring was investigated. When *p*-tolualdehyde (**1f**) was used in the cyclization reaction with anthranilamide (**1a**), the corresponding aminal **3f** was obtained in high yield (83%) and with good enantiomeric excess of 70% ee. On the other hand, when *m*- or *o*-tolualdehyde were employed in aminalization reaction, a sig-

Table 2: Catalyst screening of the aminalization reaction between **1a** and **2a**.



entry	catalyst	time [h]	yield [%][a]	ee [%][b]
1	–	40	n.d.	n.d.
2	**I**	16	95	0
3	**II**	21	96	80
4	**III**	168	60	2
5	**IV**	168	n.d.	n.d.

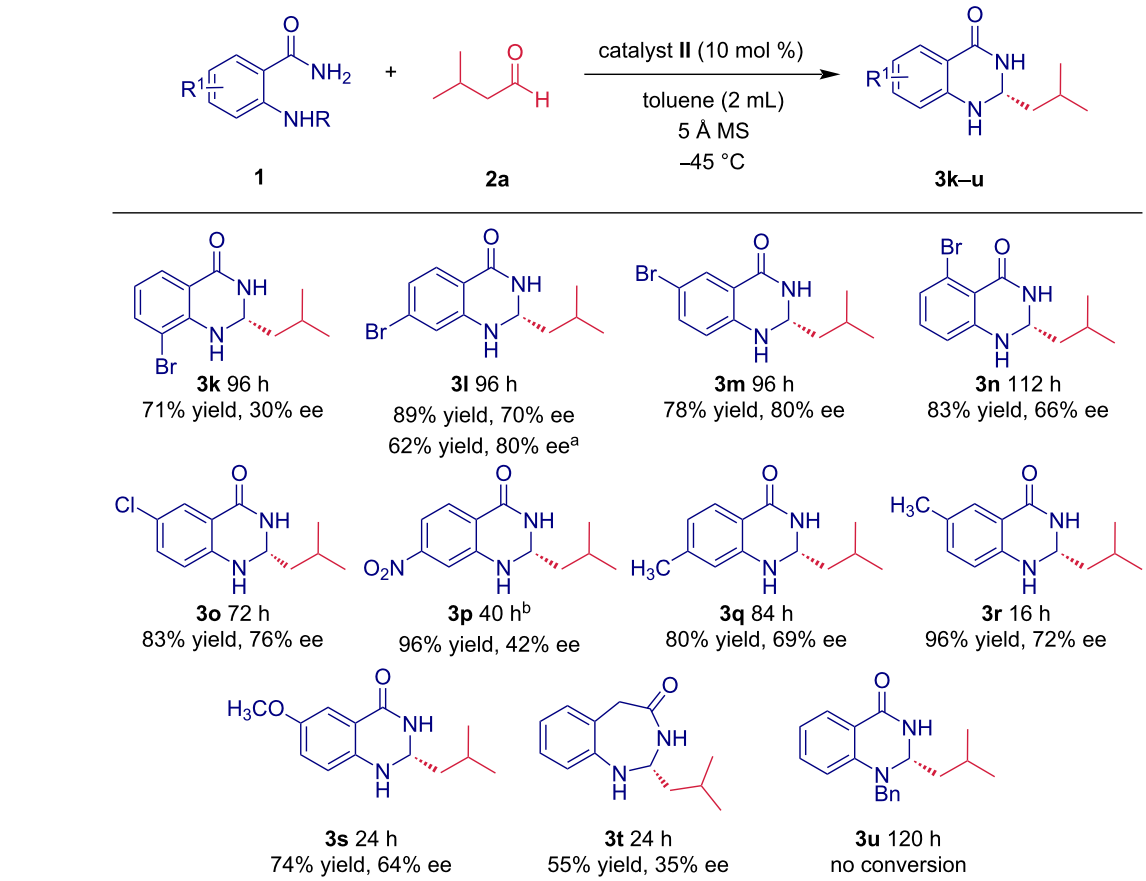
[a]Isolated yield; [b]determined by chiral HPLC.



Scheme 1: The substrate scope of the aminalization reaction for different aldehydes. [a]After recrystallization; [b]reaction run at 1 mmol scale.

nificant drop in the enantioselectivity was observed. Aminals **3g** and **3h** were obtained with 36 and 20% ee, respectively. We have also tested the reaction between anthranilamide (**1a**) and isovaleraldehyde (**2a**) in 1 mmol scale. The obtained results suggested that the reaction proceeded with slightly lower efficiency giving product **3a** in 83% yield and 71% ee. On the other hand, we found that the desired product of aminalization reaction could be readily obtained in higher enantiomeric purity after crystallization from ethyl acetate. This was demonstrated for products **3a** and **3f**, that were obtained in enantiomeric purities of 93% and 97% ee, respectively (Scheme 1).

Next, we turned our attention to the substitution of anthranilamide (Scheme 2). First, the effect of bromine as a slightly electron-withdrawing substituent on the aromatic ring was investigated. The position of bromine on the aromatic ring had a dramatic effect on the enantiomeric purity of the formed products **3k–n**. When a bromine substituent is introduced in the "3" position of anthranilamide, the enantiomeric enrichment of aminal **3k** reached only 30% ee. In contrast, substitution with bromine either in position "4" and "5" led to a formation of products **3l** and **3m** with enantiomeric purities of 70% ee and 80% ee, respectively. Finally, reaction with anthranilamide substituted with bromine in position "6" led to corresponding aminal **3n** with an enantiomeric excess of 66% ee. We also increased the enantiomeric purity of **3l** from 70% to 80% ee after crystallization from ethyl acetate. When anthranilamide substituted with a chlorine in the "5" position was used, the enantioselectivity of the reaction reached a value of 76% ee, and the yield of the corresponding aminal **3o** exceeded 80%. Next, the effect of a strongly electron-withdrawing nitro group present on anthranilamide moiety was investigated. The reaction carried out in toluene did not reach a complete conversion even after a prolonged reaction time. When more polar THF was used as the solvent, the corresponding product **3p** was obtained after 40 hours in an excellent yield of 96%; however, the enantiomeric purity of **3p** was only 42% ee. Anthranilamides containing electron-donating methyl and methoxy groups were also well-tolerated in the aminalization reaction. For example, reaction with anthranilamide bearing a methyl group in the "4" position delivered product **3q** in good yield (80%) and enantiopurity (69% ee). A higher yield (96%) and enantiopurity (72% ee) was reached with anthranilamide **1r**, having a methyl group in the position "5". To further broaden the scope of the aminalization reaction, we prepared 2-(2-aminophenyl)acetamide (**1t**) and tested it in the reaction with isovaleraldehyde (**2a**) to access benzodiazepinone derivatives. The reaction proceeded smoothly with complete conversion within 24 hours, yielding the desired benzodiazepinone derivative **3t** in 55%. However, the enantiomeric purity dropped significantly to 35% ee. Additionally, we tested the influence of substitution of the aromatic amine and prepared the benzyl-protected anthranilamide **1u**. Unfortu-



Scheme 2: The substrate scope of the intermolecular aminalization reaction for anthranilamide derivatives. [a]After recrystallization; [b]THF used as a reaction solvent.

nately, the reaction between **1u** and isovaleraldehyde (**2a**) did not deliver the corresponding product **3u** even after a prolonged reaction time.

To determine the absolute configuration of aminals **3a–t**, derivative **3l** was subjected to X-ray crystallographic analysis. The absolute configuration of the stereogenic center (C1) was assigned as *R* (Figure 2, for details see Supporting Information File 1) [36], which is in agreement with the configuration of aminals obtained by List and co-workers [14].

Conclusion

In summary, we have reported an organocatalytic asymmetric aminalization reaction between aldehydes and anthranilamides catalyzed by a PCCP catalyst as a cheap and readily available option to conventional chiral BINOL phosphoric acids. The reaction tolerates a wide range of substitutions of anthranilamides and aromatic and aliphatic aldehydes, yielding the corresponding dihydroquinazolinones in excellent yields (up to 97%) and enantiopurities up to 80% ee. We demonstrated that bulkiness of aldehydes negatively affected the enantiocontrol of

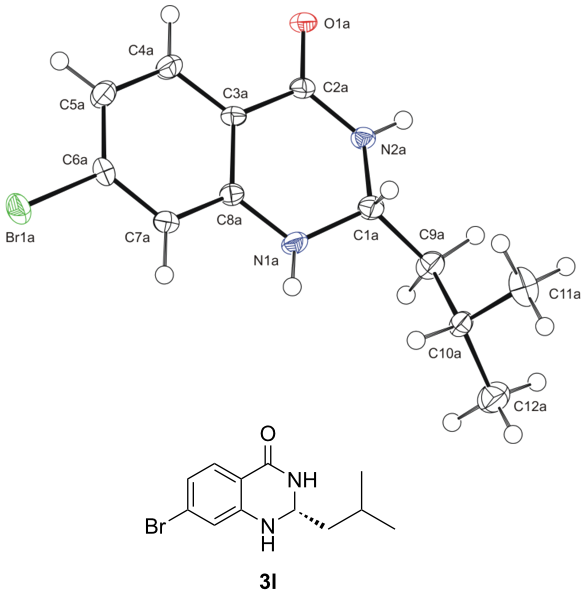


Figure 2: X-ray single-crystal structure of aminal **3l** with the displacement ellipsoids drawn at the 30% probability level.

the process, and highly enantiomerically enriched dihydroquinazolinones can be achieved by crystallization (up to 97% ee). The developed methodology can also be used to form tetrahydrobenzodiazepinones; however, a significant drop in the yield and enantioselectivity was observed.

Supporting Information

Supporting Information File 1

General synthetic procedures, characterization of compounds, X-ray experimental data, and copies of ^{1}H and ^{13}C NMR spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-160-S1.pdf]

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ORCID® iDs

Martin Kamlar - https://orcid.org/0000-0001-9115-9858
Robert Reiberger - https://orcid.org/0000-0001-7878-9310
Ivana Císařová - https://orcid.org/0000-0002-9612-9831
Jan Veselý - https://orcid.org/0000-0001-5198-8950

Preprint

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Recent advances in organocatalytic asymmetric aza-Michael reactions of amines and amides

Pratibha Sharma, Raakhi Gupta and Raj K. Bansal*

Review

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Address:
Department of Chemistry, The IIS (deemed to be University), Jaipur 302 020, India

Email:
Raj K. Bansal* - bansal56@gmail.com

* Corresponding author

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Abstract

Nitrogen-containing scaffolds are ubiquitous in nature and constitute an important class of building blocks in organic synthesis. The asymmetric aza-Michael reaction (aza-MR) alone or in tandem with other organic reaction(s) is an important synthetic tool to form new C–N bond(s) leading to developing new libraries of diverse types of bioactive nitrogen compounds. The synthesis and application of a variety of organocatalysts for accomplishing highly useful organic syntheses without causing environmental pollution in compliance with 'Green Chemistry" has been a landmark development in the recent past. Application of many of these organocatalysts has been extended to asymmetric aza-MR during the last two decades. The present article overviews the literature published during the last 10 years concerning the asymmetric aza-MR of amines and amides catalysed by organocatalysts. Both types of the organocatalysts, i.e., those acting through non-covalent interactions and those working through covalent bond formation have been applied for the asymmetric aza-MR. Thus, the review includes the examples wherein cinchona alkaloids, squaramides, chiral amines, phase-transfer catalysts and chiral bifunctional thioureas have been used, which activate the substrates through hydrogen bond formation. Most of these reactions are accompanied by high yields and enantiomeric excesses. On the other hand, N-heterocyclic carbenes and chiral pyrrolidine derivatives acting through covalent bond formation such as the iminium ions with the substrates have also been included. Wherever possible, a comparison has been made between the efficacies of various organocatalysts in asymmetric aza-MR.

Introduction

The Michael reaction though discovered about 135 years ago [1,2] continues to attract attention of the chemists owing to its potential of making a vast variety of organic compounds particularly of pharmacological importance accessible. Over the years, its many versions known as aza-Michael, thio-Michael, oxa-Michael, phospha-Michael, etc. have been developed and

well exploited for their synthetic applications [3-7]. The reaction involving a nitrogen-based nucleophile as the Michael donor is known as the aza-Michael reaction (aza-MR). In view of its ability to introduce a nitrogen-containing functionality at the β-position of an activated alkenyl- or alkynyl-substrate, over the years, it has developed as an important synthetic strategy for the preparation of a large variety of β-amino carbonyl and similar motifs which are present in many bioactive natural products [8,9], antibiotics [10-12] and chiral auxiliaries [13-15]. However, the reaction of many nitrogen-nucleophiles, such as aromatic amines, amides, imides, etc. require the use of an appropriate catalyst to undergo a Michael addition with a suitable acceptor. In view of this, chemists endeavoured to develop different types of catalysts, particularly the chiral catalysts to accomplish asymmetric aza-MRs. The development of metal-free small organic molecules as catalysts has been a landmark advancement in organic synthesis in the recent past [16]. MacMillan and co-workers for the first time in the year 2000 termed these catalysts as 'Organocatalysts' [17]. It was followed by intense activity and phenomenal rise in the number of publications in this field. These organocatalysts have been found compatible with many aspects of 'Green Chemistry' on the one hand, and highly selective in many organic syntheses on the other hand [17]. It has an added advantage that a large number of enantiomerically pure organocatalysts can be accessed from the chiral pool. Both types of organocatalysts, namely those acting through non-covalent bonding as well as those working by making covalent bonding have been employed for accomplishing asymmetric aza-MRs.

There are several review articles available on organocatalytic asymmetric aza-MRs, each highlighting a certain aspect of the reaction. While Sánchez-Roselló et al. [18] classified these reactions on the basis of the nature of the substrates, Nayak et al. [19] and Bhanja et al. [20] focused on the stereoselective synthesis of nitrogen heterocycles via Michael cascade reactions. Recently, Vinogradov et al. [21] reviewed the synthesis of pharmacology-relevant nitrogen heterocycles via stereoselective aza-MRs. On the other hand, Enders et al. [22], Wang et al. [23] as well as Krishna et al. [24] highlighted the scope and catalytic performances of some organocatalysts in asymmetric aza-MRs. However, the last three review articles are almost 10 years old and they do not cover the application of many important organocatalysts, such as thioureas and nitrogen heterocyclic carbenes (NHCs) used for the asymmetric aza-MRs. Furthermore, in the last review article [24], the application of organocatalysts is included as a small part of a general review. In view of this, we considered it prudent to compile this mini review exclusively based on the application of all categories of the organocatalysts and highlighting their efficacies covering the literature of the last ten years.

Review

In the present review, the known stereoselective syntheses of pharmacology-oriented nitrogen containing heterocyclic scaffolds via non-covalent bonding and covalent bonding organocatalytic aza-MRs has been systematized. This classification is especially useful for researchers to understand both the non-covalent and covalent organocatalysis.

It is intended to overview the literature of the last 10 years, i.e., from 2011 through 2020 only. Nevertheless, wherever necessary, earlier references may also be cited to maintain coherence. Furthermore, nitrogen nucleophiles comprise a large variety of compounds; however, in order to comply with the requirements of a mini review, additions of amines and amides only will be included.

1. Non-covalent bonding organocatalytic aza-Michael reactions

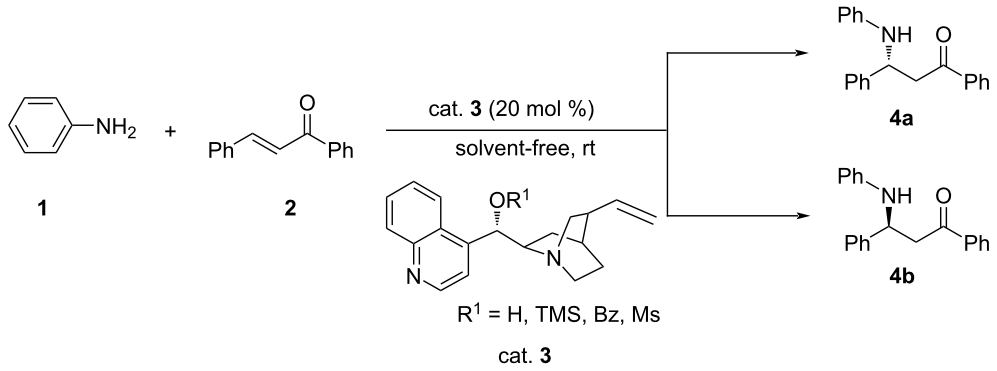
Organocatalysts catalyzing aza-MRs through mainly hydrogen bonding include cinchona alkaloids, squaramide derivatives, phase-transfer catalysts and bifunctional thiourea derivatives.

1.1 Reactions catalyzed by chiral cinchona alkaloid derivatives

Cai et al. prepared and used a number of organocatalysts from Cinchona alkaloids for the aza-MR of aniline (**1**) with chalcone (**2**) to obtain the adducts **4** in poor to very good yields (24 to >99%) with poor to moderate ee (9 to 55%). A complete reversal of stereoselectivity was observed on introducing a benzoyl group in cinchonine and cinchonidine. It was demonstrated that racemization occurred in suitable solvents under mild conditions due to retro-MR of the initially formed Michael adduct (Scheme 1) [25]. The proposed catalytic cycle involved generation of the active complex through hydrogen bonding between catalyst and aniline followed by interaction with chalcone via π–π stacking of aromatic rings and hydrogen bonding leading to the Michael adduct.

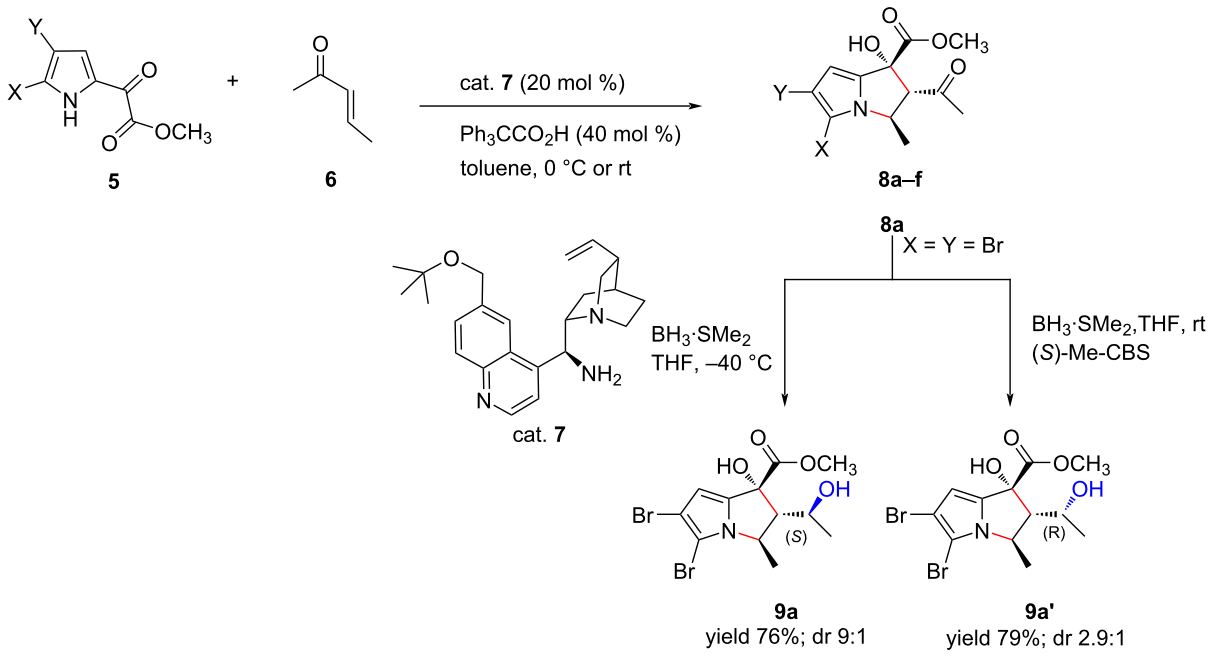
Likewise, Lee et al. reported cinchona-based primary amine catalyzed cascade aza-Michael-aldol reaction of α,β-unsaturated ketones **6** with 2-(1*H*-pyrrol-2-yl)-2-oxoacetates **5** where triphenylacetic acid was used as an additive. This cascade reaction afforded highly functionalized chiral pyrrolizines **8** in good yields (70–91%) with excellent levels of stereocontrol (≈92% ee, >20:1 dr in all cases). The ketone group in the cascade product was reduced asymmetrically to a chiral secondary hydroxy group (Table 1) [26].

In this case, the role of Ph_3CCO_2H as additive is to furnish the conjugate base $Ph_3CO_2^-$ anion which subsequently deproto-



Scheme 1: Asymmetric aza-Michael addition catalyzed by cinchona alkaloid derivatives.

Table 1: Asymmetric cascade aza-Michael–aldol reactions of α,β-unsaturated ketones with pyrroles.

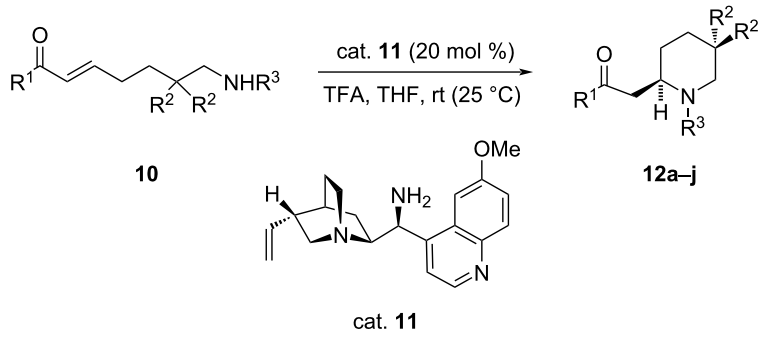


8	X	Y	Yield [%]	ee [%]	dr
a	Br	Br	86	91	>20:1
b	Cl	Br	91	90	>20:1
c	I	Br	75	92	>20:1
d	Br	Cl	86	90	>20:1
e	Cl	I	73	90	>20:1
f	I	I	70	92	>20:1

nates pyrrole to provide the stronger nucleophilic pyrrolide anion [27].

Similarly, Liu et al. accomplished an asymmetric intramolecular aza-Michael addition of various enone carbamates **10** using a chiral cinchona-based primary-tertiary diamine as catalyst to obtain 2-substituted piperidines **12** in good yields (75–95%) with up to 99% ee. Several sulfonic acids and carboxylic acids were tested as co-catalysts and trifluoroacetic acid (TFA) was found to give the best results [28]. Here the role of the co-catalyst is to assist in the formation of the iminium intermediate (Table 2) [29]. It appears that in this case, both activation mech-

Table 2: Intramolecular aza-Michael addition of conjugated ketones.



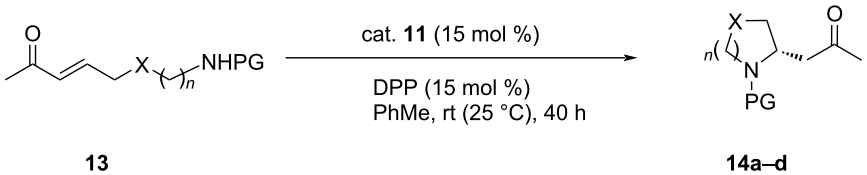
12	R^1	R^2	R^3	Yield [%]	ee [%]
a	Me	H	Cbz	95	98 (*R*)
b	Me	H	Boc	94	90
c	Me	Me	Cbz	97	99
d	Et	H	Cbz	94	96 (*R*)
e	iBu	H	Cbz	96	99
f	*n*-pentyl	H	Cbz	93	96 (*R*)
g	Ph	H	Cbz	95	96
h	4-Me-C_6H_4	H	Cbz	75	96
i	4-MeO-C_6H_4	H	Cbz	trace[a]	ND[b]
j	4-O_2N-C_6H_4	H	Cbz	80	85

[a]The starting material was mainly recovered. [b]ND = not determined.

anisms, namely through hydrogen bonding and iminium ion formation are operating.

Using the same chiral cinchona-based primary-tertiary diamine as catalyst (cat. **11**), Zhai et al. developed a highly efficient intramolecular enantioselective aza-Michael addition of carbamates, sulfonamides and acetamides **13** bearing an α,β-unsaturated ketone to synthesize a series of 2-substituted five- and six-membered heterocycles in good yields (up to 99%) and excellent enantioselectivity (92–97.5% ee) (Table 3). As in an earlier

Table 3: Intramolecular enantioselective aza-Michael addition.



14	X	*n*	PG	Yield [%]	ee [%][a]
a	O	2	Boc	97	97
b	O	1	Boc	96	94
c[b]	S	2	Cbz	55	95
d	S	1	Cbz	91	92

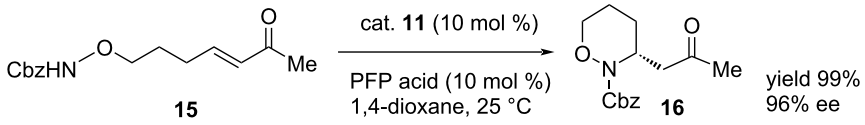
[a]Determined by means of chiral-phase HPLC analysis. [b]Reaction time = 4 days.

case [29], several acids were tested as co-catalysts and trifluoroacetic acid and diphenyl hydrogenphosphate (DPP) were found to give the best results [30].

Cheng et al. reported an intramolecular 6-*exo*-*trig* aza-MR of hydroxylamine-derived enone **15** for the synthesis of chiral 3-substituted 1,2-oxazinanes **16**. The catalyst **11** was used in this case also and pentafluoropropionic acid (PFP) was used as a co-catalyst. In the presence of 1,4-dioxane solvent, products chiral 3-substituted 1,2-oxazinanes (**16**) were obtained in 99% yield with good ee of 96% (Scheme 2) [31].

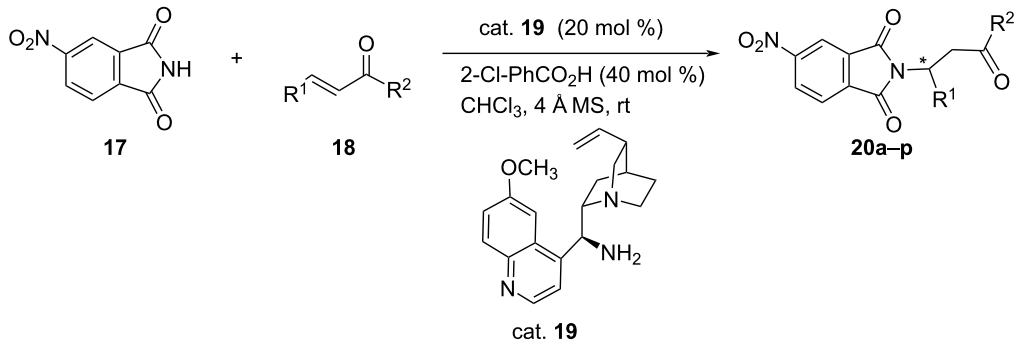
Following a similar strategy, Ma et al. accomplished a highly enantioselective aza-Michael addition of 4-nitrophthalimide (**17**) with α,β-unsaturated ketones **18** using 9-*epi*-9-amino-9-deoxyquinine **19** as the catalyst, the corresponding Michael adducts being obtained in moderate to good yields (49–98%) with excellent ee (95–99%) (Table 4) [32].

Jakkampudi et al. [33] adopted a different approach for the use of cinchona-based organocatalysts. Instead of using the cinchona derivative alone, they employed a mixture of cinchona derivative and amino acid such as D-proline, termed as the



Scheme 2: Intramolecular 6-*exo*-*trig* aza-Michael addition reaction.

Table 4: Asymmetric aza-Michael addition of 4-nitrophthalimide to α,β-unsaturated ketones.



20	R^1	R^2	Yield [%]	ee [%]
a	Ph	Ph	55	>99
b	2-Cl-C_6H_4	Ph	61	95
c	3-Cl-C_6H_4	Ph	65	98 (s)
d	4-Cl-C_6H_4	Ph	56	99
e	4-F-C_6H_4	Ph	60	>99
f	4-Br-C_6H_4	Ph	62	99
g	4-Me-C_6H_4	Ph	69	99
h	4-NO_2-C_6H_4	Ph	49	>99
i	Ph	4-Cl-C_6H_4	54	99
j	4-F-C_6H_4	4-F-C_6H_4	71	99
k	iPr	Me	75	97
l	*n*-Pr	Me	88	96
m	*n*-Bu	Me	89	95
n	*n*-Pen	Me	98	95
o	*n*-Hex	Me	90	96
p	Me	Et	51	95

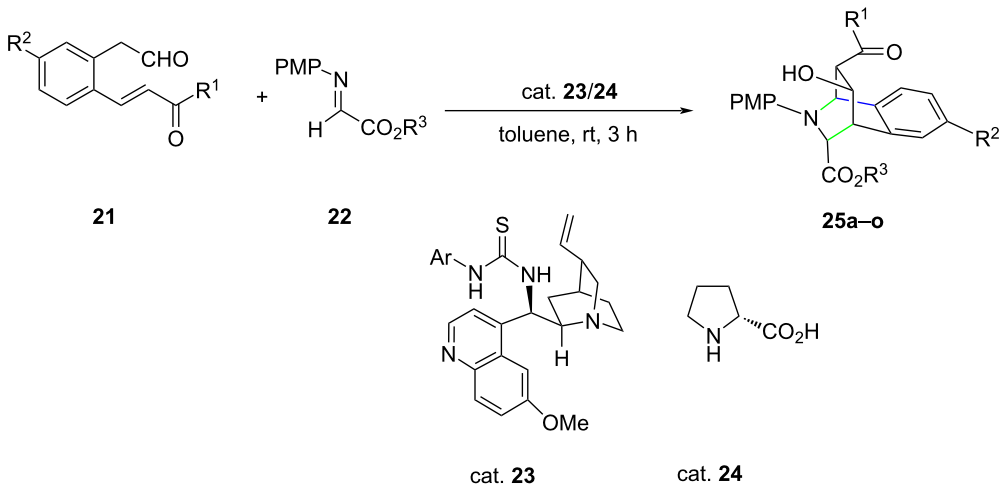
modularly designed organocatalyst (MDO) for the synthesis of bridged tetrahydroisoquinoline derivatives. It was perceived that the MDO self-assembled in situ from amino acids and cinchona alkaloid derivatives. For example, on reacting (*E*)-2-[2-(3-aryl-3-oxoprop-1-en-1-yl)phenyl]acetaldehydes **21** with ethyl or benzyl (*E*)-2-[(4-methoxyphenyl)imino]acetates **22** in the presence of the MDO **23/24** (quinidinethiourea + D-proline), instead of the expected domino Mannich/Michael product, the bridged tetrahydroisoquinoline product **25a** was obtained in high yield (90%) and excellent dr (94:6) and ee value (99%) (Table 5). The controlled reactions using **23** and **24** as the catalyst gave the product in very poor yield. It was concluded that the catalytic activity of the MDO was the result of the cooperative action of both constituents. Several examples of such MDOs are included in the paper. The reported yield varies from 56–90% with excellent ee ≈ 99% in all cases.

1.2. Reactions catalyzed by chiral squaramide derivatives

Squaramides are related to cinchona alkaloids but are much more effective organocatalysts than the latter due to the ability of dual hydrogen bonding besides a tertiary nitrogen atom of quinuclidine nucleus which may serve both as an H-bond acceptor and a base in asymmetric Michael addition reactions [34,35].

In 2015, Zhao et al. synthesized spiro[pyrrolidine-3,3'-oxindoles] **29** in single step by asymmetric cascade aza-Michael/

Table 5: Diastereoselective synthesis of bridged 1,2,3,4-tetrahydroisoquinoline derivatives using modularly designed organocatalyst.



25	R^1	R^2	R^3	Yield [%]	ee [%]	dr
a	C_6H_5	H	Et	90	>99	94:6
b	4-F-C_6H_4	H	Et	81	>99	97:3
c	4-Cl-C_6H_4	H	Et	90	99	92:8
d	4-Br-C_6H_4	H	Et	80	>99	90:10
e	4-NC-C_6H_4	H	Et	77	99	87:13
f	4-Me-C_6H_4	H	Et	76	99	97:3
g	4-MeO-C_6H_4	H	Et	79	97	96:4
h	3-Cl-C_6H_4	H	Et	72	>99	88:12
i[a]	2-F-C_6H_4	H	Et	–	–	–
j[a]	2-Cl-C_6H_4	H	Et	–	–	–
k	C_6H_5	F	Et	73	>99	90:10
l	C_6H_5	MeO	Et	74	99	91:9
m	Me	H	Et	56	92	86:14
n	C_6H_5	H	Bn	75	99	89:11
o	4-Br-C_6H_4	H	Bn	77	>99	93:7

[a]Formation of a complex mixture was observed.

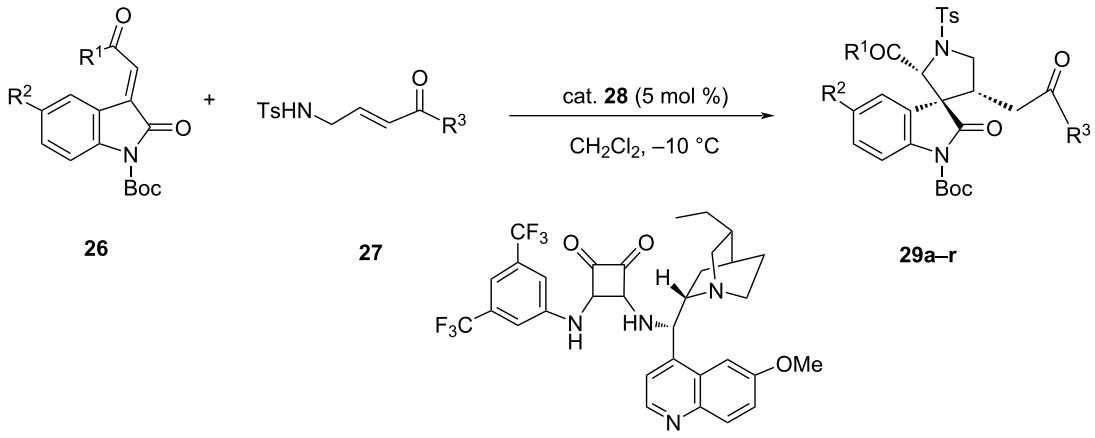
Michael addition reaction between 4-tosylaminobut-2-enoates **27** and 3-ylideneoxindoles **26** catalyzed by a chiral bifunctional tertiary amine, squaramide (cat. **28**) which afforded the corresponding adducts in good yields ranging from 72–99% with excellent diastereoselectivity (up to >99:1 dr) and enantioselectivity (>99% ee) (Table 6) [36].

In another report, Yang et al. accomplished a highly asymmetric cascade aza-Michael/Michael addition reaction for the synthesis of tetrahydroquinolines and tetrahydrochromanoquinolines catalyzed by a squaramide catalyst. The corresponding adducts were obtained in excellent yields with excellent diastereoselectivities and enantioselectivities (up to >99:1 dr, 99% ee) [37].

Following a similar strategy, Zhou et al. obtained a series of optically active tetrahydrobenzofuro[3,2-*b*]quinolines and tetrahydrobenzo[4,5]thieno[3,2-*b*]quinolines **33** in high yields ranging from 35–99% and excellent diastereo- (>20:1 dr), and enantioselectivities (up to ≈99% ee) (Scheme 3) [38].

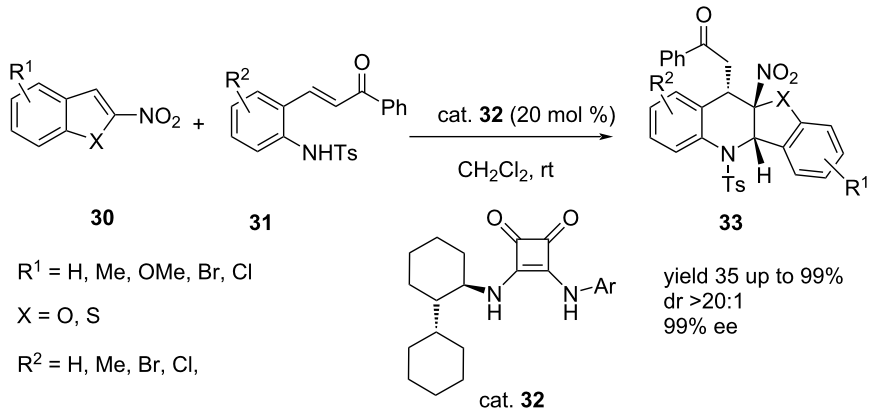
Roy et al. accomplished an enantioselective intramolecular aza-Michael addition for the synthesis of dihydroisoquinoline and tetrahydropyridines from Michael reaction of *ortho*-homo-

Table 6: Synthesis of spiro[pyrrolidine-3,3'-oxindoles] via asymmetric cascade aza-Michael reaction catalyzed by squaramide.



cat. **28**

29	R^1	R^2	R^3	Yield [%]	ee [%]	dr
a	Ph	H	Me	72	98	96:4
b	Ph	H	O*t*-Bu	99	>99	93:7
c	Ph	H	OBn	99	>99	88:12
d	Ph	H	OEt	99	>99	65:35
e	4-FC_6H_4	H	O*t*-Bu	99	>99	88:12
f	4-ClC_6H_4	H	O*t*-Bu	99	>99	89:11
g	2-BrC_6H_4	H	O*t*-Bu	91	>99	85:15
h	4-BrC_6H_4	H	O*t*-Bu	99	>99	92:8
i	4-MeC_6H_4	H	O*t*-Bu	95	>99	96:4
j	3-$MeOC_6H_4$	H	O*t*-Bu	88	>99	92:8
k	4-$MeOC_6H_4$	H	O*t*-Bu	94	>99	89:11
l	2-naphthyl	H	O*t*-Bu	92	>99	89:11
m	2-thienyl	H	O*t*-Bu	96	>99	92:8
n	C_6H_5	F	O*t*-Bu	99	>99	89:11
o	C_6H_5	Cl	O*t*-Bu	99	>99	88:12
p	C_6H_5	Br	O*t*-Bu	99	>99	93:7
q	C_6H_5	Me	O*t*-Bu	99	>99	97:3
r	C_6H_5	OMe	O*t*-Bu	99	>99	99:1



Scheme 3: Asymmetric aza-Michael/Michael addition cascade reaction of 2-nitrobenzofurans and 2-nitrobenzothiophenes with 2-aminochalcones catalyzed by squaramide derivative.

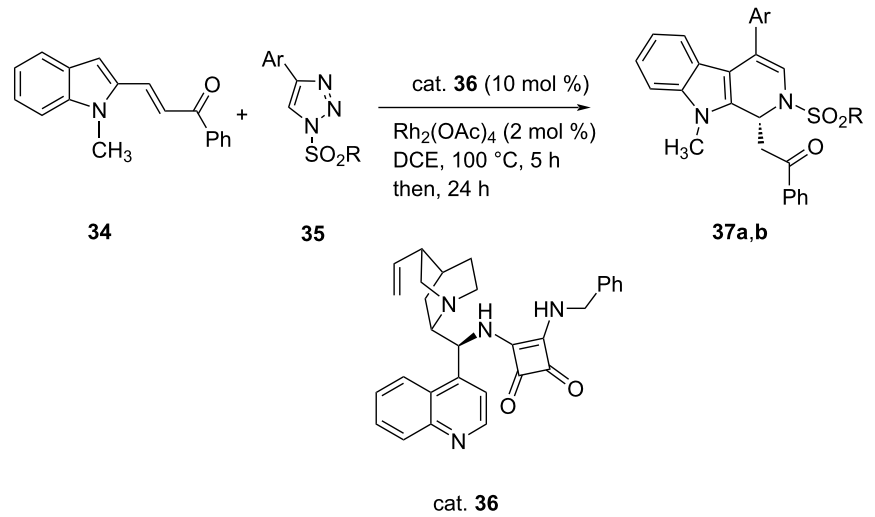
formyl chalcone with various amines by using squaramide catalyst. The reaction occurred with good yields and excellent enantioselectivity [39].

Similarly, Li et al. reported an asymmetric cascade aza-Michael addition of 2-tosylaminoenones with unsaturated pyrazolones using squaramide as catalyst. The reaction proceeded smoothly under mild conditions to afford the corresponding spiro[pyrazolone-tetrahydroquinolines] in high yields (up to 99%) with excellent diastereoselectivities (up to >25:1 dr) and high enantioselectivities (up to 65–91%) [40].

Rajasekar et al. developed an efficient one-pot tandem rhodium(II)/chiral squaramide relay catalysis for the enantioselective construction of dihydro-β-carbolines **37** from the Michael reaction of suitably substituted indole derivatives **34** with *N*-sulfonyl-1,2,3-triazoles **35** in good yields (up to ≈72%) and excellent enantioselectivity (up to 99% ee) (Table 7) [41].

In an interesting study, Wu et al. screened a number of cinchona derivatives and squaramides for their relative catalytic efficacies for the enantioselective aza-Michael additions between

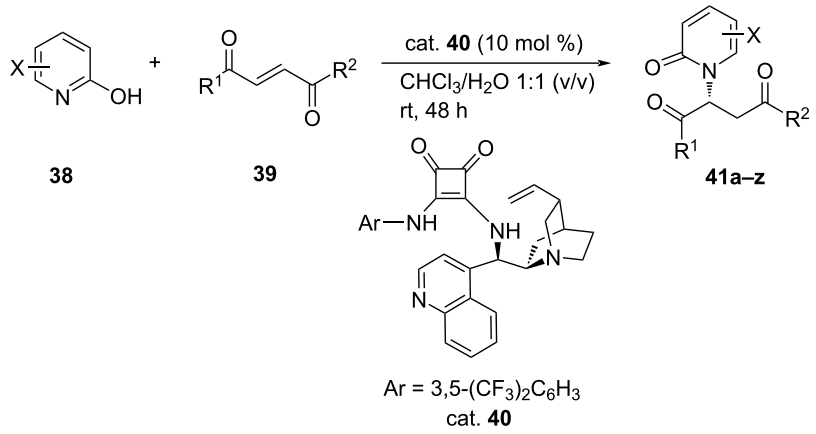
Table 7: Asymmetric aza-Michael synthesis of dihydro-β-carbolines.



37	Ar	R	Yield [%]	ee [%]
a	Ph	Ph	71	99
b	Ph	Me	72	80

halogenated 2-hydroxypyridines (pyridin-2(1*H*)-ones) **38** and α,β-unsaturated 1,4-diketones or 1,4-ketoesters **39** in different solvents. The best results (yield 96%, ee >91%) were obtained on using squaramide catalyst in chloroform. However, for others, the yields ranged from 50–98% with good to excellent enantioselectivity (47–98% ee). The observed results were rationalized with density functional theory calculations (Table 8) [42].

Table 8: Asymmetric aza-Michael synthesis of *N*-substituted 2-pyridones.



41	X	R^1	R^2	Yield [%]	ee [%]
a	5-Br	Ph	Ph	98	98
b	5-I	Ph	Ph	78	91
c	5-F	Ph	Ph	60	74
d	H	Ph	Ph	50	44
e	3-Cl	Ph	Ph	88	93
f	3-Br	Ph	Ph	93	92
g	3-I	Ph	Ph	82	73
h	4-Br	Ph	Ph	60	47
i	6-Cl	Ph	Ph	0	–
j	5-Cl	*p*-F-C_6H_4	*p*-F-C_6H_4	93	93
k	5-Br	*p*-F-C_6H_4	*p*-F-C_6H_4	95	>99
l	5-I	*p*-F-C_6H_4	*p*-F-C_6H_4	87	97
m	3-Cl	*p*-F-C_6H_4	*p*-F-C_6H_4	82	99
n	3-Br	*p*-F-C_6H_4	*p*-F-C_6H_4	88	97
o	3-I	*p*-F-C_6H_4	*p*-F-C_6H_4	90	99
p	5-Cl	*p*-NC-C_6H_4	*p*-NC-C_6H_4	85	94
q	5-Br	*p*-NC-C_6H_4	*p*-NC-C_6H_4	73	97
r	5-Cl	*p*-Me-C_6H_4	*p*-Me-C_6H_4	70	35
s	5-Br	*p*-Me-C_6H_4	*p*-Me-C_6H_4	76	82
t	5-I	*p*-Me-C_6H_4	*p*-Me-C_6H_4	75	67
u	5-Cl	*p*-MeO-C_6H_4	*p*-MeO-C_6H_4	0	–
v	5-Cl	OEt	Ph	90	78
w	5-Br	OEt	Ph	82	80
x	5-F	OEt	Ph	83	63
y	3-Cl	OEt	Ph	70	90
z	3-Br	OEt	Ph	78	90
aa	4-Br	OEt	Ph	73	60
ab	3-Cl	OEt	*p*-F-C_6H_4	90	80

1.3 Reactions catalyzed by chiral amines

He and co-workers developed heterogeneous synergistic catalysis using chiral amines SBA-15 (cat. **44**), which promote aza-Michael–Henry cascade reactions between 2-aminobenzaldehydes **42** and β-nitrostyrenes **43** to obtain chiral 3-nitro-1,2-dihydroquinolines **45** in good yields with up to 98% ee (Table 9) [43].

1.4 Reactions catalyzed by chiral phase-transfer catalysts

Chiral phase-transfer catalysts (PTC) have been recognized as versatile catalysts for the asymmetric aza-Michael addition reactions. Mahe et al. reported an effective, eco-friendly and cost-effective enantioselective synthesis of 3,5-diarylpyrazolines **49** by using phase-transfer methodology. They carried out a set of reactions between chalcones **46** and *N*-*tert*-butoxycarbonylhydrazine (**47**) in the presence of cesium carbonate and an *N*-benzylquininium salt as catalyst (cat. **48**) (solid–liquid phase-transfer conditions) to give the corresponding adducts in 40–90% yields with excellent ee of up to 99% (Table 10) [44].

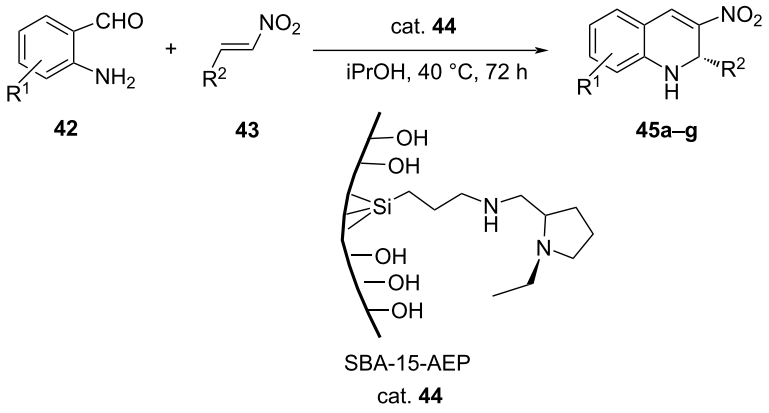
A different type of asymmetric aza-Michael addition was developed by Wang et al. They carried out asymmetric conjugate amination of *tert*-butylbenzyloxycarbamate (**50**) to β-nitrostyrene **51** under neutral phase-transfer conditions in the presence of chiral bifunctional tetraalkylammonium bromide (cat. **52**) in water-rich biphasic solvent. The reaction proceeded with high ee values of up to 95% and very good yields (≈99%) in all cases (Table 11) [45].

Guo et al. synthesized a variety of benzoindolizidines (**56**) from α,β-unsaturated aminoketones **54** through intramolecular domino aza-Michael addition/alkylation reactions. The reactions were carried out in the presence of cinchona alkaloid-derived quaternary ammonium salts (cat. **55**) as the phase-transfer catalyst. The products were obtained in high yields (53–93%) with high enantioselectivities (40–76% ee) (Table 12) [46].

Lebrun et al. developed a new method to synthesize optically active isoindolinones via asymmetric intramolecular aza-MR by using phase-transfer catalysts. Alkenylated benzamide was used as the substrate in this reaction. The resulting compounds were found to be useful intermediates for the synthesis and development of benzodiazepine-receptor agonists [47].

In 2018, Sallio et al. worked on the same reaction by using different PTCs in order to improve yield and diastereomeric excess. They incorporated PTC and chiral auxiliary and reacted

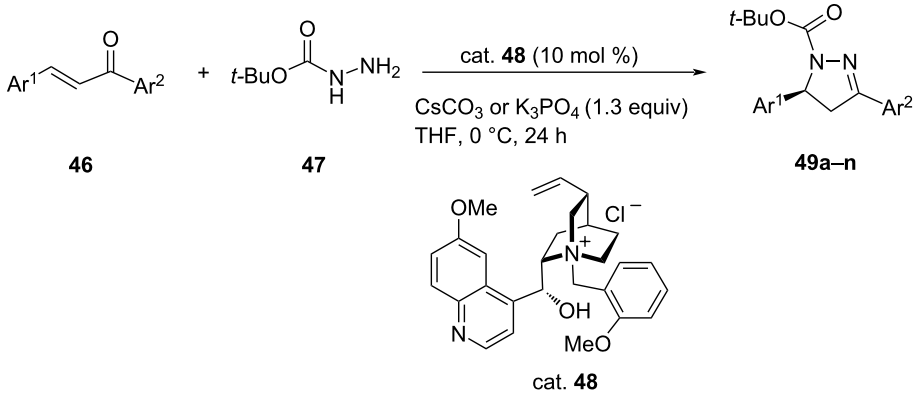
Table 9: Asymmetric aza-Michael–Henry cascade reaction.



45	R^1 in 42	R^2	Yield [%][a]	ee [%][b]
a	H	2,3-$(MeO)_2$-C_6H_3	67 (65)	98 (98)
b	H	4-Me-C_6H_4	60 (59)	90 (93)
c	H	2,4-$(Cl)_2$-C_6H_3	45 (40)	97 (96)
d	H	3,4-$(Cl)_2$-C_6H_3	42 (38)	95 (97)
e	3-MeO	Ph	52 (50)	95 (99)
f	5-Cl	Ph	55 (53)	98 (99)
g	3,5-Br_2	Ph	68 (67)	99 (98)

[a]Determined by ^{1}H NMR. [b]Determined by HPLC. The data in parentheses are reproduced results.

Table 10: Asymmetric aza-Michael addition for the formation of (S)-(–)-pyrazoline.



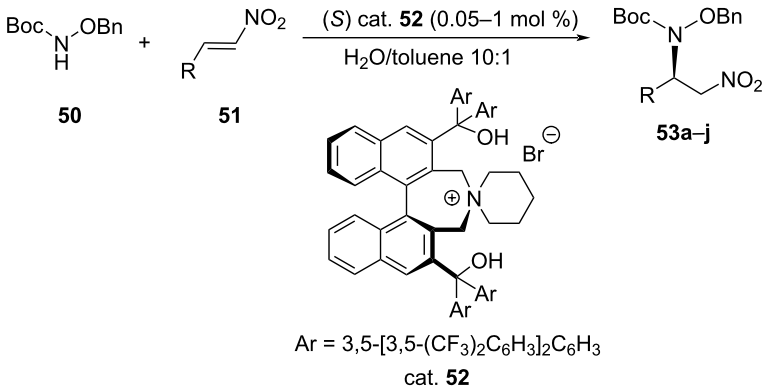
46 **47** **49a–n**

cat. **48**

49	Ar^1	Ar^2	Yield [%]	ee [%]
a	Ph	Ph	77	92 (–)
b	Ph	4-$MeOC_6H_4$	71	90 (–)
c	Ph	4-FC_6H_4	72	90 (–)
d	Ph	4-FC_6H_4	62	92 (–)
e	Ph	2-$MeOC_6H_4$	89	92 (–)
f	Ph	2-$MeOC_6H_4$	52	94 (–)
g	Ph	2-thienyl	66	87 (–)
h	Ph	2-thienyl	60	91 (–)
i	Ph	3,4-$(Cl)_2C_6H_3$	40 (62)[a]	92 (–)
j	4-$MeOC_6H_4$	Ph	60	89 (+)
k	4-ClC_6H_4	Ph	70	88 (–)
l	2-MeC_6H_4	Ph	62	89 (–)
m	3-$MeOC_6H_4$	Ph	61	91 (–)
n	2-thienyl	Ph	46	78 (–)

[a]Yield determined by NMR analysis of the crude reaction mixture using an internal standard.

Table 11: Asymmetric aza-Michael addition reaction catalyzed by phase-transfer catalyst.



50 **51** **53a–j**

Ar = 3,5-[3,5-$(CF_3)_2C_6H_3$]$_2C_6H_3$

cat. **52**

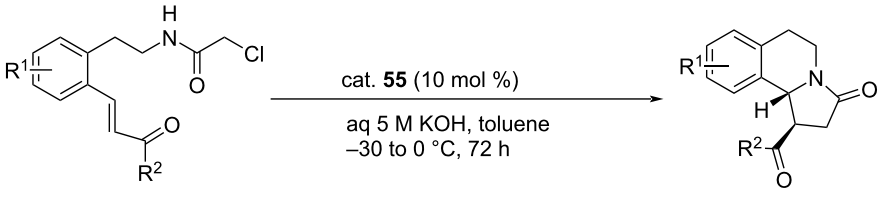
53	Conditions[a]		R	Yield (%)		ee [%]	
	A	B		A	B	A	B
a	A	B	Ph	91	90	90	93

Table 11: Asymmetric aza-Michael addition reaction catalyzed by phase-transfer catalyst. (continued)

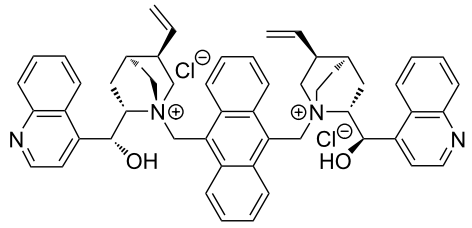
b	A	B	4-Me-C_6H_4	93	90	90	91
c	A	B	4-BrC_6H_4	91	89	91	94
d	A	B	3-FC_6H_4	70	62	90	93
e	A	B	4-TBSOC_6H_4	94	92	92	95
f	A	B	2-naphthyl	85	70	90	91
g	A	B	2-thienyl	93	81	90	94
h	A	B	2-furyl	90	82	90	93
i	A	B	$(CH_3)_2CHCH_2$	95	99	77	82
j	A	B	*t*-Bu	97	99	79	83

[a]Conditions A: cat. (0.05 mol %) at rt or 0 °C, conditions B: cat. (1 mol %) at 0 °C.

Table 12: Asymmetric aza-Michael/alkylation reaction catalyzed by cinchona alkaloid-derived quaternary ammonium salts.



54 **56a–o**



cat. **55**

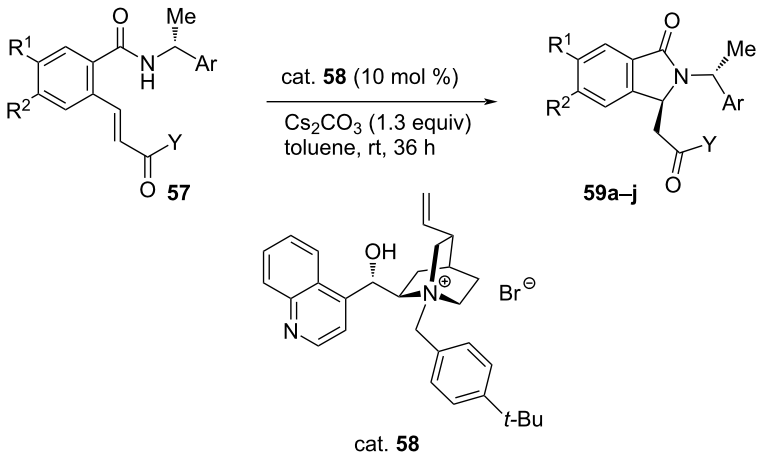
56	R^1	R^2	Yield [%]	ee [%]
a	H	Ph	91	76
b	H	4-MeC_6H_4	84	69
c	H	4-MeOC_6H_4	53	65
d	H	Ph-C_6H_4	71	75
e	H	2-naphthyl	91	72
f	H	4-FC_6H_4	88	50
g	H	4-ClC_6H_4	93	80
h	H	4-BrC_6H_4	93	65
i	H	2-furyl	87	54
j	H	2-thienyl	91	68
k	H	2-Py	89	63
l	2-Br	Ph	86	85
m	2-NO_2	Ph	75	85
n	3-MeO	Ph	87	40
o	H	Me	–	–

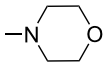
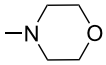
a variety of chiral phthalimidines **57** to obtain isoindolinones **59** in good yields (≈85%) with excellent de ranging 48–96% (Table 13) [48].

1.5 Catalysis by chiral bifunctional thioureas

Thioureas constitute one of the most important class of organocatalysts [49].

Table 13: Asymmetric aza-Michael synthesis of isoindolinones.



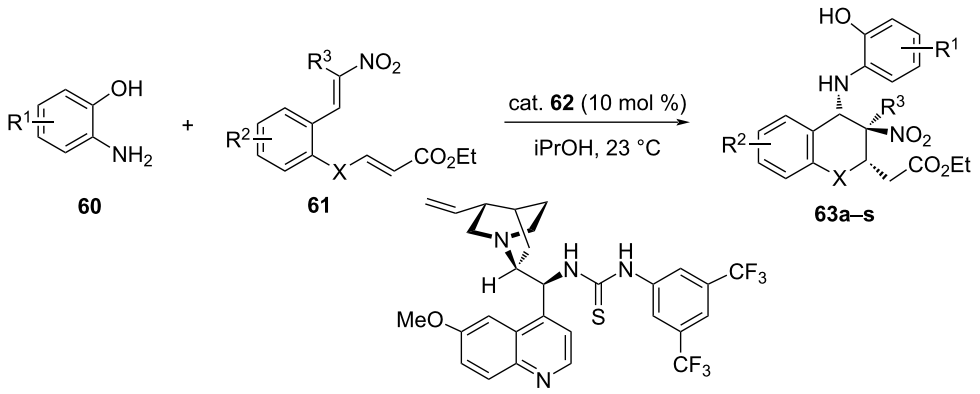
59	R^1	R^2	Ar	Y	Yield [%]	de [%]
a	H	H	Ph		75	>96
b	H	H	Ph		78	>96
c	H	H	Ph		79	56
d	H	H	Ph		80	44
e	H	H	PMP[a]		82	82
f	H	H	PMP		80	98
g	H	H	PMP		85	98
h	H	H	PMP		83	48
i	H	H	PMP		79	67
j	MeO	MeO	PMP		78	98

[a]PMP = *p*-methoxyphenyl.

Wang et al. reported a cascade aza-Michael/Michael reaction of anilines **60** to nitroolefin enoates **61** using chiral bifunctional thiourea as catalyst (cat. **62**). It provided a mild and efficient approach to the synthesis of three stereocentered polysubstituted chiral 4-aminobenzopyrans **63** in high yields (71–96%) with excellent stereoselectivities of up to >99% ee (Table 14) [50].

In an interesting report, five organocatalysts belonging to three categories, namely cinchona alkaloid bases, bifunctional squaramides and thioureas were screened for the enantioselective *N*-alkylation of isoxazolin-5-ones via a 1,6-aza-Michael addition of isoxazolin-5-ones **64** to *p*-quinone methides (*p*-QMs) **65** to give isoxazolin-5-ones **67** bearing a chiral diarylmethyl

Table 14: Asymmetric aza-Michael addition reaction catalysed by chiral bifunctional thiourea.



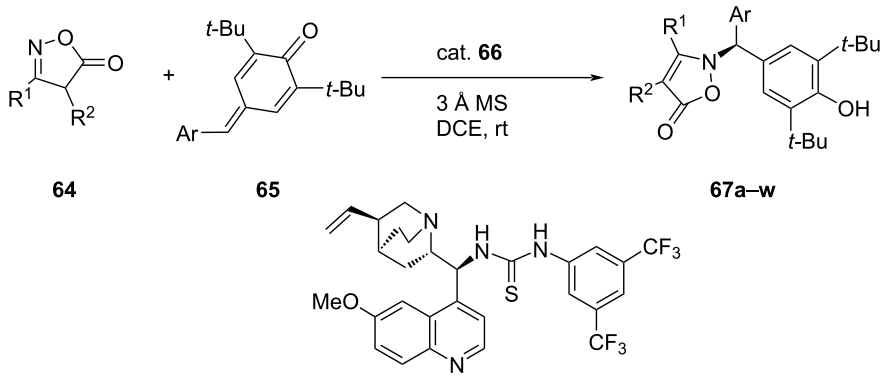
63	R^1	R^2	R^3	X	Yield [%]	ee [%]	dr
a	H	H	Me	O	96	96	>95:5
b	H	4-F	Me	O	71	>99	>95:5
c	H	4-Cl	Me	O	92	94	>95:5
d	H	4-Br	Me	O	84	94	>95:5
e	H	4-Me	Me	O	92	94	>95:5
f	H	4-MeO	Me	O	94	94	95:5
g	4-Me	5-MeO	Me	O	83	96	>95:5
h	4-Me	4-Br	Me	O	82	94	>95:5
i	5-Me	4-Br	Me	O	85	93	>95:5
j	6-Me	H	Me	O	94	93	>95:5
k	6-Me	5-MeO	Me	O	81	94	>95:5
l	4-Me	H	Me	O	94	96	>95:5
m	4-Br	H	Me	O	94	>99	>95:5
n	4-Cl	H	Me	O	89	93	>95:5
o	4-*t*-Bu	H	Me	O	91	94	>95:5
p	H	H	Et	O	91	96	>95:5
q	H	H	Bn	O	89	93	>95:5
r	H	H	Me	S	95	91	65:35
s	H	H	Me	S	93	94	95:5

moiety attached to the N atom. The best result in terms of enantioselectivity (85% ee) was obtained with quinine-derived thiourea in dichloroethane as the solvent. The scope of the reaction was also investigated *vis-a-vis* the effect of the substitution on the isoxazolinone ring and *p*-quinone methide (*p*-QM) partner. (Table 15) [51].

Takemoto and co-workers investigated three catalytic systems, namely arylboronic acid alone, its dual combination with chiral thiourea and integrated catalyst having boronic acid functionality in the chiral thiourea molecule. The dual combination of arylboronic acid with chiral thiourea was found as effective as arylboronic acid alone for the intermolecular asymmetric Michael addition of alk-2-enoic acids **68** with *O*-benzylhydroxylamine (**69**) giving racemic mixture of the product in poor yield. However, the integrated catalyst having boronic acid functionality in the chiral thiourea molecule gave the desired β-benzyloxyamino acid as the single product in a satisfactory yield. Thus, a series of these catalysts was screened. The best results in term of the yield (83%) and ee (90%) were obtained while using the catalyst having a *p*-nitrophenyl group on the other side of thiourea moiety in CCl_4 in the presence of 4 Å molecular sieves (Table 16). The yields ranged 57–89% with ee 70–97% [52].

A similar chiral multifunctional thiourea/boronic acid was used as an organocatalyst by Michigami et al. for the enantioselective synthesis of *N*-hydroxyaspartic acid derivatives **76** with

Table 15: Enantioselective 1,6-aza-Michael addition of isoxazolin-5-ones to *p*-quinone methides.



67	R^1	R^2	Ar	Yield [%]	ee [%][a]
a	Me	H	Ph	65	87
b	Et	H	Ph	51	81
c	Pr	H	Ph	50	81
d	Ph	H	Ph	77	54
e	Pr	H	Ph	78	89
f	Me	Me	Ph	66	62
g	Me	H	*p*-MeC_6H_4	62	88
h	Me	H	*p*-$MeOC_6H_4$	74	84
i	Me	H	*p*-ClC_6H_4	43	48
j	Me	H	*p*-$O_2NC_6H_4$	47	89
k	Me	H	*o*-$MeOC_6H_4$	81	94
l	Me	H	*o*-ClC_6H_4	94	96
m	Me	H	*o*-BrC_6H_4	43	90
n	Me	H	*m*-$MeOC_6H_4$	20	25
o	Me	H	*m*-ClC_6H_4	36	81
p	Me	H	*m*-$O_2NC_6H_4$	56	77
q	Pr	H	*p*-$MeOC_6H_4$	75	79
r	Pr	H	*p*-ClC_6H_4	78	88
s	Pr	H	*p*-$O_2NC_6H_4$	80	86
t	Pr	H	*o*-ClC_6H_4	76	92
u	Pr	H	*m*-$MeOC_6H_4$	82	82
v	Pr	H	*m*-ClC_6H_4	80	88
w	Pr	H	Ph	71	86

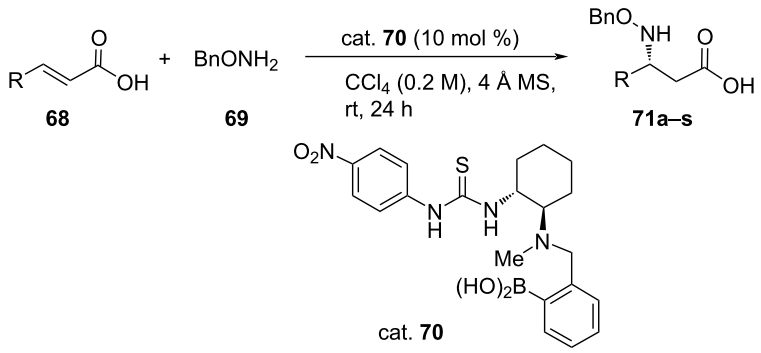
[a]Determined by HPLC using a chiral stationary phase.

perfect regioselectivity and high enantioselectivity (Table 17) [53].

Likewise, Miyaji et al. reported an efficient method for the synthesis of 2-substituted indolines **79** via intramolecular aza-Michael addition of α,β-unsaturated carboxylic acid derivatives **77** in the presence of bifunctional thiourea organocatalysts (cat. **78**) (Table 18). The product was obtained in moderate to good yield of 53–99% with an ee of 74–93% [54].

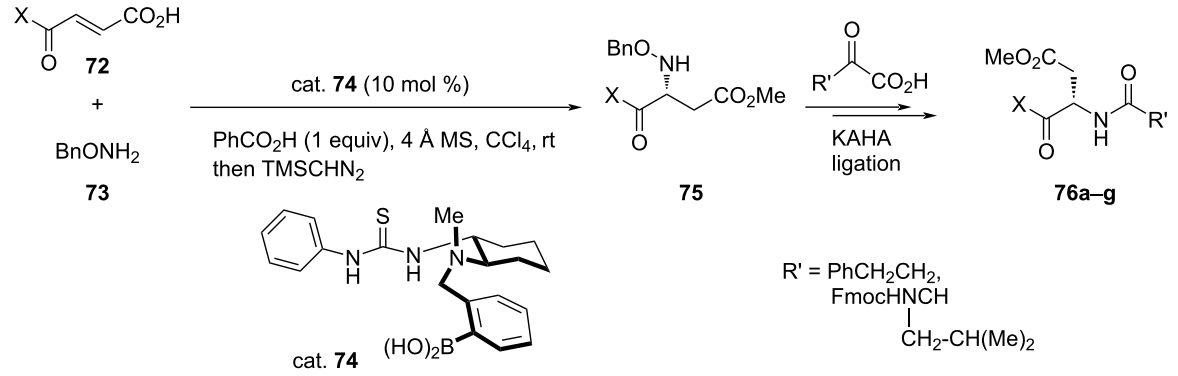
Liu et al. accomplished a catalytic cascade aza-Michael–Henry-dehydration protocol for the preparation of chiral 3-nitro-1,2-dihydroquinolines **83** from the reaction of *N*-protected amino-benzaldehydes **80** with substituted nitroolefins **81** by using

Table 16: Asymmetric intermolecular aza-Michael addition of (*E*)-3-substituted-2-enoic acid.



71	R	Yield [%]	ee [%]
a	Me	75	97
b	Et	84	90
c	Pr	72	90
d	*n*-C_5C_{11}	76	88
e	*n*-C_7C_{15}	75	86
f	$CH(CH_3)_2$	57	76
g	CH_2-OBn	89	85
h	$(CH_2)_3$-OBz	86	91
i	$(CH_2)_2$-SMe	78	87
j	$(CH_2)_3$-NHCbz	80	71
k	$(CH_2)_2$-C_6H_4-CF_3-4	76	83
l	$(CH_2)_2$-C_6H_4-MeO-4	88	87
m	$(CH_2)_2$-C_6H_4-Br-2	85	88
n	$(CH_2)_2$-C_6H_3-3,4-$(OMe)_2$	81	86
o	$(CH_2)_2$-2-naphthyl	90	87
p	$(CH_2)_3$-Ph	81	91
q	$(CH_2)_4$-Ph	84	88
r	CH_2-Ph	80	71
s	Ph	0	–

Table 17: Asymmetric aza-Michael addition reaction for the synthesis of *N*-hydroxyaspartic acid derivatives catalyzed by chiral multifunctional thiourea/boronic acid.



76	X	Yield [%]	ee [%]	dr
a	*t*-BuO	88	93	–

Table 17: Asymmetric aza-Michael addition reaction for the synthesis of *N*-hydroxyaspartic acid derivatives catalyzed by chiral multifunctional thiourea/boronic acid. (continued)

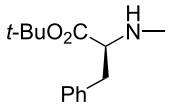
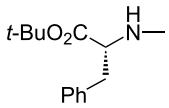
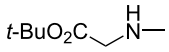
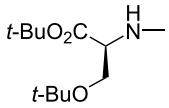
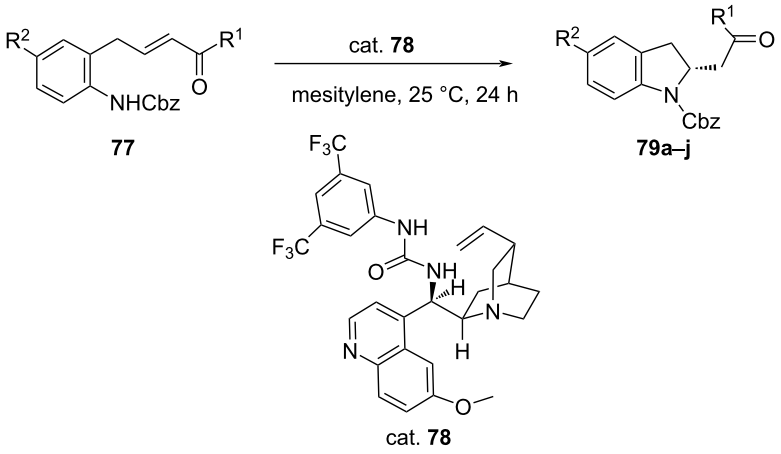
b	BnO	50	91	–
c	EtO	49	94	–
d		40	–	67:33
e		60	–	75:25
f		66	63	–
g		81	85	73:37

Table 18: Intramolecular aza-Michael addition catalyzed by bifunctional thiourea.

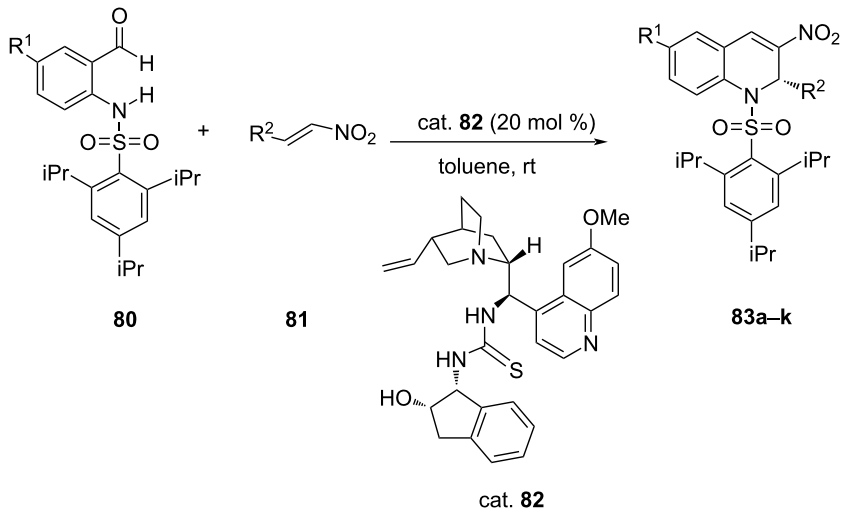


79	R^1	R^2	Yield [%]	ee [%]
a	Ph	H	99	87
b	4-$CH_3OC_6H_4$	H	73	84
c	4-$CF_3C_6H_4$	H	79	88
d	2-naphthyl	H	83	88
e	4-BrC_6H_4	H	75	91
f	Ph	CH_3O	82	83
g	Ph	F	69	82
h	Ph	Cl	82	84
i	4-BrC_6H_4	CH_3O	53	93
j	CH_3	H	18	74

tertiary amine-thiourea catalyst (cat. **82**). This cascade reaction afforded aza-Michael adducts in 77–92% yields with high ee (up to 90%) (Table 19) [55].

Du et al. developed an enantioselective catalytic tandem aminolysis/aza-Michael addition for the asymmetric total synthesis of two natural *Apocynaceae* alkaloids, (+)-deethylibophyllidine

Table 19: Intramolecular aza-Michael addition reaction catalyzed by tertiary amine-thiourea.



83	R^1	R^2	Yield [%]	ee [%]
a	H	Ph	81	90
b	H	4-FC_6H_4	77	82
c	H	4-BrC_6H_4	91	85
d	H	4-NCC_6H_4	92	87
e	H	4-MeC_6H_4	83	81
f	H	4-$MeOC_6H_4$	75	84
g	H	3-ClC_6H_4	90	87
h	H	3-BrC_6H_4	86	89
i	H	3-MeC_6H_4	83	81
j	H	$CH(Me)_2$	86	70
k	Cl	Ph	78	88

(**88**) and (+)-limaspermidine (**89**) from the reaction of *para*-dienone imide **84** with benzylamine (**85**) in the presence of bifunctional thiourea organocatalyst (Scheme 4) [56].

1.6 Reactions catalyzed by chiral binol-derived phosphoric acids

Binol-derived chiral phosphoric acids have been shown to catalyze the reactions via single or double hydrogen bonding [57,58].

Saito et al. accomplished the chiral phosphoric acid-catalyzed intramolecular aza-Michael addition reaction of *N*-unprotected 2-aminophenyl vinyl ketones **90** to obtain chiral 2-substituted 2,3-dihydro-4-quinolones **92** in very good yields (67–95%) with high ee (82–97%) (Table 20) [59].

Following a similar approach, Yang et al. reported asymmetric aza-Michael additions of anilines **94** to β-nitrostyrenes **93** using a chiral binol-derived phosphoric acid diester catalyst (cat. **95**). They succeeded in preparing β-nitroamines **96** in good yields (65–85%), but with only a moderate level of ee (19–70%) (Table 21) [60].

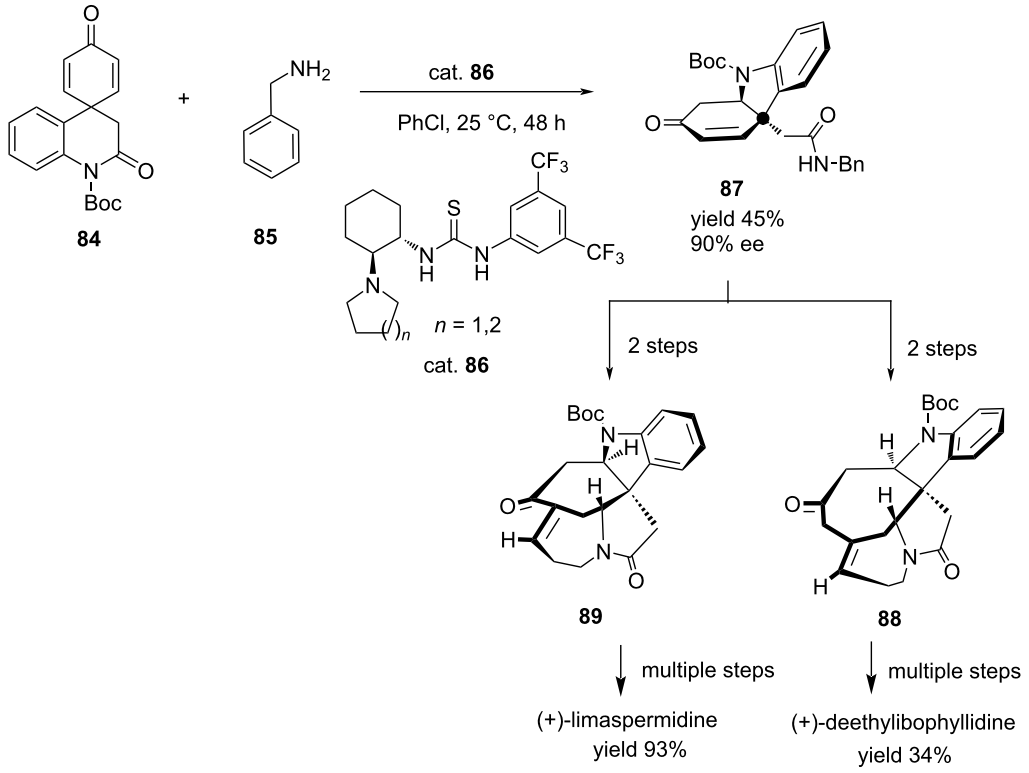
Feng et al. accomplished an asymmetric intramolecular aza-Michael addition of activated α,β-unsaturated ketones **97** by using chiral *N*-triflylphosphoramide as catalyst (cat. **98**). The products, namely 2-aryl-2,3-dihydro-4-quinolones **99** were obtained in good yields of up to 95% and good ee (58–72%) (Table 22) [61].

2. Covalent-bonding organocatalysis of aza-Michael reactions

This category of organocatalysts includes N-heterocyclic carbenes and pyrrolidine derivatives.

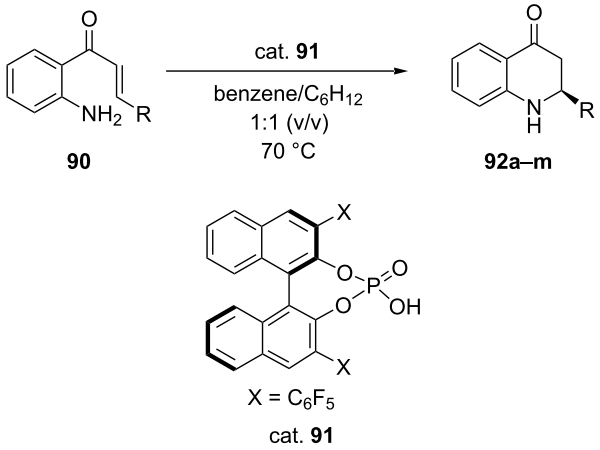
2.1 Catalysis by N-heterocyclic carbenes (NHC)

In recent years, NHCs have been used as organocatalysts for a wide variety of reactions [62].



Scheme 4: Asymmetric aza-Michael addition of *para*-dienone imide to benzylamine.

Table 20: Intramolecular aza-Michael addition reaction catalyzed by chiral phosphoric acid.

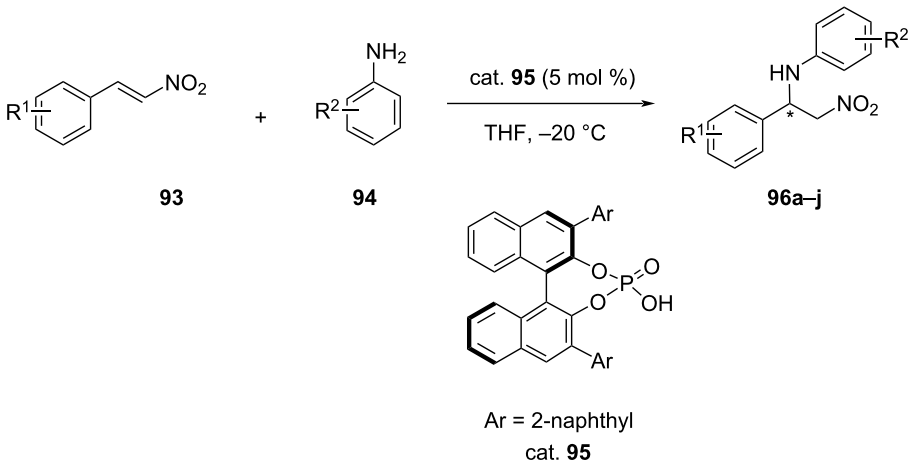


92	R	Yield [%]	ee [%]
a	Ph	95	93
b	2-FC_6H_4	71	90
c	2-ClC_6H_4	90	93
d	2-BrC_6H_4	90	94
e	2-MeC_6H_4	97	88
f	3-BrC_6H_4	73	84
g	3-MeC_6H_4	95	86

Table 20: Intramolecular aza-Michael addition reaction catalyzed by chiral phosphoric acid. (continued)

h	3-$MeOC_6H_4$	95	92
i	4-FC_6H_4	quant	87
j	4-ClC_6H_4	67	82
k	4-MeC_6H_4	quant	97
l	2-naphthyl	82	81
m	*t*-Bu	64	88

Table 21: Asymmetric aza-Michael addition of aniline to β-nitrostyrenes.



96	R^1	R^2	Yield [%]	ee [%]
a	4-Br	4-BrC_6H_4	82	19
b	4-Cl	4-BrC_6H_4	81	30
c	2-OMe	4-BrC_6H_4	65	44
d	4-OMe	4-BrC_6H_4	–	–
e	2-Br	4-BrC_6H_4	85	45
f	2,3-$(OMe)_2$	4-BrC_6H_4	85	70
g	4-Me	Ph	70	30
h	4-Me	4-MeC_6H_4	75	30
i	4-Me	4-MeC_6H_4	70	42
j	4-Me	2-naphthyl	64	48

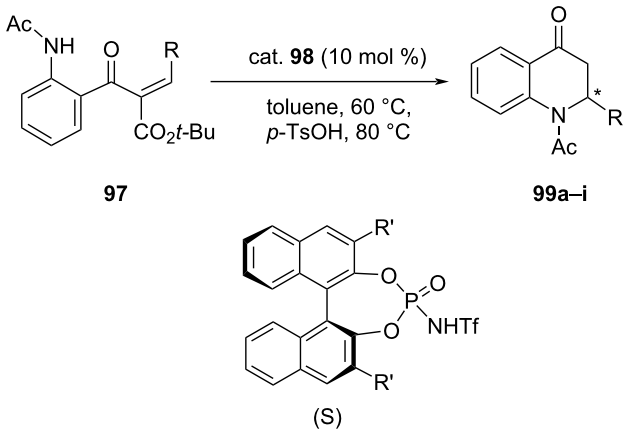
Wang et al. investigated the use of several 1,2,4-triazolo-annelated chiral NHCs as organocatalysts to catalyze enantioselective aza-MR between primary amines (**100**) and β-trifluoromethyl-β-arylnitroolefins **101** and the best results (yield 99%, ee 91%) were obtained in the reaction of benzylamine (R^1 = Ph) on using the NHC precursor as shown below in the presence of hexafluoroisopropanol (HFIP) as additive along with molecular sieves (4 Å) (Table 23) [63]. The role of HFIP is to act as proton shuttle, i.e., to assist in 1,3-prototropic shift.

2.2 Catalysis by chiral pyrrolidine derivatives

Chiral pyrrolidine derivatives, such as (*S*)-proline are widely used as organocatalysts [54,64].

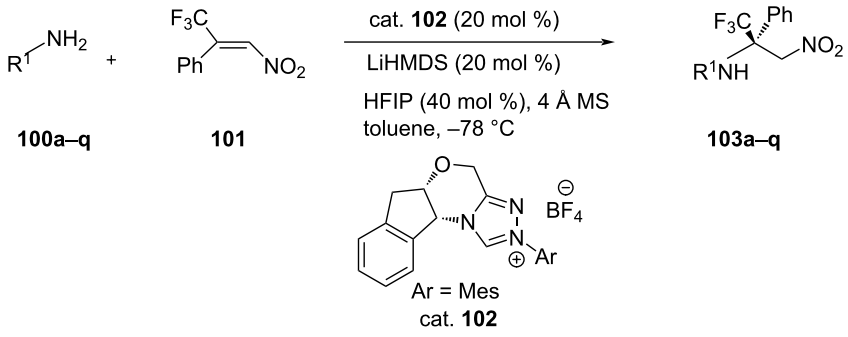
Lee et al. synthesized bromopyrrole alkaloids **107** via aza-Michael addition of 4,5-dibromo-1*H*-pyrrole-2-carbonitrile **104** to Bz-protected (*E*)-4-hydroxybut-2-enal **105** in the presence of (*S*)-α,α-bis[3,5-bis(trifluoromethyl)phenyl]-2-pyrrolidinemethanol trimethylsilyl ether as the organocatalyst (cat.

Table 22: Intramolecular aza-Michael addition reaction catalyzed by chiral *N*-triflylphosphoramide.



99	R	Yield [%]	ee [%]
a	Ph	95	97 (–)
b	4-BrC_6H_4	90	58 (–)
c	4-ClC_6H_4	90	67 (–)
d	4-$NO_2C_6H_4$	77	20 (–)
e	4-MeC_6H_4	98	82 (–)
f	4-$MeOC_6H_4$	94	60 (–)
g	2-$MeOC_6H_4$	95	4 (+)
h	1-naphthyl	81	76 (+)
i	2-naphthyl	98	76 (–)

Table 23: Aza-Michael addition of primary amines to β-trifluromethyl-β-phenylnitroolefin catalyzed nitrogen heterocyclic carbene.



103	R^1	Yield [%]	ee [%]
a	$C_6H_5CH_2$-	90	91
b	2-$MeC_6H_4CH_2$-	67	91
c	4-$MeOC_6H_4CH_2$-	89	92
d	3,5-$(MeO)_2C_6H_3CH_2$-	56	86
e	$C_6H_5(CH_2)_2$-	85	86
f	4-$BrC_6H_4(CH_2)_2$-	68	87
g	$CH_3(CH_2)_2$-	80	92

Table 23: Aza-Michael addition of primary amines to β-trifluromethyl-β-phenylnitroolefin catalyzed nitrogen heterocyclic carbene. (continued)

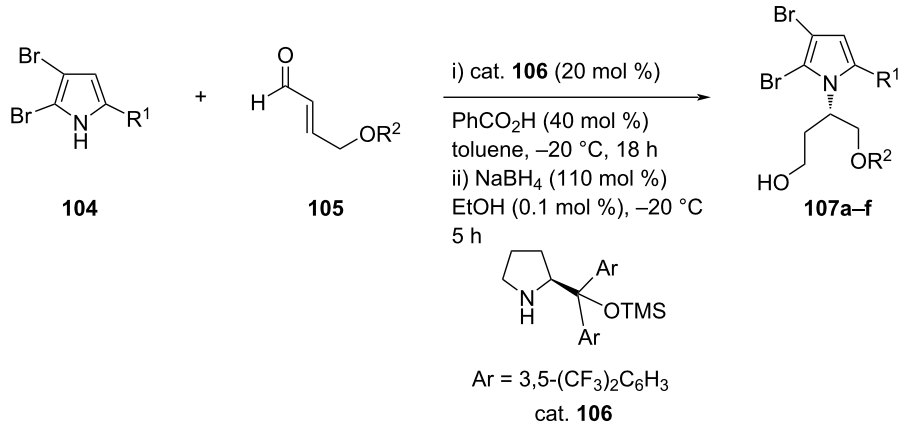
h	$C_7H_{15}CH_2$-	87	95
i	$C_6H_5(CH_2)_3$-	82	93
j	$(CH_3)_2CH(CH_2)_2$-	79	89
k	cyclopropyl-	79	97
l	cyclobutyl-	78	94
m	2-pyridylethyl-	87	93
n	$BocHN(CH_2)_2$	79	91
o	$MeO(CH_2)_3$-	87	87
p	$(Me)_2N(CH_2)_2$-	99	91
q	2-thienyl$(CH_2)_2$-	98	93

106) and using $PhCO_2H$ as the acid additive. Desired products were obtained in good yields ≈78% with excellent enantioselectivities of up to 93% (Table 24) [65]. The role of the additive is to assist in the formation of the iminium intermediate from the reaction of pyrrolidine with the aldehyde group.

Following a similar approach, Guo et al. accomplished the first organocatalytic asymmetric aza-Michael addition of purine bases **108** to aliphatic α,β-unsaturated aldehydes **109** and synthesized biologically active acyclonucleoside **110** via an iminium-ion activation mechanism. The initially formed product was reduced in situ to afford the final product in 82–89% yield and 89–96% ee (Table 25) [66].

In a similar method, Joie et al. accomplished an asymmetric organocatalytic quadruple cascade reaction of various α-ketoamides **111** with aromatic α,β-unsaturated aldehydes **112** to obtain tetraaryl-substituted 2-azabicyclo[3.3.0]octadienones **114** in good yields (34–71%) with excellent diastereo- and enantioselectivities (84–97%). The reaction occurred via an aza-Michael/aldol condensation/vinylogous Michael addition/aldol condensation sequence (Table 26) [67].

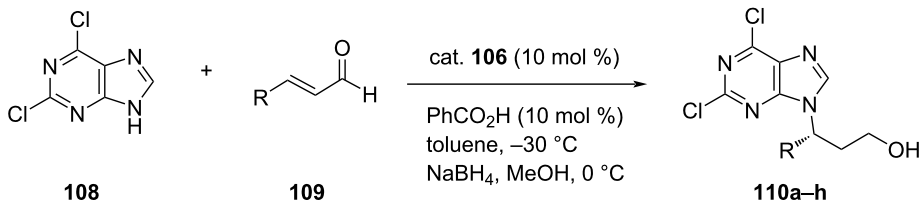
Table 24: Asymmetric aza-Michael additions of pyrroles to protected (*E*)-4-hydroxybut-2-enals.



107	R^1	R^2	Yield [%]	ee [%]
a	CN	Bz	70	76
b	CO_2CH_3	Bz	n.d.[a]	–
c	CN	TBS	78	80
d	CN	TBDPS	77	87
e	CN	TBDPS	76	91
f	CN	TBDPS	76	93

[a]Not determined.

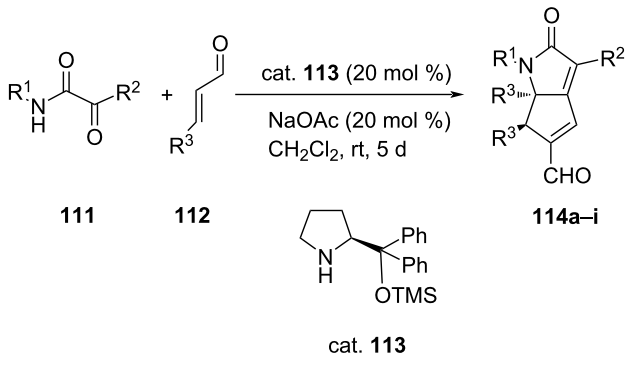
Table 25: Asymmetric aza-Michael addition of purine bases to aliphatic α,β-unsaturated aldehydes.



108 **109** **110a–h**

110	R	Yield [%]	ee [%]
a	Me	87	89
b	Et	89	91
c	*n*-Pr	87	96
d	*n*-Bu	86	94
e	*n*-pentyl	85	96
f	*n*-hexyl	87	96
g	CH_2OTBS	82	96
h	Ph	trace	–

Table 26: Asymmetric aza-Michael organocatalytic quadruple cascade reaction.



111 **112** **114a–i**

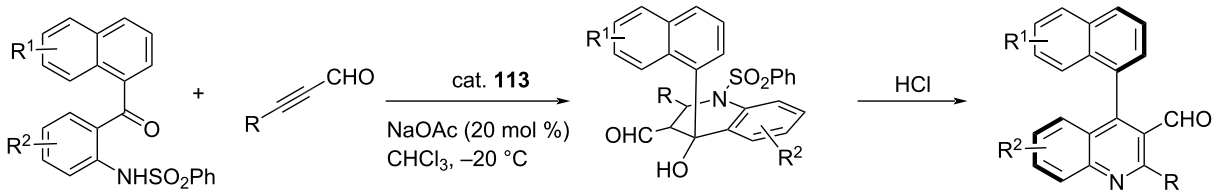
cat. **113**

114	R^1	R^2	R^3	Yield [%]	ee [%][a]
a	Ph	Ph	Ph	63	97
b	Ph	Ph	4-$MeOC_6H_4$	51	89 (91)
c	Ph	Ph	4-ClC_6H_4	34	85 (95)
d	Ph	Ph	2,3-$(OCH_2O)C_6H_3$	56	84 (87)
e	4-$MeOC_6H_4$	Ph	Ph	66	92 (91)
f	3-ClC_6H_4	Ph	Ph	69	91 (95)
g	4-$O_2NC_6H_4$	Ph	Ph	58	95
h	Ph	4-MeC_6H_4	Ph	70	88
i	Ph	4-ClC_6H_4	Ph	71	95

[a]Values in brackets correspond to the results obtained with the catalyst (*R*)-**113**.

Recently, the synthesis of axially chiral 4-naphthylquinoline-3-carbaldehydes **117** has been reported via Michael/Aldol cascade reaction of alkynals **116** with *N*-(2-(1-naphthoyl)phenyl)benzenesulfonamides **115** using the same pyrrolidine catalyst **113**. The products were obtained in excellent yields and enantioselectivities (Table 27) [68]. In this context, the presence of a strong electron-withdrawing sulfonyl group was found to be essential. On comparing efficacies of different sulfonyl

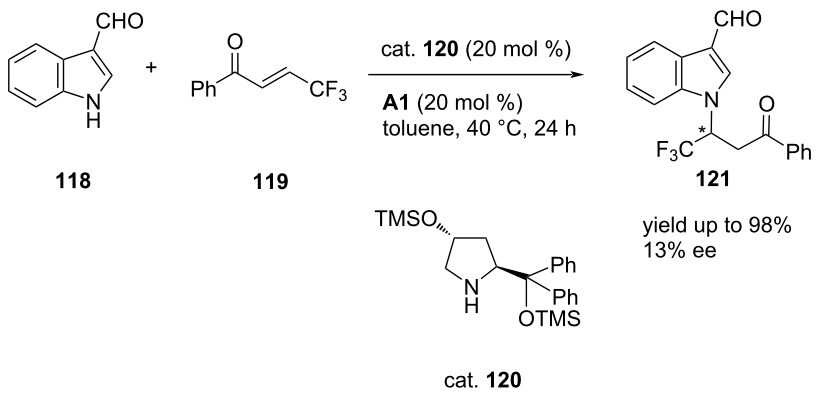
Table 27: Asymmetric synthesis of chiral 4-naphthylquinoline-3-carbaldehydes.



117	R^1	R^2	R	Yield [%]	ee [%]
a	H	H	4-ClC_6H_4	97	93
b	H	H	Ph	94	95
c	H	H	4-FC_6H_4	86	94
d	H	H	4-BrC_6H_4	95	94
e	H	H	4-MeC_6H_4	81	94
f	H	H	4-$MeOC_6H_4$	86	95
g	H	H	3-ClC_6H_4	92	91
h	H	H	3-MeC_6H_4	88	93
i	H	H	3-$MeOC_6H_4$	83	93
j	H	H	*n*-C_5H_{11}	85	87
k	4-Me	H	4-ClC_6H_4	82	92
l	4-MeO	H	4-ClC_6H_4	91	90
m	4-F	H	4-ClC_6H_4	83	94
n	H	6-Cl	4-ClC_6H_4	90	94
o	H	7-Cl	4-ClC_6H_4	91	91
p	H	7-Cl	Ph	95	96
q	H	7-Cl	4-BrC_6H_4	95	94
r	H	7-Cl	3-MeC_6H_4	90	95
s	H	7-Cl	*n*-C_5H_{11}	88	90

groups, benzenesulfonyl moieties with electron-donating groups were found to be most effective. Furthermore, the utility of the newly developed method was demonstrated by preparing useful chiral 4-naphthylquinolines from the resulting products [68].

Chang-Jiang et al. developed a catalytic strategy by using a combination of prolinol silyl ether (cat. **120**) and benzoic acid (**A1**) catalysts to bring about reaction between 3-formyl-substituted indoles or pyrroles **118** and diverse electrophiles, including carbonyls, imines and other Michael acceptors (Scheme 5)



Scheme 5: Asymmetric synthesis of chiral *N*-functionalized heteroarenes.

[69]. The reaction with secondary amines occurred via the formation of HOMO raised dearomative aza-dienamine-type intermediates, which undergo direct aza-Michael addition to β-trifluoromethyl enones to afford *N*-functionalized heteroarenes **121** efficiently in moderate to excellent yields, albeit with low to fair enantioselectivity. However, asymmetric aza-Michael additions of these heteroarenes with crotonaldehyde yielded the adducts in moderate to good enantioselectivity under dual catalysis of chiral amines (Scheme 5) [69].

Conclusion

The asymmetric aza-Michael reaction being a useful synthetic strategy for constructing C–N bonds to make a variety of nitrogen-containing chiral scaffolds of wide applications in the fields of pharmaceuticals, organic synthesis building blocks and accessible catalysis continues to attract attention of the chemists. During the last two decades, many new chiral organocatalysts have been developed for accomplishing these reactions with the nitrogen nucleophiles, such as aromatic amines and amides which are otherwise averse to reacting. The organocatalysts have emerged as catalysts of choice due to various reasons, such as their compatibility with the 'Green Chemistry' and possibility of tailoring them according to the requirements. Efforts are directed towards enhancing not only the yields of the products but also enantio- and diastereoselectivities of the aza-Michael reactions. New strategies have been adopted while making optimum utilization of the efficacies of the catalysts. Of these strategies, cascade reactions of the Michael addition in conjunction with one or more reactions leading to overall very high yields and ee are noteworthy. Another strategy of interest appears to be the generation of organocatalysts of enhanced efficacy in situ by mixing squaramides with amino acids again giving >99% ee. It may be perceived that in the coming years, more sophisticated methodologies will be developed with the advent of new organocatalysts to accomplish asymmetric aza-Michael reactions of even the so far unexplored and obstinate amines and amides substrates.

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ORCID® iDs

Raakhi Gupta - https://orcid.org/0000-0003-0732-5134
Raj K. Bansal - https://orcid.org/0000-0002-8154-9817

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N-Sulfinylpyrrolidine-containing ureas and thioureas as bifunctional organocatalysts

Viera Poláčková[1], Dominika Krištofíková[1], Boglárka Némethová[1], Renata Górová[2], Mária Mečiarová[1] and Radovan Šebesta[*1]

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Address:
[1]Department of Organic Chemistry,Faculty of Natural Sciences, Comenius University in Bratislava, Mlynská dolina, Ilkovičova 6, 842 15 Bratislava, Slovakia and [2]Department of Analytical Chemistry, Faculty of Natural Sciences, Comenius University in Bratislava, Mlynská dolina, Ilkovičova 6, 842 15 Bratislava, Slovakia

Email:
Radovan Šebesta[*] - radovan.sebesta@uniba.sk

* Corresponding author

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Abstract

The synthesis of bifunctional *N*-sulfinylureas and thioureas with an appended pyrrolidine unit is presented. These organocatalysts were evaluated in Michael additions of aldehydes to nitroalkenes both under solvent-free conditions and in solution. The *N*-sulfinylurea catalyst was more efficient than the corresponding thiourea. For some substrates, enantioselectivities reached 98% ee. The stereogenic center on the sulfur did not have a considerable influence on the catalytic reactions. Under ball-milling conditions, the Michael adducts were obtained in good yields but with slightly lower enantiomeric purities than in solution. DFT calculations elucidated its mode of action and confirmed a dual activation mode, which combines enamine activation of aldehydes and hydrogen-bond activation of nitroalkenes.

Introduction

Asymmetric organocatalysis became one of the strategic ways for the efficient synthesis of chiral compounds [1]. Bifunctional catalysis has proven to be a successful concept in asymmetric organocatalysis [2-8]. An amine unit with a hydrogen-bond donating skeleton is highly efficient from among various possible combinations of catalytic moieties within an organocatalyst. This idea has been inspired by proline catalysis itself, in which the carboxylic function acts as an ancillary hydrogen-bond donor for the direction of one of the reagents [9]. Amines serve as basic units and nucleophilic components capable of carbonyl compounds activation via enamine or iminium ion formation [10,11]. In particular, pyrrolidine became a privileged structural motif central to many catalyst designs [12]. This fact stems from the success of diarylprolinol silyl ethers as chiral organocatalysts, which were independently introduced by Hayashi [13] and Jørgensen [14]. These compounds were used in a large

number of stereoselective syntheses, including total syntheses of natural compounds [15]. The pyrrolidine moiety has been successfully combined with thiourea [16-18] and the squaramide unit [19,20]. Thioureas and squaramides often feature the electron-withdrawing group attached to one of the nitrogen atoms to increase the acidity of the hydrogen-bond donating unit. This notion has often been realized with substituted aryls such as 3,5-bis(trifluoromethyl)phenyl. Ellman introduced a different approach and developed *N*-sulfinylureas. An additional potentially useful feature is the stereogenic center on sulfur. *tert*-Butanesulfinamide is highly useful in stereoselective synthesis as a stereoinducing group [21]. Thus, *N*-sulfinylureas and thioureas are a new class of organocatalysts, with the sulfinyl group acting both as an acidifying and a chiral controlling moiety. A variety of *N*-sulfinylureas catalyzed aza-Henry reaction, including enantioselective H-bonding-catalyzed additions to aliphatic *N*-Boc-imines with high stereoselectivity [22]. A broad range of β-aminonitroolefins were reduced to chiral β-aminonitroalkanes in high yields and excellent enantioselectivities using trichlorosilane as a reducing agent and an *N*-sulfinylurea as bifunctional organocatalyst [23]. The enantio- and diastereoselective addition of Meldrum's acids to nitroalkenes via *N*-sulfinylurea catalysis gave products that were readily converted to pharmaceutically relevant compounds [24,25]. A sulfinylurea organocatalyst catalyzed a highly selective Michael addition of thioacetic acid to aromatic and aliphatic nitroalkenes to produce chiral β-aminothiols, compounds of pharmaceutical interest [26]. Similarly, the enantioselective addition of thioacids to trisubstituted nitroalkenes was catalyzed by several *N*-sulfinylureas providing the 1,2-nitrothioacetates in good yields and enantioselectivities [27]. A sulfinylurea catalyst was also applied to catalyze the addition of 3-substituted pyrazol-5-ones to trisubstituted nitroalkenes. The adducts were obtained with good yields and enantioselectivities up to 91:9 er [28].

Inspired by the previous successful applications of sulfinylureas and thioureas as organocatalysts, we have designed four new *N*-sulfinyl-*N*'-(pyrrolidinylmethyl)urea and *N*-sulfinyl-*N*'-(pyrrolidinylmethyl)thiourea bifunctional organocatalysts. The main design principles are outlined in Figure 1. The catalysts feature a pyrrolidine unit, which should engage in enamine activation of enolizable carbonyl compounds. The urea or thiourea moiety shall provide hydrogen-bond donating ability. Furthermore, these compounds possess a sulfinyl group with an additional stereogenic center on the sulfur. To verify the influence of a matched/mismatched combination of chirality, we employed both enantiomers of *tert*-butyl sulfinamide with the (*S*)-enantiomer of the pyrrolidine building block.

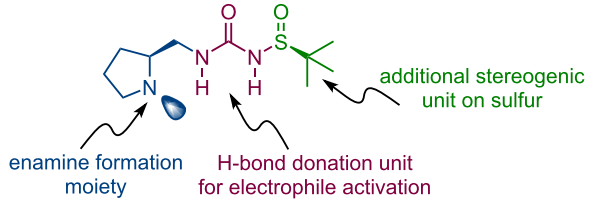


Figure 1: Catalyst design principles.

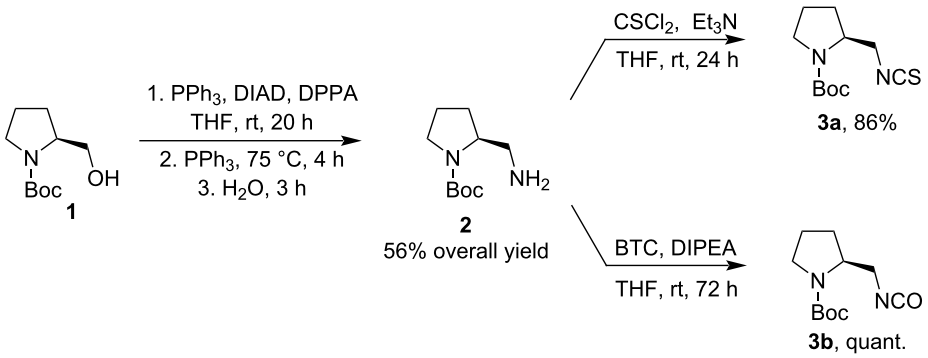
The introduction of green chemistry principles into chemical transformations is an important goal toward sustainable production and manufacturing. Asymmetric organocatalysis can benefit and accommodate many sustainability techniques [29]. Mechanochemistry can increase the sustainability profile of a chemical process by reducing potentially harmful organic solvents and bring other benefits such as substantially shortened reaction times. A handful of asymmetric organocatalytic transformations were successfully performed under solvent-free ball-milling conditions [30,31]. In this context, we describe the synthesis of new pyrrolidine appended sulfinylurea and thiourea organocatalysts and their assessment in Michael additions of aldehydes to nitroalkenes. Furthermore, we have evaluated the suitability of these catalysts under solvent-free conditions. With the help of DFT calculations, we elucidated the mode of action of these catalysts.

Results and Discussion

Synthesis of catalysts

We have started the synthesis of the catalysts from Boc-protected (*S*)-prolinol (**1**), from which the key intermediate, pyrrolidine derivative **2**, can be obtained in three steps according to the literature procedure [32]. Using this method, we obtained the product **2** in a yield comparable (56% overall yield) to that described in the literature. However, the difficult chromatographic separation after each step prompted us to apply a Mitsunobu and Staudinger reaction for the preparation of amine **2** (Scheme 1) [33]. This one-pot reaction gave the desired amine **2** in 56% yield. Then, the corresponding isothiocyanate **3a** was prepared by reaction of amine **2** with CS_2 and DCC according to the reported procedure. However, this method gave product **3a** in only 44% yield. Therefore, we decided to prepare isothiocyanate **3a** using thiophosgene in dry THF with Et_3N. This procedure afforded the corresponding isothiocyanate **3a** in 86% yield (Scheme 1). Isocyanate **3b** was also synthesized from amine **2**. The reaction with bis(trichloromethyl)carbonate (BTC) afforded the crude product **3b**, which was sufficiently pure for use in the next reaction step without further purification (Scheme 1).

The next steps of the catalyst synthesis were the attachment of *tert*-butanesulfinamide **4** to iso(thio)cyanates **3a** and **3b** with



Scheme 1: Synthesis of isothiocyanate **3a** and isocyanate **3b**.

concomitant formation of the urea or thiourea moiety, respectively. The corresponding *N*-Boc-protected precursors of the desired catalysts, **5a** and **5b**, were obtained in low to good yields. The removal of the Boc-protecting group with trifluoroacetic acid afforded the desired *N*-sulfinylthioureas (*S*,*R*)- and (*S*,*S*)-**C1** as well as *N*-sulfinylureas (*S*,*R*)- and (*S*,*S*)-**C2** in excellent yields (Scheme 2).

Application of thioureas **C1** and ureas **C2** in the Michael addition of aldehydes to nitroalkenes

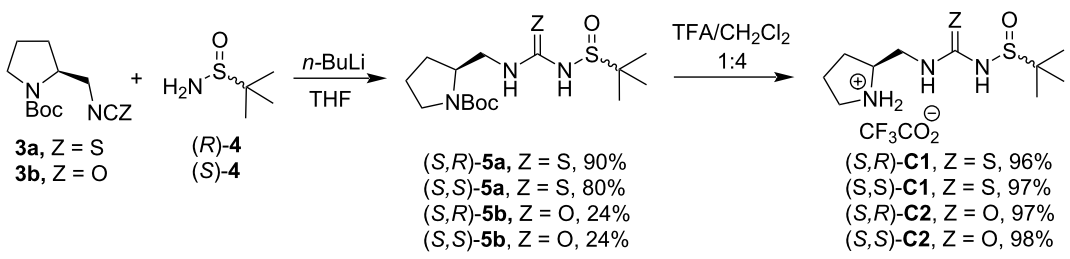
Michael addition in solution

As the first benchmark transformation, we opted for the Michael addition of butanal (**6a**) to β-nitrostyrene (**7a**) catalyzed by (*S*,*R*)-**C2** (Scheme 3). The reaction in CH_2Cl_2 at 5 °C with Et_3N as a base gave 45% of adduct **8a** with 86:14 dr and 24:76 er for both diastereomers. Slightly better yields (63%) were achieved in $CHCl_3$ at room temperature with Et_3N or NMP as a base, but both diastereoselectivity as well as enantioselectivity remained unchanged. We have used thiourea (*S*,*R*)-**C1** for this Michael addition, too, but the catalyst was not successful for this reaction (not shown).

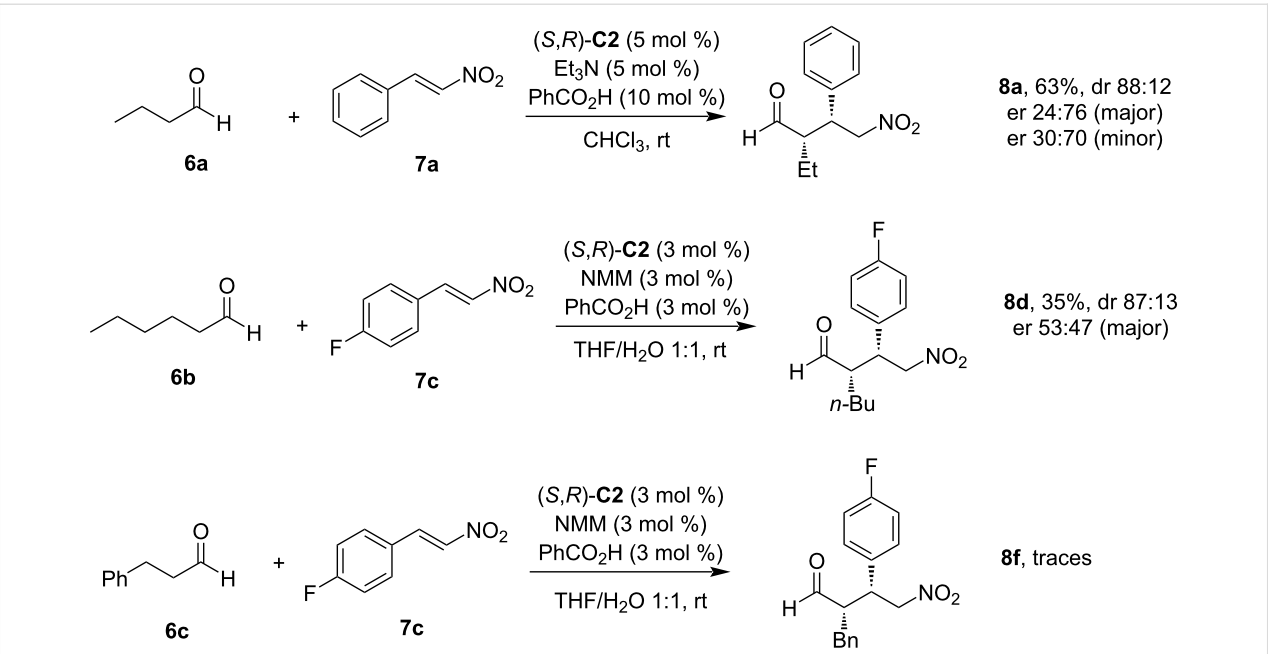
Only traces of the Michael adduct were obtained in the solution reaction of butanal (**6a**) with 1-methoxy-4-(2-nitrovinyl)benzene (**7b**). Hexanal (**6b**) reacted successfully with 4-fluoro-β-nitrostyrene (**7c**) and gave product **8d** under all conditions tested (in solution, solvent-free, and ball-milling conditions, vide infra). Again, small amounts of catalyst (*S*,*R*)-**C2** gave the best chemical yield. Catalyst (*S*,*R*)-**C2** (3 mol %) in solution (NMM as the base, THF/H_2O 1:1) provided the product in only 35% yield, but with high diastereomeric purity of 87:13 dr. However, this result could not be obtained with thiourea (*S*,*R*)-**C1**, which provided only traces of product **8d**. The Michael addition was not successful when 3-phenylpropanal (**6c**) was reacted with 4-fluoro-β-nitrostyrene (**7c**). In the presence of catalyst (*S*,*R*)-**C2** only traces of product **8f** (THF/H_2O, NMM as the base, and additive $PhCO_2H$) were obtained (Scheme 3).

Michael acceptors containing heterocyclic groups have been studied only sparingly, but the corresponding chiral compounds with heterocyclic substituents are of high biological and medicinal relevance [34,35]. Therefore, we have decided to evaluate sulfinylurea and thiourea catalysts **C1** and **C2** also with (*E*)-2-(2-nitrovinyl)furan (**9**) and (*E*)-3-(2-nitrovinyl)pyridine (**11**) as Michael acceptors. As Michael donor, we chose 3-phenylpropanal (**6c**).

The Michael addition of 3-phenylpropanal (**6c**) with (*E*)-2-(2-nitrovinyl)furan (**9**) under initial reaction conditions with (*S*,*R*)-**C1** (10 mol %) in THF/H_2O with NMM as the base and



Scheme 2: Synthesis of sulfinylthioureas **C1** and ureas **C2**.



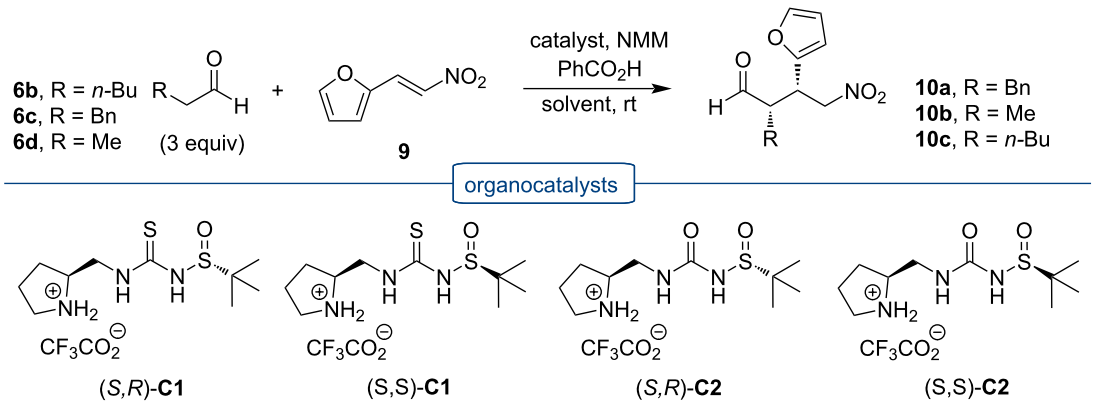
Scheme 3: Synthesis of adducts **8a**,**d**,**f** in solution.

with $PhCO_2H$ as acid additive gave product **10a** in 31% yield after 72 hours with a diastereomeric ratio of 86:14 and high enantiomeric purity of 95:5 er for the major diastereomer (Table 1, entry 1). Using chloroform/isopropyl alcohol 9:1 as the solvent mixture afforded after 120 hours, aldehyde **10a** in 45% yield with 83:17 dr and 97:3 er (Table 1, entry 2). The Michael addition in methanol catalyzed by only 3 mol % (*S,R*)-**C1** after 72 hours provided only 18% yield, but with high enantiomeric purity (99:1, Table 1, entry 5). The reaction without a base did not provide the desired product **10a** (Table 1, entry 6). Moreover, a reaction performed with other acidic additives (phenylboronic acid, *p*-toluenesulfonic acid) provided after 72 hours only 18% and 23% yield of the product with compromised diastereomeric and enantiomeric purity (Table 1, entries 3 and 4). When, we applied 3 mol % of catalyst (*S,R*)-**C1** during 48 hours, we obtained 73% yield with diastereomeric purity 83:17 and high enantiomeric purity, similar to the reaction performed in methanol (99:1 er, Table 1, entry 7). Using the same conditions as with catalyst (*S,R*)-**C1**, we also used 3 mol % (*S,S*)-**C1** (Table 1, entry 8). The yield and diastereomeric and enantiomeric purity were very similar as with catalyst (*S,R*)-**C1**. However, a further reduction of the catalyst loading to 1 mol % of (*S,S*)-**C1**, required a longer reaction time, up to 216 hours and this Michael addition gave only 27% yield of the product (Table 1, entry 11). Additionally, attempting the Michael addition of 3-phenylpropanal (**6c**) to nitroalkene **9** catalyzed by (*S,S*)-**C1** without any acid additive resulted in a very low yield after 48 hours (29%, Table 1, entry 9) with a diastereomeric purity of 80:20 dr. We also tested the Boc-protected derivative (*S,S*)-**5b** as the catalyst (Table 1, entry 10). The Michael addition catalyzed by (*S,S*)-**5b** provided racemic product **10a** in 23% yield. This result confirms the essential role of the pyrrolidine unit in the enamine formation during the reaction. Michael addition reactions catalyzed with sulfinylureas (*S,R*)-**C2** and (*S,S*)-**C2** provided the products within 24 hours in good yields (63% and 88%, respectively) but with lowered diastereomeric and enantiomeric purities (Table 1, entries 12 and 13).

In terms of the stereochemical outcome, both sulfinylthioureas **C1** and urea **C2** afforded the same enantiomer as the main product. Furthermore, both diastereomers of both catalysts also directed the Michael addition toward the same enantiomer. These results suggest that the main stereogenic element in the catalyst structure is the pyrrolidine unit. The stereogenic center on the sulfur plays only a minor role, probably because it is far away from the reaction center.

Catalyst (*S,R*)-**C2** catalyzed the Michael addition of propanal (**6d**) and hexanal (**6b**) to nitroalkene **9**. The reaction in the presence of 3 mol % (*S,R*)-**C2** provided the product **10b** in 70% yield and 85:15 dr and 75:25 er (Table 1, entry 14). Here, we have also tested the influence of only basic additive on the reaction and the product was obtained with 73% yield (Table 1, entry 15). The reaction without a base went much less efficiently (Table 1, entry 16), similarly to the reaction performed without acid additive and base (Table 1, entry 17). The product **10c** by Michael addition of hexanal **6b** to nitroalkene **9** was ob-

Table 1: Michael additions of aldehydes **6b–d** with nitroalkene **9**.



entry	catalyst (mol %)[a]	solvent	time (h)	yield of **10** (%)	dr	er major/minor
1	(*S,R*)-**C1** (10)	THF/H_2O 1:1	72	31 (**10a**)	86:14	95:5/98:2
2	(*S,R*)-**C1** (10)	$CHCl_3$/iPrOH 9:1	120	45 (**10a**)	83:17	97:3/97:3
3	(*S,R*)-**C1** (3)[b]	THF/H_2O 4:1	72	23 (**10a**)	67:33	n.d.
4	(*S,R*)-**C1** (3)[c]	THF/H_2O 4:1	72	18 (**10a**)	50:50	n.d.
5	(*S,R*)-**C1** (3)	MeOH	72	18 (**10a**)	88:12	99:1/99:1
6	(*S,R*)-**C1** (3)[d]	MeOH	72	– (**10a**)	–	–
7	(*S,R*)-**C1** (3)	THF/H_2O 1:1	48	73 (**10a**)	83:17	99:1/99:1
8	(*S,S*)-**C1** (3)	THF/H_2O 1:1	48	72 (**10a**)	89:11	99:1/99:1
9	(*S,S*)-**C1** (3)[e]	THF/H_2O 1:1	48	29 (**10a**)	80:20	n.d.
10	(*S,S*)-**5b** (3)	THF/H_2O 1:1	48	23 (**10a**)	55:45	50:50
11	(*S,S*)-**C1** (1)	THF/H_2O 1:1	216	27 (**10a**)	86:14	n.d.
12	(*S,R*)-**C2** (3)	THF/H_2O 1:1	24	63 (**10a**)	86:14	68:32/85:15
13	(*S,S*)-**C2** (3)	THF/H_2O 1:1	24	88 (**10a**)	88:12	70:30/87:13
14	(*S,R*)-**C2** (3)	THF/H_2O 1:1	24	70 (**10b**)	85:15	75:25/73:27
15	(*S,R*)-**C2** (3)	THF/H_2O, no acid	24	73 (**10b**)	87:13	73:27/75:25
16	(*S,R*)-**C2** (3)	THF/H_2O, no base	24	25 (**10b**)	87:13	74:26/71:29
17	(*S,R*)-**C2** (3)	THF/H_2O, no acid, no base	24	44 (**10b**)	86:14	73:27/71:29
18	(*S,R*)-**C2** (3)	THF/H_2O 1:1	24	40 (**10c**)	77:23	86:14

[a]Catalyst, *N*-methylmorpholine (NMM) and acid loading was the same; [b]$PhB(OH)_2$ was used instead of $PhCO_2H$; [c]*p*TSA was used instead of $PhCO_2H$; [d]the reaction was performed without any basic additive; [e]the reaction was performed without any acid additive.

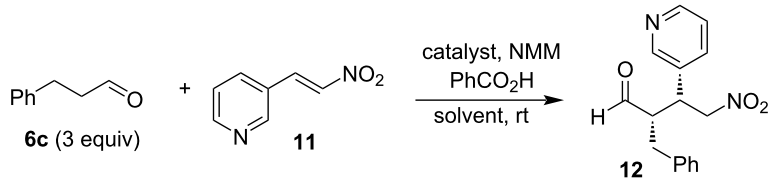
tained with only 40% yield with comparable diastereoselectivity (Table 1, entry 18). The aliphatic aldehydes propanal (**6d**) and hexanal (**6b**) provided medium yields and diastereoselectivity and enantioselectivity.

The Michael addition of 3-phenylpropanal (**6c**) to (*E*)-3-(2-nitrovinyl)pyridine (**11**) required long reaction times (120 h) in solution, similar to those for the reaction with (*E*)-2-(2-nitrovinyl)furan (**9**) and they provided racemic adduct **12** in 14 or 64% yield with poor or no diastereoselectivity (Table 2, entries 1 and 2). The change of solvent made it possible to obtain the products in a shorter time. Reactions catalyzed with 3 mol % (*S,R*)-**C1** and (*S,S*)-**C1** in MeCN gave product **12** in 38 or 39% yield with dr 80:20 and 88:12 and er 38:62 and 39:61 (Table 2, entries 3 and 4). Slightly higher yields and similar diastereolectivities were achieved with urea-derived catalysts (*S,R*)-**C2** and (*S,S*)-**C2**, but nitroaldehyde **12** was obtained in racemic form (Table 2, entries 5 and 6).

Michael additions under solvent-free reaction conditions

To evaluate the applicability of the new catalysts **C1** and **C2**, we decided to test them in the Michael addition under solvent-free conditions. Ball-milling experiments were conducted in a mixer mill, in which the milling vessels perform radial oscillations with vibrational frequencies from 3 to 30 Hz. These reactions were realized in stainless steel milling jars with an internal volume of 5 mL and with stainless steel balls (Ø 5 mm). We

Table 2: Michael addition of 3-phenylpropanal (**6c**) to nitroalkene **11**.



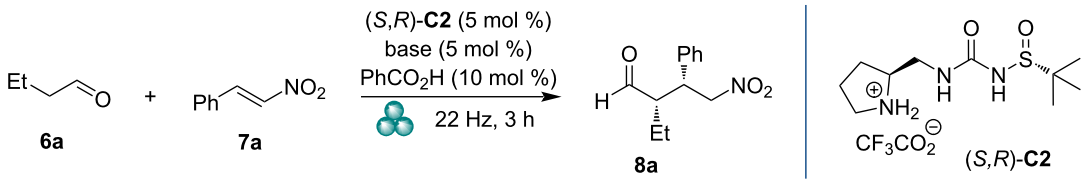
entry	catalyst (mol %)[a]	solvent	time (h)	yield of **12** (%)[b]	dr	er major/minor
1	(*S*,*R*)-**C1** (15)	$CHCl_3$/iPrOH 9:1	120	14	56:44	50:50/50:50
2	(*S*,*R*)-**C1** (10)	THF/H_2O 4:1	120	64	67:33	50:50/50:50
3	(*S*,*R*)-**C1** (3)	MeCN	22	38	80:20	38:62/57:43
4	(*S*,*S*)-**C1** (3)	MeCN	48	39	88:12	39:61/60:40
5	(*S*,*R*)-**C2** (3)	MeCN	22	56	81:19	49:51/51:49
6	(*S*,*S*)-**C2** (3)	MeCN	22	65	80:20	48:52/50:50

[a]Catalyst, *N*-methylmorpholine (NMM) and acid loading was the same.

have started with an evaluation of the solvent-free conditions for the reaction of butanal (**6a**) and nitrostyrene (**7a**) using sulfinylurea catalyst (*S*,*R*)-**C2**.

A relatively high yield (81%) of Michael adduct **8a** was formed in 3 hours of milling, with triethylamine as the base (Table 3, entry 1). The diastereoselectivity and enantioselectivity reached comparable values as in the solvent conditions. The chemical yield of adduct **8a** dropped to 51%, when the excess of butanal (**6a**) was reduced from 3 to 1.5 equivalents. The diastereoselectivity increased to 93:7 and the enantioselectivity for the major enantiomer was 19:81 and 16:84 for the minor enantiomer, re-

Table 3: Optimization of reaction conditions for solvent-free Michael additions.[a]



entry	base	yield of **8a** (%)	dr	er (major/minor)
1	Et_3N	81	84:16	26:74/28:72
2[b]	Et_3N	51	93:7	19:81/16:84
3	NMP	59	83:17	24:76/20:80
4	iPr_2EtN	77	75:25	24:76/29:71
5	DABCO	66	80:20	23:77/22:78
6	$K_3PO_4{\cdot}3H_2O$	82	86:14	25:75/27:73
7[b]	$K_3PO_4{\cdot}3H_2O$	53	86:14	22:78/19:81
8	NMM	70	71:29	33:67/28:72
9	K_2CO_3	71	60:40	45:55/51:49
10	pyrrole	75	62:38	52:48/54:46
11	–	traces[c]	–	–

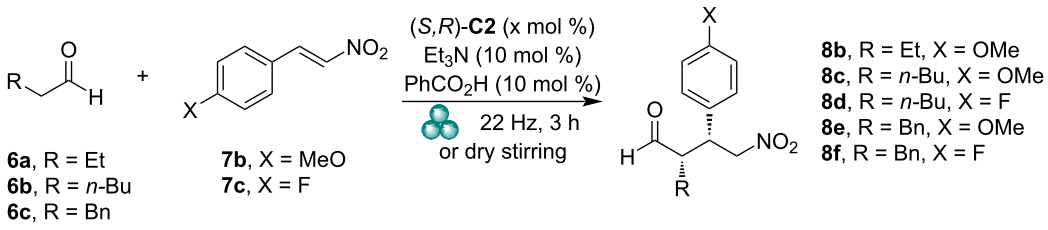
[a]Reaction conditions: the catalyst (0.016 mmol), base (0.016 mmol), nitroalkene (0.33 mmol), butyraldehyde (1 mmol), benzoic acid (0.03 mmol) and NaCl (1.2 g) were added to ball mill reactor in one portion, milling frequency 22 Hz, milling time 3 h; [b]1.5 equiv of aldehyde **6a**; [c]reaction proceeded without any base and acid.

spectively (Table 3, entry 2). A base exchange had no significant influence, neither on yields nor on selectivities. Reactions under ball milling with *N*-methylpyrrole (NMP), iPr_2EtN, DABCO, $K_3PO_4·3H_2O$, *N*-methylmorpholine (NMM) (Table 3, entries 3–8) proceeded with yields of 53–82%. The highest value of diastereoselectivity was achieved only with triethylamine as the base (dr 93:7) but unfortunately with a comparable enantioselectivity (Table 3, entry 2). When the excess of butanal (**6a**) was reduced from 3 to 1.5 equivalents, the yield again decreased (Table 3, cf. entries 2 and 7). The Michael addition of aldehyde **6a** to nitroalkene **7a** with K_2CO_3 and pyrrole (10 mol %) as the base, respectively, afforded adduct **8a** in 71 and 75% yield, with diastereoselectivity of 60:40 and 62:38 and in a racemic form (Table 3, entries 9 and 10). Only traces of adduct **8a** were detected in the reaction mixture when the reaction in the ball mill was carried out without any base and any acid additive (Table 3, entry 11).

Furthermore, we have continued with the evaluation of catalyst (*S,R*)-**C2** in the Michael addition of aldehydes **6a**–**c** to functionalized nitrostyrenes **7b** and **7c**. These reactions were conducted using a ball-milling set-up as well as solvent-free stirring at 30 °C. The experimental results of the addition reactions of aldehydes **6a**–**c** with nitrostyrenes **7b**,**c** catalyzed with (*S,R*)-**C2** are summarized in Table 4.

The aliphatic aldehyde **6a** in the Michael addition with 4-methoxy-β-nitrostyrene (**7b**) catalyzed by catalyst (*S,R*)-**C2** gave the corresponding Michael adduct exclusively by using the ball-mill method. The Michael addition was carried out in the presence of Et_3N as the base and provided only 32% yield of the product with low diastereoselectivity and enantioselectivity (Table 4, entry 1). The aliphatic aldehyde **6b** with 4-methoxy-β-nitrostyrene (**7b**) gave the Michael addition product **8c** by the solvent-free method by stirring at 30 °C. Ten mol % of catalyst (*S,R*)-**C2** gave 32% yield after 48 hours. The best result in terms of yield and diastereoselectivity was obtained by a small amount of catalyst (*S,R*)-**C2**. Already 2.5 mol % of (*S,R*)-**C2** provided the product in 75% yield and 71:29 dr and 33:67 er, respectively. A higher catalyst loading of 5 mol % under solvent-free stirring gave 67% yield and 55:45 dr and 50:50 er (Table 4, entries 2–4). Hexanal (**6b**) also reacted successfully with 4-fluoro-β-nitrostyrene (**7c**) and gave the product **8d** under solvent-free and ball-mill conditions. Again a small amount of catalyst (*S,R*)-**C2** (2.5 mol %) gave the best chemical yield, 70% using solvent-free, neat stirring at 30 °C. In comparison, the ball-mill reaction afforded 66% of the product (Table 4, entries 5–7). The Michael addition of aldehyde **6c** gave under dry stirring products **8e** and **8f** in 76 and 79% yield with comparable diastereoselectivity and enantioselectivity (Table 4, entries 8 and 9).

Table 4: Michael addition of aldehyde **6a–c** to nitroalkenes **7a** and **7b**.[a]



entry	catalyst loading (mol %)	method	yield (%)	dr	er (major/minor)
1	5	ball-milling	32 (**8b**)	64:36	52:48/54:46
2	2.5	dry stirring (4 d)	75 (**8c**)	71:29	33:67/70:30
3	5	dry stirring (48 h)	67 (**8c**)	55:45	50:50/50:50
4	10	dry stirring (48 h)	32 (**8c**)	64:36	35:65/62:38
5	2.5	dry stirring (48 h)	70 (**8d**)	64:36	35:65/65:35
6	5	dry stirring (72 h)	67 (**8d**)	72:28	34:66/68:32
7	2.5	ball-milling	66 (**8d**)	71:29	35:65/65:35
8	5	dry stirring (72 h)	76 (**8e**)	57:43	33:67/65:35
9	5	dry stirring (72 h)	79 (**8f**)	63:27	36:64/64:36

[a]The catalyst (2.5–10 mol %), base (10 mol %) and a half volume of aldehyde (total 5 equiv used), were added to a 10 mL vial vessel. After 5 min, the remaining volume of aldehyde was added to the mixture. Benzoic acid (10 mol %) was added after 5 min stirring and 10 min later, nitroalkene (1 equiv) was added.

DFT calculations of catalyst structure and reaction stereo-course

To understand the catalyst operation, we have conducted DFT calculations of its structure and reaction course. All calculations were realized using Turbomole program package [36,37]. Geometric optimizations were performed using PBEh-3c functional [38]. This functional is a composite scheme based on the well-known PBE0 functional [39,40]. PBEh-3c corrects for the basis set superposition error and accounts for the long-range London dispersion interactions. Geometrical optimizations were performed with the Karlsruhe split-valence def2-SV(P) basis set [41]. Energies were refined using the Minnesota M06-2X functional [42] and valence triple-zeta def2-TZVP basis set [43]. The lowest energy conformers of both catalyst (*S*,*R*)- and (*S*,*S*)-**C2** (Figure 2a) have *anti-syn* arrangement of the urea unit. Figure 2b shows the enamine intermediate likely formed between aldehyde **6c** and catalyst (*S*,*R*)-**C2**. The urea unit adopts an *anti-anti* arrangement upon coordination of a nitroalkene via hydrogen bonds (Figure 2c).

The reaction likely proceeds via initial enamine formation from the aldehyde and catalyst. The coordination of the nitroalkene via hydrogen bonding with the (thio)urea moiety will bring it in the vicinity of the enamine from the *re*-face. The major enantiomer of the Michael adduct (*S*,*S*)-**10** is formed via *re*-attack on the nitroalkene. The nitroalkene is in *synclinal* orientation with respect to the enamine double bond. The alternative *si*-attack on the nitroalkene provides the minor diastereomer (*S*,*R*)-**10**. The enantiomeric products (*R*,*R*)- and (*R*,*S*)-**10** could be formed via the Michael addition from the *si*-face of the enamine. In this case, the nitroalkene could not be activated by hydrogen bonding via the (thio)urea moiety, however, it is also probably less sterically hindered (Figure 3a). The DFT calculated transition states support this analysis. The transition state **TS-major-re-SR-cat** leading to the major stereoisomer of the Michael adducts has the lowest Gibbs free energy of activation of 40.4 kJ·mol^{-1}. The Gibbs free energies of activations for the (*S*,*S*)-**C2** catalyst are only slightly higher than those for the (*S*,*R*)-**C2** catalyst. These calculations support the experimental observation that the configuration of the sulfur stereogenic center does not play an important role in the Michael addition (Figure 3b). The stereochemical outcome of the Michael addition is dictated mainly by the configuration of the proline unit. The calculated transition states for the Michael addition with both diastereomeric catalysts (*S*,*R*)- and (*S*,*S*)-**C2** are displayed in Figure 3c.

After the Michael addition, the initial products formed are iminium salts with the catalysts, which are hydrolyzed to the isolated Michael adducts **10**. A representative reaction profile is depicted in Figure 4.

Conclusion

We have designed and synthesized bifunctional pyrrolidine-containing sulfinylureas and thioureas. These catalysts operate via enamine activation of aldehydes and hydrogen-bond activation of the electrophilic component, in this study – nitrostyrenes. These catalysts were effective in the Michael addition of aldehydes to nitroalkenes, affording the corresponding adducts in medium to high diastereomeric and enantiomeric

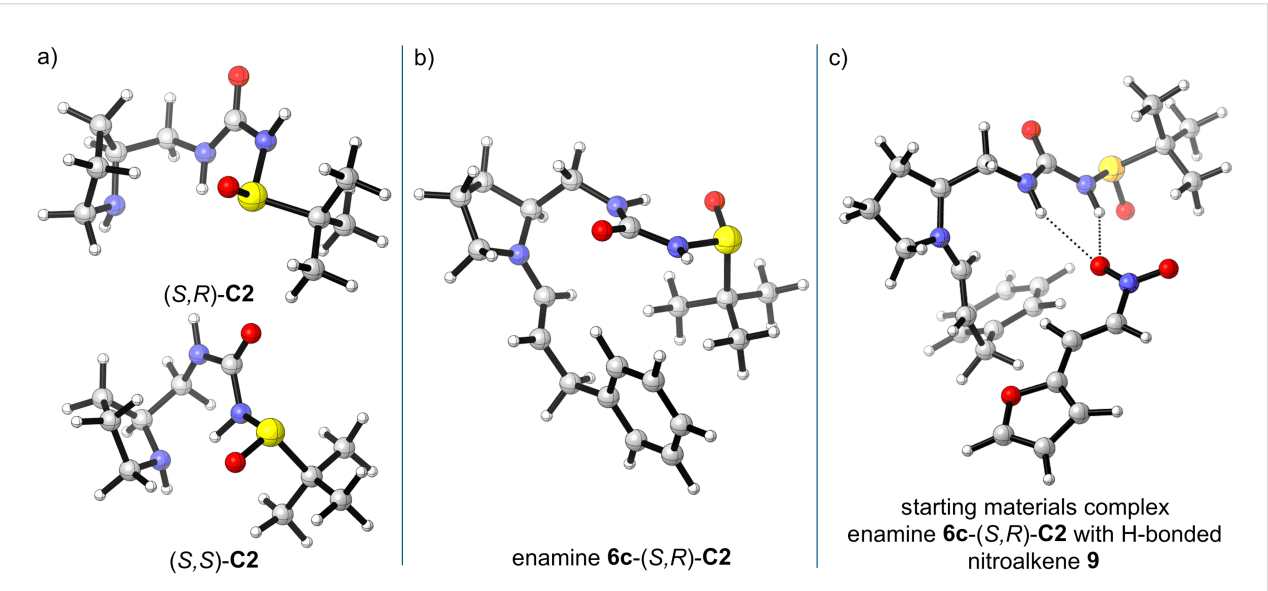


Figure 2: DFT-calculated (PBEh-3c/def2-SV(P)//M06-2X/def2-TZVP) structures of catalyst (*S*,*R*) and (*S*,*S*)-**C2**, enamine between aldehyde **6c** and (*S*,*R*)-**C2**; enamine **6c**-(*S*,*R*)-**C2** and hydrogen-bonded nitroalkene **9**.

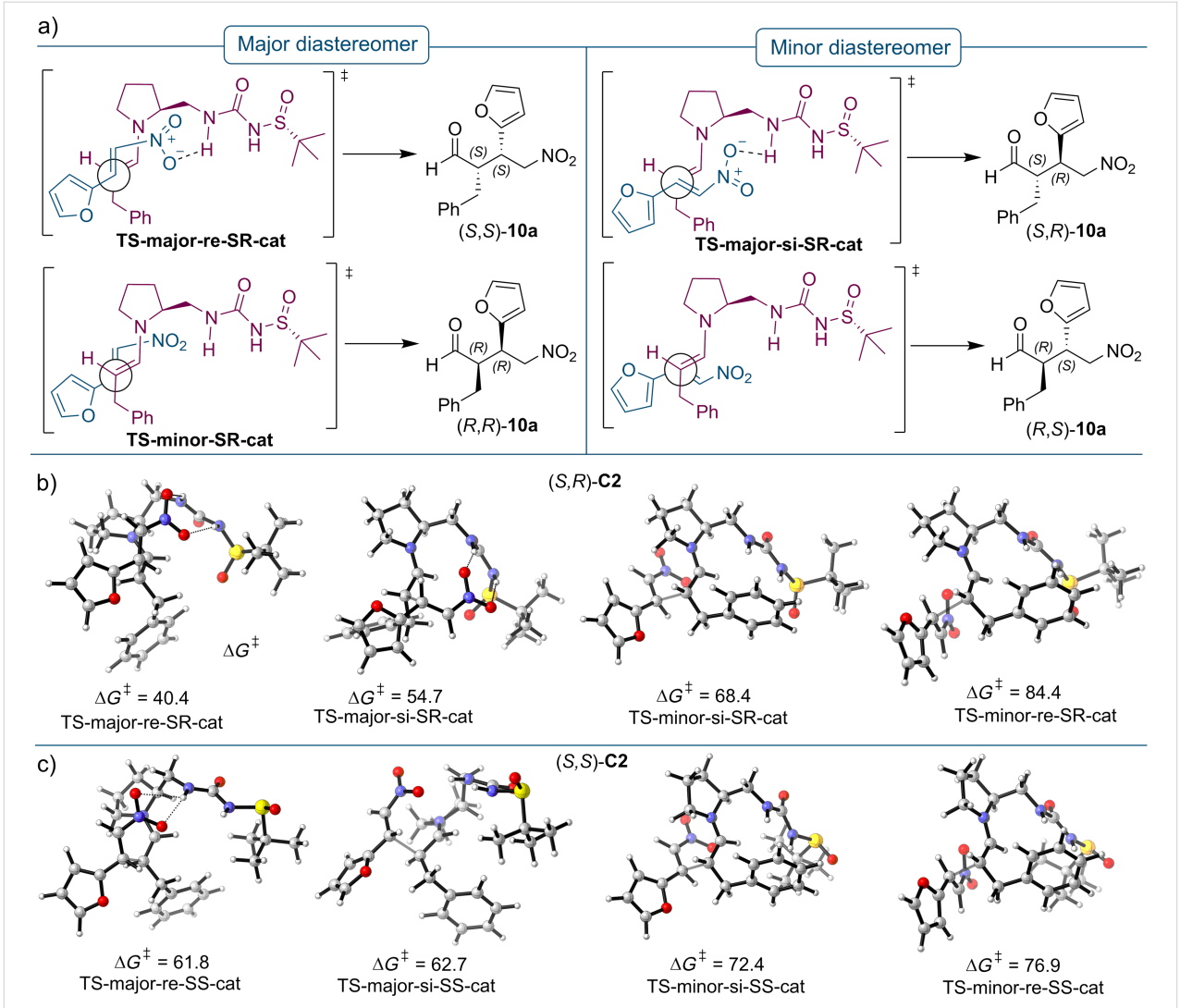


Figure 3: a) Arrangements of reactants in the transition states; b) DFT-calculated (PBEh-3c/def2-SV(P)//M06-2X/def2-TZVP) transition states with catalyst (*S*,*R*)-**C2**; c) calculated transition states with catalyst (*S*,*S*)-**C2**; Gibbs free energies of activation in kJ/mol.

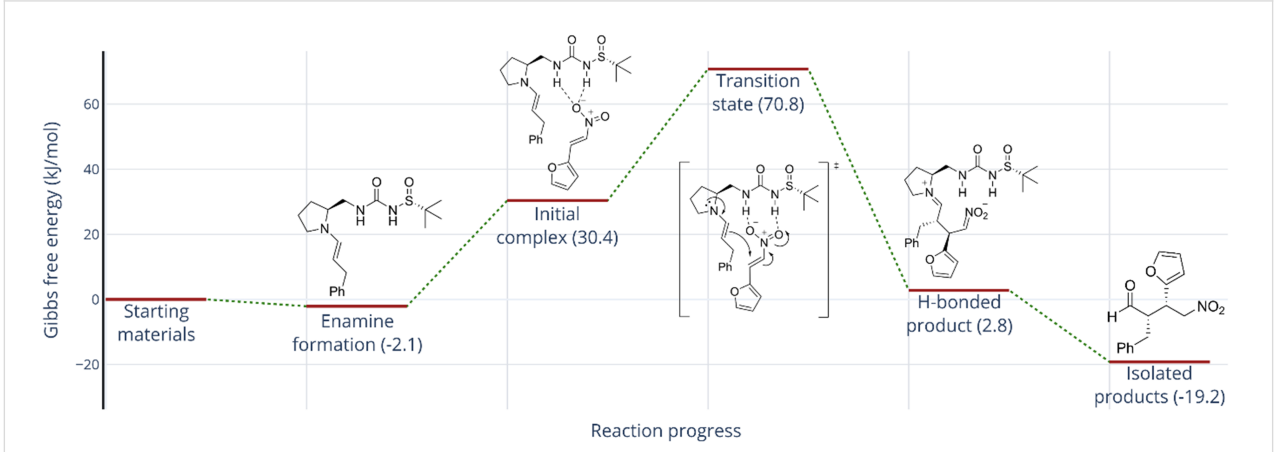


Figure 4: DFT-calculated (PBEh-3c/def2-SV(P)//M06-2X/def2-TZVP) reaction profile for the Michael addition of 3-phenylpropanal (**6c**) and nitroalkene **9** using catalyst (*S*,*R*)-**C2**.

purities. The reactions under solvent-free conditions performed considerably faster than those under classical conditions in solution, with comparable or better yields, without any significant effect on selectivity. Sulfinylurea catalysts were more active than the corresponding thioureas. The additional stereogenic center on the sulfur plays only a minor role on the stereoselectivity of the reaction, which is governed mainly by the configuration of the proline moiety. DFT calculations elucidated the stereochemical action of the catalysts in organocatalytic Michael addition and suggested the possibilities of further improvement in catalyst design.

Experimental

Synthesis of catalysts

(S)-tert-Butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (**2**)

The solution of PPh_3 (1.64 g, 6.3 mmol) and *N*-Boc-(*S*)-prolinol (**1**, 1.0 g, 5.0 mmol) in dry THF (10 mL) was cooled in an ice-water bath, and subsequently, diisopropyl azodicarboxylate (DIAD, 1.21 g, 6.0 mmol) and diphenylphosphoryl azide (DPPA, 1.65 g, 6.0 mmol) were added dropwise under argon atmosphere. The mixture was allowed to reach room temperature and stirred for 20 h. The reaction mixture was then warmed to 75 °C and refluxed for 2 h, subsequently, PPh_3 (1.64 g, 6.3 mmol) in THF (10 mL) was added, and the reaction mixture was refluxed for further 2 h. After that, the reaction mixture was cooled to room temperature, water (1 mL) was added, and the mixture was stirred for 3 h. Then, the solvent was removed under vacuum and the pH of the residue was adjusted to around 2 with 1 M HCl. The aqueous phase was washed with Et_2O (3 × 25 mL). The pH of the aqueous phase was adjusted to 13 with 2 M NaOH, and extracted with DCM (6 × 20 mL). The organic phase was dried with Na_2SO_4 and concentrated under reduced pressure to afford the product in 56% yield. R_f 0.11 (hexane/ethyl acetate 3:1); ^{1}H NMR (300 MHz, CD_3OD) δ 3.82–3,64 (m, 1H), 3.48–3.24 (m, 4H), 2.81 (dd, *J* = 12.7, 4.5 Hz, 1H), 2.57 (dd, *J* = 12.7, 7.8 Hz, 1H), 2.01–1.78 (m, 4H), 1.46 (s, 9H) ppm. Spectral data agree with those in the literature [32].

(*S*)-*tert*-Butyl 2-(isothiocyanatomethyl)pyrrolidine-1-carboxylate (**3a**)

The solution of Et_3N (0.13 g, 1.3 mmol) and *(S)-tert*-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (**2**, 0.08 g, 0.4 mmol) in dry THF (4 mL) was cooled in an ice–water bath and next it was added dropwise into cooled $CSCl_2$ (0.12 g, 1.1 mmol) under argon atmosphere. The reaction mixture was stirred for 30 min in an ice–water bath and 24 h at room temperature. Cold water (60 mL) was then added, and the aqueous phase was extracted with Et_2O (3 × 40 mL). The combined organic phase was washed with aq saturated solution of $NaHCO_3$ (3 × 40 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent, hexane/ethyl actate 7:1→5:1), affording the product as dark orange oil in 86% yield. R_f 0.5 (hexane/EtOAc 3:1); IR (ATR): 2971, 2089, 1390, 1700, 1162 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98–3.84 (m, 2H); 3.68–3.57 (m, 1H), 3.53–3.35 (m, 2H), 2.13–2.03 (m, 1H), 1.99–1.81 (m, 3H), 1,47 (s, 9H) ppm.

(S)-tert-Butyl 2-(isocyanatomethyl)pyrrolidine-1-carboxylate (**3b**)

BTC (0.33 g, 1.11 mmol) was dissolved in dry THF (10 mL) and the solution was cooled to 0 °C. Then, *N,N*-diisopropylethylamine (DIPEA, 1.14 g, 8.84 mmol) was added dropwise, followed by a solution of *(S)-tert*-butyl 2-(aminomethyl)pyrrolidine-1-carboxylate (**2**, 0.44 g, 2.21 mmol) in dry THF (10 mL) during 30 min. The reaction mixture was stirred for 72 h at room temperature. The solvent was removed in vacuo and the residue was dissolved in DCM (60 mL) and washed with 0.1 M HCl (2 × 30 mL). The organic phase was dried over Na_2SO_4 and the crude reaction mixture was used in the next reaction step without further purification.

General procedure for preparation of *N*-sulfinylthiourea pre-catalysts (*S*,*R*)-**5a** and (*S*,*S*)-**5a**

A stirred solution of *(R)-tert*-butanesulfinamide or *(S)-tert*-butanesulfinamide (0.09 g, 0.75 mmol) in THF (5 mL) was cooled to 0 °C under argon atmosphere. Butyllithium in hexane (0.35 g, 0.82 mmol) was added dropwise, and the solution was stirred for 15 min. The cooling bath was removed and the solution of (*S*)-*tert*-butyl 2-(isothiocyanatomethyl)pyrrolidine-1-carboxylate (**3a**, 0.20 g, 0.82 mmol) in dry THF (5 mL) was added dropwise over 15 min and stirring continued at rt for four days. The reaction was quenched with water (0.3 mL) and the mixture was stirred for 30 min. The resulting mixture was concentrated in vacuo and the desired product was isolated by column chromatography on silica gel (EtOAc/MeOH/NH_4OH 60:1:0.6→50:1:0.5).

(S)-tert-Butyl 2-((3-((*R*)-*tert*-butylsulfinyl)thioureido)methyl)pyrrolidine-1-carboxylate ((*S*,*R*)-**5a**)

$[\alpha]_D^{20}$ −87.8 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.17 (s, 1H), 6.85 (s, 1H), 4.17–4.09 (m, 1H), 3.83–3.72 (m, 1H), 3.44–3.32 (m, 3H), 2.10–2.00 (m, 1H), 1.97–1.82 (m, 2H), 1.77–1.64 (m, 1H), 1.49 (s, 9H), 1.31 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.9, 157.2, 80.8, 57.6, 55.8, 53.3,47.3, 29.5, 28.5, 23.9, 22.1 ppm; IR (ATR): 3270, 2973, 1685, 1161, 1107, 1038 cm^{-1}; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{29}N_3O_3S_2$, 364.1723; found, 364.1725; $[M + Na]^+$ calcd, 386.1543; found, 386.1544.

(*S*)-*tert*-Butyl 2-((3-((*S*)-*tert*-butylsulfinyl)thioureido)methyl)pyrrolidine-1-carboxylate ((*S*,*S*)-**5a**)

$[\alpha]_D^{20}$ +30.5 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.22 (s, 1H), 6.96 (s, 1H), 4.17–4.09 (m, 1H), 3.76–3.67 (m, 1H), 3.49–3.38 (m, 2H), 3.36–3.31 (m, 1H), 2.13–2.04 (m, 1H), 1.97–1.81 (m, 2H), 1.78–1.69 (m, 1H), 1.46 (s, 9H), 1.30 (s, 9H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 182.3, 157.3, 80.6, 57.4, 55.9, 53.7, 47.5, 29.9, 28.5, 24.0, 22.2 ppm; IR (ATR): 3307, 2973, 1653, 1159, 1237, 1058 cm^{-1}; HRMS (*m*/*z*): $[M + Na]^+$ calcd for $C_{15}H_{29}N_3O_3S_2$, 386.1543; found, 386.1543; $[M + H]^+$ calcd, 364.1729; found, 364.1722.

General procedure for the preparation of *N*-sulfinylurea pre-catalysts (*S*,*R*)-**5b** and ((*S*,*S*)-**5b**)

A stirred solution of *(R)-tert*-butanesulfinamide or *(S)-tert*-butanesulfinamide (0.07 g, 0.6 mmol) in THF (5 mL) was cooled to −30 °C under argon atmosphere. Butyllithium in hexane (0.28 g, 0.66 mmol) was added dropwise and the solution was stirred for 15 min. The solution of (*S*)-*tert*-butyl 2-(isocyanatomethyl)pyrrolidine-1-carboxylate (**3b**, 0.15 g, 0.66 mmol) in dry THF (5 mL) was added dropwise during 15 min, the cooling bath was removed, and stirring was continued at rt for 22 h. The reaction was then quenched with water (0.3 mL) and the mixture was stirred for 30 min. The resulting mixture was concentrated and the desired product was isolated by column chromatography on silica gel (EtOAc/MeOH/NH_4OH 60:1:0.6→50:1:0.5).

(*S*)-*tert*-Butyl 2-((3-((*R*)-*tert*-butylsulfinyl)ureido)methyl)pyrrolidine-1-carboxylate ((*S*,*R*)-**5b**)

$[\alpha]_D^{20}$ −87.3 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.22 (s, 1H), 6.96 (s, 1H), 4.17–4.09 (m, 1H), 3.76–3.67 (m, 1H), 3.49–3.38 (m, 2H), 3.36–3.31 (m, 1H), 2.13–2.04 (m, 1H), 1.97–1.81 (m, 2H), 1.78–1.69 (m, 1H), 1.46 (s, 9H), 1.30 (s, 9H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 182.3, 157.3, 80.6, 57.4, 55.9, 53.7, 47.5, 29.9, 28.5, 24.0, 22.2 ppm; IR (ATR): 3307, 2973, 1653, 1159, 1237, 1058 cm^{-1}; HRMS (*m*/*z*): $[M + H]^+$ calcd for $C_{15}H_{29}N_3O_4S$, 348.1957; found, 348.1952; $[M + Na]^+$ calcd, 370.1776; found, 370.1771.

(*S*)-*tert*-Butyl 2-((3-((*S*)-*tert*-butylsulfinyl)ureido)methyl)pyrrolidine-1-carboxylate ((*S,S*)-**5b**)

$[\alpha]_D^{20}$ +33.9 (*c* 0.5, MeOH); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.32 (s, 1H), 4.02–3.72 (m, 1H), 3.52–3.15 (m, 4H), 2.01–1.65 (m, 5H), 1.46 (s, 9H), 1.26 (s, 9H) ppm; ^{13}C NMR (151 MHz, $CDCl_3$) δ 156.7, 154.4, 79.6, 57.2, 56.1, 47.0, 45.1, 29.1, 28.5, 23.8, 22.3 ppm; IR (ATR): 3349, 2966, 1665, 1516, 1166, 1060 cm^{-1}; HRMS (*m*/*z*): $C_{15}H_{29}N_3O_4S$, $[M + H]^+$ calcd for $C_{15}H_{29}N_3O_4S$, 348.1957; found, 348.1950; $[M + Na]^+$ calcd, 370.1776; found, 370.1769.

General procedure for the preparation of the catalysts **C1a**, **C1b**, **C2a**, **C2b**

The Boc-protected pre-catalyst **5a** or **5b** (0.1 mmol) was dissolved in cold dry CH_2Cl_2 (1 mL) and TFA (0.37 g, 3.3 mmol) was added. The reaction mixture was stirred at room temperature for 3 h. The solvent was removed in vacuo and the catalysts were obtained as their trifluoroacetate salts.

(*S*)-2-((3-((*R*)-*tert*-Butylsulfinyl)thioureido)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate ((*S*,*R*)-**C1**)

$[\alpha]_D^{20}$ −17.8 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.53 (s, 1H), 9.40 (s, 1H), 9.16 (s, 1H), 9.01 (s, 1H), 4.33–4.17 (m, 2H), 3.63–3.31 (m, 3H), 2.30–2.00 (m, 3H), 1.85–1.67 (m,1H), 1.33, 1.31 (s, 9H); ^{13}C NMR (75 MHz, D_2O) δ 184.6, 162.9 (q, *J* = 5.3 Hz), 116.3 (q, *J* = 291.7 Hz), 59.8, 56.9, 45.5, 38.7, 27.1, 22.6, 21.7 ppm; IR (ATR): 3231, 2981, 1672, 1578, 1362, 1199, 1128, 1016 cm^{-1}; HRMS (*m*/*z*): $[M - CF_3COOH + H]^+$ calcd for $C_{12}H_{22}F_3N_3O_3S_2$, 264.1199; found, 264.1200; $[M - CF_3COOH + Na]^+$ calcd, 286.1018; found, 286.1019.

(*S*)-2-((3-((*S*)-*tert*-Butylsulfinyl)thioureido)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate ((*S*,*S*)-**C1**)

$[\alpha]_D^{20}$ +34.2 (*c* 1.0, MeOH); ^{1}H NMR (600 MHz, D_2O) δ 3.93–3.87 (m, 1H), 3.81–3.74 (m, 2H), 3.61–3.57 (m, 1H), 3.28–3.13 (m, 3H), 2.15–2.03 (m, 1H), 1.98–1.83 (m, 3H), 1.75–1.70 (m, 1H), 1.68–1.60 (m, 1H), 1.17 (s, 9H) ppm; ^{13}C NMR (151 MHz, D_2O) δ 184.5, 162.7 (q, *J* = 35.7 Hz), 117.1 (q, *J* = 286.9 Hz), 67.8, 59.9, 56.9, 45.5, 27.1, 22.5, 21.6 ppm; IR (ATR): 2969, 2721, 1660, 1551, 1316, 1153, 1044 cm^{-1}; HRMS (*m*/*z*): $[M - CF_3COOH + H]^+$ calcd for $C_{12}H_{22}F_3N_3O_3S_2$, 264.1199; found, 264.1198; $[M - CF_3COOH + Na]^+$ calcd, 286.1018; found, 286.1016.

(*S*)-2-((3-((*R*)-*tert*-Butylsulfinyl)ureido)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate ((*S*,*R*)-**C2**)

$[\alpha]_D^{20}$ −38.8 (*c* 1.0, MeOH); ^{1}H NMR (300 MHz, D_2O) δ 7.22 (bs, 1H), 7.05 (bs, 1H), 6.87 (bs, 1H), 3.72–3.08 (m, 5H), 2.12–1.87 (m, 3H), 1.63 (ddd, *J* = 17.2 Hz; 12.8 Hz; 8.6 Hz; 1H), 1.17 (s, 9H) ppm; ^{13}C NMR (151 MHz, D_2O) δ 162.9 (q, *J* = 17.3 Hz), 116.3 (q, *J* = 291.7 Hz), 60.4, 56,4, 45.5, 40.7, 26.8, 22.7, 21.4 ppm; IR (ATR): 3259, 2977, 1670, 1577, 1424, 1173, 1019 cm^{-1}; HRMS (*m*/*z*): $[M - CF_3COOH + H]^+$ calcd for $C_{12}H_{22}F_3N_3O_4S$, 248.1427; found, 248.1428.

(*S*)-2-((3-((*S*)-*tert*-Butylsulfinyl)ureido)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate ((*S*,*S*)-**C2**)

$[\alpha]_D^{20}$ +15.4 (*c* 0.25, MeOH); ^{1}H NMR (600 MHz, D_2O) δ 3.63–3.56 (m, 1H), 3.36 (dd, *J* = 15.2; 4.2 Hz, 1H), 3.26 (dd, *J* = 15.2, 7.6 Hz, 1H), 3.22–3.14 (m, 2H), 2.02 (dt, *J* = 12.6, 7.7 Hz, 1H), 1.98–1.84 (m, 2H), 1.61 (dq, *J* = 17.0, 8.6 Hz, 1H), 1.17, 1.16 (s, 9H) ppm; ^{13}C NMR (151 MHz, D_2O) δ 162.9 (q, *J* = 35.7 Hz), 161.0, 116.1 (q, *J* = 290.2 Hz), 60.7, 45.3, 40.6, 26.7, 22.9, 21.4, 18.1 ppm; IR (ATR): 3353, 2971, 1660, 1576, 1428, 1124, 1057 cm^{-1}; HRMS (*m*/*z*): [M − CF_3COOH + H]$^+$ calcd for $C_{12}H_{22}F_3N_3O_4S$, 248.1427; found, 248.1424.

Representative procedure for enantioselective Michael additions under solution conditions

The catalyst (0.015 mmol) and base (NMM, 2 mg, 0.015 mmol) were dissolved in the solvent (0.7 mL) and, after 10 min, the nitroalkene (0.5 mmol) in the solvent (0.7 mL) was added. After 10 min of stirring, the aldehyde (1.5 mmol) was added dropwise, and an acidic additive (0.015 mmol) was added. The resulting reaction mixture was stirred at room temperature for the appropriate reaction time. The reaction course was monitored by TLC. After completion of the reaction, the resulting mixture was concentrated in vacuo. The residue was diluted with water (10 mL). The layers were separated, and the aqueous layer was extracted with DCM (4 × 5 mL). The organic layer was then dried over Na_2SO_4 and concentrated. The desired products were isolated by flash column chromatography using silica gel as stationary phase.

Mechanochemical procedure for enantioselective Michael additions

The catalyst (0.016 mmol), base (0.016 mmol), nitroalkene (0.33 mmol), appropriate aldehyde (1 mmol), benzoic acid (0.03 mmol), and NaCl (1.2 g) were added to the ball mill reactor in one portion. The resulting mixture was mechanically activated for 3 h. The crude reaction mixture was dissolved in CH_2Cl_2 and NaCl was separated by simple filtration. The solvent was then evaporated under vacuum and the crude reaction mixtures were purified by column chromatography on silica gel.

Representative procedure for solvent-free enantioselective Michael additions

The catalyst (2.5–10 mol %), base (2.5–10 mol %), and half of volume of the aldehyde (total 5 equiv used) were added to a 10 mL vial vessel. After 5 min, the remaining volume of the aldehyde was added to the mixture. After further 5 min stirring, benzoic acid (10 mol %) was added and 10 min later, the nitroalkene (1 equiv) was added. The resulting reaction mixture was stirred at room temperature for the appropriate reaction time. The crude reaction mixture was purified by column chromatography using silica gel.

Supporting Information

Supporting information contains characterization data for Michael adducts, pictures of NMR spectra, pictures of HPLC chromatograms, and DFT computational details.

Supporting Information File 1

Characterization data, copies of spectra, and DFT computational details
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-176-S1.pdf]

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ORCID® iDs

Renata Górová - https://orcid.org/0000-0001-6668-5469
Mária Mečiarová - https://orcid.org/0000-0003-1378-2972
Radovan Šebesta - https://orcid.org/0000-0002-7975-3608

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Solvent-free synthesis of enantioenriched β-silyl nitroalkanes under organocatalytic conditions

Akhil K. Dubey[1] and Raghunath Chowdhury*[1,2,§]

Full Research Paper

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Address:
[1]Bio-Organic Division, Bhabha Atomic Research Centre, Trombay, Mumbai 400085, India and [2]Homi Bhabha National Institute, Anushaktinagar, Mumbai-400094, India

Email:
Raghunath Chowdhury* - raghuc@barc.gov.in

* Corresponding author
§ Fax: +91-22-25505151

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Abstract

An enantioselective 1,4-conjugate addition of nitromethane to β-silyl α,β-unsaturated carbonyl compounds catalyzed by bifunctional squaramide catalysts has been developed. This methodology offers both enantiomers of β-silyl nitroalkanes in good to excellent yields (up to 92%) and enantioselectivities (up to 97.5% ee) under solvent-free conditions at room temperature. Control experiments reveal that the presence of a β-silyl group in the enones is crucial for high reactivity under the optimized reaction conditions.

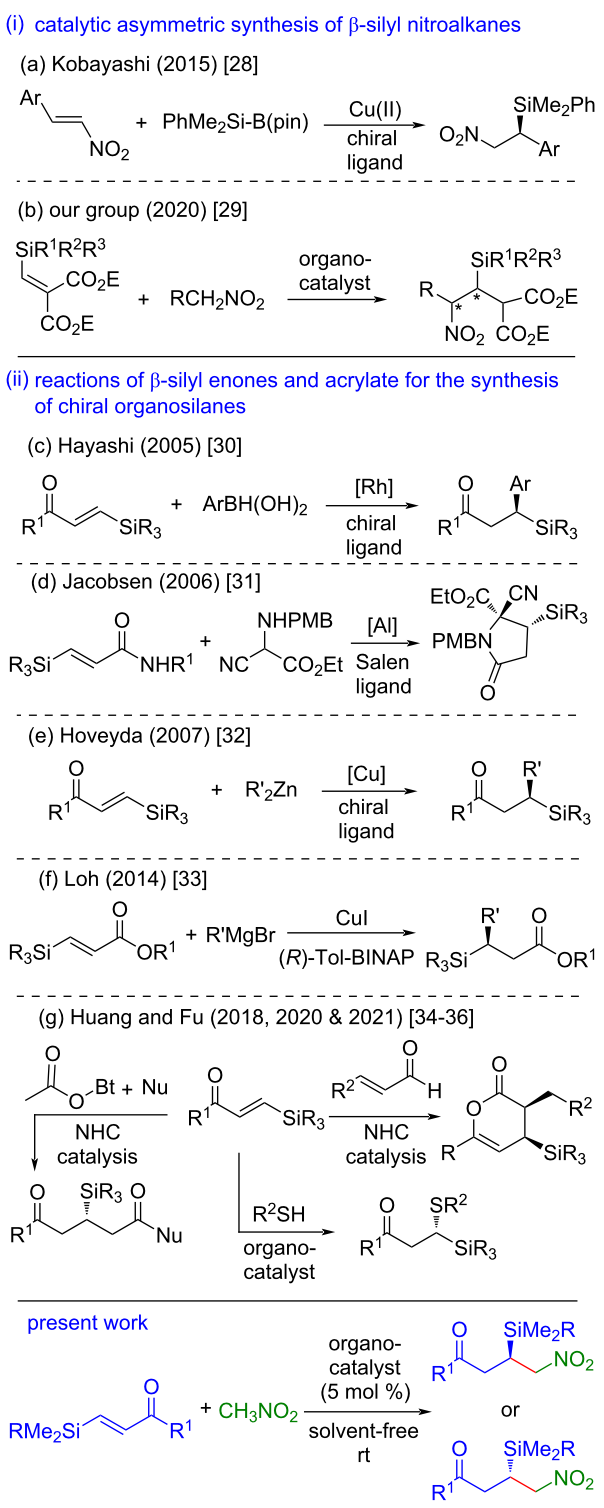
Introduction

Enantioenriched organosilanes are attractive molecules in organic synthesis owing to their potential applications in stereoselective synthesis [1,2]. The unique sterical and electronical features of the C–Si bond can induce stereodifferentiation at the adjacent prostereogenic center in organic transformations [2]. In addition, the C–Si bond can be oxidized to a hydroxy group by Tamao–Fleming oxidation [3,4] or to an alkene unit via protodesilylation [5,6]. Many complex natural products, bioactive molecules, and drug molecules have been synthesized on exploitation of the above-mentioned properties of organosilanes [2,7-14]. A number of efficient catalytic enantioselective methods has been developed for the synthesis of chiral organosilanes [15-24]. Out of the chiral organosilanes, nitrosilanes are important synthetic targets as they are precursors of valuable β-aminosilanes [25-27]. Although there is huge success in the synthesis of enantioenriched organosilanes, catalytic routes to synthesize chiral β-nitrosilanes and in general nitrosilanes have not been well explored. Kobayashi and co-workers realized the synthesis of enantioenriched β-nitrosilanes through a Cu(II)–chiral bipyridine complex catalyzed enantioselective silyl transfer reaction to nitroalkenes using Suginome's silylboron reagent (Scheme 1a) [28]. Recently, we have reported the synthesis of chiral β-nitrosilanes via an organocatalytic conjugate addition of nitromethane to β-silylmethylene

malonates (Scheme 1b) [29]. As the catalytic enantioselective route is limited to accessible β-nitrosilanes, there is an urgent need to develop efficient catalytic protocols to deliver enantioenriched β-nitrosilanes from easily available starting materials.

Metal-catalyzed reaction of various nucleophiles to β-silyl α,β-unsaturated carbonyl compounds were documented as one of the straightforward and atom-economic approaches for the facile synthesis of chiral organosilanes (Scheme 1c–f) [30-33]. Recently, the aforementioned reaction under organocatalytic conditions has gained attention [34-36]. In this context, Huang, Fu and co-workers reported carbene-catalyzed enantioselective formal [4 + 2] annulation reactions of β-silyl enones with enals and with active acetic esters (Scheme 1g) for the preparation of chiral organosilanes [34-36]. Very recently, during the final stage of our work, the same group disclosed an organocatalyzed conjugate addition of thiols to β-silyl enones for the synthesis of chiral α-mercaptosilanes (Scheme 1g) [36].

As a part of our ongoing program for the development of asymmetric catalytic approaches for the synthesis of enantioenriched organosilanes [29,37,38], we present herein an organocatalyzed conjugate addition reaction of nitromethane to β-silyl enones to afford chiral β-silyl nitroalkanes (Scheme 1). Notably, the developed method was not only carried out under solvent-free conditions at room temperature but was found to be tolerant to moisture and air. Therefore, this method offers an attractive and robust option for the preparation of chiral β-silyl nitroalkanes. In sharp contrast to the aforesaid reaction, organocatalytic conjugate addition reactions of nitroalkanes to enones have been well studied [39-43]. To the best of our knowledge, organocatalyzed or metal-catalyzed enantioselective conjugate additions of nitroalkanes to β-silyl enones are not yet known.

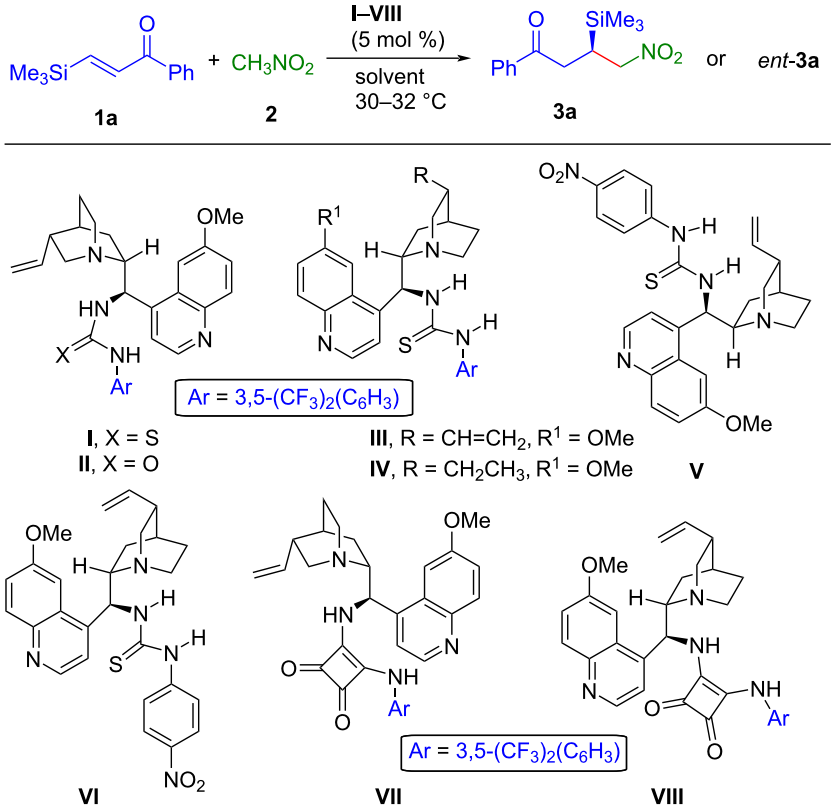


Scheme 1: Selected methods for the synthesis of enantioenriched β-silyl nitroalkanes, synthesis of chiral organosilanes from β-silyl α,β-unsaturated carbonyl compounds, and the present work.

Results and Discussion

The optimization study began with the conjugate addition reaction between β-TMS enone **1a** and nitromethane (**2**) as the model reaction. An uncatalyzed background reaction was not observed while performing the model reaction in toluene as a solvent at 30 °C for 24 h. To our delight, when the same reaction was carried out in presence of 5 mol % catalyst **I** in toluene at 30 °C for 48 h, the desired product **3a** was obtained in 84% yield with 60% ee (Table 1, entry 1). Catalyst **II** was found to be unproductive as only 25% conversion of β-TMS enone **1a** was observed (Table 1, entry 2). Gratifyingly, catalyst **III** furnished product *ent*-**3a** in 85% yield (Table 1, entry 3) with excellent enantioselectivity (94% ee). Whereas catalyst **IV** gave *ent*-**3a** in 85% yield with slightly lower enantioselectivity (91% ee) as compared to catalyst **III** (Table 1, entry 4). Catalyst **V** also led to product **3a** in 66% yield and 78% ee (Table 1, entry 5). Catalyst **VI**, a pseudoenantiomer of catalyst **V** delivered *ent*-**3a** in 78% yield with 80% ee (Table 1, entry 6). The catalytic performance of the squaramide catalysts was also explored for the model reaction. Catalyst **VII** afforded the

Table 1: Catalysts screening and optimization of reaction conditions.[a]



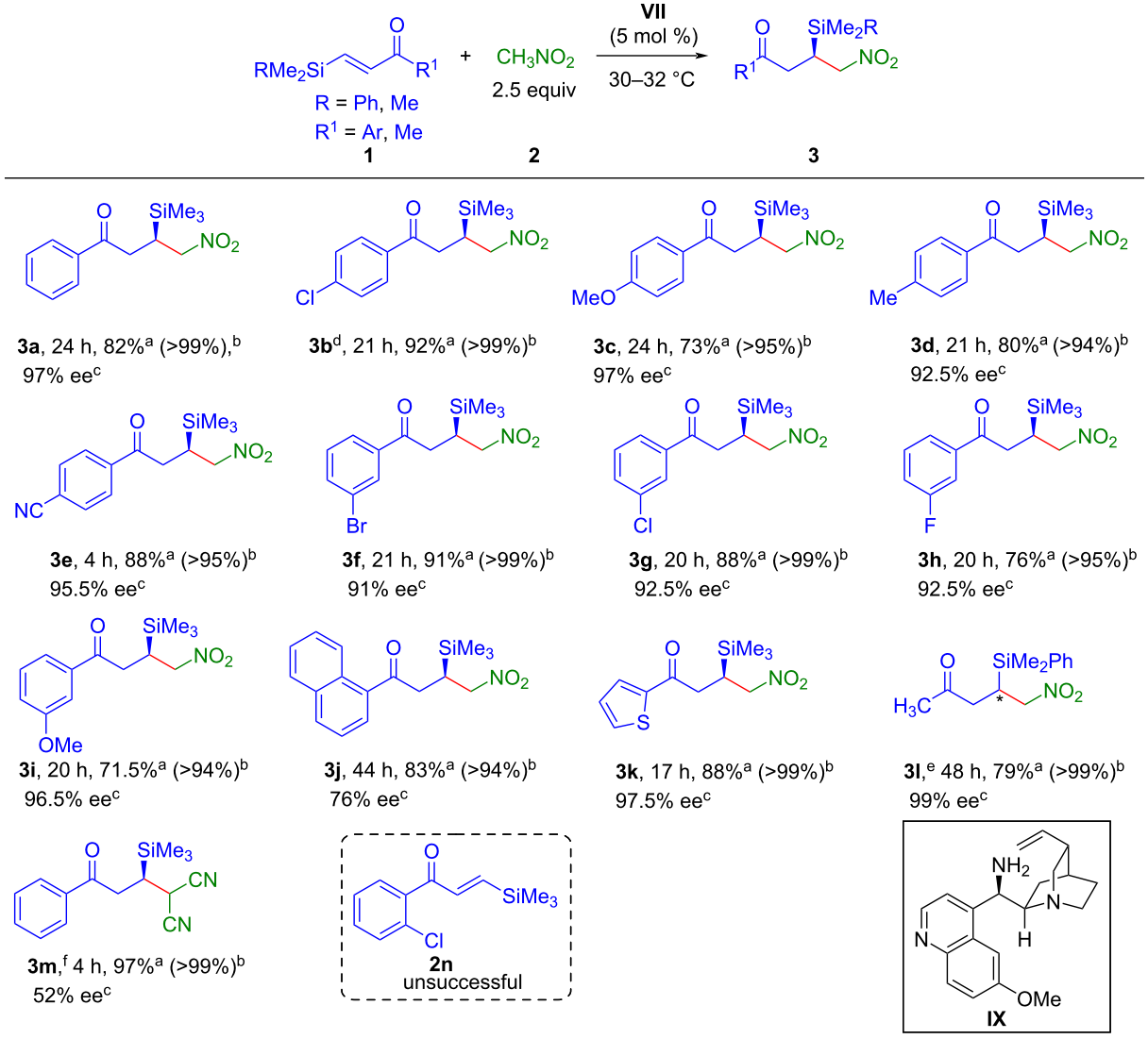
Entry	Cat.	Solvent (mL)	**2a** (equiv)	Time (h)	Yield (%)[b]	ee (%)[c]
1	**I**	toluene (0.4)	10	48	84 (98)	60
2	**II**	toluene (0.4)	10	48	ND (25)	ND
3	**III**	toluene (0.4)	10	48	85 (>99)	–94[d]
4	**IV**	toluene (0.4)	10	48	85 (>99)	–91[d]
5	**V**	toluene (0.4)	10	48	66 (90)	78
6	**VI**	toluene (0.4)	10	48	78 (97)	–80[d]
7	**VII**	toluene (0.4)	10	48	78 (>99)	97
8	**VII**	toluene (0.2)	10	42	78 (>99)	97
9	**VII**	toluene (0.1)	10	24	80 (>99)	97
10	**VII**	–	10	24	83 (>99)	97
11	**VII**	–	5	24	82 (>99)	97
12	**VII**	–	2.5	24	82 (>99)	97
13[e]	**VII**	–	10	24	56 (85)	97
14	**VIII**	–	2.5	24	80 (>97)	–94[d]

[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.5–2.0 mmol), catalyst (0.01 mmol, 5 mol %) in toluene or neat at 30–32 °C. [b]Isolated yield after column chromatography, % of conversion of the starting material **1a** is given in parentheses, determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by HPLC using a chiralpak OD-H column. [d]Opposite enantiomer. [e]2.5 mol % of the catalyst **VII** was used.

conjugate addition product **3a** in 78% yield with excellent enantiopurity of 97% ee (Table 1, entry 7). A solvent survey (see Supporting Information File 1 for details) revealed that toluene is the most suitable solvent. Next, we targeted to make the reaction more time economical under mild conditions. For this purpose, the reaction was performed at different concentrations of the reaction mixture (Table 1, entries 8–11). It was observed that time required for completion of the reaction decreased with an increase of concentration of the reaction mixture while the enantiopurity of the product **3a** remained unchanged (Table 1, entries 7–9). Next, the model reaction was performed using 10 equivalents of nitromethane (**2**) in the presence of

5 mol % catalyst **VII** under solvent-free conditions, and was complete within 24 h without affecting the enantioselectivity of product **3a** (Table 1, entry 10). Reducing the loading of nitromethane (**2**) to 5 equivalents, a slight drop in yield (82%) of product **3a** was observed whereas the enantioselectivity (97% ee) remained the same (Table 1, entry11). Upon further reduction in the loading of nitromethane (**2**) to 2.5 equivalents, the yield (82%), enantioselectivity (97% ee), and reaction time were not affected (Table 1, entry 12). Moreover, the reaction became sluggish when conducting the reaction with 2.5 mol % of the catalyst **VII** while keeping other parameters fixed (Table 1, entry 13). Performing the reaction with catalyst **VIII**, the pseudoenantiomeric catalyst of **VII**, furnished *ent*-**3a** in 80% yield and 94% ee (Table 1, entry 14). From the aforementioned studies, compromising slight lower yield of **3a**, we set up the optimization conditions as: For **3a**, **1a** (0.2 mmol), **2** (0.5 mmol), 5 mol % of catalyst **VII** at 30–32 °C (Table 1, entry 12) and for *ent*-**3a**, **1a** (0.2 mmol), **2** (0.5 mmol), 5 mol % of catalyst **VIII** at 30–32 °C (Table 1, entry 14).

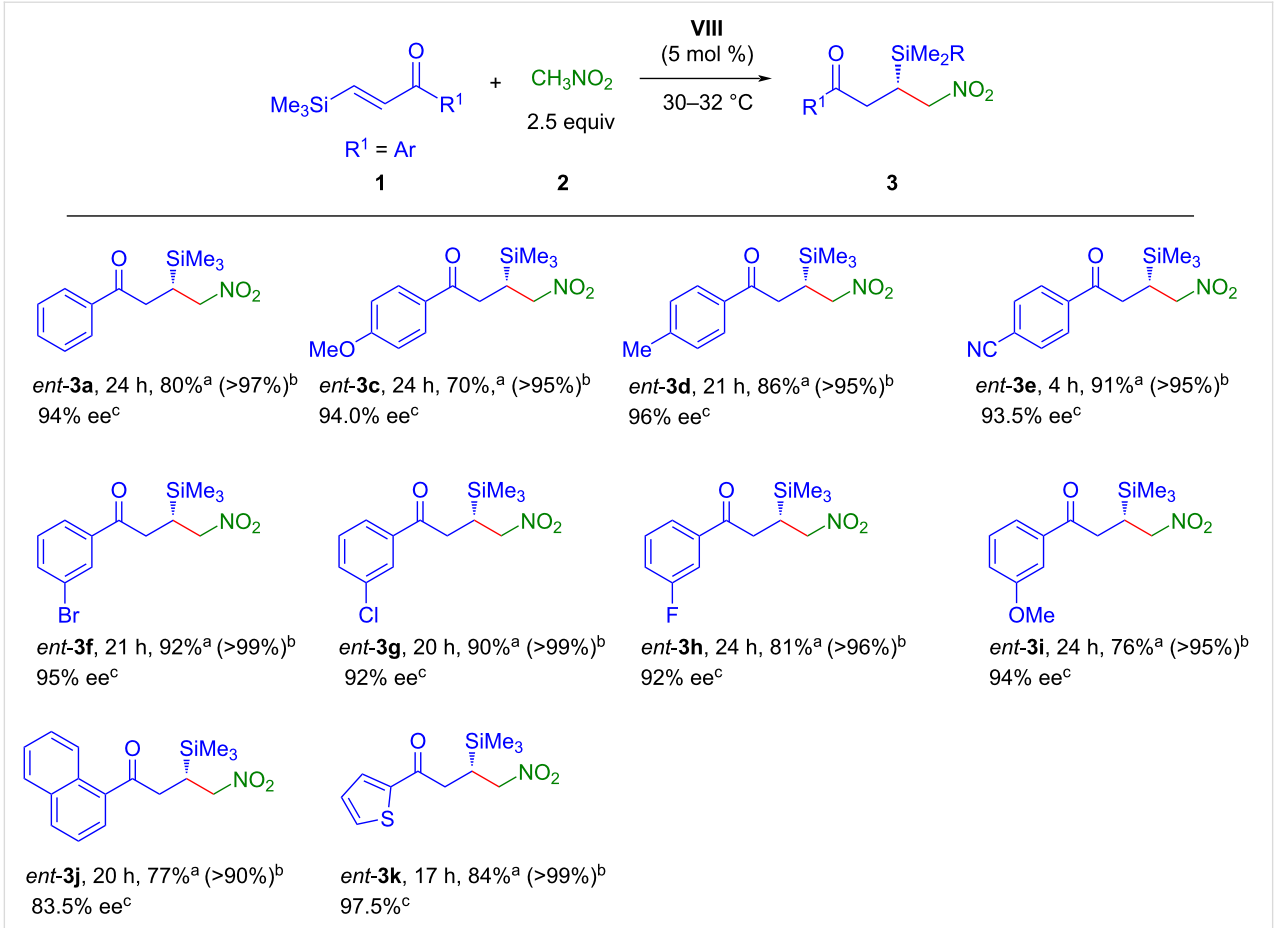
With the acceptable optimized reaction conditions in hand, we next investigated the generality and limitations of this enantioselective conjugate addition reaction. Under the optimized reaction conditions, the conjugate addition reaction of nitromethane (**2**) to a variety of β-silylenones **1** was carried out and the results are summarized in Scheme 2. β-Silylenones bearing electron-



Scheme 2: Scope of substrates. Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol), catalyst **VII** (0.01 mmol, 5 mol %) at 30 °C. [a]Isolated yield of **3** after column chromatography. [b]Conversion in % of the starting material **1** is given in parentheses, determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by HPLC using a chiral stationary phase. [d]Enantiomers could not be separated by AD-H, OD-H, OJ-H, and AS-H columns. [e]Reaction conditions for **3l**: **1l** (0.2 mmol), **2** (2 mmol), catalyst **IX** (0.04 mmol, 20 mol %), benzoic acid (0.08 mmol, 40 mol %) in 0.9 mL toluene as the solvent (see Supporting Information File 1). [f]Malonitrile (0.6 mmol, 3 equiv) was used.

donating, electron-withdrawing groups and halogen substituents in the *meta* or *para* position of the phenyl ring reacted smoothly and furnished the desired products **3a–k** in good to excellent yields (71.5–92%) and enantioselectivities (76–97.5% ee). The β-silylenone with a strong electron-withdrawing group (cyano) attached to the phenyl ring, was found to be most reactive as the reaction completed within 4 h and afforded the product **3e** in good yield (88%) and enantioselectivity (95.5% ee). The β-silylenone with a naphthyl substituent also took part in the conjugate addition reaction and gave the corresponding product **3j** in good yield (83%) and enantioselectivity (76% ee). The reaction also tolerated a 2-thienyl-substituted β-silylenone and the desired product **3k** was obtained in good yield (88%) and enantioselectivity (97.5% ee). However, β-silylbutenone **1l** failed to participate in the conjugate addition reaction with nitromethane under the optimized reaction conditions. Pleasingly, using 9-amino-9-deoxyepihydroquinidine (**IX**)–benzoic acid as organocatalyst system (see Supporting Information File 1 for details) promoted the addition reaction and product **3l** was formed in good yield (79%) and excellent enantioselectivity (99% ee). The conjugate addition reaction between malononitrile and β-silylenone **1a** was also investigated using 5 mol % of catalyst **VII** under the optimized reaction conditions. To our delight, the reaction completed within 4 h and the desired product **3m** was isolated in excellent yield (97%) with moderate enantioselectivity (52% ee). β-Silylenone **2n** bearing a *o*-chloro substituent in the aromatic ring remained unreactive under the optimized reaction conditions probably due to steric hindrance.

The facile synthesis of both enantiomers of the targeted compounds is of paramount importance since biological activities are dictated by the absolute configuration of the products. To our delight, catalyst **VIII**, the pseudoenantiomeric catalyst of **VII**, allowed to synthesize the enantiomeric products *ent*-**3** (Scheme 3) in high yields and enantioselectivities comparable to the corresponding enantiomers **3** under the optimized reaction conditions. The same set of β-silylenones was explored and an almost similar trend in reactivities, yields as well as enantioselectivities was observed.



Scheme 3: Synthesis of *ent*-**3**. Reaction conditions: **1** (0.2 mmol), **2** (0.5 mmol), catalyst **VIII** (0.01 mmol, 5 mol %) at 30 °C. [a]Isolated yield of *ent*-**3** after column chromatography. [b]Conversion in % of the starting material **1** is given in the parentheses, determined by ^{1}H NMR analysis of the crude reaction mixture. [c]Determined by HPLC using chiral stationary phase.

To probe the role of the β-silyl group, the reaction of *tert*-butyl-substituted enone **3o** and nitromethane (**2**) was conducted under the standard reaction conditions using catalyst **VII** or **VIII**, affording only trace amounts of products **4** or *ent*-**4** even after stirring for 48 h [44]. When the same reaction was performed in the presence of 10 equivalents of nitromethane using catalyst **VII**, the product **4** was isolated in 26% yield and 89.5% ee after 96 h whereas the catalyst **VIII** led to *ent*-**4** in 25% yield and 95% ee (Scheme 4). This observation confirmed that the presence of the β-silyl group in the enones played a key role in the high reactivity under the optimized reaction conditions.

The stereochemistry of the silicon-substituted chiral center in compound *ent*-**3k** was found to adopt "(*S*)" configuration which was unambiguously established by single crystal X-ray diffraction analysis (Figure 1) [45].

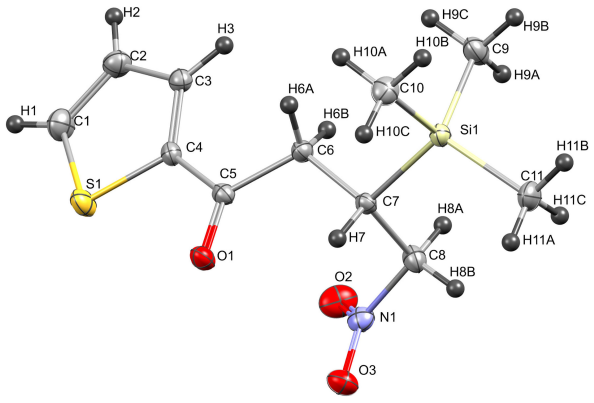
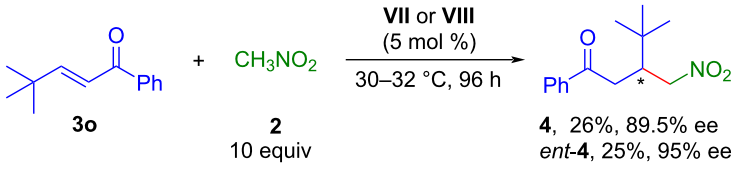


Figure 1: Single crystal X-ray structure of *ent*-**3k** (CCDC 2097263).

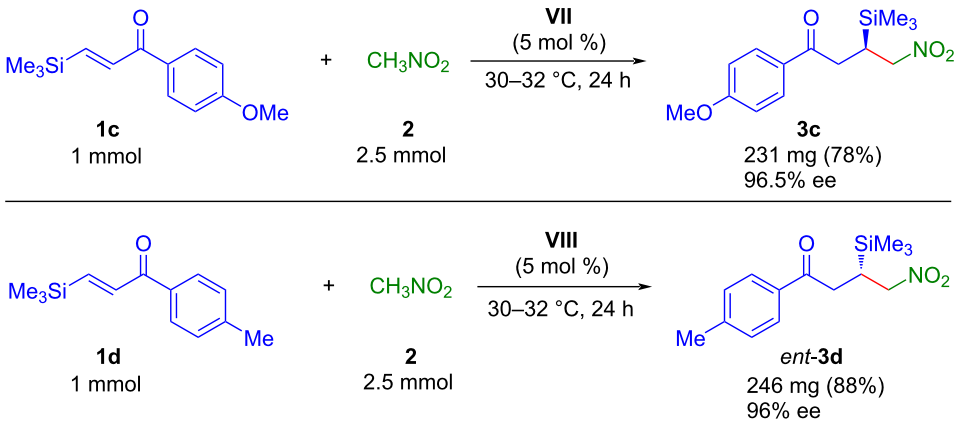
To prove the scalability of this synthetic method, we examined the synthesis of **3c** and *ent*-**3d** in a 1 mmol scale (Scheme 5). The products **3c** and *ent*-**3d** were isolated even with better yields while the enantiomeric excess was unperturbed.

Conclusion

In summary, we have outlined bifunctional squaramide-catalyzed 1,4-conjugate addition reaction of nitromethane to β-silyl α,β-unsaturated carbonyl compounds to access a series of chiral β-silyl nitroalkanes in high yields and good to excellent enantioselectivities at room temperature. The notable features of this reaction are access to both the (*R*) and (*S*) enantiomers of the products, solvent-free synthesis, mild reaction conditions, low catalyst loading, and use of only a small excess of nitromethane (2.5 equivalents with respect to limiting reagent).



Scheme 4: Organocatalytic 1,4-conjuagte addition of nitromethane (**2**) to enone **3o**.



Scheme 5: Preparative scale synthesis of **3c** and *ent*-**3d**.

Supporting Information

Supporting Information File 1

Experimental data and copies of spectra.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-17-177-S1.pdf]

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ORCID® iDs

Raghunath Chowdhury - https://orcid.org/0000-0002-0395-7014

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44. The ratio of **3o**/**4** = 90:10 (determined by ^{1}H NMR analysis of the crude reaction mixture).
45. The crystallographic data (CCDC 2097263) for *ent*-**3k**, can be obtained free of charge from the Cambridge crystallographic Data Centre via http://www.ccdc.cam.ac.uk/data_request/cif.

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Bifunctional thiourea-catalyzed asymmetric [3 + 2] annulation reactions of 2-isothiocyanato-1-indanones with barbiturate-based olefins

Jiang-Song Zhai and Da-Ming Du*

Full Research Paper

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Address:
School of Chemistry and Chemical Engineering, Beijing Institute of Technology, No.5 Zhongguancun South Street, Beijing 100081, People's Republic of China

Email:
Da-Ming Du* - dudm@bit.edu.cn

* Corresponding author

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Abstract

Bifunctional thiourea-catalyzed asymmetric [3 + 2] annulation reactions of 2-isothiocyanato-1-indanones with barbiturate-based olefins have been developed to afford chiral dispiro[indene-pyrrolidine-pyrimidine]s. Through this strategy, the target products could be obtained in good to excellent yields with excellent stereoselectivities. In addition, the synthetic utility was verified through a gram-scale synthesis, one-pot three-component reactions and further transformation experiments of the products.

Introduction

Indane scaffolds exist in various biologically active natural products and pharmaceutical compounds with antipsychotic and antifungal activities, such as SB 209670, indatraline, tefludazine, mutisianthol, rasagiline, and ramelteon (Figure 1) [1-5]. Therefore, this structural motif has attracted great attention of researchers in the field of synthetic organic chemistry and pharmaceutical chemistry all over the world. In the previous few decades, a large number of strategies emerged to construct heterocyclic compounds with this skeleton or similar ones [6-10], aiming to explore biological activity and medicinal value conveniently and comprehensively. However, as we know, the construction of these compounds is mostly carried out through transition-metal-catalyzed cyclization reactions [11-14], whereas strategies using bifunctional chiral thiourea catalysts are rarely reported. In 2018, Du's group reported a novel cascade reagent with the indane framework, namely, 2-isothiocyanato-1-indanone (Scheme 1a) [15], but research on its participation in the construction of chiral compounds has been relatively low [16,17].

On the other hand, as a kind of vital spiroheterocyclic derivatives, spirobarbiturates show a wide range of significant pharmacological and physiological activities in the medical and biological fields (Figure 2) [18-21]. For instance, compound **A**

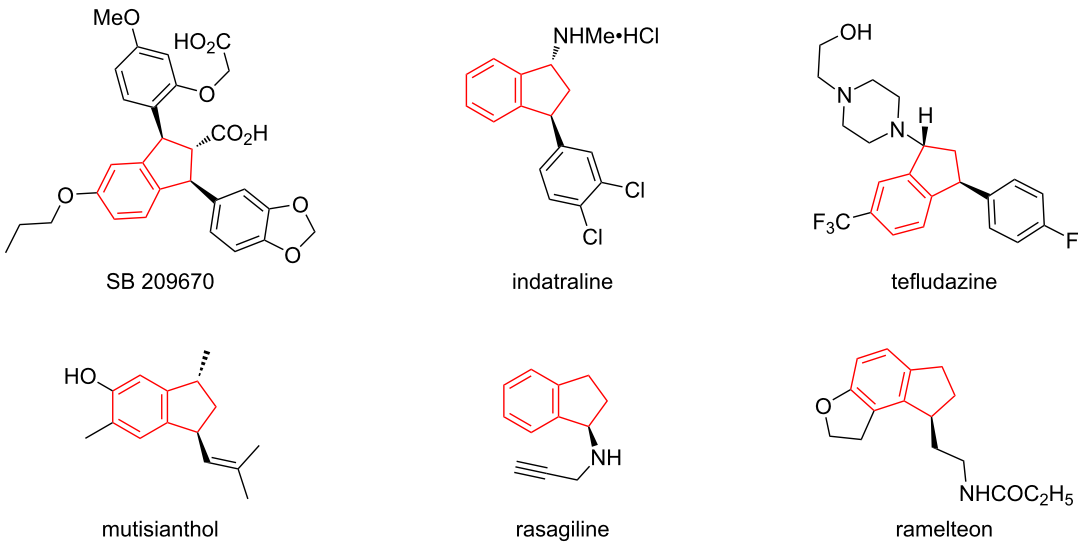
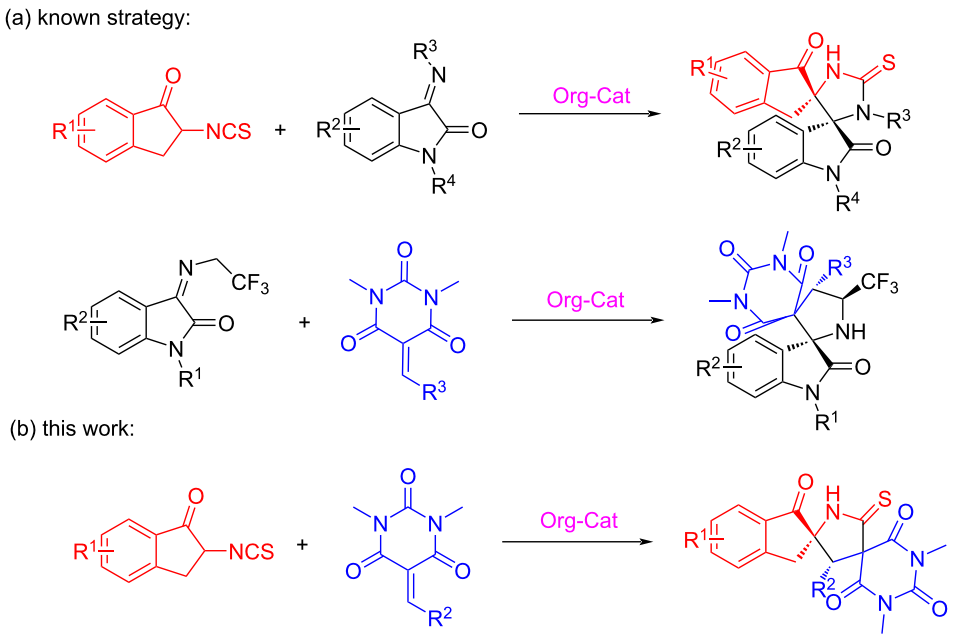


Figure 1: Selected examples of natural products and drugs possessing the indane scaffold.



Scheme 1: Known strategies and conceptual advance of this contribution.

displays anticonvulsant activity and compound **C** can be used as an antifungal agent [22,23]. This impels the quest to develop a series of synthons or new methodologies to construct the spirobarbiturates with diverse structures. In recent years, good progress has been achieved in the construction of racemates of spirobarbiturates and the enantioselective synthesis [24-29], but only limited progress has been made in the construction of bispirobarbiturates [30,31]. In 2019, for example, An and co-workers reported an asymmetric Michael/Mannich [3 + 2] cycloaddition reaction between *N*-(2,2,2-trifluoroethyl)isatin ketimines and barbiturate-based olefins (Scheme 1a) [32]. Based on the current knowledge, the construction of dispirobarbiturates containing the indane skeleton has not been reported yet.

In light of the prominent bioactivities and the pharmacological activity of the above two framework compounds, the combination of these two species may be potential drug candidates.

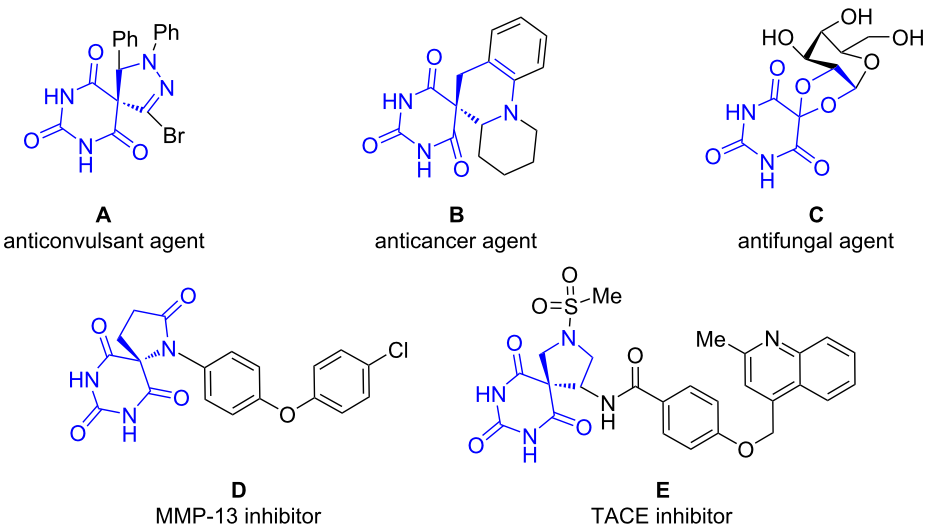


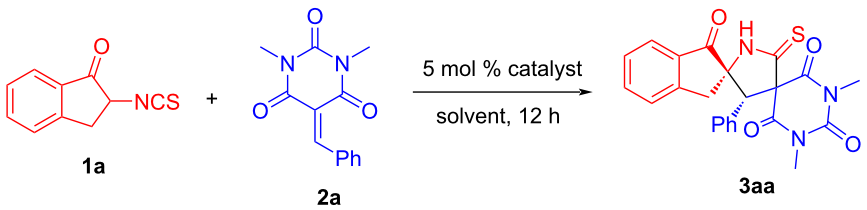
Figure 2: Selected examples of bioactive spirobarbiturates.

Therefore, it is of great significance to develop a new strategy to construct a series of spirobarbiturates derived from indanone. Combining current researches of these two compounds, we report the first organocatalytic asymmetric Michael addition/cyclization reaction between barbituric acid-derived olefins and indanones (Scheme 1b). Under the action of the bifunctional thiourea catalyst, a series of target products in excellent yields with excellent stereoselectivities can be obtained under mild conditions in this reaction. Notably, this protocol provides direct access to indanone-derived spirobarbiturates, which are difficult to access with other methods.

Results and Discussion

To verify the feasibility of the reaction, the domino Michael addition/cyclization reaction of 2-isothiocyanato-1-indanone (**1a**) and barbiturate-based olefin **2a** was used as a model reaction, which was carried out in dichloromethane (DCM) with 5 mol % quinine-derived squaramide **C1** at room temperature. The results are summarized in Table 1. We were pleased to find that the domino Michael addition/cyclization reaction could complete in the presence of 5 mol % **C1** at room temperature in 12 h providing the desired product **3aa** in 55% yield with excellent stereoselectivity (>20:1 dr, 97% ee) (Table 1, entry 1). Due to

Table 1: Optimization of the reaction conditions[a].



1a + **2a** → **3aa**

Entry	Solvent	Catalyst	Yield[b] (%)	dr[c]	ee[d] (%)
1	DCM	**C1**	55	>20:1	97
2	DCM	**C2**	57	>20:1	89
3	DCM	**C3**	61	>20:1	97
4	DCM	**C4**	81	>20:1	97
5	DCM	**C5**	79	>20:1	96
6	DCM	**C6**	65	>20:1	94
7	DCM	**C7**	84	>20:1	94
8	DCM	**C8**	82	>20:1	96

Table 1: Optimization of the reaction conditions[a]. (continued)

9	$CHCl_3$	**C4**	83	>20:1	94
10	PhMe	**C4**	80	>20:1	95
11	THF	**C4**	81	>20:1	86
12	MeCN	**C4**	79	>20:1	94
13	DCE	**C4**	72	>20:1	96
14	dioxane	**C4**	81	>20:1	96
15	EtOAc	**C4**	74	>20:1	93
16[e]	DCM	**C4**	76	>20:1	94

[a]Unless otherwise specified, the reactions were carried out with **1a** (0.12 mmol), **2a** (0.10 mmol) and catalyst (5 mol %) in solvent (1.0 mL) at room temperature for 12 h. [b]Isolated yield after column chromatography purification. [c]Determined by ^{1}H NMR analysis. [d]Enantiomeric excess (ee) was determined by HPLC analysis. [e]2.5 mol % catalyst was used and reaction time was 18 h.

the excellent stereoselectivity of the target product **3aa**, the reaction conditions were further optimized to increase its yield.

Subsequently, a number of organocatalysts (Figure 3) were evaluated for this domino process (Table 1, entries 2–8). From the experimental results, it was found that the yield of product did not increase significantly with the cinchona alkaloid-derived squaramide catalysts (Table 1, entries 2 and 3). Consequently, we decided to explore the effects of different types of catalysts on the reaction. Through experiments, it can be found that thiourea catalysts (**C4**–**C7**) can catalyze the reaction to obtain higher yields while keeping the stereoselectivity basically unchanged. Then we chose the **C4** catalyst with the best reaction effect as the optimal catalyst to explore the influence of other

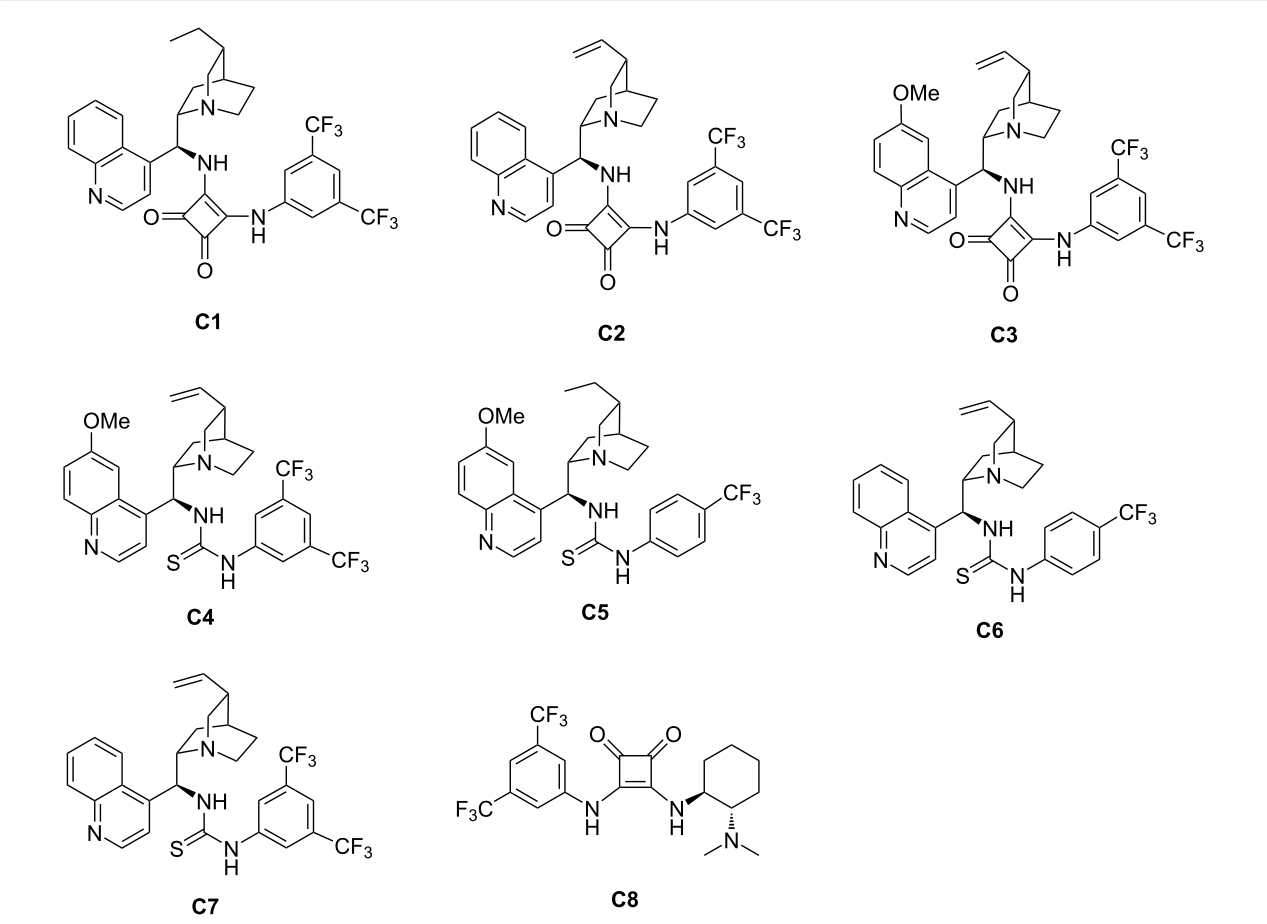
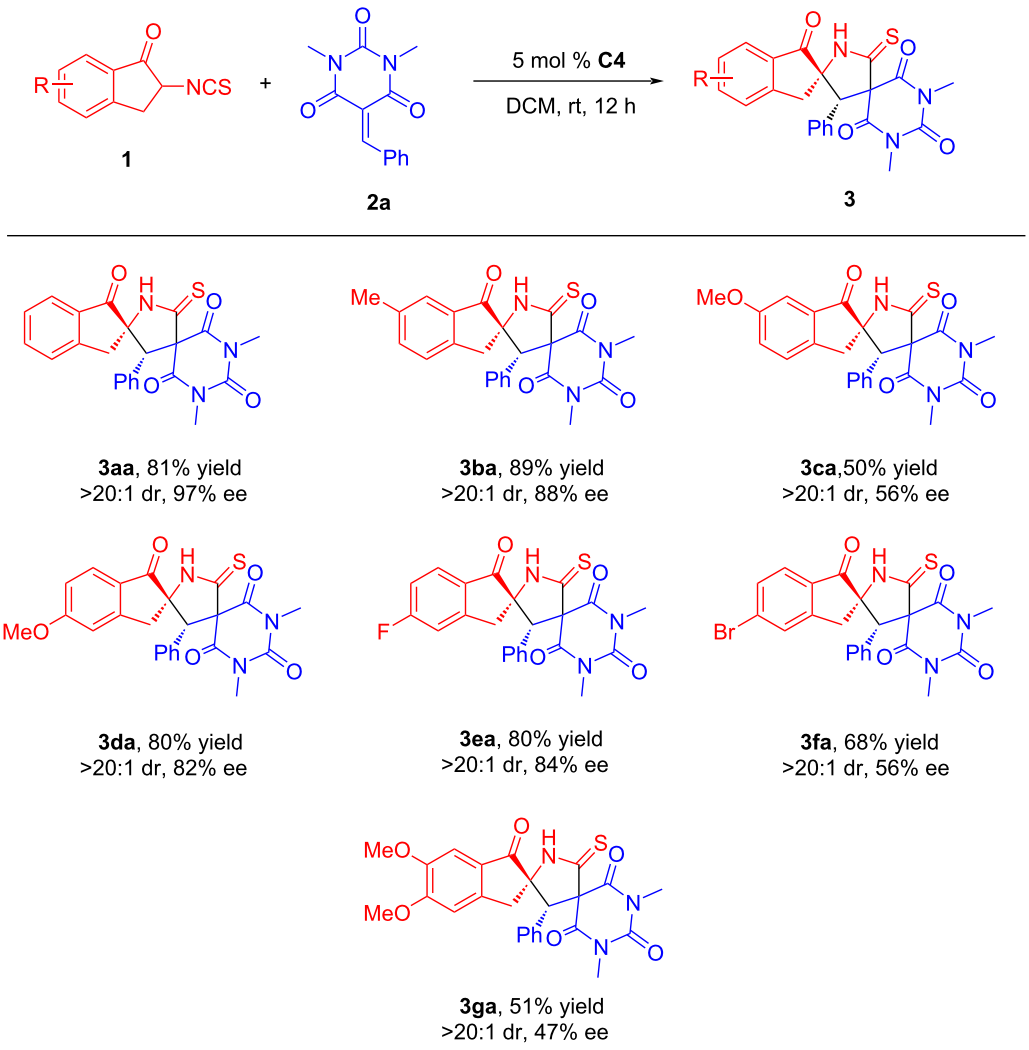


Figure 3: The screened organocatalysts.

reaction conditions such as solvent type and catalyst loading on the reaction (Table 1, entries 9–16). The experimental results show that the solvent has a non-negligible effect on the reaction and dichloromethane (DCM) has the best reaction effect in the annulation system (Table 1, entries 9–15). Hereafter, we tried to reduce the catalyst loading to further improve the reaction yield and enantioselectivity, but it did not meet our expectations (Table 1, entry 16). Taking into account the ease of operation of the experiment and for economic reasons, we did not explore the effect of increasing the catalyst loading and changing the reaction temperature on the reaction. Based on the above evaluation, we finally selected 2-isothiocyanato-1-indanones **1** and barbiturate-based olefins **2** with a molar ratio of 1.2:1 to react for 12 h at room temperature in DCM using 5 mol % of catalyst **C4** as the optimum reaction conditions.

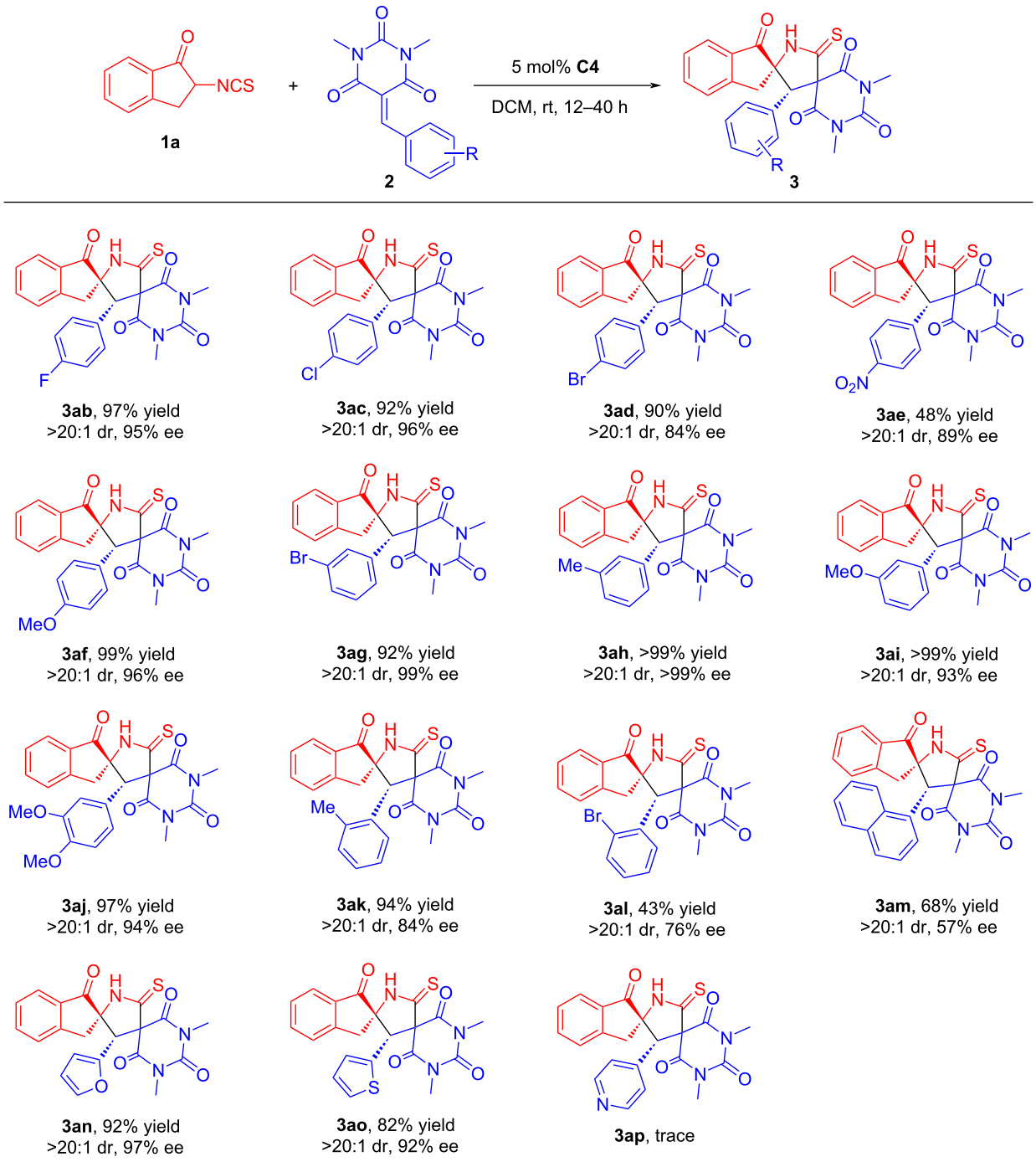
With the optimum reaction conditions established, we then commenced to probe the substrate scope and limitations of this reaction. As summarized in Scheme 2, a variety of 2-isothiocyanato-1-indanones **1** were firstly tested under the optimized conditions. When a methyl substituent is located at the 6-position of the indanone, the reaction yield of the product **3ba** was higher than that of the model reaction, but the enantioselectivity was partially reduced. When the 5-position of the indanone was substituted by either F or a MeO group, the yield remained nearly unchanged, however, the enantioselectivity was slightly reduced. On the other hand, when the 5-position of the indanone was substituted by Br, the 6-position was substituted by a MeO group, and the 5 and 6-positions are simultaneously substituted by a MeO group, the yields and stereoselectivities of the reactions significantly dropped. This indicates that the position of



Scheme 2: Substrate scope of 2-isothiocyanato-1-indanones. The reactions were carried out with **1** (0.12 mmol), **2a** (0.10 mmol), and catalyst (5 mol %) in solvent (1.0 mL) at room temperature for 12 h. The yields refer to the isolated products after column chromatography. The diastereoisomeric ratios (dr values) were determined by ^{1}H NMR spectroscopy and the enantiomeric excess (ee) values were determined by HPLC analysis.

the substituent has a great influence on the reaction. Gratifyingly, the diastereoselectivities of the reactions were maintained.

To further explore the generality of this reaction, structurally diverse barbiturate-based olefins **2** were examined under the standard conditions by reacting with **1a**. As shown in Scheme 3, in addition to substrates **3ae** and **3al**, it appeared that the reaction could well tolerated the presence of electron-donating and electron-withdrawing groups on the benzene ring of substrates **2**, and afforded most of the products **3** in excellent chemical yields (90 to >99%) and stereoselectivities (>20:1 dr,



Scheme 3: Substrate scope of barbiturate-based olefins. The reactions were carried out with **1a** (0.12 mmol), **2** (0.10 mmol) and catalyst **C4** (5 mol %) in solvent (1.0 mL) at room temperature for 12–40 h. The yields refer to isolated products after column chromatography. The diastereoisomeric ratios (dr values) were determined by ^{1}H NMR spectroscopy and the enantiomeric excess (ee) values were determined by HPLC analysis.

84–>99% ee). Possibly due to the influence of steric hindrance, reactions involving substrate **2** with *ortho*-substitution on the benzene ring has lower yields and worse enantioselectivities than those with *meta*-substitution and *para*-substitution. Meanwhile, the enantioselectivities of the products **3am** and **3ao** were partially decreased when the R^1 group was substituted by naphthyl and thienyl, respectively. It was a good result that R^1 was substituted by furyl. Unfortunately, when the R^1 was a pyridyl group, the product was obtained in trace amounts. This may be partly related to the poor solubility of this substrate.

The absolute configuration of the chiral product **3ae** was unambiguously identified on the basis of single-crystal X-ray diffraction analysis as (2*S*,3'*S*) (Figure 4) [33]. The configurations of the other products were assigned by analogy to **3ae**.

In order to further prove the application value of this asymmetric domino Michael addition/cyclization reaction, a gram-scale experiment was performed under the optimized conditions. As exemplified in Scheme 4, the desired dispiro[indene-pyrrolidine-pyrimidine] **3ah** could be obtained in 94% yield with excellent stereoselectivity (>20:1 dr, >99% ee), which indicated this strategy shows promising prospects for mass production.

Moreover, two different transformations of the product **3ah** are shown to validate synthetic utility of the reaction. As demonstrated in Scheme 5, the dispiro[indene-pyrrolidine-pyrimidine] **3ah** could be easily oxidized to compound **4** with *m*-chloroperbenzoic acid under mild conditions, and compound **4** can basically maintain the original excellent stereoselectivity (Scheme 5a). Meanwhile, we are pleased that methylation of **3ah** took place easily to afford product **5** in 95% chemical yield with 99% ee and >20:1 dr under the basic reaction conditions (Scheme 5b).

A one-pot reaction of three available starting materials was tested using CH_2Cl_2 as the solvent. The one-pot reaction of 1,3-dimethylbarbituric acid (**6**), benzaldehyde (**7**), and 2-isothiocyanato-1-indanone (**1a**) proceeded smoothly to provide the desired product **3aa** in 80% yield with 95% ee and >20:1 dr (Scheme 6a). In addition, the one-pot reaction of 1,3-dimethylbarbituric acid (**6**), *m*-bromobenzaldehyde (**8**), and 2-isothiocyanato-1-indanone (**1a**) was also investigated, and the reaction

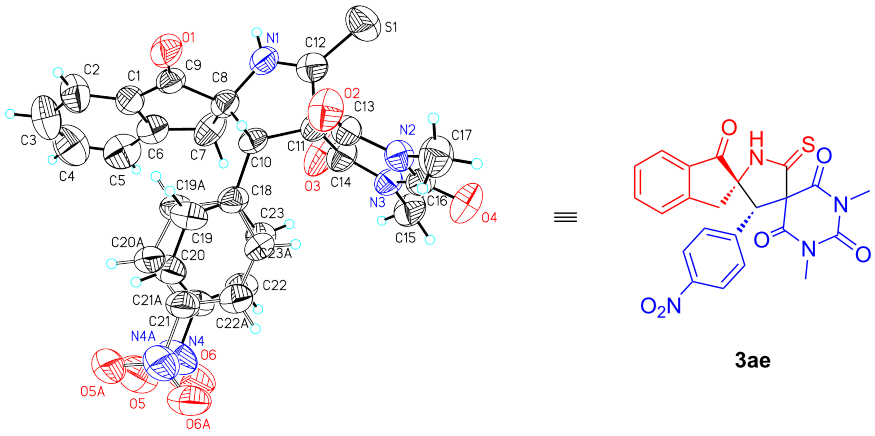
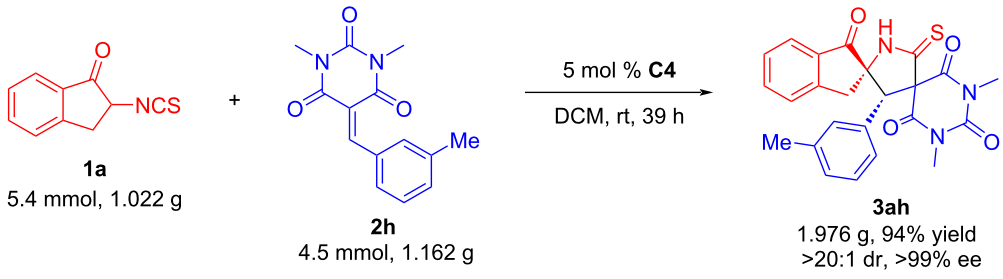
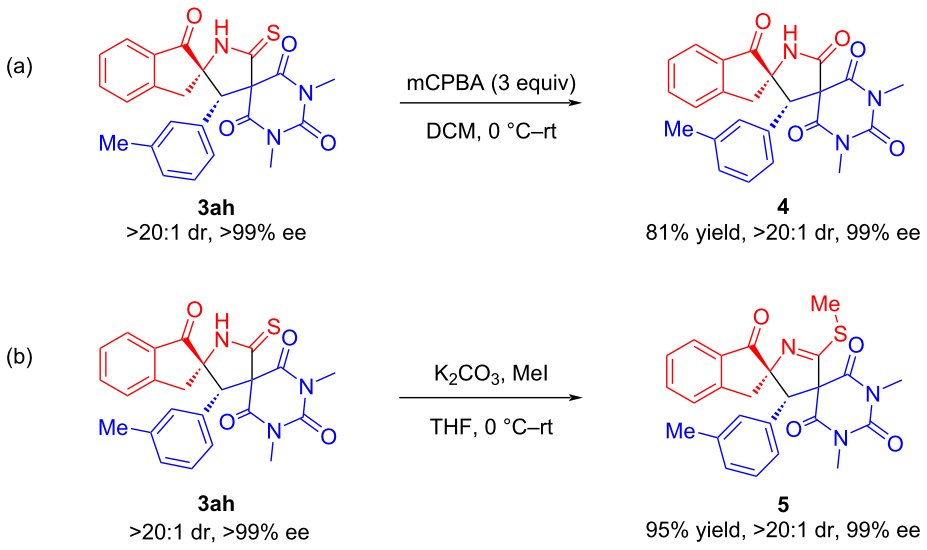


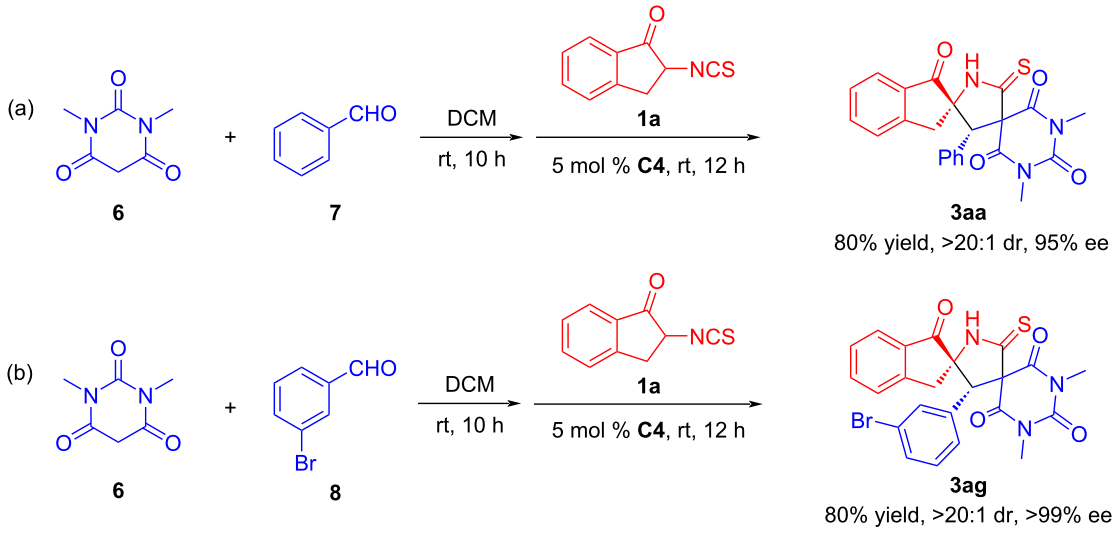
Figure 4: X-ray crystal structure of **3ae** (displacement ellipsoids are drawn at the 50% probability level).



Scheme 4: Gram-scale synthesis of **3ah**.



Scheme 5: Further transformation of **3ah**.



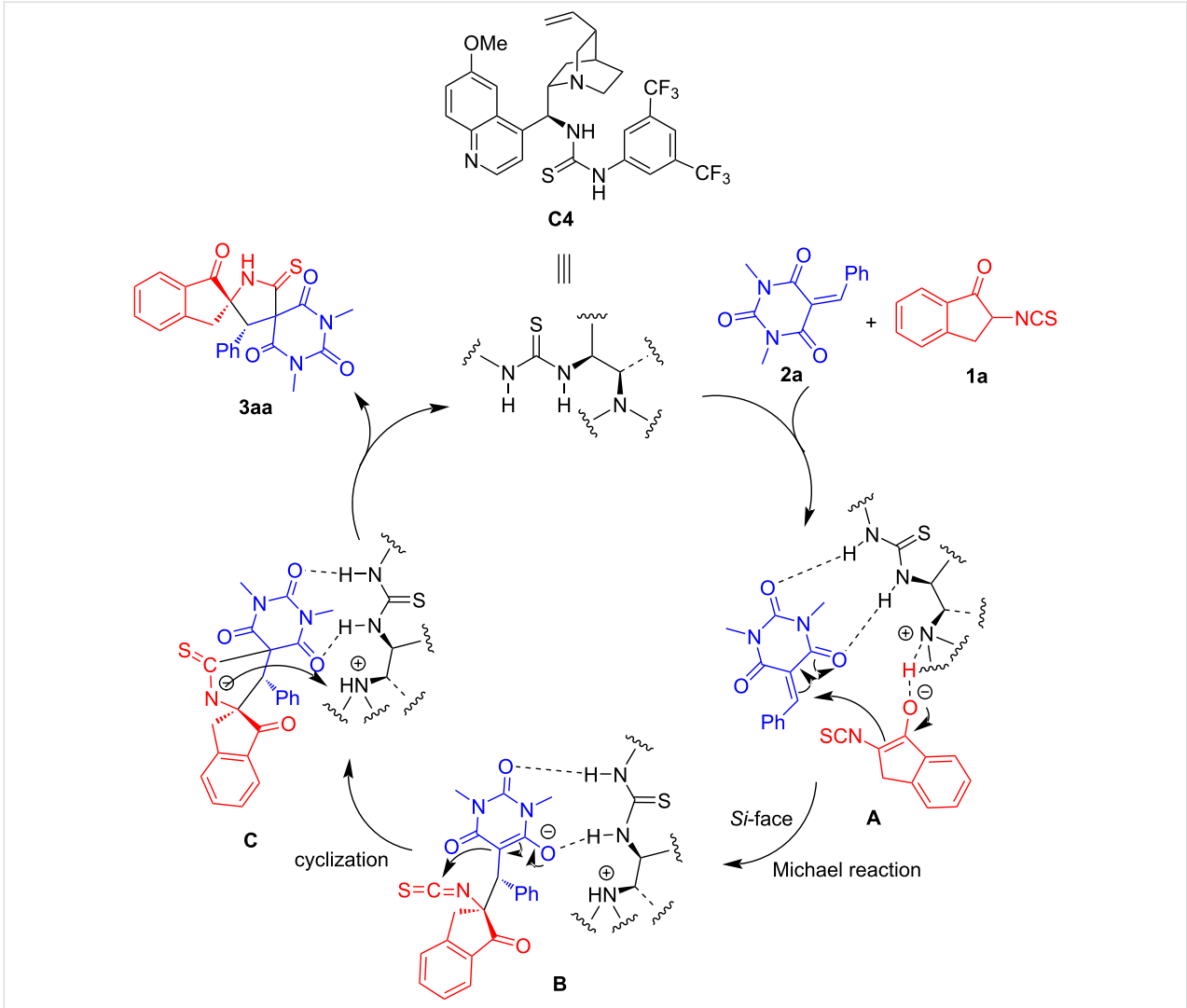
Scheme 6: One-pot three-component reaction.

yield (80%) was lower than before, but the stereoselectivity (>20:1 dr, >99% ee) could still be maintained (Scheme 6b). This one-pot three-component reaction would be more convenient for potential industrial applications.

Finally, in order to understand the enantioselective formation process of product **3**, we proposed the possible mechanisms for the [3 + 2] cyclization reaction of **1a** and **2a** based on the previously published work. As illustrated in Scheme 7, in this cycle, it is reasonable that the catalyst **C4** activates barbiturate-based olefins **2a** through the action of hydrogen bonds, and then the 2-isothiocyanato-1-indanone **1a** tautomerizes to form the corresponding enol under the action of catalyst **C4**. Simultaneously, deprotonated **1a** attacks the double bond of **2a** from the *Si* face via intermediate **A**, resulting in a Michael addition reaction. Then the electron-deficient isothiocyanate moiety is attacked by newly generated α-carbon center from barbiturate-based olefins **2a** to form intermediate **B**. Finally, the catalyst **C4** is removed in intermediate **C** and the product **3aa** is obtained.

Conclusion

In summary, we have successfully developed an exceptionally efficient strategy for the enantioselective construction of indanone-derived spirobarbiturates through a simple organocat-



Scheme 7: Proposed reaction mechanism.

alytic domino Michael/cyclization reaction. This annulation reaction can be easily performed under air atmosphere and mild conditions with 5 mol % catalyst loading. By using bifunctional thiourea catalyst, a series of structurally diverse indanone-derived spirobarbiturates could be obtained in high yields and excellent diastereo- and enantioselectivities (up to >99% yield, >20:1 dr and >99% ee). In addition, a gram-scale synthesis, one-pot three-component reactions and further transformation experiments of the products were also demonstrated with excellent stereoselectivities. We believe that the availability of these compounds will provide promising candidates for chemical biology and drug discovery.

Experimental

General information

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. Column chromatography was performed with silica gel (200–300 mesh). Melting points were determined with an XT-4 melting-point apparatus and are uncorrected. ^{1}H NMR spectra were measured with a Bruker Ascend 400 MHz spectrometer, chemical shifts are reported in δ (ppm) units relative to tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were measured at 100 MHz with a 400 MHz spectrometer or at 176 MHz with a 700 MHz spectrometer, chemical shifts are reported in δ (ppm) units relative to tetramethylsilane and referenced to solvent peak ($CDCl_3$, δ = 77.00 ppm; DMSO-d_6, δ = 39.43 ppm). High-resolution mass spectra were measured with an Agilent 6520 Accurate-Mass Q-TOF MS system equipped with an electrospray ionization (ESI) source. Optical rotations were measured with a Krüss P8000 polarimeter at the indicated concentration with the units of g/100 mL. Enantiomeric excesses were determined by chiral HPLC analysis using an Agilent

1200 LC instrument with a Daicel Chiralpak IB, IC, or ADH column.

The following compounds were prepared following procedures reported in the literature: **1a**–**g** [15], **2a**–**o** [34], and chiral organocatalysts [35-38].

1. Procedure for the synthesis of racemates of **3**

To a dried small bottle were added **1** (0.06 mmol), **2** (0.05 mmol), Et_3N (1.0 mg, 0.01 mmol, 0.2 equiv), and DCM (1.0 mL). The mixture was stirred at room temperature for 12 h, then the reaction mixture was concentrated and directly purified by silica gel column chromatography to afford the racemates of **3**.

2. Procedure for the synthesis of chiral compounds **3**

To a dried small bottle were added **1** (0.12 mmol), **2** (0.10 mmol), chiral organocatalyst **C4** (2.7 mg, 0.005 mmol, 5 mol %), and DCM (1.0 mL). The mixture was stirred at room temperature for 12–40 h, then the reaction mixture was concentrated and directly purified by silica gel column chromatography to afford the desired products **3**.

3. Gram-scale synthesis of **3ah**

2-Isothiocyanato-2,3-dihydro-1*H*-inden-1-one (**1a**, 1.022 g, 5.4 mmol), 1,3-dimethyl-5-(3-methylbenzylidene)pyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (**2h**, 1.162 g, 4.5 mmol), and catalyst **C4** (122.4 mg, 5 mol %) were dissolved in dry DCM (45 mL) at room temperature. After stirring at room temperature for 39 h, the reaction mixture was concentrated, and directly purified by silica gel column chromatography (dichloromethane/ethyl acetate/petroleum ether 1:1:5) to afford the desired product **3ah** as white solid (1.976 g, 94% yield) with >20:1 dr and >99% ee.

4. Synthetic procedure for compound **4**

The synthesis of compound **4** was similar to the reported method in the literature [39]. In a 5 mL small bottle, compound **3ah** (44.8 mg, 0.10 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (2 mL) and the bottle was placed in an ice-water bath. Then *m*-CPBA (≈85%, 60.9 mg, 0.30 mmol, 3.0 equiv) was added to the reaction mixture at 0 °C. After completion of the addition, the reaction mixture was slowly warmed to room temperature and allowed to stir overnight. The residue was purified by silica gel column chromatography (petroleum ether/ethyl acetate 2:1) to give pure compound **4** as a white solid (35.1 mg, 81% yield).

5. Synthetic procedure for compound **5**

The synthesis of compound **5** was similar to the reported method in the literature [39]. To an oven dried 5 mL small bottle were added compound **3ah** (44.8 mg, 0.10 mmol, 1.0 equiv), dry K_2CO_3 (21.0 mg, 0.23 mmol, 1.50 equiv), and THF (2 mL). The solution was cooled to 0 °C and iodomethane (12.5 µL, 0.20 mmol, 2.0 equiv) was added dropwise to the reaction mixture. After completion of the addition, the reaction mixture was gradually warmed to room temperature and allowed to stir overnight. The residue was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate 4:1) to give pure compound **5** as white solid (44.0 mg, 95% yield).

6. One-pot three-component reaction for the synthesis of **3aa**

1,3-Dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (15.6 mg, 0.10 mmol) and benzaldehyde (10.6 mg, 0.10 mmol) were dissolved in anhydrous CH_2Cl_2 (1.0 mL) and stirred at room temperature for 10 h. Then, catalyst **C4** (2.7 mg, 5 mol %) and compound **1a** (22.7 mg, 0.12 mmol) were added. After stirring at room temperature for another 12 h, the reaction mixture was concentrated and directly purified by silica gel column chromatography (dichloromethane/ethyl acetate/petroleum ether 1:1:5) to afford the desired product **3aa** as white solid (35.5 mg, 80% yield) with >20:1 dr and 95% ee.

7. One-pot three-component reaction for the synthesis of **3ag**

1,3-Dimethylpyrimidine-2,4,6(1*H*,3*H*,5*H*)-trione (15.6 mg, 0.10 mmol) and *m*-bromobenzaldehyde (18.5 mg, 0.10 mmol) were dissolved in anhydrous CH_2Cl_2 (1.0 mL) and stirred at room temperature for 10 h. Then, catalyst **C4** (2.7 mg, 5 mol %) and compound **1a** (22.7 mg, 0.12 mmol) were added. After stirring at room temperature for another 12 h, the reaction mixture was concentrated and directly purified by silica gel column chromatography (dichloromethane/ethyl acetate/petroleum ether 1:1:5) to afford the desired product **3ag** as a white solid (41.0 mg, 80% yield) with >20:1 dr and >99% ee.

Supporting Information

Supporting Information File 1

Characterization data, copies of NMR spectra, and HPLC chromatograms of products.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-3-S1.pdf]

Supporting Information File 2

Crystallographic data of compound **3ae**.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-18-3-S2.cif]

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ORCID® iDs

Da-Ming Du - https://orcid.org/0000-0002-9924-5117

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