New advances in asymmetric organocatalysis II

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Towards an asymmetric β-selective addition of azlactones to allenoates

Behzad Nasiri‡1,2, Ghaffar Pasdar‡1, Paul Zebrowski1, Katharina Röser1, David Naderer1 and Mario Waser*1

Abstract

We herein report the asymmetric organocatalytic addition of azlactones to allenoates. Upon using chiral quaternary ammonium salt catalysts, i.e., Maruoka’s binaphthyl-based spirocyclic ammonium salts, the addition of various azlactones to allenoates proceeds in a β-selective manner with moderate levels of enantioselectivities (up to 83:17 er). Furthermore, the obtained products can be successfully engaged in nucleophilic ring opening reactions, thus giving highly functionalized α-amino acid derivatives.

Introduction

The development of asymmetric synthesis routes to access non-natural amino acids has for decades been one of the most heavily investigated tasks in organic synthesis and catalysis-oriented research [1-13]. As a consequence, a broad variety of conceptually orthogonal strategies to access differently functionalized non-natural α-amino acids (α-AA) [2-7] as well as β-amino acids (β-AA) [8-13] have been introduced and there is still considerable interest in the development of new concepts and synthesis approaches. Our group has a longstanding focus on the development of asymmetric organocatalytic methods to access non-natural chiral α- and β-AA [14-19]. Hereby we are especially interested in utilizing simple (prochiral) starting materials and carry out stereoselective α-functionalizations by reacting them with suited C- or heteroatom electrophiles. α-Amino acid-derived azlactones I are amongst the most commonly utilized starting materials to access more diverse chiral α,α-disubstituted amino acids (Scheme 1A) [20-22]. More specifically, these compounds can be engaged in a variety of asymmetric α-carbo- and α-heterofunctionalization reactions by utilizing different catalysis strategies [20-22]. We have recently carried out systematic investigations concerning the syntheses of advanced β-AA by means of asymmetric α-carbofunctional-
ization reactions and during these studies we also realized that the masked β-AA derivatives 2 undergo enantioselective β-addition to allenoates 3 under chiral ammonium salt catalysis (Scheme 1B) [18]. Interestingly, hereby we also found that the use of alternative catalyst systems (i.e., tertiary phosphines) allows for a γ-selective addition of 2 to the allenoate instead, thus resulting in two complementary catalyst-controlled pathways [18]. Based on these previous results, and also the well-documented different reactivity trends of allenoates 3 when using different organocatalysts and activation modes [23–27], we were thus wondering if we could extend this ammonium salt-catalyzed β-selective allenoate functionalization strategy to other amino acid classes. Azlactones 1 have previously been used for γ-selective additions to allenoates under chiral phosphine catalysis [28]. In addition, glycine Schiff base derivatives [29] as well as α-amino acid-based thiazolones [30] have successfully been used for asymmetric β-selective additions to allenoates when using chiral ammonium salt catalysts or chiral organobase catalysts. However, to the best of our knowledge the β-selective asymmetric addition of azlactones 1 to allenoates 3 delivering highly functionalized α,α-disubstituted α-amino acid derivatives 5 has so far not been systematically addressed (for recent other β-selective additions of enolates precursors to allenoates please see references [31–34]). Thus, we now became interested in testing this transformation under asymmetric ammonium salt catalysis [35–38] and the results of these investigations are outlined in this contribution (Scheme 1C).

Results and Discussion

We started our investigations by testing the quaternary ammonium salt-catalyzed addition of azlactone 1a to allenoate 3a (Table 1 gives an overview of the most significant results obtained hereby). First experiments using cinchona alkaloid-based quaternary ammonium salts A showed that the expected β-addition product 5a could be accessed under typical phase-transfer conditions, but with low selectivities and yields only when using these catalysts (Table 1, entries 1–4, other cinchona alkaloid-based ammonium salt derivatives as well as free base cinchona alkaloids were tested too but did not allow for any improvement). Using the established and commercially available Maruoka catalysts B1 and B2 [39] next turned out to be more promising (Table 1, entries 5–8). Testing the bis-CF3-substituted B1 first allowed for 75:25 er, but with moderate yield only when carrying out the reaction in toluene in the presence of 3 equiv of K2CO3 (Table 1, entry 5). Lower amounts of base (Table 1, entry 6) or other solvents, as exemplified for CH2Cl2 (Table 1, entry 7, similar non-selective results were obtained when using THF), were found to be less-suited however. Testing the 3,4,5-trifluorobenzene-decorated catalyst B2 with K2CO3 in toluene next (Table 1, entry 8) allowed for a slightly higher selectivity but still gave only a relatively low yield. Spirohindane-based salts C emerged as promising alternative for quaternary ammonium salt catalysts recently [40,41] and were also the catalysts of choice in our recently developed β-selective allenoate addition of isoxazolidinones 2 (compare with Scheme 1B [18]). Unfortunately, these catalysts were found to be less-suited for our azlactone protocol, as exemplified for derivative C1 (Table 1, entry 9). Accordingly, we carried out our final optimization using Maruoka’s catalyst B2 (Table 1, entries 10–14). By testing different bases and lower temperatures as well as lower catalyst loadings we identified the use of 3 equiv Cs3CO3 in toluene (0.05 M) at room temperature as the best-suited conditions (Table 1, entry 13), allowing for the synthesis of 5a in moderate yield (61%) and enantioselectivity (81:19 er).

With optimized conditions for the synthesis of enantioenriched (−)-5a at hand, we next investigated the generality of this protocol. As outlined in Scheme 2, differently substituted allenoates were reasonably well tolerated (see products 5a–d), albeit some erosion in enantioselectivity was observed when using a tert-butyl ester containing allenoate (product 5d). Various α-arylmethyl-substituted azlactones 1 performed similarly as compared to the parent system 1a (products 5e–i), and analogous α-alkyl-substituted derivatives were reasonably well accepted too (5j–o). When varying the aryl substituent in position 2 of the oxazolone core (compare products 5a, 5g, and 5p) we found that increasing the steric bulk (5p) leads to a somewhat lower enantioselectivity, while the methoxy-substituent

Scheme 1: General use of azlactones 1 to access more advanced α-AA derivatives (A), our recently reported ammonium salt-catalyzed β-selective addition of compounds 2 to allenoates 3 (B), and the herein investigated β-selective addition of azlactones 1 to allenoates 3 (C).
Table 1: Optimization of the addition of azlactone 1a to allenoate 3a.  

<table>
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<th>Entry</th>
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</table>

[^a]: Unless otherwise stated, all reactions were carried out by stirring 1a (0.1 mmol), the allenoate (2 equiv), the indicated base and the catalyst, in the given solvent (0.05 M based on 1a) at the given temperature for 24 h.  
[^b]: Isolated yield.  
[^c]: Determined by HPLC using a chiral stationary phase, (-)-5a was obtained as the major enantiomer when using the (R,R)-configured catalysts B.

Table data does not have a strong impact on the yield. It should, however, be stated that some of the methoxy-containing products, i.e., the α-alkyl-substituted 5j and 5k tend to undergo partial nucleophilic ring opening by residual water during column chromatography. Unfortunately, attempts to assign the absolute configuration of products 5 failed, as we have not been able to obtain any crystals suited for single crystal X-ray diffraction analysis.

Finally, we also tested the suitability of products 5 to access acyclic α-AA derivatives by means of nucleophilic azlactone-opening reactions. Gratifyingly primary amines can be easily utilized under reflux conditions to access the amide derivatives 6a and 6b straightforwardly (Scheme 3), thus demonstrating the versatility of compounds 5 to access more complex acyclic α-AA derivatives in a straightforward manner.

**Conclusion**

The development of novel catalytic methods for the asymmetric synthesis of non-natural amino acid derivatives is a contemporary task and we herein introduce an organocatalytic protocol for the β-selective addition of various azlactones 1 to allenoates 3. Upon using Maruoka’s spirocyclic binaphthyl-based quaternary ammonium salts B as catalysts this transformation can be achieved with enantioselectivities up to 83:17 er. Furthermore, the herein accessed cyclic products 5 could be successfully engaged in ring-opening reactions with different
amines, thus giving access to the acyclic α-amino acid-based amides 6 straightforwardly.

**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. All NMR spectra were referenced on the solvent residual peak (CDCl$_3$: $\delta$ 7.26 ppm for $^1$H NMR and $\delta$ 77.16 ppm for $^{13}$C NMR). NMR data are reported as follows: chemical shift ($\delta$ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), coupling constants (Hz), relative integration value. High-resolution mass spectra were obtained using a Thermo Fisher Scientific LTQ Orbitrap XL spectrometer with an Ion Max API source and analyses were made in the positive ionization mode if not otherwise stated. Infrared (IR) spectra were recorded on a Bruker Alpha II FTIR spectrometer with diamond ATR-module using the OPUS software package and are reported in terms of frequency of absorption (cm$^{-1}$). HPLC was performed using a Shimadzu Prominance system with a diode array detector with a CHIRALPAK AD-H, CHIRAL ART Amylose-SA, (250 × 4.6 mm, 5 µm) chiral stationary phase. Optical rotations were recorded on a Schmidt + Haensch Polarimeter Model UniPol L1000 at 589 nm ($[\alpha]_D$ values are listed in deg/(dm(g/cm$^3$))); concentration $c$ is given in g/100 mL).

Unless otherwise stated, all chemicals were purchased from commercial suppliers and used without further purification. Dry solvents were obtained from an MBraun-SPS-800 solvent purification system. All reactions were carried out under argon atmosphere unless stated otherwise. Azlactones 1 and allenoates 3 were synthesized according to previously published procedures [18,42-44].

**General procedure**

An oven-dried Schlenk tube equipped with a stirring bar was charged with azlactone 1 (0.05–0.1 mmol), catalyst B2 (10 mol % related to 1), and Cs$_2$CO$_3$ (3 equiv). Then the respective allenoate 3 (2 equiv) and toluene (0.05 M with respect to 1) were added and the mixture was stirred at room temperature for 24 h (Ar atmosphere). The crude product was passed through a short column of silicagel (rinsed with DCM and EtOAc), concentrated under reduced pressure, and subsequently purified by preparative TLC (silica gel, heptanes/EtOAc 4:1) to obtain the products 2 in the given yields and enantiopurities.
Details for the parent compound 5a (details for the other targets can be found in Supporting Information File 1). Obtained as a colorless oil in 61% yield (81:19 er) on 0.1 mmol scale. [α]D\textsuperscript{22} = −11.4 (c 1.1, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}, 298.0 K) δ/ppm = 7.85 (dd, J = 8.6, 1.4 Hz, 2H), 7.54 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.53 Hz, 2H), 7.24–7.11 (m, 5H), 5.79 (s, 1H), 5.37 (s, 1H), 4.14–3.90 (m, 2H), 3.52–3.16 (m, 4H), 1.15 (t, J = 7.1 Hz, 3H); \textsuperscript{13}C NMR (75 MHz, CDCl\textsubscript{3}, 298.0 K) δ/ppm = 177.4, 171.0, 160.3, 139.1, 133.8, 132.6, 130.5, 128.6, 128.0, 127.8, 127.3, 125.6, 118.1, 75.9, 60.9, 44.9, 39.3, 13.9; IR (neat): 3080, 3070, 2917, 1815, 1732, 1656, 1393, 1378, 1244, 1224, 1191, 1175, 1093, 1059, 1030, 974, 893, 694 cm\textsuperscript{−1}; HRESIMS m/z: [C\textsubscript{22}H\textsubscript{24}NO\textsubscript{4} + H]\textsuperscript{+} calcld for 364.1543; found, 364.1554; HPLC: (Chiralpak SA, eluent: n-hexane/iPrOH = 100:2, 0.5 mL·min\textsuperscript{−1}, 20 °C, λ = 254 nm) retention times: t\textsubscript{major} = 16.15 min, t\textsubscript{minor} = 17.00 min.

Supporting Information
Supporting Information File 1
Full experimental and analytical details and copies of NMR spectra and HPLC traces.

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Data Availability Statement
All data that supports the findings of this study is available in the published article and/or the supporting information to this article.

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References

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Primary amine-catalyzed enantioselective 1,4-Michael addition reaction of pyrazolin-5-ones to α,β-unsaturated ketones

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Abstract

The enantioselective 1,4-addition reaction of pyrazolin-5-ones to α,β-unsaturated ketones catalyzed by a cinchona alkaloid-derived primary amine–Brønsted acid composite is reported. Both enantiomers of the anticipated pyrazole derivatives were obtained in good to excellent yields (up to 97%) and high enantioselectivities (up to 98.5% ee) under mild reaction conditions. In addition, this protocol was further expanded to synthesize highly enantioenriched hybrid molecules bearing biologically relevant heterocycles.

Introduction

N-Heterocycles are attractive molecules owing to their extensive applications in small-molecule drugs, natural products, and agrochemical products [1-3]. Among the N-heterocycles, pyrazole is an important structural scaffold, found in several marketed drugs and bioactive molecules (Figure 1) [4-7]. In addition, this moiety is an integral part of various agrochemical products and chelating agents [4-9]. Given the importance and widespread applications of pyrazoles, considerable efforts have been devoted to develop new protocols to access structurally diverse pyrazole derivatives [4-7,10-12].

4-Unsubstituted pyrazolin-5-ones are well known precursors for the construction of optically active structurally diverse pyrazoles [10-12]. In this context, the organocatalyzed asymmetric Michael addition of 4-unsubstituted pyrazolin-5-ones to a variety of Michael acceptors has emerged as one of the most powerful strategies to access enantioenriched pyrazole derivatives [10-21]. In the majority of these cases, the reactivities of the pyrazolin-5-one derivatives were harnessed under non-covalent catalysis via bifunctional hydrogen-bonding organocatalysts. The C-4 nucleophilicity of pyrazolin-5-ones was also
explored in enantioselective reactions with α,β-unsaturated carbonyl compounds through covalent catalysis with chiral amine-based catalysts; however, it has achieved limited success [10-21].

Among the developed organocatalyzed enantioselective 1,4-addition reactions of pyrazolin-5-ones, the catalytic asymmetric reactions of pyrazolin-5-ones with α,β-unsaturated ketones are comparatively less studied. In 2009, Zhao’s group were the first who reported a chiral amine-catalysedaza-Michael addition reaction of pyrazolin-5-ones with α,β-unsaturated ketones to access β-(3-hydroxypyrazol-1-yl)ketones (Scheme 1a) [22]. The developed reaction was restricted to α,β-unsaturated ketones with aliphatic substituents (Scheme 1a) [22]. Ji and Wang disclosed organocatalyzed [5 + 1] double Michael additions between pyrazolones and dienones (Scheme 1b) [23]. Very recently, the Chimni group reported a cinchona-derived squaramide-catalyzed 1,4-Michael addition reaction of pyrazolin-5-ones with 2-enolpyridazines (Scheme 1c) [24]. Recently, we developed an organocatalyzed asymmetric Michael addition reaction of 4-monosubstituted pyrazolin-5-ones with α,β-unsaturated ketones using cinchona alkaloid-derived primary amine catalysts. The developed protocol delivered both enantiomers of the desired products in good to excellent yields and enantioselectivities.

**Results and Discussion**

At the outset, the reaction between commercially available benzylideneacetone (1a) and 3-methyl-1-phenyl-2-pyrazolin-5-one (2a) was studied in the presence of a panel of primary amine catalysts (see Table S1 in Supporting Information File 1) in toluene at room temperature (30–32 °C). When the test reaction was conducted in the presence of 15 mol % of 9-amino-9-deoxy-epicinchonidine (I) as catalyst [30] for 12 h and treated with Ac2O followed by DABCO, the reaction gave the conjugate addition product 3aa in 58–62% yield with 74% ee (Table 1, entry 1). On the other hand, 9-amino-9-deoxyepicinchonine (II) [30] furnished the opposite enantiomer ent-3aa in 62% yield and 66% ee (Table 1, entry 2). Among the screened organocatalysts (see Table S1 in Supporting Information File 1), the catalyst I imparted the highest enantioselectivity (74% ee) of the Michael product 3aa (Table 1, entry 1). Different solvents (see details in Supporting Information File 1) were screened for the test reaction using 15 mol % of catalyst I. Among them, CHCl3 turned out to be the optimal solvent, as the product 3aa was isolated in reproducible yield (77%) and enantioselectivity 74% ee (Table 1, entry 3). Next, we explored a variety of achiral and/or chiral Brønsted acids A1–6 as additives in order to increase the yield and the enantioselectivity of the reaction (Table 1, entries 4–9). A marked increase in both the yield and enantioselectivity of the product 3aa was observed. Among the screened Brønsted acids A1–6, the combination of 15 mol % of the catalyst I and 30 mol % of (±)-mandelic acid (A5) was found to be superior in terms of enantioselectivity (92% ee) of the product 3aa (Table 1, entry 8). When the catalyst loading was lowered (10 mol % of I/20 mol % of A5), the desired product 3aa was obtained in 71% yield and 91% ee (Table 1, entry 10). Lowering the temperature (~20 °C) of the reaction improved the enantioselectivity of the product 3aa slightly but decreased its yield (Table 1, entry 11). Subsequently, the effect of concentration on the reaction outcome was also studied. In dilute conditions, both the yield and enantioselectivity of the product 3aa were improved to 80% and 94%, respectively, at room temperature (Table 1, entry 12).

Taking into account the results of the optimization studies mentioned above, the catalytic system I (15 mol %)/A5 (30 mol %) in CHCl3 (1 mL) at room temperature (30–32 °C) was selected as the optimum reaction conditions (Table 1, entry 12). Under identical optimized reaction conditions, the catalytic system II (15 mol %)/A5 (30 mol %) furnished ent-3aa in 76% yield and 87.5% ee (Table 1, entry 13).

**Figure 1:** Selected examples of drugs and bioactive molecules bearing a pyrazole core.
Scheme 1: Representative examples of asymmetric organocatalytic conjugate addition of pyrazolin-5-ones to \( \alpha, \beta \)-unsaturated ketones and present study.

With the optimal reaction conditions at hands, the 1,4-conjugate addition reaction of a series of \( \alpha, \beta \)-unsaturated ketones \( \mathbf{1} \) with pyrazolin-5-one (2a) were studied next (Scheme 2). Aryl \( \alpha, \beta \)-unsaturated ketones bearing a halogen, electron-withdrawing, or electron-donating group at the para-position of the benzene ring were compatible and led to the corresponding products \( \mathbf{3ba–fa} \) in good to excellent yields (72–97\%) and enantioselectivities (90–95\% ee). The \( \alpha, \beta \)-unsaturated ketone \( \mathbf{1f} \) with a strong electron-withdrawing group (cyano) in the para-position of the benzene ring, was found to be more reactive as the reaction was completed within 4 h and the desired Michael adduct \( \mathbf{3fa} \) was isolated in 89\% yield and 92\% ee. Notably, the \( \alpha, \beta \)-unsaturated ketone with a substituent in the meta-position of the benzene ring was also tolerated and the desired product \( \mathbf{3ga} \) was isolated in good yield (82\%) and excellent enantioselectivity (95\% ee). To our delight, the \( \alpha, \beta \)-unsaturated ketone with a substituent in the ortho-position of the benzene ring, led to the product \( \mathbf{3ha} \) in good yield (76.5\%) and highest enantioselectivity (98.5\% ee). Moreover, 1-naphthyl-substituted and 2-thienyl-substituted \( \alpha, \beta \)-unsaturated ketones also took part in the reaction and the desired products \( \mathbf{3ia} \) and \( \mathbf{3ja} \) were isolated in good yields (77.5\% and 80\%, respectively) and enantioselectivity.
Table 1: Optimization of reaction conditions.\(^a\)

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</tbody>
</table>

\(^a\)Reaction conditions: 1a (0.3 mmol), 2a (0.2 mmol), 15 mol % of catalyst I or II in 0.5 mL toluene (entries 1 and 2) or catalyst I (15 mol %) and 30 mol % A in 0.5 mL CHCl\(_3\) for 12-14 h. Next, Ac\(_2\)O (0.52 mmol, 50 \(\mu\)L) was added followed by DABCO (0.1 mmol, 11 mg) and the reaction mixture was further stirred for 2 h at 30-32 °C. \(^b\)Isolated yield of 3aa or ent-3aa after column chromatography. \(^c\)Enantiomeric excess (ee) was measured by HPLC analysis using a chiralcel OD-H column. \(^d\)The yield of the reaction product varied from 58–62%. \(^e\)The reaction was performed in the presence of 10 mol % I and 20 mol % A5. \(^f\)The reaction was performed at -20 °C using 15 mol % of catalyst I in combination with 30 mol % A5 in 0.5 mL CHCl\(_3\) for 24 h. \(^g\)The reaction was carried out using 15 mol % of catalyst I or II in combination with 30 mol % A5 in 1.0 mL CHCl\(_3\) for 14 h at 30-32 °C. Next, Ac\(_2\)O (0.52 mmol, 50 \(\mu\)L) was added followed by DABCO (0.1 mmol, 11 mg) and the reaction mixture was further stirred for 2 h at 30-32 °C.

Next, we explored the scope of pyrazolin-5-ones 2 (Scheme 2, lower part) with diverse substituents (Br, Cl, F, Me or CN) in the para-position of the N-aryl group. These substrates reacted smoothly with \(\alpha,\beta\)-unsaturated ketone 1c and the corresponding products 3cb–cf were obtained in good yields (61–85.5%) and good to excellent enantioselectivities (84.5–95% ee). In addition, pyrazolone 2g with a substituent in the meta-position of the N-aryl group also participated in the reaction and the desired product 3cg was isolated in 87% yield and 95% ee. Notably, a phenyl substituent at the C3 position of pyrazolone 2h was found to be compatible, and the desired product 3ch was obtained in 87% yield and 90% ee.

In general, enantiomers of a bioactive molecule have different biological activities. Therefore, there is a huge demand to develop methods to access both enantiomers of a chiral compound. We turned our attention to the synthesis of enantiomeric products ent-3. Under identical optimized reaction conditions...
Scheme 2: Scope of substrates. Reaction conditions: 1 (0.3 mmol), 2 (0.2 mmol), 15 mol % of catalyst I, 30 mol % of A5, in 1.0 mL CHCl₃, 30–32 °C. Next, Ac₂O (0.52 mmol, 50 µL) was added followed by DABCO (0.1 mmol, 11 mg) and the reaction mixture was further stirred for 2 h at 30–32 °C. aIsolated yield of 3 or ent-3 after column chromatography. bEnantiomeric excess (ee) was measured by HPLC analysis using a stationary phase chiral column. cValues in parentheses represent % ee after single recrystallization. dReaction time for the first step was 4 h.
Scheme 3: Synthesis of pyrazole-benzofuran and pyrazole–indole hybrid molecules. Reaction conditions: 1m or 1n (0.3 mmol), 2a (0.2 mmol), 15 mol % of catalyst I (15 mol %)/A5 (30 mol %). To our delight, the enantiomeric products ent-3ma–ent-3na (Scheme 2) were obtained in good to excellent yields (71–97%) and enantioselectivities (83.5–98% ee).

Molecules containing two or more biologically relevant heterocycle motifs are receiving attention in drug discovery research [31-33]. The enantioselective synthesis of such hybrid molecules is fascinating but at the same time challenging. Pyrazoles [4-7], benzofurans [34], and indoles [35,36] are popular scaffolds as they are prevalent in many bioactive molecules. Compounds bearing both pyrazole and indole moieties or pyrazole and benzofuran moieties (Figure 1) are highly attractive since such compounds might be endowed with potent biological activities.

Under the disclosed optimized reaction conditions, the reaction between pyrazolin-5-one (2a) and indole-derived α,β-unsaturated ketone 1m was performed. The resulting hybrid molecule 3ma was isolated in 96% yield and 90% ee (Scheme 3). On the other hand, the reaction of pyrazolin-5-one (2a) with benzofuran-derived α,β-unsaturated ketone 1n delivered the product 3na in 85.5% yield and 95.5% ee (Scheme 3). Moreover, by employing the catalytic composite II (15 mol %) and A5 (30 mol %) under otherwise identical optimized reaction conditions, the corresponding enantiomeric products (ent-3ma and ent-3na) were obtained (Scheme 3) in good yields (91.5% and 85.5%, respectively) and enantioselectivities (84% ee and 91.5% ee, respectively).

The practical utility of the developed method was demonstrated by carrying out the synthesis of 3aa on a 1 mmol scale under the optimized reaction conditions (Scheme 4). The product 3aa was isolated in slightly lower yield and similar enantioselectivity compared to the 0.2 mmol scale reaction.

Subsequently, we turned our attention to determine the absolute configuration of the newly formed chiral center. Under the disclosed optimized conditions, the product ent-3ba was isolated as white solid with 85% ee and the enantiopurity of the prod-

Scheme 4: Synthesis of 3aa on preparative scale.
uct could be enriched to 98% ee by single recrystallization. The absolute stereochemistry was determined to be “R” on the basis of single-crystal X-ray crystallography data of ent-3ba (Figure 2) [37]. The stereochemistry of the products in this series was assigned by analogy.

Based on the observed absolute configuration of product ent-3ba and preceding literature reports [38,40], a plausible mechanistic pathway is outlined in Scheme 5. Initially, in the presence of one equivalent Brønsted acid additive A5, the catalyst II generates the monoprotonated diamine II-A5. The condensation of the primary amine moiety in II-A5 with the carbonyl group of the α,β-unsaturated ketone 1b in presence of the Brønsted acid leads to the formation of the iminium ion assembly 4 (Scheme 5). It is known that Brønsted acids facilitate the iminium ion formation step [38,39] and the counterion of the acid plays an important role in the stereocontrolling event [38,40]. On the other hand, the protonated quinuclidine nitrogen atom of the catalyst II (in the iminium ion assembly) activates the pyrazol-5-one 2a through hydrogen bonding and forms the corresponding enol. Simultaneously, the enol form of the pyrazol-5-one attacks the Re-face of the α,β-unsaturated ketone 1b to provide the intermediate 5 (Scheme 5), which after hydrolysis leads to product ent-3ba'. In situ acetyla-

**Figure 2:** Single crystal X-ray structure of ent-3ba (CCDC 2234286).

**Scheme 5:** Proposed reaction mechanism.
tion of the ent-3ba’ using acetic anhydride and DABCO, furnishes the desired product ent-3ba.

Conclusion
In summary, we have realized the Michael addition reaction of 4-unsubstituted pyrazolin-5-ones to α,β-unsaturated ketones under organocatalytic conditions. The developed protocol was efficiently applied to diverse α,β-unsaturated ketones and a pool of pyrazolin-5-ones. The formed Michael adducts were isolated in good to excellent yields and enantioselectivities. The method also led to enantioenriched hybrid molecules bearing pyrazole–indole moieties and pyrazole–benzofuranone moieties. It is worth mentioning that the current protocol delivers both enantiomers of the Michael adducts.

Experimental
General procedure for the synthesis of 3 and ent-3.
In an oven-dried 4 mL glass vial fitted with a magnetic stirring bar, the mixture of catalyst I (15 mol %, ≈9.0 mg) and (±)-mandelic acid (30 mol %, 9.0 mg) or catalyst II (15 mol %, ≈9.0 mg) and (±)-mandelic acid (30 mol %) in CHCl3 (1.0 mL) was stirred at room temperature (30–32 °C) for 5 min. Next, α,β-unsaturated ketone (0.3 mmol, 1.5 equiv) was added in one portion and the reaction mixture was further stirred for 5 min. Then, the pyrazolin-5-one 2 (0.2 mmol, 1.0 equiv) was added to the mixture and stirred for 4–14 h. Once the pyrazolin-5-one 2 was consumed (monitored by TLC), Ac2O (50 µL, ≈0.52 mmol, 2.6 equiv) and DABCO (11 mg, 50 mol %) were sequentially added. The resulting reaction mixture was further stirred for 2 h at room temperature. The crude reaction mixture was purified by silica gel (230–400 mesh) column chromatography (petroleum ether/EtOAc as the eluent) to give the product 3 or ent-3.

Supporting Information
Supporting Information File 1
Additional optimization studies, characterization data of compounds 3aa–na and ent-3aa–ent-3na, 1H, 13C NMR spectra of 3aa–na, 1H NMR of ent-3aa–ent-3na and their HPLC traces and single crystal data of ent-3ba.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-20-136-S1.pdf]

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Data Availability Statement
All data that supports the findings of this study is available in the published article and/or the supporting information to this article.

References
37. The crystallographic data (CCDC 2234286) for ent-3ba, can be obtained free of charge from the Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/data_request/cif.

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