

Enantioselective Stetter Reactions Catalyzed by Bis(amino)cyclopropenylienes: Important Role for Water as an Additive

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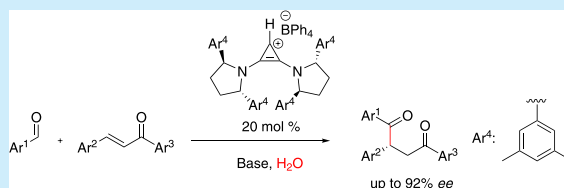


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ABSTRACT: The first highly enantioselective intermolecular Stetter reaction using simple enones is reported. A series of novel chiral BAC structures were designed and prepared. They were tested in the Stetter reaction with simple aldehydes and enones. The products were generated in excellent yields and enantioselectivities (up to 94% *ee*). Surprisingly, a substoichiometric amount of water was crucial to obtain high enantioselectivities. Chiral BACs were also shown to catalyze 1,6-conjugate addition reactions with paraquinone methides enantioselectively.



Synthetic access to 1,4-dicarbonyl motifs is limited due to their unusual polarity pattern. The Stetter reaction provides a direct and convergent synthetic route for constructing 1,4-dicarbonyls using a strategic C–C bond formation.¹ Seminal work by Enders disclosed the first intramolecular enantioselective Stetter reaction.² Although the intramolecular variant is well explored,³ highly enantioselective intermolecular Stetter reactions have remained a challenge.⁴ Representative examples are shown in Scheme 1. Enders and colleagues first demonstrated an enantioselective intermolecular Stetter reaction with aromatic aldehydes and chalcone in which moderate yields and enantioselectivities were obtained (Scheme 1a).^{4b} Rovis and co-workers obtained excellent results by using highly electrophilic glyoxamides and arylidene malonates as reaction partners (Scheme 1b).^{4c} We later reported β,γ -unsaturated α -ketoesters as effective partners in these reactions.^{4h} Despite a number of other reports in this area, a high level of enantioselectivity for the intermolecular Stetter reaction involving simple enones and aldehydes remains elusive.

BACs have proved to be quite stable carbenes.⁵ In 2013, we showed that they are competent catalysts for the Stetter reaction.^{6,7} However, when chiral pre-catalyst **1** was used, the product was obtained with only a modest 36% *ee* (Scheme 1c). The excellent reactivity profile of BACs motivated us to design and synthesize new chiral backbones that would better impart enantioselectivity for this challenging transformation.

We reasoned that the poor enantioselectivity observed when using pre-catalyst **1** is due to the free C–N bond rotation illustrated in Figure 1a. We hypothesized that more rigid structures would lead to higher enantioselectivities due to a better-defined chiral environment near the reaction center.

Rigidifying the catalyst's structure via the introduction of additional fused rings to the structure of **1** was deemed

impractical from the point of view of catalyst synthesis. Instead, we opted to restrict rotation around the C–N bonds by the use of bulky C2-symmetric amino substituents (Figure 1b). Most chiral NHC catalysts are devoid of symmetry, leading to *E/Z* isomerism of the corresponding Breslow intermediates, which can negatively affect the enantioselectivity. The Breslow intermediates derived from our new C2-symmetric pre-catalysts do not feature *E/Z* isomerism, which limits the number of available reaction pathways. Pre-catalysts **2** and **3** were prepared from the known chiral piperidine and pyrrolidine, respectively. Following initial screening results (vide infra), the bulkier pre-catalysts **4** and **5** were also prepared. Pre-catalysts **1**–**5** were evaluated in a model Stetter reaction (Table 1).

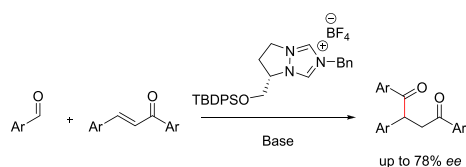
The reaction using piperidine-derived pre-catalyst **2** showed a notable improvement in enantioselectivity compared to the one using pre-catalyst **1**, thereby validating the approach of restricting C–N bond rotation through steric hindrance (entries 1 and 2). Not surprisingly, this increase in enantioselectivity was accompanied by a decrease in reactivity. The level of enantioselectivity was maintained when using pyrrolidine-derived pre-catalyst **3**, but a much better conversion of 92% was obtained (entry 3). It is not clear at this point whether the improved reactivity profile of **3** compared to that of **2** is due to the size of the heterocycles or to the presence of aromatic rings in **3**. The tunability of aromatic substituents allowed the exploration of other diaryl-

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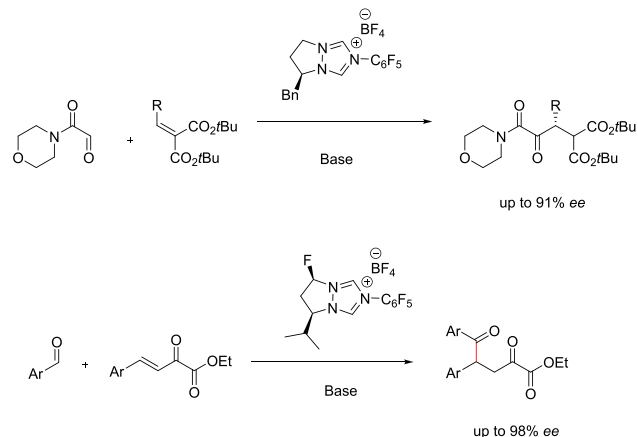
Scheme 1. Selected Examples of Enantioselective Intermolecular Stetter Reactions

Prior work

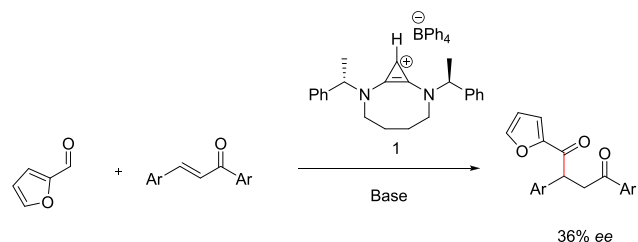
a. Using simple enones (Enders)



b. Using highly electrophilic reaction partners (Rovis, Gravel)

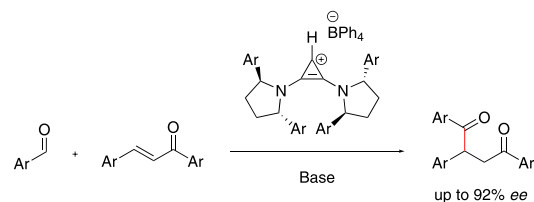


c. Using a chiral BAC (Gravel)



This work:

d. Highly enantioselective Stetter reactions using simple enones



substituted pyrrolidine-derived pre-catalysts. We surmised that, by modulating the steric and electronic properties of these aryl substituents, an increase in enantioselectivity could be obtained. To this effect, aryl groups with increased bulk could possibly enhance the rigidity of the catalyst and/or the facial selectivity on the acceptor. Simple visual inspection suggested that ortho substituents or branched alkyl groups (such as *t*-Bu and *i*-Pr) at the meta position are too bulky, and they might shut down the reactivity of the catalyst. Meta-methyl substitution therefore seemed to be a reasonable choice. Thus, pre-catalyst 4 was synthesized and tested.

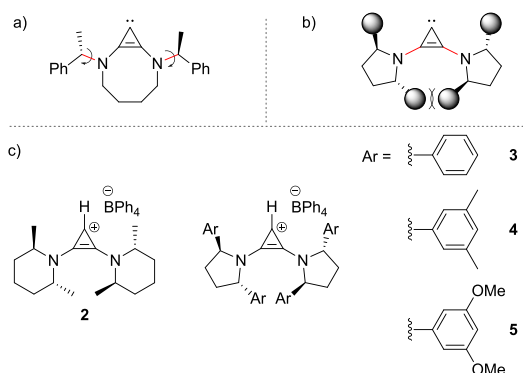


Figure 1. (a) Undesired C–N bond rotation. (b) C₂-symmetric design with hindered C–N bond rotation. (c) Chiral pre-catalysts used in this study.

Table 1. Pre-Catalyst Screening^a

entry	pre-catalyst	conversion ^b (%)	ee ^c (%)
1	1	>99	10
2	2	45 ^d	55
3	3	92	57
4	4	82	85
5	5	32	60

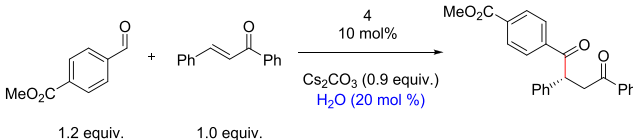
^aReactions were run with 1.2 equiv of aldehyde, 10 mol % of pre-catalyst, and 0.7 equiv of Cs₂CO₃ in CH₂Cl₂ in the presence of 4 Å molecular sieves for 4 h at rt under argon. ^bConversions determined by ¹H NMR analysis of the crude reaction mixture. ^cee determined by HPLC analysis using a chiral stationary phase. ^d15% of pre-catalyst was used.

Gratifyingly, a great improvement in the enantioselectivity was obtained while maintaining a reasonable level of reactivity (entry 4). Next, we turned our efforts to varying the electronic properties of the catalyst. In the presence of electron-rich 5, the enantioselectivity observed was similar to that using pre-catalyst 3, but the conversion dropped significantly (entry 5). Unfortunately, brief attempts to prepare a fluorinated version of 3 failed. Nevertheless, the results obtained with 4 were sufficiently encouraging to optimize this reaction and explore its scope.

Of concern was that our initial results were not reproducible. The enantioselectivity ranged from 85 to 94% ee and the conversion from 30 to 90%. Interestingly, we observed a correlation between enantioselectivity and conversion: a higher yield led to a lower selectivity and vice versa (results not shown). We suspected that adventitious water played a role in the variability of our results, so we decided to carefully control the amount of water present in the reaction vessel. We screened the model reaction with various amounts of water, and the best result was obtained in the presence of 20 mol % water (80% conversion, 90% ee; see the [Supporting Information](#)). More importantly, the results became highly reproducible. We reasoned that the improvement of enantioselectivity in the presence of water might be due to hydrogen bonding. Various additives with hydrogen bonding ability were therefore tested, but water proved to be optimal (see the [Supporting Information](#)).

Optimization of the other reaction parameters is presented in Table 2. Lowering the temperature from -10 to -25 °C led

Table 2. Optimization of the Reaction Conditions^a



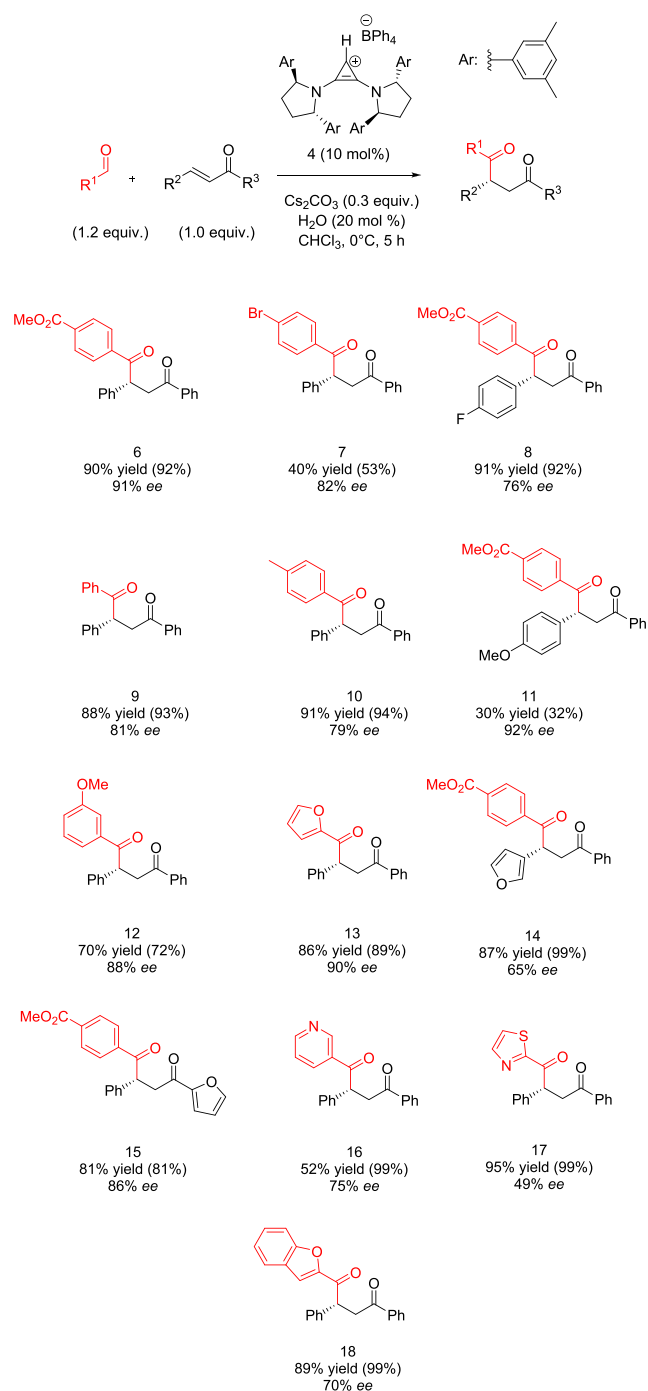
entry	solvent	<i>T</i> (°C)	<i>t</i> (h)	yield ^b (%)	ee (%)
1	CHCl ₃	-10	4	80	90
2	CHCl ₃	-25	4	19	96
3	CHCl ₃	0	4	91	91
4	CHCl ₃	0	0.75	60	91
5	CHCl ₃	0	2	84	90
6	CHCl ₃	0	24	93	88
7	DCM	0	4	92	82
8	THF	0	4	83	77
9	CH ₃ CN	0	4	8	75
10	<i>p</i> -dioxane	0	4	83	85
11	DMF	0	4	57	0
12 ^c	CHCl ₃	0	4	92	91

^aReactions were run on a 0.07 mmol scale. ^bYield determined by ¹H NMR analysis using an internal standard. ^c0.3 equiv of Cs₂CO₃ was used.

to an increase in enantioselectivity, but that was accompanied by a dramatic drop in conversion (entries 1 and 2). Lower solubility of the pre-catalyst at this temperature could be an explanation for this observation.⁸ Surprisingly, the conversion could be increased at 0 °C while maintaining the high level of enantioselectivity (entry 3). Varying the reaction time showed that very little racemization occurs over time (entries 4–6). A solvent screen revealed that chloroform is superior to the other solvents (entries 7–11). Finally, we found that the amount of base could be lowered without a measurable impact on the reaction outcome (entry 12).

With the optimized reaction conditions in hand, we set out to explore the generality of this transformation (Scheme 2). The reaction is tolerant to electron-withdrawing and mild electron-donating groups on both reactants. The use of electron-poor aromatic aldehydes leads to the highest enantioselectivities (6–8), but the products derived from benzaldehyde or electron-rich aromatic aldehydes are still obtained in good enantiomeric excess (9, 10). The use of an electron-rich acceptor led to the Stetter product in modest yield but with very high enantioselectivity (11). Product 12 was formed from meta-anisaldehyde, implying that the reaction is sterically tolerant to substituents at the meta position (12). Further investigation demonstrated that heteroaromatic aldehydes are well tolerated. The furfural-derived product 13 was formed in high yield and with high enantioselectivity. Acceptors containing a heterocyclic substituent also led to the desired products efficiently, although the product formed from the β -heterocyclic acceptor only had a modest enantiomeric excess (14, 15). The successful formation of furyl-containing Stetter products is synthetically significant, as this moiety is susceptible to further modifications such as photo-oxygenation⁹ and Diels–Alder reactions.¹⁰ Other heteroaromatic aldehydes were also tested and led to the desired products. The use of 3-pyridinecarboxaldehyde and 2-thiazolecarboxaldehyde gave the Stetter products with excellent conversions

Scheme 2. Substrate Scope^a



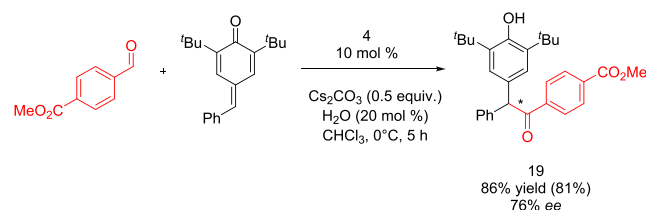
^aReactions were run on a 0.15 mmol scale. Yields are of pure, isolated products; yields indicated in parentheses were determined by ¹H NMR analysis using an internal standard.

and diminished enantioselectivities (16, 17). Benzofuran-2-carboxaldehyde also coupled with chalcone but in the absence of water. The reaction using this particular substrate proved to be highly water sensitive. Lack of water led to a higher conversion; however, the enantioselectivity was inferior, confirming the significant influence of water on the enantioselectivity of this reaction. It is worth noting that the use of ortho-substituted aromatic aldehydes or aliphatic aldehydes did not lead to the desired Stetter products. Although an extensive survey of Michael acceptors was not

carried out, β -alkyl-substituted acceptors were found to be unreactive under the optimized conditions, as were β,γ -unsaturated α -ketoesters. The absolute configuration of product **9** was determined by polarimetry and comparison with reported values.^{4b} The absolute configuration of other substrates was assigned by analogy.

Anand and co-workers recently reported a BAC-catalyzed 1,6-addition of aldehydes onto para-quinone methides to form racemic α,α -diaryl ketones.^{7a} Inspired by their report, we wondered if the reported reaction can be done enantioselectively using a chiral BAC catalyst. Gratifyingly, in the presence of **4**, the desired product **19** was formed in excellent yield and good enantioselectivity (Scheme 3). No further

Scheme 3. Enantioselective 1,6-Addition



optimization of this reaction was attempted, but it clearly demonstrates that our new family of C2-symmetric BACs represents a generally useful template for enantioselective umpolung reactions.

In conclusion, we have developed the first chiral BACs capable of catalyzing reactions in high enantioselectivity. This was demonstrated by their application to challenging intermolecular Stetter reactions. Significantly, it led to the first highly enantioselective Stetter reactions using simple enones such as chalcone and related acceptors. In contrast to most NHC-catalyzed reactions, the use of water as an additive was necessary to obtain high enantioselectivities. The broader generality of C2-symmetric BACs was also shown through the enantioselective 1,6-conjugate addition of aldehydes onto para-quinone methides. Computational studies for the origin of enantioselectivity as well as the unusual role of water in this reaction are currently underway. One avenue of investigation involves transition states for which a water molecule forms a hydrogen bonding network between the Breslow intermediate and the acceptor during the C–C bond forming step. Another possible role for water is in assisting with catalyst turnover during the ejection step. The results of these studies will be reported in due course.

■ ASSOCIATED CONTENT

SI Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acs.orglett.0c03879>.

Experimental procedures, characterization data, and NMR spectra (PDF)

FAIR data, including the primary NMR FID files, for compounds **1**–**19** (ZIP)

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Notes

The authors declare no competing financial interest.

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