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Enantioselective Brønsted Base Catalysis with Chiral Cyclopropenimines

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Supporting Information

ABSTRACT: Cyclopropenimines are shown to be a highly effective new class of enantioselective Brønsted base catalysts. A chiral 2,3-bis(dialkylamino)cyclopropenimine catalyzes the rapid Michael reaction of a glycine imine substrate with high levels of enantioselectivity. A preparative scale reaction to deliver 25 g of product is demonstrated, and a trivial large scale synthesis of the optimal catalyst is shown. In addition, the basicity of a 2,3-bis(dialkylamino)cyclopropenimine is measured for the first time and shown to be approximately equivalent to the P_1-*t*Bu phosphazene base. An X-ray crystal structure of the protonated catalyst is shown along with a proposed mechanistic and stereochemical rationale.

Due to the prevalence of chemical reactions involving proton transfer as a key mechanistic event, Brønsted bases have become indispensable tools for the practice of organic synthetic chemistry.[1] Of particular interest in recent years has been the development of chiral Brønsted bases capable of catalyzing proton transfer reactions enantioselectively for the production of optically enriched products.[2] Although enantioselective Brønsted base catalysis holds great promise, this area has arguably lagged far behind the development of other modes of asymmetric catalysis.

In general, a Brønsted base catalyst must possess a strength of basicity properly tuned to the acidity of a given substrate. In this regard, strong, neutral organic bases such as DBU (diazabicycloundecene) or TMG (tetramethylguanidine) have proven highly useful as reagents or catalysts for numerous transformations.[2] However, the amidine and guanidine functionalities upon which these and related reagents are built have inherent limitations of basicity, which has inhibited the development of broadly effective chiral catalysts based on these structures. Significantly stronger basicities can be realized with phosphazene[3] or phosphatrane[4] structures, and a number of these reagents have become important additions to the Brønsted base arsenal. Nevertheless, broadly effective chiral catalysts based on these functionalities have not yet been realized. Clearly, there exists a strong need for novel Brønsted bases that provide potent yet tunable basicity, are trivial to prepare, and offer unique opportunities for asymmetric transition state organization. In this regard, we report here the development of 2,3-bis(dialkylamino)cyclopropenimines as a highly effective platform for chiral Brønsted base catalysis.

The signature feature of the cyclopropenimine scaffold[5] is the presence of a latent cyclopropenium ion, which is revealed upon protonation of the imino nitrogen (Figure 1). As the smallest ring

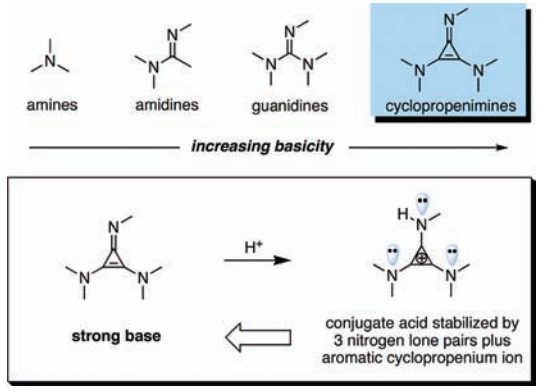

Figure 1. Cyclopropenimines as strong Brønsted bases.

system that satisfies Hückel's rules, the 2π-electron cyclopropenium ion[6,7] provides substantial aromatic resonance stabilization to the conjugate acid of the cyclopropenimine. In comparison to the analogous guanidines, this additional stabilization renders 2,3-bis(dialkylamino)cyclopropenimines highly basic.

Although the principle behind the strong basicity of cyclopropenimines is well appreciated, to the best of our knowledge no measurement of this basicity has been reported,[8] and the use of cyclopropenimines as reagents or catalysts is unknown.[9] We have measured the acidity of the conjugate acid (pK_{BH+}) of cyclopropenimine **1** in acetonitrile (26.9) and found it to be comparable to the bicyclic guanidine TBD (26.03) and the phosphazene base P_1-*t*Bu (26.98), both considered to be exceptionally strong "superbases" (Figure 2).[10] Notably,

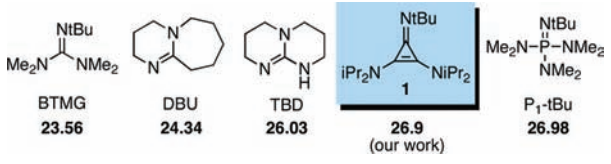

Figure 2. Basicity of cyclopropenimine **1** and several common strong organic bases. Bold numbers are pK_{BH+} values in acetonitrile.

cyclopropenimine **1** is 3 orders of magnitude more basic than a comparable guanidine, BTMG (23.56). These findings confirm for the first time that 2,3-bis(dialkylamino)cyclopropenimines are indeed potent Brønsted bases.

We hypothesized that the strong basicity of cyclopropenimines might offer advantages in terms of reactivity and reaction

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scope for Brønsted base catalyzed transformations. To test this hypothesis, we selected the Michael reaction of glycine imine **2** with methyl acrylate **3**[11] as a forum for comparison to reported chiral guanidine catalysts. In this regard, we have identified cyclopropenimine **5** as a highly effective catalyst, which at 10 mol % loading effects the production of adduct **4** in essentially quantitative yield and 91% ee in only 5 min under neat conditions. When the reaction was performed in ethyl acetate, product was obtained in quantitative yield and with 98% ee in 1 h. In comparison to the high performance of this cyclopropenimine catalyst, reported chiral guanidine catalysts have been far less effective. For example, 20 mol % of guanidine **6** catalyzes the production of **4** in high yield and good ee only after 3 days of reaction time at high concentration (neat).[12,13] Notably, these guanidine catalyzed reactions have not been viable in solution. This comparison clearly illustrates the potential of cyclopropenimines to serve as a powerful new platform for chiral Brønsted base catalysis.

A selection of the optimization studies we conducted to arrive at the conditions shown in eq 1 is shown in Table 1.

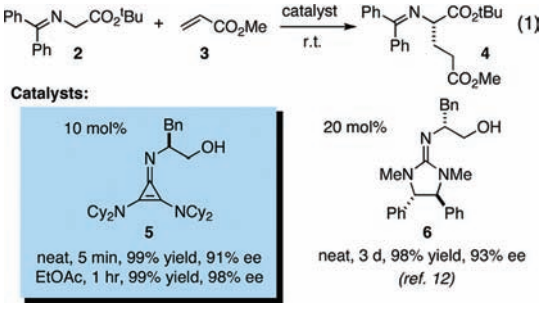
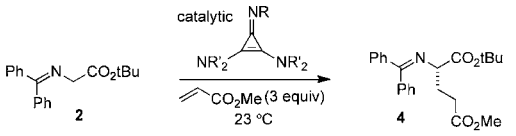


Table 1. Optimization of Enantioselective Cyclopropenimine Catalyzed Michael Addition[a]



entry	catalyst (mol%)	solvent (M)	time (h)	conv. (%)	ee (%)
1	**5** (10)	THF (0.20)	24	86	89
2	**5** (10)	Et_2O (0.20)	2	>95	98
3	**5** (10)	dioxane (0.20)	8	>95	98
4	**5** (10)	MeCN (0.20)	1	>95	28
5	**5** (10)	$EtCO_2Me$ (0.20)	10	>95	95
6	**5** (10)	EtOAc (0.20)	2	>95	98
7	**5** (10)	EtOAc (0.35)	1	>95	98
8	**5** (5)	EtOAc (0.35)	6	>95	98
9	**5** (2.5)	EtOAc (0.35)	18	>95	97
10	**5** (1)	EtOAc (0.35)	24	78	97
11	**7** (10)	EtOAc (0.35)	24	11	0
12	**8** (10)	EtOAc (0.35)	24	40	87

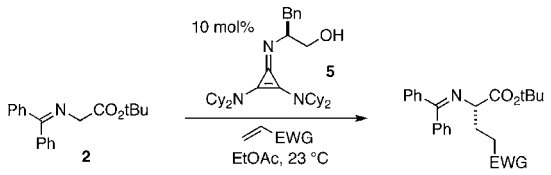
[a]Conversion determined by ^{1}H NMR versus Bn_2O standard.

In terms of solvent, ethers including THF, Et_2O, and dioxane were viable media for this process using catalyst **5** (entries 1−3) albeit with significant variation in reaction time. The reaction was fast in acetonitrile but enantioselectivity was greatly compromised (entry 4), which may be a reflection of the propensity for this solvent to engage in H-bonding and thus to disrupt transition state organization. On the other hand, ester solvents such as methyl propionate (entry 5) and, optimally, ethyl acetate (entry 6) proved to be most convenient. Reactions can be significantly accelerated by increasing concentration, with a concentration of 0.35 M resulting in the optimized reaction shown in eq 1 (entry 7). Reduction of catalyst loading down to 2.5 mol % could be achieved without loss of conversion or enantioselectivity (entries 8−9). Even the use of only 1 mol % catalyst was possible although in this case the conversion after 24 h was reduced to 78% (entry 10).

In terms of catalyst structure, we found the presence of a hydroxyl group to be crucial for both reactivity and enantioselectivity, with catalysts such as **7** producing low conversions of product with 0% ee (entry 11). Sterically demanding dialkylamino substituents at the 2 and 3 positions were also found to be important for optimal performance. Interestingly, the diisopropylamine derived catalyst **8** was markedly less efficient and selective than catalyst **5** under the same conditions (entry 12).

A screen of Michael acceptors revealed that various acrylate esters are also viable substrates for catalyst **5**. Thus in addition to methyl acrylate (Table 2, entry 1), *n*-butyl, *tert*-butyl, and

Table 2. Substrate Scope of Michael Acceptors[a]



entry	electrophile	time (h)	yield (%)	ee (%)
1	CO_2Me	1	99	98
2	CO_2nBu	1.5	99	98
3	CO_2tBu	12	98	99
4	CO_2Bn	1	97	98
5	COMe	0.25	97	95
6	CN	30	97	77
7[b]	SO_2Ph	24	89	41
8		1	97	95 (6:1 dr)

[a]Yield based on isolated and purified product. [b]Yield determined by ^{1}H NMR versus Bn_2O standard.

benzyl acrylates also participated in nearly quantitative yield and with high enantioselectivity (entries 2−4). Notably, *tert*-butyl acrylate reacted significantly slower than either methyl or *n*-butyl acrylate, which is consistent with the hypothesis that interaction of the catalyst with the ester carbonyl via H-bonding plays an important role in the catalysis of this reaction. Methyl vinyl ketone was quite reactive, proceeding to full conversion in only 15 min (entry 5). In contrast, both acrylonitrile (entry 6) and phenyl vinyl sulfone (entry 7) reacted dramatically slower and with greatly diminished enantioselectivity. We speculate that differences in H-bonding geometry between these substrates and the carboxylate substrates may account for these disparities. Lastly, a chalcone substrate reacted with high efficiency to produce the Michael addition adduct in high yield and 95% ee as a 6:1 mixture of diastereomers (entry 8).

One of the most attractive features of 2,3-bis(dialkylamino)-cyclopropenimines is their extreme ease of synthesis. As a prime example, we have developed a trivial large scale synthesis

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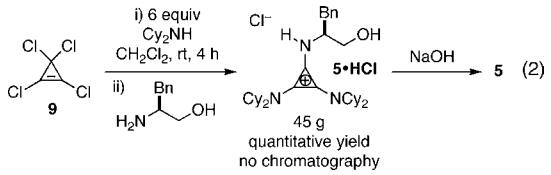
of catalyst **5** starting from inexpensive and readily available materials (eq 2).[14] Thus tetrachlorocyclopropene[15] (**9**) was



(2)

treated with an excess of dicyclohexylamine for 4 h, followed by the addition of phenylalaninol. From this procedure the salt **5·HCl** was isolated in essentially quantitative yield as a crystalline solid. As discussed below, we have found it most convenient to store the catalyst as its HCl salt, and we have prepared as much as 45 g in a single run. The generation of cyclopropenimine **5** requires only a simple wash with an aqueous inorganic base and can be used without purification after concentration from solvent.

The crystalline nature of **5·HCl** allowed an X-ray structure to be obtained (Parkin group, Columbia University), which revealed several key structural features (Figure 3). First, the

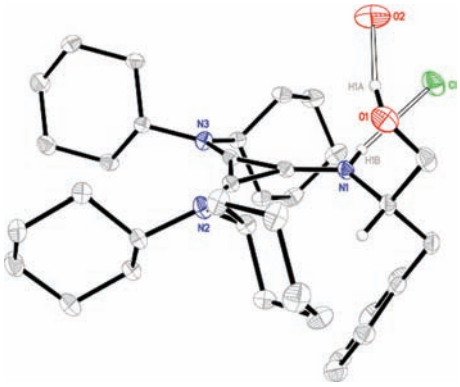
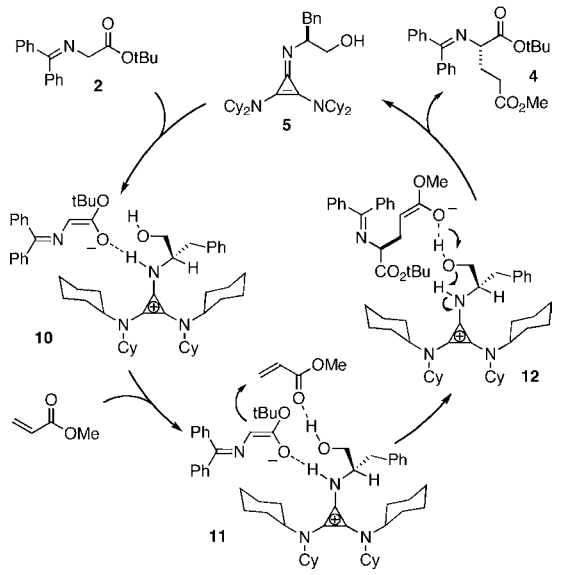


Figure 3. Molecular structure of protonated cyclopropenimine **5·HCl** cocrystallized with a molecule of H_2O.

steric demand of the dicyclohexylamino groups causes these substituents to torque out of planarity with the cyclopropenium ring.[16] This phenomenon is likely the reason for the slightly diminished basicity of **5** relative to other cyclopropenimines. Second, the chiral appendage appears to be oriented with the proton directed toward a cyclohexyl ring so as to minimize steric conflict. We propose this element of organization is key to the observed high levels of stereocontrol. Finally, it can be seen that the chloride counterion is H-bonded to the H-bearing amino group, rather than associated with the cationic cyclopropenium ring,[17] and that a cocrystallized molecule of water is H-bonded to the hydroxyl group. It can be readily imagined that such interactions are involved in transition state organization of the conjugate addition of glycine imine **2**.

The structure of protonated **5** allows us to propose a tentative mechanistic and stereochemical rationale for this transformation (Scheme 1). Thus we suggest that the catalyst **5** deprotonates glycine imine **2** to generate the cyclopropenium enolate salt **10**. This complex is presumed to involve a H-bond with the N−H of the cyclopropenium, but the precise organization of **10** is at this time unknown. Nevertheless, because the alcohol moiety of the catalyst was found to be required for enantioselectivity, we speculate that methyl acrylate is directed for conjugate attack via H-bonding with the pendant hydroxyl

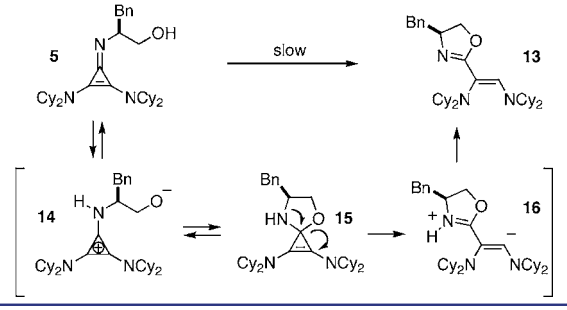
Scheme 1. Stereochemical Rationale for Cyclopropenimine 5 Catalyzed Enantioselective Conjugate Addition of 2 to Methyl Acrylate



(cf. **11**). Rapid proton transfer from the cyclopropenium ion to the resultant enolate as shown in structure **12** then closes the catalytic cycle.

It should be noted that the activity of catalyst **5** was observed to slowly diminish over several days when stored at rt. Analysis of a pure sample over the course of 30 days indeed revealed a steady conversion ($t_{1/2} \approx 12$ days; see Supporting Information) from the cyclopropenimine **5** to a new compound, which we have identified as **13** (Scheme 2). A reasonable proposal for the

Scheme 2. Decomposition Pathway of Cyclopropenimine 5



production of this compound is that internal deprotonation of the pendant hydroxyl of **5** generates the alkoxy cyclopropenium **14**, which can then cyclize to the oxazolidine **15**. Destructive ring opening to produce vinyl anion **16** followed by proton transfer would then lead to the observed product **13**.

Importantly, this decomposition pathway was greatly slowed by storing the cyclopropenimine **5** at −20 °C, with a sample still 94% intact after 30 days. Alternatively, we have found that the HCl salt of **5** is indefinitely stable at rt, and given that conversion of **5·HCl** to **5** requires only a simple wash with an aqueous base, we have found it most convenient to store the catalyst as its acid co-salt.

Finally, we have investigated the performance of cyclopropenimine **5** for asymmetric catalysis on a preparative scale. Thus the addition of glycine imine **2** to methyl acrylate was

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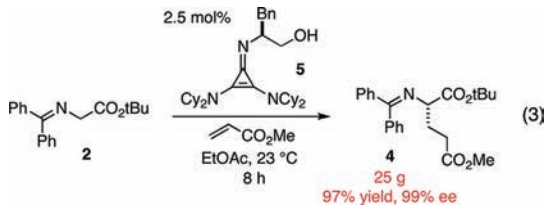
performed to produce 25 g (97% yield, 99% ee) of the product **3** in 8 h using 2.5 mol % of catalyst **5** (eq 3). Given that **5** can



be easily generated in significant quantities (see eq 2), it seems that catalysis with chiral cyclopropenimines should be amenable to relatively large-scale applications.

In summary, the experimental verification of the high basicity of cyclopropenimines provides an important addition to the so-called "superbase" arsenal.[1] The exceptional performance of the chiral cyclopropenimine **5** versus related guanidine bases suggests that these new catalysts may enable important developments in the area of enantioselective Brønsted base catalysis. The extraordinary ease of preparation of cyclopropenimines and their amenability to use on a multigram scale as we have demonstrated should make cyclopropenimines suitable to a range of applications.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and product characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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