Organocatalysis

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A Chiral Bis(betaine) Catalyst for the Mannich Reaction of Azlactones and Aliphatic Imines**

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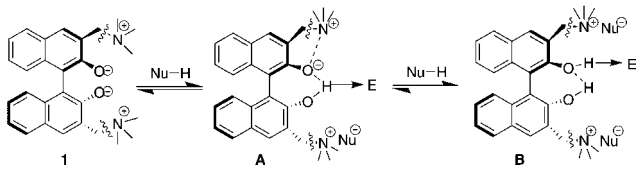
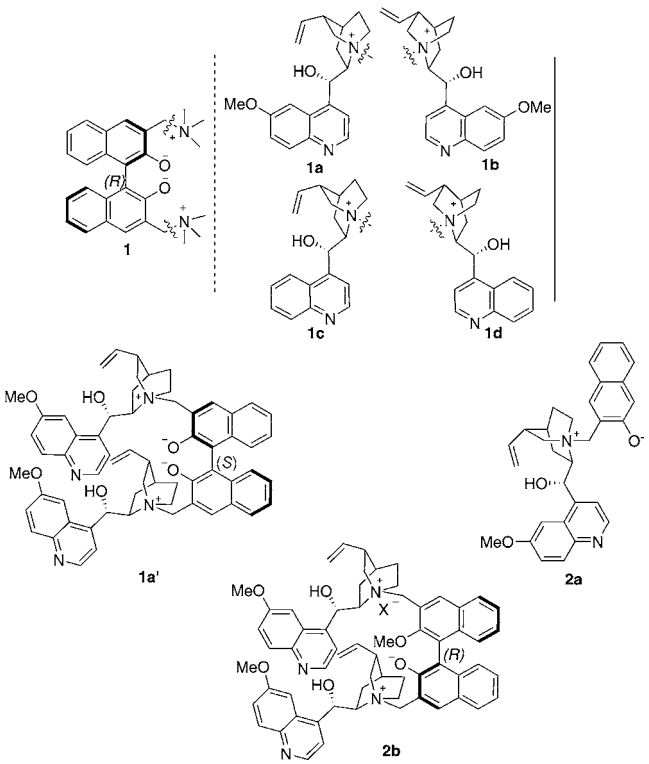
The design of novel and efficient chiral catalysts capable of inducing substantial stereochemical outcomes has been a longstanding frontier in organic synthesis.[1,2] In recent decades, the design of highly efficient chiral catalysts has encompassed the incorporation of two catalytically active centers into a single chiral molecule with the assumption that cooperative catalysis might occur between the two catalytic sites. Numerous chiral catalysts of this type have been discovered and have enabled a wide range of enantioselective transformations.[3–13] In particular, great advances have been made with the dinuclear metal complexes which have enabled bimetallic cooperative catalysis and have been exploited to accelerate numerous asymmetric transformations.[3–7] However, those dinuclear organocatalysts having multiple catalytic centers, wherein each catalytically active site is bifunctional, have been investigated to a lesser extent for asymmetric protocols.[8–13]

Recently, Ooi and co-workers demonstrated that artificial chiral betaines were promising chiral organocatalysts in base-catalyzed asymmetric protocols.[14] In particular, the monobetaines, having a binaphthyl backbone, stereoselectively activated nucleophiles having acidic protons, thus allowing the discovery of highly enantioselective transformations. These betaines contain a basic aryl oxide moiety and an ammonium cation. We and others have demonstrated that the introduction of a binol backbone as an extra chiral element into Schiff base ligands for bimetallic catalysts is beneficial to the stereocontrol.[6,7] On the other hand, binol and its derivatives have been employed as Brønsted acids in asymmetric catalysis, wherein an intramolecular hydrogen bond between the two hydroxy groups exists to assist in the single hydrogen-bonding activation.[15–18] Inspired by these achievements, we designed chiral bis(betaine) organocatalysts of type **1** (Schemes 1 and 2), which contain two chiral ammonium moieties, two basic naphthoxides, as well as axial chirality. Upon encountering nucleophiles (H-Nu), the bis(betaine) might participate in a deprotonation and in turn be transformed into the chiral Brønsted acidic nucleophilic species **A** or **B** which have Brønsted-acid-assisted Brønsted acid functionalities. Both **A** and **B** are principally capable of activating the incoming electrophiles (E) through a hydrogen-bonding interaction. As such, these compounds would be potentially ideal chiral catalysts for promoting stereoselective nucleophilic addition reactions involving nucleophiles having acidic protons. We describe herein a highly enantioselective Mannich reaction of azlactones and imines (up to 99% *ee*) catalyzed by the newly designed bis(betaine)s **1** (Scheme 2), thus demonstrating the potential of **1** in asymmetric catalysis.



Scheme 1. The general consideration for the design of bis(betaine) organocatalysts.



Scheme 2. Organobases evaluated in this study.

The designed bis(betaine)s **1** and monobetaines **2** were easily accessed by using classical transformations starting from binol and naturally occurring cinchona alkaloids (for

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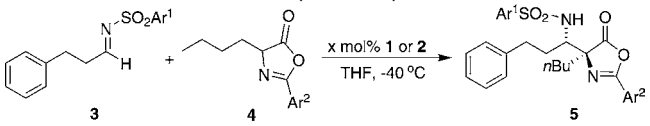
a detailed procedure see the Supporting Information). α,β-Diamino acids are prevalent in many biologically active compounds,[19] and a direct Mannich reaction is one of the most straightforward approaches for accessing these molecules.[19d,20] Recently, the Mannich reactions of 4-substituted azlactones and α-substituted nitroacetates for synthesizing α-tetrasubstituted diamino acids have attracted much attention.[3,14a,c,21–26] However, very few reports have described access to the highly enantioselective variants of aliphatic imines.[14a,21,22] Thus, we focused our initial study on the catalytic Mannich reaction of N-tosyl imine **3a** and 4-butyl-2-phenyloxazol-5(4*H*)-one (**4a**) in THF at −40 °C in the presence of 5 mol% **1a**, which was derived from quinidine (Table 1). As anticipated, the reaction worked well to give the desired product **5aa** in 78% yield with an *anti*/*syn* ratio of 2.5:1. We were encouraged by the isolation of *anti*-**5aa** in 81% *ee* (Table 1, entry 1). Additional investigation into the effect of the 4-aryl substituent of the azlactones **4** indicated that the introduction of an alkyl substituent to the phenyl group of the azlactones enhanced both the yield and enantioselectivity (entries 1–3 and 5), whereas 4-chlorophenyl and 3,5-dimethylphenyl azlactones gave comparable enantioselectivities (entry 1 versus 4 and 6). Among the azlactones examined, **4g**, bearing a 2-naphthyl substituent, provided the highest level of enantioselectivity for the major product *anti*-**5ag** (entry 7). Further optimization showed that the use of 10 mol% of the catalyst **1a** provided 96% *ee* for *anti*-**5ag** (entry 8).[27] Under these optimized reaction conditions, other betaines derived from cinchona alkaloids were evaluated (entries 9–14). Interestingly, the quinine-derived base **1b** offered the enantiomer of *anti*-**5ag** with a high level of enantioselectivity, but with poor diastereoselectivity (entry 9), thus suggesting that the stereochemistry was governed by the chirality of the alkaloid moiety. A similar outcome was observed in the reactions catalyzed by cinchonine- and cinchonidine-derived bis(betaine)s **1c** and **1d**, both of which provided moderate enantioselectivities (entries 10 and 11). The monobetaines **2a** and **2b** showed excellent catalytic activity, but afforded a much lower *ee* value than the bis(betaine) **1a** (entries 12 and 13), thus indicating that the stereochemical control benefits greatly from the axial chirality of the binol moiety. The catalyst **1a′**, which was derived from (*S*)-binol and quinidine, delivered a lower enantioselectivity than **1a**, further demonstrating that the axial chirality has an impact on the stereoselectivity (entry 14 versus 8). A further enhancement in the enantioselectivity was achieved when 4-isopropylphenylsulfonyl imine **3b** was employed as a substrate (97% *ee*, entry 15).

Moreover, we investigated the effect of the stoichiometry of trifluoroacetic acid (TFA) and **1a** on the reaction. The enantioselectivity fell when the amount of TFA increased (Table 2). The addition of 10 mol% TFA, principally generating a monoanion of type **A** (Scheme 1), also showed catalytic activity despite the erosion in the stereoselectivity and yield (entry 3), thus indicating the feasibility of forming intermediate **B** (Scheme 1). However, the reaction was almost inhibited upon addition of 15 mol% TFA (entry 4).

The substrate scope with respect to aliphatic imines and azlactones was then investigated under the optimized reaction conditions (Table 3).[28] A variety of 4-substituted azlactones participated in the Mannich reaction with high yields and excellent levels of enantioselectivity (entries 1–7). More interestingly, the azlactone **4m** containing a thioether, which may add more synthetic utility,[29] cleanly underwent the

Table 1: Evaluation of chiral catalysts and optimization of conditions.[a]



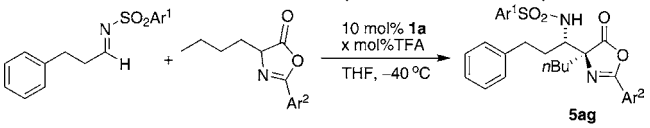
3a: Ar^1 = 4-$CH_3C_6H_4$
3b: Ar^1 = 4-*i*PrC_6H_4

4a: Ar^2 = Ph
4b: Ar^2 = 4-MeC_6H_4
4c: Ar^2 = 4-*t*BuC_6H_4
4d: Ar^2 = 4-ClC_6H_4
4e: Ar^2 = 3-MeC_6H_4
4f: Ar^2 = 3, 5-$Me_2C_6H_3$
4g: Ar^2 = 2-naphthyl

Entry	3	4	Cat. [%]	5	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	**3a**	**4a**	**1a** (5)	**5aa**	78	2.5:1	81
2	**3a**	**4b**	**1a** (5)	**5ab**	93	3:1	83
3	**3a**	**4c**	**1a** (5)	**5ac**	98	3.8:1	84
4	**3a**	**4d**	**1a** (5)	**5ad**	95	2:1	81
5	**3a**	**4e**	**1a** (5)	**5ae**	99	3:1	88
6	**3a**	**4f**	**1a** (5)	**5af**	99	2.5:1	81
7	**3a**	**4g**	**1a** (5)	**5ag**	97	3:1	90
8[b]	**3a**	**4g**	**1a**(10)	**5ag**	86	2.7:1	96
9[b]	**3a**	**4g**	**1b**(10)	**5ag**	95	1:1	87(9)[f]
10[b]	**3a**	**4g**	**1c**(10)	**5ag**	82	1.3:1	76(10)
11[b]	**3a**	**4g**	**1d**(10)	**5ag**	99	2:1	68(70)[f]
12[b]	**3a**	**4g**	**2a**(10)	**5ag**	94	1.5:1	76(26)
13[b]	**3a**	**4g**	**2b**(10)	**5ag**	94	1:1.4	77(29)
14[b]	**3a**	**4g**	**1a′**(10)	**5ag**	88	1:1	63(7)
15[b]	**3b**	**4g**	**1a**(10)	**5bg**	91	2.6:1	97

[a] Unless otherwise noted, reactions were carried out with **3** (0.1 mmol), **4** (0.15 mmol), and **1a** (5 mol%) in THF (0.5 mL) at −40 °C for 24 h. [b] Reactions were carried out with **3** (0.1 mmol), **4** (0.12 mmol), and the catalyst (10 mol%) in THF (0.5 mL) at −40 °C for 24 h. [c] Yield of isolated product. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Enantiomeric excess was determined by HPLC analysis and the *ee* value within parentheses is for the minor diastereomer. [f] An opposite enantiomer was obtained. THF = tetrahydrofuran.

Table 2: The effect of the stoichiometry of TFA and the catalyst **1a**.[a]

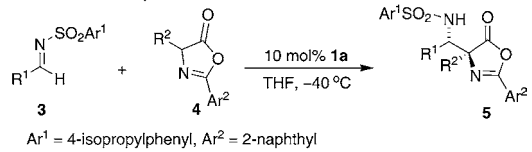


3a: Ar^1 = 4-$CH_3C_6H_4$ **4g**: Ar^2 = 2-naphthyl

Entry	x (mol%)	Yield [%][b]	d.r.[c]	*ee* [%][d]
1	0	86	2.7:1	96
2	5	92	3.5:1	82
3	10	66	1.7:1	72
4	15	–	–	–

[a] Reactions were carried out with **3a** (0.1 mmol), **4g** (0.12 mmol), **1a** (10 mol%) and TFA (*x* mol%) in THF (0.5 mL) at −40 °C for 24 h. [b] Yield of isolated product. [c] Determined by ^{1}H NMR analysis of the crude reaction mixture. [d] Enantiomeric excess of *anti* isomer was determined by HPLC analysis.

Table 3: Substrate scope for imines.[a]



3c: R^1 = Et
3d: R^1 = CH_3
3e: R^1 = *n*Pr
3f : R^1 = *n*Bu
3g: R^1 = $Me(CH_2)_7$
3h: R^1 = $CH_2{=}CH(CH_2)_2$
3i : R^1 = $CH_2{=}CH(CH_2)_8$
3j: R^1 = Me_2CHCH_2

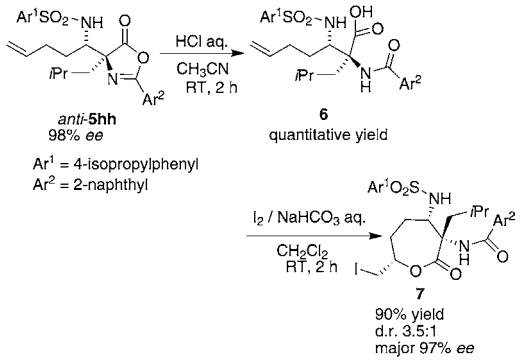
4h: R^2 = Me_2CHCH_2
4i: R^2 = $Me(CH_2)_4$
4j: R^2 = Me
4k: R^2 = $PhCH_2$
4l: R^2 = $MeCH_2$
4m: R^2 = $MeS(CH_2)_2$

Entry	3	4	5	Yield [%][c]	d.r.[d]	*ee* [%][e]
1	**3b**	**4h**	**5bh**	86	3.5:1	96
2	**3b**	**4i**	**5bi**	93	3:1	96
3[b]	**3b**	**4j**	**5bj**	86	2:1	99
4	**3c**	**4h**	**5ch**	90	7:1	97
5	**3c**	**4k**	**5ck**	98	2.7:1	96
6	**3c**	**4l**	**5cl**	92	3.4:1	98
7	**3c**	**4m**	**5cm**	96	2.9:1	98
8	**3d**	**4h**	**5dh**	89	4.6:1	96
9	**3e**	**4h**	**5eh**	95	5.9:1	97
10	**3f**	**4h**	**5fh**	93	4:1	96
11	**3g**	**4h**	**5gh**	99	4:1	96
12[f]	**3h**	**4h**	**5hh**	89	5.2:1	98
13	**3i**	**4h**	**5ih**	89	4.2:1	96
14	**3j**	**4h**	**5jh**	76	3.4:1	98

[a] Unless otherwise noted, reactions were carried out with **3** (0.1 mmol), **4** (0.12 mmol), and **1a** (10 mol%) in THF (0.5 mL) at −40 °C for 24 h. [b] The reaction was carried out at −50 °C. [c] Yield of isolated product. [d] Determined by ^{1}H NMR analysis of the crude reaction mixture. [e] Enantiomeric excess of *anti* isomer was determined by HPLC analysis. [f] Absolute configuration of **5hh** was determined to be (2*S*,3*S*) by X-ray diffraction analysis.

reaction to furnish the major diastereomer in 98% *ee* (entry 7). The protocol was also applicable to different aliphatic imines (entries 8–14). Linear aliphatic imines reacted with the azlactone **4h** to give the desired products with high levels of enantioselectivity (entries 8–11). More significantly, the introduction of a C=C bond to **3** was well tolerated with excellent enantioselectivities (entries 12 and 13). Moreover, the branched aliphatic imine **3j** afforded a product with 98% *ee* (entry 14). It is worth noting that the *syn* products were always obtained from the catalysts reported by Ooi and co-workers.[21] Therefore, the current protocol represents an important complement to the known highly enantioselective Mannich-type reactions.[3,14a,c,21–26]

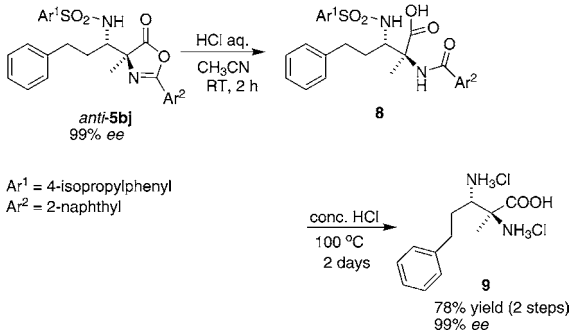
The caprolactone structural motif has been found in many biologically active natural products.[30] Moreover, they are important monomers in the preparation of biologically compatible materials.[31] The chiral caprolactones can be accessed in high optical purity starting from the current Mannich reaction (Scheme 3). The treatment of *anti*-**5hh** with aqueous hydrochloride furnished an α,β-diamino acid derivative **6** in quantitative yield, which then underwent an iodocyclization[32] to afford the highly functionalized chiral caprolactone **7** in 90% yield with a diastereomeric ratio of 3.5:1. The major diastereomer of **7** was obtained with an



Scheme 3. The application of the protocol in the synthesis of highly functionalized chiral caprolactone.

excellent enantioselectivity of 97% *ee*.[33] The flexibility and synthetic significance of caprolactone with multiple functionalities of type **7** implies the potential usefulness of the current protocol.

In addition, the resulting products **5** can be easily deprotected under acidic conditions. For example, the compound **5bj** was first hydrolyzed into the acid **8**. Subsequently, the treatment of **8** with concentrated hydrochloric acid at 100 °C smoothly generated the corresponding α,β-diamino acid dihydrochloride **9** in a high yield without the loss of the enantioselectivity (Scheme 4).



Scheme 4. Deprotection of *anti*-**5bj** to prepare α,β-diamino acid dihydrochloride.

In summary, we have developed a new type of chiral bis(betaine) base for the Mannich reaction of azlactones and aldimines. The synergism among the multiple functionalities within these organobases provided high levels of enantioselectivity (94–99% *ee*) for a variety of aliphatic imines and azlactones. Importantly, the catalyst can be easily modified for different reactions through changes to both the binaphthyl and cinchona motifs. Moreover, the strategy presented in this work has led to a versatile platform for the design of chiral organobase catalysts. Further studies will be focused on the reaction mechanism and the development of other base-catalyzed asymmetric reactions by using the chiral bis(betaine) bases.

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[27] The use of a catalyst derrived from quinine and (*S*)-binol gave 90% yield, 2.6:1 d.r. (*anti*/*syn*), and −96% *ee* (*anti* isomer).

[28] We examined the Mannich reaction of azlactone (**4g**) with *N*-Ts benzaldimine under the optimized reaction conditions, however, 85% yield and 30% *ee* (for major isomer) were obtained.

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[33] The relative configurations of the major and minor product **7** were determined by NOESY analysis.