Organocatalysis

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Enantioselective 1,3-Dipolar Cycloaddition of Cyclic Enones Catalyzed by Multifunctional Primary Amines: Beneficial Effects of Hydrogen Bonding**

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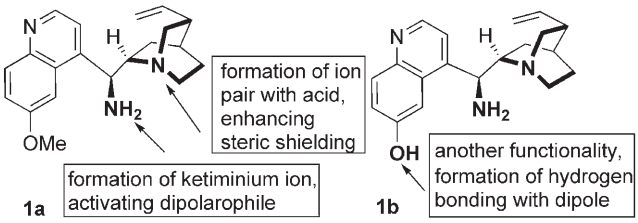
Organocatalytic asymmetric reactions provide an environmentally benign approach to a variety of optically pure compounds.[1] In particular, the development of organocatalysts bearing two or more activating functionalities has provoked increasing attention, because a concerted interaction among multifunctional catalyst and reactants can generally lead to more efficient catalysis and enantiocontrol.[2] Most bifunctional organocatalysts combine a Brønsted acid and Lewis base in one molecule to activate an electrophile and nucleophile, respectively. However, this strategy has not been applied to organocatalytic cycloaddition reactions.[3]

Asymmetric [3+2] dipolar cycloaddition is one of the most powerful protocols to synthesize chiral five-membered heterocycles, which usually have biological importance,[4] and MacMillan et al. developed the first elegant amine-catalyzed 1,3-dipolar cycloaddition of enals through a LUMO-lowering strategy.[5] However, despite great progress in iminium catalysis,[6] the organocatalytic 1,3-dipolar cycloaddition of enones still remains to be explored, probably because of the lack of suitable amine catalysts.[7] Recently, we established that 9-amino-9-deoxyepicinchona alkaloids could serve as excellent iminium catalysts for enones.[8] This finding encouraged us to investigate the undeveloped organocatalytic 1,3-dipolar cycloaddition of enones.

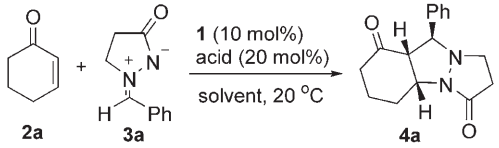
9-Amino-9-deoxyepiquinine (**1a**; 10 mol%, Scheme 1) in combination with acid (20 mol%) smoothly catalyzed the 1,3-dipolar cycloaddition of 2-cyclohexen-1-one (**2a**) and azomethine imine[9] **3a** to give the desired tricyclic product **4a** with excellent diastereoselectivity (d.r. > 99:1) at 20°C. Unfortunately, only low to moderate *ee* values could be obtained (Table 1, entries 1–3). 9-Amino-9-deoxyepiquinidine (**1c**; 10 mol%, Scheme 2) exhibited higher catalytic activity, while a similar *ee* value was obtained (Table 1, entry 4).

We realize that **1a** could activate dipolarophile **2a** by the formation of ketiminium ion, but has no direct contact with



Scheme 1. Design of the second-generation primary amine catalyst.

Table 1: Screening of the organocatalytic 1,3-dipolar cycloaddition of 2-cyclohexen-1-one (**2a**) and azomethine imine **3a**.[a]



Entry	Catalyst	Acid	Solvent	*t* [h]	Yield [%][b]	*ee* [%][c]
1	**1a**	TFA	THF	16	56	51
2	**1a**	*p*-TSA	THF	20	37	55
3	**1a**	L-CSA	THF	20	19	60
4	**1c**	L-CSA	THF	36	82	−59
5	**1b**	*p*-TSA	THF	12	52	78
6	**1b**	L-CSA	THF	24	96	87
7	**1b**	D-CSA	THF	24	89	89
8	**1b**	D-CSA	CH_2Cl_2	36	96	88
9	**1b**	D-CSA	toluene	36	89	89
10	**1b**	D-CSA	EtOAc	36	96	89
11	**1b**	D-CSA	DME	36	44	78
12	**1b**	D-CSA	*i*PrOH	24	23	61
13[d]	**1b**	D-CSA	THF	36	60	95
14[e]	**1b**	D-CSA	THF	36	22	96
15	**1a**	D-CSA	THF	42	52	51
16[d]	**1a**	D-CSA	THF	144	44	46
17[d,f]	**1b**	TIPBA	THF	36	89	90
18[d,f]	**1d**	TIPBA	THF	36	82	−86

[a] Unless otherwise noted, reactions were performed with 0.2 mmol of **2a**, 0.1 mmol of **3a**, 0.01 mmol of **1**, and 0.02 mmol of acid in 0.5 mL solvent at 20°C. [b] Yield of isolated product. [c] Determined by chiral HPLC analysis, d.r. > 99:1. [d] Addition of 10 mg 4-Å M.S. [e] Addition of 25 mg 4-Å M.S. [f] At 40°C. CSA = camphor-10-sulfonic acid; TIPBA = 2,4,6-triisopropylbenzenesulfonic acid; DME = 1,2-dimethoxyethane.

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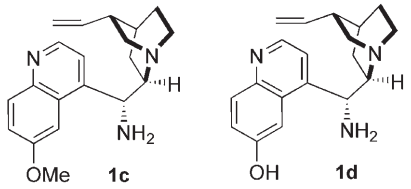


Scheme 2. Structures of amine catalysts derived from quinidine.

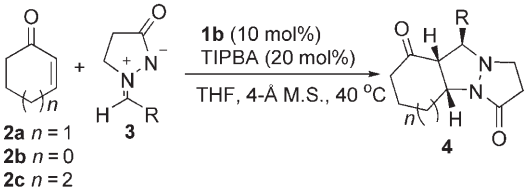
1,3-dipole **3a**. We envisage that the introduction of a hydroxy group in the primary amine catalyst **1b** (Scheme 1),[10,11] which might form a hydrogen bond[12] with the carbonyl group of dipole **3a**, would be helpful for enantiocontrol, as a synergistic interaction between the organocatalyst and the two reactants could be created.[4j,13] Indeed, both the reactivity and enantioselectivity were dramatically improved when the reaction was catalyzed by **1b** salt (Table 1, entries 5–7), and a higher *ee* value was attained with D-CSA (Table 1, entry 7). Other solvents like CH_2Cl_2, toluene, and EtOAc were also tolerated (Table 1, entries 8–10), but both reaction rate and *ee* values were decreased in DME or 2-propanol (Table 1, entries 11 and 12).

As H_2O would be generated during the formation of an active iminium intermediate, the expected hydrogen-bonding interaction might be affected. Consequently, a molecular sieve (M.S., 4 Å) was added to remove the trace amount of water. In this way, the *ee* value was raised to 95%, although the reaction time had to be extended, probably because the hydrolysis of the iminium salt to release the catalyst would be retarded after the completion of cycloaddition (Table 1, entry 13). Moreover, the reaction became very sluggish when more M.S. was introduced to further reduce the H_2O content (Table 1, entry 14). In comparison, there were no beneficial effects on the *ee* value when catalyst **1a** was applied in the presence of M.S. (Table 1, entries 15 versus 16), which also verified that the OH group of **1b** played a crucial role in this reaction.

Inspired by recent studies on counterion-directed iminium catalysis,[14] a more bulky additive, TIPBA, was tested and excellent *ee* values were obtained even at 40 °C. The reaction rate was also greatly enhanced (Table 1, entry 17). In addition, 6′-hydroxy-9-amino-9-deoxyepiquinidine (**1d**) was prepared from quinidine[10] and good results were obtained, although the product had the opposite configuration (Table 1, entry 18). Hence, both enantiomers of the cycloaddition product could be attained.

Having established the optimal conditions, the scope of the dipolar cycloaddition reaction was explored with a variety of cyclic enones **2** and azomethine imines **3** (Table 2). In general, better results were obtained with catalysis by **1b**/TIPBA salt at 40 °C with addition of 4-Å M.S.[10] Excellent diastereoselectivity (d.r. > 99:1) was noted in all reactions. For **2a**, high enantioselectivities were achieved with azomethine imines bearing various aryl (Table 2, entries 2–10), heteroaryl (Table 2, entry 11), and alkyl substituents (Table 2, entries 12–14). Azomethine imines with an electron-donating substituent displayed higher reactivity, and excellent results were obtained even with 2 mol% of **1b** (Table 2, entry 9).

Table 2: Asymmetric 1,3-dipolar cycloaddition of cyclic enones **2** and azomethine imines **3**.[a]



Entry	2	R (3)	t [h]	4	Yield [%][b]	ee [%][c]
1	**2a**	Ph (**3a**)	36	**4a**	89	90
2	**2a**	*p*-ClC_6H_4 (**3b**)	60	**4b**	73	92[d]
3	**2a**	*m*-ClC_6H_4 (**3c**)	72	**4c**	73	95
4[e]	**2a**	*o*-ClC_6H_4 (**3d**)	18	**4d**	80	94
5	**2a**	*p*-BrC_6H_4 (**3e**)	48	**4e**	73	92
6	**2a**	*p*-FC_6H_4 (**3f**)	48	**4f**	70	92
7	**2a**	*p*-$MeOC_6H_4$ (**3g**)	36	**4g**	99	92
8[f]	**2a**	*p*-$MeOC_6H_4$ (**3g**)	48	**4g**	99	93
9[g]	**2a**	*p*-$MeOC_6H_4$ (**3g**)	120	**4g**	67	93
10	**2a**	3,4-$(MeO)_2C_6H_3$ (**3h**)	20	**4h**	88	86
11	**2a**	2-furanyl (**3i**)	96	**4i**	99	95
12	**2a**	*i*Pr (**3j**)	40	**4j**	76	91
13	**2a**	cyclohexyl (**3k**)	24	**4k**	94	92
14	**2a**	*n*Pr (**3l**)	40	**4l**	76	87
15[h]	**2b**	Ph (**3a**)	60	**4m**	78	90
16[h]	**2b**	*p*-$MeOC_6H_4$ (**3g**)	24	**4n**	91	95
17[h]	**2b**	*p*-BrC_6H_4 (**3e**)	60	**4o**	72	93
18	**2c**	*p*-$MeOC_6H_4$ (**3g**)	60	**4p**	76	93
19[i]	**2a**	*m*-ClC_6H_4 (**3c**)	60	**4c**	72	−90
20[i]	**2a**	*p*-$MeOC_6H_4$ (**3g**)	40	**4g**	95	−85
21[i]	**2a**	cyclohexyl (**3k**)	40	**4k**	83	−85
22[i]	**2b**	*p*-$MeOC_6H_4$ (**3g**)	40	**4n**	75	−90

[a] Unless otherwise noted, reactions were performed with 0.2 mmol of **2**, 0.1 mmol of **3**, 10 mol% of **1b**, and 20 mol% of TIPBA in 0.5 mL THF at 40 °C. [b] Yield of isolated product. [c] Based on chiral HPLC analysis. [d] The absolute configuration of **4b** was determined by X-ray analysis (Figure 1),[15] and other products were assigned by analogy. [e] Without adding M.S. [f] With 5 mol% of **1b**. [g] With 2 mol% of **1b**. [h] With 20 mol% of **1b**. [i] With **1d** as catalyst.

In addition, remarkable *ee* values were obtained in the cycloaddition of 2-cyclopenten-1-one (**2b**), although 20 mol% of catalyst was required for the achievement of high yields (Table 2, entries 15–17). Furthermore, 2-cyclohepten-1-one (**2c**) was tested and a high enantioselectivity was attained (Table 2, entry 18). On the other hand, the opposite enantiomeric cycloaddition products were prepared with high *ee* values when catalyzed by **1d**/TIPBA salt under the same conditions (Table 2, entries 19–22).[16,17]

On the basis of the absolute configuration of **4b** (see Figure 1), we propose a plausible catalytic mode, albeit very naive, for the reaction of **2a** and **3b** (Scheme 3). The ketiminium cation between **1b** and enone **2a** might adopt a *trans* conformation, and a hydrogen bond would be formed from the OH group of **1b** and the carbonyl group of **3b** to produce concerted communication. As a result of the steric hindrance from the ion pair of the tertiary amine moiety,[8] high *endo*- and *re*-face selectivity would be enforced to give the desired cycloaddition product. Nevertheless, the exact catalytic mechanism still needs more investigation.

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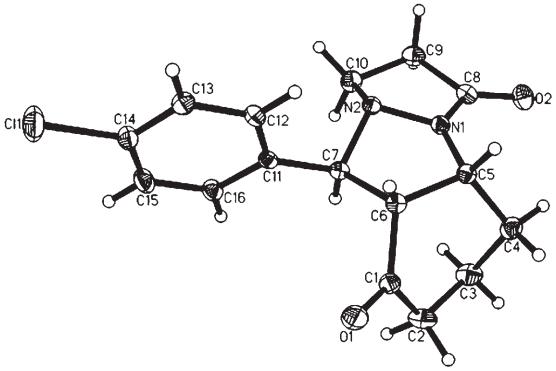
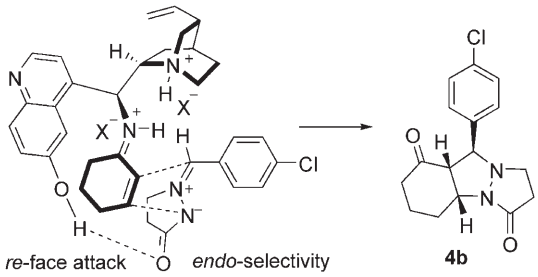


Figure 1. X-ray structure of enantiomerically pure **4b**. Thermal ellipsoids are set at 30% probability.



Scheme 3. Proposed cycloaddition mode of **2a** and **3b** catalyzed by multifunctional salt of **1b**.

In conclusion, we have developed the first organocatalytic and highly enantioselective 1,3-dipolar cycloaddition of cyclic enones and azomethine imines, by employing novel multifunctional primary amine catalysts derived from cinchona alkaloids. The additional and synergistic hydrogen-bonding interaction of catalyst and 1,3-dipole is essential for enantiocontrol, and excellent stereoselectivities were achieved for a broad spectrum of substrates (d.r. > 99:1, up to 95% *ee*). We hope that this work will give some hints in the development of new multifunctional organocatalysts and asymmetric reactions.

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Keywords: amines · cycloaddition · enantioselectivity · enones · organocatalysis

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[15] CCDC-655245 (**4b**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[16] Currently only a low *ee* value (< 30 %) was obtained for acyclic enones. Further studies on such substrates and synthetic utility of the new heterocycles are being explored.

[17] The preparation, and potential cycloaddition reaction, of acyclic azomethine imine from *N*-Boc-*N*′-benzylhydrazine (Boc = *tert*-butoxycarbonyl) and benzaldehyde was unsuccessful.

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