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Asymmetric Organocatalytic Three-Component 1,3-Dipolar Cycloaddition: Control of Stereochemistry via a Chiral Brønsted Acid Activated Dipole

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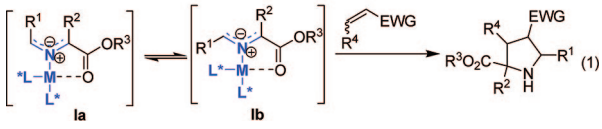
1,3-Dipolar cycloaddition of azomethine ylide to electron-deficient olefins yields chiral pyrrolidines, an important class of heterocyclic compounds with widespread applications to the synthesis of biologically active compounds and natural products.[1] These cycloaddition reactions represent an important class of synthetic methods and have inspired much research interest in the development of asymmetric catalytic variants.[1,2] Elegant studies in this field have often centered on chiral Lewis acid (LA) catalyzed asymmetric 1,3-dipolar additions with azomethine ylides, in which the stereochemistry is controlled via a chiral metal complex bonded intermediate **Ia** or **Ib** (eq 1).[2,3] Very recently, high stereoselectivities were observed with the first organocatalytic asymmetric 1,3-dipolar addition of an azomethine ylide to α,β-unsaturated aldehydes.[4] This reaction was catalyzed by chiral secondary amines through the reversible formation of iminium ions with α,β-unsaturated aldehydes, which served to reduce the energy of the lowest unoccupied molecular orbital of the dipolarophiles.[5] However, this procedure did not include dipolarophiles other than unsaturated aldehydes.[4]

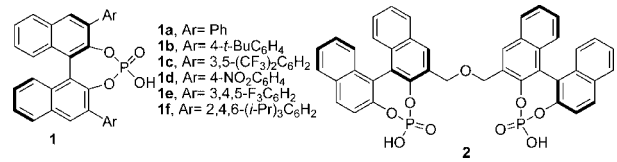
Control of Stereochemistry with Chiral LA-Bonded Dipole.



Control of Stereochemistry with Chiral BH-Bonded Dipole

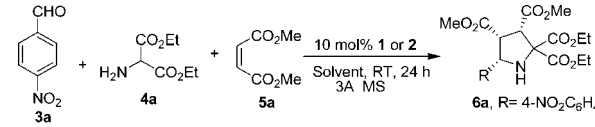
Chiral Brønsted acids (BH), in particular, chiral phosphoric acids, provide sufficient acidity required for the activation of imines leading to many new asymmetric procedures,[6] including multicomponent reactions.[7] We envisioned that they are theoretically able to form a chiral azomethine ylide dipole **IIa** or **IIb** with an azomethine compound that would undergo an enantioselective 1,3-dipolar cycloaddition with dipolarophiles (eq 2). Herein, we report that an asymmetric, catalytic, and three-component 1,3-dipolar cycloaddition between aldehydes, amino esters, and electron-deficient olefins could be realized by using the chiral BH activated dipole to control the stereochemistry, yielding multiply substituted pyrrolidines with high enantioselectivity (up to 99% ee). This procedure allows a rapid diversity-oriented synthesis[8] of chiral pyrrolidine derivatives.

To validate our hypothesis, we performed a three-component reaction of *para*-nitrobenzaldehyde (**3a**) and diethyl aminomalonate (**4a**) with dimethyl maleate (**5a**) under the influence of 10 mol % of BINOL-derived phosphoric acid **1a** in the presence of 3 Å molecular sieves in dichloromethane. To our delight, a cycloaddition reaction smoothly furnished an endodiastereomer **6a** in 78% yield, albeit with a low ee (Table 1, entry 1). Encouraged by this preliminary result, a number of chiral phosphoric acids derived from BINOL were evaluated. It appeared that none of these catalysts provided a satisfactory enantioselectivity, although they showed good catalytic efficiency (entries 1–6). Strikingly, a bisphosphoric acid, derived from (*R*,*R*)-linked BINOL that was initially designed as a chiral ligand,[9] was the most promising catalyst and provided an almost quantitative yield and excellent enantioselectivity of 98% ee (entry 7). Halogen-containing solvents were most suitable for the reaction, providing better results than those obtained with other solvents (entries 7–12). No variation in the stereoselectivity was observed by carrying out the reaction at 0 °C (entry 13).



Having established the optimal procedure, we next investigated the effect of aldehydes in reactions with **4a** and **5a** (Table 2). A wide range of aldehydes including aromatic, α,β-unsaturated, and aliphatic variants could be tolerated, leading to the formation of

Table 1. Screening Catalysts and Optimization of Reaction Conditions[a]



entry	catalyst	solvent	yield (%)[b]	ee (%)[c]
1	**1a**	CH_2Cl_2	78	8
2	**1b**	CH_2Cl_2	74	6
3	**1c**	CH_2Cl_2	88	25
4	**1d**	CH_2Cl_2	87	46
5	**1e**	CH_2Cl_2	83	43
6	**1f**	CH_2Cl_2	78	23
7	**2**	CH_2Cl_2	96	98
8	**2**	$CHCl_3$	92	97
9	**2**	$PhCH_3$	88	88
10	**2**	$ClCH_2CH_2Cl$	98	97
11	**2**	CH_3CN	84	58
12	**2**	THF	72	12
13	**2**	CH_2Cl_2	97	98[d]

[a] The reaction was carried out in 0.2 mmol scale in a solvent (2 mL) with 3 Å MS (300 mg), and the ratio of **3a**/**4a**/**5a** is 1.2/1/5. [b] Isolated yield based on **6a** and **4a**. [c] Determined by HPLC. [d] The reaction was performed at 0 °C for 72 h.

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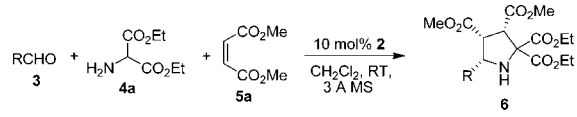
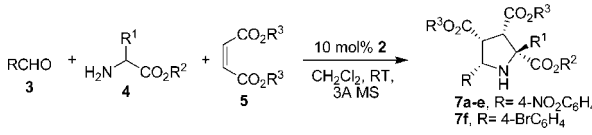
Table 2. Scope of Aldehydes of the Asymmetric Three-Component 1,3-Dipolar Addition Reactions[a]



entry	6	R	time (h)	yield (%)[b]	ee (%)[c]
1	**6b**	3-$NO_2C_6H_4$	24	95	99
2	**6c**	2-$NO_2C_6H_4$	48	97	96
3	**6d**	4-CNC_6H_4	24	94	95
4	**6e**	4-$MeO_2CC_6H_4$	24	88	98
5	**6f**	4-BrC_6H_4	72	89	99
6	**6g**	4-FC_6H_4	72	94	98
7	**6h**	3-ClC_6H_4	72	92	90[d]
8	**6i**	2-BrC_6H_4	96	67	94[d]
9	**6j**	4-ClC_6H_4	72	97	93
10	**6k**	2-Cl,4-FC_6H_3	96	82	97[d]
11	**6l**	Ph	48	93	91[d]
12	**6m**	4-$MeOC_6H_4$	96	87	90[d]
13	**6n**	1-nphthyl	96	90	84[d]
14	**6o**	2-nphthyl	96	92	87[d]
15	**6p**	4-MeOPhCH=CH	96	75	93[d]
16	**6q**	4-MePhCH=CH	96	70	92[d]
17	**6r**	*c*-C_6H_{11}	96	74	76[d,e]

[a] The reaction was carried out in 0.2 mmol scale in dichloromethane (2 mL) with 3 Å MS (300 mg), and the ratio of **3/4a/5a** was 1.2/1/5. [b] Isolated yield based on **6** and **4**. [c] Determined by HPLC. [d] The ratio of **3/4/5a** is 1/1.2/10. [e] Reacted with dimethyl aminomalonate (**4b**).

Table 3. Scope of Amino Esters and Dipolarophiles of the Asymmetric Three-Component 1,3-Dipolar Addition Reactions[a]



entry	7	R^1	R^2	R^3	time (h)	yield (%)[b]	ee (%)[c]
1	**7a**	CO_2Et	Et	Et	36	95	90
2	**7b**	CO_2Et	Et	Bu	36	77	81
3	**7c**	CO_2Me	Me	Me	48	95	96[d]
4	**7d**	CO_2Me	Me	Et	48	92	91[d]
5	**7e**	Ph	Me	Me	60	92[e]	97[f]
6	**7f**	Ph	Me	Me	60	93[e]	97[f,g]

[a] The reaction was carried out in 0.2 mmol scale in dichloromethane (2 mL) with 3 Å MS (300 mg), and the ratio of **3a/4/5** was 1.2/1/5. [b] Isolated yield based on **7** and **4**. [c] Determined by HPLC. [d] The reaction was performed at 0 °C. [e] Isolated yield based on **5a** and **7**. [f] In the presence of 20 mol % of **2** in $CHCl_3$ at 50 °C, and the ratio of **3/4c/5a** is 5/4/1. [g] The reaction with 4-BrC_6H_4CHO.

desired adducts in high yields and excellent enantioselectivities. Regardless of the substituent on the benzene ring, benzaldehyde derivatives furnished five-membered heterocycles with 90–99% ee (entries 1–12). Either α- or β-naphthaldehyde served as a good substrate to yield **6n** or **6o** with 84 or 87% ee, respectively (entries 13 and 14). Significantly, the azomethine ylides generated in situ from α,β-unsaturated aldehydes, which have not yet been evaluated as substrates for the chiral Lewis acid catalyzed 1,3-dipolar addition, successfully reacted with **5a** in high enantioselectivity (entries 15 and 16). An attempt to use an aliphatic aldehyde substrate led to a fairly good reaction with a moderate enantioselectivity (entry 17). The relative and absolute configurations of **6f** were assigned by the X-ray analysis (see Supporting Information).

The scope and limitations of the protocol with regard to amino esters **4** and dipolarophiles were also explored (Table 3). The stereoselectivity of the [3 + 2] dipolar addition reaction seemed highly sensitive to the dipolarophiles and particularly suffered from the presence of bulky substituents on the maleates **5**. For example, although ethyl and butyl maleates were both highly reactive, they gave comparably lower enantioselectivities than dimethyl maleate (entries 1 and 2). The enantioselectivity was significantly reduced with dimethyl fumarate.[10] An almost racemic [3 + 2] adduct was obtained using *N*-methyl maleimide as the dipolarophile.[11] However, no obvious change in the enantioselectivity was observed employing dimethyl aminomalonate (**4b**) to replace **4a** as a reaction component (entries 3 and 4). Importantly, α-phenylglycine methyl ester (**4c**) was also able to undergo the three-component 1,3-dipolar additions, affording adducts with four contiguous stereogenic centers including a quaternary carbon with high enantiomeric excesses (entries 5 and 6). Notably, the few reported chiral Lewis acid catalyzed dipolar addition reactions involving structural analogues of **4c**-derived azomethines with dipolarophiles have mostly shown enantioselectivities of <81% ee.[3c,e,12]

In conclusion, we have described a Brønsted acid catalyzed three-component asymmetric 1,3-dipolar addition reaction[13] between aldehydes, amino esters, and dipolarophiles by a new bisphosphoric acid derived from the linked BINOL, furnishing multiply substituted pyrrolidines in high yields with excellent enantioselectivities under mild conditions. The procedure is easy to perform and allows a rapid, diversity-oriented, and enantioselective synthesis of pyrrolidine derivatives. The concept that the stereoselectivity may be controlled by use of a chiral Brønsted acid bonded dipole may lead to new findings in asymmetric catalytic 1,3-dipolar addition reactions with dipolarophiles other than electron-deficient olefins.

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Supporting Information Available: Experimental details and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) The reaction provided 92% yield, 2/1 dr, and 73% ee.
(11) The reaction provided 95% yield with 2% ee.
(12) Exceptionally, *N*-phenyl maleimide reacted with an imino ester derived from 2-naphthaldehyde and alanine methyl ester in 92% ee; see ref 3e.
(13) After submission of this manuscript, an excellent work by Yamamoto concerns Brønsted acid catalyzed 1,3-diploar addition of nitrones published on the Web: Jiao, P.; Nakashima, D.; Yamamoto, H. *Angew. Chem., Int. Ed.* **2008**, *47*, 2411.

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