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Direct Assembly of Aldehydes, Amino Esters, and Anilines into Chiral Imidazolidines via Brønsted Acid Catalyzed Asymmetric 1,3-Dipolar Cycloadditions

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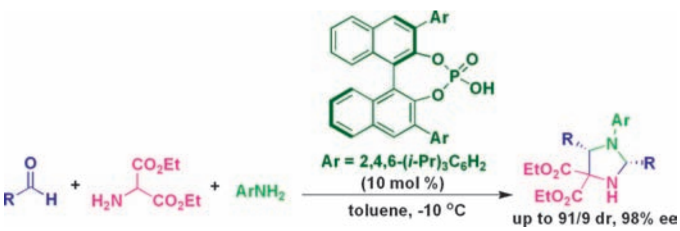
ABSTRACT



A chiral Brønsted acid catalyzed 1,3-dipolar cycloaddition reaction directly assembles aldehydes, amino esters, and anilines into synthetically useful chiral imidazolidines with high levels of stereoselectivity (up to 91/9 dr and 98% ee).

Optically active imidazolidines are important intermediates with broad applications in organic synthesis.[1] The 1,3-dipolar cycloaddition of azomethine ylides to imines with concomitant creation of multiple stereogenic centers represents an efficient and atom-economical method for the manufacture of these compounds. Numerous highly enantioselective 1,3-dipolar additions between azomethine ylides and electron-deficient olefins have been developed through the use of either the metal-based or organic catalysts.[2−4] However, only a few diastereoselective 1,3-dipolar cycloadditions of azomethine ylides with imines that utilized preformed chiral reaction components to control stereoselectivities have been available for furnishing enantioenriched imidazolidines.[5] To

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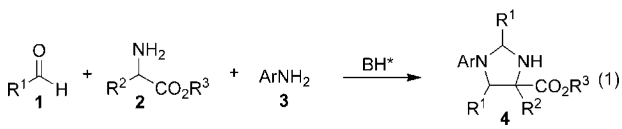
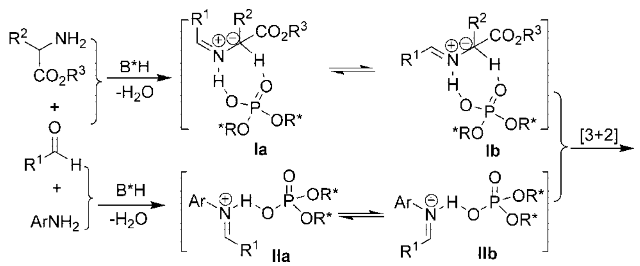
date, the catalytic asymmetric 1,3-dipolar cycloaddition of azomethine ylides to imines has not been reported, and we believe this represents a considerable challenge.[6] Herein, we present the first asymmetric catalytic three-component 1,3-dipolar cycloaddition between azomethine ylides and imines that directly assembles aldehydes, amino esters, and anilines into chiral imidazolidines with high levels of enantioselectivity (eq 1).



During our recent efforts to develop Brønsted acid catalyzed asymmetric multicomponent reactions, we have demonstrated that chiral phosphoric acids[7] effectively furnish Biginelli reactions, Mannich reactions, and cyclization of enals with anilines and 1,3-dicarbonyls.[8] Most recently, we established a three-component 1,3-dipolar cycloaddition reaction wherein the phosphoric acid controlled the stereochemistry by presumably forming a chiral dipole, **Ia** or **Ib**, with an azomethine ylide.[9] An imine generated in situ from an aldehyde and an amine could be activated by formation of an iminium species, either **IIa** or **IIb**, with a Brønsted acid and showed high reactivity toward nucleophiles.[7,8] We questioned whether the iminium intermediates would be captured by the chiral Brønsted acid activated dipole **Ia** or **Ib** to thereby undergo an enantioselective [3 + 2] cycloaddition (Scheme 1).

Scheme 1. Proposed Phosphoric Acid Catalyzed 1,3-Dipolar Cycloaddition of Imines with Azomethine Ylides



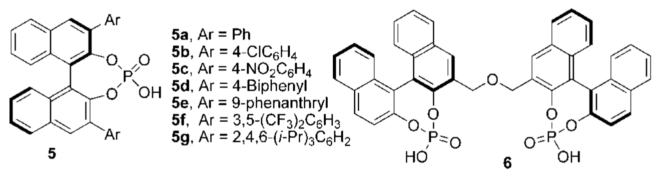


Figure 1. Catalysts evaluated in this study.

In our initial experiments, the benzaldehyde (**1a**), diethyl aminomalonate (**2a**), and *p*-anisidine (**3a**) smoothly underwent 1,3-dipolar cycloaddition in toluene under the catalysis of a phosphoric acid **5a**, furnishing the desired imidazolidine **4a** in 90% yield, but with unsatisfactory stereoselectivity (Table 1, entry 1). A survey of various binol-based catalysts demonstrated that the phosphoric acid **5g**, bearing the most sterically congested substituents, gave superior stereoselectivity (entries 2−7). However, the bis-phosphoric acid **6**, which delivered high ee in the 1,3-dipolar cycloaddition of azomethine ylides to maleates, exhibited poor stereoselectivity (entry 8). Screening of solvents suggested that toluene is most suitable for the reaction (entries 7 and 9−11). The aniline substituent played a crucial role in the stereochemistry (entries 12−16). Accordingly, excellent enantioselectivities were observed with *m*-toluidine and 4-*tert*-butoxyaniline (entries 14 and 16).

Having established the optimal conditions, we then examined the scope of the aldehydes that could participate in the cycloaddition reaction with either *m*-toluidine (**3d**) or 4-*tert*-butoxyaniline (**3f**). As shown in Table 2, electronically poor and neutral aromatic aldehydes reacted smoothly with 4-*tert*-butoxyaniline (**3f**) to afford *syn*-imidazolidines in high yields with excellent enantioselectivities (entries 1−7 and 10−14). Although electronically rich benzaldehydes showed much less reactivity in the reaction involving the 4-*tert*-butoxyaniline component, they underwent facile reactions with *m*-toluidine (**3d**) in high enantioselectivities (entries 8 and 9). The diastereoselectvity was found highly dependent on the substituent of aldehydes. Generally, *para*-substituted

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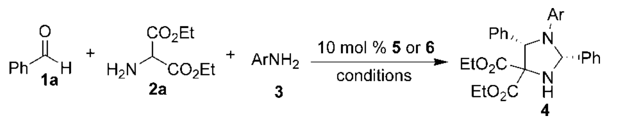
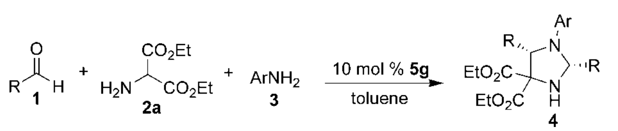
Table 1. Optimization of Reaction Conditions[a]



entry	catalyst	4 (Ar)	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**5a**	*p*-MeOC_6H_4 (**4a**)	toluene	90	67/33	7[e] (6)
2	**5b**	*p*-MeOC_6H_4 (**4a**)	toluene	84	52/48	8 (15)
3	**5c**	*p*-MeOC_6H_4 (**4a**)	toluene	83	56/44	2 (6)
4	**5d**	*p*-MeOC_6H_4 (**4a**)	toluene	89	68/32	15 (1)
5	**5e**	*p*-MeOC_6H_4 (**4a**)	toluene	82	53/47	8 (41[e])
6	**5f**	*p*-MeOC_6H_4 (**4a**)	toluene	85	82/18	5[e] (1)
7	**5g**	*p*-MeOC_6H_4 (**4a**)	toluene	98	73/27	82 (41)
8	**6**	*p*-MeOC_6H_4 (**4a**)	toluene	84	48/52	40[e] (5)
9	**5g**	*p*-MeOC_6H_4 (**4a**)	CH_2Cl_2	94	39/61	23 (54)
10	**5g**	*p*-MeOC_6H_4 (**4a**)	$CHCl_3$	97	52/48	61 (38)
11	**5g**	*p*-MeOC_6H_4 (**4a**)	$(CH_2Cl)_2$	85	30/70	31 (50)
12	**5g**	Ph (**4b**)	toluene	89	78/22	89 (42)
13	**5g**	*m*-MeOC_6H_4 (**4c**)	toluene	86	59/41	87 (57)
14	**5g**	*m*-MeC_6H_4 (**4d**)	toluene	86	79/21	91 (36)
15	**5g**	*p*-ClC_6H_4 (**4e**)	toluene	96	66/34	89 (62)
16	**5g**	*p*-(*t*-BuO)C_6H_4 (**4f**)	toluene	77	75/25	90 (46)[f]

[a] The reaction was carried out at 0.2 mmol scale in toluene (2 mL) with 3 Å MS (200 mg) at −10 °C for 36 h, and the ratio of **1a/2a/3** was 3:1:1.2. [b] Isolated yield based on **2a**. [c] Determined by ^{1}HNMR. [d] Determined by HPLC, the ee in parentheses is for the minor diastereomer. [e] The opposite enantiomer was obtained. [f] Reaction time was 60 h.

Table 2. Scope of Aldehydes[a]



entry	4	R	yield (%)[b]	dr[c]	ee (%)[d]
1	**4g**	4-$NO_2C_6H_4$	73	91/9	98
2	**4h**	4-BrC_6H_4	85	82/18	95
3	**4i**	4-CNC_6H_4	90	90/10	98
4	**4j**	4-$MeO_2CC_6H_4$	89	91/9	98
5	**4k**	4-$CF_3C_6H_4$	84	83/17	94
6	**4l**	4-ClC_6H_4	91	79/21	95 (20)
7	**4m**	4-FC_6H_4	89	76/24	93 (33)[e]
8	**4n**	4-$CH_3C_6H_4$	85	75/25	88 (15)[f,g]
9	**4o**	3-$CH_3OC_6H_4$	99	63/37	90 (15)[f,g]
10	**4p**	3-BrC_6H_4	82	84/16	95
11	**4q**	2-BrC_6H_4	87	65/35	90 (65)
12	**4r**	2-ClC_6H_4	76	48/52	85 (66)
13	**4s**	2-FC_6H_4	78	45/55	89 (60)
14	**4t**	1-naphthyl	99	88/12	90[e]
15	**4u**	c-C_3H_5	63	*j*	40[g,h]
16	**4v**[i]	Ph≡	86	34/66	76 (58)[f,g]

[a] Unless indicated otherwise, the reaction involving 4-*tert*-butoxyaniline (**3f** was carried out in 0.2 mmol scale in toluene (2 mL) with 3 Å MS (200 mg) at −10 °C for 60 h, and the ratio of **1/2a/3** was 3/1/1.2. [b] Isolated yield based on **2a**. [c] Determined by ^{1}HNMR. [d] Determined by HPLC, the *ee* in parentheses is for the minor diastereomer. [e] Stirred for 100 h. [f] At −20 °C. [g] Reactions with *m*-toluidine (**3d**). [h] The ratio of **1/2a/3** was 5:3:1. [i] Using **5e** as a catalyst. [j] The *anti*-diastereomer was not observed by ^{1}HNMR.

benzaldehydes gave much higher diastereomeric ratios than *ortho*-substituted ones (entries 1−8 and 11−13). Interestingly, 2-fluoro- and 2-chlorobenzaldehydes favored *anti*-diastereomers (entries 12 and 13), opposite to those observed with *para*- and *meta*-substituted benzaldehydes. 1-Naphthaldehyde was also a good reaction partner, giving a good diastereomeric ratio and high enantioselectivity (entry 14). Notably, the protocol is amenable to aliphatic aldehydes such as cyclopropanecarboxaldehyde,[10] albeit with a moderate stereoselectivity (entry 15). Importantly, ynals, a class of challenging reaction acceptors under organocatalytic conditions, were tolerated in the dipolar cycloaddition catalyzed by **5e** favoring the *anti*-product as exemplified by phenylpropiolaldehyde (entry 16). The relative and absolute stereochemistry of **4h** was assigned by X-ray analysis (Figure 2), and the stereochemistry of the other products was assigned by analogy.

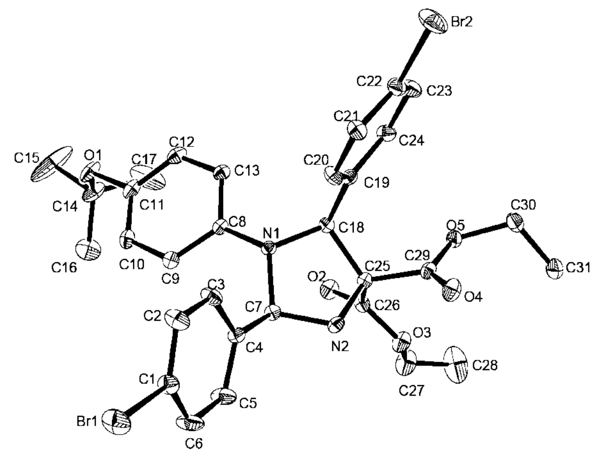


Figure 2. X-ray crystal structure of **4h** with ellipsoids set at 10% probability. Hydrogen atoms are omitted for clarity.

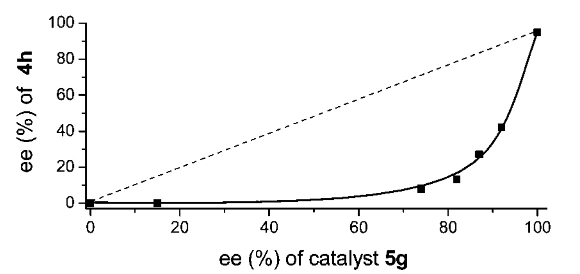


Figure 3. Relation between enantiomeric excess of **4h** and that of **5g**.

A preliminary mechanistic study was conducted by measuring the nonlinear effect (NLE). Plotting the ee of the catalyst **5g** versus that of the product **4h** led to a negative NLE (Figure 3), implying that two molecules of phosphoric acids may participate in the catalysis via the pathway shown in Scheme 1.[11]

(10) Cyclohexanecarboxaldehyde also reacted with *m*-toluene (**3d**) to afford imidazoline in a 32% yield after 6 days, but we failed to resolve the product by chiral HPLC and therefore the ee is not reported.

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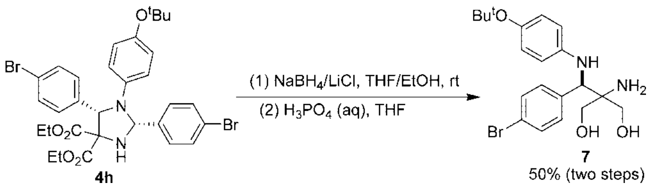
Scheme 2. Synthetic Application of Imidazolidines



Optically pure vicinal diamines and amino alcohols have been widely used in organic synthesis, either as chiral auxiliaries or ligands,[12] and the present 1,3-dipolar cycloaddition reaction may be applied to the synthesis of these compounds (Scheme 2). The exposure of imidazolidine **4h** to a combined reductive reagent of sodium borohydride and lithium chloride in a solvent mixture of ethanol and THF,[13] followed by a one-pot hydrolysis with aqueous phosphoric acid in THF, generated a chiral β,γ-diamino alcohol **7** in an overall 50% yield.

In summary, we have disclosed the first catalytic asymmetric 1,3-dipolar cycloaddition that directly assembles aldehydes, amino esters, and anilines into synthetically useful chiral imidazolidines with high levels of stereoselectivity. Two molecules of Brønsted acids participated in the catalysis by the activation of both azomethine ylides and imines. This reaction has further demonstrated that the chiral Brønsted acid activated dipoles are versatile intermediates for the creation of new enantioselective 1,3-dipolar cycloadditions. Additional related studies will be reported in due course.

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

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