Organocatalytic asymmetric intramolecular [3+2] cycloaddition: A straightforward approach to access multiply substituted hexahydrochromeno[4,3-b]pyrrolidine derivatives in high optical purity†

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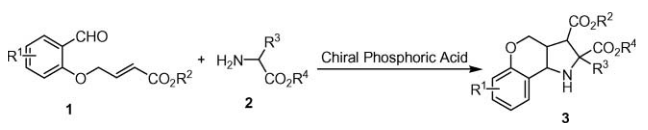
A chiral phosphoric acid-catalyzed intramolecular 1,3-dipolar cycloaddition of 4-(2-formylphenoxy)butenoates with amino esters provides hexahydromeno[4,3-b]pyrrolidine derivatives in high enantioselectivity (up to 94% ee).

Hexahydromeno[4,3-b]pyrrolidine and its structural analogues have received considerable attention from synthetic and biological chemists, because they constitute key subunits widely present in biologically active and natural products, and serve as building blocks in organic synthesis.[1] For example, these compounds have been non-competitive antagonists of the muscular nicotin receptor.[2] Moreover, they have been used as conformationally restricted nicotine or rivastigmine analogues,[3] and, therefore, hold great potential to be acetylcholinesterase inhibitors.[4] In addition, similar structural scaffolds widely occur in a large number of natural compounds, as exemplified by martinelline[5] and sceletium alkaloid A_4.[6] The significance of this heterocyclic skeleton in organic and medicinal chemistry has led to a great demand for efficient synthetic methods, particularly those capable of producing highly enantiomerically enriched hexahydromeno[4,3-b]pyrrolidine derivatives. Although several transformations have been available for the construction of these skeletons, some protocols exploited metal-based chiral catalysts to control the stereoselectivity[7] and the others merely gave racemic compounds under rigorous reaction conditions in the absence of catalysts.[8] Consequently, an enantioselective catalytic procedure for the facile construction of polycyclic pyrrolidine skeletons in one-pot under mild reaction conditions remains highly desirable with respect to synthetic efficiency and atom economy.

Most recently, we found that azomethines could be activated by phosphoric acids by forming chiral azomethine ylide dipoles capable of undergoing 1,3-dipolar cycloaddition reactions with electronically poor C=C double bonds and imines, leading to the emergence of several straightforward methods for structurally diverse synthesis of nitrogenous five-membered heterocycles with high optical purity.[9] Recognizing the importance of hexahydromeno[4,3-b]pyrrolidine derivatives and a paucity of efficient approaches to access these molecules, we have great interest in the development of an enantioselective intramolecular 1,3-dipolar cycloaddition of 4-(2-formylphenoxy)butenoates of type **1** with amino esters **2** using phosphoric acids as chiral catalysts[10] (Scheme 1). Herein, we will present our efforts on the discovery of the first organocatalytic asymmetric intramolecular 1,3-dipolar cycloaddition reaction for the synthesis of hexahydromeno[4,3-b]pyrrolidine derivatives in high enantioselectivity.



Scheme 1 The phosphoric acid-catalyzed intramolecular 1,3-dipolar cycloaddition.

An initial experiment of (*E*)-ethyl-4-(2-formylphenoxy)but-2-enoate (**1a**) and methyl-2-amino-2-phenylacetate (**2a**) under the influence of 10 mol% of a BINOL-derived phosphoric acid **4a** in the presence of 3 Å molecular sieves in chloroform was carried out. As we expected, the intramolecular [3+2] cycloaddition reaction occurred to give the desired product **3a** in 41% yield and 85 : 15 dr, but the enantioselectivity was low (33% ee, Table 1, entry 1). Encouraged by this preliminary result, a number of 3,3′-disubstituted binol-derived phosphoric acids **4** (Fig. 1) were evaluated to recruit the optimal catalyst (entries 2–9). As can be seen from Table 1, the reaction performance was highly dependent on the structure of phosphoric acids. The sterically bulky 3,3′-substituents of phosphoric acids were seemingly deleterious to the catalytic activity and stereoselectivity. For example, the use of phosphoric acids bearing bulky 3,3′-substituents as catalysts, which showed high stereoselectivity in many transformations,[10a–c] rendered an almost non-selective reaction (entries 2–4). **4g** turned

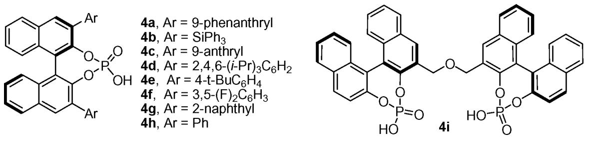


Fig. 1 Catalysts evaluated in this study.

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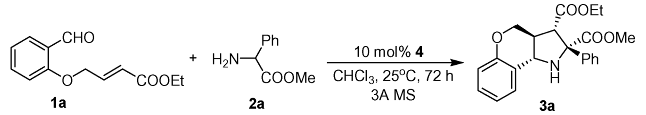
Table 1 Screening of chiral phosphoric acids[a]



Entry	4	Yield (%)[b]	dr[c]	ee (%)[d]
1	**4a**	41	85 : 15	33
2	**4b**	9	90 : 10	3
3	**4c**	34	83 : 17	3
4	**4d**	37	87 : 13	1
5	**4e**	11	74 : 26	25
6	**4f**	38	93 : 7	32
7	**4g**	64	93 : 7	59
8	**4h**	28	88 : 12	58
9	**4i**	15	83 : 17	2

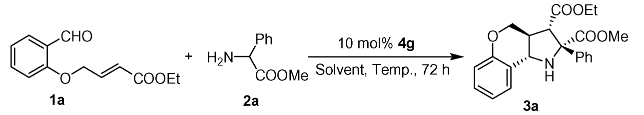
[a] The reaction was carried out at 0.1 mmol scale in chloroform (1 mL) with 3 Å MS (200 mg) at 25 °C for 72 h and the ratio of **1a** : **2a** was 1.2 : 1. [b] Isolated yield based on **2a**. [c] The dr refers to the ratio of **3a** to its isomers and was determined by ^1H NMR of crude product. [d] Determined by HPLC.

out to be the optimal catalyst and gave the highest levels of stereochemical outcome (entries 5–8). Surprisingly, bisphosphoric acid **4i**, which gave excellent enantioselectivity for 1,3-dipolar cycloaddition,[9a,c] also delivered an almost racemic product (entry 9).

With the optimal organocatalyst in hand, the reaction parameters including solvents, molecular sieves and temperature were investigated and the results are summarized in Table 2. Screening of solvents found that toluene was the best media for the reaction in terms of conversion and stereoselectivity (entries 1–4). However, no reaction occurred in THF (entry 3). Variation of molecular sieves from 3 to 4 and 5 Å suggested that 3 Å molecular sieves turned out to be the best additive in terms of enantioselectivity (entries 4–6). Either lowering or elevating the temperature afforded unsatisfactory results (entries 8–9). Particularly, the reaction did not work upon being conducted at 0 °C (entry 7). The best results were obtained by performing the reaction at a higher concentration (entry 10).

Having the optimal conditions, we first investigated the generality of the protocol for various α-arylglycine methyl esters (Table 3). Both electronically rich and poor arylglycine methyl esters were well tolerated and furnished the desired products in good yields and with high to excellent enantioselectivity. Generally, the electronically deficient α-arylglycine methyl esters provided higher enantioselectivity than the electronically rich derivatives (entries 1–6 *vs.* 7). Specifically, methyl-2-amino-2-(2-fluorophenyl) acetate

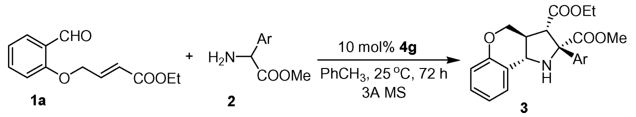
Table 2 Optimization of reaction conditions[a]

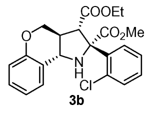
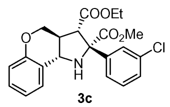
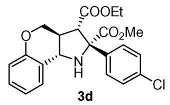
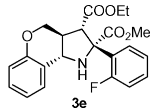
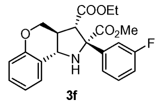
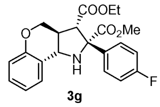
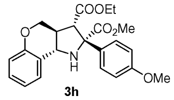


Entry	Solvent	T/°C	MS	Yield (%)[b]	dr[c]	ee (%)[d]
1	CH_2Cl_2	25	3 Å	65	88 : 12	83
2	$CHCl_3$	25	3 Å	64	93 : 7	59
3	THF	25	3 Å	<5	—	ND
4	Toluene	25	3 Å	81	99 : 1	90
5	Toluene	25	4 Å	95	99 : 1	84
6	Toluene	25	5 Å	48	90 : 10	59
7	Toluene	0	3 Å	NR	—	ND
8	Toluene	10	3 Å	51	85 : 15	89
9	Toluene	40	3 Å	87	97 : 3	66
10	Toluene	25	3 Å	94	99 : 1	91[e]

[a] The reaction was carried out at 0.1 mmol scale in solvent (1 mL) with MS (200 mg) for 72 h and the ratio of **1a** : **2a** was 1.2 : 1. [b] Isolated yield based on **2a**. [c] The dr refers to the ratio of **3a** to its isomers and was determined by ^1H NMR of crude product. [d] Determined by HPLC. [e] The reaction was performed in toluene (0.5 mL).

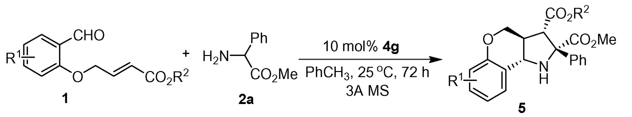
Table 3 Scope of α-arylglycine methyl esters[a]

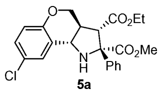
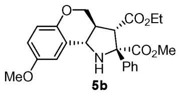
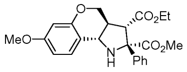
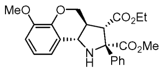
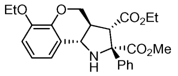
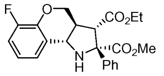
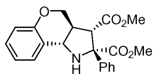


Entry	2 (Ar)	3	Yield (%)[b]	dr[c]	ee (%)[d]
1	2-ClC_6H_4 (**2b**)	 **3b**	89	98 : 2	87
2	3-ClC_6H_4 (**2c**)	 **3c**	86	99 : 1	92
3	4-ClC_6H_4 (**2d**)	 **3d**	80	97 : 3	90
4	2-FC_6H_4 (**2e**)	 **3e**	93	99 : 1	94
5	3-FC_6H_4 (**2f**)	 **3f**	82	99 : 1	90
6	4-FC_6H_4 (**2g**)	 **3g**	84	97 : 3	91
7	4-$MeOC_6H_4$ (**2h**)	 **3h**	65	97 : 3	81

[a] The reaction was carried out at 0.2 mmol scale in toluene (1 mL) with 3 Å MS (400 mg) at 25 °C for 72 h and the ratio of **1a** : **2** was 1.2 : 1. [b] Isolated yield based on **2**. [c] The dr refers to the ratio of **3** to its isomers and was determined by ^1H NMR of crude product. [d] Determined by HPLC.

Table 4 Scope of aldehydes[a]



Entry	**1** (R_1, R_2)	**5**	Yield (%)[b]	dr[c]	ee (%)[d]
1	R_1 = 5-Cl R_2 = Et **(1b)**	 **5a**	60	98 : 2	53
2	R_1 = 5-OMe R_2 = Et **(1c)**	 **5b**	56	94 : 6	68
3	R_1 = 4-OMe R_2 = Et **(1d)**	 **5c**	42	95 : 5	90
4	R_1 = 3-OMe R_2 = Et **(1e)**	 **5d**	54	95 : 5	70
5	R_1 = 3-OEt R_2 = Et **(1f)**	 **5e**	76	98 : 2	78
6	R_1 = 3-F R_2 = Et **(1g)**	 **5f**	63	97 : 3	68
7	R_1 = H R_2 = Me **(1h)**[e]	 **5g**	84	99 : 1	74

[a] The reaction was carried out at 0.2 mmol scale in toluene (1 mL) with 3 Å MS (400 mg) at 25 °C for 72 h and the ratio of **1** : **2a** was 1.2 : 1. [b] Isolated yield based on **2a**. [c] The dr refers to the ratio of **5** to its isomers and was determined by ^{1}H NMR of crude product. [d] Determined by HPLC.

(**2e**) was the most suitable substrate to undergo the cycloaddition reaction in 93% yield and 94% ee (entry 4). These outcomes are actually particularly significant in view of formidable challenges present in the construction of enantioenriched polycyclic pyrrolidine compounds bearing quaternary stereogenic centers.[11] The relative and absolute stereochemistry was assigned by X-ray crystallography (see ESI†), and other products were assigned by analogy.

Further exploration was focused on the generality of the protocol for different aldehydes (Table 4). Variation of the electronic properties of the substituent at either C3 or C5 of (*E*)-ethyl-4-(2-formylphenoxy)but-2-enoate was tolerable, with good yields ranging from 54 to 76% and moderate to good enantioselectivities ranging from 53 to 78% ee (entries 1–2 and 4–6). Notably, the cycloaddition reaction with (*E*)-ethyl-4-(2-formylphenoxy)but-2-enoate (**1d**) bearing an electronically donating substituent at C4 proceeded in a moderate yield, but with excellent enantioselectivity (entry 3). The replacement of the (*E*)-ethyl-4-(2-formylphenoxy)but-2-enoate (**1a**) with (*E*)-methyl-4-(2-formylphenoxy)but-2-enoate (**1h**) was also able to provide good yield and enantioselectivity (entry 7).

In summary, we have disclosed a Brønsted acid-catalyzed asymmetric intramolecular 1,3-dipolar cycloaddition of aldehydes bearing dipolarophile functionalities with α-aryl amino esters. The phosphoric acid **4g** enabled the reaction to give hexahydromeno[4,3-b]pyrrolidine derivatives in high yield and enantioselectivity (up to 94% yield, 94% ee). This reaction provided a straightforward entry to privileged polycyclic pyrrolidine architectures, which hold great potential in the development of related compounds as medicinal and pharmaceutical agents.

Acknowledgements

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