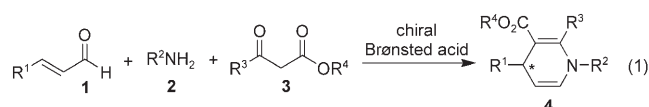


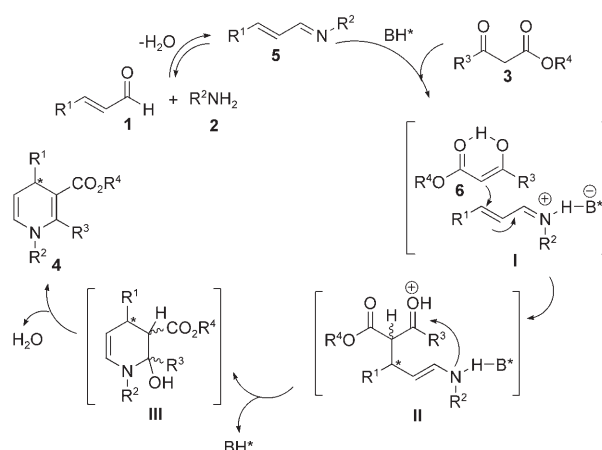
Organocatalytic Asymmetric Three-Component Cyclization of Cinnamaldehydes and Primary Amines with 1,3-Dicarbonyl Compounds: Straightforward Access to Enantiomerically Enriched Dihydropyridines**

Jun Jiang, Jie Yu, Xi-Xi Sun, Qin-Quan Rao, and Liu-Zhu Gong*

Dihydropyridines (DHPs), in particular 4-aryl-substituted 1,4-dihydropyridines, have been recognized as an important class of organic calcium-channel modulators for the treatment of cardiovascular diseases^[1] since the first description of the pharmacology of these compounds by Loev et al.^[2] Structural modification led to a large family of compounds containing the 1,4-dihydropyridine moiety. In a series of biological assays, these compounds were found to have a broad range of other pharmaceutical activities.^[3] The absolute configuration of the stereogenic center of chiral DHPs has considerable influence on their biological activity.^[4] The application of chiral dihydropyridines in the synthesis of alkaloids has been reported,^[5] and the use of optically pure C4-substituted 1,4-dihydropyridines as chiral models of NAD(P)H has also received much attention.^[6] Therefore, efficient methods for the synthesis of optically active 1,4-dihydropyridines would be of great value for drug discovery and organic synthesis. Until now, however, optically active DHPs could only be accessed by asymmetric synthesis with chiral auxiliaries and by resolution.^[4a,5] Despite the large number of procedures that yield DHPs,^[7,8] a catalytic asymmetric synthesis of highly enantiomerically enriched 4-aryl-substituted 1,4-dihydropyridines has not appeared, and thus remains an important challenge. Herein, we report an asymmetric three-component cyclization of an α,β -unsaturated aldehyde **1**, a primary amine **2**, and an acetoacetate **3** in the presence of a chiral Brønsted acid as a catalyst to give chiral 1,4-dihydropyridines **4**^[8] with excellent enantioselectivities of up to 98% *ee* [Eq. (1)].



Our initial proposal for the Brønsted acid catalyzed cyclization reaction of an α,β -unsaturated aldehyde **1**, a primary amine **2**, and an acetoacetate **3** is outlined in Scheme 1. Under acidic conditions, α,β -unsaturated alde-



Scheme 1. Proposed mechanism for the cyclization reaction of α,β -unsaturated aldehydes and primary amines with 1,3-dicarbonyl compounds under the catalysis of a chiral Brønsted acid.

hydes **1** condense with primary amines **2** to form α,β -unsaturated imines **5** with a 1-aza-1,3-butadiene structure, and acetoacetates **3** enolize into their tautomers **6**, which are nucleophiles. The chiral Brønsted acid (BH^*) makes imines **5** more electron deficient by forming a hydrogen bond with the N atom and thereby promotes the Michael addition of **6** to **5** via a possible transition state **I**. The resulting intermediate **II** undergoes cyclization to give **III**.^[9,10] Finally, intermediate **III** undergoes a dehydration reaction to afford optically active dihydropyridines **4**.

Recently, chiral phosphonic acids have been recognized as efficient catalysts for asymmetric nucleophilic addition to imines.^[11,12] In particular, we have demonstrated that these chiral Brønsted acids can catalyze some important multi-component reactions with high enantioselectivity.^[13] Although chiral phosphonic acids had not been used to activate 1-aza-1,3-butadienes for cycloaddition reactions,

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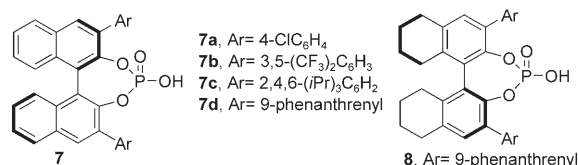
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these previous successes led us to believe that **7** and **8** may promote enantioselective cyclization reactions of α,β -unsaturated



rated aldehydes **1** with primary amines **2** and acetoacetates **3** via the proposed key transition structures **IV** and **V** (Figure 1) to generate optically active DHPs **4** through a reaction sequence similar to that shown in Scheme 1.

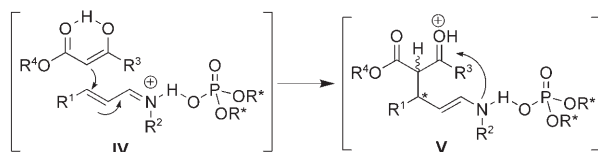
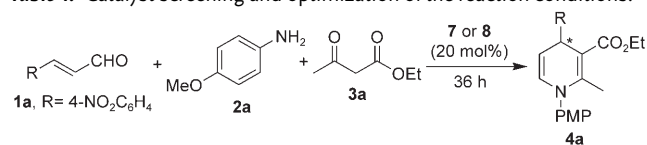


Figure 1. The proposed key transition structures for the phosphonic acid-catalyzed cyclization reaction of α,β -unsaturated aldehydes and amine with 1,3-dicarbonyls.

The initially tested three-component cyclization reaction of *p*-nitrocinnamaldehyde (**1a**) and *p*-anisidine (**2**) with ethyl acetoacetate (**3a**) proceeded smoothly in the presence of the chiral phosphonic acid **7a** (20 mol %) in chloroform at room temperature to furnish the desired product **4a** in 72 % yield, albeit with just 19 % *ee* (Table 1, entry 1). The screening of phosphonic acids **7b–d** and **8** revealed that an increase in the size of the substituents at the 3,3'-positions of the catalyst led

Table 1: Catalyst screening and optimization of the reaction conditions.^[a]



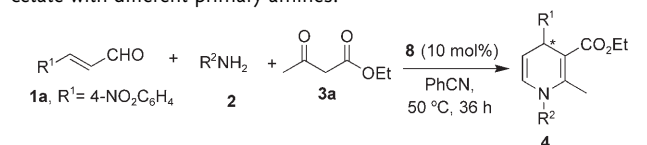
Entry	Catalyst	Solvent	<i>T</i> [°C]	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	7a	CHCl ₃	25	72	19
2	7b	CHCl ₃	25	85	19
3	7c	CHCl ₃	25	62	31
4	7d	CHCl ₃	25	67	73
5	8	CHCl ₃	25	69	64 ^[d]
6	7d	CHCl ₃	40	80	80
7	7d	CHCl ₃	50	85	82
8	8	CHCl ₃	50	86	72 ^[d]
9	7d	PhCN	50	82	89
10	8	PhCN	50	83	90 ^[d]
11 ^[e]	8	PhCN	50	82	92 ^[d]

[a] A solution of **1a** (0.3 mmol), **2a** (0.2 mmol), **3a** (0.4 mmol), and the indicated catalyst in CHCl₃ or PhCN (1.5 mL) was stirred for 36 h. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC; (*S*)-**4a** was obtained unless otherwise indicated. [d] The product was (*R*)-**4a**. [e] The reaction was carried out with 10 mol % of **8**. PMP = *p*-methoxyphenyl.

to enhanced enantioselectivity (Table 1, entries 2–5). Thus, **7d** and **8**, which afforded **4a** in fairly good yields and enantioselectivities (Table 1, entries 4 and 5), were found to be the most promising catalysts for the reaction. Optimization of the reaction conditions indicated that an increase in the reaction temperature led to higher enantioselectivity (Table 1, entries 6–8). We tested various solvents and observed the highest enantioselectivity when the reaction was carried out in PhCN. Thus, **4a** was formed in the presence of the phosphonic acids **7d** and **8** in PhCN at 50 °C with 89 and 90 % *ee*, respectively (Table 1, entries 9–10). The enantioselectivity could be improved to 92 % *ee* by using 10 mol % of **8** (Table 1, entry 11).

Next, we explored the scope of the reaction with respect to the aniline component by using *p*-nitrocinnamaldehyde and ethyl acetoacetate as the other two reactants. Both the reaction efficiency and the enantioselectivity were found to depend significantly on the substituent on the aromatic ring (Table 2). The reaction in which *p*-anisidine was used as the

Table 2: Cyclization reaction of *p*-nitrocinnamaldehyde and ethyl acetoacetate with different primary amines.^[a]



Entry	R ² (2)	4	Yield [%] ^[b]	<i>ee</i> [%] ^[c]
1	4-MeOC ₆ H ₄ (2a)	4a	82	92
2	3-MeOC ₆ H ₄ (2b)	4b	53	97
3	4-CH ₃ C ₆ H ₄ (2c)	4c	57	96
4	3-MeC ₆ H ₄ (2d)	4d	53	90
5	4-ClC ₆ H ₄ (2e)	4e	60	89

[a] Reaction conditions: **1a** (0.3 mmol), **2** (0.2 mmol), **3a** (0.4 mmol), **8** (0.02 mmol), PhCN (1.5 mL). [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC.

primary amine component furnished the desired heterocycle in high yield with excellent enantioselectivity (Table 2, entry 1). The best enantioselectivity of 97 % *ee* was observed for the reaction of *m*-toluidine, although the yield of the product was comparatively low (Table 2, entry 2). In contrast to the trend observed with the anisidine substrates, the reaction of *p*-toluidine proceeded with higher enantioselectivity than that of *m*-toluidine (96 versus 90 % *ee*; Table 2, entries 3 and 4). Even lower enantioselectivity was observed for the reaction of 4-chloroaniline (Table 2, entry 5). Thus, an electron-withdrawing substituent on the aniline appears to have a negative effect on the stereoselectivity of the cyclization.

We then investigated the generality of the protocol with respect to the other two substrates, the β -ketoester **3** and the α,β -unsaturated aldehyde **1** (Table 3). A range of β -ketoesters was first examined in the reaction with *p*-nitrocinnamaldehyde (**1a**) and *p*-anisidine (**2a**; Table 3, entries 1–4). The enantioselectivity was highly dependent on the size of the ester moiety. Thus, cyclization reactions with ethyl and isopropyl acetoacetate provided the product with 92 % *ee*

Table 3: Cyclization reaction of cinnamaldehydes and *p*- or *m*-anisidine with 1,3-dicarbonyl compounds.^[a]

Entry	R ¹	2	R ²	R ³	4	Yield [%] ^[b]	ee [%] ^[c]
1	4-NO ₂ C ₆ H ₄	2a	Me	Et	4a	82	92
2	4-NO ₂ C ₆ H ₄	2a	Me	<i>i</i> Pr	4f	81	92
3	4-NO ₂ C ₆ H ₄	2a	Me	allyl	4g	75	82
4	4-NO ₂ C ₆ H ₄	2a	Me	Me	4h	93	81
5	4-NO ₂ C ₆ H ₄	2b	Me	Et	4b	53	97
6	4-NO ₂ C ₆ H ₄	2b	Me	<i>i</i> Pr	4i	48	95
7	4-NO ₂ C ₆ H ₄	2b	Me	allyl	4j	52	95
8	4-NO ₂ C ₆ H ₄	2b	Me	Me	4k	47	91
9	4-NO ₂ C ₆ H ₄	2a	Et	Me	4l	38	91
10	Ph	2a	Me	<i>i</i> Pr	4m	40	81
11	2,3-Cl ₂ C ₆ H ₃	2a	Me	Et	4n	72	87
12	2,3-Cl ₂ C ₆ H ₃	2b	Me	Et	4o	72	96
13	3-NO ₂ C ₆ H ₄	2a	Me	Et	4p	70	91
14	2-NO ₂ C ₆ H ₄	2a	Me	Et	4q	72	94
15	2-NO ₂ C ₆ H ₄	2b	Me	Et	4r	37	98
16	2-NO ₂ C ₆ H ₄	2a	Me	Me	4s	85	88
17	2-NO ₂ C ₆ H ₄	2b	Me	Me	4t	53	96
18	2-MeOC ₆ H ₄	2a	Me	<i>i</i> Pr	4u	50	82
19	2-ClC ₆ H ₄	2a	Me	Et	4v	74	94
20	2-ClC ₆ H ₄	2b	Me	Et	4w	69	97
21	2-CF ₃ C ₆ H ₄	2a	Me	Et	4x	75	96
22	2-BrC ₆ H ₄	2a	Me	Et	4y	70	93
23 ^[d]	<i>n</i> Pr	2a	Me	Et	4z	31	66

[a] A solution of **1** (0.3 mmol), **2a** or **2b** (0.2 mmol), **3** (0.4 mmol), and **8** (0.02 mmol) in PhCN (1.5 mL) was stirred at 50 °C for 24 h. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC. [d] The reaction was carried out with 20 mol % of **8** and 4-Å molecular sieves (100 mg). The reaction mixture was stirred at 60 °C for 48 h.

(Table 3, entries 1 and 2). However, much lower enantioselectivities were observed for methyl and allyl acetoacetate (Table 3, entries 3 and 4). The equivalent reactions with *m*-anisidine in place of *p*-anisidine as a reaction component proceeded with considerably higher enantioselectivities (91–97% *ee*), although the products were formed in lower yields (Table 3, entries 5–8). Methyl propionylacetate was found to be less reactive than the acetoacetates and underwent cyclization with **1a** and **2a** to give the corresponding product in lower yield; however, high enantioselectivity was observed (91% *ee*; Table 3, entry 9).

Next, various α,β -unsaturated aldehydes were examined as substrates for the cyclization reaction. The substituent on the aromatic ring of the cinnamaldehyde had a dramatic effect on the stereoselectivity. Cinnamaldehyde itself underwent the cyclization reaction to furnish the desired product with fairly good enantioselectivity (Table 3, entry 10). The reaction of 2,3-dichlorocinnamaldehyde, **2a**, and ethyl acetoacetate delivered the dihydropyridine **4n** in 72% yield with 87% *ee* (Table 3, entry 11). The desired product was formed with much higher enantioselectivity (96% *ee*) in the reaction of the same aldehyde and 1,3-dicarbonyl compound with **2b** (Table 3, entry 12). High enantioselectivity was observed with *m*-nitrocinnamaldehyde (91% *ee*; Table 3, entry 13). The

cyclization reactions of *ortho*-substituted cinnamaldehydes and acetylacetates with **2a** or **2b** proceeded with high enantioselectivities (82–97% *ee*; Table 3, entries 14–22), which were highly dependent on the substituents of the three reaction components. The reaction of a β -alkyl-substituted unsaturated aldehyde led to the product in low yield with 66% *ee* (Table 3, entry 23).

Further studies on the cyclization reaction of acetylacetone and *p*- or *m*-anisidine (**2a,b**) with various cinnamaldehydes revealed that the use of acetylacetone as a reaction component led to lower enantioselectivities than those observed with the structurally analogous acetoacetates. Accordingly, the dihydropyridines **9** were furnished in moderate yields with good *ee* values (73–88% *ee*; Table 4).

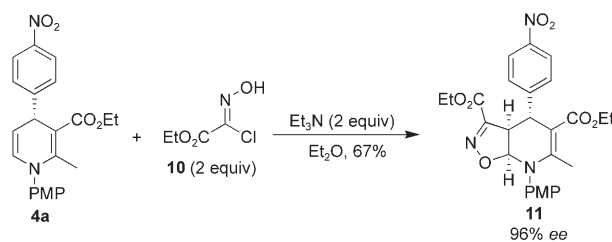
Table 4: Cyclization reaction of cinnamaldehydes and acetylacetone with primary amines.^[a]

Entry	9	R ¹	R ²	Yield [%] ^[b]	ee [%] ^[c]
1	9a	4-NO ₂ C ₆ H ₄	PMP	60	81
2	9b	2-NO ₂ C ₆ H ₄	PMP	69	88
3	9c	2-BrC ₆ H ₄	PMP	63	73
4	9d	2,3-Cl ₂ C ₆ H ₃	PMP	72	77
5	9e	3-NO ₂ C ₆ H ₄	PMP	64	79
6	9f	3-NO ₂ C ₆ H ₄	3-MeOC ₆ H ₄	52	87
7	9g	2-CF ₃ C ₆ H ₄	3-MeOC ₆ H ₄	48	86

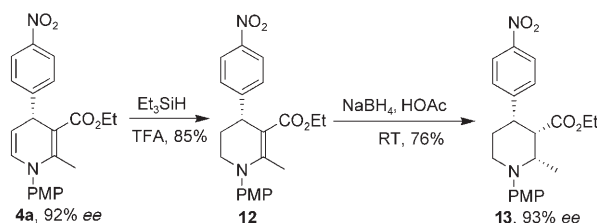
[a] A solution of **1** (0.3 mmol), **2a** or **2b** (0.2 mmol), **3c** (0.4 mmol), and **8** (0.02 mmol) in PhCN (1.5 mL) was stirred at 50 °C for 24 h. [b] Yield of the isolated product. [c] The *ee* value was determined by HPLC.

The highly enantiomerically enriched dihydropyridines obtained by this method are multifunctional compounds that can be converted into other optically active heterocycles by conventional reactions. For example, upon the treatment of **4a** with **10** in the presence of triethylamine, a 1,3-dipolar addition^[14] occurred to give the heterocycle **11** in 67% yield with 96% *ee* (Scheme 2).

The reduction of **4a** with trimethylsilane in the presence of trifluoroacetic acid (TFA) produced the tetrahydropyridine **12** in 85% yield (Scheme 3).^[15] Compound **12** was reduced further with NaBH₄ in acetic acid to give the trisubstituted piperidine **13** in 76% yield with the same *ee* value; no other diastereomers were observed.^[16] Chiral tetrahydropyridines and multisubstituted piperidines are



Scheme 2. Application of a dihydropyridine in the synthesis of another optically active heterocycle.



Scheme 3. Application of a dihydropyridine in the synthesis of a tetrahydropyridine and a piperidine.

important synthetic intermediates and common substructures found in biologically active natural products and synthetic pharmaceuticals.^[17,18] Thus, the chiral DHPs formed in the three-component cyclization are of broad importance.

The absolute configuration of **4a** was assigned by X-ray crystallographic analysis of compound **14** (Figure 2), which

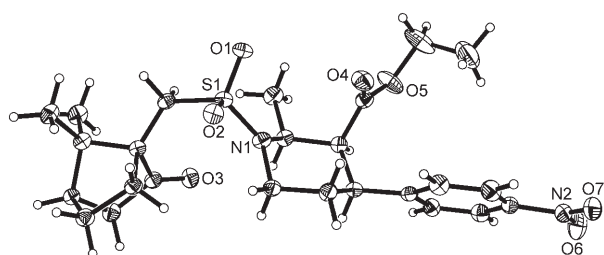
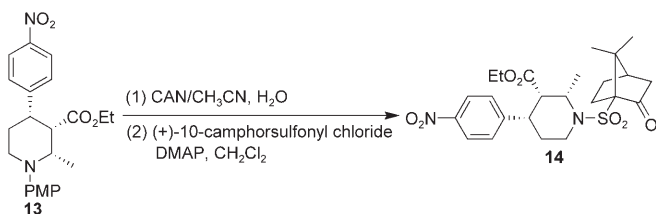


Figure 2. X-ray crystal structure of **14**; thermal ellipsoids at 50% probability.

was prepared from **13** by removal of the PMP protecting group with ceric ammonium nitrate (CAN), followed by treatment with (+)-10-camphorsulfonyl chloride (Scheme 4).



Scheme 4. Synthesis of compound **14**. DMAP = 4-dimethylaminopyridine.

The configuration of **13** was thus assigned as 2*S*,3*S*,4*S* on the basis of the X-ray crystal structure of **14**. As no reaction occurred at the stereogenic center in **4a** during its transformation into **13** (Scheme 2), **4a** was assigned the *S* configuration.

In summary, an asymmetric catalytic three-component cyclization reaction between a cinnamaldehyde, an aromatic primary amine, and a 1,3-dicarbonyl compound enables the straightforward synthesis of enantiomerically enriched 4-aryl-substituted 1,4-dihydropyridines with high enantioselectivity (up to 98% *ee*). The application of the resulting DHPs in the synthesis of optically active heterocyclic compounds through 1,3-dipolar addition and diastereoselective reduction enhances

the importance of this asymmetric cyclization reaction. This study also indicates that the application of Brønsted acids, in particular chiral phosphonic acids, might be extended to the promotion of other asymmetric addition reactions of suitable nucleophiles to 1-aza-1,3-butadienes.

Experimental Section

General Procedure: A solution of the aldehyde (0.3 mmol), the primary amine (0.2 mmol), and the chiral phosphonic acid (0.02 mmol) in PhCN (1.5 mL) was stirred at 25 °C for 15 min. The β -dicarbonyl compound (0.4 mmol) was then added, and the resulting mixture was stirred at 50 °C for 1 day. (The reaction was monitored by TLC.) Flash column chromatography of the reaction mixture on silica gel (eluent: petroleum ether/ethyl acetate 50:1) yielded the pure product.

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