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Organocatalytic asymmetric multicomponent reactions of aromatic aldehydes and anilines with β-ketoesters: facile and atom-economical access to chiral tetrahydropyridines†

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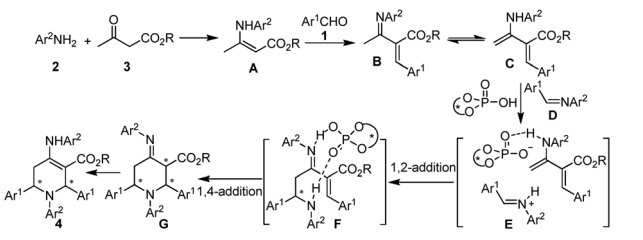
The first catalytic asymmetric pseudo five-component (AB_2C_2 type) reaction is reported. A spirocyclic chiral phosphoric acid catalyzed one-pot multicomponent reaction of aromatic aldehydes, anilines and β-ketoesters and afforded highly functionalized enantioenriched tetrahydropyridines with high levels of stereocontrol.

Asymmetric multicomponent reactions (AMCRs) have emerged as a powerful strategy in organic and medicinal chemistry as they are facile, efficient and have a high degree of atom economy.[1] These features make AMCRs well suited for the easy construction of diversified chiral heterocyclic scaffolds from readily available starting materials.[2] The functionalized tetrahydropyridine ring systems represent an important class of heterocycles in organic chemistry.[3] In recent times, many methods have been reported describing the one-pot, pseudo five-component (AB_2C_2) synthesis of highly functionalized tetrahydropyridines, based on various catalysts from the multicomponent reaction of β-ketoesters, aldehydes and amines.[4] However, development of a catalytic enantioselective multicomponent variant, which allows the rapid construction of optically active tetrahydropyridines, remains an elusive problem. We now report the recently introduced chiral SPINOL-derived phosphoric acid catalyzed, one-pot, enantioselective MCR of aromatic aldehydes **1**, anilines **2** and β-ketoesters **3** to obtain enantioenriched tetrahydropyridines **4** with high levels of stereocontrol.

Over the past decade, as an environmentally benign and practical methodology for asymmetric synthesis, enantioselective organocatalysis has been hotly pursued.[5] Chiral cyclic phosphoric acids have been recognized as efficient organocatalysts for a variety of enantioselective transformations.[6] Recently, our group has developed a novel class of spirocyclic SPINOL-phosphoric acids derived from chiral 1,1′-spirobiindane-7,7′-diol, which effectively catalyzed the highly enantioselective Friedel–Crafts reaction, Pictet–Spengler reaction, Biginelli reaction and Povarov reaction.[7] List, Hu and Zhou also independently reported that SPINOL-phosphoric acids could afford higher enantioselectivity than BINOL-derived counterparts in some cases.[8] These previous successes led us to envision that SPINOL-phosphoric acids would effectively catalyze the enantioselective multicomponent reaction of aromatic aldehydes **1**, anilines **2** and β-ketoesters **3** to generate enantioenriched tetrahydropyridines **4**.

Our initial proposal for the SPINOL-phosphoric acid catalyzed multicomponent reaction is shown in Scheme 1. Under acidic conditions, aromatic amine **2** condenses with β-ketoester **3** to form enamine **A**, which may react with aromatic aldehyde **1** to give the Knoevenagel-type product **B**. Then, tautomerisation of imine to the enamine produces a diene **C**. Another equivalent of amine and aldehyde react to generate the corresponding imine **D**. Sequentially, a possible transition state **E** is formed *via* protonation of the imine **D** with a SPINOL-phosphoric acid catalyst, followed by hydrogen-bonding between the enamine NH of **C** and Lewis basic phosphoryl oxygen. A pseudo-intramolecular 1,2-addition reaction of the chiral contact ion pairs *via* transition state **E** would then give iminium **F**.[9] The resulting intermediate **F** undergoes an intramolecular 1,4-addition reaction to afford **G**. Finally, intermediate **G** tautomerizes to provide optically active tetrahydropyridines **4**.

In our initial study, we examined the pseudo five-component model reaction between two equivalents of aromatic aldehyde **1a**,



Scheme 1 Proposed chiral SPINOL-phosphoric acid-catalyzed AMCR.

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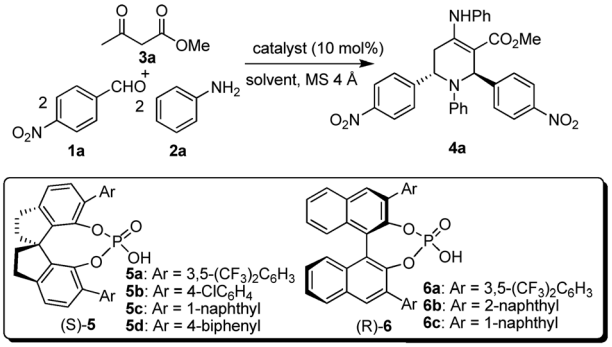
Table 1 Optimization of reaction conditions[a]

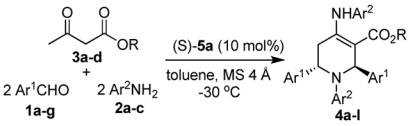


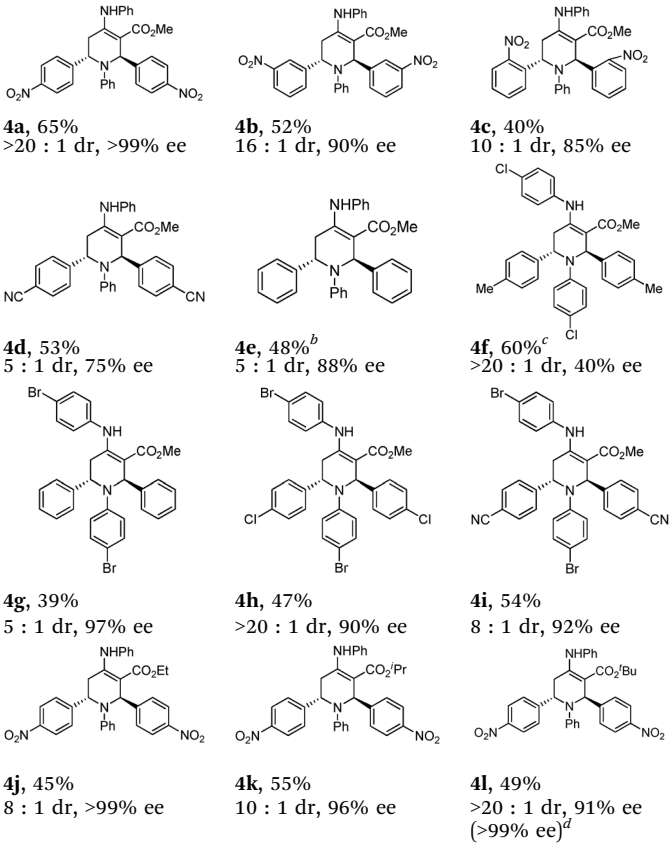
Entry	Catalyst	Solvent	T (°C)	Yield[b] (%)	dr[c]	ee[d] (%)
1	**5a**	$ClCH_2CH_2Cl$	rt	79	5.1 : 1	73
2	**5a**	CH_2Cl_2	rt	92	3.2 : 1	33
3	**5a**	CH_3CN	rt	15	4 : 1	63
4	**5a**	Xylene	rt	71	6.8 : 1	72
5	**5a**	Toluene	rt	87	2.5 : 1	81
6	**5a**	Toluene	−15	82	3.7 : 1	86
7	**5a**	Toluene	−30	76	4.2 : 1	89
8[e]	**5a**	Toluene	−30	81	2.1 : 1	84
9[f]	**5a**	Toluene	−30	72	13.6 : 1	93
10[g]	**5a**	Toluene	−30	65	>20 : 1	>99
11	**5b**	Toluene	−30	5	2.7 : 1	>99
12	**5c**	Toluene	−30	25	1 : 1.7	>99
13	**5d**	Toluene	−30	Trace	—	—
14	**6a**	Toluene	−30	40	3.6 : 1	87
15	**6b**	Toluene	−30	0	—	—
16	**6c**	Toluene	−30	0	—	—
17	**6b**	Toluene	50	65	10 : 1	20

[a] Reaction conditions: catalyst (10 mol%, 0.01 mmol), **1a** (0.2 mmol), **2a** (0.2 mmol), **3a** (0.1 mmol), MS 4 Å (0.1 g), solvent (1 mL), 3 days. [b] Yield of the isolated isomers. [c] dr = *trans*/*cis*; determined by ^{1}H NMR analysis of the crude product. [d] Determined by chiral HPLC analysis. [e] Solvent (0.5 mL). [f] Solvent (2 mL). [g] Solvent (3 mL).

two equivalents of amine **2a**, and one equivalent β-ketoester **3a**. Indeed, the reaction proceeded using a 10 mol% chiral phosphoric acid catalyst in the presence of powdered 4 Å molecular sieves to afford the desired optically active tetrahydropyridine **4a**, as summarized in Table 1. Screening of the solvent effect revealed that all the reactions proceeded smoothly to give the desired product **4a** in good yields, except acetonitrile, with 10 mol% chiral SPINOL-phosphonic acid **5a** at room temperature (entries 1–5). Toluene proved to be a promising solvent, affording product **4a** with 81% ee (entry 5). Lowering the temperature to −15 °C or −30 °C slightly improved the diastereo- and enantioselectivity of the reaction (entries 6 and 7). It is notable that a subsequent concentration survey revealed that concentration remarkably changed the diastereo- and enantioselectivity (entries 7–10). Low concentration further improved the diastereoselectivity to >20 : 1 and enantioselectivity to >99% (entry 10). We also tested other chiral phosphoric acids. Interestingly, the screening of SPINOL-phosphonic acids **5a–d** revealed that the 6,6′-substituents on the SPINOL backbone remarkably effected the catalytic activity and diastereoselectivity, while excellent enantioselectivity (>99% ee) was provided by all except **5d** (entries 10–13). Of BINOL-phosphoric acids **6**, catalyst **6a** gave the desired product in 40% yield with 3.6 : 1 dr and 87% ee, whereas no catalytic activity was observed with **6b** and **6c** in this model reaction under the current conditions (entries 14–16). When the model reaction was carried out at 50 °C using catalyst **6b**, the catalytic activity could be improved, but affording only 20% ee (entry 17). Thus, the most suitable reaction conditions for the model reaction were established (entry 10).

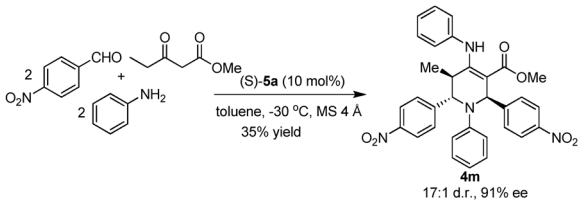
Table 2 Scope of the reaction[a]



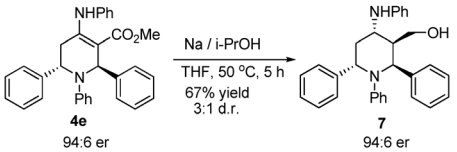


[a] Reaction conditions: **5a** (10 mol%, 0.01 mmol), **1** (0.2 mmol), **2** (0.2 mmol), **3** (0.1 mmol), MS 4 Å (0.1 g), toluene (3 mL), −30 °C, 3 days. Yields given are for the isolated *trans* isomer. Diastereomeric ratios (dr = *trans*/*cis*) were determined by ^{1}H NMR. ees of the major diastereomers were determined by chiral HPLC. [b] At −15 °C. [c] At 35 °C with 20 mol% **5a**. [d] Data in parentheses were obtained after single recrystallization.

With these reaction conditions identified, our attention turned to examination of the scope of the multicomponent reaction between aromatic aldehydes **1**, anilines **2** and β-ketoesters **3** (Table 2). The substituent on the aromatic ring of the aldehyde had a dramatic effect on the activity and stereoselectivity. The reactions involving the electron-withdrawing aldehydes proceeded smoothly in moderate yields with good diastereoselectivities (up to >20 : 1 dr) in favor of the *trans* isomer, which delivered the corresponding products **4a–4d** with good to excellent enantioselectivities (up to >99% ee). Benzaldehyde could deliver product **4e** with 5 : 1 dr and 88% ee. An electron-rich substituent on the aromatic aldehyde appears to have a remarkably negative effect on the reaction activity.



Scheme 2 Synthesis of tetrahydropyridine **4m**.



Scheme 3 Synthesis of chiral piperidine.

Throughout our studies, the multicomponent reaction involving an electron-rich substrate did not occur under the standard optimized reaction conditions, whereas by increasing the temperature to 35 °C and the catalyst loading to 20 mol%, the reaction activity could be improved, albeit affording only low enantioselectivity, as exemplified by 4-methyl-phenyl substituted tetrahydropyridine **4f**, which was obtained in 60% yield with >20 : 1 dr and only 40% ee. Pleasingly, a bromo-substituent on the aniline, which can participate in subsequent transformations such as cross-coupling reactions, was well tolerated in this cyclization reaction to generate tetrahydropyridine derivatives **4g–4i** in acceptable chemical yields of the *trans* isomer with good diastereoselectivities (5 : 1 → 20 : 1 dr) and excellent enantioselectivities (90–97% ee).

Next, various β-ketoesters **3** were examined. Variation of the alkyl substituent of β-ketoesters **3** could be well tolerated to provide the desired products **4j–4l** with good diastereoselectivities (8 : 1 → 20 : 1 dr) and excellent enantioselectivities (91 → 99% ee). The size of the ester moiety slightly influenced the reaction stereoselectivity, with small steric alkyl substrates delivering products with better enantiocontrol. Notably, tetrahydropyridine **4l** was obtained with >99% ee after one recrystallization. A single crystal X-ray analysis of **4l** determined its configuration as (2*R*,6*S*).[10] Furthermore, the fully substituted tetrahydropyridine derivative **4m** was also obtained with excellent diastereo- and enantioselectivity (17 : 1 dr and 91% ee) (Scheme 2).

As a further demonstration of the utility of this current protocol, the reduction of **4e** produced the enantiomerically enriched piperidine **7** in 67% yield of the major isomer with maintained enantioselectivity (Scheme 3). The absolute configuration of product **7** was assigned as (2*S*,3*R*,4*S*,6*S*).[10]

In conclusion, we have developed a chiral SPINOL-phosphoric acid catalyzed pseudo five-component (AB_2C_2 type) reaction between β-ketoesters, aromatic aldehydes and anilines for the straightforward synthesis of enantiomerically enriched tetrahydropyridines with high diastereoselectivities and enantioselectivities. Notably, this organocatalytic asymmetric multicomponent reaction provides excellent stereocontrol, atom economy, and the products are valuable for the synthetic application to optically active piperidines.

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