

# Diphenylprolinol Methyl Ether: A Highly Enantioselective Catalyst for Michael Addition of Aldehydes to Simple Enones

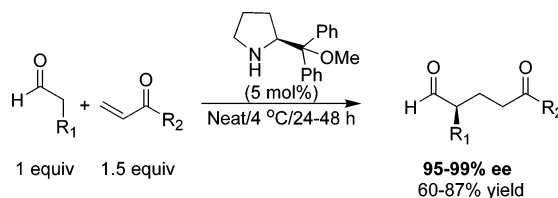
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## ABSTRACT



Diphenylprolinol methyl ether catalyzes intermolecular Michael addition of simple aldehydes to relatively nonactivated enones with the highest enantioselectivities reported to date (95–99% ee) and significantly lower catalyst loadings than have been typical in this arena.

The development of asymmetric Michael additions for C–C bond formation is an important challenge in organic synthesis. Metal-based catalysis has long been the dominant approach,<sup>1</sup> but recently organocatalytic methods have drawn growing attention.<sup>2</sup> Many successes have been realized by applying organocatalysts to highly reactive Michael donors or acceptors. For example, Michael additions of malonate diesters<sup>3</sup> or nitroalkanes<sup>4</sup> to simple enones have been reported. Alternatively, in pioneering work by Barbas et al. and other groups, simple ketones or aldehydes have been

added to activated Michael acceptors such as nitroalkenes or alkylidenemalonates.<sup>5</sup> In contrast, Michael additions of simple aldehydes to simple enones have received little attention. Melchiorre and Jørgensen found modest enantioselectivities for such additions catalyzed by chiral pyrrolidines.<sup>6</sup> List et al. subsequently reported highly enantioselective *intramolecular* examples catalyzed by a MacMillan imidazolidinone.<sup>7</sup> Very recently, we described enantioselective catalysis (ee up to 92%) of intermolecular aldehyde/enone reactions by chiral imidazolidinones in conjunction with a catechol cocatalyst.<sup>8</sup>

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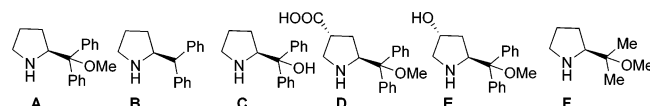
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(8) Peelen, T. J.; Chi, Y.; Gellman, S. H. *J. Am. Chem. Soc.* **2005**, ASAP (DOI: 10.1021/ja0532584). In this study, an enamine intermediate was observed. High catalyst loading (20 mol %) was required, and the ee values were 82–92%.

Here we report that diphenylprolinol methyl ether (**A**),<sup>9</sup> a modest excursion beyond previously explored pyrrolidines, can catalyze intermolecular Michael addition of simple aldehydes to simple enones with the highest enantioselectivities reported to date (95–99% ee) and significantly lower catalyst loading (1–5 mol %) than has been typical in this arena. We show that higher catalyst loading depresses enantioselectivity, apparently because of product racemization catalyzed by the pyrrolidine. With some substrates, the use of a cocatalyst is necessary for optimal results.

We initially examined six substituted pyrrolidines (1 mol % each) as potential catalysts for reaction between hydrocinnamaldehyde and methyl vinyl ketone (Table 1). Pyrro-

**Table 1.** Initial Studies of Michael Addition of Hydrocinnamaldehyde to Methyl Vinyl Ketone



Reaction scheme: 1 equiv of hydrocinnamaldehyde + 3 equiv of methyl vinyl ketone  $\xrightarrow[Neat/rt/24\text{ h}]{1\text{ mol\% catalyst}}$  Michael adduct.

entry	catalyst	conversion (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	<b>A</b>	60	97
2	<b>B</b>	28	80
3	<b>C</b>	<1	nd <sup>c</sup>
4	<b>D</b>	33	99
5	<b>E</b>	27	96
6	<b>F</b>	15	77

<sup>a</sup> Measured by <sup>1</sup>H NMR of the crude reaction mixture. <sup>b</sup> Determined by a <sup>1</sup>H NMR ee assay using chiral amines; for details, see Supporting Information. <sup>c</sup> Not determined.

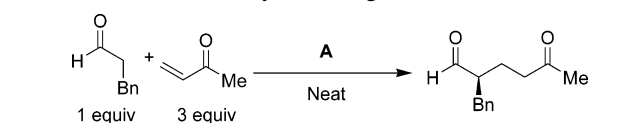
lidine **A** performed best, providing excellent enantioselectivity<sup>10</sup> and good conversion. Quaternary substitution on the substituent adjacent to the nitrogen seems to be important for optimal reactivity and enantioselectivity, since **B**, lacking the methoxy group, is inferior to **A**. Pyrrolidine **B** is typical of the catalysts evaluated in the seminal study of Melchiorre and Jørgensen,<sup>6</sup> and the results we obtained with **B** are consistent with their findings. The oxygen atom in **A** must be etherified, as diphenylprolinol (**C**) was completely inactive. We suspect that **C** forms a stable cyclic aminal upon reaction with the aldehyde.<sup>11</sup> Pyrrolidines **D** and **E** gave excellent enantioselectivities but lower conversion than was obtained with **A**; perhaps the electron-withdrawing ring substituents (carboxyl or hydroxyl) diminish the nucleophilic

reactivity of the nitrogen atom. Pyrrolidine **F**, which differs from **A** in having methyl groups in place of phenyl groups on the ring substituent, provides substantially lower yield and enantioselectivity than does **A**.

The catalytic reaction appears to proceed via the enamine formed by reaction of the pyrrolidine and the aldehyde.<sup>6</sup> In light of this hypothesis, it seemed surprising that **B** provided lower conversion to product than did **A**, since one might have predicted that the lesser degree of substitution on the “side chain” of **B** would lead to more rapid enamine formation and more rapid enamine reaction with enone for **B** than for **A**.

Table 2 shows the effect of catalyst loading on conversion and product ee for Michael addition catalyzed by **A**. The

**Table 2.** Effect of Catalyst Loading



entry	catalyst (mol %)	time (h)	temperature	conversion (%) <sup>a</sup>	ee (%) <sup>b</sup>
1	20	7	rt	94	65
2	5	24	rt	99	86
3	2	24	rt	90	>95
4	1	24	rt	60	>95
5	5	24	4 °C	90	>95

<sup>a</sup> Measured by <sup>1</sup>H NMR of crude reaction mixture. <sup>b</sup> Determined by a <sup>1</sup>H NMR ee assay using chiral amines.

reaction is nearly complete in 7 h when 20 mol % **A** is used, but enantioselectivity is quite modest under these conditions. Use of lower catalyst proportions leads to slower product formation but higher enantioselectivity, as seen by comparing results obtained with 5, 2, and 1 mol % **A** after 24 h. This trend suggests that the pyrrolidine may play two roles under the reaction conditions: catalysis of the Michael addition, via enamine formation with the starting aldehyde, and catalysis of product epimerization, via enamine formation with the product aldehyde.<sup>12</sup> Indeed, when pure Michael adduct and pyrrolidine **A** were mixed, a steady erosion of adduct enantiomeric excess was observed. We find that products with the highest ee are obtained when the adduct is separated from the catalyst as soon as the reaction nears completion.

Table 3 shows results obtained under optimized conditions (5 mol % **A**, 4 °C, 24–48 h) with six simple aldehydes and two enones. Enantioselectivities are excellent (>95%), and yields are good to excellent in all cases. Although some of these reactions proceed well with only the pyrrolidine as a catalyst, others require the use of the catechol **G** as a cocatalyst.<sup>13</sup> We recently discovered that catechols could serve as cocatalysts for Michael additions that proceed by

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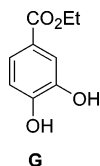
(12) For an example of  $\alpha$ -substituted aldehyde product racemization by catalyst, see: List, B. *J. Am. Chem. Soc.* **2002**, *124*, 5656–5657.

**Table 3.** Michael Addition of Aldehydes to Enones

product	R <sub>1</sub> , R <sub>2</sub>	additive <b>G</b> (mol %)	reaction		
			time (h)	yield (%) <sup>a</sup>	ee (%)
1	Me, Me	20	36	82	97 <sup>c</sup>
2	Et, Me	0	36	75	97 <sup>c</sup>
3	Pr, Me	0	36	69	>95 <sup>d</sup>
4	<i>i</i> -Pr, Me	0	36	65	98 <sup>c</sup>
5	<i>n</i> -Hex, Me	0	24	85	>95 <sup>d</sup>
6	Bn, Me	0	24	82	>95 <sup>d</sup>
7	Me, Et	20	48	70	99 <sup>c</sup>
8	Et, Et	20	48	68	95 <sup>c</sup>
9	Pr, Et	20	48	69	>95 <sup>d</sup>
10	<i>i</i> -Pr, Et	20	48	60 <sup>b</sup>	99 <sup>c</sup>
11	<i>n</i> -Hex, Et	20	24	87	>95 <sup>d</sup>
12	Bn, Et	20	24	87	>95 <sup>d</sup>

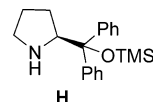
<sup>a</sup> Yield of isolated product after column chromatography on silica gel. <sup>b</sup> Reaction at room temperature. <sup>c</sup> Determined by chiral stationary phase GC of the corresponding carboxylic acids; the ee of the parent aldehydes were also determined by a <sup>1</sup>H NMR ee assay, giving ee higher than 95% in all cases. <sup>d</sup> Determined by a <sup>1</sup>H NMR ee assay using chiral amines.

nucleophilic activation of aldehydes (enamine formation);<sup>14</sup> our current hypothesis is that the catechol electrophilically activates the enone, via hydrogen bond donation to the carbonyl oxygen.<sup>8,15</sup>



As our work was being completed, Hayashi et al. reported that enantiomerically pure diphenylprolinol silyl ethers, another modest excursion beyond previously explored pyrrolidine,<sup>5,6</sup> could be used for enantio- and diastereoselective addition of simple aldehydes to  $\beta$ -monosubstituted nitroalkenes.<sup>16</sup> This paper followed closely upon reports from

Jørgensen et al. that such silyl ethers catalyze the  $\alpha$ -fluorination<sup>17</sup> and  $\alpha$ -sulfenylation<sup>18</sup> of aldehydes with high enantioselectivity. We compared **A** and the analogous trimethylsilyl ether (**H**), both at 1 mol %, as catalysts for the Michael addition shown in Table 1. The TMS ether provided enantioselectivity comparable to that obtained with **A**, but **H** was a less efficient catalyst, giving only 20% Michael adduct conversion (vs 60% conversion with **A**).<sup>19</sup>



We have conducted a preliminary assessment of pyrrolidine catalysis of aldehyde Michael additions to acceptors bearing  $\beta$ -substituents, reactions that are important because two adjacent stereogenic centers are created. Michael addition of isovaleraldehyde to  $\beta$ -substituted alkylidenemalonates<sup>5c,d</sup> proceeds with high diastereo- and enantioselectivity in the presence of **A**. In contrast, **A** is only a poor catalyst for Michael addition of aldehydes to cyclopentenone or acyclic  $\beta$ -substituted enones. No Michael addition at all was detected with cyclohexenone.

Our results show that pyrrolidine **A** is an outstanding organocatalyst for Michael addition of simple aldehydes to simple enones. Among the substrates we have examined, however, small variations in structure can hinder the desired reaction. In some cases such as replacement of methyl vinyl ketone with ethyl vinyl ketone, which causes a small increase in steric constraint, the reactivity deficit can be remedied by introduction of an achiral catechol cocatalyst. In other cases such as use of  $\beta$ -substituted enones, which present a more demanding steric challenge, more sophisticated catalyst design will be necessary to achieve useful reactivity. Enzymes frequently employ bifunctional catalysis to promote intrinsically difficult reactions, and we therefore speculate that covalent linkage<sup>20</sup> between the optimized enamine moiety represented by **A** and the putative enone-activating moiety represented by catechol **G** will allow efficient utilization of  $\beta$ -substituted enones. It is noteworthy in this context that **D** and **E**, which bear potential linkage sites, retain the excellent enantioselectivity manifested by **A**, although the reactivity of **D** and **E** is somewhat reduced relative to that of **A**. Use of chiral preorganized segments to connect complementary catalytic groups could provide both high catalytic activity and high stereochemical induction.

(13) (a) Without catechol cocatalyst, these reactions gave only 1–35% conversion after 48 h, except for reaction of hydrocinnamaldehyde and ethyl vinyl ketone (63% conversion). (b) The use of catechol cocatalyst enhances the reaction rates in all cases.

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**Supporting Information Available:** Experimental details, chromatograms, and NMR spectra for ee determination. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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