

# Chiral Brønsted Acid-Catalyzed Enantioselective Multicomponent Mannich Reaction: Synthesis of *anti*-1,3-Diamines Using Enecarbamates as Nucleophiles

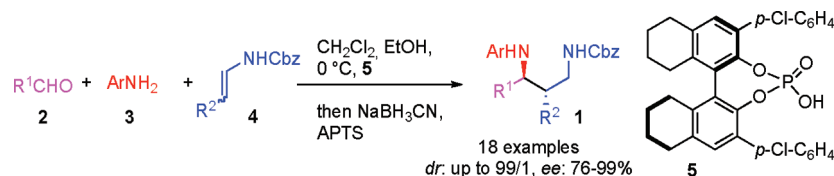
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## ABSTRACT



Reaction of aldehydes **2**, anilines **3**, and enecarbamates **4** in dichloromethane in the presence of EtOH and a catalytic amount of chiral phosphoric acid **5** afforded the Mannich adducts which were in situ reduced to *anti*-1,3-disubstituted 1,3-diamines **1** in excellent diastereoselectivity and enantioselectivity.

Enantiomerically enriched 1,3-diamines are very important chiral building blocks in the synthesis of natural products, pharmacologically active compounds, and ligands.<sup>1</sup> For this reason, much effort has been devoted to the development of new effective methods to access these compounds.<sup>2</sup> However, only few direct asymmetric syntheses of 1,3-diamines have

been described, contrary to their 1,2-diamine counterparts.<sup>3</sup> Kobayashi and Terada<sup>4</sup> have developed an elegant two-step synthesis of 1,3-diamines by reaction of enamides (enecarbamates)<sup>5</sup> with preformed *N*-acylimines or *N*-acyl aminoether followed by reduction of the resulting aminoethers. We report herein the first multicomponent synthesis of 1,3-diamines **1** via an enantioselective Mannich reaction of aldehydes **2**, anilines **3**, and enecarbamates **4** in the presence of ethanol and a chiral phosphoric acid **5**. The direct condensation products were the aminoethers **6**, which without isolation were in situ reduced to 1,3-diamines **1** (Scheme 1).

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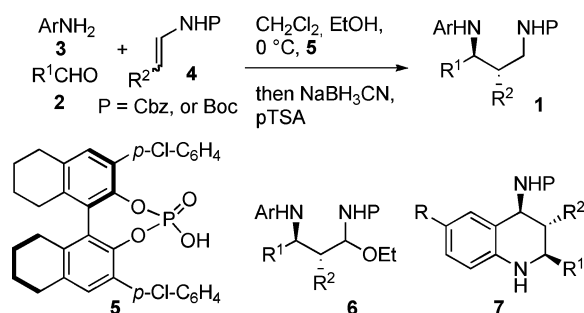
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**Scheme 1.** Catalytic Enantioselective Three-Component Synthesis of 1,3-Diamines



We have recently reported a chiral phosphoric acid **5**-catalyzed enantioselective Povarov reaction for the synthesis of tetrahydroquinolines **7**.<sup>6–8</sup> Inspired by Lavilla's observation that a classic Povarov reaction pathway can be

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**Table 1.** One-Pot Synthesis of 1,3-Diamines: A Survey of Reaction Conditions<sup>a</sup>

| entry | Ar                                                      | EtOH (equiv) | yield <b>6</b> (%) <sup>b</sup> | yield <b>7</b> (%) <sup>b</sup> | yield <b>1</b> (%) <sup>b,c</sup> | ee (%) <sup>d</sup> |
|-------|---------------------------------------------------------|--------------|---------------------------------|---------------------------------|-----------------------------------|---------------------|
| 1     | <i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>              | 17           | <b>6a</b> (21)                  | <b>7a</b> (50)                  | <b>1a</b> (32) <sup>d</sup>       | 77                  |
| 2     | Ph                                                      | 17           | <b>6b</b> (77)                  | <b>7b</b> (11)                  | <b>1b</b> (51) <sup>d</sup>       | 92                  |
| 3     | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub>               | 17           | <b>6c</b> (85)                  | -                               | <b>1c</b> (82) <sup>d</sup>       | 92                  |
| 4     | <i>p</i> -ClC <sub>6</sub> H <sub>4</sub>               | 17           | <b>6d</b> (85)                  | -                               | <b>1d</b> (76) <sup>d</sup>       | 90                  |
| 5     | <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | 17           | <b>6e</b> (72)                  | -                               | <b>1e</b> (70) <sup>d</sup>       | 93                  |
| 6     | <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | 10           | <b>6e</b> (63)                  | -                               | <b>1e</b> (81) <sup>d</sup>       | 94                  |
| 7     | <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | 5            | <b>6e</b> (55)                  | -                               | <b>1e</b> (64) <sup>d</sup>       | 95                  |
| 8     | <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | 17           | -                               | -                               | <b>1e</b> (86) <sup>e</sup>       | 96                  |
| 9     | <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> | 17           | -                               | -                               | <b>1e</b> (72) <sup>e,f</sup>     | 92                  |

<sup>a</sup> General conditions: **2a/3/4/5** = 1.1/1.0/1.5/0.1 in CH<sub>2</sub>Cl<sub>2</sub> (*c* = 0.1) at 0 °C. <sup>b</sup> Yields refer to chromatographically pure products. <sup>c</sup> Reduction conditions: NaBH<sub>3</sub>CN (20 equiv), pTSA (10 equiv) in EtOH (*c* = 0.05). <sup>d</sup> Yields calculated from **6.4b** was used. <sup>e</sup> Sequential one-pot 4CR/reduction process, yields calculated from **3**. <sup>f</sup> Reaction performed at rt. <sup>g</sup> Enantiomeric excess was determined by chiral HPLC analysis. For details see Supporting Information.

interrupted by a suitable external nucleophile,<sup>9</sup> we set out to examine the **5**-catalyzed enantioselective reaction of benzaldehyde (**2a**), 4-methoxyaniline (**3a**), and benzyl *N*-vinylcarbamate (**4a**) using EtOH (17 equiv) as a trapping reagent to intercept the initial Mannich adduct.<sup>10</sup> Under these conditions, we did isolate the four-component adduct **6a** as a mixture of two diastereoisomers (21%), together with the Povarov adduct **7a** (R = OMe, R<sup>1</sup> = Ph, R<sup>2</sup> = H, P = Cbz, 50%, entry 1, Table 1). Using electron-neutral aniline (**3b**, Ar = Ph) as an input, the Mannich adduct **6a** (R<sup>1</sup> = Ar = Ph, R<sup>2</sup> = H, P = Cbz) was isolated as a major product in 77% yield (entry 2).<sup>10</sup> With electron-poor 4-chloroaniline (**3c**, Ar = 4-ClPh) and 4-nitroaniline (**3d**, Ar = 4-NO<sub>2</sub>Ph), the four-component Mannich adducts **6c** and **6e** were formed exclusively at the expense of the tetrahydroquinolines (entries 3–5). Reducing the amount of EtOH resulted in the low yield of **6** (entries 5–7). We stress that in the absence of EtOH under otherwise identical conditions, only Povarov products **7** (R = Cl or NO<sub>2</sub>) were obtained.

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Reduction of aminoether **6** to 1,3-diamines **1** was next investigated and was best realized using an ethanol solution of NaBH<sub>3</sub>CN in the presence of pTSA. These conditions being perfectly compatible with the Mannich reaction, a one-pot Mannich reaction/reduction process was performed and was found to give 1,3-diamine in higher yield than the two-step procedure (entries 8 vs 5 and 6). Overall, the reaction of benzaldehyde, 4-nitroaniline, and *N*-benzyl enecarbamate under optimized conditions afforded directly **1e** in 86% yield and 96% ee (entry 8). *N*-Boc vinylcarbamate (**4b**) can also be used as a nucleophile to provide **1d** in 65% yield and 90% ee (entry 4).

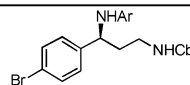
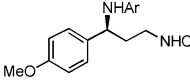
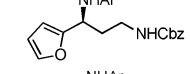
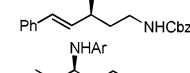
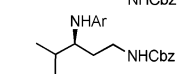
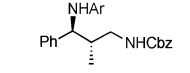
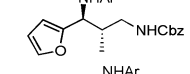
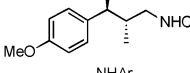
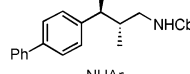
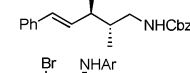
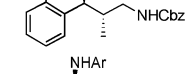
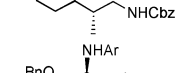
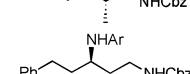
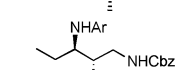
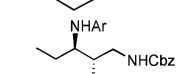
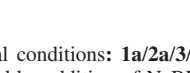
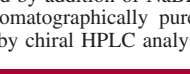
Using 4-nitroaniline (**3d**) as a fixed input, we next examined the scope of this one-pot synthesis of 1,3-diamines varying the aldehyde and enecarbamate structures (Table 2). The enantiomeric excesses and yields of products resulting from aromatic aldehydes were generally high irrespective of the electronic nature of the aromatic rings (**1f–1i**, entries 1–4). A heteroaromatic aldehyde such as furan-2-carbaldehyde (**2d**) and an  $\alpha,\beta$ -unsaturated aldehyde (cinnamaldehyde, **2e**) were suitable substrates to afford the corresponding diamines in good to excellent yields and ee's (entries 3, 4, 8, and 11). Most remarkably, the one-pot process worked well with an array of enolizable  $\alpha$ - and  $\beta$ -branched aldehydes to give the corresponding diamines in good yields with high enantioselectivities (entries 5, 6, and 13–17).<sup>11</sup>

The potential of this catalytic approach is further demonstrated using substituted enecarbamates as nucleophiles. Reaction of aniline **3d**, (*E*)-benzyl-prop-1-enylcarbamate (**4c**, R<sup>2</sup> = Me), or (*E*)-benzyl-pent-1-enylcarbamate (**4d**, R<sup>2</sup> = <sup>*n*</sup>Pr) with a range of aliphatic and aromatic aldehydes afforded the *anti* 1,3-diamines **1l–1u** with excellent diastereomeric (*anti*/*syn* > 95/5) and enantiomeric excesses.<sup>12</sup> The (*Z*)-**4c**, although less reactive than the (*E*)-**4c**, displayed the same selectivity as its (*E*)-counterpart, affording the *anti*-isomer as a major product. Thus the reaction of (*Z*)-**4c** with propionaldehyde (**2f**) afforded the *anti*-adduct **1r** in 62% yield with 90% ee (cf. entries 13 and 17).<sup>13</sup> A *Z/E* isomerization of enecarbamate under these reaction conditions was apparently faster than its addition to the imine.<sup>12,14,15</sup>

The 4-nitrophenyl group was removed following a two-step procedure reported recently by Snapper and Hoveyda.<sup>16</sup> Thus, reduction of **1k** (Zn, NH<sub>4</sub>Cl) followed by oxidative cleavage of the resulting aniline in the presence of PhI(OAc)<sub>2</sub> afforded amine **8** in 40% nonoptimized yield (Scheme 2).

A mechanistic proposal for this one-pot process is outlined in Scheme 3. Condensation of an aniline and an aldehyde

**Table 2.** Scope of the Enantioselective Brønsted Acid-Catalyzed One-Step Synthesis of 1,3-Diamines<sup>a</sup>

| $\begin{array}{c} \text{ArNH}_2 \\ \mathbf{3} \\ \text{R}^1\text{CHO} \\ \mathbf{2} \end{array} + \begin{array}{c} \text{NHCbz} \\ \text{R}^2 \\ \mathbf{4} \end{array} \xrightarrow[\text{then NaBH}_3\text{CN, pTSA}]{\text{CH}_2\text{Cl}_2, \text{EtOH, } 0^\circ\text{C, } \mathbf{5}}$ $\begin{array}{c} \text{ArHN} \\ \text{R}^1 \\ \mathbf{1} \end{array}$<br>Ar = <i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub> |                                                                                      |                        |                     |                 |
|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|------------------------|---------------------|-----------------|
| entry                                                                                                                                                                                                                                                                                                                                                                                                                               | <b>1</b>                                                                             | yield (%) <sup>b</sup> | ee (%) <sup>c</sup> |                 |
| 1                                                                                                                                                                                                                                                                                                                                                                                                                                   |    | <b>1f</b>              | 79                  | 79              |
| 2                                                                                                                                                                                                                                                                                                                                                                                                                                   |    | <b>1g</b>              | 74                  | 94              |
| 3                                                                                                                                                                                                                                                                                                                                                                                                                                   |    | <b>1h</b>              | 86                  | 83              |
| 4                                                                                                                                                                                                                                                                                                                                                                                                                                   |    | <b>1i</b>              | 92                  | 76              |
| 5                                                                                                                                                                                                                                                                                                                                                                                                                                   |    | <b>1j</b>              | 97                  | 88              |
| 6                                                                                                                                                                                                                                                                                                                                                                                                                                   |    | <b>1k</b>              | 76                  | 90              |
| 7                                                                                                                                                                                                                                                                                                                                                                                                                                   |   | <b>1l</b>              | 80                  | 84              |
| 8                                                                                                                                                                                                                                                                                                                                                                                                                                   |  | <b>1m</b>              | 72                  | 83              |
| 9                                                                                                                                                                                                                                                                                                                                                                                                                                   |  | <b>1n</b>              | 70                  | 85              |
| 10                                                                                                                                                                                                                                                                                                                                                                                                                                  |  | <b>1o</b>              | 78                  | 82              |
| 11                                                                                                                                                                                                                                                                                                                                                                                                                                  |  | <b>1p</b>              | 81                  | >99             |
| 12                                                                                                                                                                                                                                                                                                                                                                                                                                  |  | <b>1q</b>              | 55                  | 84              |
| 13                                                                                                                                                                                                                                                                                                                                                                                                                                  |  | <b>1r</b>              | 79 <sup>d</sup>     | 91 <sup>d</sup> |
| 14                                                                                                                                                                                                                                                                                                                                                                                                                                  |  | <b>1s</b>              | 70 <sup>d</sup>     | 89 <sup>d</sup> |
| 15                                                                                                                                                                                                                                                                                                                                                                                                                                  |  | <b>1t</b>              | 89 <sup>d</sup>     | 97 <sup>d</sup> |
| 16                                                                                                                                                                                                                                                                                                                                                                                                                                  |  | <b>1u</b>              | 95 <sup>d</sup>     | 90 <sup>d</sup> |
| 17                                                                                                                                                                                                                                                                                                                                                                                                                                  |  | <b>1r</b>              | 62 <sup>d</sup>     | 90 <sup>d</sup> |

<sup>a</sup> General conditions: **1a/2a/3/4/5** = 1.5/1.1/1/17/0.1 in CH<sub>2</sub>Cl<sub>2</sub> (*c* = 0.1) followed by addition of NaBH<sub>3</sub>CN/pTSA = 20/10 in EtOH. <sup>b</sup> Yields refer to chromatographically pure products. <sup>c</sup> Enantiomeric excess was determined by chiral HPLC analysis. <sup>d</sup> Reaction performed at –30 °C.

would give imine **9**, which was susceptible to nucleophilic addition of ethanol leading to aminoether **10**.<sup>17</sup> However, this step was degenerative since **10** was readily converted

(11) In all these examples, aminoethers **6** were formed as a mixture of two diastereomers without appreciable diastereoselectivity.

(12) The *anti* stereochemistry was determined by conversion of isolated aminoether **6** into the Povarov adduct **7** under acidic conditions and detailed NMR studies of the resulting tetrahydroisoquinoline.

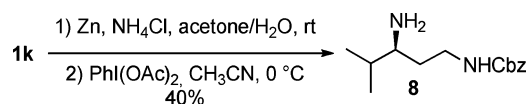
(13) Terada has recently shown that stereochemical outcome in the addition of enecarbamate to aminoether depended on the geometry of the starting enecarbamate. See ref 4c.

(14) For Lewis acid-catalyzed *E/Z* isomerization, see: Matsubara, R.; Kobayashi, S. *Angew. Chem., Int. Ed.* **2006**, *45*, 7993.

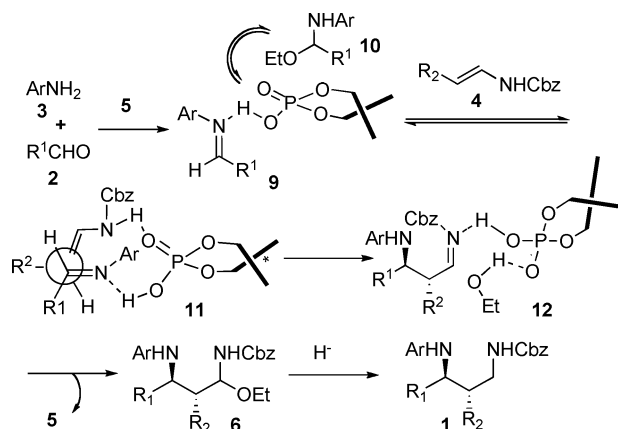
(15) For phosphoric acid-catalyzed *E/Z* isomerization, see: Baudequin, C.; Zamfir, A.; Tsogoeva, S. B. *Chem. Commun.* **2008**, 4637.

(16) Wieland, L. C.; Vieira, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 570.

**Scheme 2.** Reaction Sequence and Stereochemical Issue



**Scheme 3.** Reaction Sequence and Stereochemical Issue



back to imine **9** under the reaction conditions. On the other hand, activation of both imine **9** and enecarbamate **4** via H-bonded transition state **11** followed by pseudointramolecular

(17) The aminoether **10** has been isolated in certain cases.

lecular *si*-face attack of (*E*)-enecarbamate to imine would afford new imine intermediate **12** with concurrent creation of two stereocenters. Trapping of the acylimine **12** by ethanol would then afford the aminoether **6**, which is reduced in situ to form the *anti* 1,3-diamine **1**. It is interesting to note that further addition of enecarbamate **4** to the *N*-acylimine **12** did not occur even when 2 equiv of **4** was used,<sup>18</sup> presumably due to (a) the presence of a large excess of EtOH and (b) the enhanced stability of the *N*-acylaminoether function in **6** relative to *N*-arylaminoether **10**.

In summary, we have developed a chiral Brønsted acid-catalyzed enantioselective three-component synthesis of 1,3-diamines via a key Mannich reaction. The reaction provides an efficient entry to *anti*-1,2-disubstituted 1,3-diamine derivatives in high yields with excellent enantioselectivities.

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**Supporting Information Available:** Catalysis optimization, spectroscopic data, ee measurement, and absolute configuration determinations for **1e** and **1l**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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(18) Reactions involving consecutive addition of two equivalents of enecarbamates to imine intermediates, see: (a) Terada, M.; Machioka, K.; Sorimachi, K. *J. Am. Chem. Soc.* **2007**, *129*, 10336. (b) Kobayashi, S.; Gustafsson, T.; Shimizu, Y.; Kiyohara, H.; Matsubara, R. *Org. Lett.* **2006**, *8*, 4923.