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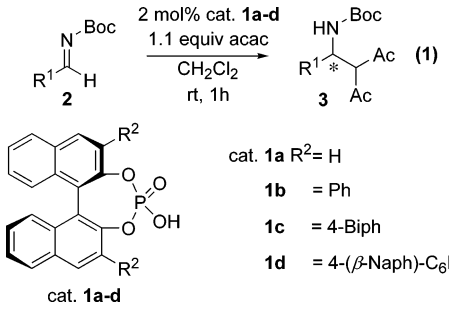
# Chiral Brønsted Acid-Catalyzed Direct Mannich Reactions via Electrophilic Activation

Daisuke Uraguchi and Masahiro Terada*

*Graduate School of Science, Department of Chemistry, Tohoku University, Sendai 980-8578, Japan*

Received February 16, 2004; E-mail: mterada@mail.tains.tohoku.ac.jp

Since List, Barbas, and MacMillan reported their landmark treatise in 2000,[1,2] carbon−carbon bond forming reactions catalyzed by small organic molecules, so-called organocatalysts, have become a rapidly growing area in synthetic organic chemistry.[3] In organocatalysis, one of the most general approaches is the activation of a carbon nucleophile by the formation of an enamine intermediate via the nucleophilic attack of a secondary amine to a carbonyl compound.[4,5] Although the electrophilic activation of a substrate by means of a Brønsted acid is, undoubtedly, the most straightforward and classical approach to the promotion of a reaction, the development of effective asymmetric transformations catalyzed by Brønsted acids is rather limited.[6−8] It is well-accepted that nearly a "proton"-like character is required for activating a substrate efficiently and hence chiral Brønsted acids *could not* provide a chiral environment to a reactive intermediate. However, recently, Jacobsen et al. have developed highly enantioselective Strecker reactions[9] and Mannich reactions[10] catalyzed by peptide-based thiourea derivatives as chiral Brønsted acids.[6,11] Their achievement has clearly indicated that a chiral Brønsted acid *could* recognize enantiotopic faces of an imine substrate via hydrogen bonding and has opened up a new avenue in asymmetric catalysis. We describe herein a new family of chiral Brønsted acid catalysts, phosphoric acid derivatives,[12] which accelerates direct Mannich reactions in a highly enantioselective fashion. This is the prominent example of asymmetric direct Mannich reactions catalyzed by chiral Brønsted acids.[4e−i,13−15]




We focused on phosphoric acids as suitable Brønsted acid catalysts because of their unique characteristics. 1) Tetradentate structure around the phosphorus(V) atom would prevent free rotation at α of the phosphorus center by formation of a ring structure. This characteristic feature cannot be found in other possible Brønsted acids, such as carboxylic and sulfonic acids, etc. 2) Their appropriate acidity[16] should catch up the imine through hydrogen bonding without loose ion-pair formation. 3) Their phosphoryl oxygen should function as a Lewis basic site, and thus a phosphoric acid could function as a bifunctional catalyst.

Indeed, preliminary studies have shown that chiral phosphoric acid (**1a**)[17,18] has extremely high catalytic activity for Mannich-type reactions. During the screening of substrates, we found that it could effectively promote the *direct* Mannich reaction between *N*-Boc-protected imine (**2**, $R^1$ = Ph) and acetyl acetone. Fortunately, resulting β-aminoketone (**3**, $R^1$ = Ph) was obtained in an optically active form (12% ee) (Table 1, entry 1). The result obviously indicates that **1a** can provide a chiral environment to a reaction intermediate. Noteworthy are the beneficial effects of the 3,3′-bisaryl substituents of the catalysts on the enantioselectivity (entries 2−4). For instance, the direct Mannich reaction under the influence of 3,3′-phenyl-substituted phosphoric acid (**1b**) produced **3** ($R^1$ = Ph) in 56% ee (entry 2). Interestingly, the simple extension of aromatic substitution to the para direction improved the enantioselectivity dramatically (entry 3). Use of **1d** as a catalyst further increased the enantioselectivity to 95% ee in 99% yield (entry 4).[19]

***Table 1.*** Optimization of Phosphoric Acids[a] (Eq 1; $R^1$ = Ph)

| entry | catalyst | yield[b] (%) | ee[c] (%) |
|---|---|---|---|
| 1 | **1a** | 92 | 12[d] |
| 2 | **1b** | 95 | 56 |
| 3 | **1c** | 88 | 90 |
| 4 | **1d** | 99 | 95 |

[a] All reactions were carried out on a 0.1 mmol reaction scale. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis. [d] The opposite enantiomer was obtained as the major isomer.

***Table 2.*** The Chiral Phosphoric Acid-Catalyzed Direct Mannich Reactions (Eq 1; Catalyst **1d** Was Used)[a]

| entry | $R^1$ | yield[b] (%) | ee[c] (%) |
|---|---|---|---|
| 1 | 4-MeO−$C_6H_4$− | 93 | 90 |
| 2 | 4-Me−$C_6H_4$− | 98 | 94 |
| 3 | 4-Br−$C_6H_4$− | 96 | 98 |
| 4 | 4-F−$C_6H_4$− | 94 | 96 |
| 5 | 2-Me−$C_6H_4$− | 94 | 93 |
| 6 | 1-Naph− | 99 | 92 |

[a] All reactions were carried out on a 0.1 mmol reaction scale. [b] Isolated yield. [c] Enantiomeric excess was determined by HPLC analysis.

The substrate scope of the direct Mannich reaction of *N*-Boc-protected arylimine derivatives is summarized in Table 2. Para- and ortho-substituted arylimines underwent addition with generally high enantioselectivity in excellent yield. This reaction was carried out on a scale as high as 1 g with no detrimental effect on yield or enantioselectivity, and a single recrystallization gave pure enantiomer in 82% yield based on **3** ($R^1$ = Ph) thus formed. It should be noted that only 1 mol % catalyst was sufficient for completion of the reaction within 2 h to give **3** ($R^1$ = Ph) in 94% ee and **1d** was recovered in over 80%.

The absolute configuration of **3** ($R^1$ = Ph) was determined by derivatization to Boc-phenylglycine methylester (**4**) (Scheme 1). **3** ($R^1$ = Ph) was converted into β-amino-α-acetoxyketone by Baeyer−Villiger oxidation, and subsequent reduction provided the corresponding diol. The oxidative cleavage of the diol by $KMnO_4$/sodium periodate gave Boc-phenylglycine without racemization,[20] and further treatment with diazomethane yielded Boc-phenylglycine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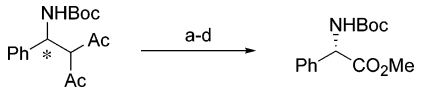
***Scheme 1.*** Absolute Configuration Determination by Phenylglycine Synthesis[a]




**3** ($R^1$ = Ph) >99% ee — **4** >99% ee

[a] Conditions: (a) Oxone, $K_2CO_3$, acetone, $CH_2Cl_2$, $H_2O$, 0 °C; (b) DIBAH, toluene, −78 °C; (c) cat. $KMnO_4$, $NaIO_4$, $Na_2CO_3$, 1,4-dioxane, $H_2O$, room temperature; (d) diazomethane, ethyl acetate, 0 °C, 46% (four steps).

methylester (**4**). The absolute configuration of **4** was assigned to be *S* by optical rotation. The results demonstrate that (*R*)-*β*-aminoketone (**3**, $R^1$ = Ph) was obtained in the reaction catalyzed by (*R*)-**1d**. This procedure also exhibits the synthetic utility of **3** to construct an α-amino acid moiety.

In summary, we communicated that the phosphoric acid derivatives of general structure **1** serve as highly effective catalysts for the direct addition of acetyl acetone to *N*-Boc-protected arylimines. The beneficial effects of the 3,3′-bisaryl substituents of the catalysts on the enantioselectivity are greatly appreciated, and thus **1d** functions as an excellent catalyst. The Brønsted acid-catalyzed direct Mannich reactions presented herein provide an attractive way to construct *β*-aminoketones under extremely mild conditions. The stereochemical course of this reaction was established through the synthesis of Boc-(*S*)-phenylglycine methylester (**4**). The transformation thus demonstrated is applicable to a useful method for the synthesis of various phenylglycine derivatives. The development of other Mannich-type reactions catalyzed by phosphoric acids as Brønsted acid catalysts is underway in our laboratory.

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**Supporting Information Available:** Representative experimental procedure and spectral data for **1d** and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

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