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# Asymmetric Transfer Hydrogenation of β,γ-Alkynyl α-Imino Esters by a Brønsted Acid

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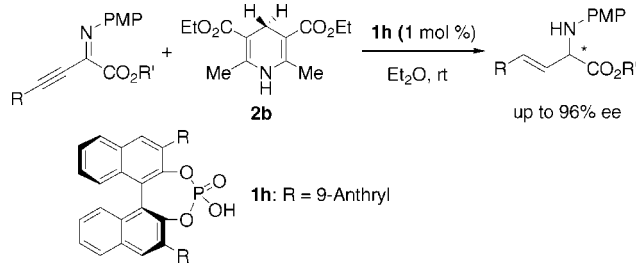
## ABSTRACT




**Asymmetric synthesis of *trans*-alkenyl α-amino esters was realized by chiral phosphoric acid catalyzed transfer hydrogenation of β,γ-alkynyl α-imino esters. Utilizing Hantzsch esters as the hydrogen donor, both the alkyne and imine moieties of β,γ-alkynyl α-imino esters were reduced to afford *trans*-alkenyl α-amino esters with up to 96% ee.**

Synthesis of optically pure α-amino acids and their derivatives constitutes an important task in organic synthesis because of their broad utilities in all disciplines of biology, medicine, and chemistry.[1] The chiral β,γ-alkenyl α-amino acids and their derivatives as a special class of these compounds have received much attention.[2] However, the synthesis of optically pure β,γ-alkenyl α-amino acids and their derivatives remains challenging. The current asymmetric synthesis of β,γ-alkenyl α-amino acids mainly relies on the chiral auxiliary approach.[3] To our knowledge, there are very limited reports on the catalytic asymmetric synthesis.[4] Recently, we and others have reported the chiral phosphoric acids[5,6] catalyzed asymmetric transfer hydrogenation of α-imino esters by employing Hantzsch ester as the hydrogen donor, providing enantiopure α-amino esters smoothly (Figure 1).[7–9] Unprecedentedly, when the β,γ-alkynyl α-imino ester was employed, both the alkyne and imine moieties

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were reduced to afford the $\beta,\gamma$-alkenyl α-amino ester. It should be noted that only a *trans*-alkene-substituted product was observed during the reduction. This reaction provides straightforward access to optically pure $\beta,\gamma$-alkenyl α-amino acid derivatives. The presence of a C=C bond in the product offers a unique and highly valuable opportunity for further transformation on the $\beta,\gamma$-position of α-amino acids.

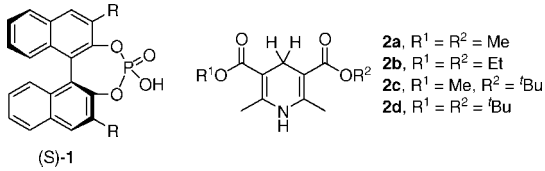
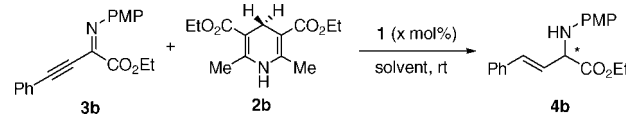



**Figure 1.** Chiral phosphoric acids and Hantzsch esters.

Herein, we report the enantioselective synthesis of *trans*-alkenyl α-amino esters by chiral phosphoric acid catalyzed transfer hydrogenation of $\beta,\gamma$-alkynyl α-imino esters with Hantzsch ester as the hydrogen donor. Excellent enantioselectivities (up to 96% ee) have been obtained, and preliminary mechanistic studies have also been carried out.

We first examined the hydrogenation of the phenylacetylenyl-substituted α-imino ester **3b** with 2.2 equiv of Hantzsch ester **2b** in $Et_2O$. With 5 mol % of **1**, all reactions proceeded smoothly at room temperature. From this survey, the sterically more congested phosphoric acids emerged as catalysts with good to excellent levels of enantioselectivity (entries 3, 6, and 8−10, Table 1). The best result was obtained with 5 mol % of **1h**

**Table 1.** Optimization of the Reaction Conditions for the Asymmetric Transfer Hydrogenation of **3b**[a]




| entry | **1**, R | $x$ (mol %) | solvent | ee[b] (%) |
|---|---|---|---|---|
| 1 | **1a**, H | 5 | $Et_2O$ | −22 |
| 2 | **1b**, phenyl | 5 | $Et_2O$ | 57 |
| 3 | **1c**, $SiPh_3$ | 5 | $Et_2O$ | −85 |
| 4 | **1d**, 3,5-$(CF_3)_2$-$C_6H_3$ | 5 | $Et_2O$ | 21 |
| 5 | **1e**, 4-$NO_2$-$C_6H_4$ | 5 | $Et_2O$ | 54 |
| 6 | **1f**, 1-naphthyl | 5 | $Et_2O$ | 82 |
| 7 | **1g**, 2-naphthyl | 5 | $Et_2O$ | <1 |
| 8 | **1h**, 9-anthryl | 5 | $Et_2O$ | 90 |
| 9 | **1i**, 9-phenanthryl | 5 | $Et_2O$ | 72 |
| 10 | **1j**, 2,4,6-($i$Pr)$_3$$C_6H_2$ | 5 | $Et_2O$ | 87 |
| 11 | **1k**, 4-biphenyl | 5 | $Et_2O$ | 26 |
| 12 | **1h**, 9-anthryl | 5 | toluene | 92 |
| 13 | **1h**, 9-anthryl | 1 | toluene | 92 |

[a] Reaction conditions: $x$ mol % of **1**, 220 mol % of **2b**, 0.05 mol/L of **3b** at room temperature for 24 h. [b] Determined by chiral HPLC analysis (Chiralcel AD-H). PMP = *p*-methoxyphenyl.

providing the *trans*-alkene-substituted α-amino ester **4b** in 90% ee (entry 8, Table 1). Interestingly, chiral phosphoric acids **1a** and **1c**, derived from (*S*)-BINOL, led to **4b** with reversed optical rotation (entries 1 and 3, Table 1).

With 5 mol % of **1h** at room temperature, the reactions could be carried out smoothly in several common solvents such as toluene (92% ee), $CH_2Cl_2$ (85% ee), THF (87% ee), and $^t$BuOMe (85% ee).[10] Toluene was chosen as the optimal solvent since the reaction in toluene led to the highest enantioselectivity (92% ee, entry 12, Table 1). Further study on the catalyst loadings disclosed that even with 1 mol % of **1h**, the reaction could afford the desired product with the same enantioselectivity (92% ee, entry 13, Table 1). Several Hantzsch esters have been tested, and **2b** was chosen as the optimal hydrogen source [85% ee (**2a**), 93% ee (**2c**), 86% ee (**2d**)].[10]

In addition, several $\beta,\gamma$-alkynyl α-imino esters bearing different ester groups were tested for the reaction. As shown

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(8) For a review, see: You, S.-L. *Chem. Asian. J.* **2007**, *2*, 820–827.

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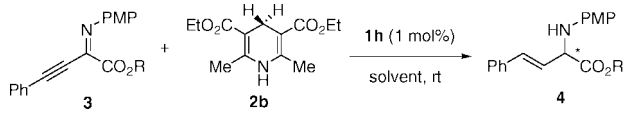
(10) See the Supporting Information for details.

in Table 2, the isolated yields of the desired products were highly dependent on the steric size of the ester groups. For methyl ester **3a**, product was obtained in only 15% yield. Moderate yields were obtained for the substrates bearing the bulky ester groups such as *i*-Pr (51% yield) and *t*-Bu (58% yield), respectively (entries 3 and 5, Table 2). Different from

**Table 2.** Effect of Ester Groups in Asymmetric Transfer Hydrogenation of **3**[a]



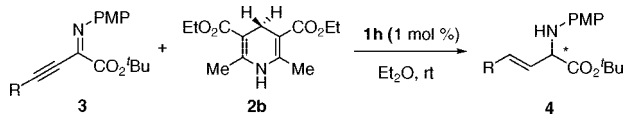

| entry | R | product | solvent | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|
| 1[d] | Me (**3a**) | **4a** | toluene | 15 | 89 |
| 2[d] | Et (**3b**) | **4b** | toluene | 34 | 92 |
| 3 | *i*Pr (**3c**) | **4c** | $Et_2O$ | 51 | 95 |
| 4 | *t*Bu (**3d**) | **4d** | toluene | 48 | 91 |
| 5 | *t*Bu (**3d**) | **4d** | $Et_2O$ | 58 | 94 |

[a] Reaction conditions: 1 mol % of **1h**, 220 mol % of **2b**, 0.05 mol/L of **3** at room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis. [d] Using **2d** instead of **2b** since product **4** cannot be isolated from the byproduct of **2b**.

the previous asymmetric transfer hydrogenation of the simply α-imino esters where different esters show dramatic effect on the enantioselectivity,[7a] there is no significant influence on the enantioselectivities by varying the ester group. For substrates **3c**,**d** bearing bulky ester groups, the yield and enantioselectivity were slightly improved by using the $Et_2O$ as the solvent.

In the presence of 1 mol % of **1h** and 2.2 equiv of **2b**, several alkynyl-substituted α-imino esters have been tested. The results are summarized in Table 3. For substrate with

**Table 3.** Asymmetric Transfer Hydrogenation of $\beta,\gamma$-Alkynyl α-Imino Esters **3**[a]



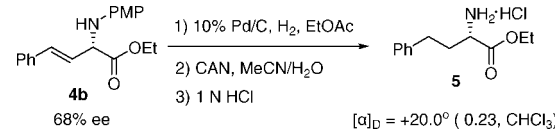

| entry | R | product | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|
| 1 | $C_6H_5$ (**3d**) | **4d** | 58 | 94 |
| 2 | 4-Me-$C_6H_4$ (**3e**) | **4e** | 42 | 95 |
| 3 | 3-Me-$C_6H_4$ (**3f**) | **4f** | 60 | 93 |
| 4 | 4−Cl-$C_6H_4$ (**3g**) | **4g** | 47 | 96 |
| 5 | 3−F-$C_6H_4$ (**3h**) | **4h** | 64 | 95 |
| 6 | 1-naphthyl (**3i**) | **4i** | 27 | 83 |
| 7 | $PhCH_2CH_2$ (**3j**) | **4j** | <5 | |

[a] Reaction conditions: 1 mol % of **1h**, 220 mol % of **2b**, 0.05 mol/L of **3** in $Et_2O$ at room temperature. [b] Isolated yields. [c] Determined by chiral HPLC analysis.

3-methyl or 4-methyl groups on the phenyl ring, moderate yields and excellent ees were obtained (42−60% yield, 93−95% ee, entries 2 and 3, Table 3). By introducing an electron-withdrawing group (4-Cl, 3-F) on the phenyl ring, the reactions also afforded the desired products with excellent ees (95−96% ee, entries 4 and 5, Table 3). Asymmetric transfer hydrogenation of 1-naphthyl bearing alkynyl-substituted α-imino ester **3i** afforded the corresponding *trans*-alkene α-amino ester with 83% ee but only in 27% yield (entry 6, Table 3). Unfortunately, no desired product was isolated when aliphatic substituent bearing substrate was used (entry 7, Table 3).

To determine the absolute configuration, product **4b** was converted to 2-amino-4-phenylbutyric ethyl ester hydrochloride **5**, as depicted in Scheme 1. The absolute configuration

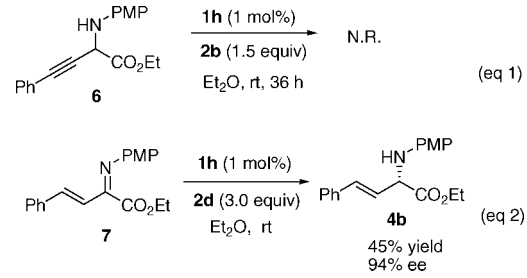
**Scheme 1.** Determination of Absolute Configuration of **4b**




was determined as *S* by comparison with the sign of optical rotation of **5** reported in the literature.[4a,c]

To investigate the mechanism of the catalytic asymmetric transfer hydrogenation of $\beta,\gamma$-alkynyl α-imino esters, the following two experiments were carried out to identify which bond (carbon−carbon triple bond or carbon-nitrogen double bond) would reduce first. As shown in Scheme 2, in the

**Scheme 2.** Investigation of the Reaction Mechanism




presence of 1 mol % of **1h**, the reaction of $\beta,\gamma$-alkynyl α-amino ester **6** with Hantzsch ester **2b** did not proceed to afford the desired product **4b** but the recovery of the starting material. On the other hand, the desired product could be obtained in 45% yield with 94% ee by reducing the *trans*-alkene-substituted α-imino ester **7** (34% yield, 92% ee by hydrogenation of **3b**, entry 2, Table 2). These above results indicated that reduction of carbon−carbon triple bond is faster than that of carbon−nitrogen double bond. It should be noted that the desired product **4b** can not be further reduced under these reaction conditions.

In conclusion, we have identified chiral phosphoric acids as efficient organocatalysts for the asymmetric transfer

hydrogenation of $\beta,\gamma$-alkynyl-α-imino esters to afford *trans*-alkenyl α-amino esters. Both of the alkyne and imine functionalities were reduced under these reaction conditions. Although the yields remain moderate, the reaction features excellent enantioselectivities, mild reaction conditions, operationally simple procedures, and relatively low catalyst loading. Further investigation of the reaction mechanism, improvement of the yields, and extension of the reaction scope are currently ongoing in our laboratory.

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**Supporting Information Available:** Experimental procedures and characterization of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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