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# Catalytic Asymmetric Hydrophosphonylation of Ketimines

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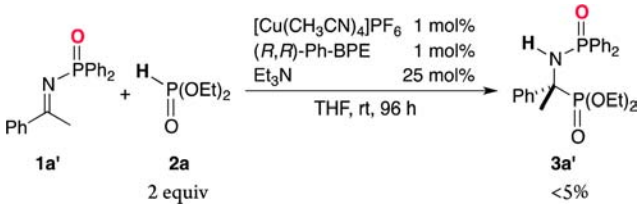
Supporting Information

**ABSTRACT:** Catalytic asymmetric hydrophosphonylation of aromatic and aliphatic *N*-thiophosphinoyl ketimines with dialkyl phosphite was efficiently promoted by as little as 0.5 mol% of catalyst loading at ambient temperature. The catalyst can be recovered for repeated use, and facile removal of the thiophosphinoyl group allowed for ready access to the phosphonic acid analogue of enantioenriched $\alpha,\alpha$-disubstituted $\alpha$-amino acids.

Phosphonic acid is regarded as an isosteric functional group for carboxylic acids, and $\alpha$-amino phosphonic acids are frequently used as surrogates for proteinogenic $\alpha$-amino acids in medicinal chemistry.[1] The most prominent feature of phosphonic acid is its tetrahedral configuration, which mimics the intermediary tetrahedral structure of the reactions of carboxylic acid derivatives.[2] Because of the increasing demand for phosphonic acid analogues of $\alpha$-amino acids, a wide variety of synthetic methodologies have been devised.[3] However, even with the significant advance in the arsenal of modern synthetic chemistry, only a few enantioselective synthetic methods are available for their $\alpha$-tetrasubstituted variants. Use of the chiral pool and chiral auxiliaries paved the way to this class of elusive synthetic targets,[4] and the first catalytic enantioselective approach was reported by Ito et al. using catalytic asymmetric allylation of $\alpha$-acetamido-$\beta$-keto phosphonates, albeit with limited generality and moderate enantioselectivity.[5,6] Nakamura and Shibata et al. demonstrated another approach using catalytic asymmetric hydrophosphonylation of *N*-mesitylenesulfonyl ketimines (Pudovik reaction) to produce tetrasubstituted $\alpha$-aryl $\alpha$-amino phosphonic acids with high enantioselectivity.[7−10] However, the reaction using aliphatic ketimines delivered the corresponding products with unsatisfactory enantioselectivity. Herein, we report a general protocol to access $\alpha$-tetrasubstituted $\alpha$-amino phosphonic acids bearing aromatic or aliphatic substituents with 0.5−2 mol% of catalyst loading. The catalyst can be recovered and used repeatedly without any loss of catalytic activity.

The catalytic asymmetric construction of a tetrasubstituted stereogenic center has been a sustained topic for decades.[11] In our continuing program in this field, we identified that *N*-thiophosphinoyl ketimines **1**[12] serve as suitable soft Lewis basic electrophiles to produce $\alpha$-tetrasubstituted amines in soft Lewis acid/hard Brønsted base cooperative catalysis.[13,14] Use of secondary phosphite **2** as the nucleophile permits direct access to tetrasubstituted $\alpha$-amino phosphonates under proton transfer conditions. An initial attempt was made with ketimine **1a** and diethyl phosphite **2a** (Table 1). With 10 mol% of the soft Lewis acid/hard Brønsted base cooperative catalyst consisting of $[Cu(CH_3CN)_4]PF_6$/$Li(OC_6H_4$-*p*-OMe), chiral phosphine ligands were screened (entries 1−5).[15] (*R*,*R*)-Ph−BPE outperformed the bisphosphine ligands with axial chirality or ferrocene-embedded bisphosphine ligands, and the desired product **3a** was obtained in 96% yield with 97% enantiomeric excess (ee) (entry 5). Given its operational simplicity and the relatively high acidity of phosphite **2a**, amine bases instead of $Li(OC_6H_4$-*p*-OMe) were examined in combination with $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph−BPE (entries 6−8). Although a coordinative amine base such as DBU led to a significant decrease in enantioselectivity (entry 6), substoichiometric amounts of trialkylamines functioned as effective Brønsted bases to produce **3a** with high enantioselectivity (entries 7,8). $Et_3N$ was selected as the optimal base because it is an inexpensive stock reagent in chemical laboratories, and the amount of $[Cu(CH_3CN)_4]PF_6$/(*R*,*R*)-Ph−BPE could be reduced to as little as 0.5 mol% to complete the reaction (entry 9).[16] The thiophosphinoyl group was indispensable in this soft Lewis acid/hard Brønsted base cooperative catalytic system. In contrast to the smooth progress of the reaction of **1a** (Table 1), the reaction of *N*-phosphinoyl ketimine **1a′**, an oxygen analogue of **1a**, barely proceeded under otherwise identical reaction conditions even after 96 h (Scheme 1),

**Scheme 1. Reaction with *N*-Phosphinoyl Ketimine 1a′**




suggesting that the soft−soft interaction of the P═S group and Cu(I) played a pivotal role in promoting the reaction.[17]

The substrate generality of the present catalytic asymmetric hydrophosphonylation protocol is summarized in Table 2. The reactivity of thiophosphinoyl ketimine **2** was partly dependent on the electronic nature of the adjacent aromatic group. The reactions using ketimines bearing electron-withdrawing $CF_3$ or halogen substituents reached completion

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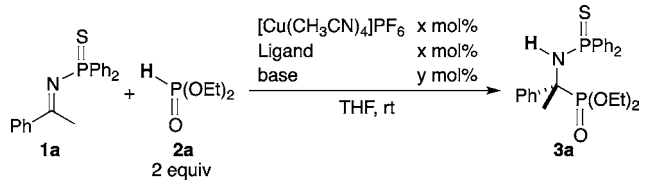
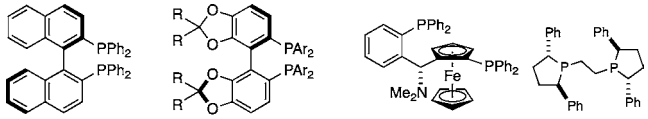
**Table 1. Catalytic Asymmetric Hydrophosphonylation of *N*-Thiophosphinoyl Ketimines[a]**

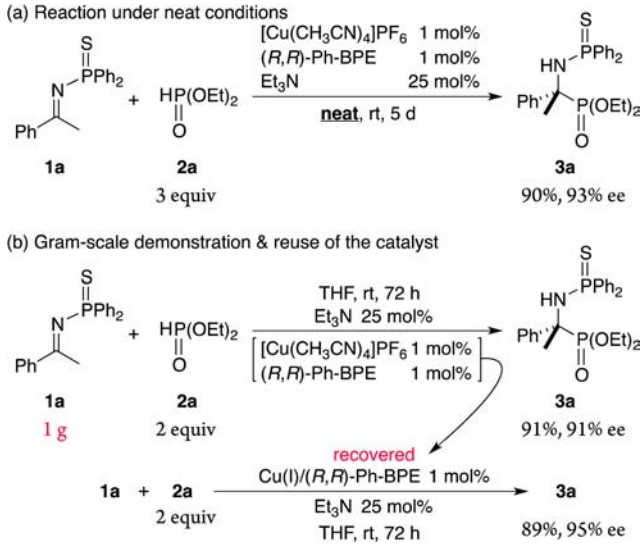



| entry | ligand | *x* | base | *y* | time (h) | yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|---|
| 1 | (*R*)-BINAP | 10 | LiOAr[d] | 10 | 24 | 63 | −75[e] |
| 2 | (*R*)-DIFLUORPHOS | 10 | LiOAr[d] | 10 | 24 | 85 | −82[e] |
| 3 | (*R*)-DTBM-SEGPHOS | 10 | LiOAi[d] | 10 | 24 | 70 | 53 |
| 4 | (*R,Rp*)-TANIAPHOS | 10 | LiOAr[d] | 10 | 24 | 31 | 66 |
| 5 | (*R,R*)-Ph-BPE | 10 | LiOAr[d] | 10 | 24 | 96 | 97 |
| 6 | (*R,R*)-Ph-BPE | 5 | DBU | 50 | 24 | 94 | 67 |
| 7 | (*R,R*)-Ph-BPE | 5 | $Cy_2NMe$ | 50 | 24 | 97 | 97 |
| 8 | (*R,R*)-Ph-BPE | 5 | $Et_3N$ | 50 | 24 | 98 | 97 |
| 9[f] | (*R.R*)-Ph-BPE | 0.5 | $Et_3N$ | 25 | 72 | 90 | 96 |

[a] **1a**: 0.1 mmol. **2a**: 0.2 mmol, 0.5 M in **1a**. [b] Determined by $^1H$ NMR analysis. [c] Determined by HPLC analysis. [d] Ar = $C_6H_4$-*p*-OMe. [e] *S* enantiomer was the major product. [f] **1a**: 0.2 mmol. **2a**: 0.4 mmol, 0.5 M in **1a**. Isolated yield.



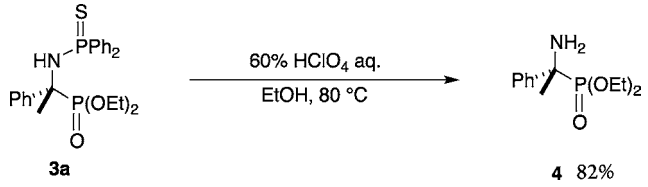

**Scheme 2. Practical Aspect**




with a 0.5 mol% catalyst loading irrespective of their *o*-, *m*-, and *p*-positions (entries 2−7). Ketimines with electron-donating substituents exhibited lower electrophilicity and a higher catalyst loading (1−2 mol%) was required, whereas enantioselectivity was generally high (entries 8−11). Of particular note is that the present catalysis is applicable to aliphatic ketimines having $sp^3$ carbons adjacent to the C=N group, which showed moderate enantioselectivity in the previously developed protocol (entries 12−15).[7] As for the other dialkyl phosphites, dimethyl and dibenzyl phosphite were compatible (entries 16, 17). A slight decrease in enantioselectivity was observed in the reaction using a ketimine having an ethyl substituent (entry 18).

The present catalysis is robust and could be applied under solvent-free conditions without temperature control (Scheme 2a). Whereas the reaction was run for five days because of the low solubility of ketimine **2a**, the operational simplicity and volume production are noteworthy. Furthermore, the Cu(I)/(*R,R*)-Ph−BPE complex was sufficiently stable to be recovered and reused.[18] The reaction mixture for hydrophosphonylation of **2a** on a 1 g scale was directly followed by silica gel chromatography to separate the product **3a** and Cu(I)/(*R,R*)-Ph−BPE complex, which was used for the second run without any loss in catalytic activity and enantioselectivity (Scheme 2b). The thiophosphinoyl group of the product **2a** was readily removed by treatment with $HClO_4$ aq./EtOH at 80 °C to give α-amino phosphonate **4** in 82% yield (Scheme 3).

**Scheme 3. Removal of Thiophosphinoyl Group**




In summary, we have developed a robust and general protocol to produce enantioenriched tetrasubstituted α-amino phosphonic acid derivetives. Ambient temperature, volumetric productivity, and reusability of the catalyst are advantageous for practical application.


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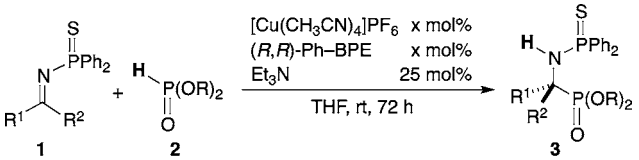
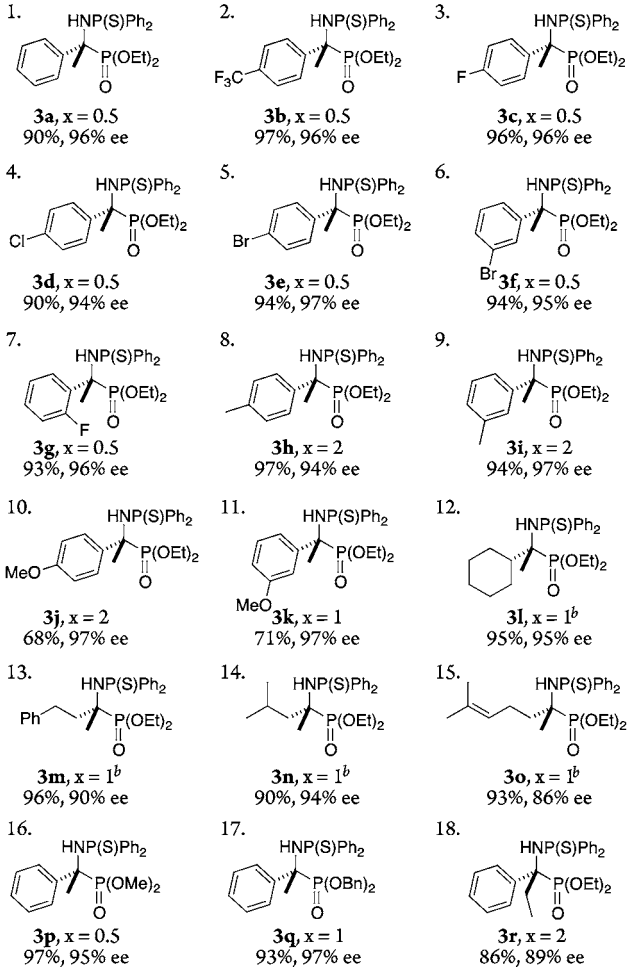
**Table 2. Substrate Generality**[a]




[a]**1**: 0.2 mmol. **2**: 0.4 mmol, 0.5 M in **1**. Isolated yield; ee was determined by HPLC analysis. [b]3 equiv of **2** were used.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Experimental procedures and characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ACKNOWLEDGMENTS

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(16) According to the suggestion from a reviewer, inorganic bases were examined. Although $NaHCO_3$ (50 mol%) was not able to promote the reaction, 50 mol% of $Na_2CO_3$ and $K_2CO_3$ was effective to afford the product **3a** in comparable yield and ee under heterogeneous conditions. Details will be reported as a full paper in due course.

(17) The inherent electrophilicity of phosphinoyl ketimine **1a′** toward the phosphite anion would be higher than that of thiophosphinoyl ketimine **1a**. In the reaction using **2a** with a stoichiometric amount (1.1 equiv) of Li($OC_6H_4$-*p*-OMe), **1a′** exhibited a higher reaction rate than **1a** (**1a**: 0 °C, 30 min, 35% yield and 60% recovery of **1a**; **1a′**: 0 °C, 30 min, 94% yield). See Supporting Information for details.

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