# Direct Catalytic Enantioselective Hydrophosphonylation of *N*-Unsubstituted Ketimines

Koki Yamada,‡ Yuta Kondo,‡ Akihiko Kitamura, Tetsuya Kadota, Hiroyuki Morimoto,* and Takashi Ohshima*

Graduate School of Pharmaceutical Sciences, Kyushu University, Maidashi 3-1-1 Higashi-ku, Fukuoka, Japan, 812-8582.

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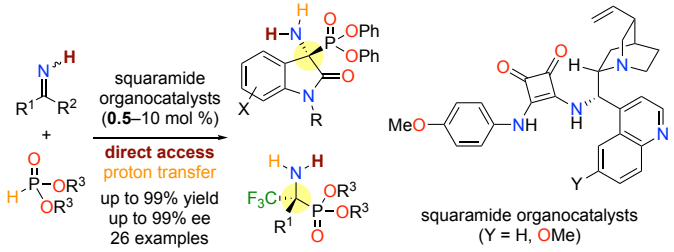
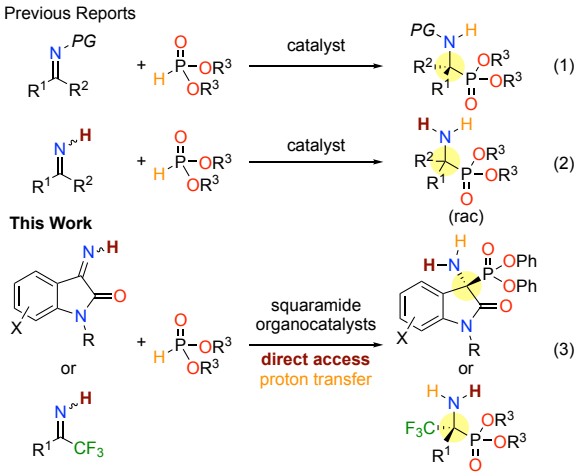



**ABSTRACT:** We report a direct catalytic enantioselective hydrophosphonylation of *N*-unsubstituted ketimines that affords *N*-unprotected α-tetrasubstituted α-aminophosphonates without protection/deprotection steps. The reaction is suitable for *N*-unsubstituted isatin-derived ketimines and *N*-unsubstituted trifluoromethyl ketimines, affording products in high yields with excellent enantioselectivity. Applications of the reaction and a proposed transition state model are also described.

Direct catalytic enantioselective hydrophosphonylation of ketimines effectively synthesizes enantioenriched α-tetrasubstituted α-aminophosphonates, which are usable α-amino acid analogs.[1-4] *N*-Substituted ketimines realize the reaction with both high yield and high enantioselectivity (Scheme 1, eq 1).[5,6] The requisite protection/deprotection steps for derivatizing the amino group, however, limit the greenness of the overall reaction sequence.

**Scheme 1. Hydrophosphonylation of Ketimines**

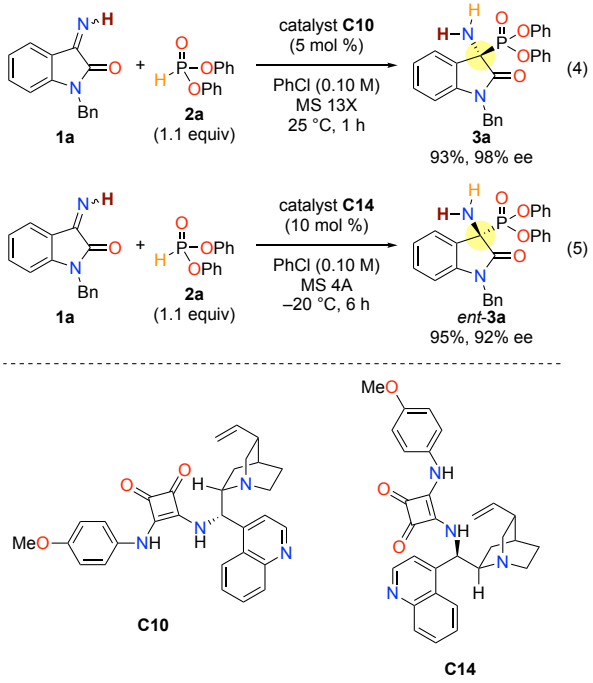



*N*-Unsubstituted ketimines are attractive substrates because they directly afford *N*-unprotected α-tetrasubstituted α-aminophosphonates without protection/deprotection steps.[7-14] Despite several reports of hydrophosphonylation reactions that directly affording *N*-unprotected products have been reported in a racemic form (eq 2),[15-18] the use of *N*-unsubstituted ketimines in catalytic enantioselective hydrophosphonylation has not, to the best of our knowledge, been reported.[19] Herein we report the first direct catalytic enantioselective hydrophosphonylation of *N*-unsubstituted ketimines (eq 3).[20] The unprecedented reactions can be realized using chiral bifunctional squaramide organocatalysts,[21-23] and high yield and excellent enantioselectivity were realized for a broad range of substrates.

To realize the catalytic enantioselective hydrophosphonylation of *N*-unsubstituted ketimines, we first selected isatin-derived ketimine **1a**.[24-27] Screening of chiral bifunctional organocatalysts revealed that thiourea organocatalysts **C1–C3**, previously used for related hydrophosphonylation reactions,[25] gave the product **3a** in moderate yields with moderate enantioselectivities (Tables S1). On the other hand, squaramide catalysts **C4–C10** gave **3a** in high yield with high enantioselectivity, and we selected catalyst **C10** for further optimization. Additional screening of the solvent and desiccant revealed that chlorobenzene and molecular sieves 13X were optimal (Table S3). Finally, phosphite **2a** was reduced to 1.1 equivalents without affecting the reactivity and selectivity (Scheme 2, eq 4). Analogous optimizations using the pseudo-enantiomer catalysts **C11–C14**

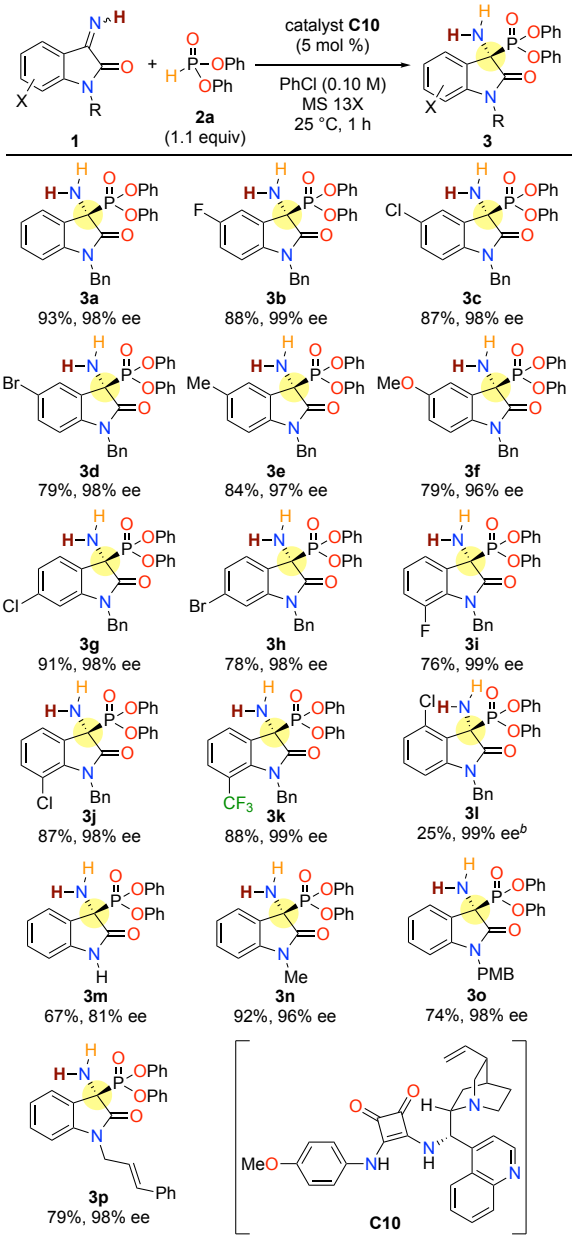
(Tables S2 and S4) revealed that catalyst **C14** was optimal to give *ent*-**3a** in high yield with high enantioselectivity under comparable reaction conditions (eq 5).

**Scheme 2. Optimized Reaction Conditions**




The scope of *N*-unsubstituted isatin-derived ketimines **1** was explored using the optimized reaction conditions and catalyst **C10** (Scheme 3). Electron-withdrawing and -donating substituents at position 5 did not affect the selectivity of **3b**–**f**, and the substituents at positions 6 and 7 also maintained both the high yield and high enantioselectivity of **3g**–**k**. Product **3l** was an exception; while enantioselectivity was excellent, the yield was low. Several substituents at the nitrogen of the isatin were tolerated to give products **3m**–**p**. The absolute configuration of **3a** was determined to be (*R*) by comparing HPLC spectra with the authentic sample of (*R*)-**3a** prepared by deprotection of a known Boc-protected product[24] (see the Supporting Information for details).

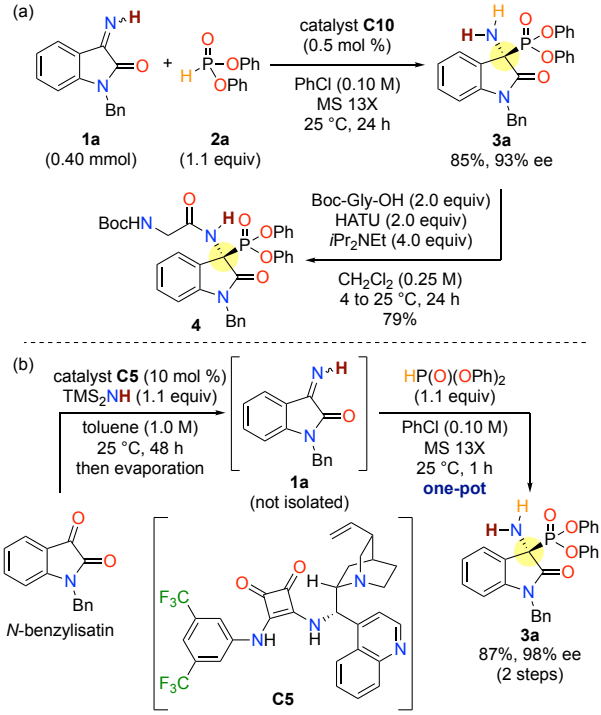
**Scheme 3. Scope of *N*-Unsubstituted Isatin-Derived Ketimines**[a]




[a]Conditions: Ketimine **1** (0.10 mmol), phosphite **2a** (1.1 equiv), catalyst **C10** (5.0 mol %), and MS 13X (50 mg) in PhCl (0.10 M) at 25 °C for 1 h. Isolated yields are reported. Ee was determined by HPLC analysis with chiral stationary phases. [b]For 3 h.

An advantage of the above reaction is that catalyst loading can be reduced to 0.5 mol % while maintaining the high enantioselectivity of **3a** (Scheme 4 (a)). *N*-Unprotected product **3a** was directly transformed into amide **4** without deprotection of the protective group. The one-pot catalytic transformation of *N*-benzylisatin to **3a** via in-situ generation of *N*-unsubstituted ketimine **1a** was realized using catalyst **C5** (Scheme 4 (b)).[14,28,29] Catalyst **C5** was essential to promote the generation of **1a**, likely due to efficient activation of the carbonyl group by hydrogen bonding.

**Scheme 4. Applications of the Hydrophosphonylation of *N*-Unsubstituted Isatin-Derived Ketimines**




A transition state model explaining the observed enantioselectivity is proposed as shown in Figure 1.[30] Phosphite **2** is deprotonated with bifunctional organocatalysts to give an ion pair. The ammonium part of the catalyst activates the *N*-unsubstituted ketimine, and the squaramide moiety holds the phosphite anion through hydrogen-bonding interactions, promoting the addition from the *Re* face of the ketimine to preferentially give (*R*) products. Density functional theory calculations supported the proposed transition state model using catalyst **C10** with isatin-derived *N*-unsubstituted ketimine **1a** and diphenyl phosphite (**2a**) (see the Supporting Information for details). The transition state energy for the major (*R*) isomer was 5 kcal/mol lower than that for the minor (*S*) isomer, consistent with the high enantioselectivity of isatin-derived *N*-unprotected products **3**.

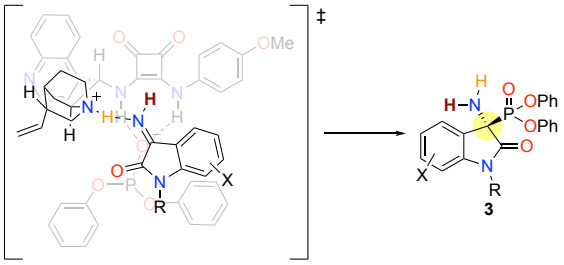
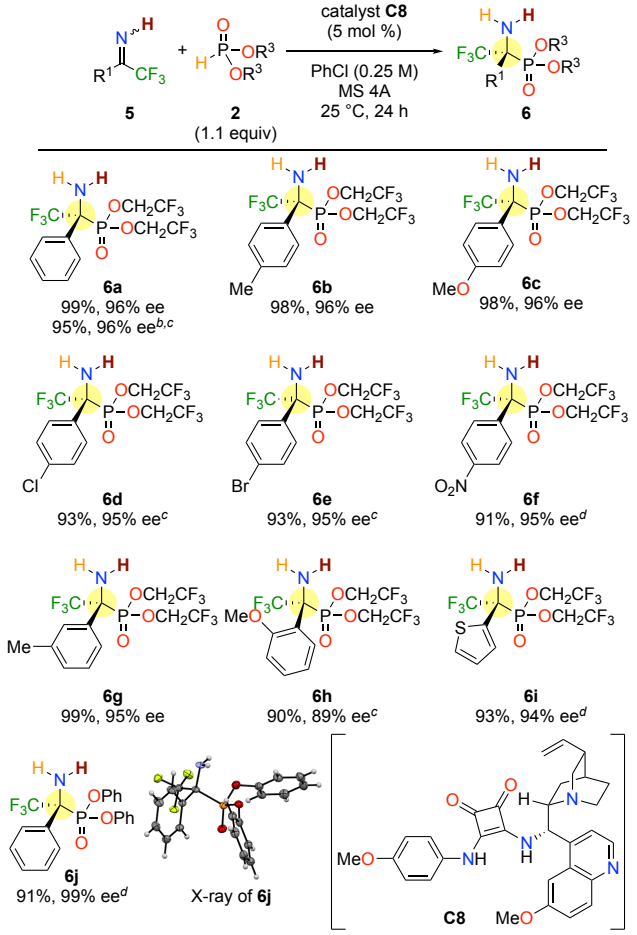


**Figure 1**. Proposed transition state model for the synthesis of **3**.

Finally, the scope was extended to *N*-unsubstituted trifluoromethyl ketimines **5** (Scheme 5).[31,32] After optimizing the reaction conditions (Tables S5 and S6), hydrophosphonylation adduct **6** was obtained in high yield with high enantioselectivity using catalyst **C8** and bis(2,2,2-trifluoroethyl) phosphite (**2b**),[33] and various electron-donating and -withdrawing substituents were tolerated. The reaction was also applicable for diphenyl phosphite (**2a**) to give product **6j**. The absolute configuration of **6j** was determined to be (*R*) by X-ray crystallographic analysis, and the transesterification of **6j** established the absolute configuration of **6a** to be (*R*) (see the Supporting Information for details).

**Scheme 5. Scope of *N*-Unsubstituted Trifluoromethyl Ketimines**[a]




[a]Conditions: Ketimine **5** (0.10 mmol), phosphite **2** (1.1 equiv), catalyst **C8** (5.0 mol %), and MS 4A (50 mg) in PhCl (0.25 M) at 25 °C for 24 h. [b]With 2.5 mol % of **C8**. [c]For 48 h.[d]With 10 mol % of **C8** for 72 h.

In conclusion, we developed a catalytic enantioselective hydrophosphonylation reaction of *N*-unsubstituted ketimines. The reaction was uniformly applicable for isatin-derived ketimines and trifluoromethyl-substituted ketimines, giving the desired products with excellent enantioselectivity. Advantages of the reaction are reduced catalyst loading, transformation of the product, and one-pot synthesis from the parent carbonyl compound. A transition state model explaining the observed enantioselectivity is also proposed. Detailed mechanistic studies and efforts to expand the scope to other *N*-unsubstituted ketimines are ongoing in our laboratory.

## ASSOCIATED CONTENT

**Supporting Information**.
This material is available free of charge via the Internet at http://pubs.acs.org.
Experimental details and characterization data of products (PDF)

## AUTHOR INFORMATION

### Corresponding Author

*E-mail: hmorimot@phar.kyushu-u.ac.jp (H.M.)
*E-mail: ohshima@phar.kyushu-u.ac.jp (T.O.)

### ORCID

Yuta Kondo: 0000-0003-4974-0096
Hiroyuki Morimoto: 0000-0003-4172-2598
Takashi Ohshima: 0000-0001-9817-6984

### Author Contributions

‡These authors contributed equally.

### Notes

The authors declare no conflict of interest.

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