OL | Organic Letters

Cite This: Org. Lett. XXXX, XXX, XXX−XXX

Letter

pubs.acs.org/OrgLett

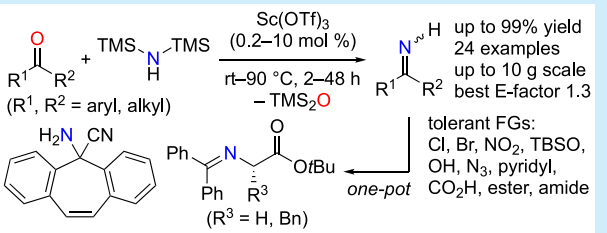
Scandium(III) Triflate Catalyzed Direct Synthesis of *N*-Unprotected Ketimines

Yuta Kondo, Tetsuya Kadota, Yoshinobu Hirazawa, Kazuhiro Morisaki,† Hiroyuki Morimoto,* and Takashi Ohshima*

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

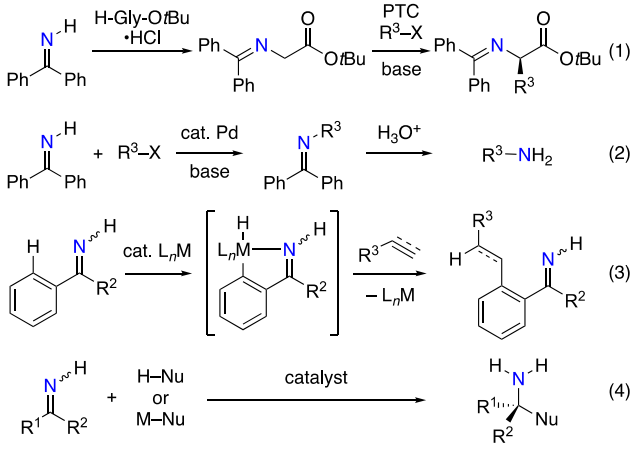
Supporting Information

ABSTRACT: *N*-Unprotected ketimines are useful substrates and intermediates for synthesizing valuable nitrogen-containing compounds, but their potential applicability is limited by the available synthetic methods. To address this issue, we report a scandium(III) triflate catalyzed direct synthesis of *N*-unprotected ketimines. Using commercially available reagents and Lewis acid catalysts, ketones were directly transformed into the corresponding *N*-unprotected ketimines in high yields with broad functional group tolerance, even in multigram scales. The reactions were readily applicable for one-pot synthesis of important compounds such as a glycine Schiff base without isolation of *N*-unprotected ketimine intermediates. Preliminary mechanistic studies to clarify the reaction mechanism are also described.



N-Unprotected ketimines are useful substrates and intermediates for synthesizing a variety of valuable nitrogen-containing compounds.[1] For example, benzophenone imine is the starting material for synthesizing a glycine Schiff base, a well-known substrate for enantioselective synthesis of unnatural amino acids using phase-transfer catalysts (PTC) (Scheme 1, eq 1),[2]

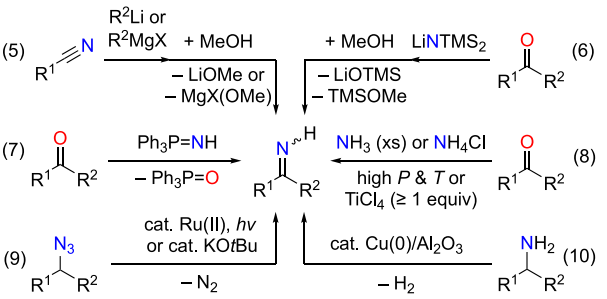
Scheme 1. Utility of *N*-Unprotected Ketimines



and is an ammonia equivalent in catalytic C−N bond-forming reactions such as the Buchwald−Hartwig amination (eq 2).[3] In addition, the recent development of catalytic methods allows for the use of *N*-unprotected ketimines in various catalytic processes such as C−H bond functionalization (eq 3)[4] and nucleophilic addition (eq 4).[5] Therefore, the development of efficient methods for *N*-unprotected ketimine synthesis can greatly contribute to the progress of catalytic synthesis of nitrogen-containing compounds.

Known synthetic methods of *N*-unprotected ketimines (Scheme 2) have several drawbacks. For example, the addition

Scheme 2. Known Synthetic Methods of *N*-Unprotected Ketimines



of organometallic reagents to nitriles, one of the most frequently used methods for synthesizing *N*-unprotected ketimines, requires the use of basic and moisture-sensitive organometallic reagents (eq 5).[6] A similar issue is encountered when using lithium bis(trimethylsilyl)amide as a nitrogen source (eq 6).[7] The aza-Wittig reaction is an effective synthetic method of *N*-unprotected ketimines, but preparing iminophosphorane and separating the large amounts of triphenylphosphine oxide as waste are problematic (eq 7).[8] The use of ammonia would be ideal for synthesizing *N*-unprotected ketimines, but the reaction is generally endergonic for ketones

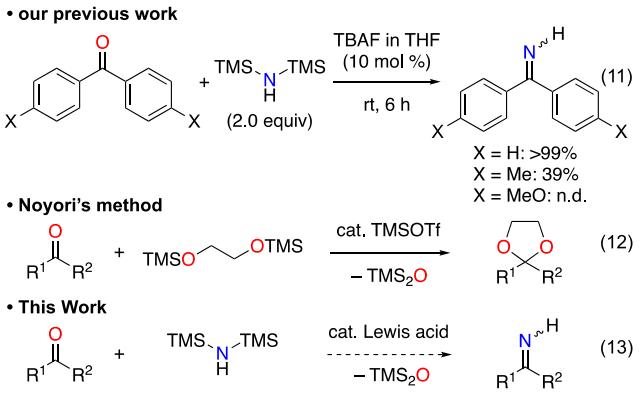
Received: November 11, 2019

DOI: 10.1021/acs.orglett.9b04038
Org. Lett. XXXX, XXX, XXX−XXX

and requires high pressure/temperature conditions or the use of stoichiometric amounts of reagents such as $TiCl_4$ (eq 8).[9] In the above cases, application to a one-pot reaction is not facile because the excess amounts of reagents and stoichiometric amounts of byproducts prohibit subsequent reactions. Although recent advances allow for catalytic synthesis of *N*-unprotected ketimines, the limited availability of the starting materials restricts their application to large-scale preparation of *N*-unprotected ketimines (eqs 9 and 10).[10]

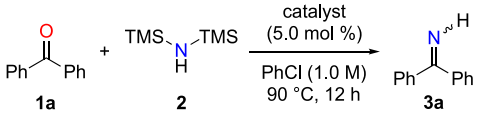
To address these issues, we recently reported TBAF-catalyzed synthesis of benzophenone imine (Scheme 3, eq 11).[11] Although the reaction proceeded under ambient conditions to give benzophenone imine in high yields, the reaction conditions could not be extended to other *N*-unprotected ketimines, significantly limiting their generality. Thus, we worked to develop a better catalytic method for synthesizing a much broader range of *N*-unprotected ketimines. To this end, we were interested in TMSOTf-catalyzed synthesis of ketals from carbonyl compounds, so-called Noyori's method,[12] for which the formation of stable hexamethyldisiloxane drives the reaction forward (eq 12). We hypothesized that a similar reaction would be promoted to afford *N*-unprotected ketimines in the presence of the appropriate Lewis acid catalysts using bis(trimethylsilyl)amine as a nitrogen source (eq 13),[13] although bis(trimethylsilyl)-amine is considered to have very low nucleophilicity.

Scheme 3. Previous Reports and the Design of This Work



To test the above hypothesis, we examined Lewis acid catalysts (Table 1). Screening of several Lewis acids[14] revealed that some Lewis acid triflates effectively catalyzed the desired reaction in good yields (entries 3, 4, 6, and 7), while TMSOTf, the catalyst for Noyori's method, did not efficiently promote the reaction (entry 2). The reaction did not proceed without a catalyst (entry 1) and TfOH was a less efficient catalyst (entry 8), suggesting that the Lewis acidic metal is essential for promoting the reaction. The Lewis acidity of the scandium metal was important, and less Lewis acidic scandium catalysts did not catalyze the reaction effectively (entries 9 and 10). The catalytic efficiency was further tested at 2 h, and scandium triflate[15] was found to be optimal for producing benzophenone imine (**3a**) in excellent yield (entry 11). Additional control experiments revealed the importance of scandium triflate rather than Brønsted acids as the catalyst, TMS_2NH as the nitrogen source, and 90 °C as the temperature for promoting the reaction effectively.[14]

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	yield (%)[b]	entry	catalyst	yield (%)[b]
1	none	n.r.	7	$Bi(OTf)_3$	>99
2	TMSOTf	20	8	TfOH	11
3	$Sc(OTf)_3$	>99	9	$Sc(NO_3)_3$	37
4	$Y(OTf)_3$	85	10	$Sc(OAc)_3$	n.r.
5	$La(OTf)_3$	n.r.	11[c]	$Sc(OTf)_3$	>99
6	$Yb(OTf)_3$	88	12[c]	$Bi(OTf)_3$	96

[a]Conditions: **1a** (0.20 mmol), **2** (1.1 equiv), and catalyst (5.0 mol %) in PhCl (1.0 M) at 90 °C for 12 h. [b]Determined by ^1H NMR analysis of the crude mixture. [c]For 2 h. n.r. = no reaction.

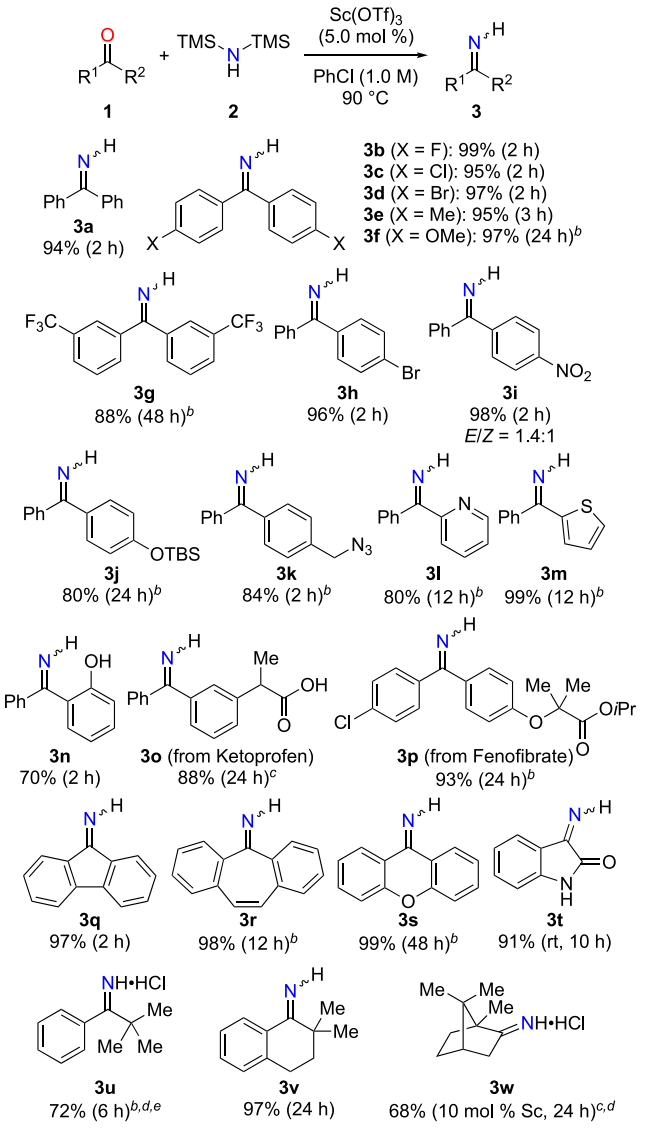
With the optimized reaction conditions in hand, we investigated the substrate scope (Scheme 4). The reaction conditions were applicable for a variety of carbonyl compounds, and benzophenone derivatives having electron-donating and -withdrawing groups, which were unsuitable substrates in our TBAF-catalyzed process,[11] afforded the desired *N*-unprotected ketimines **3b–g** in good yields. The reaction conditions were also applicable for functionalized ketones, and chloro, bromo, nitro, silyloxy, hydroxy, pyridyl, thienyl, amide, and azido moieties were tolerated. Notably, the present catalytic method allowed us to synthesize *N*-unprotected ketimines **3o** and **3p**, which are derived from biologically active carbonyl compounds possessing carboxylic acid and ester moieties, respectively, for which conventional synthetic methods are not readily applicable. Cyclic ketones were also good substrates, and the corresponding *N*-unprotected ketimines **3q–t** were obtained in excellent yields. Finally, alkyl-substituted ketones gave the corresponding *N*-unsubstituted ketimines **3u–w**.[16] Of note, the *N*-unprotected ketimines **3a**, **3b**, **3e**, **3f**, **3g**, **3i**, **3n**, **3q**, **3r**, and **3t** are the substrates/reagents used in the literature.[2−5]

To showcase the practicality of our catalytic method, we performed a large-scale synthesis of *N*-unprotected ketimines (Scheme 5). We successfully synthesized the frequently used substrates benzophenone imine (**3a**) and trifluoromethyl ketimine **3x** in gram scale with reduced catalyst loading (eqs 14 and 15). Moreover, benzophenone imine (**3a**) was successfully synthesized even in decagram scale using an ordinary academic laboratory setup with reasonable reagent and catalyst costs (eq 16),[14] and the product was directly isolated by distillation from the reaction vessel with minimal waste formation, as reflected by the small E-factor (1.3),[17] which is comparable to the level of the bulk chemical synthesis in industry (from 1 to 5) and much smaller than the conventional synthetic method of **3a** using Grignard reagents (9.1) or our TBAF-catalyzed method (20.9).[14]

One benefit of our method over other synthetic protocols is that the coproduct of the reaction is hexamethyldisiloxane, which is unreactive for most reaction conditions. To take advantage of this feature, we investigated one-pot synthesis of several important compounds via *N*-unprotected ketimines (Scheme 6). The one-pot processes from ketones were indeed feasible, and glycine Schiff base **4** was isolated in multigram scale after recrystallization (eq 17). Pronucleophile **5**[18] was synthesized in two step with good yields, for which the isolated *N*-unprotected ketimine **3q** was used according to the previous protocol (eq 18). Further, the Strecker adduct **6**, an

DOI: 10.1021/acs.orglett.9b04038
Org. Lett. XXXX, XXX, XXX−XXX

Scheme 4. Substrate Scope[a]

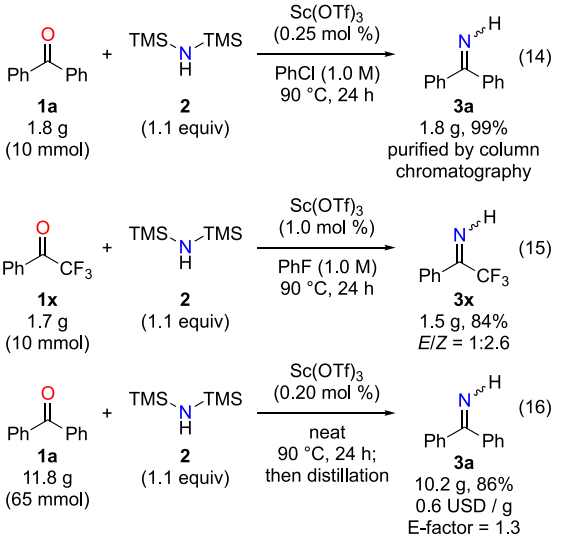


[a]Conditions: **1** (0.20 mmol), **2** (1.1 equiv), $Sc(OTf)_3$ (5.0 mol %) in PhCl at 90 °C unless otherwise noted, and isolated yield was reported. *E*/*Z* ratio was also reported where applicable. [b]1.5 equiv of **2** were used. [c]2.0 equiv of **2** were used. [d]Isolated after treatment with 1 M HCl in Et_2O. [e]At 1.0 mmol scale.

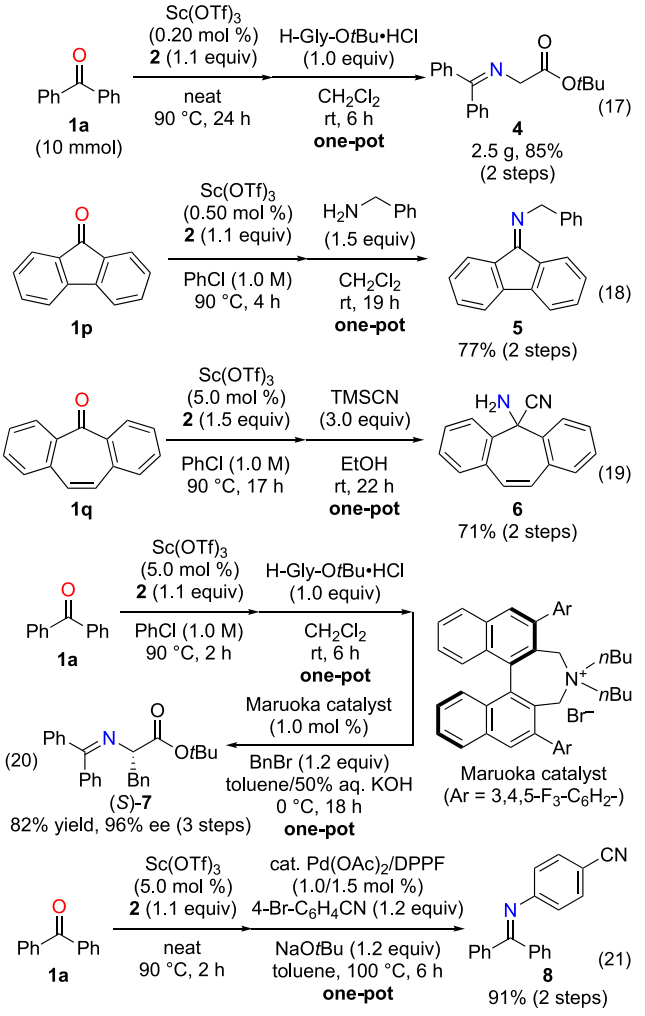
intermediate for the synthesis of a biologically active compound,[19] was obtained without isolating the *N*-unprotected ketimine **3r**, improving the synthetic efficiency (eq 19). Moreover, the one-pot process was successfully extended to one-pot phase-transfer catalysis with the Maruoka catalyst[20] to give (*S*)-**7** in high yield and enantioselectivity over three steps (eq 20). To the best of our knowledge, this is the first example of one-pot synthesis of **7** from benzophenone (**1a**). The one-pot sequence can be extended to Pd-catalyzed reaction,[3] giving the Buchwald−Hartwig amination product **8** in good overall yield (eq 21).

Finally, we performed preliminary mechanistic studies to elucidate the reaction mechanism (Scheme 7). First, similar to our previous TBAF-catalyzed process, hexamethyldisiloxane (**9**) was observed after the reaction, suggesting that bis(trimethylsilyl)amine (**2**) works as an oxygen scavenger (eq 22). Second, the addition of desiccants such as molecular

Scheme 5. Large-Scale Synthesis of *N*-Unprotected Ketimines



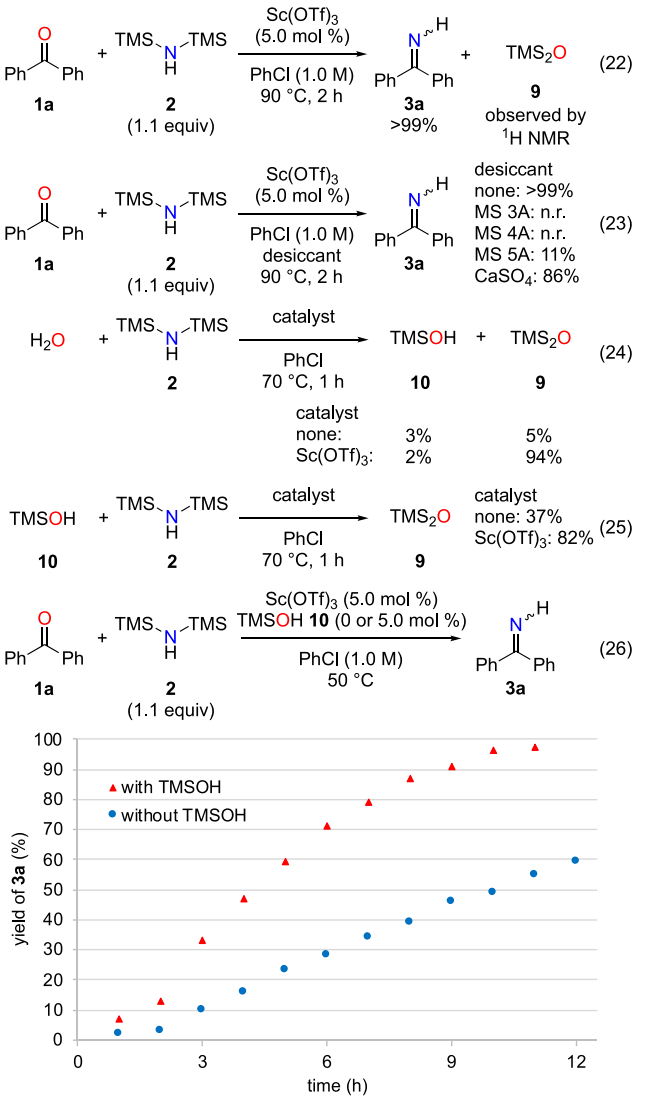
Scheme 6. Application to One-Pot Reactions



sieves retarded the reaction (eq 23), implying that the presence of a trace amount of water in the reaction mixture is important for promoting the reaction. Third, H_2O or trimethylsilanol (**10**) reacted with **2** to give **10** and/or **9**, respectively, and the

DOI: 10.1021/acs.orglett.9b04038
Org. Lett. XXXX, XXX, XXX−XXX

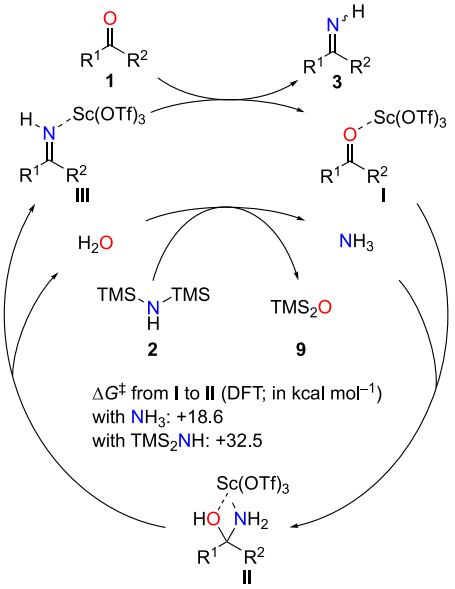
Scheme 7. Preliminary Mechanistic Studies



reaction was accelerated in the presence of $Sc(OTf)_3$ (eqs 24 and 25). Lastly, an induction period was observed at 50 °C, whereas the addition of a catalytic amount of **10** reduced the induction period (eq 26). These results are consistent with the mechanism by which **2** reacts with H_2O or **10** to produce less sterically crowded amine species such as NH_3 that act as effective nucleophiles for addition to carbonyl compounds.[21]

On the basis of the above experimental information, we propose the following possible reaction mechanism (Scheme 8). The reaction is initiated by the reaction of bis(trimethylsilyl)amine (**2**) with a trace amount of water in the reaction mixture to generate ammonia along with TMS_2O (**9**). The addition of ammonia to the carbonyl compounds **1** is accelerated in the presence of $Sc(OTf)_3$ through complex **I** to give addition intermediate **II**. To note, ammonia gave a much lower activation energy for the addition step than **2** alone according to DFT calculations,[14] consistent with our proposed mechanism. Intermediate **II**, in turn, eliminates water to give complex **III**, and product **3** is released through the coordination of **1** to give complex **I**. Finally, water reacts with **2** to give ammonia, which again reacts with **I** to close the catalytic cycle.[22]

Scheme 8. Proposed Mechanism



In conclusion, we developed a Lewis acid catalyzed direct synthesis of *N*-unprotected ketimines. Using a combination of commercially available bis(trimethylsilyl)amine and catalytic amounts of scandium triflate, ketones were directly transformed into *N*-unprotected ketimines in high yields with a broad substrate scope and functional group tolerance, even in multigram scale. The reactions were readily applicable to the one-pot synthesis of important compounds such as a glycine Schiff base without isolation of *N*-unprotected ketimine intermediates. Preliminary mechanistic studies revealed that generation of the less-crowded nitrogen nucleophile efficiently promoted the reaction. We anticipate that the present method will facilitate future development of catalytic reactions via *N*-unprotected ketimines. Further studies to expand the reaction are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.9b04038.

Experimental details and characterization data of products (PDF)

■ AUTHOR INFORMATION

Corresponding Authors

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

ORCID

Hiroyuki Morimoto: 0000-0003-4172-2598
Takashi Ohshima: 0000-0001-9817-6984

Present Address

†K.M.: Institute for Chemical Research, Kyoto University, Kyoto 611-0011, Japan.

Notes

The authors declare the following competing financial interest(s): Part of the work in this letter has been filed in a patent application.

DOI: 10.1021/acs.orglett.9b04038
Org. Lett. XXXX, XXX, XXX−XXX

■ ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research on Innovative Areas (JSPS KAKENHI Grant JP15H05846 in Middle Molecular Strategy to T.O.) and Grants-in-Aid for Scientific Research (B) (JSPS KAKENHI Grant JP17H03972 to T.O.) and (C) (JSPS KAKENHI Grant JP18K06581 to H.M.) from JSPS, Basis for Supporting Innovative Drug Discovery and Life Science Research (BINDS) (Grant JP19am0101091) from AMED, the Takeda Science Foundation and the Uehara Memorial Foundation. Y.K. and K.M. thank JSPS for Research Fellowships for Young Scientists. The computations were carried out using the computer resources offered under the category of General Projects by the Research Institute for Information Technology at Kyushu University.

■ REFERENCES

(1) For selected recent reviews of *N*-unprotected ketimines, see: (a) Klinkenberg, J. L.; Hartwig, J. F. Catalytic Organometallic Reactions of Ammonia. *Angew. Chem., Int. Ed.* **2011**, *50*, 86−95. (b) Yu, Z.; Jin, W.; Jiang, Q. Brønsted Acid Activation Strategy in Transition-Metal Catalyzed Asymmetric Hydrogenation of N-Unprotected Imines, Enamines, and N-Heteroaromatic Compounds. *Angew. Chem., Int. Ed.* **2012**, *51*, 6060−6072. (c) Kim, J.; Kim, H. J.; Chang, S. Synthetic Uses of Ammonia in Transition-Metal Catalysis. *Eur. J. Org. Chem.* **2013**, *2013*, 3201−3213. (d) Legnani, L.; Bhawal, B. N.; Morandi, B. Recent Developments in the Direct Synthesis of Unprotected Primary Amines. *Synthesis* **2017**, *49*, 776−789. (e) Corma, A.; Navas, J.; Sabater, M. J. Advances in One-Pot Synthesis through Borrowing Hydrogen Catalysis. *Chem. Rev.* **2018**, *118*, 1410−1459.

(2) For selected recent reviews for the synthesis of amino acid derivatives using glycine Schiff bases, see: (a) Shirakawa, S.; Maruoka, K. Recent Developments in Asymmetric Phase-Transfer Reactions. *Angew. Chem., Int. Ed.* **2013**, *52*, 4312−4348. (b) Tan, J.; Yasuda, N. Contemporary Asymmetric Phase Transfer Catalysis: Large-Scale Industrial Applications. *Org. Process Res. Dev.* **2015**, *19*, 1731−1746. (c) O'Donnell, M. J. Benzophenone Schiff bases of glycine derivatives: Versatile starting materials for the synthesis of amino acids and their derivatives. *Tetrahedron* **2019**, *75*, 3667−3696. For selected earlier contributions, see: (d) O'Donnell, M. J.; Polt, R. L. A mild and efficient route to Schiff base derivatives of amino acids. *J. Org. Chem.* **1982**, *47*, 2663−2666. (e) O'Donnell, M. J.; Bennett, W. D.; Wu, S. The stereoselective synthesis of α-amino acids by phase-transfer catalysis. *J. Am. Chem. Soc.* **1989**, *111*, 2353−2355.

(3) For selected reviews, see: (a) Hartwig, J. F. *Organotransition Metal Chemistry: From Bonding to Catalysis*; University Science Books: Sausalito, CA, 2010; pp 907−914. (b) Ruiz-Castillo, P.; Buchwald, S. L. Applications of Palladium-Catalyzed C−N Cross-Coupling Reactions. *Chem. Rev.* **2016**, *116*, 12564−12649. For selected examples using benzophenone imine and its derivatives as an ammonia equivalent, see: (c) Wolfe, J. P.; Åhman, J.; Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. An Ammonia Equivalent for the Palladium-Catalyzed Amination of Aryl Halides and Triflates. *Tetrahedron Lett.* **1997**, *38*, 6367−6370. (d) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. Palladium-Catalyzed C−N(sp2) Bond Formation: N-Arylation of Aromatic and Unsaturated Nitrogen and the Reductive Elimination Chemistry of Palladium Azolyl and Methyleneamido Complexes. *J. Am. Chem. Soc.* **1998**, *120*, 827−828. (e) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. Amination Reactions of Aryl Halides with Nitrogen-Containing Reagents Mediated by Palladium/Imidazolium Salt Systems. *J. Org. Chem.* **2001**, *66*, 7729−7737. (f) Huang, H.; Chen, W.; Xu, Y.; Li, J. I^-/TBHP catalyzed C_{sp3}−N/C_{sp2}−N bond formation via oxidative coupling with benzophenone imine in water. *Green Chem.* **2015**, *17*, 4715−4719. (g) Peacock, D. M.; Roos, C. B.; Hartwig, J. F. Palladium-Catalyzed Cross Coupling of Secondary and Tertiary Alkyl Bromides with a Nitrogen Nucleophile. *ACS Cent. Sci.* **2016**, *2*, 647−652. (h) Xu, K.; Wang, Y.-H.; Khakyzadeh, V.; Breit, B. Asymmetric synthesis of allylic amines via hydroamination of allenes with benzophenone imine. *Chem. Sci.* **2016**, *7*, 3313−3316. (i) Yang, J.; Ruan, P.; Yang, W.; Feng, X.; Liu, X. Enantioselective carbene insertion into the N−H bond of benzophenone imine. *Chem. Sci.* **2019**, *10*, 10305.

(4) For a review of C−H functionalization using *N*-unprotected ketimines as a substrate, see: (a) Sambiagio, G.; Schönbauer, D.; Blieck, R.; Dao-Huy, T.; Pototschnig, G.; Schaaf, P.; Wiesinger, T.; Zia, M. F.; Wencel-Delord, J.; Besset, T.; Maes, B. U. W.; Schnürch, M. A comprehensive overview of directing groups applied in metal-catalysed C−H functionalisation chemistry. *Chem. Soc. Rev.* **2018**, *47*, 6603−6743. For selected examples, see: (b) Ueura, K.; Satoh, T.; Miura, M. Rhodium-Catalyzed Arylation Using Arylboron Compounds: Efficient Coupling with Aryl Halides and Unexpected Multiple Arylation of Benzonitrile. *Org. Lett.* **2005**, *7*, 2229−2231. (c) He, R.; Huang, Z.-T.; Zheng, Q.-Y.; Wang, C. Manganese-Catalyzed Dehydrogenative [4 + 2] Annulation of N−H Imines and Alkynes by C−H/N−H Activation. *Angew. Chem., Int. Ed.* **2014**, *53*, 4950−4953. (d) Kim, J. H.; Greßies, S.; Glorius, F. Cooperative Lewis Acid/Cp^*Co^{III} Catalyzed C−H Bond Activation for the Synthesis of Isoquinolin-3-ones. *Angew. Chem., Int. Ed.* **2016**, *55*, 5577−5581. (e) Xu, W.; Yoshikai, N. N−H Imine as a Powerful Directing Group for Cobalt-Catalyzed Olefin Hydroarylation. *Angew. Chem., Int. Ed.* **2016**, *55*, 12731−12735. For selected examples of formal [3 + 2] annulation reaction via *N*-unsubstituted ketimine-directed C−H bond activation, see: (f) Sun, Z.-M.; Chen, S.-P.; Zhao, P. Tertiary Carbinamine Synthesis by Rhodium-Catalyzed [3 + 2] Annulation of N-Unsubstituted Aromatic Ketimines and Alkynes. *Chem. - Eur. J.* **2010**, *16*, 2619−2627. (g) Tran, D. N.; Cramer, N. Enantioselective Rhodium(I)-Catalyzed [3 + 2] Annulations of Aromatic Ketimines Induced by Directed C—H Activations. *Angew. Chem., Int. Ed.* **2011**, *50*, 11098−11102. (h) Tran, D. N.; Cramer, N. Rhodium-Catalyzed Dynamic Kinetic Asymmetric Transformations of Racemic Allenes by the [3 + 2] Annulation of Aryl Ketimines. *Angew. Chem., Int. Ed.* **2013**, *52*, 10630−10634. (i) Jin, X.; Yang, X.; Yang, Y.; Wang, C. Rhenium and base co-catalyzed [3 + 2] annulations of N−H ketimines and alkynes to access unprotected tertiary indenamines through C−H bond activation. *Org. Chem. Front.* **2016**, *3*, 268−272.

(5) For selected recent examples of catalytic addition reactions to *N*-unprotected ketimines, see: (a) Sukach, V. A.; Golovach, N. M.; Pirozhenko, V. V.; Rusanov, E. B.; Vovk, M. V. Convenient enantioselective synthesis of β-trifluoromethyl-β-aminoketones by organocatalytic asymmetric Mannich reaction of aryl trifluoromethyl ketimines with acetone. *Tetrahedron: Asymmetry* **2008**, *19*, 761−764. (b) Hara, N.; Tamura, R.; Funahashi, Y.; Nakamura, S. N-(Heteroarenesulfonyl)prolinamides-Catalyzed Aldol Reaction between Acetone and Aryl Trihalomethyl Ketones. *Org. Lett.* **2011**, *13*, 1662−1665. (c) Rassukana, Y. V.; Yelenich, I. P.; Vlasenko, Y. G.; Onys'ko, P. P. Asymmetric synthesis of phosphonotrifluoroalanine derivatives via proline-catalyzed direct enantioselective C−C bond formation reactions of N−H trifluoroacetimidoyl phosphonate. *Tetrahedron: Asymmetry* **2014**, *25*, 1234−1238. (d) Jang, H.; Romiti, F.; Torker, S.; Hoveyda, A. H. Catalytic diastereo- and enantioselective additions of versatile allyl groups to N−H ketimines. *Nat. Chem.* **2017**, *9*, 1269−1275. (e) Morisaki, K.; Morimoto, H.; Ohshima, T. Direct access to *N*-unprotected tetrasubstituted propargylamines via direct catalytic alkynylation of *N*-unprotected trifluoromethyl ketimines. *Chem. Commun.* **2017**, *53*, 6319−6322. (f) Sawa, M.; Morisaki, K.; Kondo, Y.; Morimoto, H.; Ohshima, T. Direct Access to N-Unprotected α- and/or β-Tetrasubstituted Amino Acid Esters via Direct Catalytic Mannich-Type Reactions Using N-Unprotected Trifluoromethyl Ketimines. *Chem. - Eur. J.* **2017**, *23*, 17022−17028. (g) Yonesaki, R.; Kondo, Y.; Akkad, W.; Sawa, M.; Morisaki, K.; Morimoto, H.; Ohshima, T. 3-Mono-Substituted BINOL Phosphoric Acids as Effective Organocatalysts in Direct Enantioselective Friedel-Crafts-Type Alkylation of N-Unprotected α-Ketiminoester. *Chem. - Eur. J.* **2018**, *24*, 15211−15214. (h) Sawa, M.;

DOI: 10.1021/acs.orglett.9b04038
Org. Lett. XXXX, XXX, XXX−XXX

Miyazaki, S.; Yonesaki, R.; Morimoto, H.; Ohshima, T. Catalytic Enantioselective Decarboxylative Mannich-Type Reaction of *N*-Unprotected Isatin-Derived Ketimines. *Org. Lett.* **2018**, *20*, 5393−5397. (i) Miyagawa, M.; Yoshida, M.; Kiyota, Y.; Akiyama, T. Enantioselective Friedel-Crafts Alkylation Reaction of Heteroarenes with N-Unprotected Trifluoromethyl Ketimines by Means of Chiral Phosphoric Acid. *Chem. - Eur. J.* **2019**, *25*, 5677−5681. (j) Zhu, J.; Huang, L.; Dong, W.; Li, N.; Yu, X.; Deng, W.-P.; Tang, W. Enantioselective Rhodium-Catalyzed Addition of Arylboroxines to N-Unprotected Ketimines: Efficient Synthesis of Cipargamin. *Angew. Chem., Int. Ed.* **2019**, *58*, 16119−16123.

(6) For selected examples via addition of organometallic reagents to nitriles, see: (a) Smith, G. E. P., Jr.; Bergstrom, F. W. The Ammono Ketone-Alcohols. I. Benzophenoneimine. *J. Am. Chem. Soc.* **1934**, *56*, 2095−2098 and references therein. (b) Pickard, P. L.; Tolbert, T. L. DIPHENYL KETIMINE. *Org. Synth.* **1964**, *44*, 51. (c) Koos, M.; Mosher, H. S. α-Amino-α-trifluoromethyl-phenylacetonitrile: A potential reagent for ^{19}F NMR determination of enantiomeric purity of acids. *Tetrahedron* **1993**, *49*, 1541−1546. (d) Hou, G.; Tao, R.; Sun, Y.; Zhang, X.; Gosselin, F. Iridium−Monodentate Phosphoramidite-Catalyzed Asymmetric Hydrogenation of Substituted Benzophenone N−H Imines. *J. Am. Chem. Soc.* **2010**, *132*, 2124−2125.

(7) For examples using LiHMDS as the nitrogen source, see: Gosselin, F.; O'Shea, P. D.; Roy, S.; Reamer, R. A.; Chen, C.-y.; Volante, R. P. Unprecedented Catalytic Asymmetric Reduction of N−H Imines. *Org. Lett.* **2005**, *7*, 355−358. See also ref 5j.

(8) For examples using iminophosphorane as the nitrogen source, see: Wannagat, U.; Münstedt, R. Über Einige Reaktionen Der Dialkylbenzylphosphinimide. *Phosphorus Sulfur Relat. Elem.* **1987**, *29*, 233. See also ref 6c.

(9) For selected examples using ammonia as the nitrogen source, see: (a) Strain, H. H. AMMONOLYSIS OF KETONES. *J. Am. Chem. Soc.* **1930**, *52*, 820−823. (b) Brenner, D. G.; Cavolowsky, K. M.; Shepard, K. L. Imino-bridged heterocycles. IV. A facile synthesis of sulfenimines derived from diaryl ketones. *J. Heterocycl. Chem.* **1985**, *22*, 805−808. (c) Verardo, G.; Giumanini, A. G.; Strazzolini, P.; Poiana, M. Ketimines From Ketones and Ammonia. *Synth. Commun.* **1988**, *18*, 1501−1511. (d) Yamashita, Y.; Matsumoto, M.; Chen, Y.-J.; Kobayashi, S. Catalytic Mannich-type reactions of α-aminoacetonitrile using fluorenylidene as a protecting and activating group. *Tetrahedron* **2012**, *68*, 7558−7563. (e) Žari, S.; Kudrjashova, M.; Pehk, T.; Lopp, M.; Kanger, T. Remote Activation of the Nucleophilicity of Isatin. *Org. Lett.* **2014**, *16*, 1740−1743.

(10) For examples of catalytic approaches to *N*-unprotected ketimines, see: (a) Lee, J. H.; Gupta, S.; Jeong, W.; Rhee, Y. H.; Park, J. Characterization and Utility of N-Unsubstituted Imines Synthesized from Alkyl Azides by Ruthenium Catalysis. *Angew. Chem., Int. Ed.* **2012**, *51*, 10851−10855. (b) Pramanik, S.; Reddy, R. R.; Ghorai, P. Transition Metal-Free Generation of *N*-Unsubstituted Imines from Benzyl Azides: Synthesis of *N*-Unsubstituted Homoallylic Amines. *J. Org. Chem.* **2015**, *80*, 3656−3663. (c) Damodara, D.; Arundhathi, R.; Likhar, P. R. Copper Nanoparticles from Copper Aluminum Hydrotalcite: An Efficient Catalyst for Acceptor- and Oxidant-Free Dehydrogenation of Amines and Alcohols. *Adv. Synth. Catal.* **2014**, *356*, 189−198.

(11) Kondo, Y.; Morisaki, K.; Hirazawa, Y.; Morimoto, H.; Ohshima, T. A Convenient Preparation Method for Benzophenone Imine Catalyzed by Tetrabutylammonium Fluoride. *Org. Process Res. Dev.* **2019**, *23*, 1718−1724.

(12) (a) Tsunoda, T.; Suzuki, M.; Noyori, R. A facile procedure for acetalization under aprotic conditions. *Tetrahedron Lett.* **1980**, *21*, 1357−1358. (b) Noyori, R.; Murata, S.; Suzuki, M. Trimethylsilyl triflate in organic synthesis. *Tetrahedron* **1981**, *37*, 3899−3910.

(13) For related Lewis acid-catalyzed synthesis of imines, see: (a) Duffaut, N.; Dupin, J.-P. Étude de l'action de silazanes et de silylamines sur quelques dérivés carbonylés. *Bull. Soc. Chim. Fr.* **1966**, 3205−3210. (b) Morimoto, T.; Sekiya, M. A Convenient Synthetic Method for Schiff Bases. The Trimethylsilyl Trifluoromethanesulfonate-Catalyzed Reaction of N,N-Bis(trimethylsilyl)amines with Aldehydes and Ketones. *Chem. Lett.* **1985**, *14*, 1371.

(14) See the Supporting Information for details.

(15) For selected reviews, see: (a) Kobayashi, S. Scandium Triflate in Organic Synthesis. *Eur. J. Org. Chem.* **1999**, *1999*, 15−27. (b) Kobayashi, S.; Sugiura, M.; Kitagawa, H.; Lam, W. W.-L. Rare-Earth Metal Triflates in Organic Synthesis. *Chem. Rev.* **2002**, *102*, 2227−2302. (c) Pellissier, H. Recent developments in enantioselective scandium-catalyzed transformations. *Coord. Chem. Rev.* **2016**, *313*, 1−37.

(16) Valerophenone also afforded the corresponding *N*-unprotected ketimine in 51% yield based on ^{1}H NMR analysis of the crude mixture, but the product was not isolable in pure form due to the concomitant formation of impurity.[14]

(17) E-factor = the amount of waste (g)/the amount of product (g). For the E-factor, see: (a) Sheldon, R. A. Organic Synthesis—Past, Present and Future. *Chem. Ind.* **1992**, 903−906. (b) Sheldon, R. A. The *E* factor 25 years on: the rise of green chemistry and sustainability. *Green Chem.* **2017**, *19*, 18−43.

(18) Chen, Y.-J.; Seki, K.; Yamashita, Y.; Kobayashi, S. Catalytic Carbon−Carbon Bond-Forming Reactions of Aminoalkane Derivatives with Imines. *J. Am. Chem. Soc.* **2010**, *132*, 3244−3245.

(19) (a) Gonzalez, J.; Carroll, F. I. Bromine-promoted cyclization of an olefinic α-aminonitrile: A practical synthesis of 5-aminocarbonyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine (ADCI). *Tetrahedron Lett.* **1996**, *37*, 8655−8658. (b) Gonzalez, J.; Carroll, F. I. Synthesis of 5-aminocarbonyl-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine. US5831095A, 1998.

(20) Kitamura, M.; Shirakawa, S.; Maruoka, K. Powerful Chiral Phase-Transfer Catalysts for the Asymmetric Synthesis of α-Alkyl- and α,α-Dialkyl-α-Amino Acids. *Angew. Chem., Int. Ed.* **2005**, *44*, 1549−1551.

(21) The reaction rate at the initial stage was improved in the presence of NH_3, supporting the assumption.[14] It is also noted that the molecular sieves that absorb NH_3 retarded the reaction significantly, consistent with the proposal.

(22) It is noted that $TMSNH_2$ as a nitrogen nucleophile cannot be ruled out, and DFT calculation showed that the activation energy for the addition step of $TMSNH_2$ was small (+13.7 kcal mol^{-1}).[14] Nevertheless, $TMSNH_2$ was known to be unstable at higher temperatures, precluding the experimental verification. For the stability of $TMSNH_2$, see: Wiberg, N.; Uhlenbrock, W. Notiz zur Darstellung von Trimethylsilylamin. *Chem. Ber.* **1971**, *104*, 2643−2645.

DOI: 10.1021/acs.orglett.9b04038
Org. Lett. XXXX, XXX, XXX−XXX