Article

A Practical Electrophilic Nitrogen Source for the Synthesis of Chiral Primary Amines by Copper-Catalyzed Hydroamination

Sheng Guo, Jeffrey C. Yang, and Stephen L. Buchwald

J. Am. Chem. Soc., Just Accepted Manuscript • DOI: 10.1021/jacs.8b10564 • Publication Date (Web): 29 Oct 2018

Downloaded from http://pubs.acs.org on October 29, 2018

Just Accepted

"Just Accepted" manuscripts have been peer-reviewed and accepted for publication. They are posted online prior to technical editing, formatting for publication and author proofing. The American Chemical Society provides "Just Accepted" as a service to the research community to expedite the dissemination of scientific material as soon as possible after acceptance. "Just Accepted" manuscripts appear in full in PDF format accompanied by an HTML abstract. "Just Accepted" manuscripts have been fully peer reviewed, but should not be considered the official version of record. They are citable by the Digital Object Identifier (DOI®). "Just Accepted" is an optional service offered to authors. Therefore, the "Just Accepted" Web site may not include all articles that will be published in the journal. After a manuscript is technically edited and formatted, it will be removed from the "Just Accepted" Web site and published as an ASAP article. Note that technical editing may introduce minor changes to the manuscript text and/or graphics which could affect content, and all legal disclaimers and ethical guidelines that apply to the journal pertain. ACS cannot be held responsible for errors or consequences arising from the use of information contained in these "Just Accepted" manuscripts.



is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Published by American Chemical Society. Copyright © American Chemical Society. However, no copyright claim is made to original U.S. Government works, or works produced by employees of any Commonwealth realm Crown government in the course of their duties.

A Practical Electrophilic Nitrogen Source for the Synthesis of Chiral Primary Amines by Copper-Catalyzed Hydroamination

Sheng Guo, Jeffrey C. Yang and Stephen L. Buchwald*

Department of Chemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts 02139, United States.

ABSTRACT: A mild and practical method for the catalytic installation of the amino group across alkenes and alkynes has long been recognized as a significant challenge in synthetic chemistry. As the direct hydroamination of olefins using ammonia requires harsh conditions, the development of suitable electrophilic aminating reagents for formal hydroamination methods is of importance. Herein, we describe the use of 1,2-benzisoxazole as a practical electrophilic primary amine source. Using this heterocycle as a new amino group delivery agent, a mild and general protocol for the copper-hydride-catalyzed hydroamination of alkenes and alkynes to form primary amines was developed. This method provides access to a broad range of chiral α -branched primary amines and linear primary amines, as demonstrated by the efficient synthesis of the antiretroviral drug Maraviroc and the formal synthesis of several other pharmaceutical agents.

INTRODUCTION

Chiral primary amines play an essential role in the preparation of natural products, active pharmaceutical ingredients, and other important derivatives because of their synthetic flexibility (Figure 1a).¹ Consequently, synthetic organic chemists have a long-standing interest in general methods for the synthesis of chiral primary amines.¹⁻² Important methods for the enantioselective synthesis of chiral primary amines include the reduction of imines and enamines,³⁻⁷ addition of nucleophiles to imines,⁸ particularly Ellman's sulfonamide,9 the reaction of a nitrogen nucleophile to allylic electrophiles,¹⁰ and biocatalytic processes.¹¹⁻¹³ Although various methods exist, they typically require a pre-existing carbon-heteroatom bond or ketone group as the handle for functionalization. In comparison, hydroamination reactions provide a direct approach to access amines from readily available alkene and alkyne precursors. Specifically, copper(I) hydride complexes have been shown to catalyze hydroamination reactions between alkenes and hydroxylamine esters.¹⁴ Despite the number of electrophilic aminating reagents that have been developed for the synthesis of chiral secondary¹⁵ and tertiary amines¹⁶⁻²⁵ as well as amides²⁶, there have not been any reports of enantioselective transformations that allow for the direct synthesis of primary amines from olefins, in part due to the lack of a suitable electrophilic amine source.

Current electrophilic primary amine reagents that provide a direct approach for the synthesis of primary amines typically suffer from instability (in the case of haloamines) or have been reported to be hazardous upon purification and isolation (in the case of *O*-(mesitylenesulfonyl)hydroxylamine, MSH).²⁷ Moreover, reagents such as methoxyamine are stable as the corresponding hydrochloride salt, but require a minimum of two equivalents of strongly basic organometallic reagents to access the active form (through neutralization and further deprotonation),²⁸ which is capable of forming the desired C–N bond. Although protected NH₃ surrogates such as oxime derivatives²⁹ or

creatively designed oxaziridines³⁰ may circumvent the problems of competitive amine deprotonation and difficult deprotections, most of these electrophiles require multistep synthesis (Figure 1b).³¹ Thus, a simple, stable, and commercially available electrophilic amine source is highly desirable.

In this work, we describe the fortuitous discovery that isoxazole can be used as a suitable electrophilic nitrogen source providing a solution to the synthesis of primary amines via the copper-hydride-catalyzed hydroamination. Previously, we reported the copper-hydride-catalyzed enantioselective 1,4dearomatization of pyridines with styrene-derived nucleophiles (Figure 1c(i)).³² While attempting to extend this method to other nitrogen-containing heterocycles, the isoxazole unexpectedly provided the Schiff base product, instead of the anticipated dihydroisoxazole product (Figure 1c(ii)). The nucleophilic substitution of isoxazole via the cleavage of the N-O bond, upon imine hydrolysis, provided a new approach for synthesis of primary amines via an unknown mode of reactivity. Based on this result coupled with the high stability and commercial availability of isoxazole, we envisioned that isoxazole and its derivatives might function as electrophilic primary amine sources.

Herein, we demonstrate the generality of this initial result and describe the preparation of primary amines (or equivalents) via the hydroamination of alkenes and alkynes using isoxazole electrophiles as new commercially available electrophilic nitrogen sources. Under mild reaction conditions, a wide range of chiral α -branched (from aryl alkenes or alkynes) and linear primary amines (from alkyl-substituted terminal alkenes or alkynes) are afforded in good-to-excellent yields with high levels of enantioselectivity (Figure 1d). Additionally, the synthetic utility of this transformation is demonstrated by the preparation of several important pharmaceuticals, as well as the one-step conversion of low-cost readily available starting materials into valuable synthetic intermediates.

59



Figure 1. a) Representative pharmaceuticals prepared from chiral primary amines. b) Current electrophilic aminating reagents used for the synthesis of primary amines. c) The discovery of isoxazole as an electrophilic aminating reagent. d) Asymmetric synthesis of primary amines by using the isoxazoles as electrophilic aminating reagents.

RESULTS AND DISCUSSION

Effect of substitution patterns of isoxazole derivatives. To arrive at the optimal isoxazole reagent for the CuH-catalyzed hydroamination of alkenes, styrene was allowed to react with a series of commercial isoxazole derivatives with varying electronic and steric properties under typical CuH catalysis conditions.¹⁸ In the presence of 5.0 mol% copper acetate, 5.5 mol% (S)-DTBM-SEGPHOS, 3.2 equivalents of dimethoxymethylsilane, and 2.0 equivalents of isoxazole, the Schiff base product was afforded in moderate yield and with excellent enantioselectivity. Evaluation of other isoxazole derivatives revealed that the 3-substituted isoxazoles could not be used for the hydroamination process regardless of their steric and electronic properties (2b, 2c). Furthermore, a comparison between the 4- (2d, 2e) and 5- (2f, 2g) substituted isoxazoles showed that, although substituents at these positions are reported to promote the undesired ring-opening decomposition of the electrophile,³³

extension of the π -conjugation at the 5 position proved to be beneficial for overall reaction efficiency. The use of 1,2-benzisoxazole, **2h**, proved to be optimal, affording the chiral Schiff base product in excellent yield and enantiopurity. Additional experiments confirmed that 3-substituted 1,2-benzisoxazole (**2i**) was also not a suitable electrophile for this system. In addition to isoxazole derivatives, we have found that the *O*-benzoyl oxime derivative **2j** also provided the desired protected primary amine under similar conditions, albeit in reduced levels of yield and enantioselectivity (see Supporting Information). Due to the lower reactivity of **2j**, higher reaction temperatures and lower reaction concentrations were required to achieve high yields and enantioselectivity.

The effectiveness of **2h** as an electrophilic amine source was benchmarked against N,N-dibenzyl-O-pivaloylhydroxylamine (Bn₂NOPiv), which was previously found to be an excellent electrophilic amine reagent for CuH-catalyzed hydroamination

reactions.³⁴⁻³⁵ In separate reactions, the overall rate of reaction with Bn₂NOPiv was found to be about twice as fast as that with 1,2-benzisoxazole (Figure 2a, entry 1,2). However, because previous mechanistic studies indicated that the rate-determining-step of CuH-catalyzed hydroamination of styrene was the regeneration of LCuH catalyst (Figure 2b, III \rightarrow I),³⁴ we speculated that the slower relative rate of reaction with 1,2-benzisoxazole was due to the slower regeneration of active LCuH species from Cu-phenolate IIIb relative to the analogous regeneration of LCuH from the copper pivalate IIIa in the reaction employing Bn₂NOPiv as the electrophile. In agreement with this hypothesis, a one-pot competition between 2h and

Table 1. Effect of substitution pattern of isoxazole derivatives

Bn₂NOPiv revealed that the alkyl-copper species **II** reacts preferentially with **2h** over Bn₂NOPiv (Figure 2a, Entry 3). These collective results indicate that, while **2h** is more reactive toward substitution with the Cu-alkyl intermediate (**II**), the resulting Cu-phenolate **IIIb** is less reactive toward reaction with the silane. The latter effect causes reactions employing **2h** to display reaction rates that are slower than reactions using Bn₂NOPiv as aminating reagents. The slower regeneration of LCuH in the isoxazole-based system has an important implication for the hydroamination of complex substrates, which is discussed below.



a) (5.0 mol%) Cu(OAc)₂, (5.5 mol%) (*S*)-DTBM-SEGPHOS, styrene (0.50 mmol), electrophile (2.0 equiv), rt, 24 h. The yield and ee were determined based on the benzamide product. b) The yield and ee were determined based on the Schiff base product. c) 40 °C, 0.5 M in THF. d) 85 °C, 0.05 M in THF, see supporting information for optimization.



*After 30 min, no **P2** was detected by ¹H-NMR but 11% **P1** was seen.

Figure 2. a) Competition experiment between electrophilic amination reagents. b) Proposed catalytic cycle

Hydroamination of alkenes and alkynes to form primary amines. Having identified 1,2-benzisoxazole as the optimal electrophilic nitrogen source, we set out to examine the scope of the alkene coupling partners of this hydroamination protocol (Table 2). The chiral Schiff base products can be quantitatively converted, in a one-pot procedure, to the corresponding primary amine without erosion of enantiomeric purity. Both the Schiff base products (**3a-l**) and the primary amines (**4a-f**) derived from

this protocol can be obtained in good yields and high enantioselectivity (\geq 93% ee). Styrenes bearing electron-withdrawing (**3g**) and electron-donating (**3h**) substituents were converted to products with good efficiency. Similarly, substrates with an electronically diverse set of *ortho*-substituents (**3b**, **3c**) were also suitable. Due to the mild reaction conditions, a variety of functional groups such as aryl chlorides (**3d**) and bromides (**3e**), esters (**3j**), sulfonamides (**4a**), carbamates (**4b**), and a thiomethyl group (4c) were tolerated. The reaction conditions also accommodated a wide range of vinyl-substituted heteroarenes, including those containing an electron-deficient heterocycles, such as pyridine (3k), 7-azaindole (4a), pyrimidine (4c), electron-rich indazole (4b), pyrazole (4d), and carbazole (4e) ring, providing α -chiral primary amines with high levels of enantioselectivity. This approach was applied to the hydroamination of complex aryl alkenes such as estrone to provide rapid access to the structurally complex Schiff base 3l.





Condition A: (2.0 - 5.0 mol%) Cu(OAc)₂, (2.2 - 5.5 mol%) (*S*)-DTBM-SEGPHOS, **2h** was added in one portion, rt. Condition B: (2.0 - 5.0 mol%) Cu(OAc)₂, (2.2 - 5.5 mol%) (*S*)-DTBM-SEGPHOS, **2h** (0.5 equiv.) was added every 2 h, 45 °C. Yield refers to isolated yield of purified product (1.0 mmol scale, average of two runs) and the ee was determined on the Schiff base product. a. cyclohexane as solvent and **2h** was added via syringe pump (30 μ L/h).

Previously, we have demonstrated that increased steric hindrance at the β -position may negatively influence the efficiency of hydroamination.¹⁵ Although sterically less-hindered β -substituted styrenes (**3i**, **3j**) provided the desired product with good yield, a significant amount of alkene reduction (~50%) was observed when the more sterically hindered substrate, cinnarizine

(4f), was subjected to our standard hydroamination conditions. The observation of salicylonitrile as a major byproduct led us to postulate that Kemp elimination of 1,2-benzisoxazole (Figure 3a) had emerged as a competing, non-productive pathway when the rate of CuH regeneration (i.e., $\mathbf{H}^* \rightarrow \text{product}$, Figure 3b) is reduced by the steric hinderance of the large β -substituent. Due

2

3

4

5

6

7

8

9

10

11

12

13

14

15

16

17

18

19

20

21

22

23

24

25

26

27

28

29

30 31 32

33

34

35

36

37

38

39 40 41

42

43

44 45

46

47 48

49

50

51 52

53

54

60

to the slowed rate of CuH regeneration, the copper-phenolate (II') can catalyze the Kemp elimination of 2 to form III'. This copper-phenolate can catalyze further Kemp elimination of 1,2benzisoxazole to give salicylonitrile (see Supporting Information for details), which in turn serves as a proton source (IV') for the reduction of the alkene. The issue of alkene reduction due to competitive Kemp elimination was addressed by employing solvents of lower polarity, which are known to slow the rate of Kemp elimination,³⁶⁻³⁷ as well as by using a syringe pump for the slow addition of 1.2-benzisoxazole (see Supporting Information for details). Presumably, the slow addition of 1,2-benzisoxazole reduces the rate of Kemp elimination versus the rate of productive catalyst turnover by keeping the concentration of 1,2-benzisoxazole low. Under these reaction conditions, cinnarizine was successfully converted to the chiral primary amine 4f in high yield and excellent levels of enantioselectivity. This simple modification of the reaction system later proved to be crucial during our subsequent synthesis of Maraviroc.

a. Base-catalyzed Kemp elimination of 1,2-benzisoxazole



Figure 3. a. Base-catalyzed Kemp elimination of 1,2-benzisoxazole. b. The proposed mechanism for alkene reduction in the hydroamination of β -sterically hindered styrenes.

Having confirmed the effectiveness of our method for the synthesis of chiral Schiff bases and primary amines using styrene substrates, we continued by investigating the anti-Markovnikov hydroamination of unactivated alkenes (Table 3). Due to the higher energy barrier for the hydrocupration of terminal alkenes,38 slightly elevated temperatures (45 °C) and slow addition of the electrophile using a syringe pump were required to obtain good yields and high levels of enantioselectivity. This protocol was successfully applied to terminal alkenes (4g-4k). As before, the protocol manifested excellent functional group tolerance, as acetals (4g), sulfonamides (4h), epoxy groups (3n), and silvl groups (30) were tolerated under the reaction conditions. Both electron-rich and electron-deficient heterocycles, such as benzothiazole (4i) and quinoline (4j), were also readily accommodated. Furthermore, the one-pot synthesis of primary amine 4k provided an alternative route for the preparation of bifemelane, a cerebral activator used for the treatment of senile dementia and glaucoma.³⁹ The hydroamination of 1,1-disubstituted alkenes also worked well with this protocol providing the a silicon-substituted stereogenic center (30), as well as demonstrating the chemoselectivity for the reaction of 1,1-disubstituted alkenes over trisubstituted ones (3p). The regioselectivity and enantioselectivity of hydroamination of 1,1-dialkyl substituted alkenes (30, 3p in Table 3) are in accord with the results previously reported by our lab.¹⁹

Table 3. Using 1,2-benzisoxazole as an electrophilic aminating reagent for the hydroamination of unactivated alkenes to primary amines



Yield refers to isolated yield of purified product (1.0 mmol scale, average of two runs). a) 1.5 equiv **2h** was added via syringe pump (15 μ L/h). b) 1.05 equiv **2j** was used. The use of the oxime ester **2j** as the electrophile for the synthesis of **3n** did not require slow addition or excess aminating reagent to achieve a moderate yield, presumably due to its comparatively higher stability at elevated temperatures. c) 1.5 equiv **2h** was added via syringe pump (10 μ L/h).

We next explored the hydroamination of alkynes. Previous work in our lab demonstrated that alkynes may be converted into alkyl amines via a sequence involving semireduction of the alkyne and hydroamination of the resultant alkene.⁴⁰ With a modified reductive hydroamination protocol, including *i*PrOH as the proton source and **2h** as the aminating reagent, we found that the aryl-substituted terminal alkynes undergo the Markovnikov hydroamination to access the corresponding chiral Schiff base products (Table 4). The reaction conditions tolerated the

electron-withdrawing (**3e**) and electron-donating (**3h**) substituents on the arene as well as the electron-rich heterocycles, such as thiophene (**3q**). Additionally, the terminal aliphatic alkynes undergo anti-Markovnikov hydroamination to access the linear primary amine product (**4l**) with the one-pot operation. The regioselectivity is in accord with the results previously reported by our lab.⁴⁰ The reductive hydroamination of alkynes to primary amines provides an alternative approach for the synthesis of the valuable primary amines.





Yield refers to isolated yield of purified product (1.0 mmol scale, average of two runs). a) 1.5 equiv **2h** was added in one portion. b) 1.5 equiv **2h** was added via syringe pump (30 μ L/h) at rt. c) 1.5 equiv **2h** was added via syringe pump (15 μ L/h) at 45 °C

Application to the synthesis of pharmaceutical agents. An important advantage of this mild enantioselective hydroamination process using 1,2-benzisoxazole as an ammonia surrogate lies in its ability to install a chiral primary amine unit onto highly functionalized late-stage synthetic intermediates. To illustrate this, a convergent strategy for the three-step synthesis of the antiretroviral drug Maraviroc, which is used for the treatment of HIV infections, is described. All three previous asymmetric synthetic routes that have been reported in the literature call for early-stage installation of the amino group, 41-44 therefore limiting the tunability of the arene fragment. As a complementary approach, our strategy introduced the amino group via copper-catalyzed asymmetric hydroamination of styrene 5c, which can be accessed in high yield from reductive amination of cinnamyl aldehyde 5a and the complex secondary amine 5b. Using similar conditions to those developed for the hydroamination of cinnarizine, the core chiral primary amine fragment 5d was isolated in 73% yield and 94% ee after hydrolytic workup. Subsequent acylation then provided Maraviroc in 59% yield over three steps (Figure 4a). This approach provides an alternative route that allows for the diversification of the arene component of drug analogs.

As another application of this method, we converted a simple hydrocarbon feedstock, indene, to 1-aminoindane (**4m**), a highly valuable synthetic precursor for important pharmaceuticals such as Rasagiline.⁴⁵ By following the slow addition protocol developed for unactivated alkenes and increasing the reaction temperature to 70 °C, 1-aminoindane (**4m**) was obtained in 69% yield and 92% ee (Figure 4b). To evaluate the scalability of this method, we have also synthesized (*S*)-3-amino-3-phenyl-1-propanol hydrochloride (**4n**), an important intermediate for the synthesis of Dapoxetine⁴⁶ from the hydroamination of cinnamyl acetate on a 10 mmol scale. This gram-scale reaction provided the Schiff base product in 94% NMR yield and 99% ee. After the hydrolysis of the imine and the ester, the hydrochloride (**4n**) can be obtained by acidification of the corresponding primary amine in good isolated yield (78%, Figure 4c). Finally, the chiral Schiff base product **3r** can also be obtained in exceptional levels of enantiopurity under our standard conditions, and this intermediate can be further hydrolyzed to the valuable chiral primary amine product for the synthesis of human leukocyte elastase inhibitor, DMP 777 (Figure 4d).⁴⁷

CONCLUSION

In conclusion, we have discovered that 1,2-benzisoxazole is effective as a practical electrophilic ammonia equivalent in CuHcatalyzed hydroamination. We described the first enantioselective hydroamination of alkenes and alkynes to primary amines that occurs by asymmetric substitution of 1,2-benzisoxazole through the N–O bond cleavage. This approach provides an efficient method to access chiral α -branched and linear primary amines under very mild conditions. During the exploration of the scope of alkenes and alkynes, a series of primary amines were prepared in excellent enantio-, regio- and chemoselectivity. Furthermore, we developed a highly convergent route to prepare anti-HIV drug Maraviroc, and demonstrated the preparation of precursors of Rasagiline mesylate, Dapoxetine hydrochloride, and DMP 777.



Figure 4. Application of the hydroamination reaction in the synthesis of some pharmaceutical agents: (a) Maraviroc, (b) Rasagiline mesylate, (c) Dapoxetine hydrochloride, (d) DMP 777

ASSOCIATED CONTENT

Supporting Information. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author

*sbuchwal@mit.edu

Notes

The authors declae no competing financial interest.

ACKNOWLEDGMENTS

The authors acknowledge the National Institutes of Health under award numbers R35-GM122483 for support of the research reported in this publication. The content of this publication is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors thank Scott McCann, Richard Liu and Andy Thomas (MIT) for advice on the preparation of this paper, Christine Nguyen for advice on the supplementary information, Bruce Adams (MIT) for assistance with NMR structure-determination, and the National Institutes of Health for a supplemental grant for the purchase of supercritical fluid chromatography (SFC) equipment (GM058160-17S1)

REFERENCES

(1) Nugent, T. C., *Chiral Amine Synthesis: Methods, Developments and Applications.* Wiley-VCH, 2010.

(2) Morandi, B.; Legnani, L.; Bhawal, B., Recent Developments in the Direct Synthesis of Unprotected Primary- Amines. *Synthesis* **2016**, *49*, 776-789.

(3) Tan, X.; Gao, S.; Zeng, W.; Xin, S.; Yin, Q.; Zhang, X., Asymmetric Synthesis of Chiral Primary Amines by Ruthenium-Catalyzed Direct Reductive Amination of Alkyl Aryl Ketones with Ammonium Salts and Molecular H2. *J. Am. Chem. Soc.* **2018**, *140*, 2024-2027.

(4) Gallardo-Donaire, J.; Hermsen, M.; Wysocki, J.; Ernst, M.; Rominger, F.; Trapp, O.; Hashmi, A. S. K.; Schafer, A.; Comba, P.; Schaub, T., Direct Asymmetric Ruthenium-Catalyzed Reductive Amination of Alkyl-Aryl Ketones with Ammonia and Hydrogen. J. Am. Chem. Soc. 2018, 140, 355-361.

- (5) Zhao, Q.; Wen, J.; Tan, R.; Huang, K.; Metola, P.; Wang, R.; Anslyn, E. V.; Zhang, X., Rhodium-catalyzed asymmetric hydrogenation of unprotected NH imines assisted by a thiourea. Angew. Chem., Int. Ed. 2014, 53, 8467-8470.
- (6) Nugent, T. C.; El-Shazly, M., Chiral amine synthesis. Recent developments and trends for enamide reduction, reductive amination, and imine reduction. Adv. Synth. Catal. 2010, 352, 753-819. 10
- (7) Li, K.; Shao, X.; Tseng, L.; Malcolmson, S. J., 2-11 Azadienes as Reagents for Preparing Chiral Amines: 12 Synthesis of 1,2-Amino Tertiary Alcohols by Cu-Catalyzed 13 Enantioselective Reductive Couplings with Ketones. J. Am. 14 Chem. Soc. 2018, 140, 598-601. 15
- (8) Jang, H.; Romiti, F.; Torker, S.; Hoveyda, A. H., 16 Catalytic diastereo- and enantioselective additions of 17 versatile allyl groups to N-H ketimines. Nat. Chem. 2017, 9, 18 1269-1275. 19
- (9) Robak, M. T.; Herbage, M. A.; Ellman, J. A., Synthesis 20 and Applications of tert-Butanesulfinamide. Chem. Rev. 21 **2010**, *110*, 3600-3740.
- 22 (10) Roggen, M.; Carreira, E. M., Stereospecific substitution 23 of allylic alcohols to give optically active primary allylic 24 amines: unique reactivity of a (P,alkene)Ir complex 25 modulated by iodide. J. Am. Chem. Soc. 2010, 132, 11917-26 9
- 27 (11) Kroutil, W.; Fischereder, E.-M.; Fuchs, C. S.; Lechner,
- H.; Mutti, F. G.; Pressnitz, D.; Rajagopalan, A.; Sattler, J. H.; 28 Simon, R. C.; Siirola, E., Asymmetric Preparation of prim-, 29 sec-, and tert-Amines Employing Selected Biocatalysts. Org. 30 Process Res. Dev. 2013, 17, 751-759. 31
- (12) Savile, C. K.; Janey, J. M.; Mundorff, E. C.; Moore, J. 32 C.; Tam, S.; Jarvis, W. R.; Colbeck, J. C.; Krebber, A.; Fleitz, 33
- F. J.; Brands, J.; Devine, P. N.; Huisman, G. W.; Hughes, G. 34 J., Biocatalytic asymmetric synthesis of chiral amines from 35 ketones applied to sitagliptin manufacture. Science 2010, 36 329, 305-9.
- 37 (13) Paetzold, J.; Backvall, J. E., Chemoenzymatic dynamic 38 kinetic resolution of primary amines. J. Am. Chem. Soc. 39 2005, 127, 17620-1.
- 40 (14) Pirnot, M. T.; Wang, Y.-M.; Buchwald, S. L., Copper 41 Hydride-Catalyzed Hydroamination of Alkenes and 42 Alkynes. Angew. Chem., Int. Ed. 2016, 55, 48-57.
- 43 (15) Niu, D.; Buchwald, S. L., Design of Modified Amine 44 Transfer Reagents Allows the Synthesis of α-Chiral 45 Secondary Amines via CuH-Catalyzed Hydroamination. J. 46 Am. Chem. Soc. 2015, 137, 9716-9721.
- 47 (16) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M., Copper-48 Catalyzed Intermolecular Regioselective Hydroamination of 49 Styrenes with Polymethylhydrosiloxane and 50 Hydroxylamines. Angew. Chem., Int. Ed. 2013, 52, 10830-51 10834.
- 52 (17) Nishikawa, D.; Hirano, K.; Miura, M., Asymmetric Synthesis of a-Aminoboronic Acid Derivatives by Copper-53 Catalyzed Enantioselective Hydroamination. J. Am. Chem. 54 Soc. 2015, 137, 15620-15623. 55

(18) Zhu, S.; Niljianskul, N.; Buchwald, S. L., Enantio- and Regioselective CuH-Catalyzed Hydroamination of Alkenes. J. Am. Chem. Soc. 2013, 135, 15746-15749.

(19) Zhu, S.; Buchwald, S. L., Enantioselective CuH-Catalyzed Anti-Markovnikov Hydroamination of 1,1-Disubstituted Alkenes. J. Am. Chem. Soc. 2014, 136, 15913-15916.

(20) Niljianskul, N.; Zhu, S.; Buchwald, S. L., Enantioselective synthesis of a-aminosilanes by coppercatalyzed hydroamination of vinylsilanes. Angew. Chem., Int. Ed. 2015, 54, 1638-1641.

(21) Yang, Y.; Shi, S.-L.; Niu, D.; Liu, P.; Buchwald, S. L., Catalytic asymmetric hydroamination of unactivated internal olefins to aliphatic amines. Science 2015, 349, 62-66.

(22) Shi, S.-L.; Wong, Z. L.; Buchwald, S. L., Coppercatalysed enantioselective stereodivergent synthesis of amino alcohols. Nature 2016, 532, 353-356.

(23) Xi, Y.; Butcher, T. W.; Zhang, J.; Hartwig, J. F., Regioselective, Asymmetric Formal Hydroamination of Unactivated Internal Alkenes. Angew. Chem., Int. Ed. 2016. 55, 776-780.

(24) Zhu, S.; Niljianskul, N.; Buchwald, S. L., A direct approach to amines with remote stereocentres by enantioselective CuH-catalyzed reductive relay hydroamination. Nat. Chem. 2016, 8, 144-150.

(25) Wang, H.; Yang, J. C.; Buchwald, S. L., CuH-Catalyzed Regioselective Intramolecular Hydroamination for the Synthesis of Alkyl-Substituted Chiral Aziridines. J. Am. Chem. Soc. 2017, 139, 8428-8431.

(26) Zhou, Y.; Engl, O. D.; Bandar, J. S.; Chant, E. D.; Buchwald, S. L., CuH-Catalyzed Asymmetric Hydroamidation of Vinylarenes. Angew. Chem., Int. Ed. 2018, 57, 6672-6675.

(27) Mendiola, J.; Rincón, J. A.; Mateos, C.; Soriano, J. F.; de Frutos, Ó.; Niemeier, J. K.; Davis, E. M., Preparation, Use, and Safety of O-Mesitylenesulfonylhydroxylamine. Org. Process Res. Dev. 2009, 13, 263-267.

(28) Mlynarski, S. N.; Karns, A. S.; Morken, J. P., Direct Stereospecific Amination of Alkyl and Aryl Pinacol Boronates. J. Am. Chem. Soc. 2012, 134, 16449-16451.

(29) Kitamura, M.; Suga, T.; Chiba, S.; Narasaka, K., Synthesis of primary amines by the electrophilic amination of Grignard reagents with 1,3-dioxolan-2-one Osulfonyloxime. Org. Lett. 2004, 6, 4619-21.

(30) Gao, H.; Zhou, Z.; Kwon, D. H.; Coombs, J.; Jones, S.; Behnke, N. E.; Ess, D. H.; Kurti, L., Rapid heteroatom transfer to arylmetals utilizing multifunctional reagent scaffolds. Nat. Chem. 2017, 9, 681-688.

(31) Gosmini, C.; Corpet, M., Recent Advances in Electrophilic Amination Reactions. Synthesis 2014, 46, 2258-2271.

(32) (a) We note that a related paper appeared while our paper was in revision: REFERENCE **DOI:** 10.1021/acs.orglett.8b03093. It involves ring opening of anthranils as a source of electrophile for Cu-catalyzed asymmetric hydroamination processes. It does not appear to allow for the easy introduction of a primary amino group. (b)

59 60

56

57 58

1

2

3

4

5

6

7

8

2

3

Gribble, M. W.; Guo, S.; Buchwald, S. L., Asymmetric Cu-Catalyzed 1,4-Dearomatization of Pyridines and Pyridazines without Preactivation of the Heterocycle or Nucleophile. *J. Am. Chem. Soc.* **2018**, *140*, 5057-5060.

- 4 (33) De Munno, A.; Bertini, V.; Lucchesini, F., On the base
 5 catalysed ring opening of 3-unsubstituted isoxazoles.
 6 Derivatives of 4- and 5-phenylisoxazole. J. Chem. Soc.,
 7 Perkin Trans. 2 1977, 1121-1124.
- 8 (34) Bandar, J. S.; Pirnot, M. T.; Buchwald, S. L.,
 9 Mechanistic Studies Lead to Dramatically Improved
 10 Reaction Conditions for the Cu-Catalyzed Asymmetric
 11 Hydroamination of Olefins. J. Am. Chem. Soc. 2015, 137,
 12 14812-14818.
- (35) In principle, Bn₂NOPiv could provide the same products (primary amines) that are synthesized in this paper by hydrogenolysis of the benzyl groups. However, because of the possibility of hydrogenating the benzyl amines we are synthesizing, we did not pursue this approach.
 (9) Provide the same product of the possibility of the possibility of the possibility of the possibility of hydrogenating the benzyl amines we are synthesizing, we did not pursue this approach.
- (36) Casey, M. L.; Kemp, D. S.; Paul, K. G.; Cox, D. D.,
 Physical organic chemistry of benzisoxazoles. I. Mechanism of the base-catalyzed decomposition of benzisoxazoles. J. Org. Chem. 1973, 38, 2294-301.
- 21 (37) D'Anna, F.; La Marca, S.; Lo Meo, P.; Noto, R., A
 22 Study of the Influence of Ionic Liquids Properties on the
 23 Kemp Elimination Reaction. *Chem. Eur. J.* 2009, *15*, 789624 7902.
- (38) Lu, G.; Liu, R. Y.; Yang, Y.; Fang, C.; Lambrecht, D.
 S.; Buchwald, S. L.; Liu, P., Ligand-Substrate Dispersion
 Facilitates the Copper-Catalyzed Hydroamination of
 Unactivated Olefins. J. Am. Chem. Soc. 2017, 139, 1654816555.
- 30 (39) Kikumoto, R.; Tobe, A.; Tonomura, S., Synthesis and
 31 antidepressant activity of substituted (ω32 aminoalkoxy)benzene derivatives. J. Med. Chem. 1981, 24,
 33 145-8.
- (40) Shi, S.-L.; Buchwald, S. L., Copper-catalyzed selective
 hydroamination reactions of alkynes. *Nat. Chem.* 2015, 7, 38-44.
- (41) Zhao, G.-L.; Lin, S.; Korotvicka, A.; Deiana, L.;
 Kullberg, M.; Cordova, A., Asymmetric Synthesis of Maraviroc (UK-427,857). Adv. Synth. Catal. 2010, 352, 2291-2298.
- 40 (42) Lou, S.; Moquist, P. N.; Schaus, S. E., Asymmetric
 41 (42) Lou, S.; Moquist, P. N.; Schaus, S. E., Asymmetric
 42 Allylboration of Acyl Imines Catalyzed by Chiral Diols. J.
 42 Am. Chem. Soc. 2007, 129, 15398-15404.
- (43) Ahman, J.; Birch, M.; Haycock-Lewandowski, S. J.;
 (44) Long, J.; Wilder, A., Process Research and Scale-up of a
 Commercializable Route to Maraviroc (UK-427,857), a
 CCR-5 Receptor Antagonist. *Org. Process Res. Dev.* 2008, *12*, 1104-1113.
- (44) Haycock-Lewandowski, S. J.; Wilder, A.; Ahman, J.,
 Development of a Bulk Enabling Route to Maraviroc (UK427,857), a CCR-5 Receptor Antagonist. *Org. Process Res.*Dev. 2008, 12, 1094-1103.
- 52 (45) Ma, G.; Xu, Z.; Zhang, P.; Liu, J.; Hao, X.; Ouyang, J.;
- Liang, P.; You, S.; Jia, X., A Novel Synthesis of Rasagiline
 via a Chemoenzymatic Dynamic Kinetic Resolution. *Org. Process Res. Dev.* 2014, *18*, 1169-1174.

(46) Torre, O.; Gotor-Fernandez, V.; Gotor, V., Lipasecatalyzed resolution of chiral 1,3-amino alcohols: application in the asymmetric synthesis of (S)-dapoxetine. *Tetrahedron: Asymmetry* **2006**, *17*, 860-866.

(47) Storace, L.; Anzalone, L.; Confalone, P. N.; Davis, W. P.; Fortunak, J. M.; Giangiordano, M.; Haley, J. J., Jr.; Kamholz, K.; Li, H.-Y.; Ma, P.; Nugent, W. A.; Parsons, R. L., Jr.; Sheeran, P. J.; Silverman, C. E.; Waltermire, R. E.; Wood, C. C., An efficient large-scale process for the human leukocyte elastase inhibitor, DMP 777. *Org. Process Res. Dev.* **2002**, *6*, 54-63.



58 59 60

56