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Highly Diastereo- and Enantioselective CuH-Catalyzed Synthesis of 2,3-Disubstituted Indolines

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S Supporting Information

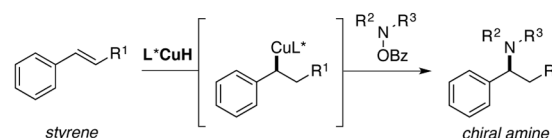
ABSTRACT: A diastereo- and enantioselective CuH-catalyzed method for the preparation of highly functionalized indolines is reported. The mild reaction conditions and high degree of functional group compatibility as demonstrated with substrates bearing heterocycles, olefins, and substituted aromatic groups, renders this technique highly valuable for the synthesis of a variety of *cis*-2,3-disubstituted indolines in high yield and enantioselectivity.

Optically active 2,3-disubstituted indolines are of considerable interest in both synthetic and medicinal chemistry due to the numerous natural products and pharmaceuticals whose structures incorporate this heterocyclic framework.¹ They also serve as key building blocks for drug discovery, as exemplified in various natural product-like chemical libraries based on the indoline framework.²

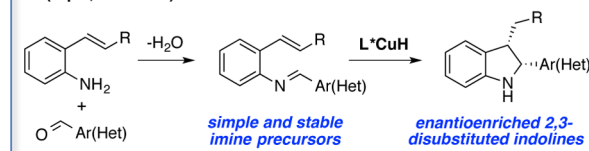
Consequently, a wide range of strategies have been developed for the asymmetric synthesis of these structures.³ Among these methods, the Brønsted acid-activated asymmetric hydrogenation of functionalized indoles is perhaps the most important strategy to their synthesis.⁴ Despite its attractiveness, the need to employ acidic reaction conditions, high pressure, and the lack of broad functional group compatibility manifested, have prevented the more widespread application of this approach. Other notable methods, such as the kinetic resolution of indolines,⁵ the Pd-catalyzed asymmetric intramolecular coupling reactions,⁶ tandem $A_N/S_N/Ar$ processes,⁷ and asymmetric sparteine-mediated reactions,⁸ have also been developed. Despite these advances, the harsh reaction conditions,^{6,8} multistep synthesis,⁵ and modest to poor yields,^{6a,7} limits their synthetic applications. To date, no direct asymmetric approach is available to access 2,3-disubstituted indolines bearing a wide variety of functional groups. In particular, incorporation of pharmaceutically important heterocycles (e.g., indoles, quinolines, pyridines) with indolines in an asymmetric fashion is not well-known. Herein, we report a straightforward approach to the synthesis of 2,3-disubstituted indolines in high diastereo- and enantioselectivities through a CuH-based strategy. This protocol tolerates a broad range of functional groups, including heteroarenes and olefins.

Recently, we and Miura and Hirano have independently reported the enantioselective CuH-catalyzed Markovnikov hydroamination of styrenes.⁹ Bearing in mind that these reactions proceed via organocopper intermediates that undergo amination with electrophilic hydroxylamine esters (eq 1), we questioned whether these species could be trapped intramolecularly with tethered imine electrophiles. In this manner a

Asymmetric CuH-Catalyzed Hydroamination of Styrenes (Eq. 1)



Asymmetric CuH-Catalyzed Synthesis of 2,3-Disubstituted Indolines (Eq. 2, this work)



rapid and synthetically valuable approach to enantioenriched indolines with two contiguous chiral centers could be realized in two steps from readily available aminostyrene and aromatic aldehyde derivatives (eq 2).

A scheme of our proposed strategy is illustrated in Figure 1. Based on literature precedent for related CuH-based systems,^{9–14} the active L^*CuH species **A** could be formed by reacting $Cu(OAc)_2$ with a chiral ligand and a stoichiometric amount of a hydrosilane.^{9a,10a,b} The olefinic moiety of **1a** could then readily insert into Cu–H bond of **A**. Based on previous

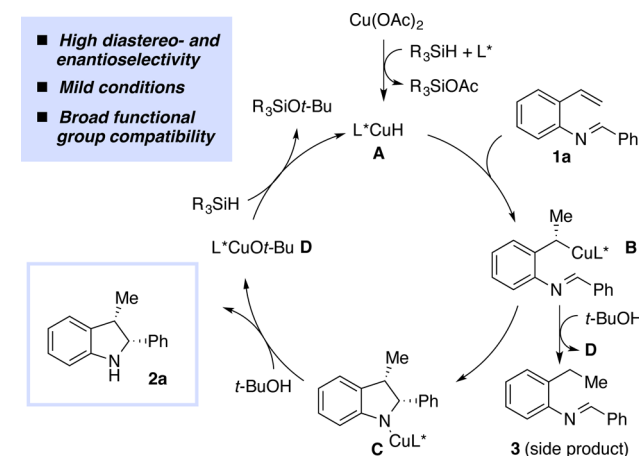


Figure 1. Proposed catalytic cycle for CuH-catalyzed synthesis of 2,3-disubstituted indolines.

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results we would expect this to occur in a highly enantioselective and in a Markovnikov fashion to form the alkylcopper intermediate **B**.^{9,10c-f} Intermediate **B** could then undergo an unprecedented cyclization with the adjacent imine to form **C**.¹¹ Subsequent protonation of **C** with *t*-BuOH would then provide the desired indoline **2a**, and generate $[L^*CuOt-Bu]$ species **D**, which is an ideal precursor for rapid regeneration of the active L^*CuH **A**.¹² In order for this approach to be successful, it is necessary that **A** react chemoselectively with the olefin over the imine.¹³ It is also necessary that the cyclization (**B** to **C**) is faster than the undesired protonation of **B** to **3**.¹⁴

To test the viability of our proposed method, we examined styrene **1a** as our model substrate. We began using our reported conditions for the hydroamination of styrene^{9a} (Table 1, entry 1).

Table 1. Reaction Optimization

entry	additives	L	solvent	yield (%) ^a	ee (%) ^b
1	-	L1	THF	9	27
2	<i>t</i> -BuOH	L1	THF	67	27
3	<i>t</i> -BuOH	L2	THF	15	-7
4	<i>t</i> -BuOH	L3	THF	15	22
5	<i>t</i> -BuOH	L4	THF	74	58
6	<i>t</i> -BuOH	L5	THF	<2	ND
7	<i>t</i> -BuOH	L6	THF	84	84
8	<i>t</i> -BuOH	L6	MTBE:THF (19:1)	92	90
9	<i>i</i> -PrOH	L6	MTBE:THF (19:1)	88	90
10	EtOH	L6	MTBE:THF (19:1)	80	89
11	MeOH	L6	MTBE:THF (19:1)	57	89
12		L6	MTBE:THF (19:1)	29	ND
13	<i>t</i> -BuOD	L6	MTBE:THF (19:1)	96	90
14	<i>t</i> -BuOD, PPh ₃ (5%)	L6	MTBE:THF (19:1)	99	90

Ar = 3,5-*t*-Bu-4-MeOC₆H₂: (R)-DTBM-SEGPHOS (L1) Ar = 3,5-MeC₆H₃: (S)-3,5-Me-MeO-BIPHEP (L2) Ar = Ph: (R)-BINAP (L3)

(R)-(S)-JOSIPHOS (L4) (S,S)-Me-DUPHOS (L5) (S,S)-Ph-BPE (L6)

^aYields were determined by ¹H NMR analysis of the crude reaction mixture using 1,1,2,2-tetrachloroethane as an internal standard.

^bEnantioselectivities were determined by chiral HPLC analysis. ND = not determined. DEMS = (EtO)₂MeSiH.

The reaction afforded the desired indoline **2a** in 9% yield and 27% *ee*, as a single *cis*-diastereomer. However, when a stoichiometric amount of *t*-BuOH was added, the yield was improved to 67%

yield, while the enantioselectivity was unchanged (entry 2). We attributed the improvement in catalyst turnover to the protonation of $[L^*Cu-N\text{-indoline}]$ **C** with *t*-BuOH (Figure 1), bypassing the slow transmetalation between **C** and R₃Si-H needed for regeneration of L^*CuH .¹⁵ We next examined several commercially available chiral bisphosphine ligands (entries 2–7), and we found that (*S,S*)-Ph-BPE proved to be best in terms of reactivity and enantioselectivity (84% yield, 84% *ee*, entry 7). Screening of solvents revealed that a mixture of MTBE/THF (19:1) was the best choice, leading to an enhanced yield and enantioselectivity (92% yield, 90% *ee*, entry 8).

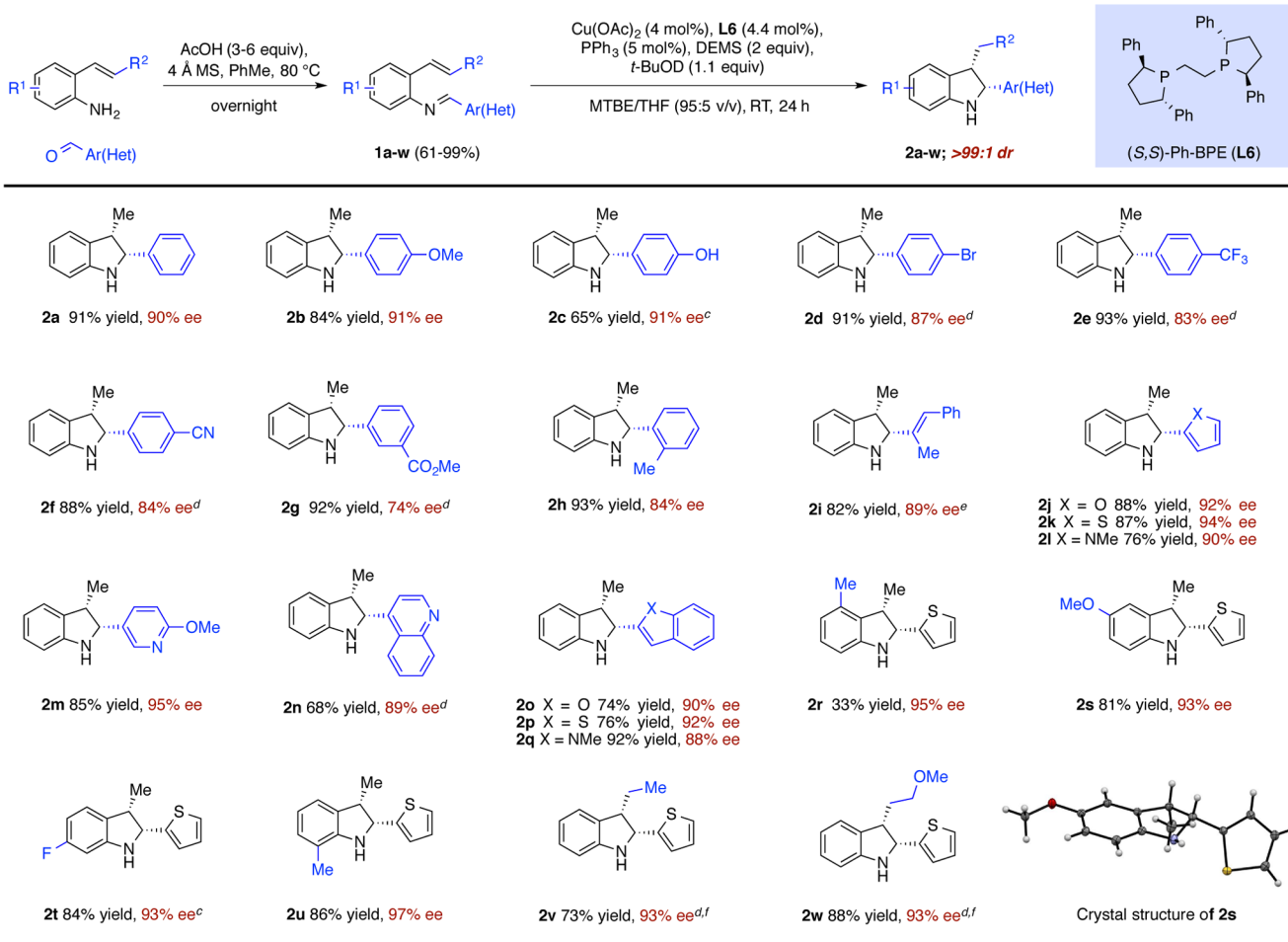
We found that the choice of alcohol was important for the yield. For example, when using *t*-BuOH (entry 8) the reduced styrene side product **3** could be detected in 3% yield. Examining the use of *i*-PrOH, EtOH, MeOH, and 2-trifluoromethyl-2-propanol, afforded the desired product **2a** in lower yields (29–88%, entries 9–12), while observing an increase in yield of the side product **3** in 5%, 15%, 36%, and 55%, respectively. When *t*-BuOD was used in lieu of *t*-BuOH, only a trace amount of **3** (<1%) could be detected, and a slight increase in yield of **2a** was obtained (96%, entry 13) compared to *t*-BuOH (92%, entry 8). We attribute this to a deuterium isotope effect; i.e., the protonolysis of **B** to **3** is slower with *t*-BuOD than with *t*-BuOH.¹⁶

Lipshutz, in related CuH-catalyzed systems, has shown that addition of triphenylphosphine as a secondary ligand, significantly improves the catalyst turnover number.¹⁷ Applying this strategy to our method, further improved the yield that could be achieved without any erosion in enantioselectivity (entry 14).

With the optimized conditions in hand, we examined the reaction scope using a variety of stable 2-alkenylimine precursors **1a–w**. These were obtained in good to excellent yields from readily available 2-alkenylanilines and aromatic aldehydes (Table 2). Generally, the reaction displayed good functional group tolerance, and in all cases (except for product **2i**), the resulting indolines were obtained exclusively as the *cis*-diastereomers.¹⁸ The reason for the observed diastereoselectivity is not clear and remains to be elucidated.

It was found that electron-neutral and -rich substituents on the phenyl ring could be transformed, thus giving *cis*-indolines **2a–c,h** in high yields and in good to excellent enantioselectivities. Electron-deficient substituents (**2d–g**) also gave satisfactory results but with slightly lower levels of enantioselectivity. For these examples, the yield was higher if the reaction was run in the absence of triphenylphosphine. The applicability of this method to access indolines bearing a phenol (**2c**), aryl bromide (**2d**), benzonitrile (**2f**), or methyl benzoate (**2g**) group is important, as these functional groups can be used as synthetic handles for further transformations. Moreover, the compatibility of a vinyl group, which is a valuable feature that can be problematic in methods using asymmetric hydrogenation,⁴ furnishes the resultant indoline **2i** in good yield and enantioselectivity. This method also tolerates a variety of heteroarenes. As illustrated in Table 2, five-membered (**2j–l**), six-membered (**2m**), and fused heterocycles (**2n–q**) could all be accommodated in good yields with excellent levels of enantioselectivity.

We next turned our attention to substrates bearing substituents on the aryl ring of styrene. We found that excellent enantioselectivities were obtained for indolines **2r–u**.¹⁹ However, indoline **2r**, with a methyl group at the 4-position displayed lower reactivity (33% yield), with 30% of the reduced imine could be also detected. We rationalize that the CuH insertion step is slower due to steric encumbrance of the methyl group in the 4-position.

Table 2. Substrate Scope^{a,b}

^aIsolated yield on 1 mmol scale (average of two runs). ^bEnantioselectivities were determined by chiral HPLC analysis. ^c3 equiv of DEMS was used. ^dReaction performed in the absence of PPh₃. ^eIsolated as a 11:1 diastereoselective ratio. ^fCu(OAc)₂ (8 mol%) and (S,S)-Ph-BPE (8.8 mol%) were used.

We also briefly examined the extension of this method to β -substituted styrenes and found that indolines **2v,w** could be obtained in high yield and excellent enantioselectivities. In these cases, 8 mol% catalyst loading was needed and best results were observed in the absence of triphenylphosphine.

In conclusion, we have developed a mild, Cu-catalyzed strategy for the highly diastereo- and enantioselective synthesis of a broad range of *cis*-2,3-disubstituted indolines. Due to the generality of the method and mild conditions employed, we believe this method will see considerable use in both academic and industrial settings.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data. 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.

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REFERENCES

- (1) For selected examples, see: (a) Crich, D.; Banerjee, A. *Acc. Chem. Res.* **2007**, *40*, 151. (b) Triggler, D. J.; Mitchell, J. M.; Filler, R. *CNS Drug Reviews* **1998**, *4*, 87. (c) Deutsch, H. F.; Evenson, M. A.; Drescher, P.; Sparwasser, C.; Madsen, P. O. *J. Pharm. Biomed. Anal.* **1994**, *12*, 1283. (d) Silvestri, R. *J. Med. Chem.* **2013**, *56*, 625. (e) Greig, N. H.; Pei, X.-F.; Soncrant, T. T.; Ingram, D. K.; Brossi, A. *Med. Res. Rev.* **1995**, *15*, 3. (f) Neelamegam, R.; Hellenbrand, T.; Schroeder, F. A.; Wang, C.; Hooker, J. M. *J. Med. Chem.* **2014**, *57*, 1488.
- (2) (a) Podoll, J. D.; Liu, Y.; Chang, L.; Walls, S.; Wang, W.; Wang, X. *Proc. Natl. Acad. Sci. U.S.A.* **2013**, *110*, 15573. (b) Poondra, R. R.; Kumar, N. N.; Nijjan, K.; Prakesch, M.; Slater-Campagna, V.; Reayi, A.; Reddy, T. P.; Choudhry, A.; Barnes, M. L.; Leek, D. M.; Daroszewska, M.; Lougheed, C.; Xu, B.; Schapira, M.; Alaoui-Jamali, M. A.; Arya, P. *J. Comb. Chem.* **2009**, *11*, 303. (c) Gan, Z. P.; Reddy, T.; Quevillon, S.; Couve-Bonnaire, S.; Arya, P. *Angew. Chem., Int. Ed.* **2005**, *44*, 1366.

(3) For recent reviews, see: (a) Liu, D.; Zhao, G.; Xiang, L. *Eur. J. Org. Chem.* **2010**, 3975. (b) Zhang, D.; Song, H.; Qin, Y. *Acc. Chem. Res.* **2011**, *44*, 447.

(4) (a) Wang, D.-S.; Chen, Q.-A.; Li, W.; Yu, C.-B.; Zhou, Y.; Zhang, X. *J. Am. Chem. Soc.* **2010**, *132*, 8909. (b) Duan, Y.; Chen, M.-W.; Chen, Q.-A.; Yu, C.-B.; Zhou, Y.-G. *Org. Biomol. Chem.* **2012**, *10*, 1235. (c) Duan, Y.; Chen, M.-W.; Ye, Z.-S.; Wang, D.-S.; Chen, Q.-A.; Zhou, Y.-G. *Chem.—Eur. J.* **2011**, *17*, 7193. (d) Wang, D.-S.; Tang, J.; Zhou, Y.-G.; Chen, M.-W.; Yu, C.-B.; Duan, Y.; Jiang, G.-F. *Chem. Sci.* **2011**, *2*, 803. (e) Li, C.; Chen, J.; Fu, G.; Liu, D.; Liu, Y.; Zhang, W. *Tetrahedron* **2013**, *69*, 6839. (f) Duan, Y.; Li, L.; Chen, M.-W.; Yu, C.-B.; Fan, H.-J.; Zhou, Y.-G. *J. Am. Chem. Soc.* **2014**, *136*, 7688. (g) Xiao, Y.-C.; Wang, C.; Yao, Y.; Sun, J.; Chen, Y.-C. *Angew. Chem. Int. Ed.* **2011**, *50*, 10661.

(5) (a) Arp, F. O.; Fu, G. C. *J. Am. Chem. Soc.* **2006**, *128*, 14264. (b) Lopez-Iglesias, M.; Busto, E.; Gotor, V.; Gotor-Fernández, V. *J. Org. Chem.* **2012**, *77*, 8049. (c) Saito, K.; Shibata, Y.; Yamanaka, M.; Akiyama, T. *J. Am. Chem. Soc.* **2013**, *135*, 11740.

(6) (a) Katayev, D.; Nakanishi, M.; Bürgi, T.; Kündig, P. E. *Chem. Sci.* **2012**, *3*, 1422. (b) Saget, T.; Lemouzy, S. J.; Cramer, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 2238.

(7) Ruano, J. L. G.; Parra, A.; Marcos, V.; Pozo, C. D.; Catalán, S.; Monteagudo, S.; Fustero, S.; Poveda, A. *J. Am. Chem. Soc.* **2009**, *131*, 9432.

(8) Kang, K. H.; Do, J.; Park, Y. S. *J. Org. Chem.* **2012**, *77*, 808.

(9) (a) Zhu, S.; Niljianskul, N.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 15746. (b) Miki, Y.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 10830.

(10) (a) Zhu, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **2014**, *136*, 15913. (b) Niljianskul, N.; Zhu, S.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2014**, *54*, 1638. For related asymmetric Cu-catalyzed Markovnikov hydroboration and aminoboration reactions of styrenes, see: (c) Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160. (d) Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Am. Chem. Soc.* **2013**, *135*, 4934. (e) Grigg, D. R.; Hovel, R. V.; Schomaker, J. M. *J. Am. Chem. Soc.* **2012**, *134*, 16131. (f) Noh, D.; Chea, H.; Ju, J.; Yun, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 6062. For reviews dealing with CuH-catalyzed reactions, see: (g) Deusch, C.; Krause, N.; Lipshutz, B. H. *Chem. Rev.* **2008**, *108*, 2916 and references therein. (h) Hesp, K. D. *Angew. Chem., Int. Ed.* **2014**, *53*, 2034. (i) Fujihara, T.; Semba, K.; Terao, J.; Tsuji, Y. *Catal. Sci. Technol.* **2014**, *4*, 1699.

(11) Although no examples of an analogous intramolecular coupling reaction have been reported, an asymmetric intermolecular CuH-catalyzed coupling between vinylarenes and (hetero)aryl N-Boc imines has recently been developed; Choi, B.; Saxena, A.; Smith, J. J.; Churchill, G. H.; Lam, H. W. *Synlett* **2015**, *26*, 350.

(12) For examples of *t*-BuOH-accelerated CuH-catalyzed reactions, see: (a) Chen, J.-X.; Daeuble, J. F.; Brestensky, D. M.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2153. (b) Chen, J.-X.; Daeuble, J. F.; Stryker, J. M. *Tetrahedron* **2000**, *56*, 2789. (c) Hughes, G.; Kimura, M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2003**, 11253. (d) Lipshutz, B. H.; Servesko, J. M.; Taft, B. R. *J. Am. Chem. Soc.* **2004**, *126*, 8352. (e) Rainka, M. P.; Aye, Y.; Buchwald, S. L. *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5821. (f) Lam, H. W.; Saxena, A.; Rupnicki, L. *J. Am. Chem. Soc.* **2009**, *131*, 10386.

(13) For CuH-catalyzed hydrosilylation of imines, see: Lipshutz, B. H.; Shimizu, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 2228.

(14) For protonation of carbon–copper bonds with alcohols in related CuH-catalyzed reactions, see: (a) Semba, K.; Fujihara, T.; Xu, T.; Terao, J.; Tsuji, Y. *Adv. Synth. Catal.* **2012**, *354*, 1542. (b) Whittaker, A. M.; Lalic, G. *Org. Lett.* **2013**, *15*, 1112. (c) Shi, S.-L.; Buchwald, S. L. *Nat. Chem.* **2015**, *7*, 38.

(15) For a conceptually related process, see: Verdaguer, X.; Lange, U. E. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1998**, *37*, 1103.

(16) Hoveyda, in related Cu-catalyzed processes, has shown that protonation of carbon–copper intermediates with MeOD-*d*₄ is significantly slower than the reaction with MeOH. Thus, $k_{\text{H}}/k_{\text{D}}$ = 2.7–3.6 have been measured. See: Jang, W.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2011**, *133*, 7859.

(17) Lipshutz, B. H.; Noson, K.; Chrisman, W.; Lower, A. *J. Am. Chem. Soc.* **2003**, *125*, 8779. See also ref 10a.

(18) This technique could also be applied on crude imines directly after solvent evaporation, as exemplified on **1a**, although the yield was somewhat lower (74% isolated yield, 90% ee). Unfortunately, no product was observed on aliphatic imines, as demonstrated on (*E*)-2-methyl-*N*-(2-vinylphenyl)propan-1-imine.

(19) The absolute configuration of **2s** was determined to be 2*R*,3*S* by X-ray analysis (see Table 2). Consequently, those of the other products were assigned by analogy.