Asymmetric Copper Hydride-Catalyzed Markovnikov Hydrosilylation of Vinylarenes and Vinyl Heterocycles

Michael W. Gribble, Jr.,† Michael T. Pirnot,‡ Jeffrey S. Bandar,‡ Richard Y. Liu, and Stephen L. Buchwald*†

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

Supporting Information

ABSTRACT: We report a highly enantioselective CuH-catalyzed Markovnikov hydrosilylation of vinylarenes and vinyl heterocycles. This method has a broad scope and enables both the synthesis of isolable silanes and the conversion of crude products to chiral alcohols. Density functional theory calculations support a mechanism proceeding by hydrocupration followed by σ-bond metathesis with a hydrosilane.

Chiral silanes undergo a number of useful transformationa,b and possess more desirable toxicological and environmental characteristics than many related main-group reagents. However, they can be difficult to prepare due to the scarcity of broadly applicable methods for the construction of C(sp^3)−Si bonds in functionalized molecules. This limitation also discourages the pursuit of silane drug-candidates, despite the promise organosilicon compounds hold for a variety of therapeutic applications. Because functionalized alkylsilanes are additionally important to many modern materials and industrial processes, selective new C−Si bond-forming reactions have the potential to be enabling technologies for researchers across a wide range of disciplines.

Late transition metal-catalyzed olefin hydrosilylation (Figure 1a) is one of the core synthetic transformations of organosilicon chemistry. The archetypal Pt-catalyzed variant is among the highest-volume industrial applications of homogeneous catalysis and the need to replace Pt in this role with more abundant metals has spurred the discovery of many anti-Markovnikov hydrosilylation catalysts based on iron, cobalt, and nickel. In contrast, Markovnikov olefin hydrosilylation catalysts are uncommon, and the synthetic capabilities of the reactions are presently limited. Hayashi’s discovery that Pd-MOP complexes catalyze highly enantioselective Markovnikov hydrosilylation with trichlorosilane was a milestone achievement in asymmetric catalysis. Although this reaction is of exceptional fundamental importance, its reported scope is limited; in particular, we are aware of no applications of this methodology to the hydrosilylation of heterocyclic or appreciably Lewis-basic olefins, presumably because they are incompatible with the sensitive trichlorosilyl group.

Our group has recently developed several functional group-tolerant Markovnikov hydrofunctionalization reactions that proceed through electrophilic interception of alkylcopper intermediates generated by asymmetric hydrocupration of vinylarenes with an active chiral copper hydride catalyst [I, Figure 1e, step (i)]. We reasoned that an asymmetric Markovnikov hydrosilylation could be achieved if the alkylcopper species (Figure 1e) could undergo stereoretentive transmetalation with a hydrosilane [Figure 1e, step
selectivity with Ph₃SiH varied with change in the solvent, although without an obvious correlation with solvent properties. Reducing the concentration of silane was deleterious for enantioselectivity, whereas conducting the reaction neat resulted in excellent levels of asymmetric induction (Table 1, entries 4 and 7). These observations suggest that rapid trapping of the alkylcopper intermediate by the silane may be a key factor for obtaining high levels of enantioselective, particularly because the hydrocupration step is known to be highly enantioselective in a variety of solvents. This notion was further supported by the observation that the more reactive PhSiH₃ underwent hydrosilylation in 96% ee even in THF solution (Table 1, entry 8).

With the goal of generating easily isolable products, we chose to use Ph₃SiH₂ in our exploration of the vinylarene scope. The results of these studies are presented in Table 2. The hydrosilylation occurred in high yield and with good to excellent enantioselectivity with substrates containing either electron-withdrawing or electron-donating groups and accommodated substituents at any of the three positions on the aryl ring. The highest levels of enantioselectivity were obtained with π-donor substituents at either the para- or ortho-positions (e.g., examples 2 and 9, Table 2). Electron-withdrawing groups were tolerated at the meta-position, and we noted that conducting the reaction at room temperature benefited the selectivity in those cases. Certain functional groups, such as the nitro group and halogens other than fluorine, were incompatible with the reaction, as were sterically demanding ortho-substituents.

Underscoring the utility of the protocol, we conducted a reaction on 10 mmol scale without significant loss of yield or enantioselectivity (eq 1).

Table 3 illustrates that a variety of vinyl heterocycles proved to be viable substrates for the reaction. Silanes 11 and 12 (Table 3A) were formed with high enantioselectivity, whereas a less electronically biased heterocycle gave product with modest asymmetric induction (example 13, Table 3A). These results mirrored the enantioselectivity trends evident in Table 2 and those our group has observed in the CuH-catalyzed hydroamination of vinylarenes.

A crystal structure of 14 (Table 3A) showed the absolute configuration of the major enantiomer to be (S), which is consistent with the mechanism shown in Figure 1e. However, we noted that several entries in Tables 1 and 2 exhibited lower ee’s than were obtained in previously reported
reactions thought to proceed by the same hydrocupration step.\(^9\) We considered two mechanistic hypotheses that might account for these discrepancies: one posits a racemization step occurring after hydrocupration (i.e., a \(\text{efecting intermediate II of Figure 1e}\)); the second invokes gradual formation of an undesired catalytically active species that undergoes hydrocupration with poor selectivity in the presence of certain substrates. In either case, one would expect that accelerating the transmetalation [Figure 1e, step (ii)], e.g., by employing the more reactive \(\text{PhSiH}_3\), would result in higher enantioselectivity.\(^{12,13}\)

We also considered that \(\text{PhSiH}_3\) might be ideal for derivatization attempts using crude products because it could be easily evaporated beforehand. Hydrosilylation with \(\text{PhSiH}_3\) occurred in <12 h at room temperature in most examples, and we were able to perform Tamao oxidations\(^{15}\) on the crude products by incorporating EDTA into the reaction mixtures (Table 3B), which suppresses copper-catalyzed disproportionation of hydrogen peroxide. The enantioinduction obtained with \(\text{PhSiH}_3\) was indeed broadly superior to that observed with \(\text{Ph}_2\text{SiH}_2\) and further appeared to be less sensitive to substrate electronic bias (compare 16, 17 [Table 3B] and 13 [Table 3A]).

To sharpen our mechanistic hypothesis,\(^{16}\) we performed density functional theory (DFT) calculations on the CuH-catalyzed hydrosilylation of styrene with \(\text{PhSiH}_3\) using bis(dicyclohexylphosphino)ethane (DCyPE) as the model ligand (Figure 2). After hydrocupration, we located a \(\sigma\)-complex C upon interaction of copper with phenylsilane. From here, \(\sigma\)-bond metathesis may proceed irreversibly through a thermally accessible four-membered transition state TS-C (+30.9 or +35.8 kcal/mol relative to B). The net reaction is energetically favorable (A vs D).

In summary, we have developed a broadly applicable base-metal-catalyzed asymmetric hydrosilylation that provides access to bench-stable silanes and chiral alcohol derivatives. The method uses mild conditions, employs commercially available catalyst precursors, and enables the functionalization of a variety of medicinally relevant heterocyclic olefins. Although our mechanistic hypotheses remain speculative at this time, we propose that they provide a useful framework for rationalizing the observed selectivity trends. We also postulate that a thorough mechanistic investigation will be of value to our group’s ongoing efforts to develop new CuH-catalyzed transformations.

### Table 3. Hydrosilylation of Vinyl Heterocycles

| Compound | Yield | Enantiomeric Excess | Conditions |
|----------|-------|---------------------|------------|
| **A**<sup>a</sup> | 68% | 97% ee | 41:1 rr (23:1 crude rr by NMR), T = 40 °C, t = 16 h |
| **B**<sup>b</sup> | 61% | 90% ee | T = 40 °C, t = 36 h |
| **C**<sup>c</sup> | 77% | 70% ee | T = rt, t = 36 h |
| **D**<sup>d</sup> | 83% | 88% ee | T = rt, t = 12 h |

<sup>a</sup> Isolated yield pertains to the regioisomer mixture. <sup>b</sup>NMR yield pertains to the major regioisomer. <sup>c</sup>2.0 equiv. silane used. <sup>d</sup>MTBE used as the solvent. <sup>e</sup>Reaction run for 36 h.

---

**Figure 2.** DFT model for copper-catalyzed hydrosilylation of styrene (\(\text{L} = \text{DCyPE}\)). M06-6-311+G(d,p) SDD/SMD(THF)//B3LYP/6-31G(d)-SDD Gibbs free energy values displayed in kcal/mol. Corresponding PBE0/6-311+G(d,p)-SDD/SMD(THF)//B3LYP/6-31G(d)-SDD values shown in brackets. Key bond distances shown in units of Å. Carbon-bonded hydrogen atoms are omitted for clarity.

---

### ASSOCIATED CONTENT

**Supporting Information**

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.6b13029.

Experimental procedures and characterization data for all compounds (PDF)

Data for \(\text{C}_{23}\text{H}_{26}\text{N}_{2}\text{O}_{3}\text{Si}\) (CIF)

### AUTHOR INFORMATION

**Corresponding Author**

*sbuchwal@mit.edu*

**ORCID**

Michael W. Gribble Jr.: 0000-0003-2088-3264

---

DOI: 10.1021/jacs.6b13029

J. Am. Chem. Soc. 2017, 139, 2192–2195

---

Journal of the American Chemical Society
Author Contributions
M.T.P. and J.S.B. made equal contributions to this work.

Notes
The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The National Institutes of Health under award number GM46059 supported research reported in this publication. M.T.P. and J.S.B. thank the National Institutes of Health for postdoctoral fellowships (1F32GM113311 [M.T.P.], GM112197 [J.S.B.]). We thank Dr. Yi-Ming Wang (MIT) for advice on the preparation of this paper, Jonathan Becker (MIT) for X-ray crystallographic analysis, and the National Institutes of Health for a supplemental grant for the purchase of supercritical fluid chromatography equipment (GM08160-17S1).

REFERENCES

(1) (a) Chan, T. H.; Wang, D. Chem. Rev. 1992, 92, 995–1006. (b) Fleming, I.; Barbero, A.; Walter, D. Chem. Rev. 1997, 97, 2063–2192.

(2) (a) Denmark, S. E.; Ambrosi, A. Org. Process Res. Dev. 2015, 19, 982–994. (b) Nakao, Y.; Hiyama, T. Chem. Soc. Rev. 2011, 40, 4893–4901.

(3) (a) Min, G. K.; Hernández, D.; Skrydstrup, T. Acc. Chem. Res. 2013, 46, 457–470. (b) Bo, Y.; Singh, S.; Duong, H. Q.; Cao, C.; Sieburth, S. M. Org. Lett. 2011, 13, 1787–1789. (c) Franz, A. K.; Wilson, S. O. J. Med. Chem. 2013, 56, 388–405.

(4) (a) See volumes III–VI of Organosilicon Chemistry: From Molecules to Materials; Auner, N., Weis, J., Eds.; Wiley-VCH: Weinheim, Germany, 1996 (III), 2000 (IV), 2004 (V), 2005 (VI).

(5) (a) Nesmeyanov, A. N.; Freidlin, R. K.; Kukhovskaya, E. C.; Petrova, R. G.; Belyavsky, A. B. Tetrahedron 1962, 17, 61–68. (b) Bart, S. C.; Lobkovsky, E.; Chirik, P. J. Am. Chem. Soc. 2004, 126, 13794–13807.

(6) (a) Tondreau, A. M.; Atienza, C. C. H.; Weller, K. J.; Nye, S. C.; Lobkovsky, E.; Chirik, P. J. Org. Chem. 2013, 78, 1441–1449. Also see: (e) Jensen, J. F.; Svendsen, B. Y.; la Cour, T. V.; Pedersen, H. L.; Johansson, M. J. Am. Chem. Soc. 2002, 124, 4558–4559.

(7) (a) Han, J. W.; Hayashi, T. Tetrahedron: Asymmetry 2014, 25, 479–484. (b) Uozumi, Y.; Hayashi, T. J. Am. Chem. Soc. 1991, 113, 9887–9888. (c) Kitayama, K.; Uozumi, Y.; Hayashi, T. J. Am. Chem. Soc. Chem. Commun. 1995, 1533–1534. (d) Hayashi, T.; Hirate, S.; Kitayama, K.; Tsuji, H.; Torii, A.; Uozumi, Y. J. Org. Chem. 2001, 66, 6426–6427.

(8) The Nishiyama group has described a rhodium-catalyzed asymmetric synthesis of bench-stable silanes, but the regioselectivity of this reaction is modest in many cases: Naito, T.; Toneda, T.; Ito, J. -I.; Nishiyama, H. Synlett 2012, 23, 2957–2960.

(9) See, for example: (a) Pirnott, M. T.; Wang, Y.-M.; Buchwald, S. L. Angew. Chem., Int. Ed. 2016, 55, 48–57. (b) Bandar, J. S.; Ascic, E.; Buchwald, S. L. J. Am. Chem. Soc. 2016, 138, 5821–5824. (c) Wang, Y.-M.; Buchwald, S. L. J. Am. Chem. Soc. 2016, 138, 5024–5027. (d) Yang, Y.; Perry, I. B.; Buchwald, S. L. J. Am. Chem. Soc. 2016, 138, 9787–9790. (e) Bandar, J. S.; Pirnott, M. T.; Buchwald, S. L. J. Am. Chem. Soc. 2015, 137, 14812–14818.

(10) Marks has proposed this mechanism for a lanthanide-catalyzed hydrosilylation of styrenes. See: Fu, P.-F.; Brand, L.; Li, Y.; Marks, T. J. Am. Chem. Soc. 1995, 117, 7157–7168. Also see ref 5k.

(11) For a mechanistically analogous Cu-catalyzed hydrosilation, see: (a) Noh, D.; Chea, H.; Ju, J.; Yun, J. Angew. Chem., Int. Ed. 2009, 48, 6062–6064. (b) Noh, D.; Yoon, S. K.; Won, J.; Lee, J. Y.; Yun, J. Chem. - Asian J. 2011, 6, 1967–1969.

(12) Dow Corning holds a patent claiming certain copper-based catalysts for the hydrosilylation of olefins. Brandstadt, K.; Cook, S.; Nguyen, B. T.; Surgenor, A.; Taylor, R.; Tzou, M.-S. Copper Containing Hydrosilylation Catalysts and Compositions Containing the Catalysts. WO 2013043792 A, March 28, 2013.

(13) See, for example: (a) Deschamps, J.; Chuzel, O.; Hennedouche, J.; Riant, O. Angew. Chem., Int. Ed. 2006, 45, 1297–1297. (b) Rendler, S.; Oestreich, M. Angew. Chem. Int. Ed. 2007, 46, 498–504. (c) Deutsch, S.; Krause, N.; Lipshutz, B. H. Chem. Rev. 2008, 108, 2916–2927.

(14) Supporting Information.

(15) Tamao, K.; Ishida, N.; Tanaka, T.; Kumada, M. Organometallics 1983, 2, 1694–1696.

(16) For a discussion of metal-catalyzed hydrosilylation mechanisms, see refs 4b and 4c.