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

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Supporting Information Placeholder

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. DFT calculations support a mechanism proceeding by hydrocupration followed by σ-bond metathesis with a hydrosilane.

Chiral silanes undergo a number of useful transformations[1a,b] and possess more desirable toxicological and environmental characteristics than many related main-group reagents.[2a,b] 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.[3a,b] This limitation also discourages the pursuit of silane drug-candidates, despite the promise organosilicon compounds hold for a variety of therapeutic applications.[3a-c] Since functionalized alkylsilanes are additionally important to many modern materials and industrial processes,[4a,b] 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 1, a) is one of the core synthetic transformations of organosilicon chemistry.[4b,c] The archetypal Pt-catalyzed variant[4b] is among the highest-volume industrial applications of homogenous catalysis,[4b,5c,i] 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,[5a-f] cobalt[5g-j] , and nickel.[5k-q] In contrast, Markovnikov olefin hydrosilylation catalysts are uncommon, and the synthetic capabilities of the reactions are presently limited.[5e,6] Hayashi's discovery that Pd-MOP complexes catalyze highly enantioselective Markovnikov hydrosilylation with trichlorosilane[7a-e] was a milestone achievement in asymmetric catalysis.[8] While 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 appreci-

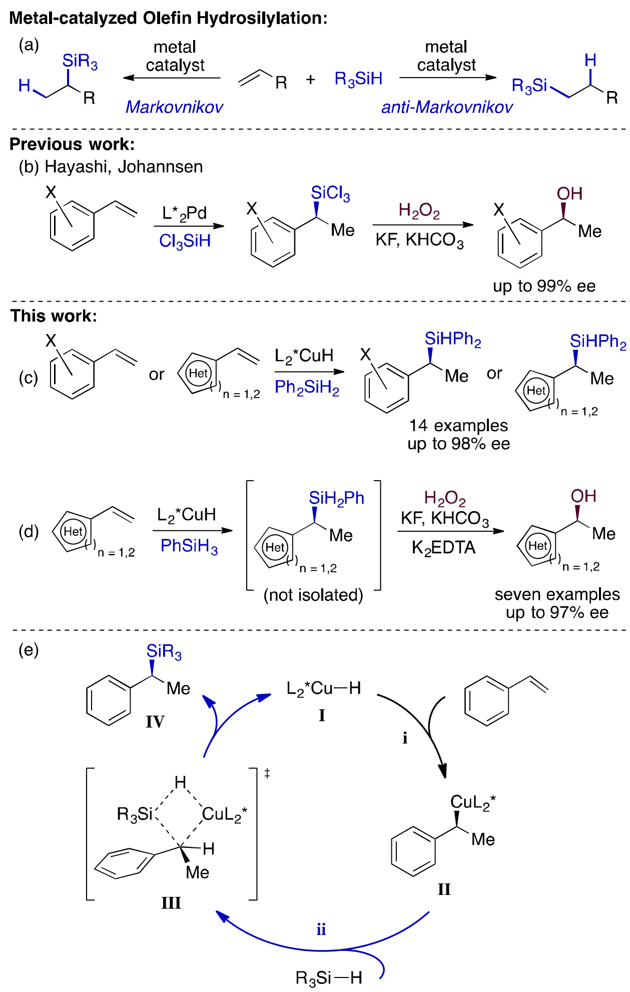
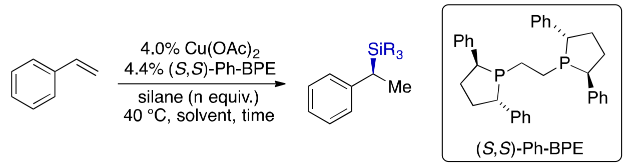


Figure 1. [a]Metal-catalyzed hydrosilylation of olefins; [b]Pd-catalyzed asymmetric Markovnikov hydrosilylation of

vinylarenes; [c,d]CuH-catalyzed asymmetric hydrosilylation of styrenes; [e]Proposed mechanism for the hydrosilylation.

Table 1. Optimization of the CuH-catalyzed Hydrosilylation of Styrene.



entry[a]	silane	n	solvent (0.5 M)	time (d)	product (%)[b]	ee (%)[c]
1	Ph_2SiH_2	3.0	THF	2	86	79
2	Ph_2SiH_2	3.0	dioxane	2	92	82
3	Ph_2SiH_2	3.0	MTBE	2	92	88
4	Ph_2SiH_2	1.2	THF	5	24	70
5	Ph_2SiH_2	1.2	2-Me-THF	5	17	72
6	Ph_2SiH_2	1.2	toluene	5	23	76
7	Ph_2SiH_2	3.6	none	2	79	**94**
8[d]	$PhSiH_3$	3.0	THF	2	91[e]	**96**
9	Me_2PhSiH	3.0	THF	2	–	nd
10	$Me(EtO)_2SiH$	3.0	THF	2	–	nd

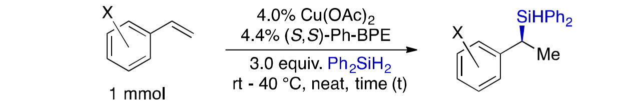
[a]Unless otherwise noted, reactions were conducted on 0.5 mmol scale; [b]Unless otherwise noted, yields were determined by GC with dodecane internal standard; [c]Determined by chiral HPLC; [d]0.2 mmol scale; [e]Isolated yield.

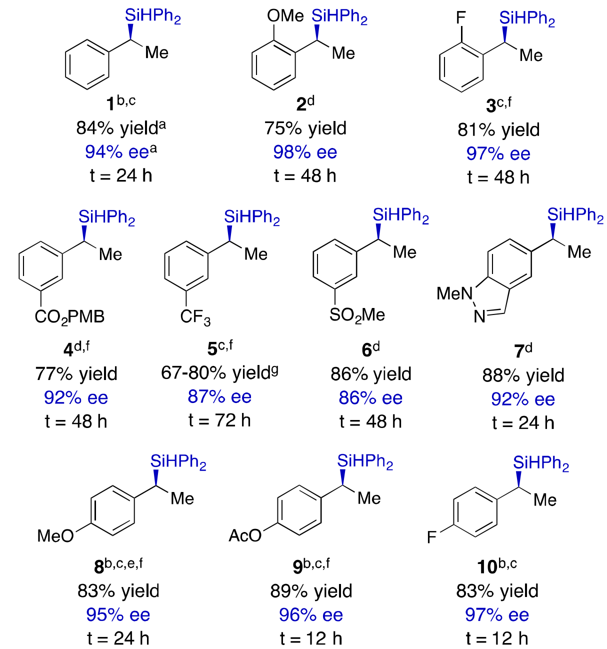
ably Lewis-basic olefins, presumably because they are incompatible with the sensitive trichlorosilyl group.

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[9a-e] with an active chiral copper hydride catalyst (**I**, Figure 1, e, step i). We reasoned that an asymmetric Markovnikov hydrosilylation could be achieved if the alkylcopper species **II** (Fig 1, e) could undergo stereoretentive transmetallation with a hydrosilane (Fig 1, e, step ii).[10,11a,b] The hypothesized transformation would constitute an attractive alternative to Pd catalysis if it could provide isolable silanes and silane-derivatives with high generality using readily available catalyst precursors. However, to our knowledge, copper-catalyzed olefin hydrosilylation has not been described in the primary literature,[12] despite pervasive use of hydrosilane reductants in copper hydride catalysis.[9a,13a-c] This observation suggested that the proposed metathesis step could be challenging and that competitive side reactions might present challenges.

With styrene as our model substrate, we observed clean formation of the desired Markovnikov hydrosilylation product using either $PhSiH_3$ or Ph_2SiH_2, but the enantioselectivity obtained with Ph_2SiH_2 was modest (Table 1, entry 1). The selectivity with Ph_2SiH_2 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

Table 2. Hydrosilylation of Vinylarenes.





[a]Unless otherwise noted, yields and enantiomeric excesses are the averages for two runs; [b]Reaction was conducted with 2.0 mol% $Cu(OAc)_2$ and 2.2 mol% (*S*,*S*)-Ph-BPE; [c]Reaction mixture was stirred in a 40 °C oil bath; [d]Reaction was conducted at ambient temperature; [e]1.5 equiv. silane were used; [f]Enantiomeric excesses were determined for the respective silanol derivatives;[14] [g]Extrema are the results from two experiments.[14]

key factor for obtaining high levels of enantioselectivity, particularly since the hydrocupration step is known to be highly enantioselective[9a-e] in a variety of solvents. This notion was further supported by the observation that the more reactive $PhSiH_3$ 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 Ph_2SiH_2 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

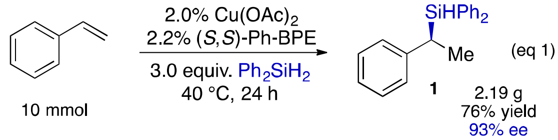
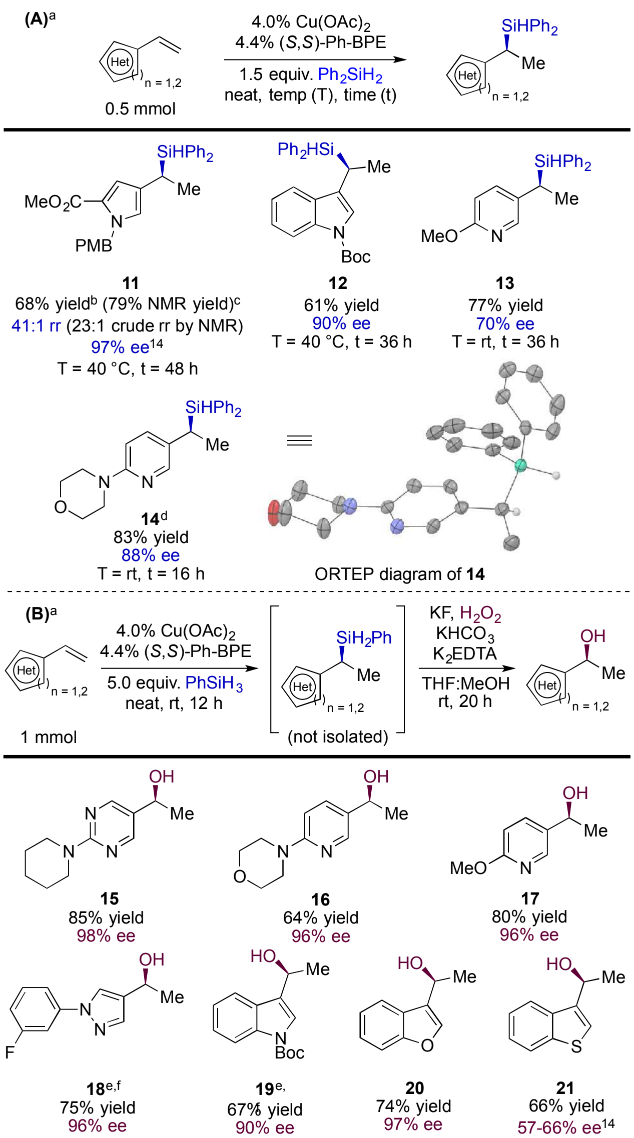


Table 3. Hydrosilylation of Vinyl Heterocycles.



[a]Yields and enantiomeric excess values are averages from two runs; [b]Isolated yield pertains to the regioisomer mixture; [c]NMR yield pertains to the major regioisomer; [d]2.0 equiv. silane used; [e]MTBE used as the solvent; [f]Reaction run for 36 h.

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 3, A) were formed with high enantioselectivity, whereas a less electronically biased heterocycle gave product with modest asymmetric induction (example **13**, Table 3, A). These results mirrored the enantioselectivity trends evident in Table 2 and those

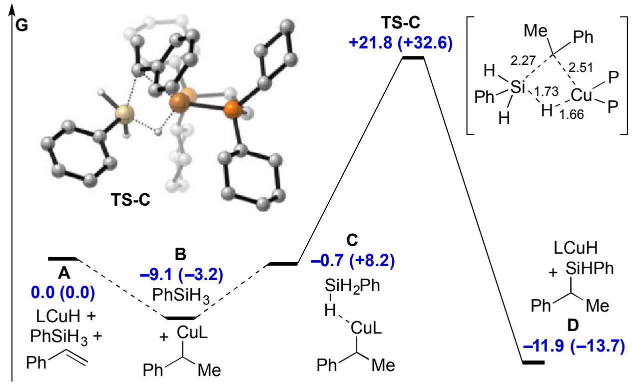


Figure 2. DFT model for copper-catalyzed hydrosilylation of styrene (L = DCyPE). M06/6-311+G(d,p) SDD/SMD(THF)//B3LYP/6-31G(d)-SDD Gibbs free energy values displayed in kcal/mol. Corresponding PBE0/6-311+G(d,p)-SDD/SMD(THF)//B3LYP/6-31G(d)-SDD values shown in brackets. Key bond distances shown in units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

our group has observed in the CuH-catalyzed hydroamination of vinylarenes.[9e]

A crystal structure of **14** (Table 3, A) showed the absolute stereochemistry of the major enantiomer to be (*S*), which is consistent with the mechanism shown in Figure 1, e.[9c,d] 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.[9c,d] We considered two mechanistic hypotheses that might account for these discrepancies: one posits a racemization step occurring after hydrocupration (i.e., affecting intermediate **II** of Figure 1, e); 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 transmetallation (Figure 1, e, step ii), e.g., by employing the more reactive $PhSiH_3$, would result in higher enantioselectivity. $PhSiH_3$ would also be ideal for derivatization attempts using crude products, since it could be easily evaporated beforehand. Hydrosilylation with $PhSiH_3$ 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 3, B), which suppresses copper-catalyzed disproportionation of hydrogen peroxide. The enantioinduction obtained with $PhSiH_3$ was indeed broadly superior to that observed with Ph_2SiH_2 and further appeared to be less sensitive to substrate electronic bias (compare **16**, **17** [Table 3, B] and **13** [Table 3, A]).

To sharpen our mechanistic hypothesis,[16] we performed DFT calculations on the CuH-catalyzed hydrosilylation of styrene with $PhSiH_3$ using bis(dicyclohexylphosphino)ethane (DCyPE) as the model ligand (Figure 2). After hydrocupration, we located a σ-complex **C** upon interaction of copper with phenylsilane. From here, σ-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 commerically available catalyst-precursors, and enables the functionalization of a variety of medicinally relevant heterocyclic olefins. While our mechanistic hypotheses remain speculative at this time, we believe they provide a useful framework for rationalizing the observed selectivity trends. We also believe that a thorough mechanistic investiation will be of value to our group's ongoing efforts to develop new CuH-catalyzed transformations.

ASSOCIATED CONTENT

Supporting Information. The Supporting Information is available free of charge on the ACS Publications website. Experimental procedures and characterization data for all compounds (PDF, CIF)

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Author Contribution

†M.T.P. and J.S.B. made equal contributions to this work.

Notes

The authors declare no competing financial interests.

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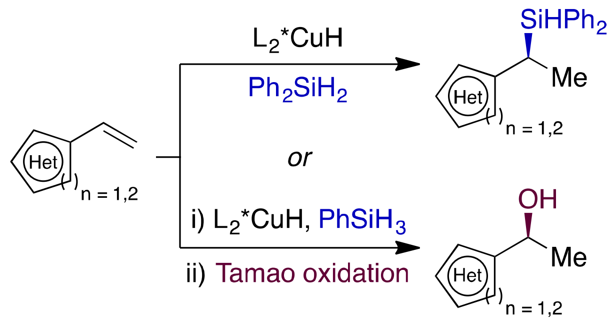

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