Communication

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J. Am. Chem. Soc., **Just Accepted Manuscript** • DOI: 10.1021/jacs.7b11707 • Publication Date (Web): 04 Dec 2017

Synthesis of Enantioenriched Allylic Silanes via Nickel-Catalyzed Reductive Cross-Coupling

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Supporting Information Placeholder

ABSTRACT: An asymmetric Ni-catalyzed reductive cross-coupling has been developed to prepare enantioenriched allylic silanes. This enantioselective reductive alkenylation proceeds under mild conditions and exhibits good functional group tolerance. The chiral allylic silanes prepared here undergo a variety of stereospecific transformations, including intramolecular Hosomi-Sakurai reactions, to set vicinal stereogenic centers with excellent transfer of chirality.

Organosilanes are valuable organic materials with applications in medicinal chemistry,[1] materials science,[2] and as reagents for organic synthesis.[3] In particular, chiral allylic silanes are versatile synthetic reagents that engage in a variety of highly stereoselective reactions. For example, the Hosomi-Sakurai reaction[4] is a powerful method for C–C bond formation that provides homoallylic alcohols with excellent transfer of chirality when enantioenriched allylic silanes are used.[5,6] Despite the utility of this and related transformations, the enantioselective preparation of chiral allylic silanes often requires multistep sequences, or the incorporation of specific functional groups to direct the formation of the C(sp^3)-Si bond. Here we describe a Ni-catalyzed asymmetric reductive cross-coupling to directly prepare enantioenriched allylic silanes from simple, readily available building blocks (Figure 1). The resulting chiral allylic silanes undergo a variety of post-coupling transformations with high levels of chirality transfer.

Chiral allylic silanes are most commonly prepared through diastereoselective or stereospecific transformations,[7] which include the Claisen rearrangement of vinyl silanes,[8] bis-silylation of allylic alcohols,[9] silylene insertion of allylic ethers,[10] and the alkenylation of 1,1-silaboronates.[11] In addition, several enantioselective transition metal-catalyzed reactions have been developed, including the hydrosilylation of dienes,[12] the silylboration of allenes[13], the insertion of metal carbenoids into Si-H bonds,[14] and conjugate addition[15] and

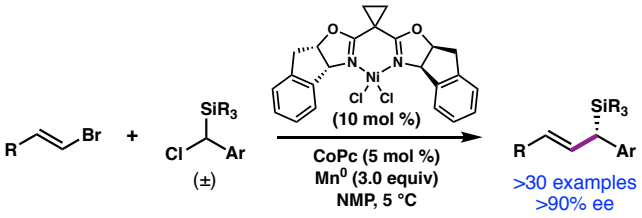
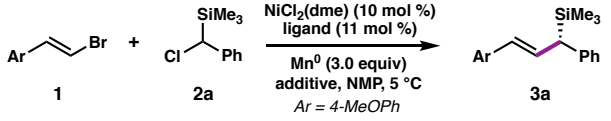


Figure 1. Synthesis of Chiral Allylic Silanes by Enantioselective Ni-Catalyzed Reductive Cross-Coupling

allylic substitution[16] reactions. Asymmetric transition metal-catalyzed cross-coupling, in which the critical silicon-bearing C(sp^3) stereogenic center is established in the C–C bond forming step, represents an alternative and highly modular approach to chiral allylic silanes. Indeed, the first synthesis of an enantioenriched chiral allylic silane was the Pd-catalyzed asymmetric cross-coupling between α-(trimethylsilyl)benzylmagnesium bromide and 1-bromo-1-propene reported by Kumada and coworkers in 1982.[5a] However, this method employs Grignard reagents as coupling partners, which are not stable to long-term storage and decreases the functional group compatibility of the reaction. We envisioned that a Ni-catalyzed asymmetric reductive alkenylation would address this limitation,[17] in that the required (chlorobenzyl)silanes are bench stable compounds and these reactions typically exhibit good functional group tolerance. Thus, a Ni-catalyzed reductive alkenylation could provide chiral allylic silanes that were not readily accessible by other methods.

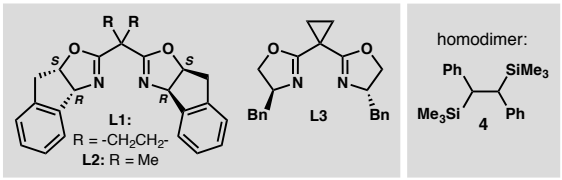
Our investigations began with the coupling between (E)-1-(2-bromovinyl)-4-methoxybenzene (**1**) and (chloro(phenyl)methyl)trimethylsilane (**2a**) using chiral bis(oxazoline) ligand **L1**, which was optimal in our previously developed enantioselective reductive alkenylation reaction (Table 1).[14] A screen of reaction parameters revealed that when the reaction is conducted at 5 °C with with *N*-methyl-2-pyrrolidone (NMP) as the solvent,[18] allylic silane **3a** was formed in low yield, but with high enantioselectivity (entry

Table 1. Optimization of Allylic Silanes



entry[a]	ligand	equiv **1**	additive[b]	yield **4** (%)[c]	yield **3a** (%)[c]	ee **3a** (%)[d]
1	L1	1.0	none	26	20	96
2	L1	1.0	NaI	22	26	97
3	L1	1.0	CoPc	13	51	96
4	L1	1.5	CoPc	9	64	97
5	L1	2.0	CoPc	8	69	97
6	L2	2.0	CoPc	22	14	41
7	L3	2.0	CoPc	9	49	–90
8[e]	L1	2.0	CoPc	9	70	97

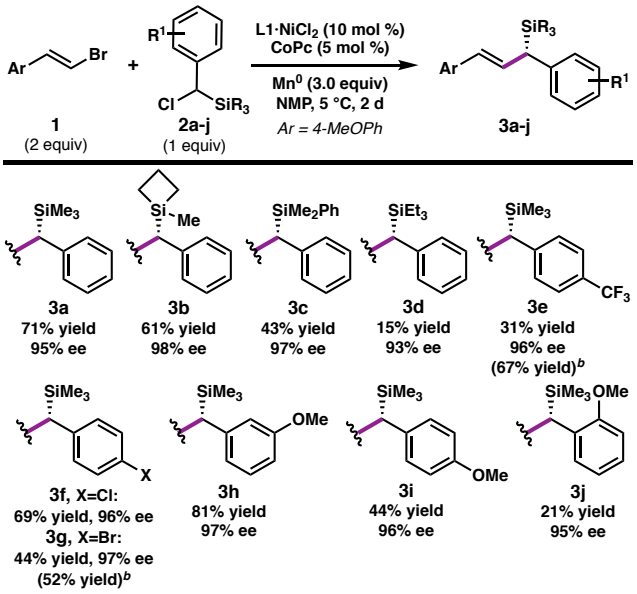
[a]Reactions conducted under N_2 on 0.1 mmol scale for 48 h. [b]NaI = 0.5 equiv; CoPc = 5 mol %. [c]Determined by ^{1}H NMR versus an internal standard. [d]Determined by SFC using a chiral stationary phase. [e]10 mol % preformed (3*R*,8*S*)-**L1**·$NiCl_2$ complex used.



1). We hypothesized that the presence of the bulky silyl group impeded the oxidative addition of **2a** to the Ni catalyst. The addition of cobalt(II) phthalocyanine (CoPc), a co-catalyst that enables the Ni-catalyzed cross-coupling of benzyl mesylates by facilitating alkyl radical generation,[19] doubled the yield of **3a** (entry 3). The yield of **3a** increased when excess vinyl bromide was used (entries 3–5); since the use of 2.0 equiv **1** proved most generally robust across a range of substrates, these conditions were used to evaluate the scope of the reaction (see Tables 2 and 3). A screen of other bis(oxazoline) ligands, e.g. **L2** and **L3**, determined that **L1** provided the highest enantioselectivity (entries 6–7). The use of isolated complex **L1**·$NiCl_2$ gave **3a** in comparable yield to the in situ generated catalyst (entry 8). Control experiments confirmed that $NiCl_2$(dme), ligand, and Mn^0 are required to form **3a**.[15] To demonstrate scalability, the cross-coupling was conducted on a 6.0 mmol scale, delivering 1.3 g of **3a** in 74% yield and 97% ee.

With the optimized conditions in hand, the scope of the silane was investigated (Table 2). Whereas strained silacyclobutane[20] **3b** was prepared in good yield and excellent ee, the corresponding triethylsilane **3d** was formed in poor yield, presumably due to the increased steric encumbrance at silicon. Substrates bearing either electron-withdrawing or electron-donating groups on the arene cross-coupled with universally high ee; however, in some cases the yield was diminished due to instability of the products (**3e**, **3g**). The presence of an *ortho* substituent on the arene also decreased the yield of the cross-coupling product (**3j**).

Table 2. Chlorobenzyl Silane Scope[a]



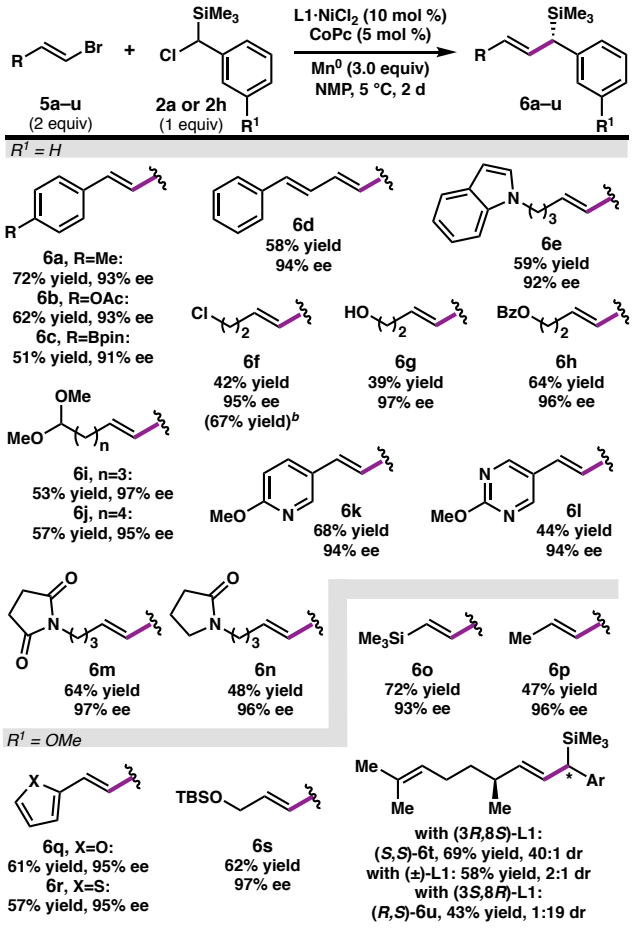
[a]Reactions conducted on 0.2 mmol scale under N_2. Isolated yields; ee is determined by SFC using a chiral stationary phase. [b]Yield determined by ^{1}NMR versus an internal standard.

The reaction tolerates a diverse array of functional groups on the alkenyl bromide partner (Table 3),[21] including aryl boronates (**6c**), esters (**6b**, **6h**), imides (**6m**), amides (**6n**), alkenyl silanes (**6o**), and alkyl halides (**6f**). For greasy substrates, *m*-methoxy silane **2h** was used as the coupling partner to facilitate product purification (**6o**–**6u**). Alkyl-substituted alkenyl bromides performed comparably to styrenyl bromides; however, a limitation of the reaction is that *Z*-alkenes and tri- and tetra-substituted alkenyl bromides failed to react. By changing which enantiomer of **L1** is employed, diastereomeric polyenes **6t** and **6u** were prepared, although the yield is decreased with the mismatched (3*S*,8*R*)-**L1** catalyst. Finally, alkenyl bromides bearing furan (**6q**), thiophene (**6r**), pyridine (**6k**), pyrimidine (**6l**), and indole (**6e**) heterocycles could be cross-coupled, giving the corresponding allylic silanes in high ee. Functional groups that were not well tolerated include aldehydes and nitriles.[22]

Although halide electrophiles were the primary focus of this study, oxygen-based electrophiles were also evaluated. We were pleased to find that mesylate **7** provided **3a** in 45% yield and 92% ee; the lower yield was due to incomplete conversion of the starting material (Scheme 1a). Enol triflate **8** underwent cross-coupling to afford **6a** in 57% yield, again with excellent enantioselectivity (Scheme 1b). Although the

yields were modest, we note that these reactions were conducted under the conditions developed for the organic halides with minimal re-optimization.

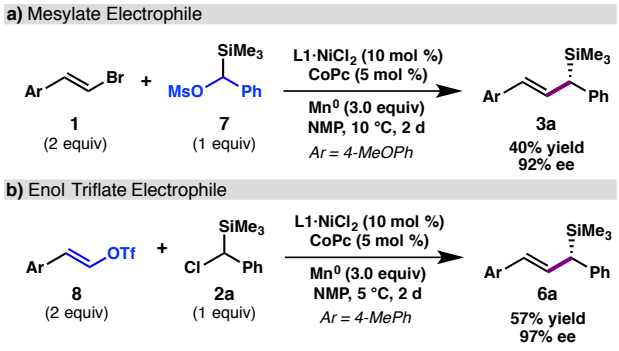
Table 3. Vinyl Bromide Scope[a]



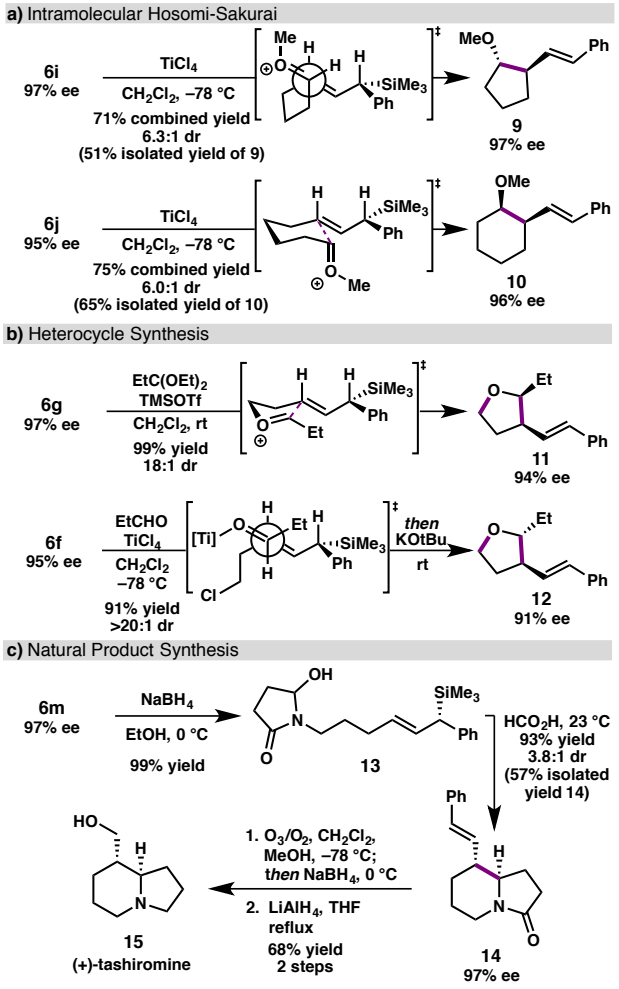
[a]Reactions conducted on 0.2 mmol scale under N_2. Isolated yields are provided; ee is determined by SFC or HPLC using a chiral stationary phase. [b]Yield determined by ^{1}NMR versus an internal standard.

This reductive cross-coupling provides rapid access to functionalized chiral allylic silanes that are useful in a variety of synthetic transformations.[23,24] For example, allylic silanes **6i** and **6j**, which contain pendant acetals, undergo stereospecific $TiCl_4$-mediated intramolecular cyclization to form the 5- and 6-membered rings **9** and **10**, respectively (Scheme 2a). The observed absolute and relative stereochemistry is consistent with an *anti*-S_E' mode of addition, which gives rise to the *trans*-substituted 5-membered ring and the *cis*-substituted 6-membered ring.[25,26,27] Either the 2,3-*cis* or 2,3-*trans* tetrahydrofurans can be prepared by Lewis-acid mediated cyclizations of alcohol **6g** or chloride **6f**, respectively; both proceed with excellent transfer of chirality (Scheme 2b).[5b,28] The utility of the method was further demonstrated in a concise enantioselective synthesis of (+)-tashiromine (Scheme 2c).[29] Sodium borohydride reduction of imide **6m** provided aminal **13**, which upon exposure to formic acidcyclized to form bicycle **14** in 93% yield as a 3.8:1 mixture of diastereomers.[30] The major diastereomer was isolated in 57% yield and 97% ee. Ozonolysis and reduction of the amide provided (+)-tashiromine.

Scheme 1. Reactions of Oxygen-Based Electrophiles



Scheme 2. Stereospecific Reactions of Chiral Allylic Silanes



In summary, a highly enantioselective cross-coupling reaction has been developed for the preparation of chiral allylic silanes. The reactions proceed under mild conditions

and tolerate a variety of functional groups. The enantioenriched allylic silanes undergo several stereospecific transformations with high transfer of chirality, which we anticipate will prove useful in an array of synthetic contexts.

ASSOCIATED CONTENT

Experimental procedures, characterization and spectral data for all compounds, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

We thank Dr. Scott Virgil and the Caltech Center for Catalysis and Chemical Synthesis for access to analytical equipment. We also thank Dr. Michael K. Takase and Mr. Lawrence M. Henling for assistance with X-ray crystallography, as well as Dr. Mona Shahgholi and Naseem Torian for assistance with mass spectrometry measurements. Fellowship support was provided by the National Science Foundation (Graduate Research Fellowship, J. L. H., A. H. C., Grant No. DGE-1144469) and Caltech SURF program (Richard H. Cox and John Stauffer Fellowships, C. M. O.). S. E. R. is an American Cancer Society Research Scholar and Heritage Medical Research Institute Investigator. Financial support from the NIH (R35GM118191-01; GM111805-01) is gratefully acknowledged.

REFERENCES

[1] (a) Showell, G. A.; Mills, J. S. *Drug. Discov. Today* **2003**, *8*, 551.(b) Min, G. K.; Hernandez, D.; Skrydstrup, T. *Acc. Chem. Res.* **2013**, *46*, 457. (c) Franz, A. K.; Wilson, S. O. *J. Med. Chem.* **2013**, *56*, 388.

[2] *Organosilicon Chemistry V: From Molecules to Materials*; Auner, N., Weis, J., Eds.; Wiley-VCH: Weinheim, Germany, 2004.

[3] Reviews: (a) Chan, T. H.; Wang, D. *Chem. Rev.* **1992**, *92*, 995. (b) Masse, C. E.; Panek, J. S. *Chem. Rev.* **1995**, *95*, 1293. (c) Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97*, 2063. (d) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, *15*, 3173.

[4] (a) Hosomi, A.; Sakurai, H. *Tetrahedron Lett.* **1976**, *17*, 1295. (b) Hosomi, A.; Endo, M.; Sakurai, H. *Chem. Lett.* **1976**, *5*, 941. (c) Kira, M.; Kobayashi, M.; Sakurai, H. *Tetrahedron Lett.* **1987**, 28,4081. (d) Kira, M.; Sato, K.; Sakaurai, H. *J. Am. Chem. Soc.* **1990**, *112*, 257. (d) Chemler, S. R.; Roush, W. R. *J. Org. Chem.* **1998**, *63*, 3800.

[5] Seminal reports: (a) Hayashi, T.; Konishi, M.; Ito, H.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4962. (b) Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963. (c) Hayashi, T.; Konishi, M.; Okamoto, Y.; Kabeta, K.; Kumada, M. *J. Org. Chem.* **1986**, *51*, 3772.

[6] (a) Jain, N. F.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1996**, *118*, 12475. (b) Hu, T.; Takenaka, N.; Panek, J. S. *J. Am. Chem. Soc.* **1999**, *121*, 9229. (c) Berger, R.; Duff, K.; Leighton, J. L. *J. Am. Chem. Soc.* **2004**, *126*, 5686. (d) Park, P. K.; O'Malley, S. J.; Schmidt, D. R.; Leighton, J. L. *J. Am. Chem. Soc.* **2006**, *128*, 2796. (e) Kim, H.; Ho, S.; Leighton, J. L. *J. Am. Chem. Soc.* **2011**, *133*, 6517.

[7] Recent catalytic asymmetric methods to prepare chiral, non-allylic silanes: (a) Chen, D.; Zhu, D.-X.; Xu, M.-H. *J. Am. Chem. Soc.* **2016**, *138*, 1498. (b) Kan, S. B. J.; Lewis, R. D.; Chen, K.; Arnold, F. H. *Science* **2016**, *354*, 1048. (c) Gribble, Jr., M. W.; Pirnot, M. T.; Bandar, J. S.; Liu, R. Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2017**, *139*, 2192.

[8] (a) Sparks, M. A.; Panek, J. S. *J. Org. Chem.* **1991**, *56*, 3431. (b) Panek, J. S.; Clark, T. D. *J. Org. Chem.* **1992**, *57*, 4323.

[9] Suginome, M.; Matsumoto, A.; Ito, Y. *J. Am. Chem. Soc.* **1996**, *118*, 3061.

[10] Bourque, L. E.; Cleary, P. A.; Woerpel, K. A. *J. Am. Chem. Soc.* **2007**, *129*, 12602.

[11] (a) Binanzer, M.; Fang, G. Y.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2010**, *49*, 4264. (b) Aggarwal, V. K.; Binanzer, M.; Carolina de Ceglie, M.; Gallanti, M.; Glasspoole, B. W.; Kendrick, S. J. F.; Sonawane, R. P.; Vazquez-Romero, A.; Webster, M. P. *Org. Lett.* **2011**, *13*, 1490.

[12] Hayashi, T.; Han, J. W.; Takeda, A.; Tang, J.; Nohmi, K.; Mukaide, K.; Tsuji, H.; Uozumi, Y. *Adv. Synth. Catal.* **2001**, *343*, 279.

[13] Ohmura, T.; Taniguchi, H.; Suginome, M. *J. Am. Chem. Soc.* **2006**, *128*, 13682.

[14] (a) Davies, H. M. L.; Hansen, T.; Rutberg, J.; Bruzinski, P. R. *Tett. Lett.* **1997**, *38*, 1741. (b) Wu, J.; Chen, Y.; Panek, J. S. *Org. Lett.* **2010**, *12*, 2112.

[15] (a) Shintani, R.; Ichikawa, Y.; Hayashi, T.; Chen, J.; Nakao, Y.; Hiyama, T. *Org. Lett.* **2007**, *9*, 4643. (b) Lee, K.-S.; Wu, H.; Haeffner, F.; Hoveyda, A. H.; *Organomet.* **2012**, *31*, 7823.

[16] Kacprzynski, M. A.; May, T. L.; Kazane, S. A.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2007**, *46*, 4554.

[17] (a) Cherney, A. H.; Reisman, S. E. *J. Am. Chem. Soc.* **2014**, *136*, 14365. (b) Suzuki, N.; Hofstra, J. L.; Poremba, K. E.; Reisman, S. E. *Org. Lett.* **2017**, *19*, 2150.

[18] See Supporting Information for additional reaction optimization data.

[19] Ackerman, L. K. G.; Anka-Lufford, L. L.; Naodovic, M.; Weix, D. J. *Chem. Sci.* **2015**, *6*, 1115.

[20] Matsumoto, K.; Oshima, K.; Utimoto, K. *J. Org. Chem.* **1994**, *59*, 7152.

[21] The absolute stereochemistry of **6c** was determined by single crystal X-ray diffraction. The stereochemical assignment of all other products were made by analogy.

[22] Use of (*E*)-4-(2-bromovinyl)benzaldehyde or (*E*)-4-(2-bromovinyl)benzonitrile provide the cross-coupled product in 0% and 34% yield, respectively.

[23] The allylic silanes can also be employed in standard Hosomi-Sakurai crotylation reactions with excellent transfer of chirality. See Supporting Information for details.

[24] The photoredox-catalyzed trifluoromethylation of chiral allylic silanes has also been reported: Mizuta, S.; Engle, K. M.; Verhoog, S.; Galicia-López, O.; O'Buill, M.; Médebielle, M.; Wheelhouse, K.; Rassias, G.; Thompson, A. L.; Gouverneur, V. *Org. Lett.* **2013**, *15*, 1250.

[25] An S_N2-type mechanism is also consistent with the stereochemical outcome. Denmark, S. E.; Willson, T. M. *J. Am. Chem. Soc.* **1989**, *111*, 3475.

[26] Diastereomers were assigned by comparison to synthetic standards. See Supporting Information.

[27] Wu, J.; Pu, Y.; Panek, J. S. *J. Am. Chem. Soc.* **2012**, *134*, 18440.

[28] Suginome, M.; Iwanami, T.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 6096.

[29] (a) McElhinney, A. D.; Marsden, S. P. *Synlett* **2005**, *16*, 2528. (b) Park, Y.; Schindler, C. S.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2016**, *138*, 14848.

[30] (a) Hiemstra, H.; Sno, M. H. A. M.; Vijn, R. J.; Speckamp, W. N. *J. Org. Chem.* **1985**, *50*, 4014. (b) Hubert, J. C.; Wijnberg, J. B. P. A.; Speckamp, W. N. *Tetrahedron* **1975**, *31*, 1437.

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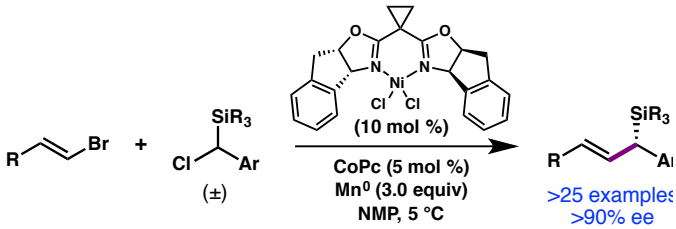

stereoconvergent reductive alkenylation