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Asymmetric Catalysis

Copper-Catalyzed Enantio- and Diastereoselective Addition of Silicon Nucleophiles to 3,3-Disubstituted Cyclopropenes

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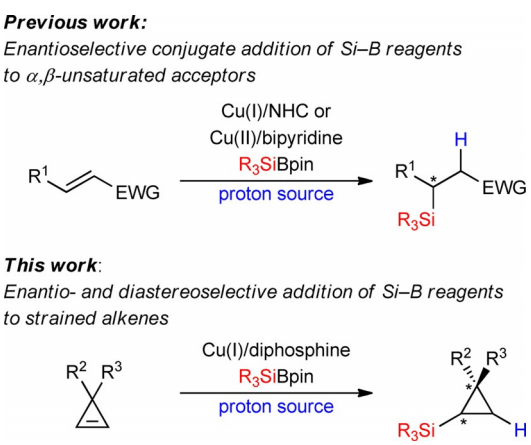
Abstract: A highly stereocontrolled *syn*-addition of silicon nucleophiles across cyclopropenes with two different geminal substituents at C3 is reported. Diastereomeric ratios are excellent throughout (d.r. $\geq$ 98:2) and enantiomeric excesses usually higher than 90%, even reaching 99%. This copper-catalyzed C–Si bond formation closes the gap of the direct synthesis of α-chiral cyclopropylsilanes.

Silylboronic acid esters are highly useful silicon pronucleophiles which have had significant impact on synthetic silicon chemistry.[1] A broad variety of enantioselective C–Si bond formations can be achieved by using these Si–B reagents,[2] and their copper-catalyzed addition across α,β-unsaturated acceptors is a prominent example (Scheme 1, top).[3] Cu^{I}-NHC[4] (NHC = N-heterocyclic carbene) as well as Cu^{II}-bipyridine[5] complexes do promote these reactions with high fidelity. A related enantioselective addition to strained alkenes, such as cyclopropenes, is not known to date (Scheme 1, bottom).[6,7] The resulting silylated cyclopropanes are versatile building blocks in organic synthesis,[8] yet is their direct preparation by C–Si bond formation at an existing cyclopropane skeleton rare.[9–12] Gevorgyan and co-workers developed palladium- and platinum-catalyzed diastereoselective insertion reactions of cyclopropenes into Si–Sn and Si–H bonds, respectively.[9] Established methods therefore start with silicon-containing substrates,[13] and a common method is the cyclopropanation of vinylsilanes.[14] A fascinating approach by Ito, Sawamura, and co-workers involving a regioselective copper-catalyzed borylation of vinylsilanes containing an allylic leaving group by a 3-*exo-tet* ring closure stands out.[15] The idea to access silylated cyclopropanes from cyclopropenes was inspired by Marek's[16] and, in particular, Tortosa's[17] work. Tortosa and co-workers have accomplished a copper-catalyzed desymmetrization of cyclopropenes by borylation.[17] We report here a highly stereoselective silylation of cyclopropenes without the aid of a directing group (Scheme 1, bottom).[18]



Scheme 1. Copper-catalyzed enantioselective addition of Si–B reagents across activated alkenes. EWG = electron-withdrawing group. R_3Si = triorganosilyl.

We started our investigation by reacting 3-phenyl-3-methylcyclopropene (**1a**) with $Me_2PhSiBpin$ (**2a**)[19a] (1.5 equiv) in the presence of $Cu(CH_3CN)_4PF_6$ as the copper precatalyst in THF at 0 °C (Table 1). NaO*t*Bu (0.5 equiv) was used as an alkoxide base and MeOH (3.0 equiv) as a proton source (see the Supporting Information for the complete set of optimization data). With no ancillary ligand, almost no conversion of the cyclopropene was seen (< 5%, entry 1). This situation changed completely in the presence of bidentate phosphine ligands. Excellent diastereoselectivity was obtained with binap ligands **L1**–**L3**, and the enantioinduction increased with the steric demand of the PAr_2 groups (entries 2–4). This high level of stereocontrol could not be further improved by changing the solvent to toluene or by lowering the reaction temperature to −20 °C (entries 5 and 6). A similar outcome was found with segphos ligands **L4** and **L5** (entries 7 and 8), and we eventually continued with **L5**, which led to the formation of the silylated cyclopropane **3aa** in good yield with a diastereomeric ratio (d.r.) $\geq$ 98:2 and an enantiomeric excess (*ee*) of 97%.

We then examined the substitution pattern of the cyclopropene (**1a**–**s**, Scheme 2). Yields were generally good, and the level of enantioselection was consistently high. 3-Arylated cyclopropenes bearing a substituent in the *para* or/and *meta* position(s) were tested, and it was found that the X group did

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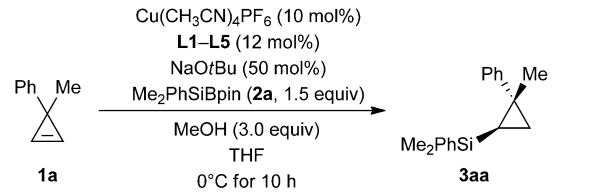
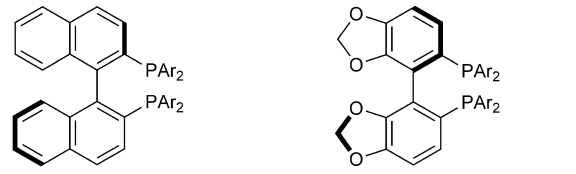
Table 1. Selected examples of the optimization reactions.[a]

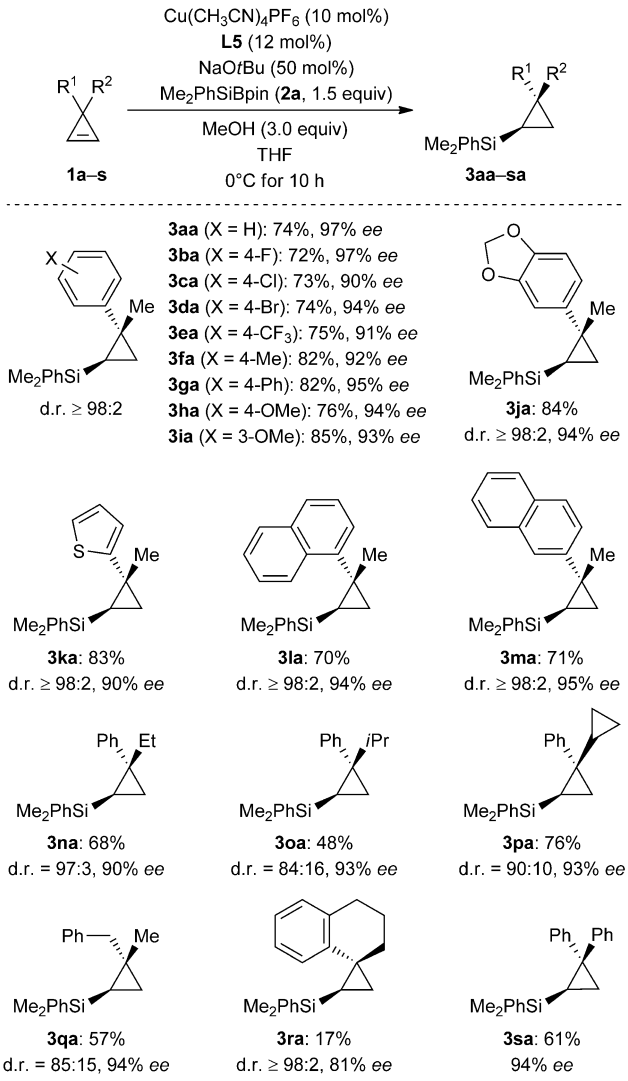




L1 (Ar = Ph): (*R*)-binap
L2 (Ar = 4-Tol): (*R*)-Tol-binap
L3 (Ar = 3,5-Xylyl): (*R*)-Xyl-binap
L4 (Ar = Ph): (*R*)-segphos
L5 (Ar = 3,5-Xylyl): (*R*)-DM-segphos

Entry	Copper/Ligand	Yield [%]	d.r.[b]	*ee* [%][c]
1	$Cu(CH_3CN)_4PF_6$	n.d.	–	–
2	$Cu(CH_3CN)_4PF_6$/**L1**	71	≥98:2	80
3	$Cu(CH_3CN)_4PF_6$/**L2**	73	≥98:2	90
4	$Cu(CH_3CN)_4PF_6$/**L3**	73	≥98:2	96
5[d]	$Cu(CH_3CN)_4PF_6$/**L3**	81	96:4	84
6[e]	$Cu(CH_3CN)_4PF_6$/**L3**	74	≥98:2	92
7	$Cu(CH_3CN)_4PF_6$/**L4**	73	97:3	92
8	$Cu(CH_3CN)_4PF_6$/**L5**	74	≥98:2	97

[a] All reactions were performed on a 0.20 mmol scale with the isolated yield determined after flash chromatography on silica gel. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis on a chiral stationary phase. [d] Toluene instead of THF. [e] Run at −20 °C. n.d. = not determined. binap = 2,2′-bis(diphenylphosphanyl)-1,1′-binaphthyl. sephos = 5,5′-bis(diphenylphosphanyl)-4,4′-bi-1,3-benzodioxol.

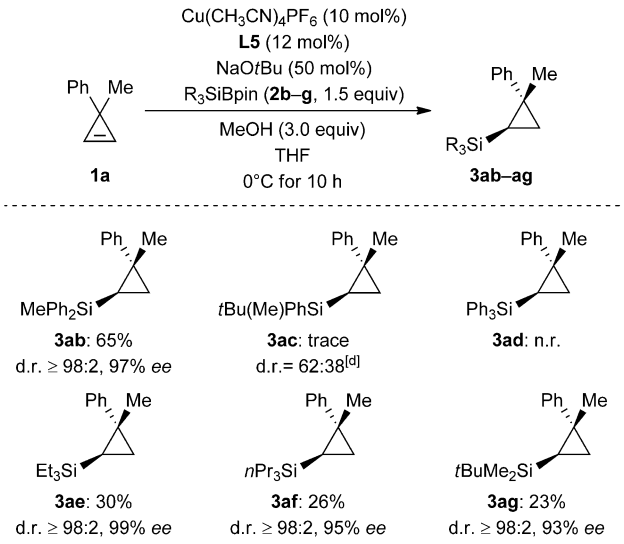


Scheme 2. Scope I: Variation of the cyclopropene.[a–c] [a] All reactions were performed on a 0.20 mmol scale with the isolated yield determined after flash chromatography on silica gel. [b] Diastereomeric ratios determined by ^{1}H NMR analysis. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phases.

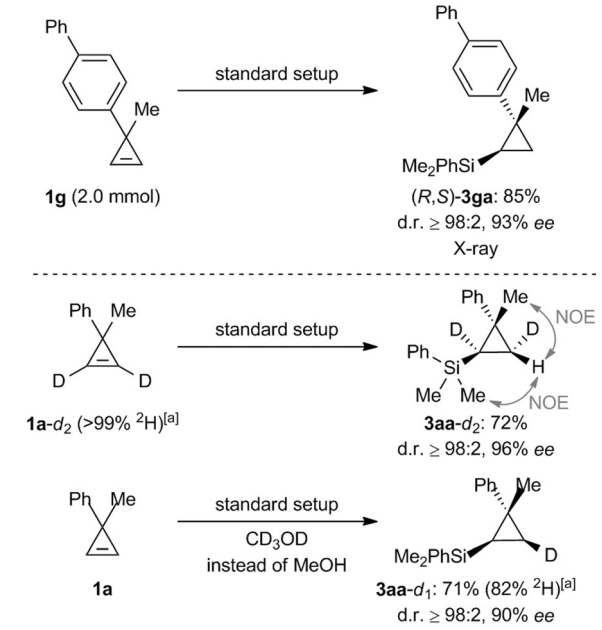
not exert any electronic effect on either yield or stereoselectivity (**1a–j**→**3aa–ja**); the silylated cyclopropanes were all isolated as single diastereomers (d.r. ≥ 98:2). Likewise, a thien-2-yl as well as naphthyl groups were tolerated (**1k–m**→**3ka–ma**). Bulkier alkyl groups instead of the methyl group at C3 of the cyclopropene had no influence on the enantiofacial selectivity, but a little on diastereoselectivity; yields were lower with increasing steric demand (**1n–p**→**3na–pa**). These results imply that the diastereoselectivity is affected by the steric discrimination of geminal substituents (Aryl/Me vs. Ph/Alkyl). This observation was also made when replacing the phenyl by a benzyl group (Ph/Me versus Bn/Me); the diastereomeric ratio dropped from ≥98:2 to 85:15 (**1q**→**3qa**). In turn, a spiro derivative reacted with high diastereoselectivity but in low yield (**1r**→**3ra**). For completion, the 3,3-diphenyl-substituted cyclopropene afforded the silylated cyclopropane in good yield and with high *ee* (**1s**→**3sa**).

We next probed the transfer of different silyl groups from silylboronic acid esters $R_3SiBpin$ **2b–g**[19] to model compound **1a** (Scheme 3). It became quickly clear at the size of the silyl group substantially influences the yield. $MePh_2SiBpin$ (**2b**) furnished acceptable 65% yield (**1a**→**3ab**). The enantiomeric excess was 97% *ee* and was even higher with another substituent in the *para* position (not shown; additional substrates in the Supporting Information). *t*Bu(Me)PhSiBpin (**2c**) did yield trace amounts of **3ac**, and the diastereomeric ratio of 62:38 is due to the stereogenicity at the silicon atom; no formation of **3ad** was seen with $Ph_3SiBpin$ (**2d**). Trialkylsubstituted Si–B reagents **2e–g**,[19b] even with a *t*Bu group attached to the silicon atom, reacted in mediocre yields. Enantio- and diastereocontrol were excellent though.

Running the reaction **1g**→**3ga** on a tenfold scale was neither detrimental to yield nor stereoselectivity (Scheme 4, top). From this sample, single crystals suitable for X-ray diffraction were obtained.[20] The absolute and relative configuration of **3ga** was found to be *R,S*. The stereochemistry of the other silylated cyclopropanes was assigned accordingly. Also, oxidative degradation of the C–Si bond in (*R,S*)-**3ga** employing the Tamao–Fleming protocol was attempted.[21] This transformation is usually low yielding due to competing ring opening.[22] The



Scheme 3. Scope II: Variation of silylboronic acid ester.[a–c] [a] All reactions were performed on a 0.20 mmol scale with the isolated yield determined after flash chromatography on silica gel. [b] Diastereomeric ratios determined by ^{1}H NMR analysis. [c] Enantiomeric excesses determined by HPLC analysis on chiral stationary phases. [d] Diastereomeric ratio determined by GLC and GC-MS analysis. n.r. = no reaction.

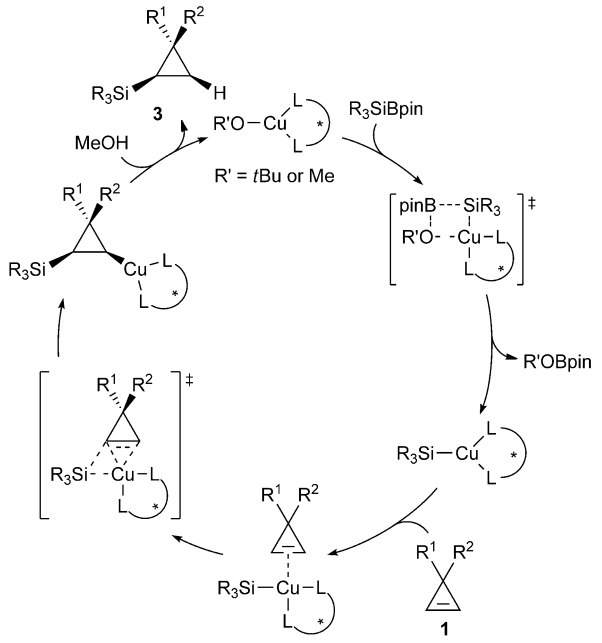


Scheme 4. Determination of the absolute configuration (top) and deuterium-labeling experiments (bottom). [a] Deuteration grade estimated by NMR analysis.

corresponding alcohol was obtained in 6% yield with d.r. ≥ 98:2 and 92% *ee* under retention of the configuration (see the Supporting Information for details).

To learn about the stereochemical course of the copper-catalyzed addition of the silicon nucleophile across the C–C double bond, we subjected dideuterated cyclopropene **1a**-d_2[23] (> 99% ^{2}H) to the standard setup (Scheme 4, bottom). Cyclopropane **3aa**-d_2 did form in 72% yield with excellent diastereo- (d.r. ≥ 98:2) and enantioselectivity (96% *ee*). The *syn*-addition of the silylcopper intermediate to the cyclopropene was confirmed by 2D NOE measurements between the ring proton in **3aa**-d_2 and the methyl groups on the ring and the silicon atom (see the Supporting Information for details). To gain further mechanistic insight, an additional deuterium-labeling experiment was performed (**1a** → **3aa**-d_1, Scheme 4, bottom). MeOH was replaced by CD_3OD as an exogenous proton source, and **3aa**-d_1 was isolated in 71% yield and 82% deuterium incorporation. This corroborates that the proton originates from the alcohol additives.

Based on these observations and literature precedence,[1,2] we propose the catalytic cycle shown in Scheme 5. The silicon nucleophile (= silylcopper complex) is generated by transmetalation of the Si–B linkage at the Cu–O bond of the in situ



Scheme 5. Proposed mechanism.

formed copper alkoxide. Cyclopropene **1** then coordinates to copper to form a π-complex followed by *syn*-addition of the Cu–Si bond across the strained alkene.[24] Diastereofacial selectivity is likely controlled by sterics with the bond formation occurring on the side of smaller R^2 (usually methyl) and opposite to larger R^1 (usually aryl). Protonation of the Cu–C bond with MeOH releases the cyclopropane **3** and closes the catalytic cycle.

In summary, we described here the first example of a highly enantio- and diastereoselective addition of silylboronic acid esters across a broad range of prochiral 3,3-disubstituted cyclopropenes. It is a *syn*-addition that does not rely on a coordinating/directing group. The silyl-substituted cyclopropanes were obtained in good yields and with superb stereoselectivity. Expansion of this methodology is currently underway in our laboratory.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: asymmetric catalysis · boron · copper · silicon · strained molecules

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