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Enantioselective Synthesis of α-Chiral Propargylic Silanes by Copper-Catalyzed 1,4-Selective Addition of Silicon Nucleophiles to Enyne-Type α,β,γ,δ-Unsaturated Acceptors

Wenbin Mao and Martin Oestreich*

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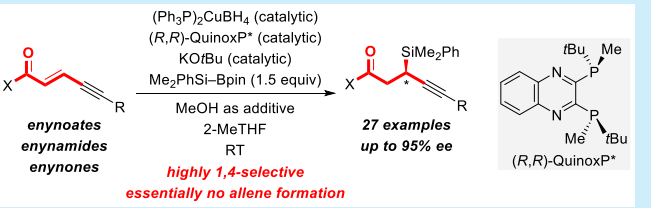
ABSTRACT: A copper-catalyzed deconjugative addition of silicon nucleophiles to a broad range of enyne-type α,β,γ,δ-unsaturated acceptors with high enantiocontrol is reported. The method is 1,4-selective with hardly any formation of the 1,6-adduct. The double-bond geometry is shown to be critical for achieving this chemoselectivity: exclusive 1,4-addition for *E* and predominant 1,6-addition for *Z*. By this, *E*-configured enynoates, enynamides, and enynones have been converted to the corresponding α-chiral propargylic silanes with excellent enantiomeric excesses.



Unlike numerous methods for the enantioselective synthesis of α-chiral allylic silanes,[1] there are essentially no general catalytic procedures to access α-chiral propargylic silanes.[2,3] One reason behind this could be that propargylic substitution typically leads to the allene motif.[4] Significant advances in enantioselective Si–C(sp^3) bond formation with silicon nucleophiles have been made in recent years,[5] particularly based on chiral copper catalysts,[6] in conjunction with Si–B reagents[7] as silicon pronucleophiles.[5] Hoveyda and co-workers had developed 1,4-selective conjugate additions to diene-type α,β,γ,δ-unsaturated acceptors (Scheme 1, top).[8,9] Knowing that 1,4-selective addition to enyne-type α,β,γ,δ-unsaturated acceptors is possible,[10,11] we asked ourselves whether this approach could be turned into an effective way to make α-chiral propargylic silanes (Scheme 1, bottom).[12] Interestingly, the same class of substrates had already been investigated by Xu, Loh, and co-workers yet with exclusive 1,6-selectivity (Scheme 1, bottom).[13] We disclose here a mild and general method for the rapid assembly of α-chiral propargylic silanes by copper-catalyzed 1,4-selective conjugate addition of silylboronic esters to enyne-type α,β,γ,δ-unsaturated acceptors.

We began our study with enynoate (*E*)-**1a** as the model substrate and Me_2PhSi–Bpin (**2a**) as the Si–B reagent (see Table 1). From a ligand screening, (*R*,*R*)-QuinoxP* (**L3**)[14] had emerged as a promising chiral ligand for this transformation, especially with regard to 1,4- over 1,6-selectivity (see Scheme S1 in the Supporting Information). 74% yield of the 1,4-adduct **3aa** with 70% ee, along with a small amount of **4aa**, were obtained in the presence of 5.0 mol % CuCl, 7.5 mol % **L3**, 20 mol % NaO*t*Bu, and 4.0 equiv MeOH in THF at room temperature (Table 1, entry 1). $(Ph_3P)_2CuBH_4$, as a precatalyst, was superior to other typical copper salts, with regard to yield and enantioinduction (Table 1, entries 1–5). The achieved 84% and 83% ee were further improved to 85% yield and 91% ee by changing the solvent from tetrahydrofuran (THF) to 2-MeTHF (Table 1, entry 6); other solvents were less effective (Table 1, entries 7–9). Various attempts with different combinations of base and alcohol additive revealed that KO*t*Bu/MeOH were optimal, affording 85% yield and 92% ee (Table 1, entries 10–14). Significantly lowering the loadings of the catalyst, the ligand, and those of the additives was not detrimental, and the enantiomeric excess remained unchanged at high isolated yield (Table 1, entry 15). Additional control experiments showed that the catalyst and the additives employed in the reaction are needed (see Table S5 in the Supporting Information), yet the reaction proceeded without the chiral ligand **L3** (Table 1, entry 16). Zinc-based silicon nucleophiles[15] $Me_2PhSiZnCl$ and $(Me_2PhSi)_2Zn$[16] did also give the 1,4-adduct regioselectively with good enantiocontrol, but the results were inferior to those obtained with the silylboronic ester (Table 1, entries 17 and 18). $Me_2PhSiLi$ and $Me_2PhSiMgHal$[17] (where Hal = Cl and Br) furnished only trace amounts of the product.

With the optimized conditions in hand, we set out to evaluate the generality of this reaction (Scheme 2, top). Various δ-aryl-substituted enynoates with an electron-donating (**1b**–**1e**) or an electron-withdrawing group (**1i**–**1k**) on the phenyl ring were suitable substrates, giving the corresponding α-chiral propargylic silanes in good to excellent yields with

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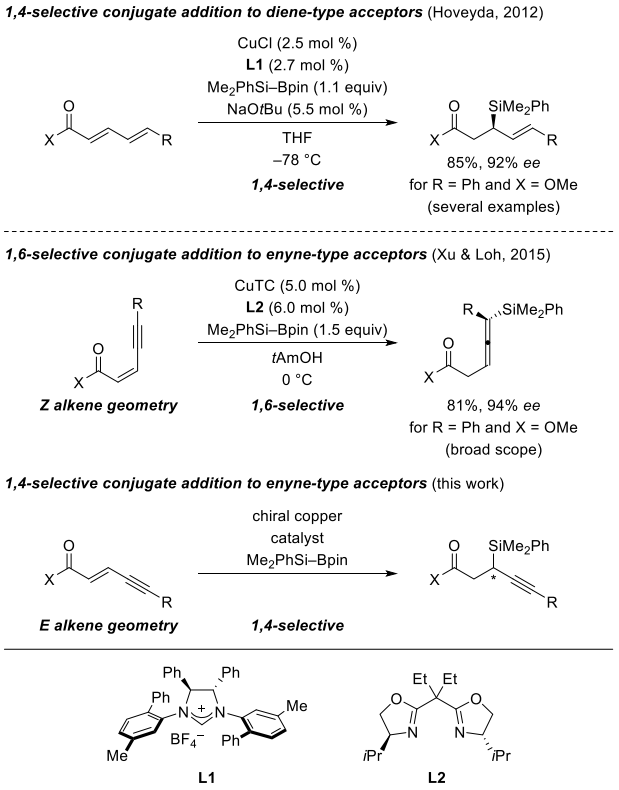
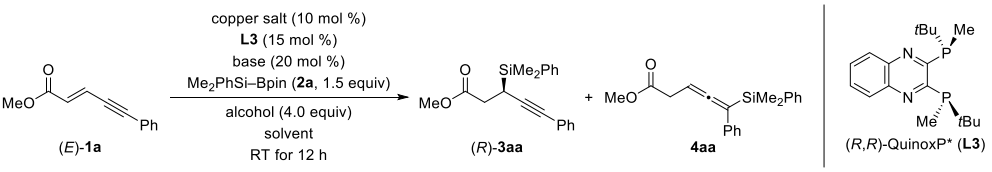
Scheme 1. 1,4-Selectivity versus 1,6-Selectivity in Conjugate Addition of Silicon Nucleophiles to α,β,γ,δ-Unsaturated Acceptors



high levels of enantioselectivity (up to 93% ee). A methyl group in either the *ortho*-, *meta*-, or *para*-position of the phenyl ring had only negligible influence (**1b**–**1d** → **3ba**–**3da**). Good functional-group compatibility was observed with tolerance of halo (**1f**–**1h** → **3fa**–**3ha**), cyano (**1j** → **3ja**), ester (**1k** → **3ka**), and boryl groups (**1l** → **3la**), thereby allowing for subsequent manipulations. Thienyl groups were also tolerated (**1m** and **1n** → **3ma** and **3na**). Enynoates with an alkyl group or a silyl group in the δ position did participate equally well, furnishing the corresponding 1,4-adducts in good yields with slightly lower enantiomeric excesses (**1o**–**1q** → **3oa**–**3qa**). The absolute configuration of **3la** was determined as *R* by X-ray diffraction analysis (see the Supporting Information for details), and all other products were assigned by analogy.

The 1,4-selectivity was excellent throughout for the above acceptors. However, a methyl substituent at the β-C atom completely steered the chemoselectivity toward the 1,6-adduct to yield the allene in 50%, along with recovered starting material with essentially no enantioinduction (**1r** → **4ra**; see the gray box in Scheme 2). Other silylboronic esters such as $MePh_2Si$–Bpin (**2b**) and Ph_3Si–Bpin (**2c**) led to different reaction outcomes (Scheme 2, bottom). While **2b** reacted with lower yield and enantioselectivity compared to **2a** (48%, 78% ee for **3ab** versus 95%, 92% ee for **3aa**), there was no reaction for bulky **2c**. The situation was even worse with Et_3Si–Bpin (**2d**) where both chemoselectivity (1,4:1,6 = 76:24) and enantioinduction (58% ee) were eroded at good yield of **3ad**. This suggests that the substitution pattern of the silyl group and its steric demand greatly influence this reaction.

Table 1. Selected Examples of the Optimization[a]



entry	copper salt	base/alcohol	solvent	1,4:1,6 ratio[b]	yield of **3aa** (%)[c]	ee of **3aa** (%)[d]
1	CuCl	NaO*t*Bu/MeOH	THF	96:4	74	70
2	CuBr	NaO*t*Bu/MeOH	THF	97:3	79	80
3	CuTC	NaO*t*Bu/MeOH	THF	>98:2	71	82
4	CuBr·SMe_2	NaO*t*Bu/MeOH	THF	>98:2	55	81
5	$(Ph_3P)_2CuBH_4$	NaO*t*Bu/MeOH	THF	>98:2	84	83
6	$(Ph_3P)_2CuBH_4$	NaO*t*Bu/MeOH	2-MeTHF	>98:2	85	91
7	$(Ph_3P)_2CuBH_4$	NaO*t*Bu/MeOH	Et_2O	>98:2	80	75
8	$(Ph_3P)_2CuBH_4$	NaO*t*Bu/MeOH	toluene	92:8	42	60
9	$(Ph_3P)_2CuBH_4$	NaO*t*Bu/MeOH	AmylOH	>98:2	33	78
10	$(Ph_3P)_2CuBH_4$	NaO*t*Bu/EtOH	2-MeTHF	>98:2	82	87
11	$(Ph_3P)_2CuBH_4$	NaO*t*Bu/H_2O	2-MeTHF	>98:2	75	88
12	$(Ph_3P)_2CuBH_4$	KO*t*Bu/MeOH	2-MeTHF	>98:2	85	92
13	$(Ph_3P)_2CuBH_4$	LiO*t*Bu/MeOH	2-MeTHF	>98:2	75	89
14	$(Ph_3P)_2CuBH_4$	Et_3N/MeOH	2-MeTHF	>98:2	80	83
15[e]	$(Ph_3P)_2CuBH_4$	KO*t*Bu/MeOH	2-MeTHF	>98:2	95 (95)[f]	92 (92)[f]
16[g]	$(Ph_3P)_2CuBH_4$	KO*t*Bu/MeOH	2-MeTHF	93:7	89	—
17[h]	$(Ph_3P)_2CuBH_4$	—	2-MeTHF	>98:2	45	90
18[i]	$(Ph_3P)_2CuBH_4$	—	2-MeTHF	>98:2	80	80

[a]All reactions were performed on a 0.10 mmol scale. [b]Determined by ^1H NMR spectroscopy. [c]Isolated yield after flash chromatography on silica gel. [d]Determined by HPLC analysis on a chiral stationary phase. [e]0.50 mol % $(Ph_3P)_2CuBH_4$, 0.75 mol % (*R*,*R*)-QuinoxP* (**L3**), 5.0 mol % KO*t*Bu, and 2.0 equiv MeOH were used. [f]Values given in parentheses for reaction on a 1.2 mmol scale. [g]Without ligand **L3**. [h]$Me_2PhSiZnCl$ instead of **2a**. [i]$(Me_2PhSi)_2Zn$ instead of **2a**. CuTC = copper(I) thiophene-2-carboxylate. 2-MeTHF = 2-methyltetrahydrofuran.

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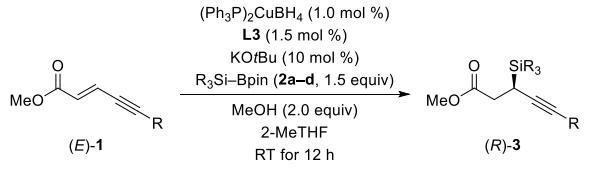
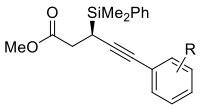
Scheme 2. Enantioselective Deconjugative 1,4-Addition of Silicon Nucleophiles to Enynoates[a]

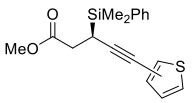


(hetero)aryl substitution



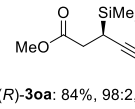
(*R*)-**3ba** (R = 4-Me): 80%, >98:2, 92% ee[b]
(*R*)-**3ca** (R = 3-Me): 76%, >98:2, 92% ee[b]
(*R*)-**3da** (R = 2-Me): 72%, >98:2, 91% ee[b]
(*R*)-**3ea** (R = 4-OMe): 94%, >98:2, 93% ee
(*R*)-**3fa** (R = 4-F): 94%, >98:2, 92% ee
(*R*)-**3ga** (R = 4-Cl): 88%, >98:2, 89% ee[c]
(*R*)-**3ha** (R = 4-Br): 69%, >98:2, 85% ee
(*R*)-**3ia** (R = 4-CF_3): 90%, >98:2, 92% ee
(*R*)-**3ja** (R = 4-CN): 61%, 94:6, 93% ee
(*R*)-**3ka** (R = 4-CO_2Me): 72%, 98:2, 90% ee
(*R*)-**3la** (R = 4-Bpin): 67%, >98:2, 92% ee

X-ray for (*R*)-**3la**

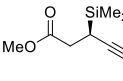


(*R*)-**3ma** (thien-2-yl): 87%, >98:2, 93% ee[b]
(*R*)-**3na** (thien-3-yl): 88%, >98:2, 93% ee[c]

alkyl substitution

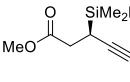


(*R*)-**3oa**: 84%, 98:2, 89% ee[b]

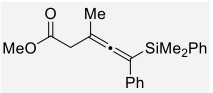


(*R*)-**3pa**: 69%, >98:2, 84% ee[b]

silyl substitution

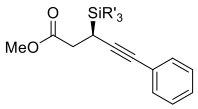


(*R*)-**3qa**: 80%, >98:2, 90% ee



4ra: 50%, <2:98, <5% ee[d]

Si–B reagents



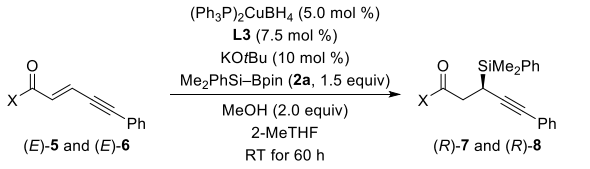
(*R*)-**3ab** (R' = $MePh_2$): 48%, 98:2, 78% ee
(*R*)-**3ac** (R' = Ph_3): trace[d]
(*R*)-**3ad** (R' = Et_3): 71%, 76:24, 58% ee[d]

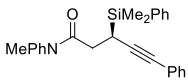
[a]All reactions were performed on a 0.20 mmol scale. The ratio of 1,4- versus 1,6-selectivity was determined by ^{1}H NMR spectroscopy. [b]5.0 mol % $(Ph_3P)_2CuBH_4$ and 7.5 mol % **L3**. [c]2.5 mol % $(Ph_3P)_2CuBH_4$ and 3.8 mol % **L3**. [d]10 mol % $(Ph_3P)_2CuBH_4$ and 15 mol % **L3**.

We next applied this procedure to enynamides and enynones (see Scheme 3). A longer reaction time (60 h instead of 12 h) was found to be necessary for the reaction of enynamides (*E*)-**5**. Tertiary enynamides (*E*)-**5a** and (*E*)-**5b** reacted in good yields and with ≥90% ee. Conversely, a free NH group as in (*E*)-**5c** and (*E*)-**5d** was detrimental to the yield, and the primary amide resulted in ∼95% ee, whereas the enantiomeric excess for the secondary amide (*E*)-**5c** was moderate; we cannot explain this difference. The yield was also high for imide (*E*)-**5e** but the enantioinduction was poor. Enynone (*E*)-**6d** proved to be a suitable substrate, delivering the 1,4-adduct (*R*)-**8aa** in 61% yield and with 71% ee.

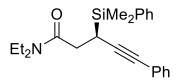
A deuteration experiment with CD_3OD instead of MeOH confirmed the alcohol additive as the proton source (Scheme 4, top). We also probed the other diastereomer (*Z*)-**1a** under the standard protocol (Scheme 4, bottom). As expected on the basis of Xu's and Loh's work (see Scheme 1, bottom),[13] 1,6-adduct **4aa** did form in 45% yield, albeit not selectively; the 1,4-adduct (*R*)-**3aa** was isolated in 34% yield. While there was hardly any enantioinduction in the formation of the allene, the α-chiral propargylic silane had an enantiomeric excess of 94%. Interestingly, its absolute configuration was the same as obtained from (*E*)-**1a**. The above stereochemical outcome could be the result of in situ *Z*-to-*E* isomerization. However,

Scheme 3. Enantioselective Deconjugative 1,4-Addition of Silicon Nucleophiles to Enynamides and Enynones[a]

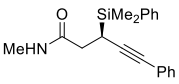




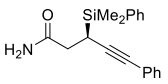
(*R*)-**7aa** from (*E*)-**5a**: 79%, 96:4, 90% ee



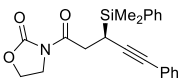
(*R*)-**7ba** from (*E*)-**5b**: 82%, 97:3, 92% ee



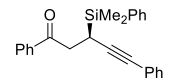
(*R*)-**7ca** from (*E*)-**5c**: 28%, 95:5, 73% ee



(*R*)-**7da** from (*E*)-**5d**: 25%, >98:2, 95% ee



(*R*)-**7ea** from (*E*)-**5e**: 89%, 98:2, 30% ee

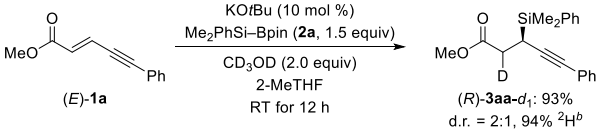


(*R*)-**8aa** from (*E*)-**6a**: 61%, >98:2, 71% ee[b]

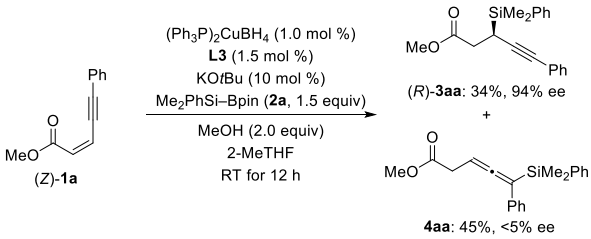
[a]All reactions were performed on a 0.20 mmol scale. The ratio of 1,4- versus 1,6-selectivity was determined by ^{1}H NMR spectroscopy. [b]1.0 mol % $(Ph_3P)_2CuBH_4$/1.5 mol % **L3** for 12 h.

Scheme 4. Control Experiments[a]

deuterium labeling



Z double bond geometry



[a]All reactions were performed on a 0.20 mmol scale. [b]Diastereomeric ratio and deuteration grade were estimated using ^{1}H NMR spectroscopy.

we have not been able to detect (*E*)-**1a** during the reaction of (*Z*)-**1a** by ^{1}H NMR spectroscopy, even in the absence of the silylboronic ester. Nevertheless, such a scenario is not unprecedented. While an in-depth analysis of the mechanism of copper-catalyzed conjugate silylation is missing, Minnaard, Feringa, and co-workers explored the 1,4-addition of Grignard reagents in great detail and made similar observations.[18]

In conclusion, a reliable and broadly applicable synthesis of α-chiral propargylic silanes has been developed. The enantioselective formation of the Si−C(sp^3) bond is achieved by a highly 1,4-selective copper-catalyzed conjugate addition of silylboronic esters to enyne-type $\alpha,\beta,\gamma,\delta$-unsaturated acceptors. The mild reaction conditions allow for very good functional-group tolerance, and the substrate scope includes enynoates, enynamides, and enynones.

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c03046.

General procedures, experimental details, characterization and spectral data for all new compounds, and crystal data and structural refinement for compound (*R*)-**3la**(PDF)

Accession Codes

CCDC 2025553 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road,Cambridge CB2 1EZ, UK; fax: + 44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

Martin Oestreich − *Institut für Chemie, Technische Universität Berlin, 10623 Berlin, Germany;* orcid.org/0000-0002-1487-9218; Email: martin.oestreich@tu-berlin.de

Author

Wenbin Mao − *Institut für Chemie, Technische Universität Berlin, 10623 Berlin, Germany;* orcid.org/0000-0001-8746-1616

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.0c03046

Notes

The authors declare no competing financial interest.

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