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Activation of the Si−B Linkage: Copper-Catalyzed Addition of Nucleophilic Silicon to Imines

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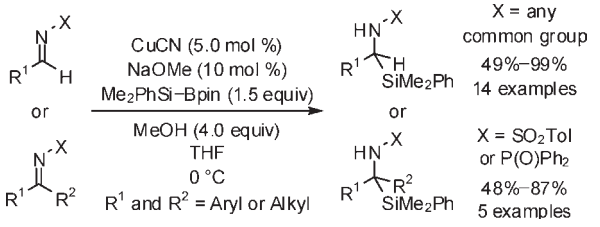
ABSTRACT



Activation of the Si−B bond through copper-catalyzed transmetalation quickly developed into a practical method to generate Cu−Si reagents. These silicon nucleophiles cleanly add to aldehyde-derived imine electrophiles to form α-silylated amines in protic media, and no carbon-to-nitrogen Brook-type rearrangement of the intermediate anion is observed. Aside from electron-withdrawing groups at the imine nitrogen atom, for example, SO_2Tol and $P(O)Ph_2$, previously delicate nitrogen substituents such as phenyl or benzhydryl are tolerated. The same protocol also allows the unprecedented addition to representative ketone-derived imines.

The Si−B bond serves as a source of nucleophilic silicon,[1] and its heterolytic cleavage is mediated by transition metal−alkoxide complexes, corresponding to a transmetalation of the silicon group from the boron atom to the transition metal. The recent development of rhodium(I)-[2] and copper(I)-catalyzed[3] protocols for Si−B bond activation and subsequent selective C−Si bond formation is currently garnering considerable attention. The emerging copper(I) catalysis is particularly attractive as the catalytically generated Cu−Si reagent represents an alternative to established silicon-based cuprates,[4] indeed opening the door to enantioselective conjugate additions[3a,c] and regioselective transformations.[3e,f]

Due to ongoing interest in silicon-containing peptide isosteres[5−7] and α-amino acids,[8] a copper-catalyzed

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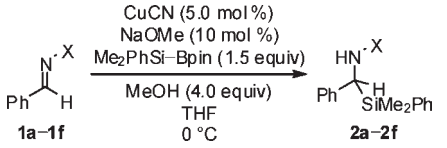
addition of silicon nucleophiles to imines to form α-silylated amines[9] would also be a useful method. There were only isolated examples of Si−Li[10] and Si−Cu[11] additions to iminium ions prior to the systematic elaboration of diastereoselective imine additions by the laboratories of Scheidt[12] and Skrydstrup,[7] employing various functionalized[6,7] Si−Li reagents.[13] Activating groups at the imine nitrogen atom, for example, S(O)*t*-Bu, are usually required,[7,12] and ketone-derived imines were not sufficiently reactive.[7a] In this Letter, we disclose a copper-catalyzed imine addition of nucleophilic silicon released from an Si−B reagent in protic medium.[14] As to the substituent at the nitrogen atom, there is no limitation, and selected ketone-derived imines also react in remarkably high yields.

Our investigation commenced with benzaldehyde-derived imines **1a**−**1f** (Table 1), and we used 1.5 equiv of Suginome's $Me_2PhSiBpin$ reagent[15] (= Si−B with pin = pinacolato) as a silicon precursor. CuCN (5.0 mol %) as the copper(I) source and excess NaOMe (2.0 equiv) had been optimal in our previous work,[3e] and this combination also performed perfectly in the imine addition. We were then able to also reduce the amount of NaOMe (10 mol %) by the addition of MeOH (4.0 equiv). The protic additive was not detrimental to the chemical stability of either the Si−B reagent or the Cu−Si reactant. It might even be beneficial in that protonation of the intermediate anion prevents carbon-to-nitrogen Brook rearrangement.[16] Reactions required less than an hour for full conversion but reaction rates decreased with, for example, CuCl or with added phosphines.[3e]

The identification of the CuCN−NaOMe−MeOH system was followed by the variation of the group at the imine nitrogen atom. As expected,[7,12] imines with electron-withdrawing groups afforded the α-silylated amines in good yields (**1a**−**1c**→**2a**−**2c**, Table 1, entries 1−3). Unexpectedly though,[12a] phenyl as well as benzyl/benzhydryl substituents were accepted as well, and excellent yields were obtained (**1d**−**1f**→**2d**−**2f**, Table 1, entries 4−6).

Table 1. Copper-Catalyzed Addition to Benzaldehyde-Derived Aldimines: Variation of the Substituent at the Nitrogen Atom

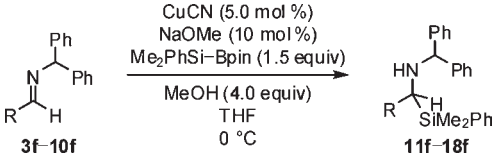


entry	aldimine	X	α-silylamine	yield (%)[a]
1	**1a**	SO_2Tol	**2a**	90
2	**1b**	$P(O)Ph_2$	**2b**	88
3	**1c**	Boc	**2c**	60
4	**1d**	Ph	**2d**	80
5	**1e**	CH_2Ph	**2e**	quant
6	**1f**	$CHPh_2$	**2f**	quant

[a] Isolated yield after flash chromatography on silica gel.

We decided to continue with the less-used benzhydryl group for the determination of the substrate scope (Table 2). All other aryl-substituted imines produced comparable yields (**3f**−**7f**→**11f**−**15f**, Table 2, entries 1−5). Relatively hindered alkyl-substituted imines required an increased amount of the Si−B reagent (**8f** and **9f**→**16f** and **17f**, Table 2, entries 6 and 7) while an imine with a tertiary alkyl group showed no conversion (**10f**, Table 2, entry 8). Yields were generally good.

Table 2. Copper-Catalyzed Addition to Benzhydryl-Substituted Aldimines: Substrate Scope



entry	aldimine	R	α-silylamine	yield (%)[a]
1	**3f**	4-ClC_6H_4	**11f**	77
2	**4f**	4-BrC_6H_4	**12f**	85
3	**5f**	4-$MeOC_6H_4$	**13f**	95
4	**6f**	1-$C_{10}H_7$	**14f**	87
5	**7f**	Fc	**15f**	71
6	**8f**[b]	Cy	**16f**	71[c]
7	**9f**[b]	*i*-Pr	**17f**	49[c]
8	**10f**[b]	*t*-Bu	**18f**	no reaction

[a] Isolated yield after flash chromatography on silica gel. [b] Used without further purification. [c] $Me_2PhSi-Bpin$ (2.0 equiv) used.

We next turned our attention to the challenging addition to ketone-derived imines, for which Skrydstrup et al. had reported a single low-yielding example.[7a] We were delighted to see that the copper-catalyzed silicon addition to activated acetophenone-derived imines proceeded in acceptable yields (**19a** and **19b**→**20a** and **20b**, Table 3, entries 1 and 2). Conversely, phenyl- and

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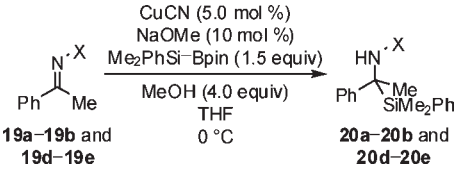
Table 3. Copper-Catalyzed Addition to Acetophenone-Derived Ketimines: Variation of the Substituent at the Nitrogen Atom

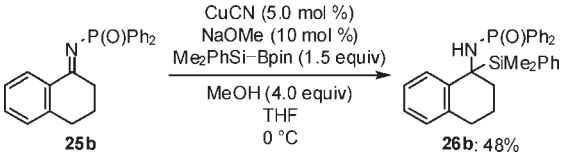


entry	aldimine	X	α-silylamine	yield (%)[a]
1	**19a**	SO_2Tol	**20a**	68
2	**19b**	$P(O)Ph_2$	**20b**	72
3	**19d**	Ph	**20d**	no reaction
4	**19e**	CH_2Ph	**20e**	no reaction

[a] Isolated yield after flash chromatography on silica gel.

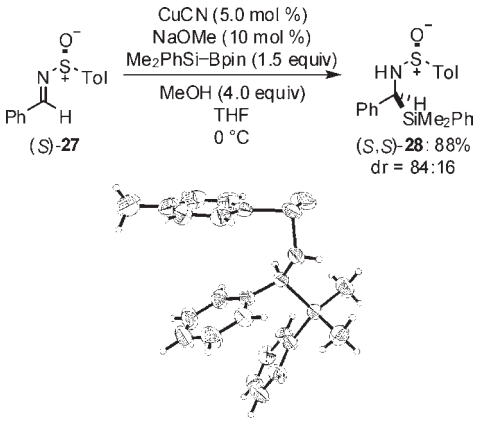
benzyl-substituted imines were not susceptible to nucleophilic attack (**19d** and **19e**, Table 3, entries 3 and 4). A few other $P(O)Ph_2$-substituted alkyl aryl imines furnished similar yields (87% for ethyl phenyl, **21b**→**22b** and 52% for 4-anisyl methyl **23b**→**24b**, see the Supporting Information). A cyclic substrate reacted in moderate yield (**25b**→**26b**, Scheme 1).

Scheme 1. One More Example of a Ketimine Addition



Although diastereocontrolled addition is not the major focus of the present study, we are aware of the high diastereoselectivities (dr ≥ 95:5) obtained by Scheidt et al.[12a] and Skrydstrup et al.[10] using the Ellman auxiliary.[17] Those *t*-Bu-substituted enantiopure sulfinylimines were, however, completely inert in the copper(I) catalysis. Assuming steric bulk to be the problem, we prepared the related aryl-substituted sulfinylimine (*S*)-**27**,[18] and that afforded the chiral α-silylated amine (*S*,*S*)-**28** in good yield with decent diastereoselectivity (Scheme 2). The relative configuration was assigned by X-ray analysis of the major diastereomer (Scheme 2), obtained in isomerically pure form after flash chromatography on silica gel. The sense of stereoinduction agrees with that rigorously established by Scheidt.[12a] We also prepared

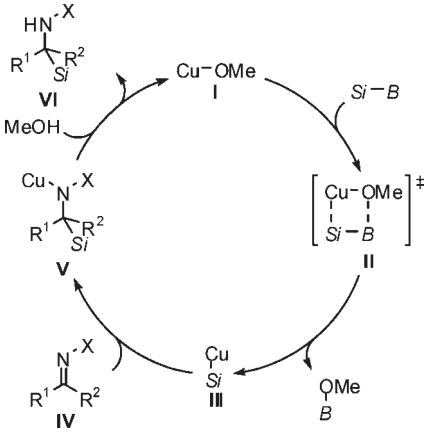
Scheme 2. Diastereoselective Addition to Chiral Aldimine with Molecular Structure of Major Diastereomer



the corresponding sulfinylimine from acetophenone [(*S*)-**29**, cf. the Supporting Information] but that showed no conversion.

The proposed catalytic cycle (Scheme 3) begins with the now generally accepted boron-to-copper transmetalation (**I**→**III**), the formal σ-bond metathesis through **II**.[3] Thus formed Cu–Si reagent **III** adds to imine **IV** to give intermediate **V** (**IV**→**V**). With added MeOH, **V** is likely to be immediately protonated (**V**→**VI**). We favor this scenario over salt metathesis with NaOMe because we do not observe any Brook-type rearrangement,[16] even with phenyl and benzyl/benzhydryl groups at the nitrogen atom.[12a]

Scheme 3. Proposed Catalytic Cycle



In summary, we accomplished a broadly applicable synthesis of α-silylated amines through copper-catalyzed addition of a silicon nucleophile to aldehyde- and ketone-derived imines. The nitrogen substituent tolerance supplements existing protocols, and the reactivity

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toward ketimines is particularly noteworthy. It also is another contribution to the versatile synthetic chemistry of the recently introduced copper-catalyzed Si−B bond activation.[3]

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Supporting Information Available. General procedure, characterization data as well as ^{1}H and ^{13}C NMR spectra for all compounds, and X-ray data. This material is available free of charge via the Internet at http://pubs.acs.org.