Asymmetric 1,2-Addition

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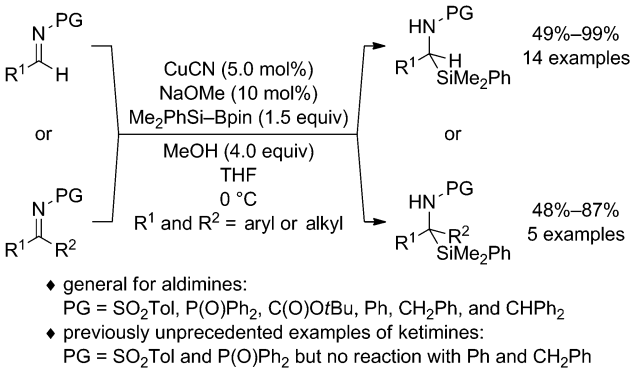
Enantioselective Addition of Silicon Nucleophiles to Aldimines Using a Preformed NHC–Copper(I) Complex as the Catalyst**

*Alexander Hensel, Kazuhiko Nagura, Lukas B. Delvos, and Martin Oestreich**

Abstract: *A remaining major challenge in the asymmetric addition of silicon nucleophiles to typical prochiral acceptors, the enantioselective 1,2-addition to aldimines, is addressed. Activation of the Si–B bond in the silicon pronucleophile by a copper(I) alkoxide with McQuade's chiral six-membered N-heterocyclic carbene as a supporting ligand releases the silicon nucleophile, which adds to various aldimines with high levels of enantioselectivity. The new method provides a catalytic asymmetric access to α-silylated amines.*

The catalytic generation of silicon nucleophiles by transmetalation of the Si–B linkage at transition-metal–oxygen bonds significantly advanced synthetic silicon chemistry.[1,2] Its impact manifests itself in the development of asymmetric variants of fundamental carbon–silicon bond-forming reactions, namely conjugate addition[3,4] and allylic substitution.[5] The 1,4-addition is particularly well investigated, and chiral diphosphine [Rh^{I}-O][3] and NHC [Cu^{I}-O][4] complexes have been identified as suitable catalysts. The latter were also crucial in solving the problem of regio- and enantiocontrolled allylic displacements.[5] Interestingly, the enantioselective 1,2-addition of silicon nucleophiles to C=X bonds (X = O or NPG with PG = protective group) proved to be a difficult task. We had disclosed racemic protocols for both acceptors,[6,7] and Riant and co-workers recently accomplished the addition to aldehydes with high levels of enantiocontrol by employing a preformed chiral diphosphine [Cu^{I}-F] complex.[8] For imines, a catalyst-controlled version is still elusive, and that may be regarded a remaining major challenge in asymmetric carbon–silicon bond formation with silicon nucleophiles. The motif of α-silylated amines is, however, particularly relevant to the area of silicon-containing peptide isosteres,[9–11] and current stereoselective approaches usually make use of either Ellman's or Davis' sulfinyl group as a chiral auxiliary.[7,12–14] Using electrophilic silicon, reverse aza-Brook rearrangements of chiral α-amino lithium/carbanion pairs have proven to be a valid alternative.[15] We disclose here the enantioselective transfer of silicon nucleophiles onto aldimines under copper(I) catalysis, employing Suginome's $Me_2PhSiBpin$[16] as the silicon pronucleophile.

The scope of our racemic copper(I)-catalyzed imine addition is certainly broad as documented by its compatibility with common protective groups at the aldimine nitrogen atom and the fact that even selected ketone-derived imines reacted in decent yields for the first time (Scheme 1).[7] However, our



Scheme 1. General copper(I)-catalyzed 1,2-addition of silicon nucleophiles to aldimines and ketimines.[7] Tol = 4-tolyl.

initial attempts to render this reaction enantioselective with representative chiral ligands did not meet with success. Asymmetric induction, if any, was extremely low with bidentate phosphines and amines, and somewhat higher enantiomeric excesses obtained with N-heterocyclic carbenes hinted that these could be the ligands of choice for this transformation.[17]

Without further progress, we abandoned the project for a while. In the meantime, we succeeded in the enantioselective preparation of α-chiral allylic silanes by a copper(I)-catalyzed allylic substitution using the Si–B reagent.[5a] This asymmetric reaction had had a track record similar to the present challenge, and problems were overcome by the use of the NHC–copper(I) complex **L1**·CuCl introduced by McQuade and co-workers.[18] With **L1**·CuCl and its cognate **L2**·CuCl in hand, we returned to the 1,2-addition to aldimines and tested procedures with catalytic (Method A) and stoichiometric (Method B) in NaOMe in various solvents (Table 1). Reactions were started at 0 °C and then slowly warmed to ambient temperature. This temperature program was found to bring about the highest enantiomeric excesses; these were significantly diminished at lower temperatures.

[*] A. Hensel,[+] Dr. K. Nagura,[+] L. B. Delvos, Prof. Dr. M. Oestreich
Institut für Chemie, Technische Universität Berlin
Strasse des 17. Juni 115, 10623 Berlin (Germany)
E-mail: martin.oestreich@tu-berlin.de
Homepage: http://www.organometallics.tu-berlin.de

[+] These authors contributed equally to this work.

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NHC = N-heterocyclic carbene.

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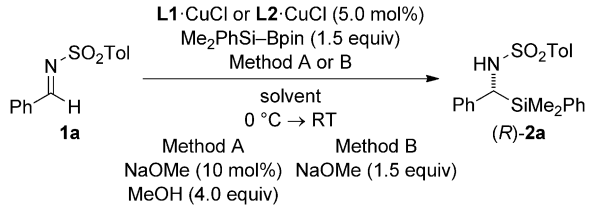
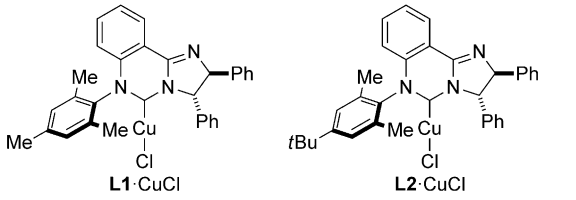
Table 1: Optimization of the reaction conditions.



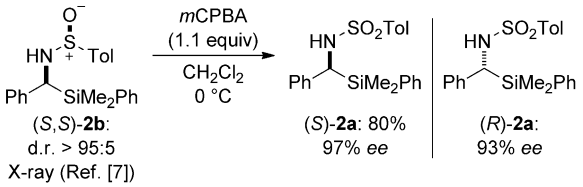


Entry	Catalyst	Method	Solvent	Yield [%][a]	*ee* [%][b]
1	**L1**·CuCl	A	THF	81	77
2	**L1**·CuCl	B	CH_2Cl_2	74	68
3	**L1**·CuCl	B	THF	49	12
4	**L1**·CuCl	B	Et_2O	67	93
5	**L1**·CuCl	B	*t*BuOMe	54	60
6	**L1**·CuCl	B	toluene	72	93
7	**L1**·CuCl	A	Et_2O	69	28
8	**L2**·CuCl	B	Et_2O	56	87

[a] Determined after purification by flash chromatography. [b] Determined by HPLC analysis using a chiral stationary phase.

Results were promising with both Method A in THF (cf. Scheme 1)[7] and Method B in CH_2Cl_2 (cf. aforementioned allylic substitution)[5a] (Table 1, entries 1 and 2). The solvent had a marked influence on the asymmetric induction. For Method B, the α-silylated amine formed in good yield and excellent 93% *ee* in either Et_2O (entry 4) or toluene (entry 6) but, in contrast to Method A, 12% *ee* was obtained when THF was used as the solvent (entry 3 vs. entry 1). Conversely, Method A was not compatible with Et_2O as the solvent, and the α-silylated amine was formed with 28% *ee* (entry 7 vs. entry 4). We cannot explain why the different methods display such a dramatic solvent dependence. Also, the level of enantiocontrol was highly dependent on several unidentified parameters, including the quality of the Si–B reagent and the base. The reaction in Et_2O (entry 4) was repeated multiple times, and enantiomeric excesses ranged from 91% to 95%, provided the use of freshly distilled Si–B reagent and a relatively new homemade batch of NaOMe. Riant and co-workers had also reported reproducibility issues in their copper(I)-catalyzed synthesis of enantioenriched α-silylated alcohols.[8] Neither these authors nor we are currently able to rationalize these observations. Catalyst **L2**·CuCl was no improvement over **L1**·CuCl (entry 8 vs. entry 4) although McQuade and co-workers had found the former to be superior in allylic substitution.[18c]

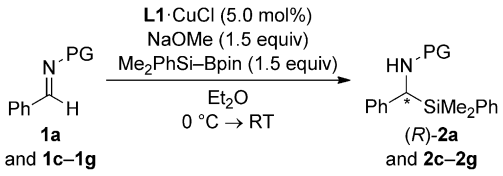
Our attempts to crystallographically establish the absolute configuration of the α-silylated amine failed. It crystallized as its racemate, even from highly enantioenriched samples, and crystals would not grow from the corresponding mother liquors containing essentially enantiomerically pure material. We had fortunately not only accomplished the related diastereoselective addition to an imine derived from Davis' auxiliary but had also been able to assign the adduct's configuration by X-ray analysis as *S* at the newly formed stereocenter.[7] Facile oxidation of that sulfinamide to the sulfonamide allowed for its chemical correlation with the α-silylated amine emerging from the enantioselective catalysis [(*S*,*S*)-**2b**→(*S*)-**2a**, Scheme 2]. As a result, catalyst **L1**·CuCl induces *R* configuration in the 1,2-addition to sulfonyl-protected imines.



Scheme 2. Determination of the absolute configuration by chemical correlation. *m*CPBA = *meta*-chloroperbenzoic acid.

With the reaction conditions optimized (Method B in Et_2O), we varied the protective group at the imine nitrogen atom (Table 2). All reactions were performed with the same batch of reagents to ensure comparability within the screening. Imines **1a**, **1c**, and **1d** with electron-withdrawing protective groups cleanly yielded the α-silylated amines **2a**, **2c**, and **2d** (entries 1–3), whereas **1e**–**1g** with phenyl and benzyl/benzhydryl substitution reacted poorly (entries 4–6). The latter results distinguish the **L1**·CuCl catalyst from the highly reactive CuCN/NaOMe/MeOH combination without added ligand (cf. Scheme 1).[7] Enantiomeric excesses were equally high with the SO_2Tol and $P(O)Ph_2$ groups, and we continued using the former with its assigned absolute configuration.

Table 2: Variation of the protective group at the nitrogen atom.



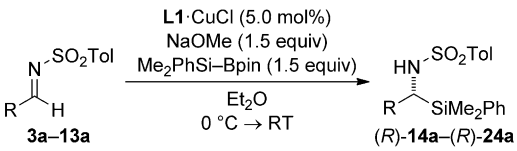
Entry	Aldimine	PG	α-Silylated amine	Yield [%][a]	*ee* [%][b]
1	**1a**	SO_2Tol	(*R*)-**2a**	85	91
2	**1c**	$P(O)Ph_2$	**2c**	59	90
3	**1d**	C(O)O*t*Bu	**2d**	76	37
4	**1e**	Ph	**2e**	10[c]	28
5	**1f**	CH_2Ph	**2f**	traces[c]	n.d.
6	**1g**	$CHPh_2$	**2g**	–[d]	–

[a] Determined after purification by flash chromatography. [b] Determined by HPLC analysis using chiral stationary phases. [c] Conversion estimated by ^{1}H NMR spectroscopy to be less than 50%. [d] No conversion. n.d. = not determined.

Imines **1a**, **1c**, and **1d** with electron-withdrawing protective groups cleanly yielded the α-silylated amines **2a**, **2c**, and **2d** (entries 1–3), whereas **1e**–**1g** with phenyl and benzyl/benzhydryl substitution reacted poorly (entries 4–6). The latter results distinguish the **L1**·CuCl catalyst from the highly reactive CuCN/NaOMe/MeOH combination without added ligand (cf. Scheme 1).[7] Enantiomeric excesses were equally high with the SO_2Tol and $P(O)Ph_2$ groups, and we continued using the former with its assigned absolute configuration.

The catalyst emerged as tolerant of electronic as well as steric variation of the aryl group at the imine carbon atom

Table 3: Substrate scope.



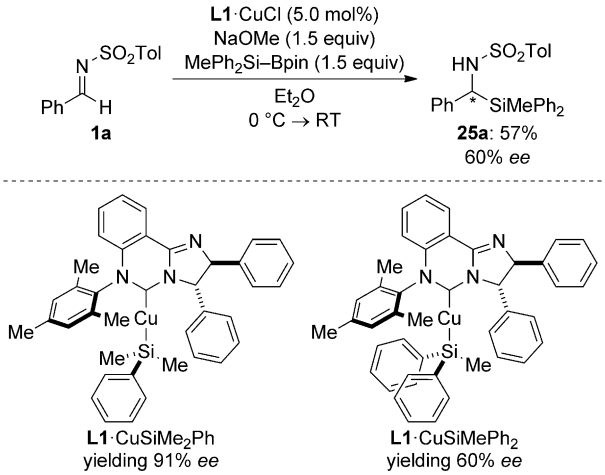
Entry	Aldimine	R	α-Silylated amine	Yield [%][a]	*ee* [%][b]
1	**3a**	*p*-MeC_6H_4	(*R*)-**14a**	76	94
2	**4a**	*p*-ClC_6H_4	(*R*)-**15a**	62	90
3	**5a**	*p*-BrC_6H_4	(*R*)-**16a**	63[c]	95
4	**6a**	*p*-$MeOC_6H_4$	(*R*)-**17a**	54	79
5	**7a**	*p*-$CF_3C_6H_4$	(*R*)-**18a**	71	91
6	**8a**	*o*-MeC_6H_4	(*R*)-**19a**	83	98
7	**9a**	*o*-BrC_6H_4	(*R*)-**20a**	76[c]	85
8	**10a**	1-naphthyl	(*R*)-**21a**	85	95
9	**11a**	cyclohexyl	(*R*)-**22a**	32	85
10	**12a**	isopropyl	(*R*)-**23a**	65	52
11	**13a**	*sec*-butyl	(*R*)-**24a**	52	89

[a] Determined after purification by flash chromatography. [b] Determined by HPLC analysis using chiral stationary phases. [c] Performed in toluene instead of Et_2O for better solubility; yields are lower in the latter but enantiomeric excesses are unchanged.

(Table 3, entries 1–8). Yields and enantiomeric excesses were unaffected by substitution in the *para* position, except for the electron-donating methoxy substituent (Table 3, entries 1–5). The situation was similar for *ortho* substitution (entries 6 and 7), including an α-naphthyl group (entry 8). It was merely the poor solubility of the aryl halides in Et_2O that was detrimental; changing the solvent to toluene improved these yields without any effect on enantioinduction (entries 3 and 7). The same protocol also allowed for the enantioselective 1,2-addition to aliphatic aldimines (Table 3, entries 9–11) but results were mixed.[19] For example, aldimines with secondary alkyl groups reacted either with good enantioselectivity (entry 9) or in good yield (entry 10). In turn, good 89% *ee* but moderate 52% yield were obtained for a substrate with a primary alkyl group as a substituent (entry 11).

We also tested bulkier $MePh_2SiBpin$[16] as a pronucleophile where one of the methyl groups of $Me_2PhSiBpin$ is replaced by a phenyl group. There are no examples of its use in enantioselective transformations involving transmetalation.[1] It added cleanly to the sulfonyl-protected aldimine but the level of enantiocontrol and the yield were significantly lower (Scheme 3, top). We explain this sharp decrease in asymmetric induction (91% *ee* for $Me_2PhSiBpin$ vs. 60% *ee* for $MePh_2SiBpin$) with the increased steric congestion around the silicon atom and copper(I) center in **L1**·$CuSiMePh_2$ (Scheme 3, bottom). The transition state of the imine addition is likely to be less compact than that involving **L1**·$CuSiMe_2Ph$.

In summary, we have reported herein the enantioselective transfer of silicon nucleophiles onto aldimines, affording α-silylated amines in a catalyst-controlled reaction for the first time. The new method closes a gap in synthetic silicon chemistry. The chiral precatalyst, the NHC–copper(I) complex **L1**·CuCl developed by McQuade and co-workers, is not sufficiently reactive to promote addition to less-activated



Scheme 3. Effect of the silicon nucleophile: $Me_2PhSiBpin$ versus $MePh_2SiBpin$.

aldimines or even ketimines. The enantioselective 1,2-addition to these acceptors is one of the future challenges.

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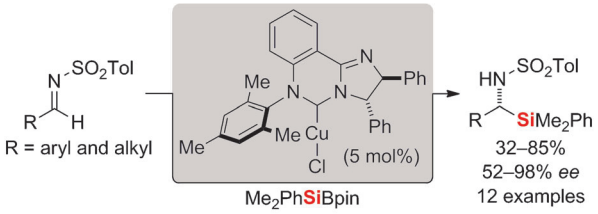
Communications

Asymmetric 1,2-Addition

A. Hensel, K. Nagura, L. B. Delvos, M. Oestreich* ——— ■■■■–■■■■

Enantioselective Addition of Silicon Nucleophiles to Aldimines Using a Preformed NHC–Copper(I) Complex as the Catalyst



The final chapter: The enantioselective addition of silicon nucleophiles to typical prochiral acceptors is now well-established methodology, except for the 1,2-addition to imines. McQuade's chiral NHC–copper(I) complex catalyzes this elusive transformation with high asymmetric induction, finally allowing for the catalyst-controlled preparation of α-silylated amines from aldimines (see scheme).