

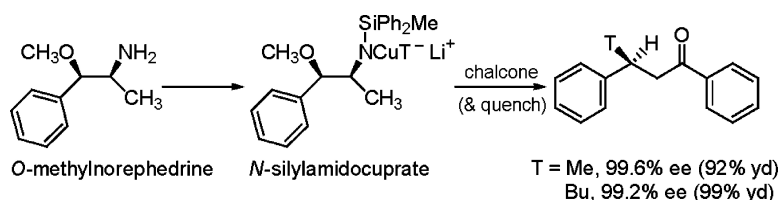
Communication

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Remarkable Effect of Silyl Groups on Asymmetric Induction in a Conjugate Addition Reaction with *O*-Methylnorephedrine-Based *N*-Silylamidocuprates¹

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Asymmetric induction in the conjugate addition reaction of organocuprates has received a great deal of attention over the past two decades, and steady progress has been made, as documented in reviews by Rossiter,² Krause,³ and Alexakis.⁴ Scalemic amidocuprates were an attractive approach,^{5–7} owing to the ready availability of the corresponding amines from the “chiral pool”; however, they have been hamstrung by low chemical or optical yields—or often both. We report herein “proof of principle” that the β -Si effect^{8,9} can be used to achieve excellent chemical and optical yields from a typical amidocuprate reaction, viz. conjugate addition of scalemic *N*-silylamidocuprates based on *O*-methylnorephedrine to chalcone.

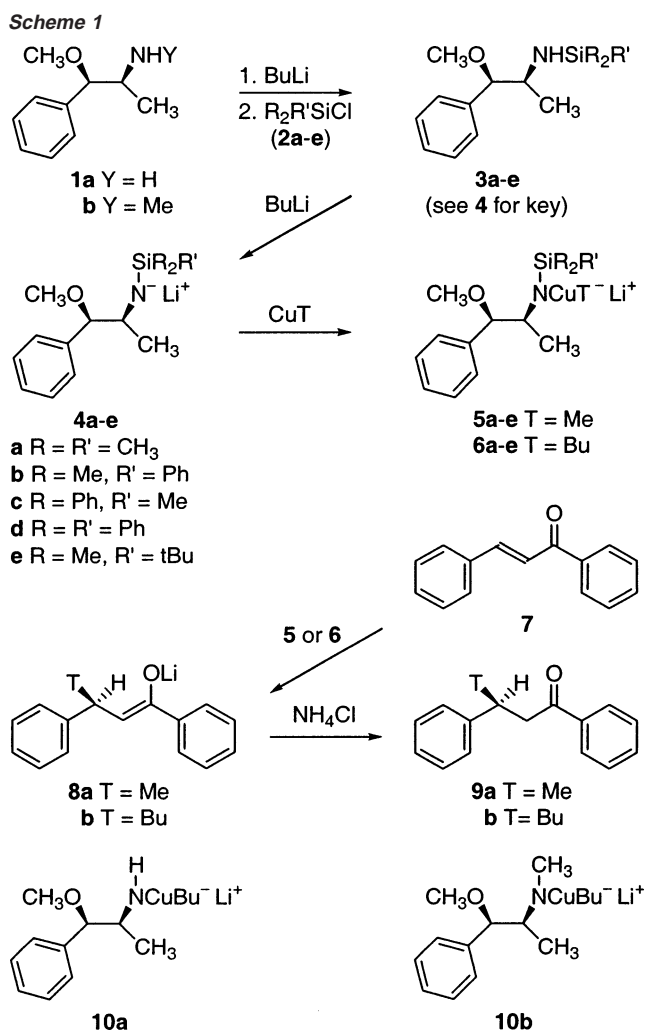
Commercially available (1*R*,2*S*)-(–)-norephedrine was converted to our starting material, (1*R*,2*S*)-*O*-methylnorephedrine **1a** by an improved method, as detailed in the Supporting Information. Pyne used **1a** as a chiral auxiliary attached to the substrate for conjugate additions of organolithium and organocopper reagents and obtained high ($\geq 90\%$) optical yields in favorable cases.¹⁰ In previous work by one of us,⁵ a heterocuprate prepared from norephedrine gave poor results, which made this ligand a good candidate for improvement.

The new silyl ligands were prepared in situ from **1a** and chlorosilanes **2a–e**, as shown in Scheme 1. Thus, solutions of **1a** in ether, dimethyl sulfide (DMS), or tetrahydrofuran (THF) were treated with 1 equiv of BuLi at -78°C to afford *N*-lithio-*O*-methylnorephedrine, and **2** was added to yield *N*-silylamines **3a–e**, which were not isolated. They were likewise lithiated to give *N*-lithio-*N*-silyl-*O*-methylnorephedrines **4a–e**, which were transferred via syringe or cannula to a -78°C suspension of MeCu, prepared from MeLi and CuI in the same solvent. The resulting methyl *N*-silylamidocuprates **5a–e** were annealed at 0°C for 0.1 h,^{11,12} and then they were cooled to -78°C for further reaction. Analogously, addition of **4a–e** to BuCu in the final stage gave butyl *N*-silylamidocuprates **6a–e**, respectively. This procedure has been referred to as “Method B”.¹³

Chalcone **7** proved to be the ideal yardstick by which to measure our results, as it has been studied by many investigators using a wide variety of reagents and ligands.^{14–22} Optical yields ranging from 0 to 97% ee (82% chemical yield)²¹ have been reported for organocopper reagents. Chemical yields range from 0 to 99% (90% ee).¹⁶

Upon aqueous workup, the initial product, enolate **8a** or **8b**, was converted to the final one, (*S*)-3-methyl-1,3-diphenyl-1-propanone **9a** or (*S*)-3-butyl-1,3-diphenyl-1-propanone **9b**, respectively. Chemical yields were measured by GLC and optical yields (ee) by HPLC with a Daicel ChiralPak AD column. All 1,4-adducts were predominantly *S*, based on Tomioka’s correlation of elution order with optical rotation.¹⁶ While the products are drawn as the *S* enantiomers in Scheme 1, minor amounts of the *R* isomer are present in all cases.²³

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The new *N*-silylamidocuprates **5a–d** and **6a–d** gave very high chemical and optical yields of 1,4-addition products in ether. The best examples are butyl cuprates **6b** and **6c**, based on dimethylphenylsilyl (DMPS) and diphenylmethylsilyl (DPMS) groups, respectively, which gave $>99\%$ ee in 99% yield (Table 1, entries 2, 3). The corresponding methyl cuprates **5b** and **5c** gave $\geq 99\%$ ee and $\geq 90\%$ yields (entries 16, 17). The chemical and optical yields with the trimethylsilyl (TMS) and triphenylsilyl (TPS) ligands were lower for both T = Bu (entries 1, 4) and T = Me (entries 15, 18); nevertheless, they were still very good. The pattern of ee—DMPS, DPMS > TMS > TPS—is the same for both the butyl and methyl series.

Since DMS is an excellent solvent for organocuprate conjugate addition reactions,²⁴ we had hoped that the optical yields with the TMS and TPS ligands might be improved in it, but in fact they

Table 1. 1,4-Addition of *N*-Silylamidocuprates to Chalcone

entry (cuprate)	T	solvent	Cu(I) salt	Si group	yd, ^a %	ee, ^b %
1 (6a)	Bu	ether	CuI	Me ₃ Si	90 ^c	97 ^c
2 (6b)				Me ₂ PhSi	99	99.6
3 (6c)				Ph ₂ MeSi	99	99.2
4 (6d)				Ph ₃ Si	90	96
5 (6e)				<i>t</i> BuMe ₂ Si	45	10
6 (6a)			Bu ₃ PCuI	Me ₃ Si	62	37
7 (6a)			Me ₂ SCuBr	Me ₃ Si	87	96
8 (6a)			CuCN	Me ₃ Si	46	10
9 (6a)		DMS	CuI	Me ₃ Si	88	93
10 (6c)				Ph ₂ MeSi	92	96
11 (6d)				Ph ₃ Si	90	94
12 (6a)		THF		Me ₃ Si	1	NM ^d
13 (6c)				Ph ₂ MeSi	9	33
14 (6d)				Ph ₃ Si	2	NM ^d
15 (5a)	Me	ether	CuI	Me ₃ Si	88	97
16 (5b)				Me ₂ PhSi	90	99.0
17 (5c)				Ph ₂ MeSi	92	99.6
18 (5d)				Ph ₃ Si	88	95
19 (10a)	Bu			none	25	10
20 (10b)				none	14	85

^a All reactions were run at $-78\text{ }^{\circ}\text{C}$ for 20 h. ^b %S – %R. ^c After 2 h at $-78\text{ }^{\circ}\text{C}$, the yield was 85%, and the ee was 96%. ^d Not measured, owing to low yield.

were slightly lower in all cases (entries 9–11). In THF the yields were very low (entries 12–14). The yields of 1,4-adduct from Bu₂CuLi·LiI were also significantly lower in THF (16%) than in ether (52%) or DMS (49%).

The use of other Cu(I) compounds as precursors was also investigated (entries 6–8). Whereas in some applications Bu₃PCuI was superior to CuI,²⁵ our results with it were much inferior. Substitution of CuBr in the preferred form of its DMS complex²⁶ gave results that were comparable to those from CuI. The use of CuCN under the same conditions gave very poor results.

To better understand the interplay between electronic and steric factors, we prepared unsubstituted amidocuprate **10a** and methyl-substituted **10b** from **1a** and **1b**, respectively. Cuprate **10a** gave a low yield and very low ee (entry 19). Upon going from H to methyl (i.e., **10a** to **10b**), the ee improved dramatically from 10% to 85%, while the yield fell from 25% to 14% (entry 20). Both effects can be attributed to the larger size of methyl vs H. Upon going from methyl to trimethylsilyl (i.e., **10b** to **6a**), substituent size again increases, and so too did the ee, from 85% to 97% (entry 1). Incredibly, the yield rebounded from 14% to 90%.

Thus, by incorporating the prometean TMS group (i.e., going from **10a** to **6a**), the ee was improved from 10% to 97%, and the yield, from 25% to 90%. The extraordinary increases in yield and ee can be attributed to the powerful activating effect of β -Si on Cu.^{8,9,27} It appears that the *tert*-butyldimethylsilyl group is too bulky for a favorable fit of **6e** with our substrate; nevertheless, the yield from this cuprate (45%) is significantly higher than from **10a** or **10b** (25% and 14%, respectively), which have much smaller substituents.

Sharpless has described “ligand-accelerated catalysis” in which a catalytic amount of ligand reacts with a reagent to form a (small amount of) a new reagent that has significantly higher reactivity toward the substrate.²⁸ As lithium reagents are highly reactive toward α -enones, we did not expect to be able to use our new cuprates for such classical catalysis.²⁹ Nevertheless, following Tanaka et al.,¹² we were able to achieve encouraging results with a “batch-catalytic” process,³⁰ e.g., after three cycles, the yield was 99% and the ee was 84%.

In conclusion, the activating effect of β -Si on organocuprate reactivity has been demonstrated to extend to the enantiomeric excesses from typical silyl derivatives of an amidocuprate with a

common substrate. On the basis of the superb results with derivatives of (1*R*,2*S*)-(–)-norephedrine, we believe the β -Si effect deserves to be tested broadly with organocuprates—and other reagents as well.²⁷

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Supporting Information Available: Typical experimental procedures, including the preparation of **1a**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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- (23) To obtain the best results, solutions of **7** were cooled with dry ice and added slowly down the walls of the reaction vessel, so that upon entering the rapidly stirred reaction mixture, they were as close as possible to $-78\text{ }^{\circ}\text{C}$. When the reaction of **6a** and **7** was run at $-50\text{ }^{\circ}\text{C}$, instead of $-78\text{ }^{\circ}\text{C}$, the ee dropped from 97% to 77%, which was not unexpected.⁵
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- (30) The reaction was run in the usual way, but when it was complete, another 1 equiv of BuLi was added, and the reaction mixture was annealed at $0\text{ }^{\circ}\text{C}$ for 0.1 h, as usual. Upon cooling to $-78\text{ }^{\circ}\text{C}$, an additional 1 equiv of **7** was added, and the reaction mixture was stirred for 2 h at $-78\text{ }^{\circ}\text{C}$ to complete cycle 2. With *n* cycles the final mol % of catalyst is 100/*n*. For example, with *n* = 5 the effective catalyst loading is 20 mol %, and the yield was 73% (80% ee).

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