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Me_3SiCl-ASSISTED 1,2-ADDITION OF ORGANOCUPRATES TO CARBONYL COMPOUNDS

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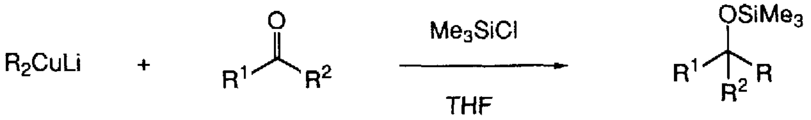
Summary: Me_3SiCl not only accelerates the 1,2-additions of organocopper reagents to carbonyl compounds, but also enhances the Cram diastereoselectivity of the addition to a chiral aldehyde.

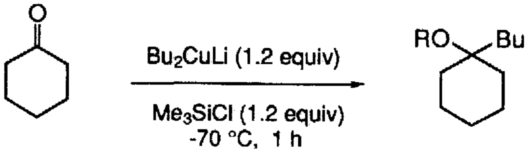
Organocuprate reagents represent a very important class of carbon nucleophiles owing to their outstanding reactivities as well as their selectivities, inter alia, chemoselectivity. Basically moderate nucleophilicity of the carbon-copper bond endows the reagent with a rather peculiar spectrum of nucleophilicity: for instance, it does not undergo 1,2-addition to saturated ketones.[1] Such failure of 1,2-addition has not seriously affected the value of the copper chemistry, however, because the reagents are generally prepared by transmetalation from more nucleophilic metal alkyls, e.g., lithium alkyls.[2] Nonetheless, it is now desirable to have some means to effect the 1,2-addition of copper reagents, because a number of useful copper reagents now available are not prepared by such conventional transmetalation reaction.[3]

We[4] and others[5] have previously reported that Me_3SiCl greatly enhances the rate of conjugate addition of copper reagents. It was thus expected that such rate enhancement would also emerge in the 1,2-addition of organocuprates onto ketones. This expectation was indeed borne out. In this Letter, we report that Me_3SiCl dramatically enhances the rate of the 1,2-addition of organocuprates to saturated ketones,[6] *and that it also enhances the Cram* diastereoselectivity in the addition of organocopper reagents to a chiral aldehyde.[7,8,9]



Reaction of Bu_2CuLi (1.2 equiv) with cyclohexanone in THF, when terminated after 1 h at -70 °C (Table I, entry 1), gave back ca. 90% of the starting ketone. The reaction in the presence of Me_3SiCl (1.2 equiv) under otherwise the same conditions, however, gave the desired 1,2-adduct as its

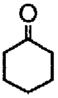
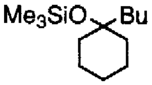
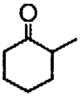
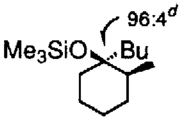
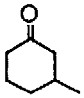
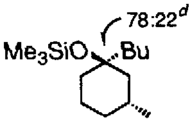
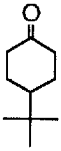
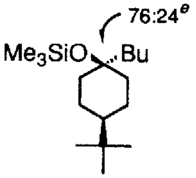
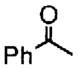
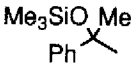
Table I. Rate Acceleration by Me_3SiCl



entry	solvent	Me_3SiCl	%yield[a]		recovery
			R = H	R = Me_3Si	
1	THF	-	0	0	89
2		+	<0.5	44	52
3	Et_2O	-	4	0	94
4		+	4	0	90

[a] Determined by quantitative GLC analysis.

Table II. Me_3SiCl-Accelerated 1,2-Addition[a]

entry	cuprate (equiv)	ketone	adduct (%equatorial attack)[b]	%yield[c]
1	Bu_2CuLi (2.0)			75[f]
2				68
3				56
4				63
5	Me_2CuLi (1.2)			74[g]

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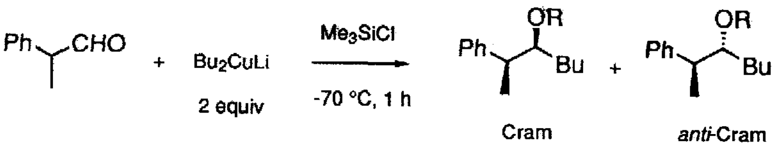
[a] Cuprates were prepared in THF from lithium alkyls and $CuBr \cdot Me_2S$, and were reacted at -70 to 25 °C in the presence of 2 equivalents of Me_3SiCl. [b] The diastereomeric ratio due to equatorial attack of the reagent versus that due axial attack. [c] Isolated yield. [d] Determined by GLC. [e] The ratio determined after acidic desilylation. [f] Isolated yield after acidic desilylation. [g] Enol silyl ether of acetophenone was also formed (18%).

Table III. Cram-Selectivity in the Addition to Chiral Aldehyde



entry	solvent	Me_3SiCl equiv	additive	%yield (Cram: anti-Cram)[a] R = Me_3Si	R = H
1	Et_2O	0	-	-	100 (3.1: 1)
2		1.2	-	2 (2.5: 1)	98 (2.5: 1)
3	THF	0	-	-	100 (1.2: 1)
4		1.2	-	71 (5.3: 1)	14 (1.3: 1)
5		1.2	[b]	73 (7.1: 1)	8 ([d])
6		1.2	[c]	96 (6.4: 1)	0 (-)
7	(BuCu)	1.2	[e]	84 (6.6: 1)	4 ([d])

[a] Determined by quantitative capillary GLC on OV-1 and OV-17. [b] With two equiv of 18-crown-6. [c] With two equiv of 12-crown-4 and 1.2 equiv of HMPA. The reaction was carried out for at -70 °C and for 1 h at -40 °C. [d] Not determined. [e] The reaction was slowly warmed from -70 °C to room temperature.

silyl ether in 44% yield (entry 2). As noted previously for the conjugate addition, the accelerating effect of Me_3SiCl emerged only for the reaction in THF (cf. entries 3 and 4). By running the reaction at -70 °C then gradually warming up to room temperature, 75% yield of the adduct was realized.

The generality of the reaction has been examined for the combinations of some typical reagents and substrates, and the results are summarized in Table II. The diastereoselectivity observed for the addition to substituted cyclohexanones are generally slightly higher than that with BuLi.

Diastereoselectivity of the addition to a chiral aldehyde has been compared for the presence and the absence of Me_3SiCl. Since an aldehyde serves as a good acceptor for cuprate addition, the reaction of Bu_2CuLi with 2-phenylpropanal (standard conditions: -70 °C for 1 h) proceeded quantitatively even in the absence of Me_3SiCl (Table III, entries 1 and 3). In ether, Me_3SiCl does not effectively participate in the reaction (entry 2). In THF, however, it does accelerate the addition, and, more interestingly, enhances the diastereofacial selectivity of the addition.

The reaction in THF gave the 1,2-adduct mainly as a silylated secondary alcohol, and little as an alcohol. There was found a notable difference in the Cram selectivity observed for these two products: while the alcohol product showed a Cram/anti-Cram ratio of 1.3:1, which is identical with the value obtained in the absence of Me_3SiCl, the silyl ether showed a much enhanced (5:1 to 6:1) Cram selectivity. This discrepancy of the selectivity clearly indicates that the pathway producing the silylated product (Me_3SiCl-dependent pathway) is independent of the one giving the unsilylated adduct (the direct pathway), and that the former is several times faster than the latter. The Cram selectivity in the Me_3SiCl-dependent reaction was slightly enhanced when the reaction was performed in the presence of both Me_3SiCl and a crown ether (18-crown-6) or HMPA (entries 5 and 6). It should be noted that the reaction in the presence of the crown ether alone is reported to show moderate anti-Cram selectivity.[7] The precise mechanisms and the mutual relationship of the two reaction pathways are presently unclear, but may well be related to a equilibration suggested previously for the Me_3SiCl-accelerated conjugate addition.[5a]

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