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Me_3SiCl ACCELERATED CONJUGATE ADDITION OF STOICHIOMETRIC ORGANOCOPPER REAGENTS

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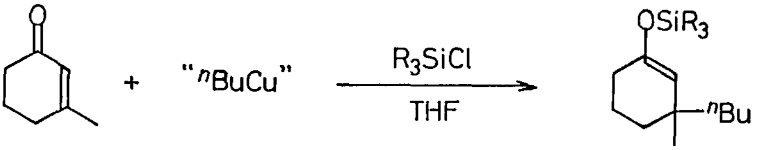
Summary: Chlorotrimethylsilane, particularly if combined with hexamethylphosphoric triamide or 4-dimethylaminopyridine, strongly promote the conjugate addition of stoichiometric organocopper reagents.

In the conjugate addition of Gilman's reagent onto an enone,[1] the inherent nature of the reagent normally necessitates the use of at least two equivalents of a lithium reagent to achieve a good result. In addition, the conditions required to effect smooth reaction are often vigorous enough to effect decomposition of the reagent, which also contributes to make the reagent stoichiometry uneconomical. Such difficulties have been overcome initially with the aid of "dummy" ligands[2] and recently by using cuprates with higher reactivities[3] or higher thermal stability.[4]

Me_3SiCl (with a polar additive) strongly accelerates the copper catalyzed conjugate addition of the Grignard reagent.[5] This observation lead us to examine the effect of chlorosilanes on the reaction of stoichiometric copper reagents, and we found that the combined chlorosilane/organocopper reagents also exhibit enhanced reactivities. Of particular note is that chlorosilanes used together with an activator such as hexamethylphosphoric triamide (HMPA) or 4-dimethylaminopyridine (DMAP), allows unreactive RCu-type reagents to undergo smooth conjugate addition, and that as the result efficient conjugate addition of the R_2CuLi-type reagent can be achieved by the use of only half an equivalent of the reagent.[6,7]

Relatively unreactive 3-methylcyclohexenone was chosen as a probe for the semiquantitative analysis of the reaction (-78 °C in THF) of Bu_2CuLi and BuCu (prepared from BuLi and $CuBr{\cdot}Me_2S$ at -78~-40 °C) (Table I). Control experiments indicated that Bu_2CuLi reacts only slowly at such a low temperature (entry 1). With added Me_3SiCl, however, the reaction completed almost instantaneously (entry 2), and the reaction mixture remained clear and yellow throughout the reaction. $^tBuMe_2SiCl$, while being ineffective by itself (entry 4), realized good level of rate acceleration if used together with HMPA (entry 5). In line with House's observation,[8] HMPA itself retarded the reaction. The rate enhancement was more prominent in THF than in ether. Reagents derived from cuprous iodide consistently gave lower yield.

BuCu was totally inert to the enone at -78 °C. While the presence of Me_3SiCl caused only moderate rate enhancement (entry 7), HMPA again intensified the effect of the chlorosilane (entries 8 and 9). Strong effect of Me_3SiCl/HMPA upon the reaction of BuCu implied that these additives would make both of the butyl groups on Bu_2CuLi available for the conjugate addition. This was indeed the case and the reaction with 0.6 equiv of the cuprate at -78 °C realized a good yield (entry 3).



(1)

Table I. Me_3SiCl-Assisted Addition onto 3-Methylcyclohexenone at -78 °C in THF

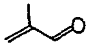
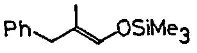
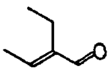
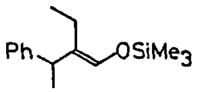
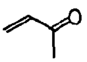
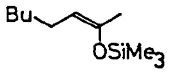
entry	Bu_2CuLi or BuCu (equiv)	R_3SiCl (2 equiv)	additive (2 equiv)	time	GLC yield (%) 1,4-adduct	recovery
1	Bu_2CuLi (2.0)	-	-	1 h	28[a]	70
2	(2.0)	Me_3SiCl	-	5 min	99	0
3	Bu_2CuLi (0.6)	Me_3SiCl	HMPA	3 h	87	13
4	(2.0)	$^tBuMe_2SiCl$	-	1 h	31	63
5	(2.0)	$^tBuMe_2SiCl$	HMPA	1 h	95	5
6	(2.0)	$^tBuMe_2SiCl$	DMAP	1 h	90	10
7	BuCu (1.2)	Me_3SiCl	-	20 min	24[a]	65
8	(1.2)	Me_3SiCl	HMPA	20 min	53[a]	33
9	(1.2)	Me_3SiCl	DMAP	20 min	57[a]	34
10	(1.2)	Me_3SiCl	HMPA	1 h	89[a]	8

[a] Isolated as a ketone after acidic quench.

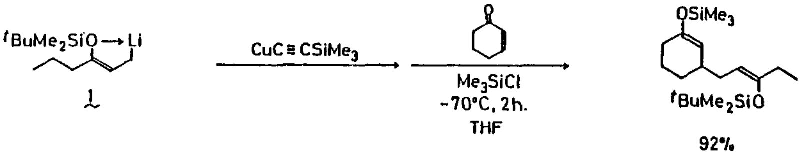
In order to probe the function of HMPA and to eventually replace this carcinogen with other reagents, we examined several other polar solvents and the reagents that are known to enhance the electrophilicity of chlorosilanes.[9] While crown ethers and common carboxamide solvents did not show significant effect, DMAP proved uniquely effective both for Me_3SiCl/BuCu (compare entries 8 and 9) and $^tBuMe_2SiCl/Bu_2CuLi$ (entries 5 and 6).[9]

Some representative substrates which pose difficulties by the conventional Gilman's reagents were examined (Table II). Note that, when the reactions were performed in the presence of chlorosilane/HMPA or DMAP, only 1.2 equiv of an alkyllithium reagent was needed to achieve full conversion of the substrate (either via RCu or R_2CuLi). The effect of Me_3SiCl was not very prominent with methyl vinyl ketone except for the interesting reversal of the geometry of the enolate double bond (67% E without Me_3SiCl[10] vs. 72% Z with Me_3SiCl/HMPA). Significant effect emerged for unsaturated aldehydes, e.g. acrolein (88% with Me_3SiCl vs. 25%[11] without Me_3SiCl) and Most noteworthy is the very high (over 90%) E-stereochemistry of the aldehyde enolate formed by the TMSCl-assisted addition. It is reported that the reactions under conventional conditions give a nearly 1:1 mixture.[11] Such E-selectivity also observed in the reaction of Me_3SiCl/catalytic organocopper reagents[5] provides a unique access to the synthesis of stereodefined aldehyde enolates unattainable by other published methods. A few selected cases indicates that this selectivity is increased by the presence of HMPA.

Table II. Me_3SiCl-Assisted Conjugate Addition at -78~-40 °C

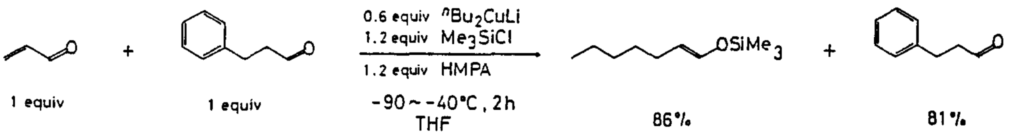
substrate	R_2CuLi or RCu	Me_3SiCl	HMPA	Product	GLC yield	E:Z
	(equiv)	(2.0 equiv)			%	
	Bu_2CuLi (1.2)	+	–		88	89:11
	(0.6)	+	+		80	98: 2
	BuCu (1.2)	+	+		71	95: 5
	Ph_2CuLi (0.6)	+	+		84	92: 8
	Ph_2CuLi (0.6)	+	+		99	97: 3
	Bu_2CuLi (0.6)	+	+		84	28:72
	BuCu (1.2)	+	+		82	15:85

In addition to the simple organocopper reagents described above, complex reagents are also subject to the effect of Me_3SiCl. A mixed homocuprate derived from **1** is basically an allylic cuprate and unreactive. Use of Me_3SiCl and HMPA as well as silylacetylide as a "dummy" ligand afforded good results (eq 2).[6b]



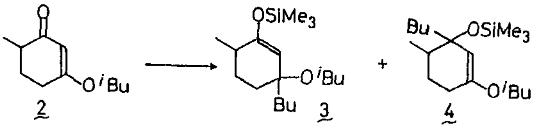
(2)

Chemoselectivity of the reaction was tested for the combination previously examined (eq 3).[5] A mixture of two aldehydes and Me_3SiCl were added at -90 °C to a solution containing 0.6 equiv of Bu_2CuLi and HMPA. GLC analysis of the reaction after 2 h below -40°C showed clean and selective reaction of the unsaturated aldehyde. The reaction without Me_3SiCl gave a complex mixture.

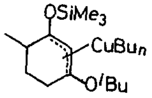


(3)

The ease with which an organocopper reagent conjugate adds to an enone shows strong correlation to the reduction potential of the enone.[12] Such correlation is considered to reflect a reaction mechanism in which electron transfer from the organometallics to the π^* orbital of the enone plays the key role. An attractive hypothesis to account for the observed rate acceleration involves coordination of Me_3SiCl with the carbonyl oxygen[13] to raise the reduction potential of the enone. Spectral studies of a mixture of methyl vinyl ketone and Me_3SiCl (with and without HMPA) in THF however revealed no sign of such coordination.[14] Nonetheless, we were intrigued by such a hypothesis and examined the reaction of 3-alkoxy enone **2** which is unreactive toward organocopper species due to its very low reduction potential.[12] The Me_3SiCl-mediated reactions of **2** with Bu_2CuLi (-78~-40 °C in THF) and BuCu (0 °C in HMPA/THF) indeed proceeded in 80--100% yield. The reaction, however, generally produced a mixture of 1,4- (**3**) and 1,2-adducts (**4**) in a ratio of 4:1 to 1:1, which varied according to very slight change of the conditions.[15] Control experiments without Me_3SiCl indicated that BuCu does not react at all under comparable conditions, and Bu_2CuLi reacts only very slowly, giving small amounts of products presumably due to in situ elimination of the 3-alkoxy group.



2 3 4



5

Recently, Corey and Boaz[7b] elegantly demonstrated that Me_3SiCl kinetically quenches the enone-cuprate addition complex, and considered this as a reason for the rate enhancement by the silane. The product distribution observed for the reaction of **2** agrees with their scheme in that the scrambling of the 1,4- and 1,2-addition pathways occurs during the C-C bond forming reaction after the formation of a nearly symmetrical silylated intermediate **5**.

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14. A similar observation was also made by Corey (ref 7b).
15. (a) The silylated adducts were not sufficiently stable for full characterization, and the product ratio was determined after conversion to methylated 3-butylcyclohexenones. The reason for the non-reproducibility is uncertain. (b) The 1,4/1,2 ratio for Me_2CuLi in ether[7c] is 1:2. We obtained a comparable number in THF.
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