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Me_3SiCl/HMPA ACCELERATED CONJUGATE ADDITION OF CATALYTIC COPPER REAGENT. STEREOSELECTIVE SYNTHESIS OF ENOL SILYL ETHER OF ALDEHYDE

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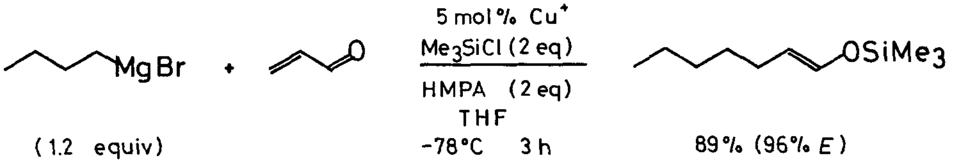
Summary: Copper-catalyzed conjugate addition of the Grignard reagents in the presence of Me_3SiCl and HMPA proceeds in much higher yield than the reaction of conventional organocopper reagents and shows very good regio-, stereo-, and chemoselectivities.

Conjugate addition of organocopper reagents,[1] originated from Kharasch's catalytic prototype,[2] undoubtedly ranks among the most important synthetic reactions.[1b] During the evolutionary course of organocopper chemistry, a belief in the superiority of stoichiometric to catalytic reagents has been cultivated; for the classical catalytic procedure is less reproducible and less selective.[1b] We wish to report here that the presence of Me_3SiCl and hexamethylphosphoric triamide (HMPA) *during* the catalytic addition reaction removes many of the drawbacks of the classical catalytic procedure, and, more importantly, opens new avenues of selectivities that have not been available even by stoichiometric reagents.[3]

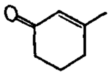
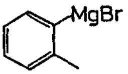
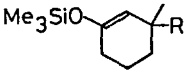
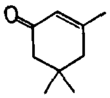
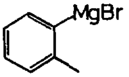
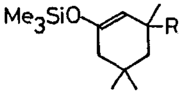
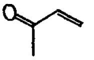
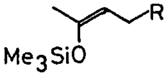
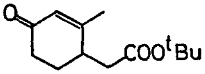
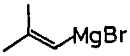
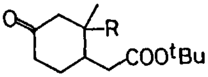
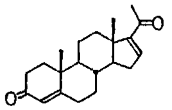
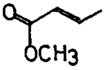
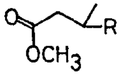


(1)

A typical result in eq 1 highlights our findings, demonstrating 1) the respectable stoichiometry required, 2) the tolerance of an unstable electrophilic partner, and 3) the high isomeric purity of the product. The use of Me_3SiCl/HMPA makes the catalytic reagent superior to the stoichiometric ones: The reaction of Gilman's reagent corresponding to eq 1 is reported to proceed in no better than 30% yield.[4] The experimental procedure[5] still retains the simplicity of the classical catalytic reaction.

It is very important to note at this point that *Me_3SiCl is not a simple enolate trap,*[6] *but accelerates the addition reaction.* Clear indication of such rate enhancement was obtained in the CuBr·Me_2S (5 mol%) catalyzed conjugate addition of *o*-tolyl- and butylmagnesium bromides onto 3-methylcyclohexenone. For such combinations of relatively unreactive compounds, the conjugate addition proceeded very slowly at -70 °C without additives (1—2% yield after 30 min). When the reaction was performed *in the presence of* Me_3SiCl (ca. 2 equiv), the yield of the conjugate adduct increased to 30--40% (4—15% of 1,2-adduct), and, with 1—2 equiv each of Me_3SiCl *and* HMPA, it became as high as 99%.[7] Under these last conditions, the ratio of 1,4-/1,2-adducts exceeded 200:1, while it was only 4:1 at best without these additives. Ether proved much inferior to THF. Under the present conditions, silylation of the Grignard reagents did not effectively competes with the conjugate addition.

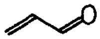
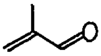
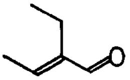
Table I. Conjugate Addition onto Unsaturated Ketones and Ester[a]

entry	Enone	RMgBr	Enol silyl ether	% yield	[E:Z]
1				77% (100%)	
2		n-C_3H_7MgBr		85	
3				80	
4		n-C_4H_9MgBr		89	
5		CH_2=CHMgBr		97	
6		n-C_4H_9MgBr		(96)	[28:72]
7		n-C_6H_{13}MgBr		91	[23:77]
8		C_6H_5MgBr		78	[46:54]
9				71[b,c]	
10		CH_3MgBr		94[d]	[2:98]
11		C_6H_5MgBr		76[b]	

[a] All reactions were carried out for 2—4 h at -78 °C according to the procedure described in footnote 5 using either 1.2 equivalent of a standardized Grignard reagent or the reagent prepared in situ from 1.5 equivalent of an organic bromide. Unless stated otherwise, yields refer to the enol silyl ether of at least 95% purity obtained by distillation. Quantitative GLC yields are in parentheses, and E:Z ratios are in brackets. The E/Z-ratio was determined capillary GLC analysis and was supported by ^{1}H NMR analysis. [b] Isolated as carbonyl compounds. [c] The reaction was performed with 4 equiv of Me_3SiCl (without HMPA). [d] Performed at -50 °C for 15 h.

Table I summarizes the results of the Me_3SiCl/HMPA accelerated reaction for various combinations of Grignard reagents and ketone- and ester-electrophiles. All results were obtained with 1.2—1.5 equiv of the Grignard reagents. Entries 9 and 10 illustrate the stereo- and chemoselective reaction. Esters also serve as electrophile of this reaction (entry 11): The yield of the reaction of PhMgBr/Me_3SiCl with crotonate was much higher (76%) than that with the corresponding Gilman's reagent (38%) and comparable with that with a higher order cuprate (75%).[8,9]

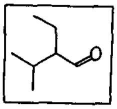
Table II. Conjugate Addition onto Unsaturated Aldehydes[a]

Entry	Enal	RMgBr (R =)	Temp (°C)	Enol Silyl Ether %yield	Enol Silyl Ether E:Z
1		n-hexyl	-78	83 (95)[b]	94:6
2		n-butyl	-78	86	97:3
3		phenyl	-78	89	86:14
4			-100	90	91:9
5		n-hexyl	-78	89	96:4
6		phenyl	-78	(91)[b]	96:4
7		phenyl	-78	89	87:13
8		n-hexyl	-100	(78)[b]	93:7
9		c-hexyl	-100	80	98.6:1.4
10		phenyl	-78	90	97:3

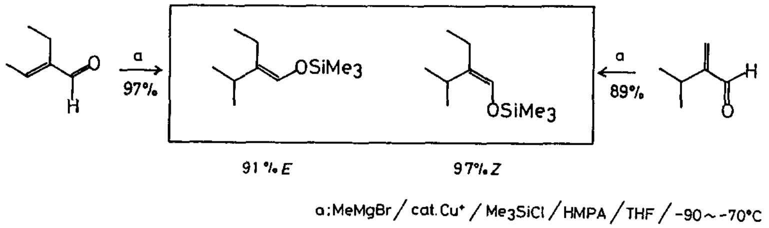
[a] See Table I. [b] Quantitative GLC yields in parentheses.

The Me_3SiCl/HMPA assisted addition reveals its highest potentiality in the reaction with enals (Table II), where none of the conventional organocopper reagents gives satisfactory results. The Grignard reagents (1.2—1.5 equiv) thus afforded aldehyde enols in almost quantitative yields.[10] Notably, the products were formed uniformly with high stereoselectivity particularly at low temperature (entries 3 and 4).

The observed selectivity formally reflects the s-trans conformation of the starting aldehydes,[11] thus providing a general synthetic route to stereodefined aldehyde enolates. For instance, both E and Z enol silyl ethers formally derived from an α-branched aldehyde **1** have been selectively prepared (eq 2). The current lack of methods for the stereoselective synthesis of aldehyde enolates would render the present reaction a useful new tool in enolate chemistry.

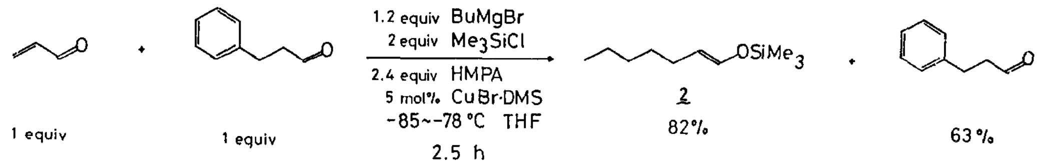


1



(2)

Finally, we describe a remarkable chemoselectivity of the reaction (eq 3). Addition of a mixture of acrolein, 3-phenylpropionaldehyde, and Me_3SiCl to a solution of butylmagnesium bromide and HMPA in THF gave the conjugate adduct **2** in 82% yield with 63% recovery of phenylpropionaldehyde. Not unexpectedly, the reaction of $BuMgBr/Cu^+$ or Bu_2CuLi at -78 °C gave a quite complex mixture containing the recovered saturated aldehyde.



(3)

Me_3SiCl has been found to accelerate the reaction of stoichiometric reagents,[14] which is the subject of the following communication.[15,16]

References

1. (a) House, H. O.; Respess, W. L.; Whitesides, G. M. J. Org. Chem. **1966**, 31, 3128. Gilman, H.; Straley, J. M. Rec. Trav. Chim. **1936**, 55, 821. (b) Review: G. H. Posner, Org. Reactions, **1972**, 19, 1.
2. Kharasch, M. S.; Tawney, P. O. J. Am. Chem. Soc. **1941**, 63, 2308.
3. (a) Reported at the Annual Meeting of the Chemical Society of Japan, April 1985, Tokyo. (b) Abstracts, *32nd Symposium on Organometallic Chemistry, Japan; November 6, Suita:* B214. (c) Cf. Nakamura, E.; Kuwajima, I. J. Am. Chem. Soc. **1984**, 106, 3368.
4. Bourgain-Commerçon, M.; Foulon, J.-P.; Normant, J. F. J. Organomet. Chem. **1982**, 228, 321. Chuit, C.; Foulon, J. P.; Normant, J. F. Tetrahedron, **1981**, 37, 1385; ibid. **1980**, 36, 2305.
5. Typical Procedure: To a cooled (-78 °C) THF (60 ml) solution of n-hexylmagnesium bromide (prepared from 35 mmol of n-hexyl bromide and 37.5 mmol of magnesium in 85--90% yield), HMPA (10.5 ml, 60 mmol), and $CuBr{\cdot}Me_2S$ (257 mg, 1.25 mmol) was added dropwise a mixture of acrolein (1.67 ml, 25 mmol) and Me_3SiCl (6.4 ml, 50 mmol) in 20 ml of THF during 30 min. After 3 h, triethylamine (7 ml) and hexane (100 ml) were added. The organic layer was washed with water to remove HMPA, and finally dried by $MgSO_4$. The 1,4-adduct (3.86 g, 83%; 94% E by GLC analysis) was obtained as an enol silyl ether by distillation (74 °C, 1 mm Hg).
6. Cf. Taylor, R. J. K. Synthesis **1985**, 364.
7. HMPA may be replaced by (less effective) polar solvents such as dimethylimidazolidinone. Conjugate addition was accelerated by $Me_2PhSiCl$ but not by tert-$BuMe_2SiCl$ or Me_3SiF.
8. Cf. Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. Tetrahedron **1984**, 40, 5005.
9. TMSCl/HMPA did not show favorable effects in the reaction with epoxides and 1,1-dialkoxycarbonylcyclopropane.
10. *Normant et al. reported the reaction of cuprates with acrolein, where* Me_3SiCl *and* triethylamine was used in situ to increase the product yield (ref 4).
11. Stereoselectivity with enones (Table I) does not conform to this "s-trans" protocol (cf. Chamberlin, A. R.; Reich, S. H. J. Am. Chem. Soc., **1985**, 107, 1440).
12. For recent observations about the function of Me_3SiCl as an activator of carbonyl groups, see; RajanBabu, T. V. J. Org. Chem. **1984**, 49, 2083. Oshino, H.; Nakamura, E.; Kuwajima, I. J. Org. Chem. **1985**, 50, 2802.
13. For the BF_3-assisted reaction of RCu reagents, in which the product is isolated as a ketone, see: Yamamoto, Y.; Yamamoto, S.; Yatagai, H.; Ishihara, Y.; Maruyama, K. J Org. Chem., **1982**, 47, 119.
14. (a) Cf. Enda, J.; Kuwajima, I. J. Am. Chem. Soc. **1985**, 107, 5495. (b) Corey, E. J.; Boaz, N. W. Tetrahedron Lett. **1985**, 26, 6015, 6019. (c) Alexakis, A.; Berlan, J.; Besace, Y. Tetrahedron Lett. **1986**, 27, 1047.
15. All conjugate adducts were characterized by spectroscopy and by elemental analysis, either as an enol silyl ether or as the carbonyl compound obtained by hydrolysis. Stereochemistry of the enol silyl ether was determined by analysis of the ^1H NMR coupling constant and/or NOE studies.
16. Financial support (to E. N.) from The Kurata Foundation (The Kurata Research Grant) and generous supply of Me_3SiCl from Toray Silicone are deeply acknowledged.

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