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Copper Reagents: A New and Efficient Solution for the Selective Addition of Metallated Propargylic Amines to Aldehydes

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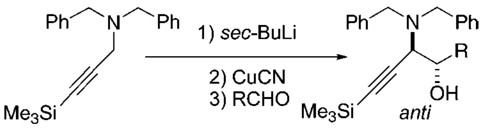
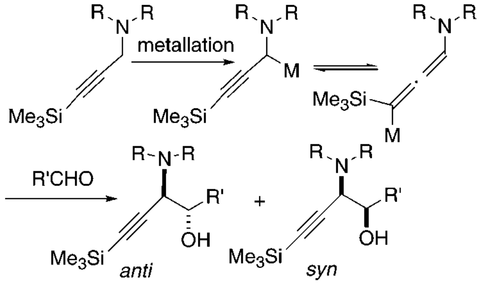
ABSTRACT



Anti α-amino-homopropargylic alcohols are prepared by addition of metallated propargylic amines to aldehydes. Among the four organometallic (LI, Zn, Ti, Cu) derivatives used, the most effective are the copper reagents.

The addition of alkoxy-subsituted allenylmetal reagents to aldehydes is widely used for the preparation of *anti*-α-alkoxy homopropargylic alcohols.[1] Surprisingly, the same reaction, using aza-substituted allenylmetal reagents, to give α-amino-homopropargylic alcohols, an interesting class of compounds considering their potential in synthesis,[2] is almost omitted. Indeed, to the best of our knowledge, there are only two reports, by Epsztein, on the synthesis of such amino alcohols by addition of metallated propargylamines amino alcohols where the anti stereomers were the major products. Unfortunately, no precise anti/syn ratio was given. Therefore, we decided to reexamine the scope and the generality of this reaction (Scheme 1). The starting propargylic amine **1** was prepared according to Scheme 2.[3] In our hand, use of *n*-BuLi or LDA was found to be ineffective, in THF, in promoting deprotonation on the propargylic position. This was quantitatively achieved using *sec*-Buli in THF, as shown by a deuteriolysis experiment that gave a mixture of deuterated propargylic and allenic amines **2** and **3** (**2**/**3** = 65/35) in quantitative yield (Scheme 2). The stereochemistry of the addition of the lithium derivative to aldehydes (Scheme 3) was then studied. The results obtained are shown in Table 1 (entries 1−7). The first point to note is that, in any case (even after transmetallation), no allenic derivatives were obtained, the only observed compounds being the propargylic amino alcohols **5a**−**g**. The configuration of *anti*-**5a** was determined by X-ray analysis[4] and by ^{1}H NMR (NOE) of

Scheme 1



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[1] Scheidt, K. A.; Bannister, T. D.; Tasaka, A.; Wendt, M. D.; Savall, B. D.; Fegley, G. J.; Roush, W. R. *J. Am. Chem. Soc.* **2002**, *124*, 6981−6990 and references therein. For addition to imines see: Poisson, J. F.; Normant, J. F. *Org. Lett.* **2001**, *3*, 1889−1891.

[2] Fleming, J. J.; Fiori, K. W.; Du Bois, J. *J. Am. Chem. Soc.* **2003**, *125*, 2028−2029.

[3] Ireland, R. E.; Anderson, R. C.; Badoud, R.; Fitzsimmons, B. J.; McGarvey, G. J.; Thaisrivongs, S.; Wilcox, C. S. *J. Am. Chem. Soc.* **1983**, *105*, 1988.

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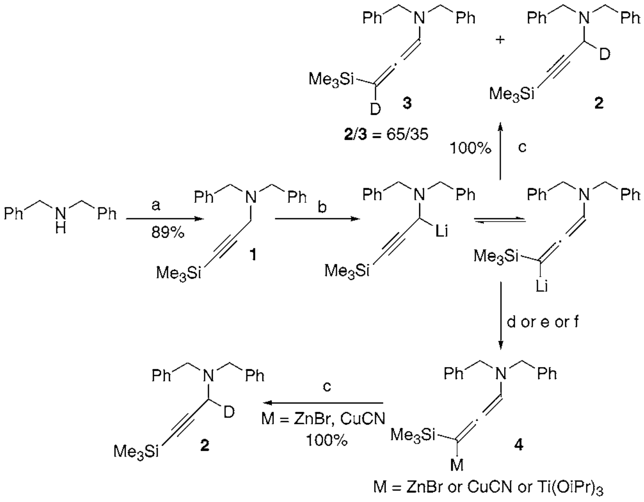
Scheme 2[a]



[a] Reactions conditions: (a) propargyl bromide, K_2CO_3, CH_3CN, purification, and then MeLi, TMSCl, THF, 0 °C. (b) *sec*-BuLi (1.1 equiv), THF, −80 to −40 °C. (c) D_2O. (d) $ZnBr_2$ (1.1 equiv), −80 °C or room temperature. (e) CuCN, 2LiCl (1.4 equiv), −80 °C to −30 °C. (f) $Ti(OiPr)_4$ (1.1 equiv), −78 °C.

Scheme 3

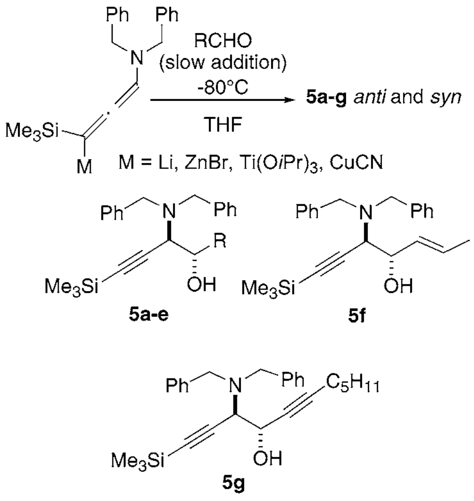


Table 1. Additions of Metallated Derivatives to Aldehydes

entry	M	R	product	anti/syn[a]	yield (%)[b]
1	Li	*t*-Bu	**5a**	67/33	73
2		*c*-hexyl	**5b**	65/35	78
3		*n*-hexyl	**5c**	62/38	82
4		*i*-Pr	**5d**	65/35	84
5		Ph	**5e**	50/50	82
6		propenyl	**5f**	63/37	79
7		hexynyl	**5g**	75/25	65
8	ZnBr	*t*-Bu	**5a**	>95/5	81
9		*c*-hexyl	**5b**	>95/5	81
10		*n*-hexyl	**5c**	85/15	81
11		*i*-Pr[c]	**5d**	90/10	86
12		*i*-Pr	**5d**	93/7	88
13		Ph	**5e**	68/32	79
14		propenyl	**5f**	88/12	83
15		heptynyl	**5g**	76/24[d]	85
16	$Ti(OiPr)_3$	*i*-Pr	**5d**	50/50	85
17	CuCN	*i*-Pr	**5d**	>95/5	86
18		*c*-hexyl	**5b**	>95/5	81
19		*n*-hexyl	**5c**	>95/5	82
20		Ph	**5e**	95/5	79
21		propenyl	**5f**	95/5	83
22		heptynyl	**5g**	93/7[d]	74

[a] Determined by ^1H NMR of the crude product. [b] Isolated product. [c] Fast addition of the aldehyde. [d] Unseparable mixture.

the corresponding oxazolidinones derived from *anti*-**5b** and *anti*-**5c**.[5] As shown in the table, with the lithium derivative, the *anti*-amino alcohols were isolated in good yields but with poor (or no) selectivity. A transmetallation of the lithiated intermediate by $ZnBr_2$[6] afforded the zinc derivative, which was quantitatively deuterated into the propargylamine **2**, probably via the allenyl zinc reagent **4**.[7] The addition of this zinc derivative to aldehydes was found to be more anti selective than the addition of the lithium derivative (Table, entries 8−15). This selectivity was sensitive to steric effects, the best results being obtained with bulky aldehydes (entries 8, 9, and 12). Furthermore, better results were obtained by a slow addition of the aldehyde (via syringe pump) into the zinc derivative (compare entries 11 and 12). Such observation is in favor of a kinetic control for the reaction. It is interesting to note that deprotonation by *sec*-BuLi and transmetallation by $ZnBr_2$ of *anti*-**5b** gave the amino alcohol completely unchanged after several hours of stirring, even at room temperature. The observed anti stereochemistry is in accordance with the classical Yamamoto−Chodkiewicz's cyclic transition state commonly involved for analoguous reactions where the formation of the *anti*-amino alcohol is favored by steric interactions (Scheme 4).[8] Nevertheless, poor selectivities were obtained with benzaldehyde, crotonaldehyde, and octynal (entries 13−15), and we decided to explore the possiblity of using the titanium derivative,[9] which was obtained by transmetallation of the lithium derivative by titanium tetraisopropoxyde. Unfortunately, and curiously, the addition of this titanium reagent to isobutyraldehyde was totally unselective (entry 16).

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[4] Crystallographic data for the structural analysis have been deposited with the crystallographic Data Center as deposition no. CCDC209061.

[5] Barret, A. G. M.; Seefeld, M. A.; White, J. P. *J. Org. Chem* **1996**, *61*, 2677−2685. Bergmeier, S. C.; Stanchina, D. M. *Tetrahedron Lett.* **1995**, *36*, 4533−4536.

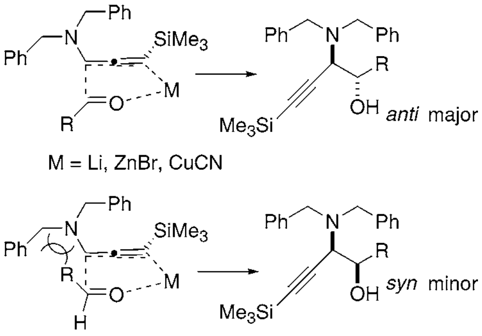
[6] We have checked that the nature of the zinc salt (ZnI_2 or $ZnBr_2$) did not affect the selectivity.

[7] Structure of these organometallic reagents is under study but is probably allenic: see ref 8.

[8] Epzstein, R. The Formation and Transformations of Allenic and α-Acetylenic Carbanions. In *Comprehensive Carbanions Chemistry*; Buncel, E., Durst, T., Eds.; Elsevier: Amsterdam, 1984; Vol. B, pp 107−175. Yamamoto, H. Propargyl and Allenyl Organometallics. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon Press: London, 1991; Vol. 2, pp 81−98.

[9] Anies, C.; Lallemand, J. Y.; Pancrazi, A. *Tetrahedron Lett.* **1996**, *37*, 5519−5522 and references therein.

Scheme 4



We then turned our attention to copper derivatives for which preparation was never reported.[10] This new copper derivative was prepared by transmetallation of the lithium derivative with CuCN, 2LiCl. Deuteriolysis afforded exclusively, and quantitatively, the propargylamine **2** (Scheme 2). We were very pleased to observe that the addition to aldehydes occurred cleanly, without the formation of any allenic derivatives. The *anti*-amino alcohols (entries 17−22) were obtained with very good stereoselectivity even for benzaldehyde (entry 20). Noteworthy are the results obtained with crotonaldehyde and octynal (entries 21 and 22). With these unsaturated aldehydes, no product resulting from a conjugate addition was observed[11] and again a significant increase of the selectivity was obtained (compare entries 14 and 15 and entries 21 and 22). In conclusion, we have shown that the addition of lithium or titanium reagents, derived from propargylic amines, to aldehydes occurs with poor selectivity. With the zinc derivative, a significant enhancement of the anti selectivity, leading to good results, is obtained except with benzaldehyde, crotonaldehyde, and octynal. With the copper derivative, which is obviously a reagent of choice for such reactions, the *anti*-amino alcohols are obtained with good selectivity, regardless of the nature of the aldehyde. We are currently studying the structure (allenyl-propargyl) of these organometallic reagents, their configurational stability, and the possible extension to the proparglic ether analogues.

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Supporting Information Available: Spectral and analytical data and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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[10] For the use of propargyl-allenyl copper reagents, see: Lam, H. W.; Pattenden, G *Angew. Chem., Int. Ed.* **2002**, *41*, 508−511. Rozema, M. J.; Knochel, P. *Tetrahedron Lett.* **1991**, *32*, 1855−1858. Bednarski, P. J.; Nelson, S. D. *J. Med. Chem.* **1989**, *32*, 203-213. de Graaf, W.; Boersma, J.; van Koten, G. *J. Organomet. Chem.* **1989**, *378*, 115−124. Ruitenberg, K.; Vermeer, P. *J. Organomet. Chem.* **1983**, *256*, 175−180. Ruitenberg, K.; Kleijn, H.; Meijer, J.; Oostveen, E. A.; Vermeer, P. *J. Organomet. Chem.* **1982**, *224*, 399−405. Michelot, D.; Linstrumelle, G. *Tetrahedron Lett.* **1976**, 275−276. Commerçon, A.; Normant, J.; Villieras, J. *J. Organomet. Chem.* **1975**, *93*, 415−421. Ganem, B. *Tetrahedron Lett.* **1974**, 4467−4470.

[11] With heptynal, a small amount (10%) of an undetermined product was obtained.