Carboalumination of 1-Alkynes and in Situ Transmetalation to Higher Order Cyanocuprates. Stereospecific Synthesis of Tri- and Disubstituted Olefins by Conjugate Addition to Enones

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Summary: A method is described for the direct carbo-alumination and in situ cuprate exchange that makes possible the conjugate addition of disubstituted (R, CH$_3$) or monosubstituted (R, H) vinyl anions to α,β-unsaturated ketones. The process results in high yields (63-95%) of conjugate addition products *without* the customary intervention of the more standard vinyl iodide and then cuprate formation.

Trisubstituted double bonds are a characteristic feature of many important natural products such as Avermectin,[1] Nargenicin,[2] Pumiliotoxin,[3] Geodiamolide,[4] and FK-506,[5] to name only a few. A number of useful synthetic methods for trisubstituted olefin synthesis have been reported,[6] especially for the conversion of propargylic alcohols to either 2- or 3-alkylated allylic alcohols.[7] In general, vinyl organometallics are among the most popular reagents for the synthesis of regio- and stereodefined olefins, and an often used method for their preparation involves carbometalation of 1-alkynes. However, this process is usually efficient only in the case of aluminum.[8] Carbocupration[9] of 1-alkynes has been extensively investigated, but the yields of the desired vinyl cuprates are often low, and, especially in the case of methyl group transfer from copper to the alkyne, reaction times are extremely long.[10]

In contrast, Zr-catalyzed carboalumination[8c] proceeds well and in high yield with a variety of substrates. The vinylalanes thus generated can in special cases be used directly as nucleophiles,[11] though they are usually converted into the corresponding vinyl cuprates in a three step
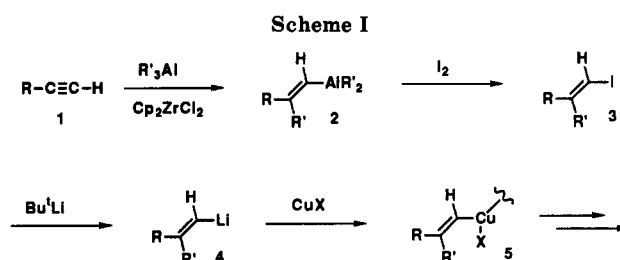
Scheme I

sequence:[12] treatment with I$_2$ to generate the vinyl iodide, metal-halogen exchange, and addition of the vinyllithium to cuprous salts (Scheme I).

Though often this multistep sequence proceeds in an acceptable yield, from a preparative standpoint it would be far more desirable to have a shorter, more direct procedure. This report describes a new synthetic method which allows the stereospecific conversion of 1-alkynes into vinyl cuprates via carboalumination followed by in situ transmetalation to a higher order (HO) cyanocuprate,[13] thereby avoiding the generation of vinyl iodides **3** and vinyllithiums **4**.

The zirconocene dichloride catalyzed carboalumination of 1-hexyne (**7**) and 1-((tert-butyldimethylsilyl)oxy)-2-(R)-methyl-4-pentyne (**9**) with AlMe$_3$ was performed under standard conditions.[8] A solution of the alane in Et$_2$O was added to a preformed mixture of 2 equiv of 1-hexynyllithium and 1 equiv of CuCN at -23 °C in THF, followed by the dropwise addition of 0.9 equiv of the enone. The yields of the vinylogous addition products in Table I are based on chromatographically purified material.

Several features of this novel ligand exchange process deserve special comment. First, only a slight excess of alkyne is used, thus synthetically precious enantiomerically pure compounds such as **9** are not wasted. The two nontransferable[15] alkyne ligands on the HO cuprate do not interfere in the addition process; the reaction is fast and

(1) Davies, H. G.; Green, R. H. *Nat. Prod. Rep.* **1986**, *3*, 87.

(2) Celmer, W. D.; Chmurny, G. N.; Moppett, C. E.; Ware, R. S.; Watts, P. C.; Whipple, E. B. *J. Am. Chem. Soc.* **1980**, *102*, 4203.

(3) Witkop, B.; Gössinger, E. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: New York, 1983; Vol. 21, Chapter 5.

(4) Chan, W. R.; Tinto, W. F.; Manchand, P. S.; Todaro, L. *J. Org. Chem.* **1987**, *52*, 3091.

(5) Tanaka, H.; Kuroda, A.; Marusawa, H.; Hatanaka, H.; Kino, T.; Goto, T.; Hashimoto, M. *J. Am. Chem. Soc.* **1987**, *109*, 5031.

(6) (a) Kocienski, P. J.; Love, C. J.; Whitby, R. J.; Costello, G.; Roberts, D. A. *Tetrahedron* **1989**, *45*, 3839. (b) Desmond, R.; Mills, S. G.; Volante, R. P.; Shinkai, I. *Tetrahedron Lett.* **1988**, *29*, 3895. (c) Maryanoff, B. E.; Reitz, A. B. *Chem. Rev.* **1989**, *89*, 863. (d) Ziegler, F. E. *Chem. Rev.* **1988**, *88*, 1423.

(7) (a) Corey, E. J.; Katzenellenbogen, J. A.; Posner, G. H. *J. Am. Chem. Soc.* **1967**, *89*, 4245. (b) Denmark, S. E.; Jones, T. K. *J. Org. Chem.* **1982**, *47*, 4595.

(8) (a) Sharma, S.; Oehlschlager, A. C. *J. Org. Chem.* **1989**, *54*, 5064. (b) Negishi, E.; Valente, L. F.; Kobayashi, M. *J. Am. Chem. Soc.* **1980**, *102*, 3298. (c) Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333. (d) Zweifel, G.; Miller, J. A. *Org. React.* **1984**, *32*, 375.

(9) (a) Normant, J. F.; Alexakis, A. *Synthesis* **1981**, 841. (b) Lipshutz, B. H. *Synthesis* **1987**, 325. (c) Foulon, J. P.; Bourgain-Commercon, M.; Normant, J. F. *Tetrahedron* **1986**, *42*, 1389.

(10) (a) Chou, S.-S. P.; Kuo, H.-W.; Wang, C.-J.; Tsai, C.-Y.; Sun, C.-M. *J. Org. Chem.* **1989**, *54*, 868. (b) Rao, S. A.; Periasamy, M. *Tetrahedron Lett.* **1988**, *29*, 4313. (c) Marfat, A.; McGuirk, P. R.; Helquist, P. *J. Org. Chem.* **1979**, *44*, 3888.

(11) (a) Bernady, K. F.; Weiss, M. J. *Tetrahedron Lett.* **1972**, 4083. (b) Hooz, J.; Layton, R. B. *Can. J. Chem.* **1973**, *51*, 2098. (c) Ashby, E. C.; Heinsohn, G. *J. Org. Chem.* **1974**, *39*, 3297. (d) Collins, P. W.; Dajani, E. Z.; Bruhn, M. S.; Brown, C. H.; Palmer, J. R.; Pappo, R. *Tetrahedron Lett.* **1975**, 4217. (e) Bernady, K. F.; Poletto, J. F.; Weiss, M. J. *Tetrahedron Lett.* **1975**, 765. (f) Bagnell, L.; Jeffery, E. A.; Meisters, A.; Mole, T. *Aust. J. Chem.* **1975**, *28*, 801. (g) Alexakis, A.; Jachiet, D. *Tetrahedron* **1989**, *45*, 6197.

(12) For recent examples, see: (a) Ley, S. V.; Anthony, N. J.; Armstrong, A.; Brasca, M. G.; Clarke, T.; Culshaw, D.; Greck, Ch.; Grice, P.; Jones, A. B.; Lygo, B.; Madin, A.; Sheppard, R. N.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1989**, *45*, 7161. (b) Baker, R.; Castro, J. L. *J. Chem. Soc., Chem. Commun.* **1989**, 378.

(13) (a) Lipshutz, B. H.; Wilhelm, R. S. *J. Am. Chem. Soc.* **1982**, *104*, 4696. (b) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A.; Parker, D. *J. Org. Chem.* **1984**, *49*, 3928.

(14) The preparation of ketone 8 is typical for the reaction procedure: A suspension of 53 mg (0.18 mmol) of zirconocene dichloride in 2 mL of dry 1,2-dichloroethane was treated at 0 °C with 0.78 mL (1.56 mmol) of a 2.0 M solution of trimethylaluminum in toluene, followed by addition of the solution of 46 mg (0.56 mmol) of 1-hexyne in 0.3 mL of 1,2-dichloroethane. The reaction mixture was stirred for 3 h at room temperature, the solvent was removed in vacuo, and 3 mL of dry Et$_2$O was added. The etheral solution of the vinylalane was added to the solution of 50 mg (0.56 mmol) of flame-dried CuCN in 2 mL of THF, which had previously been treated at -23 °C with 2.24 mL (1.12 mmol) of a 0.5 M solution of 1-hexynyllithium in THF/hexane. After the reaction mixture was stirred for 5 min at -23 °C, a solution of 48 mg (0.50 mmol) of cyclohexenone in 1 mL of Et$_2$O was added dropwise, and stirring at -23 °C was continued for another 30 min. The mixture was quenched into a 9:1 saturated ammonium chloride/ammonium hydroxide solution and extracted three times with Et$_2$O, and the combined organic layers were dried (MgSO$_4$), filtered through silica gel, and chromatographed (silica gel, EtOAc/hexane, 1:5) to yield 92 mg (95%) of ketone 8.

(15) Corey, E. J.; Beames, D. J. *J. Am. Chem. Soc.* **1972**, *94*, 7210.

Table I. Carboalumination Followed by in Situ Cuprate Formation/Conjugate Addition Reactions with $(C_4H_9C_2)_2CuCNLi_2$[14]

enone	alkyne	alane	product[a]	yield
6	7	AlMe$_3$	8	95%[14]
6	9	AlMe$_3$	10	92%
11	9	AlMe$_3$	12	72%
13	7	AlMe$_3$	14	63%
15	7	AlMe$_3$	16	64%
6	7	Dibal-H	17	72%

[a] All products were fully characterized by IR, NMR, MS, and C, H analyses.

efficient (typically 4–5 h overall reaction time), and the desired products can easily be isolated from the reaction mixture. Spectroscopic investigation[16] of the addition product **12** shows an axial addition of the vinyl organometallic and a clean *E* stereochemistry of the double bond, thus rendering a radical mechanism[11d] unlikely. Addi-

(16) The vicinal coupling constants of the spiroketal ring hydrogens correspond nicely to an axial enone addition product:

$J_{A,B}$: 15.8 Hz
$J_{A,C}$: 5.9 Hz
$J_{B,C}$: 4 Hz
$J_{C,D}$: 10.2 Hz
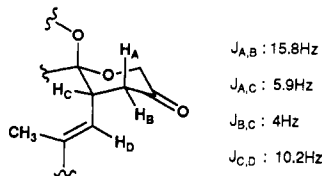
Additionally, the olefin geometry can be assigned based upon the characteristic ^{13}C NMR resonances of the methyl substituent in *E*- and *Z*-trisubstituted olefin systems (16 and 24 ppm, respectively; cf. Jones, T. K.; Mills, S. G.; Reamer, R. A.; Askin, D.; Desmond, R.; Volante, R. P.; Shinkai, I. *J. Am. Chem. Soc.* **1989**, *111*, 1157. Ragan, J. A.; Nakatsuka, M.; Smith, D. B.; Uehling, D. E.; Schreiber, S. L. *J. Org. Chem.* **1989**, *54*, 4267).

Scheme II
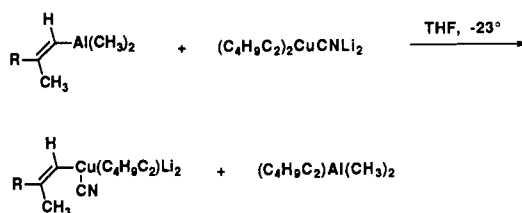
tionally, no addition of the vinylalanes or their corresponding ate complexes to cyclohexenone could be observed in the absence of the HO cuprate.

Based upon these observations and published precedence[17] for the transmetalation of vinylstannanes to HO cuprates the following hypothetical reaction mechanism is proposed (Scheme II).

The transfer of the vinyl ligand from aluminum to copper is triggered by the release of one of the ligands of the copper ate complex, possibly leading to an intermediate aluminum ate complex.[18] The driving force for this fast (ca. 5 min at –23 °C) and apparently quantitative ligand exchange reaction is not entirely clear at the moment, but presumably involves, similar to the vinylstannane case,[17] preferential and thermodynamically favoured transfer of a vinyl group from Al[11] and one of the two acetylene ligands from Cu.[15,19] The in situ generated HO cyanocuprate then adds in the expected fashion[9b] to α,β-enones.

In a similar way, hydroalumination[20] of 1-hexyne with Dibal-H followed by in situ cuprate formation with (C_4-H_9C_2)$_2$CuCNLi$_2$ and conjugate addition to cyclohexenone leads in 72% yield to the *E*-olefin **17**, thus expanding the scope of the process to disubstituted double bonds.

In summary, the new protocol for in situ cuprate formation from vinylalanes allows the direct use of the versatile zirconocene dichloride catalyzed carboalumination of 1-alkynes for conjugate addition reactions and the straightforward stereospecific synthesis of trisubstituted alkenes. Overall ease and simplicity besides an economic use of reactive agents are the main features of this new example of a synthetically useful ligand exchange between metal centers.[21]

(17) Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.

(18) Two interesting observations deserve to be mentioned at this point. First, a vinylalane ate complex does *not* transfer the vinyl ligand to the HO cyanocuprate under the standard reaction conditions, nor does a combination of vinylalane and lower order Me$_2$CuLi lead to any enone addition product.

(19) (a) Kang, J.; Cho, W.; Lee, W. K. *J. Org. Chem.* **1984**, *49*, 1838. (b) House, H. O.; Umen, M. *J. Org. Chem.* **1973**, *38*, 3893. (c) Corey, E. J.; Floyd, D.; Lipshutz, B. H. *J. Org. Chem.* **1978**, *43*, 3418. (d) Acker, R. D. *Tetrahedron Lett.* **1978**, 2399. (e) Hamon, L.; Levisalles, J. *J. Organomet. Chem.* **1983**, *251*, 133.

(20) Zweifel, G.; Steele, R. B. *J. Am. Chem. Soc.* **1967**, *89*, 2753.

(21) Collman, J.; Hegedus, L. S.; Norton, J. R.; Finke, R. G. In *Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987.