J|A|C|S
COMMUNICATIONS

Controlling Regiochemistry in Negishi Carboaluminations. Fine Tuning the Ligand on Zirconium

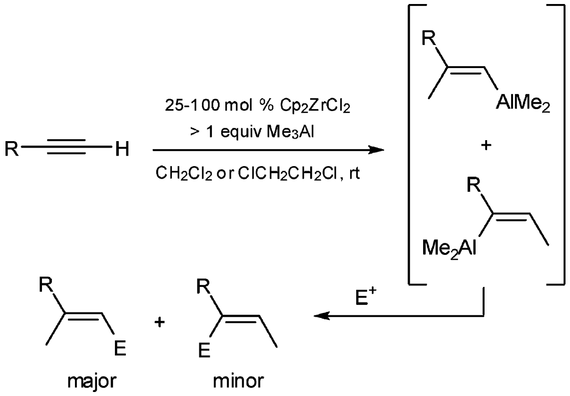
Bruce H. Lipshutz,* Tom Butler, and Asher Lower

Department of Chemistry & Biochemistry, University of California, Santa Barbara, California 93106

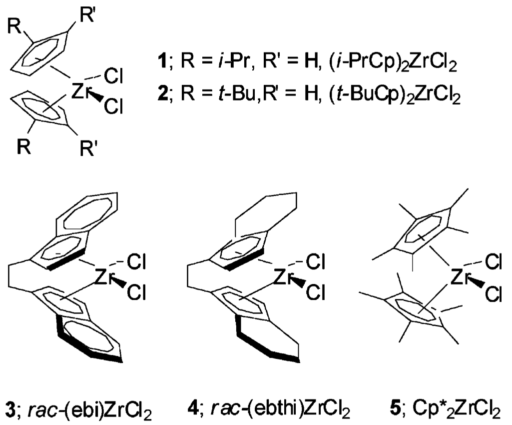
Received August 8, 2006; E-mail: lipshutz@chem.ucsb.edu

Among various "name" reactions[1] in organometallic chemistry is the Negishi carboalumination, initially reported close to three decades ago.[2] Today, it is a textbook method, especially valued for the stereospecific functionalization of readily available alkynes. As originally described,[3] the combination of zirconocene dichloride (Cp_2ZrCl_2, 25−100 mole percent) and trimethylaluminum (TMA, $\geq$1 equiv) in a chlorinated solvent (dichloromethane, DCM or 1,2-dichloroethane, DCE) leads to a net cis-addition of TMA across the (commonly terminal) acetylene, affording a mix of *E*-vinylalane and the corresponding regioisomer usually on the order of ca. 95:5 (Scheme 1).[3−5]

Scheme 1. Traditional Negishi Carboalumination



The reactivity of Cp_2ZrCl_2/TMA can be dramatically increased on the basis of the breakthrough observation by Wipf and co-workers,[6] where introduction of either water or methyl aluminoxanes (MAO) (1 equiv relative to TMA) both leads to a faster carboalumination at lower temperatures (−78 °C) and drops the required level of zirconium catalyst to ca. 5%. Notwithstanding these impressive advances, left unsolved is the question of regioselectivity, which can be variable depending upon substrate, solvent, and temperature of the carboalumination. Moreover, subsequent C−C bond forming cross-couplings are rare given the reduced reactivity of the oxygen-bearing vinylalane intermediates generated under these modified conditions.[6] A new procedure that provides not only improved regiocontrol but additional benefits with respect to environmental concerns and convenient room-temperature reactions may offer opportunities for expanded use and perhaps industrial applications. In this communication we disclose a solution to these long-standing issues, highlighting the influence of the zirconium catalyst in controlling the regiochemistry of a Negishi carboalumination.

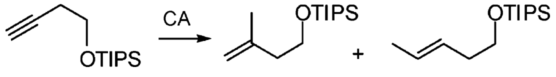


1; R = *i*-Pr, R' = H, (*i*-PrCp)$_2$ZrCl$_2$
2; R = *t*-Bu, R' = H, (*t*-BuCp)$_2$ZrCl$_2$

3; *rac*-(ebi)ZrCl$_2$ **4**; *rac*-(ebthi)ZrCl$_2$ **5**; Cp*$_2$ZrCl$_2$

Figure 1. Zirconocene dichlorides studied in Negishi carboalumination.

Table 1. Effect of Ligand and Solvent on Regiochemistry of Carboalumination (CA) at Room Temperature



6 **7** **8**

entry	catalyst	solvent	regiochemistry[a]
1	Cp_2ZrCl_2	DCE[b]	< 96:4
2	*rac*-(ebi)ZrCl$_2$[c] (**3**)	DCE[b]	100:0
3	Cp_2ZrCl_2	$PhCH_3$	< 94:6
4	*rac*-(ebi)ZrCl$_2$[c] (**3**)	$PhCH_3$	99.8:0.2
5	*rac*-(ebthi)ZrCl$_2$[d] (**4**)	$PhCH_3$	100:0
6	(*i*-PrCp)$_2$ZrCl$_2$ (**1**)	$PhCH_3$	100:0[e]
7	(*t*-BuCp)$_2$ZrCl$_2$ (**2**)	$PhCH_3$	NR[f]
8	Cp*ZrCl$_2$ (**5**)	$PhCH_3$	NR[f]
9	*rac*-(ebi)ZrCl$_2$[c] (**3**)	$PhCF_3$	94:6

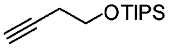
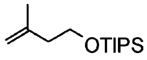
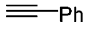
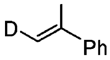
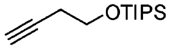
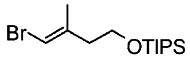
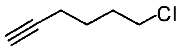
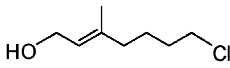
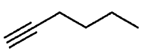
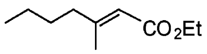
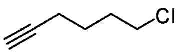
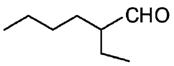
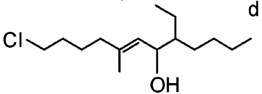
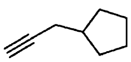
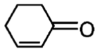
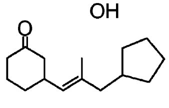
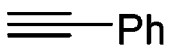
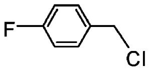
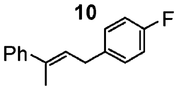
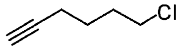
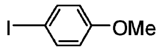
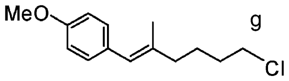
[a] Ratio of **7**:**8**, determined by GC. [b] DCE = 1,2-dichloroethane. [c] ebi = 1,2-ethylene-1,1′-bis(η^5-indenyl). [d] ebthi = 1,2-ethylene-1,1′-bis(η^5-tetrahydroindenyl). [e] Low conversion (ca. 20%) after 24 h at room temperature. [f] NR = no reaction.

Although mechanistic details are limited, both TMA and Cp_2ZrCl_2 are known to be essential for carboalumination of an alkyne.[7] Reasoning that steric factors in the Zr/Al catalyst should exert a major influence on the observed regioselectivity, we studied several commercially available zirconocene dichlorides **1**−**5** in place of Cp_2ZrCl_2 (Figure 1).[8]

Considerable effort was also made to eliminate use of chlorinated solvents, such as the typically employed class 1 solvent DCE or reclassified (to class 2) solvent DCM.[9] As illustrated in Table 1, with the use of alkyne **6** as a model substrate, the ligands on Zr were observed to have a dramatic effect on the ratio of terminal/internal vinylalane formed, as reflected in products of protio quenched **7** and **8**. The amount of Zr catalyst could be minimized to the 5% range, while inclusion of inexpensive MAO (5%)

10.1021/ja065769b CCC: $33.50

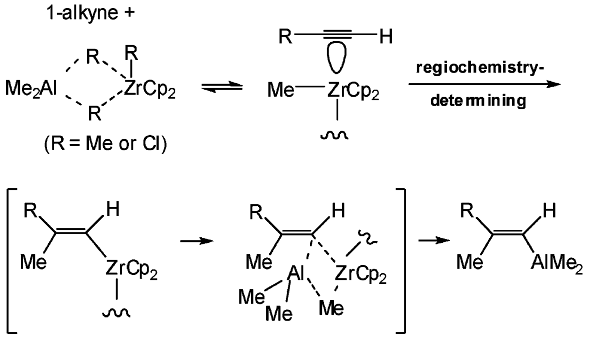
Table 2. Representative Examples: Carboalumination/Couplings

entry	alkyne	E^+	product	yield(%)[a]	regiochemistry[b]
A		H_2O		82	>99:1 [c]
B		D_2O		78	99.3:0.7
C		NBS		74	>99:1 [c]
D		HCHO		85	99.9:0.1
E		Cl-CO_2Et		88	>99:1 [c]
F			 [d]	84	>99:1 [c]
G	 9		 [e] 10	84	>99:1 [c]
H			 [f]	82	99.7:0.3
I			 [g]	87	99.9:0.1

[a] Isolated, chromatographically purified material. [b] Determined by GC analyses. [c] Other regioisomer not detected. [d] An 8:1 ratio of diastereomers. [e] Used CuCN (0.10 equiv) as catalyst; cf. ref 15. [f] Used catalytic Ni(0); cf. refs 16 and 18. [g] Used catalytic Ni(0); cf. ref 23.

compensated for the drop in reaction rate expected as the percentage of zirconocene dichloride was lowered. Increasing the amount of MAO while maintaining the Zr catalyst within the 5% level afforded significantly lower yields between vinylalanes and electrophiles (other than H^+) in subsequent reactions. Thus, while traditional parameters led to a <96/4 ratio (entry 1), the Brintzinger catalyst **3**[10] gave a regiospecific carboalumination in DCE (entry 2). Switching to far "greener" toluene decreased selectivity to an even greater extent using Cp_2ZrCl_2 (entry 3). By contrast, racemic (ebi)-$ZrCl_2$ (the Brintzinger zirconocene, **3**) again gave close to 100% of the *E*-alane-derived product (entry 4). The tetrahydroindenyl analogue **4**[11] also led to an especially discriminating reagent, giving (albeit at a greatly reduced rate) exclusively the desired regioisomer in toluene at room temperature (entry 5). Likewise, zirconocene catalyst **1** was found to be very effective in this hydrocarbon solvent (entry 6), although presumably for steric reasons led to a marked decrease in the rate of carboalumination. Catalyst **2**, with each cyclopentadiene substituted with a *t*-butyl group (entry 7),[8] as with the pentamethylcyclopentadiene (Cp*) analogue (entry 8) and in line with this trend, completely inhibited carboalumination. Use of the DCM replacement solvent, $PhCF_3$,[12] surprisingly negated the selectivity of the Brintzinger catalyst (compare entries 2 and 4 with entry 9), an observation not readily understood since the polarity of $PhCF_3$ is similar to that of DCM. Nonetheless, by fine-tuning the nature of the ligand on zirconium,[13] a balance in reactivity is achieved, reflecting accessibility of the Lewis acidic metal orbital to the acetylene (e.g., as viewed for Zr,[14] Scheme 2) and selectivity manifested in the minimization of steric interactions in the transition state that directs the ligated metal to the least hindered site in a terminal alkyne.

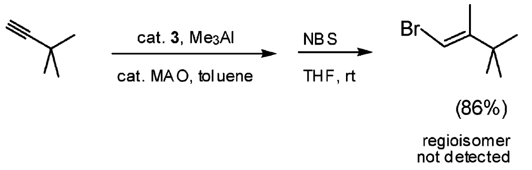
Scheme 2. A Proposed Mechanism Featuring Addition of the Alkyne to the Zr Catalyst



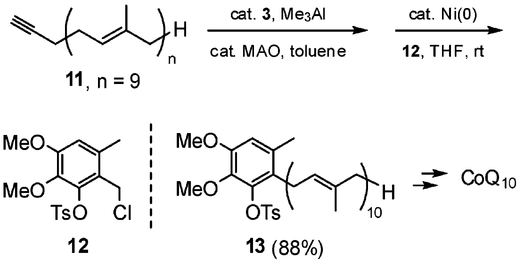
Several 1-alkynes were treated under these new conditions using the combination of 5 mol % of the Brintzinger zirconocene catalyst, 5 mol % MAO, and excess (1.5 equiv) TMA in toluene at ambient temperatures (Table 2). The electrophiles (E^+) chosen are representative of the various quenching/cross-coupling options available to vinylalanes and are commonly used in synthesis. Thus, installation of a proton (entry A), deuteron (entry B), halogen (entry C), hydroxymethyl (entry D), carboethoxy (entry E), and a substituted alcohol (entry F) all took place in good yields. After the carboalumination of alkyne **9**, a CuCN-catalyzed[15] 1,4-addition of the in situ formed vinylalane intermediate occurred to smoothly produce ketone **10** (entry G). Two group 10 metal-catalyzed C−C bond formations between a carbometallated alkyne and a benzylic chloride (entry H)[16] and an aryl iodide (entry I) could also be readily achieved. Notably, independent of subsequent handling of intermediate vinylalanes, the initial regioselectivity of the carboalumination in each case was uniformly high.

While branching at the propargylic site was anticipated to further encourage C_{sp2}−metal bond formation at the alkyne terminus, the steric impact on rate remained to be addressed. Thus, *t*-butylacetylene was carboaluminated overnight using our standardized reaction parameters (Scheme 3). Subsequent quenching with NBS led to the derived *E*-vinyl bromide in good isolated yield. By capillary GC, none of the regioisomer could be detected.

Scheme 3. Carboalumination of an α-Branched Alkyne



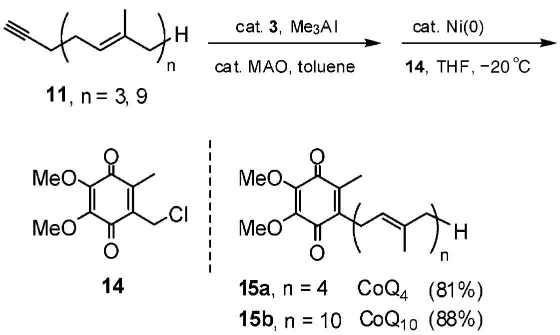
Scheme 4. Synthesis of a Precursor (**13**) to Coenzyme Q_{10}



Carboalumination of the 48-carbon polyenyne **11**[17] (Scheme 4), derived from the nine prenoidal unit allylic alcohol solanesol, in toluene at room temperature using 5% Cp_2ZrCl_2, 5% MAO, and Me_3Al leads to only a 90:10 mix of regioisomeric vinylalanes. Switching to catalyst **3**, however, upon subsequent Ni(0)-catalyzed cross-coupling[18] with benzylic chloride **12**, leads to known coenzyme Q_{10} (CoQ_{10}) precursor **13** in excellent isolated yield.[19]

An alternative, more direct route to this series of naturally occurring quinones uses known[19] chloromethylated *para*-quinone **14**. Carboalumination/coupling of farnesyl-derived acetylene **11** (n = 3)[20] led to the lower homologue, CoQ_4 (**15a**; Scheme 5), in good isolated yield (98.8:1.2 regiochemistry). Identical conditions applied to **11**, n = 9, led in one pot to CoQ_{10} (**15b**; regioselectivity $\geq$98.5%).[21,22]

Scheme 5. Synthesis of CoQ_4 and CoQ_{10}



In summary, new technology has been developed that significantly advances the fundamental utility of Negishi carboaluminations.[24] From mechanistic considerations, selection of the appropriate ligand on zirconium has been found to impart a very high degree of regiocontrol to these valued multicomponent couplings. Catalyst levels on the order of 5% are effective, the inexpensive additive MAO can be employed in limited quantities to accelerate carboaluminations, and the process can now be effected in an environmentally friendly solvent, toluene, at ambient temperatures.

Acknowledgment. Financial support provided by Zymes, LLC (Hasbrouck Heights, NJ) is gratefully acknowledged. We are indebted to Boulder Scientific Co. for supplying most of the zirconocenes used in this study.

Supporting Information Available: Procedures and spectral data for all new products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Kurti, L.; Czako, B. In *Strategic Applications of Named Reactions in Organic Synthesis*; Elsevier: Burlington, MA, 2005.
(2) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252.
(3) *Metallocenes in Regio- and Stereoselective Synthesis*; Takahashi, T., Ed.; Spinger Verlag: Heidelberg, Germany, 2005.
(4) For ligand variation in ethyl alumination, see Shibata, K.; Aida, T.; Inoue, S. *Tetrahedron Lett.* **1992**, *33*, 1077.
(5) Yoshida, T.; Negishi, E. *J. Am. Chem. Soc.* **1981**, *103*, 4985. Negishi, E. *Chem. Scr.* **1989**, *29*, 457. Negishi, E.; Takahashi, T. *Acc. Chem. Res.* **1994**, *27*, 124. Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639. Matsushita, H.; Negishi, E. *Org. Synth.* **1984**, *63*, 31. Negishi, E. *Pure Appl. Chem.* **1981**, *53*, 2333.
(6) (a) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed.* **1993**, *32*, 1068. (b) Rebe, S.; Wipf, P. *Chem. Commun.* **2001**, 299. (c) Wipf, P.; Nunes, R. L.; Rebe, S. *Helv. Chim. Acta* **2002**, *85*, 3478.
(7) Negishi, E.; Kondakov, D. Y.; Choueiry, D.; Kasai, K.; Takahashi, T. *J. Am. Chem. Soc.* **1996**, *118*, 9577.
(8) For a listing of zirconocene dichlorides at Boulder Scientific from which **1**−**5** were selected, see http://www.bouldersci.com/.
(9) ICH Harmonised Tripartite Guideline, Q3C Impurities: Residual Solvents. cf. http://www.ich.org/LOB/media/MEDIA423.pdf.
(10) Wild, W. P.; Zsolnai, L.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *232*, 233. Wild, F. W. R. P.; Wasiucionek, M.; Huttner, G.; Brintzinger, H. H. *J. Organomet. Chem.* **1982**, *288*, 63.
(11) Brintzinger, H. H.; Fischer, D.; Mülhapt, R.; Rieger, B.; Waymouth, R. M. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 1143. Brunner, H.; Schindler, H. D. *J. Organomet. Chem.* **1973**, *55*, C71. Tirouflet, J.; Dormond, A.; LeBlanc, J. C.; LeMoigne, F. *Tetrahedron Lett.* **1973**, 257. Fryzuk, M. D.; Bosnich, B. *J. Am. Chem. Soc.* **1978**, *100*, 5491.
(12) Jones, M. B.; Platz, M. S. *J. Org. Chem.* **1991**, *56*, 1694.
(13) Resconi, L.; Piemontesi, F.; Camurati, I.; Sudmeijer, O.; Nifant'ev, I. E.; Ivchenko, P. V.; Kuz'mina, L. G. *J. Am. Chem. Soc.* **1998**, *120*, 2308.
(14) It is appreciated that early work by Negishi and co-workers indicates that direct carboalumination by a zirconium-modified alane is equally plausible; cf. Negishi, E.; Van Horn, D. E.; Yoshida, T. *J. Am. Chem. Soc.* **1985**, *107*, 6639.
(15) Lipshutz, B. H.; Dimock, S. H. *J. Org. Chem.* **1991**, *56*, 5761.
(16) Negishi, E.; Matsushita, H.; Okukado, N. *Tetrahedron Lett.* **1981**, *22*, 2715.
(17) Lipshutz, B. H.; Mollard, P.; Pfeiffer, S.; Chrisman, W. *J. Am. Chem. Soc.* **2002**, *124*, 14282.
(18) Lipshutz, B. H.; Bulow, G.; Lowe, R.; Stevens, K. *J. Am. Chem. Soc.* **1996**, *118*, 5512.
(19) Lipshutz, B. H.; Kim, S.; Mollard, P.; Stevens, K. *Tetrahedron* **1998**, *54*, 1241.
(20) Lipshutz, B. H.; Bulow, G.; Fernandez-Lazaro, F.; Kim, S.; Lowe, R.; Mollard, P.; Stevens, K. *J. Am. Chem. Soc.* **1999**, *121*, 11664.
(21) Negishi, E.; Liou, S.-Y.; Xu, C.; Huo, S. *Org. Lett.* **2002**, *4*, 261.
(22) Lipshutz, B. H.; Lower, A.; Berl, V.; Schein, K.; Wetterich, F. *Org. Lett.* **2005**, *7*, 4095.
(23) Negishi, E.; Baba, S. *J. Chem. Soc., Chem. Commun.* **1976**, 596.
(24) Standard carboalumination of alkynes (1.0 mmole scale) using catalytic *rac*-(ebi)$ZrCl_2$, catalytic MAO, and excess Me_3Al: To a flame dried argon purged 25 mL round bottomed (rb) flask was added *rac*-ethylenebis-(indenyl)zirconocene dichloride **3** (20.9 mg, 0.05 mmol, 5.0 mol %), followed by the dropwise addition at room temperature of Me_3Al (2.0 M solution in toluene, 0.75 mL, 1.50 mmol, 1.5 equiv). While stirring at room temperature, MAO (10% w/w solution in toluene, 33 μL, 0.05 mmol, 5 mol %) was then added. The alkyne (1.00 mmol) was then introduced, and the homogeneous golden orange solution was stirred at room temperature until TLC analysis (5% CH_2Cl_2/petroleum ether) indicated that the carboalumination was complete.

JA065769B