

Enhancing Regiocontrol in Carboaluminations of Terminal Alkynes. Application to the One-Pot Synthesis of Coenzyme Q₁₀

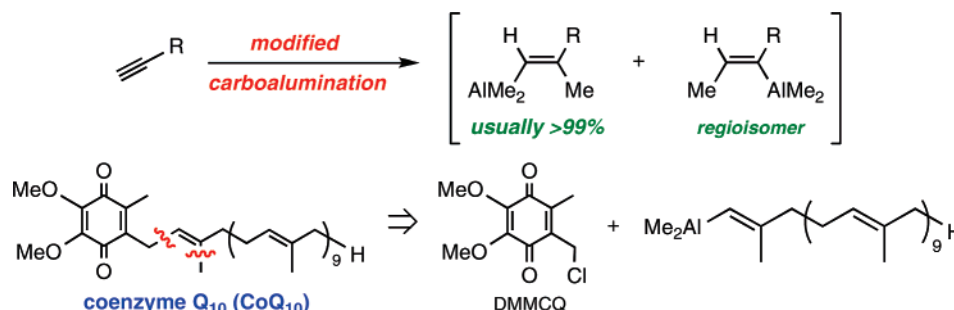
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ABSTRACT



Two new “generations” of methodological advances are reported for the Negishi carboalumination of terminal alkynes. Use of simple, inexpensive additives that alter the Al–Zr complex formed between Me₃Al and Cp₂ZrCl₂ give rise to an especially effective reagent mix that results in virtually complete control of regiochemistry upon carboalumination of 1-alkynes. One timely application to coenzyme Q₁₀ is highlighted. Regioisomers from subsequent coupling, which would otherwise be very difficult to separate, are avoided.

The now classical Negishi carboalumination (CA) reaction applied to terminal alkynes is routinely effected by prior mixing of Me₃Al (trimethylaluminum; TMA) and ≥ 25 mol % of Cp₂ZrCl₂ (zirconocene dichloride; Figure 1) in 1,2-dichloroethane (DCE).¹ While the stereochemistry of addition is essentially all *cis*, the regiochemistry is usually at best 95:5, and thus can present separation issues especially for reactions run on a larger scale. An improvement may occur by using the impressive Wipf modification based on addition of either water or MAO² (Scheme 1), although ratios on simple substrates up to only 97:3 have occasionally been seen. For this modest enhancement, the CA needs to be performed at -70 °C. Thus, even a 90% yielding reaction is at a disadvantage, since an additional 5–10% will be lost

as the regioisomeric product. Should this happen on scale-up, the loss would also likely present major economic issues, since separation depending upon the target can be nontrivial. One solution has recently been put forth,³ where the Cp

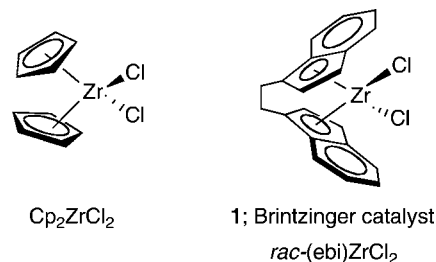
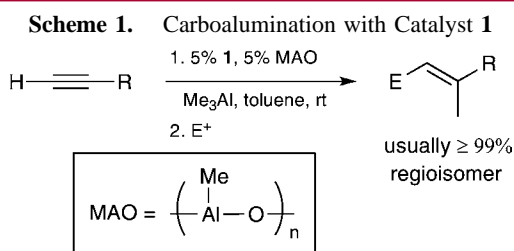


Figure 1. Zirconocene catalysts.

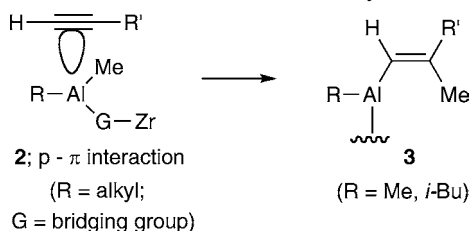
(1) (a) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252.
(b) Negishi, E.; Baba, S. *J. Chem. Soc., Chem. Commun.* **1976**, 596.
(2) Wipf, P.; Lim, S. *Angew. Chem., Int. Ed.* **1993**, *32*, 1068.



ligands on zirconium are replaced by the racemic ethylene bridged bis-indenyl analogue, (ebi)ZrCl₂ (i.e., the Brintzinger catalyst, **1**).⁴ Together with catalytic quantities of MAO, a very selective CA takes place in toluene at rt (Scheme 1). While straightforward procedurally, catalyst **1** is quite expensive relative to the cost of Cp₂ZrCl₂. From an academic perspective, given the requirement that both Al and Zr be present within the catalytically active species,⁵ there might be a simpler alternative that relies on changes at aluminum rather than at the ligand(s) on zirconium. In this Letter we disclose our latest efforts in this area leading to simplified and economically attractive new procedures for gaining essentially total control of regiochemistry in Negishi carboalumination reactions.

Fundamental mechanistic studies on carboalumination by Negishi and Takahashi⁵ suggest that an Al p-orbital-alkyne- π interaction directs a bimetallic aggregate **2** to the sterically and stereochemically favored terminal position (Scheme 2).

Scheme 2. Potential Interaction of Catalyst with Alkyne

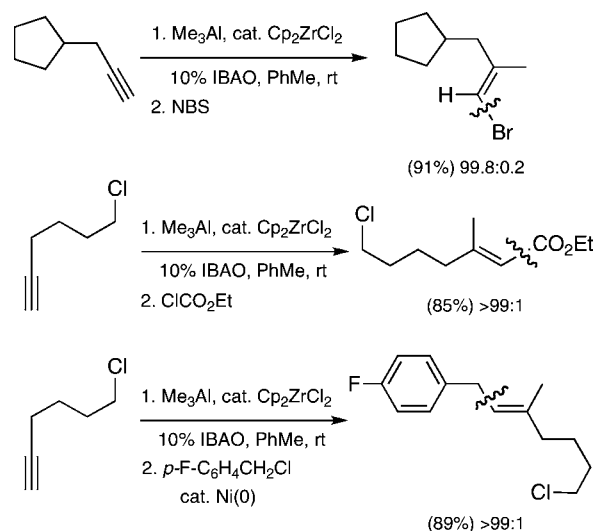


Thus, a bulkier residue R on aluminum in **2** should enhance regioselectivity. This would necessitate a “mixed” alane (i.e., **2**, R \neq Me) which, on the other hand, could also sterically retard rates of carboalumination to an intolerable degree, as already seen with variations of ligands on zirconium (e.g., Cp₂ZrCl₂).³

To generate such a mixed alane in situ, advantage could be taken of the rapid exchange of ligands on aluminum at room temperature.⁵ Given the nontransferable nature of isobutyl groups on Al (e.g., as in DIBAL), MAO’s isobutyl analogue,⁶ isobutylaluminumoxane (IBAO), might undergo

ligand exchange to a mixed cluster **2** (R = *i*-Bu; Scheme 2). The newly positioned isobutyl group could exert the desired influence on the observed regioselectivity favoring, at least initially, **3** (R = *i*-Bu). It was eventually discovered that by equilibrating only 5% Cp₂ZrCl₂, 10% of inexpensive IBAO, and Me₃Al, all in toluene at room temperature for only 15 min, a reagent was formed that effects highly selective carboalumination. After the usual removal of solvent under vacuum and redissolution in THF, introduction of an electrophilic coupling partner affords the desired *E*-alkenyl product. Scheme 3 shows a few representative examples, all

Scheme 3. Representative Examples for CA with IBAO



of which reflect $>99\%$ control of regiochemistry in the carboalumination step. In the specific case of nutraceutical coenzyme Q₁₀,⁷ one immediate application of this new technology, the 48-carbon side chain precursor **5**³ was prepared from solanesol (**4**, Scheme 4),⁸ a waste product from

Scheme 4. Preparation of the CoQ₁₀ Side Chain Precursor



tobacco plants. Treatment of **5** under these modified carboalumination conditions, which required 0.25 equiv of

(3) Lipshutz, B. H.; Butler, T.; Lower, A. *J. Am. Chem. Soc.* **2006**, *128*, 15396.

(4) 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.

(5) Negishi, E.; Kondakov, D. Y.; Choueiry, D.; Kasai, K.; Takahashi, T. *J. Am. Chem. Soc.* **1996**, *118*, 9577.

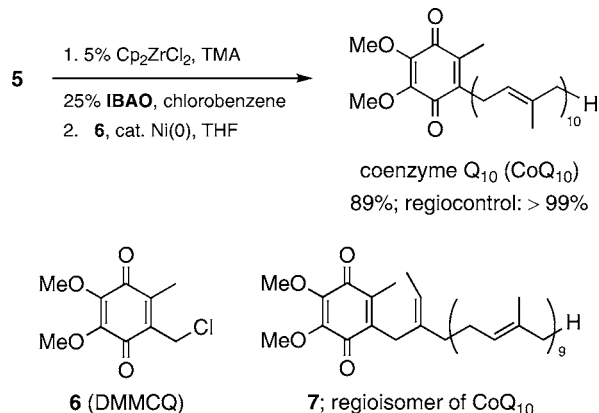
(6) Negishi, E. *Organometallics in Organic Synthesis*; Wiley, New York, 1980; Vol. 1.

(7) Littarru, G. P. *The Fourth Conference of the International Coenzyme Q₁₀ Association*; IOS Press: Amsterdam, The Netherlands, 2006. Littarru, G. P. *Energy and Defense. Facts and Perspectives on CoQ₁₀ in Biology and Medicine*; Casa Editrice Scientifica Internazionale, 1994; p 1.

(8) (a) Rowland, R. L.; Latimer, P. H.; Giles, J. A. *J. Am. Chem. Soc.* **1956**, *78*, 4680. (b) Sheen, S. J.; Davis, D. L.; DeJong, D. W.; Chaolin, S. F. *J. Agric. Food Chem.* **1978**, *26*, 259.

IBAO in chlorobenzene in this case, followed by Ni-catalyzed cross-coupling with the 6-chloromethylated 2,3-dimethoxy-5-methyl-*p*-benzoquinone **6** (DMMCQ)³ afforded CoQ₁₀ directly in good yield and with excellent regioselectivity (Scheme 5). Most noteworthy is the ratio of regio-

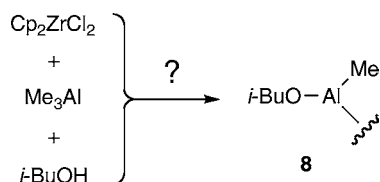
Scheme 5. Carboalumination/Coupling with IBAO



isomeric products: that is, the desired quinone (CoQ₁₀) to its regioisomer **7** associated with this one-pot process as determined by both NMR and HPLC analyses (>99%). Routinely, 7–10% of isomer **7** is formed following the traditional approach to carboalumination.^{1,6}

The rationale of building bulk around Al in a Zr/Al complex to gain regioselectivity in Negishi carboaluminations of 1-alkynes, while presumably manifested by ligand exchange of isobutyl (from IBAO) for methyl, could potentially be solved in several ways. For example, using residues on aluminum with steric demands in between those of the two alkyl moieties studied (Me or *i*-Bu) might be enough to encourage the Al/Zr complex to migrate in the desired direction. Alternatively, ligands on aluminum other than alkyl were also envisioned, the simplest and most expedient being oxygen based (i.e., an Al–OR bond). Thus, with alcohol as an additive rather than MAO or IBAO, the catalyst should be altered by insertion of an alkoxy rather than alkyl group. Of several alcohols examined with the 48-carbon alkyne **5** as the benchmark substrate, an isobutanol-modified catalyst **8** (Scheme 6) led to complete carboalumination at ambient

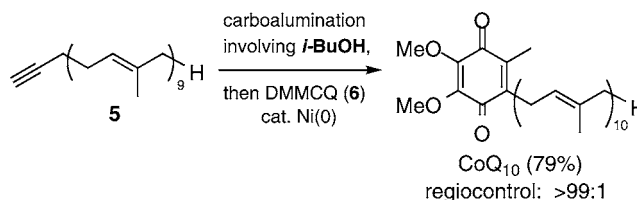
Scheme 6. Presumed Influence of *i*-BuOH on Catalyst



temperature. Other alcohols were unproductive, either in terms of conversion in the carboalumination step (*t*-BuOH, PhOH), or subsequent coupling of the derived vinylalane

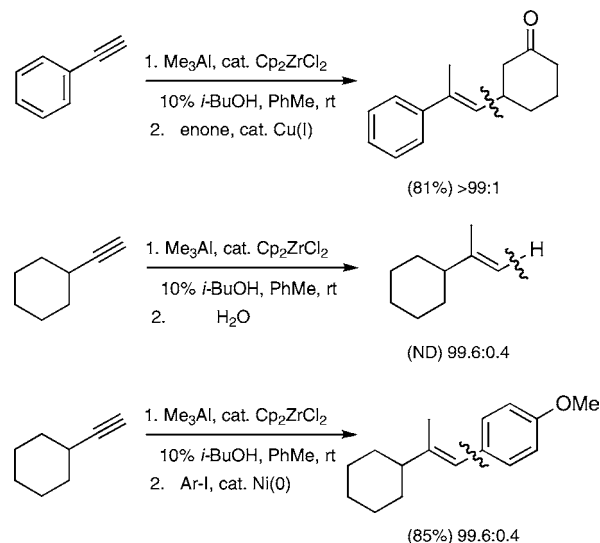
bearing the alkoxy moiety (MeOH). Success with isobutanol, however, necessitated a switch from toluene to dichloromethane (DCM), both class 2 solvents, to achieve reasonable rates of carboalumination. Under these new conditions the observed ratio of CoQ₁₀:isomer **7** was >99:1, although the isolated yield was somewhat lower than expected (Scheme 7).

Scheme 7. *i*-BuOH-Modified Carboalumination/Coupling to CoQ₁₀



The generality of this latest route to highly stereo- and regio-defined alkenes is suggested by the examples illustrated in Scheme 8. Unlike the case above leading to CoQ₁₀, more

Scheme 8. Representative Examples of Carboalumination with *i*-BuOH



typical 1-alkynes could be carboaluminated in *toluene* in the presence of only 10% *i*-BuOH. Each is representative of standard reactions of vinylalanes (e.g., [1] a copper(I)-catalyzed conjugate addition;⁹ [2] simple proton quenching of the vinylalane; and [3] a Ni-catalyzed cross-coupling to an aryl iodide).¹ The presumed alkoxy-substituted vinylalane intermediates are noticeably of lower reactivity than those formed by using the MAO- or IBAO-derived (alkyl-substituted) reagents. Nonetheless, carboalumination progresses at quite reasonable rates (2–4 h) at substrate concentrations of ca. 1.3 M in toluene, and subsequent bond formations

(9) Lipshutz, B. H.; Dimock, S. H. *J. Org. Chem.* **1991**, *56*, 5761.

occur as usual in THF in good yields and excellent regioselectivities based on GC analyses.

In summary, the evolution of carboalumination chemistry of terminal alkynes, dating back to the seminal contribution of Negishi,¹ has now seen several “generations” of development. As testimony to the insight of its creator, the sequence, in a sense, has come full circle. That is, all of the reagents as originally put forth in 1978,¹ albeit in modified amounts, are to be found in the latest process: Cp_2ZrCl_2 (reduced from 25 to 5 mol %), excess Me_3Al (reduced from 2 to 1.5 equiv), and DCM or toluene as solvent (environmentally preferred alternatives to DCE). Through the expediency of an additive (catalytic IBAO), or introduction of a simple alcohol (isobutanol) to the Negishi recipe, regiochemistry of net cis-

addition of Me_3Al to a 1-alkyne can be essentially fully controlled.

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Supporting Information Available: Representative procedures for carboalumination, along with full spectral data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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