A Novel Route to Coenzyme Q_n

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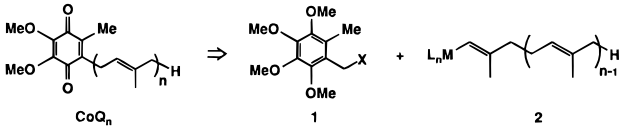
The ubiquinones, also commonly called coenzyme Q_n (n = 1−12), constitute essential cellular components of many life forms. In humans, CoQ_{10} is the predominant member of this class of polyprenoidal natural products and is well-known to function primarily as a redox carrier in the respiratory chain.[1] Several approaches to the ubiquinones have been developed over the past 3−4 decades, attesting to their importance. Recent contributions[2] have invoked such varied approaches as Lewis acid-induced prenoidal stannane additions to quinones,[2a] reiterative Pd(0)-catalyzed couplings of doubly activated prenoidal chains with allylic carbonates bearing the required aromatic nucleus in protected form,[2b] and a Diels−Alder, retro Diels−Alder route to arrive at the quinone oxidation state directly.[2c,d] Nonetheless, all are lengthy, linear rather than convergent, and/or inefficient. Moreover, problems in controlling double bond stereochemistry using, *e.g.*, a copper(I)-catalyzed allylic Grignard−allylic halide coupling can lead to complicated mixtures of geometrical isomers that are difficult to separate given the hydrocarbon nature of the side chains.[3] An alternative disconnection that relies on the well-known[4] maintenance of olefin geometry in group 10 coupling reactions was envisioned, potentially involving a vinyl organometallic and a benzylic halide (Scheme 1). We now report that such couplings, using the appropriate reaction partners and based on *unprecedented* Ni(0) catalysis, are quite general and can be used to directly afford known precursors[5] to various CoQ_n, as well as related systems such as found with vitamins K_1 and K_2.

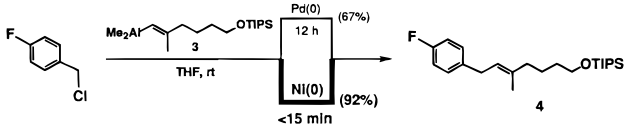
Initially, it was anticipated that Pd(0)-catalyzed cross-coupling of a vinylalane (**2**, $L_nM = Me_2Al$) with benzylic electrophile **1** would result in the desired C−C bond, notwithstanding the existence of but a single (partial) report on such a carboalumination−benzylic coupling process.[6] Studies using model vinylalane **3**[7] and *p*-fluorobenzyl chloride in the presence of 5 mol % $Pd(PPh_3)_4$ gave coupling product **4** in 67% yield after 12 h at room temperature. By contrast, switching to cataytic Ni(0)[8] afforded 92% of **4** in <15 min (Scheme 2). More relevant to the CoQ_n issue, and a far more challenging coupling, is the case of chloride **1**, X = Cl.[9] Treatment of this halide with the C_{19} vinylalane **5** and 5 mol % Ni(0) afforded CoQ_4 precursor **6**, again in high isolated yield (87%), *in minutes* at room temperature. *Even lesser amounts of catalyst, as low as 0.5 mol %, are equally effective.*[10] Only traces of product were observed using Pd(0) under identical conditions, while refluxing the reaction mixture for 12 h returned no starting material and only 68% of **6** (Scheme 3).

Extension of this approach to the protected hydroquinone precursors of CoQ_3 (**8**) and CoQ_5 (**9**) could also be accomplished under similar conditions (Scheme 4). Acetylenic chains (**7**) employed were constructed from commercially available prenoidal alcohols or halides. Likewise, precursors to vitamins[11] K_1

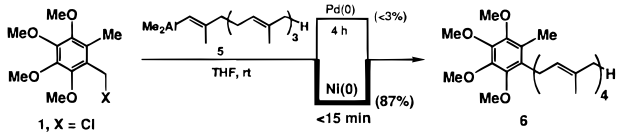
Scheme 1



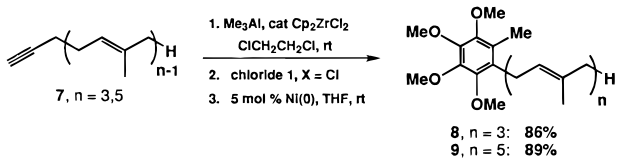
Scheme 2



Scheme 3



Scheme 4



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(1) (a) Lenaz, G. *Coenzyme Q. Biochemistry, Bioenergetics, and Clinical Applications of Ubiquinone*; Wiley-Interscience: New York, 1985. (b) Trumpower, B. L. *Function of Ubiquinones in Energy Conserving Systems*; Academic Press: New York, 1982. (c) Thomson, R. H. *Naturally occuring quinones*, 3rd ed.; Academic Press: New York, 1987. (d) Bliznakov, E. G.; Hunt, G. L. *The Miracle Nutrient Coenzyme Q_{10}*; Bantom Books: New York, 1987.

(2) (a) Naruta, Y. *J. Org. Chem.* **1980**, *45*, 4097. (b) Eren, D.; Keinan, E. *J. Am. Chem. Soc.* **1988**, *110*, 4356 and references therein. (c) Van Lient, W. B. S.; Steggerda, W. F.; Esmeijer, R.; Lugtenburg, J. *Rec. Trav. Chim. Pays-Bays* **1994**, *113*, 153. (d) Rüttimann, A.; Lorenz, P. *Helv. Chim. Acta* **1990**, *73*, 790. (e) Terao, S.; Kato, K.; Shiraishi, M.; Morimoto, H. *J. Chem. Soc., Perkin Trans. 1* **1978**, 1101.

(3) Yanagisawa, A.; Nomura, N.; Noritake, Y.; Yamamoto, H. *Synthesis* **1991**, 1130.

(4) Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*; University Science Books: Mill Valley, CA, 1994.

(5) Oxidation of protected hydroquinone precursors leads directly to the corresponding CoQ_n.[2]

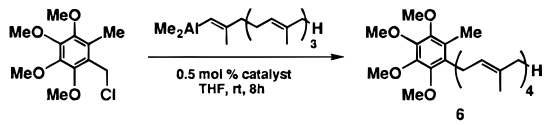
(6) Negishi, E. I.; Matsushita, H.; Okukado, N. *Tetrahedron Lett.* **1981**, *22*, 2715.

(7) Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252. 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.

(8) Ni(0) has been generated in this study *via* two methods. (1) Treatment of $Ni(acac)_2$ in THF with DIBAL-H in the presence of 4 equiv of PPh_3, *cf.:* Negishi, E. I.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (2) Treatment of $NiCl_2(PPh_3)_2$ with 2 equiv of *n*-BuLi in the presence of 2 equiv of PPh_3, *cf.* the preparation of $Pd(PPh_3)_4$ *via* reduction of $Pd(PPh_3)_2Cl_2$ with *n*-BuLi in the presence of 2 equiv of PPh_3: Negishi, E.; Takahashi, T.; Akiyoshi, K. *J. Chem. Soc., Chem. Commun.* **1986**, 1338.

(9) Prepared by chloromethylation of the corresponding aromatic, *cf.*: Shunk, C. H.; Wolf, D. E.; McPherson, J. F.; Linn, B. O.; Folkers, K. *J. Am. Chem. Soc.* **1960**, *82*, 5914.

(10) Preliminary studies with catalyst levels as low as *0.5 mol % Ni(0) at ambient temperatures* have led to equally efficient couplings, *e.g.*, en route to CoQ_4 precursor **6**. As with simpler systems, Pd(0) was ineffective under these conditions.



(11) (a) Tso, H-H.; Chen, Y-J. *J. Chem. Res.* **1995**, 104. (b) Kozhevnikov, I. V.; Kulikov, S. M.; Chukaeva, N. G.; Kirsanov, A. T.; Letunova, A. B.; Blinova, V. I. *React. Kinet. Catal. Lett.* **1992**, *47*, 59. (c) Schmid, R.; Antoulas, S.; Rüttimann, A.; Schmid, M.; Vecchi, M.; Weiser, H. *Helv. Chim. Acta* **1990**, *73*, 1276. (d) Review: Rüttimann, A. *Chimia* **1986**, *40*, 290 and references therein. Masaki, Y.; Hashimoto, K.; Kaji, K. *Chem. Pharm. Bull.* **1984**, *10*, 3959. (e) Godschalx, J. P.; Stille, J. K. *Tetrahedron Lett.* **1983**, *24*, 1905. (f) Dötz, K. H.; Pruskil, I. *J. Organomet. Chem.* **1981**, *209*, C4. (g) Chenard, B. L.; Manning, M. J.; Raynolds, P. W.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 378.

S0002-7863(96)01285-1 CCC: $12.00

Scheme 5

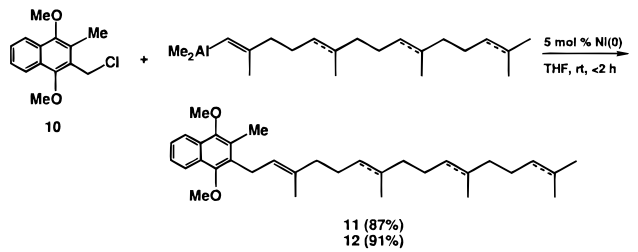
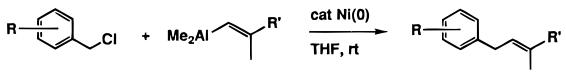
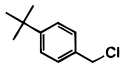
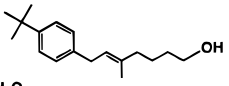
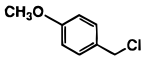
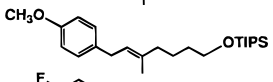
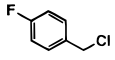
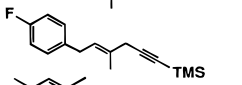
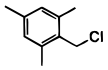
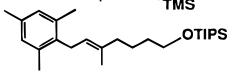
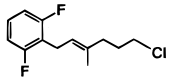
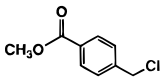
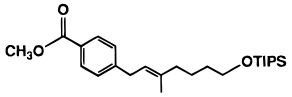
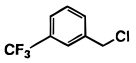
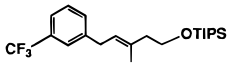


Table 1. Ni(0)-Catalyzed Reactions of Vinylalanes with Benzylic Chlorides[a]



Entry	Benzylic chloride	Product[b]	Yield[c]
1			81[d]
2			84[d]
3			77
4			86
5			93
6			86
7			89

[a] All reactions were run using 5 mol % Ni(0), unless specified otherwise. [b] Fully characterized by IR, NMR, MS, and HRMS data. [c] Isolated, chromatographically purified materials. [d] Run using 10 mol % Ni(0).

(**11**; racemic)[12] and $K_{2(20)}$ (**12**; CoQ_4 side chain) could be efficiently prepared using this protocol (Scheme 5).

The generality of this new coupling sequence for realizing allylated aromatics *not* related to the ubiquinones has also been investigated, using a variety of benzylic chlorides and vinylic alanes (Table 1).[13] Clearly, both electron-rich and electron-poor aromatics participate with equal facility. Importantly, there is reason to believe that good functional group compatibility is maintained (*e.g.*, entry 6).

(12) Alkyne preparation: Addition of 1-(triisopropylsilyl)propynyllithium to *in situ* generated iodide (from 3,7,11-trimethyldodecanol; Wiley Organics), followed by tetrabutylammonium fluoride deprotection and column chromatography (pentane), afforded the alkyne in 67% overall yield. Educt **10** is a known precursor, *cf.*: Adams, R.; Geissman, T. A.; Baker, B. R.; Teeter, H. M. *J. Org. Chem.* **1940**, *63*, 528.

In conclusion, a conceptually unique strategy has been uncovered for preparing CoQ_n and vitamin K precursors involving vinylalanes and benzylic chlorides. The rapidity and efficiency of the process derives from catalysis *via* inexpensive Ni(0), rather than Pd(0). The potential here for the former catalyst to mediate cross-couplings of this type was not only previously unappreciated but, in fact, unknown. Further developments which rely on a novel linchpin approach toward precursors of the higher, extremely expensive homologues of those prepared herein (*i.e.*, CoQ_{6-9})[14] are in progress and will be reported in due course.

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Supporting Information Available: Spectral data for all precursors to CoQ_{3-5}, vitamins K_1 and $K_{2(20)}$, and new compounds in Table 1 (29 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, can be ordered from the ACS, and can be downloaded from the Internet; see any current masthead page for ordering information and Internet access instructions.

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(13) A general procedure for the preparation of **6** is as follows. Carboalumination: To a 10 mL round-bottom Schlenk flask (equipped with a medium ground glass filter frit) was added zirconocene dichloride (73 mg, 0.25 mmol) under an argon atmosphere. A solution of trimethylaluminum (0.75 mL, 2.0 M in hexane, 1.5 mmol) was added at 0 °C and stirred under reduced pressure until the hexane was removed. 1,2-Dichloroethane was added (1.0 mL), and the solution was allowed to stir and warm to room temperature over 30 min. To this solution was added alkyne **7** ($n = 4$, 244 mg, 1.0 mmol), and the mixture was stirred at 0 °C for 30 min, after which carboalumination was complete, as determined by GC. The dichloroethane was pumped off *in vacuo*, and freshly distilled hexane (2 mL) was added, which was then also removed *in vacuo*. Additional hexane (5 mL) was then added to the flask to precipitate the zirconium salts. The hexane layer was removed by carefully decanting and filtering through the frit, with great care taken to avoid contamination by the zirconium salts. The leftover salts were not washed. The orange hexane solution was concentrated under reduced pressure and dissolved in THF (2.0 mL). Nickel-catalyzed coupling: To a 5 mL round-bottom flask were added *bis*(triphenylphosphine)nickel(II) chloride (Aldrich, 22 mg, 0.033 mmol) and triphenylphosphine (18 mg, 0.067 mmol) under an argon atmosphere at room temperature. THF (1.0 mL) was added, followed by *n*-butyllithium (0.136 mL, 0.49 M in hexane, 0.067 mmol). The deep red solution was allowed to stir for 30 min, at which time benzyl chloride **1** (174 mg, 0.67 mmol) was added, and the subsequent dark blue solution was stirred for an additional 5 min. The solution containing the nickel catalyst was then transferred *via* cannula to the vinylalane at room temperature, and the cross-coupling reaction followed by GC analysis. When the reaction was complete (<15 min in this case), the solution was diluted with diethyl ether (10 mL) and quenched at 0 °C by carefully adding 1.0 M HCl dropwise (3 mL). The mixture was allowed to stir for an additional 5 min and then extracted with diethyl ether. The combined organic layers were dried ($Na_2SO_4/MgSO_4$) and concentrated *in vacuo*. Silica gel column chromatography of the residue (petroleum ether) afforded **6** (0.281 g, 87%) as a viscous, clear oil: $R_f = 0.10$ (2% acetone/pentane); IR (neat) 2931, 2856, 1470, 1454, 1446, 1417, 1406, 1350, 1107, 1068, 1041 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 5.09−5.02 (m, 4H), 3.89 (s, 3H), 3.88 (s, 3H), 3.77 (s, 3H), 3.77 (s, 3H), 3.31 (d, $J = 6.5$ Hz, 2H), 2.12 (s, 3H), 2.08−1.92 (m, 12H), 1.75 (s, 3H), 1.66 (s, 3H), 1.58 (s, 3H), 1.57 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.85, 147.67, 144.92, 144.67, 135.05, 134.96, 134.84, 131.17, 129.23, 125.34, 124.40, 124.22, 124.13, 122.87, 61.17, 61.04, 60.61, 39.70, 26.76, 26.62, 25.78, 25.64, 17.64, 16.20, 15.96, 11.67; HREIMS calcd for $C_{31}H_{48}O_4$ M^+ 484.3553, found 484.3548.

(14) According to the 1995 edition of the Sigma catalog, CoQ_6 is listed at $571.30/50 mg (or $11,426/g), while CoQ_9 is $376.30/10 mg (or $37,630/g).