Heterogeneous Catalysis: Ni/C-Catalyzed Cross-Couplings en route to Allylated Aromatics: Application to a Precursor to Coenzyme Q_{10}

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Warmly dedicated to Professor Dieter Seebach on the occasion of his retirement from the ETH.

Abstract: The readily available, heterogeneous, and inexpensive catalyst nickel-on-charcoal (Ni/C) can be used to mediate couplings between vinyl alanes and benzylic chlorides under very mild conditions and in good yields. Although such allylated aromatics are themselves important compounds, as demonstrated in this work, their syntheses under the 'green chemistry' conditions used can smoothly arrive at precursors to valued quinone natural products, such as the nutraceutical coenzyme Q₁₀.

Key words: heterogeneous catalysis, nickel-on-charcoal, crosscouplings, allylated aromatics, coenzyme Q₁₀

In a recent report from these laboratories, an especially efficient synthesis of coenzyme Q₁₀ (CoQ₁₀; ubiquinone) was disclosed.¹ The key coupling reaction which accomplishes a net attachment of the 50 carbon side-chain to the presursor to the *p*-quinone head group was effected in a convergent, one-pot sequence.² The ingredients combined in this process included the benzylic chloride 1 and vinylic alane 2, the latter species derived in situ from alkyne 3 via carboalumination (Scheme 1).

The catalyst behind the success of this strategy is a nickel(0) complex generated from NiCl₂(Ph₃P)₂ in the presence of n-BuLi (2 equiv). When used at the 3 mole percent level in THF at room temperature, the CoQ_{10} skeleton was produced in close to 90% isolated overall yield.¹ In looking for ways to alter the process so as to make it even more environmentally benign as well as potentially more economically attractive, use of Ni(0) impregnated onto a solid support was considered.³ A heterogeneous alternative might offer a simplified (non-aqueous) workup, as well as opportunities for recycling of the catalyst. In this contribution we present our preliminary work on the development of cross-couplings between various benzylic chlorides and vinylic alanes mediated by catalytic



Scheme 2

amounts of readily available and inexpensive nickel-oncharcoal (Ni/C) (Scheme 2).

Previously, we have described several Ni/C-catalyzed reactions (e.g., Negishi,4a Kumada,4b Suzuki,4c aminations,^{4d} reductions^{4e}), all of which required reaction temperatures close to or at the reflux point of the medium. For the vinyl alanes used in this study, prepared in standard fashion by carboalumination of their precursor terminal alkynes (1.2 equiv Me₃Al, 0.25 equiv Cp₂ZrCl₂, 1,2dichloroethane, r.t.),⁵ it was therefore unexpected to find that allylated aromatics could be formed cleanly at ambient temperatures. The general procedure arrived at relies on 5 mol% Ni/C as catalyst, prepared from Ni(II)/C by simple pre-treatment with 10 mol% BuLi in THF at 25 °C for 5 minutes.⁶ Introduction of the vinyl alane followed by the chloromethylated aromatic leads to efficient C-C bond formation. Representative examples are illustrated in Table 1.

In general, these data suggest that (1) reactions go to completion in reasonable times without resorting to unusually high concentrations (ca. 0.25–0.30 M); (2) both electronrich and electron-poor substrates react with all-hydrocarbon-derived or ω -functionalized vinyl alanes at roughly comparable rates; and (3) isolated yields tend to be quite good. One heteroaromatic case studied, thiazole 4, did not require any procedural changes en route to allylated product 5 (Scheme 3).



Scheme 1

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| Entry | Chloride | Vinyl Alane ^a | Time (h) | Product ^b | Yield (%) ^c |
|-------|------------|---|----------|---|------------------------|
| 1 | F 6 | Me ₂ AI | 4 | C_6H_{13} | 94 |
| 2 | | Me ₂ AI | 17 | CI 13 | 90 |
| 3 | F 6 | Me ₂ AI | 9 | OTIPS | 84 |
| 4 | CI CF3 | Me ₂ Al | 10 | CF ₃ 15 | 91 |
| 5 | CI | Me ₂ Al | 13 | OTIPS OMe 16 | 78 |
| 6 | | Me ₂ Al | 10 | | 87 |
| 7 | OEt OMe | Me ₂ Al C ₆ H ₁₃ | 16 | $\bigcup_{\substack{OMe}}^{OEt} C_6 H_{13}$ | 84 |

| Table 1 | Ni(0)/C-Catalyzed | Couplings of Benzylic | Chlorides with Vinylic Alanes |
|---------|-------------------|-----------------------|-------------------------------|
|---------|-------------------|-----------------------|-------------------------------|

 $^{\rm a}$ Formed via standard $Cp_2ZrCl_2\mbox{-}catalyzed$ carboalumination conditions.

^b Fully characterized by IR, NMR, MS, and HRMS data.

^c Isolated, chromatographically purified material.

A disubstituted allylated aromatic of *E*-configuration could also be constructed, in this case relying on an initial hydrozirconation followed by transmetalation to the corresponding vinyl alane 7 (Scheme 4). Treatment of 7 with benzylic chloride **6** under the influence of Ni(0)/C at room temperature led to **8** in 88% overall isolated yield. Fortunately, this carboalumination/Ni(0)-catalyzed process could be applied to the fully adorned CoQ_{10} nucleus. Thus, following the usual protocol, the pentasubstituted benzylic chloride **1** could be coupled with the 49 carbon vinyl alane side-chain **2** to arrive at the decaprenoid prod-



Scheme 3



Scheme 5

uct **9** in 85% yield after workup (i.e., filtration) and passage through a short plug of silica gel (Scheme 5).

The potential for recycling of Ni/C in these ambient temperature couplings was tested in the case of 4-fluorobenzyl chloride (6; Table 1, entry 1). After the initial reaction with alane 10 was complete, the catalyst was filtered and then dried at 100 °C under vacuum for six hours. Reactivation of the Ni/C (i.e., by treatment with BuLi) and subsequent re-exposure to the identical reaction conditions led to complete consumption of educt and afforded the expected product 11 in essentially the same yield (Scheme 6).

To simplify the procedure further, the coupling above (Scheme 6) was repeated with fresh reagents, and upon complete consumption of p-fluorobenzyl chloride, the mixture was centrifuged to settle the charcoal. The reac-

tion solution was then removed and after solvent evaporation in vacuo, the product was purified to afford **11**, again in high yield (Scheme 7). The Ni/C left behind was recharged with additional vinyl alane and a different halide [3-chlorobenzyl chloride (**12**)]. Thus, *without reactivation of the catalyst*, this second cross-coupling proceded to completion at room temperature in the expected timeframe (cf. Table 1, entry 2). Isolation led to the newly coupled product **13** in good yield. Thus, the inexpensive catalyst Ni/C does not lose significant activity over (at least) two consecutive independent cross-couplings, obviating reactivation by preliminary treatment with additional BuLi.

Analysis of the extent of nickel bleed from the charcoal into solution was determined by ICP AES (inductively coupled plasma atomic emission spectroscopy)⁷ on a crude reaction mixture. Filtration of a Ni/C-catalyzed re-



Scheme 7

Scheme 6

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action between the vinyl alane from oct-1-yne and 3-CF₃C₆H₄CH₂-Cl led to the observation that 0.24% of the 5% Ni/C (i.e., 2.359 ppm) had been released from the solid support. This value is very much in line with those observed previously⁴ for completed reactions run at reflux that had been first cooled to room temperature, then filtered, and ultimately digested using *aqua regia*. In our recent study on the nature of Ni/C,⁸ it was shown that couplings are taking place within the charcoal matrix but are mediated by free nickel in solvent therein. Thus, it appears that elevated temperatures are clearly not required (at least in this situation) in order to enhance the rate at which coupling partners enter into, or product exits from, the pores of the solid support.

In summary, it has been demonstrated that nickel-on-charcoal in the presumed Ni(0) state is a viable, efficient, and 'green' catalyst for effecting allylations of aromatic rings. Couplings between vinylic alanes and chloromethylated aromatics occur under mild conditions and in good yields. The potential for this general process to be applied to the synthesis of an established coenzyme Q_{10} precursor has also been successfully documented. Further studies and applications on this and related catalyst systems will be reported in due course.

Reactions were performed in oven-dried glassware under argon with Teflon coated stir bars and dry septa. THF was freshly distilled from Na/benzophenone ketyl prior to use. Hexanes and pentane were freshly distilled from CaH2 prior to use. Ni/C was stored and weighed out as a black powder in a glove box. All commercially available reagents were distilled either from CaH₂ or molecular sieves under an inert atmosphere before use. Oct-1-yne, hex-5-yn-1-ol, 6-chlorohex-1-yne, 4-fluorobenzyl chloride (6), 3-(trifluoromethyl)benzyl chloride, and 3-methoxybenzyl chloride were purchased from Aldrich. 4-Chloromethylthiazole hydrochloride was purchased from Lancaster, and converted to the free-base with Et₃N and CH₂Cl₂. Petroleum ether used had bp 35-60 °C. Column chromatography was performed using Davisil Grade 633 Type 60A silica gel. TLC analysis was performed on commercial Kieselgel 60 F254 silica gel plates. NMR spectra were obtained on Varian Inova systems using CDCl₃ or CD₃CN solvents with proton and carbon resonance at 400 MHz and 100 MHz, respectively. FTIR spectra were obtained on an ATI Mattson Infinity series spectrometer neat on NaCl plates, and are reported in cm⁻¹. Mass spectral data were acquired on a VF Autospec or an analytical VG-70-250 HF instrument.

1-Fluoro-4-[(*E*)-3-methylnon-2-enyl]benzene (11); Typical Procedure

Carboalumination: To a 10 mL round-bottom flask under argon was added Cp₂ZrCl₂ (73 mg, 0.25 mmol). A solution of Me₃Al (0.75 mL, 2.0 M in hexanes, 1.5 mmol) was added at 0 °C via syringe and the solution stirred under reduced pressure until the hexanes were removed. ClCH₂CH₂Cl was added (1 mL) and the solution was allowed to stir and warm to r.t. over 10 min. To this solution was added oct-1-yne (147.5 μ L, 1 mmol) and the mixture was stirred at 0 °C for 30 min, after which time carboalumination was complete (as determined by GC). The solvent was removed in vacuo and freshly distilled hexanes (2 mL) were then added to the flask so as to precipitate the zirconium salts. The vinylalane in hexanes was then transferred to a second flask via cannula (*with great care taken to*

avoid contamination by the zirconium salts), and the hexanes were removed in vacuo. The yellow hexanes solution was concentrated under reduced pressure and the residue dissolved in THF (2 mL).

Nickel-on-Charcoal Catalyzed Coupling: To a 10 mL round bottom flask was added Ni/C (67.3 mg, 0.04 mmol) and Ph₃P (21 mg, 0.08 mmol) under argon at r.t. THF (1 mL) was added followed by BuLi (31 μ L, 2.55 M in hexanes, 0.08 mmol). The solution was allowed to stir at r.t. for 5 min. The vinylalane was then transferred via cannula to the Ni/C catalyst at r.t. 4-Fluorobenzyl chloride (**6**; 96 μ L, 0.80 mmol) was added at r.t., and the cross-coupling reaction was followed by GC analysis. When the reaction was complete (usually <4 h), the solution was diluted with Et₂O (10 mL) and quenched at 0 °C by carefully adding 1 M HCl dropwise (3 mL). The mixture was filtered and the aq layer was extracted with Et₂O (3×10 mL). The combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. Silica gel column chromatography afforded product **11** as a clear viscous oil (176 mg, 94%).

tert-Butyl{[(*E*)-7-(2-chlorophenyl)-5-methylhept-5-enyl]oxy}-dimethylsilane (13)

The TBDMS protected hex-5-yn-1-ol (184 mg, 1 mmol), Me₃Al (1.5 mL, 3.0 mmol, 2 M in hexanes), Cp₂ZrCl₂ (146 mg, 0.50 mmol), and ClCH₂CH₂Cl (1 mL) were used in the carboalumination following the procedure above with the exception that the carboalumination was allowed to stir at r.t. for 6 h. Ph₃P (21 mg, 0.08 mmol), BuLi (33 μ L, 2.45 M), THF (1 mL), and 1-chloro-2-(chlorometh-yl)benzene (**12**; 100 μ L, 129 mg, 0.8 mmol) were used in the cross-coupling reaction following the typical procedure above. The reaction was allowed to stir at r.t. for 17 h. Upon typical aqueous acidic quench, chromatography of the residue on silica gel with 2% CH₂Cl₂-petroleum ether afforded 253 mg of the title compound (90%) as a clear oil; (2% CH₂Cl₂-petroleum ether).

IR (neat): 2930, 2858, 1654, 1468, 1254, 1101, 837 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ =7.34 (dd, *J* = 1.6, 7.8 Hz, 1 H), 7.25–7.10 (m, 3 H), 5.29 (tq, *J* = 0.8, 7.2 Hz, 1 H), 3.62 (t, *J* = 6.4 Hz, 2 H), 3.45 (d, *J* = 7.2 Hz, 2 H), 2.06 (t, *J* = 7.2 Hz, 3 H), 1.71 (s, 3 H), 1.52–1.45 (m, 4 H), 0.9 (s, 9 H), 0.05 (s, 6 H).

 ^{13}C NMR (100 MHz, CDCl₃) δ = 136.45, 137.54, 135.25, 130.13, 129.52, 127.32, 126.92, 121.35, 63.35, 39.62, 32.64, 32.15, 26.20, 24.29, 18.60, –5.03.

MS (EI): m/z (%) = 295 (60, M – C₄H₉), 143 (18), 129 (22), 125 (29), 115 (18), 75 (100).

HRMS (EI): m/z calcd for $C_{20}H_{33}$ ClOSi (M – C_4H_9) 295.1285; found 295.1287.

{[(*E*)-7-(4-Fluorophenyl)-5-methylhept-5-enyl]oxy}(triisopropyl)silane (14)

TIPS-protected hex-5-yn-1-ol (190.6 μ L, 254 mg, 1 mmol), Me₃Al (1.50 mL, 3 mmol, 2 M in hexanes), Cp₂ZrCl₂ (146 mg, 0.5 mmol), and ClCH₂CH₂Cl (1 mL) were used in the carboalumination following the procedure above with the exception that the carboalumination was allowed to stir at r.t. for 3 h. Ni/C (58.9 mg, 0.035 mmol), Ph₃P (18.3 mg, 0.07 mmol), BuLi (26 μ L, 0.07 mmol, 2.70 M), THF (1 mL), and 4-fluorobenzyl chloride (**6**; 83.8 μ L, 101 mg, 0.7 mmol) were used in the cross coupling reaction following the procedure above. The reaction was allowed to stir at r.t. for 9 h. Chromatography of the residue on silica gel with hexanes afforded 222 mg of the title compound **15** (84%) as a clear oil; R_f 0.13 (hexanes).

IR (neat): 2938, 2865, 1508, 1462, 1221, 1107, 882 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.37–7.30 (m, 1 H), 7.15–7.11 (m, 1 H), 6.98–6.94 (m, 2 H), 5.31 (tq, *J* = 1.2, 16.3 Hz, 1 H), 3.70 (t, *J* = 6.1 Hz, 2 H), 3.33 (d, *J* = 7.4 Hz, 2 H), 2.07 (t, *J* = 7.1 Hz, 2 H), 1.70 (s, 3 H), 1.57–1.50 (m, 4 H), 1.07–1.06 (m, 21 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 136.49, 134.02, 128.72, 128.66, 123.01, 115.27, 112.88, 63.50, 39.59, 33.55, 32.80, 24.31, 18.27, 16.18, 12.23.

MS (EI): *m/z* (%) = 335 (100, M – 43), 239 (5), 161 (10), 149 (29), 131 (49), 109 (80)

HRMS (EI): m/z calcd for $C_{23}H_{39}FOSi$, M^+ 335.2216; found 335.2206.

tert-Butyl(dimethyl)({(*E*)-5-methyl-7-[3-(trifluoromethyl)phe-nyl]hept-5-enyl}oxy)silane (15)

TBDMS-protected hex-5-yn-1-ol (297 μ L, 212 mg, 1 mmol), Me₃Al (1.50 mL, 3 mmol, 2 M in hexanes), Cp₂ZrCl₂ (146 mg, 0.5 mmol), and ClCH₂CH₂Cl (1 mL) were used in the carboalumination following the procedure above with the exception that the carboalumination was allowed to stir at r.t. for 5 h. Ni/C (58.9 mg, 0.035 mmol), Ph₃P (18.3 mg, 0.07 mmol), BuLi (26 μ L, 0.07 mmol, 2.70 M), THF (1 mL), and 3-(trifluoromethyl)benzyl chloride (108.6 μ L, 136 mg, 0.7 mmol) were used in the cross coupling reaction following the procedure above. The reaction was allowed to stir at r.t. for 10 h. Chromatography of the residue on silica gel using hexanes afforded 234 mg of the title compound **16** (91%) as a clear oil; R_f 0.13 (hexanes).

IR (neat): 2930, 1331, 1256, 1164, 1128, 836, 775, 702 cm⁻¹.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 7.21-7.19$ (m, 1 H), 6.81–6.74 (m, 3 H), 5.34 (tq, J = 1.2, 7.1 Hz, 1 H), 3.62 (t, J = 6.1 Hz, 2 H), 3.34 (d, J = 7.4 Hz, 2 H), 2.05 (t, J = 7.1 Hz, 2 H), 1.70 (s, 3 H), 1.59–1.39 (m, 4 H), 0.90 (s, 9 H), 0.05 (s, 6 H).

¹³C NMR (100 MHz, CDCl₃): δ = 142.91, 137.68, 131.91, 128.90, 125.22, 125.18, 122.80, 122.77, 122.13, 63.27, 39.56, 34.15, 32.60, 26.17, 24.26, 18.58, 16.25, -5.08.

MS (EI): *m*/*z* (%) = 329 (6, M – 57), 247 (17), 233 (50), 159 (19), 143 (58), 77 (100), 55 (33).

HRMS (EI): m/z calcd for $C_{21}H_{33}F_3OSi$, M⁺ 329.1550; found 329.1549.

Triisopropyl{[(*E*)-7-(3-methoxyphenyl)-5-methylhept-5-enyl]oxy}silane (16)

TIPS-protected hex-5-yn-1-ol (190.6 μ L, 254 mg, 1 mmol), Me₃Al (1.50 mL, 3 mmol, 2 M in hexanes), Cp₂ZrCl₂ (146 mg, 0.5 mmol), and ClCH₂CH₂Cl (1 mL) were used in the carboalumination following the procedure above with the exception that the carboalumination was allowed to stir at r.t. for 3 h. Ni/C (67.3 mg, 0.04 mmol), Ph₃P (21 mg, 0.08 mmol), BuLi (40 μ L, 0.08 mmol, 2.45M), THF (1 mL), and 3-methoxybenzyl chloride (116 μ L, 125 mg, 0.8 mmol) were used in the cross coupling reaction following the procedure above. The reaction was allowed to stir at r.t. for 13 h. Chromatography of the residue on silica gel using hexanes afforded 234 mg of the title compound **17** (78%) as a clear oil; R_f 0.11 (hexanes).

IR (neat): 2941, 1600, 1464, 1257, 1106, 909, 734 cm⁻¹.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 7.24-7.16$ (m, 1 H), 6.82–6.71 (m, 3 H), 5.35 (tq, J = 1.2, 7.1 Hz, 1 H), 3.69 (t, J = 6.1 Hz, 2 H), 3.36 (d, J = 6.8 Hz, 2 H), 2.07 (t, J = 6.5 Hz, 2 H), 1.72 (s, 3 H), 1.63–1.44 (m, 4 H), 1.08–1.07 (m, 21 H).

¹³C NMR (100 MHz, CDCl₃): δ = 159.84, 143.69, 136.75, 129.44, 122.97, 120.94, 114.21, 111.17, 63.53, 55.30, 39.66, 34.41, 32.83, 24.29, 18.26, 16.20, 12.23.

MS (EI): *m*/*z* (%) = 347 (100, M – 43), 131 (12), 121 (21), 103 (16), 75 (19), 61 (12).

HRMS (EI): m/z calcd for $C_{24}H_{42}O_2Si$, M^+ 347.2412; found 347.2412.

1-Chloro-2-[(*E*)-7-chloro-3-methylhept-2-enyl]benzene (17)

6-Chlorohex-1-yne (120 μ L, 1.0 mmol), Me₃Al (0.75 mL, 1.50 mmol, 2 M in hexanes), Cp₂ZrCl₂ (73 mg, 0.25 mmol), and ClCH₂CH₂Cl (1.0 mL) were used in the carboalumination following the procedure above with the exception that the carboalumination was allowed to stir at r.t. for 3 h. Ni/C (67.3 mg, 0.04 mmol), Ph₃P (21 mg, 0.08 mmol), BuLi (32 μ L, 0.08 mmol, 2.45 M), THF (1 mL), and 1-chloro-2-(chloromethyl)benzene (**12**; 100 mg, 0.80 mmol), dissolved in THF (0.5 mL) were used in the cross-coupling reaction following the procedure above with the exception that pentane was used to crash out the zirconocene salts instead of hexanes. The reaction was allowed to stir at r.t. for 10 h. Chromatography of the residue (5% CH₂Cl₂-petroleum ether) afforded 177.8 mg of the title compound **17** (87%) as a clear oil; R_f 0.58 (5% CH₂Cl₂-petroleum ether).

IR (neat): 2932, 2860, 1470, 1442, 1049, 750 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.35 (dd, *J* = 1.2, 7.6 Hz, 2 H), 7.24–7.12 (m, 3 H), 5.31 (tq, *J* = 1.2, 7.2 Hz, 1 H), 3.56 (t, *J* = 6.4 Hz, 2 H), 3.46 (d, *J* = 7.2 Hz, 2 H), 2.08 (t, *J* = 7.2 Hz, 2 H), 1.81–1.72 (m, 5 H), 1.63–1.50 (m, 2 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 139.30, 136.77, 134.16, 130.15, 129.56, 127.42, 126.97, 121.95, 45.28, 39.02, 32.31, 32.22, 25.21, 16.24.

MS (EI): *m/z* (%) = 256 (16, M⁺), 167 (34), 166 (12), 165 (100), 138 (25), 129 (23), 125 (35), 69 (34), 57 (33), 43 (33).

HRMS (EI): *m*/*z* calcd C₁₄H₁₈Cl₂ 256.0786; found 256.0785.

1-Ethoxy-4-methoxy-2-methyl-3-[(*E*)-3-methylnon-2-enyl]-naphthalene (18)

Oct-1-yne (75 μ L, 0.5 mmol), Me₃Al (0.38 mL, 0.75 mmol, 2 M in hexanes), Cp₂ZrCl₂ (37 mg, 0.12 mmol), and ClCH₂CH₂Cl (0.5 mL) were used in the carboalumination following the procedure above with the exception that the carboalumination was allowed to stir at r.t. for 1 h. Ni/C (33.7 mg, 0.02 mmol), Ph₃P (10.5 mg, 0.04 mmol), BuLi (16 μ L, 0.04 mmol, 2.45M), THF (1 mL), and 2-chlorometh-yl-4-ethoxy-1-methoxy-3-methylnaphthalene (106.0 mg, 0.40 mmol), dissolved in THF (0.5 mL), were used in the cross-coupling reaction following the procedure above with the exception that pentane was used to crash out the zirconocene salts instead of hexanes. The reaction was allowed to stir at r.t. for 16 h. Chromatography of the residue (1% Et₂O–petroleum ether) afforded 118.5 mg of the title compound **19** (84%) as a clear oil; R_f 0.39 (1% Et₂O–petroleum ether).

IR (neat): 2927, 2856, 1591, 1347, 1063 cm⁻¹.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 8.08-8.03$ (m, 2 H), 7.49–7.43 (m, 2 H), 5.10 (tq, J = 1.2, 6.4, 1 H), 4.00 (q, J = 6.8 Hz, 2 H), 3.89 (s, 3 H), 3.58 (dd, J = 0.8, 6.2 Hz, 2 H), 2.39 (s, 3 H), 1.99 (t, J = 7.6 Hz, 2 H), 1.82 (d, J = 0.8 Hz, 3 H), 1.54 (t, J = 7.2 Hz, 3 H), 1.42–1.35 (m, 2 H), 1.30–1.20 (m, 7 H), 0.87 (t, J = 7.2 Hz, 3 H).

 13 C NMR (100 MHz, CDCl₃): δ = 150.15, 149.07, 136.25, 131.29, 127.82, 127.59, 127.17, 125.54, 125.35, 122.91, 122.62, 122.23, 70.68, 61.52, 39.85, 31.96, 29.18, 28.10, 26.66, 22.87, 16.51, 16.12, 14.30, 12.64.

MS (EI): *m*/*z* (%) = 354 (100, M⁺), 325 (17), 213 (45), 201 (18), 198 (16), 187 (10), 71 (12), 57 (17), 55 (10), 43 (25).

HRMS (EI): *m*/*z* calcd C₂₄H₃₄O₂ 354.2559; found 354.2547.

4-[(*E*)-7-{[*tert*-Butyl(dimethyl)silyl]oxy}-3-methylhept-2-enyl]-thiazole (5)

In a 10 mL round bottom flask was added 4-chloromethylthiazole hydrochloride (184 mg, 1 mmol), CH_2Cl_2 (2 mL), and Et_3N (1 mL). This mixture was allowed to stir for 15 min to generate the free amine. The mixture was extracted with Et_2O and filtered. The or-

ganic layer was concentrated in vacuo and azeotropically dried with toluene (3 ×). TBDMS-protected hex-5-yn-1-ol (297 µL, 212 mg, 1 mmol), Me₃Al (1.50 mL, 3 mmol, 2 M in hexanes), Cp₂ZrCl₂ (146 mg, 0.5 mmol), and ClCH₂CH₂Cl (1 mL) were used in the carboalumination following the procedure above with the exception that the carboalumination was allowed to stir at r.t. for 5 h. Ni/C (67.3 mg, 0.04 mmol), Ph₃P (21 mg, 0.08 mmol), BuLi (30 µL, 0.08 mmol), 2.45M), THF (1 mL), and 4-chloromethylthiazole (4; 106 mg, 0.8 mmol) were used in the cross-coupling reaction following the procedure above, with the exception that the reaction was allowed to stir at r.t. for 17 h and the quench was performed with H₂O instead of 1 M HCl. Chromatography of the residue (EtOAc–petroleum ether, 2:1) afforded 217 mg of the title compound **5** (83%) as a clear oil; R_f 0.41 (EtOAc–petroleum ether, 2:1).

IR (neat): 3073, 2930, 2858, 1649, 72, 1462, 1388, 1361, 1255, 1105, 836, 775 $\rm cm^{-1}.$

¹H NMR (400 MHz, CD₃CN): δ =9.57–9.56 (m, 1 H), 7.71–7.50 (m, 1 H), 5.43 (tq, *J* = 1.2, 3.7 Hz, 1 H), 4.68 (d, *J* = 10.1 Hz, 2 H), 3.62 (t, *J* = 6.1 Hz, 2 H), 2.03 (t, *J* = 6.1 Hz, 2 H), 1.70 (s, 3 H), 1.51–1.43 (m, 4 H), 0.89 (s, 9 H), 0.04 (s, 6 H).

¹³C NMR (100 MHz, CD₃CN): δ = 147.19, 110.42, 63.63, 38.13, 33.19, 26.34, 24.60, 22.44, -5.07.

MS (EI): *m*/*z* (%) = 325 (9, M⁺), 270 (10), 269 (20), 268 (100), 262 (88), 183 (66), 152 (17), 86 (12) 51 (13).

HRMS (EI): m/z calcd for C₁₇H₃₁NOSSi, M⁺ 325.1892; found 325.1896.

1-Fluoro-4-[(E)-non-2-enyl]benzene (8)

To a 10 mL round-bottom flask under argon was added Schwartz's reagent Cp2Zr(H)Cl (188 mg, 95%, 0.70 mmol), THF (2 mL), and oct-1-yne (103 µL, 0.70 mmol). The mixture was stirred at r.t. for 30 min, after which time the hydrozirconation was complete (as determined by TLC). The mixture was cooled to 0 °C, and diethylaluminum chloride (88 µL, 0.70 mmol) was added dropwise and allowed to stir for 1 h at 0 °C and 2 h at r.t. After the transmetalation was complete, the THF was removed in vacuo and freshly distilled hexanes (2 mL) were added and then also removed in vacuo. Additional hexanes (5 mL) were then added to the flask so as to precipitate the zirconium salts. The alane in hexanes was then transferred to a second flask via cannula (with great care taken to avoid contamination by the zirconium salts), and the hexanes were removed in vacuo. The yellow hexanes solution was concentrated under reduced pressure and the residue dissolved in THF (1.5 mL). To a 10 mL round bottom flask was added Ni/C (32 mg, 0.02 mmol) and Ph₃P (10.5 mg, 0.04 mmol) under argon at r.t. THF (0.5 mL) was added followed by BuLi (15 µL, 2.55 M in hexanes, 0.04 mmol). The solution was allowed to stir at r.t. for 5 min. The alane was then transferred via cannula to the Ni/C catalyst at r.t. 4-Fluorobenzyl chloride (6; 48 µL, 0.40 mmol) was added at r.t., and the cross-coupling reaction was followed by GC analysis. After 16 h, the reaction was complete and the mixture was diluted with Et₂O (10 mL) and quenched at 0 °C by carefully adding 1 M HCl dropwise (3 mL). The mixture was filtered and the combined organic layers were dried (Na₂SO₄) and concentrated in vacuo. Chromatography of the residue on silica gel with pentane afforded 78 mg of the title compound (88%) as a clear oil; $R_f 0.60$ (pentane).

IR (neat): 2926, 2855, 1601, 1508, 1466, 1222, 1156, 1092, 967, 822 cm⁻¹.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 7.15-7.12$ (m, 2 H), 7.00–6.94 (m, 2 H), 5.57–5.46 (m, 2 H), 3.30 (d, J = 4.9 Hz, 2 H), 1.44–1.30 (m, 10 H), 0.89 (t, J = 7.4 Hz, 3 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 132.58, 130.03, 129.95, 128.74, 115.32, 115.11, 38.41, 32.70, 31.92, 29.62, 29.07, 22.85, 22.56, 14.31.

MS (EI): *m*/*z* (%) = 220 (21), 135 (66), 122 (100), 109 (68).

HRMS (EI): m/z calcd for $C_{15}H_{21}F$, M⁺ 220.1635; found 220.1627.

Toluene-4-sulfonic Acid 2-(3,7,11,15,19,23,27,31,35,39-Decamethyltetraconta-2,6,10,14,18,22,26,-30,34,38-decaenyl)-5,6-dimethoxy-3-methylphenyl Ester (9)

The alkyne **3** (200 mg, 0.31 mmol) dissolved in ClCH₂CH₂Cl (0.25 mL), Me₃Al (0.31 mL, 0.61 mmol, 2 M in hexanes), Cp₂ZrCl₂ (45 mg, 0.15 mmol), and ClCH₂CH₂Cl (0.3 mL) were used in the carboalumination following the procedure above with the exception that the carboalumination was allowed to stir at r.t. for 5 h. Ni/C (25.7 mg, 0.017 mmol), Ph₃P (8.9 mg, 0.034 mmol), BuLi (10 μ L, 0.034 mmol, 2.45 M), THF (0.9 mL), and the tosylated benzyl chloride **1** (90.8 mg, 0.25 mmol), dissolved in THF (0.4 mL), were used in the cross coupling reaction following the procedure above with the exception that pentane was used to crash out the zirconocene salts instead of hexanes. The reaction was allowed to stir at r.t. for 12 h. Chromatography of the residue (5% CH₂Cl₂–petroleum ether) afforded 208.1 mg of the title compound **10** (85%) as a clear oil; R_f 0.28 (5% CH₂Cl₂–petroleum ether).

IR (neat): 2963, 2919, 2853, 1741, 1500, 1449, 1372, 1177, 1115, 760 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 7.94 (d, *J* = 8.4 Hz, 2 H), 7.34 (d, *J* = 8.4 Hz, 2 H), 6.65 (s, 1 H), 5.12 (m, 9 H), 5.02 (t, *J* = 7.2 Hz, 1 H), 3.82 (s, 3 H), 3.48 (s, 3 H), 3.32 (d, *J* = 6.4 Hz, 2 H), 2.46 (s, 3 H), 2.25 (s, 3 H), 2.07 (m, 18 H), 1.99 (m, 18 H), 1.69 (s, 6 H), 1.61 (s, 21 H), 1.60 (s, 3 H), 1.58 (s, 3 H).

 13 C NMR (100 MHz, CDCl₃): δ = 151.05, 144.71, 142.51, 135.69, 135.21, 135.12, 135.08, 132.95, 131.45, 129.56, 128.42, 127.26, 124.59, 124.43, 124.31, 121.99, 113.15, 60.64, 56.20, 39.94, 39.92, 39.87, 26.95, 26.90, 26.79, 26.58, 25.91, 21.91, 19.97, 17.88, 16.42, 16.23.

MS (FAB): m/z (%) = 1004 (M⁺), 355 (17), 219 (45), 181 (100).

HRMS (FAB): m/z calcd $C_{66}H_{98}NaO_5S$ 1025.7032; found 1025.7077.

1-Fluoro-4-[(E)-3-methylnon-2-enyl]benzene (11)

Ni/C Re-use Experiment with Regeneration by BuLi (Scheme 6): Ni/ C was reclaimed by filtration of a prior, acid quenched reaction. It was collected on a filter paper, washed with Et₂O, azeotropically dried with toluene (3 \times 1 mL), and finally heated at 100 °C under high vacuum for 6 h. The Ni/C was then used according to the general procedure detailed above with the following reagents: oct-1yne (150 µL, 110 mg, 1 mmol), Me₃Al (0.75 mL, 1.5 mmol, 2 M in hexanes), Cp2ZrCl2 (73 mg, 0.25 mmol), and ClCH2CH2Cl (1 mL) were used in the carboalumination following the procedure above. Ni/C (67.5 mg, 0.04 mmol), Ph₃P (21 mg, 0.08 mmol), BuLi (33 µL, 0.08 mmol, 2.45 M), THF (1 mL), and 4-fluorobenzyl chloride (6; 100 µL, 116 mg, 0.8 mmol) were used in the cross-coupling reaction following the procedure above. The reaction was allowed to stir at r.t. for 4 h. Standard workup followed by chromatography of the residue on silica gel with pentane afforded 172.1 mg of the title compound (92%) as a clear oil; R_f 0.71 (pentane).

IR (neat): 2959, 2927, 2856, 1642, 1508, 1223 cm⁻¹.

¹H NMR (400 MHz, $CDCl_3$): $\delta = 7.20-7.10 \text{ (m, 2 H)}$, 7.05–6.90 (m, 2 H), 5.32 (tq, J = 1.2, 7.4 Hz, 1 H), 3.34 (d, J = 7.2 Hz, 2 H), 2.04 (t, J = 7.2 Hz, 2 H), 1.71 (s, 3 H), 1.50–1.40 (m, 2 H), 1.35–1.20 (m, 6 H), 0.9 (t, J = 6.8 Hz, 3 H).

 ^{13}C NMR (100 MHz, CDCl₃): δ = 162.62, 160.20, 137.64, 137.10, 129.82, 129.74, 122.79, 115.31, 115.10, 39.90, 33.55, 31.99, 29.21, 28.12, 22.89, 16.26, 14.32.

MS (EI): m/z (%) = 234 (17, M⁺), 149 (100), 122 (22), 109 (45).

HRMS (EI): m/z calcd for C₁₆H₂₃F, M⁺ 234.1784, found 234.1782.

1-Fluoro-4-[(E)-3-methylnon-2-enyl]benzene (11)

Ni/C Re-use Experiments Without Regeneration; (Scheme 7): Unlike the general procedure, these reactions were conducted in a centrifuge tube so as to be able to settle the Ni/C once the first reaction was complete. Oct-1-yne (150 µL, 110 mg, 1 mmol), Me₃Al (0.75 mL, 1.5 mmol, 2 M in hexanes), Cp₂ZrCl₂ (73 mg, 0.25 mmol), and ClCH₂CH₂Cl (1 mL) were used in the carboalumination following the procedure above. Ni/C (67.5 mg, 0.04 mmol), Ph₂P (21 mg, 0.08 mmol), BuLi (33 µL, 0.08 mmol, 2.45 M), THF (1 mL), and 4-fluorobenzyl chloride (6; 100 µL, 116 mg, 0.8 mmol) were used in the cross-coupling reaction following the procedure above. The reaction was allowed to stir at r.t. for 4 h. Upon completion of the reaction, the reaction vessel was placed in the centrifuge for 10 min. After that time, the solution was transferred via syringe to a round bottom flask containing aq sat. NH4Cl solution. To the reaction tube was added anhyd THF (1 mL) and the mixture was stirred for 5 min. The reaction vessel was again placed in the centrifuge for 10 min. The liquid layer was again removed via syringe and added to the same round bottom flask. The second reaction was then started. Upon typical aqueous acidic quench, column chromatography of the residue on silica gel with pentane afforded 175.6 mg of the title compound (94%) as a clear oil. (See above experimental for IR, ¹H NMR, 13C NMR, and MS data.)

tert-Butyl{[(*E*)-7-(2-chlorophenyl)-5-methylhept-5enyl]oxy}dimethylsilane (13)

Ni/C Re-use, Second experiment, Without Regeneration by BuLi: In the same reaction vessel containing the previously used Ni/C was added TBDMS protected hex-5-yn-1-ol (184 mg, 1 mmol), Me₃Al (1.5 mL, 3.0 mmol, 2 M in hexanes), Cp₂ZrCl₂ (146 mg, 0.50 mmol), and ClCH₂CH₂Cl (1 mL) were used in the carboalumination following the procedure above with the exception that the carboalumination was allowed to stir at r.t. for 6 h. Ph₃P (21 mg, 0.08 mmol), THF (1 mL), and 1-chloro-2-(chloromethyl)benzene (**12**; 100 µL, 129 mg, 0.8 mmol) were used in the cross-coupling reaction following the procedure above. The reaction was allowed to stir at r.t. for 16 h. Upon typical aqueous acidic quench, chromatography of the residue on silica gel with 2% CH₂Cl₂-petroleum ether afforded 248 mg of the title compound (88%) as a clear oil; R_f 0.25 (2% CH₂Cl₂-

petroleum ether). (See above experimental (Table 1, entry 2) for IR, ¹H, NMR, ¹³C NMR, and MS data).

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References

- (1) Lipshutz, B. H.; Mollard, P.; Pfeiffer, S. S.; Chrisman, W., submitted.
- (2) For a related study using Ni(0) under *homogeneous* conditions, see: (a) Lipshutz, B. H.; Kim, S.-K.; Mollard, P.; Stevens, K. L. *Tetrahedron* **1998**, *54*, 6999. (b) Lipshutz, B. H.; Bulow, G.; Stevens, K. L.; Lowe, R. *Tetrahedron* **1996**, *52*, 7265.
- (3) Lipshutz, B. H. Adv. Synth. Catal. 2001, 343, 313.
- (4) (a) Lipshutz, B. H.; Blomgren, P. A. J. Am. Chem. Soc. 1999, 121, 5819. (b) Lipshutz, B. H.; Tomioka, T.; Blomgren, P. A.; Sclafani, J. A. Inorg. Chim. Acta 1999, 296, 164.
 (c) Lipshutz, B. H.; Sclafani, J. A.; Blomgren, P. A. Tetrahedron 2000, 56, 2139. (d) Lipshutz, B. H.; Ueda, H. Angew. Chem., Int. Ed. 2000, 39, 4492; Angew. Chem. 2000, 112, 4666. (e) Lipshutz, B. H.; Tomioka, T.; Sato, K. Synlett 2001, 970.
- (5) (a) Van Horn, D. E.; Negishi, E. J. Am. Chem. Soc. 1978, 100, 2252. (b) Negishi, E.; Van Horn, D. E.; Yoshida, T. J. Am. Chem. Soc. 1985, 107, 6639. (c) Matsushita, H.; Negishi, E. Org. Synth. 1984, 63, 31. (d) Negishi, E. Pure Appl. Chem. 1981, 53, 2333.
- (6) Lipshutz, B. H.; Tasler, S. Adv. Synth. Catal. 2001, 343, 327.
- (7) Inductively Coupled Plasma Mass Spectrometry; Montaser, A., Ed.; Wiley-VCH: New York, 1998.
- (8) Lipshutz, B. H.; Tasler, S.; Chrisman, W.; Spliethoff, B.; Tesche, B. J. Org. Chem. in press.