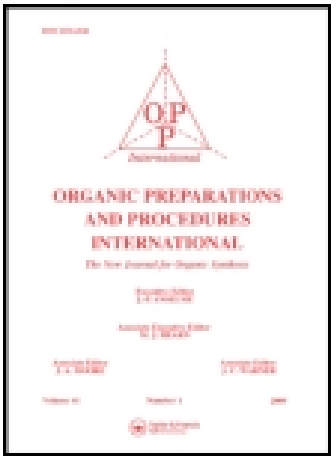

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OPPI BRIEF

Alternate and Step-Economic Synthesis of the β-Methylstyrene Chelating Pre-ligand of the Hoveyda-Grubbs' II Catalyst

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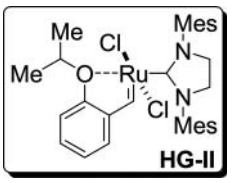
The Hoveyda-Grubbs (HG)[1] series of olefin metathesis catalysts are more selective, recyclable, and heat, air and moisture stable than their predecessors.[2] β-Methylstyrenes, such as *E*-1-isopropoxy-2-propenylbenzene (**3**, *Scheme 1*), are currently preferred as pre-ligands for the synthesis of the second generation of the HG catalysts (HG-II),[3] because they are less costly, easier to prepare, more stable and less prone to undergo spontaneous polymerization or homo-dimerization than the styrenes unsubstituted at the β-position, originally used for that purpose.[4,5]



Previous syntheses of compound **3** (*Scheme 1*), the chelating pre-ligand of HG-II and related olefin metathesis catalysts,[6] involved several steps, some of which were slow or tedious, requiring long reaction times,[3] or proceeded only in moderate yields,[3] employed high excess of alkylating agents, stoichiometric amounts of organometallic reagents,[7] or afforded undesirable *E/Z* mixtures of olefins.[8] In addition, an approach to related β-methylstyrenes via the Wittig reaction has been found to proceed in relatively low yields, and required the removal and disposal of large amounts of triphenylphosphine oxide; therefore, it was discarded as a viable route toward **3**.[3,7]

We have recently reported an efficient one-pot sequential homo-bimetallic catalytic propenylation of haloarenes with allyltri(*n*-butyl)tin under palladium catalysis and optimized the reaction conditions.[9,10] As a further application of this novel strategy, with impact in fine chemistry, herein we report an alternate and convenient, step-economic synthesis of **3**, from commercial 2-halophenols **8a**,**b** (*Scheme 2*).

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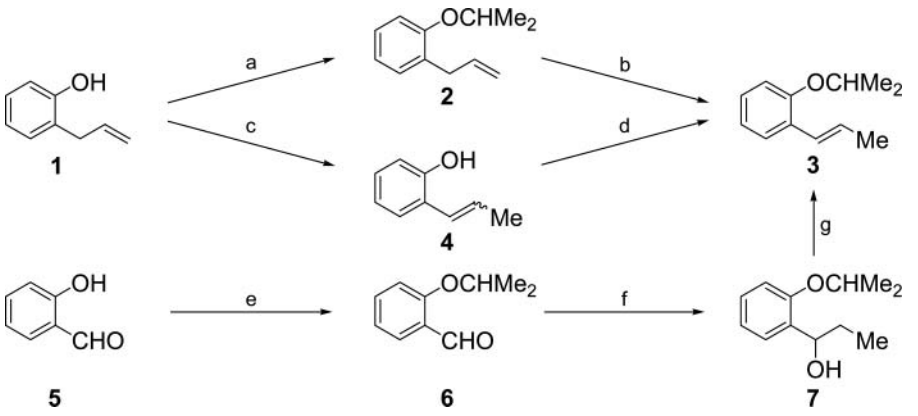


Scheme 1

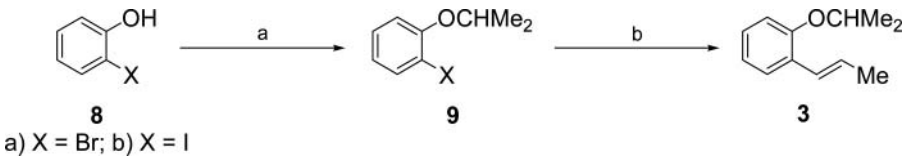
a) K_2CO_3, Cs_2CO_3 (cat.), *i*-PrI, DMF, 40°C, 24–48 h (93%); b) $RhCl_3.3H_2O$ (cat.), *p*-TsOH.H_2O (cat.), 90% aq. EtOH, reflux, 5 h (71%, *E/Z* = 14.3:1) or CH_2=CHOTMS, Grubbs II (cat.), CH_2Cl_2, 35°C, 24 h (66%); c) 1. $(PPh_3)_2Cl_2Ru$, 70°C, 17.5 h; 2. $P(CH_2OH)_3$ [> 99% (GC), *E/Z* = 45:55]; d) K_2CO_3 (2 equiv.), *i*-PrBr (2 equiv.), DMF, 60°C, 48 h (93%); e) K_2CO_3, *i*-PrBr, DMF, 60°C, 9 h; f) EtMgCl, THF, −15°C; g) TsOH, PhMe, 90°C, 1.5 h (58% overall, *E/Z* = 96:4).

The Williamson etherification of **8a** or **8b** was performed with 2-bromopropane and K_2CO_3 in EtOH[1] (*Scheme 2*), to afford **9a** and **9b** in 84% and 86% yield respectively, after 5 h of heating under reflux. This contrasted with previous preparations of **9a,b** involving comparatively poor eco-friendly solvents, strong bases,[12] or the relatively more expensive isopropyl iodide.

Next, the key homo-bimetallic catalytic reaction of allyltri(*n*-butyl)tin with the bromoethers **9a,b** was carried out in the presence of $Pd(PPh_3)_2Cl_2$ in diglyme at 130°C for 14 h. This process cleanly executed the Stille cross-coupling to the allyl intermediate[3] which further underwent an *in situ* palladium-catalyzed conjugative double bond migration to give compound **3**.

Removal of triphenylphosphine by oxidation to triphenylphosphine oxide with H_2O_2,[13] followed by treatment of the crude extract of the reaction with an activated fluorous silica gel phase (10% w/w),[14] led to the complete elimination of all tin residues (GC-MS analysis), affording the expected product **3** in yields of 73% and 60% from **9a** and **9b**, respectively.

The present two-step alternative approach to **3** complements previously reported syntheses of this important and valuable *β*-methylstyrene derivative. It can be easily carried out in a short time transforming the sequence into a cost-competitive process, counterbalancing the expense of the chemicals involved. The wider scope of the present route and its adaptability to access similar compounds with various functional groups[10] make it



Scheme 2

a) Me_2CHBr, K_2CO_3, EtOH, reflux, 5h (**9a**, 84%; **9b**, 86%); b) *n*-$Bu_3SnCH_2CH{=}CH_2$, $Pd(PPh_3)_2Cl_2$, LiCl, PPh_3, Diglyme, 130°C, 6 h; c) 130°C, 8 h (73% from **9a**; 60% from **9b**).

useful for the preparation of related otherwise less accessible, pre-ligand members of this family.[15] The availability of redundant pathways for the synthesis of small molecules with relevance in fine chemistry is always desirable, because of the potential economic value of such compounds. This is especially critical when intellectual property protection conditions restrict the use of the patent-protected processes.[6,7]

Experimental Section

The reactions were carried out under dry argon atmospheres, employing oven-dried glassware. Ethanol was dried by treatment with Mg turnings and a catalytic amount of I_2, and distilled from the resulting magnesium ethoxide. Diglyme was distilled from sodium benzophenone ketyl.[16] Anhydrous solvents were stored in dry Schlenk tubes. The remaining reagents were used as received. The IR spectra were acquired on a Shimadzu Prestige 21 spectrophotometer, as thin films. The ^{1}H and ^{13}C NMR spectra were recorded at 300.13 and 75.48 MHz respectively, on a Bruker Avance 300 spectrometer, employing $CDCl_3$ [δ_H 7.26 (residual $CHCl_3$) and δ_C 76.9 ppm] as internal standard. Chemical shifts are reported in δ scale and the coupling constants (J) are given in Hertz. The GC-MS data were obtained on a Shimadzu QP2010 *plus* instrument (EI = 70 eV). The high resolution MS were obtained on a Bruker MicroTOF-Q II instrument. Detection of the ions was performed with electrospray ionization in positive ion mode. The compounds gave single spots when run on Kieselgel 60 GF_{254} TLC plates, employing hexane-EtOAc as the solvent system. The chromatographic spots were detected by exposing the plates to UV light (254 nm), followed by spraying with *p*-anisaldehyde/sulfuric acid reagent in EtOH and careful heating up to 120°C.

General Procedure for the Synthesis of 1-halo-2-isopropoxybenzenes (9a and 9b)

A mixture of the 2-halophenol (**8a**,**b** 1.156 mmol), 192 mg (1.2 equiv. anhydrous K_2CO_3 (1.20 equiv.) and sodium iodide (4 mg) in absolute EtOH (3 mL) was magnetically stirred at ambient temperature under argon. The 2-bromopropane (1.20 equiv.), was added slowly and the mixture was then refluxed for 5 h, cooled to ambient temperature prior to the removal of the solvent under reduced pressure. Addition of EtOAc (50 mL) gave a solution which was washed successively with 1M NaOH and brine (15 mL each). The organic phase was dried over Na_2SO_4, and evaporated under reduced pressure to give a residue that was purified by flash column chromatography.

1-Bromo-2-isopropoxybenzene (9a)[17]

Oil; yield: 84%. IR (film): 602, 748, 953, 1030, 1107, 1275, 1385, 1472, 1587, 2978 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.38 (d, J = 5.9, 6H, CH*Me*$_2$), 4.55 (septet, J = 5.9, 1H, OC*H*Me$_2$), 6.81 (dt, J = 1.2 and 7.6, 1H, 3-H), 6.91 (dd, J = 0.6 and 7.9, 1H, 5-H), 7.22 (dt, J = 1.5 and 8.0, 1H, 4-H), 7.53 (dd, J = 1.6 and 7.9, 1H, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1 (*Me*$_2$-CH), 72.1 (Me$_2$−*C*H), 113.8 (1-C), 115.9 (5-C), 121.9 (3-C), 128.2 (4-C), 133.5 (6-C), 154.6 (2-C). MS (EI, 70 eV): *m/z* (%) 172 (100), 174 (95), 214 [M]$^+$ (25), 216 [M+2]$^+$ (25).

1-Iodo-2-isopropoxybenzene (9b)[18]

Oil; yield: 86%. IR (film): 648, 748, 953, 1045, 1126, 1273, 1381, 1470, 1577, 2931, 2978 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.39 (d, J = 5.9, 6H, CH*Me*$_2$), 4.56 (septet, J

= 5.9, 1H, OC*H*Me$_2$), 6.69 (dt, J = 1.6 and 8.0, 1H, 3-H), 6.85 (dd, J = 1.6 and 8.0, 1H, 5-H), 7.25 (dt, J = 1.6 and 8.0, 1H, 4-H), 7.78 (dd, J = 1.6 and 8.0, 1H, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.1 (*Me*$_2$-CH), 72.1 (Me$_2$-*C*H), 88.6 (1-C), 114.4 (3-C), 122.5 (5-C), 129.3 (4-C), 139.6 (6C), 156.8 (2-C). MS (EI, 70 eV): *m/z* (%) 65 (37), 93 (34), 220 [M-C_3H_6]$^+$ (100), 262 [M]$^+$ (25).

E-1-Isopropoxy-2-propenylbenzene (3)

A degassed solution containing the aryl bromide (**9a**, 183 mg, 0.852 mmol), anhydrous LiCl (286 mg, 6.82 mmol), Ph_3P (112 mg, 0.426 mmol) and Pd(Ph_3P)$_2Cl_2$ (71.7 mg, 0.102 mmol) in anhydrous diglyme (2 mL, final concentration of **9a** *ca.* 0.15 M) was treated dropwise with allyltri(*n*-butyl)tin (0.32 mL, 1.02 mmol). The reaction mixture was heated at 130°C under an argon atmosphere. A sample taken at 6 h and worked up allowed the isolation of *1-allyl-2-isopropoxybenzene*.[3]

IR (film): 605, 734, 864, 995, 1046, 1174, 1287, 1372, 1383, 1489, 1587, 1638, 2931, 2978, 3077 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.33 (d, J = 6.0 Hz, 6H), 3.37 (d, J = 6.7 Hz, 2H), 4.54 (septet, J = 6.0 Hz, 1H), 5.00–5.09 (m, 2H), 5.93–6.03 (m, 1H), 6.83–6.89 (m, 2H), 7.12–7.18 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 22.2, 34.6, 69.9, 113.0, 115.2, 120.2, 127.1, 129.7, 129.9, 137.2, 155.5. MS (EI, 70 eV): *m/z* (%) 91 (13), 115 (12), 119 (46), 133 (46), 134 (100), 135 (10), 176 [M]$^+$ (66), 177 [M+1]$^+$ (9). MS found: 176.1207; $C_{12}H_{16}O$ requires *m/z*: 176.1201.

When the reaction was heated during 14 h, complete consumption of the starting material took place, as determined by GC analysis. Then, the reaction mixture was allowed to attain ambient temperature and was diluted with 25 mL of hexanes and filtered through a short pad of Florisil and Celite (1:1). The filtrate was washed successively with saturated NaF (4 × 10 mL), H_2O (3 × 10 mL), brine (15 mL) and H_2O_2 (10 mL of a 0.12% P/V solution), dried over Na_2SO_4 and evaporated *in vacuo*. The oily residue was re-dissolved in CH_2Cl_2 and stirred an additional period of 12 h with 200 mg activated fluorous silica. Filtration and evaporation of volatiles afforded 90 mg (73%) of the expected β-methylstyrene (**3**), as a colorless oil.

IR (film): 606, 782, 862, 959, 1049, 1176, 1289, 1383, 1484, 1596, 1655, 2876, 2933, 3070 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.35 (d, J = 5.9, 6H, *Me*$_2$-CH), 1.90 (dd, J = 1.5 and 6.6, 3H, *Me*-CH=CH-Ar), 4.57 (septet, J = 5.9, 1H, Me$_2$-C*H*), 6.22 (dq, J = 6.0, 13.9 and 15.2, 1H, Me-C*H*=CH-Ar), 6.72 (dq, J = 1.5 and 15.9, 1H, CH_3-CH=C*H*-Ar), 6.85–6.90 (m, 2H, ArH), 7.14 (dt, J = 1.5 and 7.7, 1H, 4-H), 7.41 (dd, J = 1.4 and 7.5, 1H, 6-H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 18.9 (*Me*-CH=CH-Ar), 22.2 (*Me*$_2$-CH-O), 70.8 (Me$_2$-*C*H), 114.3 (6-C), 120.7 (5-C), 125.8 (2-C), 125.9 (CH_3-*C*H=CH-Ar), 126.4 (CH_3-CH=*C*H-Ar), 127.5 (3-C), 128.2 (5-C), 154.6 (1-C). MS (EI, 70 eV): *m/z* (%) 77 (10), 91 (24), 105 (13), 107 (9), 115 (17), 117 (12), 119 (69), 133 (54), 134 (100), 147 (12), 176 [M]$^+$ (52), 177 [M+1]$^+$ (7). MS found *m/z* = 176.1198; $C_{12}H_{16}O$ (M^+) requires *m/z* = 176.1201. The spectral data were in full agreement with those described.[2,3,5,8]

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