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Rhenium-Catalyzed Aromatic Propargylation

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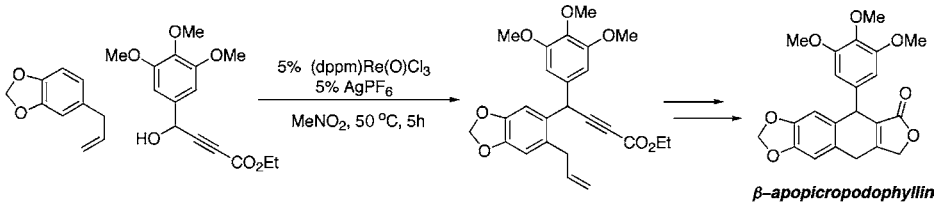
ABSTRACT



A mild aromatic propargylation reaction, employing an air- and moisture-tolerant rhenium–oxo complex ((dppm)ReOCl$_3$) as a catalyst and a propargyl alcohol as the electrophile, is described. The reaction tolerates a broad range of functional groups and regioselectively affords propargylic arenas without formation of the isomeric allenyl adducts. The potential of this rhenium(V)-catalyzed reaction is exemplified by application of the propargylation to the synthesis of *O*-methyldetrol, mimosifoliol, and *β*-apopicropodophyllin.

Classically, the conversion of aromatic C−H bonds into C−C bonds has involved Friedel−Crafts reactions that employ a Lewis acid catalyst for the activation of an alkyl halide.[1] The need for stoichiometric amounts of catalyst[2] and other limitations of traditional Friedel−Crafts reactions has prompted considerable interest in developing alternative methods. While a variety of transition metal complexes have been employed as catalysts for C−H functionalization,[3] the use of high oxidation state complexes is relatively unexplored.[4]

We have recently reported a method for the etherification and allylation of simple alcohols with propargylic alcohols employing an air- and moisture-tolerant rhenium(V) complex, (dppm)Re(O)Cl$_3$ (**1**), as a catalyst.[5] We envisioned that replacement of the alcohol nucleophile with an aromatic compound would allow for the catalytic propargylation of aryl C−H bonds with propargyl alcohols.[6] Herein we report the development and synthetic application of an air- and moisture-tolerant method for the catalytic functionalization of aromatic C−H bonds.

Reaction of 1,2,3-trimethoxybenzene with propargyl alcohol **2**, under the reaction conditions developed for our propargylic etherification reaction (5% **1**, CH_3CN, 65 °C), produced only poor yields of the desired adduct **3**. We reasoned that activation of the propargyl alcohol may involve substitution of one of the chloride ligands in **1** by the alcohol, and therefore the activity of the catalyst could be improved by abstraction of a chloride. Gratifyingly, 5 mol % **1** in the presence of 5 mol % potassium hexafluorophosphate as a halide abstractor afforded **3** in 90% yield from the coupling of 1,2,3-trimethoxybenzene (1.5 equiv) with **2** (eq 1).

With these reaction conditions in hand, we examined the scope of nucleophile that would participate in the rhenium-

(1) (a) Olah, G. A.; Krishnamurti, R.; Prakash, G. S. S. In *Comprehensive Organic Synthesis*: Trost, B. M., Fleming I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 1.8. (b) Olah, G. A. *Friedel−Crafts and Related Reactions*; Interscience Publishers: New York, 1964.

(2) Recently, catalytic amounts of rare earth triflates have been employed. (a) Kobayshi, S.; Suguira, M.; Kitagawa, H.; Lam, W. W. L. *Chem. Rev.* **2002**, *102*, 2227. (b) Evans, D. A.; Scheidt, K. A.; Fandrick, K. R.; Lam, H. W.; Wu, J. *J. Am. Chem. Soc.* **2003**, *125*, 10780. For an organocatalytic Friedel−Crafts reaction, see: Paras, N. A.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2001**, *123*, 4370.

(3) For a review, see: Kakiuchi, F.; Chatani, N. *Adv. Synth. Catal.* **2003**, *345*, 1077.

(4) For Pt(IV)-catalyzed C−H functionalization, see: Pastine, S. J.; Youn, S. W.; Sames, D. *Tetrahedron* **2003**, *59*, 8859.

(5) (a) Sherry, B. D.; Radosevich, A. T.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 6076. (b) Luzung, M. R.; Toste, F. D. *J. Am. Chem. Soc.* **2003**, *125*, 15760.

(6) For Ru-catalyzed propargylations, see: (a) Nishibayashi, Y.; Yoshikawa, M.; Inada, Y.; Hidai, M.; Uemura, S. *J. Am. Chem. Soc.* **2002**, *124*, 11846. (b) Nishibayashi, Y.; Inada, Y.; Yoshikawa, M.; Hidai, M.; Uemura, S. *Angew. Chem., Int. Ed.* **2003**, *42*, 1495. For propargylations involving stoichiometric amounts of transition metals, see: (c) Grove, D. D.; Corte, J. R.; Spencer, R. P.; Pauly, M. E.; Rath, N. P. *J. Chem. Soc., Chem. Commun.* **1994**, 49. (d) Müller, T. J. J. *Eur. J. Org. Chem.* **2001**, 2021.

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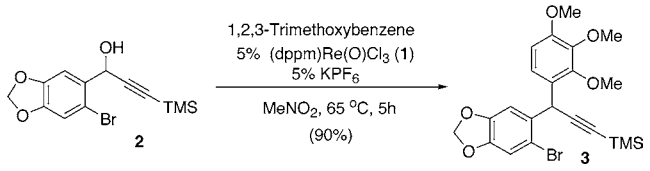
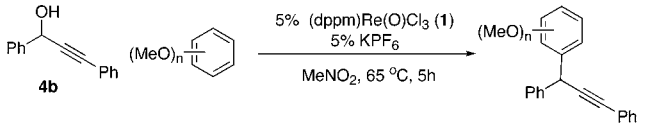
Scheme 1



catalyzed aryl propargylation (Scheme 2). The reaction proceeds well with 1,2,4-trimethoxybenzene (1.05 equiv) as a nucleophile affording **6a** as a single regioisomer. Furthermore, aromatic compounds that did not participate in the ruthenium-catalyzed propargylation[6a] such as anisole (**5c**) and 1,3-dimethoxybenzene (**5b**) are excellent nucleophiles in the rhenium-catalyzed reaction, although the latter was accompanied by 9% of a dipropargylated adduct. Additionally, the presence of an aryl bromide did not have a noticeable effect on the course of the rhenium-catalyzed propargylation of **5d**.

Scheme 2

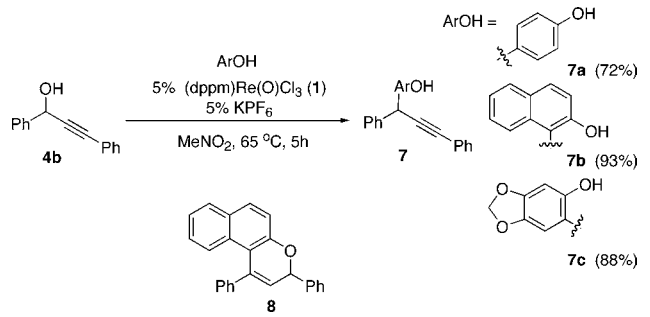


5a 1,2,4-MeO
b 1,3-MeO
c 1-MeO
d 2,4-MeO, 1-Br

6a 2,4,5-MeO (76%)
b 2,4-MeO (83%)
c 4-MeO (80%)
d 2,4-MeO, 5-Br (88%)

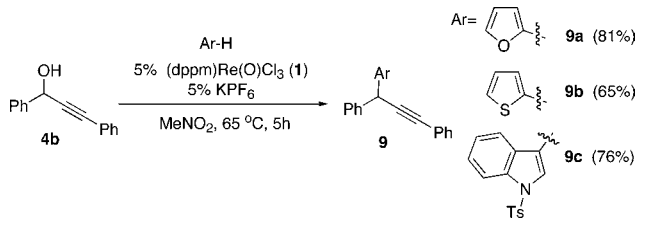
The propargylation of phenols, catalyzed by a cationic ruthenium complex[6b] or protic acid,[7] generally results in the formation of the benzopyran (e.g., **8**). Therefore, the alkyne is often protected as its cobalt complex,[6c] allowing for selective reaction with the alcohol. We envisioned that our rhenium-catalyzed reaction might allow for the propargylation of phenols without the need for formation of the stoichiometric cobalt−alkyne complex or protection of the phenolic hydroxyl group. We were pleased to find that 5 mol % **1** efficiently catalyzed the propargylation of a variety of phenols (1.05−1.5 equiv) while avoiding competitive O-alkylation[8] and formation of the benzopyran (Scheme 3).

Scheme 3



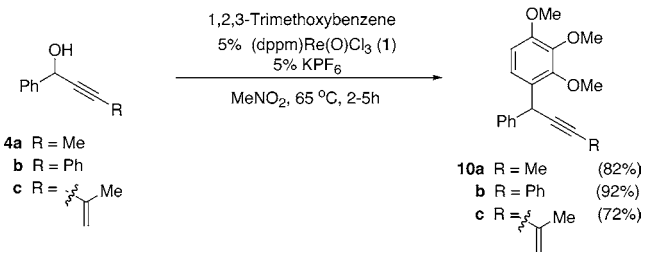
Heteroaromatic compounds can also be propargylated with propargyl alcohols using rhenium(V)−oxo complex **1** as a catalyst (eq 4). For example, 5 mol % **1** catalyzes the selective propargylation of furan and thiophene at the α-position, affording **9a** and **9b**, respectively. In accord with other electrophilic substitutions, propargylation of *N*-tosylindole (1.05 equiv) occurs selectively at C-3, giving **9c** in 76% yield.

Scheme 4



The reaction could also be extended to propargyl alcohols bearing a variety of alkyne substituents, including enyne **4c** that contains a 1,1-disubstituted olefin that is susceptible to protonation (Scheme 5). Notably, the reaction remains

Scheme 5



4a R = Me
b R = Ph
c R =

10a R = Me (82%)
b R = Ph (92%)
c R = (72%)

completely selective for formation of the propargyl adduct,[9] even when the alkyne is substituted with phenyl and vinyl groups. In contrast to the ruthenium-catalyzed reaction,[6a] propargyl alcohols derived from terminal alkynes were not viable substrates.

The rhenium-catalyzed propargylation allows for the rapid and atom economical (water is the only byproduct) synthesis of compounds containing a benzhydryl moiety from simple starting materials (Scheme 6). For example, reaction of **11** with 2,5-dimethoxyphenol, catalyzed by 5 mol % **1**, afforded **12**, which was converted into mimosifoliol[10] in two steps.

(7) For a recent example, see: Zhao, W.; Carreira, E. M. *Org. Lett.* **2003**, *5*, 4153.

(8) O-Alkylation is faster in the reaction of phenols with benzylic carbocations in 50:50 TFE/water. Tsuji, Y.; Toteva, M. M.; Garth, H. A.; Richard, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 15455.

(9) These substituents would be expected to result in increased cationic character at the alkynyl carbon (allenyl cation). (a) Olah, G. A.; Porter, R. D.; Kelly, D. P. *J. Am. Chem. Soc.* **1971**, *93*, 464. (b) Siehl, H.-U.; Kaufmann, F.-P. *J. Am. Chem. Soc.* **1992**, *114*, 4937.

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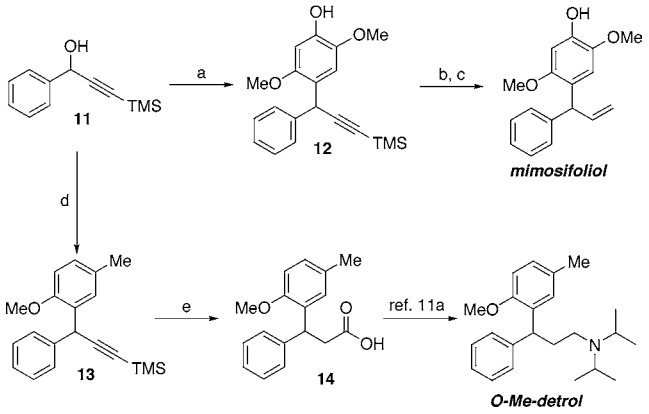
Scheme 6. Synthesis of Mimosifoliol and *O*-Me-Detrol[a]



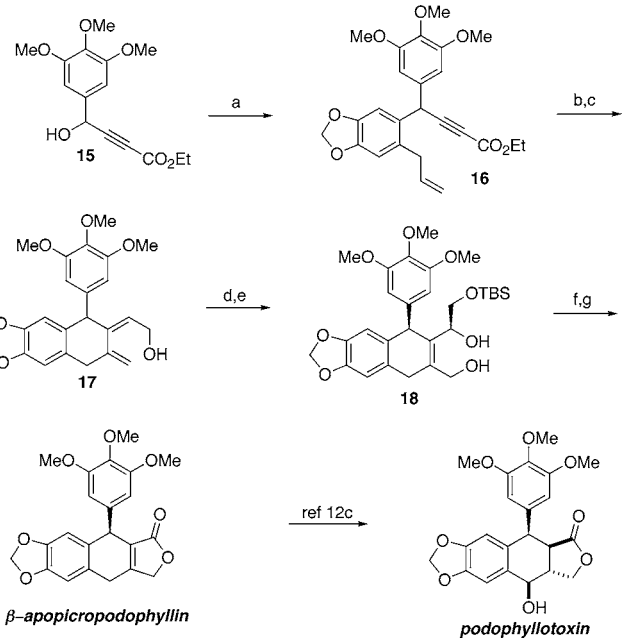
[a] Reagents and conditions: (a) 2,5-dimethoxyphenol, 5 mol % (dppm)Re(O)Cl_3, 5 mol % KPF_6, $MeNO_2$, 65 °C, 69%. (b) TBAF, THF, 0 °C, 92%. (c) H_2, Pd/$BaSO_4$, quinoline, EtOAc, rt, 91%. (d) 4-methylanisole, 5 mol % (dppm)Re(O)Cl_3, 5 mol % KPF_6, $MeNO_2$, 65 °C, 90%. (e) Cy_2BH, THF, 0 °C, then NaOH, H_2O_2, 90%.

Similarly, detrol (tolterodine) is available from Re(V)-catalyzed functionalization of 4-methylanisole with propargyl alcohol **11**. The TMS-protected acetylene (**13**) smoothly underwent hydroboration to carboxylic acid **14**, which can be converted into *O*-Me-detrol.[11]

We also envisioned that the rhenium-catalyzed propargylation reaction could provide rapid entry into cytotoxic aryltertralin lactones such as podophyllotoxin.[12] To this end, rhenium-catalyzed coupling of ethyl propiolate **15** with safrole yielded **16** in 66% as a ~6:1 mixture of separable regioisomers.[13] Iodination followed by DIBAL-H reduction provided a vinyl iodide[14] that was employed in an intramolecular Heck reaction[15] to afford diene **17**. After silyl protection of the alcohol, the diene was photooxygenated and reduced with Al(Hg)[16] to give diol **18**. Deprotection of the silyl ether, followed by one-pot $Pb(OAc)_4$ diol cleavage and PDC oxidation, gave *β*-apopicropodophyllin. The conversion of *β*-apopicropodophyllin to podophyllotoxin has been previously described.[12c]

In summary, we have developed a mild rhenium-catalyzed reaction of aromatic compounds with propargyl alcohols for the conversion of aryl and heteroaryl C−H bonds into C−C bonds. The reaction is tolerant of air and moisture, and in many cases requires only a slight excess of the nucleophile

Scheme 7. Formal Synthesis of (±)-Podophyllotoxin[a]



[a] Reagents and conditions: (a) safrole, 5 mol % (dppm)Re(O)Cl_3, 5 mol % $AgPF_6$, $MeNO_2$, 50 °C, 66%. (b) (i) NaI, AcOH, 115 °C, 76−92%; (ii) DIBAL-H, CH_2Cl_2, 0 °C, 77%. (c) $Pd(OAc)_2$, PPh_3, Ag_2CO_3, PhH, 50 °C, 91%. (d) TBSCl, TEA, DMAP, CH_2Cl_2, rt, 89%. (e) (i) O_2, *hν*, TPP, CCl_4, 0 °C, 80%; (ii) Al(Hg), THF, H_2O, rt, 96%. (f) TBAF, THF, 0 °C, 96%. (g) $Pb(OAc)_4$, $NaHCO_3$, CH_2Cl_2, 0 °C, 15 min, then PDC, 39%.

and gives water as the only byproduct. This reaction provides a powerful and practical alternative for the construction of aryl C−C bonds as exemplified by its application to synthesis of benzhydryl-containing compounds such as podophyllotoxin. The regioselectivity of the propargylation is consistent with that of electrophilic aromatic substitution; however, the exact nature of the electrophile derived from the propargyl alcohol remains unclear.[17] Studies on the mechanism of the propargylation reaction and development of this class of reactions are ongoing in our laboratories.

Acknowledgment. We gratefully acknowledge the UC Cancer Research Coordinating Committee, Merck Research Laboratories, Amgen, Inc., and Eli Lilly & Co. for financial support. J.J.K.S. thanks Eli Lilly & Co. for a graduate fellowship. The Center for New Directions for Organic Synthesis is supported by Bristol-Myers Squibb as a Sponsoring Member and Novartis Pharma as a Supporting Member.

Supporting Information Available: Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) Small amount of a dimer of **15** was also isolated (see Supporting Information)

(14) Piers, E.; Harrison, C. L.; Zetina-Rocha, C. *Org. Lett.* **2001**, *3*, 3245.

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(16) Nicolaou, K. C.; Gunzer, J. L.; Shi, G.-Q.; Agrios, K. A.; Gartner, P.; Yang, Z. *Chem. Eur. J.* **1999**, *5*, 646.

(17) Reaction of **4b** and 2-naphthol catalyzed by cationic ruthenium[6b] complexes affords pyran **8**, while our rhenium-catalyzed reaction exclusively produces propargyl adduct **7b** (Scheme 3). This suggests that the reactions are proceeding through different mechanisms or nucleophilic attack on different electrophilic intermediates.