Rhenium-Catalyzed Aromatic Propargylation

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ABSTRACT

A mild aromatic propargylation reaction, employing an air- and moisture-tolerant rhenium−oxo complex ((dppm)ReOCl₃) 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 aryls 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. The need for stoichiometric amounts of catalyst 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, the use of high oxidation state complexes is relatively unexplored. 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)Cl₃ (1), as a catalyst. 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. 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, CH₃CN, 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(V)-catalyzed reaction.
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 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.

The propargylation of phenols, catalyzed by a cationic ruthenium complex or protic acid, generally results in the formation of the benzopyran (e.g., 8). Therefore, the alkyne is often protected as its cobalt complex 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 and formation of the benzopyran (Scheme 3).

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 in two steps.

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.

The reaction could also be extended to propargyl alcohols bearing a variety of alkyne substituents, including enyne that contains a 1,1-disubstituted olefin that is susceptible to protonation (Scheme 5). Notably, the reaction remains completely selective for formation of the propargyl adduct, even when the alkyne is substituted with phenyl and vinyl groups. In contrast to the ruthenium-catalyzed reaction, propargyl alcohols derived from terminal alkynes were not viable substrates.

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(7) For a recent example, see: Zhao, W.; Carreira, E. M. Org. Lett. 2003, 5, 4153.
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 arylertralin 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 reaction15 to afford diene 17. After silyl protection of the alcohol, the diene was photogenerated 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-apicicropodophyllin. The conversion of β-apicicropodophyllin to podophyllotoxin has been previously described.12

In summary, we have developed a mild rhenium-catalyzed reaction of aromatic compounds with propargyl alcohols for the conversion of ary1 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 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.

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

1327

(17) Reaction of 4b and 2-naphthol catalyzed by cationic ruthenium6 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.