Dehydrative Alkylation

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Ruthenium-Catalyzed *ortho*-Alkylation of Phenols with Alcohols by Dehydrative Coupling**

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alcohols · C–C coupling · C–H activation · phenols · ruthenium

The development of direct and efficient methods for the formation of C–C bonds is a major area of research in organic chemistry. Transition-metal-catalyzed coupling reactions are now commonplace in synthesis, and generally rely on the initial oxidative addition of a metal into a C–X bond (X = halide, aryl sulfonate).[1] This method requires the presence of an appropriate C–X group and often generates stoichiometric amounts of HX, which must be removed from the reaction mixture, typically by the addition of a base. A more attractive approach is the direct activation of C–H bonds. This alternative route produces fewer waste products and may give access to alternative derivatives of the starting materials.

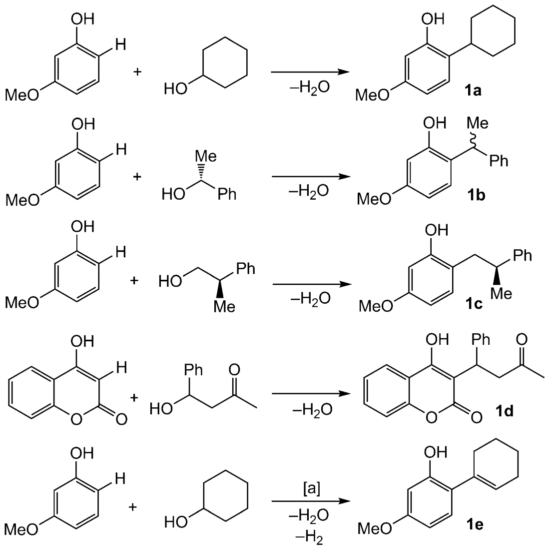
Pioneering examples of transition-metal-catalyzed C–H bond activation include Murai's coupling of arylketones with alkenes[2] and Oi's arylation of 2-arylpyridines.[3] Each of these methods involves aryl systems and makes use of a directing effect through chelation, in which coordination of a Lewis basic group to the metal leads to regioselective insertion into the C–H bond in the *ortho* position to the directing group. While such C(sp^2)–H activations are most common,[4] examples of C(sp^3)–H activation have also been reported.[5]

After activation of the C–H bond, substitution usually takes place to give C–C, C–N, and C–O in the *ortho* position to the directing group of aryl derivatives.[6] Cases also exist in which metal insertion leads to greater reactivity in arene rings in the position *para* to the C–M bond.[7]

While Pd is the most common metal used for such transformations,[8] several other metals have also been exploited, including Ru, Rh, Ni, Ir, and Cu.[9]

The ability to activate C–H bonds in order to generate new C–C bonds is perhaps one of the most important transformations addressed by current research. The focus of this highlight is the recent report from Yi and co-workers on a ruthenium-catalyzed alkylation or alkenylation of phenols with alcohols.[10] A key feature of this process is that alcohols can be used as coupling reagents, in which the C–O bond is broken, while the energetically more favorable alkoxylation or oxidation does not occur. A second major advantage to the process is the formation of H_2O as the only by-product.

The process involves the coupling of phenols with primary and secondary alcohols to give the corresponding *ortho*-alkylated phenols in high yields (91–95%; Scheme 1). The presence of a methoxy group in the 3-position, although not a requirement for the success of the reaction, enhances the rate of reaction and directs the alkylation in the 6-position. Consequences of coupling with this procedure include the loss of stereochemistry at the carbon atom attached to the OH group (**1b**), but retention of stereochemistry at the adjacent carbon atom (**1c**). The reaction was also shown to be applicable to the formation of biologically relevant molecules, such as the anticoagulant warfarin (**1d**).



Scheme 1. General Conditions: Ar-H (1.0 mmol), alcohol (1.2 mmol), Ru catalyst **3b** (1 mol%), cyclopentene (0.1 mmol), toluene (2 mL), 100 °C, 8 h, yields: 91–95%. [a] 3.0 mmol of cyclopentene was used.

It was found that the reaction proceeds more rapidly with the addition of 0.1 equivalents of alkene, with cyclopentene proving to be the most effective. By increasing the amount of cyclopentene from 0.1 to 3 equivalents, it was found that

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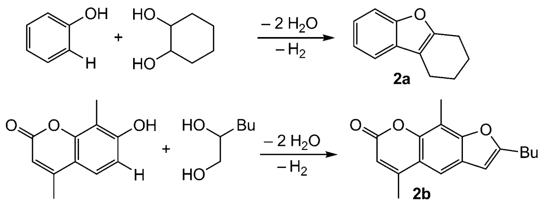
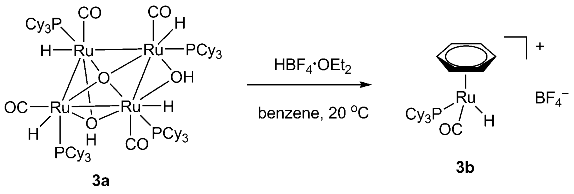
dehydrogenation of the coupled product takes place, with cyclopentene acting as a dehydrogenation agent,[11] to give alkenylation product **1e**. This methodology was extended to the formation of benzofurans from phenols and 1,2-diols (Scheme 2). Presumably, the reaction proceeds via the dehydrogenated coupled product, followed by loss of H_2O to give the corresponding benzofurans. As with the previous coupling reaction, this process gives the products in high yields, and has been applied to the synthesis of α-substituted furanocoumarin (**2b**), commonly used as a photosensitizer for the treatment of psoriasis.

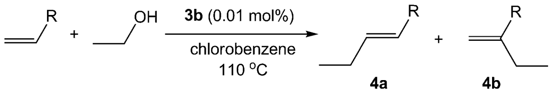


Scheme 2. General Conditions: Ar-H (1.0 mmol), diol (1.2 mmol), Ru catalyst **3b** (1 mol%), cyclopentene (3.0 mmol), toluene (2 mL), 100 °C, 8 h, yields: **2a** 86%, **2b** 67%.

The selected catalyst for these processes is the tetrafluoroborate salt of $[(C_6H_6)(PCy_3)(CO)RuH]^+$ (**3b**), which is synthesized by a protonation reaction of complex **3a** using $HBF_4{\cdot}OEt_2$ in benzene (Scheme 3).[12] The monomeric Ru complex, defined by X-ray crystallography and multinuclear NMR, has previously been shown to catalyze the C–H bond-activated coupling of alkenes with aryl ketones,[13] aryl amides,[14] alkenes,[15] and, most noteworthy, primary alcohols.[16] The latter of these examples involves the activation of an alkenyl C–H bond, followed by dehydrative coupling with primary and secondary alcohols to give substituted alkenes (Scheme 4). The stereo- ($E/Z = 20{:}1$) and regioselectivity (**4a**/**4b** = 9:1) are reasonably high and can be further enhanced by the presence of bulky R groups. This process requires no directing group and yields ranged from 71–97%, with catalyst loadings as low as 0.01 mol%.

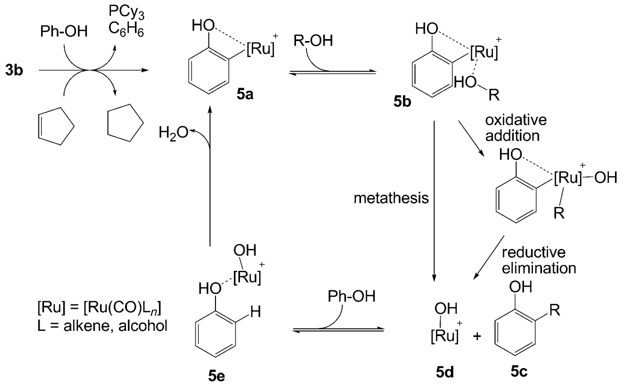


Scheme 3. Synthesis of the active Ru catalyst.[12]



Scheme 4. Coupling of terminal alkenes with alcohols.[16]

The proposed mechanisms for the reactions catalyzed by $[(C_6H_6)(PCy_3)(CO)RuH]^+$, discussed above, follow similar pathways to one another. In the case of the phenol/alcohol coupling (Scheme 5), initial loss of both C_6H_6 and PCy_3 from the Ru complex is accompanied by the insertion of Ru into the *ortho* C–H bond of phenol. Cyclopentene acts as a hydrogen acceptor to form cyclopentane and the chelated Ru species **5a**. Coordination of the alcohol to Ru is followed by breaking of both the alcohol C–O bond and the Ru–C bond, followed by formation of a new C–C bond to give the coupled phenol and the Ru–OH species **5d**. A second phenol then coordinates to the Ru center with the OH group before elimination of H_2O completes the catalytic cycle. Evidence for such a mechanism includes the observation of cyclopentane and free benzene in the reaction mixture, an extensive *ortho*-H/D exchange pattern as a result of a rapid and reversible C–H bond activation, and a large $^{12}C/^{13}C$ kinetic isotope effect at the *ortho* carbon atom, suggesting C–C bond formation as the rate-limiting step. It is proposed that the formation of **5c** from intermediate **5b** proceeds either through an oxidative addition of the C–O bond, followed by C–C reductive elimination, or through a σ-bond metathesis coupling mechanism.[17]



Scheme 5. Plausible mechanism for the Ru-catalyzed coupling of phenol and alcohols.

The coupling reactions outlined in this highlight represent significant advances in the area of metal-catalyzed C–C bond formation. More generally, C–H bond activation is an important process in derivatizing carbon frameworks, expanding the toolbox of organic transformations in a manner that is more atom-economical and greener than traditional methods. One of the major drawbacks of this methodology is the need for reaction conditions including inert atmosphere because of the sensitivity of many transition-metal catalysts to molecular O_2. While rare examples exist of C–H oxidative coupling under aerobic conditions,[18] this limitation remains a challenge for the development of practical C–C bond-formation methods.

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