Oxidative Coupling

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Oxidative Catalytic Coupling Reactions: Selective Formation of C–C and C–X Bonds Using Radical Processes**

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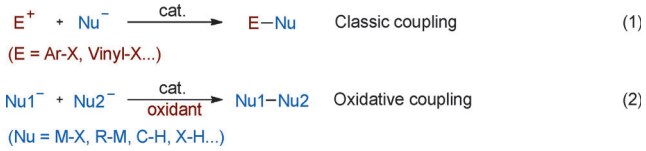
C–C bonds · C–X bonds · oxidative coupling · radical reactions · sustainable chemistry

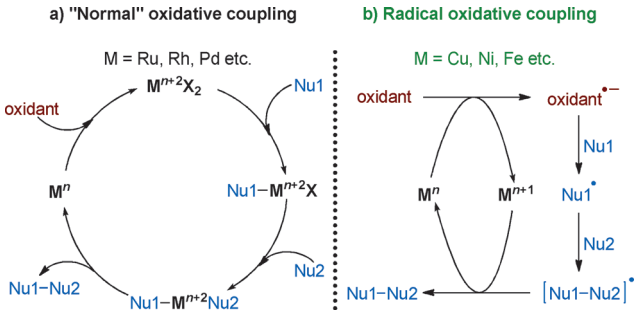
Transition-metal-catalyzed coupling reactions have provided important innovations for synthetic chemistry over the past decades. Nowadays, they constitute a powerful method for the construction of carbon–carbon and carbon–heteroatom bonds.[1] Along with the rapid development of organometallic chemistry, many kinds of metal catalysts and ligands were discovered and applied in coupling reactions, thus greatly improving their efficiency and applicability.[2] Most studies in this field have focused on classic coupling reactions between an electrophile and a nucleophile [Scheme 1, Eq. (1)]. By suitable variations of the substrates and reaction conditions, coupling processes of two nucleophiles are also possible; these processes are known as "oxidative couplings" [Scheme 1, Eq. (2)].[3] In this case, an additional oxidant is required to remove the two extra electrons for the bond-formation process.



Scheme 1. Classic and oxidative coupling reactions.

Nucleophiles include anions in salts (MX), organometallic reagents (R–M), hydrocarbons (C–H), and also X–H compounds, such as amines, alcohols, and carboxylic acids. Moreover, a number of electrophiles, such as the broadly used organohalides, are directly or indirectly prepared from the corresponding nucleophiles. The use of nucleophiles for bond construction in the presence of a green oxidant such as oxygen allows synthetic procedures to be more efficient, and waste production can be minimized. An important challenge of this approach is chemoselectivity, as unwanted homocoupling of the nucleophiles and direct reaction of the nucleophiles with the oxidant may occur. Despite these problems, a number of excellent results have recently been reported.[3,4]

In general, oxidative coupling reactions were achieved through a double-electron-transfer process, and the final bond-formation step occurred through the reductive elimination of two nucleophiles from a high-valent metal catalyst (Scheme 2a). Precious metal catalysts (including Ru,[5] Rh,[6] and Pd[7]) are most commonly used for these reactions. Recently, single electron transfer (SET) processes were applied to oxidative coupling reactions, which leads to so-called radical oxidative couplings (Scheme 2b).[8] Several remarkable examples developed by Lei et al. demonstrated the ability of non-precious-metal sources (Cu, Ni, Fe, etc.) to act as efficient catalysts of this type of transformations; these reactions are highlighted below.



Scheme 2. General reaction mechanisms for oxidative coupling processes.

In early 2013, Lei and co-workers reported a radical oxidative coupling of aldehydes and alkenes in the presence of a copper catalyst and *tert*-butyl hydroperoxide (TBHP) as the oxidant (Scheme 3).[9] Both alkenes and aldehydes are easily available substrates, even on industrial scales. The direct coupling of aldehydes with alkenes results in the straightforward construction of α,β-unsaturated ketones, and neither the aldehyde nor the alkene need to be prefunctionalized. The mechanism follows the general reaction pathway shown in Scheme 2. SET between the low-valent copper

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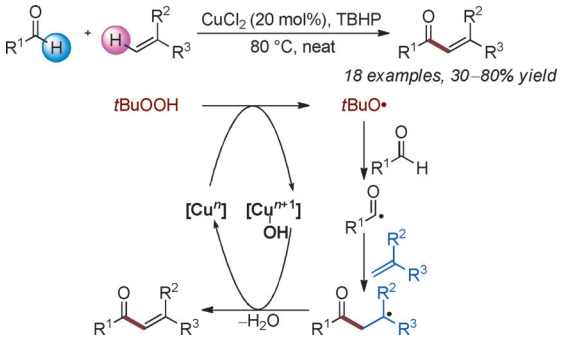
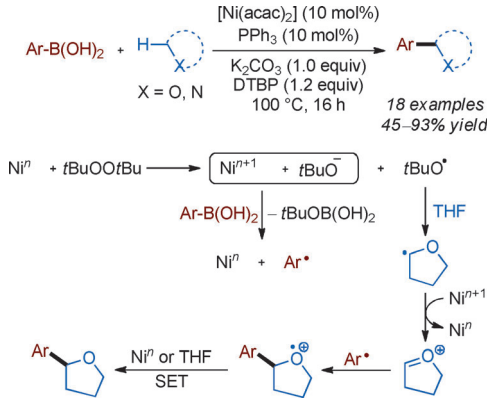


Scheme 3. Copper-catalyzed radical oxidative coupling of alkenes with aldehydes.

species and TBHP generates the *tert*-butyloxyl radical, which initiates the coupling process (Scheme 3). The key C–C-bond-formation step occurs through the radical addition of the acryl radical to the olefin.

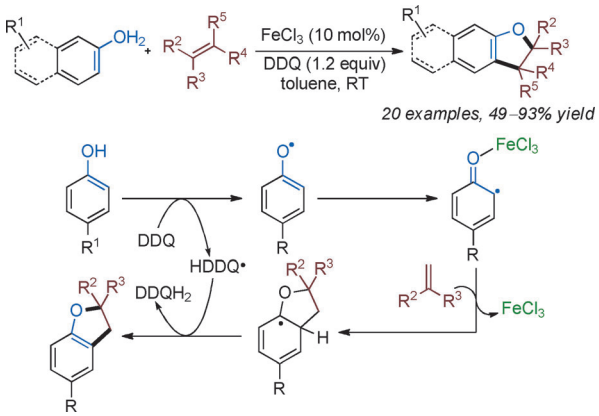
Shortly after, a nickel-catalyzed oxidative arylation of *ortho*-C(sp^3)–H bonds that are adjacent to the oxygen atom of tetrahydrofuran (THF) or 1,4-dioxane with aryl boronic acids was reported by the same group (Scheme 4).[10] THF and 1,4-dioxane moieties frequently occur as part of the structures of



Scheme 4. Nickel-catalyzed radical oxidative coupling of C(sp^3)–H bonds with aryl boronic acids. acac = acetylacetonato.

important organic compounds.[11] However, direct functionalization of the THF or 1,4-dioxane rings is a challenging task owing to a lack of reactivity. Remarkably, these cyclic ethers are suitable substrates for a nickel-catalyzed radical oxidative coupling reaction. A radical-trapping experiment with 1,1-diphenylethene confirmed the co-existence of THF and aryl radicals during the reaction process. As a result, the following reaction mechanism is proposed (Scheme 4). The two above-mentioned radicals are initially generated with the aid of the nickel catalyst and DTBP (di-*tert*-butyl peroxide); they then undergo the subsequent SET and radical-addition processes to afford the final product.

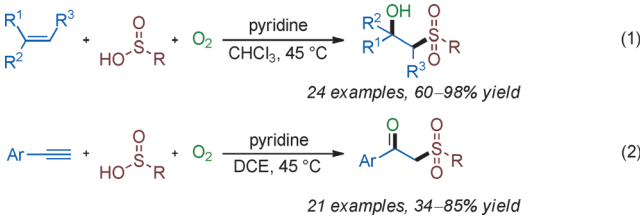
Apart from copper and nickel catalysts, less-expensive and environmentally benign iron catalysts also promote radical oxidative couplings. In this respect, Lei and co-workers reported a novel iron-catalyzed radical oxidative



Scheme 5. Iron-catalyzed radical oxidative coupling and cyclization of phenols with alkenes.

coupling reaction of phenols and olefins (Scheme 5).[12] When simple phenols are employed in oxidative coupling reactions, the generation of the desired product usually occurs with concomitant formation of homocoupled by-products as well as higher-molecular-weight polymers or C–O connected phenol portions, such as quinol ethers. In contrast, when $FeCl_3$ was utilized as the catalyst in the presence of 2,3-dichloro-5,6-dicyano-1,4-benzoqinone (DDQ) as the oxidant, a highly selective oxidative coupling/cyclization reaction occurred at room temperature. Based on detailed studies by electron paramagnetic resonance (EPR) spectroscopy and in situ IR experiments, a putative mechanism was proposed (Scheme 5). First, DDQ oxidizes phenol, which leads to the corresponding phenol radical. By stabilizing the resonance structure of the phenol radical, $FeCl_3$ acts as a Lewis acid catalyst to promote the radical transfer from an oxygen-centered to a carbon-centered radical, which subsequently leads to a rapid radical addition to the alkene to deliver the cyclization product.

Apart from radical oxidative couplings catalyzed by non-precious metals, a metal-catalyst-free aerobic oxysulfonylation of alkenes and alkynes that leads to β-hydroxysulfones and β-keto sulfones was developed (Scheme 6).[13] This method not only features an effective and operationally simple formation of new C–O and C–S bonds in a one-pot fashion, but also enabled the activation of dioxygen by sulfinic acids in the absence of any additional initiators. Moreover, this transformation demonstrates that under suitable reaction conditions, radical oxidative coupling reactions can be accomplished even without the assistance of a metal catalyst as the radical initiator.



Scheme 6. Metal-catalyst-free radical oxidative coupling of alkenes or alkynes with aryl sulfinic acids and oxygen. DCE = 1,2-dichloroethane.

In summary, novel radical oxidative coupling reactions are achieved by single-electron-transfer processes with the assistance of non-precious-metal catalysts, or even under metal-catalyst-free conditions. These reactions are interesting alternatives to well-established methods for the formation of C–C and C–X bonds.

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