Photoredox Catalysis

DOI: 10.1002/anie.201408748

Oxidative Photoredox-Catalytic Activation of Aliphatic Nucleophiles for C(sp^3)–C(sp^2) Cross-Coupling Reactions**

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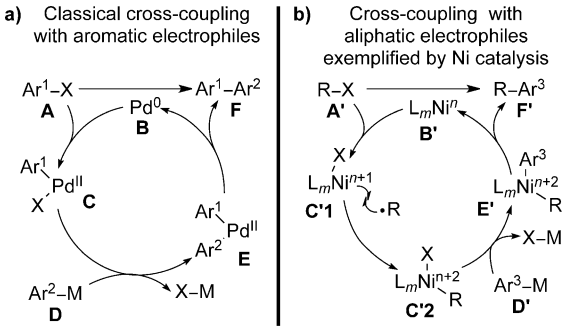
amino acids · cross-coupling · nickel · persistent radical effect · photoredox catalysis

Transition-metal-catalyzed cross-coupling reactions are a powerful tool for the formation of C(sp^2)–C(sp^2) bonds in organic chemistry.[1] They proceed by the two-electron oxidative addition of a low-valent transition-metal complex **B**, here palladium(0), to an aromatic or vinylic electrophile **A** (Scheme 1 a). The resulting organometallic complex **C** is



Scheme 1. Simplified catalytic cycles for cross-coupling with aromatic and aliphatic electrophiles.

subject to transmetalation by the nucleophile **D**, affording organometallic intermediate **E**, which undergoes reductive elimination of the product **F** and regenerates the catalyst **B**. In contrast, C(sp^3)–C(sp^2) bond formation by cross-coupling reactions is by far more diverse and less general. If the electrophile is aliphatic, the oxidative addition step is usually slow, and importantly, once an alkyl metal intermediate forms, β-hydride elimination is fast and outcompetes coupling. This limitation was overcome in the late 1990s by using predominately third-row transition-metal catalysts, such as low-valent titanium, iron, cobalt, and nickel complexes (Scheme 1 b).[2] Here, alkyl halide electrophiles **A′** are activated by single-electron-transfer (SET) reduction by the catalyst **B′** leading to transient radical intermediates **C′1**, which couple to give the oxidized complex **C′2**, which reacts further by transmetalation with **D′** and reductive elimination from intermediates **E′**.[2]

If the aliphatic component is the nucleophile in cross-coupling reactions, its transmetalation by the transition-metal catalyst becomes the critical step. It may be fast for Grignard or alkylzinc reagents in Kumada–Corriu or Negishi coupling reactions, but especially alkylboron nucleophiles in Suzuki–Miyaura-type coupling reactions are a challenge and no general conditions exist to use them in coupling reactions.[3]

Recently, photoredox catalysis (PRC) was very successfully established to activate organic molecules for radical or polar reactions[4] and it proved also useful for activation in transition-metal catalysis.[5] Akita et al. reported the first example in a copper-free Sonogashira coupling, although the mode of activation is not understood.[6] More recently, the Sanford and Glorius groups applied photoredox catalysis for the reductive activation of aryldiazonium salts in dual-catalytic cross-coupling processes (Scheme 2).[7] In both methods, a polar reaction step, a directed C–H insertion of substrate **1a**[7a] or a gold-catalyzed intramolecular alkoxyauration of alcohol **1b**,[7b] form nucleophilic organometallic intermediates **H**/**H′**, which are unreactive toward coupling partners without further activation. Both research groups activate the electrophilic aryldiazonium salts **2** by reductive photoredox catalysis mediated by excited [Ru(bpy)$_3$X$_2$] (bpy = bipyridyl) affording reactive aryl radicals **I**, which are able to couple with complexes **H**/**H′**. The resulting complex intermediates **J** are in turn oxidized by the oxidized photocatalyst to complexes **K**, which are now activated for facile reductive elimination to the products **3a** and **3b** and release of the palladium(II) and gold(I) catalysts **G**. A related reductive photoredox activation of **2** and coupling with gold-catalyzed ring expansion was developed by Toste,[7c] whereas a C(sp^3)–C(sp^2) trifluoromethylation of arylboronic acids using the [Ru(bpy)$_3$]Cl$_2$/CuOAc catalyst system was reported by Sanford et al. (not shown).[7d]

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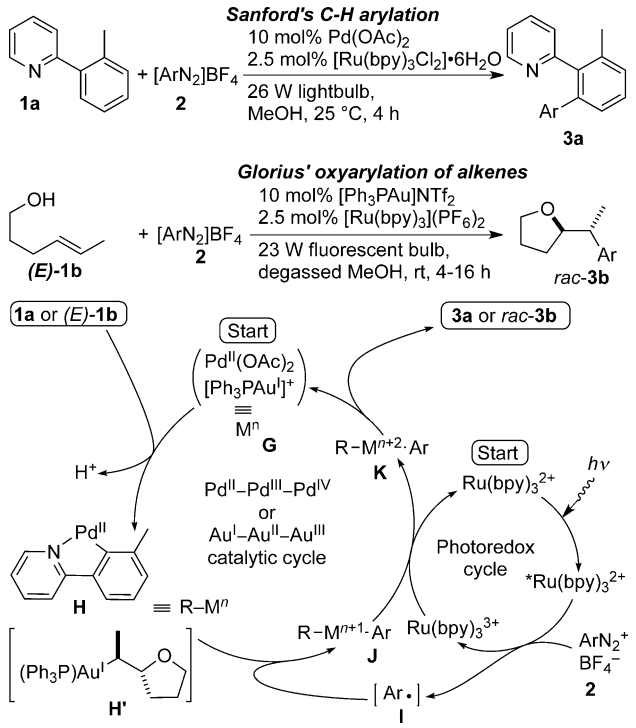
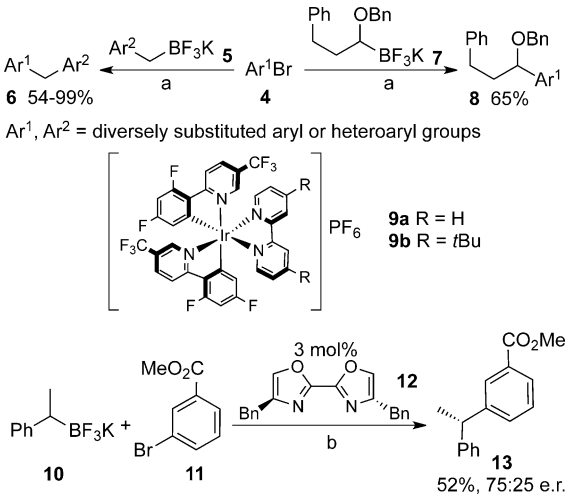
[**] Generous financial support by the Institute of Organic Chemistry and Biochemistry, Academy of Sciences of the Czech Republic (RVO:61388963), the Gilead Sciences & IOCB Research Centre, and the COST action CM1201 "Biomimetic Radical Chemistry" is acknowledged.



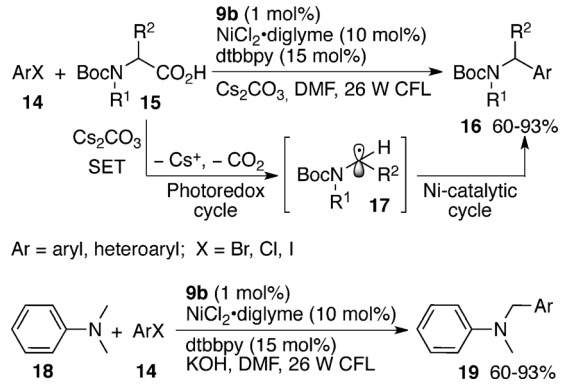
Scheme 2. Photoredox-catalyzed reductive activation of aromatic electrophiles for transition-metal-catayzed coupling reactions.

The oxidative SET activation of organometallic nucleophiles has been much less developed. Akita et al. recently reported the generation of carbon-centered radicals from aliphatic organotrifluoroborates by oxidative photoredox catalysis using Ir^{III} or Ru^{II} catalysts.[8] Their coupling with the persistent radical TEMPO or addition to electron-deficient alkenes enabled the formation of C–O and C–C bonds.

Based on these developments, now a dual-catalytic cross-coupling strategy was established, in which oxidative photoredox catalysis activates the alkyl nucleophiles for facile transition-metal-catalyzed cross-coupling reactions with aryl electrophiles.[9] Molander and colleagues[9a] coupled alkyltrifluoroborate nucleophiles **5** and **7** with aryl halides **4** by applying the catalyst system consisting of iridium complex **9a** and $[Ni(cod)_2]$ (cod = cyclooctadiene) to obtain diarylmethanes **6** and branched ethers **8**, respectively (Scheme 3). Electrophilic and protic functional groups as well as diverse heteroaryl bromides are tolerated in **4** under the reaction conditions, while substrates **5** may carry electronically and sterically diverse *ortho*, *meta*, and *para* substituents. Importantly, the coupling of **5** proceeds selectively in the presence of aryltrifluoroborates, which did not react under these conditions. The method can be applied to chiral, but racemic alkyltrifluoroborates **10**. In the presence of ligand **12** the coupling provides enantioenriched product **13**. The stereoconvergence provides a strong indication that the coupling does not proceed by a concerted transmetalation, but that an sp^2-hybridized intermediate derived from **10** must be involved.



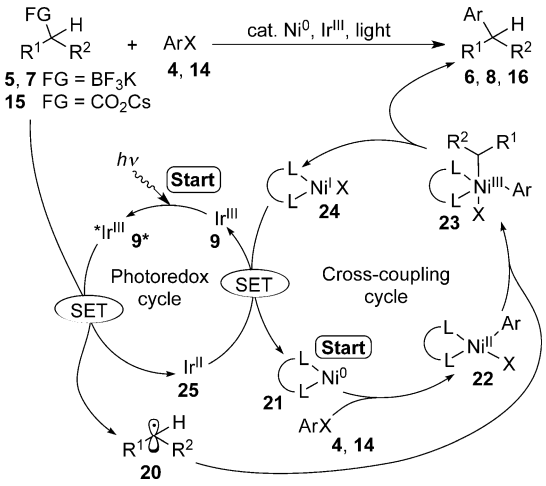
Scheme 3. Molander's dual-catalytic cross-coupling of alkyltrifluoroborates with aryl halides. Conditions: a) **9a** (2 mol%), $[Ni(cod)_2]$ (3 mol%), dtbbpy (3 mol%), 3.5 equiv 2,6-lutidine, 95:5 acetone/MeOH, 26W CFL, 24 h; b) **9a** (2 mol%), $[Ni(cod)_2]$ (3 mol%), **12** (3 mol%), dtbbpy (3 mol%), 3.5 equiv 2,6-lutidine, 95:5 THF/MeOH, blue LED, 24 h. dtbbpy = 4,4′-di-*tert*-butyl-2,2′-biyridine, CFL = compact fluoresent lightbulb.



Scheme 4. MacMillan's dual-catalytic cross-coupling reactions using amino acids or anilines. Boc = *tert*-butoxycarbonyl, DMF = dimethylformamide.

An equally efficient approach was jointly developed by the MacMillan and Doyle groups[9b] using amino acids **15** as the aliphatic coupling partner, thus enabling the use of readily available carboxylic acids as formal nucleophiles in $C(sp^3)$–$C(sp^2)$ cross-coupling reactions (Scheme 4). Both electron-rich and electron-deficient aryl halides **14**, including heteroaryl halides, furnished racemic benzylic amines **16** with high functional group tolerance. A variety of amino acid derivatives, and also 2-tetrahydrofurancarboxylic and phenylacetic acids are convenient substrates. The method capitalizes on the facile SET oxidation of the α-amino carboxylate salts derived from **15** by the photocatalyst and subsequent decarboxylation to α-amino radicals **17**. *N*,*N*-Dimethylaniline **18** was similarly coupled with aryl halides **14** to furnish *N*-benzylic anilines **19**.

The cooperative dual-catalytic cycle is similar for both methodologies. In the photocatalyzed activation step, iridium



Scheme 5. Catalytic cycle for the photoredox-activated nickel-catalyzed cross-coupling reactions.

catalyst **9** is excited by irradiation with visible light (Scheme 5). The excited complex **9*** oxidizes electron-rich substrates **5**, **7**, or **15** to the corresponding radicals **20**, which subsequently enter the low-valent nickel-catalyzed cross-coupling cycle. In parallel, oxidative addition of nickel complex **21** to aryl halides **4** or **14** initiates the cross-coupling catalytic cycle by formation of nickel(II) complex **22**. Coupling of radicals **20** with **22** provides nickel(III) complexes **23**, which afford cross-coupling products **6**, **8**, or **16** and Ni^{I} halide **24** by reductive elimination. The latter is reduced by iridium(II) complex **25**, thus reactivating both catalysts. This catalytic cycle is supported by racemic alkyltrifluoroborates **10** providing an enantioenriched product **13**. The stereoconvergence arises from the facial preference of the coupling of prochiral planar radical **20** to the chiral [bis(oxazoline)]Ni^{II} complex **22**.

The main innovation of the methodology is the replacement of the problematic limiting two-electron transmetalation step of the alkyl nucleophile by SET oxidation and subsequent coupling of the highly reactive transient radicals **20** with the long-lived persistent nickel(II) species **22** according to the persistent radical effect[10] resulting in facile high-yielding cross-coupling under very mild conditions. Substrates possessing β-hydrogen atoms and functional groups are well tolerated. Significantly, the classical reactivity pattern is reversed allowing the selective coupling of $C(sp^3)$ nucleophiles like benzyltrifluoroborates in the presence of a less oxidizable $C(sp^2)$ nucleophile like phenyltrifluoroborate. Currently, the main limitations are that this strategy can only be applied to alkyl nucleophiles that are easily oxidizable, like alkyltrifluoroborates, carboxylic acid salts, and anilines. Future efforts must be directed toward achieving high enantioselectivity in asymmetric cross-couplings of secondary alkyl nucleophiles. Both limitations should be overcome by fine-tuning of the photoredox catalyst and the chiral ligand at the nickel catalyst.[4,2c]

In summary, the reported oxidative photoredox activation/cross-coupling methodology is a very elegant strategy to overcome reactivity limitations in traditional cross-coupling reactions. The photoredox/nickel interwoven dual catalysis will not only enable more efficient cross-coupling reactions with weak nucleophiles, but serve as a blueprint for how to strategically achieve currently difficult asymmetric C–C bond formations, which will in turn serve well to provide tailored solutions for organic synthesis as well as for materials-oriented, medicinal, and biological chemistry.

Received: September 2, 2014
Published online: October 16, 2014

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