Cross-dehydrogenative coupling (CDC) is the class of reaction developed by Chao-Jun Li (McGill U)\textsuperscript{17} that results in the formation of C-C or C-N bond directly from two unmodified C-H bonds (C-C bond formation) or C-H and N-H bonds (C-N bond formation) (Figure 1). Formally, the reaction occurs with a loss of an equivalent of H\textsubscript{2}, although hydrogen gas is really the byproduct since the formation of C-C or C-N bond with a loss of H\textsubscript{2} is thermodynamically unfavorable and thus requires the use of an oxidant (Cu(ІІ), Ag(I) salts, CAN, benzoquinone, peroxides, O\textsubscript{2}, hypervalent iodine, persulfates etc.) as the driving force.

Figure 1: General scheme for cross-dehydrogenative coupling.

Although the same transformations can be achieved by alternative methods, the advantage of CDC approach is that direct tandem oxidation of simple C-H and N-H bonds allows use of simple and readily available reagents and reduces number of steps towards the desired molecule. On the other hand, some challenges are yet to be overcome including low reactivity of some C-H bonds, overoxidation, selective C-H bond functionalization, dimerization etc.

CDC reactions are used to construct bonds between sp\textsuperscript{3}-sp\textsuperscript{3}, sp\textsuperscript{3}-sp\textsuperscript{2}, sp\textsuperscript{2}-sp (including Heck-type reaction), sp\textsuperscript{2}-sp (Sonogashira type) and sp-sp (Glaser reaction) carbon atoms, as well as C(sp\textsuperscript{3})-N. Because CDC is a group of reaction in which the mechanism and reactivity various dramatically depending on the substrate. These couplings, however, can be roughly divided in four groups (by the proposed mechanism): CDC \textit{via} Heck-type mechanism, direct arylation, CDC \textit{via} ionic intermediates and CDC \textit{via} radical intermediates.\textsuperscript{1}

**CDC via Heck-type Mechanism**

Heck-type mechanism\textsuperscript{2} is typical of sp\textsuperscript{2}-sp\textsuperscript{2} CDCs including arene-alkene, alkene-alkene, arene-benzoquinone coupling; sp\textsuperscript{3}-sp\textsuperscript{2}; and formal sp\textsuperscript{3}-sp\textsuperscript{2} including enolate-alkene, allyl-arene coupling. As follows from the name, the mechanism is very similar with the Heck Reaction. Palladium\textsuperscript{3} salts are usually the catalyst of choice, although the same reactivity may be achieved with other transition metals such as Rh(ІІ), Ru(ІІІ) and Ir(І) complexes. The mechanism involves the electrophilic palladation of arene ring (ligand assisted or base mediated C-H insertion) with a Pd(ІІ) catalyst to generate arylpalladium intermediate. Subsequent carbopalladation of olefin leads to alkylpalladium complex that undergoes syn-β-H elimination to yield styrenyl product and Pd(0). The final step of the catalytic cycle is oxidation of Pd(0) to Pd(ІІ). In an alternative mechanism, the Pd(ІІ) catalyst is proposed to coordinate to the olefin, which enhances its electrophilicity and propensity to undergo nucleophilic addition with electron-rich aromatic rings (Figure 2).

Figure 2: General mechanism for Pd-catalyzed cross-dehydrogenative coupling via Heck-type pathway: alkenylation by...
C-H palladation (left) and alkenylation by intermolecular carbopalladation (right).

Catalytic systems are usually not too complex and require no or only a simple ligand such as phosphines, N-protected amino acids or sulfoxides. Inorganic or organic base can also be employed. When more than one product may be formed, the regioselectivity is normally achieved by installation of a directing group on the aromatic ring, whereas the pyridyl-based groups are the most extensively employed to direct transition-metal-catalyzed C–H activation reactions (both ortho- and meta-).4

Figure 3: Selected examples on the ortho- and meta- Pd-catalyzed cross-dehydrogenative alkenylation.

Diract Arylation

Direct arylation (also known as 2-fold C-H activation) is used to construct a bond between two arenes.5 Direct arylation strategy is an alternative to such well-known and widely used methods as: Suzuki, Negishi, Stille, Hiyama, Kumada cross-couplings etc, which require independent synthesis and isolation of aryl halide (or pseudohalide) and arylmetal starting materials. Direct arylation can be achieved with electron-rich arenes, arenes bearing pyridine, amide, carbamate, and other oxazoline directing groups, pyridine N-oxides and other electron-deficient arenes. Palladium(II) complexes are almost exclusively used. The method is considered as atom economical approach towards bi- and poly-aryl motifs, which are common structures in medicinal chemistry and material science. The mechanism involves 2-fold C-H activation (either ligand assisted or base mediated) leading to the formation of Pd(II) bis-aryl complex, which undergoes reductive elimination and produces biaryl and Pd(0). The final step of the catalytic cycle is oxidation of Pd(0) to Pd(II) (Figure 4).

Figure 4: General mechanism for cross-dehydrogenative coupling involving direct arylation.
The regioselectivity is usually controlled by thermodynamic factors (e.g., formation of the most stable intermediate through activation of the most acidic C-H bond or through the attack of the most nucleophilic position, Figure 5a) and by installation of a directing group (Figure 5b).

Figure 5: Selected examples of cross-dehydrogenative coupling involving two arenes.

**CDC via Ionic Intermediates**

Unlike first two mechanisms CDC via ionic intermediates can be promoted by a number of transition metals including Pd, Ru, Zr, Ni, Cu, Fe, Co etc., whereas the last three are the most widely employed. The ionic mechanism predominantly relies on single electron transfer (SET) pathway, although some exceptions are known. Mechanistically C-C/N bond formation occurs between an electrophilic carbon species (carbocation) and a carbon- or nitrogen-based nucleophile (amine, amide, carbanion, enamine, heteroaromatic). Carbocations are generated in situ by C-H bond oxidation of a suitable precursor, whereas carbanions can be prepared by deprotonation of relatively acidic C-H or N-H bonds. As a source of carbocations, amines, ethers, allylic and benzylic compounds are usually employed. Oxidant choice depends on a substrate, although organic hydroperoxides were shown to be most efficient in many cases. The catalysis normally performed without ligand additive and simple TM salts are employed (halides, carboxylates, nitrates etc.) While it is hard to derive a single mechanism, the Ionic Intermediates pathway can be demonstrated on the iron(III) catalyzed CDC of ethers with N-nucleophiles, leading to a facile formation of a hemiaminal moiety (which present in a number of bioactive natural products) (Figure 6).

Figure 6: Iron catalyzed cross-dehydrogenative coupling of ethers and N-nucleophiles via Ionic Intermediates pathway.

**CDC via Radical Intermediates**

The radical Intermediates mechanism is very similar to the one described above (Ionic), except that no ionic intermediates are formed. The newly generated carbon-centered radical directly reacts with another active specie (e.g., carbocation, carbanion, C-C multiple bond) forming another radical, which later on gets oxidized either by an oxidant (Figure 7) or
transition metal (Figure 8)\textsuperscript{10} realizing the desired product. The radical CDC is exclusively promoted by first-row transition metal complexes such as Cu, Fe, Mn (in some cases vanadium oxo-species) via single-electron transfer type pathway. Selective C-H bond oxidation to a radical can be achieved with phenols, electron-rich arenes, benzylic compounds and C(sp\textsuperscript{3})-H bond α- to carbonyl or heteroatom (O or N).

The radical CDC is essential in the synthesis of binaphtols\textsuperscript{11} and related compounds and can be achieved enantioselectively when chiral ligand is used (i.e. Salan, (R)-α-methylbenzylamine etc.).\textsuperscript{12}

![Figure 7: General mechanism for Cu-catalyzed cross-dehydrogenative phenolyc coupling.](image)

Cross-dehydrogenative coupling is a rapidly advancing field and may occur via a wide array of pathways. Therefore some valuable transformations including Au-catalyzed dehydrogenative cyclization between allenes and arenes,\textsuperscript{13} Cu and Ni-catalyzed cross-coupling of alkynes,\textsuperscript{14} Cu and Pd-catalyzed CDC of aldehydes and arenes making ketones etc.,\textsuperscript{15} were not described. In many cases involving C(sp\textsuperscript{3})-H and sometimes C(sp\textsuperscript{2})-H bonds CDC may occur without transition metal catalyst. Finally, it is worth noting, that CDC approach is widely used by nature to construct C-C bonds in living organisms, which primarily involves catalysis promoted by cytochrome P450 (CYP) enzymes in the presence of O\textsubscript{2} as the terminal oxidant.\textsuperscript{16}
References


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Contributors

- Kirill Korvinson (City University of New York)