Cross-Coupling

International Edition: DOI: 10.1002/anie.201503204
German Edition: DOI: 10.1002/ange.201503204

Nickel-Catalyzed C–O/C–H Cross-Coupling Reactions for C–C Bond Formation

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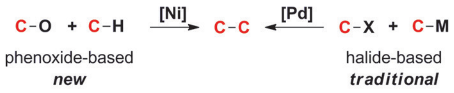
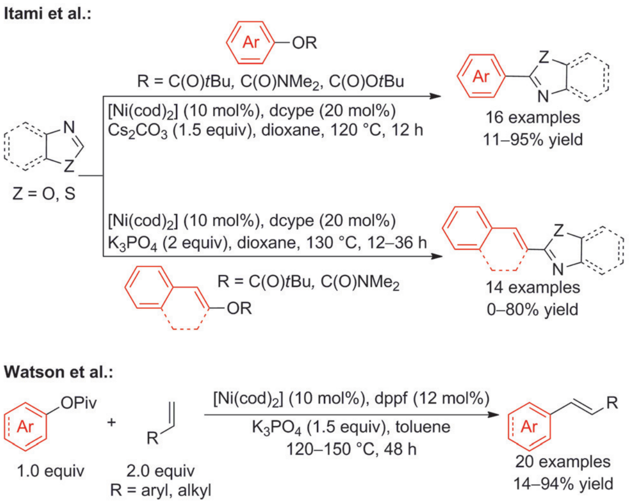
asymmetric catalysis · C–H activation ·
C–O activation · cross-coupling · nickel catalysis

Over the past decades, transition-metal-catalyzed cross-coupling reactions of halogenated compounds have been well established and now serve as powerful methods for constructing C–C bonds.[1] Nevertheless, new cross-coupling methods, especially greener and more efficient ones, are still being explored because of the problems associated with halogenated compounds, such as toxicity, availability, and cost. Phenoxide derivatives are abundant and readily accessible chemicals. Coupling reactions that employ phenoxide derivatives as substitutes for halogenated compounds have recently attracted much attention, and a couple of such reactions have been successfully developed.[2] However, owing to the inert nature of the C–O bond, chemically reactive counterparts, such as organoboron, organozinc, or Grignard reagents, have to be used in these couplings. On the other hand, the direct, selective transformation of ubiquitous C–H bonds is an ideal short-cut for organic synthesis because it avoids the prefunctionalization of starting materials. A direct C–O/C–H cross-coupling would thus significantly contribute to advancing current C–C bond-forming methods. Herein, we highlight recent progress in the development of nickel-catalyzed C–O/C–H (phenoxide/activated hydrocarbon) cross-couplings (Scheme 1).[3–9,11]

A significant breakthrough in this area was achieved by the Itami group in 2012.[3] It was found that by using [Ni(cod)$_2$]/dcype (cod = 1,5-cyclooctadiene, dcype = Cy$_2$PCH$_2$CH$_2$PCy$_2$) as the catalyst, naphthalen-2-yl could be readily coupled with benzoxazole in the presence of Cs$_2$CO$_3$ in dioxane at 120 °C to produce the coupling product in 95 % yield (Scheme 2). The phosphine ligand has a great influence on this coupling process, and the use of dcype is essential for achieving an efficient reaction. For example, PCy$_3$, which efficiently mediates C–O/C–M cross-couplings, was totally ineffective in this C–O/C–H coupling. Similarly, Ph$_2$PCH$_2$CH$_2$PPh$_2$ (dppe), Et$_2$PCH$_2$CH$_2$PEt$_2$ (depe), and 2,2′-bipyridyl, ligands that are popularly used in nickel-catalyzed C–H/C–X couplings, were also not suitable for this C–O/C–H cross-coupling. Various biaryl compounds, including derivatives with functional groups, were readily prepared by this nickel-catalyzed cross-coupling of phenoxide derivatives and azoles. For naphthalenyl derivatives, pivalates, carbamates, or carbonates could be used as the leaving group, whereas more reactive triflates were necessary when phenyl derivatives were employed. Later, Itami and co-workers also reported a nickel-catalyzed C–O/C–H cross-coupling that leads to alkenyl-substituted arenes.[4] By slightly modifying the reaction conditions, the [Ni(cod)$_2$]/dcype system also catalyzed the alkenylation of azoles with enol pivalates and enol carbamates. Interestingly, only *E* enols were reactive in this reaction whereas *Z* enol derivatives remained intact.



Scheme 1. Transition-metal-catalyzed C–C bond-forming reactions.



Scheme 2. Nickel-catalyzed C–O/C(sp^2)–H cross-couplings.

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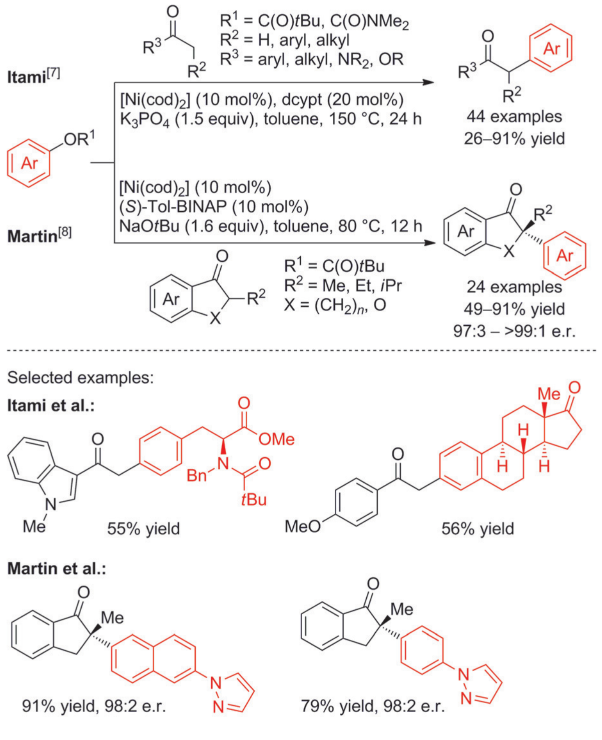
These findings are the first examples of C−O/C−H (phenoxide/activated hydrocarbon) cross-couplings.[3–11]

Meanwhile, the Watson group reported a nickel-catalyzed cross-coupling between phenoxide derivatives and terminal alkenes in 2012.[6] In the presence of an in situ generated [Ni(dppf)] catalyst (dppf = 1,1′-bis(diphenylphosphanyl)ferrocene), both aryl and alkenyl pivalates could be coupled with styrenes and α-substituted terminal olefins. This Heck-type coupling provides a facile access to *E* olefins, albeit at a high temperature and with an excess of alkene (Scheme 2).

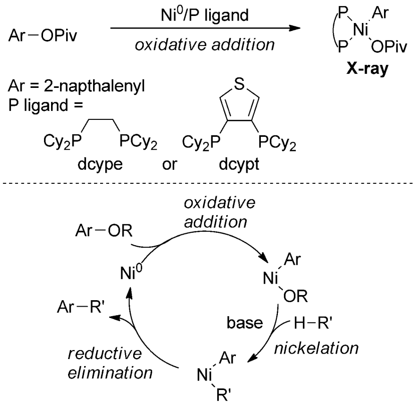
Recently, Itami and co-workers disclosed a new cross-coupling reaction between phenoxide and carbonyl derivatives, which affords the corresponding α-aryl carbonyl compounds.[7] Switching the phosphine ligand to dcypt (for the structure of dcypt, see Scheme 4) was crucial for accomplishing this novel nickel-catalyzed α-arylation reaction. Ketones, esters, and amides could be readily coupled with the phenoxide derivatives of pivalates and carbamates. Importantly, this reaction tolerates various functional groups, such as methoxy, amino, fluorine, and heterocyclic substituents. The synthetic potential of this reaction was further demonstrated by the preparation of complex molecules with indole, amino acid, or estrone fragments (Scheme 3).



Scheme 3. Nickel-catalyzed α-arylations of carbonyl compounds.

By using [Ni(cod)$_2$]/(*S*)-Tol-BINAP as the catalyst, an asymmetric α-arylation was successfully developed by Martin and co-workers.[8] Impressively, quaternary stereogenic centers could be generated by the α-arylation of prochiral ketones with aryl esters in high yields and with high selectivity (up to > 99:1 e.r.; Scheme 3).

The detailed mechanistic aspects of these nickel-catalyzed C−O/C−H cross-couplings clearly remain to be explored in the future, but a traditional Ni^0/Ni^{II} cycle has already been proposed. Itami et al. isolated arylnickel(II) pivalates with a phosphine ligand (dcype, dcypt), which were assumed to be generated by the oxidative addition of a C−O bond to Ni^0.[7,9] They also confirmed that nickelation of the C−H bond was the rate-determining step. Therefore, they proposed the Ni^0/Ni^{II} catalytic cycle depicted in Scheme 4. These reactions have also been studied using density functional theory (DFT) calculations by the groups of Houk, Fu, and Itami.[11] On the other hand, regarding the activation of C−O bonds by nickel, Martin et al. recently proposed a different mechanism that involves novel Ni^I complexes and/or ate complexes.[10]



Scheme 4. Isolated key intermediates and a proposed mechanism for the nickel-catalyzed C−O/C−H cross-coupling.

From the synthetic point of view, the above-mentioned reactions still have a few shortcomings, including high temperatures, long reaction times, high catalyst loadings, and stoichiometric amounts of a base. Nevertheless, these studies have marked a milestone in the area of C−O/C−H cross-couplings for C−C bond formation. It is expected that forthcoming studies on the optimization of these reactions, mechanistic aspects, and synthetic applications will assure this C−O/C−H coupling as an invaluable method for C−C bond formation.

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 8600–8602
Angew. Chem. **2015**, *127*, 8722–8724

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Received: April 8, 2015
Revised: May 7, 2015