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Nickel-Catalyzed Decarbonylative C–H Coupling Reactions: A Strategy for Preparing Bis(heteroaryl) Backbones**

*Arkaitz Correa, Josep Cornella, and Ruben Martin**

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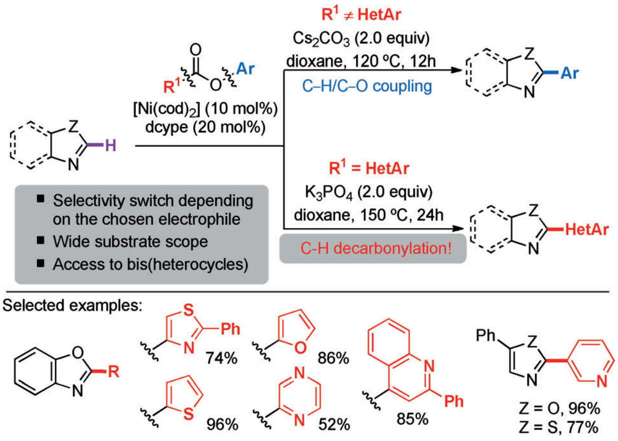
decarbonylative coupling · nickel

Nitrogen-containing heterocycles rank among the most important motifs in many bioactive natural products, medicinally important compounds, and organic materials.[1] Despite recent advances in C–C bond-forming reactions, the direct coupling of two different heteroaromatic motifs still constitutes a remarkable synthetic challenge.[2] The most commonly employed strategy to produce bis(heteroaryl) linkages is the metal-catalyzed cross-coupling of metalloheteroarenes (C–M) and haloheteroarenes (C–X). This type of couplings has evolved from a standard laboratory procedure to a daily utilized technique in industrial-scale synthesis.[2,3] In spite of their high efficiency, these methods suffer from the high cost and moisture sensitivity of the required organometallic reagents and the generation of significant amounts of halide-containing waste. While other oxidative C–H bond-functionalization processes have also been described,[4] the requirement for stoichiometric amounts of silver- or copper-based oxidants does not make these protocols attractive enough from a pharmaceutical point of view. Therefore, the development of new catalytic protocols that can face all these challenges, while readily giving access to bis(heteroaryl) cores with a diverse set of substituents would be a highly desirable goal in organic synthesis.

Prompted by the pioneering decarboxylative arylation processes described by Goossen et al. in 2006,[5] benzoic acid derivatives have emerged as advantageous coupling partners in a wide range of C–H arylation processes toward biaryls because of their general low cost, high stability, and ready availability.[6,7] Although significant progress has been made with aryl sulfonates or sulfamates, only few reports exist on the use of simpler and cheaper acyloxy derivatives.[8] This is likely due to the reluctance of metal complexes to undergo C(sp^2)-OR oxidative addition and the known aptitude of these electrophiles for hydrolysis under basic reaction conditions. In line with this concept, the use of decarbonylative reactions has become an alternative method for the elaboration of complex organic structures. In 1982, Blaser and Spencer reported a Pd-catalyzed Heck-type coupling of alkenes with aroyl chlorides through a decarbonylation event.[9] Subsequently, the groups of Stephan and DeVries,[10] and Goossen[11] extended this methodology to aromatic carboxylic anhydrides and isoprenyl or aryl esters, thus avoiding the generation of halide-containing waste. Ni-catalyzed reactions were also found to be highly competent to promote decarbonylative reactions, with the advantage of Ni being less expensive than Pd. Among these methods, the procedures developed by Trost[12a] as well as the elegant decarbonylative coupling reactions with organozinc reagents reported by Rovis[12b] and Johnson[12c] are particularly attractive. Herein we discuss a remarkable contribution that features a conceptually novel Ni-catalyzed decarbonylative C–H coupling of azoles and phenyl esters en route to bis(heteroaryl) motifs.[13]

In early 2012, Itami et al. implemented a C–H arylation of azoles with C–O electrophiles, catalyzed by the combination [Ni(cod)$_2$]/dcype (cod = 1,5-cyclooctadiene, dcype = 1,2-bis(dicyclohexylphosphino)ethane) (Scheme 1, top pathway).[14] This catalyst system was found to be highly active for the coupling of esters, carbamates, sulfamates, triflates, tosylates, and mesylates with several compounds with an acidic C–H



Scheme 1. Ni-catalyzed C–H/C–O and decarbonylative coupling reactions.

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[*] Dr. A. Correa, Dr. J. Cornella, Dr. R. Martin
Institute of Chemical Research of Catalonia (ICIQ)
Av. Països Catalans, 16, 43007 Tarragona (Spain)
E-mail: rmartinromo@iciq.es

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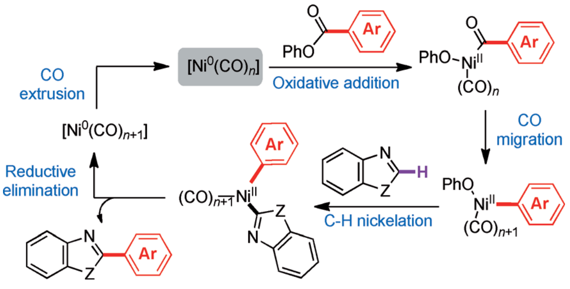
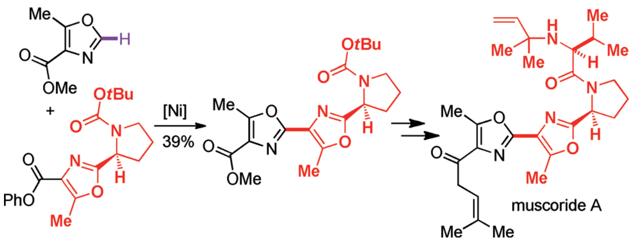
group, such as benzoxazoles, oxazoles, benzothiazoles, and thiazoles. Not surprisingly, the use of simpler alkyl ethers (C–OMe) as electrophiles did not give any conversion at all, thus illustrating the greater inertness associated with the C–OMe bond.[15] Interestingly, the coupling of benzoxazole with phenyl thiophene-2-carboxylate did not afford the expected C–H/C–O coupling process, but the formation of the corresponding bis(heteroaryl) backbone (Scheme 1, bottom pathway).[13] The selectivity switch that accompanies the utilization of different C–O electrophiles suggests that this protocol could be used as a strategic advance in the development of future coupling reactions. A wide variety of heteroaromatic phenyl esters, including furans, thiophenes, pyridines, thiazoles, and quinolones were smoothly coupled with benzoxazoles, oxazoles, and thiazoles, to access bis(heteroaryl) motifs in a straightforward fashion (Scheme 1).

The authors reasonably assumed that the described decarbonylative C–H arylation protocol involved a Ni^0/Ni^{II} catalytic cycle (Scheme 2).[13] Presumably, the reaction is initiated by an oxidative addition of the C–O bond to low-valent Ni^0 species. Subsequently, a CO migration affords an Ar-$Ni^{II}(CO)_{n+1}$-OPh ($n = 0$ or 1) intermediate that would undergo subsequent C–H nickelation with the corresponding azole. A final reductive elimination from the putative Ni^{II} intermediate would deliver the desired bis(heteroaryl) compound with concomitant formation of a $[Ni^0(CO)_{n+1}]$ species. In line with the proposed mechanism, experiments performed under CO atmosphere inhibited the reaction. Remarkably, no significant kinetic isotopic effect was observed, hence supporting the notion that C–H bond cleavage is not involved in the rate-limiting step of the reaction. A more in-depth mechanistic study will, no doubt, provide valuable information about the nature of the reaction intermediate within the catalytic cycle. The synthetic challenges, though, should not be underestimated; unlike Pd-catalyzed processes, the isolation of reaction intermediates in Ni-catalyzed cross-coupling reactions is much more challenging because of the innate ability of Ni complexes to undergo single-electron-transfer processes. Still, we anticipate that a better understanding of these Ni-catalyzed reactions will definitely open up new opportunities in organometallic chemistry.



Scheme 2. Proposed catalytic cycle.

Unlike the Ni-catalyzed decarbonylative coupling reactions described by Rovis[12b] and Johnson,[12c] the approach described by Itami et al.[13] does not require the use of stoichiometric amounts of metal species. Indeed, the ability to use simpler arenes as coupling partners undoubtedly represents an additional bonus in C–H decarbonylative reactions and hold great promise for the utilization of these techniques as a tool to achieve molecular diversity. Indeed, the potential of the Ni-catalyzed decarbonylation was nicely illustrated in the synthesis of muscoride A, a natural product with exceptional antibacterial activity (Scheme 3).[13] The flexibility of the approach by Itami et al. will likely enable the preparation of a new set of analogues of the muscoride family.



Scheme 3. Application of coupling reactions to the total synthesis of muscoride A.

In summary, the use of arene carboxylates as an advantageous source of carbon nucleophiles is essential for developing greener chemical processes. The novel decarbonylative C–H arylation reported by Itami et al. will open up new opportunities and stimulate the development of new concepts and ideas within the field of Ni-catalyzed reactions, which is probably one of the most vibrant and promising branches of current research in organic and organometallic chemistry.

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