JOURNAL OF THE AMERICAN CHEMICAL SOCIETY

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Nickel-Catalyzed C–H/C–O Coupling of Azoles with Phenol Derivatives

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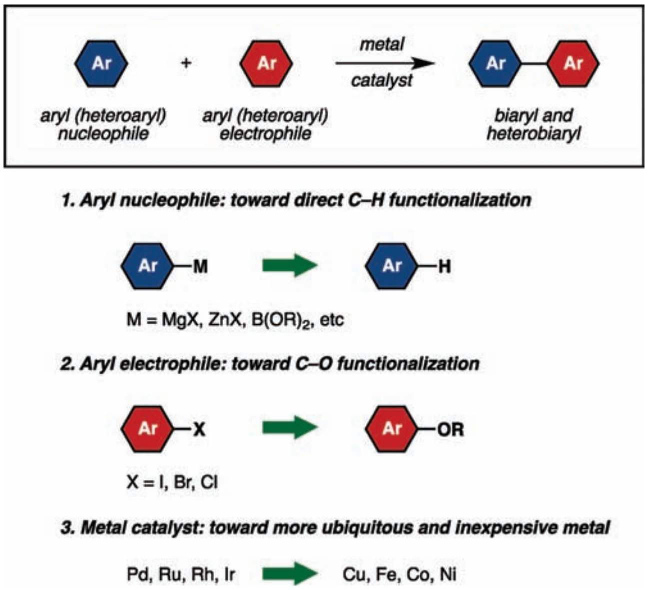
S *Supporting Information*

ABSTRACT: The first nickel-catalyzed C–H bond arylation of azoles with phenol derivatives is described. The new Ni(cod)$_2$/dcype catalytic system is active for the coupling of various phenol derivatives such as esters, carbamates, carbonates, sulfamates, triflates, tosylates, and mesylates. With this C–H/C–O biaryl coupling, we synthesized a series of privileged 2-arylazoles, including biologically active alkaloids. Moreover, we demonstrated the utility of the present reaction for functionalizing estrone and quinine.

The development of efficient methods for constructing privileged biaryl structures is a topic of utmost importance in various fields of chemistry. Although the Pd-catalyzed cross-coupling reactions of metalated arene/heteroarene and halogenated arene/heteroarene species are undoubtedly among the most reliable methods for making biaryls and heterobiaryls,[1] significant academic efforts are underway to make metal-catalyzed biaryl couplings "greener" chemical processes (Scheme 1). Among many aspects of biaryl coupling, efforts are being directed toward replacing conventional aryl nucleophiles (Mg, Zn, B, etc.), electrophiles (aryl halides), and metal catalysts (Pd) used in conventional cross-coupling (C–M/C–X coupling) by more inexpensive, readily available, and less toxic participants.

Scheme 1. Recent Directions in Catalyzed Biaryl Coupling



For example, significant progress has been made in the development of aromatic C–H bond arylation with aryl halides (C–H/C–X coupling).[2,3] Oxidative C–H bond arylation reactions using arylboron reagents (C–H/C–B coupling)[4] or arenes (C–H/C–H coupling)[5] are also known. Though these direct arylation reactions are typically catalyzed by Pd, Rh, Ir, and Ru complexes,[2] catalytic systems using inexpensive metals such as Cu,[6] Ni,[7] Fe,[8] and Co[9] are also emerging, indicating another clear direction for the advancement of biaryl coupling. The search for new aryl electrophiles to replace aryl halides is also being actively investigated. For example, new Ni-based catalytic systems have recently been developed for cross-coupling of aryl C–O bonds of some phenol derivatives (e.g., aryl ethers and esters) with arylmetal species (C–M/C–O coupling).[10–13] The advantage of using phenol derivatives as aryl electrophiles is apparent, as they are often ready available and inexpensive. Herein we report on our recent findings that Ni(cod)$_2$/dcype [cod = 1,5-cyclooctadiene, dcype =1,2-bis(dicyclohexylphosphino)ethane] serves an efficient catalyst for the direct arylation of azoles with various phenol derivatives (C–H/C–O coupling). This represents important progress in the advancement of biaryl coupling chemistry (Scheme 1).

Motivated by the fact that arylated azoles are privileged structures present in many biologically active natural products, pharmaceuticals, and optoelectronic materials,[7d] we selected azoles as heteroarene substrates for C–H/C–O biaryl coupling.[14] After careful and thorough investigation, we discovered the new Ni(cod)$_2$/dcype catalyst. For example, the reaction of benzoxazole (**1A**, 1.0 equiv) and naphthalen-2-yl pivalate (**2a**, 1.5 equiv) in the presence of Ni(cod)$_2$ (10 mol %), dcype (20 mol %), and Cs_2CO_3 (1.5 equiv) in 1,4-dioxane at 120 °C (representing our standard conditions) afforded the corresponding coupling product (**3Aa**) in 95% isolated yield (Scheme 2).

Listed in Scheme 3 are some examples of variations from the standard conditions. Among various reaction parameters, a dramatic ligand effect of dcype is notable. For example, we found that tricyclohexylphosphine (PCy$_3$), the standard ligand for activating aryl C–O bonds for C–M/C–O coupling,[11,12] was totally ineffective for the present C–H/C–O coupling. Similarly 1,3-bis(2,6-diisopropylphenyl)imidazolium chloride (IPr·HCl) was ineffective. Structurally similar ethyl- and phenyl-substituted ligands (depe and dppe) as well as

Received: October 31, 2011
Published: December 8, 2011

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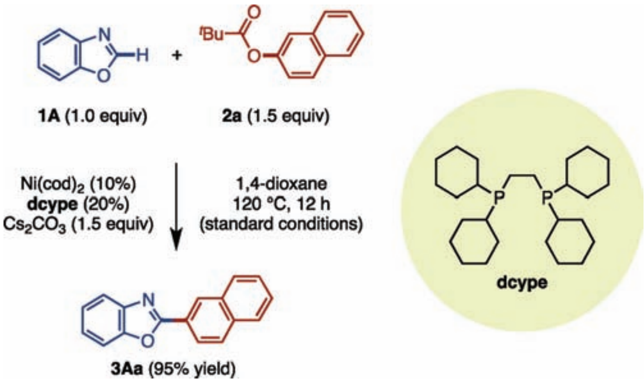
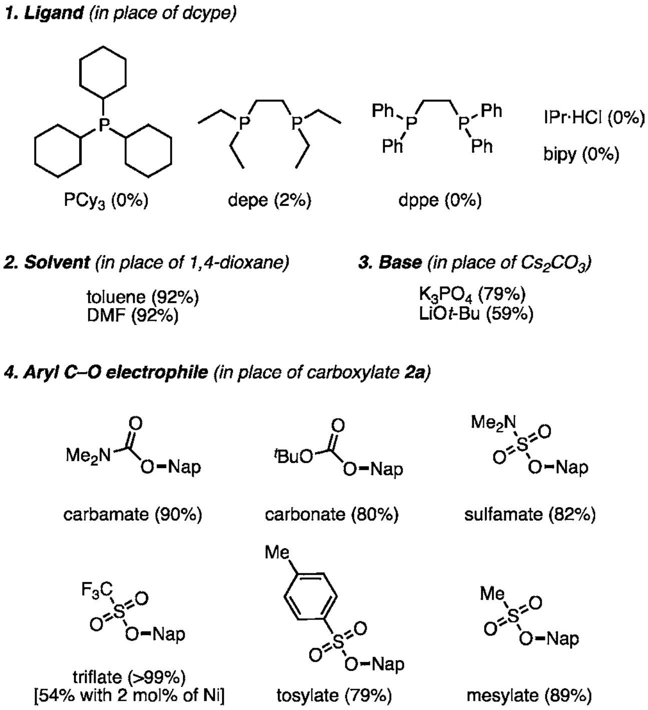
Scheme 2. Discovery of the $Ni(cod)_2$/dcype Catalyst for C−H/C−O Biaryl Coupling



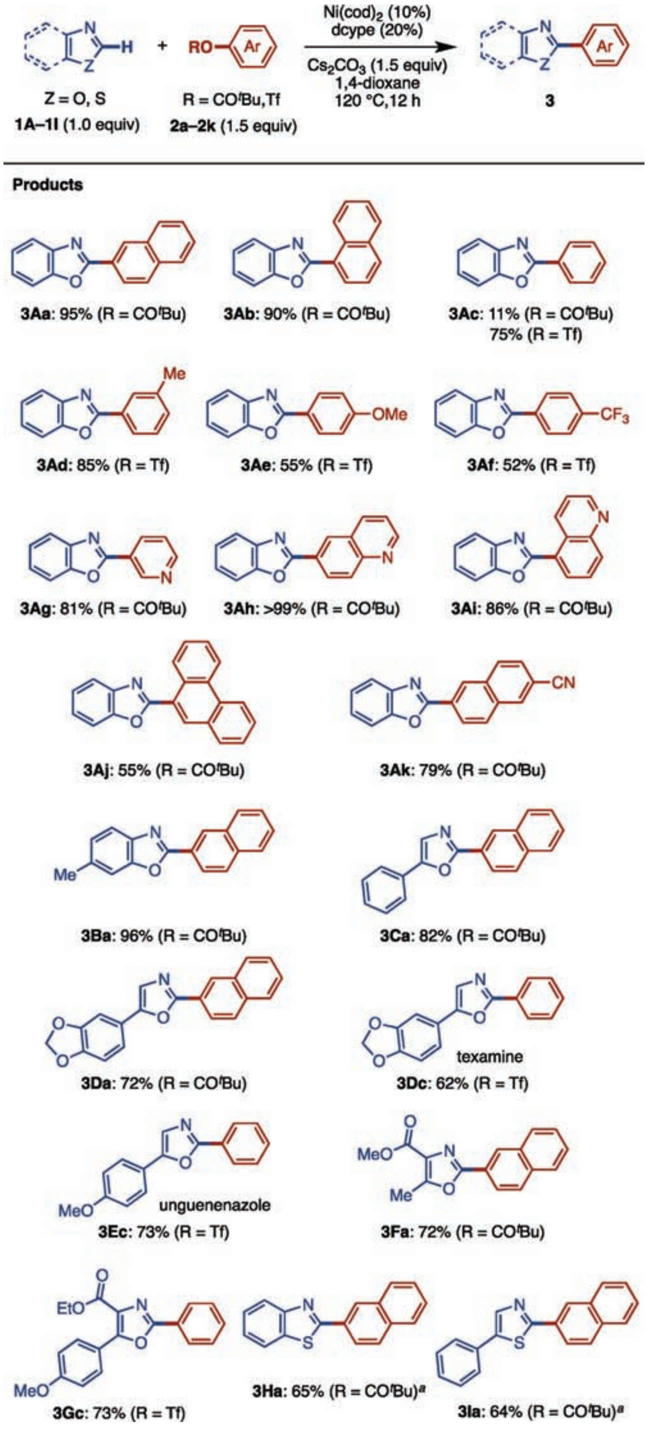
Scheme 3. Influence of Parameters in the Coupling of 1A and 2a



2,2′-bipyridyl (bipy), our standard ligand for Ni-catalyzed C−H/C−X coupling,[7a,d] were also not effective. As shown in Scheme 3, usable solvents and bases are not limited to 1,4-dioxane and Cs_2CO_3, respectively. Gratifyingly, we found that the present $Ni(cod)_2$/dcype catalyst is active for the coupling of other phenol derivatives such as carbamates, carbonates, sulfamates, triflates, tosylates, and mesylates (80−99% yield). We also confirmed that the reaction also takes place with catalyst loadings as low as 2 mol % (54% yield with triflate). Although the mechanism of the C−H/C−O biaryl coupling remains unknown,[15] the observed striking ligand effect is notable. In particular, PCy_3[11,12,16] and N-heterocyclic carbenes,[17] which are known to be able to activate aryl C−O bonds, do not promote the present C−H/C−O biaryl coupling.

On the basis of these findings, we then examined the direct arylation of various 1,3-azoles with aryl pivalates and triflates as representative C−O coupling partners (Scheme 4). **1A** was successfully coupled with 1-naphthyl, 2-naphthyl, 3-pyridinyl, 6-quinolinyl, 5-quinolinyl, and 9-phenanthrenyl pivalates, giving the corresponding coupling products in moderate to excellent yields. For installing substituted phenyl groups onto azoles, we found that the use of the corresponding triflates is more effective. Under these conditions, both electron-rich and electron-deficient phenol derivatives were successfully coupled with **1A**. Aryl−methoxy[11,12a] and aryl−cyano[18] bonds, which could be activated with Ni catalysts, were well-tolerated under the present conditions. In addition to benzoxazoles, oxazoles, thiazoles, and benzothiazoles were found to react smoothly with phenol derivatives to furnish the corresponding coupling

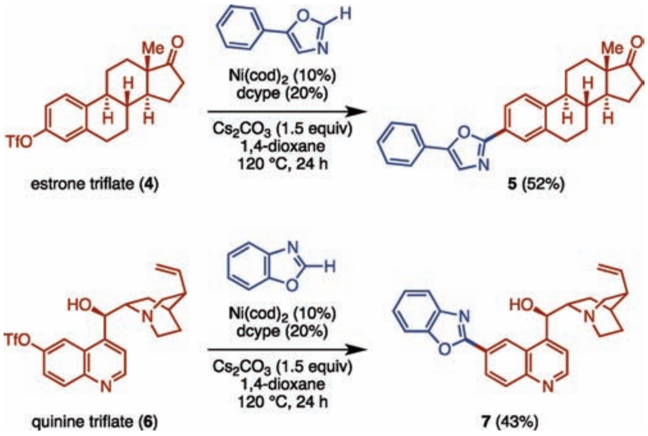
Scheme 4. C−H/C−O Biaryl Coupling Catalyzed by the Ni/dcype System



products.[19] During these investigations, we successfully achieved concise syntheses of the oxazole alkaloids texamine (**3Dc**)[20] and unguenenazole (**3Ec**).[21]

We believe that the C−H/C−O biaryl coupling should find use in the rapid identification of new biologically active compounds by a late-stage functionalization of naturally occurring privileged structures.[22] Thus, to demonstrate the feasibility of this approach, we investigated the Ni-catalyzed C−H/C−O coupling for functionalization of estrone and quinine (Scheme 5). The coupling of estrone triflate (**4**) with 5-phenyloxazole proceeded smoothly under our standard conditions to afford heteroarylated estrone **5** in 52% yield. The C−H/C−O coupling of quinine triflate (**6**)[23] with benzoxazole also occurred, giving the quinine−benzoxazole hybrid molecule **7**, albeit with somewhat lower efficiency. Notably, the hydroxyl, amine, and olefinic functionalities were well-tolerated under the coupling conditions. The successful application to the functionalization of the quinine structure, which is known to be sensitive under acidic, basic, and redox conditions, speaks well for the potential of the present nickel catalysis for further development and applications.

Scheme 5. Ni-Catalyzed Arylation of Complex Steroid and Alkaloid Scaffolds



In summary, we have discovered the first nickel-catalyzed C−H/C−O coupling reaction of azoles with phenol derivatives. Under Ni(cod)$_2$/dcype catalysis, various pivalates, triflates, tosylates, mesylates, carbamates, carbonates, and sulfamates can be used as phenol derivatives. The present findings not only push the limit of biaryl coupling into the C−H/C−O manifold but also should open an avenue for a range of new catalytic C−O bond transformations of phenol derivatives with Ni(cod)$_2$/dcype. Works along this line, mechanistic investigations of the C−H/C−O coupling, and the development of a second-generation catalyst with much broader scope are now the focus of our ongoing efforts.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Detailed experimental procedures and spectral data for all compounds, including scanned images of ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ACKNOWLEDGMENTS

This work was supported by the Funding Program for Next Generation World-Leading Researchers from JSPS (220GR049 to K.I.) and the Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" (23105517 to J.Y.) from MEXT. We thank Dr. Jean Bouffard for fruitful discussions and critical comments.

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(15) A possible mechanism might be Ni^0/Ni^{II} redox catalysis via (i) C−O oxidative addition of a phenol derivative **2** (Ar−OR) to Ni^0 to form Ar−Ni^{II}−OR, (ii) C−H nickelation of an azole **1** (Az−H) with Ar−Ni^{II}−OR to generate Ar−Ni^{II}−Az, and (iii) reductive elimination of an arylazole product **3** (Ar−Az) with the regeneration of Ni^0 catalyst.

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