JACS JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Communication
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Decarbonylative C−H Coupling of Azoles and Aryl Esters: Unprecedented Nickel Catalysis and Application to the Synthesis of Muscoride A

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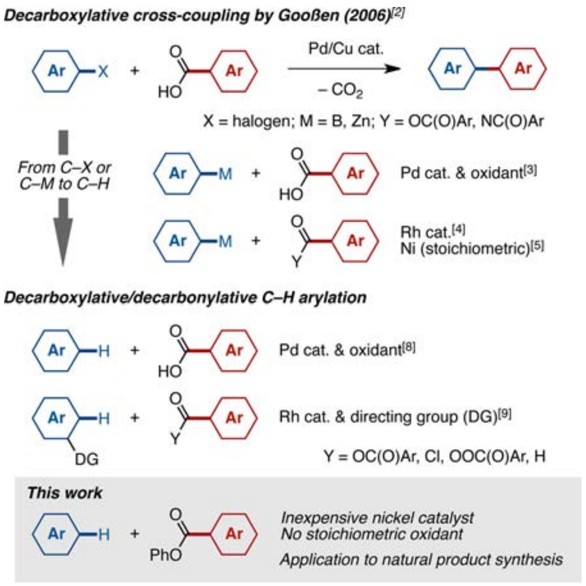
S Supporting Information

ABSTRACT: A nickel-catalyzed decarbonylative C−H biaryl coupling of azoles and aryl esters is described. The newly developed catalytic system does not require the use of expensive metal catalysts or silver- or copper-based stoichiometric oxidants. We have successfully applied this new C−H arylation reaction to a convergent formal synthesis of muscoride A.

Aroyl compounds, such as aromatic carboxylic acids, acid chlorides, anhydrides, and esters, have received significant attention as useful aryl sources in metal-catalyzed decarboxylative or decarbonylative biaryl coupling reactions.[1] In comparison with typical cross-coupling partners such as metalloarenes or haloarenes, aroyl compounds are usually inexpensive, stable, and readily available. We herein report a novel nickel-catalyzed decarbonylative C−H arylation of azoles with aryl esters and its application to natural product synthesis (Scheme 1).

In 2006, Gooßen and co-workers reported the breakthrough finding that decarboxylative biaryl coupling of aromatic carboxylic acids and haloarenes can be promoted by palladium−copper bimetallic catalysis (Scheme 1).[2] Since this epoch-making discovery, a number of variant coupling reactions have been reported. For example, palladium-catalyzed oxidative decarboxylative coupling using metalloarenes was reported,[3] and decarbonylative arylation of aroyl compounds with metalloarenes was achieved by using a rhodium catalyst[4] or a stoichiometric nickel complex (Scheme 1).[5]

Scheme 1. Decarboxylative/Decarbonylative Biaryl Coupling



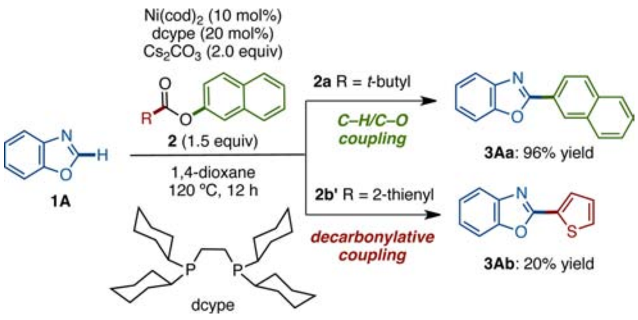
In recent years, with the advent of C−H functionalization chemistry,[6,7] efforts have been directed toward the development of decarboxylative or decarbonylative arylation of aroyl compounds with simple aromatic compounds. In 2008, Crabtree and co-workers reported a palladium-catalyzed decarboxylative C−H arylation of aromatic carboxylic acids with heteroarenes or with polyfluorobenzenes (Scheme 1).[8a] In the same year, Yu and co-workers developed a rhodium-catalyzed decarbonylative C−H coupling of 2-pyridylbenzenes and acyl chlorides (Scheme 1).[9a] Following these contributions, various decarboxylative[8] and decarbonylative[9] C−H arylation reactions of aroyl compounds have been reported. We herein describe a new nickel-based catalytic system with a number of advantages, which we believe to be a useful addition to the existing repertoire of decarboxylative/decarbonylative C−H arylation tools (Scheme 1). This catalytic system does not require the use of expensive metal catalysts or silver- or copper-based stoichiometric oxidants.

We have already reported that azoles can be coupled with phenol derivatives in a C−H/C−O coupling fashion under the catalytic influence of Ni(cod)$_2$/dcype [cod =1,5-cyclooctadiene; dcype =1,2-bis(dicyclohexylphosphino)ethane].[7i,10] For example, benzoxazole (**1A**) can be coupled with naphthalen-2-yl pivalate (**2a**; R = *t*-Bu) using this nickel catalyst and Cs$_2$CO$_3$ in 1,4-dioxane at 120 °C to give the corresponding C−H/C−O coupling product **3Aa** in 96% yield (Scheme 2). Quite surprisingly, however, when a similar naphthalen-2-yl thiophene-2-carboxylate (**2b′**; R = 2-thienyl) was used as the substrate, the thienyl-transferred product **3Ab** was produced in 20% yield without the formation of **3Aa**. When the coupling partner **2b′** was changed to phenyl thiophene-2-carboxylate (**2b**), the reaction also gave **3Ab** in 20% yield. After an extensive screening of catalysts, bases, temperature, and reaction time, optimal conditions for this decarbonylative C−H coupling were identified: Ni(cod)$_2$/dcype (1:2 ratio), K$_3$PO$_4$

Received: June 21, 2012
Published: August 7, 2012

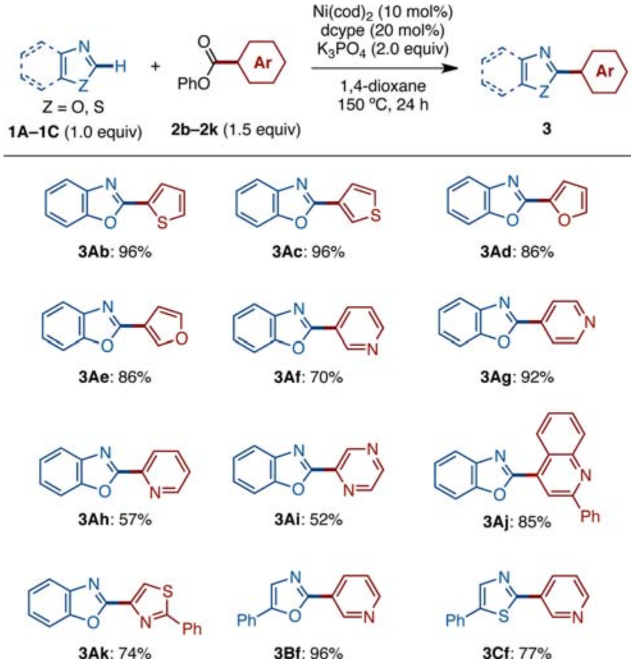
dx.doi.org/10.1021/ja306062c | J. Am. Chem. Soc. 2012, 134, 13573−13576

Scheme 2. Discovery of Nickel-Catalyzed Decarbonylative C−H Coupling



(2.0 equiv), 1,4-dioxane, 150 °C, 24 h.[11] Under these conditions, the yield of **3Ab** increased to 96% (Scheme 3).

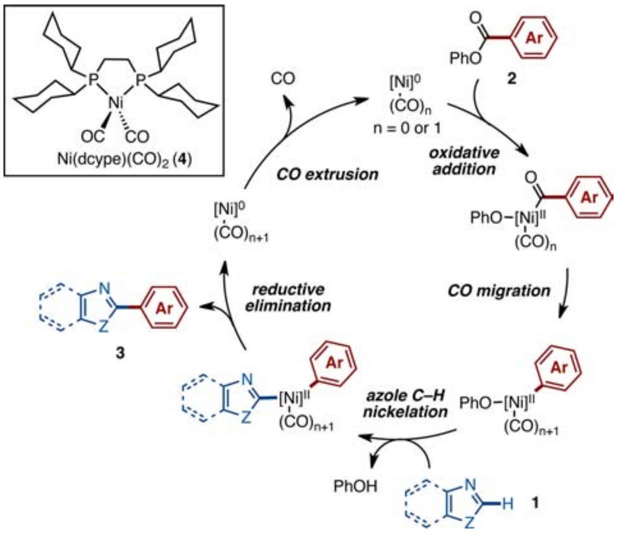
Scheme 3. Substrate Scope



With optimized conditions in hand, various azoles and aryl esters were tested (Scheme 3). The coupling of **1A** with phenyl thiophene-3-carboxylate (**2c**) also afforded the corresponding coupling product **3Ac** in 96% yield. Furancarboxylic acid phenyl esters, such as phenyl furan-2-carboxylate (**2d**) and phenyl furan-3-carboxylate (**2e**), reacted with **1A** to produce heterobiaryls **3Ad** and **3Ae**, respectively, in excellent yields. Electron-deficient azine esters, such as phenyl pyridine-3-carboxylate (**2f**), phenyl pyridine 4-carboxylate (**2g**), phenyl quinoline-4-carboxylate derivative **2j**, and phenyl 2-phenyl-thiazole-4-carboxylate (**2k**), were coupled with **1A** to give the corresponding products **3Af**, **3Ag**, **3Aj**, and **3Ak** in good to excellent yields, whereas phenyl pyridine-2-carboxylate (**2h**) and phenyl pyrazine-2-carboxylate (**2i**) gave products in moderate yields. In addition, oxazole (**1B**) and thiazole (**1C**) derivatives were found to react smoothly with heteroaromatic phenyl esters to furnish the corresponding coupling products **3Bf** and **3Cf**.

In this study, we extensively investigated the coupling of heteroaromatic esters[12] because (i) heteroarylated azoles (the products) are privileged structures in pharmaceutically relevant molecules and natural products[10d] and (ii) heteroaromatic esters (the starting materials) can be prepared readily by common heteroarene synthesis methods (e.g., Hantzsch dihydropyridine synthesis, Feist−Bénary furan synthesis, and Knorr pyrrole synthesis). Thus, in the present decarbonylative coupling strategy, ester groups that often result from heteroaromatic syntheses can be directly used as "leaving groups" for further transformations.

Scheme 4. A Plausible Mechanism for the Decarbonylative C−H Biaryl Coupling Using a Ni−dcype Catalytic System

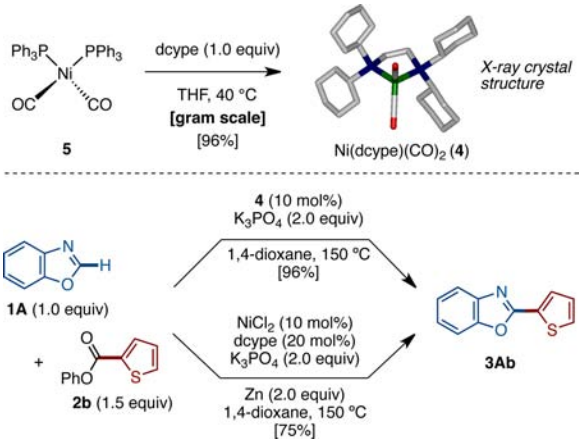


A plausible mechanism for this decarbonylative C−H arylation reaction is shown in Scheme 4. The reaction might undergo a Ni^0/Ni^{II} redox catalysis involving (i) oxidative addition of the phenyl ester C−O bond to Ni^0; (ii) CO migration onto the nickel center to produce an $Ar-Ni^{II}(CO)_{n+1}-OPh$ species (n = 0, 1);[13] (iii) C−H nickelation of azole (Het−H) with $Ar-Ni^{II}(CO)_{n+1}-OPh$ to generate $Ar-Ni^{II}(CO)_{n+1}-Het$;[14] and (iv) reductive elimination to release the coupling product (Het−Ar) and generate a $Ni^0(CO)_{n+1}$ species. Although the seemingly inactive complex Ni(dcype)-$(CO)_2$ (**4**) would be produced after two turnovers, the active Ni^0 catalyst could be regenerated by thermal extrusion of CO from **4**.[15]

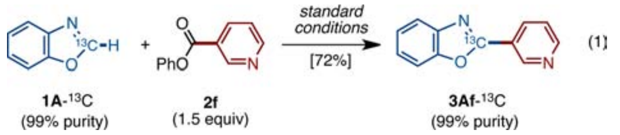
To shed further light on the reaction mechanism, we prepared the assumed intermediate **4** as a possible precatalyst. After some experimentation, we found that complexation of dcype with dicarbonylbis(triphenylphosphine)nickel (**5**) in tetrahydrofuran (THF) at 40 °C afforded **4** in 96% yield (Scheme 5). The preparation of **4** performed well on a gram scale (1.5 g), and the structure of **4** was determined by single-crystal X-ray diffraction analysis. Complex **4** turned out to be air-stable in the solid state, showing no sign of decomposition after 1 month. Most importantly, complex **4** was found to be a competent catalyst, as **3Ab** was obtained in 96% yield from the reaction of **1A** and **2b** in the presence of catalytic amounts of **4** (10 mol %). In an effort to establish more user-friendly conditions, we also found that the use of stable and less expensive $NiCl_2$ in combination with zinc powder also promotes the decarbonylative C−H coupling (Scheme 5).

While the proposed mechanism shown in Scheme 4 seemed reasonable, details regarding the elementary steps of the

Scheme 5. Preparation of Ni(dcype)(CO)$_2$ and Development of Alternative Protocols for Decarbonylative C–H Coupling

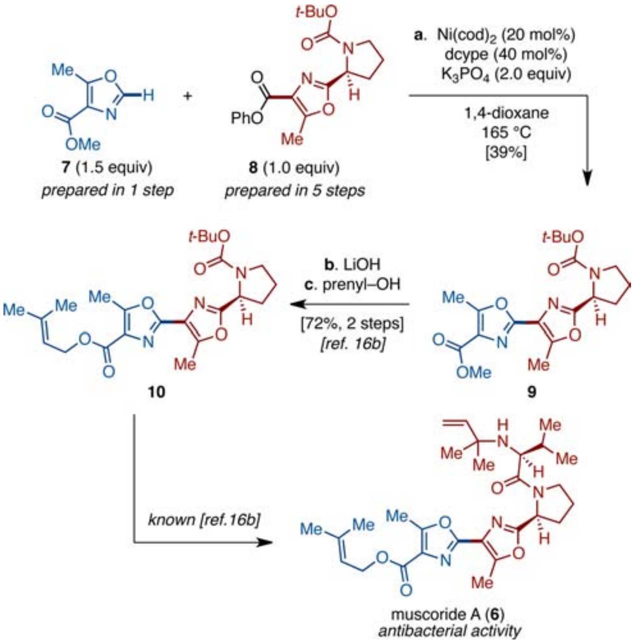


assumed mechanism remained unclear. For example, there was a possibility that the C2 carbon atom of the azole portion of the coupling product could originate from the aryl ester carbonyl carbon by a ring-opening/closing process of the azole rather than the azole starting material as assumed. Thus, we carried out a ^{13}C labeling experiment to verify the origin of the C2 carbon in the product (eq 1). When ^{13}C-labeled benzoxazole (**1A**-^{13}C, 99% purity) and ester **2f** were subjected to our standard conditions, the corresponding coupling product (**3Af**-^{13}C, 99% purity) was obtained in 72% yield. This result is in agreement with the proposed azole C–H arylation pathway. However, some of the mechanistic details still remain unclear, including the effects of the dcype ligand and K$_3$PO$_4$ in the catalytic cycle. Further detailed studies to elucidate the reaction mechanism are currently underway.



Finally, we applied the nickel-catalyzed decarbonylative C–H arylation to the synthesis of muscoride A (**6**), a natural product with antibacterial activity (Scheme 6). **6** was isolated by Sakakibara in 1995,[16a] and its total synthesis has been accomplished by Wipf,[16b] Pattenden,[16c] and Ciufolini.[16d] Although all of these groups adopted linear approaches, we imagined that our decarbonylative C–H coupling would allow an efficient synthesis of **6** in a convergent manner. Thus, two azole esters **7** (1.5 equiv) and (−)-**8** (1.0 equiv), which were readily prepared in one step and five steps respectively, were successfully coupled under our standard conditions to afford the corresponding coupling product (−)-**9** in 39% yield. Subsequently, (−)-**9** was treated with LiOH, after which condensation with prenyl alcohol afforded (−)-**10** in 72% yield over the two steps.[16b,17] Since the conversion of (−)-**10** to (−)-**6** was described previously by Wipf,[16b] the work reported here represents a formal synthesis of **6**. If the synthesis were planned and executed with typical cross-coupling substrates (aryl halides and organometallic reagents) instead, it would have become much less efficient, with many added steps.

Scheme 6. Formal Synthesis of Muscoride A (6) Using Nickel-Catalyzed Decarbonylative C–H Coupling



In summary, we have established the first nickel-catalyzed decarbonylative C–H biaryl coupling of azoles with aryl esters. This reaction operates on an inexpensive catalyst system and performs without stoichiometric oxidants. In addition to preliminary mechanistic experiments, we successfully applied this newly developed reaction to a convergent formal synthesis of muscoride A (**6**). In combination with common heteroaromatic synthesis, where ester groups are typically coinstalled onto a heterocycle, the present decarbonylative coupling method should find many uses in the construction of complex heterocyclic frameworks. Further mechanistic investigations of decarbonylative C–H coupling and the development of a second-generation catalyst with 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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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We thank Dr. Yasutomo Segawa for assistance with X-ray crystal structure analysis. This work was supported by the Funding Program for Next Generation World-Leading Researchers from JSPS (220GR049 to K.I.), a Grant-in-Aid for Scientific Research on Innovative Areas "Molecular Activation Directed toward Straightforward Synthesis" (23105517 to J.Y.) from MEXT, and a SUNBOR Grant from the Suntory Institute for Bioorganic Research (to J.Y.).

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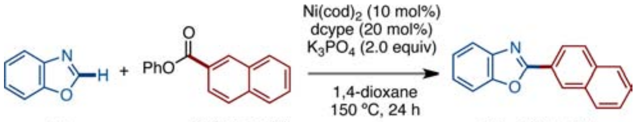
(11) See the Supporting Information for details and further screening of reaction conditions.

(12) General aromatic esters also coupled with azoles under nickel catalysis. For example, **1A** was coupled with phenyl 2-naphthoate (**2l**) under our standard conditions to afford the corresponding coupling product **3Aa** in 82% yield.



1A **2l** (1.5 equiv) **3Aa**: 82% yield

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(14) Kinetic isotope effect (KIE) experiments were carried out using the reactions of **2b** with **1A** and its C2-deuterated derivative ([D]-**1A**) under our catalytic conditions. As no significant KIE was observed ($k_H/k_D = 1.24$), it is likely that the C−H bond cleavage of the 1,3-azole is not the rate-limiting step in the catalytic reaction.

(15) When the coupling reaction of **1A** and **2b** catalyzed by **4** was conducted under a CO atmosphere, the yield of **3Ab** decreased to 9% yield (96% yield under Ar; see Scheme 5). This result is in line with the CO extrusion mechanism.

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(17) The NMR data for methyl ester **9** did not match completely with those in the previous report (see ref 16b). Therefore, **9** was converted to prenyl ester **10**, which we confirmed to display ^{1}H and ^{13}C NMR data identical to those reported in ref 16b.