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Communication

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Isolation, Structure, and Reactivity of an Arylnickel(II) Pivalate Complex in Catalytic C−H/C−O Biaryl Coupling

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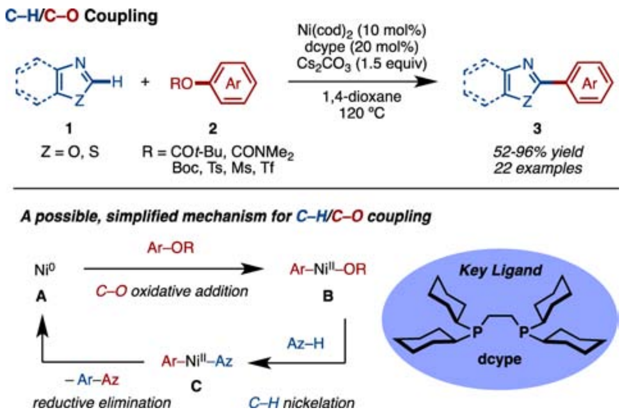
Supporting Information

ABSTRACT: We describe mechanistic studies of a C−H/C−O biaryl coupling of 1,3-azoles and aryl pivalates catalyzed by Ni(cod)$_2$/dcype. This study not only supports a catalytic cycle consisting of C−O oxidative addition, C−H nickelation, and reductive elimination but also provides insight into the dramatic ligand effect in C−H/C−O coupling. We have achieved the first synthesis, isolation and structure elucidation of an arylnickel(II) pivalate, which is an intermediate in the catalytic cycle after oxidative addition of a C−O bond. Furthermore, kinetic studies and kinetic isotope effect investigations reveal that the C−H nickelation is the turnover-limiting step in the catalytic cycle.

Invention, understanding, and utilization of a new mode of inert bond activation by transition-metal catalysts offer great opportunities in organic synthesis. In particular, when coupled with strategic synthetic approaches, the activation of ubiquitous and inert bonds such as C−H and C−O bonds can lead to an unconventional, streamlined method for assembling molecules.[1] In parallel to the experimental screening for optimizing reaction conditions, mechanistic studies such as kinetics, isolation and reaction of a possible intermediate as well as computational analysis are crucial for the rational design of catalysts, conditions, and new transformations.[2] We report herein a mechanistic study of our recently discovered nickel catalysis that can activate both C−H bonds in 1,3-azoles and C−O bonds in phenol derivatives, leading to the synthesis of heterobiaryls directly from these substrates.

In 2012, as a part of our campaign exploring nickel catalysis in C−H functionalization,[3] we discovered that a C−H/C−O biaryl coupling of 1,3-azoles **1** and phenol derivatives **2**, such as aryl pivalates, takes place in the presence of catalytic amounts of Ni(cod)$_2$/dcype (cod = 1,5-cyclooctadiene, dcype = 1,2-bis(dicyclohexylphosphino)ethane) to yield the corresponding heterobiaryls **3** in good to excellent yields (Scheme 1).[3c] Although this reaction was developed based on our mechanistic blueprint of a Ni^0/Ni^{II} redox catalytic cycle (Scheme 1) consisting of (i) C−O bond oxidative addition of the phenol derivative (Ar−OR) to Ni(0) **A** to form an Ar−Ni−OR complex **B**, (ii) C−H nickelation of an azole (Az−H) to yield Ar−Ni−Az complex **C**, and (iii) reductive elimination to afford the coupling product (Ar−Az) and regenerate Ni(0) species **A**, there was no evidence for this pathway at that time. Moreover, we were not able to provide any rationale for the dramatic ligand effects (the use of dcype is essential, and other ligands including highly reputed PCy$_3$ are totally ineffective)[4] in this C−H/C−O coupling. Thus, we aimed at gaining an understanding of the mechanism of the C−H/C−O coupling and the ligand effect by the isolation of intermediates supported by kinetic studies.

Scheme 1. C−H/C−O Coupling Catalyzed by Ni/dcype



We began our study by examining the C−O oxidative addition of phenol derivatives to Ni(0) species. There are many reports proposing a similar Ni^0/Ni^{II} oxidative additions in the catalytic conversion of aromatic C−O bonds; the most notable example being the cross-coupling of phenol derivatives and organometallic reagents (C−M/C−O coupling) catalyzed by a Ni/PCy$_3$ catalyst (PCy$_3$ = tricyclohexylphosphine).[5−7] However, the isolation and characterization of key catalytic intermediates supporting pathway have not been successful so far.[8] Very recently, Martin et al. proposed an interesting oxidative addition mechanism that proceeds through a Ni(I) species as a part of their mechanistic study on the reduction of methoxyarenes using a Ni/PCy$_3$ catalyst and hydrosilanes as the hydrogen source.[8c]

Our investigation commenced by monitoring the stoichiometric reaction of naphthalen-2-yl pivalate (**2a**) with Ni(cod)$_2$/dcype using ^{31}P NMR spectroscopy (solvent: d^8-toluene) to identify the C−O oxidative addition intermediate. When the mixture was heated at 100 °C, two new downfield peaks (δ = 63.7 and 61.7 ppm) appeared alongside the signal for the Ni(cod)$_2$/dcype complex itself (δ = 60.3 ppm) (Figure 1).[9] As the two

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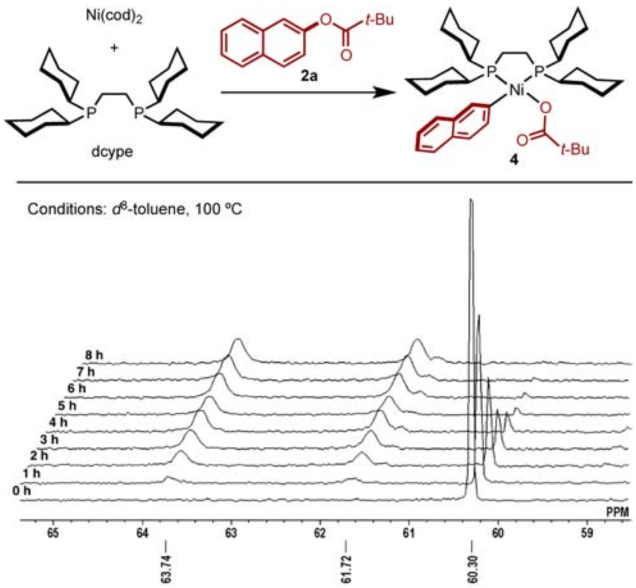


Figure 1. Monitoring the reaction of **2a** with Ni(cod)$_2$/dcype using ^{31}P NMR spectroscopy. The ^{31}P chemical shift of Ni/dcype complex and **4** appears at 60.8 ppm (for dcype) and 61.7 and 63.8 ppm (for **4**), respectively.

phosphorus atoms of dcype are in different chemical environments, it was assumed that the aromatic C−O bond underwent an oxidative addition to the nickel center. Additionally, the fact that the NMR spectra are displayed with clarity suggests that the reaction does not generate a Ni(I) species.

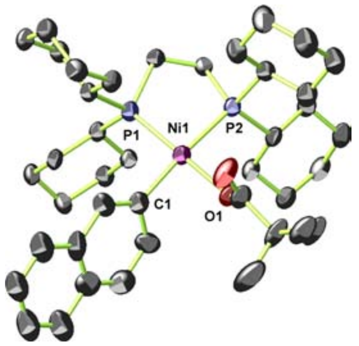
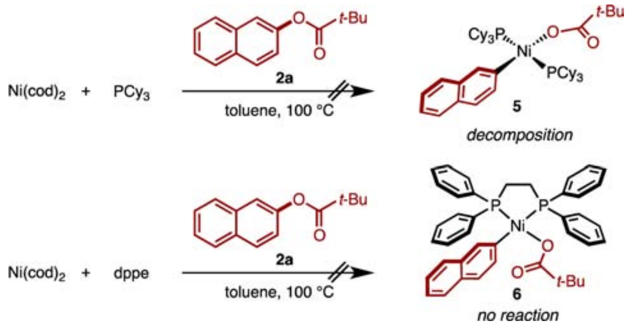


Figure 2. ORTEP drawing of one of two independent molecules of **4**. Hydrogen atoms are omitted for clarity; thermal ellipsoids are drawn at 50% probability. Selected bond lengths (Å) and angles (°): Ni1−C1 = 1.940(6), Ni1−O1 = 1.919(4), Ni−P1 = 2.1401(16), Ni1−P2 = 2.2192(17), P1−Ni1−P2 = 88.56(8), P1−Ni1−C1 = 91.85(18), C1−Ni1−O1 = 88.8(2), O1−Ni1−P2 = 89.89(13), P1−Ni1−O1 = 175.10(14), P2−Ni1−C1 = 168.9(2).

Encouraged by this result, we next attempted the isolation of the presumed nickel complex (Figure 2). After a stoichiometric reaction, the solvent was completely removed to afford a crude orange solid. The resulting solid was recrystallized from toluene/hexane to give orange crystals in 80% isolated yield. The structure of resulting mononuclear Ni(II) complex **4** (C−O oxidative addition complex) was unambiguously confirmed by X-ray crystallographic analysis.[10] The X-ray crystal structure showed that the Ni atom is in a square-planar geometry surrounded by two phosphines, a carbon, and an oxygen atom. The dcype ligand is indeed coordinated to the Ni atom in a *cis*-configuration. Most importantly, this Ni complex **4** not only matches our proposed intermediate **B** but also represents the first isolation and characterization of a Ar−Ni(II)−OR species via the oxidative addition of an aromatic C−O bond to a Ni(0) species. It should also be noted that virtually no decomposition of Ni complex **4** has been detected after extended (>3 months) exposure to air, indicating the effect of dcype in the stability of nickel complexes.[11]

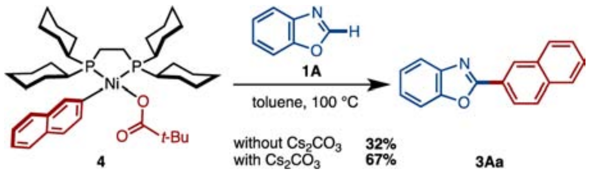
Next, we investigated the dcype ligand effect on the oxidative addition of the aromatic C−O bond to the Ni(0) species (Scheme 2). As reference ligands in this study, we selected PCy$_3$ and dppe (1,2-diphenylphosphinoethane), which do not promote the catalytic C−H/C−O coupling.[3c] When PCy$_3$ was employed in the stoichiometric reaction with Ni(cod)$_2$ and **2a**, the corresponding oxidative addition complex **5** was not isolated. Instead, the reaction afforded 2,2′-binaphthyl, which is likely generated by disproportionation of **5** as similarly to the production of biaryl from Ar−Ni−X (X = halogen).[12] In the case of the reaction using dppe, the oxidative addition complex **6** was not observed, and the substrate **2a** remained almost unchanged. According to these results, the dcype ligand might play two roles in the oxidative addition of aryl C−O bonds as well as in the catalytic reaction. The first is that the electron-donating cyclohexyl moieties on phosphorus atoms help increase the electron density of Ni(0) center to facilitate the C−O oxidative addition. The other is that the bidentate structure of dcype could stabilize the generated Ar−Ni(II)−OR species after the oxidative addition.

Scheme 2. Attempted Oxidative Addition of 2a to Ni/PCy$_3$ or Ni/dppe



With plausible oxidative addition intermediate **4** in hand, we next examined the stoichiometric reaction of **4** and benzoxazole (**1A**) (Scheme 3). The reaction of **1A** with **4** in toluene at 100 °C provided naphthalen-2-yl benzoxazole (**3Aa**), the product of C−H/C−O coupling, in 32% yield. The reaction yield was improved by the addition of 1.0 equiv of Cs$_2$CO$_3$, providing a 67% yield of **4**. These results suggest that nickel complex **4** is likely involved in the catalytic cycle. Although we were not able to observe the assumed diarylnickel(II) intermediate **C**, we assume that the product **3Aa** is formed by C−H nickelation and reductive elimination (Scheme 1). The observation that product can be

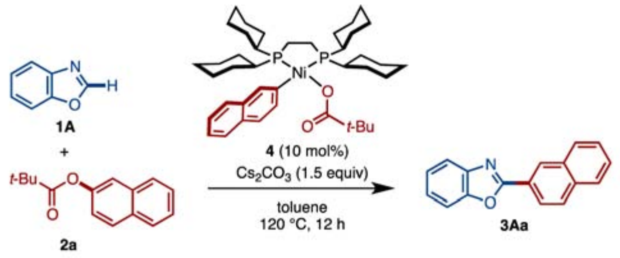
Scheme 3. Stoichiometric Reaction of 1A with 4



formed without additive indicates the existence of C−H nickelation pathway from arylnickel(II) pivalate **4** through a concerted metalation−deprotonation mechanism.[13] The rate acceleration by Cs_2CO_3 indicates the occurrence of ligand exchange from pivaloyl to carbonate to generate a more active nickel intermediate, $Ar-Ni-OCO_2Cs$. However, we must stress that more extensive investigations are needed to prove this particular step.

As a part of our studies investigating the reactivity of oxidative addition complex **4**, we then attempted to use **4** as a catalyst (precursor) in the C−H/C−O coupling (Table 1). When the coupling of **1A** and **2a** was conducted in the presence of **4** (10 mol %) and Cs_2CO_3 in toluene at 120 °C for 12 h, the product **3Aa** was formed but only in 8% yield (entry 1). We hypothesized that the product was formed as in the stoichiometric reaction shown in Scheme 3 but the regenerated Ni(0) species decomposed under the reaction conditions. Moreover, we also came to assume that some additional ligands are present in the catalytic reaction to prevent Ni(0) decomposition. To verify this hypothesis, cod, which is present in the optimized catalytic conditions as shown in Scheme 1, was added in the coupling using **4** as a catalyst. Indeed, by adding cod, the desired product **3Aa** was obtained in 70% yield (entry 2). These results clearly show not only the possible involvement of **4** in the catalytic cycle but also that cod plays a key role in the catalytic cycle as Ni(0)-stabilizing ligand.

Table 1. C−H/C−O Coupling Catalyzed by 4



entry	variation	yield of **3Aa**
1	none	8%
2	added 1,5-COD	70%

To further elucidate the mechanism of the C−H/C−O coupling, we conducted kinetic studies by using *in situ* IR experiments to observe the initial rate of reaction,[14] the results of which are summarized in Figure 3. The kinetic profile for **2a** demonstrated that the reaction rate of C−H/C−O coupling of **1A** with **2a** is zero-order in [**2a**]. In contrast to [**2a**], first-order kinetic profiles were observed for [**1A**] and [$Ni(cod)_2$/dcype]. The kinetic profiles in each substrate suggest that the turnover-limiting step of this Ni-catalyzed reaction is the C−H nickelation step. Furthermore, it was found that the active catalyst is a monometallic nickel species because a first-order dependence on the amount of catalyst was observed.

Finally, kinetic isotope effect (KIE) experiments were carried out using the reactions of **2a** with **1A** and its C2-deuterated derivative ([**D**]-**1A**) under optimized conditions (Figure 4).[15] Since an initial KIE was observed (k_H/k_D = 2.4), it is likely that the C−H nickelation (C−H cleavage) of 1,3-azole is the rate-determining step in the catalytic reaction.

Taking all the experimental data into consideration, we propose the mechanism of C−H/C−O coupling shown in Scheme 4. The key Ni(0) species, L-Ni^0-dcype (**A**) (L = cod), is first generated from $Ni(cod)_2$ and dcype. The dissociation of L would generate a coordinatively unsaturated Ni^0-dcype complex (not shown in Scheme 4), which undergoes the C−O bond oxidative addition with aryl pivalate **2** to afford arylnickel(II) pivalate **B** (R = CO*t*-Bu). The turnover-limiting, Cs_2CO_3-accelerated C−H nickelation of **B** with azoles produces a diarylnickel(II) intermediate **C**. Finally, the reductive elimination of **C** produces the coupling product **3** and Ni^0-dcype, which

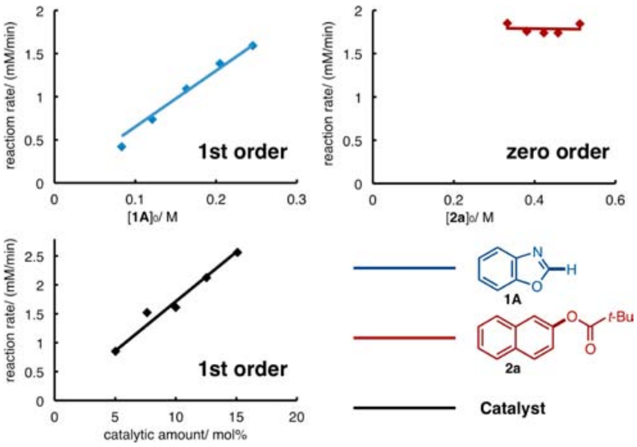


Figure 3. Kinetic profiles of Ni-catalyzed C−H/C−O coupling.

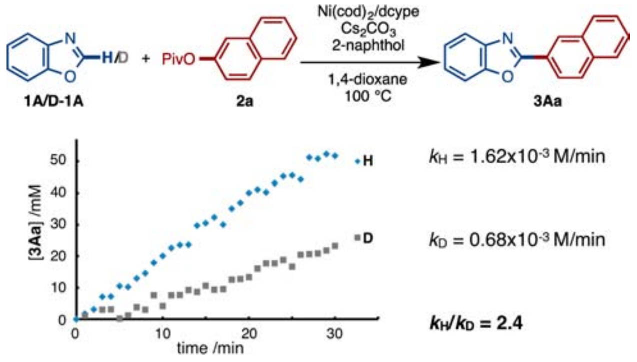
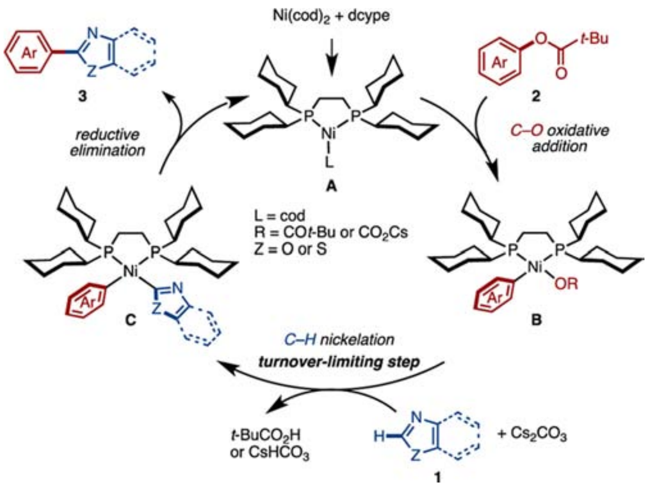


Figure 4. Investigation of KIE.

Scheme 4. Possible Mechanism for C−H/C−O Coupling



should be trapped by L to regenerate the metastable L-Ni^0-dcype complex (**A**).

In summary, we have thoroughly studied the mechanism of C−H/C−O coupling of 1,3-azoles and aryl pivalates catalyzed by Ni-dcype. The first synthesis, isolation, and characterization of a C−O oxidative addition complex, arylnickel(II) pivalate **4**, were achieved using the key ligand, dcype. The catalytic cycle consisting of C−O oxidative addition, C−H nickelation, and reductive elimination has been supported by a number of stoichiometric and catalytic reactions using **4**, kinetic studies, and KIE experiments. The C−H nickelation step is likely to be the turnover-limiting step in the catalytic cycle. Moreover, control experiments using other ligands provided insight into the two important roles of dcype ligand in C−H/C−O coupling: (1) facilitation of the oxidative addition of C−O bonds and (2) stabilization of the intermediate after oxidative addition. Based on insights obtained regarding the effect of dcype, the design and development of more active nickel catalysts are ongoing in our laboratory.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures and data and kinetic data. 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.

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■ REFERENCES

(1) Selected reviews on inert bond activation: (a) Godula, K.; Sames, D. *Science* **2006**, *312*, 67. (b) Alberico, D.; Scott, M. E.; Lautens, M. *Chem. Rev.* **2007**, *107*, 174. (c) Davies, H. W. L.; Manning, J. R. *Nature* **2008**, *451*, 417. (d) Ackermann, L.; Vicente, R.; Kapdi, A. R. *Angew. Chem., Int. Ed.* **2009**, *48*, 9792. (e) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (f) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (g) Yamaguchi, J.; Yamaguchi, A.; Itami, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 8960. (h) Amii, H.; Uneyama, K. *Chem. Rev.* **2009**, *109*, 2119. (i) Tobisu, M.; Chatani, N. *Chem. Soc. Rev.* **2008**, *37*, 300.

(2) Selected examples: (a) Garcia-Cuadrado, D.; de Mendoza, P.; Braga, A. A. C.; Maseras, F.; Echavarren, A. M. *J. Am. Chem. Soc.* **2007**, *129*, 6880. (b) Lewis, J. C.; Berman, A. M.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 2493. (c) Musaev, D. G.; Kaledin, A.; Shi, B.-F.; Yu, J.-Q. *J. Am. Chem. Soc.* **2012**, *134*, 1690. (d) Jiao, L.; Herdtweck, E.; Bach, T. *J. Am. Chem. Soc.* **2012**, *134*, 14563. (e) Tan, Y.; Barrios-Landeros, B.; Hartwig, J. F. *J. Am. Chem. Soc.* **2012**, *134*, 3683.

(3) (a) Canivet, J.; Yamaguchi, J.; Ban, I.; Itami, K. *Org. Lett.* **2009**, *11*, 1733. (b) Yamamoto, T.; Muto, K.; Komiyama, M.; Canivet, J.; Yamaguchi, J.; Itami, K. *Chem.—Eur. J.* **2011**, *17*, 10113. (c) Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 169. (d) Amaike, K.; Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 13573. (e) Meng, L.; Kamada, Y.; Muto, K.; Yamaguchi, J.; Itami, K. *Angew. Chem., Int. Ed.* **2013**, *52*, 10048.

(4) See ref 3c for the ligand effect in Ni-catalyzed C−H/C−O coupling.

(5) Other examples of Ni-catalyzed C−H arylations: (a) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 1737. (b) Kobayashi, O.; Uraguchi, D.; Yamanaka, T. *Org. Lett.* **2009**, *11*, 2679. For C−H/C−M coupling, see: (c) Tobisu, M.; Hyodo, I.; Chatani, N. *J. Am. Chem. Soc.* **2009**, *131*, 12070. (d) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *ChemCatChem* **2010**, *2*, 1403. (e) Hachiya, H.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2010**, *49*, 2202. (f) Hyodo, I.; Tobisu, M.; Chatani, N. *Chem. Asian J.* **2012**, *7*, 1357. (g) Hyodo, I.; Tobisu, M.; Chatani, N. *Chem. Commun.* **2012**, *48*, 308. For recent examples of C−H alkylation, see: (h) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2013**, *135*, 5308. (i) Xin, P.-Y.; Niu, H.-Y.; Qu, G.-R.; Ding, R.-F.; Guo, H.-M. *Chem. Commun.* **2012**, *48*, 6717.

(6) Recent reviews: (a) Li, B.-J.; Yu, D.-G.; Sun, C.-L.; Shi, Z.-J. *Chem.—Eur. J.* **2011**, *17*, 1728. (b) Rosen, B. M.; Quasdorf, K. W.; Wilson, D. A.; Zhang, N.; Resmerita, A.-M.; Garg, N. K.; Percec, V. *Chem. Rev.* **2011**, *111*, 1346. (c) Yu, D.-G.; Li, B.-J.; Shi, Z.-J. *Acc. Chem. Res.* **2010**, *43*, 1486. (d) Yamaguchi, J.; Muto, K.; Itami, K. *Eur. J. Org. Chem.* **2013**, 19. (e) Mesganaw, T.; Garg, N. K. *Org. Process Res. Dev.* **2013**, *17*, 29.

(7) Ni/PCy$_3$-catalyzed C−B/C−O biaryl coupling using phenol derivatives (ethers, esters, carbamates, carbonates, sulfamates, phosphates, and metal salts): (a) Tobisu, M.; Shimasaki, T.; Chatani, N. *Angew. Chem., Int. Ed.* **2008**, *47*, 4866. (b) Quasdorf, K. W.; Tian, X.; Garg, N. K. *J. Am. Chem. Soc.* **2008**, *130*, 14422. (c) Guan, B.-T.; Wang, Y.; Li, B.-J.; Yu, D.-G.; Shi, Z.-J. *J. Am. Chem. Soc.* **2008**, *130*, 14468. (d) Quasdorf, K. W.; Riener, M.; Petrova, K. V.; Garg, N. K. *J. Am. Chem. Soc.* **2009**, *131*, 17748. (e) Antoft-Finch, A.; Blackburn, T.; Snieckus, V. *J. Am. Chem. Soc.* **2009**, *131*, 17750. (f) Xi, L.; Li, B.-J.; Wu, Z.-H.; Lu, X.-Y.; Guan, B.-T.; Wang, B.-Q.; Zhao, K.-Q.; Shi, Z.-J. *Org. Lett.* **2010**, *12*, 884. (g) Quasdorf, K. W.; Antoft-Finch, A.; Liu, P.; Silberstein, A. L.; Komaromi, A.; Blackburn, T.; Ramgren, S. D.; Houk, K. N.; Snieckus, V.; Garg, N. K. *J. Am. Chem. Soc.* **2011**, *133*, 6352. (h) Chen, H.; Huang, Z.; Hu, X.; Tang, G.; Xu, P.; Zhao, Y.; Cheng, C.-H. *J. Org. Chem.* **2011**, *76*, 2338. (i) Yu, D.-G.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2011**, *50*, 7097. (j) Ramgren, S. D.; Hie, L.; Ye, Y.; Garg, N. K. *Org. Lett.* **2013**, *15*, 3950.

(8) Mechanistic studies of oxidative addition of C−O bonds to nickel: (a) Li, Z.; Zhang, S.-L.; Fu, Y.; Guo, Q.-X.; Liu, L. *J. Am. Chem. Soc.* **2009**, *131*, 8815. (b) Kelly, P.; Lin, S.; Edouard, G.; Day, M. W.; Agapie, T. *J. Am. Chem. Soc.* **2012**, *134*, 5480. (c) Cornella, J.; Gómez-Bengoa, E.; Martin, R. *J. Am. Chem. Soc.* **2013**, *135*, 1997. Mechanistic studies of the oxidative addition of a C−O bond to ruthenium: (d) Ueno, S.; Mizushima, E.; Chatani, N.; Kakiuchi, F. *J. Am. Chem. Soc.* **2006**, *128*, 16516.

(9) As monitored by ^{31}P NMR, the oxidative addition completed within 2 h, which is much faster than the catalytic reaction (12 h). See the SI for details.

(10) An asymmetric unit contains two independent molecules having only slightly different bond lengths and angles between them. One of them is omitted for clarity. See the SI for details.

(11) Though stable in solid state, complex **4** gradually decomposes in solution when exposed to air atmosphere.

(12) Yamamoto, T.; Wakabayashi, S.; Osakada, K. *J. Organomet. Chem.* **1992**, *428*, 223.

(13) For reviews, see: (a) Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118. (b) Ackermann, L. *Chem. Rev.* **2011**, *11*, 1315.

(14) See the SI for details.

(15) Simmons, E. M.; Hartwig, J. F. *Angew. Chem., Int. Ed.* **2012**, *51*, 3066.