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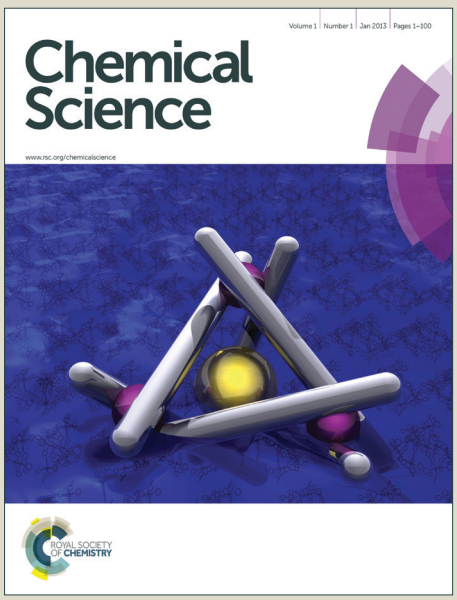





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ARTICLE

# C–H Arylation and Alkenylation of Imidazoles by Nickel Catalysis: Solvent-accelerated Imidazole C–H Activation

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The first nickel-catalyzed C–H arylation and alkenylation of imidazoles with phenol and enol derivatives is described. Under the influence of $Ni(OTf)_2$/dcype/$K_3PO_4$ (dcype: 1,2-bis(dicyclohexylphosphino)ethane) in *t*-amyl alcohol, imidazoles can undergo C–H arylation with phenol derivatives. The C–H arylation of imidazoles with chloroarenes as well as that of thiazoles and oxazoles with phenol derivatives can also be achieved with this catalytic system. By changing the ligand to dcypt (3,4-bis(dicyclohexylphosphino)thiophene), enol derivatives could also be employed as coupling partners achieving the C–H alkenylation of imidazole as well as thiazoles and oxazoles. Thus, a range of C2-arylated and alkenylated azoles can be synthesized using this newly developed nickel-based catalytic systems. The key to success of C–H coupling of imidazoles is the use of tertiary alcohol as solvent. This also allows using air-stable nickel(II) salt as a catalyst precursor.

## Introduction

Imidazoles including benzimidazoles are recognized as important chemical motifs since they are frequently found in a range of natural products, and exploited as core structures in pharmaceuticals, agrochemicals, and organic materials. Because of high versatility of imidazole-containing compounds (particularly C2-arylated and alkenylated imidazoles; Figure 1),[1] functionalization and derivatization thereof are of significant importance in synthetic organic chemistry. Numerous synthetic methods to construct C2-aryl and alkenyl imidazoles have been reported thus far. Although cyclization and annulation reactions have found wide use, these methods often suffer from multi-step reaction sequences.[2] Transition metal-catalyzed cross-coupling reactions of arylmetal compounds and aryl halides have also been employed, albeit requiring the pre-functionalization of metalated or halogenated imidazoles prior to the coupling reactions.[3]

In recent years, transition metal-catalyzed C–H functionalization approach has attracted attention as it enables rapid and straightforward synthesis of various functional heteroarenes.[4] Within this class of reactions, C–H arylation and alkenylation of imidazoles using transition-metal catalysts have been reported, mainly involving palladium[5] and rhodium.[6] In 2009, Daugulis and coworkers discovered a Cu-catalyzed C–H arylation of imidazoles, which allowed the use of an inexpensive transition metal catalyst.[7]

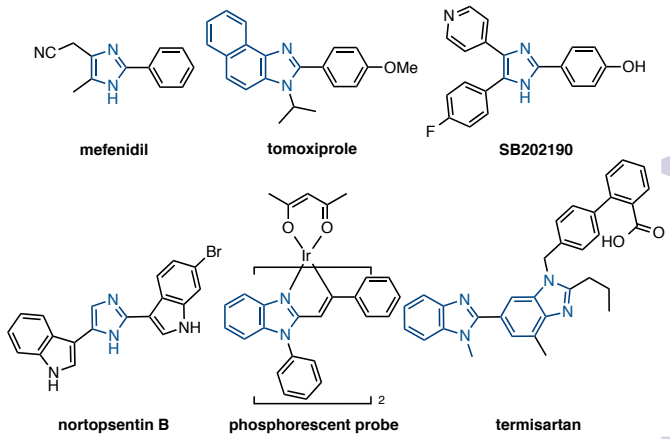


**Figure 1.** C2-Arylated and alkenylated imidazoles and benzimidazoles in natural products, pharmaceuticals, and organic materials.

In our studies in catalytic C–H functionalization,[8] we have developed several unique nickel catalysts[9] that facilitate the C–H arylation of 1,3-azoles, such as oxazoles and thiazoles, with haloarenes (C–H/C–X coupling)[10], phenol derivatives (C–H/C–O coupling)[11], and arenecarboxylates (decarbonylative C–H coupling)[12]. The advantage of our recent nickel-based catalytic systems[11] is not only its low cost, but also its ability to activate and couple phenol derivatives (C–O electrophiles).[13,14] However, imidazoles and benzimidazoles still remained as challenging substrates for our nickel-catalyzed C–H coupling campaign. Herein, we report the first general protocol for Ni-catalyzed C–H arylation as well as alkenylation of imidazoles (Figure 2).

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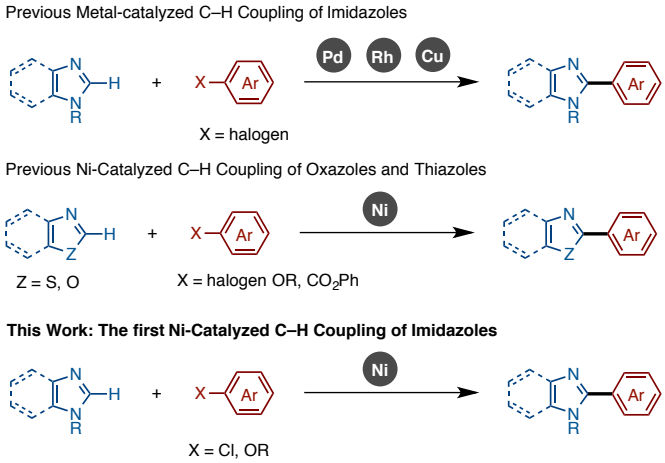



**Figure 2**. Transition metal-catalyzed C–H arylation of imidazoles and benzimidazoles.

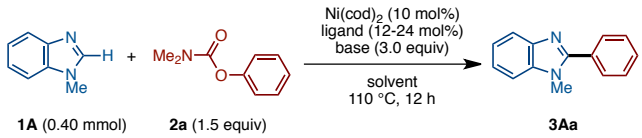
## Results and discussion

### C–H Arylation of Imidazoles with Phenol Derivatives

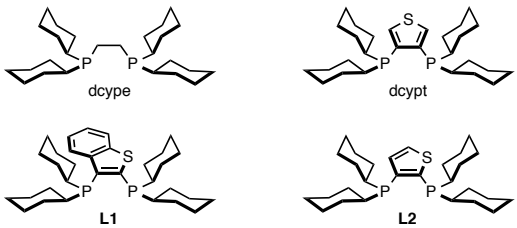
Among the myriad nickel catalysts for C–H arylation reported over the past decade from our group,[10-12] Miura,[15] and Chatani,[16] our $Ni(cod)_2$/dcype (cod = 1,5-cyclooctadiene; dcype = 1,2-bis(dicyclohexylphosphino)ethane) catalyst with $Cs_2CO_3$ as the base in 1,4-dioxane as the solvent is well suited for direct coupling of 1,3-azoles and phenol derivatives (C–H/C–O coupling). The selection of an appropriate ligand is crucial, as this reaction proceeds only when dcype was used. In contrast, this catalytic system was not affected by the choice of base and solvent since C2-functionalized azoles could be formed in the absence of base. Through several mechanistic investigations including the isolation of a catalytic intermediate, kinetic studies,[11c] and theoretical calculations,[11d] we had previously identified the ligand effect and a plausible catalytic cycle for the reaction. In particular, DFT calculations provided significant insight regarding the mechanism of C–H nickelation steps: the formation of a Cs-Ni cluster was found to play a key roll to accelerate the C–H nickelation. However, experimentally and computationally, it had also been revealed that new catalytic conditions need to be developed for the C–H coupling of imidazoles.

With these considerations in mind, we focused on the investigation of base and solvent effects by using *N*-methylbenzimidazole (**1A**) and phenyl carbamate **2a** as model substrates (Table 1). Our previous $Ni(cod)_2$/dcype-based catalytic conditions employing $Cs_2CO_3$ and 1,4-dioxane afforded no coupling products (entry 1). Intensive and thorough investigation led to the discovery that the combination of $K_3PO_4$ and *t*-amyl alcohol (*t*-AmylOH) could facilitate the C–H arylation of **1A** to afford **3Aa** in 83% yield (entry 2). The replacement of *t*-AmylOH with *t*-BuOH gave **3Aa** in slightly lower yield (entry 3). When the base and/or the solvent were changed, the reaction efficiency was diminished. For example, the use of aprotic solvents and secondary alcohol solvents was completely ineffective for this reaction (entries 4–6). Additionally, the reaction in the presence of $Cs_2CO_3$ or LiO*t*-Bu resulted in lower yields than with $K_3PO_4$ (entries 7 and 8). While we initially imagined that *in situ*-generated potassium tertiary alkoxides might be the reactive species, this seems not to be the case; the use of KO*t*-Bu completely shut down the catalytic activity (entry 9). Regarding the ligand effect, $PCy_3$ and an *N*-heterocyclic carbene ligand were inactive for the present reaction (entries 10 and 11). Our thiophene-based diphosphine ligand, dcypt (3,4-bis(dicyclohexylphosphino)thiophene),[17] as well as other dcype derivatives such as **L1** and **L2** furnished **3Aa** in moderate yields (entries 12–14). To our delight, the replacement of $Ni(cod)_2$ to $Ni(OTf)_2$ as pre-catalyst maintained the catalytic activity (entry 15). Considering significant advantage of using air-stable $Ni(OTf)_2$, we decided to use $Ni(OTf)_2$/dcype catalyst and $K_3PO_4$ in *t*-AmylOH for further studies.

**Table 1.** Screening of reaction conditions.[a]

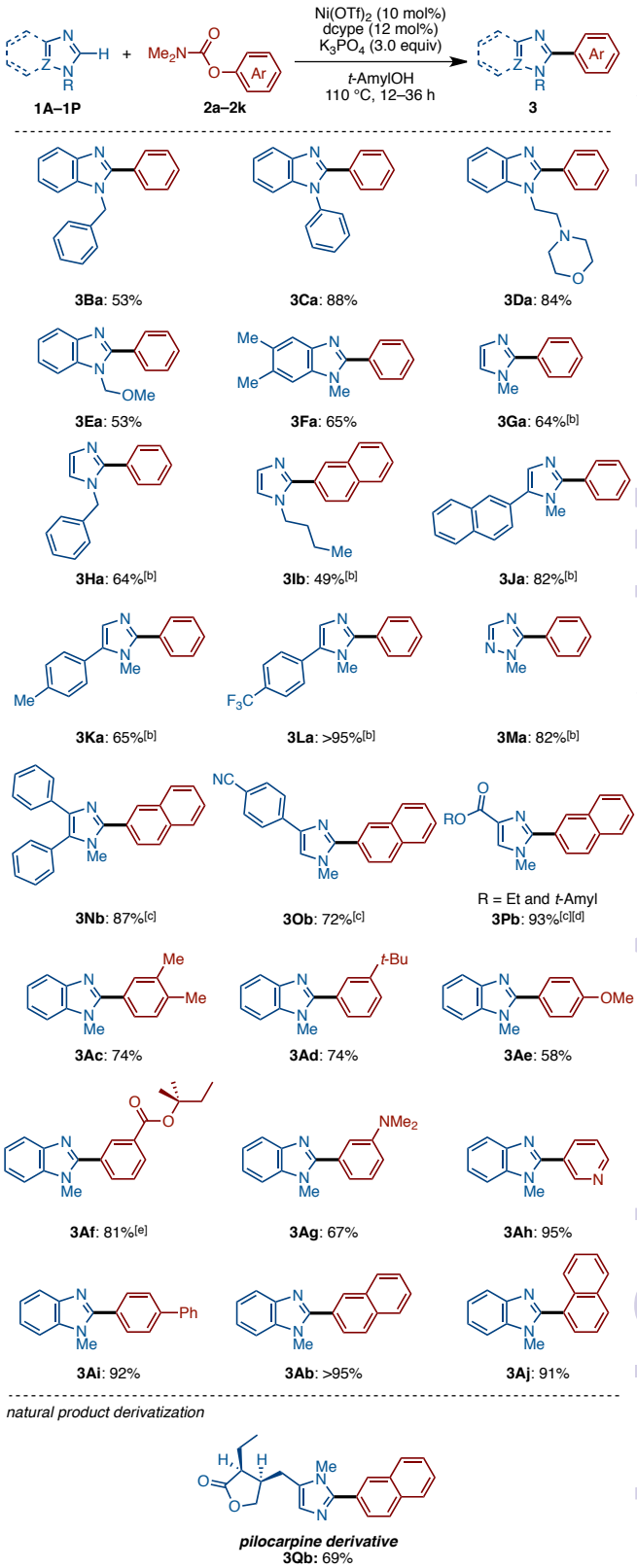



| entry | ligand | base | Solvent | **3Aa** (%)[b] |
|---|---|---|---|---|
| 1 | dcype | $Cs_2CO_3$ | 1,4-dioxane | 0 |
| 2 | dcype | $K_3PO_4$ | *t*-AmylOH | 83 |
| 3 | dcype | $K_3PO_4$ | *t*-BuOH | 70 |
| 4 | dcype | $K_3PO_4$ | 1,4-dioxane | 0 |
| 5 | dcype | $K_3PO_4$ | DMF | 0 |
| 6 | dcype | $K_3PO_4$ | *i*-PrOH | 0 |
| 7 | dcype | $Cs_2CO_3$ | *t*-AmylOH | 44 |
| 8 | dcype | LiO*t*-Bu | *t*-AmylOH | 59 |
| 9 | dcype | KO*t*-Bu | *t*-AmylOH | 0 |
| 10 | $PCy_3$ | $K_3PO_4$ | *t*-AmylOH | 0 |
| 11 | IPr·HCl | $K_3PO_4$ | *t*-AmylOH | 0 |
| 12 | dcypt | $K_3PO_4$ | *t*-AmylOH | 55 |
| 13 | **L1** | $K_3PO_4$ | *t*-AmylOH | 53 |
| 14 | **L2** | $K_3PO_4$ | *t*-AmylOH | 64 |
| 15[c] | dcype | $K_3PO_4$ | *t*-AmylOH | 82 |




[a] Unless otherwise noted, reaction conditions were as follows: **1A** (0.40 mmol), **2a** (1.5 equiv), $Ni(cod)_2$ (10 mol%), ligand (bidentate: 12 mol%, monodentate: 24 mol%), base (3.0 equiv), solvent (1.6 mL), 110 °C, 12 h. [b] GC yield. [c] $Ni(OTf)_2$ (10 mol%) was used.

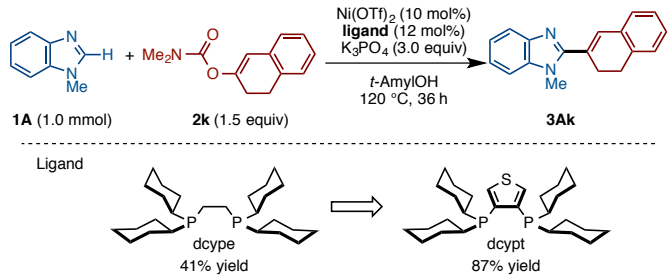
We then examined the substrate scope of $Ni(OTf)_2$/dcype-catalyzed C–H arylation (C–H/C–O coupling) of imidazoles **1** with carbamates of phenol derivatives **2** (Scheme 1). Several *N*-substituted benzimidazoles such as *N*-benzyl (**1B**), phenyl (**1C**), morpholinoethyl (**1D**), and methoxymethyl benzimidazoles (**1E**) underwent C–H/C–O coupling to afford the corresponding products in moderate to excellent yields. In addition to benzimidazoles, imidazoles were also coupled with phenol derivatives **2** successfully, although it was necessary to use $Ni(cod)_2$ as the catalyst precursor as well as a longer reaction time. In general, the coupling proceeds smoothly with substrates having electron-withdrawing groups on the phenyl rings at the C5 position of imidazole ring. For example, the reaction of trifluoromethyl-substituted 5-arylimidazole furnished triaryl **3La** in superior yield (>95%) than that for methyl-substituted triaryl **3Ka** (65%). Although the reason remains unclear at this stage, dcypt ligand gave better results for the coupling of C4-substituted imidazoles (**1N**, **1O**, and **1P**). Notably, triazole **1M** also underwent C–H/C–O coupling with **2a** to afford 5-phenyl *N*-methyl-1,2,4-triazole (**3Ma**) in 82% yield. Regarding aryl electrophiles, a broad functional group tolerance was observed. An amino group or nitrogen heterocycle, which often behaves as a catalyst-deactivating group, did not inhibit the reaction; **3Da**, **3Ag**, and **3Ah** were obtained in good to excellent yields. Although transesterification took place with *t*-AmylOH when ethoxycarbonyl-substituted phenol electrophile **2f** was used, the product **3Af** was generated in good yield. Delightfully, we could directly functionalize pilocarpine (**1Q**), which is a drug for the treatment of dry mouth,[18] in 69% yield without any lactone opening or epimerization at the α-position of the carbonyl group. It should be emphasized that this coupling reaction proceeds with high regioselectivity at the C2 position of the imidazole rings.




**Scheme 1.** Substrate scope of imidazole C–H arylation with phenol derivatives. [a] Unless otherwise noted, reaction conditions were as follows: **1** (0.40 mmol), **2** (1.5 equiv), $Ni(OTf)_2$ (10 mol%), dcype (12 mol%), $K_3PO_4$ (3.0 equiv), *t*-AmylOH (1.6 mL), 110 °C, 12–36 h. [b] $Ni(cod)_2$ (10 mol%) was used. [c] $Ni(cod)_2$ (10 mol%) and dcypt (12 mol%) was used. [d] Starting from ethyl 4 imidazolecarboxylate **1P**. (R = Et: 33%; *t*-Amyl: 60%). [e] Starting from methy 3-((dimethylcarbamoyl)oxy)benzoate (**2f**).

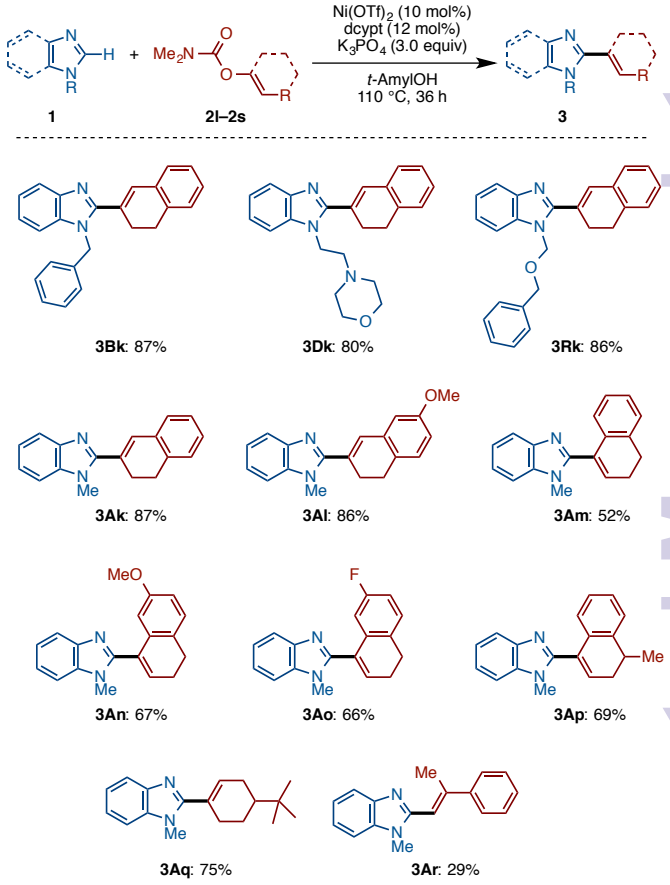
### C–H Alkenylation of Imidazoles with Enol Derivatives

With our previous success of Ni-catalyzed C–H alkenylation of oxazoles with enol derivatives,[11b,19] we envisioned that alkenylation of imidazoles would be feasible under $Ni(OTf)_2$/diphosphine/$K_3PO_4$/*t*-AmylOH system. The use of C–O alkenyl electrophiles for coupling reactions is advantageous because they can be easily prepared from the corresponding ketones and aldehydes. Motivated by the fact that alkenyl group is a versatile platform in organic synthesis, we next embarked on the development of C–H/C–O alkenylation of imidazoles (Scheme 2). Although the coupling reaction of **1A** and **2k** under $Ni(OTf)_2$/dcype catalysis is feasible, it provided alkenylated product **3Ak** in only 41% yield. While changes in base and solvent did not lead to the improvement of the reaction yield, the $Ni(OTf)_2$/dcypt catalyst dramatically boosted the reaction efficiency, providing the coupling product **3Ak** in 87% yield.




**Scheme 2.** Dramatic effect of dcypt ligand in the C–H alkenylation of imidazoles.

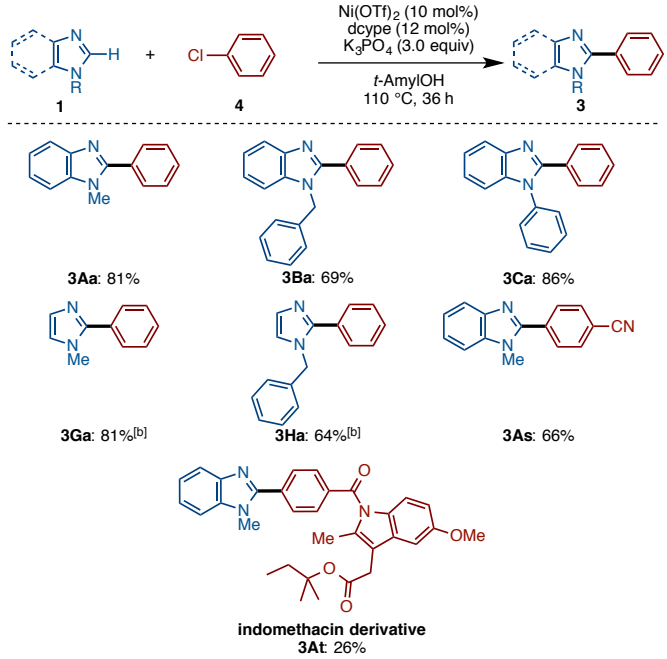
It turns out that this newly discovered $Ni(OTf)_2$/dcypt catalytic system can effectively facilitate the imidazole C–H alkenylation with broad scope (Scheme 3). As with the case of biaryl couplings, several *N*-alkylated benzimidazoles (such as **1D** and **1R**) could couple with enol carbamates. Both enol carbamates synthesized from α- and β-tetralones were reactive under the $Ni(OTf)_2$/dcypt catalyst to afford the coupling products **3Al–3Ap**. Cyclohexenyl benzimidazoles could be synthesized from cyclohexanone derived electrophiles. Aldehyde-derived enol derivative **2r** also coupled with **1A**, but its rather fast decomposition under the reaction conditions turned out to be somewhat problematic. It has been known that C–OMe[14a,e] and C–F bonds[20] could be cleaved with nickel complexes, but these groups were completely tolerated in the present Ni-catalyzed coupling reaction.




**Scheme 3.** Scope of imidazole C–H alkenylation under $Ni(OTf)_2$/dcypt. [a] Unless otherwise noted, reaction conditions were as follows: **1** (1.0 mmol), **2** (1.5 equiv), $Ni(OTf)_2$ (10 mol%), dcypt (12 mol%), $K_3PO_4$ (3.0 equiv), *t*-AmylOH (4.0 mL), 120 °C, 36 h.

### C–H Arylation of Imidazoles with Chloroarenes

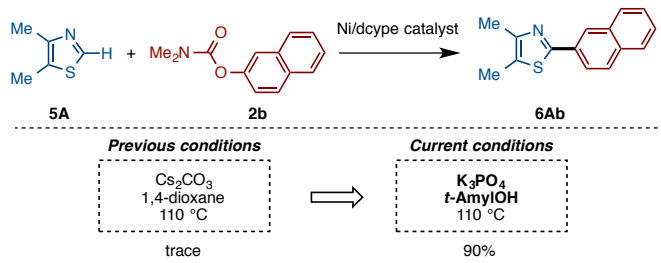
While we mainly focused on the use of C–O electrophiles in this study, it was found that the newly developed $Ni(OTf)_2$/dcype/$K_3PO_4$/*t*-AmylOH system is also effective for the imidazole arylation with chloroarenes. As shown in Scheme 4, a range of imidazoles and benzimidazoles cross-coupled with chlorobenzene derivatives under the standard conditions. *N*-Methyl, phenyl, and benzyl benzimidazoles underwent C–H arylation with chlorobenzene (**4a**) to deliver phenylated imidazoles in good yield. *N*-Methyl and benzyl imidazoles also reacted as well. Nitrile-substituted aryl chloride **4s** furnished the corresponding product **3As** in good yield. Although the reaction yield was low (26%), we could apply indomethacin derivative **4t** to the reaction to give **3At,** but with significant amounts of homodimerization by-product. Very interestingly, the reactions of aryl iodides and bromides in turn resulted in poor or zero yields of product.




**Scheme 4.** C-H arylation of imidazoles with chloroarenes under $Ni(OTf)_2$/dcype. [a] Unless otherwise noted, reaction conditions were as follows: 1 (0.40 mmol), **4** (1.5 equiv), $Ni(OTf)_2$ (10 mol%), dcype (12 mol%), $K_3PO_4$ (3.0 equiv), *t*-AmylOH (1.6 mL), 110 °C, 36 h. [b] $Ni(cod)_2$ (10 mol%) was used.

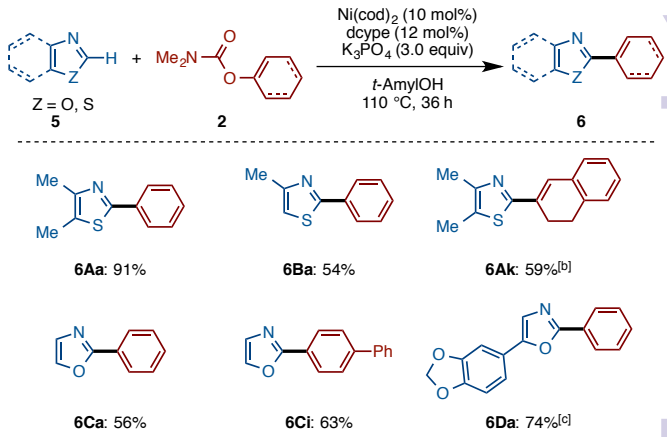
## C–H Arylation and Alkenylation of Other 1,3-Azoles.

The present catalytic protocols were found to be applicable not only for imidazoles, but also for thiazoles and oxazoles. While our previous catalyst employing $Ni(cod)_2$/dcype/$Cs_2CO_3$ in 1,4-dioxane was effective for oxazoles and thiazoles (in particular for benzo-fused substrates),[11] coupling was not efficient for relatively electron-rich azoles. For example, the reaction of 4,5-dimethylthiazole (**5A**) with naphthyl carbamate **2b** under the previous conditions furnished no coupling product. Thus, we applied our new protocol with $K_3PO_4$ and *t*-AmylOH to the reaction of previously unreactive azole **5A**. Gratifyingly, **5A** and **2b** cross-coupled very smoothly under the present conditions to furnish **6Ab** in 90% yield (Scheme 5).




**Scheme 5.** Comparison of previous and current conditions for the reaction of thiazole **5A**.

Depicted in Scheme 6 are the results of the Ni-catalyzed reactions of other 1,3-azoles. In addition to thiazoles, oxazoles were also found to be good substrates, generating the corresponding coupling products in good yields. Although previous alkenylation reactions with C–O electrophiles were limited to the reaction of oxazoles, the present Ni-catalyzed reaction in *t*-AmylOH was also applicable to thiazoles.

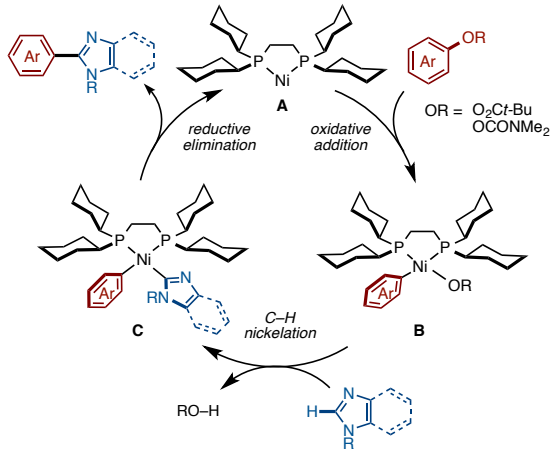



**Scheme 6.** C–H arylation and alkenylation of oxazoles and thiazoles under $Ni(OTf)_2$/dcype/$K_3PO_4$ in *t*-AmylOH. [a] Unless otherwise noted, reaction conditions were as follows: **5** (0.40 mmol), **2** (1.5 equiv), $Ni(OTf)_2$ (10 mol%), dcypt (12 mol%), $K_3PO_4$ (3.0 equiv), *t*-AmylOH (1.6 mL), 110 °C, 36 h. [b] $Ni(OTf)_2$ (10 mol%) and dcypt (12 mol%) was used. [c] $Ni(OTf)_2$ (10 mol%) and dcypt (12 mol%) was used.

## Plausible Mechanism

We succeeded in developing new catalytic systems to significantly expand the C–H/C–O coupling of 1,3-azoles with phenol/enol-based electrophiles, but we feel that the basic catalytic cycle under $Ni(OTf)_2$/diphosphine/$K_3PO_4$/*t*-AmylOH should be similar to those operating with previous conditions. First, $Ni(OTf)_2$ should be reduced to nickel(0) species by the action of diphosphine (dcype or dcypt) and/or an imidazole substrate to initiate a Ni(0)/Ni(II) redox cycle shown in Figure 2. Oxidative addition of C–O or C–Cl bond of electrophile to Ni(0) **A** affords intermediate **B**. Then, base-promoted C–H nickelation of imidazoles, followed by reductive elimination would furnish the coupling products with regeneration of the active Ni(0) species. Previously, we successfully isolated and characterized intermediate **B** by using naphthalen-2-yl pivalates as a C–O electrophile,[11c] which supports our hypothesized catalytic cycle. The remaining question is how the new conditions (particularly the activation modes of $K_3PO_4$ and *t*-AmylOH) allowed imidazoles to participate in this catalytic cycle. We are currently investing to uncover these phenomena experimentally and theoretically.

**Figure 2.** A plausible catalytic cycle.




## Conclusions

In summary, we have established a general protocol for the nickel-catalyzed C–H couplings of imidazoles. The newly discovered conditions, employing a catalytic amount of $Ni(OTf)_2$/dcype or $Ni(OTf)_2$/dcypt and $K_3PO_4$ in *t*-AmylOH, enable a direct C–C bond-forming reaction of imidazoles including C–H/C–O arylations and alkenylations. The C–H arylation of imidazoles with chloroarenes as well as that of thiazoles and oxazoles with phenol/enol derivatives can also be achieved with this catalytic system. The key to success in the new nickel-catalyzed system is the choice of a tertiary alcohol as solvent, as neither aprotic solvents nor secondary alcohols were effective. We believe that the present method provides significant opportunities to synthesize and derivatize valuable functionalized imidazoles.

## Acknowledgements

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