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Nickel-Catalyzed C–H Arylation of Benzoxazoles and Oxazoles: Benchmarking the Influence of Electronic, Steric and Leaving Group Variations in Phenolic Electrophiles

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Graphical Abstract

Keywords

homogeneous catalysis; nickel; arylation; C–H activation; azoles; pivalates; sulfonates; carbamates

1. Introduction

1.1 Significance

Transition metal-catalyzed direct arylation is an established method for the construction of biaryl bonds.¹ The vast majority of currently known direct arylations use aryl halides as electrophiles.^{1–3} Recently, there has been an increasing interest to employ phenolic electrophiles in place of aryl halides for several reasons.^{4–5} First, unlike aryl halides, the phenol precursors to phenolic electrophiles can be obtained from natural sources. Second, the synthesis of phenol derivatives often requires less harsh conditions than for aryl halides. Third, several *ortho*-substituted phenol derivatives can be accessed via directed *ortho*-

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Supplementary Data. Supplementary data containing ¹H NMR spectra (for new substrates and all catalysis products) and ¹³C NMR spectra (for all new compounds) can be found.

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lithiation strategies. Finally, phenolic electrophiles might exhibit complementary reactivity to aryl halides, thereby enabling the selective functionalization of these electrophiles at different stages of complex molecule synthesis.^{4–5} In light of these advantages several reports on transition metal catalyzed direct arylation using C–O electrophiles have been published.^{4–5} Among these, nickel-catalyzed direct arylations exhibit the broadest scope of electrophiles.^{6–8} For example, Pd-catalyzed transformations are limited to the use of sulfonates and phosphates.^{9–11} In contrast, nickel-catalyzed direct arylations are known with sulfonates, carboxylates, carbamates, sulfamates and carbonates.⁶ This advantage of Ni-catalysis can be harnessed to its fullest potential for synthetic applications once a comprehensive understanding of the relative reactivity and scope of the various phenolic electrophiles is realized. To this end, this manuscript details the *first systematic investigation of the Ni-catalyzed arylation of oxazoles with electronically and sterically diverse pivalates, tosylates, mesylates and carbamates*. The following sections detail the state-of-the-art for Ni-catalyzed arylations using C–O electrophiles and present the important questions that this manuscript seeks to address.

1.2 Background

The Itami group published the first report on Ni-catalyzed C–H arylation of azoles using phenolic electrophiles in 2012.^{6a} The reaction of benzoxazole with 2-naphthyl sulfonate, pivalate, carbonate, sulfamate and carbamate affords the desired product in excellent yields using the Ni(COD)₂/dcype catalyst system (Scheme 1a). The reaction of benzoxazole was explored with electronically varied phenyl triflates (Scheme 1b). While the reaction with phenyl triflate leads to the phenylated product in good yield (75%), the yields with electron-rich and electron-deficient triflates are significantly lower (55% and 52%). The use of electronically varied, aryl pivalates, tosylates, mesylates, carbamates and carbonates is not reported.

The reaction of azoles with pivalates bearing extended π -systems affords the products in good yields (Scheme 2a). Interestingly, however, the reaction with phenyl pivalate leads to the product in only 11% yield (Scheme 2b). In 2015, one example for the coupling of benzoxazole with aryl pivalate was reported in the context of sequential Suzuki coupling/decarbonylative C–H arylation (Scheme 2c).^{6c} The higher efficiency of C–H arylation using biphenyl pivalate (Scheme 2c) versus phenyl pivalate (Scheme 2b) may be due to the difference in the ligands employed for these reactions (dcype vs dcypt).

Recently, a more general example for the arylation of imidazoles with carbamates was published.^{6b} The reaction of *N*-methyl benzimidazole with electronically varied carbamates leads to products in modest to good yields (Scheme 3a). Three examples for the arylation of oxazoles were also reported with either phenyl carbamate or biphenyl carbamate to afford the products in modest yields (Scheme 3b).

As part of our program on Pd- and Ni-catalyzed reactions using C–O electrophiles,¹² we published the first report on the Ni-catalyzed intramolecular arylation of non-heteroaromatic C–H bonds using pivalate electrophiles (Scheme 4).^{12b} Our results are consistent with the reports by the Itami group with respect to the electronic effect of the aryl electrophile (Scheme 1b vs. Scheme 4). The reactions of electron-rich and electron-deficient pivalate-

bearing substrates afford the corresponding dibenzofuran products in lower yields than obtained with their unsubstituted counterpart. Furthermore, these reactions are most effective using pivalates. The use of carbamates, sulfonates and carbonates afford the product in lower yields.

1.3 Challenges and goals

The results detailed in Schemes 1–4 above are significant contributions to the field of Ni-catalyzed C–H arylations using C–O electrophiles. However, these reports also provoke several important unanswered questions that are detailed below:

1. The arylations presented in Schemes 1–2 are to date the only reported examples for Ni-catalyzed coupling of azoles with aryl tosylates, mesylates, pivalates and carbonates. The use of electronically and sterically varied aryl tosylates and mesylates remains elusive. Furthermore, the scope of aryl pivalates for these arylations is limited primarily to the use of electrophiles bearing extended π -systems (Scheme 2a). While Scheme 2 illustrates the two published examples for the efficient use of aryl pivalates lacking extended π -systems (3-pyridyl and biphenyl pivalate), it is ambiguous whether these reaction conditions can be extended to the use of other electronically varied aryl pivalates. Hence, a systematic investigation of Ni-catalyzed arylations with respect to electronic and steric perturbations on the C–O electrophiles is necessary to delineate the scope of these transformations.
2. A systematic study exploring the electronic influence of the C–H substrate on the efficiency of Ni-catalyzed azole arylations using various aryl electrophiles is hitherto unknown.
3. A comparative study benchmarking the relative performance and scope of various C–O electrophiles for Ni-catalyzed arylations is not reported. Such investigations are necessary to understand the similarities and differences in the reaction parameters to accomplish arylations using various phenolic electrophiles.
4. Finally, the relative rates of Ni-catalyzed azole arylations using electrophiles bearing different leaving groups remains unknown. The knowledge of relative rates is critical to judiciously engage the various C–O electrophiles selectively at different stages in the synthesis of complex molecules.

As part of our program on transition metal catalyzed arylations using C–O electrophiles,¹² this manuscript systematically addresses the aforementioned unanswered questions. Importantly, the results described herein will inform future mechanistic and synthetic investigations in the field of Ni-catalyzed C–H arylations.

2. Results and Discussion

2.1 Optimization of arylation using pivalates

Our studies commenced with the optimization of Ni-catalyzed direct arylation of 5-methyl benzoxazole (**1**) with *para*-methoxyphenyl pivalate (**AOPiv**). As shown in Table 1, the

original reaction parameters reported by the Itami group affords product **1a**, albeit in low yield (entry 1).^{6a} The use of xylene instead of dioxane affords comparable yields of **1a** (entries 1 and 2). The most significant increase in reaction efficiency was achieved using more equivalents of the pivalate electrophile leading to **1a** in 83% yield (entry 4). The use of K₃PO₄ (vs Cs₂CO₃, entries 4 and 5) or higher temperatures (entries 4 and 6) afford **1a** in similar yields. The use of Ni(OTf)₂ as the catalyst also affords product **1a**, albeit in lower yield than that obtained using Ni(COD)₂ (entries 6–7).^{6b} Interestingly, the use of dcyp^{6,13} instead of dcyp affords **1a** in excellent yields even with 1.5 equiv of the pivalate (entries 6 and 8). No product is obtained in the absence of Ni(COD)₂ or the ligand (entries 9–10). These optimization results suggest that high yields of **1a** can be obtained either using dcyp (with 3.0 equiv of pivalate, entry 6) or dcyp (with 1.5 equiv of pivalate, entry 8). Our further investigations mainly focussed on the use of dcyp conditions since this ligand is commercially available. However, dcyp was used in instances where product yields were particularly low with dcyp.

2.2 Scope of pivalates for arylation of 5-methylbenzoxazole

The coupling of 5-methyl benzoxazole (**1**) with electronically and sterically varied pivalates was explored. As depicted in Scheme 5, electron-rich, electron-neutral, and electron-deficient pivalates participate in these reactions to afford the products in good to excellent yields. However, small variations in reaction conditions are needed for efficient reactions with electron-rich versus electron-deficient pivalates. For example, relatively electron-neutral and electron-rich pivalates perform well under the optimal conditions for the reaction of *p*-methoxyphenyl pivalate (Scheme 5, products **1a–1d**). However, electron-deficient pivalates afford the corresponding products **1f–1g** in good yields with 1.5 equivalents of the electrophile at 140 °C. Furthermore, dcyp is more effective than dcyp for arylations using these electron-deficient electrophiles. Finally, ester-substituted aryl pivalates lead to products (**1h** and **1i**) in higher yields with K₃PO₄ than Cs₂CO₃. Interestingly, sterically hindered *ortho*-methylphenyl pivalate affords product **1j** in low yield.

2.3 Scope of azoles in reactions with pivalates

The reaction of pivalates with diverse azole substrates was explored next (Scheme 6). These transformations are compatible with ethers, fluorine, trifluoromethyl and benzylic alkyl groups. Benzoxazoles are generally more effective than phenyl oxazoles (cf. **2c–6c** vs. **8c–10c**). Analogous to 5-methylbenzoxazole reactions, the scope of phenyl oxazole arylation is also general with respect to the electronics on the pivalate electrophile (**8c** and **8f**). Additionally, there is a noticeable electronic effect with respect to the C–H substrate for these arylations. Electron-rich and electron-neutral substrates **8** and **9** participate in these reactions to afford the products (**8c** and **9c**) in lower yields (57% and 63%) than the electron-deficient oxazole **10** under identical reaction conditions (86% yield of **10c**).¹⁴ Similarly product **4c** is obtained in lower yield than **3c** under the same conditions (68% versus 91% for **4c** and **3c** respectively). The lower yields of **8c**, **9c** and **4c** compared to **10c** and **3c**, could partly be due to the diminished acidity of the azole C–H bond undergoing functionalization. The yield of **4c** is enhanced (90% yield), however, using dcyp as the ligand.

2.4 Arylation using sulfonates

We next explored reaction conditions for coupling of azoles with tosylates and mesylates (Scheme 7). This is an advance over the previously published report,^{6a} which primarily focused on the use of the more expensive and less bench-stable triflates (Scheme 1).

The couplings of 5-methyl benzoxazole with electronically varied tosylates results in lower yields of products compared to reactions of the corresponding pivalates (Scheme 7a vs Scheme 5). Improved yields are obtained with the more atom-economical mesylates (Scheme 7b). Similar to our observation with pivalates (Scheme 5), an *ortho*-substituted mesylate affords the product (**1j**) in lower yields than *para*- and *meta*-substituted mesylates. Finally, the trends for couplings using electronically varied azoles are comparable to those observed using pivalates (Scheme 7c).

2.5 Arylation using carbamates

The scope of the arylations with carbamates is shown in Scheme 8. These reactions are more effective with K₃PO₄ instead of Cs₂CO₃.^{6b} Under the optimal conditions the scope of these reactions are similar to that of pivalates and mesylates described above.

2.6 Competition studies

As mentioned in the introduction, to date Ni-catalysis exhibits the broadest scope of phenolic electrophiles (bearing different leaving groups) for direct arylations.⁶ This broad scope can be synthetically useful if one electrophile can be selectively engaged in direct arylations in the presence of other electrophiles. To this end, we conducted systematic competition studies to evaluate the relative reactivity of various electrophiles. The reaction of 5-methyl benzoxazole with equimolar amounts of two electronically similar electrophiles with different leaving groups was explored (Table 2). The relative amounts of products **1c** and **1b** obtained from these competition reactions reflect the relative rates of the reaction of the two electrophiles in the reaction vessel. For example, the reaction of equimolar amounts of PhOPiv (1.5 equiv) and *p*-MeC₆H₄OCONEt₂ (1.5 equiv) with 5-methylbenzoxazole (1.0 equiv) affords **1c** and **1b** in 71% and 16% yields respectively (entry 1). These results (see also entry 4) suggest that the pivalate outcompetes the carbamate in these arylations, which is consistent with the better leaving group ability of pivalates. Similarly, and as expected, the mesylate undergoes arylation at a faster rate than the carbamate (entries 3 and 6). Interestingly, the vastly different leaving group abilities of mesylate versus pivalate translate into a small difference in the relative rates for the direct arylation using these electrophiles (entries 2 and 5). These results imply the following order for the relative rates of arylation: mesylate > pivalate > carbamate.

Importantly, the reactivity order in these studies is the same regardless of which electrophile has phenyl or *p*-tolyl group (cf. entries 1–3 vs. 4–6). Overall, the results in entries 1–6 suggest that the highest difference in relative rates exists between mesylates and carbamates. Furthermore, the degree of selectivity between two leaving groups can be altered with different ligands. When competition studies were done using dcype instead of dcyp (entries 7–9), the differences in relative reaction rates decreased for all three combinations of leaving groups. The comparison between the results in entries 1–3 vs. 7–9 exemplifies the potential

for further ligand optimizations to enhance the selectivity between electrophiles bearing different leaving groups.

As detailed above the highest difference in relative rates of arylation is exhibited in the competition between the mesylate and the carbamate electrophiles (Table 2, entries 3, 6 and 9). Consistent with this observation the reaction of 5-methyl benzoxazole with the electrophile bearing both the mesylate and the carbamate groups affords the product (**A**) resulting from the selective functionalization of the mesylate group (Scheme 9). Product **B** obtained via diarylation of **1** is also observed. Importantly, however, product (**C**) resulting from the selective functionalization of the carbamate is not observed.¹⁵ These results lend credence to the applicability of the competition studies detailed in Table 2 to the selective functionalization of leaving groups at different stages in the context of multi-step syntheses.

3. Conclusion

This manuscript details the first systematic elucidation of the electronic and steric influences of diverse azoles and phenolic electrophiles in Ni-catalyzed direct arylations. The first general report on the direct arylation of azoles with pivalates is described. The reaction of azoles with aryl tosylates, mesylates, and carbamates are also presented. Four variables critical to the optimization of these reactions are: base (Cs_2CO_3 or K_3PO_4), electrophile equivalents (1.5 or 3.0 equiv), ligands (dcype to dcypt), and temperature (100–140 °C). Establishing the general scope of these Ni-catalyzed arylations set the stage for investigating the relative rates of arylations with electrophiles bearing different leaving groups. Competition studies reveal the following order for relative rates of arylation: mesylates > pivalates > carbamates. Furthermore, these studies demonstrate the important role of ligand optimization in further enhancing the selectivity between electrophiles. Detailed mechanistic investigations to elucidate the differences in optimal reaction parameters for various combinations of azoles/electrophiles are underway and will be reported in due course. Such studies are pivotal to further broadening the scope and selectivity for these Ni-catalyzed arylations.

4. Experimental

4.1 General

NMR spectra were obtained on a Bruker 400 (399.96 MHz for ^1H ; 100.57 MHz for ^{13}C) spectrometer. ^1H NMR chemical shifts are reported in parts per million (ppm) relative to TMS, with the residual solvent peak used as an internal reference. Multiplicities are reported as follows: singlet (s), doublet (d), doublet of doublets (dd), triplet of doublets (td), triplet (t), quartet (q), doublet of triplets (dt), triplet of triplets (tt), multiplet (m), and broad resonance (br). IR spectra were obtained on a Thermo scientific Nicolet iS5 iD5 ATR spectrometer. Melting points were obtained on a Thomas Hoover melting point apparatus.

4.2 Materials

1,2-Bis(dicyclohexylphosphino)ethane (dcype) and 5-methylbenzoxazole were obtained from Aldrich and used as received. Benzoxazole was obtained from TCI America and used as received. $\text{Ni}(\text{COD})_2$ and $\text{Ni}(\text{OTf})_2$ were obtained from Strem chemical and used as

received. Cesium carbonate, TosMic (Tosylmethylisocyanide) and K_3PO_4 were obtained from Acros and used as received. Benzoxazole substrates (**4**, **5** and **6**) were prepared using literature procedures.¹⁶ Phenyl oxazole substrates **8–10** were prepared using literature procedures.¹⁷ The pivalates, tosylates, mesylates and carbamates were prepared using literature procedures.¹⁸ 2-Fluoro-4-methoxy benzaldehyde, and 2-fluoro-5-methyl benzaldehyde were obtained from Matrix Scientific and used as received. 2-Fluoro-5-(trifluoromethyl) benzaldehyde was obtained from Alfa Aesar and used as received. K_2CO_3 was obtained from JT Baker and used as received. 3,4-Bis-(dicyclohexylphosphino)thiophene (dcypt) was prepared using a literature procedure.¹⁹ Anhydrous *p*-xylene and 1,4-dioxane were obtained from Aldrich and used as received. Other solvents were obtained from Fisher Chemical or VWR Chemical and used without further purification. Flash chromatography was performed on EM Science silica gel 60 (0.040–0.063 mm particle size, 230–400 mesh) and thin layer chromatography was performed on Analtech TLC plates pre-coated with silica gel 60 F₂₅₄.

4.3 Synthesis and Characterization of Substrates

4.3.1. 5-(2-fluoro-4-methoxyphenyl)-1,3-oxazole (11)—To an oven dried 20 mL scintillation vial under ambient atmosphere, was added 2-fluoro-4-methoxy benzaldehyde (617 mg, 4.00 mmol, 1.0 equiv), TosMic (929 mg, 4.76 mmol, 1.2 equiv), K_2CO_3 (1.82 g, 13.2 mmol, 3.3 equiv) and MeOH (8.5 mL). The vial was sealed with a Teflon lined cap and stirred at 70 °C for 2 h. Two of these same reactions were set up and combined for purification. At the end of the reaction the reaction vials were cooled to room temperature and the reaction mixture was filtered to remove the solid residues. The filtrate was concentrated and chromatographed on a silica gel column using 80/20 hexanes/EtOAc (R_f = 0.30 in 80% hexanes/20% ethyl acetate) yielded product **11** as a light yellow solid (1.27 g, 82% yield). mp = 63–64 °C. IR (neat): 1628, 1574, 1509, 1486, 1465, 1332, 1308, 1268, 1245, 1192, 1160, 1098, 1040, 1019, 951, 915, 834, 640, 629, 569 cm^{-1} . 1H NMR ($CDCl_3$): δ 7.90 (s, 1H), 7.66 (t, J = 8.6 Hz, 1H), 7.37 (d, J = 3.8 Hz, 1H), 6.79 (dd, J = 8.4, 2.5 Hz, 1H), 6.72 (dd, J = 12.6, 2.5 Hz, 1H), 3.84 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 160.8 (d, J = 10.7 Hz), 159.6 (d, J = 251 Hz), 149.5, 146.0 (d, J = 3.0 Hz), 126.8 (d, J = 5.0 Hz), 123.7 (d, J = 11.6 Hz), 110.5 (d, J = 2.9 Hz), 108.9 (d, J = 13.7 Hz), 102.0 (d, J = 24.3 Hz), 55.6. HRMS Calcd for $C_{10}H_8FNO_2$ 193.0539; Found: 193.0538.

4.3.2. 5-(2-fluoro-5-methylphenyl)-1,3-oxazole (12)—To an oven dried 20 mL scintillation vial under ambient atmosphere, was added 2-fluoro-5-methyl benzaldehyde (552 mg, 4.00 mmol, 1.0 equiv), TosMic (929 mg, 4.76 mmol, 1.2 equiv), K_2CO_3 (1.82 g, 13.2 mmol, 3.3 equiv) and MeOH (8.5 mL). The vial was sealed with a Teflon lined cap and stirred at 70 °C for 2 h. Two of these same reactions were set up and combined for purification. At the end of the reaction the reaction vials were cooled to room temperature and the reaction mixture was filtered to remove the solid residues. The filtrate was concentrated and chromatographed on a silica gel column using 80/20 hexanes/EtOAc (R_f = 0.46 in 80% hexanes/20% ethyl acetate) yielded product **12** as a light yellow solid (1.42 g, 100% yield). mp = 73–74 °C. IR (neat): 1500, 1215, 1112, 1093, 1044, 954, 814, 757, 642 cm^{-1} . 1H NMR ($CDCl_3$): δ 7.94 (s, 1H), 7.56 (d, J = 7.2 Hz, 1H), 7.49 (d, J = 3.9 Hz, 1H), 7.12–7.02 (multiple peaks, 2H), 2.38 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 157.0 (d, J = 247 Hz),

150.0, 146.0 (d, $J = 3.0$ Hz), 133.9 (d, $J = 3.6$ Hz), 130.1 (d, $J = 8.0$ Hz), 126.3 (d, $J = 2.9$ Hz), 125.5 (d, $J = 12.4$ Hz), 115.55 (d, $J = 20.5$ Hz), 115.58 (d, $J = 14.5$ Hz), 20.6. HRMS Calcd for $C_{10}H_8FNO$ 177.0590; Found: 177.0587.

4.3.3. 5-[2-fluoro-5-(trifluoromethyl)phenyl]-1,3-oxazole (13)—To an oven dried 20 mL scintillation vial under ambient atmosphere, was added 2-fluoro-5-trifluoromethyl benzaldehyde (768 mg, 4.00 mmol, 1.0 equiv), TosMic (929 mg, 4.76 mmol, 1.2 equiv), K_2CO_3 (1.82 g, 13.2 mmol, 3.3 equiv) and MeOH (8.5 mL). The vial was sealed with a Teflon lined cap and stirred at 70 °C for 2 h. Two of these same reactions were set up and combined for purification. At the end of the reaction the reaction vials were cooled to room temperature and the reaction mixture was filtered to remove the solid residues. The filtrate was concentrated and chromatographed on a silica gel column using the Biotage flash purification system ($R_f = 0.50$ in 90% hexanes/10% ethyl acetate) yielded product **13** as a pale yellow solid (778 mg, 42% yield). mp = 43–44 °C. IR (neat): 1509, 1342, 1319, 1265, 1233, 1165, 1141, 1072, 1041, 949, 899, 891, 847, 826, 682, 640, 619, 585 cm^{-1} . 1H NMR ($CDCl_3$): δ 8.07 (dd, $J = 6.5, 2.2$ Hz, 1H), 8.00 (s, 1H), 7.62–7.58 (m, 1H), 7.59 (d, $J = 4.1$ Hz, 1H), 7.30 (t, $J = 9.5$ Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 160.2 (d, $J = 256$ Hz), 150.7, 144.5 (d, $J = 3.3$ Hz), 127.5 (qd, $J = 33, 3.6$ Hz), 126.9 (d, $J = 13.0$ Hz), 126.7 (dq, $J = 9.5, 3.6$ Hz), 123.7 (m), 123.4 (q, $J = 270$ Hz), 117.0 (d, $J = 14.5$ Hz), 116.7 (d, $J = 22.4$ Hz). HRMS Calcd for $C_{10}H_5F_4NO$ 231.0307; Found: 231.0312.

4.3.4. (3-methanesulfonylphenyl) N,N-diethyl carbamate (electrophile in Scheme 9)—To an oven dried 100 mL Schlenk flask was added NaH (70.1 mg, 2.92 mmol, 1.1 equiv) and anhydrous THF (2.3 mL) in the glove box. The flask was secured with a septum, taken out of the glove box and cooled to 0 °C. A solution of (3-hydroxyphenyl)methanesulfonate (500 mg, 2.66 mmol, 1.0 equiv) in THF (2.3 mL) was added dropwise to the NaH solution at 0 °C. The resulting mixture was stirred for 1 h at 0 °C. To the resulting mixture was added *N,N*-diethylcarbamoyl chloride dropwise at 0 °C. The reaction mixture was allowed to warm to room temperature and was stirred at room temperature overnight. The solution was then cooled to 0 °C and quenched with water. The solution was transferred to a separatory funnel, diluted with EtOAc (20 mL) and washed with NaCl (20 mL). The aqueous and organic layers were separated and the aqueous layer was extracted with EtOAc (3 $\times$ 20 mL). The combined organic layers were washed with brine (20 mL), dried over $MgSO_4$ and concentrated under vacuum. The crude product was purified using chromatography on silica gel ($R_f = 0.30$ in 70% hexanes/30% ethyl acetate) to yield product as a light yellow, viscous oil (492 mg, 64% yield). IR (neat): 2976, 1714, 1472, 1417, 1364, 1265, 1239, 1219, 1181, 1152, 1114, 1078, 965, 924, 878, 818, 778, 752, 709, 683 cm^{-1} . 1H NMR ($CDCl_3$): δ 7.42–7.37 (m, 1H), 7.15–7.12 (multiple peaks, 3H), 3.46–3.36 (multiplet, 4H), 3.15 (s, 3H), 1.27–1.19 (multiplet, 6H). ^{13}C NMR ($CDCl_3$): δ 153.4, 152.3, 149.3, 130.0, 120.8, 118.5, 116.0, 42.3, 41.9, 37.3, 14.2, 13.3.

4.4 C–H Arylation of Aryl Pivalates

General Procedure (A) for C–H Arylations for solid electrophiles— $Ni(COD)_2$, ligand (dcype or dcypt), base (CS_2CO_3 or K_3PO_4), aryl electrophile (pivalates, mesylates or carbamates) and azole were weighed into in an oven dried 20 mL scintillation vial in the

glove box. Xylene was added, the vial was sealed with a Teflon lined cap, taken out of the glove box and the reaction mixture was allowed to stir at the indicated temperature for the indicated time. The reaction mixture was cooled to room temperature and filtered through a 1.0 inch plug of silica gel, eluting with Et₂O (125 mL). The filtrate was concentrated and chromatographed on a silica gel column to afford the product. General Procedure (B) for C–H Arylations for solid electrophiles: Tosylate was weighed into an oven dried 20 mL scintillation vial. The vial was taken into the glove box and Ni(COD)₂, ligand (dcype or dcpyt), base (Cs₂CO₃ or K₃PO₄), and azole were added to it. Xylene was added, the vial was sealed with a Teflon lined cap, taken out of the glove box and the reaction mixture was allowed to stir at the indicated temperature for the indicated time. The reaction mixture was cooled to room temperature and filtered through a 1.0 inch plug of silica gel, eluting with Et₂O (125 mL). The filtrate was concentrated and chromatographed on a silica gel column to afford the product.

General Procedure (C) for C–H Arylations for liquid electrophiles—Ni(COD)₂, ligand (dcype or dcpyt), base (Cs₂CO₃ or K₃PO₄), and azole were weighed into in an oven dried 20 mL scintillation vial in the glove box. A xylene solution of the aryl electrophile (pivalates, mesylates or carbamates) was added to the reaction mixture. The reaction vial was sealed with a Teflon lined cap, taken out of the glove box and the reaction mixture was allowed to stir at the indicated temperature for the indicated time. The reaction mixture was cooled to room temperature and filtered through a 1.0 inch plug of silica gel, eluting with Et₂O (125 mL). The filtrate was concentrated and chromatographed on a silica gel column to afford the product.

General Procedure (D) for C–H Arylations for liquid electrophiles and liquid azoles—Ni(COD)₂, ligand (dcype or dcpyt), and base (Cs₂CO₃ or K₃PO₄) were weighed into in an oven dried 20 mL scintillation vial in the glove box. A xylene (1.0 mL) solution of the pivalate and a xylene (1.0 mL) solution of the azole was added to the reaction mixture. The reaction vial was sealed with a Teflon lined cap, taken out of the glove box and the reaction mixture was allowed to stir at the indicated temperature for the indicated time. The reaction mixture was cooled to room temperature and filtered through a 1.0 inch plug of silica gel, eluting with Et₂O (125 mL). The filtrate was concentrated and chromatographed on a silica gel column to afford the product.

4.4.1 Procedures and spectral characterization of arylation products using pivalates (Scheme 5)

4.4.1.1. 2-(4-methoxyphenyl)-5-methyl-1,3-benzoxazole (1a): Following general procedure C, 4-methoxy phenyl pivalate (312 mg, 1.50 mmol, 3.0 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.30 in 90% hexanes/10% ethyl acetate) yielded product **1a** as a white solid (106 mg, 89% yield). mp = 109–110 °C. The spectroscopic data is identical to that previously reported in the literature.^{12c}

4.4.1.2. 2-(4-methylphenyl)-5-methyl-1,3-benzoxazole (1b): Following general procedure **A**, 4-methyl phenyl pivalate (288 mg, 1.50 mmol, 3.0 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.30 in 95% hexanes/5% ethyl acetate) yielded product **1b** as a white solid (105 mg, 94% yield). mp = 135–136 °C. The spectroscopic data is identical to that previously reported in the literature.^{10c}

4.4.1.3. 2-phenyl-5-methyl-1,3-benzoxazole (1c): Following general procedure **C**, phenyl pivalate (134 mg, 0.75 mmol, 3.0 equiv), 5-methylbenzoxazole (33.3 mg, 0.250 mmol, 1.0 equiv), Ni(COD)₂ (6.90 mg, 0.025 mmol, 0.10 equiv), dcype (21.1 mg, 0.05 mmol, 0.20 equiv), Cs₂CO₃ (122 mg, 0.375 mmol, 1.5 equiv), and anhydrous xylene (1.0 mL) were combined in a 4 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.39 in 95% hexanes/5% ethyl acetate) yielded product **1c** as a white solid (49.0 mg, 94% yield). mp = 104–106 °C. The spectroscopic data is identical to that previously reported in the literature.²⁰

4.4.1.4. 2-(3-methoxyphenyl)-5-methyl-1,3-benzoxazole (1d): Following general procedure **C**, *meta*-methoxy phenyl pivalate (312 mg, 1.50 mmol, 3.0 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.34 in 90% hexanes/10% ethyl acetate) yielded product **1d** as a white solid (106 mg, 89% yield). mp = 107–110 °C. The spectroscopic data is identical to that previously reported in the literature.^{10c}

4.4.1.5. 2-(4-fluorophenyl)-5-methyl-1,3-benzoxazole (1e): Following general procedure **C**, *para*-fluoro phenyl pivalate (294 mg, 1.50 mmol, 3.0 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcyp (47.7 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 24 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.4 in 95% hexanes/5% ethyl acetate) yielded product **1e** as a white solid (106 mg, 93% yield). mp = 132–134 °C. The spectroscopic data is identical to that previously reported in the literature.²¹

4.4.1.6. 2-[3-(trifluoromethyl)phenyl]-5-methyl-1,3-benzoxazole (1f): Following general procedure **C**, *meta*-trifluoromethyl phenyl pivalate (185 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcyp (47.7 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction

mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.42 in 95% hexanes/5% ethyl acetate) yielded product **1f** as a white solid (118 mg, 85% yield). mp = 115–117 °C. The spectroscopic data is identical to that previously reported in the literature.²²

4.4.1.7. 2-[4-(trifluoromethyl)phenyl]-5-methyl-1,3-benzoxazole (1g): Following general procedure **A**, *para*-trifluoromethyl phenyl pivalate (185 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.41 in 95% hexanes/5% ethyl acetate) yielded product **1g** as a white solid (70.4 mg, 51% yield). mp = 127–130 °C. The spectroscopic data is identical to that previously reported in the literature.²³

4.4.1.8. ethyl 3-(5-methyl-1,3-benzoxazol-2-yl)benzoate (1h): Following general procedure **C**, 3-(2,2-dimethyl-1-oxopropoxy)-ethyl ester benzoic acid (188 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.01 mmol, 0.20 equiv), K₃PO₄ (159 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.40 in 90% hexanes/10% ethyl acetate) yielded product **1h** as a white solid (106 mg, 76% yield). mp = 97–98 °C. ¹H NMR (CDCl₃): δ 8.89 (t, J = 1.7 Hz, 1H), 8.43 (dt, J = 7.8, 1.5 Hz, 1H), 8.21 (dt, J = 7.8, 1.5 Hz, 1H), 7.61 (t, J = 7.8 Hz, 1H), 7.58 (s, 1H), 7.49 (d, J = 8.3 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 4.45 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 1.45 (t, J = 7.1 Hz, 3H). ¹³C NMR (CDCl₃): δ 165.7, 162.1, 149.0, 142.1, 134.5, 132.1, 131.45, 131.37, 129.0, 128.4, 127.7, 126.5, 120.0, 110.0, 61.3, 21.5, 14.3. IR (neat): 1716, 1455, 1423, 1311, 1285, 1247, 1195, 1123, 1109, 1056, 1021, 948, 921, 889, 823, 804, 765, 756, 710, 677, 614, 597 cm⁻¹. HRMS Calcd for C₁₇H₁₅NO₃ 281.1052; Found: 281.1061.

4.4.1.9. ethyl 4-(5-methyl-1,3-benzoxazol-2-yl)benzoate (1i): Following general procedure **A**, 4-(2,2-dimethyl-1-oxopropoxy)-ethyl ester benzoic acid (188 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), K₃PO₄ (212 mg, 1.00 mmol, 2.0 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.40 in 90% hexanes/10% ethyl acetate) yielded product **1i** as a white solid (101 mg, 72% yield). mp = 153–154 °C. ¹H NMR (CDCl₃): δ 8.31 (d, J = 8.3 Hz, 2H), 8.19 (d, J = 8.3 Hz, 2H), 7.58 (s, 1H), 7.48 (d, J = 8.3 Hz, 1H), 7.20 (d, J = 8.4 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 2.50 (s, 3H), 1.43 (t, J = 7.1 Hz, 3H). ¹³C NMR (CDCl₃): δ 165.8, 161.9, 149.0, 142.1, 134.6, 132.6, 131.0, 129.9, 127.2, 126.8, 120.1, 110.0, 61.2, 21.4, 14.2. IR (neat): 1715, 1407, 1267, 1250, 1101, 1055, 1012, 804, 777, 714 cm⁻¹. HRMS Calcd for C₁₇H₁₅NO₃ 281.1052; Found: 281.1058.

4.4.1.10. 2-(2-methylphenyl)-5-methyl-1,3-benzoxazole (1j): Following general procedure **C**, *ortho*-methyl phenyl pivalate (288 mg, 1.50 mmol, 3.0 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.1 mmol, 0.20 equiv), K₃PO₄ (318 mg, 1.50 mmol, 3.0 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 24 h. Chromatography on a silica gel column using 50/50 CH₂Cl₂/hexanes (R_f = 0.30 in 50% CH₂Cl₂/50% hexanes) yielded product **1j** as a white solid (48.3 mg, 44% yield). mp = 75–77 °C. The spectroscopic data is identical to that previously reported in the literature.

4.4.2 Procedures and Spectral Characterization of Arylation products using pivalates (Scheme 6)

4.4.2.1. 2-phenyl-1,3-benzoxazole (2c): Following general procedure **D**, phenyl pivalate (267 mg, 1.50 mmol, 3.0 equiv), benzoxazole (59.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.25 in 95% hexanes/5% ethyl acetate) yielded product **2c** as a white solid (88.6 mg, 91% yield). mp = 101–103 °C. The spectroscopic data is identical to that previously reported in the literature.^{10c}

4.4.2.2. 2-phenyl-5-methoxy-1,3-benzoxazole (3c): Following general procedure **C**, phenyl pivalate (134 mg, 0.75 mmol, 3.0 equiv), 5-methoxybenzoxazole (37.3 mg, 0.250 mmol, 1.0 equiv), Ni(COD)₂ (6.90 mg, 0.025 mmol, 0.10 equiv), dcype (21.1 mg, 0.05 mmol, 0.20 equiv), Cs₂CO₃ (122 mg, 0.375 mmol, 1.5 equiv), and anhydrous xylene (1.0 mL) were combined in a 4 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.42 in 90% hexanes/10% ethyl acetate) yielded product **3c** as a white solid (51.4 mg, 91% yield). mp = 75–78 °C. The spectroscopic data is identical to that previously reported in the literature.²⁴

4.4.2.3. 2-phenyl-6-methoxy-1,3-benzoxazole (4c)

Using dcype: Following general procedure **C**, phenyl pivalate (134 mg, 0.75 mmol, 3.0 equiv), 6-methoxybenzoxazole (37.3 mg, 0.250 mmol, 1.0 equiv), Ni(COD)₂ (6.90 mg, 0.025 mmol, 0.10 equiv), dcype (21.1 mg, 0.05 mmol, 0.20 equiv), Cs₂CO₃ (122 mg, 0.375 mmol, 1.5 equiv), and anhydrous xylene (1.0 mL) were combined in a 4 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 18 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.34 in 90% hexanes/10% ethyl acetate) yielded product **4c** as a white solid (38.2 mg, 68% yield).

Using dcypt: Following general procedure **C**, phenyl pivalate (267 mg, 1.50 mmol, 3.0 equiv), 6-methoxybenzoxazole (74.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 18 h. Chromatography on a silica gel

column using 90/10 hexanes/EtOAc ($R_f = 0.34$ in 90% hexanes/10% ethyl acetate) yielded product **4c** as a white solid (115 mg, 90% yield). mp = 64–67 °C. The spectroscopic data is identical to that previously reported in the literature.²⁵

4.4.2.4. 2-phenyl-6-methyl-1,3-benzoxazole (5c): Following general procedure **C**, phenyl pivalate (267 mg, 1.50 mmol, 3.0 equiv), 6-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 20 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc ($R_f = 0.39$ in 95% hexanes/5% ethyl acetate) yielded product **5c** as a white solid (98.7 mg, 94% yield). mp = 92–94 °C. The spectroscopic data is identical to that previously reported in the literature.²¹

4.4.2.5. 2-phenyl-4-methyl-1,3-benzoxazole (6c): Following general procedure **D**, phenyl pivalate (267 mg, 1.50 mmol, 3.0 equiv), 4-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 18 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc ($R_f = 0.40$ in 95% hexanes/5% ethyl acetate) yielded product **6c** as a white solid (95.2 mg, 91% yield). mp = 91–93 °C. The spectroscopic data is identical to that previously reported in the literature.²⁶

4.4.2.6. 2-phenyl-1,3-benzothiazole (7c): Following general procedure **C**, phenyl pivalate (267 mg, 1.50 mmol, 3.0 equiv), benzothiazole (67.9 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcyp (47.7 mg, 0.10 mmol, 0.20 equiv), K₃PO₄ (318 mg, 1.50 mmol, 3.0 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 19 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc ($R_f = 0.30$ in 95% hexanes/5% ethyl acetate) yielded product **7c** as a white solid (64.4 mg, 61% yield). mp = 112–114 °C. The spectroscopic data is identical to that previously reported in the literature.²¹

4.4.2.7. 2,5-diphenyl-1,3-oxazole (8c): Following general procedure **C**, phenyl pivalate (214 mg, 1.20 mmol, 3.0 equiv), phenyl oxazole (58.1 mg, 0.400 mmol, 1.0 equiv), Ni(COD)₂ (11.0 mg, 0.04 mmol, 0.10 equiv), dcype (33.8 mg, 0.08 mmol, 0.20 equiv), Cs₂CO₃ (195 mg, 0.6 mmol, 1.5 equiv), and anhydrous xylene (1.6 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 21 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc ($R_f = 0.30$ in 95% hexanes/5% ethyl acetate) yielded product **8c** as a white solid (50.2 mg, 57% yield). mp = 72–74 °C. The spectroscopic data is identical to that previously reported in the literature.²⁷

4.4.2.8. 5-(4-methoxyphenyl)-2-phenyl-1,3-oxazole (9c): Following general procedure **C**, phenyl pivalate (134 mg, 0.75 mmol, 3.0 equiv), 5-(4-methoxyphenyl)-1,3-oxazole (43.8 mg, 0.250 mmol, 1.0 equiv), Ni(COD)₂ (6.90 mg, 0.025 mmol, 0.10 equiv), dcype (21.1 mg, 0.05 mmol, 0.20 equiv), Cs₂CO₃ (122 mg, 0.375 mmol, 1.5 equiv), and anhydrous xylene (1.0 mL) were combined in a 4 mL scintillation vial. The reaction mixture was allowed to

stir at 140 °C for 21 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.29 in 95% hexanes/5% ethyl acetate) yielded product **9c** as a white solid (39.4 mg, 63% yield). mp = 80–82 °C. The spectroscopic data is identical to that previously reported in the literature.²⁸

4.4.2.9. 5-[4-(trifluoromethyl)phenyl]-2-phenyl-1,3-oxazole (10c): Following general procedure **C**, phenyl pivalate (134 mg, 0.75 mmol, 3.0 equiv), 5-[4-(trifluoromethyl)phenyl]-1,3-oxazole (53.3 mg, 0.250 mmol, 1.0 equiv), Ni(COD)₂ (6.90 mg, 0.025 mmol, 0.10 equiv), dcype (21.1 mg, 0.05 mmol, 0.20 equiv), Cs₂CO₃ (122 mg, 0.375 mmol, 1.5 equiv), and anhydrous xylene (1.0 mL) were combined in a 4 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 21 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.32 in 95% hexanes/5% ethyl acetate) yielded product **10c** as a white solid (61.9 mg, 86% yield). mp = 106–108 °C. The spectroscopic data is identical to that previously reported in the literature.²⁹

4.4.2.10. 5-phenyl-2-[3-(trifluoromethyl)phenyl]-1,3-oxazole (8f): Following general procedure **C**, *meta*-trifluoromethylphenyl pivalate (185 mg, 0.75 mmol, 1.5 equiv), phenyloxazole (72.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcyp (47.7 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.36 in 90% hexanes/10% ethyl acetate) yielded product **8f** as a white solid (68.0 mg, 47% yield). mp = 127–129 °C. The spectroscopic data is identical to that previously reported in the literature.³⁰

4.4.2.11. 5-phenyl-2-[2-methylphenyl]-1,3-oxazole (8j): Following general procedure **C**, *ortho*-methylphenyl pivalate (230 mg, 1.20 mmol, 3.0 equiv), phenyloxazole (58.1 mg, 0.400 mmol, 1.0 equiv), Ni(COD)₂ (11.0 mg, 0.04 mmol, 0.10 equiv), dcype (33.8 mg, 0.08 mmol, 0.20 equiv), Cs₂CO₃ (195 mg, 0.600 mmol, 1.5 equiv), and anhydrous xylene (1.6 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 120 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.30 in 95% hexanes/5% ethyl acetate) yielded product **8j** as a white solid (54.0 mg, 57% yield). mp = 87–89 °C. The spectroscopic data is identical to that previously reported in the literature.^{10b}

4.4.2.12. 5-(2-fluoro-4-methoxyphenyl)-2-phenyl-1,3-oxazole (11c): Following general procedure **C**, phenyl pivalate (267 mg, 1.5 mmol, 3.0 equiv), 5-(2-fluoro-4-methoxyphenyl)-oxazole (96.7 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcyp (47.7 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.75 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 20 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.27 in 90% hexanes/10% ethyl acetate) yielded product **11c** as a white solid (105 mg, 78% yield). mp = 93–95 °C. ¹H NMR (CDCl₃): δ 8.11 (dd, J = 8.0, 1.8 Hz, 2H), 7.77 (t, J = 8.6 Hz, 1H), 7.50–7.45 (multiple peaks, 4H), 6.82 (dd, J = 8.8, 2.6

Hz, 1H), 6.75 (dd, $J = 12, 2.5$ Hz, 1H), 3.86 (s, 3H). ^{13}C NMR (CDCl_3): δ 159.7 (d, $J = 249$ Hz), 160.7 (d, $J = 10.9$ Hz), 160.2, 145.8 (d, $J = 3.5$ Hz), 130.3, 128.8, 127.3, 126.6, 126.2, 125.7 (d, $J = 11.7$ Hz), 110.5 (d, $J = 2.9$ Hz), 109.2 (d, $J = 13.4$ Hz), 102.1 (d, $J = 24.6$ Hz), 55.7. IR (neat): 1628, 1499, 1480, 1464, 1443, 1325, 1308, 1286, 1269, 1192, 1116, 1021, 961, 955, 837, 814, 779, 706, 688, 633, 618, 579 cm^{-1} . HRMS Calcd for $\text{C}_{16}\text{H}_{12}\text{FNO}_2$ 269.0852; Found: 269.0842.

4.4.2.13. 5-(2-fluoro-5-methylphenyl)-2-phenyl-1,3-oxazole (12c): Following general procedure C, phenyl pivalate (267 mg, 1.5 mmol, 3.0 equiv), 5-(2-fluoro-5-methylphenyl)-oxazole (88.8 mg, 0.500 mmol, 1.0 equiv), $\text{Ni}(\text{COD})_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), Cs_2CO_3 (244 mg, 0.75 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 20 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc ($R_f = 0.30$ in 95% hexanes/5% ethyl acetate) yielded product **12c** as a white solid (96.2 mg, 76% yield). mp = 86–87 °C. ^1H NMR (CDCl_3): δ 8.15–8.13 (multiple peaks, 2H), 7.65 (d, $J = 7.0$ Hz, 1H), 7.57 (d, $J = 3.9$ Hz, 1H), 7.53–7.47 (multiple peaks, 3H), 7.12–7.04 (multiple peaks, 2H), 2.42 (s, 3H). ^{13}C NMR (CDCl_3): δ 160.7, 157.1 (d, $J = 247$ Hz), 145.7 (d, $J = 3.6$ Hz), 133.9 (d, $J = 3.6$ Hz), 130.4, 129.8 (d, $J = 8.0$ Hz), 128.7, 127.6 (d, $J = 12.8$ Hz), 127.2, 126.3, 126.0 (d, $J = 2.9$ Hz), 115.9 (d, $J = 13.1$ Hz), 115.6 (d, $J = 20.9$ Hz), 20.7. IR (neat): 1504, 1478, 1448, 1382, 1238, 1216, 1135, 1070, 1054, 967, 881, 861, 831, 814, 778, 757, 706, 691, 670, 659, 555 cm^{-1} . HRMS Calcd for $\text{C}_{16}\text{H}_{12}\text{FNO}$ 253.0903; Found: 253.0897.

4.4.2.14. 5-[2-fluoro-5-(trifluoromethyl)phenyl]-2-phenyl-1,3-oxazole (13c): Following general procedure C, phenyl pivalate (134 mg, 0.75 mmol, 3.0 equiv), 5-(2-fluoro-5-trifluoromethylphenyl)-oxazole (57.8 mg, 0.250 mmol, 1.0 equiv), $\text{Ni}(\text{COD})_2$ (6.9 mg, 0.025 mmol, 0.10 equiv), dcypt (23.8 mg, 0.05 mmol, 0.20 equiv), Cs_2CO_3 (122 mg, 0.375 mmol, 1.5 equiv), and anhydrous xylene (1.0 mL) were combined in a 4 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 20 h. Chromatography on a silica gel column using 93/7 hexanes/EtOAc ($R_f = 0.26$ in 93% hexanes/7% ethyl acetate) yielded product **13c** as a white solid (70.4 mg, 91% yield). mp = 143–144 °C. ^1H NMR (CDCl_3): δ 8.17–8.12 (multiple peaks, 3H), 7.67 (d, $J = 4.0$ Hz, 1H), 7.61–7.50 (multiple peaks, 4H), 7.31 (t, $J = 9.5$ Hz, 1H). ^{13}C NMR (CDCl_3): δ 161.6, 160.2 (d, $J = 255$ Hz), 144.2 (d, $J = 3.1$ Hz), 130.9, 129.1, 128.9, 127.5 (qd, $J = 33.1, 3.5$ Hz), 126.8, 126.6, 126.3 (m), 123.5 (q, $J = 270$ Hz), 123.3 (m), 117.4 (d, $J = 14.4$ Hz), 116.7 (d, $J = 22.0$ Hz). IR (neat): 1509, 1350, 1335, 1316, 1234, 1179, 1116, 1076, 1054, 900, 845, 780, 712, 699, 692, 682, 676, 588 cm^{-1} . HRMS Calcd for $\text{C}_{16}\text{H}_9\text{F}_4\text{NO}$ 307.0620; Found: 307.0626.

4.4.3 Procedures and spectral characterization of arylation products using tosylates (Scheme 7a)

4.4.3.1. 2-phenyl-5-methyl-1,3-benzoxazole (1c): Following general procedure B, phenyl tosylate (186 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), $\text{Ni}(\text{COD})_2$ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs_2CO_3 (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 100 °C

for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc ($R_f = 0.26$ in 95% hexanes/5% ethyl acetate) yielded product **1c** as a white solid (63.2 mg, 60% yield). The spectroscopic data is identical to that obtained using phenyl pivalate (*vide supra*).

4.4.3.2. 2-(4-methoxyphenyl)-5-methyl-1,3-benzoxazole (1a): Following general procedure **B**, 4-methoxy phenyl tosylate (209 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 100 °C for 20 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc ($R_f = 0.40$ in 90% hexanes/10% ethyl acetate) yielded product **1a** as a white solid (83.3 mg, 70% yield). The spectroscopic data is identical to that obtained using *paramethoxyphenyl* pivalate (*vide supra*).

4.4.3.3. 2-(3-methoxyphenyl)-5-methyl-1,3-benzoxazole (1d): Following general procedure **B**, *meta*-methoxy phenyl tosylate (209 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcyp (47.7 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 120 °C for 18 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc ($R_f = 0.31$ in 90% hexanes/10% ethyl acetate) yielded product **1d** as a white solid (52.7 mg, 44% yield). The spectroscopic data is identical to that obtained using *meta*-methoxyphenyl pivalate (*vide supra*).

4.4.3.4. 2-[3-(trifluoromethyl)phenyl]-5-methyl-1,3-benzoxazole (1f): Following general procedure **B**, *meta*-trifluoromethyl phenyl tosylate (237 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcyp (47.7 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 120 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc ($R_f = 0.42$ in 95% hexanes/5% ethyl acetate) yielded product **1f** as a white solid (37.3 mg, 27% yield). The spectroscopic data is identical to that obtained using *meta*-trifluoromethylphenyl pivalate (*vide supra*).

4.4.4 Procedures and spectral characterization of arylation products using mesylates (Schemes 7b and 7c)

4.4.4.1. 2-phenyl-5-methyl-1,3-benzoxazole (1c): Following general procedure **A**, phenyl mesylate (129 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 120 °C for 22 h. Chromatography on a silica gel column using 96/4 hexanes/EtOAc ($R_f = 0.28$ in 96% hexanes/4% ethyl acetate) yielded product **1c** as a white solid (86.2 mg, 82% yield). The spectroscopic data is identical to that obtained using phenyl pivalate (*vide supra*).

4.4.4.2. 2-(4-methylphenyl)-5-methyl-1,3-benzoxazole (1b): Following general procedure A, 4-methyl phenyl mesylate (140 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 94/6 hexanes/EtOAc (R_f = 0.45 in 94% hexanes/6% ethyl acetate) yielded product **1b** as a white solid (69.8 mg, 62% yield). The spectroscopic data is identical to that obtained using *para*-methylphenyl pivalate (*vide supra*).

4.4.4.3. 2-(4-methoxyphenyl)-5-methyl-1,3-benzoxazole (1a): Following general procedure A, 4-methoxy phenyl mesylate (151 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 120 °C for 22 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.25 in 90% hexanes/10% ethyl acetate) yielded product **1a** as a white solid (94.4 mg, 79% yield). The spectroscopic data is identical to that obtained using *para*-methoxyphenyl pivalate (*vide supra*).

4.4.4.4. 2-(3-methoxyphenyl)-5-methyl-1,3-benzoxazole (1d): Following general procedure C, *meta*-methoxy phenyl mesylate (303 mg, 1.50 mmol, 3.0 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 18 h. Chromatography on a silica gel column using 91/9 hexanes/EtOAc (R_f = 0.31 in 91% hexanes/9% ethyl acetate) yielded product **1d** as a white solid (92.1 mg, 77% yield). The spectroscopic data is identical to that obtained using *meta*-methoxyphenyl pivalate (*vide supra*).

4.4.4.5. 2-[3-(trifluoromethyl)phenyl]-5-methyl-1,3-benzoxazole (1f): Following general procedure C, *meta*-trifluoromethyl phenyl mesylate (144 mg, 0.600 mmol, 1.5 equiv), 5-methylbenzoxazole (53.3 mg, 0.400 mmol, 1.0 equiv), Ni(COD)₂ (11.0 mg, 0.04 mmol, 0.10 equiv), dcyp (38.1 mg, 0.08 mmol, 0.20 equiv), Cs₂CO₃ (195 mg, 0.600 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 21 h. Chromatography on a silica gel column using 94/6 hexanes/EtOAc (R_f = 0.29 in 94% hexanes/6% ethyl acetate) yielded product **1f** as a white solid (62.5 mg, 56% yield). The spectroscopic data is identical to that obtained using *meta*-trifluoromethylphenyl pivalate (*vide supra*).

4.4.4.6. 2-(2-methylphenyl)-5-methyl-1,3-benzoxazole (1j): Following general procedure C, *ortho*-methyl phenyl mesylate (279 mg, 1.50 mmol, 3.0 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcype (42.3 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was

allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 97/3 hexanes/EtOAc (R_f = 0.34 in 97% hexanes/3% ethyl acetate) yielded product **1j** as a white solid (32.9 mg, 30% yield). The spectroscopic data is identical to that previously reported in the literature.²⁷

4.4.4.7. 2,5-diphenyl-1,3-oxazole (8c): Following general procedure **A**, phenyl mesylate (258 mg, 1.50 mmol, 3.0 equiv), phenyl oxazole (72.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.75 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.40 in 95% hexanes/5% ethyl acetate) yielded product **8c** as a white solid (63.7 mg, 58% yield). The spectroscopic data is identical to that obtained using phenyl pivalate (*vide supra*).

4.4.4.8. 5-(4-methoxyphenyl)-2-phenyl-1,3-oxazole (9c)

Using dcypt and Cs₂CO₃: Following general procedure **A**, phenyl mesylate (258 mg, 1.50 mmol, 3.0 equiv), 5-(4-methoxyphenyl)-1,3-oxazole (87.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.40 in 90% hexanes/10% ethyl acetate) yielded product **9c** as a white solid (44.6 mg, 35% yield). The spectroscopic data is identical to that obtained using phenyl pivalate (*vide supra*).

Using dcypt and K₃PO₄: Following general procedure **A** in a 4 mL scintillation vial, phenyl mesylate (64.6 mg, 0.375 mmol, 1.5 equiv), 5-(4-methoxyphenyl)-1,3-oxazole (43.8 mg, 0.250 mmol, 1.0 equiv), Ni(COD)₂ (6.9 mg, 0.025 mmol, 0.10 equiv), dcypt (23.8 mg, 0.05 mmol, 0.20 equiv), K₃PO₄ (159 mg, 0.750 mmol, 3.0 equiv), and anhydrous xylene (1.0 mL) were combined. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.40 in 90% hexanes/10% ethyl acetate) yielded product **9c** as a white solid (32.1 mg, 52% yield). The spectroscopic data is identical to that obtained using phenyl pivalate (*vide supra*).

4.4.4.9. 5-[4-(trifluoromethyl)phenyl]-2-phenyl-1,3-oxazole (10c): Following general procedure **A**, phenyl mesylate (258 mg, 1.50 mmol, 3.0 equiv), 5-[4-(trifluoromethyl)phenyl]-1,3-oxazole (107 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), Cs₂CO₃ (244 mg, 0.750 mmol, 1.5 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.32 in 95% hexanes/5% ethyl acetate) yielded product **10c** as a white solid (111 mg, 77% yield). The spectroscopic data is identical to that obtained using phenyl pivalate (*vide supra*).

4.4.5 Procedures and spectral characterization of arylation products using carbamates (Scheme 8)

4.4.5.1. 2-phenyl-5-methyl-1,3-benzoxazole (1c): Following general procedure C, *N,N*-diethyl-phenyl carbamate (145 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), K₃PO₄ (318 mg, 1.50 mmol, 3.0 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 23 h. Chromatography on a silica gel column using 94/6 hexanes/EtOAc (R_f = 0.45 in 94% hexanes/6% ethyl acetate) yielded product **1c** as a white solid (86.4 mg, 83% yield). The spectroscopic data is identical to that obtained using phenyl pivalate (*vide supra*).

4.4.5.2. 2-(4-methylphenyl)-5-methyl-1,3-benzoxazole (1b): Following general procedure C, *N,N*-diethyl-4-methyl phenyl carbamate (152 mg, 0.733 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), K₃PO₄ (318 mg, 1.50 mmol, 3.0 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.30 in 95% hexanes/5% ethyl acetate) yielded product **1b** as a white solid (87.9 mg, 79% yield). The spectroscopic data is identical to that obtained using *para*-methylphenyl pivalate (*vide supra*).

4.4.5.3. 2-(4-methoxyphenyl)-5-methyl-1,3-benzoxazole (1a): Following general procedure C, *N,N*-diethyl-4-methoxy phenyl carbamate (167 mg, 0.750 mmol, 3.0 equiv), 5-methylbenzoxazole (33.3 mg, 0.250 mmol, 1.0 equiv), Ni(COD)₂ (6.9 mg, 0.025 mmol, 0.10 equiv), dcypt (23.8 mg, 0.05 mmol, 0.20 equiv), K₃PO₄ (159 mg, 0.75 mmol, 3.0 equiv), and anhydrous xylene (1.0 mL) were combined in a 4 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 20 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.28 in 90% hexanes/10% ethyl acetate) yielded product **1a** as a white solid (40.3 mg, 67% yield). The spectroscopic data is identical to that obtained using *para*-methoxyphenyl pivalate (*vide supra*).

4.4.5.4. 2-(3-methoxyphenyl)-5-methyl-1,3-benzoxazole (1d): Following general procedure C, *N,N*-diethyl-*meta*-methoxyphenyl carbamate (83.7 mg, 0.375 mmol, 1.5 equiv), 5-methylbenzoxazole (33.3 mg, 0.250 mmol, 1.0 equiv), Ni(COD)₂ (6.9 mg, 0.025 mmol, 0.10 equiv), dcypt (23.8 mg, 0.05 mmol, 0.20 equiv), K₃PO₄ (159 mg, 0.750 mmol, 3.0 equiv), and anhydrous xylene (1.0 mL) were combined in a 4 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.34 in 90% hexanes/10% ethyl acetate) yielded product **1d** as a white solid (49.6 mg, 83% yield). The spectroscopic data is identical to that obtained using *meta*-methoxyphenyl pivalate (*vide supra*).

4.4.5.5. 2-[3-(trifluoromethyl)phenyl]-5-methyl-1,3-benzoxazole (1f): Following general procedure C, *N,N*-diethyl-*meta*-trifluoromethylphenyl carbamate (195 mg, 0.750 mmol, 1.5 equiv), 5-methylbenzoxazole (66.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), K₃PO₄ (318 mg, 1.50 mmol,

3.0 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.41 in 95% hexanes/5% ethyl acetate) yielded product **1f** as a white solid (91.0 mg, 66% yield). The spectroscopic data is identical to that obtained using *meta*-trifluoromethylphenyl pivalate (*vide supra*).

4.4.5.6. 2-(2-methylphenyl)-5-methyl-1,3-benzoxazole (1j): Following general procedure C, *ortho*-methyl phenyl carbamate (60.7 mg, 0.293 mmol, 3.0 equiv), 5-methylbenzoxazole (13.3 mg, 0.100 mmol, 1.0 equiv), Ni(COD)₂ (2.80 mg, 0.01 mmol, 0.10 equiv), dcypt (9.50 mg, 0.02 mmol, 0.20 equiv), K₃PO₄ (63.7 mg, 0.300 mmol, 3.0 equiv), and anhydrous xylene (0.4 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. The reaction mixture was cooled to room temperature and diluted with EtOAc. Hexadecane (0.100 mmol) was added and an aliquot of this reaction mixture was analyzed using GC/MS, which showed 22% yield of product **1j**.

4.4.5.7. 2,5-diphenyl-1,3-oxazole (8c): Following general procedure C, *N,N*-diethyl-phenyl carbamate (145 mg, 0.75 mmol, 1.5 equiv), phenyl oxazole (72.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), K₃PO₄ (318 mg, 1.50 mmol, 3.0 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 95/5 hexanes/EtOAc (R_f = 0.30 in 95% hexanes/5% ethyl acetate) yielded product **8c** as a white solid (71.1 mg, 64% yield). The spectroscopic data is identical to that obtained using phenyl pivalate (*vide supra*).

4.4.5.8. 5-(4-methoxyphenyl)-2-phenyl-1,3-oxazole (9c): Following general procedure C, *N,N*-diethyl-phenyl carbamate (145 mg, 0.75 mmol, 1.5 equiv), 5-(4-methoxyphenyl)-1,3-oxazole (87.6 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), K₃PO₄ (318 mg, 1.50 mmol, 3.0 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22 h. Chromatography on a silica gel column using 90/10 hexanes/EtOAc (R_f = 0.40 in 90% hexanes/10% ethyl acetate) yielded product **9c** as a white solid (44.8 mg, 36% yield). The spectroscopic data is identical to that obtained using phenyl pivalate (*vide supra*).

4.4.5.9. 5-[4-(trifluoromethyl)phenyl]-2-phenyl-1,3-oxazole (10c): Following general procedure C, *N,N*-diethyl-phenyl carbamate (145 mg, 0.75 mmol, 1.5 equiv), 5-[4-(trifluoromethyl)phenyl]-1,3-oxazole (107 mg, 0.500 mmol, 1.0 equiv), Ni(COD)₂ (13.8 mg, 0.05 mmol, 0.10 equiv), dcypt (47.7 mg, 0.10 mmol, 0.20 equiv), K₃PO₄ (318 mg, 1.50 mmol, 3.0 equiv), and anhydrous xylene (2.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 22.5 h. Chromatography on a silica gel column using 94/6 hexanes/EtOAc (R_f = 0.27 in 94% hexanes/6% ethyl acetate) yielded product **10c** as a white solid (74.1 mg, 51% yield). The spectroscopic data is identical to that obtained using phenyl pivalate (*vide supra*).

4.4.6 Procedures for competition studies (Table 2 and Scheme 9)

4.4.6.1: Procedures for competition studies with two liquid electrophiles (Table 2, entries 1 and 7): Ni(COD)₂ (2.80 mg, 0.01 mmol, 0.1 equiv), ligand (dcype or dcpyt) (8.6 or 9.5 mg, 0.02 mmol, 0.2 equiv), Cs₂CO₃ (48.9 mg, 0.15 mmol, 1.5 equiv), and 5-methylbenzoxazole (13.3 mg, 0.100 mmol, 1.0 equiv) were weighed into in an oven dried 4 mL scintillation vial in the glove box. A xylene solution (0.2 mL) of the phenyl electrophile (0.15 mmol, 1.5 equiv) and a xylene solution (0.2 mL) of *p*-MeC₆H₄ electrophile (0.15 mmol, 1.5 equiv) were added to the reaction mixture. The reaction vial was sealed with a Teflon lined cap, taken out of the glove box and the reaction mixture was allowed to stir at 140 °C for 22 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (1 mL) and filtered through silica gel, eluting with EtOAc (2 mL). Hexadecane (0.029 mL, 1.0 equiv) was added to the reaction mixture. An aliquot of the reaction mixture was analyzed using GC/MS and the calibrated GC yield of the product against the hexadecane standard was calculated.

4.4.6.2: Procedures for competition studies with two solid electrophiles (Table 2, entries 2 and 8): Ni(COD)₂ (2.80 mg, 0.01 mmol, 0.1 equiv), ligand (dcype or dcpyt) (8.6 or 9.5 mg, 0.02 mmol, 0.2 equiv), Cs₂CO₃ (48.9 mg, 0.15 mmol, 1.5 equiv), 5-methylbenzoxazole (13.3 mg, 0.100 mmol, 1.0 equiv), phenyl electrophile (0.15 mmol, 1.5 equiv), *p*-MeC₆H₄ electrophile (0.15 mmol, 1.5 equiv) and xylene (0.4 mL) were added to an oven dried 4 mL scintillation vial. The reaction vial was sealed with a Teflon lined cap, taken out of the glove box and the reaction mixture was allowed to stir at 140 °C for 22 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (1 mL) and filtered through silica gel, eluting with EtOAc (2 mL). Hexadecane (0.029 mL, 1.0 equiv) was added to the reaction mixture. An aliquot of the reaction mixture was analyzed using GC/MS and the calibrated GC yield of the product against the hexadecane standard was calculated.

4.4.6.3: Procedures for competition studies with solid phenyl electrophile and liquid *p*-Mephenyl electrophile (Table 2, entries 3 and 9): Ni(COD)₂ (2.80 mg, 0.01 mmol, 0.1 equiv), ligand (dcype or dcpyt) (8.6 or 9.5 mg, 0.02 mmol, 0.2 equiv), Cs₂CO₃ (48.9 mg, 0.15 mmol, 1.5 equiv), 5-methylbenzoxazole (13.3 mg, 0.100 mmol, 1.0 equiv), and phenyl electrophile (0.15 mmol, 1.5 equiv) were added to an oven dried 4 mL scintillation vial. A xylene (0.4 mL) solution of *p*-MeC₆H₄ electrophile (0.15 mmol, 1.5 equiv) was added to the reaction vial. The reaction vial was sealed with a Teflon lined cap, taken out of the glove box and the reaction mixture was allowed to stir at 140 °C for 22 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (1 mL) and filtered through silica gel, eluting with EtOAc (2 mL). Hexadecane (0.029 mL, 1.0 equiv) was added to the reaction mixture. An aliquot of the reaction mixture was analyzed using GC/MS and the calibrated GC yield of the product against the hexadecane standard was calculated.

4.4.6.4: Procedures for competition studies with liquid phenyl electrophile and solid *p*-Mephenyl electrophile (Table 3, entries 4–6): Ni(COD)₂ (2.80 mg, 0.01 mmol, 0.1 equiv), ligand (dcype or dcpyt) (8.6 or 9.5 mg, 0.02 mmol, 0.2 equiv), Cs₂CO₃ (48.9 mg, 0.15 mmol, 1.5 equiv), 5-methylbenzoxazole (13.3 mg, 0.100 mmol, 1.0 equiv), and *p*-MeC₆H₄ electrophile (0.15 mmol, 1.5 equiv) were added to an oven dried 4 mL scintillation vial. A

xylene (0.4 mL) solution of the phenyl electrophile (0.15 mmol, 1.5 equiv) was added to the reaction vial. The reaction vial was sealed with a Teflon lined cap, taken out of the glove box and the reaction mixture was allowed to stir at 140 °C for 22 h. The reaction mixture was cooled to room temperature, diluted with EtOAc (1 mL) and filtered through silica gel, eluting with EtOAc (2 mL). Hexadecane (0.029 mL, 1.0 equiv) was added to the reaction mixture. An aliquot of the reaction mixture was analyzed using GC/MS and the calibrated GC yield of the product against the hexadecane standard was calculated.

4.4.6.5. 2-[3-*N,N*-diethylcarbamoyl phenyl]-5-methyl-1,3-benzoxazole (product A in Scheme 9): Following general procedure C, (3-methanesulfonylphenyl) *N,N*-diethyl carbamate (215 mg, 0.75 mmol, 3.0 equiv), 5-methyl benzoxazole (33.3 mg, 0.250 mmol, 1.0 equiv), Ni(COD)₂ (6.9 mg, 0.025 mmol, 0.10 equiv), dcypt (23.8 mg, 0.05 mmol, 0.20 equiv), Cs₂CO₃ (122 mg, 0.37 mmol, 1.5 equiv), and anhydrous xylene (1.0 mL) were combined in a 20 mL scintillation vial. The reaction mixture was allowed to stir at 140 °C for 24 h. Chromatography on a silica gel column using 95/5 to 93/7 EtOAc/hexanes (R_f = 0.13 in 93% hexanes/7% ethyl acetate) yielded product (25 mg, 30% yield). ¹H NMR (CDCl₃): δ 8.07 (dt, *J* = 7.8, 1.4 Hz, 1H), 8.00 (t, *J* = 1.9 Hz, 1H), 7.55 (s, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 1H), 7.33-7.31 (m, 1H), 7.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 3.50-3.39 (m, 4H), 2.49 (s, 3H), 1.31-1.21 (m, 6H).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
 Literature Precedent for Azole Arylation

Scheme 3.

Literature Precedent for Azole Arylation Using Carbamates

Scheme 4.

Literature Precedent for Intramolecular C–H Arylation

Scheme 5. Scope of Pivalates for C–H Arylation^{a,b}

[^a] General conditions: azole (1.0 equiv), pivalate (3.0 equiv), Ni(COD)₂ (0.1 equiv), dcype (0.2 equiv), Cs₂CO₃ (1.5 equiv), *p*-xylene, 140 °C. [^b] Isolated yields. [^c] General conditions but with dcyp^t (0.2 equiv). [^d] General conditions but with dcyp^t (0.2 equiv), pivalate (1.5 equiv). [^e] General conditions but with pivalate (1.5 equiv) and K₃PO₄ (1.5 equiv). [^f] General conditions but with pivalate (1.5 equiv) and K₃PO₄ (2.0 equiv). [^g] General conditions but with dcyp^t (0.2 equiv), and K₃PO₄ (3.0 equiv).

Scheme 6. Scope of Azoles for Arylation Using Pivalates^{a,b}

[^a] General conditions: azole (1.0 equiv), pivalate (3.0 equiv), Ni(COD)₂ (0.1 equiv), dcypt (0.2 equiv), Cs₂CO₃ (1.5 equiv), *p*-xylene, 140 °C. [^b] Isolated yields. [^c] General conditions with dcypt (0.2 equiv). [^d] General conditions with dcypt (0.2 equiv), and K₃PO₄ (3.0 equiv). [^e] General conditions with dcypt (0.2 equiv), and pivalate (1.5 equiv). [^f] General conditions at 120 °C.

Scheme 7. Arylation of Oxazoles Using Sulfonates^{a,b}

[^a] General conditions: azole (1.0 equiv), sulfonate (1.5 equiv), Ni(COD)₂ (0.1 equiv), dcype (0.2 equiv), Cs₂CO₃ (1.5 equiv), *p*-xylene, 120 °C. [^b] Isolated yields. [^c] General conditions at 100 °C. [^d] General conditions with dcyp (0.2 equiv). [^e] General conditions at 140 °C. [^f] General conditions with sulfonate (3.0 equiv) at 140 °C. [^g] General conditions with dcyp (0.2 equiv) at 140 °C. [^h] General conditions with dcyp (0.2 equiv), sulfonate (3.0 equiv) at 140 °C. [ⁱ] General conditions with dcyp (0.2 equiv), and K₃PO₄ (3.0 equiv) at 140 °C.

Scheme 8. Arylation of Oxazoles Using Carbamates^{a,b}

[^a] General conditions: azole (1.0 equiv), carbamate (1.5 equiv), Ni(COD)₂ (0.1 equiv), dcypt (0.2 equiv), K₃PO₄ (3.0 equiv), *p*-xylene, 140 °C. [^b] Isolated yields. [^c] General conditions with carbamate (3.0 equiv). [^d] Calibrated GC yield against hexadecane as the internal standard.

Scheme 9.
Intramolecular Competition Study

Optimization of Arylation Using Pivalates

^eGeneral conditions but with 3.0 equiv of pivalate in the absence of Ni(COD)₂.

Competition Studies

entry	X	Y	ligand	yield of 1c ^a (%)	yield of 1b ^a (%)	1c:1b
1	OPiv	OCONEt ₂	dcypt	71	16	4.4:1
2	OMs	OPiv	dcypt	68	15	4.5:1
3	OMs	OCONEt ₂	dcypt	57	1%	n/a
4	OCONEt ₂	OPiv	dcypt	32	62	0.52:1
5	OPiv	OMs	dcypt	10	77	0.13:1
6	OCONEt ₂	OMs	dcypt	1%	59	n/a
7	OPiv	OCONEt ₂	dcype	67	25	2.7:1
8	OMs	OPiv	dcype	72	23	3.1:1
9	OMs	OCONEt ₂	dcype	55	6	9.2:1

^a Calibrated GC yield against hexadecane as the internal standard.