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Nickel-Catalyzed *N*-Arylation of Amides with (Hetero)aryl Electrophiles by Using a DBU/NaTFA Dual-Base System

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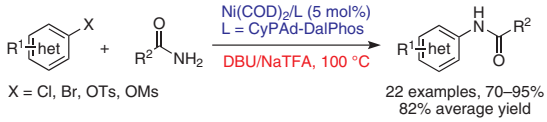

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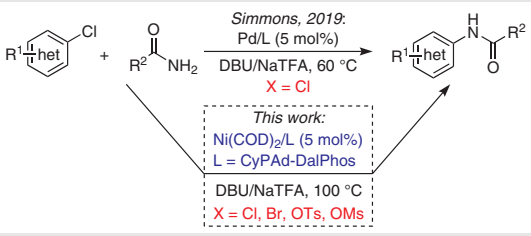
Abstract The first nickel-catalyzed *N*-arylation of amides with (hetero)aryl (pseudo)halides employing an organic amine base is described. By using a bis(cyclooctadienyl)nickel/8-[2-(dicyclohexylphosphinyl)phenyl]-1,3,5,7-tetramethyl-2,4,6-trioxa-8-phosphaadamantane catalyst mixture in combination with DBU/NaTFA as a dual-base system, a diversity of (hetero)aryl chloride, bromide, tosylate, and mesylate electrophiles were successfully cross-coupled with structurally diverse primary amides, as well as a selection of secondary amide, lactam, and oxazolidone nucleophiles.

Key words nickel catalysis, C–N cross-coupling, amides, arylation

The ubiquitous nature of amides in biologically relevant molecules and functional materials[1] provides motivation for developing practical methods of preparing derivatives of such compounds, including metal-catalyzed syntheses.[2] The Pd-catalyzed *N*-arylation of amides through intermolecular C(sp^2)–N cross-couplings with (hetero)aryl electrophiles, as developed initially by Shakespeare[3] and by Buchwald and co-workers,[4] represents an effective means of accessing *N*-arylated amides. Continual advances in ancillary ligand design[5] have given rise to highly effective Pd-based catalysts for the *N*-arylation of primary and secondary amides with a variety of (hetero)aryl electrophiles.[6] Notwithstanding such progress, the cost and scarcity of Pd, as well as the pursuit of an expanded substrate scope, provides impetus for the development of nonprecious-metal catalysts for use in these transformations.[7] In this vein, Cu-based catalysts have proven highly effective in mediating the *N*-arylation of amides.[8] Although such catalysts are typically ineffective for use with inexpensive and abundant (hetero)aryl chloride or phenol-derived electrophiles, some important breakthroughs have been made in this regard.[9] In 2016, we reported the first broadly useful Ni-catalyzed C(sp^2)–N cross-coupling of primary amides and (hetero)aryl electrophiles, spanning both halides and phenol derivatives, by use of the air-stable precatalyst (PAd-DalPhos)Ni(*o*-tolyl)Cl (PAd-DalPhos = **L1**; see Scheme 2 below).[10,11]

Until recently, metal catalyst systems for amide *N*-arylation commonly made use of strong bases (e.g., *t*-BuONa) or relatively weak inorganic bases (e.g., Cs_2CO_3, K_3PO_4, and K_2CO_3), with the latter being required when employing substrates featuring base-sensitive addenda. While generally effective, the poor solubility of such inorganic bases in organic reaction media gives rise to a number of complications, including clogging/stirring issues and unpredictable reaction kinetics associated with the batch-specific morphology of the base (e.g., particle size). An elegant solution to this problem was reported by Simmons and co-workers in 2019,[12] whereby a combination of a weak-amine Brønsted base (1,8-diazabicyclo[5.4.0]undec-7-ene; DBU) and sodium trifluoroacetate (NaTFA) was employed successfully in Pd-catalyzed C(sp^2)–N cross-couplings of (hetero)aryl chlorides with primary amides or anilines (Scheme 1). The advantage of the DBU/NaTFA dual-base system, besides being readily available and inexpensive, is that the NaTFA additive helps sequester any soluble halide anions from DBU·HX,



Scheme 1 Palladium-catalyzed C–N cross-coupling of amides employing an organic amine 'dual-base' system (DBU/NaTFA), and the nickel-catalyzed transformations reported herein.

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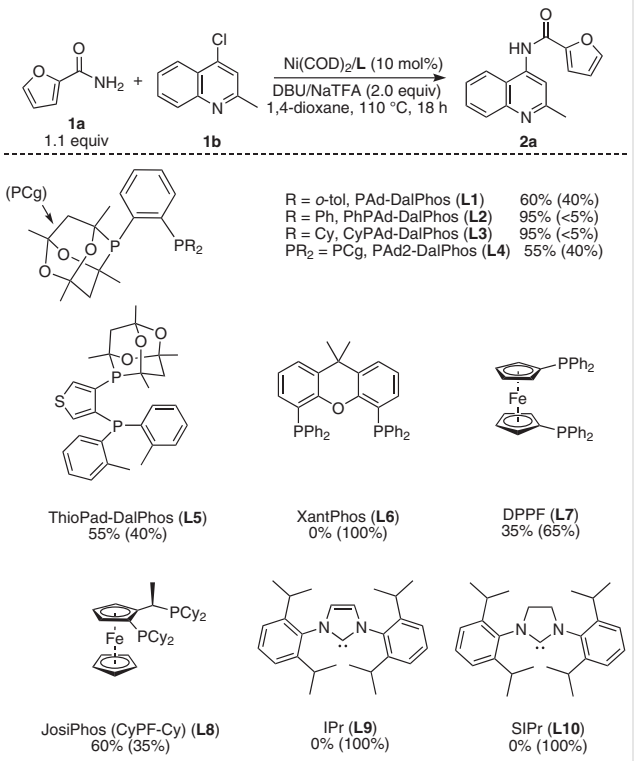
which have been shown to coordinate to catalytic intermediates, thereby inhibiting catalysis.[12] Newman and coworkers recently employed DBU in high-throughput screenings of Pd-catalyzed amination chemistry, thereby demonstrating the utility of mild organic amine bases in cross-coupling reactions in batch and flow processes.[13]

As part of our ongoing research program focused on developing new and synthetically useful Ni-catalyzed cross-coupling chemistry, we recently reported a successful application of the Simmons[12] dual-base strategy in the *N*-arylation of fluoroalkylamines with (hetero)aryl electrophiles by using (PAd2-DalPhos)Ni(*o*-tolyl)Cl (PAd2-DalPhos = **L2**; see Scheme 2 below) as a precatalyst.[14] The success of these C(sp^2)–N cross-couplings involving generally poor fluoroalkylamine nucleophiles akin to amides,[15] when paired with the dearth of reports documenting Ni-catalyzed amide cross-couplings of this type generally,[16] led us to explore the utility of DalPhos and other prominent ligands in the development of the first Ni-catalyzed amide cross-couplings of (hetero)aryl (pseudo)halides in the presence of a weak organic amine base. The results of these investigations are disclosed below.

We began by investigating the cross-coupling of 2-furamide (**1a**) and 4-chloroquinaldine (**1b**) employing catalyst mixtures of 10 mol% of $Ni(COD)_2$ (COD = 1,5-cyclooctadienyl) with 10 mol% of each of the ligands **L1**–**10** (Scheme 2). Included in our ligand screen were the DalPhos ligands **L1**–**5**,[17] which have proved successful in Ni-catalyzed C(sp^2)–N cross-coupling, as well as other commercially available bisphosphine and NHC ancillary ligands that have been fruitful in Pd-catalyzed C(sp^2)–N cross-couplings of amides (**L6** and **L7**) or in the Ni-catalyzed C(sp^2)–N cross-coupling of alternative nucleophiles (**L8**–**10**). Poor to moderate conversions into the product **2a** were observed for ligands outside the DalPhos family, the most successful being JosiPhos (CyPF-Cy) (**L8**), which showed comparable catalytic abilities to some DalPhos ligands (**L1**, **L4**, and **L5**). However, PhPAd-DalPhos (**L2**) and CyPAd-DalPhos (**L3**) afforded high conversions into **2a**. To differentiate the catalytic performance of these two ligands, the catalyst loading was decreased [5 mol% of $Ni(COD)_2$ and **L**]. At this loading, and following a brief examination of solvent and temperature in which toluene and 100 °C proved optimal, CyPAd-DalPhos (**L3**) proved to be superior to PhPAd-DalPhos (**L2**), affording **2a** in 88% isolated yield (Scheme 3).

Attempts were made to employ the air-stable precatalysts (L)Ni(*o*-tolyl)Cl (L = **L2**,[17f] **L3**[17b]), which have historically shown superior capabilities to those of the analogous $Ni(COD)_2$/L mixtures in C(sp^2)–N cross-coupling.[18] However, with the dual-base system under the conditions examined in our study, such precatalysts showed inferior performance, requiring higher catalyst loadings and elevated temperatures to achieve comparable conversions. For example (**L3**)Ni(*o*-tolyl)Cl, in the presence or absence of added COD, proved inferior (88% versus >95% conversion into **2a**) to

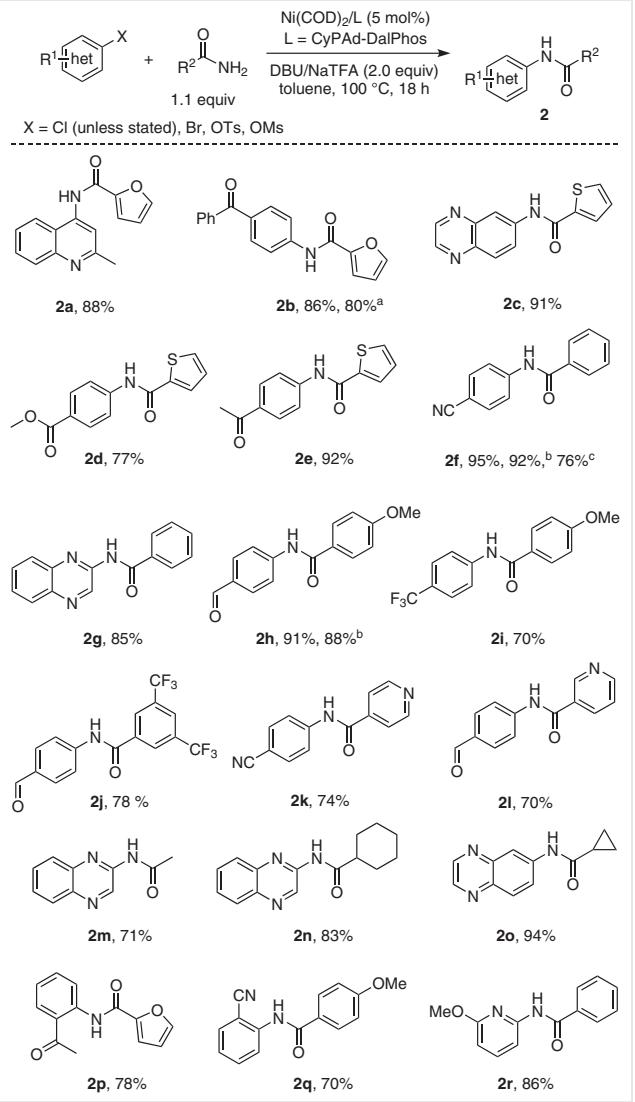


Scheme 2 Ligand screen for the Ni-catalyzed C–N cross-coupling of amides by using DBU/NaTFA, employing 2-furamide (**1a**) and 4-chloroquinaldine (**1b**; 0.12 mmol scale, 0.12 M) as test substrates. Conversions were estimated on the basis of calibrated GC data and are reported as the percentage of **2a**, with the percentage of residual **1b** shown in parentheses; the mass balance is attributable to unidentified products.

$Ni(COD)_2$/CyPAd-DalPhos (**L3**) catalyst mixtures (Ni/L = 5 mol% each, toluene, 100 °C; see Supporting Information, Table S1) in the formation of **2a** from **1a** and **1b**. When the temperature was reduced to 80 °C, the $Ni(COD)_2$/CyPAd-DalPhos system still afforded a high conversion into **2a**, whereas the precatalyst (**L3**)Ni(*o*-tolyl)Cl afforded negligible amounts of **2a**, with unreacted **1b**. Therefore, we continued our synthetic investigations by employing $Ni(COD)_2$/CyPAd-DalPhos (**L3**).

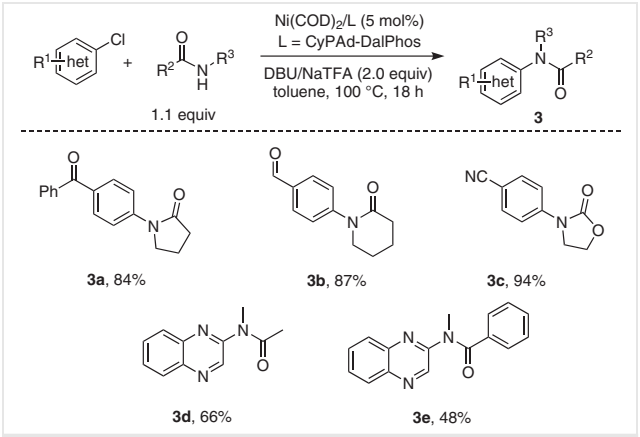
In exploring the scope of reactivity, we determined that the use of 5 mol% $Ni(COD)_2$/CyPAd-DalPhos (**L3**) in toluene at 100 °C for 18 hours generally represented the most effective conditions, although several reactions were found to proceed efficiently at temperatures as low as 80 °C. An array of functionalized (hetero)aryl (pseudo)halides (X = Cl, Br, OTs, OMs) were successfully cross-coupled to (hetero)aromatic or alkyl primary amides, affording isolated yields of ≥70% (Scheme 3).[19] The heterocyclic amides 2-furamide and thiophene-2-carboxamide were shown to be competent coupling partners with both aryl and hetaryl (quinaldine and quinoxaline) electrophiles to give secondary amides **2a–e**. Electronically varied benzamides were also well tol-

erated, including those bearing electron-donating (4-methoxybenzamide) or electron-withdrawing [3,5-bis(trifluoromethyl)benzamide] groups, leading to **2f–j**. The ability to conduct gram-scale reactions was demonstrated by a successful synthesis of amide **2f** (1.37 g, 85% isolated yield) from 4-chlorobenzonitrile (1.0 g).[20] Throughout, control experiments established that negligible conversion was achieved in the absence of $Ni(COD)_2$/CyPAd-DalPhos. Moreover, on focusing on the formation of **2f** specifically, the exclusion of NaTFA resulted in poor conversions (<5% for Ar-OTs; ~50% for ArCl). Nicotinamide and isonicotinamide were shown to produce fruitful pairings, giving **2k** and **2l**, respectively. The primary alkyl amides acetamide, cyclohexanecarboxamide, and cyclopropanecarboxamide were compatible with the heterocyclic electrophiles 2-chloroquinoxaline and 6-chloroquinoxaline, affording products **2m–o**. Cross-couplings employing 2-chlorobenzonitrile and 2′-chloroacetophenone were performed to investigate tolerance toward *ortho*-substitution of the electrophile; these reactants proved compatible, forming products **2p** and **2q**. Pyridine electrophiles could also be employed in this chemistry (**2r**). This method is partially limited, in that electron-rich aryl electrophiles (e.g., 4-chloroanisole) were found to be generally poor reaction partners under the conditions employed, as negligible conversions of the starting materials were observed. However, the dual-base system tolerated a variety of functional groups that typically display sensitivity to strong bases, including carbonyl-containing (aldehyde, ketone, ester), nitrile, or trifluoromethyl groups. Note that there was no evidence of any Ni-mediated bond activation with potentially vulnerable groups such as ester, nitrile, or cyclopropyl fragments, thereby demonstrating the functional-group tolerance of this catalyst system.



Scheme 3 Scope of the Ni-catalyzed C–N cross-coupling of primary amides with (hetero)aryl (pseudo)halides. The reaction time is unoptimized. Yields of isolated products are reported. X = Cl unless otherwise noted. [a] X = Br. [b] X = OTs. [c] X = OMs.

We also observed that the catalyst system successfully cross-coupled lactams of various ring sizes to give products **3a** and **3b** (Scheme 4). An oxazolidone substrate was also found to be compatible with this chemistry, affording product **3c**. Proof-of-principle experiments leading to tertiary amides **3d** and **3e** established the viability of using acyclic secondary amide nucleophiles in this chemistry, although these are significantly more challenging than primary or cyclic secondary amide substrates. Examples of such Ni-catalyzed transformations are limited to a single report from Sankar and Babu, involving exclusively the 2-picolinamide group as a ligand/directing group for the transformation.[11b]



Scheme 4 Ni-catalyzed C–N cross-coupling of secondary amides with (hetero)aryl chlorides. The reaction time is unoptimized. Yields of isolated products are reported.

In summary, we have established the first Ni-catalyzed C(sp^2)–N cross-coupling of amides and (hetero)aryl (pseudo)halides with a combination of DBU as a weak amine Brønsted base and NaTFA as a halide scavenger. Having

identified Ni(COD)$_2$/CyPAd-DalPhos as the optimal catalyst system for use under these dual-base conditions, a series of primary and secondary amides were cross-coupled with a variety of (hetero)aryl halide and sulfonate electrophiles. The results disclosed herein further establish Ni-catalyzed C(sp^2)–N cross-coupling as a complementary and competitive alternative to Pd and Cu catalysis.

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Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/a-1337-6459.

References and Notes

(1) *The Amide Linkage: Selected Structural Aspects in Chemistry, Biochemistry and Materials Science*; Arthur, G.; Breneman, C. M.; Liebman, J. F., Ed.; Wiley-Interscience: New York, **2000**.
(2) Dunetz, J. R.; Magano, J.; Weisenburger, G. A. *Org. Process Res. Dev.* **2016**, *20*, 140.
(3) Shakespeare, W. C. *Tetrahedron Lett.* **1999**, *40*, 2035.
(4) Yin, J.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1101.
(5) *Ligand Design in Metal Chemistry: Reactivity and Catalysis*; Stradiotto, M.; Lundgren, R. J., Ed.; Wiley: Chichester, **2016**.
(6) For lead references, see: (a) Ikawa, T.; Barder, T. E.; Biscoe, M. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2007**, *129*, 13001. (b) Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 16720. (c) Crawford, S. M.; Lavery, C. B.; Stradiotto, M. *Chem. Eur. J.* **2013**, *19*, 16760. (d) Young, I. S.; Glass, A.-L.; Cravillion, T.; Han, C.; Zhang, H.; Gosselin, F. *Org. Lett.* **2018**, *20*, 3902.
(7) *Catalysis Without Precious Metals*; Bullock, R. M., Ed.; Wiley-VCH: Weinheim, **2010**.
(8) For lead references and a review, see: (a) Goldberg, I. *Ber. Dtsch. Chem. Ges.* **1906**, *39*, 1691. (b) Klapars, A.; Antilla, J. C.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 7727. (c) Monnier, F.; Taillefer, M. *Top. Organomet. Chem.* **2013**, *46*, 173.
(9) (a) De, S.; Yin, J.; Ma, D. *Org. Lett.* **2017**, *19*, 4864. (b) Chang, R. K.; Clairmont, B. P.; Lin, S.; MacArthur, A. H. R. *Organometallics* **2019**, *38*, 4448.
(10) Lavoie, C. M.; MacQueen, P. M.; Stradiotto, M. *Chem. Eur. J.* **2016**, *22*, 18752.
(11) For other examples of Ni-catalyzed amide cross-couplings employing aryl chlorides, see: (a) Moghaddam, F. M.; Tavakoli, G.; Moafi, A.; Saberi, V.; Rezvani, H. R. *ChemCatChem* **2014**, *6*, 3474. (b) Sankar, R.; Babu, S. A. *Asian J. Org. Chem.* **2017**, *6*, 269.
(12) Beutner, G. L.; Coombs, J. R.; Green, R. A.; Inankur, B.; Lin, D.; Qiu, J.; Roberts, F.; Simmons, E. M.; Wisniewski, S. R. *Org. Process Res. Dev.* **2019**, *23*, 1529.
(13) Kashani, S. K.; Jessiman, J. E.; Newman, S. G. *Org. Process Res. Dev.* **2020**, *24*, 1948.
(14) McGuire, R. T.; Yadav, A. A.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2020**, in press DOI: 10.1002/anie.202014340.
(15) Meanwell, N. A. *J. Med. Chem.* **2018**, *61*, 5822.
(16) The following report contains a single entry involving a Ni-catalyzed C(sp^2)–N cross-coupling of an aryl bromide and an amide employing DBU as the base: Kawamata, Y.; Vantourout, J. C.; Hickey, D. P.; Bai, P.; Chen, L.; Hou, Q.; Qiao, W.; Barman, K.; Edwards, M. A.; Garrido-Castro, A. F.; deGruyter, J. N.; Nakamura, H.; Knouse, K.; Qin, C.; Clay, K. J.; Bao, D.; Li, C.; Starr, J. T.; Garcia-Irizarry, C.; Sach, N.; White, H. S.; Neurock, M.; Minteer, S. D.; Baran, P. S. *J. Am. Chem. Soc.* **2019**, *141*, 6392.
(17) (a) Lavoie, C. M.; MacQueen, P. M.; Rotta-Loria, N. L.; Sawatzky, R. S.; Borzenko, A.; Chisholm, A. J.; Hargreaves, B. K. V.; McDonald, R.; Ferguson, M. J.; Stradiotto, M. *Nat. Commun.* **2016**, *7*, 11073. (b) Tassone, J. P.; MacQueen, P. M.; Lavoie, C. M.; Ferguson, M. J.; McDonald, R.; Stradiotto, M. *ACS Catal.* **2017**, *7*, 6048. (c) Lavoie, C. M.; Stradiotto, M. *ACS Catal.* **2018**, *8*, 7228. (d) Clark, J. S. K.; Ferguson, M. J.; McDonald, R.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 6391. (e) Clark, J. S. K.; McGuire, R. T.; Lavoie, C. M.; Ferguson, M. J.; Stradiotto, M. *Organometallics* **2019**, *38*, 167. (f) Tassone, J. P.; England, E. V.; MacQueen, P. M.; Ferguson, M. J.; Stradiotto, M. *Angew. Chem. Int. Ed.* **2019**, *58*, 2485.
(18) Hazari, N.; Melvin, P. R.; Beromi, M. M. *Nat. Rev. Chem.* **2017**, *1*, 0025.
(19) **N-Arylation of Amides with Aryl Electrophiles (Figures 3 and 4); General Procedure**
In a N_2-filled glovebox, a screw-capped vial containing a magnetic stirrer bar was charged with Ni(COD)$_2$ (5 mol%), CyPAd-DalPhos (5 mol%), the appropriate aryl (pseudo)halide (0.45 mmol, 1.0 equiv, 0.12 M), DBU (2.0 equiv), NaTFA (2.0 equiv), and the appropriate amide (1.1 equiv), followed by the addition of toluene (3.75 mL). The vial was sealed with a cap containing a PTFE septum, removed from the glovebox, and placed in a temperature-controlled aluminum heating block set to 100 °C for 18 h, with magnetic stirring. The vial was then removed from the heating block and left to cool to rt. The crude reaction mixture was filtered through a short plug of Celite and silica gel (3:1 v/v), eluting with EtOAc. The volatile materials were evaporated in vacuo, and the crude product was purified by flash-column chromatography.
N-(2-Methylquinolin-4-yl)-2-furamide (2a)
Synthesized according to the general procedure and purified by flash column chromatography (silica gel; 30% EtOAc–hexanes) to give a pale-yellow solid; yield: 100 mg (0.40 mmol, 88%).
^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.87 (s, 1 H), 8.34 (s, 1 H), 8.08 (d, J = 8.4 Hz, 1 H), 7.87 (d, J = 8.3 Hz, 1 H), 7.71 (ddd, J = 8.3, 7.1, 1.2 Hz, 1 H), 7.62–7.61 (m, 1 H), 7.57–7.54 (m, 1 H), 7.36–7.35 (m, 1 H), 6.64 (dd, J = 3.5, 1.8 Hz, 1 H), 2.76 (s, 3 H). ^{13}C{^{1}H} UDEFT NMR (125.8 MHz, $CDCl_3$): δ = 160.2, 156.3, 148.3, 147.5, 145.0, 140.1, 129.8, 125.9, 118.8, 118.4, 116.7, 113.2, 111.3, 25.8. HRMS-ESI: m/z [M + H]$^+$ calcd for $C_{15}H_{13}N_2O_2$: 253.0972; found: 253.0980.
N-(4-Benzoylphenyl)-2-furamide (3a)
Synthesized according to the general procedure and purified by flash column chromatography (silica gel; 20% EtOAc–hexanes) to give a colorless solid; yield: 100 mg (0.38 mmol, 84%). ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.87–7.84 (m, 2 H), 7.79–7.76 (m, 4

H), 7.60–7.56 (m, 1 H), 7.49–7.46 (m, 2 H), 3.93 (t, J = 7.1 Hz, 2 H), 2.66 (t, J = 8.1 Hz, 2 H), 2.21 (quintet, J = 7.6 Hz, 2 H). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ = 195.8, 174.8, 143.2, 138.0, 133.1, 132.3, 131.4, 130.0, 128.4, 118.8, 48.7, 33.0, 18.1. HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{17}H_{15}NNaO_2$: 288.0995; found: 288.0998.

(20) **N-(4-Cyanophenyl)benzamide (2f); Gram-Scale Synthesis**

In a N_2-filled glovebox, an oven-dried 250 mL round-bottomed Schlenk flask was charged with $Ni(COD)_2$ (100 mg, 0.363 mmol), CyPAd-DalPhos (178 mg, 0.363 mmol), 4-chlorobenzonitrile (1.0 g, 7.27 mmol), benzamide (0.969 g, 8.00 mmol), NaTFA (1.98 g, 14.5 mmol), DBU (2.17 mL, 14.5 mmol), and toluene (60 mL). A magnetic stirrer bar was added and the flask was sealed with a rubber septum, removed from the glovebox, and placed in an oil bath preheated to 100 °C. A reflux condenser was attached to the reaction vessel under a positive pressure of N_2, and magnetic stirring was initiated. After 18 h (unoptimized), the crude reaction mixture was cooled to rt and filtered through a short plug of Celite and silica gel (3:1 v/v), eluting with EtOAc. Volatile materials were evaporated in vacuo, and the crude product was purified by flash-column chromatography (silica gel, 20% EtOAc–hexanes) to give a pale-yellow solid; yield: 1.37 g (6.18 mmol, 85%).

^1H NMR (500 MHz, $CDCl_3$): δ = 8.01 (s, 1 H), 7.88–7.86 (m, 2 H), 7.81–7.79 (m, 2 H), 7.67–7.64 (m, 2 H), 7.61–7.58 (m, 1 H), 7.53–7.50 (m, 2 H). $^{13}C\{^1H\}$ UDEFT NMR (125.8 MHz, $CDCl_3$): δ = 166.0, 142.2, 134.3, 133.5, 132.7, 129.2, 127.3, 120.1, 118.9, 107.6. HRMS-ESI: m/z [M + Na]$^+$ calcd for $C_{14}H_{10}N_2NaO$: 245.0685; found: 245.0686.