

# Site-Selective C–H/C–N Activation by Cooperative Catalysis: Primary Amides as Arylating Reagents in Directed C–H Arylation

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*Supporting Information*



**ABSTRACT:** Direct C–H arylation of non-acidic C(sp<sup>2</sup>)–H bonds with primary amides as arylating reagents via highly chemoselective C–H/C–N/C–C cleavages has been accomplished for the first time. The key to the success is the cooperative combination of rhodium(I) catalysis and Lewis base catalysis, which can promote activation of inert C–N bonds in generic primary amides after selective N-*tert*-butoxycarbonyl activation in a highly efficient manner. Notably, this report constitutes the first biaryl synthesis enlisting common primary amides by N–C bond activation. This report also discloses for the first time the potential of generic, acyclic secondary amides as arylating reagents in directed C–H arylation. Considering the fundamental importance of biaryls and the key role of primary amides in organic synthesis, we expect that this concept by synergistic catalysis for aryl–aryl coupling will unlock broad catalytic applications.

**KEYWORDS:** C–H activation, C–N activation, amides, arylation, arylating reagents, cooperative catalysis

Amides are among the most important and prevalent functional groups in drug discovery, polymers and chemical industry.<sup>1</sup> While numerous methods for the functionalization of amide bonds by selective N–C cleavage<sup>2–6</sup> have been developed utilizing amide Nlp to C=O ground-state destabilization<sup>7,8</sup> (barrier to rotation, amide bond resonance in primary amides of 15–20 kcal/mol), cross-coupling of generic primary amides remains a challenging task. Despite the prevalence of primary amides as fundamental building blocks in pharmaceuticals, agrochemicals and electronic materials,<sup>9,10</sup> chemical methods that induce site-selective N–C insertion/decarbonylation and catalytically generate aryl electrophiles have remained elusive to direct catalytic pathways.<sup>4–6</sup>

Transition-metal-catalyzed C–H activation has been established as a very attractive method for the preparation of biaryl motifs.<sup>11</sup> Invention of new methods and arylating reagents for the site-selective construction of biaryls utilizing non-acidic C(sp<sup>2</sup>)–H bonds has a wide-ranging impact on the field.<sup>12–14</sup> Recently, a number of elegant processes for the selective activation/C–H cross-coupling of C(sp<sup>2</sup>)–O bonds has been developed.<sup>15</sup> Significant advances have been made in the development of biaryl synthesis, involving C–X and C–C cleavage that enable a range of

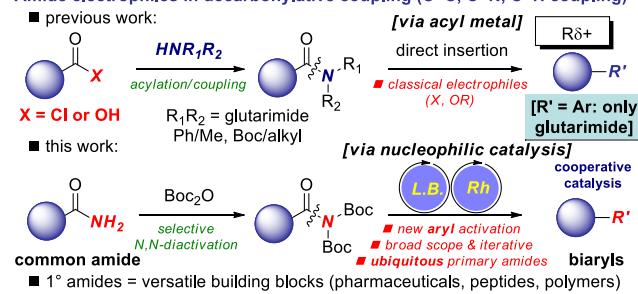
functional groups to selectively participate in the assembly of biaryls.<sup>16,17</sup> Herein, we describe a new concept for aryl–aryl coupling that utilizes primary amides as arylating reagents via highly chemoselective C–N/C–C/C–H cleavages in the absence of oxidants, enabled by the union of cooperative rhodium(I) and Lewis base catalysis.<sup>18</sup> Notably, the method represents the first biaryl synthesis enlisting common primary amides by N–C bond activation (Figure 1).<sup>4–6</sup> This reaction manifold differs from the direct acyl Negishi cross-coupling using Ni catalysis, wherein metal insertion proceeds directly into the amide N–C bond.<sup>8e</sup> The catalytic cooperative strategy has great potential in overriding the inherent reactivity<sup>8c</sup> and may pave the way for the generic application of common acyclic amides<sup>9,10</sup> as aryl donor components in the synthesis of aryl–aryl motifs.<sup>12</sup>

Notable features of our findings include: (1) the first use of common primary amides as arylating reagents via redox-neutral decarbonylation; (2) cooperative catalytic system to selectively access aryl metal intermediates.

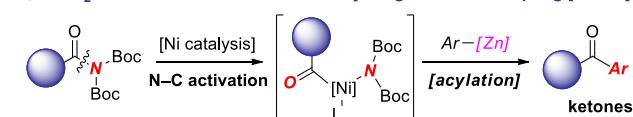
Based on our previous work in electrophilic activation of amides and metal-catalysis, we propose the mechanism shown in Figure 2. Initial amide transacylation enabled by *N,N*-diacylation of the amide bond<sup>19</sup> (E<sub>R</sub> = 7.6 kcal/mol)

with an appropriate Lewis base produces acylammonium intermediate (nucleophilic cycle). In a simultaneous organometallic cycle, Rh(I), undergoes selective oxidative addition into weak acylammonium bond<sup>20,21</sup> to generate a highly reactive acyl-Rh(III) intermediate. The feasibility of this proposed manifold heavily relies on the propensity of the acyl-Rh(III) intermediate to undergo controlled decarbonylation.<sup>22</sup> The subsequent chelation-directed ortho-C–H arylation by aryl-Rh(III)<sup>23</sup> gives diarylrhodium(III), releasing the Lewis base catalyst. The diarylrhodium(III) undergoes reductive elimination to generate the biaryl C–

**Amide electrophiles in decarbonylative coupling (C–C, C–N, C–H coupling)**

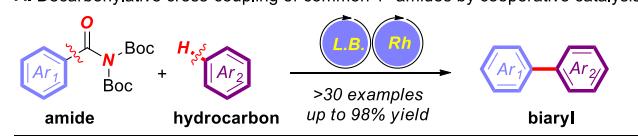


***N,N*-Boc<sub>2</sub>-activated 1° amides in direct acyl Negishi cross-coupling [ref. 8e]**

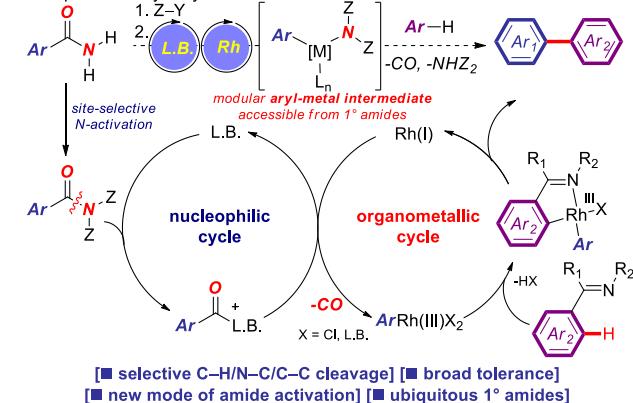


**Figure 1.** Decarbonylative cross-coupling of amides by N–C bond activation: current state-of-the-art and present work.

**A. Decarbonylative cross-coupling of common 1° amides by cooperative catalysis**



**B. Proposed catalytic cycle**



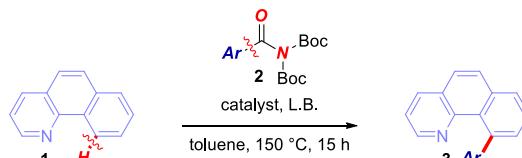
**Figure 2.** Proposed mechanism for site-selective C–H arylation with common 1° amides as arylating reagents by cooperative catalysis.

H activation product and releases the Rh(I) catalyst to complete the cycle. Given the marked increase in electrophilicity of the N–C(O) bond following selective N-*tert*-butoxycarbonyl activation,<sup>19</sup> we presumed that the nucleophilic capture of the amide bond would be facile. Protinating the carbonyl group of the N–carbamate would further increase the propensity of the amide bond for metal insertion.<sup>24</sup> Finally, the mild conditions associated with Rh(I)-catalysis<sup>23</sup> would obviate the undesired cleavage of

the N–carbamate, which is a common side reaction with nucleophilic Ni(o) and Pd(o)-catalytic systems,<sup>2–6</sup> thus resulting in a broadly applicable process.

The reaction conditions were first optimized for the cross-coupling of *N,N*-di-Boc-activated amide (**1**) with benzo[*h*]quinoline as the model substrate for investigation (Table 1, entry 1). The optimized conditions utilize  $[\text{Rh}(\text{cod})\text{Cl}]_2$  (5 mol%),  $n\text{-Bu}_3\text{N}$  (30 mol%),  $\text{H}_2\text{O}$  (1.5 equiv) in toluene at 150 °C, affording the desired product in quantitative yield. Several points should be noted: (1) all *N,N*-di-Boc activated amides are prepared directly in one-step from the corresponding benzamides, including substrates with Lewis basic sites.<sup>25</sup> This represents a substantial departure from the cross-coupling of other types of amides that have been largely thus far limited to the coupling of less common tertiary amides that are ultimately

**Table 1. Optimization of the Reaction Conditions<sup>a</sup>**



entry	catalyst	nucleophile	additive	yield (%) <sup>b</sup>
1	$[\text{Rh}(\text{cod})\text{Cl}]_2$	$\text{Bu}_3\text{N}$	$\text{H}_2\text{O}$	>98
2	$[\text{Rh}(\text{cod})_2\text{BF}_4$	$\text{Bu}_3\text{N}$	$\text{H}_2\text{O}$	70
3	$[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$	$\text{Bu}_3\text{N}$	$\text{H}_2\text{O}$	53
4	$[\text{Rh}(\text{CO})_2\text{Cl}]_2$	$\text{Bu}_3\text{N}$	$\text{H}_2\text{O}$	35
5	$\text{RhCl}(\text{PPh}_3)_3$	$\text{Bu}_3\text{N}$	$\text{H}_2\text{O}$	<5
6	$[\text{Rh}(\text{cod})\text{Cl}]_2$	$\text{Et}_3\text{N}$	$\text{H}_2\text{O}$	97
7	$[\text{Rh}(\text{cod})\text{Cl}]_2$	$\text{DIEA}$	$\text{H}_2\text{O}$	29
8	$[\text{Rh}(\text{cod})\text{Cl}]_2$	isoquinoline	$\text{H}_2\text{O}$	<5
9	$[\text{Rh}(\text{cod})\text{Cl}]_2$	pyridine	$\text{H}_2\text{O}$	18
10	$[\text{Rh}(\text{cod})\text{Cl}]_2$	quinoline	$\text{H}_2\text{O}$	73
11	$[\text{Rh}(\text{cod})\text{Cl}]_2$	DMAP	$\text{H}_2\text{O}$	<5
12	$[\text{Rh}(\text{cod})\text{Cl}]_2$	$\text{Bu}_3\text{N}$	-	59
13	$[\text{Rh}(\text{cod})\text{Cl}]_2$	-	$\text{H}_2\text{O}$	20
14	$[\text{Rh}(\text{cod})\text{Cl}]_2$	-	-	19
15	$[\text{Rh}(\text{cod})\text{Cl}]_2$	$\text{K}_2\text{CO}_3$	-	<5
16 <sup>c</sup>	$[\text{Rh}(\text{cod})\text{Cl}]_2$	$\text{Bu}_3\text{N}$	$\text{H}_2\text{O}$	20
17 <sup>d</sup>	$[\text{Rh}(\text{cod})\text{Cl}]_2$	$\text{Bu}_3\text{N}$	$\text{H}_2\text{O}$	79
18	$[\text{Rh}(\text{cod})\text{Cl}]_2$	$\text{Bu}_3\text{N}$	$\text{H}_3\text{BO}_3$	98

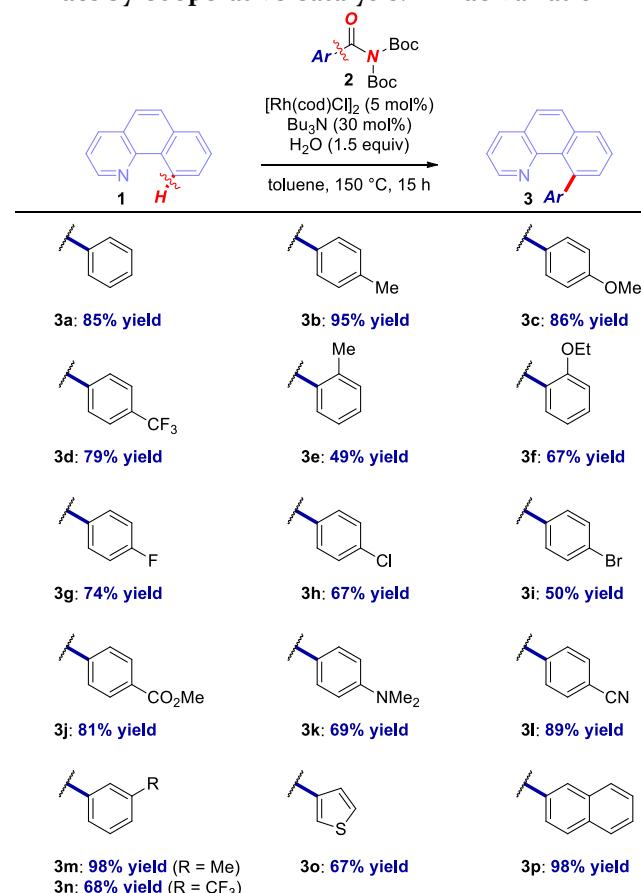
<sup>a</sup>Conditions: **1** (1.0 equiv), amide (1.5 equiv), catalyst (5 mol%), L.B. (30 mol%), additive (1.5 equiv), toluene (0.25 M), 150 °C, 15 h. <sup>b</sup>GC/H NMR yields. <sup>c</sup> $\text{Bu}_3\text{N}$  (1.0 equiv). <sup>d</sup> $\text{H}_2\text{O}$  (3.0 equiv). L.B. = Lewis base.

derived from carboxylic acids or aryl chlorides<sup>2–6</sup> (cf. ubiquitous primary amides).<sup>9,10</sup> (2) The cooperative catalytic cycle bypasses the direct metal insertion into the amide bond, thus providing a powerful catalytic approach that can be triggered by complementary reactivity to the conventional activation.<sup>18</sup> (3) The high chemoselectivity of the process toward decarbonylation bodes well for the development of direct arylation reactions with other elec-

trophiles,<sup>26</sup> and hinges upon high capability of Rh(I) to facilitate decarbonylation.

Selected key optimization results are presented in Table 1. Various catalysts were tested, and  $[\text{Rh}(\text{cod})\text{Cl}]_2$  showed the best activity (entries 1-5). Of note, Wilkinson's catalyst showed poor reactivity in the coupling. Other Lewis bases can also be used; however,  $n\text{-Bu}_3\text{N}$  provided consistently the best results (entries 6-11). Water acts as an essential additive in this coupling (entries 12-14). Water can be substituted with  $\text{H}_3\text{BO}_3$  without a significant decrease in the reaction efficiency (entries 18). We hypothesize that the amide bond is activated by switchable O/O-coordination of the N-carbamate.<sup>24</sup> The inclusion of an inorganic base,  $\text{K}_2\text{CO}_3$ , inhibits the reaction (entry 15 cf. 14).<sup>16i</sup> As expected, no product formation is observed in the absence of rhodium catalyst and minimal product formation is

**Scheme 1. C-H Arylation of Benzo[*h*]quinoline with Amides by Cooperative Catalysis: Amide Variation<sup>a,b</sup>**

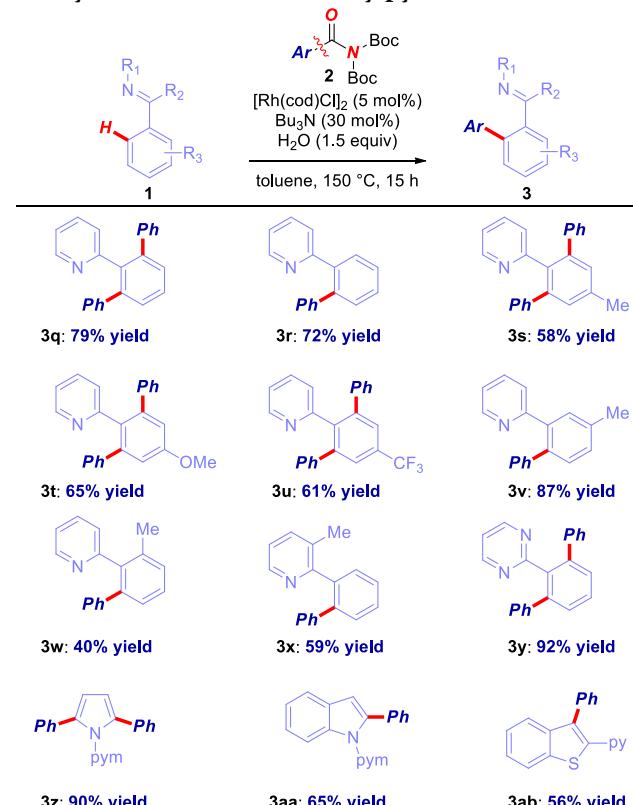


<sup>a</sup>Conditions: **1** (1.0 equiv), amide (1.5 equiv),  $[\text{Rh}(\text{cod})\text{Cl}]_2$  (5 mol%),  $\text{Bu}_3\text{N}$  (30 mol%),  $\text{H}_2\text{O}$  (1.5 equiv), toluene (0.25 M), 150 °C, 15 h. <sup>b</sup>I-solated yields. See SI for details.

observed in the absence of Lewis base (<20%) (entries 13-14). The optimized stoichiometry is critical to match the efficiency of both cycles (entries 16-17). Finally, it should be noted that the process is highly practical; the reaction can be conducted in the presence of ambient air in excellent yields.

With our newly developed arylation in hand the substrate scope of this deamidative C-C/C-H coupling was investigated. As shown in Scheme 1, a wide range of electronically-diverse amides can be employed in this transformation (**3a-3d**). Notably, bulky ortho-substituted amides can be tolerated, albeit in slightly diminished yields (**3e-3f**). Of particular note, the latter substrate directly utilizes 2-ethoxybenzamide (anti-inflammatory drug),<sup>27</sup> thus highlighting the capacity of the method to engage common substrates bearing primary amide bond. Particularly noteworthy is the functional group tolerance of this method, including fluorides (**3g**), chlorides (**3h**), bromides (**3i**), esters (**3j**), anilines (**3k**), and nitriles (**3l**) that would be problematic with Grignard reagents. Meta-substitution is well-tolerated (**3m-3n**). Furthermore, heterocycles (**3o**) and polyarenes (**3p**) are compatible with the reaction conditions, despite their capacity to undergo deamidative decomposition. The arylation using 3-pyridyl amide containing additional basic nitrogen proceeds in unoptimized 49% yield (not shown). The scope with respect to the directing

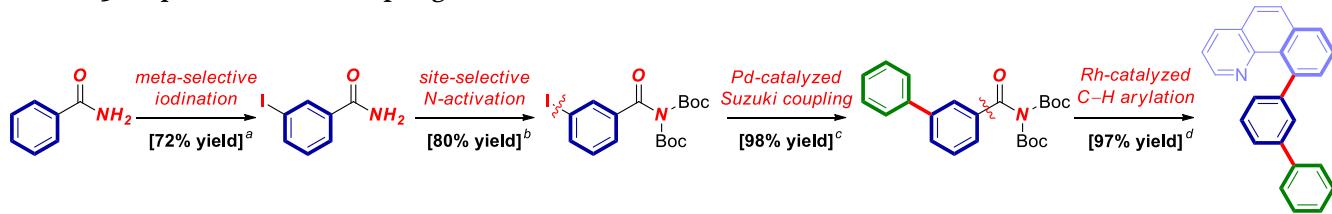
**Scheme 2. C-H Arylation with Amides by Cooperative Catalysis: Variation of 2-Phenylpyridine<sup>a,b</sup>**



<sup>a</sup>Conditions: **1** (1.0 equiv), amide (1-3 equiv),  $[\text{Rh}(\text{cod})\text{Cl}]_2$  (5 mol%),  $\text{Bu}_3\text{N}$  (30 mol%),  $\text{H}_2\text{O}$  (1.5 equiv), toluene (0.25 M), 150 °C, 15 h. <sup>b</sup>I-solated yields. See SI for details.

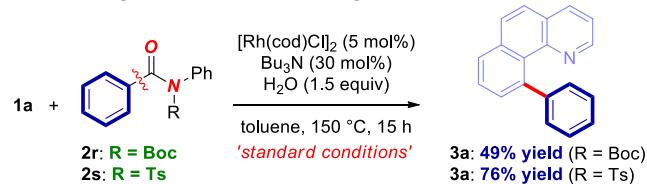
group component was next evaluated (Scheme 2). Typically, excess of the amide was used, resulting in double C-H arylation (**3q**). This highly efficient process results in selective breaking of 6 different bonds (96.1% efficiency per bond). The example with stoichiometric amount (**3r**) illustrates that monoarylation is possible with high

**Scheme 3. Sequential Cross-Coupling<sup>a</sup>**

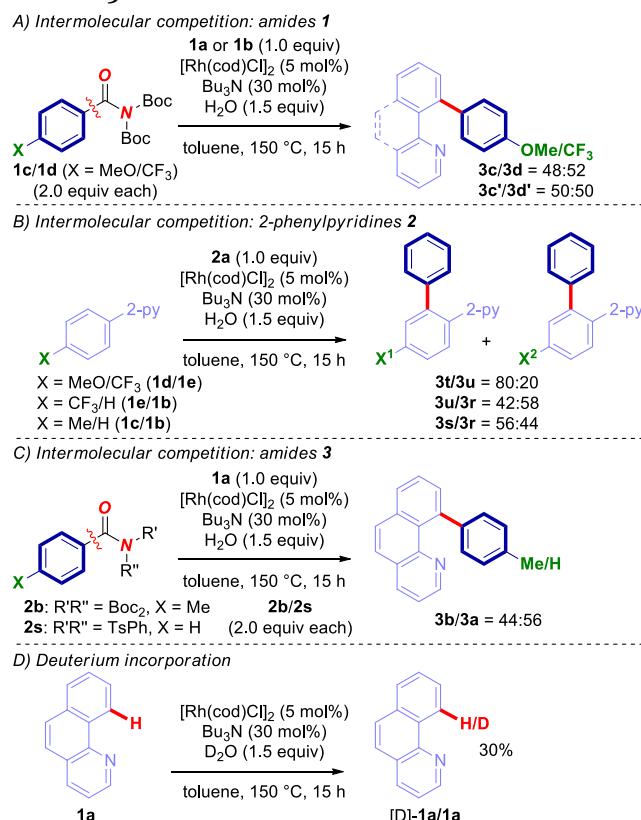


<sup>a</sup>Conditions: a)  $I_2$ ,  $NaIO_4$ ,  $H_2SO_4$ , 23 °C; b)  $Boc_2O$ ,  $Et_3N$ ,  $CH_2Cl_2$ , 23 °C; c)  $Pd(OAc)_2$ ,  $PhB(OH)_2$ ,  $Na_2CO_3$ ,  $EtOH:H_2O$ , 23 °C; d) standard conditions.

**Scheme 4. C-H Arylation with Common Secondary Amides by Cooperative Catalysis**



**Scheme 5. Mechanistic Studies**



selectivity. Substrates bearing para- (**3s-3u**) and meta-substituents (**3v**) on the 2-phenylpyridine component were successfully coupled in good yields. The more sterically-demanding ortho-methyl substrate successfully coupled, albeit in lower yield (**3w**). Conversely, ortho-substitution on the pyridine was well-tolerated, resulting in high selectivity for monoarylation (**3x**). Furthermore, substrates bearing other heterocycles, such as pyrimidine (**3y**), pyrrole (**3z**), indole (**3aa**) and benzothiophene (**3ab**) were successfully coupled with amides to afford the biaryl products in good to excellent yields.

The potential of primary benzamides to serve as a directing group was demonstrated in the sequential meta-iodination, Suzuki cross-coupling/C-H arylation (Scheme 3). Importantly, Suzuki cross-coupling could be readily performed in the presence of the electrophilic *N,N*-di-Boc moiety, allowing for a strategically valuable disconnection akin to Weinreb amides,<sup>28</sup> but via a decarbonylative pathway.

Intriguingly, although these reaction conditions were optimized for *N,N*-di-Boc-benzamides, we found that acyclic *N,N*-Ph/Boc and *N,N*-Ph/Ts amides that are readily prepared from common secondary<sup>2,4c</sup> amides underwent arylation in 49–76% yields (Scheme 4). Importantly, this observation shows the potential of cooperative catalytic strategy to engage common secondary acyclic amides as arylating reagents for directed C-H arylation.

Several studies were performed to gain insight into the mechanism (Scheme 5). (1) Intermolecular competition experiments between differently substituted amides ( $R = 4\text{-MeO}/4\text{-CF}_3$ ) revealed that the coupling is relatively insensitive to the electronics of electrophile (1:1). (2) Further competition experiments with differently substituted 2-phenylpyridines revealed the electron-rich arenes are inherently more reactive ( $R = 4\text{-MeO}/4\text{-CF}_3$ , 4:1). (3) The following order of reactivity of amide electrophiles has been established:  $N,N\text{-Boc}_2 \approx N,N\text{-Ts}/\text{Ph} >> N,N\text{-Boc}/\text{Ph}$ . In addition, anilides ( $N,N$ -alkyl/Ph) and  $N,N$ -dialkyl amides are recovered unchanged from these conditions, attesting to the potential of the method in chemoselective synthesis and consistent with the electrophilicity of the amide bond undergoing N-C cleavage.<sup>19</sup> (4) Deuterium incorporation experiments revealed reversibility of the C-H activation step at the ortho-position of **1a**. (5) A TON of 480 in Rh in the arylation of **1a** with **2a** has been determined, showing highly efficient catalysis. Overall, these mechanistic findings strongly support reversible C-H functionalization by electrophilic substitution pathway.<sup>15e</sup> Further studies to elucidate the mechanism are ongoing.

In summary, we have developed the first method for arylation of non-acidic ( $sp^2$ )-H bonds with primary amides as the arylating reagent. The key to the successful development is the use of cooperative rhodium(I) catalysis and Lewis base catalysis, which can promote activation of inert C-N bonds in ubiquitous primary amides after selective *N-tert*-butoxycarbonyl activation in a highly efficient manner by an orchestrated sequence of C-N, C-C and C-H cleavages. Considering that primary amides are among the most important amide derivatives in small organic molecules and prevalent intermediates in pharmaceuticals and biologically active materials, we expect

that this study will be of great interest. Equally importantly, this process provides a novel method for generating aryl electrophiles, and may unlock a broad range of arylations by synergistic catalysis mechanisms. Studies toward expanding the reaction scope to other precursors as well as on further developments of C–N activation technologies are actively pursued in our laboratory and will be reported in due course.

## ASSOCIATED CONTENT

### Supporting Information

Procedures and analytical data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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## REFERENCES

- (1) (a) Greenberg, A.; Breneman, C. M.; Liebman, J. F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; Wiley-VCH: New York, 2003. (b) Pattabiraman, V. R.; Bode, J. W. *Nature* **2011**, *480*, 471-479. (c) Ruider, S.; Maulide, N. *Angew. Chem. Int. Ed.* **2015**, *54*, 13856-13858.
- (2) For reviews on N–C functionalization, see: (a) Takise, R.; Muto, K.; Yamaguchi, J. *Chem. Soc. Rev.* **2017**, DOI: 10.1039/c7cs00182g. (b) Meng, G.; Shi, S.; Szostak, M. *Synlett* **2016**, *27*, 2530-3540. (c) Liu, C.; Szostak, M. *Chem. Eur. J.* **2017**, *23*, 7157-7173.
- (3) (a) *Science of Synthesis: Cross-Coupling and Heck-Type Reactions*, Molander, G. A.; Wolfe, J. P.; Larhed, M., Eds.; Thieme: Stuttgart, 2013. (b) *Metal-Catalyzed Cross-Coupling Reactions and More*, de Meijere, A.; Bräse, S.; Oestreich, M., Eds.; Wiley: New York, 2014. (c) *New Trends in Cross-Coupling*; Colacot, T. J., Ed.; The Royal Society of Chemistry: Cambridge, 2015.
- (4) For representative acyl coupling, see: (a) Hie, L.; Nathel, N. F. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y. F.; Liu, P.; Houk, K. N.; Garg, N. K. *Nature* **2015**, *524*, 79-83. (b) Meng, G.; Szostak, M. *Org. Lett.* **2015**, *17*, 4364-4367. (c) Lei, P.; Meng, G.; Szostak, M. *ACS Catal.* **2017**, *7*, 1960-1965. (d) Meng, G.; Lei, P.; Szostak, M. *Org. Lett.* **2017**, *19*, 2158-2161. (e) Amani, J.; Alam, R.; Badir, S.; Molander, G. A. *Org. Lett.* **2017**, *19*, 2426-2429. (f) Ni, S.; Zhang, W.; Mei, H.; Han, J.; Pan, Y. *Org. Lett.* **2017**, *19*, 2536-2539. (g) Lei, P.; Meng, G.; Shi, S.; Ling, Y.; An, J.; Szostak, R.; Szostak, M. *Chem. Sci.* **2017**, *8*, 6525-6530 and references cited therein.
- (5) For representative decarbonylative coupling, see: (a) Meng, G.; Szostak, M. *Angew. Chem. Int. Ed.* **2015**, *54*, 14518-14522. (b) Shi, S.; Meng, G.; Szostak, M. *Angew. Chem. Int. Ed.* **2016**, *55*, 6959-6953. (c) Meng, G.; Szostak, M. *Org. Lett.* **2016**, *18*, 796. (d) Dey, A.; Sasmai, S.; Seth, K.; Lahiri, G. K.; Maiti, D. *ACS Catal.* **2017**, *7*, 433-437. (e) Yue, H.; Guo, L.; Liao, H. H.; Cai, Y.; Zhu, C.; Rueping, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 4282-4285. (f) Yue, H.; Guo, L.; Lee, S. C.; Liu, X.; Rueping, M. *Angew. Chem. Int. Ed.* **2017**, *56*, 3972-3976. (g) Srimontree, W.; Chatupheeraphat, A.; Liao, H. H.; Rueping, M. *Org. Lett.* **2017**, *19*, 3091-3094. (h) Shi, S.; Szostak, M. *Org. Lett.* **2017**, *19*, 3095-3098 and references cited therein.
- (6) For representative tandem coupling, see: Walker, J. A.; Vickerman, K. L.; Humke, J. N.; Stanley, L. M. *J. Am. Chem. Soc.* **2017**, *139*, 10228-10231 and references cited therein.
- (7) For classic studies on amide destabilization in bridged lactams, see: (a) Tani, K.; Stoltz, B. M. *Nature* **2006**, *441*, 731-734. (b) Greenberg, A.; Venanzi, C. A. *J. Am. Chem. Soc.* **1993**, *115*, 6951-6957. (c) Aubé, J. *Angew. Chem. Int. Ed.* **2012**, *51*, 3063-3065.
- (8) For pertinent studies on amide destabilization in N–C cross-coupling, see: (a) Szostak, R.; Shi, S.; Meng, G.; Lalancette, R.; Szostak, M. *J. Org. Chem.* **2016**, *81*, 8091-8094. (b) Pace, V.; Holzer, W.; Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. *Chem. Eur. J.* **2016**, *22*, 14494-14498. (c) Szostak, R.; Meng, G.; Szostak, M. *J. Org. Chem.* **2017**, *82*, 6373-6378. (d) See, ref. 1c. (e) For acyl-Negishi coupling using *N,N*-Boc<sub>2</sub>-amides, see: Shi, S.; Szostak, M. *Org. Lett.* **2016**, *18*, 5872-5875.
- (9) (a) Roughley, S. D.; Jordan, A. M. *J. Med. Chem.* **2011**, *54*, 3451-3479. (b) Kaspar, A. A.; Reichert, J. M. *Drug Discov. Today* **2013**, *18*, 807-817. (c) Marchildon, K. *Macromol. React. Eng.* **2011**, *5*, 22-54. (d) Chen, Y.; Turlik, A.; Newhouse, T. *J. Am. Chem. Soc.* **2016**, *138*, 1166-1169.
- (10) (a) Larock, R. C. *Comprehensive Organic Transformations*; Wiley: New York, 1999. (b) Zabicky, J. *The Chemistry of Amides*; Interscience: New York, 1970.
- (11) Select reviews on C–H activation: (a) Yu, J. Q. *Science of Synthesis: Catalytic Transformations via C–H Activation*; Thieme: Stuttgart, 2015. (b) Chen, Z.; Wang, B.; Zhang, J.; Yu, W.; Liu, Z.; Zhang, Y. *Org. Chem. Front.* **2015**, *2*, 1107-1295. (c) Daugulis, O.; Roane, J.; Tran, L. D. *Acc. Chem. Res.* **2015**, *48*, 1053-1064. (d) Miao, J.; Ge, H. *Eur. J. Org. Chem.* **2015**, 7859-7868. (e) Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. *Adv. Synth. Catal.* **2014**, *356*, 17-117. (f) Engle, K. M.; Mei, T. S.; Wasa, M.; Yu, J. Q. *Acc. Chem. Res.* **2012**, *45*, 788-802. (g) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960-9009. (h) Yeung, C. S.; Dong, V. M. *Chem. Rev.* **2011**, *111*, 1215-1292. (i) Lyons, T.; Sanford, M. *Chem. Rev.* **2010**, *110*, 1147-1169.
- (12) (a) Hussain, I.; Singh, T. *Adv. Synth. Catal.* **2014**, *356*, 1661-1696. (b) *Modern Arylation Methods*, Burke, A. J.; Marques, C. S., Eds.; Wiley-VCH: Weinheim, 2015.
- (13) For a comprehensive review on C–H arylation with organometallics, see: Giri, R.; Thapa, S.; Kafle, A. *Adv. Synth. Catal.* **2014**, *356*, 1395-1411.
- (14) For a recent C–H arylation of primary amines, see: Liu, Y.; Ge, H. *Nat. Chem.* **2017**, *9*, 26-32.
- (15) Ni: (a) Amaike, K.; Muto, K.; Yamaguchi, J.; Itami, K. *J. Am. Chem. Soc.* **2012**, *134*, 13573-13576. (b) Muto, K.; Yamaguchi, J.; Lei, A.; Itami, K. *J. Am. Chem. Soc.* **2013**, *135*, 16384-16387. (c) Muto, K.; Hatakeyama, T.; Yamaguchi, J.; Itami, K. *Chem. Sci.* **2015**, *6*, 6792-6798. Co: (d) Song, W.; Ackermann, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 8251-8254. Rh: (e) Tobisu, M.; Yasui, K.; Aihara, Y.; Chatani, N. *Angew. Chem. Int. Ed.* **2017**, *56*, 1877-1880.
- (16) Select examples: Halides/pseudohalides: (a) Kametani, Y.; Satoh, T.; Miura, M.; Nomura, M. *Tetrahedron Lett.* **2000**, *41*, 2655-2659. (b) Daugulis, O.; Zaitsev, V. G.; *Angew. Chem. Int. Ed.* **2005**, *44*, 4046-4048. (c) Berman, A. M.; Lewis, J. C.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2008**, *130*, 14926-14927. (d) Kim, M.; Kwak, J.; Chang, S. *Angew. Chem. Int. Ed.* **2009**, *48*, 8935-8939. (e) Ackermann, L.; Althammer, A.; Born, R. *Angew. Chem. Int. Ed.* **2006**, *45*, 2619-2622. (f) Roger, J.; Doucet, H. *Org. Biomol. Chem.* **2008**, *6*, 169-174. Organometallics: (g) Sun, C. L.; Li, B. J.; Shi, Z. *J. Chem. Commun.* **2010**, *46*, 677-685. Arenes: (h) Zhao, X.; Yeung, C. S.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 5837-5844. Aroyl halides: (i) Zhao, X.; Yu, Z. *J. Am. Chem. Soc.* **2008**, *130*, 8136-8137. Anhydrides: (j) Jin, W.; Yu, Z.; He, W.; Ye, Y.

W.; Xiao, W. *J. Org. Lett.* **2009**, *11*, 1317-1320. (k) Pan, F.; Lei, Z. Q.; Wang, H.; Li, H.; Sun, J.; Shi, Z. *J. Angew. Chem. Int. Ed.* **2013**, *52*, 2063-2067. Aldehydes: (l) Shuai, Q.; Yang, L.; Guo, X.; Basle, O.; Li, C. *J. Am. Chem. Soc.* **2010**, *132*, 12212-12213.

(17) For pertinent examples of decarboxylative cross-coupling, see: (a) Gooßen, L. J.; Deng, G.; Levy, L. M. *Science* **2006**, *313*, 662-664. (b) Gooßen, L. J.; Rodriguez, N.; Melzer, B.; Linder, C.; Deng, G.; Levy, L. M. *J. Am. Chem. Soc.* **2007**, *129*, 4824-4833. (c) Wei, Y.; Hu, P.; Zhang, M.; Su, W. *Chem. Rev.* **2017**, *117*, 8864-8907.

(18) Select reviews on cooperative catalysis: (a) Peters, R. *Cooperative Catalysis: Designing Efficient Catalysts for Synthesis*; Wiley-VCH: 2015. (b) Du, Z.; Shao, Z. *Chem. Soc. Rev.* **2013**, *42*, 1337-1378. (c) Allen, A. E.; MacMillan, D. W. C. *Chem. Sci.* **2012**, *3*, 633-658.

(19) Davidsen, S. K.; May, P. D.; Summers, J. B. *J. Org. Chem.* **1991**, *56*, 5482-5485.

(20) (a) Blakey, S. B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2003**, *125*, 6046-6047. (b) Buszek, K. R.; Brown, N. *Org. Lett.* **2007**, *9*, 707-710.

(21) Reviews on acyl-metal intermediates: (a) Gooßen, L. J.; Rodriguez, N.; Gooßen, K. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100-3120. (b) Dzik, W. I.; Lange, P. P.; Gooßen, L. J. *Chem. Sci.* **2012**, *3*, 2671-2678.

(22) Johnson, J. B.; Rovis, T. *Acc. Chem. Res.* **2008**, *41*, 327-338.

(23) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624-655.

(24) Cox, C.; Lectka, T. *Acc. Chem. Res.* **2000**, *33*, 849-858.

(25) See the Supporting Information.

(26) Bera, M.; Agasti, S.; Chowdhury, R.; Mondal, R.; Pal, D.; Maiti, D. *Angew. Chem. Int. Ed.* **2017**, *56*, 5272-5276 and references cited therein.

(27) Lemke, T. L.; Williams, D. A. *Foye's Principles of Medicinal Chemistry*, Lippincott: Philadelphia, 2013.

(28) Nahm, S.; Weinreb, S. M. *Tetrahedron Lett.* **1981**, *22*, 3815-3818.