Palladium/NHC (NHC = N-Heterocyclic Carbene)-Catalyzed Suzuki–Miyaura Cross-Coupling of Alkyl Amides

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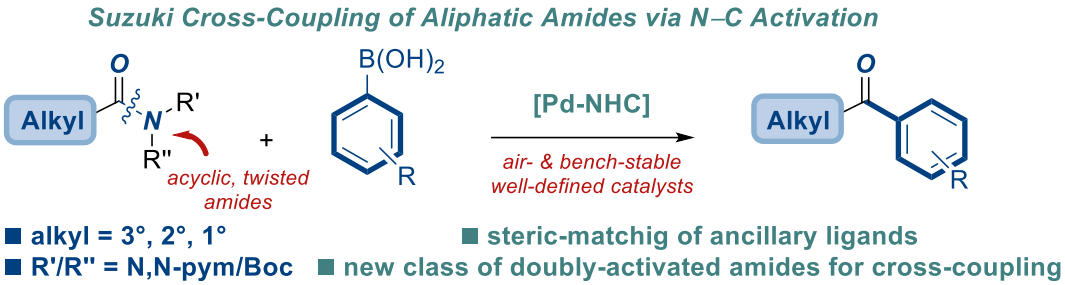
Supporting Information



ABSTRACT: We report the Pd-catalyzed Suzuki-Miyaura cross-coupling of aliphatic amides. Although tremendous advances have been made in the cross-coupling of *aromatic* amides, C–C bond formation from *aliphatic* amides by selective N–C(O) cleavage has remained a major challenge. This long-standing problem in Pd-catalysis has been addressed herein by a combination of (1) the discovery of N,N-pym/Boc amides as a class of readily accessible amide based reagents for cross-coupling, and (2) steric-tuning of well-defined Pd(II)-NHC catalysts for cross-coupling. The methodology is effective for the cross-coupling of an array of 3°, 2° and 1° aliphatic amide derivatives. The catalyst system is user-friendly since the catalysts are readily-available, air- and bench-stable. Mechanistic studies strongly support amide bond twist and external $n_N \rightarrow \pi^*_{C=O/Ar}$ delocalization as a unified enabling feature of N,N-pym/Boc amides in selective N–C(O) bond activation. The method provides a rare example Pd-NHC-catalyzed cross-coupling of aliphatic acyl amide electrophiles.

KEYWORDS: *cross-coupling; Pd–NHCs; N–C activation; alkyl amides; amide resonance; twisted amides*

Since 2015, marking the first reports on selective N–C(O) bond activation of amides by transition-metal-catalysis, tremendous progress has been achieved in the development of powerful methods for cross-coupling of amide bonds (Figure 1A).[1,2] The selective activation of amides is particularly attractive due to the ubiquitous presence of amides in all facets of organic synthesis.[3,4] In this context, major advances in the oxidative addition of N–C(O) bonds to transition metals have been achieved by ground-state-destabilization of the amide bond,[5,6] enabling to overcome the $n_N \rightarrow \pi^*_{C=O}$ conjugation barrier (amidic resonance, 15-20 kcal/mol in planar amides) by twist and electronic delocalization.[7]

Nevertheless, despite significant progress, C–C bond formation from *aliphatic* amide derivatives has remained a major challenge.[8] At present, there is only report by Garg and coworkers on a Ni-catalyzed Suzuki–Miyaura cross-coupling of aliphatic amides (Figure 1A).[9] In this elegant study, Garg's group developed a Ni(0)-NHC-catalyst system using a combination of $Ni(cod)_2$ and benzo-fused benz-ICy (ICy-bimy) as supporting ligand [$Ni(cod)_2$, 5 mol%; benz-ICy, 10 mol%, K_3PO_4, H_2O, toluene, 120 °C]. Later, to address the inherent sensitivity of Ni(0) to air, the same group reported a clever solution by employing paraffin capsules.[10] This scarcity of methods for the selective C–C bond formation from *aliphatic* amides is not surprising since previous computational studies showed that aliphatic amides suffer from high activation barrier of the N–C(O) bond to oxidative addition (cf. *aromatic* amides).[11]

Our laboratory has studied amide bond activation and transition-metal-NHC catalysis.[12] As a part of these efforts, herein, we report the first Pd-catalyzed Suzuki-Miyaura cross-coupling of *aliphatic* amides (Figure 1B). This method has

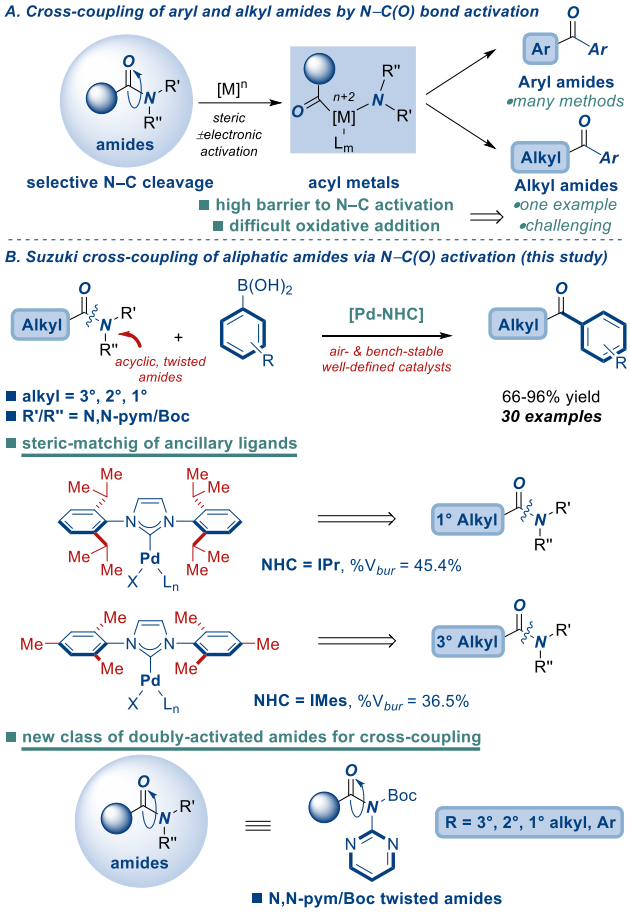
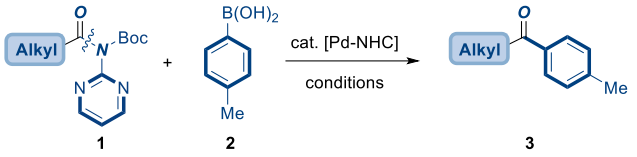


Figure 1. (A) Challenges in cross-coupling of amides by selective N–C cleavage. (B) Pd-NHC-catalyzed cross-coupling of aliphatic amides by ancillary ligand steric matching and amide development (this work).

been achieved by a combination of (1) the discovery of N,N-pym/Boc amides as a new class of readily accessible amide based reagents for cross-coupling, and (2) steric-tuning of well-defined Pd(II)-NHC catalysts for cross-coupling.[13] The method is effective for the cross-coupling of a broad array of 3°, 2° and 1° aliphatic amide derivatives. The method takes advantage of the highly-reactive, air- and moisture-stable Pd(II)–NHC precatalysts by steric matching with the properties of the amide bond, offering a new platform for Pd-catalyzed cross-coupling of *aliphatic* amide derivatives.[14] The method represents the first Pd-catalyzed cross-coupling of amides with potential applications ranging from functionalization of amides in biomolecules and pharmaceuticals to industrial N–C cross-coupling. The method further introduces a new activating group that allows for tuning of amide resonance by a combined N-acyl and N-pyrimidyl activation for a broad range of cross-couplings.

Reaction Design. From the outset of our study, we questioned whether highly reactive Pd-NHC catalysts bearing strongly σ-donating NHC ligands, which have shown to be effective in C(acyl)–N activation, could promote productive cross-coupling of *aliphatic* amides. Such a method would be highly advantageous due to the accessibility of Pd(II)-NHC precatalysts and their well-established tuning potential through modification of ancillary and throw-away ligands.[12–14]

Table 1. Optimization of Pd-NHC-Catalyzed Suzuki–Miyaura Cross-Coupling of Alkyl Amides[a]



amide	entry	catalyst	yield (%)
A.	1	[Pd(IPr)(3-Cl-py)Cl_2]	<2
	2	[Pd(IPent)(3-Cl-py)Cl_2]	<2
	3	[Pd(IPr)(cin)Cl]	<2
	4	[Pd(IPr)(1-*t*-Bu-ind)Cl]	<2
	5	[Pd(IMes)(3-Cl-py)Cl_2]	>95
	6	[Pd(I*t*Bu)(3-Cl-py)Cl_2]	31
3° alkyl	7	[Pd(IMes)(allyl)Cl]	42
	8	[[Pd(IMes)(μ-Cl)Cl]$_2$	79
	9	[[Pd(IPr)(μ-Cl)Cl]$_2$	14
B.	10	[Pd(IPr)(3-Cl-py)Cl_2]	60
	11	[Pd(IPent)(3-Cl-py)Cl_2]	<2
	12	[Pd(IPr)(cin)Cl]	17
	13	[Pd(IPr)(1-*t*-Bu-ind)Cl]	46
	14	[Pd(IMes)(3-Cl-py)Cl_2]	92
	15	[Pd(I*t*Bu)(3-Cl-py)Cl_2]	20
2° alkyl	16	[Pd(IMes)(allyl)Cl]	37
	17	[[Pd(IMes)(μ-Cl)Cl]$_2$	72
	18	[[Pd(IPr)(μ-Cl)Cl]$_2$	26
C.	19	[Pd(IPr)(3-Cl-py)Cl_2]	95
	20	[Pd(IPent)(3-Cl-py)Cl_2]	31
	21	[Pd(IPr)(cin)Cl]	28
	22	[Pd(IPr)(1-*t*-Bu-ind)Cl]	40
	23	[Pd(IMes)(3-Cl-py)Cl_2]	86
	24	[Pd(I*t*Bu)(3-Cl-py)Cl_2]	18
1° alkyl	25	[Pd(IMes)(allyl)Cl]	30
	26	[[Pd(IMes)(μ-Cl)Cl]$_2$	55
	27	[[Pd(IPr)(μ-Cl)Cl]$_2$	37

[a]Conditions: **1** (1.0 equiv), 4-Tol-B(OH)$_2$ (2.0 equiv), [Pd] (3 mol%), K_2CO_3(3.0 equiv), dioxane (0.20 M), 80 °C, 15 h. See SI for details.

Initial attempts using a range of typical amides employed for C(acyl)–N activation, such as N-Ts, N-Boc or N-acyl-glutarimides, were ineffective resulting in no or trace quantities of the cross-coupling products (see SI). Evidently, the combination of ground-state-destabilization and steric properties of the N-substituents required to alter the $n_N \rightarrow \pi^*_{C=O}$ conjugation is not compatible with the cross-coupling of *aliphatic* amides. Thus, we set out to devise a new class of amides that would (1) electronically and sterically facilitate oxidative addition by decreasing amidic resonance, and (2) accommodate sterically-demanding substitution. After very significant experimentation, we found that N,N-pym/Boc amides undergo effective cross-coupling under Pd(II)-NHC conditions. Selected optimization results are presented in Table 1.

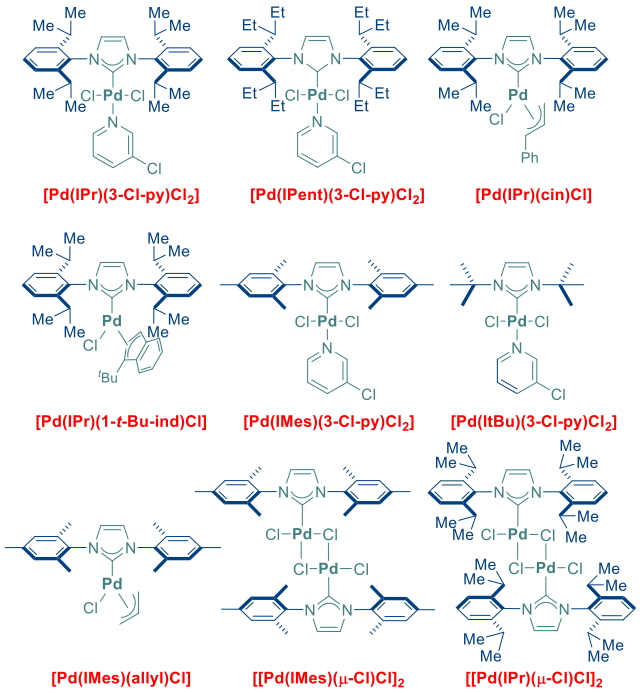


Figure 2. Structures of palladium-NHC precatalysts.

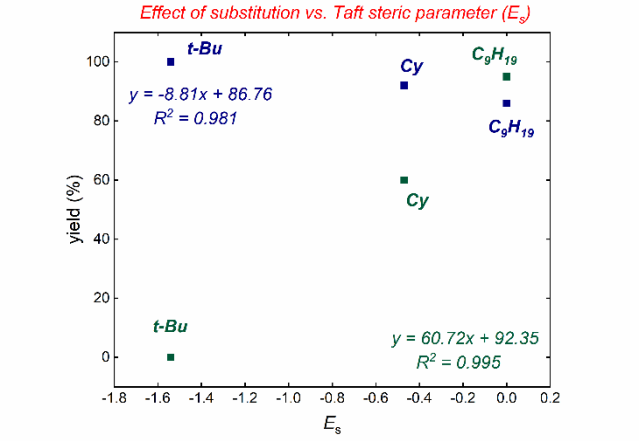


Figure 3. Yield vs. Taft steric parameter. Blue squares indicate cross-coupling of 3°, 2° and 1° amide using [Pd(IMes)(3-Cl-py)Cl_2] system; green indicate cross-coupling using [Pd(IPr)(3-Cl-py)Cl_2] system.

Reaction Optimization. Although no productive coupling was observed using [Pd(IPr)(3-Cl-py)Cl_2] as a catalyst bearing IPr ligand (IPr =1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene), as well as more sterically-demanding [Pd(IPent)(3-Cl-py)Cl_2] and analogues with allyl-type throw-away ligands, such as [Pd(IPr)(cin)Cl] and [Pd(IPr)(1-*t*-Bu-ind)Cl](Figure 2), we were delighted to find that less sterically-demanding [Pd(IMes)(3-Cl-py)Cl_2] afforded the cross-coupling products in excellent yield (Table 1A). Furthermore, [Pd(I*t*Bu)(3-Cl-py)Cl_2] and [Pd(IMes)(allyl)Cl] bearing an aliphatic N-wingtip and allyl throw-away ligand on Pd, respectively, were less effective, while high conversion was observed using the fast-activating chloro dimer precatalyst, [[Pd(IMes)(μ-Cl)Cl]$_2$. In contrast, the use of analogous [[Pd(IPr)(μ-Cl)Cl]$_2$ resulted in low conversion. Overall, these results suggest that for the coupling of sterically-demanding aliphatic amide derivatives, Pd–NHC catalysts bearing less bulky ancillary ligands, such as IMes (%V_{bur} = 36.5%) are preferred over more sterically-demanding ancillary ligands, such as IPr (%V_{bur} = 45.4%) or IPent (%V_{bur} = 49.0%).[15]

Interestingly, the optimization using 2° and 1° aliphatic amides indicated a major change in catalyst reactivity (Table 1B and 1C). As such, in the cross-coupling of a 2° amide, a gradual shift of the reactivity towards less sterically-demanding NHC ligands was observed (Table 1B). While [Pd(IMes)(3-Cl-py)Cl_2] bearing the IMes ligands is still the preferred catalyst, there is a significant improvement of [Pd(IPr)(3-Cl-py)Cl_2], including its allylcongeners, while [Pd(IPent)(3-Cl-py)Cl_2] is still ineffective. Further, in moving to a 1° amide, now [Pd(IPr)(3-Cl-py)Cl_2] bearing IPr ligand is the preferred catalyst, closely followed by [Pd(IMes)(3-Cl-py)Cl_2]. Likewise, moderate reactivity is finally observed using the most sterically-demanding in the series [Pd(IPent)(3-Cl-py)Cl_2]. Interestingly, the dimeric NHC–Pd give relatively low performance compared with pyridinyl-chelated monomeric NHC–Pd. We hypothesize that nitrogen ligands might play a role in affecting the activity of Pd by re-coordination to monoligated Pd(0) and stabilizing the reactive species.[12b]

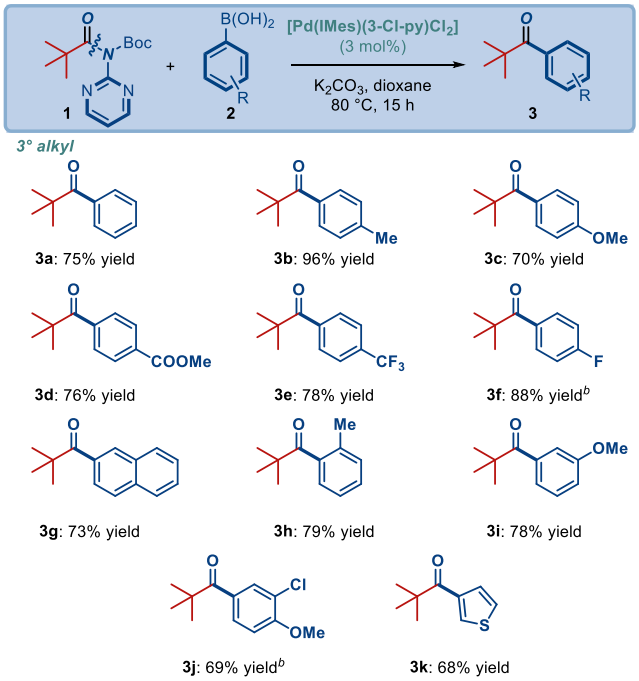
There is an excellent Taft correlation between the Taft steric parameter (E_S) of the aliphatic substituent and the cross-coupling yield of 3°, 2° and 1° amides using [Pd(NHC)(3-Cl-py)Cl_2] catalysts bearing IMes and IPr ligands in Table 1 (Figure 3).[16] Overall, the optimization results (1) provide the first examples of Pd-catalyzed cross-coupling of sterically-hindered aliphatic amides, and (2) demonstrate that a steric match between the NHC ancillary ligand and steric properties of the *aliphatic* amide bond is required for effective coupling.

Reaction Scope. With the optimized conditions in hand, we investigated the scope of this novel Pd-catalyzed cross-coupling of aliphatic amides (Schemes1-4). As such, the cross-coupling of most demanding 3° amides proceeded with excellent levels of efficiency using a range of electronically- and sterically-differentiated aryl boronic acids (Scheme 1), including neutral (**3a**), electron-rich (**3b-3c**), electron-deficient (**3d-3f**), naphthyl (**3g**), ortho-substituted (**3h**), meta-substituted (**3i-3j**) and heterocyclic boronic acids (**3k**). It is noteworthy that sensitive electrophilic functional groups that could be problematic in conventional methodologies, such as an ester (**3d**) or halide (**3j**) are tolerated in the coupling. The scope of cross-coupling of 2° amides proceeded with equally high levels of efficiency (Scheme 2). For comparison, exactly the same set of aromatic boronic acids was employed, delivering the cross-coupling products **4a-4k** in 72-92% yields using [Pd(IMes)(3-Cl-py)Cl_2] as a catalyst. Furthermore, the scope could be extended to the least sterically-demanding 1° amides (Scheme 3) using representative electron-neutral (**5a**), electron-rich (**5b**), electron-deficient (**5c**) and sterically-hindered (**5d**) aryl boronic acids. Finally, different aliphatic amides have been subjected to the reaction conditions to demonstrate generality of the cross-coupling (Scheme 4). As such, phenethyl derivative that is poised for decarbonylation/β-hydride elimination was well-tolerated in the coupling (**6a**).[17] Moreover, heterocyclic substitution such as 4-tetrahydro-2*H*-pyranyl (**6b**) and 4-piperidynyl (**6c**) was well accommodated in the coupling. Furthermore, the scope could be extended to sterically-hindered 3° adamantyl amides (**6d**). Finally, aromatic amides (**6e**) are

also suitable substrates for the cross-coupling without modification of the reaction conditions, attesting to the generality of the catalyst system. Preliminary studies indicate that 3-pyridinyl and 3-furyl boronic acids undergo cross-coupling in 25% and 79% yield, respectively (3° amide).

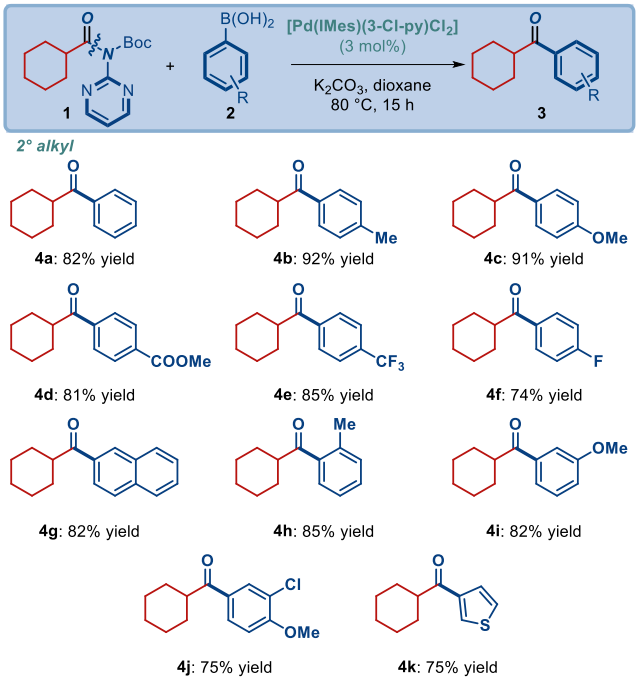
Mechanistic Studies. In consideration of the unique activity of aliphatic amides in the cross-coupling, preliminary experiments were conducted (Scheme 5). (1) Intermolecular competition experiments demonstrated that electron-rich boronic acids react preferentially with 3° amides (4-MeO:4-CF_3 = 76:24) and 2° amides (4-MeO:4-CF_3 = 64:36), while similar reactivity is observed with 1° amides (4-MeO:4-CF_3 = 50:50). There is an excellent Taft correlation between the Taft steric parameter (E_S) of the aliphatic substituent and the 4-MeO/4-CF_3 cross-coupling selectivity (Y = -1.39X + 1.05, R^2 = 0.99, see SI). We have further found that the coupling proceeds more rapidly when the amounts of boronic acid and K_2CO_3 are increased. A yield of 26% was obtained after 15 min with 2.0 equiv of 4-Tol-$B(OH)_2$, while a yield of 48% was obtained after the same time with 4.0 equiv of 4-Tol-$B(OH)_2$ and 6.0 equiv of K_2CO_3 (**3b**). Overall, these studies indicate that transmetallation might become a rate-determining step in the cross-coupling of more sterically hindered aliphatic amides. (2) Further competition experiments between different aliphatic and aromatic amides indicate the following order of the relative reactivity: 3° < 2° << 1° ≈ Ar, highlighting the challenge of the cross- coupling of 3° and 2° aliphatic amide derivatives and underscoring the high efficiency of the present system.

Scheme 1. Pd-NHC-Catalyzed Suzuki–Miyaura Cross-Coupling of 3°Alkyl Amides[a]



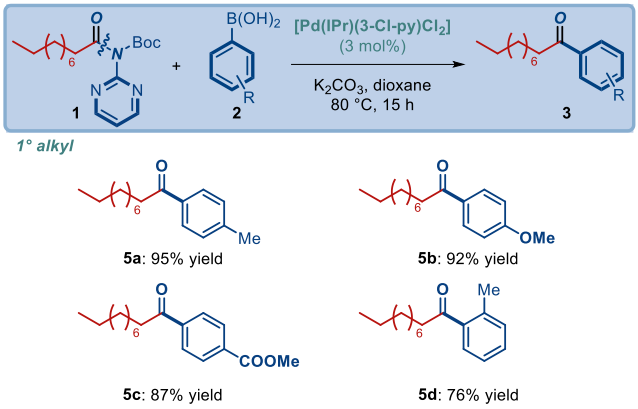
[a]Conditions: amide (1.0 equiv), Ar-$B(OH)_2$ (2.0 equiv), [Pd-NHC] = [Pd(IMes)(3-Cl-py)Cl_2] (3 mol%), K_2CO_3 (3.0 equiv), dioxane (0.20 M), 80℃, 15 h. Isolated yields. [c]120 ℃. [b][Pd-NHC] (6 mol%). See SI for details.

Scheme 2. Pd-NHC-Catalyzed Suzuki–Miyaura Cross-Coupling of 2° Alkyl Amides[a]



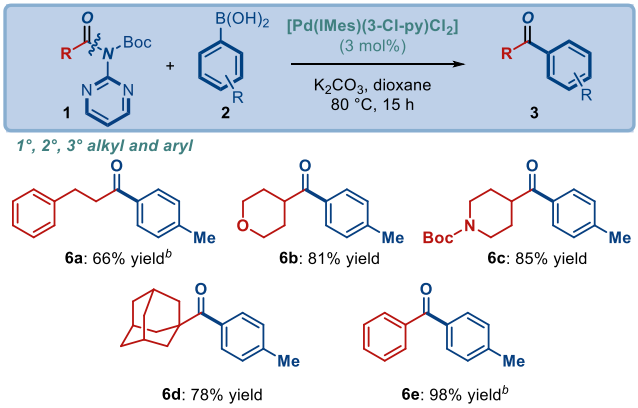
[a]See Scheme 1.

Scheme 3. Pd-NHC-Catalyzed Suzuki–Miyaura Cross-Coupling of 1° Alkyl Amides[a]



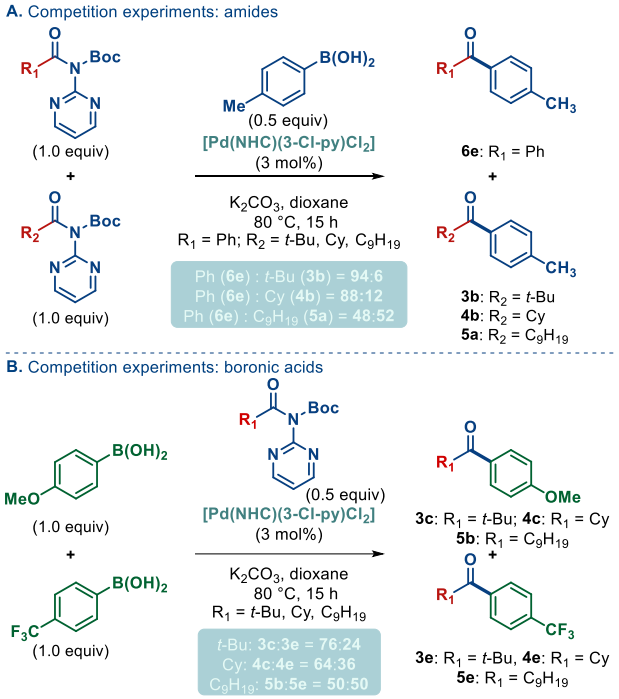
[a]See Scheme 1. [Pd-NHC] = [Pd(IPr)(3-Cl-py)Cl_2] (3 mol%).

Scheme 4. Pd-NHC-Catalyzed Suzuki–Miyaura Cross-Coupling of Various Amides[a]



[a]See Scheme 1. [b][Pd-NHC] = [Pd(IPr)(3-Cl-py)Cl_2] (3 mol%).

Scheme 5. Competition Experiments



Structural Studies. To gain insight into the structural parameters that enable high reactivity of N,N-Boc/pym amides, the x-ray structure of a model amide was determined (Figure 4). Interestingly, the amide bond is moderately twisted (τ = 28.7°, χ_N = 9.3°, χ_C = 2.5°) and the N–C(O) and C=O bond lengths are 1.404Å and 1.220Å, which corresponds to approximately 30% of the maximum possible twist value as determined by Winkler-Dunitz parameters (see SI for description of structural parameters of amide bond).[18] The C(O)–N bond is antiperiplanar to the C=O bond of the Boc moiety (161.6°), and the N–$C_{(pym)}$ bond is antiperiplanar to the C–O bond of the Boc group (148.9°). These values can be compared with the model N-acyl-glutarimide (τ = 87.5°, χ_N = 5.6°, χ_C = 1.3°; N–C(O) = 1.475Å, C=O = 1.200 Å) and the model N,N-pym/Me amide (τ = 20.9°, χ_N = 5.2°, χ_C = 3.9°; N–C(O) = 1.378 Å, C=O = 1.225Å), both of which are ineffective in the coupling of alkyl amides.

It is further interesting to note that the amide shows early stage of acylium formation as determined by carbonyl bending angle (ξ) parameter recently introduced by Stoltz and co-workers.[19] As such, ξ of 2.1° can be compared with the most twisted 7-hypoquinuclidone BF_3 complex (ξ of 5.8°) and representative acyclic twisted amide, N-benzoyl-glutarimide, ξ of 3.5°. Thus, the structure of N,N-Boc/pym amide indicates early stage of N–C breaking triggered by amide bond twist and external $n_N \rightarrow \pi^*_{C=O/Ar}$ delocalization.

Amidic Resonance. Computations were employed to determine the effect of N,N-Boc/pym substitution on amide bond destabilization (Scheme 6). (1) Resonance energy (RE) of the amide bond determined by the COSNAR method established by Greenberg and co-workers (RE = 6.4 kcal/mol) indicate strong destabilization of the N–C bond.[3a,20] This value can be compared with RE of representative N,N-pym/Me amide (RE

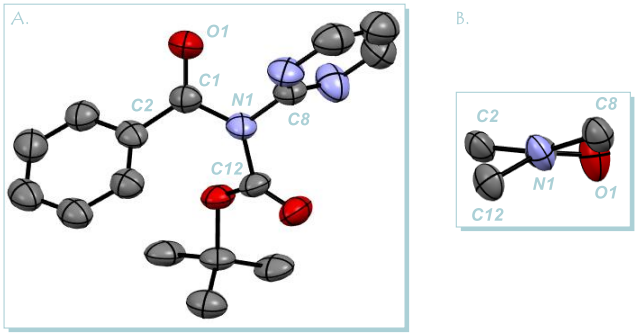


Figure 4. (a) Crystal structure of **1h**. (b) Newman projection along the N–C(O) bond. Bond lengths (Å) and angles (deg): N1–C1, 1.404; C1–O1, 1.220; C2–C1, 1.478; N1–C8, 1.422; N1–C12, 1.444; C2–C1–N1–C8, 154.70; O1–C1–N1–C12, 147.84; O1–C1–N1–C8, –22.85; C2–C1–N1–C12, –34.62. See SI for details. The structure has been deposited with the Cambridge Crystallographic Data Center, CCDC, 2114044.

Scheme 6. A) Effect of Amide Twisting; B) Graphical Representation of Double Destabilization Mechanism

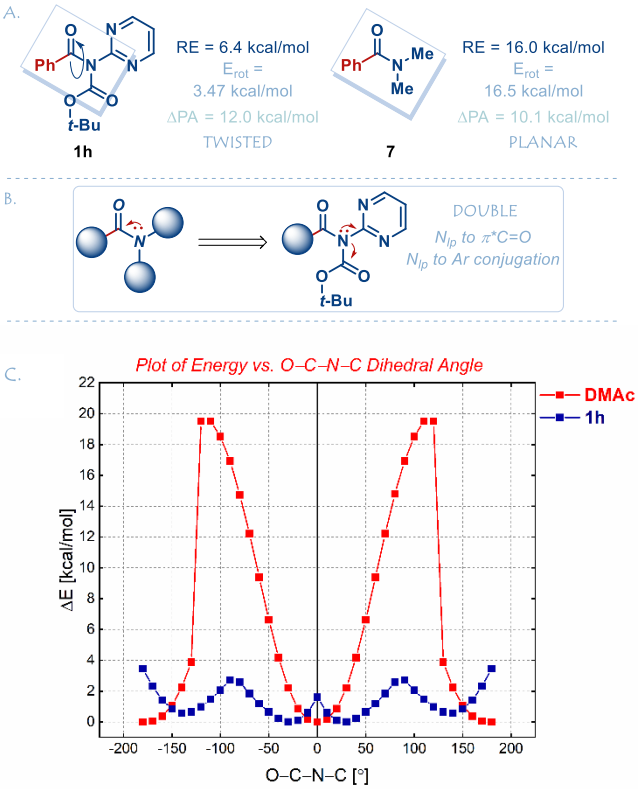


Figure 5. Rotational profile of **1h** and planar DMAc (N,N-dimethylacetamide). Expanded rotational profile of **1h** is shown in the SI.

= 6.7 kcal/mol) and N,N-Boc/Ph amide (RE = 7.1 kcal/mol). This value is much lower than in typical N,N-dialkyl amides (RE = 18.3 kcal/mol, DMAc). (2) Rotational profile determined by systematic rotation along the O–C–N–$C_{(Boc)}$ dihedral angle identified energy minimum at ca. 30° O–C–N–C angle (τ = 40.33°; χ_N = 18.28°) in an anti O–C–N–$C_{(Ar)}$ conformation (ca. 131.7° O–C–N–$C_{(Ar)}$ dihedral angle), and energy maximum (3.5 kcal/mol) at ca. 180° O–C–N–C dihedral angle (τ = 8.89°; χ_N = 12.81°) in a syn O–C–N–$C_{(Ar)}$ conformation

(ca. 12.8° O–C–N–$C_{(Ar)}$ dihedral angle) (Figure 5). The plot further indicates a significantly lowered barrier to rotation compared with planar amides. (3) Determination of N-/O-protonation affinities (ΔPA) indicates that the amide strongly favors coordination at the amide oxygen (vs. amide nitrogen, ΔPA = 12.0 kcal/mol). Interestingly, protonation of the oxygen of the Boc moiety is favored over the amide oxygen (ΔPA = 18.8 kcal/mol vs. amide nitrogen) and protonation of the pyrimidine ring nitrogen is favored over amide nitrogen (ΔPA = 25.0 kcal/mol vs. amide oxygen). Thus, O-coordination of the external groups at the nitrogen atom is an additional factor activating the N–C(O) bond for cleavage.

Thus, we conclude that the combination of N-Boc and N-pym activation results in an attractive framework that enables altering of amidic bond resonance through $n_N \rightarrow \pi^*_{C=O/Ar}$ delocalization and enhances external conjugation of the nitrogen lone pair outside the amide acyl bond undergoing N–C scission.

In conclusion, we have reported the Pd-catalyzed Suzuki-Miyaura cross-coupling of *aliphatic* amides. Most crucially, this generic approach advances the versatile Pd-NHC-catalyzed amide N–C(O) bond activation platform of *aromatic* amides to *aliphatic* amides. This approach was shown to be effective for an array of 3°, 2° and 1° aliphatic amide derivatives. Another important aspect of this work involves steric matching of the properties of amide bond and NHC ancillary ligand as well as introduction of N,N-Boc/pym amides as doubly-activated class of amide electrophiles for general N–C(O) bond cross-coupling manifolds. The catalyst system is robust, air-stable, well-defined and amenable to facile modification by ancillary and throw-away ligand tuning. Given the importance of amide bond cross-coupling methods, we anticipate that this approach will find broad application in organic synthesis and complement nucleophilic yet inherently air-sensitive Ni(0)-NHC systems.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, CIF file for amide **1h**, computational details. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) For reviews on N–C functionalization, see: (a) Meng, G.; Zhang, J. Szostak, M. Acyclic Twisted Amides. *Chem. Rev.* **2021**, *121*, 12746–12783. (b) Boit, T. B.; Bulger, A. S.; Dander, J. E.; Garg, N. K. Activation of C−O and C−N Bonds Using Non-Precious-Metal Catalysis. *ACS Catal.* **2020**, *10*, 12109–12126. (c) Bourne-Branchu, Y.; Gosmini, C.; Danoun, G. N-Boc-Amides in Cross-Coupling Reactions. *Chem. Eur. J.* **2019**, *25*, 2663–2674. (d) Chaudhari, M. B.; Gnanaprakasam, B. Recent Advances in the Metal-Catalyzed Activation of Amide Bonds. *Chem. Asian J.* **2019**, *14*, 76–93. (e) Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. Amide activation: an emerging tool for chemoselective synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7899–7925. (f) Takise, R.; Muto, K.; Yamaguchi, J. Cross-Coupling of Aromatic Esters and Amides. *Chem. Soc. Rev.* **2017**, *46*, 5864–5888. (g) Dander, J. E.; Garg, N. K. Breaking Amides using Nickel Catalysis. *ACS Catal.* **2017**, *7*, 1413–1423.

(2) For selected studies, see: (a) Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. Reversible Twisting of Primary Amides via Ground State N–C(O) Destabilization: Highly Twisted Rotationally Inverted Acyclic Amides. *J. Am. Chem. Soc.* **2018**, *140*, 727–734. (b) Dey, A.; Sasmal, S.; Seth, K.; Lahiri, G. K.; Maiti, D. Nickel-catalyzed deamidative step-down reduction of amides to aromatic hydrocarbons. *ACS Catal.* **2017**, *7*, 433−437. (c) Ni, S.; Zhang, W.; Mei, H.; Han, J.; Pan, Y. Ni-catalyzed reductive cross-coupling of amides with aryl iodide electrophiles via C−N bond activation. *Org. Lett.* **2017**, *19*, 2536−2539. (d) Medina, J. M.; Moreno, J.; Racine, S.; Du, S.; Garg, N. K. Mizoroki−Heck cyclizations of amide derivatives for the introduction of quaternary centers. *Angew. Chem., Int. Ed.* **2017**, *56*, 6567−6571. (e) Weires, N. A.; Caspi, D. D.; Garg, N. K. Kinetic modeling of the nickel-catalyzed esterification of amides. *ACS Catal.* **2017**, *7*, 4381−4385. (f) Dander, J. E.; Baker, E. L.; Garg, N. K. Nickel-catalyzed transamidation of aliphatic amide derivatives. *Chem. Sci.* **2017**, *8*, 6433−6438. (g) Deguchi, T.; Xin, H.-L.; Morimoto, H.; Ohshima, T. Direct catalytic alcoholysis of unactivated 8-aminoquinoline amides. *ACS Catal.* **2017**, *7*, 3157−3161. (h) Yue, H.; Guo, L.; Liao, H.-H.; Cai, Y.; Zhu, C.; Rueping, M. Catalytic ester and amide to amine interconversion: nickel-catalyzed decarbonylative amination of esters and amides by C−O and C−C bond activation. *Angew. Chem., Int. Ed.* **2017**, *56*, 4282−4285. (i) Yue, H.; Guo, L.; Lee, S.-C.; Liu, X.; Rueping, M. Selective reductive removal of ester and amide groups from arenes and heteroarenes through nickel-catalyzed C−O and C−N bond activation. *Angew. Chem., Int. Ed.* **2017**, *56*, 3972−3976. (j) Hu, J.; Wang, M.; Pu, X.; Shi, Z. Nickel catalysed retro-hydroamidocarbonylation of aliphatic amides to olefins. *Nat. Commun.* **2017**, *8*, 14993−14999. (k) Meng, G.; Shi, S.; Szostak, M. Palladium-catalyzed Suzuki−Miyaura cross-coupling of amides via site-selective N−C bond cleavage by cooperative catalysis. *ACS Catal.* **2016**, *6*, 7335−7339. (l) Wu, H.; Li, Y.; Cui, M.; Jian, J.; Zeng, Z. Suzuki coupling of amides via palladium-catalyzed C−N cleavage of N-acylsaccharins. *Adv. Synth. Catal.* **2016**, *358*, 3876−3880. (m) Shi, S.; Meng, G.; Szostak, M. Synthesis of biaryls via nickel-catalyzed Suzuki−Miyaura coupling of amides by carbon−nitrogen cleavage. *Angew. Chem., Int. Ed.* **2016**, *55*, 6959−6963. (n) Hu, J.; Zhao, Y.; Liu, J.; Zhang, Y.; Shi, Z. Nickel-catalyzed decarbonylative borylation of amides: evidence for acyl C−N bond activation. *Angew. Chem., Int. Ed.* **2016**, *55*, 8718−8722. (o) Weires, N. A.; Baker, E. L.; Garg, N. K. Nickel-catalysed Suzuki−Miyaura coupling of amides. *Nat. Chem.* **2016**, *8*, 75−79. (p) Baker, E. L.; Yamano, M. M.; Zhou, Y.; Anthony, S. M.; Garg, N. K. A two-step approach to achieve secondary amide transamidation enabled by nickel catalysis. *Nat. Commun.* **2016**, *7*, 11554−11558. (q) Simmons, B. J.; Weires, N. A.; Dander, J. E.; Garg, N. K. Nickel-catalyzed alkylation of amide derivatives. *ACS Catal.* **2016**, *6*, 3176−3179. (r) Hie, L.; Baker, E. L.; Anthony, S. M.; Desrosiers, J.-N.; Senanayake, C.; Garg, N. K. Nickel-catalyzed esterification of aliphatic amides. *Angew. Chem., Int. Ed.* **2016**, *55*, 15129−15132. (s) Li, X.; Zou, G. Acylative Suzuki coupling of amides: acyl-nitrogen activation via synergy of independently modifiable activating groups. *Chem. Commun.* **2015**, *51*, 5089−5092. (t) Yada, A.; Okajima, S.; Murakami, M. Palladium-catalyzed intramolecular insertion of alkenes into the carbon−nitrogen bond of *β*-lactams. *J. Am. Chem. Soc.* **2015**, *137*, 8708−8711. (u) Meng, G.; Szostak, M. General Olefin Synthesis by

the Palladium-Catalyzed Heck Reaction of Amides: Sterically-Controlled Chemoselective N−C Activation. *Angew. Chem., Int. Ed.* **2015**, *54*, 14518−14522.

(3) (a) Ruider, S.; Maulide, N. Strong Bonds Made Weak: Towards the General Utility of Amides as Synthetic Modules. *Angew. Chem. Int. Ed.* **2015**, *54*, 13856–13858. (b) Pattabiraman, V. R.; Bode, J. W. Rethinking Amide Bond Synthesis. *Nature* **2011**, *480*, 471–479. (c) Greenberg, A.; Breneman, C. M.; Liebman, J. F. *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*; Wiley-VCH: New York, 2003. For further examples of N–C bond activation, see: (d) Chen, C.; Liu, P.; Luo, M.; Zeng, X. Kumada Arylation of Secondary Amides Enabled by Chromium Catalysis for Unsymmetric Ketone Synthesis under Mild Conditions. *ACS Catal.* **2018**, *8*, 5864-5858. (e) Ni, S.; Li, C. X.; Mao, Y.; Han, J.; Wang, Y.; Yang, H.; Pan, Y. Ni-catalyzed deaminative cross-electrophile coupling of Katritzky salts with halides via C–N bond activation. *Sci. Adv.* **2019**, *5*, 9516. (f) Zhang, Z. B.; Ji, C. L.; Yang, C.; Chen, J.; Hong, X.; Xia, J. B. Nickel-Catalyzed Kumada Coupling of Boc-Activated Aromatic Amines via Nondirected Selective Aryl C–N Bond Cleavage. *Org. Lett.* **2019**, *21*, 1226-1231. (g) Liu, L.; Zhou, D.; Liu, M.; Zhou, Y.; Chen, T. Palladium-Catalyzed Decarbonylative Alkynylation of Amides. *Org. Lett.* **2018**, *20*, 2741-2744.

(4) For lead references on amide bonds in drug discovery and polymer chemistry, see: (a) Kaspar, A. A.; Reichert, J. M. Future Directions for Peptide Therapeutics Development. *Drug Discov. Today* **2013**, *18*, 807–817. (b) Roughley, S. D.; Jordan, A. M. The Medicinal Chemist's Toolbox: An Analysis of Reactions Used in the Pursuit of Drug Candidates. *J. Med. Chem.* **2011**, *54*, 3451–3479. (c) Marchildon, K. Polyamides: Still Strong After Seventy Years. *Macromol. React. Eng.* **2011**, *5*, 22–54. (d) Brunton, L.; Chabner, B.; Knollman, B. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*; MacGraw-Hill: New York, 2010.

(5) (a) *New Trends in Cross-Coupling*; Colacot, T. J., Ed.; The Royal Society of Chemistry: Cambridge, 2015, pp. 1-864. (b) *Metal-Catalyzed Cross-Coupling Reactions and More*, de Meijere, A.; Bräse, S.; Oestreich, M., Eds.; Wiley: New York, 2014, pp. 1-1576. (c) *Science of Synthesis: Cross-Coupling and Heck-Type Reactions*, Molander, G. A.; Wolfe, J. P.; Larhed, M., Eds.; Thieme: Stuttgart, 2013, pp. 1-928.

(6) (a) Johansson-Seechurn, C. C. C.; Kitching, M. O.; Colacot, T. J.; Snieckus, V. A Historical Contextual Perspective to the 2010 Nobel Prize. *Angew. Chem. Int. Ed.* **2012**, *51*, 5062–5085. (b) Brennführer, A.; Neumann, H.; Beller, M. Palladium-Catalyzed Carbonylation Reactions of Aryl Halides and Related Compounds. *Angew. Chem. Int. Ed.* **2009**, *48*, 4114–4133. (c) Gooßen, L. J.; Rodriguez, N.; Gooßen, K. Carboxylic Acids as Substrates in Homogeneous Catalysis. *Angew. Chem. Int. Ed.* **2008**, *47*, 3100–3120.

(7) Pauling, L. *The Nature of the Chemical Bond*; Oxford University Press: London, 1940, pp. 1-429.

(8) Li, G.; Ma, S.; Szostak, M. Amide Bond Activation: The Power of Resonance. *Trends Chem.* **2020**, *2*, 914-928.

(9) Boit, T. B.; Weires, N. A.; Kim, J.; Garg, N. K. Nickel-catalyzed Suzuki–Miyaura coupling of aliphatic amides. *ACS Catal.* **2018**, *8*, 1003–1008.

(10) Mehta, M. M.; Boit, T. B.; Dander, J. E.; Garg, N. K. Ni-catalyzed Suzuki–Miyaura cross-coupling of aliphatic amides on the benchtop. *Org. Lett.* **2020**, *22*, 1–5. For more studies about paraffin capsules, see: (b) Dander, J. E.; Morrill, L. A.; Nguyen, M. M.; Chen, S.; Garg, N. K. Breaking amide C−N bonds in an undergraduate organic chemistry laboratory. *J. Chem. Educ.* **2019**, *96*, 776−780. (c) Dander, J. E.; Weires, N. A.; Garg, N. K. Benchtop delivery of Ni(cod)2 using paraffin capsules. *Org. Lett.* **2016**, *18*, 3934−3936.

(11) Hie, L.; Fine Nathel, N. F.; Shah, T.; Baker, E. L.; Hong, X.; Yang, Y.-F.; Liu, P.; Houk, K. N.; Garg, N. K. Conversion of amides to esters by the Nickel-catalysed activation of amide C–N bonds. *Nature* **2015**, *524*, 79–83.

(12) (a) Zhao, Q.; Meng, G.; Li, G.; Flach, C.; Mendelsohn, R.; Lalancette, R.; Szostak, R; Szostak, M. IPr# - highly hindered, broadly applicable N-heterocyclic carbenes. *Chem. Sci.* **2021**, *12*, 10583–10589. (b) Xia, Q.; Shi, S.; Gao, P.; Lalancette, R.; Szostak, R.; Szostak, M. [(NHC)PdCl$_2$(Aniline)] Complexes: Easily Synthesized, Highly Active Pd(II)−NHC Precatalysts for Cross-Coupling Reactions. *J. Org. Chem.* **2021**, *86*, 15648–15657. (c) Zhou, T.; Ma, S.; Nahra, F.; Obled, A. M. C.; Poater, A.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P.; Szostak, M. [Pd(NHC)(μ-Cl)Cl]$_2$: Versatile and Highly Reactive Complexes for Cross-Coupling Reactions that Avoid Formation of Inactive Pd(I) Off-Cycle Products. *iScience* **2020**, *23*, 101377. (d) Shi, S.; Nolan, S. P.; Szostak, M. Well-Defined Palladium(II)-NHC (NHC = N-Heterocyclic Carbene) Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective Acyl CO–X (X = N, O) Cleavage. *Acc. Chem. Res.* **2018**, *51*, 2589–2599. (e) Lei, P.; Meng, G.; Szostak, M. General Method for the Suzuki-Miyaura Cross-Coupling of Amides Using Commercially Available, Air- and Moisture-Stable Palladium/NHC (NHC = N-Heterocyclic Carbene) Complexes. *ACS Catal.* **2017**, *7*, 1960–1965. (f) Lei, P.; Meng, G.; Shi, S.; Ling, Y.; An, J.; Szostak, R.; Szostak, M. Suzuki-Miyaura Cross-Coupling of Amides and Esters at Room Temperature: Correlation with Barriers to Rotation around C–N and C–O Bonds. *Chem. Sci.* **2017**, *8*, 6525–6530. (g) Lei, P.; Meng, G.; Ling, Y.; An, J.; Szostak, M. Pd-PEPPSI: Pd-NHC precatalyst for Suzuki−Miyaura cross-coupling reactions of amides. *J. Org. Chem.* **2017**, *82*, 6638−6646. (h) Meng, G.; Szostak, R.; Szostak, M. Suzuki−Miyaura cross-coupling of N-acylpyrroles and pyrazoles: planar, electronically activated amides in catalytic N−C cleavage. *Org. Lett.* **2017**, *19*, 3596−3599. (i) Meng, G.; Lalancette, R.; Szostak, R.; Szostak, M. N-Methylamino pyrimidyl amides (MAPA): highly reactive, electronically-activated amides in catalytic N−C(O) cleavage. *Org. Lett.* **2017**, *19*, 4656−4659. (j) Lei, P.; Meng, G.; Ling, Y.; An, J.; Nolan, S. P.; Szostak, M. General method for the Suzuki−Miyaura cross-coupling of primary amide-derived electrophiles enabled by [Pd(NHC)(cin)Cl] at room temperature. *Org. Lett.* **2017**, *19*, 6510−6513.

(13) Hopkinson, M. N.; Richter, C.; Schedler, M.; Glorius, F. An overview of N-heterocyclic carbenes. *Nature* **2014**, *510*, 485-496. (b) *N-Heterocyclic Carbenes*, Nolan, S. P., Ed.; Wiley: Weinheim, 2014, pp. 1-543. (c) Peris, E. Smart N-Heterocyclic Carbene Ligands in Catalysis. *Chem. Rev.* **2018**, 118, 9988-10031.

(14) (a) Marion, N.; Nolan, S. P. Well-Defined N-Heterocyclic Carbenes-Palladium(II) Precatalysts for Cross-Coupling Reactions. *Acc. Chem. Res.* **2008**, *41*, 1440–1449. (b) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. Palladium Complexes of N-Heterocyclic Carbenes as Catalysts for Cross-Coupling Reactions—A Synthetic Chemist's Perspective. *Angew. Chem., Int. Ed.* **2007**, *46*, 2768–2813.

(15) For reviews on steric and properties of N-heterocyclic carbenes, see: (a) Gomez-Suarez, A.; Nelson, D. J.; Nolan, S. P. Quantifying and understanding the steric properties of N-heterocyclic carbenes. *Chem. Commun.* **2017**, *53*, 2650-2660. (b) Clavier, H.; Nolan, S. P. Percent buried volume for phosphine and N-heterocyclic carbene ligands: steric properties in organometallic chemistry. *Chem. Commun.* **2010**, *46*, 841-861. (c) Huynh, H. V. Electronic Properties of N-Heterocyclic Carbenes and Their Experimental Determination. *Chem. Rev.* **2018**, *118*, 9457-9492.

(16) (a) Harper, K. C.; Bess, E. N.; Sigman, M. S. Multidimensional steric parameters in the analysis of asymmetric catalytic reactions. *Nat. Chem.* **2012**, *4*, 366–374. (b) Sigman, M. S.; Miller, J. J. Examination of the Role of Taft-Type Steric Parameters in Asymmetric Catalysis. *J. Org. Chem.* **2009**, *74*, 7633-7643.

(17) (a) Mueller, J. A.; Goller, C. P.; Sigman, M. S. Elucidating the Significance of *β*-Hydride Elimination and the Dynamic Role of Acid/Base Chemistry in a Palladium-Catalyzed Aerobic Oxidation of Alcohols. *J. Am. Chem. Soc.* **2004**, *126*, 9724-9734. (b) Shultz, L. H.; Brookhart, M. Measurement of the Barrier to *β*-Hydride Elimination in a *β*-Agostic Palladium-Ethyl Complex: A Model for the Energetics of Chain-Walking in (α-Diimine)PdR$^+$ Olefin Polymerization Catalysts. *Organometallics* **2001**, *20*, 3975–3982.

(18) Winkler, F. K.; Dunitz, J. D. The Non-Planar Amide Group. *J. Mol. Biol.* **1971**, *59*, 169-182.

(19) Liniger, M.; VanderVelde, D. G.; Takase, M. K.; Shahgholi, M.; Stoltz, B. M. Total Synthesis and Characterization of 7-Hypoquinuclidonium Tetrafluoroborate and 7-Hypoquinuclidone BF_3 Complex. *J. Am. Chem. Soc.* **2016**, *138*, 969–974.

(20) (a) Greenberg, A.; Moore, D. T.; DuBois, T. D. Small and Medium-Sized Bridgehead Bicyclic Lactams: A Systematic ab Initio Molecular Orbital Study. *J. Am. Chem. Soc.* **1996**, *118*, 8658–8668. (b) Greenberg, A.; Venanzi, C. A. Structures and Energetics of Two Bridgehead Lactams and Their N- and O-Protonated Forms: An ab Initio Molecular Orbital Study. *J. Am. Chem. Soc.* **1993**, *115*, 6951–6957.