Acyl- and Decarbonylative Suzuki Coupling of *N*-Acetyl Amides: Electronic-Tuning of Twisted, Acyclic Amides in Catalytic Carbon–Nitrogen Bond Cleavage

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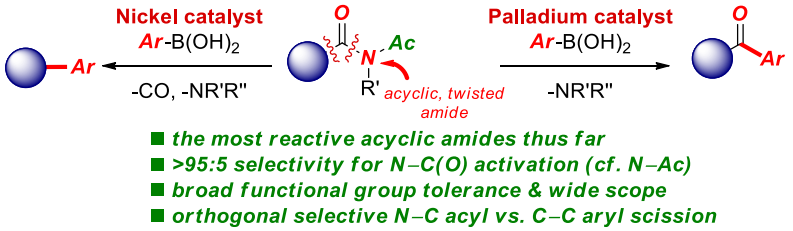
Supporting Information



KEYWORDS: *amides, N–C activation, cross-coupling, Suzuki-Miyaura coupling, decarbonylation, biaryl coupling*

ABSTRACT: We report the Pd-catalyzed acyl and the Ni-catalyzed biaryl Suzuki-Miyaura cross-coupling of *N*-acetyl-amides with arylboronic acids by selective N–C(O) cleavage. Activation of the amide bond by *N*-acylation provides electronically-destabilized, acyclic, non-planar amide, which readily undergoes cross-coupling with a wide range of boronic acids to produce biaryl ketones or biaryls in a highly efficient manner. Most crucially, the presented results introduce *N*-acetyl-amides as reactive acyclic amides in the emerging manifold of transition-metal-catalyzed amide cross-coupling. The scope and origin of high selectivity are discussed. Mechanistic studies point to re-modeling of amidic resonance and amide bond twist as selectivity determining features in a unified strategy for cross-coupling of acyclic amides. Structural studies, mechanistic investigations as well as beneficial effects of the *N*-acyl substitution on cross-coupling of amides are reported.

Cross-coupling reactions of amides have been established as a powerful route to functionalization of the ubiquitous amide bond essential in organic synthesis (Figure 1).[1,2] Direct insertion of a transition metal into the traditionally-inert amide bond generates a versatile acyl-metal intermediate **A** as an enabling platform for chemical synthesis.[3,4] Amides are particularly attractive targets for metal-induced functional-group interconversion[5] due to their fundamental significance as versatile synthetic intermediates and central role as key building blocks in the production of biologically-active compounds.[6, 7] As a result, converting common amides into high value functional groups has a transformative effect on synthetic design.

In principle, transformations at the C(acyl) amide bond are founded on the steric and electronic re-modeling of amidic resonance that further benefits from trigonal nitrogen geometry enabling controlled variation of sterics and amidicity.[8–10] The development of well-defined amide precursors permits a rational approach to cross-coupling reactions of amides and sets the stage for methodological advances.[11–16] One main obstacle is that the cleavage of the N–X bond (X = Ts, Boc) is a major side reaction in Pd(0) and Ni(0)-catalyzed amide N–C(O) cross-coupling, which limits, in particular, the scope of valuable decarbonylative processes of amides to N-cyclic amides.[17–22] Thus, the development of new amide precursors that are compatible with various reaction pathways is critical to fully exploit the potential of amides in cross-coupling.[1–4]

Herein, we report the first Pd-catalyzed acyl and Ni-catalyzed decarbonylative Suzuki-Miyaura cross-coupling of *N*-acetyl-amides with arylboronic acids (Figure 2). Most crucially, the presented results introduce *N*-acetyl-amides as the most reactive acyclic amides developed thus far in the emerging manifold of transition-metal-catalyzed amide cross-coupling. Notable features of our findings include: (i) unprecedented N–C(O) cleavage reactivity induced by the acyl group (ii) exceptionally high stability under the reaction conditions that avoids shutting-off N–X scission, (iii) reagent-controlled fully chemoselective divergent[23] acyl and decarbonylative coupling, (iv) the first example of the biaryl Suzuki-Miyaura cross-coupling[24] of simple acyclic amides, (v) in contrast to the recently reported precursors, versatile synthesis from secondary and primary amides that engenders a broad generality of this reactivity platform. As a key design element, structural

and mechanistic studies point to re-modeling of amidic resonance[9,10] and amide bond twist[8] as selectivity determining features in a unified strategy for cross-coupling of acyclic amides. We expect *N*-acetyl amides as generic precursors in

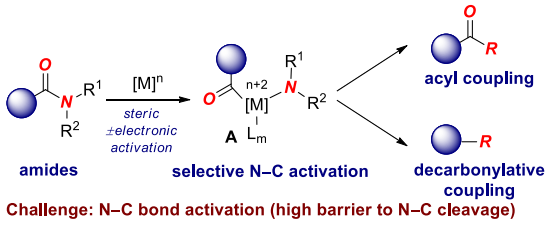


Figure 1. Metal-catalyzed activation of amides.

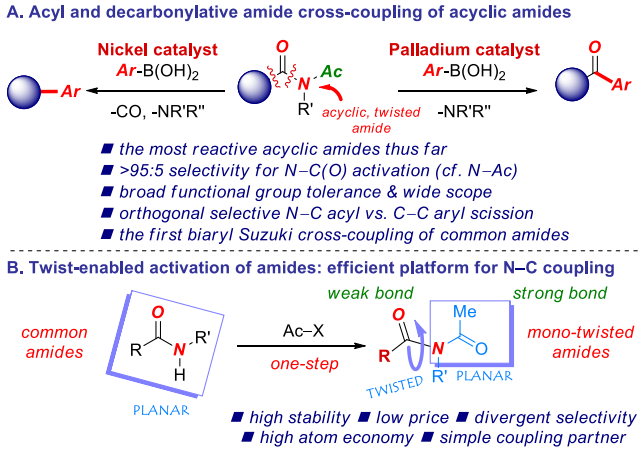


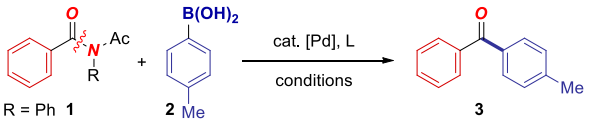
Figure 2. (a) Acyl and decarbonylative cross-coupling of acyclic amides. (b) Twist-enabled activation of the amide bond (this work).

amide bond cross-coupling to greatly expand the scope of direct functionalization of amides due to the inherent steric and electronic advantages that determine the reactivity and selectivity of these processes.[2,9,10]

Recently, our laboratory introduced *N*-acyl-glutarimides for the cross-coupling reactions by N–C(O) amide cleavage.[22] These cyclic amide precursors have now been established as by far the most reactive amide derivatives in the powerful amide bond cross-coupling manifold, enabling the development of more than 10 previously unknown catalytic modes of reactivity of the amide bond.[1–4,22] Despite the success of *N*-acyl-glutarimides, these precursors lack generality in that they cannot be prepared from common and readily available primary and secondary amides. A critical design feature of *N*-acyl-glutarimides is the combination of amide bond twist and resonance destabilization in a rotationally-inverted amide scaffold.[9b] Drawing from our mechanistic insights,[9d] we envisioned that glutarimide ring de-construction could retain the capacity of amides to undergo facile metal insertion under mild conditions (Figure 2B), while enabling a broad range of common acyclic amides to be employed as viable precursors to acyl-metal intermediates **A** in the coupling (Figure 1). To test this concept, we selected acyl Suzuki-Miyaura cross-coupling as a representative transformation.

After extensive optimization, we established than the reaction of *N*-acetyl amide **1** with 4-Tol-B(OH)$_2$ (2.0 equiv) in the presence of Pd(OAc)$_2$ (3 mol%) and PCy$_3$HBF$_4$ (12 mol%) in combination with K_2CO_3 (2.5 equiv) and H_3BO_3 (2.0 equiv) in toluene at 60 °C resulted in a quantitative conversion to the biaryl ketone **3** (Table 1, entry 1). Furthermore, the reaction at 40 °C afforded **3** in 82% yield (Table 1, entry 2), demonstrating the superior reactivity of *N*-Ac-amide **1** over other precursors.[2] Selected optimization results are summarized in Table 1. Exploration of different solvents and bases revealed that a

Table 1. Optimization of Palladium-Catalyzed Cross-Coupling of *N*-Ac Amides by N–C Cleavage[a]



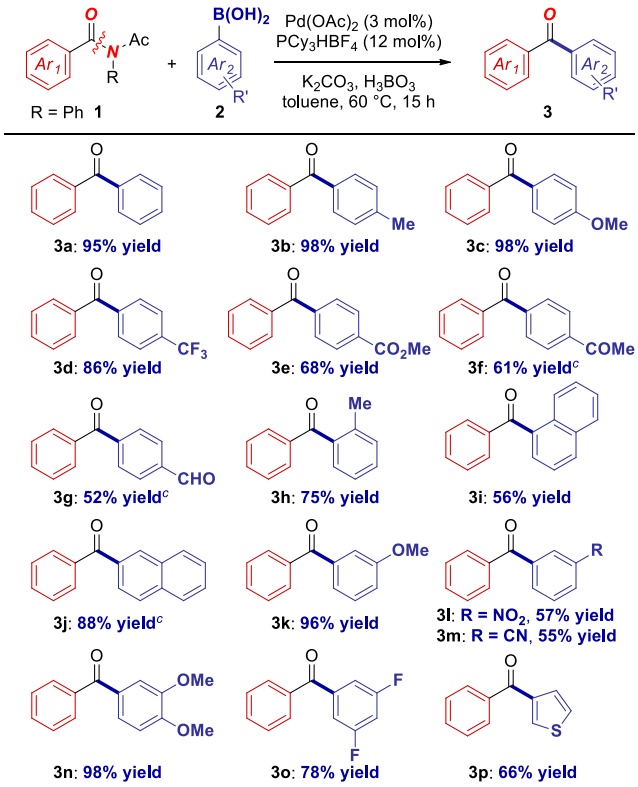
entry	catalyst	ligand	base	solvent	yield (%)
1	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_2CO_3	toluene	>98
2[b]	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_2CO_3	toluene	82
3	Pd(OAc)$_2$	PCy$_3$HBF$_4$	Na_2CO_3	THF	92
4	Pd(OAc)$_2$	PCy$_3$HBF$_4$	Na_2CO_3	dioxane	62
5	Pd(OAc)$_2$	PCy$_3$HBF$_4$	Na_2CO_3	toluene	70
6	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_2CO_3	THF	91
7	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_2CO_3	dioxane	89
8	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_3PO_4	THF	49
9	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_3PO_4	dioxane	53
10	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_3PO_4	toluene	72
11[c]	Pd(OAc)$_2$	PCy$_3$HBF$_4$	Na_2CO_3	THF	82
12[c]	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_2CO_3	THF	27
13[c]	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_3PO_4	THF	35
14	Pd(OAc)$_2$	PCy$_2$Ph	K_2CO_3	toluene	44
15	Pd(OAc)$_2$	PCyPh$_2$	K_2CO_3	toluene	<2
16	Pd(OAc)$_2$	PPh$_3$	K_2CO_3	toluene	<2
17	Pd(OAc)$_2$	P(*o*-Tol)$_3$	K_2CO_3	toluene	<2
18	Pd(OAc)$_2$	P(*n*-Bu)$_3$	K_2CO_3	toluene	89
19	Pd(OAc)$_2$	P(*t*-Bu)$_3$	K_2CO_3	toluene	<5
20	Pd(OAc)$_2$	XPhos	K_2CO_3	toluene	79
21	Pd(OAc)$_2$	XantPhos	K_2CO_3	toluene	10
22[d]	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_2CO_3	toluene	84
23[e]	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_2CO_3	toluene	91
24[f]	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_2CO_3	toluene	76
25[g]	Pd(OAc)$_2$	PCy$_3$HBF$_4$	K_2CO_3	toluene	83

[a]Conditions: amide (0.20 mmol, 1 equiv), Ar-B(OH)$_2$ (0.40 mmol, 2.0 equiv), catalyst (3 mol%), ligand (12 mol%), base (2.5 equiv), H_3BO_3 (2.0 equiv), solvent (0.20 M), 60 °C, 15 h. [b]40 °C. [c] Without H_3BO_3. [d]ligand (3 mol%). [e]ligand (6 mol%). [f]Ar-B(OH)$_2$ (1.2 equiv). [g]Ar-B(OH)$_2$ (1.5 equiv). See SI for details.

combination of K_2CO_3 and toluene was optimal (entries 3-10). Interestingly, we found that the addition of boric acid to presumably induce switchable N-/O-activation of the amide bond[9b] and prevent protodeboronation[24] had a positive effect on the coupling (entries 11-13). We hypothesize that H_3BO_3 promotes the coupling by protonation of the acyl oxygen atom, which further decreases amidic resonance and activates the amide bond towards the coupling. Most notably, the nature of the ligand had a profound impact on the coupling and PCy$_3$ proved to be the most effective (entries 14-21). This phosphine emerges as a privileged ligand in Pd-catalyzed amide bond activation, presumably due to highly electron-rich nature and well-fitted steric impact on the Pd center (cf. *t*-Bu$_3$P).[3] Exami-

nation of different Pd/ligand stoichiometry revealed that efficient coupling ensues with a close to 1:1 Pd:ligand ratio, consistent with facile insertion/transmetallation in the catalytic cycle (entries 22-23). Finally, even when the amount of boronic acid was decreased to 1.2-1.5 equiv, the desired ketone was obtained in good yields at 60 °C (76-83%), providing an entry point for future studies (entries 24-25), and consistent with a rate-determining transmetallation. Importantly, under the optimized conditions, scission of the alternative N–C

Scheme 1. Boronic Acid Scope in the Palladium-Catalyzed Cross-Coupling of *N*-Ac Amides[a,b]



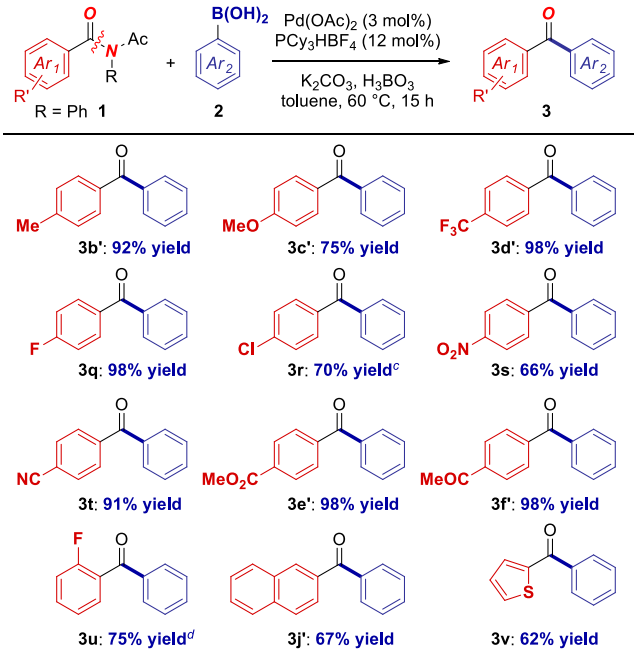
[a]Conditions: amide (0.20 mmol, 1.0 equiv), Ar-B(OH)$_2$ (0.40 mmol, 2.0 equiv), Pd(OAc)$_2$ (3 mol%), PCy$_3$HBF$_4$ (12 mol%), K$_2$CO$_3$ (2.5 equiv), H$_3$BO$_3$ (2.0 equiv), toluene (0.20 M), 60 °C, 15 h. [b]Isolated yields. [c]120 °C. See SI for details.

bond shutting-off the reactivity was not observed, indicating high propensity of the *N*-acyl-amide to undergo chemoselective N–C(O) oxidative addition.

With optimal reaction conditions in hand, we next turned our attention to the scope of boronic acids that can participate in this reaction (Scheme 1). As shown, a wide range of boronic acids bearing electron-neutral (**3a**), electron-donating (**3b-c**) and electron-withdrawing (**3d-g**) substituents is compatible with this coupling. Particularly noteworthy is that electrophilic-functional groups that would be problematic in the classic organometallic additions,[25] including esters (**3e**), ketones (**3f**) and aldehydes (**3g**) are well-tolerated. Furthermore, steric-hindrance (**3h-i**), polyaromatics (**3i-j**) and electrophilic nitro (**3l**) and cyano groups (**3m**) can be readily employed in this coupling. Finally, fluorinated boronic acids (**3o**) and heteroaromatics (**3p**) important from the medicinal chemistry[26] and functional materials standpoints[27] deliver the biaryl ketone products in good to excellent yields.

We next turned out attention to the scope of *N*-acetyl-amides that can participate in this coupling (Scheme 2). As shown, substrates with electron-donating (**3b'-c'**) and withdrawing (**3d'-f'**, **3q-t**) substituents reacted well under our optimized conditions. Moreover, an aryl chloride (**3r**) was tolerated under the reaction conditions, providing handle for sequential cross-coupling. Of note, this rare selectivity[28] in transition-metal-catalyzed amide activation (amide > Cl) indicates high and synthetically-useful N–C(O) coupling reactivity of *N*-acetyl amides. Perhaps most notably this method can be

Scheme 2. Amide Scope in the Palladium-Catalyzed Cross-Coupling of *N*-Ac Amides[a,b]



[a]Conditions: amide (0.20 mmol, 1.0 equiv), Ar-B(OH)$_2$ (0.40 mmol, 2.0 equiv), Pd(OAc)$_2$ (3 mol%), PCy$_3$HBF$_4$ (12 mol%), K$_2$CO$_3$ (2.5 equiv), H$_3$BO$_3$ (2.0 equiv), toluene (0.20 M), 60 °C, 15 h. [b]Isolated yields. [c]PhB(OH)$_2$ (1.2 equiv). [d]PhB(OH)$_2$ (3.0 equiv), K$_2$CO$_3$ (4.5 equiv), 120 °C. See SI for details.

applied to a wide variety of amides bearing electrophilic groups, including nitro (**3s**), cyano (**3t**), ester (**3e'**) and ketone (**3f'**) that would be incompatible with the classic Weinreb ketone synthesis,[25] demonstrating a significant advantage from the practical standpoint. Furthermore, ortho-fluoro-substitution (**3u**) poised for derivatization by S$_N$Ar is well-tolerated. Finally, polyaromatic amides prone to decarbonylation (**3j'**)[12d] as well as heterocyclic amides (**3v**) delivered the desired product in good yields. In general, other by-products than the PhN(Ac) leaving group have not been observed. At the present stage of reaction development aliphatic amides are beyond the scope of the reaction. Alkyl boronic acids as well as *N*-heterocycles, such as pyridine, indole and quinoline, have not been tested. Future studies will be aimed at expanding the substrate scope of amide bond cross-coupling.

We were pleased to find that the method can also be applied to the coupling of challenging *N*-Ac/alkyl amides (Scheme 3),[2] demonstrating a broad generality of the *N*-acetyl activation platform.

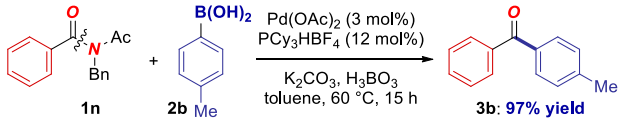
Furthermore, the coupling using Pd-NHC catalysts is feasible (Scheme 4).[29] The use of well-defined Pd(II)-NHC

precatalysts provides significant advantages in cross-coupling manifolds.[30]

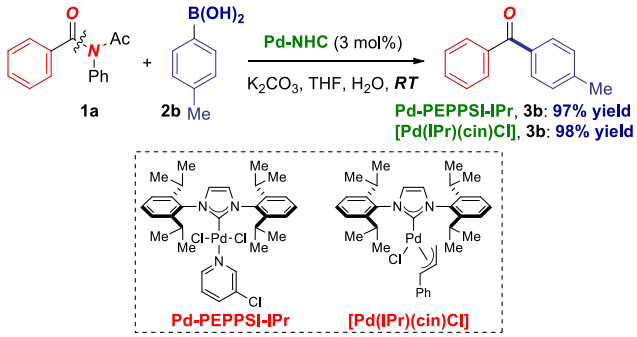
Turnover numbers (TON) of 970, 3100, 3500 were determined for the cross-coupling of amide **1a** ($Pd(OAc)_2/PCy_3$, 0.10 mol%, 60 °C; 0.025 mol%, 60 °C; Pd-PEPPSI-IPr, (IPr)Pd(cin)Cl, 0.025 mol%, 60 °C) (Scheme 5). This is the highest TON determined for Pd-catalyzed amide N–C activation reported to date for both Pd-PR_3 and Pd-NHC catalysts,[29] clearly demonstrating the high activity and the advantage of *N*-acetyl-amides in the Suzuki-Miyaura cross-coupling.

To gain insight into the mechanism, preliminary experiments were conducted (Scheme 6). (1) Electron-deficient amides are inherently more reactive (4-CF_3:4-MeO = 91:9). (2) Electron-rich nucleophiles react preferentially (4-MeO:4-CF_3 = 77:23). (3) The reactivity order with respect to the amide activating group is as follows: *N*-Ac/R >> *N*-R/Ts, *N*-

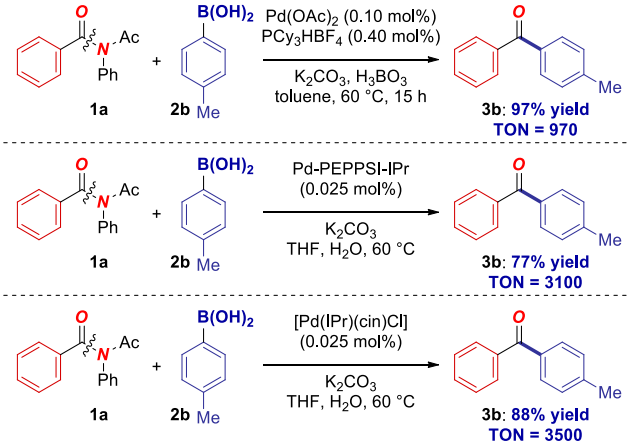
Scheme 3. Cross-Coupling of *N*-Ac/Alkyl Amides



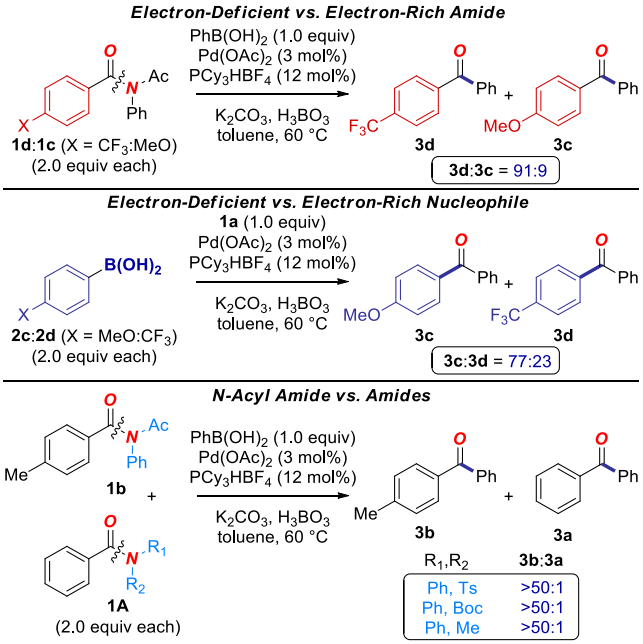
Scheme 4. Cross-Coupling using Pd(II)-NHC Catalysts



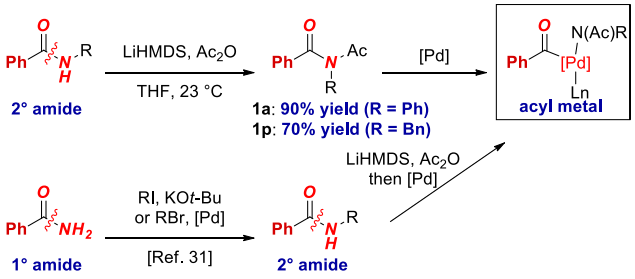
Scheme 5. Determination of TON in the Cross-Coupling of *N*-Ac Amides



Scheme 6. Competition Experiments



Scheme 7. Synthesis of *N*-Ac Amides from 1° or 2° Amides



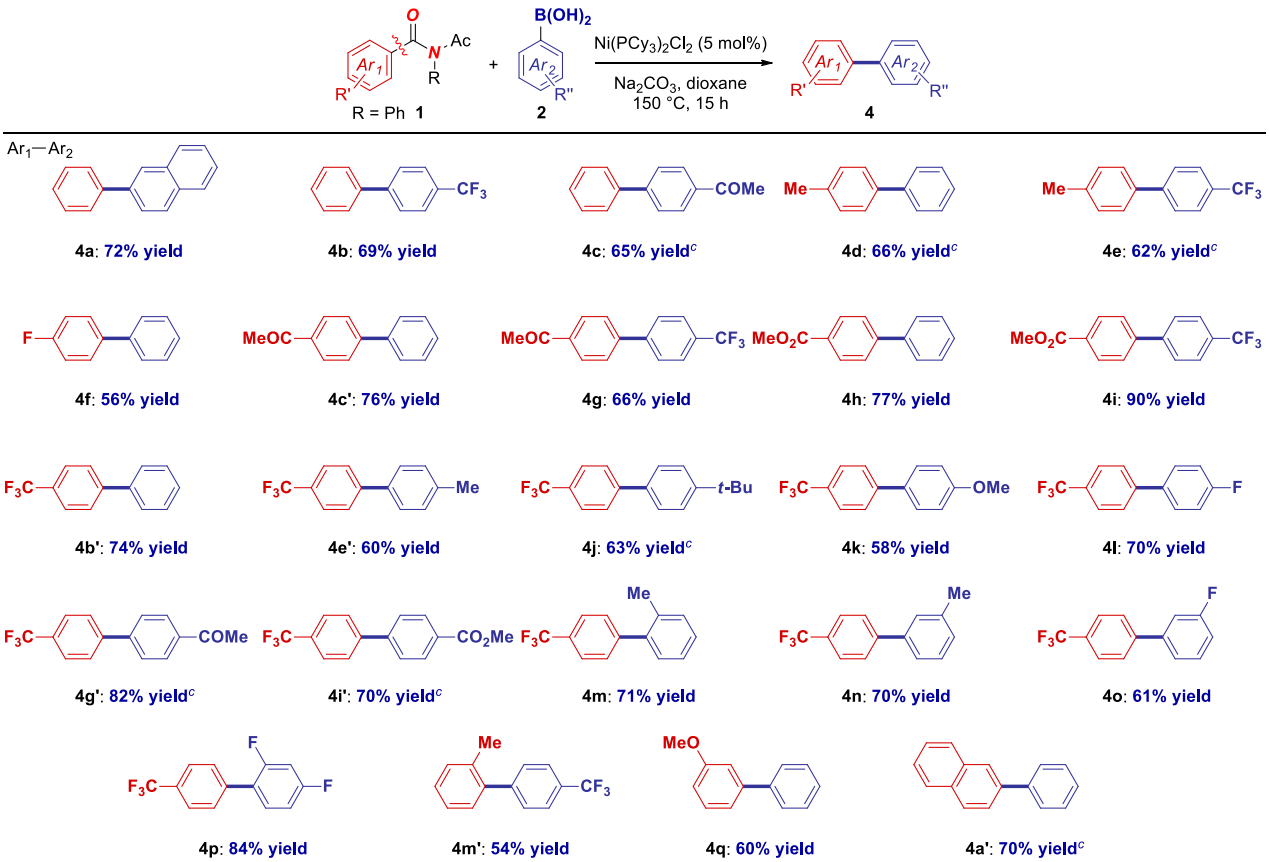
R/Boc, *N*-Ar/R (anilide). Clearly, the high reactivity of *N*-acyl-amides provides the advantage in the amide bond activation platform.

To further expand the synthetic utility of *N*-Ac-amides, we demonstrated that *N*-Ac amides can be readily prepared from unactivated secondary amides by chemoselective *N*-acylation (Scheme 7). Since methods for the synthesis of secondary amides from primary amides are well-established,[31] the *N*-Ac-amide reactivity platform provides rapid entry to acyl-metal intermediates **A** (Figure 1) from common unactivated amides. Hence, as a pivotal synthetic advantage, the amide bond cross-coupling could thus benefit from engaging common amides in this cross-coupling platform.

Having established the high reactivity of *N*-Ac-amides, we next sought to demonstrate the generality of these amide precursors. Considering the tremendous importance of biaryl Suzuki-Miyaura cross-coupling in the field of organic synthesis,[24] we selected decarbonylative Suzuki-Miyaura coupling as a representative transformation. Since thus far only one example of decarbonylative Suzuki-Miyaura cross-coupling of amides has been reported, we were attracted to this challenge.[12b] The use of acyclic amides in biaryl Suzuki cross-coupling would represent a significant advance for implementing the biaryl transform in cross-coupling reactions.

After extensive optimization (see SI for optimization details), we identified conditions to effect decarbonylative

Scheme 8. Nickel-Catalyzed Suzuki-Miyaura Biaryl Synthesis through Cross-Coupling of *N*-Ac Amides[a,b]



[a]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (1.5 equiv), Ni(PCy$_3$)$_2$Cl$_2$ (5 mol%), base (4.5 equiv), dioxane (0.25 M), 150 °C, 15 h. [b]Isolated yields. [c]Ar-B(OH)$_2$ (3.0 equiv). See SI for details.

Suzuki-Miyaura cross-coupling of *N*-Ac-amides with exquisite decarbonylation selectivity (Scheme 8). We found that a catalytic system based on inexpensive, 3d transition metal, Ni, [Ni(PCy$_3$)$_2$Cl$_2$, 5 mol%] in the presence of Na$_2$CO$_3$ as a base in dioxane at 150 °C provided optimum results. Other Ni(II) precatalysts, bases and solvents were screened (see SI), and provided inferior results. The high reactivity of the developed catalyst system is highlighted in the Suzuki biaryl coupling of 24 unique substrate combinations to produce biaryls bearing electronically-differentiated substitution on both the boronic acid and the amide coupling component (Scheme 8, **4a-q**). Importantly, electron-neutral (**4a**, **4d**, **4f**, **4c'**, **4h**), electron-rich (**4e'**, **4j**, **4k**) and even electron-deficient nucleophiles (**4b**, **4c**, **4e**, **4g**, **4i**, **4l**) that are typically less reactive in transmetallation[32] are well-tolerated in this coupling. Furthermore, the reaction is compatible with the synthesis of highly electron-deficient poly-fluorinated biaryls (**4l**, **4g**, **4i'**, **4o-p**) that have widespread application in academic and industrial research.[26] Importantly, ketone-containing substrates that are problematic in the related Suzuki-Miyaura cross-coupling of esters[18b] are well-tolerated (**4c**, **4c'**, **4g**, **4g'**). The reaction is also compatible with steric hindrance as demonstrated by the synthesis of ortho-substituted biaryls from either the boronic acid (**4m**) or amide component (**4m'**). Overall, the high efficiency and selectivity of this reaction compares very well with the known examples of the Suzuki biaryl coupling of amides and esters. The superb selectivity for decarbonylation (>20:1 in all examples examined) bodes well for the general use of *N*-Ac-amides in decarbonylative reactions of amides in lieu of aryl halides and pseudohalides.[3,24]

Studies were conducted to gain insight into the mechanism of the biaryl coupling and compare the reactivity with N-glutarimides, thus far the only other type of amides to undergo decarbonylative Suzuki coupling (Scheme 9). (1) Intermolecular competition experiments revealed that electron-deficient arenes are inherently more reactive (4-CO$_2$Me:4-Me = 86:14, cf. glutarimide, 4-CO$_2$Me:4-Me = 87:13), consistent with oxidative insertion. (2) Furthermore, intermolecular competition experiments revealed that the electronic nature of boronic acid does not significantly affect the reactivity[11b] (4-*t*-Bu:4-CO$_2$Me = 56:44, cf. glutarimide, 4-4-*t*-Bu:4-CO$_2$Me = 49:51). (3) Moreover, sterically-demanding amides are less reactive than their non-hindered counterparts (4-Me:2-Me = 78:22, cf. glutarimide, 4-Me:2-Me = 21:79), while the steric hindrance on boronic acid does not significantly affect the reactivity (4-Me:2-Me = 54:46, cf. glutarimide, 4-Me:2-Me = 40:60). Collectively, the studies provide strong support for amide bond activation by oxidative insertion of Ni(0) into the N–C(O) bond to afford acyl-Ni(II) intermediate. The high chemoselectivity for the N–C(O) activation results from ground state destabilization of the amide bond.[9b] The high selectivity for decarbonylative vs. acyl coupling suggests facile decarbonylation under the reaction conditions.

To gain insight into the structural factors that control the high reactivity of *N*-Ac-amides, the X-ray structure of **1a** was

determined (Figure 3). Remarkably, the amide shows approximately half-twisted amide bond (τ = 43.0°, χ_N = 10.9°, χ_C = 3.4°). The N–C(O) and C=O bond lengths are 1.422 Å and 1.213 Å. In contrast, the *N*-Ac bond is virtually planar;

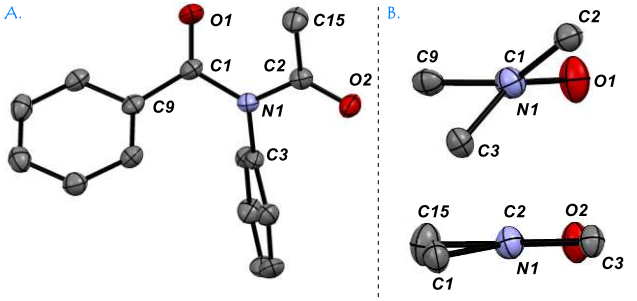
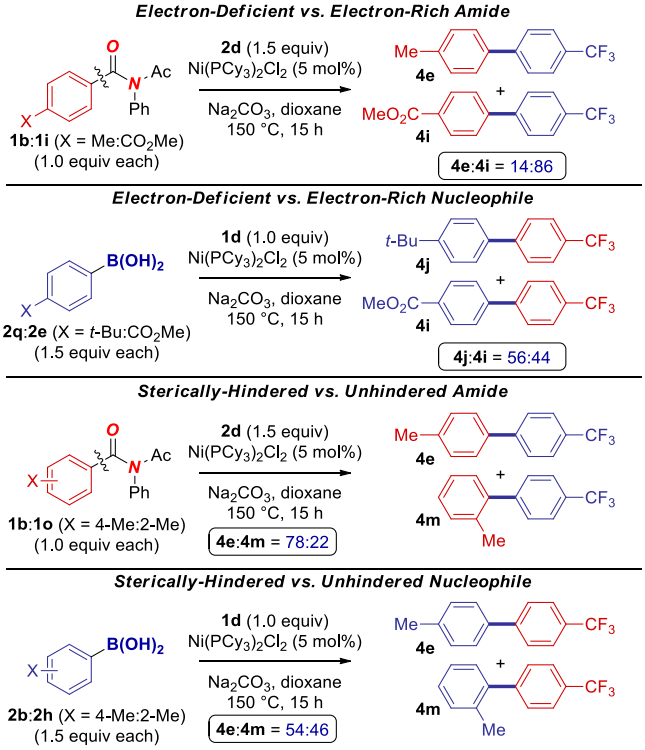


Figure 3. (a) Crystal structure of **1a**. (b) Newman projection along the N–C(O) bond (PhCO–, top; Ac–, bottom). Bond lengths (Å) and angles (deg): N1–C1, 1.422(2); C1–O1, 1.213(2); C9–C1, 1.479(2); N1–C2, 1.395(2); C2–O2, 1.209(2), C15–C2, 1.509(2); C9–C1–N1–C2, –140.8(2); O1–C1–N1–C3, –133.3(2); O1–C1–N1–C2, 35.8(2); C9–C1–N1–C3, 50.1(2); C15–C2–N1–C3, –179.3(1); O2–C2–N1–C1, –170.6(1); O2–C2–N1–C3, –1.5(2); C15–C2–N1–C1, 11.6(2). Note much weaker N1–C1(O) than N1–C2(O) bond.

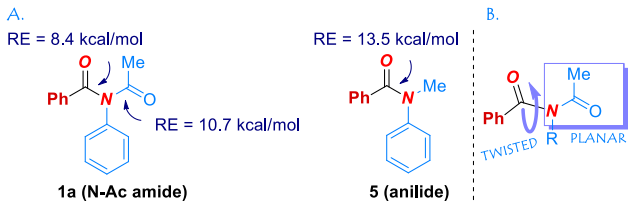
Scheme 9. Competition Experiments



(τ = 5.1°, χ_N = 10.9°, χ_C = 2.2°). The N–C(O) and C=O bond lengths of 1.395 Å and 1.209 Å in the *N*-Ac moiety further indicate a more pronounced resonance stabilization of the *N*-Ac amide bond. The *N*-Ac C=O bond in **1a** is antiperiplanar to the N–C(O) bond (170.6°), while the C–Me bond is antiperiplanar to the N–Ar bond (179.3°). While compared with the amide bond distortion in N-benzoyl-glutarimide[9b] (τ = 87.5°, χ_N = 5.6°, χ_C = 1.3°; N–C(O) = 1.475 Å, C=O = 1.200 Å), these values indicate less pronounced destabilization in **1a**, the significant twist of the amide bond provides strong support for high chemoselectivity of the N–C(O) cleavage as a result of ground state destabilization by rotation. Cleavage of the alternative *N*-Ac bond is disfavored due to $n_N \rightarrow \pi^*_{C=O}$ conjugation, as expected for a typical planar amide.[10] The unique activity of *N*-Ac amides can thus be explained by classical amidic resonance, whereby the diminution of the resonance is achieved by resonance and steric effects.

Next, we conducted computational studies to determine the effect of *N*-Ac substitution on amide bond destabilization (Scheme 10 and SI). (1) Resonance energy (RE) determined by the COSNAR method[8b] show that (i) amidic resonance in **1a** (RE = 8.4 kcal/mol) is lower than in the planar amides, and this value is within the range for metal insertion under mild, chemoselective conditions;[29a] (ii) RE of the *N*-Ac group (RE = 10.7 kcal/mol) confirms the energetic preference for activation of the twisted amide bond. (2) Rotational profile of **1a** was determined by systematic rotation along the O–C–N–$C_{(Ar)}$ dihedral angle (Figure 4), and it identified the energy minimum at ca. 40° O–C–N–C angle (τ = 33.15°; χ_N = 14.92°) in a syn O–C–N–$C_{(Me)}$ conformation (ca. 25.1° O–C–N–$C_{(Me)}$ dihedral angle). The energy maximum is located at ca.180° O–C–N–C dihedral angle (τ = 12.62°; χ_N = 15.96°) in an antiperiplanar O–C–N–$C_{(Me)}$ destabilizing conformation (ca. 164.0°

Scheme 10. A) Effect of Acyl Group; B) Graphical Representation of Acyl-Twisting Destabilization Mechanism[a]



[a]Note a gradual increase of RE by changing a single *N*-substituent at the nitrogen atom. RE of $MeCONMe_2$ = 18.3 kcal/mol.[11]

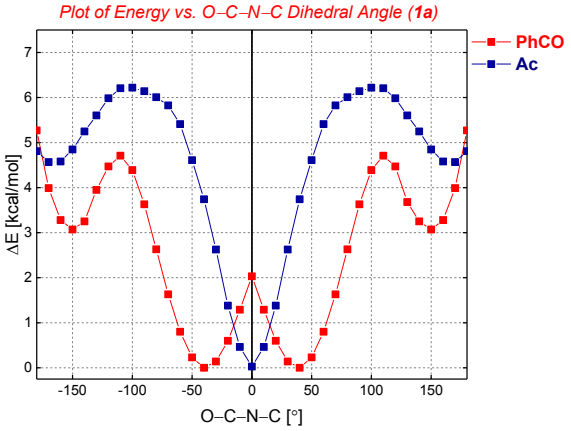


Figure 4. Rotational profile (**1a**, ΔE, kcal/mol, vs. O–C–N–C [°]). PhCO (red) indicates rotation along the PhCO–N axis; Ac (blue) indicates rotation along the Ac–N axis. Rotational profile including planar DMAc (N,N-dimethylacetamide, ΔE = 19.51 kcal/mol) is shown in the Supporting Information.

O–C–N–$C_{(Me)}$ dihedral angle). In contrast, systematic rotation along the O–C–N–$C_{(Ar)}$ dihedral angle for the Ac group (Figure 4) reveals the energy minimum at ca. 0° O–C–N–C angle (τ = 9.35°; χ_N = 15.07°), while the energy maximum is located at ca. 80° O–C–N–C dihedral angle (τ = 85.93°; χ_N = 12.91°),

as expected for planar amides.[10] Thus, rotational profiles provide further evidence for the chemoselective N–C(O) cross-coupling in *N*-Ac amides. (3) Determination of N-/O-protonation affinities (ΔPA) in **1a** indicates that this amide strongly favors protonation at the amide oxygen atom (ΔPA = 15.8 kcal/mol, the planar *N*-Ac amide bond). Interestingly, protonation at the oxygen of the *N*-Ac group is strongly favored over the O-protonation of the twisted amide bond (ΔPA = 10.9 kcal/mol, the twisted amide). Thus, O-protonation of the *N*-Ac group is an additional factor activating the N–C(O) twisted amide bond[33] towards selective scission due to enhanced Nlp conjugation.

Collectively, the structural and energetic parameters determined for the amide bond in **1a** indicate amide twist and electronic destabilization imposed by the amide framework as empowering features for N–C(O) activation, thus providing the basis for chemoselective utilization of *N*-Ac amides in a wide range of cross-coupling protocols by acyl- and decarbonylative pathways.

In conclusion, we have reported the first Pd-catalyzed acyl and Ni-catalyzed decarbonylative Suzuki-Miyaura cross-coupling of *N*-acetyl-amides with arylboronic acids. The methods developed here represent divergent approaches to the widespread utilization of common acyclic amides in organic chemistry. Most crucially, this report introduces *N*-acetyl-amides as the most reactive acyclic amides developed thus far in the burgeoning manifold of transition-metal-catalyzed amide cross-coupling. The methods allow for a rapid access to a variety of biaryl ketones and biaryls from easily accessible acyclic amides with exceptional coupling selectivity. The high reactivity of *N*-Ac-amides allowed for the first example of the biaryl Suzuki-Miyaura cross-coupling of simple acyclic amides.[34] These biaryl products represent some of the most important building blocks in organic chemistry. Mechanistic and structural interrogations provided evidence for re-modeling of amidic resonance and amide bond twist as selectivity determining features in the cross-coupling of amides. We fully expect that knowledge gained in this study will inspire the development of new synthetic methods. We anticipate *N*-Ac-amides to be exploited as generic precursors in amide bond cross-coupling enabling previously inaccessible reactivity of the amide bond. Future studies will be aimed at investigating new amide electrophiles for cross-coupling.

ASSOCIATED CONTENT

Supporting Information

Experimental details, characterization data, CIF file for amide **1a**, 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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