N-Acyl-Carbazoles and N-Acyl-Indoles: Electronically-Activated Amides for N–C(O) Cross-Coupling by N_{lp} to Ar Conjugation Switch

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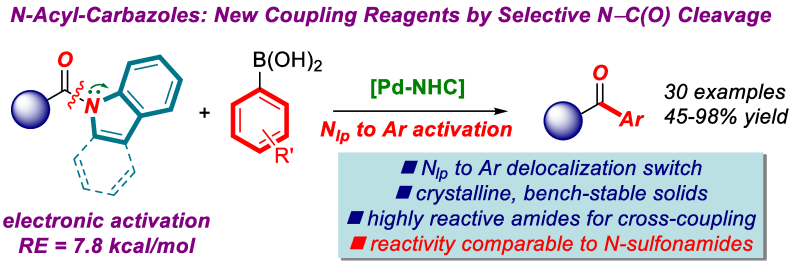
Supporting Information



ABSTRACT: The development of new amide precursors for selective, catalytic activation of carbon–nitrogen bonds in amides is a fundamental objective of this emerging reactivity manifold. We report the palladium-catalyzed Suzuki–Miyaura cross-coupling of N-acyl-carbazoles and N-acyl-indoles with arylboronic acids by a highly selective N–C(O) cleavage. The key amide bond ground-state-destabilization stems from N_{lp} to Ar conjugation and enables for the first time to achieve reactivity similar to N-acyl-sulfonamide and N-acyl-carbamate activation in simple anilides.

Activation of amide bonds by selective oxidative insertion into the N–C(O) bond is a particularly attractive strategy for generating acyl-metals from amides.[1,2] Traditionally, the selective activation of N–C(O) amide bonds has been a major challenge due to the classic amidic resonance ($n_N \rightarrow \pi^*_{C=O}$ conjugation, RE, resonance energy, 15-20 kcal/mol in planar amides) (Figure 1A-B).[3] In this context, the development of catalytic amide bond cross-couplings is of broad interest to selectively functionalize organic molecules due to the ubiquity of amide bonds in organic synthesis, polymers and drug discovery.[4,5]

Recently, methods for ground-state-destabilization of amide bonds in acyclic amides have been reported.[6–9] The most common is $n_N \rightarrow \pi^*_{C(O)=O}$ and $n_N \rightarrow \pi^*_{S=O}$ delocalization in N-acyl-carbamates and N-acyl-sulfonamides.[7] Alternatively, N-acyl-glutarimides[8] and N-acyl-mono-amides[9] represent twisted tri- and di-imides that rely on $n_N \rightarrow \pi^*_{C(R)=O}$ destabilization. This activation concept leads to the twisting of amide bonds out of planarity and enables the catalytic generation of acyl-metals by a combined steric and electronic destabilization.[10–12]

In contrast, few methods for selective activation of comparatively planar, electronically-activated N-Ar amides have been reported.[13–15] These studies are predominantly limited to N-methyl-anilides (RE = 13.5 kcal/mol),[13] which have been successfully utilized in the oxidative addition of N–C(O) bond to Ni; however, are generally much less reactive than other amide precursors and unreactive using other metals. Although N-acyl-pyrroles (RE = 9.3 kcal/mol) have been shown to be reactive electrophiles in the oxidative addition of N–C(O) bonds using Pd, these substrates are unsuitable as amides for general cross-coupling reactions due to their well-recognized hydrolytic instability triggered by the release of the azolide ring.[16–18]

As a part of our ongoing research interest in amide bond activation, we recently questioned whether N_{lp} to Ar conjugation switch in N-Ar amides might be used to effect highly selective oxidative insertion into the amide N–C(O) bond (Figure 1C).

Herein, we report the palladium-catalyzed Suzuki–Miyaura cross-coupling of N-acyl-carbazoles and N-acyl-indoles with arylboronic acids by highly selective N–C(O) bond cleavage. The following features of our findings are noteworthy: (1) Most importantly, this study introduces N-acyl-indoles and in particular N-acyl-carbazoles as highly effective amide bond electrophiles for selective activation of the N–C(O) bond. (2) The key amide bond ground-state-destabilization stems from N_{lp} to Ar conjugation in a flat carbazole ring, enabling for the first time to achieve reactivity similar to N-sulfonamide and N-carbamate activation in simple anilides. (3) Mechanistic studies provide key insight into bond destabilization of the amide bond. Overall, we expect that bench- and hydrolytically-stable N-acyl-azolides that permit facile N–C(O) activation will provide a very attractive approach to the generation of acyl-metals from amides for a variety of coupling reactions.

In agreement with our previous studies, we hypothesized that diminution of amidic resonance in anilides might be rendered possible by channeling the $n_N \rightarrow \pi^*_{C=O}$ resonance into another functional group.

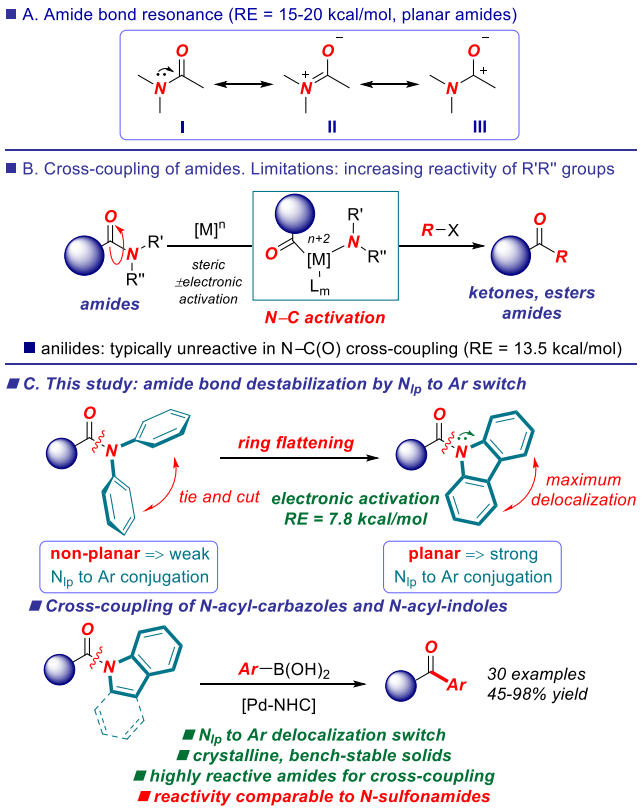
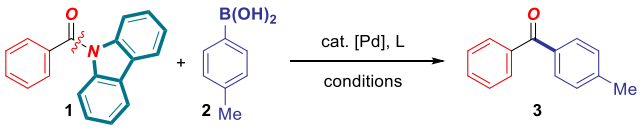


Figure 1. (a) Amide bond resonance. (b) Activation of amides and derivatives. (c) This work: N_{lp} to Ar conjugation switch, N-acyl-carbazoles: new class of highly reactive amides for N–C(O) cross-coupling.

After significant experimentation optimizing amide bond geometry, we identified N-acyl-carbazoles as suitable substrates for this process. The amide bond in a model N-benzoyl-carbazole (**1a**) is relatively planar[16c,d] (τ = 25.1°; χ_N = 3.2°, Winkler-Dunitz parameters, N–C(O) bond length of 1.400 Å, C=O of 1.212 Å), which can be compared with a model predominantly planar N-methyl-anilide (N–C(O) bond length of 1.355 Å, C=O of 1.230 Å).[13]

Selected optimization studies of the Suzuki–Miyaura cross-coupling of N-benzoyl-carbazole (**1a**) with 4-tolylboronic acid are presented in Table 1. The optimized conditions utilize Pd–PEPPSI–IPr (3 mol%), K_2CO_3 (4.5 equiv) in THF at 80 °C (Table 1, entry 1, see Figure SI-1 for catalyst structures). The use of other bases, including K_3PO_4, Na_2CO_3, Cs_2CO_3 and KOH was less successful (entries 2-5). The low yields using Na_2CO_3 and Cs_2CO_3 are likely a balance in precatalyst activation and acyl-metal stability. Several other solvents were examined, such as toluene, dioxane and DCE, and provided inferior results (entries 6-8). Higher temperature was also compatible with this reaction, consistent with the stability of N-acyl-carbazole moiety under these conditions (entry 9). Interestingly, the screen of various Pd(II)–NHC catalysts indicated that catalysts bearing allyl-type throw-away ligands, such as Pd(IPr)(cin)Cl, Pd(IPr)(1-*t*-Bu-ind)Cl, Pd(IPr)(allyl)Cl are also effective in this reaction, delivering the coupling product in good to high yields (entries 10-12). In contrast, there is a significant impact of the steric demand of the NHC ancillary ligand, with both less-sterically demanding IMes and more-hindered IPent giving low yield of the cross-coupling product (entries 13-14). Finally, we also tested the use of

Table 1. Optimization of Cross-Coupling of N-Acyl-Carbazoles[a]



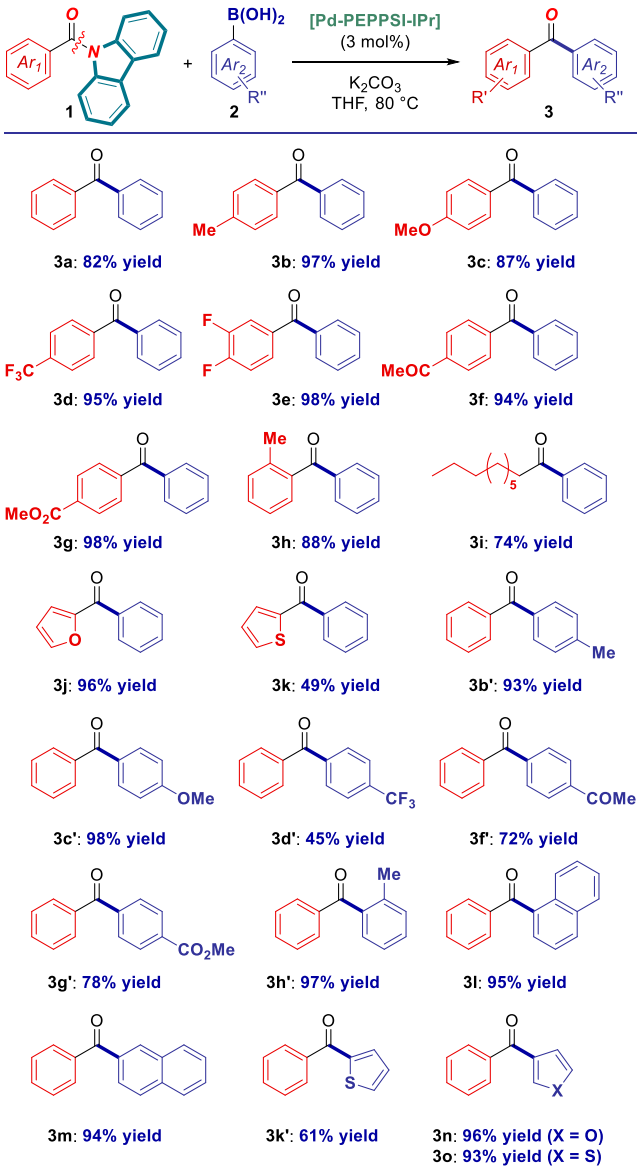
entry	catalyst	base	solvent	yield (%)[b]
1	[Pd–PEPPSI–IPr]	K_2CO_3	THF	93
2	[Pd–PEPPSI–IPr]	K_3PO_4	THF	52
3	[Pd–PEPPSI–IPr]	Na_2CO_3	THF	<5
4	[Pd–PEPPSI–IPr]	Cs_2CO_3	THF	17
5	[Pd–PEPPSI–IPr]	KOH	THF	13
6	[Pd–PEPPSI–IPr]	K_2CO_3	toluene	89
7	[Pd–PEPPSI–IPr]	K_2CO_3	dioxane	51
8	[Pd–PEPPSI–IPr]	K_2CO_3	DCE	28
9[c]	[Pd–PEPPSI–IPr]	K_2CO_3	THF	86
10	[Pd(IPr)(cin)Cl]	K_2CO_3	THF	92
11	[Pd(IPr)(1-*t*-Bu-ind)Cl]	K_2CO_3	THF	81
12	[Pd(IPr)(allyl)Cl]	K_2CO_3	THF	71
13	[Pd–PEPPSI–IPent]	K_2CO_3	THF	50
14	[Pd–PEPPSI–IMes]	K_2CO_3	THF	15
15[d]	$Pd(OAc)_2/PCy_3HBF_4$	K_2CO_3	THF	12

[a]Conditions: amide (1.0 equiv), 4-Tol-$B(OH)_2$ (3.0 equiv), catalyst (3 mol%), base (4.5 equiv), solvent (0.25 M), 80 °C, 15 h. [b]GC/^{1}H NMR yields. [c]120 °C. [d]$Pd(OAc)_2$ (3 mol%), PCy_3HBF_4 (12 mol%), H_3BO_3 (2.0 equiv), 80 °C. cin = cinnamyl; ind = indenyl; PEPPSI = 3-Cl-pyridine.

Pd/phosphane conditions, which resulted in low conversion (entry 15); thus, the high σ-donation of the NHC ligand using bench-stable, well-defined Pd(II)–NHCs is highly beneficial for the coupling.

With the optimized conditions in hand, the scope of this transformation was examined with respect to the amide component (Scheme 1). As shown, this amide bond activation is well-compatible with neutral (**3a**), electron-donating (**3b-3c**) and electron-withdrawing (**3d-3g**) substituents on the amide. It is particularly noteworthy that electrophilic functional groups that would be problematic in classical addition of hard organometallics, such as ketones (**3f**) and esters (**3g**) are tolerated under these catalytic conditions. Furthermore, steric-hindrance (**3h**), aliphatic amides (**3i**) and heterocyclic amides conjugated at the deactivating, electron-rich position (**3j-3k**) were easily tolerated. Next, we examined the scope of the reaction with respect to the boronic acid component (Scheme 1). As shown, electron-neutral (**3b'**), electron-rich (**3c'**) and electron-deficient (**3d'**, **3f'-3g'**) arylboronic acids were successful substrates, albeit a lower yield using electron-withdrawing groups has been noted (*vide infra*). Furthermore, sterically-hindered boronic acids (**3h'**), polyaromatic boronic acids (**3l-3m**) and heterocyclic boronic acids (**3k'**, **3n-3o**) furnished the cross-coupling products in good to high yields. Note that the moderate yield for the thienyl product is likely a result of amide deactivation by resonance. At the present stage, alcohols are not compatible with the reaction conditions. Non-activated amides are recovered unchanged. (4-Aminophenyl)boronic acid is not tolerated. Note that the reaction time has not been optimized.

Scheme 1. [Pd–NHC]-Catalyzed Suzuki-Miyaura Cross-Coupling of N-Acyl-Carbazoles[a]

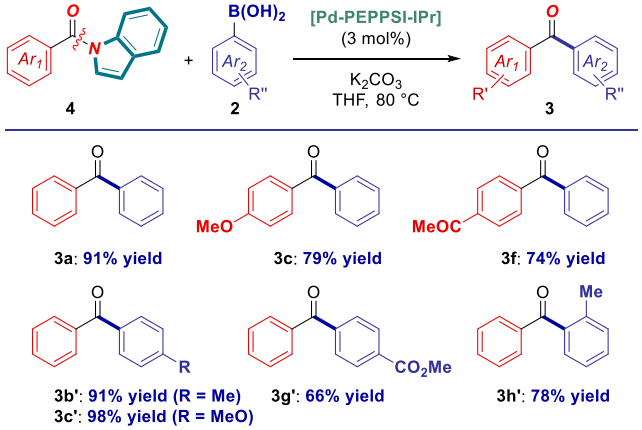


[a]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (3.0 equiv), [Pd] (3 mol%), K_2CO_3 (4.5 equiv), THF (0.25 M), 80 °C, 15 h. See Supporting Information (SI) for details.

Encouraged by the success of the Suzuki–Miyaura cross-coupling of N-acyl-carbazoles, we investigated the cross-coupling of N-acyl-indoles (Scheme 2). Similar to N-acyl-carbazoles, N-acyl-indoles are important structural motifs in numerous biologically active compounds and as synthetic intermediates.[16] We were pleased to find that the conditions optimized for the cross-coupling of N-acyl-carbazoles are also suitable for the cross-coupling of N-acyl-indoles. As shown using representative examples, electronic- (**3a**, **3c**, **3f**, **3b'**, **3c'**, **3g'**) and steric variation (**3h'**) is well-accommodated in the cross-coupling of N-acyl-indoles, indicating the generality of the reaction conditions.

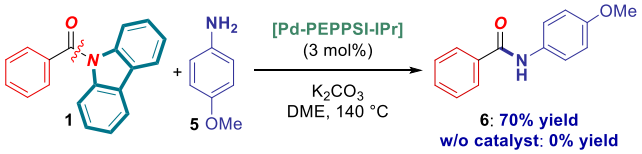
We were further interested to test N-acyl-carbazoles as precursors in acyl-Buchwald-Hartwig-type reactions (Scheme 3).[2a] We were pleased to find that a model N-benzoyl-carbazole underwent smooth transamidation under Pd–NHC conditions. It is expected that this class of reagents will provide an attractive means to trigger various reactions of amides. Note that the Suzuki-Miyaura coupling takes place under chemoselective conditions to transamidation of amides.[2a]

Scheme 2. [Pd–NHC]-Catalyzed Suzuki-Miyaura Cross-Coupling of N-Acyl-Indoles[a]

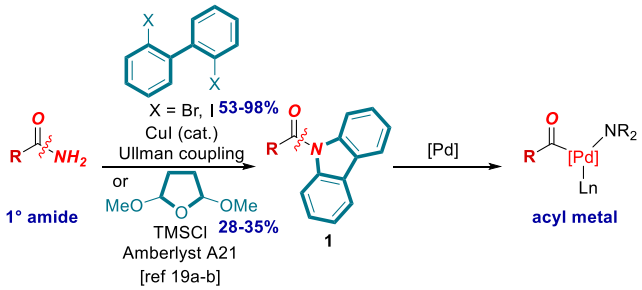


[a]Conditions: see Scheme 1.

Scheme 3. [Pd–NHC]-Catalyzed Acyl-Buchwald-Hartwig Cross-Coupling of N-Acyl-Carbazoles



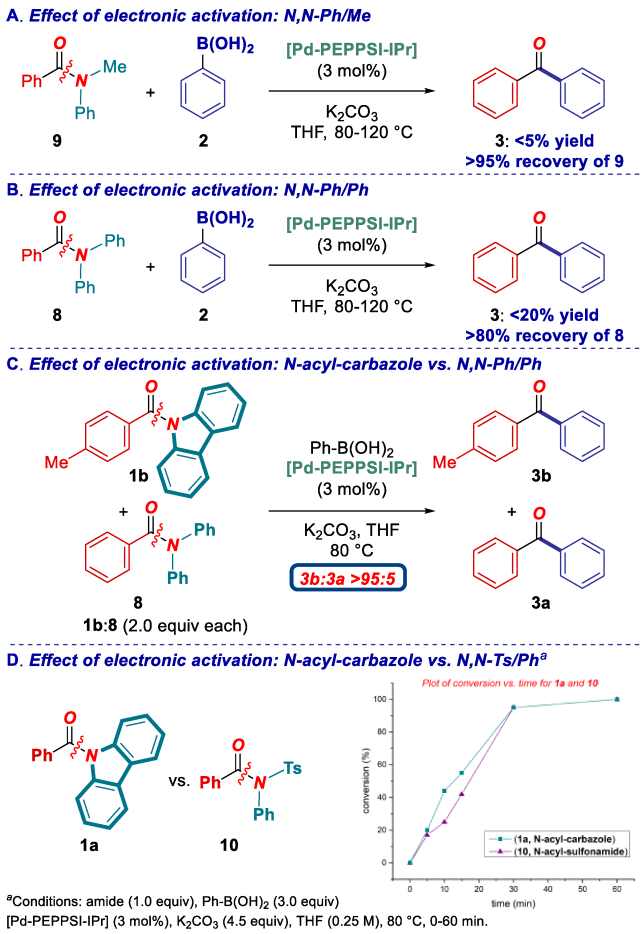
Scheme 4. Synthesis of *N*-Acyl-Carbazoles from 1° Amides



The synthetic advantage of N-acyl-carbazoles stems from the well-established stability of the amide bond to hydrolysisconditions, resulting in bench-stable, easily-handled, amide-based acyl-transfer reagents.[16] Furthermore, N-acyl-carbazoles are readily prepared from 1° amides by double N-arylation[19a] or by acid-catalyzed double electrophilic cyclization using 2,5-dimethoxytetrahdyrofuran[19b] (Scheme 4). This disconnection permits to generate acyl-metal intermediates from common 1° amides. While several other strategies for activating primary amides directly have been reported, including N,N-Boc$_2$,[7d] N-pyrimidyl,[10] and N-Ac activation,[9] N-acyl-carbazoles benefit from the stability of N-Ar linkage cf. other precursors.

Intrigued by the high reactivity of N-acyl-carbazoles in the cross-coupling, we conducted selectivity and kinetic studies (Scheme 5). (1) Selectivity experiments demonstrated that N-acyl-carbazoles are significantly more reactive than N-methyl-anilides (Scheme 5A) and N-phenyl-anilides (Scheme 5B). (2)

Scheme 5. Selectivity Studies



[a]Conditions: amide (1.0 equiv), Ph-B(OH)$_2$ (3.0 equiv) [Pd-PEPPSI-IPr] (3 mol%), K_2CO_3 (4.5 equiv), THF (0.25 M), 80 °C, 0-60 min.

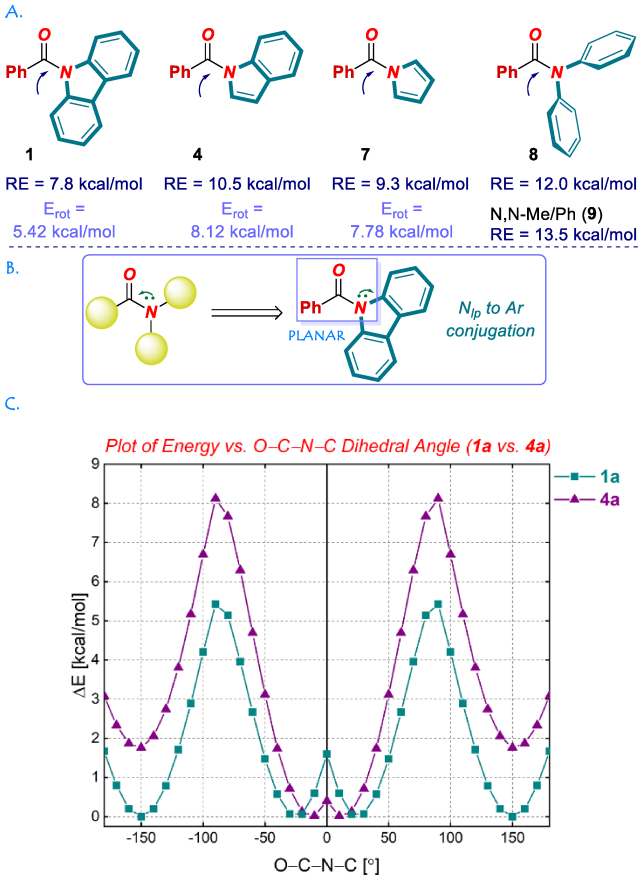
Furthermore, intermolecular competition experiments demonstrated full selectivity for the cross-coupling of N-acyl-carbazoles vs. N-phenyl-anilides (Scheme 5C). (3) Most importantly, kinetic studies demonstrated comparable reactivity of N-acyl-carbazoles to N,N-Ph/Ts sulfonamide activation (Scheme 5D). N-Acyl-carbamates have not been used in kinetic studies due to low stability of N-Boc linkage under the reaction conditions. *Thus, N-carbazolyl activation permits to achieve reactivity similar to N-sulfonamide activation in simple anilides.*[2–18]

Furthermore, intermolecular competition experiments with differently substituted amides and boronic acids showed that electron-deficient amides are more reactive (4-CF_3:4-MeO = 85:15) (Scheme SI-1), while electron-rich boronic acids are more reactive (4-MeO:4-CF_3 = 73:27) (Scheme SI-1), consistent with metal insertion as the rate limiting step.

The development of new amide bond precursors with rationally-modified amidic resonance is fundamental for the future progress of amide bond cross-coupling.[2–18] In agreement with our design, N-acyl-carbazoles are predisposed for N–C(O) activation by N_{lp} to Ar conjugation. The delocalization is much enhanced by the flat carbazole ring (Figure 1B).

To gain insight into the energetic parameters of the amide bond, we conducted computational studies on ground-state-destabilization in N-acyl-carbazoles (Scheme 6). As summarized in Scheme 6, N-acyl-carbazoles should be benchmarked two-directionally against anilides (such as, N-Me-anilide and

Scheme 6. Effect of Activating Group: Amides Employed in Computational Studies and Rotational Profile[a]



[a]Note a gradual decrease of RE by changing N-substituents at the nitrogen atom. RE of planar DMAc, $MeCONMe_2$ = 18.3 kcal/mol. See SI.

N-Ph-anilide)[13] and N-acyl-azolides (such as, N-acyl-pyrrole and N-acyl-indole).[14–16]

(1) Thus, resonance energy determined using the COSNAR method[20] showed that resonance in **1a** (RE = 7.8 kcal/mol) is significantly lower than in **7-9** (**4a**: 10.5 kcal/mol; **7**: 9.3 kcal/mol; **8**: 12.0 kcal/mol; **9**: 13.5 kcal/mol). Note that in this series, N-acyl-pyrrole is hydrolytically-unstable.[16] The low RE of **1a** can be compared with N-Ts amides (8.0 kcal/mol).[7c,d]

(2) Rotational profiles determined by systematic rotation along the O–C–N–C dihedral angle showed the energy minimum at ca. 20° O–C–N–C angle for **1a** (τ = 26.48°; χ_N = 8.41°), and 10° O–C–N–C angle for **4a** (τ = 14.38°; χ_N = 7.67°) in a syn O–C–N–Ar conformation (ca. 10° O–C–N–C dihedral angle), while the energy maximum is located at ca. 90° O–C–N–C dihedral angle for **1a** (τ = 71.97°; χ_N = 34.36°, 5.42 kcal/mol) and 90° O–C–N–C dihedral angle for **4a** (τ = 73.16°; χ_N = 31.90°, 8.12 kcal/mol) for **1a**. These values can be compared with the barrier of ca. 7.78 kcal/mol in N-acyl-pyrroles and 7.01 kcal/mol in N-Ts amides.

(3) ΔPA, the difference between N-/O-protonation affinities, indicated that **1a** favors protonation at oxygen (ΔPA = 10.7 kcal/mol), which is significantly lower than in **7** (ΔPA = 21.4 kcal/mol; cf. **4a**: 17.4 kcal/mol; **8**: 14.2 kcal/mol; **9**: 11.0 kcal/mol). Thus, while N-activation of **1** by N-protonation is

unlikely, PA values are consistent with high hydrolytic stability of N-acyl-carbazoles.[16] An interesting point regarding RE of N-acyl-carbazoles vs. pyrroles vs. indoles might be derived from C7–H steric interaction (indole). Studies to further address this trend are ongoing and will be published separately.

Diminution of amidic resonance can be performed by both steric and electronic factors.[2–6] The high feasibility of N-acyl-carbazoles in oxidative insertion stems from N_{lp} to Ar conjugation, wherein the presence of carbazole π-system and the planarity of the ring with respect to the amide N_{lp} ensures maximum delocalization switch away from the amide bond.[4,6] *This amide bond delocalization concept is likely to find applications in catalytic reactions of the amide bond[7–18] as well as the design of more active amide bond analogues.[2–6]*

In summary, we have developed the palladium-catalyzed Suzuki–Miyaura cross-coupling of N-acyl-carbazoles and N-acyl-indoles with arylboronic acids by highly selective N–C(O) bond cleavage. The reaction is performed using bench-stable and operationally-convenient Pd(II)-NHC precatalysts, and a variety of reaction partners are compatible. This reaction exploits N-acyl-indoles and especially N-acyl-carbazoles as highly effective amide bond electrophiles for selective oxidative insertion into the N–C(O) bond. This activation concept of amide bonds by electronic conjugation sets the stage for simple N-Ar amides to be broadly applied in various catalytic processes by N–C(O) bond activation. N-acyl-carbazoles are bench-stable, easy to handle and generate acyl-metals from 1° amides. Mechanistic studies provided key insight into amide bond ground-state-destabilization and for the first time showed that the reactivity of N-acyl-carbazoles is similar to that of N-acyl-sulfonamides. Further development of amide cross-coupling reactions and new catalytic applications will be closely tied to the discovery of more effective amide bond electrophiles. Full account on amide bond geometry optimization will be forthcoming.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, cartesian coordinates and energies. This material is available free of charge via the Internet at http://pubs.acs.org.

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