N-Methylamino Pyrimidyl Amides (MAPA): Highly Reactive, Electronically-Activated Amides in Catalytic N–C(O) Cleavage

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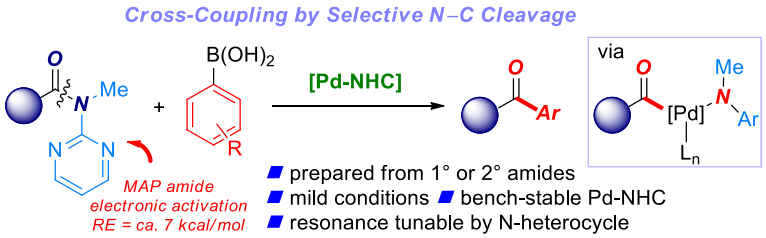
Supporting Information



ABSTRACT: Despite recent progress in catalytic cross-coupling technologies, the direct activation of *N*-alkyl-*N*-aryl amides has been a challenging transformation. Here, we report the first cross-coupling of *N*-methylamino pyrimidyl amides (MAPA) enabled by the controlled $n_N \rightarrow \pi_{Ar}$ conjugation and the resulting remodeling of the partial double bond character of the amide bond. The new mode of amide activation is suitable for generating acyl-metal intermediates from *unactivated* primary and secondary amides.

Direct activation of N–C amide bonds is receiving increasing attention in organic synthesis.[1–5] This mode of reactivity induces traditionally difficult to achieve insertion of a low-valent metal catalyst into the inert N–C(O) moiety ($n_N \rightarrow \pi^*_{C=O}$ conjugation, barrier to rotation in planar amides of 15-20 kcal/mol),[6] thus enabling amides to participate in acyl- and decarbonylative cross-coupling reactions of high synthetic value. In a broader context, the amide bond activation methods are a subset of a more general strategy to catalytically activate bench-stable carboxylic acid derivatives under redox neutral conditions,[7] including esters,[1a] wherein the amide bond offers the major advantage of selective tuning of the amide bond geometry by tricoordinate nitrogen that is unavailable in other acyl-precursors.[8] Considering that the amide bond is a preeminent motif in various bioactive and pharmaceutically-relevant compounds,[9] as well as, historically, an irreplaceable intermediate in organic synthesis,[10] new methods for selective manipulation of amides will beyond doubt find wide application within the field.

Recent developments have provided a plethora of examples for constructing carbon–heteroatom and carbon–carbon bonds through direct N–C amide bond activation, whereby the amide bond is engineered by specifically-designed *N*-substituents that result in the amide bond ground-state steric destabilization by steric distortion (amide bond twist).[1–5,8] In contrast, direct methods to activate the amide bond in electronically-biased amides are noticeably lacking. In particular, the direct activation of *N*-alkyl-*N*-aryl amides has been a challenging transformation because of the high resonance energy of the amide bond in these precursors (RE, resonance energy, 13.5 kcal/mol).[11] Note that these anilides already feature significantly decreased amidic resonance (cf. planar amides, 15-20 kcal/mol) as a consequence of electronic activation; however, these values are still prohibitive for synthetically useful Pd insertion under mild conditions. Here, we introduce *N*-methylamino pyrimidyl amides (MAPA) as highly-reactive, electronically-activated amides for catalytic N–C(O) cleavage (Figure 1). The following features of our findings are noteworthy: (1) we demonstrate high reactivity of MAP amides under versatile Pd-catalysis[12] using user-friendly, operationally simple protocols, providing rapid entry to biaryl ketones; (2) since MAP amides can be readily prepared from *unactivated primary or secondary amides*, our method offers a rapid entry to metal-catalyzed coupling of common amides; (3) we demonstrate the advantageous effect of Pd-NHC catalysis[13] over Pd-phosphines in the amide bond cross-coupling manifolds. Note that the use of bench-stable, commercially-available, well-defined Pd-NHC precatalysts offers a major practical advantage;[14] (4) Mechanistic studies strongly support external N–C(O) amide bond $n_N \rightarrow \pi_{Ar}$ conjugation pathway. Collectively, our study opens the door for using *N*-alkyl-*N*-aryl amide electrophiles in a wide range of cross-coupling manifolds via acyl- and decarbonylative pathways in a rational and predictable manner.

In the present study, we were inspired by our recent development of the reactivity scale of the amide bond, wherein the amide bond resonance of approx. 10 kcal/mol represents a guideline for synthetically useful Pd-insertion into the amide bond.[3c] In this respect, the use of anilides is synthetically limited because of the low

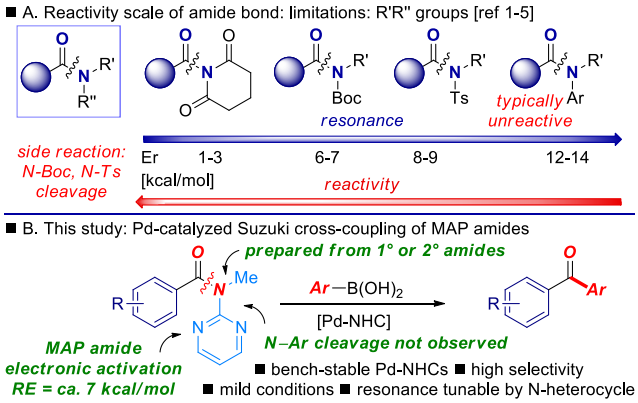


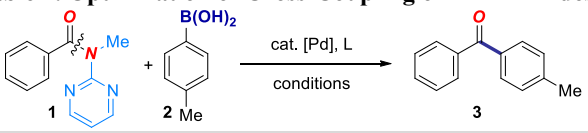
Figure 1. (a) Activation of amides and derivatives. (b) This work: coupling of MAP amides enabled by selective $n_N \rightarrow \pi_{Ar}$ delocalization.

reactivity of the amide bond (RE of 13.5 kcal/mol, *N*-Me-*N*-Ph-benzamide). The key electronic interaction[15] in our design is the $n_N \rightarrow \pi_{Ar}$ delocalization into the pyrimidine ring, which, as we demonstrate, can be readily translated into other heterocycles, resulting in a gradually-varying resonance and, thus, a generic activation mode of the amide bond. Note that this new gradual $n_N \rightarrow \pi_{Ar}$ delocalization mechanism is not readily available by other destabilization methods of the amide bond, including steric distortion and Nlp to C=O delocalization.[8]

After extensive optimization, we identified *N*-methylamino pyrimidyl amides[16] as suitable electrophiles for the process. Selected optimization results are presented in Table 1. We observed the desired cross-coupling product in our proof-of-concept reaction using $Pd(OAc)_2/PCy_3$ catalyst system and H_3BO_3 as the promoter (entry 1). The acid can protonate *N*-heterocycle, resulting in cis-trans isomer switch and selective metal-insertion along the isomerization pathway.[17] From an early stage we indentified the use of acid as essential for the formation of the desired product using Pd/phosphine catalysis (entries 1-10). After extensive screening of various conditions, the yield was increased to 50% (entry 7). At this point, we examined Pd-NHC-based catalysts systems.[3c,d] After experimentation, we found that (IPr)Pd(cinnamyl)Cl promoted the desired reaction with significantly improved efficiency (entry 11). As expected, strong σ-donation of the NHC ligand facilitates oxidative addition, while flexible steric bulk stabilizes the active catalyst and promotes reductive elimination.[13] Importantly, the reaction temperature could be decreased to 65 °C without a deleterious effect (entry 12). A further improvement was realized by using water as an additive, presumably to enhance solubility (entry 14). As expected, the transformation was found to be strongly dependent on the Pd-NHC catalyst used, with (IPr)Pd(cinnamyl)Cl providing the optimal results (entries 14-16). Interestingly, the use of acid with Pd-NHC catalysis was ineffective (entry 17), indicating that *N*-protonation is not required for this catalysis to occur. The finding that Pd-NHC act as superior catalysts to $Pd\text{-}PR_3$ systems underscores the potential of well-defined Pd(II)-NHCs as privileged catalysts for amide N–C cleavage reactivity.

With the optimal conditions in hand, the scope of the reaction with respect to the boronic acid component was evaluated (Scheme 1). As shown, the protocol exhibits broad tolerance, including neutral (**3a-c**), electron-rich (**3d**), electron-deficient (**3e**) and ortho-substituted (**3f-h**) substrates. Importantly,

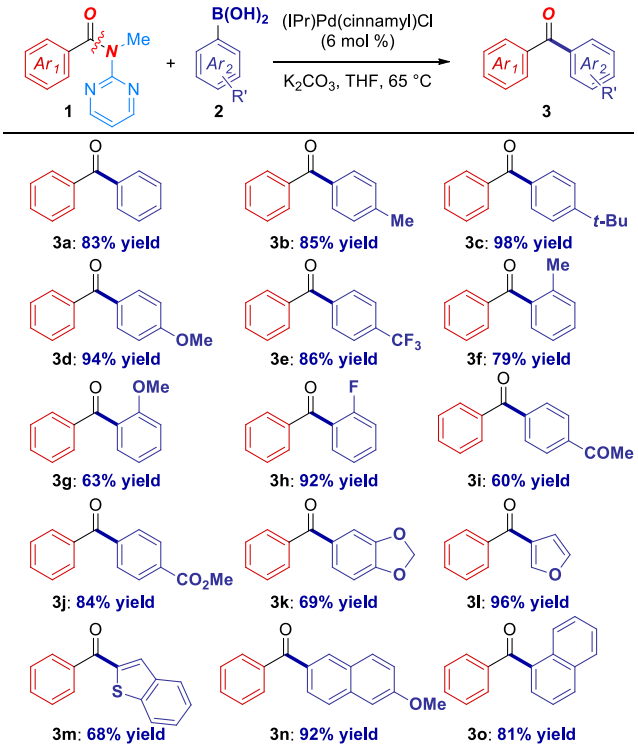
Table 1. Optimization of Cross-Coupling of MAP Amides[a]



entry	catalyst	ligand	additive	solvent	yield (%)[b]
1[c]	$Pd(OAc)_2$	PCy_3HBF_4	H_3BO_3	THF	12
2[d]	$Pd(OAc)_2$	PCy_3HBF_4	H_3BO_3	THF	20
3[c]	$Pd(OAc)_2$	PCy_3HBF_4	TFA	THF	<2
4[c]	$Pd(OAc)_2$	PCy_3HBF_4	HBF_4	THF	21
5	$Pd(OAc)_2$	PCy_3HBF_4	-	THF	<2
6[c]	$Pd(OAc)_2$	PCy_3HBF_4	H_2O	THF	<2
7[d,f]	$Pd(OAc)_2$	PCy_3HBF_4	H_3BO_3	THF	50
8[g]	$Pd_2(dba)_3$	PCy_3HBF_4	-	dioxane	<2
9[d]	$Pd(OAc)_2$	PCy_3HBF_4	H_3BO_3	CH_3CN	17
10[d]	$Pd(OAc)_2$	PCy_3HBF_4	H_3BO_3	THF	5
11	(IPr)Pd(cinnamyl)Cl		-	THF	82
12	(IPr)Pd(cinnamyl)Cl		-	THF	85
13	$Pd(OAc)_2$	IPrHCl	-	THF	<2
14[e]	(IPr)Pd(cinnamyl)Cl		H_2O	THF	89
15[e]	(SIPr)Pd(cinnamyl)Cl		H_2O	THF	76
16[e]	(IPr)Pd(allyl)Cl		H_2O	THF	70
17[d]	(IPr)Pd(cinnamyl)Cl		H_3BO_3	THF	<2

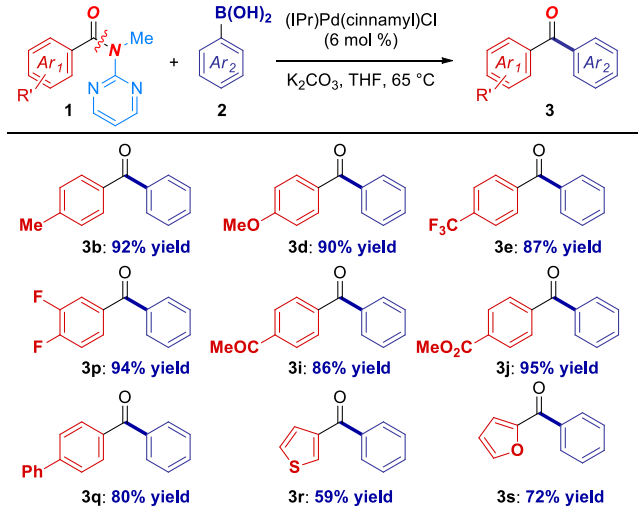
[a]Conditions: amide (1.0 equiv), R-$B(OH)_2$ (2.0 equiv), catalyst (6 mol %), K_2CO_3 (3.0 equiv), additive (2.0-10.0 equiv), solvent (0.25 M), 65-110 °C, 15 h. Entries 1-11: [Pd] (3 mol %), ligand (12 mol %). [b]GC/^{1}H NMR yields. [c]Additive (2.0 equiv). [d]Additive (4.0 equiv). [e]Additive (10 equiv). [f](0.50 M). [g]Na_2CO_3 (3.0 equiv). Entries 1-11: 110 °C. Entries 12-17: 65 °C.

Scheme 1. Boronic Acid Scope[a,b]



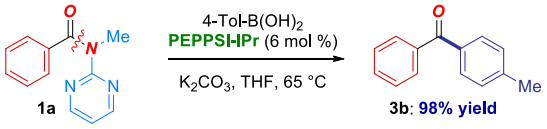
[a]Conditions: amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd] (6 mol %), K_2CO_3 (3.0 equiv), THF (0.25 M), H_2O, 65 °C, 15 h. [b]Isolated yields.

Scheme 2. Amide Scope[a,b]

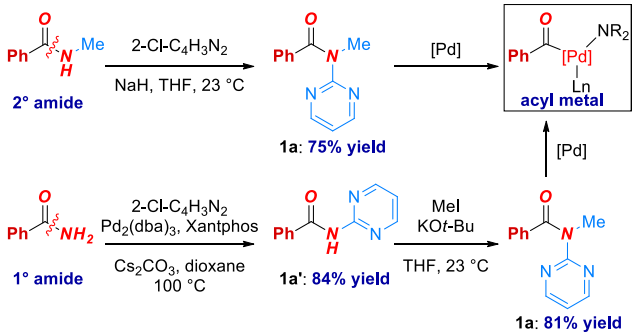


[a,b]See Scheme 1.

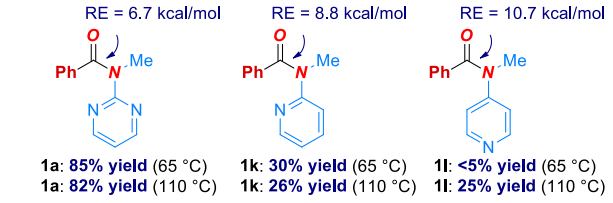
Scheme 3. Cross-Coupling using PEPPSI-IPr



Scheme 4. Synthesis of MAP Amides from 1° or 2° Amides



Scheme 5. Effect of Directing Group: Amides Employed in Computational Studies[a]



[a]Note a gradual increase of RE by changing a single *N*-substituent on the aromatic ring. RE of Ph-C(O)NMePh = 13.5 kcal/mol.[11] Note that RE of Ph-C(O)NMeAr (Ar = 4-CF_3-C_6H_4) = 11.8 kcal/mol.[11]

electrophilic functional groups, such as ketones (**3i**) and esters (**3j**) are readily accommodated. Moreover, heterocycles such as benzodioxole (**3k**), furan (**3l**), and benzothiophene (**3m**) are tolerated. Interestingly, high efficiency is observed for polyaromatic substrates (**3n-o**), including sterically-demanding arenes (**3o**). We next focused on the scope of the amide cross-coupling partner (Scheme 2). MAP amides afford high efficiency in the cross-coupling, regardless of electronic substitution (**3b-e**), including deactivated amides such as **3d**. Furthermore, polyfluorinated amides (**3p**) relevant from the medicinal chemistry point of view are compatible. Importantly, electrophilic functional groups such as ketones (**3j**) and

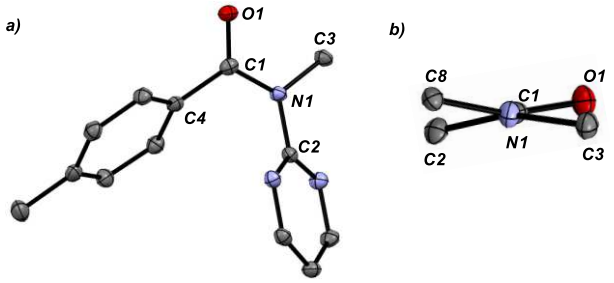


Figure 2. (a) Crystal structure of **1b**. (b) Newman projection along the N–C(O) bond. Bond lengths (Å) and angles (deg): N1–C1, 1.378(2); C1–O1, 1.225(1); C4–C1, 1.497(2); N1–C2, 1.407(1); N1–C3, 1.469(1); C4–C1–N1–C3, 159.8(1); O1–C1–N1–C2, 158.5(1); O1–C1–N1–C3, –16.3(2); C4–C1–N1–C2, –25.4(2). Note short N1–C2 bond.

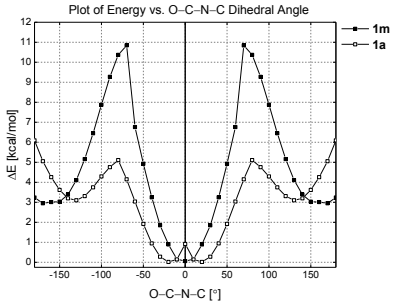


Figure 3. Rotational profile (**1a**, ΔE, kcal/mol, vs. O–C–N–C [°]). *N*-Me-*N*-Ph-benzamide (**1m**) is shown for comparison.

esters (**3j**) are well-tolerated. Moreover, conjugated biaryl amides (**3q**) that are prone to decarbonylation[4d] and heterocyclic amides (**3r-s**), including those substituted at the electron-rich 2-position (**3s**) couple with good levels of reactivity. Cross-coupling of sterically-hindered *o*-methyl benzoic acid derived amide proceeds in 84% unoptimized yield (4-MeO-C_6H_4-B(OH)$_2$) (not shown). At the present stage, aliphatic amides have not been tested.

The coupling could be performed using the synthetically attractive, well-defined PEPPSI-IPr type of precatalysts[18] without modification of the reaction conditions (Scheme 3), highlighting the versatility of our protocol.

Primary and secondary amides are some of the most common intermediates in organic synthesis.[9,10] Since MAP amides can be readily prepared from *unactivated primary or secondary amides* (Scheme 4),[16] our method offers a rapid entry to acyl-metal intermediates from generic unactivated amides.

Initial rates revealed the following reactivity: (**1a**) ($v_{initial}$ = 6.9 x 10^{-2} mM s^{-1}) (see Supporting Information, SI), which can be compared with the coupling of *N*,*N*-Ph,Boc benzamide under the same reaction conditions ($v_{initial}$ = 7.5 x 10^{-2} mM s^{-1}). The high reactivity of *N*-alkyl MAP amide is unprecedented and bodes well for applications in amide bond cross-coupling.

Studies were performed to evaluate the capacity for N-directed Pd insertion into the N–C(O) bond. Towards this end, *N*-Me-*N*-2-pyridyl (**1k**) and *N*-Me-*N*-4-pyridyl (**1l**) amides were prepared and subjected to the reaction (Scheme 5). These substrates underwent the coupling in 25-26% yield, consistent

with electronic $n_N \rightarrow \pi_{Ar}$ activation (cf. directed Pd-insertion), which is further supported by RE values (vide infra).

The X-ray structure of **1b** was determined (Figure 2). The amide shows relatively planar amide bond (τ = 20.9°, χ_N = 5.2°, χ_C = 3.9°). The N–C(O), C=O and N–Ar bond lengths are 1.378 Å , 1.225 Å, and 1.407 Å. Compared with the corresponding *N*-Me-*N*-2-pyridyl (τ = 15.0°, χ_N = 8.4°, χ_C = 4.0°; N–C(O) = 1.366 Å; C=O = 1.226 Å, N–Ar = 1.428 Å),[17] and *N*-Me-*N*-Ph benzamide (τ = 9.1°, χ_N = 6.6°, χ_C = 2.1°; N–C(O) = 1.355 Å; C=O = 1.232 Å, N–Ar = 1.437 Å),[11] these values indicate a gradual increase in $n_N \rightarrow \pi_{Ar}$ conjugation.

Computations were employed to probe the energetics of the amide bond undergoing N–C cleavage (see SI): (1) Resonance energies (RE) determined by the COSNAR method indicate that the conjugation is in the following order: **1a**, 6.7 kcal/mol; **1k**, 8.8 kcal/mol; **1l**, 10.7 kcal/mol. In agreement with our design, RE in **1a** is much lower than in anilides (RE = 13.5 kcal/mol). (2) Rotational profile in **1a** along the O–C–N–$C_{(Ar)}$ dihedral angle confirms electronic destabilization (vs. twist) (Figure 3). The plot of **1a** vs. the corresponding anilide (**1m**) clearly indicates that *N*-substitution results in a significantly lowered barrier to rotation. (3) Resonance energy in *N*-ring protonated **1a**, **1k**, and **1l** are as follows: **1a**, 3.0 kcal/mol; **1k**, 5.0 kcal/mol, **1l**, 2.4 kcal/mol, clearly demonstrating that *N*-coordination significantly weakens amidic resonance. (4) The difference between N-/O-protonation affinities (ΔPA) indicates that **1a, 1k** and **1l** strongly favor coordination at the amide oxygen (vs. amide nitrogen, ΔPA = 9.0, 7.8, 11.5 kcal/mol). However, protonation of the ring nitrogen is favored in **1a**, **1k** and **1l** (ΔPA = 2.6, 4.0, 16.1 kcal/mol).

Collectively, the structural and energetic parameters of the amide bond in MAP amides indicate that $n_N \rightarrow \pi_{Ar}$ delocalization is the major factor enabling selective N–C activation. *The capacity to switch RE in a rational manner could open up new avenues for activating amides in N–C coupling reactions.*

In summary, we have developed the first method for the direct activation of *N*-methylamino pyrimidyl amides (MAPA) by selective N–C amide bond cleavage. The reported reaction uses commercially-available and bench-stable Pd-NHC precatalysts, occurs with high N–C activation chemoselectivity and is operationally simple. Most importantly, this report introduces MAP amides as resonance-controlled, practical alternatives to anilides for a range of catalytic coupling reactions via acyl- and decarbonylative pathways. In these amides, the N–X cleavage reaction, the most common side process in the amide bond activation is not observed. MAP amides provide rapid entry to acyl metal intermediates from unactivated primary and secondary amides. Mechanistic studies strongly support $n_N \rightarrow \pi_{Ar}$ delocalization. Studies on expanding the scope of the amide bond cross-coupling are underway.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, and X-ray crystallographic data for **1b** (PDF, CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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ACKNOWLEDGMENT

Rutgers University and the NSF (CAREER CHE-1650766) are gratefully acknowledged for support. The Bruker 500 MHz spectrometer was supported by the NSF-MRI grant (CHE-1229030).

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