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Sterically Controlled Pd-Catalyzed Chemoselective Ketone Synthesis via N−C Cleavage in Twisted Amides

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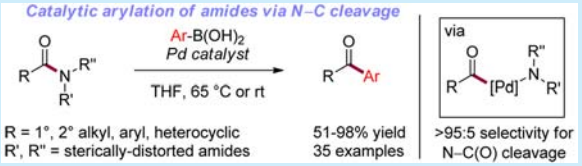
Supporting Information

ABSTRACT: Highly chemoselective, palladium(0)-catalyzed, direct cross-coupling between boronic acids and geometrically activated amides is reported. The reaction proceeds via selective activation of the N−C(O) bond, shows excellent functional group tolerance, and delivers the versatile ketone products in high yields. The observed reactivity is consistent with a decrease of $n_N \rightarrow \pi^*_{C=O}$ conjugation resulting from destabilization of the amide ground state. Notably, the method provides direct access to acyl-metal intermediates from sterically distorted, bench-stable amide precursors under mild catalytic conditions.



Palladium-catalyzed cross-couplings have revolutionized bond forming strategies in modern organic chemistry.[1] In particular, cross-couplings of carboxylic acid derivatives that forge new carbon−acyl bonds are among the most powerful transformations for the chemoselective formation of ketones that have been extensively utilized in the synthesis of pharmaceuticals, functional materials, peptides, and complex target synthesis.[2] Importantly, the downstream products of these technologies are often not available by other methods.[3] A number of elegant solutions to increase the substrate scope and include a wide range of cross-coupling partners has been reported by the groups of Negishi,[4a,b] Fukuyama,[4c] Liebeskind and Srogl,[4d,e] Yamamoto,[4f] and Gooßen,[4g] among others.[4h−j] Despite these significant advances, however, the use of amides as electrophilic precursors to form acyl-palladium intermediates for catalytic cross-coupling reactions with organometallic reagents is virtually unknown (Figure 1).[5]

This surprising gap in synthetic chemistry is due to the high activation energy required for the N−C(O) bond scission in amides due to $n_N \rightarrow \pi^*_{C=O}$ conjugation[6] as well as low propensity of amines to act as leaving groups.[7] The use of amides as acyl electrophiles in metal-catalyzed reactions with organometallic reagents would offer a unique opportunity to expand the scope of ketone synthesis by providing new strategic C−C bond disconnection, especially when high stability of the acyl precursor, directing effect of the amide bond, or orthogonal cross-coupling conditions are required.[8]

Herein we report the first general, highly chemoselective palladium(0)-catalyzed cross-coupling of amides with boronic acids by exploiting the ground state amide distortion. The method provides direct access to ketone products, tolerating sensitive functional groups such as ketones, esters, aldehydes, N-heterocycles, and halides, and proceeds with complete N−C(O) [cf. R−NC(O)] selectivity. We demonstrate that the rate of metal insertion into the N−C(O) bond is controlled by the ground-state destabilization (Winkler−Dunitz distortion parameters: τ, χ_N, χ_C).[9] Notably, this study sets the stage for myriad transition metal catalyzed reactions of amide bonds via acyl-metal intermediates.

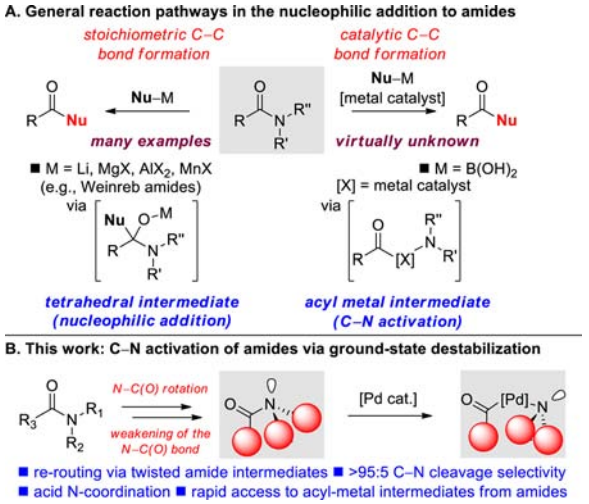


Figure 1. (a) General strategies for nucleophilic addition to amides. (b) This work: the first general chemoselective addition of boronic acids to amides via ground-state distortion.

Twisted amides are amides in which the classical $n_N \rightarrow \pi^*_{C=O}$ conjugation (barrier to rotation of ca. 15−20 kcal/mol) has been modulated by geometrical features.[10] Seminal studies by Pracejus,[11a] Kirby,[11b] Stoltz,[11c] and others have demonstrated the utility of these amides in the formation of C−C and C−X (X = O, N) bonds. Developments in the functionalization of the R−NC(O) bond and further mechanistic insights have been provided by the groups of Aubé,[11d] Greenberg,[11e,f] Brown,[11g,h] and Lectka.[11i] We have recently demonstrated that the N-/O-protonation aptitude in such amides is directly correlated with

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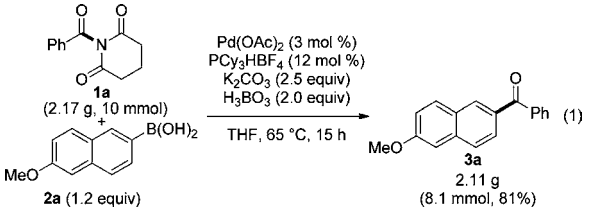
additive distortion parameters ($\Sigma\tau + \chi_N$).[12] Considerable advancements in the synthesis and reactivity of sterically distorted amides have been reported.[13] Booker-Milburn and co-workers have developed an elegant method for solvolysis of amides by a proton-switch mechanism utilizing sterically distorted tmp (tmp = 2,2,6,6-tetramethylpiperidine) amides.[14] However, no method currently exists for the metal-catalyzed cross-coupling of amides destabilized in the ground state despite the ready availability of an array of amides characterized by a wide range of distortion and the fact that such a process would open new vistas in transition metal catalyzed C−C bond formation.[1−5]

Our strategy to achieve a broadly useful, modular, sterically controlled cross-coupling of amides to access ketones involved the following steps: (i) oxidative addition of Pd into the N−C(O) bond; (ii) transmetalation with organoboron organometallics; (iii) reductive elimination to give the ketone product.[1−5] Importantly, amides can be used as precursors to access a wide variety of end products by functionalization and/or elementary reactions of the acyl metal intermediate.[1,2] A critical feature of our protocol is the capacity of amides to undergo N-activation via N-coordination (cf. O-coordination),[10−12] a well-established process that results in a disruption of the amide bond resonance and should facilitate palladium insertion into the inert N−C(O) bond.[15] We anticipated that in amides in which the sum of distortion parameters ($\Sigma\tau + \chi_N$) is close to 50°, palladium insertion should be thermodynamically favorable.[12] Furthermore, we hypothesized that the use of electron-rich ligands on Pd would favor insertion into the N−C(O) bond.[16] As a third feature, we anticipated that acidic additives would activate the N−C(O) bond and favor ligand dissociation from the acyl metal intermediate.[10]

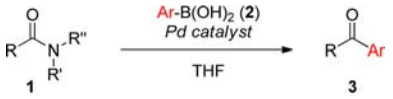
While this article was under preparation, a Pd-catalyzed cross-coupling of electronically activated amides was reported.[17] The method reported herein shows the following advantages: (i) mild reaction conditions, including room temperature; (ii) high functional group tolerance (ketones, aldehydes, halides); (iii) generality of the activation mode across amide functions; (iv) a fully tunable N−C(O) bond activation mode.[10−13] Moreover, since N-acylation of amides is well-established,[3] the present method can be used to cross-couple RC(O)−NH_2 bonds, which is not possible via electronic activation. Finally, complete recovery of electronically activated amides[17] is observed under our conditions (see Supporting Information (SI)), setting the stage for reagent-controlled sequential transformations.

The following gram scale procedure is representative: a mixture of **1a** (2.17 g, 10 mmol), boronic acid (2.42 g, 12 mmol), and $Pd(OAc)_2$ (67.4 mg, 0.3 mmol) was stirred in the presence of PCy_3HBF_4, K_2CO_3, and H_3BO_3 in THF at 65 °C to afford 2.11 g of ketone **3a** (81% yield) (eq 1).



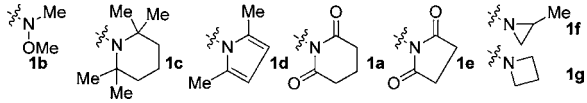
Evaluation of the amide-bond cross-coupling strategy was first examined by screening a range of electronically and sterically distorted amides[10−23] in the reactions with phenylboronic acid as a coupling partner[18] in the presence of palladium catalytic systems under various conditions (Table 1). While Weinreb

Table 1. Optimization of the Amide Bond Geometry[a]



entry	1	τ (deg)	χ_N (deg)	conv (%)	yield (%)
1	**1b**	1.2	16.3	<5	<5
2	**1c**	34.1	17.0	10	9
3	**1d**	39.7	8.4	25	<5
4	**1a**	87.8	6.8	>98	98
5	**1e**	45.9	10.7	55	54
6	**1f**	14.3	69.6	<5	<5
7	**1g**	5.1	33.1	<5	<5

[a]Conditions: Ph-B$(OH)_2$ (1.2 equiv), $Pd(OAc)_2$ (3 mol %), ligand (12 mol %), THF, 25−120 °C. See SI for full details.



amides (entry 1),[19] tmp amides (entry 2),[14] and acylpyrroles (entry 3)[11g] provided a trace or none of the desired ketone product, by using the imide derivative **1a** (entry 4)[13] the proposed cross-coupling was indeed feasible, providing the ketone product in excellent 98% yield. Furthermore, less distorted systems such as imide **1e** (entry 5)[13] resulted in a dramatic decrease in efficiency, consistent with previous studies on amide bond activation. A survey of pyramidalized aziridinyl (entry 6) and azetidinyl (entry 7) amides resulted in little or no product formation, consistent with the reactive properties of pyramidalized (cf. twisted) amides.[20] The optimization results in Table 1 demonstrate for the first time that metal insertion into the N−C(O) bond of twisted amides is feasible and that the rate of coupling is proportional to the degree of distortion. Importantly, under these conditions cleavage of the alternative R−NC(O) bond was not observed, attesting to the high chemoselectivity and/or reversibility of the insertion.[11d]

Table 1-SI presents key results obtained during the optimization of the reaction (see SI).

With the optimized conditions in hand, we tested the preparative scope of the reaction using **1a** as a standard electrophile (Scheme 1). The reaction tolerates a wide range of aromatic boronic acids bearing sensitive functional groups, such as ketones (**3d**), nitriles (**3h**), and aryl halides (**3i**), that provide synthetic handles for further functionalization. Electron-donating (**3c**) and electron-withdrawing (**3e**) boronic acids gave products in high yields. Steric hindrance on the boronic acid component [(**3f**) and (**3g**)] is well-tolerated. Heteroaromatic boronic acids, such as thienyl (**3j**), furyl (**3k**), benzothienyl (**3l**), and indolyl (**3m**), underwent coupling with high reaction efficiency.[21] Additional examples of the boronic acid substrate scope are presented in Scheme 3 and include other functional groups poised for synthetic manipulations, such as aldehydes, nitro groups, esters, and vinyl moieties.

Next, we turned our attention to the scope of amides (Scheme 2). Particularly noteworthy is the functional group tolerance of our protocol, accommodating para-cyano- (**3o**), nitro- (**3p**), chloro- (**3q**), and fluoro- (**3r**) substituents. Steric hindrance in the ortho-position on the aromatic ring was well-tolerated (**3f**). Naphthyl- (**3t**) and heteroaromatic (**3j**) amides underwent coupling with high reaction efficiency. Primary (**3u**) and secondary (**3v**) aliphatic amides coupled in moderate to good yields; however, a tertiary aliphatic amide (**3w**) was unreactive

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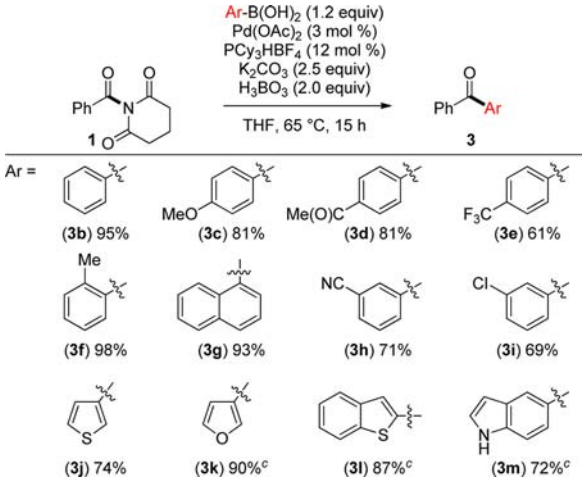
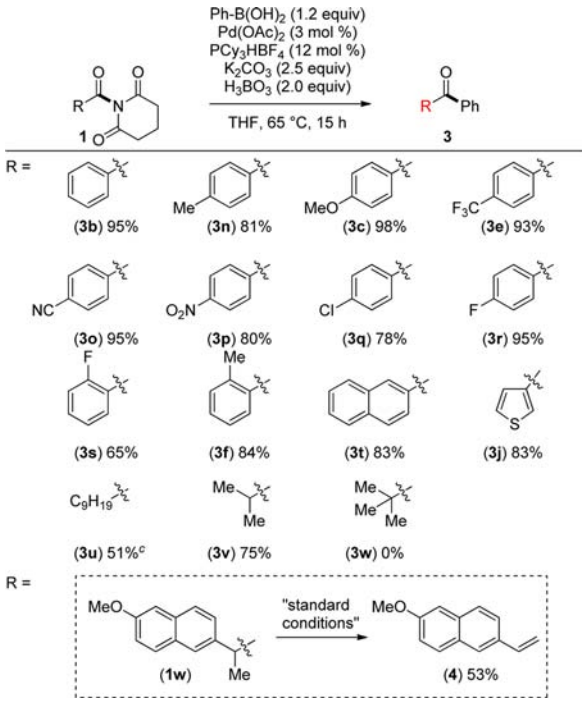
Scheme 1. Boronic Acid Scope in the Pd-Catalyzed Cross-Coupling of Amides[a,b]



[a]See Table 1. [b]Isolated yields. [c]120 °C, Ar−B(OH)$_2$ (2.0 equiv). See SI for full experimental details.

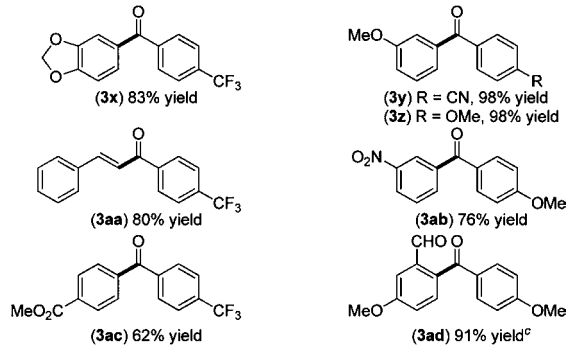
Scheme 2. Amide Scope in the Pd-Catalyzed Cross-Coupling of Amides[a,b]



[a]See Scheme 1 footnote a. See SI for full experimental details. [b]See Scheme 1 footnote b. See SI for full experimental details. [c]See Scheme 1 footnote c. See SI for full experimental details.

under these reaction conditions.[4g] Interestingly, a substrate bearing activated β-hydrogens (**1w**) underwent tandem decarbonylation/β-hydride elimination to give the styrenyl derivative in good yield.[22] Decarbonylation followed by β-hydride elimination has been reported in related reactions of aliphatic carboxylic acid derivatives.[22] The high efficiency bodes well for the application of this protocol to biomass conversion.[22c] Additional examples of the cross-coupling are shown in Scheme 3. These examples further present a variety of functionalized

Scheme 3. Synthesis of Aryl Ketones from Amides and Boronic Acids: Additional Substrate Scope[a,b]

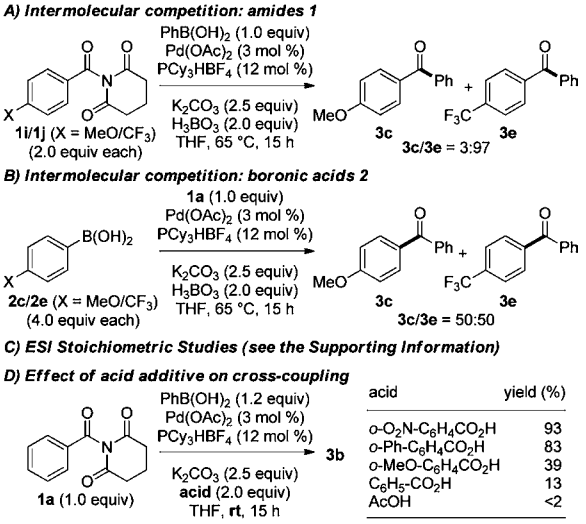


[a]See Scheme 1 footnote a. See SI for full experimental details. [b]See Scheme 1 footnote b. See SI for full experimental details. [c]See Scheme 1 footnote c. See SI for full experimental details.

boronic acids that could be coupled with a range of distorted amides to give electronically diverse products in high yields.

Several studies were conducted to gain preliminary insight into the reaction mechanism (Scheme 4 and SI). (1) Intermolecular

Scheme 4. Studies Designed to Probe the Mechanism of the Pd-Catalyzed Cross-Coupling of Amides



competition experiments with differently substituted amides (Scheme 4A) revealed that electron-deficient arenes are inherently more reactive substrates, consistent with metal insertion into the N−C(O) bond.[1,2] (2) Intermolecular competition experiments with differently substituted boronic acids (Scheme 4B) indicated no preference for electron-donating nucleophiles, consistent with coordination of the amino group to the boron atom (see SI).[23] (3) Intermolecular competition experiments with sterically differentiated amides and boronic acids (see SI) revealed that steric effects on the nucleophile play an important role in these cross-couplings, consistent with boron coordination.[1,2] (4) Electrospray ionization mass spectrometry (ESI/MS) analysis using stoichiometric palladium revealed intermediates corresponding to the acyl-Pd species containing a single phosphane ligand, consistent with the proposed mechanism and optimization studies.[24] (5) The effect of the acidic additive was probed by using substituted aryl carboxylic

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acids (Scheme 4D). The cross-coupling rate was found to be inversely proportional to the pK_a of the acid.[25]

Overall, these preliminary studies are consistent with a mechanism involving activation of the amide N−C(O) bond.[26,27] The high chemoselectivity of the N−C(O) cleavage results from ground state destabilization of the amide bond by rotation.[27] Cleavage of the alternative R−NC(O) bond is thermodynamically disfavored due to steric hindrance and conjugation of the imide carbonyl groups.[13] Furthermore, in the acyl-Pd intermediate the ligand dissociation is favored by low nucleophilicity of amines that are eliminated,[7] and by coordination of acid to the nitrogen atom,[26] enhancing the overall N−C(O) coupling selectivity. Further studies on the mechanism are ongoing.

In conclusion, we have reported the first general method for the palladium-catalyzed cross-coupling of amides with boronic acids via sterically controlled N−C(O) bond activation. This method complements classical stoichiometric techniques for ketone synthesis from amides via nucleophilic addition (e.g., Weinreb amides). More importantly, the work presented herein provides a blueprint for the generation of acyl-metal intermediates directly from amides, setting the stage for an array of transition metal catalyzed transformations of amide bonds.[17]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02209.

Experimental procedures and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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