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N-Acylsaccharins: Stable Electrophilic Amide-Based Acyl Transfer Reagents in Pd-Catalyzed Suzuki–Miyaura Coupling via N–C Cleavage

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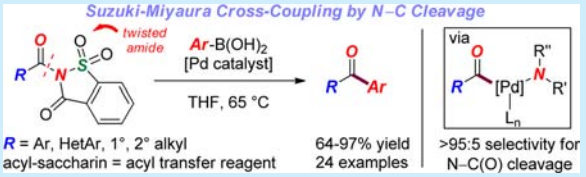
Supporting Information

ABSTRACT: The development of efficient catalytic methods for N–C bond cleavage in amides remains an important synthetic challenge. The first Pd-catalyzed Suzuki–Miyaura cross-coupling of *N*-acylsaccharins with boronic acids by selective N–C bond activation is reported. The reaction enables preparation of a variety of functionalized diaryl and alkyl-aryl ketones with broad functional group tolerance and in good to excellent yields. Of general interest, *N*-acylsaccharins serve as new, highly reactive, bench-stable, economical, amide-based, electrophilic acyl transfer reagents via acyl-metal intermediates. Mechanistic studies strongly support the amide N–C(O) bond twist as the enabling feature of *N*-acylsaccharins in the N–C bond cleavage.



The incorporation of the acyl group into organic molecules is a fundamental transformation in biological and synthetic chemistry.[1,2] In this context, the transition-metal-catalyzed acylation of organometallic reagents has emerged as a powerful strategy to produce functionalized ketones with numerous applications in pharmaceutical, dye, and agrochemical industries.[3,4] A number of methods and reagents have been developed over the past years, including palladium- and nickel-catalyzed cross-coupling reactions of acyl chlorides, thioesters, and anhydrides.[5] By contrast, the transition-metal-catalyzed acylation by N–C cleavage[6] in amides represents a significant challenge due to $n_N \rightarrow \pi^*_{C=O}$ conjugation and the resulting partial double bond character of the amide bond.[7] The amide bond resonance prohibits direct metal insertion into the N–C(O) bond in planar amides. As a consequence, there have been very few reports on the cross-coupling of amides with organometallic reagents[8−10] despite the potential versatility of amides as acylating reagents and the fundamental role of amides in biology and medicinal chemistry.[7b] In 2015, in consideration of the amidic resonance, our laboratory introduced the concept of amide bond ground-state destabilization to enable a range of metal-catalyzed transformation of amides by N–C cleavage in generic C–C bond-forming reactions (Figure 1A).[8] Independently, palladium- and nickel-catalyzed cross-coupling of amides with boronic acids[9] and nickel-catalyzed borylation by N–C cleavage have been developed.[10] Unsurprisingly, all amides utilized to date contain destabilized (twisted) amide bonds,[11] while *N*-glutarimide amides introduced by our laboratory showed thus far the highest reactivity in a range of cross-coupling reactions employing Pd, Rh, and Ni catalysis.[8]

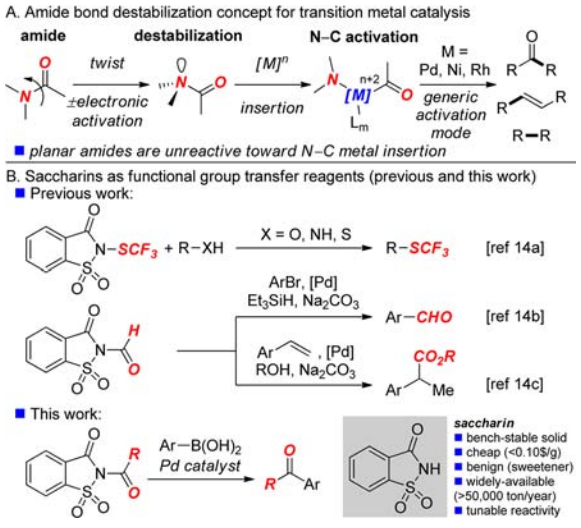


Figure 1. (a) Activation of amides by N–C cleavage. (b) Saccharins as functional group transfer reagents: previous and this work.

Continuing this theme, we became interested in using *N*-acylsaccharins as selective amide-based acyl transfer reagents in transition-metal catalysis.[12] The use of halo-saccharins as electrophilic reagents has been widely studied.[13] Recently, some notable examples have advanced the scope of saccharins as efficient functional group transfer reagents for trifluoromethyl-

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thiolation,[14a] formylation,[14b] and alkoxycarbonylation[14c] reactions (Figure 1B). Herein, we detail the first example of palladium-catalyzed Suzuki−Miyaura cross-coupling[15] of *N*-acylsaccharins with boronic acids by N−C bond cleavage. *N*-Acylsaccharins serve as new, highly reactive, bench-stable, economical, amide-based, electrophilic acyl transfer reagents for C−C bond forming reactions via acyl-metal intermediates by selective N−C bond cleavage. This finding opens the door for using *N*-acylsaccharins in a wide range of transition-metal-catalyzed reaction manifolds.[3−5]

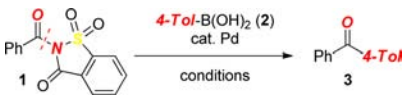
N-Acylsaccharins offer several major advantages: (a) saccharin is a cheap, widely accessible commodity chemical produced on >50,000 ton scale annually with a bulk price of <$0.10/gram;[16] (b) the presence of an electron-withdrawing sulfonyl moiety results in an enhanced electrophilicity of the acyl-carbonyl group; (c) saccharin is commonly used as an artificial sweetener and is virtually nontoxic; (d) *N*-acylsaccharins are bench-stable and easy to handle crystalline solids, with no decomposition observed over a period of 3 months at ambient conditions; (e) the geometric properties of *N*-acylsaccharins (vide infra) allow fine-tuning of the reactivity of the amide N−C bond by distortion, resulting in a new class of highly chemoselective acyl transfer reagents with orthogonal functional group tolerance to other carbonyl groups, while avoiding the handling of moisture sensitive and corrosive halides in transition metal catalyzed manifolds.[17]

N-Acylsaccharins are easily synthesized in an average yield of 87% by the reaction of saccharin with acyl chlorides in *N*,*N*-dimethylacetamide following the known procedure[18] and isolated by recrystallization (see Supporting Information).

We began our studies by examining the coupling of *N*-benzoylsaccharin with 4-tolylboronic acid under a variety of conditions. Table 1 summarizes key results from the optimization experiments. The desired coupling proceeds in an excellent >95% yield in the presence of $Pd(OAc)_2$ (3 mol %), PCy_3HBF_4 (12 mol %), K_2CO_3 (2.5 equiv), and H_3BO_3 (2.0 equiv) in THF at 65 °C (entries 1−10). Interestingly, triaryl phosphines can also be successfully employed as ligands in the reaction (entries 11−16), suggesting higher reactivity of *N*-acylsaccharins than *N*-glutarimide amides.[8] We determined that the conditions employing PCy_2Ph proved to be the most general across the range of substrates examined, and subsequently used PCy_2Ph in the substrate scope studies. The use of structurally related $PCyPh_2$ was ineffective, revealing subtleties of our protocol. Several other optimization results deserve a comment. A high yield is obtained using PPh_3, indicative of facile Pd(0) insertion into the N−C bond.[3−6] Similarly, >80% yield is obtained with an equimolar Pd/ligand ratio (entry 9), suggesting high reactivity of the N−C bond toward metal insertion.[8d] The use of acid is critical for high reactivity, likely as a result of switchable O-/O-coordination (entry 17) (vide infra).[19] Importantly, full selectivity for N−C insertion/coupling is observed under the optimized conditions, with products resulting from $C-SO_2$ insertion and decarbonylation not detected.[20]

With the optimized conditions in hand, the scope of the reaction was next investigated (Table 2). As shown, a variety of boronic acids can be employed, yielding the desired ketone products with high efficiency, including electron-donating (**3b**−**3c**), electron-withdrawing (**3d**), and sterically hindered (**3e**−**3g**) boronic acids. Moreover, highly electron-rich (**3h**) and electron-deficient (**3i**) boronic acids are competent coupling partners. Of particular interest are the products containing electrophilic

Table 1. Optimization of Pd-Catalyzed Suzuki−Miyaura Cross-Coupling of *N*-Acylsaccharins by N−C Cleavage[a]



entry	catalyst	ligand	solvent	yield (%)
1	$Pd(OAc)_2$	PCy_3HBF_4	THF	97
2	$PdCl_2$	PCy_3HBF_4	THF	61
3	$Pd(dba)_2$	PCy_3HBF_4	THF	56
4	$Pd_2(dba)_3$	PCy_3HBF_4	THF	57
5	$Pd(PPh_3)_4$	PCy_3HBF_4	THF	77
6	$Pd(OAc)_2$	PCy_3HBF_4	dioxane	68
7	$Pd(OAc)_2$	PCy_3HBF_4	DCE	44
8	$Pd(OAc)_2$	PCy_3HBF_4	toluene	18
9[b]	$Pd(OAc)_2$	PCy_3HBF_4	THF	81
10	$Pd(OAc)_2$	–	THF	<5
11	$Pd(OAc)_2$	PPh_3	THF	91
12	$Pd(OAc)_2$	PCy_2Ph	THF	89
13	$Pd(OAc)_2$	DPPP	THF	30
14	$Pd(OAc)_2$	DPPB	THF	50
15	$Pd(OAc)_2$	DPPE	THF	45
16	$Pd(OAc)_2$	DPPM	THF	35
17[c]	$Pd(OAc)_2$	PCy_3HBF_4	THF	79
18[d]	$Pd(OAc)_2$	PCy_3HBF_4	THF	87

[a]Conditions: **1** (1 equiv), 4-Tol-$B(OH)_2$ (2.0 equiv), catalyst (3 mol %), ligand (12 mol %), K_2CO_3 (2.5 equiv), H_3BO_3 (2.0 equiv), 65 °C, 15 h. [b]ligand (3 mol %). [c]Without H_3BO_3. [d]4-Tol-$B(OH)_2$ (1.2 equiv).

handles (**3j**) and medicinally relevant heterocycles (**3k**−**3l**). The scope of the amide component is also broad. Electron-rich (**3b′**−**3c′**) and electron-deficient (**3d′**) *N*-acylsaccharins provided the desired product in high yield (vide infra). Notably, electrophilic functional handles such as fluoro- (**3m**), chloro- (**3n**), ester- (**3o**), and nitro- (**3p**) at the para-position are perfectly accommodated. Moreover, ortho-coordinating (**3q**), sterically hindered (**3e′**), and heterocyclic (**3r**) amides underwent smooth acylation. Finally, 1° (**3s**) and 2° (**3t**) alkyl amides are efficient coupling partners, affording the valuable alkyl aryl ketones in good yields. Overall, the scope of the cross-coupling of *N*-acylsaccharins compares very favorably with other examples of Suzuki cross-coupling by the amide N−C cleavage reported to date.[8,9] Importantly, the present process is advantageous in terms of economy and availability of saccharin as an acyl-transfer reagent.[1,2,16]

To gain insight into the role of amide bond twist on the high reactivity of *N*-acylsaccharins, the X-ray structure of **1a** was determined (Figure 2). The X-ray structure confirms that **1a** contains a highly distorted amide bond[11] ($\tau = 23.0°$, $\chi_N = 12.5°$, $\chi_C = 1.0°$).[21] The N−C(O) and C═O bond lengths are 1.421 and 1.208 Å. The acyl C═O bond is antiperiplanar to the N−C(O) bond and bisects the O−S−O angle.

Computations were employed to probe the role of amide resonance in the high reactivity of *N*-acylsaccharins: (1) the rotational profile of **1a** determined by systematic rotation along the O−C−N−C dihedral angle (Figure 3) shows ground state distortion in *N*-acylsaccharins. The energy minimum is located at a ca. 150° O−C−N−C angle ($\tau = 27.26°$; $\chi_N = 8.88°$). The energy maximum is located at a ca. −20° O−C−N−C dihedral angle ($\tau = 10.96°$; $\chi_N = 17.46°$) in a $1,3_{(C=O/C=O)}$ eclipsing interaction, as expected. The rotational barrier was determined to be 4.87 kcal/mol. (2) The resonance energy (RE) of **1a**

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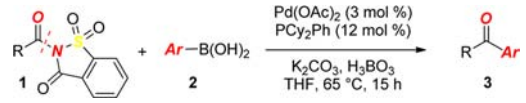
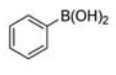
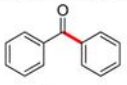
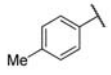
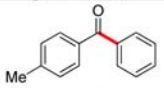
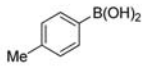
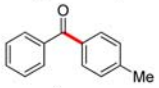
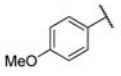
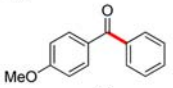
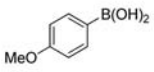
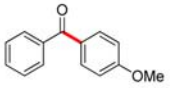
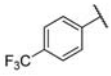
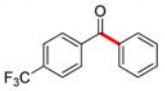
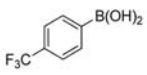
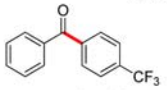
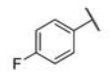
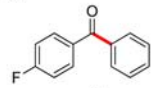
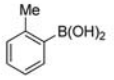
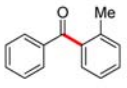
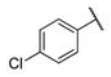
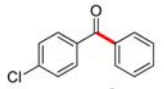
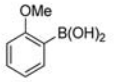
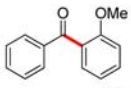
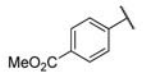
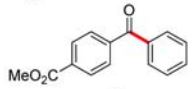
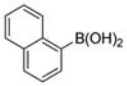
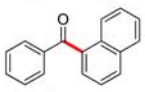
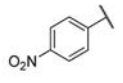
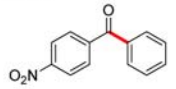
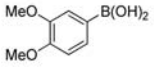
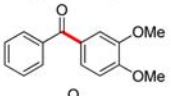
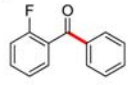
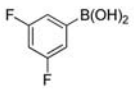
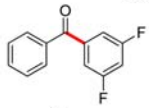
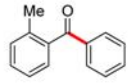
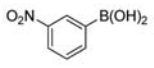
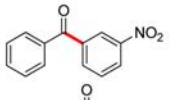
Table 2. Pd-Catalyzed Suzuki–Miyaura Cross-Coupling of *N*-Acylsaccharins by N–C Cleavage: Substrate Scope[a]



entry	3	boronic acid	product (3)	yield (%)	entry	3	amide (R)	product (3)	yield (%)
1	3a			80	13	3b'			95
2	3b			87	14	3c'			91
3	3c			95	15	3d'			97
4	3d			64	16	3m			93
5	3e			91	17	3n			72
6	3f			84	18	3o			89
7	3g			93	19	3p			71
8	3h			94	20	3q			91
9[b]	3i			89	21	3e'			89
10[b]	3j			68	22	3r			88
11	3k			77	23	3s			92
12	3l			86	24	3t			91

[a] **1** (1.0 equiv), Ar–$B(OH)_2$ (2.0 equiv), $Pd(OAc)_2$ (3 mol %), ligand (12 mol %), K_2CO_3 (2.5 equiv), H_3BO_3 (2.0 equiv), THF, 65 °C. [b] 120 °C. See Supporting Information for details.

Figure 2. (a) Crystal structure of **1a**. (b) Inset shows Newman projection along the N–C(O) bond. Selected bond lengths (Å) and angles (deg): N1–C8, 1.421(3); C8–O1, 1.208(3); C8–C9, 1.487(3); C9–C8–N1–S1, 162.8(1); O1–C8–N1–C1, 151.3(2); O1–C8–N1–S1, −16.3(3); C9–C8–N1–C1, −29.7(3).

Figure 3. Rotational profile (**1a**, Δ*E*, kcal/mol, vs O–C–N–C [deg]).

determined by the COSNAR method indicates that the conjugation in **1a** practically disappears (RE = 2.0 kcal/mol).[19b] (3) The difference between N-/O-protonation affinities (ΔPA) in **1a** verifies that *N*-saccharins favor protonation at oxygen (ΔPA = 11.8 kcal/mol), and that the protonation of the *N*-acyl group is favored over the ring amide (ΔPA = 5.0 kcal/mol) and sulfonamide oxygens (ΔPA = 5.3, 10.9 kcal/mol).[19] Overall, the structural and energetic parameters of the amide bond in *N*-acylsaccharins strongly support ground-state

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destabilization[11] as the enabling factor for N−C activation under mild conditions.

Synthetic mechanistic studies were conducted (see Supporting Information): (1) Intermolecular competitions established that electron-deficient aromatic amides are inherently more reactive (4-CF_3/4-MeO > 20:1). (2) Electron-rich nucleophiles couple preferentially (4-MeO/4-CF_3 = 2.4:1). (3) An approximately 2-fold increase in yield is observed when $PhB(OH)_2$ and K_2CO_3 are doubled at low conversion. These effects suggest that transmetalation is most likely the rate-determining step.[15] (4) A turnover number of 304 was determined. (5) Intermolecular competition studies showed higher reactivity of *N*-acylsaccharins as compared with *N*-glutarimides,[8] suggesting significant potential of *N*-acylsaccharins as acyl-transfer reagents in a broad range of organometallic manifolds.

In conclusion, we have developed *N*-acylsaccharins as new, amide-based, electrophilic reagents for transition-metal-catalyzed acyl transfer reactions by selective N−C bond cleavage. These reagents are shelf-stable, easy-to-use, and readily available from the cheap and benign saccharin. The high reactivity was demonstrated in the Pd-catalyzed Suzuki−Miyaura cross-coupling to give a variety of functionalized ketones. Mechanistic studies support the amide bond distortion as a chemoselectivity-determining feature in N−C cleavage.[22] Studies to expand the scope of coupling partners are currently underway.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01836.

Experimental procedures, characterization data, (PDF)
X-ray crystallographic data for **1a** (CIF)

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Notes

The authors declare no competing financial interest.

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