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N-Acylsuccinimides: Twist-Controlled, Acyl-Transfer Reagents in Suzuki-Miyaura Cross-Coupling by N–C Amide Bond Activation

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The palladium-catalyzed Suzuki-Miyaura cross-coupling of N-acylsuccinimides as versatile acyl-transfer reagents via selective amide N–C bond cleavage is reported. The method is user-friendly since it employs commercially-available, air-stable reagents and catalysts. The cross-coupling is enabled by half-twist of the amide bond in N-acylsuccinimides. These highly effective, crystalline acyl-transfer reagents present major advantages over perpendicularly twisted N-acylglutarimides, including low price of the succinimide activating ring, selective metal insertion under redox neutral conditions and high stability of the amide bond towards reaction conditions. Mechanistic studies indicate that oxidative addition is the rate limiting step in this widely applicable protocol.

Over the past two years, amides have emerged as important building blocks in transition-metal-catalyzed cross-coupling reactions.[1,2] Two general manifolds have been established, namely acyl- and decarbonylative cross-couplings,[3,4] wherein the facility of metal insertion is controlled by amide geometry,[5] electronics[6] and/or catalyst system[7] (Fig 1A). In particular, acyl-Suzuki-Miyaura cross-coupling has proved to be a popular tool for testing new amide-based reagents for selective metal insertion into the typically inert amide N–C bond ($n_N \rightarrow \pi^*_{C=O}$ conjugation, 15-20 kcal/mol in planar amides).[8]

In this context, N-acylglutarimides, introduced by our group in 2015,[9] have been demonstrated as the most reactive amide derivatives in metal-catalyzed N–C activation to date,[10] owing to the perpendicular twist of the amide bond and electronic activation. A wide range of other preactivated amide-based reagents such as N-Boc-carbamates,[11] N-Ts-sulfonamides,[12] N,N-di-Boc_2 amides,[13] N-acyl-saccharins,[14] N-Ms-sulfonamides,[15] N-acyl-pyrroles[16] and N-Me-pyrimidines[17] have been successfully employed as cross-coupling partners in the acyl Suzuki reaction by N–C activation (Fig. 1B). Recently, we introduced N-acylsuccinimides as highly effective, bench-stable, crystalline, amide-based acyl transfer reagents in Ni-catalyzed Negishi cross-coupling.[18] Our mechanistic studies indicated that the amide bond in N-acylsuccinimides is approximately half-twisted (Fig. 2).[5a] This allows for selective fine-tuning of metal insertion under redox-neutral conditions by amide bond geometry to afford acyl-metal intermediates of broad synthetic appeal.[19]

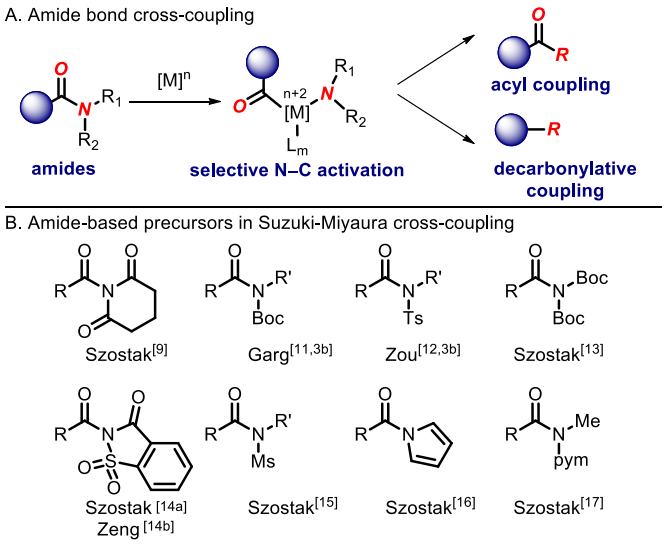

Fig. 1 (A) Amide bond cross-coupling, (B) Amide-based precursors in Suzuki-Miyaura cross-coupling.

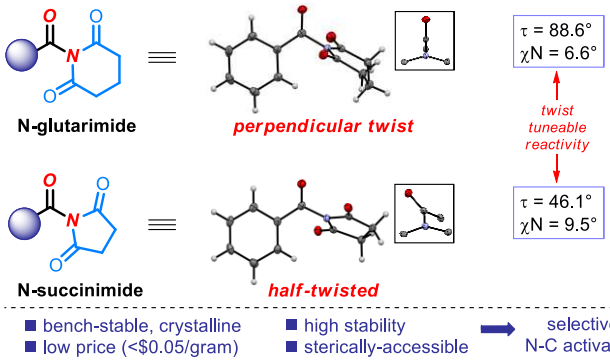

Fig. 2 Amide bond activation by twist: perpendicular glutarimides vs. half-twisted succinimides.

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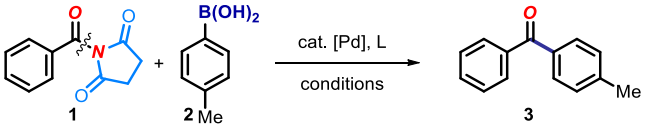
Herein, we disclose the Pd-catalyzed Suzuki-Miyaura cross-coupling of N-acylsuccinimides as versatile acyl-transfer reagents via selective amide N–C bond cleavage. The following key features render N-acylsuccinimides synthetically-appealing in N–C cross-coupling reactions: (1) low price and wide-availability of succinimide (<$0.05/gram); (2) high-bench stability; (3) N-acylsuccinimides are crystalline solids easily purified by crystallization; (4) higher stability of N-acylsuccinimides than N-glutarimide amides as a consequence of lower twist of the amide bond; and (5) the 5-membered activating ring is more sterically-accessible than the 6-membered glutarimide, while its cyclic nature prevents side reactions by the undesired cleavage of the σ N–C bond.[20,21]

During the course of this work, Zeng and co-workers reported a related process.[22] The catalytic system developed by our group uses air-stable reagents and is more catalytically reactive than the Zeng's system. Furthermore, we report mechanistic studies that shed light on the catalytic activation of N-acylsuccinimides in the Suzuki-Miyaura cross-coupling.

The reaction was optimized using commercially-available benzoylsuccinimide (Table 1). Our initial efforts centered on the catalytic system using H_3BO_3 to promote switchable O-/O-coordination of the amide bond in the twisted N-acylsuccinimide (Table 1, entries 1-2).[5a] Encouragingly, we found that the reaction of **1a** with 4-tolylboronic acid in the presence of H_3BO_3 and K_2CO_3 as a base delivered the desired acylation product in quantitative yield (entry 1). Furthermore, appreciable conversion was obtained at ambient conditions, attesting to the high catalytic activity of this catalytic system (entry 3). Nevertheless, based on our previous experience in acyl Suzuki cross-couplings, we sought to develop a more general catalyst system in the absence of acidic additives. Pleasingly, we found that a catalyst system consisting of $Pd(OAc)_2$, PCy_3HBF_4 and Na_2CO_3 in dioxane provided superior efficiency (entry 4). Higher temperature led to substantially higher yields (entry 5). This observation suggests that the reaction proceeds via direct metal insertion (cf. switchable activation of the succinimide under acidic conditions).[23] The use of Na_2CO_3 as a base and dioxane as a solvent is superior to other base/solvent combinations (entries 6-7). Furthermore, evaluation of other ligands, including less nucleophilic PPh_3 and more sterically-demanding P*t*-Bu_3HBF_4 proved significantly less effective (entries 8-10). Collectively, these results confirm that PCy_3 serves as a privileged ligand in Pd-PR_3-catalyzed Suzuki-Miyaura acyl cross-coupling of amide-based reagents by N–C activation. Importantly, our user-friendly method uses bench-stable PCy_3HBF_4, which is an added bonus over the air-sensitive PCy_3 employed by Zeng.

The scope of the Suzuki-Miyaura cross-coupling of N-acylsuccinimides was then investigated (Table 2). Importantly, the reaction tolerates electron-neutral (**3a**), electron-rich (**3b**) and electron-deficient (**3c**) boronic acids. Thus, the method is insensitive to electronic properties on the boronic acid component, resulting in a general process (cf. catalytic system reported by Zeng). Pleasingly, steric-hindrance is well-tolerated as exemplified by the coupling of ortho-tolyl boronic acid. Importantly, highly electrophilic carbonyl groups, such as

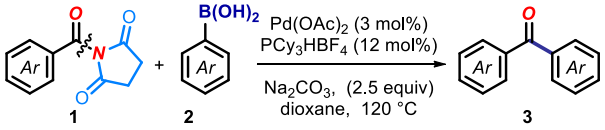
Table 1 Optimization of Pd-Catalyzed Suzuki-Miyaura Cross-Coupling of N-Acylsuccinimides[a]

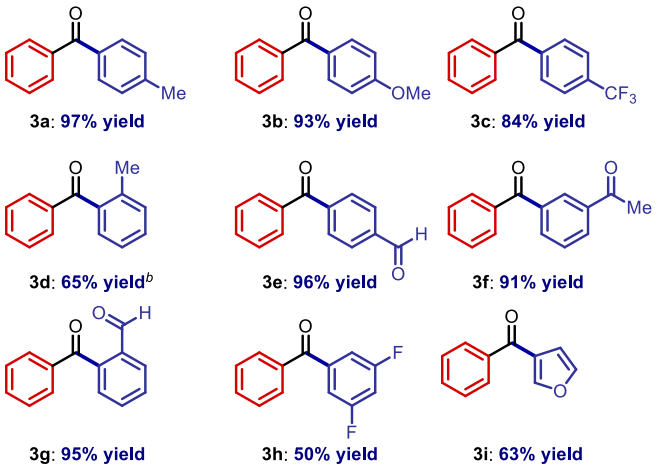


Entry	Catalyst	Ligand	Base	Acid	Solvent	Yield (%)[b]
1	$Pd(OAc)_2$	PCy_3HBF_4	K_2CO_3	H_3BO_3	THF	>95
2	$Pd(OAc)_2$	PCy_3HBF_4	K_2CO_3	-	THF	<5
3	$Pd(OAc)_2$	PCy_3HBF_4	K_2CO_3	H_3BO_3	THF	54
4	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	-	Dioxane	>95
5	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	-	Dioxane	75
6	$Pd(OAc)_2$	PCy_3HBF_4	K_2CO_3	-	Dioxane	10
7	$Pd(OAc)_2$	PCy_3HBF_4	Na_2CO_3	-	Toluene	19
8	$Pd(OAc)_2$	PCy_2Ph	Na_2CO_3	-	Dioxane	47
9	$Pd(OAc)_2$	PPh_3	Na_2CO_3	-	Dioxane	7
10	$Pd(OAc)_2$	P*t*Bu_3HBF_4	Na_2CO_3	-	Dioxane	6

[a]Amide (1.0 equiv), 4-Tol-$B(OH)_2$ (2.0 equiv), base (2.5 equiv), $Pd(OAc)_2$ (3 mol%), ligand (12 mol%), acid (1.5 equiv), solvent (0.25 M), *T*, 15 h. [b]Determined by ^{1}H NMR and/or GC-MS. *T*: Entries 1-2: 60 °C, entry 3: 23 °C, entries 4, 6-10: 120 °C, entry 5: 100 °C.

Table 2 Pd-Catalyzed Suzuki-Miyaura Cross-Coupling of N-Acylsuccinimdes: Boronic Acid Scope[a]

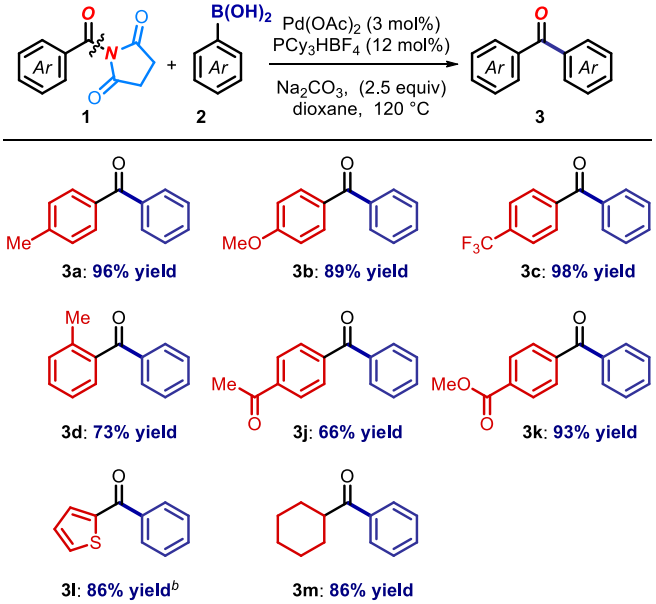




[a]Conditions: amide (1.0 equiv), $ArB(OH)_2$ (2.0 equiv), $Pd(OAc)_2$ (3 mol%), PCy_3HBF_4 (12 mol%), Na_2CO_3 (2.5 equiv), dioxane (0.25 M), 120 °C, 15 h. [b]$ArB(OH)_2$ (3.0 equiv), Na_2CO_3 (4.5 equiv). See ESI for details.

aldehydes and ketones placed at various positions around the aromatic ring on the boronic acid component (**3e-3g**) are well-tolerated. It is worthwhile to note that ketones and aldehydes are incompetent substrates in the classic Weinreb ketone synthesis. Also note that the alternative method reported by Zeng does not tolerate carbonyl functional groups. Furthermore, fluorinated aromatics (**3h**) highly relevant from the medicinal chemistry standpoint and heterocycles (**3i**) are well-tolerated. In agreement with the cyclic structure of the

Table 3 Pd-Catalyzed Suzuki-Miyaura Cross-Coupling of N-Acylsuccinimdes: N-Acylsuccinimide Scope[a]



[a]Conditions: amide (1.0 equiv), $ArB(OH)_2$ (2.0 equiv), $Pd(OAc)_2$ (3 mol%), PCy_3HBF_4 (12 mol%), Na_2CO_3 (2.5 equiv), dioxane (0.25 M), 120 °C, 15 h. [b]$ArB(OH)_2$ (3.0 equiv), Na_2CO_3 (4.5 equiv). See ESI for details.

succinimide ring, in all cases the reaction proceeded in a highly selective fashion for the activation of the N–C amide bond (cf. undesired cleavage of the σ N–C bond).

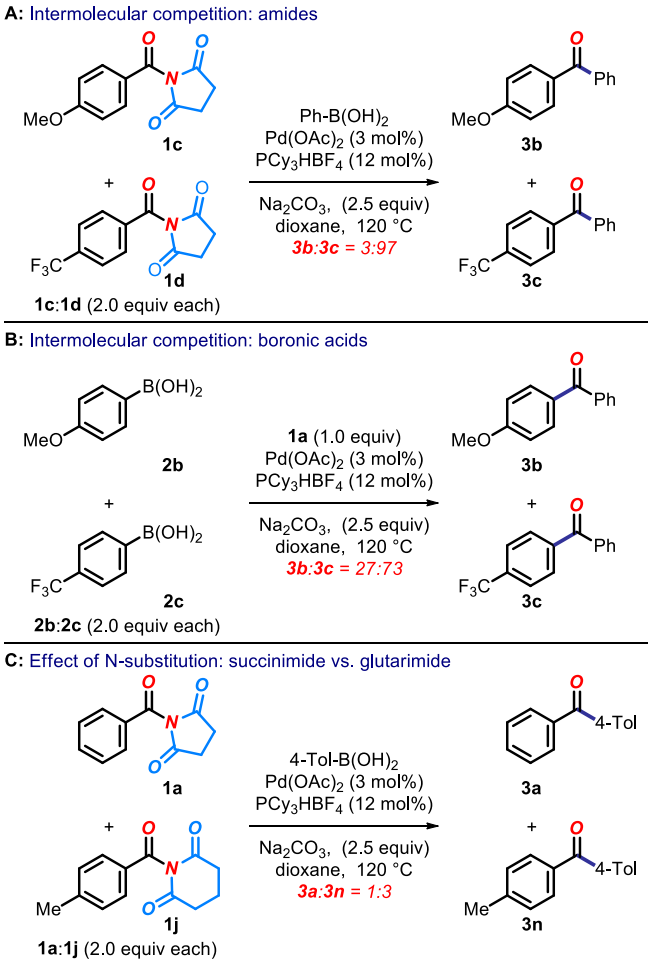
We next focused on the scope of N-acylsuccinimide coupling partner as illustrated in Table 3. Similar to the scope of the boronic acid coupling partner, the reaction delivered high yields of the coupling products irrespective of the electronic properties of the amide component, including electron-neutral, electron-donating and electron-withdrawing substituents (**3a-c**). Likewise, steric-hindrance on the amide is well-tolerated (**3d**). Perhaps most importantly, amides bearing electrophilic carbonyl groups, such as ketones and esters are also compatible (**3j-k**, vide supra). Finally, we were pleased to find that heterocyclic (**3l**) as well as aliphatic amides (**3m**) are competent substrates for the reaction. Overall, the scope of our method using the catalytic system based on $Pd(OAc)_2$, PCy_3HBF_4 and Na_2CO_3 compares very favorably with the process reported by Zeng[22] in terms of reaction efficiency, generality and functional group tolerance, in particular with respect to the synthetically-valuable carbonyl groups.[24]

We have conducted studies to gain insight into the catalytic mechanism of this reaction:

(1) Intermolecular competition experiments with differently substituted amides revealed that electron-deficient arenes are more reactive (4-CF_3:4-MeO = 97:3, cf. glutarimide, 4-CF_3:4-MeO, 97:3)[9a] (Scheme 1A).

(2) Further competition experiments revealed preference for electron-deficient boronic acids (4-CF_3:4-MeO = 73:27, cf. glutarimide, 4-CF_3:4-MeO = 75:25)[9a] (Scheme 1B).

(3) As expected on the basis of amide twist, the reaction is slightly less selective for the cross-coupling of N-acylsuccinimides cf. N-acylglutarimides (Scheme 1C). Nevertheless, this is compensated



Scheme 1 Mechanistic selectivity studies.

by the compelling availability and bargain price of the succinimide activating group.

(4) While the reaction proceeds more rapidly upon increasing the amounts of boronic acid and base (Na_2CO_3, 2.5 equiv, 4-Tol-$B(OH)_2$, 2.0 equiv, 1 h, 26% conversion; Na_2CO_3, 5.0 equiv, 4-Tol-$B(OH)_2$, 4.0 equiv, 1 h, 31% conversion), the increase is much lower than previously observed using N-acylglutarimides (54% to >98%).[9b]

(5) A turnover number (TON) of 130 was determined under these conditions at 0.25 mol% Pd loading.

Overall, these mechanistic findings suggest that metal insertion may be the rate limiting step in the coupling.

In conclusion, we have developed a general and operationally-simple method for Suzuki-Miyaura cross-coupling of N-acylsuccinimides. The key features of our protocol include high efficiency, air-stable and commercially-available reagents and catalysts. The reaction employs new cross-coupling reagents, N-acylsuccinimides, which are activated for selective metal insertion by half-twist of the amide bond. Besides the great potential applications of N-acylsuccinimides in a wide range of transition-metal catalyzed cross-couplings, these reagents could also inspire future research to address tunable distortion of the amide bond. Further studies on the development of cross-coupling reactions of amides, including aliphatic amides, and detailed

mechanistic investigations are underway and will be reported in due course.

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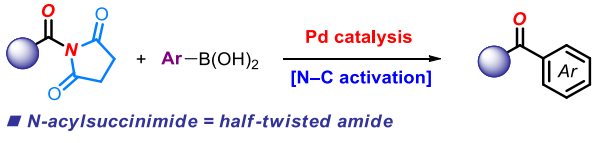

■ *N-acylsuccinimide = half-twisted amide*