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Palladium-catalyzed decarbonylative Suzuki–Miyaura cross-coupling of amides by carbon–nitrogen bond activation†

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Palladium-catalyzed Suzuki–Miyaura cross-coupling or aryl halides is widely employed in the synthesis of many important molecules in synthetic chemistry, including pharmaceuticals, polymers and functional materials. Herein, we disclose the first palladium-catalyzed decarbonylative Suzuki–Miyaura cross-coupling of amides for the synthesis of biaryls through the selective activation of the N–C(O) bond of amides. This new method relies on the precise sequence engineering of the catalytic cycle, wherein decarbonylation occurs prior to the transmetallation step. The reaction is compatible with a wide range of boronic acids and amides, providing valuable biaryls in high yields (>60 examples). DFT studies support a mechanism involving oxidative addition, decarbonylation and transmetallation and provide insight into high N–C(O) bond activation selectivity. Most crucially, the reaction establishes the use of palladium catalysis in the biaryl Suzuki–Miyaura cross-coupling of the amide bond and should enable the design of a wide variety of cross-coupling methods in which palladium rivals the traditional biaryl synthesis from aryl halides and pseudohalides.

Introduction

Palladium-catalyzed cross-coupling reactions are fundamental methods for the construction of many important molecules in chemical synthesis and these reactions are widely used to expediate the synthesis of target motifs.[1–3] In particular, due to broad generality, predictable functional group tolerance, high reaction selectivity and operational-simplicity, palladium-catalyzed cross-couplings have enabled rapid progress in the development of improved medicines, precise electronic devices, and multifunctional dyes that broadly benefit society.[4–6]

While typical Suzuki–Miyaura cross-couplings employ aryl halides as electrophiles, unconventional C–X (X = O, N, S) cross-coupling partners have attracted significant attention because they enable an orthogonal selectivity paradigm.[4–6] In this context, amides (X = $CONR_2$) are particularly attractive as aryl electrophiles in the Suzuki–Miyaura cross-coupling because amides are among the most widespread functional groups in chemical science,[7] including in the synthesis of pharmaceuticals, and play an essential role as linkages in peptides and proteins.[8,9] While significant progress has been achieved in cross-coupling of amides enabled by selective metal insertion into the N–C(O) amide bond ($n_N \rightarrow \pi^*_{CaO}$ conjugation, 15–20 kcal mol^{-1} in planar amides),[10–14] the palladium-catalyzed Suzuki–Miyaura biaryl cross-coupling of amides has been a major challenge (Fig. 1A).

Herein, we disclose the first palladium-catalyzed decarbonylative Suzuki–Miyaura cross-coupling of amides for the

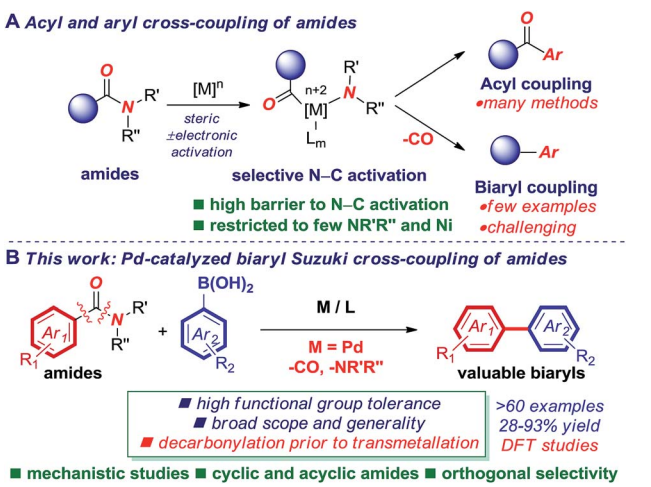

Fig. 1 (A) Acyl- and decarbonylative cross-coupling of amides. (B) Pd-catalyzed decarbonylative biaryl cross-coupling of amides enabled by sequence engineering (this study).

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synthesis of biaryls (Fig. 1B). This new method relies on the precise sequence engineering of the catalytic cycle, wherein decarbonylation occurs prior to the transmetallation step. The reaction proceeds through the selective activation of the N–C(O) bond of both cyclic and acyclic amides. DFT studies were conducted and support a mechanism involving oxidative addition, decarbonylation and transmetallation, and provide insight into the origin of the high N–C(O) bond activation selectivity. The reaction shows unprecedented generality and functional group tolerance in decarbonylative amide bond cross-coupling, providing valuable biaryls in high yields (>60 examples). Most crucially, the reaction establishes versatile palladium catalysis for the synthesis of high-value biaryls from amides, rivaling the substrate scope achieved with the traditional Suzuki cross-coupling of aryl halides.

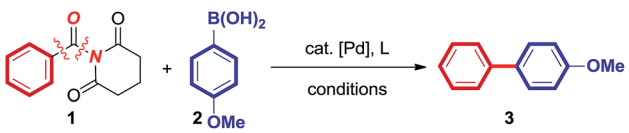
Results and discussion

The decarbonylative biaryl Suzuki–Miyaura cross-coupling of amides is a challenging reaction, in which several elementary organometallic steps must occur in a well-engineered sequence.[15–18] To date, very few examples of the biaryl Suzuki–Miyaura cross-coupling of amides have been reported; all of them limited to nickel-catalysis.[15] The high reactivity of Ni has been ascribed to a facile CO migration, which permitted for transmetallation preceding decarbonylation.[18] However, Ni-catalyzed biaryl Suzuki coupling of amides has been severely limited to specific substrate combinations and showed narrow functional group tolerance.

In consideration of the tremendous utility of Pd-catalyzed cross-couplings in organic synthesis,[19,20] we questioned whether general palladium catalysis might be applied for the decarbonylative biaryl Suzuki–Miyaura cross-coupling of amides by N–C(O) bond activation. Our investigation started with evaluation of the coupling of a challenging, electronically-neutral *N*-benzoyl glutarimide (**1**) with 4-methoxyphenyl boronic acid (**2**) in the presence of various Pd catalysts (Table 1); note that this combination is unsuccessful using Ni catalysis. After very extensive optimization (Table 1 and ESI†), we found that a catalytic system using Pd(dppf)Cl_2 (5 mol%) in the presence of close to a stoichiometric amount of boronic acid (1.2 equiv.) and $NaHCO_3$ (3.0 equiv.) in dioxane at 160 °C, delivered the desired biaryl product in 90% yield and >10 : 1 biaryl : ketone selectivity (entry 1). Interestingly, a comparable efficiency was observed using Pd(dppb)Cl_2 (5 mol%) as the precatalyst (entry 2). The use of a weak base is crucial (entries 8–15). From the outset, we hypothesized that the use of a weak base would slow down transmetallation,[21] permitting for decarbonylation preceding aryl transfer. Furthermore, the effect of boronic acid stoichiometry (entries 1–8) as well as the counterion (entries 19–20) is the key in determining the selectivity for the formation of biaryl, as expected from decarbonylation *vs.* transmetallation selectivity. It is worthwhile to note the impact of the reaction temperature on the selectivity (entries 21 and 22). The use of precatalysts[22] (entries 1–3 *vs.* 19 and 20) simplifies the reaction set-up and facilitates CO de-insertion. It is further important to note that both bidentate and monodentate phosphane ligands are similarly effective (entries 1–7), consistent with the importance of decarbonylation prior to generating the aryl-Pd intermediate.[17,18]

With optimized conditions in hand, the scope of this novel Suzuki–Miyaura biaryl cross-coupling of amides was next investigated (Table 2). The functional group tolerance and generality of this Pd-catalyzed method is remarkable. A broad range of electron neutral, electron-donating and electron-withdrawing boronic acids is compatible (**3a–3f**), all using the challenging electron-neutral, parent amide electrophile that is not suitable using Ni. Substitution at the meta-position with electronically-diverse boronic acids is well-tolerated (**3g–3i**). Sterically-hindered, polyaromatic, heterocyclic, including dioxolane, pyridine and thiophene boronic acids coupled with high levels of selectivity (**3j–3o**). Strikingly, the reaction is compatible with halides, including chlorides, as well as phenols, aldehydes, esters and nitriles (**3p–3s**), providing effective handles for further functionalization by established methods. In addition, electronically-diverse amides bearing representative electron-withdrawing, electron-donating and

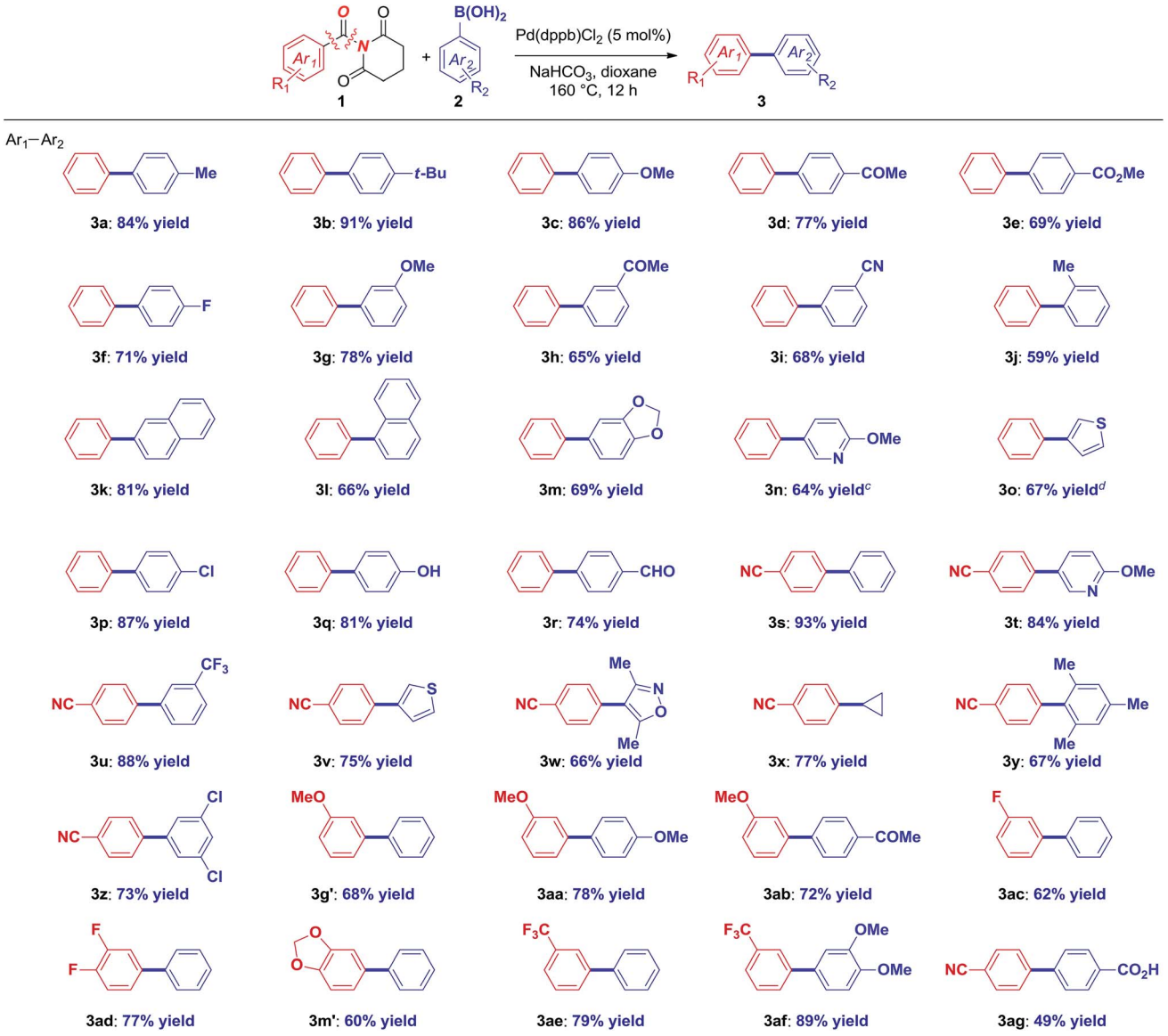
Table 1 Reaction optimization: Pd-catalyzed decarbonylative Suzuki–Miyaura cross-coupling[a]



Entry	Catalyst	Base	2 (equiv.)	Yield 3[b] (%)	Selectivity[c]
1	Pd(dppf)Cl_2	$NaHCO_3$	1.2	90	>10 : 1
2	Pd(dppb)Cl_2	$NaHCO_3$	1.2	88	90 : 10
3	Pd(PCy_3)$_2Cl_2$	$NaHCO_3$	1.2	83	84 : 16
4	Pd(dppf)Cl_2	$NaHCO_3$	2.0	82	86 : 14
5	Pd(PCy_3)$_2Cl_2$	$NaHCO_3$	2.0	70	72 : 26
6	Pd(PPh_3)$_2Cl_2$	$NaHCO_3$	2.0	67	69 : 31
7	Pd(dcypf)Cl_2	$NaHCO_3$	2.0	65	66 : 34
8	Pd(PCy_3)$_2Cl_2$	$NaHCO_3$	1.05	83	85 : 15
9[d]	Pd(PCy_3)$_2Cl_2$	K_2CO_3	2.0	<10	6 : 94
10[d]	Pd(PCy_3)$_2Cl_2$	K_3PO_4	2.0	<2	<5 : >95
11[d]	Pd(PCy_3)$_2Cl_2$	$KHCO_3$	2.0	50	53 : 47
12[d]	Pd(PCy_3)$_2Cl_2$	Na_2CO_3	2.0	15	56 : 44
13[d]	Pd(PCy_3)$_2Cl_2$	KF	2.0	<2	<5 : >95
14[d]	Pd(PCy_3)$_2Cl_2$	KOAc	2.0	<2	<5 : >95
15[d]	Pd(PCy_3)$_2Cl_2$	—	2.0	<2	nd
16[d,e]	Pd(PCy_3)$_2Cl_2$	$NaHCO_3$	2.0	<2	<5 : >95
17[d,f]	Pd(PCy_3)$_2Cl_2$	$NaHCO_3$	2.0	16	55 : 45
18[d,g]	Pd(PCy_3)$_2Cl_2$	$NaHCO_3$	2.0	31	51 : 49
19[h]	Pd(OAc)$_2$/PCy_3	$NaHCO_3$	1.2	<2	<5 : >95
20[h]	$PdCl_2$/PCy_3	$NaHCO_3$	1.2	63	79 : 21
21[i]	Pd(dppb)Cl_2	$NaHCO_3$	1.2	78	80 : 20
22[j]	Pd(dppb)Cl_2	$NaHCO_3$	1.2	47	53 : 47

[a] Conditions: amide (1.0 equiv.), Ar–B(OH)$_2$, [Pd] (5 mol%), base (3 equiv.), dioxane (0.125 M), 160 °C, 12 h. [b] GC/1H NMR yields. [c] Refers to biaryl : ketone selectivity. [d] [Pd] (3 mol%). Note that in entries 9, 10, 13 and 14, the ketone is formed in 92–98% yields. [e] Toluene. [f] DME. [g] NMP. [h] [Pd] (10 mol%), L (20 mol%). Entry 19: ketone formed in 71%. [i] 140 °C. [j] 120 °C. See ESI for full details.

Table 2 Palladium-catalyzed decarbonylative Suzuki–Miyaura biaryl cross-coupling of *N*-acyl-glutarimide amides with boronic acids[a,b]

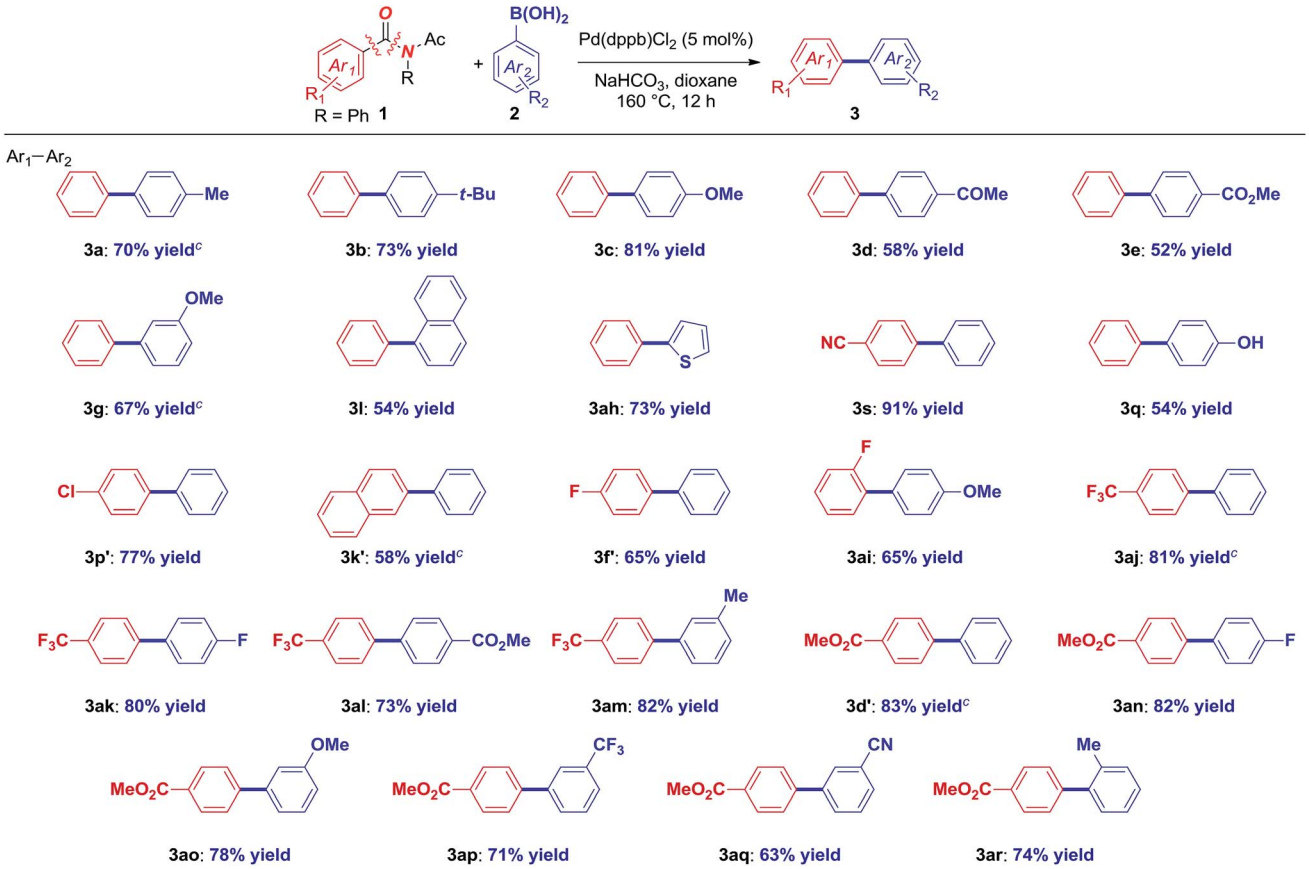


[a] Conditions: amide (1.0 equiv.), Ar–B(OH)$_2$ (1.2 equiv.), $NaHCO_3$ (3 equiv.), Pd(dppb)Cl_2 (5 mol%), dioxane (0.125 M), 160 °C, 12 h. [b] Isolated yields. [c] Ar–B(OH)$_2$ (3 equiv.), base (4.5 equiv.). [d] Pd(dppf)Cl_2 (5 mol%). See ESI for details.

important fluorine-containing substituents are transferred with high selectivity across various boronic acids (**3s–3ag**), including such groups as prone to O–N cleavage isoxazolyl, aliphatic cyclopropyl, and sterically-hindered mesityl (**3w–3y**). The synthetic potential is highlighted in the cross-coupling of carboxyphenylboronic acid (**3ag**). Since amides can be ultimately derived from carboxylic acids, this preliminary result suggests the viability of iterative cross-coupling and is performed in the presence of an electrophilic nitrile handle, which serves as another orthogonal amide precursor. These results are for the first time comparable to the scope achieved using the classical Suzuki cross-coupling of halides and pseudohalides,[1–6] and are unprecedented for any cross-coupling of amides to date.[10–18]

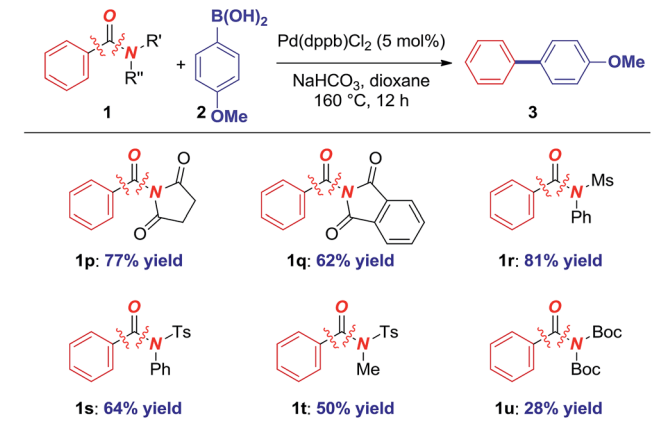
Remarkably, the optimized conditions are suitable for the cross-coupling of acyclic *N*-acetyl (*N*–Ac) amides (Table 3). A broad range of boronic acids and amides, including neutral, electron-rich and electron-withdrawing coupling partners, is compatible (**3a–3ah**). Notably, Pd-catalysis enables the coupling of an array of sensitive functional groups, such as halides, ethers, esters and nitriles (**3c**, **3e**, **3s**, **3q**, **3p′**) with high selectivity. Furthermore, the reaction delivers fluorinated biaryls of great importance in medicinal chemistry (**3f′–3am**) as well as biaryls bearing multiple electrophilic handles (**3aq**) as well as steric hindrance (**3ar**). It is noteworthy that the cleavage of the *N*-activating group, the main hurdle in decarbonylative cross-coupling of acyclic amides, is not observed under these mild conditions. This very rare use

Table 3 Palladium-catalyzed decarbonylative Suzuki–Miyaura biaryl cross-coupling of *N*-acyl-amides with boronic acids[a,b]



[a] Conditions: amide (1.0 equiv.), Ar–B(OH)$_2$ (1.5 equiv.), $NaHCO_3$ (3 equiv.), Pd(dppb)Cl_2 (5 mol%), dioxane (0.125 M), 160 °C, 12 h. [b] Isolated yields. [c] Ar–B(OH)$_2$ (1.2 equiv.). See ESI for details.

Table 4 Palladium-catalyzed decarbonylative Suzuki–Miyaura biaryl cross-coupling of various amides with boronic acids[a]



[a] See Table 2.

of acyclic amides in decarbonylative cross-coupling significantly expands the scope of biaryl Suzuki synthesis of amides and suggests a broad generality of this reactivity platform.

Furthermore, other amides, including *N*-succinimide (**1p**), *N*-phthalimide (**1q**), atom-economic *N*-Ms (**1r**) and acyclic *N*-Ts sulfonamides (**1s–1t**) are suitable substrates for the coupling (Table 4). Interestingly, even the highly challenging *N*-Boc$_2$ amide (**1u**) that is prepared directly from 1° amide[14c] and prone to deactivation by a facile *N*-Boc cleavage afforded a promising yield in the coupling. These preliminary results bode well for the development of general biaryl syntheses from various amides, which is beyond the scope of Ni catalysis.

Several additional points should be noted: (1) at this stage, cross-coupling of alkenyl-amides proceeds in 30% unoptimized yield (1-cinnamoylpiperidine-2,6-dione). (2) Full selectivity for the cross-coupling of aryl bromides in the presence of amide electrophiles is observed. This allows to establish the following order of reactivity: Ar–Cl < Ar–C(O)–NR_2 < Ar–Br. (3) Di-methyl and di-phenyl amides are recovered unchanged from the reaction, as expected from the amidic resonance (PhCONMe$_2$, RE = 16.5 kcal mol^{-1}; PhCONPh$_2$, 12.7 kcal mol^{-1}). (4) Ar–Bpin are not suitable substrates under the reaction conditions (<20% yield); pleasingly, MIDA boronates are competent nucleophiles (4-chlorophenyl MIDA boronate, 72% yield). (5) Although at this

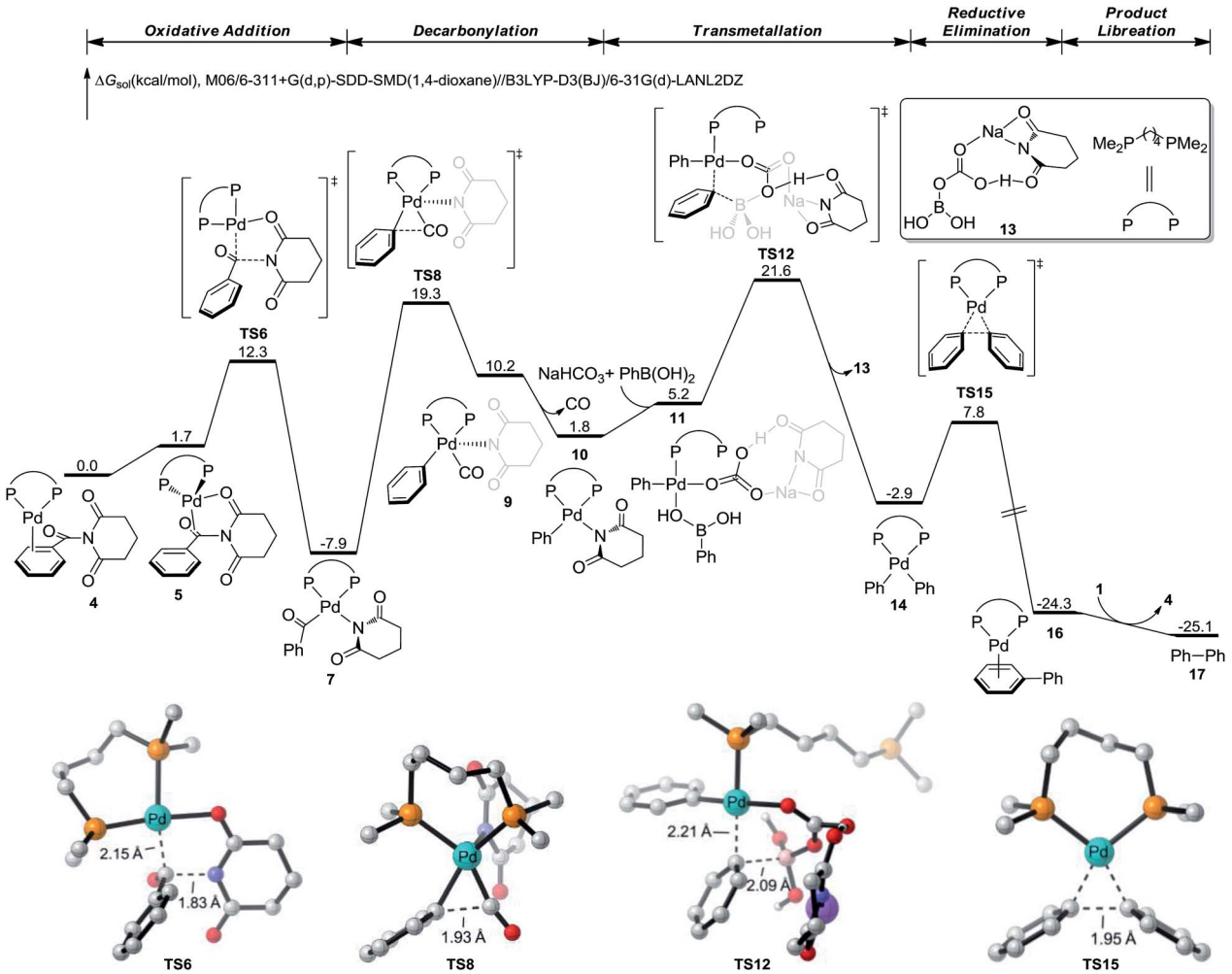


Fig. 2 DFT-calculated reaction energy profile of Pd-catalyzed decarbonylative biaryl Suzuki–Miyaura cross-coupling of amides. See ESI† for computational details.

stage tetra-*ortho*-substituted biaryls are beyond the scope of the reaction, the cross-coupling of unactivated 1-benzoylpiperidine-2,6-dione with mesitylene-2-boronic acid proceeds in promising 48% yield. Further studies are in progress to develop improved conditions and new ligands for decarbonylative cross-coupling reactions of amides.

DFT studies were conducted to gain insight into the reaction mechanism (Fig. 2), using the experimental amide substrate **1** and mode ligand dmpe.[11a,18,23] The substrate-coordinated complex **4** undergoes a facile C–N bond cleavage occurs *via* **TS6**, leading to the acylpalladium intermediate **7**. Subsequent decarbonylation occurs through **TS8** to generate the arylpalladium species **9**. **9** then undergoes the CO dissociation, and subsequent transmetallation *via* **TS12** generates the $LPd(Ph)_2$ intermediate **14**. In **TS12**, the base complexes with the boronic acid, which promotes the efficiency of the rate-determining transmetallation and lowers the overall reaction barrier. This is consistent with previous mechanistic studies,[24] and corroborated the importance of weak base for the reaction success (Table 1).[25] From **14**, the aryl–aryl reductive elimination is quite efficient through **TS15**, leading to the product-coordinated complex **16**. **16** eventually undergoes the product extrusion and regenerates the palladium(0) catalyst. Based on the DFT-computed free energy profile, the on-cycle resting state is the acylpalladium intermediate **7**. The rate-determining step is the transmetallation *via* **TS12**, which requires a overall barrier of 29.5 kcal mol^{-1} (**7** to **TS12**).

We conducted additional competition studies to shed light on the mechanism (Fig. 3). (1) Intermolecular competition experiments revealed that electron-deficient boronic acids couple preferentially (4-Ac : 4-MeO = 93 : 7, glutarimide; 4-Ac : 4-MeO = 92 : 8, *N*–Ac), consistent with coordination of the leaving group to boron, while electron-poor amides are more reactive (4-CN : 4-H >95 : 5, glutarimide; 4-CF_3 : 4-H, 82 : 18, *N*–Ac), consistent with facility of metal insertion.[11] (2) Furthermore, the reaction is not significantly affected by steric hindrance on either boronic acid (4-Me : 2-Me = 54 : 46, glutarimide; 4-Me : 2-Me = 47 : 53, *N*–Ac) or amide (4-Me : 2-Me = 55 : 45, *N*–Ac), consistent with decarbonylation preceding transmetallation.[21]

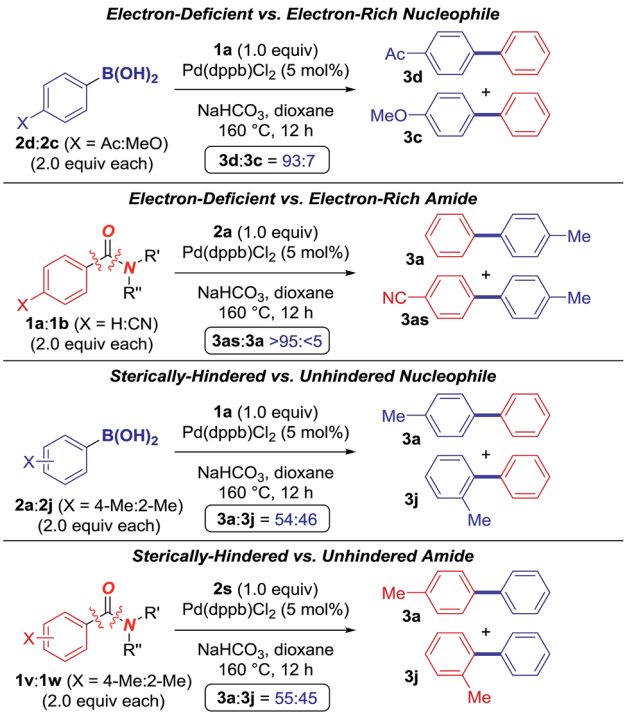


Fig. 3 Intermolecular competition experiments.

Conclusions

In conclusion, we have developed the first palladium-catalyzed decarbonylative Suzuki–Miyaura cross-coupling of amides for the synthesis of biaryls. A catalyst system derived from a Pd(II) precatalyst and a mild base enabled the direct route to biaryls from amides by selective carbon–nitrogen bond cleavage. This Pd-catalyzed reaction shows high generality and is compatible with a broad range of electronically-diverse cross-coupling partners. Furthermore, we demonstrated that a wide range of amides including both *N*-cyclic and *N*-acyclic are readily amendable to the cross-coupling. The key finding enabling the synthesis of biaryls was realization that decarbonylation must occur prior to the transmetallation step in palladium catalytic cycle. DFT studies demonstrated that mechanism involving decarbonylation prior to transmetalation is likely operative. Given the great importance of palladium-catalyzed Suzuki–Miyaura cross-couplings in chemical science, we believe that this reaction has a significant potential to enhance the utility of amides in cross-coupling reactions of general interest.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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