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Palladium-catalyzed Suzuki–Miyaura coupling of amides by carbon–nitrogen cleavage: general strategy for amide N–C bond activation†

Guangrong Meng and Michal Szostak*

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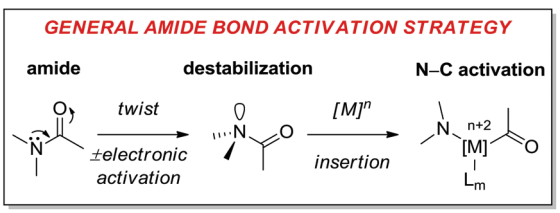
The first palladium-catalyzed Suzuki–Miyaura cross-coupling of amides with boronic acids for the synthesis of ketones by sterically-controlled N–C bond activation is reported. The transformation is characterized by operational simplicity using bench-stable, commercial reagents and catalysts, and a broad substrate scope, including substrates with electron-donating and withdrawing groups on both coupling partners, steric-hindrance, heterocycles, halides, esters and ketones. The scope and limitations are presented in the synthesis of >60 functionalized ketones. Mechanistic studies provide insight into the catalytic cycle of the cross-coupling, including the first experimental evidence for Pd insertion into the amide N–C bond. The synthetic utility is showcased by a gram-scale cross-coupling and cross-coupling at room temperature. Most importantly, this process provides a blueprint for the development of a plethora of metal catalyzed reactions of typically inert amide bonds *via* acyl-metal intermediates. A unified strategy for amide bond activation to enable metal insertion into N–C amide bond is outlined (Scheme 1).

1. Introduction

Transition-metal catalyzed cross-coupling reactions have revolutionized the synthesis of pharmaceuticals, fine chemicals, materials and polymers.[1,2] In this context, biaryl synthesis by means of Suzuki–Miyaura coupling is one of the most common reactions conducted in both industrial and academic settings, with examples ranging from mg to multi-ton scale annually.[3] This process proceeds *via* aryl metal electrophiles, and a variety of electrophilic coupling partners (LG = C–X, C–O, C–N) for the Suzuki–Miyaura biaryl synthesis have been reported.[4] An alternative yet equally powerful Suzuki–Miyaura disconnection proceeds *via* acyl metal electrophiles giving valuable ketone products,[5] which are some of the most important intermediates in organic synthesis due to the presence of polar functional handle enabling an array of downstream elaborations.[6] A handful of acyl electrophiles (LG = C(O)–X, X = halide, SR, OR) for the Suzuki–Miyaura ketone synthesis have been reported, including acyl chlorides,[7] anhydrides,[8] thioesters,[9] and esters,[10] among others (Fig. 1A).[11] In contrast, the use of significantly more challenging amides (amide bond resonance of 15–20 kcal mol^{-1})[12] has not been reported prior to 2015[1–5] despite the key role of amides as bench-stable intermediates in organic chemistry and the importance of amides in biology as building blocks of proteins and peptides.[13]



Scheme 1 Amide bond destabilization concept for metal catalysis.

The major challenge in using amides as electrophilic precursors in transition metal catalysis is the high activation energy required for the N–C(O) bond scission due to $n_N \rightarrow \pi_{C=O}^*$ conjugation (Fig. 1B).[14] Undoubtedly, the use of amides as acyl electrophiles in metal-catalyzed reactions with organometallic reagents would expand the scope of ketone synthesis by providing new strategic C–C bond disconnection.[1–5] More importantly, such a reaction would enable a new mode of elaboration of the traditionally inert N–C amide bonds[14] with wide-ranging implications in synthetic chemistry and biology.

In 2015, our laboratory introduced a new generic mode of activation of amide bonds in transition metal catalysis by geometric distortion (Fig. 1C and Scheme 1).[15a,b] This concept stems from our long-standing interest (M.S.) in chemicophysical properties of amides,[16] activation of amide bonds[17]

Department of Chemistry, Rutgers University, 73 Warren Street, Newark, NJ 07102, USA. E-mail: michal.szostak@rutgers.edu

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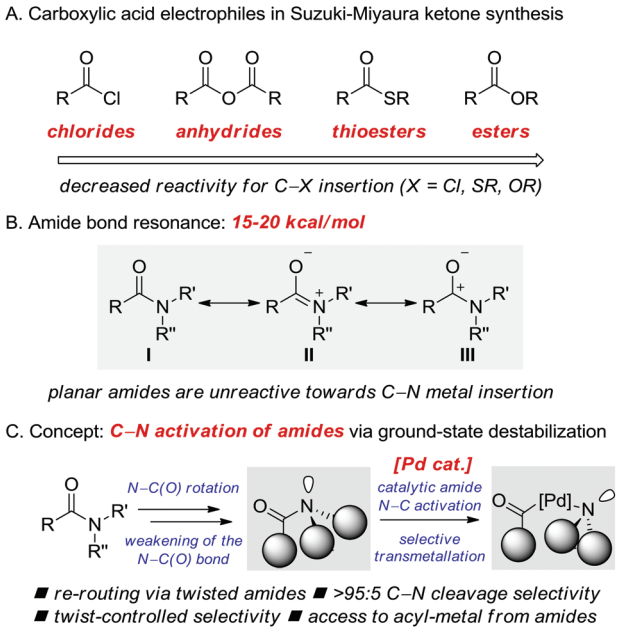


Fig. 1 (a) Reactivity of carboxylic acid derivatives in Suzuki–Miyaura ketone synthesis. (b) Amide bond resonance. (c) Concept: activation of N–C amide bond enabled by ground-state destabilization.

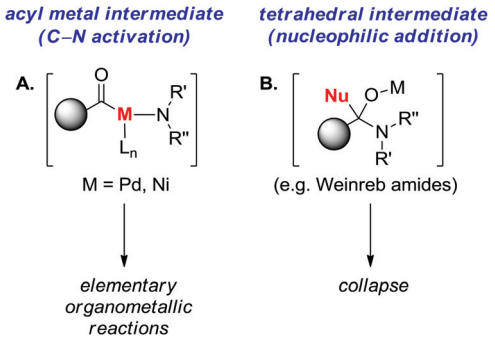


Fig. 2 Intermediates involved in nucleophilic addition to amides: (a) N–C activation intermediate. (b) Tetrahedral intermediate.

and metal-mediated activation of inert bonds with low-valent metals.[18] *Specifically, based on theoretical studies and literature precedents we proposed that metal insertion into an inert amide bond (amide bond resonance of 15–20 kcal mol^{-1}) can proceed only if the* $n_N \rightarrow \pi_{C=O}^*$ *conjugation is disrupted*. Furthermore, we have unambiguously established by introducing an additive distortion parameter ($\sum\tau + \chi_N$)[16] that in amides in which the sum of distortion parameters ($\sum\tau + \chi_N$) is close to 50°, metal insertion should be thermodynamically favourable. Specifically, amide bond distortion (transient or permanent)[17] of approximately 50° is required for productive metal insertion into the amide bond.

We are convinced that the field of transition metal catalyzed amide bond activation will become a major field of research because of (1) the many inherent benefits of amides as acyl or even aryl electrophilic precursors in metal catalysed reactions;[1–5] (2) thousands of potential metal-catalyzed transformations that could be exploited (Fig. 2)[1–5] after the fundamental steps for N–C activation have been demonstrated and the rationale for the development of new reactions has been outlined; (3) the potential to employ the amide bond activation in molecular biology for peptide modification,[13] which for obvious reasons is not feasible with other acyl electrophiles. As such, we expect that the amide bond activation by disrupting amide bond resonance can be applied across many transition metal catalyzed reactions in organic synthesis, and this concept represents a generic mode of transition metal catalyzed inert bond activation.[19]

In our initial communication, in 2015, we reported the first example of palladium-catalysed Suzuki–Miyaura ketone synthesis from amides by steric activation.[15a] Subsequently, we reported[15b] the first palladium-catalysed decarbonylative Heck reaction[20] of amides for the synthesis of olefins *via* N–C activation. These two reactions established that amides can serve as generic acyl and aryl electrophiles for the construction of C–C bonds using Pd.[15h] Independently, in elegant studies, Garg[15c] and Zou[15d] reported the use of twisted imides for the synthesis of ketones under nickel[15c,d] and palladium catalysis.[15d] Altogether, these reactions constitute the first examples of the elusive class of metal catalysed amide bond transformations for the synthesis of carbon–carbon bonds in organic synthesis.[1–5] In principle, there are certain advantages of each of the three protocols reported independently in 2015 by us,[15a] Zou[15d] and Garg[15c] (Fig. 3). We focused on palladium catalysis and boronic acids as nucleophiles of choice because, beyond any doubt, Pd-catalysis is the most established and the most commonly used transition metal catalysis manifold in academia and industry,[1–5] but also due to stability and commercial

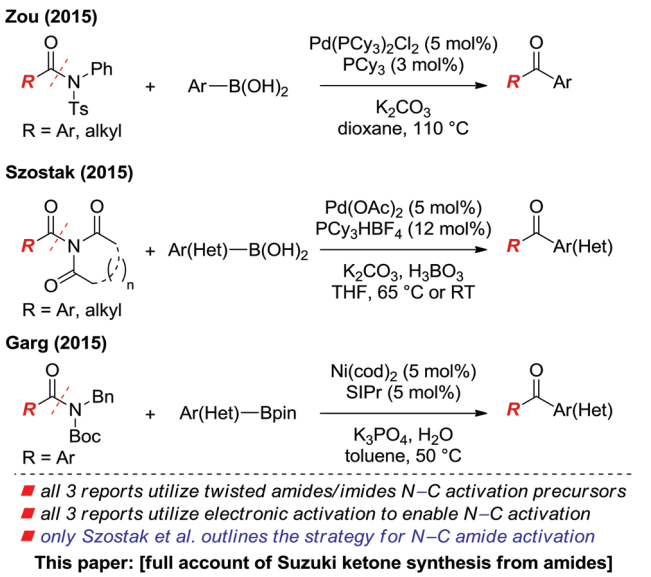


Fig. 3 Suzuki–Miyaura ketone synthesis from amides presented in chronological order of publications.

availability of boronic acids.[3b] Garg employs more sustainable Ni-catalysts, however, the reaction requires the use of an extremely air-sensitive $Ni(cod)_2$ precatalyst and glove-box set-up,[4c] typically not-commercial boronic ester nucleophiles are used and the reaction is sensitive to the amount of water. In contrast, Zou reported the use of Pd- and Ni-catalysis under high temperature conditions. The generic substrate scope is illustrated in Fig. 3, with only our process tolerating alkyl electrophiles, heterocyclic boronic acids and coupling under mild conditions; however, it should be noted that the scope of the reaction reported by Zou is broader in terms of alkyl (but not aryl) electrophiles as it tolerates sterically hindered alkyl electrophiles (see Results section for discussion).

In terms of the amide component, it is clear that ground state distortion[21] and electronic activation[22] enable the observed reactivity in all three cases (discussed below). It is important to note that in all three cases, amides are readily available from carboxylic acid precursors using standard methods,[23] thus enabling a new powerful transition metal catalyzed amide bond disconnection *via* acyl-metal intermediates.[24]

In this manuscript, we report a full account of the palladium-catalyzed Suzuki–Miyaura ketone synthesis from amides by steric activation. Detailed studies on the reaction discovery, reaction optimization, scope and limitations, as well as studies on the practical utility in organic synthesis and mechanistic studies are described. Most importantly, the generic strategy for amide bond activation by transition metals and potential benefits of the amide bond activation manifold are outlined.

2. Results and discussion

2.1. Reaction discovery

Following our long-standing research interests (M.S.) in amide bonds and catalysis,[16–18] in September 2014, we initiated a research program based on the activation of amides with a goal of discovering unknown reactivity modes of the fundamental amide functional group in organic chemistry.[15a,b] On the basis of our theoretical studies,[16] we hypothesized that bench-stable amides could be employed as acylating cross-coupling partners with organometallic reagents by identifying an appropriate amide precursor and catalyst system. We focused on Pd-catalyzed Suzuki–Miyaura coupling with boronic acids because of the major benefits of this reagent/catalyst combination.[1–5] Moreover, we were interested in developing a process that would operate at low temperatures, with high functional group tolerance and wide substrate scope, employing bench-stable, robust reagents under user-friendly conditions. This would be of particular importance for general applications of the metal-catalyzed amide bond activation platform in organic synthesis.[19]

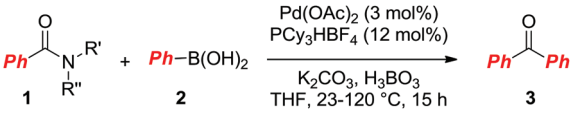
Our strategy to achieve a broadly useful, modular, sterically-controlled cross-coupling of amides to access ketones involved the following steps: (1) oxidative addition of Pd into the N–C(O) bond; (2) transmetallation with organoboron organometallic; and (3) reductive elimination to give the ketone product. Importantly, amide can be used as a precursor to access a wide variety of end-products by functionalization and/or elementary reactions of the acyl metal intermediate (Fig. 2).[1–5] A critical feature of our protocol is the capacity of amides to undergo N-activation *via* N-coordination (*cf.* O-coordination), a well-established process in the chemistry of non-planar amides, that results in a disruption of the amide bond resonance and should facilitate palladium insertion into the inert N–C(O) bond.[16,25] Based on the theoretical studies,[16] we anticipated that in amides in which the sum of distortion parameters ($\sum\tau + \chi_N$) is close to 50°,[26] palladium insertion should be thermodynamically favourable. Thus, amide bond distortion of approximately 50° (transient or permanent) would be required to effect metal insertion into the N–C bond under mild conditions.

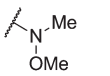
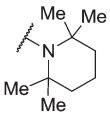
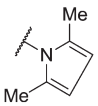
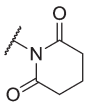
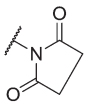
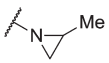
We further hypothesized that the use of electron-rich ligands on Pd would favour metal insertion into the N–C(O) bond.[4b] As a third design feature, we anticipated that acidic additives would activate the N–C(O) bond and favour ligand dissociation from the acyl metal intermediate to overcome the low propensity of amines to act as leaving groups.[27]

Evaluation of the amide-bond cross-coupling strategy was first examined by screening a range of electronically- and sterically-distorted amides[17,21,22] in the reactions with phenylboronic acid as a coupling partner in the presence of palladium catalytic systems under various conditions. Selected screened examples are presented in Table 1. Overall, we investigated the coupling of approximately >20 derivatives. While Weinreb amides (entry 1), tmp amides (entry 2), and acylpyrroles (entry 3) provided trace or no quantities of the desired ketone product, we were delighted to find that by using the twisted amide **1d** (entry 4)[17] the proposed cross-coupling was indeed feasible, providing the ketone product in excellent 98% yield. Furthermore, less distorted systems such as amide **1e** (entry 5)[17] resulted in a dramatic decrease in efficiency, consistent with our hypothesis on the importance of amide bond distortion to disrupt $n_N \rightarrow \pi_{C=O}^*$ conjugation, and previous studies on amide bond activation.[14] 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 amides.[28] The optimization results in Table 1 demonstrated for the first time that metal insertion into the N–C(O) bond of amides is feasible, and that the rate of coupling is proportional to the degree of distortion.[29] 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.[30]

The results presented in Table 1 validate the generic mode of amide bond activation by steric distortion to disrupt amide resonance. It is noteworthy that the reaction efficiency (*i.e.* the rate of metal insertion into the inert amide N–C bond, *vide infra*) correlates with the additive amide bond distortion parameter ($\sum\tau + \chi_N$).[16] Remarkably, the predicted distortion barrier of approximately 50° was found to be sufficient to enable Suzuki–Miyaura coupling of amides (entry 5).[25] However, it is

Table 1 Development of Suzuki–Miyaura cross-coupling of amides: amide optimization[a]



Entry	NR′R″	1	τ (°)	χ_N (°)	$\sum(\tau+\chi_N)$ (°)	Yield (%)
1		**1a**	1.2	16.3	17.5	<5
2		**1b**	34.1	17.0	51.1	9
3		**1c**	39.7	8.4	48.1	<5
4		**1d**	87.8	6.8	94.6	98
5		**1e**	45.9	10.7	56.6	54
6		**1f**	14.3	69.6	83.9	<5
7		**1g**	5.1	33.1	38.2	<5

[a] Conditions: amide (0.2 mmol), Ph-B(OH)$_2$ (2.0 equiv.), Pd(OAc)$_2$ (3 mol%), ligand (12 mol%), K_2CO_3 (2.5 equiv.), additive (2.5 equiv.), THF (0.25 M), rt–120 °C, 15 h. Conversions were determined by ^{1}H NMR or GC *vs.* internal standard.

also clear that steric effects exert a significant influence on the rate of metal insertion (entries 2 and 3), as expected.[17] It should also be noted that the twisted imides reported by Garg and Zou (Fig. 3) are well-established to contain non-planar amide bonds.[17,29] The distinct advantage of amides **1d–1e** lies in the ease of modulating steric and electronic environment of the amide bond by distortion, which leads to the reactivity that cannot be easily achieved with other non-planar amides, for example, such as reported by Garg and Zou. It should also be noted that all three types of amides are prepared from the same synthetic precursors.[23]

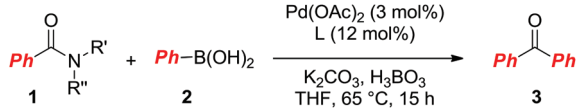
As discussed in the introduction, amide bond resonance (principally, a planar amide bond can be compared to a 40% sp^2–sp^2 double bond) effectively prevents metal insertion into a planar amide bond.[12,13] From a synthetic standpoint, the ability to promote previously elusive transformations of amides *via* generic transition metal catalyzed activation modes with high functional group compatibility represents a significant advance for implementing neutral, bench-stable, readily accessible amides as electrophilic precursors in cross-coupling manifolds.[14] Rather not surprisingly, these results make it very clear that amide bond ground-state destabilization is required for metal insertion into the amide bond.[17] *Thus, these studies establish a strong connection between fundamental research on twisted amides and properties of non-planar amide bonds to guide the rational development of transition metal catalyzed amide bond activation reactions of general utility in organic synthesis.*[31]

2.2. Reaction optimization

Encouraged by the successful coupling of amide **1d** guided by the initial hypothesis, comprehensive optimization studies were undertaken in order to provide insights into the factors controlling this new Suzuki–Miyaura coupling protocol. Key results obtained during optimization of the reaction are presented in Tables 2–9. We chose the reaction of amide **1d** (Ar = Ph) with phenylboronic acid (**2a**, Ar = Ph) as our model system (see scheme in Table 2).

As for related cross-couplings of carboxylic acid derivatives[8a–e] we anticipated that the choice of a phosphane ligand would have a significant effect on the reaction efficiency. Evaluation of the effect of ligand on the Suzuki–Miyaura coup-

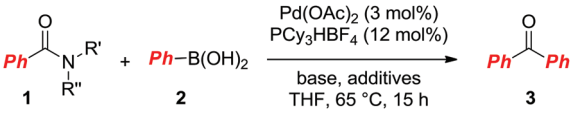
Table 2 Effect of ligands on Suzuki–Miyaura cross-coupling of amides[a]



Entry	Ligand	Yield (%)
1	PCy_3HBF_4	>95
2	PCy_3	40
3	$P(n\text{-}Bu)_3$	5
4	$PMet\text{-}Bu_2HBF_4$	80
5	PMe_3HBF_4	—
6	$P(n\text{-}Bu)_3HBF_4$	—
7	$Pt\text{-}Bu_3HBF_4$	8
8	$PCy_2(CH_2)_2PCy_2HBF_4$	—
9	$PCy_2(CH_2)_4PCy_2HBF_4$	—
10	BINAP	—
11	PCy_2Ph	56
12	$PCyPh_2$	—
13	PPh_3	7
14	$P(4\text{-}CF_3\text{-}C_6H_4)_3$	34
15	$P(4\text{-MeO-}C_6H_4)_3$	—
16	$P(2\text{-Me-}C_6H_4)_3$	—
17	$P(3\text{-Me-}C_6H_4)_3$	11
18	$P(4\text{-Me-}C_6H_4)_3$	11
19	$P(2\text{-Fur})_3$	—
20	Xphos	—
21	DIPHOS	—
22	DPPF	—
23	DPPP	10
24	DPPB	—

[a] Conditions: amide (0.2 mmol), Ph-B(OH)$_2$ (2.0 equiv.), Pd(OAc)$_2$ (3 mol%), ligand (12 mol%), (6 mol%) for chelating ligands, K_2CO_3 (2.5 equiv.), H_3BO_3 (2.0 equiv.), THF (0.25 M), 65 °C, 15 h. R′R″ = (**1d**). Conversions were determined by ^{1}H NMR or GC *vs.* internal standard.

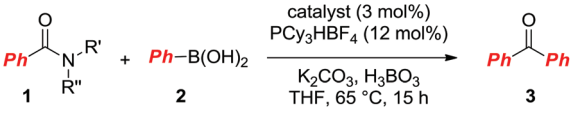
Table 3 Development of Suzuki–Miyaura cross-coupling of amides: general optimization of reaction conditions[a]



Entry	K_2CO_3 (equiv.)	Ph-B(OH)$_2$ (equiv.)	Additive	T (°C)	Yield (%)
1	—	2.0	H_2O (2.5)	65	<5
2	2.5	2.0	H_2O (2.5)	65	—
3	2.5	2.0	—	65	71
4	2.5	2.0	—	rt	8
5	2.5	2.0	H_3BO_3 (2.5)	65	>95
6	—	2.0	H_3BO_3 (2.5)	65	45
7	2.5	2.0	H_3BO_3 (2.5)	rt	83
8	2.5	1.2	H_3BO_3 (2.5)	65	93
9	2.5	2.0	H_3BO_3 (1.0)	65	70
10[b]	—	2.0	H_3BO_3 (2.5)	65	—
11[b]	2.5	2.0	H_3BO_3 (2.5)	65	—
12[c]	2.5	2.0	H_3BO_3 (2.5)	65	91

[a] Conditions: amide (0.2 mmol), Ph-B(OH)$_2$ (1.2–2.0 equiv.), Pd(OAc)$_2$ (3 mol%), ligand (12 mol%), K_2CO_3 (2.5 equiv.), additive (0–2.5 equiv.), THF (0.25 M), rt–65 °C, 15 h. R′R″ = (**1d**). Conversions were determined by ^{1}H NMR or GC *vs.* internal standard. [b] Without PCy_3HBF_4. [c] With 5.0 equiv. of H_2O.

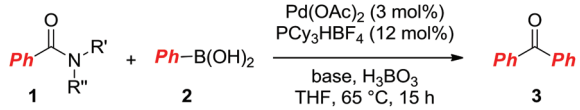
Table 4 Effect of catalysts on Suzuki–Miyaura cross-coupling of amides[a]



Entry	Catalyst	Yield (%)
1	$Pd(OAc)_2$	>95
2	$PdCl_2(PPh_3)_2$	—
3	$PdCl_2$	47
4	$Pd(dba)_2$	85
5	$Pd_2(dba)_3$	87
6	$Pd_2(dba)_3CHCl_3$	61
7	$Pd(PPh_3)_4$	—
8	Pd/C	—

[a] Conditions: amide (0.2 mmol), Ph-B(OH)$_2$ (2.0 equiv.), catalyst (3 mol%), ligand (12 mol%), K_2CO_3 (2.5 equiv.), H_3BO_3 (2.0 equiv.), THF (0.25 M), 65 °C, 15 h. R′R″ = (**1d**). Conversions were determined by ^{1}H NMR or GC *vs.* internal standard.

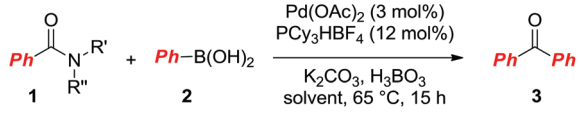
Table 5 Effect of bases on Suzuki–Miyaura cross-coupling of amides[a]



Entry	Base	Yield (%)
1	K_2CO_3	>95
2	K_2HPO_4	74
3	KH_2PO_4	76
4	KOAc	64
5	$KHCO_3$	61
6	$NaHCO_3$	70
7	$CaCO_3$	48
8	K_3PO_4	5
9	Cs_2CO_3	—
10	NaOAc	5
11	KF	—
12	—	47
13[b]	K_2CO_3	89

[a] Conditions: amide (0.2 mmol), Ph-B(OH)$_2$ (2.0 equiv.), Pd(OAc)$_2$ (3 mol%), ligand (12 mol%), base (2.5 equiv.), H_3BO_3 (2.0 equiv.), THF (0.25 M), 65 °C, 15 h. R′R″ = (**1d**). Conversions were determined by ^{1}H NMR or GC *vs.* internal standard. [b] K_2CO_3 (1.0 equiv.).

Table 6 Effect of solvents on Suzuki–Miyaura cross-coupling of amides[a]

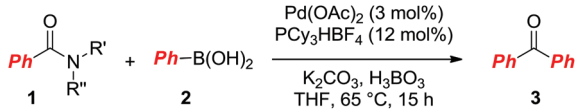


Entry	Solvent	Yield (%)
1	THF	>95
2	Toluene	84
3	Dioxane	82
4	Acetone	64
5	Benzene	75
6	CH_3CN	42
7	DMSO	24

[a] Conditions: amide (0.2 mmol), Ph-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.), solvent (0.25 M), 65 °C, 15 h. R′R″ = (**1d**). Conversions were determined by ^{1}H NMR or GC *vs.* internal standard.

ling of amides is presented in Table 2. Among a variety of phosphane ligands screened, PCy_3HBF_4 provided optimal results (entry 1). Notably, the phosphonium salt[32] showed higher efficiency than in the absence of cocatalytic additive (entries 1 and 2). A range of other phosphane ligands furnished the desired Suzuki–Miyaura coupling product in promising yields (entries 4, 11, 14); however, it appears that both steric and electronic effects play a critical role in the observed coupling. As shown, increasing steric demand around the metal center resulted in a decrease of the coupling selectivity (*e.g.* P*t*-Bu$_3$, entry 7; PM*et*-Bu$_2$, entry 4). However, less sterically demanding and bidentate alkyl phosphane ligands (*e.g.* P*n*-Bu$_3$, entry 3; PMe_3, entry 5; dcpe, entry 8) also resulted in a dramatic decrease in efficiency, showing that subtle changes in the ligand structure influence elementary steps of the C–N coupling. The latter may suggest that a trans configuration of the ligand is required for the efficient coupling, albeit this points requires further study. Moreover, the coupling was achieved using the aromatic diphosphane ligand PCy_2Ph (entry 11). Strikingly, the related $PCyPh_2$ did not generate substantial amounts of the ketone product (entry 12). Steric hin-

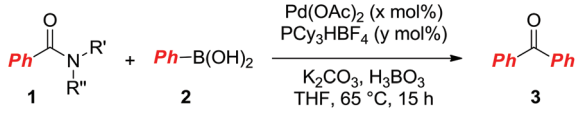
Table 7 Effect of solvent concentration on Suzuki–Miyaura cross-coupling of amides[a]



Entry	Concentration (M)	Yield (%)
1	0.05	20
2	0.10	80
3	0.25	>95
4	1.0	49

[a] Conditions: amide (0.2 mmol), Ph-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 (x M), 65 °C, 15 h. R′R″ = (**1d**). Conversions were determined by ^{1}H NMR or GC *vs.* internal standard.

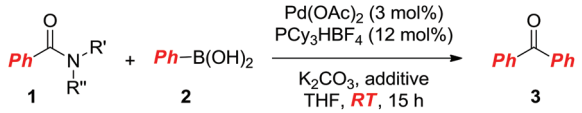
Table 8 Effect of catalyst/ligand stoichiometry on Suzuki–Miyaura cross-coupling of amides[a]



Entry	$Pd(OAc)_2 : PCy_3HBF_4$ ($x : y$)	Yield (%)
1	1 : 1	65
2	1 : 2	60
3	1 : 3	93
4	1 : 4	>95
5	1 : 5	68

[a] Conditions: amide (0.2 mmol), Ph-B(OH)$_2$ (2.0 equiv.), Pd(OAc)$_2$ (3 mol%), ligand (y mol%), K_2CO_3 (2.5 equiv.), H_3BO_3 (2.0 equiv.), THF (0.25 M), 65 °C, 15 h. R′R″ = (**1d**). Conversions were determined by ^{1}H NMR or GC *vs.* internal standard.

Table 9 Effect of additives on Suzuki–Miyaura cross-coupling of amides at room temperature[a]



Entry	Additive	Yield (%)	pK_a
1	*p*-Nitrobenzoic acid	45	3.41
2	*o*-Nitrobenzoic acid	93	2.16
3	*o*-Phenylbenzoic acid	83	3.46
4	*o*-Methylbenzoic acid	<2	3.91
5	*o*-Methoxybenzoic acid	39	4.08
6	Benzoic acid	13	4.19
7	Acetic acid	<2	4.75
8[b]	*o*-Nitrobenzoic acid	9	2.16

[a] Conditions: amide (0.2 mmol), Ph-B(OH)$_2$ (2.0 equiv.), Pd(OAc)$_2$ (3 mol%), ligand (12 mol%), K_2CO_3 (2.5 equiv.), additive (2.0 equiv.), THF (0.25 M), rt, 15 h. R′R″ = (**1d**). Conversions were determined by ^{1}H NMR or GC *vs.* internal standard. [b] 2-Nitrobenzoic acid (0.2 equiv.).

drance on the aromatic monophosphane ligands had a significant influence on the coupling (tri(*o*-tolyl)phosphane, entry 16), while higher conversions were observed with tri(*m*-tolyl) phosphane (entry 17) and tri(*p*-tolyl)phosphane (entry 18), showing an increase of reactivity with small cone angles.[33] Moreover, varying the electronic property at the position *para* to the phosphorus in tri(aryl)phosphane ligands had a great impact on the reaction, with electron withdrawing substituents facilitating the coupling (entry 14), and electron donating substituents giving a trace quantity of the desired product (entry 15). The reaction with other ligands known to promote Suzuki–Miyaura coupling of related acyl electrophiles[8a–e] (entries 19–24) did not generate significant amounts of the ketone products, suggesting interplay between the steric and electronic environment of the ligand in our protocol, and emphasizing the challenge of N–C amide bond activation. Overall, the bench-stable PCy_3HBF_4 was found to be the best ligand in terms of reaction efficiency, stability and low cost, comparing very favourably with the Ni(cod)$_2$/SIPr system.[15c]

No other by-products such as decarbonylated products of over-addition products were detected in the reaction mixture.[7–10] Control experiments demonstrated that all of the reaction parameters (Pd, ligand) are essential for efficient coupling, in line with our mechanistic proposal.

Key optimization results evaluating the effect of acidic additives are presented in Table 3. In line with our original hypothesis, we anticipated that the use of acidic additives would have a significant impact on the reaction efficiency by protonating the amide nitrogen and facilitating ligand dissociation during the catalytic cycle.[16,25] Moreover, a study by Gooßen on the Suzuki–Miyaura coupling of anhydrides suggested a non-innocent behaviour of water on the catalyst turnover.[8e] In contrast, we determined that catalyst turnover was not observed under aqueous conditions and that the base was required for coupling in our case (Table 3, entries 1 and 2). Optimization of the temperature revealed that catalytic turnover of Pd ensues at room temperature, but the process was inefficient under these conditions (entries 3 and 4). Careful optimization of acidic additives revealed that H_3BO_3 gave the best results in terms of yield and reaction efficiency (entry 5, *vide infra*). Notably, under these new conditions, the base is not required for the coupling (entry 6). Remarkably, 83% yield of the ketone product was observed at room temperature (entry 7). Control experiments demonstrated that the use of acid results in high material recovery (entry 8 and 9). The coupling did not take place in the absence of phosphane ligand under these conditions (entries 10 and 11), consistent with the proposed catalytic cycle. Furthermore, the reaction was surprisingly robust in the presence of water (entry 12).[8a–e,15c] Interestingly, in contrast to previous reports on Suzuki–Miyaura coupling of anhydrides,[8e] amide recovery is observed under aqueous conditions (entries 1 and 2), highlighting a potential to achieve orthogonal cross-coupling[34] of these two classes of acyl electrophiles (entries 1and 2 *vs.* 12).

Optimization of palladium complexes is shown in Table 4. Various palladium catalysts were tested, and Pd(OAc)$_2$ showed

the best catalytic activity (entry 1). Other palladium complexes were also found to catalyze the reaction (entries 2–8). Of particular note is the fact that $Pd(PPh_3)_2Cl_2$ (entry 2) and $Pd(PPh_3)_4$ (entry 7) precatalysts failed to give the desired coupling product, in contrast to related Suzuki–Miyaura cross-coupling of acyl electrophiles. However, other Pd(II) and Pd(0) precatalysts such as $PdCl_2$, $Pd(dba)_2$, $Pd_2(dba)_3$ and $Pd_2(dba)_3$ $CHCl_3$ (entries 3–6) afforded the coupling product in good to high yields, highlighting the importance of ligand coordination to the metal center in our N–C activation protocol. The coupling with a heterogenous catalyst,[35] Pd/C (10 wt%), was ineffective (entry 8).

The effect of base on the cross-coupling of amides is summarized in Table 5. It is well-established that a choice of base plays a critical role in the Suzuki–Miyaura cross-coupling reactions.[36] We have determined that the highest yields in our palladium-catalyzed Suzuki–Miyaura coupling of amides are observed in the presence of base, with K_2CO_3 giving the best results (entry 1). Importantly, a range of bases featuring different counterions affords the coupling product in good to high yields (entries 2–7), suggesting a non-specific role of this additive. Remarkably, modest yield is still obtained in the absence of a base (entry 12), which provides an entry point to the highly useful Suzuki–Miyaura cross-coupling under neutral conditions. Interestingly, some bases were found to have a deleterious effect on the cross-coupling, thus revealing a non-innocent behaviour of the base under these conditions (entries 8–11). The coupling in a presence of only 1.0 equiv. of K_2CO_3 indicates high reactivity of the catalyst system for N–C activation (entry 13).

The effect of solvents on the Suzuki–Miyaura cross-coupling of amides is presented in Table 6. THF was found to be the optimum solvent for the reaction (entry 1). Importantly, a number of other solvents proved to be effective for the reaction, including toluene, dioxane, acetone and benzene (entries 2–5). In contrast, lower yields were obtained for reactions performed in polar solvents such as acetonitrile and DMSO (entries 5–7), suggesting incompatibility with the reagent system. Consequently, THF was selected as the best solvent for optimization experiments.

The effect of solvent concentration on the reaction efficiency is shown in Table 7. A study across four different concentrations indicated that the cross-coupling can be performed at reasonably high concentrations without any negative impact on the reaction efficiency and N–C coupling selectivity (entries 1–4).

Optimization of the palladium/phosphane ratio is presented in Table 8. The screening of five different phosphane loadings revealed that equimolar ratio is sufficient for the reaction (entry 1); however, the best results were obtained using 3 and 4 equivalents of the phosphane ligand with respect to $Pd(OAc)_2$ (entries 3 and 4). Interestingly, higher phosphane loading results in a decrease of the reaction efficiency (entry 5), which may suggest saturation of the coordination sphere of a catalytically-active Pd(0) species in the catalytic cycle.[37] Saturation of Pd(0) by additional phosphane ligands in the Suzuki–Miyaura cross-coupling of anhydrides has been reported by Yamamoto.[8a–c] The requirement for 1 equiv. of phosphane ligand in the Suzuki–Miyaura coupling of amides (entry 1) was later confirmed in the stoichiometric ESI-MS experiments (see Mechanistic studies section).

The effect of different acidic additives on the cross-coupling of amides is summarized in Table 9. The effect of the acidic additive was probed by evaluating substituted aryl carboxylic acids with varying acidity (entries 1–7). Elegant studies by Larrosa on the Pd(0)/(II)-catalyzed arylation of indoles demonstrated an inverse correlation of the reaction rate with the acid pK_a.[38] The authors proposed that the acid serves as a weakly coordinating counterion to Pd(II) forming an electrophilic Pd(II) species. Similarly, in our Suzuki–Miyaura cross-coupling of amides by N–C activation, the cross-coupling efficiency was found to be inversely proportional to the pK_a of the acid. Remarkably, the use of *o*-nitrobenzoic acid resulted in a full conversion (93% yield) at room temperature, highlighting the mild conditions of the current protocol. To our knowledge, this reaction represents the mildest conditions for the amide N–C activation/C–C cross-coupling reported to date.[14] Interestingly, a plot of yield (%) *vs.* pK_a for acids presented in Table 9 gives a linear correlation ($Y = -0.021X + 4.66$, $R^2 = 0.80$, outlier: *o*-methylbenzoic acid, discussed below), thus clearly indicating that acidity of the additive plays an important role in the amide cross-coupling. The correlation improves to $R^2 = 0.95$ excluding *o*-phenylbenzoic acid. However, several differences between the two systems can be readily noted. The indole arylation appears to be much less sensitive to steric hindrance at the *ortho* position of the acid additive than the amide cross-coupling reported herein. This is expected given different steric environment around the Pd center and the amide bond;[39,40] the protonation sites in the respective reactions. Based on the amide bond distortion and previous studies, we tentatively propose that the acid serves to protonate the nitrogen atom of the amide bond[16,25] and facilitates ligand (*i.e.* glutarimide) dissociation[27] in the catalytic cycle. The effect of acidic additives provides compelling evidence that amide N–C bond activation is distinguished from the coupling of other acyl electrophiles[1–5] and demonstrates how a judicious choice of the reaction conditions could be utilized for effecting mild N–C amide bond cleavage.

Overall, the optimization results in Tables 2–9 demonstrate the unique features of the amide N–C bond activation platform as set against other acyl electrophiles. Furthermore, the results showcase the superior reactivity of the selected amide precursor for N–C amide activation.[15a,b] The observed reactivity, including N-coordination and ligand effects, strengthens the original hypothesis on disrupting the amide bond resonance to enable low valent metal insertion into the inert amide bond.

2.3. Reaction scope

With the optimized conditions in hand, a comprehensive evaluation of preparative scope of the palladium-catalyzed Suzuki–Miyaura coupling with amides was performed. The

scope of the reaction was evaluated using a representative set of boronic acids and amide electrophiles. Moreover, the effect of electronic variation on efficiency of the cross-coupling was systematically evaluated with a range of additional examples with functionalized coupling partners. The scope of the reaction is presented in three sections: (i) the scope of the boronic acid component (Chart 1); (ii) the scope of the amide component (Chart 2); and (iii) additional examples (Chart 3). Note that additional examples of boronic acid scope are included in Chart 3.

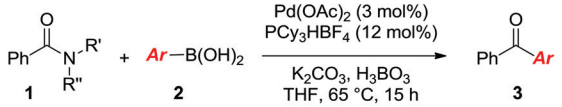
2.3.1. Scope of boronic acid component. The scope of the boronic acid component was tested using **1d** as a standard electrophile (Chart 1). As shown, the reaction tolerates a wide range of aromatic boronic acids bearing numerous sensitive functional groups (entries 1–30). Electronically-diverse boronic acids, including electron-neutral (entry 1), electron-donating (entries 2–4) and electron-withdrawing (entries 5–9) boronic acids bearing substituents at the *para*-position of the aromatic ring gave products in high to excellent yields. Importantly, the reaction tolerates a range of functional groups poised for further functionalization such as nitro (entry 6), cyano (entry 7), ester (entry 8), ketone (entry 9), vinyl (entry 10). In particular, the selective activation of the typically considered inert amide bond in the presence of ester and ketone moieties shows the synthetic potential of the amide bond activation platform. In the 4-substitued boronic acid series, the yields are generally high; however, a trend can be noted indicating that strongly electron withdrawing substituents on the boronic acid component, such as trifluoromethyl (entry 5) or cyano (entry 7) result in lower yields under these conditions. It is well-established that electron-rich aromatic systems are generally more reactive in transmetallation. Note, however, that strongly electron donating 4-MeO substituent (entry 4) and strongly electron withdrawing 4-NO_2 substituent (entry 6) gave similar yields of the ketone product, suggesting that transmetallation is not the only factor contributing to the reactivity in these couplings (see Mechanistic discussion section). Moreover, we were pleased to find that a range of electronically-varied substituents in the *meta* position of the boronic acid (Cl–, MeO–, CN–, NO_2–) gave the desired product in high yields with little or no difference in the reaction efficiency (entries 11–14), attesting to the generality of our protocol. Furthermore, steric-hindrance on the boronic acid component is well-tolerated (entry 15). The reaction could be extended to the naphthyl boronic acids with different connectivity and substitution, obtaining good yields in all cases (entries 16–18). In particular, high yield of the coupling of sterically-demanding 1-naphthyl boronic acid (entry 17) should be noted, consistent with sterically-induced reductive elimination (see Mechanistic discussion section).[41] These examples clearly differentiate our protocol from the Ni(0)/SIPr-catalyzed amide bond activation, which is sensitive to steric hindrance.[15c] The excellent chemoselectivity of our protocol was further illustrated by the coupling of medicinally relevant heteroaromatic boronic acids, such as thienyl (entries 19–21), furyl (entry 22), benzothienyl (entry 23) and indolyl (entry 24) with high reaction efficiency. Unsurprisingly, we found that for optimum results in the coupling of heteroaromatic boronic acids, the reaction conditions need to be optimized with regard to electronic properties of the boronic acid in some cases; however, a general set of conditions across heteroaromatic boronic acids was found by performing the reaction at higher temperature to facilitate the coupling. Notably, these optimized conditions tolerate unstable 2-heteroaryl boronic acids[42] (entries 20, 21 and 23), delivering products in high yields.

Limitations. Several limitations of the scope of the boronic acid component can be noted at present: (1) although mono-*ortho*-substituted boronic acids coupled in excellent yields (entries 15 and 17), 2,6-disubsitituted boronic acids are not tolerated (entry 25). These extremely sterically-hindered boronic acids are well-known to be notoriously difficult substrates for Suzuki–Miyaura reactions of aryl halides.[4a] (2) The use of aliphatic boronic acids results in the recovery of amide (entry 26). Similar to sterically-hindered boronic acids, alkyl boronic acids are well-established to be less reactive in Suzuki–Miyaura coupling reactions of aryl halides.[43] Unsurprisingly, the Suzuki–Miyaura coupling of acyl-electrophiles with alkyl boronic acids is unknown at present. (3) Boronic acids bearing strongly electron withdrawing groups are not tolerated (entries 27 and 28), which is consistent with slower transmetallation in these cases.[40] (4) Some boronic acids prone to protodeboronation are not compatible with the reaction conditions (entries 29 and 30).[42] However, the successful coupling of 2-thienyl and 2-benzothienyl boronic acids (entries 20 and 23) demonstrates that the current protocol can be extended to the sensitive substrates by fine-tuning of the reaction conditions.

Additional examples of the boronic acid substrate scope are presented in Chart 3, and include other functional groups poised for further synthetic manipulations, such as aldehyde and vinyl moieties as well as medicinally relevant 1,3-dioxolane.

Overall, the results in Chart 1 demonstrate the broad scope of this novel cross-coupling reaction with respect to the boronic acid component and compare favourably with other reported methods for cross-coupling of carboxylic acid derivatives.[5] The scope of the boronic acid component is the broadest reported to date for Suzuki–Miyaura ketone synthesis by N–C amide activation.[15]

2.3.2. Scope of amide component. Next, we turned our attention to the scope of amides that can participate in this new cross-coupling protocol (Chart 2). The scope of amides was evaluated using phenylboronic acid as a standard nucleophile (entries 1–20). As shown, the scope of the amide component is also very broad. Aromatic amides containing electron-neutral (entry 1), electron-donating (entries 2 and 3) and electron-withdrawing (entries 4–8) substituents at the *para*-position coupled in high to excellent yields. Particularly noteworthy is the functional group tolerance of our protocol, accommodating ester (entry 5), ketone (entry 6), nitrile (entry 7) and nitro (entry 8) moieties. In these cases, complete selectivity for activation of the typically inert amide N–C bond was observed, underscoring the synthetic potential of this cross-



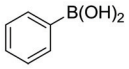
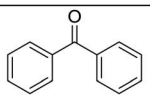
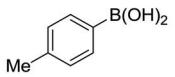
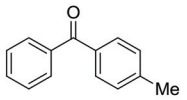
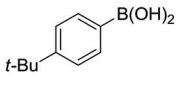
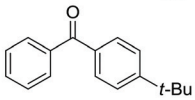
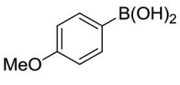
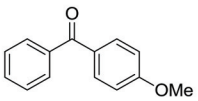
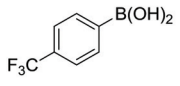
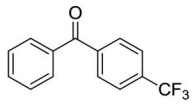
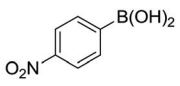
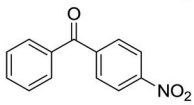
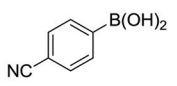
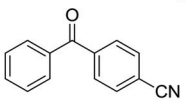
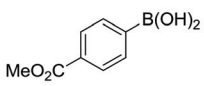
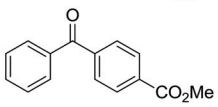
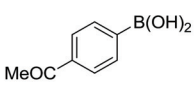
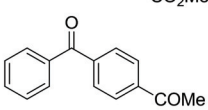
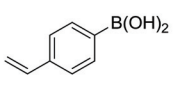
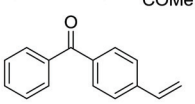
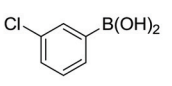
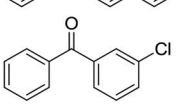
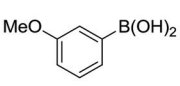
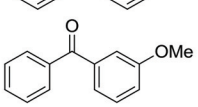
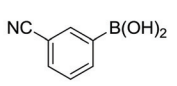
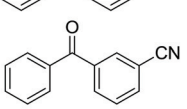
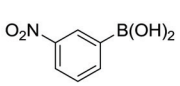
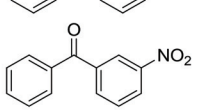
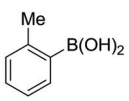
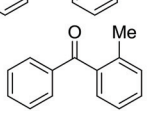
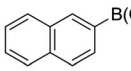
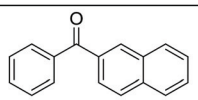
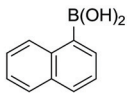
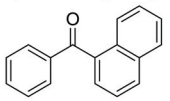
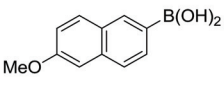
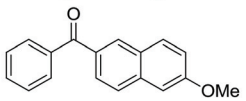
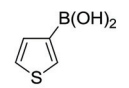
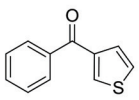
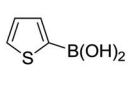
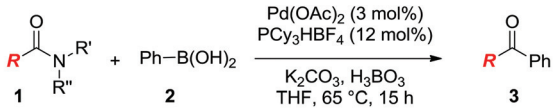
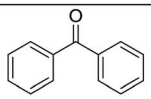
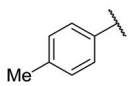
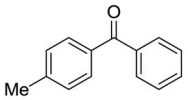
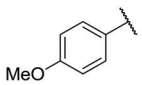
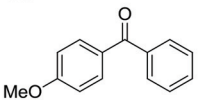
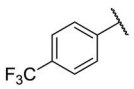
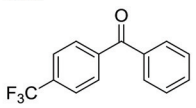
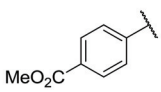
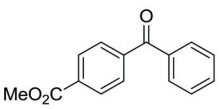
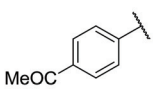
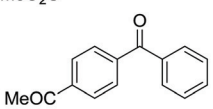
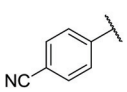
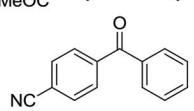
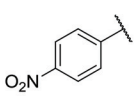
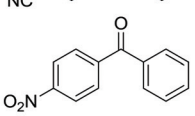
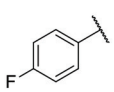
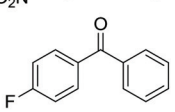
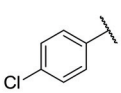
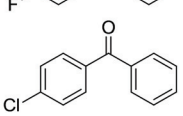
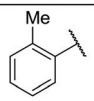
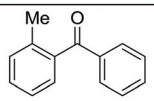
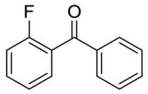
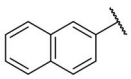
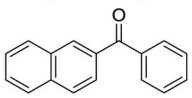
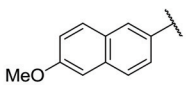
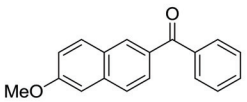
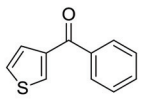
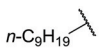
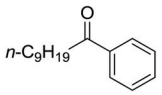
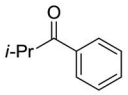
Entry	Boronic Acid	3	Product	Yield (%)
1		**3a**		95
2		**3b**		71
3		**3c**		82
4		**3d**		81
5		**3e**		61
6		**3f**		82
7		**3g**		42
8[b]		**3h**		62
9		**3i**		81
10		**3j**		79
11		**3k**		69
12		**3l**		86
13		**3m**		71
14		**3n**		69
15		**3o**		99
16		**3p**		76
17		**3q**		93
18		**3r**		81
19		**3s**		74
20		**3t**		54
21[b]		**3u**		81 (67)[c]
22[b]		**3v**		90 (41)[c]
23[b]		**3w**		87 (71)[c]
24[b]		**3x**		72
25		**3ya**	-	<5
26		**3ta**	-	<5
27		**3ua**	-	<5
28		**3va**	-	<5
29		**3wa**	-	<5
30		**3xa**	-	<5

Chart 1 Palladium-catalyzed Suzuki–Miyaura coupling of amides: boronic acid scope. Conditions: amide (0.2 mmol), Ph-B(OH)$_2$ (1.2 equiv.), Pd(OAc)$_2$ (3 mol%), ligand (12 mol%), K_2CO_3 (2.5 equiv.), H_3BO_3 (2.0 equiv.), THF (0.25 M), 65 °C, 15 h. R′R″ = (**1d**). Isolated yields. [a] 4-CF$_3$-C$_6$H$_4$ amide. [b] 120 °C. [c] Yield at 65 °C. See ESI† for full experimental details.



Entry	Amide (R)	3	Product	Yield (%)
1		**3a**		95
2		**3b'**		81
3		**3d'**		99
4		**3e'**		93
5		**3h'**		68
6		**3i'**		51
7		**3g'**		95
8		**3f'**		80
9		**3y**		95
10		**3z**		78
11		**3o'**		84
12		**3aa**		65
13		**3p'**		83
14		**3r'**		78
15		**3s'**		83
16[a]		**3ab**		51
17		**3ac**		75
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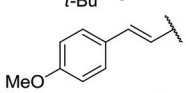
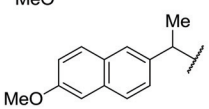
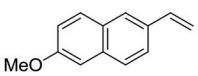
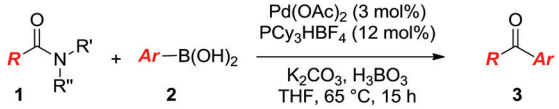
19		**3za**	-	<5
20		**4**		53

Chart 2 Palladium-catalyzed Suzuki–Miyaura coupling of amides: amide scope. Conditions: amide (0.2 mmol), Ph-B(OH)$_2$ (1.2 equiv.), Pd(OAc)$_2$ (3 mol%), ligand (12 mol%), K_2CO_3 (2.5 equiv.), H_3BO_3 (2.0 equiv.), THF (0.25 M), 65 °C, 15 h. R'R'' = (**1d**). Isolated yields. [a] 120 °C. See ESI† for details.

coupling activation platform. The resulting products are versatile precursors to a wide range of medicinally-relevant heterocycles. Moreover, this protocol could be further applied to substrates bearing *para*-fluoro and even *para*-chloro substituents on the aromatic ring (entries 9 and 10). To our knowledge, the functional group tolerance for aryl chlorides in Suzuki–Miyaura ketone synthesis with acyl electrophiles is uncommon, thus providing a handle for further manipulation and attesting to the unique potential of the amide bond N–C activation platform. This feature distinguishes our protocol from the related N–C amide bond Suzuki–Miyaura reactions reported by Zou[15d] and Garg.[15c] Moreover, steric hindrance in the *ortho*-position on the aromatic ring is well-tolerated (entry 11) as are coordinating substituents (entry 12). Furthermore, electronically-differentiated naphthyl (entries 13 and 14) and heteroaromatic amides (entry 15) underwent coupling with high reaction efficiency. Note that the presence of the ether moiety on the naphthyl ring provides functional handle for C–O Suzuki–Miyaura aryl couplings, which are particularly facile for ketone containing substrates.[44] Moreover, we were pleased to find that primary and secondary aliphatic amides can also be accommodated by our protocol (entries 16 and 17), affording the ketone product in good yields. Alkyl amides have not been reported in the Ni(0)/SIPr-catalyzed Suzuki–Miyaura amide synthesis,[15c] while these substrates can be coupled using Pd-catalyzed protocols,[15d] providing yet another advantage of Pd-catalysis in the activation of inert amide N–C bonds.



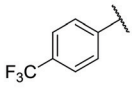
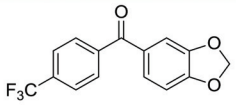
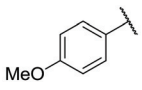
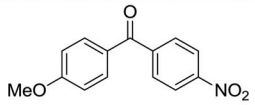
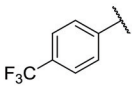
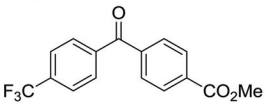
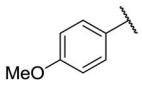
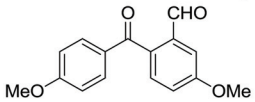
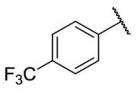
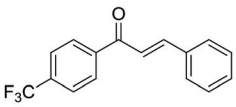
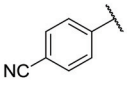
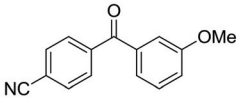
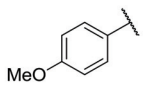
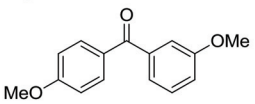
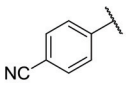
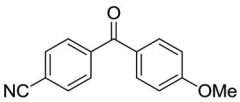
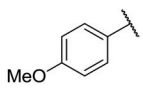
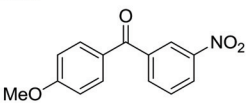
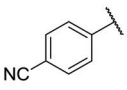
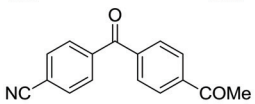
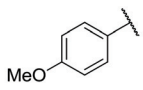
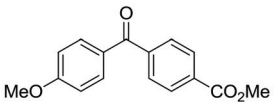
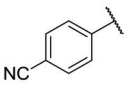
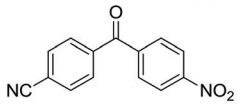
Entry	Amide (R)	3	Product	Yield (%)	Entry	Amide (R)	3	Product	Yield (%)
1		**3ad**		83	7		**3aj**		57
2		**3ae**		62	8[a]		**3ak**		91 (60)[b]
3		**3af**		80	9		**3al**		99
4		**3ag**		99	10		**3am**		88
5		**3ah**		76	11		**3an**		36
6		**3ai**		59	12		**3ao**		<20

Chart 3 Palladium-catalyzed Suzuki–Miyaura coupling of amides: additional examples scope. See Charts 1 and 2. [a] 120 °C. [b] Yield at 65 °C.

Limitations. Several limitations of our protocol with respect to the amide component can be noted at present: (1) tertiary aliphatic amides are unreactive under our optimized reaction conditions, resulting in quantitative recovery of the amide (entry 18). This provides a chemoselective reagent system that distinguishes between functional groups with apparently similar reactivity.[34] By contrast, the protocol reported by Zou is non-selective in the coupling of aliphatic amides.[15d] (2) Vinylamides are not compatible with our reaction conditions (entry 19). It is well-established that styryl-acyl electrophiles are much less reactive in related Suzuki–Miyaura cross-couplings of acyl electrophiles[8a–c] due to olefin coordination to the palladium center.[45] (3) Substrates bearing activated β-hydrogens undergo side reactions, with the major pathway proceeding *via* thermodynamic tandem decarbonylation/β-hydride elimination (entry 20). Decarbonylation, followed by β-hydride elimination has been reported in related reactions of aliphatic carboxylic acid derivatives.[46] The high efficiency of this process bodes well for the application of the current protocol to biomass degradation to give styrenes *via* amide intermediates.[46a] Divergent elimination/cross-coupling of such activated amides is currently under investigation in our laboratory.

Overall, the examples presented in Chart 2 demonstrate the generality and efficiency of this new cross-coupling. Notably, numerous examples demonstrate that the same ketone product can be accessed by either boronic acid (Chart 1) or amide disconnection (Chart 2), which allows to select the most economically-viable precursor for the synthesis, and highlights the robustness of our protocol.

2.3.3 Scope of additional examples. Additional examples of the Suzuki–Miyaura cross-coupling of amides are shown in Chart 3. Evaluation of the cross-coupling scope with respect to additional examples was performed to systematically probe the effect of electronic variation on both coupling partners on efficiency of the cross-coupling (entries 1–12). As shown, the coupling of amide bearing electron-withdrawing CF_3-substituent at the *para*-position of the aromatic ring with electron-rich, electron-deficient and electron-neutral boronic acid furnished the ketone products in good to high yields (entries 1–3). Similarly, the coupling of an electron-rich aromatic amide with electron-rich (entry 4), highly electron-deficient (entries 5–7) and highly sensitive (entry 8) boronic acids posed no significant problems. Of note is the reaction efficiency using boronic acids with complementary substitution of the highly electron-withdrawing NO_2 substituent (entries 5 *vs.* 7), which mirrors the effects observed in Chart 1 (entries 6 *vs.* 14).

The high reaction efficiency with electron-rich amides is unexpected. It is well-established that electron-rich electrophiles are generally much slower for oxidative addition (see Mechanistic discussion section).[40] Furthermore, highly electron deficient aromatic amide bearing CN substituent underwent cross-coupling with electron-rich boronic acids in excellent yields (entries 9 and 10), demonstrating that our protocol accommodates simultaneous variation of electron-

deficient and electron-donating substituents on both coupling partners.

Note that Chart 3 also includes other functionalized boronic acids that give ketone products poised for further synthetic manipulations such as vinyl (entry 3) and even aldehyde (entry 8) moieties, as well as medicinally relevant heterocycles (1,3-dioxolane, entry 1).

Limitations. At present the reaction is not compatible with cross-coupling of highly electron-deficient amides with highly-electron-deficient boronic acids (entries 11 and 12), which could be explained by slow transmetallation, leading to side-reactions. This is the only combination of substrates that has been found to result in low reaction efficiency using our protocol to date.

Taken together, the examples summarized in Charts 1–3 present a variety of functionalized boronic acids that could be coupled with a broad range of distorted amides *via* amide N–C bond activation platform.

2.4. Evaluation of the utility in organic synthesis

The reaction should be benchmarked against: (i) Suzuki–Miyaura cross-coupling of traditional acyl electrophiles; and (ii) Suzuki–Miyaura cross-coupling of amides.

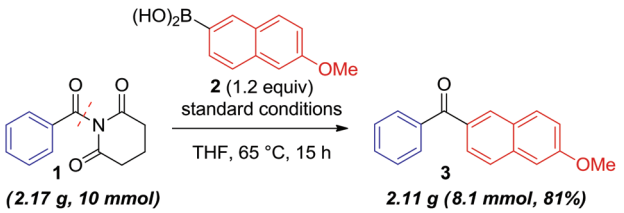
The palladium-catalyzed Suzuki–Miyaura ketone synthesis from acyl electrophiles (R–C(O)–X, X = Cl, SR, OR) has been reported.[5,7–10] The palladium[15d] and nickel[15c,d] catalyzed Suzuki–Miyaura ketone synthesis of amides has been reported at the same time as our initial report. The advantages and disadvantages of the three methods reported almost simultaneously by us, Zou and Garg (Fig. 3) have been thoroughly discussed in the introduction and throughout the substrate scope discussion.

Several important points pertaining to the advantages of the Suzuki–Miyaura ketone synthesis by N–C amide bond activation using the method described herein should be noted:

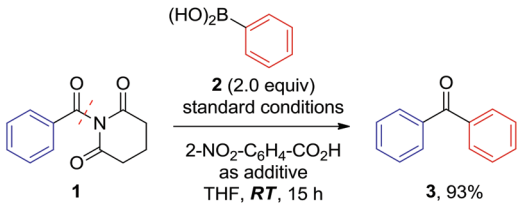
(1) The Suzuki–Miyaura cross-coupling of amides utilizing our protocol entails all advantages of using amides as neutral, bench-stable, and readily-available precursors in organic synthesis. Amide synthesis by direct condensation of carboxylic acids leads towards a waste-minimized process. Moreover, since *N*-acylation of amides is well-established,[23] the present method can be used to convert RC(O)–NH_2 bonds into ketones in late synthetic stages.

(2) The protocol is user-friendly and operationally simple. The reaction employs air-stable and commercially available catalysts, ligands and reagents. In addition, the reaction shows high tolerance to water. Taken together, these factors compare very favourably with $Ni(cod)_2$-catalyzed processes,[15c] and the use of moisture sensitive acyl chlorides[7] and anhydrides[8] as acyl electrophiles in palladium-catalyzed protocols.

(3) The reaction shows high functional group tolerance, which is superior not only to other examples of N–C bond activation, but also compares very favourably with more established processes such as Liebeskind–Srogl coupling of neutral substrates.[9] Note that the latter process typically employs stoichiometric amount of copper or complex molecular templates.



Scheme 2 Gram scale Suzuki–Miyaura ketone synthesis from amides.



Scheme 3 Room temperature Suzuki–Miyaura ketone synthesis from amides.

(4) The Suzuki–Miyaura cross-coupling of amides utilizing our protocol can be executed on a gram-scale without a noticeable decrease in yield (Scheme 2), demonstrating robustness of the method.

(5) The Suzuki–Miyaura cross-coupling of amides using our protocol can be accomplished under exceedingly mild conditions at room temperature (Scheme 3). This is the lowest temperature for the amide N–C bond activation/C–C cross-coupling reported to date.[14] We believe that the exceptional functional group tolerance of our protocol is also related to ease of the N–C amide bond activation by our catalyst system.

(6) Our preliminary experiments demonstrated that the Suzuki–Miyaura cross-coupling of amides can be accomplished in high yields under neutral, base-free, acid-free conditions (not shown). This finding sets the stage for the cross-coupling of sensitive substrates, including enantiomerically-enriched peptidyl amides.[13]

(7) Most importantly, the Suzuki–Miyaura cross-coupling of amides by N–C activation by distortion outlines a concept and introduces a strategy for the generic activation mode of amide bonds by transition metal catalysis. We have clearly defined and demonstrated that in order to achieve metal insertion into the amide N–C bond, the amide bond conjugation must be disrupted (Scheme 1, Introduction). Accordingly, fully-tuneable N–C amide bond activation controlled by distortion is possible, which allows to (i) differentiate between apparently similar functional groups, including amide functional groups (see Scheme 5, Mechanistic studies); (ii) identify a specific catalyst system that would distinguish between apparently similar amide functional groups for a desired transformation.[34] Based on this concept, a range of other transition metal catalyzed reactions of amide bonds is to be expected.

2.5. Mechanistic studies

Studies were conducted to gain preliminary insight into the reaction mechanism. Specifically, a series of experiments was performed in order to elucidate relative reactivity of the reaction components and gather evidence for direct Pd insertion into the amide N–C bond. An in-depth mechanistic discussion will be a subject of a separate report.

(1) A Hammett correlation study, employing cross-coupling of differently substituted amides **1d** with phenylboronic acid, showed a large positive ρ-value of 2.06 (R^2 = 0.94) (Fig. 4), which can be compared with the ρ-value of 0.89 for the palladium-catalyzed Suzuki–Miyaura coupling of benzoic anhydrides[8b] using $PhB(OH)_2$ and the ρ-value of 2.0 for the nickel-catalyzed Suzuki–Miyaura coupling of aryl tosylates[47] using 4-TolB$(OH)_2$. In addition, a good correlation was obtained by plotting $\log(k_{obs})$ *vs.* Hammett–Brown σ^+ constants (ρ-value of 1.31, R^2 = 0.99), which suggests that resonance effects are involved in stabilization of the reactive center. The large positive ρ-value suggests that electron-deficient arenes are inherently more reactive substrates, consistent with metal insertion into the N–C(O) bond. As expected, electron-withdrawing groups facilitate oxidative addition; resonance effects are involved in stabilization of the acyl-Pd(II) intermediate.

(2) A Hammett correlation study, employing cross-coupling of differently substituted aryl boronic acids with phenyl amide **1d**, showed a small positive ρ-value of 0.24 (R^2 = 0.99) (Fig. 5), which can be compared with the ρ-value of 0.72 for the palladium-catalyzed Suzuki–Miyaura coupling of boronic acids with acetic benzoic anhydride[8c] and the ρ-value of 0.81 for the nickel-catalyzed Suzuki–Miyaura coupling of phenyl tosylate.[47] Plotting of $\log(k_{obs})$ *vs.* Hammett-Brown σ^+ constants gives a ρ-value of 0.14, R^2 = 0.87). A small positive ρ-value indicates that electron deficient boronic acids are more reactive in the cross-coupling. This electronic effect has been described in the literature and is consistent with coordination of the amino group to boronic acids with high Lewis acidity.[48]

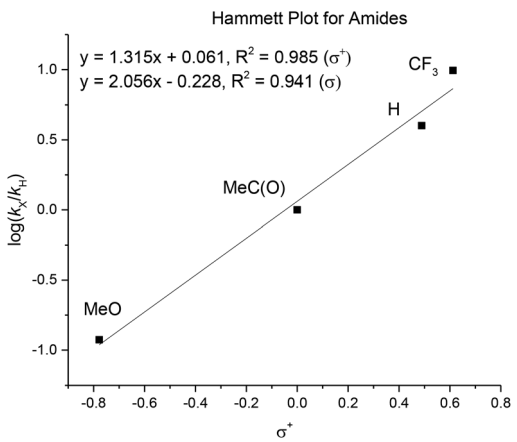


Fig. 4 Plot of log *k* *vs.* σ^+ for Suzuki–Miyaura arylation of amides with boronic acids: effects of substituents on aryl amide.

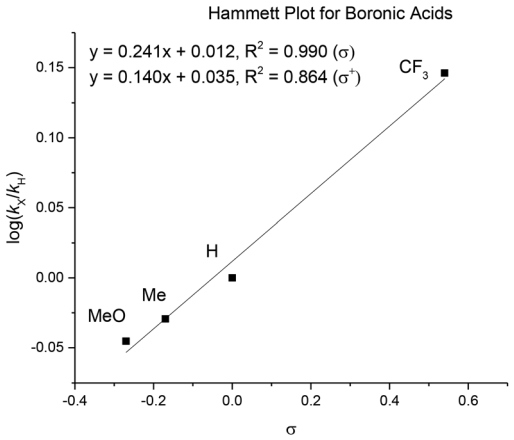
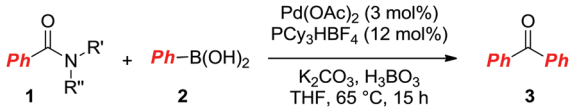


Fig. 5 Plot of log *k* *vs.* σ for Suzuki–Miyaura arylation of amides with boronic acids: effects of substituents on boronic acid.

Table 10 Effect of base/boronic acid stoichiometry on the reaction rate[a]



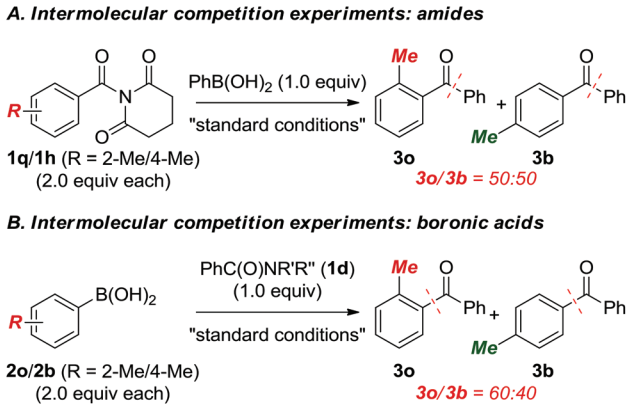
Entry	K_2CO_3 (equiv.)	Ph-B$(OH)_2$ (equiv.)	Time (h)	Conversion (%)
1	1.5	2.0	2	54
2	3.0	4.0	2	98

[a] Conditions: amide (0.2 mmol), Ph-B$(OH)_2$ (2.0–4.0 equiv.), $Pd(OAc)_2$ (3 mol%), ligand (12 mol%), K_2CO_3 (1.5–3.0 equiv.), H_3BO_3 (2.0 equiv.), THF (0.25 M), 65 °C, 2 h. R′R″ = (**1d**).

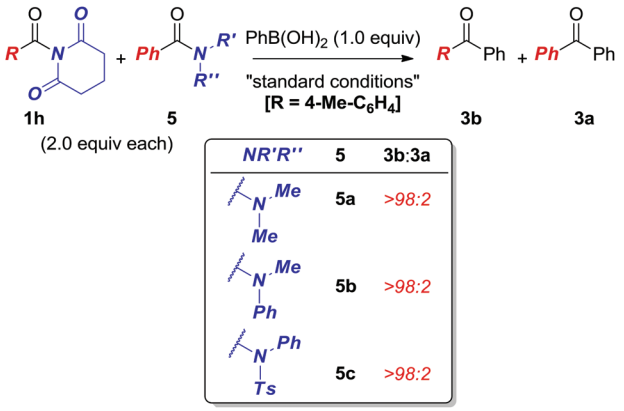
(3) To gain insight into the factors involved in transmetallation, cross-coupling of amide **1d** with phenylboronic acid with the increasing amount of base and boronic acid was performed (Table 10). As shown, the cross-coupling proceeds more rapidly when the amount of boronic acid and base is increased (K_2CO_3, 2.0 equiv., $PhB(OH)_2$, 1.5 equiv., 2 h, 54% conversion; K_2CO_3, 4.0 equiv., $PhB(OH)_2$, 3.0 equiv., 2 h, >98% conversion), consistent with the importance of transmetallation in the catalytic cycle.[49]

(4) Intermolecular competition experiments with sterically-hindered amides and boronic acids were carried out to determine the relative reactivity of sterically-hindered substrates (Scheme 4). These experiments revealed that the sterically-hindered 2-tolyl amide and the prototype 4-tolyl amide react at a similar rate (Scheme 4A), while sterically-hindered nucleophiles react preferentially (Scheme 4B). These effects are consistent with sterically-induced reductive elimination.[41]

(5) Catalyst turnover number (TON) in the cross-coupling of amide **1d** with phenylboronic acid of 320–350 at 0.1–0.2 mol% $Pd(OAc)_2$ loading was determined (Table 11). The observed reactivity compares favourably with the previously reported

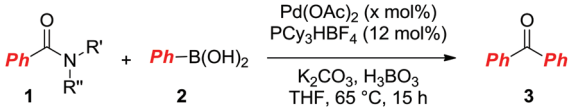


Scheme 4 Relative reactivity of hindered substrates in Suzuki–Miyaura ketone synthesis *via* N–C activation: (a) amides. (b) boronic acids.



Scheme 5 Relative reactivity experiments between amide (**1d**) and planar amides and non-planar amides reported to undergo N–C activation.

Table 11 Determination of catalyst turnover number[a]



Entry	$Pd(OAc)_2$ (mol%)	Yield (%)	TON
1	3.0	>98	33
2	0.2	69	345
2	0.1	32	320

[a] Conditions: amide (0.2 mmol), Ph-$B(OH)_2$ (2.0 equiv.), $Pd(OAc)_2$ (x mol%), ligand (12 mol%), K_2CO_3 (2.5 equiv.), H_3BO_3 (2.0 equiv.), THF (0.25 M), 65 °C, 15 h. R′R″ = (**1d**).

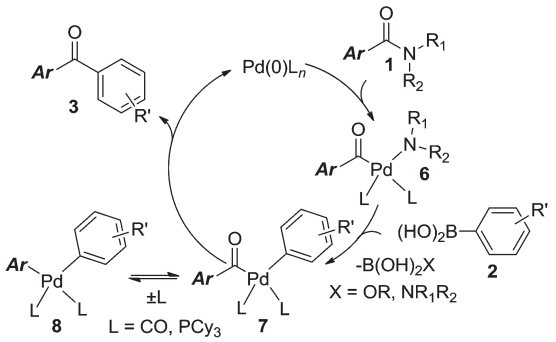
examples of Suzuki–Miyaura cross-coupling of carboxylic acid derivatives, and indicates highly efficient catalysis.[7–10] This is the highest TON observed to date for N–C amide bond activation.[14,15h]

(6) Competition experiments established the following order of reactivity in the palladium-catalyzed Suzuki–Miyaura coupling of amide **1d** with phenylboronic acid: Ph–I > Ph–Br > Ph–$C(O)NR_2$ ≫ Ar–Cl (see ESI†). Moreover, we established the following reactivity order of carboxylic acid electrophiles: Ar–$C(O)NR_2$ ≈ $(Ar–CO)_2O$ ≫ Ar–CO_2R (see ESI†). These experiments attest to the high reactivity of the selected amide precursor.[15a,b]

(7) Complete selectivity for the cross-coupling of sterically-distorted amide **1d** in the presence of planar amides (*N*,*N*-dimethylbenzamide),[12] as well as amides previously reported to undergo N–C activation under nickel[15c] and palladium[15d] catalysis is observed (Scheme 5). The low reactivity of amides **5** was confirmed in individual experiments using our catalyst system, in which full recovery of these amides was observed. Thus, synthetically valuable chemoselective cross-coupling of amides **1d** in the presence of planar and other non-planar amides can be readily achieved under our optimized conditions.

(8) Electrospray ionization mass spectrometry (ESI/MS) analysis of the reaction between amide **1d** and the developed catalyst system using stoichiometric palladium was performed (see ESI†).[50] Intermediates corresponding to acyl-Pd species containing a single phosphane ligand, as well as aryl-Pd species were detected, consistent with the optimization studies. Notably, this is the first experimental evidence for direct Pd(0) insertion into the inert amide N–C bond. The propensity of acyl-Pd intermediates to undergo decarbonylation is well-established.[40]

2.5.1. Proposed mechanism. A possible mechanism is presented in Scheme 6. The first step involves oxidative addition of Pd(0) into the amide N–C bond to afford acyl-Pd(II) intermediate. Step two of the proposed catalytic cycle involves ligand exchange and transmetallation to give acyl-palladium intermediate, which equilibrates with aryl-palladium(II) species.[40] The final step involves base-mediated C–C bond formation by reductive elimination to afford the ketone product and regenerate the catalyst. An alternative mechanism involving Pd(II) cycle[51] can be ruled out on the basis of ESI/MS experiments and control experiments using conditions typical for Pd(II) catalytic cycle.



Scheme 6 Proposed mechanism of palladium-catalyzed Suzuki–Miyaura ketone synthesis from amides *via* N–C activation.

The key step in the mechanism is activation of the amide N–C bond. In the cross-coupling, acid coordination to the amidic nitrogen appears to play a substantial role in assisting the N–C cleavage. The high chemoselectivity for the N–C(O) activation results from ground state destabilization of the amide bond. Cleavage of the alternative R–NC(O) bond is not observed. In the acyl-Pd intermediate, ligand dissociation is favoured by low nucleophilicity of amines that are eliminated, and by coordination of acid to the Lewis basis nitrogen, enhancing the overall N–C(O) cleavage selectivity. Based on the mechanistic studies, we tentatively propose that transmetallation and ligand dissociation may be kinetically relevant steps in the cross-coupling.[52] Further in-depth studies are currently ongoing to clarify this mechanism.

3. Conclusions

3.1. Method

In conclusion, we have reported the first palladium-catalyzed Suzuki–Miyaura cross-coupling of amides with boronic acids for the synthesis of ketones by sterically-controlled N–C bond activation. The method provides versatile ketone products in excellent yields from readily available amides, tolerates a wide range of functional groups, steric hindrance and electronic variation on both coupling partners, including an array of sensitive functionalities (ester, ketone, aldehyde, cyano, nitro, chloride, olefin, heterocycles), and is characterized by operational simplicity utilizing bench-stable, commercially available reagents and catalysts. The scope and limitations of this methodology were presented in the synthesis of >60 functionalized ketones. Mechanistic studies provided insight into the catalytic cycle of the cross-coupling, including the first experimental evidence for Pd insertion into the amide N–C bond. The synthetic utility was further showcased by a gram-scale cross-coupling and cross-coupling at room temperature. Furthermore, catalyst turnover number of >300 was demonstrated for the reaction.

3.2. Generic mode of activation

We have outlined a strategy for transition metal catalyzed activation of amide N–C bonds. The large rotation barrier around planar N–C amide bonds (amide bond resonance of 15–20 kcal mol^{-1}) resulting from the partial double bond character of amides (approx. 40% sp^2–sp^2 double bond) renders metal insertion into the amide bond energetically unfavourable. Thus, in order to achieve metal insertion into the amide N–C bond, the amide bond $n_N \rightarrow \pi_{C=O}^*$ conjugation must be disrupted. Beyond any reasonable doubt, this represents a new generic activation mode of amide bonds because the acylmetal species generated by metal insertion can be utilized across many transition metal catalyzed reactions in organic synthesis, as already demonstrated by us and others. Based on our results and literature precedents, we propose that amide bond distortion (transient or permanent) of approximately 50° (additive distortion parameter, $\sum\tau + \chi_N$) is required for productive metal insertion into the amide bond. Fundamental studies on twisted amides and properties of non-planar amide bonds will guide the rational development of transition metal catalyzed amide bond activation reactions of general utility in organic synthesis.

3.3. Potential benefits

In light of the key role of amides as bench-stable intermediates in organic chemistry and the importance of amides in biology as building blocks of proteins and peptides, we are convinced that the field of transition metal catalyzed amide bond activation will become a major field of research. In addition to polymer and fine-chemical industry, at present, reactions involving amide bonds account for 20% of all reactions performed in pharmaceutical research laboratories world-wide, with the amide functional group present in 55% of potential pharmaceuticals.[53] Clearly, practical, direct and catalytic methods for amide bond manipulation are in great demand.

Further investigations into activation of inert bonds by transition metal catalysis are underway in our laboratory.

4. Experimental section

4.1. General methods

All starting materials reported in the manuscript have been previously described in literature or prepared by the method reported previously. Amides were prepared by standard methods. All experiments involving palladium were performed using Schlenk or glovebox techniques under argon or nitrogen atmosphere unless stated otherwise. All solvents were purchased at the highest commercial grade and used as received or after purification by passing through activated alumina columns or distillation from sodium/benzophenone under nitrogen. All chemicals were purchased at the highest commercial grade and used as received. Reaction glassware was oven-dried at 140 °C for at least 24 h or flame-dried prior to use, allowed to cool under vacuum and purged with argon (three cycles). ^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on Bruker spectrometers at 500 (^{1}H NMR) and 125 MHz (^{13}C NMR). All shifts are reported in parts per million (ppm) relative to residual $CHCl_3$ peak (7.27 and 77.2 ppm, ^{1}H NMR and ^{13}C NMR, respectively). All coupling constants (J) are reported in hertz (Hz). Abbreviations are: s, singlet; d, doublet; t, triplet; q, quartet; brs, broad singlet. GC-MS chromatography was performed using Agilent HP6890 GC System and Agilent 5973A inert XL EI/CI MSD using helium as the carrier gas at a flow rate of 1 mL min^{-1} and an initial oven temperature of 50 °C. High-resolution mass spectra (HRMS) were measured on a 7 T Bruker Daltonics FT-MS instrument. All flash chromatography was performed using silica gel, 60 Å, 300 mesh. TLC analysis was carried out on glass plates coated with silica gel 60 F254, 0.2 mm thickness. The plates were visualized using a 254 nm ultraviolet lamp or aqueous potassium permanganate solutions. ^{1}H NMR, ^{13}C NMR, MS and HRMS data are given for all

compounds in the ESI† Experimental for characterization purposes.

4.2. General procedure for amide synthesis

An oven-dried round-bottomed flask (100 mL) equipped with a stir bar was charged with amine (8.84 mmol, 1.0 equiv.), triethylamine (2.0 equiv.), 4-dimethylaminopyridine (0.25 equiv.) and dichloromethane (50 mL), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Acyl chloride (typically, 1.1 equiv.) was added dropwise to the reaction mixture with vigorous stirring at 0 °C, and the reaction mixture was stirred overnight at room temperature. After the indicated time, the reaction mixture was diluted with Et_2O (20 mL) and filtered. The organic layer was washed with HCl (1.0 N, 30 mL), brine (30 mL), dried, and concentrated. The crude product was purified by recrystallization to give analytically pure amide.

4.3. General procedure for Pd-catalyzed Suzuki–Miyaura coupling

An oven-dried vial equipped with a stir bar was charged with an amide substrate (1.0 equiv.), potassium carbonate (2.5 equiv.), boric acid (2.0 equiv.), boronic acid (1.2 equiv.), $Pd(OAc)_2$ (0.03 equiv.), and PCy_3HBF_4 (0.12 equiv.), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. Tetrahydrofuran (0.80 mL) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 65 °C, and stirred for the indicated time at 65 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^1H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain selectivity, conversion and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel afforded the title product.

4.4. Representative procedure for large-scale coupling

An oven-dried 100 mL round-bottomed flask equipped with a stir bar was charged with 1-benzoylpiperidine-2,6-dione (2.17 g, 10 mmol, 1.0 equiv.), (6-methoxynaphthalen-2-yl) boronic acid (2.42 g, 1.2 equiv., 12 mmol), $Pd(OAc)_2$ (0.0674 g, 0.03 equiv., 0.3 mmol), PCy_3HBF_4 (0.442 g, 0.12 equiv., 1.2 mmol), potassium carbonate (3.45 g, 2.5 equiv., 25 mmol) and boric acid (1.24 g, 2.0 equiv., 20 mmol), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. THF (40 mL) was added with vigorous stirring at room temperature, the reaction was placed in a preheated oil bath at 65 °C, and stirred at 65 °C for 15 h. The reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (20 mL), filtered, and concentrated. The reaction mixture was analyzed by ^1H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain selectivity, conversion and yield using internal standard. Purification by chromatography on silica gel afforded the title product as a white solid (2.11 g, 80.6%). Characterization data are included in the ESI.†

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Notes and references

1 (*a*) A. de Meijere, S. Bräse and M. Oestreich, *Metal-Catalyzed Cross-Coupling Reactions and More*, Wiley, 2014; (*b*) G. Molander, J. P. Wolfe and M. Larhed, *Science of Synthesis: Cross-Coupling and Heck-Type Reactions*, Thieme, 2013; (*c*) E. Negishi, *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley, 2002.

2 C. C. C. Johansson-Seechurn, M. O. Kitching, T. J. Colacot and V. Snieckus, *Angew. Chem., Int. Ed.*, 2012, **51**, 5062.

3 (*a*) N. Miyaura and A. Suzuki, *Chem. Rev.*, 1995, **95**, 2457; (*b*) A. J. J. Lennox and G. C. Lloyd-Jones, *Chem. Soc. Rev.*, 2014, **43**, 412; (*c*) T. J. Colacot, *New Trends in Cross-Coupling*, The Royal Society of Chemistry, 2015.

4 (*a*) T. E. Barder, S. D. Walker, J. R. Martinelli and S. L. Buchwald, *J. Am. Chem. Soc.*, 2005, **127**, 4685; (*b*) A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed.*, 2002, **41**, 4176; (*c*) F. S. Han, *Chem. Soc. Rev.*, 2013, **42**, 5270.

5 (*a*) R. K. Dieter, *Tetrahedron*, 1999, **55**, 4177; (*b*) A. Zapf, *Angew. Chem., Int. Ed.*, 2003, **42**, 5394; (*c*) L. J. Gooßen, N. Rodriguez and K. Gooßen, *Angew. Chem., Int. Ed.*, 2008, **47**, 3100; (*d*) M. Blangetti, H. Rosso, C. Prandi, A. Deagostino and P. Venturello, *Molecules*, 2013, **18**, 1188.

6 M. B. Smith and J. March, *Advanced Organic Chemistry*, Wiley, 2007.

7 (*a*) N. A. Bumagin and D. N. Korolev, *Tetrahedron Lett.*, 1999, **40**, 3057; (*b*) M. Haddach and J. R. McCarthy, *Tetrahedron Lett.*, 1999, **40**, 3109. For seminal reports on organometallic addition to acyl chlorides, see: Organotin: (*c*) D. Milstein and J. K. Stille, *J. Org. Chem.*, 1979, **44**, 1613. Organozinc: (*d*) E. Negishi, V. Bagheri, S. Chatterjee, F. T. Luo, J. A. Miller and A. T. Stoll, *Tetrahedron Lett.*, 1983, **24**, 5181. Organoboron (tetraphenylborate): (*e*) C. S. Cho, K. Itotani and S. Uemura, *J. Organomet. Chem.*, 1993, **443**, 253. Review: (*f*) J. Yang, M. Deng and T. Yu, *Chin. J. Org. Chem.*, 2013, **33**, 693.

8 (*a*) R. Kakino, I. Shimizu and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, 2001, **74**, 371; (*b*) R. Kakino, S. Yasumi, I. Shimizu and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 137; (*c*) R. Kakino, H. Narahashi, I. Shimizu and A. Yamamoto, *Bull. Chem. Soc. Jpn.*, 2002, **75**, 1333; (*d*) L. J. Gooßen and K. Ghosh, *Angew. Chem., Int. Ed.*, 2001, **40**, 3458; (*e*) L. J. Gooßen and K. Ghosh, *Eur. J. Org. Chem.*, 2002, 3254. Review: (*f*) W. I. Dzik, P. P. Lange and L. J. Gooßen, *Chem. Sci.*, 2012, **3**, 2671.

9 (*a*) L. S. Liebeskind and J. Srogl, *J. Am. Chem. Soc.*, 2000, **122**, 11260. Review: (*b*) H. Prokopcova and C. O. Kappe, *Angew. Chem., Int. Ed.*, 2009, **48**, 2276. Cu-catalyzed addition of boronic acids: (*c*) J. M. Villalobos, J. Srogl and

L. S. Liebeskind, *J. Am. Chem. Soc.*, 2007, **129**, 15734; (*d*) L. S. Liebeskind, H. Yang and H. Li, *Angew. Chem., Int. Ed.*, 2009, **48**, 1417; (*e*) Z. Zhang, M. Lindale and L. S. Liebeskind, *J. Am. Chem. Soc.*, 2011, **133**, 6403. Organozinc reagents: (*f*) H. Tokuyama, S. Yokoshima, T. Yamashita and T. Fukuyama, *Tetrahedron Lett.*, 1998, **39**, 3189. Review: (*g*) T. Fukuyama and H. Tokuyama, *Aldrichimica Acta*, 2004, **37**, 87. Recent development: (*h*) K. Kunchithapatham, C. C. Eichman and J. P. Stambuli, *Chem. Commun.*, 2011, **47**, 12679.

10 (*a*) H. Tatamidani, K. Yokota, F. Kakiuchi and N. Chatani, *J. Org. Chem.*, 2004, **69**, 5615; (*b*) H. Tadamidami, F. Kakiuchi and N. Chatani, *Org. Lett.*, 2004, **6**, 3597.

11 Selected recent examples of the use of boronic acids in organic synthesis: (*a*) M. Sidera and S. P. Fletcher, *Nat. Chem.*, 2015, **7**, 935; (*b*) J. W. B. Fyfe, C. P. Seath and A. J. B. Watson, *Angew. Chem., Int. Ed.*, 2014, **53**, 12077; (*c*) S. E. Walker, J. A. Jordan-Hore, D. G. Johnson, S. A. Macgregor and A. L. Lee, *Angew. Chem., Int. Ed.*, 2014, **53**, 13876; (*d*) A. Bonet, M. Odachowski, D. Leonori, S. Essafi and V. K. Aggarwal, *Nat. Chem.*, 2014, **6**, 584; (*e*) L. Li, S. Zhao, A. Joshi-Pangu, M. Diane and M. Biscoe, *J. Am. Chem. Soc.*, 2014, **136**, 14027; (*f*) Z. He, A. Zajdlik, J. D. St. Denis, N. Assem and A. K. Yudin, *J. Am. Chem. Soc.*, 2012, **134**, 9926; (*g*) J. Barluenga, M. Tomas-Gamasa, F. Aznar and C. Valdes, *Nat. Chem.*, 2009, **1**, 494. Aryl ketone synthesis by C–H activation: (*h*) F. Szabo, J. Daru, D. Simko, T. Z. Nagy, A. Stirling and Z. Novak, *Adv. Synth. Catal.*, 2013, **355**, 685.

12 C. R. Kemnitz and M. J. Loewen, *J. Am. Chem. Soc.*, 2007, **129**, 2521.

13 A. Greenberg, C. M. Breneman and J. F. Liebman, *The Amide Linkage: Structural Significance in Chemistry, Biochemistry and Materials Science*, Wiley-VCH, 2003.

14 A comprehensive review on C–N activation: K. Ouyang, W. Hao, W. X. Zhang and Z. Xi, *Chem. Rev.*, 2015, **115**, 12045.

15 (*a*) G. Meng and M. Szostak, *Org. Lett.*, 2015, **17**, 4364; (*b*) G. Meng and M. Szostak, *Angew. Chem., Int. Ed.*, 2015, **54**, 14518; (*c*) N. A. Weires, E. L. Baker and N. K. Garg, *Nat. Chem.*, 2016, **8**, 75; (*d*) X. Li and G. Zou, *Chem. Commun.*, 2015, **51**, 5089. Transesterification: (*e*) L. Hie, N. F. F. Nathel, T. K. Shah, E. L. Baker, X. Hong, Y. F. Yang, P. Liu, K. N. Houk and N. K. Garg, *Nature*, 2015, **524**, 79. Suzuki–Miyaura coupling with borinic acids: (*f*) X. Li and G. Zou, *J. Organomet. Chem.*, 2015, **794**, 136. Highlight: (*g*) S. Ruider and N. Maulide, *Angew. Chem., Int. Ed.*, 2015, **54**, 13856. For rhodium(I) catalyzed C–H activation by amide bond N–C cleavage, see: (*h*) G. Meng and M. Szostak, *Org. Lett.*, 2016, **18**, DOI: 10.1021/acs.orglett.6b00058.

16 (*a*) R. Szostak, J. Aubé and M. Szostak, *Chem. Commun.*, 2015, **51**, 6395; (*b*) R. Szostak, J. Aubé and M. Szostak, *J. Org. Chem.*, 2015, **80**, 7905.

17 M. Szostak and J. Aubé, *Chem. Rev.*, 2013, **113**, 5701.

18 (*a*) M. Szostak, M. Spain, A. J. Eberhart and D. J. Procter, *J. Am. Chem. Soc.*, 2014, **136**, 2268; (*b*) M. Szostak, M. Spain, A. J. Eberhart and D. J. Procter, *J. Org. Chem.*, 2014, **79**, 11988; (*c*) M. Szostak, B. Sautier and D. J. Procter, *Chem. Commun.*, 2014, **50**, 2518; (*d*) M. Szostak, M. Spain and D. J. Procter, *Angew. Chem., Int. Ed.*, 2013, **52**, 7237; (*e*) M. Szostak, B. Sautier, M. Spain, M. Behlendorf and D. J. Procter, *Angew. Chem., Int. Ed.*, 2013, **52**, 12559; (*f*) S. Shi and M. Szostak, *Org. Lett.*, 2015, **17**, 5144; (*g*) F. Hu and M. Szostak, *ChemCatChem*, 2015, **7**, 1061; (*h*) F. Hu, M. Patel, F. Luo, C. Flach, R. Mendelsohn, E. Garfunkel, H. He and M. Szostak, *J. Am. Chem. Soc.*, 2015, **137**, 14473. See also ref. 17 and 28.

19 (*a*) B. M. Trost, *Science*, 1983, **219**, 245; (*b*) N. Z. Burns, P. S. Baran and R. W. Hoffmann, *Angew. Chem., Int. Ed.*, 2009, **48**, 2854; (*c*) J. F. Hartwig, *Nature*, 2008, **455**, 314.

20 For recent reviews on the Heck reaction, see: (*a*) M. Oestreich, *The Mizoroki-Heck Reaction*, Wiley, 2009; (*b*) D. McCartney and P. J. Guiry, *Chem. Soc. Rev.*, 2011, **40**, 5122; (*c*) A. L. Lee, *Org. Biomol. Chem.*, 2016, DOI: 10.1039/C5OB01984B.

21 M. Hutchby, C. E. Houlden, M. F. Haddow, S. N. Tyler, G. C. Lloyd-Jones and K. I. Booker-Milburn, *Angew. Chem., Int. Ed.*, 2012, **51**, 548.

22 S. A. Glover, *Tetrahedron*, 1998, **54**, 7229.

23 (*a*) B. M. Trost and I. Fleming, *Comprehensive Organic Synthesis*, Pergamon Press, 1991; (*b*) H. Lundberg, F. Tinnis, N. Selander and H. Adolfsson, *Chem. Soc. Rev.*, 2014, **43**, 2714; (*c*) G. Prabhu, Basavaprabhu, N. Narendra, T. M. Vishwanatha and V. V. Sureshbabu, *Tetrahedron*, 2015, **71**, 2785.

24 A. Brennführer, H. Neumann and M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 4114.

25 (*a*) A. Greenberg and C. A. Venanzi, *J. Am. Chem. Soc.*, 1993, **115**, 6951; (*b*) A. Greenberg, D. T. Moore and T. D. DuBois, *J. Am. Chem. Soc.*, 1996, **118**, 8658; (*c*) C. Cox and T. Lectka, *Acc. Chem. Res.*, 2000, **33**, 849; (*d*) K. B. Wiberg, *Acc. Chem. Res.*, 1999, **32**, 922.

26 F. K. Winkler and J. D. Dunitz, *J. Mol. Biol.*, 1971, **59**, 169. Winkler–Dunitz distortion parameters: τ (twist angle), χ_N (pyramidalization at N) and χ_C (pyramidalization at C) describe the magnitude of rotation around the N–C(O) bond, pyramidalization at N and C; τ is 0° for planar amide bonds and 90° for fully orthogonal bonds; χ_N and χ_C are 0° for planar bonds, and 60° for fully pyramidalized amide bonds.

27 C. Laurence and J. F. Gal, *Lewis Basicity and Affinity Scales: Data and Measurement*, Wiley-Blackwell, 2009.

28 M. Szostak and J. Aubé, *Org. Biomol. Chem.*, 2011, **9**, 27.

29 Y. Otani, O. Nagae, Y. Naruse, S. Inagaki, M. Ohno, K. Yamaguchi, G. Yamamoto, M. Uchiyama and T. Ohwada, *J. Am. Chem. Soc.*, 2003, **125**, 15191.

30 Pd: (*a*) Y. Lei, A. D. Wrobleski, J. E. Golden, D. R. Powell and J. Aubé, *J. Am. Chem. Soc.*, 2005, **127**, 4552. Ni: (*b*) M. Tobisu, K. Nakamura and N. Chatani, *J. Am. Chem. Soc.*, 2014, **136**, 5587.

31 (*a*) L. N. Yakhontov and M. V. Rubtsov, *Russ. J. Gen. Chem.*, 1957, **27**, 83; (*b*) H. Pracejus, *Ber.*, 1959, **92**, 988;

(*c*) A. J. Kirby, I. V. Komarov, P. D. Wothers and N. Feeder, *Angew. Chem., Int. Ed.*, 1998, **37**, 785; (*d*) K. Tani and B. M. Stoltz, *Nature*, 2006, **441**, 731; (*e*) M. Szostak, L. Yao, V. W. Day, D. R. Powell and J. Aubé, *J. Am. Chem. Soc.*, 2010, **132**, 8336; (*f*) J. Clayden and W. J. Moran, *Angew. Chem., Int. Ed.*, 2006, **45**, 7118; (*g*) J. Aubé, *Angew. Chem., Int. Ed.*, 2012, **51**, 3063.

32 M. R. Netherton and G. C. Fu, *Org. Lett.*, 2001, **3**, 4295.

33 P. W. N. M. van Leeuwen, P. C. J. Kamer, J. N. H. Reek and P. Dierkes, *Chem. Rev.*, 2000, **100**, 2741.

34 Recent reviews on chemoselective organic reactions: (*a*) N. A. Afagh and A. K. Yudin, *Angew. Chem., Int. Ed.*, 2010, **49**, 262; (*b*) J. Mahatthananchai, A. Dumas and J. W. Bode, *Angew. Chem., Int. Ed.*, 2012, **51**, 10954.

35 (*a*) M. Seki, *Synthesis*, 2006, 2975; (*b*) F. X. Felpin, *Synlett*, 2014, 1055; (*c*) L. Djakovitch and F. X. Felpin, *ChemCatChem*, 2014, **6**, 2175.

36 C. Amatore, G. Le Duc and A. Jurand, *Chem. – Eur. J.*, 2013, **19**, 10082.

37 R. Martin and S. L. Buchwald, *Acc. Chem. Res.*, 2008, **41**, 1461.

38 N. Lebrasseur and I. Larrosa, *J. Am. Chem. Soc.*, 2008, **130**, 2926.

39 S. R. Neufeldt and M. S. Sanford, *Acc. Chem. Res.*, 2012, **45**, 936.

40 R. H. Crabtree, *The Organometallic Chemistry of the Transition Metals*, Wiley, 2009.

41 G. Mann, C. Incarvito, A. L. Rheingold and J. F. Hartwig, *J. Am. Chem. Soc.*, 1999, **121**, 3224.

42 (*a*) K. Billingsley and S. L. Buchwald, *J. Am. Chem. Soc.*, 2007, **129**, 3358; (*b*) T. Kinzel, Y. Zhang and S. L. Buchwald, *J. Am. Chem. Soc.*, 2010, **132**, 14073.

43 H. Doucet, *Eur. J. Org. Chem.*, 2008, 2013.

44 (*a*) M. Tobisu and N. Chatani, *Acc. Chem. Res.*, 2015, **48**, 1717; (*b*) J. Cornella, C. Zarate and R. Martin, *Chem. Soc. Rev.*, 2014, **43**, 8081.

45 J. B. Johnson and T. Rovis, *Angew. Chem., Int. Ed.*, 2008, **47**, 840.

46 (*a*) L. J. Gooßen and N. Rodriguez, *Chem. Commun.*, 2004, 724; (*b*) Y. Liu, K. E. Kim, M. B. Herbert, A. Fedorov, R. H. Grubbs and B. M. Stoltz, *Adv. Synth. Catal.*, 2014, **356**, 130; (*c*) A. John, L. T. Hogan, M. A. Hillmyer and W. B. Tolman, *Chem. Commun.*, 2015, **51**, 2731.

47 (*a*) D. Zim, V. R. Lando, J. Dupont and A. L. Monteiro, *Org. Lett.*, 2001, **3**, 3049. For comparison with Pd(0) insertion into aryl iodides, see: (*b*) C. Amatore and F. Pfluger, *Organometallics*, 1990, **9**, 2276.

48 T. Moriya, N. Miyaura and A. Suzuki, *Synlett*, 1994, 149.

49 D. V. Partyka, *Chem. Rev.*, 2011, **111**, 1529.

50 (*a*) P. A. Enquist, P. Nilsson, P. Sjöberg and M. Larhed, *J. Org. Chem.*, 2006, **71**, 8779; (*b*) A. Svennebring, P. J. R. Sjöberg, M. Larhed and P. Nilsson, *Tetrahedron*, 2008, **64**, 1808; (*c*) L. S. Santos, *Eur. J. Org. Chem.*, 2008, 235.

51 (*a*) C. Zhou and R. C. Larock, *J. Org. Chem.*, 2006, **71**, 3551; (*b*) S. Lin and X. Lu, *J. Org. Chem.*, 2007, **72**, 9757; (*c*) C. Qin, H. Wu, J. Cheng, X. Chen, M. Liu, W. Zhang, W. Su and J. Ding, *J. Org. Chem.*, 2007, **72**, 4102.

52 (*a*) C. Amatore and A. Jutand, *Acc. Chem. Res.*, 2000, **33**, 314; (*b*) L. J. Gooßen, D. Koley, H. L. Hermann and W. Thiel, *J. Am. Chem. Soc.*, 2005, **127**, 11102; (*c*) J. Jover, N. Fey, M. Purdie, G. C. Lloyd-Jones and J. N. Harvey, *J. Mol. Catal. A: Chem.*, 2010, **324**, 39; (*d*) A. J. J. Lennox and G. C. Lloyd-Jones, *Angew. Chem., Int. Ed.*, 2013, **52**, 7362.

53 S. D. Roughley and A. M. Jordan, *J. Med. Chem.*, 2011, **54**, 3451.

