Green Solvent Selection for Suzuki–Miyaura Coupling of Amides

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ABSTRACT: A range of environmentally friendly solvents was evaluated in the Suzuki-Miyaura coupling of amides in an attempt to provide the first solvent selection guide for the powerful C–C coupling by amide bond cleavage. Of the 14 solvents and 10 Pd–NHC catalysts (NHC = *N*-heterocyclic carbene) considered, *i*-PrOAc was identified as the recommended, environmentally-friendly solvent for the coupling. The obtained data permit for an overall ranking of recommended solvents in the Suzuki–Miyaura coupling of amides, with methyl *t*-butyl ether (MTBE), cyclopentyl methyl ether (CPME), diethyl carbonate (DEC), *p*-cymene, dimethylcarbonate (DMC) and anisole as alternative recommended solvents in terms of health, safety and environmental ranking for the coupling. The data should facilitate the replacement of hazardous solvents with green organic solvents in the biorelevant manifold of amide bond coupling for the further implementation of amide bond activation methods.

Keywords: *solvents; amide cleavage; amide activation; N–C(O) activation; Pd–NHCs; N-heterocyclic carbenes; Suzuki cross-coupling*

INTRODUCTION

Amide bond cross-coupling is a powerful transformation that is vital for transforming traditionally inert amide bonds into cross-coupling synthons through the cleavage of N–C bonds under mild and modular transition-metal-catalyzed conditions (Figure 1).[1–29] The immense potential of the amide bond cross-coupling stems from the inherent presence of amides in biomolecules, polymers, and as the most common functional group in pharmaceutical development.[30–38]

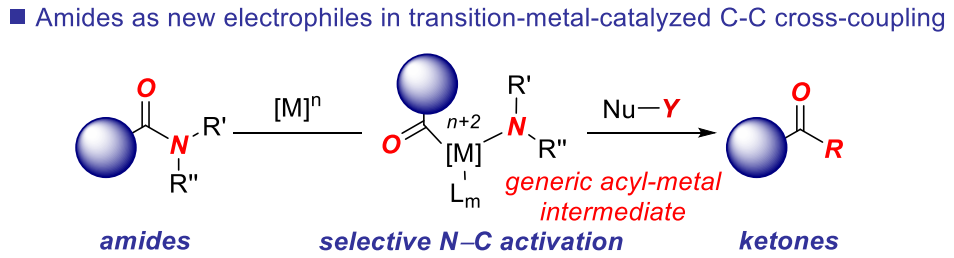


Figure 1. Amides as electrophiles in the Suzuki–Miyaura cross-coupling.

The fundamental impact of solvents on the environment and the synthesis of active pharmaceutical ingredients has led to the development of a number of green solvent selection guides to reduce the environmental and health concerns.[39–55] In consideration of the pervasive presence of solvents in chemical transformations, wherein solvents constitute up to 90% of the non-aqueous waste in the synthesis of APIs, it is critical to use environmentally friendly and greener solvents in modern chemical processes.[47–55] Evaluation of health, safety and environmental criteria of the most common solvents define sets of recommended solvents, while minimizing the environmental and health impact.[47–49]

However, the most common solvent for the Pd-catalyzed Suzuki–Miyaura coupling of amides is tetrahydrofuran (THF), which is classified as hazardous or problematic at best by all solvent selection guides.[47–55] To address the urgent need for the replacement of hazardous solvents in the biorelevant manifold of amide bond cross-coupling, we present the first solvent selection guide for the powerful Suzuki–Miyaura C–C coupling by amide bond cleavage. We show that of the 14 solvents and 10 Pd–NHC catalysts (NHC = *N*-heterocyclic carbene) considered (see Table 1 and Figure 3), *i*-PrOAc[47–49] is the recommended, environmentally-friendly solvent for the coupling, in agreement with the recent

solvent selection guides in terms of sustainability, health impact and stability,[39–57] while methyl *t*-butyl ether (MTBE)[58–60], cyclopentyl methyl ether (CPME)[61–64], diethyl carbonate (DEC)[65–67], *p*-cymene (pCy)[68–71], dimethylcarbonate (DMC)[65,72,73] and anisole[47–49] should be considered as alternative recommended solvents. The data should facilitate green organic solvent selection for the further implementation of amide bond activation methods. It is also important to note that *i*-PrOAc is inexpensive and has already found common applications in process chemistry, which should facilitate its application in amide bond cross-coupling.

Pd-NHCs (NHC = *N*-heterocyclic carbene) have been identified as the most active catalysts for the Suzuki–Miyaura coupling of amides.[1–16,74–76] The high activity of these catalysts hinges upon strong σ-donation of the NHC ancillary ligand, while accommodating steric requirements for the oxidative addition of the N–C(O) bond to the monoligated NHC–Pd(0) and reductive elimination steps by flexible N-wingtip substitution.[76–80] As an added advantage Pd–NHCs are applied as air- and moisture-stable Pd(II) precatalysts, which facilitates their rapid adoption into the synthetic toolbox.[77–85]

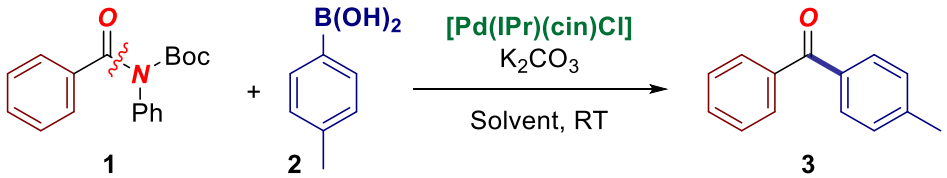
RESULTS AND DISCUSSION

For the study, we selected 14 solvents outlined in Table 1. In general, the solvent selection was guided by the environmental and health impact as defined by solvent selection guides.[39–55] We have also focused on selecting the solvents that are readily available in both academic and industrial laboratories, inexpensive and readily removable from the reaction mixtures (*vide infra*). It should be noted that alcohols are not suitable solvents for amide coupling due to facile amide bond alcoholysis of the twisted amide bond,[8] while ketones are unsuitable due to aldol type side reactions observed in amide bond cross-coupling.[74] Neolyst CX31, [Pd(IPr)(cin)Cl],[75] was selected for the initial evaluation due to the versatility, robustness and commercial availability of this Pd-NHC catalyst.[86]

As shown in Table 1, we were pleased to find that several green recommended solvents performed extremely well in the model Suzuki–Miyaura cross-coupling of amide (**1a**) with 4-Tol-B(OH)$_2$ (**2a**, 2

equiv) in the presence of Neolyst CX31 (3 mol%) and K_2CO_3 (3 equiv) as a base.[9] As such, this initial evaluation identified 2-MeTHF,[87–89] cyclopentyl methyl ether (CPME),[61–64] *i*-PrOAc,[47–49] *p*-cymene,[68–71] diethyl carbonate (DEC),[65–67] methyl *t*-butyl ether (MTBE),[61–64] ethyl acetate (EA),[47–49] anisole[47–49] and dimethyl carbonate (DMC)[65,72,73] as the superior green solvents to THF in the coupling. Other solvents, such as propylene carbonate (PC),[65] eucalyptol (1,8-cineole),[90,91] γ-valerolactone (GVL)[92,93] and ethyl levulinate[94,95] resulted in lower yields. All cross-coupling products were isolated by chromatography on silica gel. We hypothesize that lower yields are a result of side reactions, low solubility of the reaction components and inefficient generation of the catalytically active species. It is also worthwhile to note that the use of high-boiling green solvents introduces additional challenges in product isolation and purification.

Table 1. Selection of Green Solvents[a]



entry	solvent	yield (%)[b]
1	THF	94
2	2-MeTHF	96
3	CPME	98
4	*i*-PrOAc	96
5	PC	37
6	*p*-cymene	98
7	DEC	98
8	MTBE	98
9	EA	98
10	anisole	97
11	1,8-cineole	24
12	DMC	98

13	GVL	63
14	ethyl levulinate	66

[a]Amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), H_2O (5.0 equiv), solvent (0.25 M), 23 °C, 15 h. [b]GC/^{1}H NMR yields.

Having identified 9 green recommended solvents for the coupling that resulted in excellent conversions in the model reaction, we conducted kinetic studies to gain further insight into the relative reaction rates (Figure 2). As shown, the kinetic profiling studies revealed *i*-PrOAc to be the most efficient solvent for the cross-coupling followed by MTBE and CPME, which showed similar kinetic profiles, and then by DEC and *p*-cymene, while other solvents examined, namely 2-MeTHF, anisole, EA, and DMC, resulted in inferior reactivity. The reactions were completely quenched after 4 h. It is interesting to note the difference in rate between *i*-PrOAc and EtOAc. While the explanation is not clear at present, we note that we have observed low reactivity in amide bond cross-coupling in EtOAc using Pd-catalysis while developing other reactions of amides by N–C(O) activation.

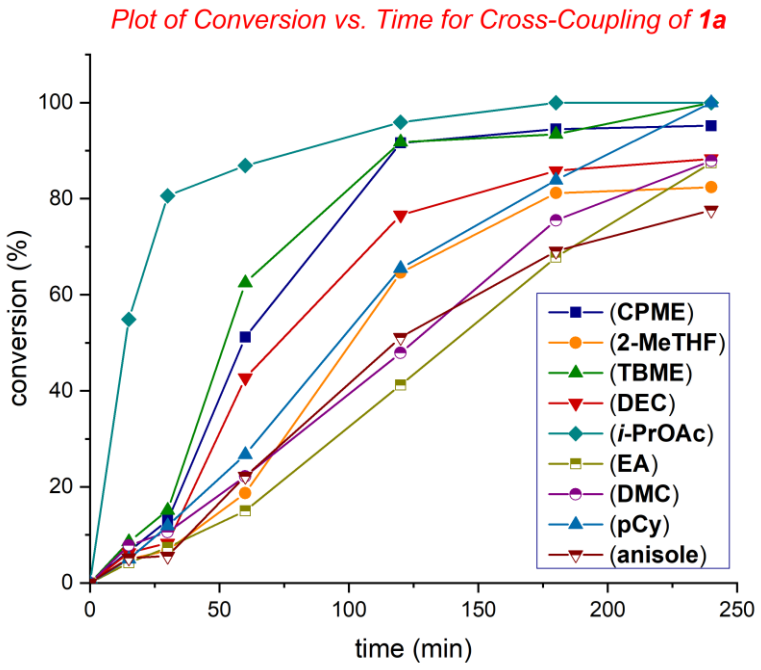


Figure 2. Kinetic profile in the Suzuki–Miyaura cross-coupling with 4-tolylboronic acid catalyzed by Pd(IPr)(cin)Cl (3 mol%) at room temperature. **1a** (1.0 equiv), 4-Tol-B(OH)$_2$ (2.0 equiv), [Pd] (3 mol%),

K_2CO_3 (3.0 equiv), H_2O (5.0 equiv), solvent (0.25 M), 23 °C, 0-240 min.

At this stage, we conducted comprehensive evaluation of Pd-NHC catalysts using *i*-PrOAc as the preferred solvent identified by the kinetic studies. As shown in Figure 3, we selected 10 Pd-NHC catalysts guided by their commercial-availability, type of the NHC scaffold and class of throw-away ligand (i.e. ligand that must dissociate from the metal centre). In general, the Pd-NHC catalysts selected can be classified as imidazolylidene (IPr, IMes) or imidazolinylidene ligands (SIPr) bearing allyl-type throw-away ligands (allyl, cin, *t*-Bu-ind), heterocyclic ligands (3-Cl-py), chloro-dimers ([Pd(IPr)(μ-Cl)Cl]$_2$) and palladacycles (SingaCycle A3).[96–102] We have also selected the sterically-demanding IPr* ligand due to its high efficiency in select cross-couplings.[97] As shown in Table 2, we found that Neolyst CX31[75] is the most efficient Pd catalyst for the coupling, closely followed by Pd–PEPPSI–IP[98] and SingaCycle A3[99], which all resulted in >90% yields in the model reaction. Two other catalysts, namely [Pd(IPr)(μ-Cl)Cl]$_2$[75,102] and the allyl-based [Pd(IPr)(*t*-Bu-ind)Cl][100] also showed promising reactivity, while other catalysts showed much lower ([Pd(IPr)(allyl)Cl][75], [Pd(SIPr)(cin)Cl][75], [Pd(IMes)(allyl)Cl][101]) or significantly lower (Pd–PEPPSI–SIPr[102], Pd–PEPPSI–IPr*[97]) reactivity. It should be noted that N-alkyl-based NHC catalysts are unsuitable for amide bond coupling.[76] In general, *N*-alkyl-NHCs feature low flexibility around the metal centre and thus are less effective in the transmetallation step, which is proposed as the rate-determining step in the Suzuki cross-coupling of aryl halides and amides.[74]

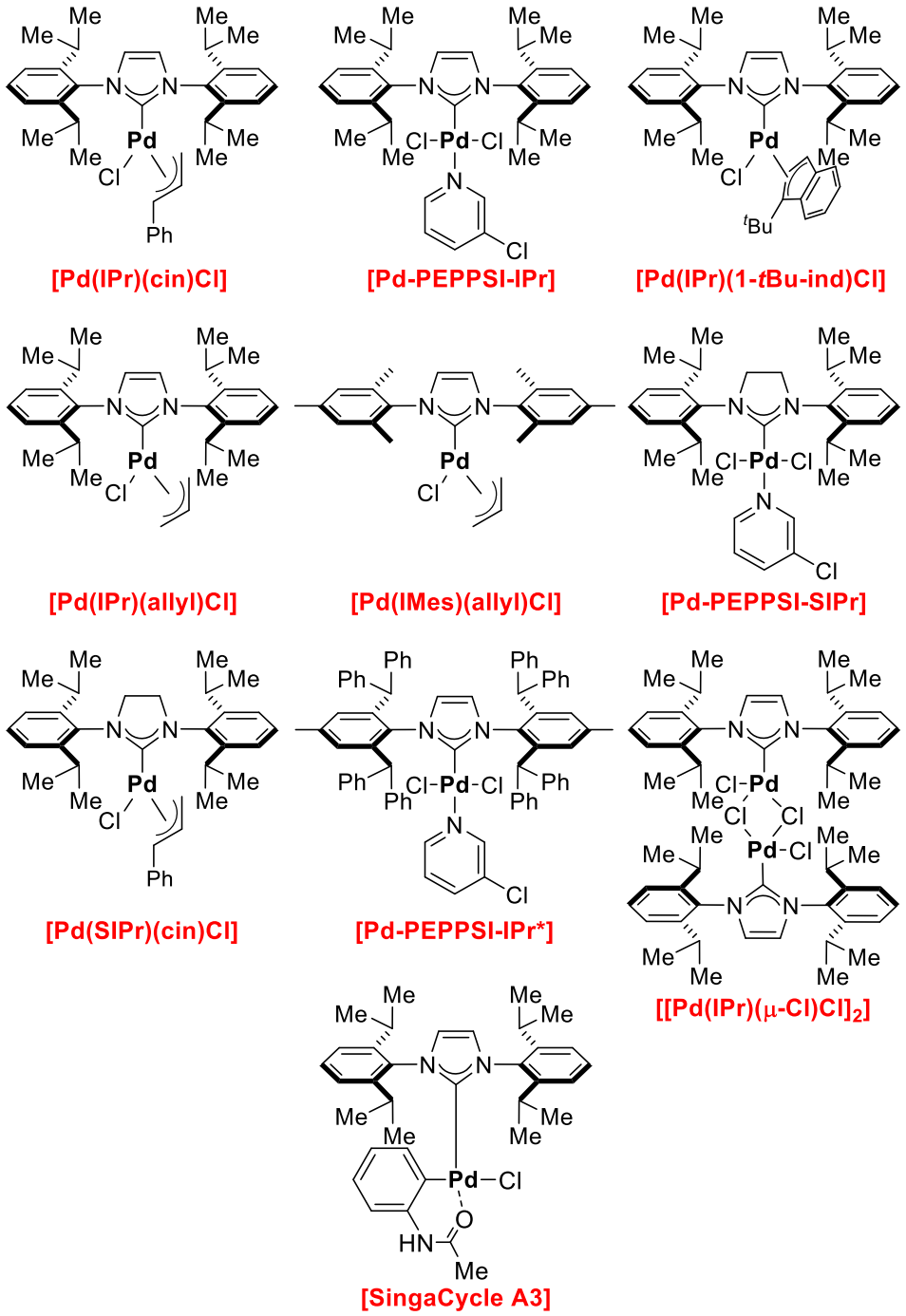
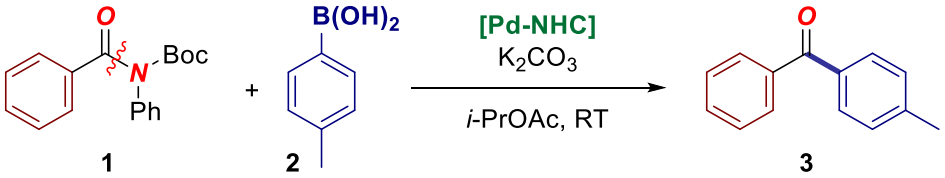


Figure 3. Structures of Pd(II)-NHC precatalysts in the Suzuki−Miyaura cross-coupling of amides.

Table 2. Selection of Pd-NHC Precatalysts[a]



1 2 3

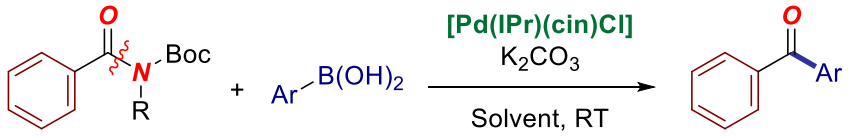
entry	catalyst	yield (%)[b]

1	Pd(IPr)(cin)Cl	96
2	Pd–PEPPSI–IPr	93
3	Pd(IPr)(*t*-Bu-ind)Cl	84
4	Pd(IPr)(allyl)Cl	52
5	Pd(IMes)(allyl)Cl	63
6	Pd–PEPPSI–SIPr	10
7	Pd(SIPr)(cin)Cl	65
8	Pd–PEPPSI–IPr*	27
9	$[Pd(IPr)(\mu\text{-}Cl)Cl]_2$	87
10	SingaCycle A3	93

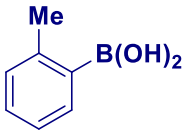
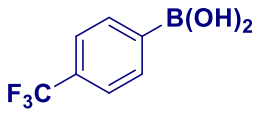
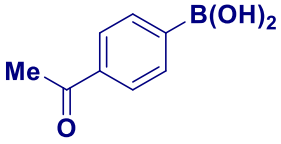
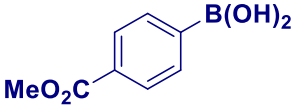
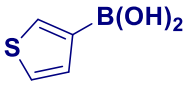
[a]Amide (1.0 equiv), Ar-$B(OH)_2$ (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), H_2O (5.0 equiv), *i*-PrOAc (0.25 M), 23 °C, 15 h. [b]GC/^{1}H NMR yields.

Next, we examined the scope utilizing the 5 most effective green solvents identified in the optimization and kinetic studies, namely *i*-PrOAc, MTBE, CPME, DEC and *p*-cymene (Tables 3 and 4). The effect of solvents on the substrate scope with respect to the boronic acid component is shown in Table 3. This study further confirmed the beneficial effect of *i*-PrOAc as the recommended green solvent for Suzuki–Miyaura coupling of amides. As shown, in the coupling using sterically-hindered 2-Tol-$B(OH)_2$ and the challenging electronically-deactivated 4-CF_3-C_6H_4-$B(OH)_2$ all solvents performed well, resulting in 57-78% and 86-98% yields, respectively. *i*-PrOAc is clearly the preferred solvent using electronically-deactivated boronic acids bearing electrophilic functional groups, such as 4-Ac-C_6H_4-$B(OH)_2$ and 4-MeO_2C-C_6H_4-$B(OH)_2$ as well as heterocyclic substrates, such as 3-thienyl boronic acid. Interestingly, MTBE and CPME are also effective solvents in the latter case, albeit the reaction is lower yielding than using *i*-PrOAc. In general, we hypothesize that the trend of solvent yield vs. activity and rate of reaction is closely dependent on several factors, including the generation of the active monoligated NHC–Pd(0), solubility of the reaction components, stability of the amide bond to the deactivating N–Boc scission and stabilization of the catalytically active NHC–Pd(0) species.

Table 3. Scope of the Suzuki–Miyaura Cross-Coupling of Amides in Green Solvents: Scope of Boronic Acids[a,b,c]



1 R = Ph **2** **3**

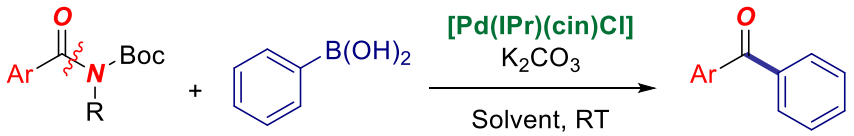
entry	boronic acid	*i*-PrOAc yield (%)	MTBE yield (%)	CPME yield (%)	DEC yield (%)	*p*-cymene yield (%)
1		58	78	57	67	72
2		97	98	90	86	96
3		65	12	5	16	11
4		86	17	11	38	<5
5		98	87	78	17	11

[a]Amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), H_2O (5.0 equiv), solvent (0.25 M), 23 °C, 15 h. [b]Isolated yields. [c]Key: red – yield < 50%; yellow – yield 50–89%; green – yield ≥ 90%.

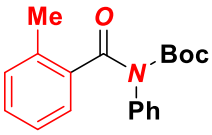
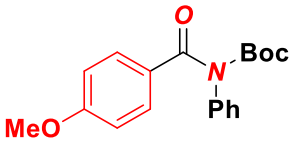
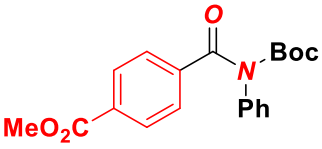
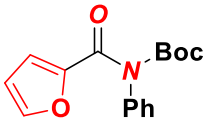
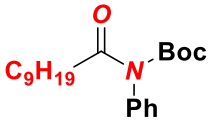
The observed reactivity trend with respect to the green solvent selection is confirmed in the scope study with respect to the amide component as shown in Table 4. Thus, *i*-PrOAc is uniformly the most effective solvent in the coupling of sterically-hindered, electronically-deactivated, electrophilic substrates, heterocyclic amides and alkyl substitution, resulting in generally high yields. Interestingly, MTBE could also be used to effectively cross-couple various amides as shown in Table 4, albeit in lower yields than *i*-PrOAc, while the performance of CPME and DEC ranges from very good (89-92%)

to low (<5%). *p*-Cymene is the least effective solvent under these conditions. Overall, the scope studies shown demonstrate *i*-PrOAc as the general solvent for coupling of a variety of amides and boronic acids through N–C bond activation. Furthermore, the coupling is also applicable to N-sulfonamide activation (N-Ph/Ts) and N-Boc_2 activation, which enables to engage other classes of amides in the coupling with the yields ranging from 87-98% to 78-95%, respectively (see SI).

Table 4. Scope of the Suzuki–Miyaura Cross-Coupling of Amides in Green Solvents: Scope of Amides[a,b,c]



1 R = Ph **2** **3**

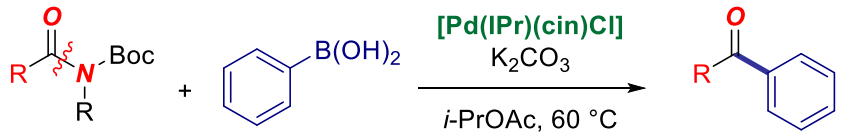
entry	amide	*i*-PrOAc yield (%)	MTBE yield (%)	CPME yield (%)	DEC yield (%)	*p*-cymene yield (%)
1		91	78	26	42	14
2		94	98	92	89	45
3		93	98	72	11	<5
4		98	98	44	<5	<5
5		84	76	41	<5	<5

[a]Amide (1.0 equiv), Ar-$B(OH)_2$ (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), H_2O (5.0 equiv), solvent (0.25 M), 23 °C, 15 h. [b]Isolated yields. [c]Key: red – yield < 50%; yellow – yield 50–89%; green – yield ≥ 90%.

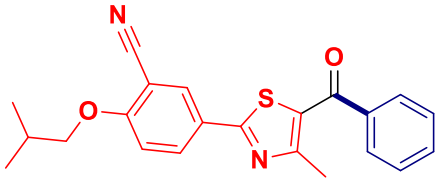
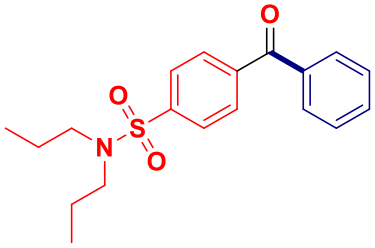
The Suzuki–Miyaura amide bond cross-coupling provides opportunities to functionalize amide

containing pharmaceuticals through late-stage functionalization. To demonstrate the utility of green solvent protocol in the Suzuki–Miyaura cross-coupling, we carried out the late-stage functionalization of *Febuxostat* (antigout)[103,104] and *Probenecid* (antihyperuricemic)[105] using *i*-PrOAc as the recommended solvent (Table 5). As shown, the cross-coupling proceeded in excellent yields, further demonstrating the functional group tolerance to electrophilic functional group and demonstrating the potential in the synthesis of active pharmaceutical agents.

Table 5. The Late-Stage Functionalization of Pharmaceuticals[a]



1 R = Ph **2** **3**

entry	product	yield (%)[b]
1		88
2		93

[a]Amide (1.0 equiv), Ar-B(OH)$_2$ (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), H_2O (5.0 equiv), *i*-PrOAc (0.25 M), 60 °C, 15 h. [b]Isolated yields.

CONCLUSIONS

In conclusion, we have presented the first green solvent selection guide for the powerful C–C coupling by amide bond cleavage. The emergence of amide bond coupling allows for the mild and chemoselective generation of C–C bonds by harnessing N–C bond cleavage. This process has a profound impact on synthetic disconnections owing to the inherent presence of amide bonds in organic

synthesis, including in drug discovery. This study identified *i*-PrOAc as the recommended green solvent for the coupling. *It should be noted that i-PrOAc ranks as one of the most preferred solvents in terms of health, safety and environmental impact in the recent solvent selection guides published by several pharmaceutical companies*.[44–55] Several other solvents, such as methyl *t*-butyl ether (MTBE), cyclopentyl methyl ether (CPME), diethyl carbonate (DEC), *p*-cymene, dimethylcarbonate (DMC) and anisole have been identified as alternative solvents for the coupling in select cases. The compatibility has been demonstrated in the late-stage functionalization of pharmaceuticals. We fully expect that the study will facilitate the development of much-needed protocols for the cross-coupling of amides using environmentally friendly and greener solvents. Future innovations in the activation of the amide bond should incorporate sustainability criteria to maximize chemical impact.[106]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at http://pubs.acs.org.

Experimental details, characterization data, and ^{1}H and ^{13}C NMR spectra.

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Author Contributions

‡P.L., Y.M. and Y.W. contributed equally.

Notes

The authors declare no competing financial interest.

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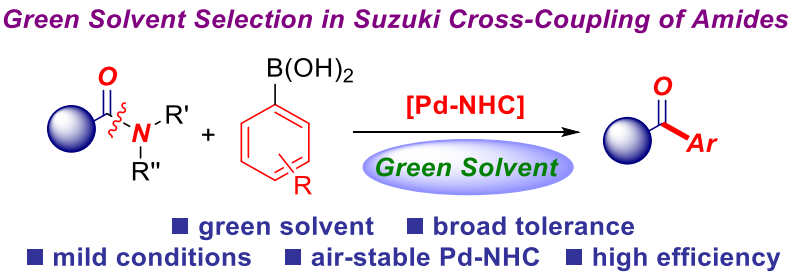

Synopsis: A range of environmentally friendly solvents was evaluated in the Suzuki-Miyaura coupling of amides to provide the first solvent selection guide for the C–C coupling by amide bond cleavage.