Green Solvent Selection for Acyl Buchwald-Hartwig Cross-Coupling of Amides (Transamidation)

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ABSTRACT: The selection of solvents is essential as a suitable reaction milieu in chemical processes of industrial and academic impact. We present an evaluation of a range of green solvents for acyl Buchwald-Hartwig cross-coupling of amides in order to provide the first green solvent selection guide for this powerful C–N to C–N' cross-coupling interconversion engaging typically inert amide bonds and resulting in a net transamidation process of historically challenging amide bonds. Out of solvents considered, MTBE (MTBE = methyl *tert*-butyl ether) and 2-MeTHF (2-MeTHF = 2-methyltetrahydrofuran) were identified as the preferred alternative solvents for the acyl-Buchwald-Hartwig cross-coupling using well-defined and robust Pd(II)–NHC (NHC = N-heterocyclic carbene) precatalysts. MTBE and, in particular, 2-MeTHF are superior solvents in this cross-coupling manifold and recommended in terms of safety, health, biodegradability and environmental score. The results indicate the replacement of hazardous solvents with green organic solvents in the biorelevant C–N to C–N' cross-coupling manifold of amides to further the burgeoning chemical repertoire of amide bond activation methods.

KEYWORDS: *N–C(O) activation, Buchwald-Hartwig amination, green solvent selection, 2-methyltetrahydrofuran, 2-MeTHF, methyl tert-butyl ether, twisted amides, activated amides*

INTRODUCTION

The Buchwald-Hartwig amination has emerged as one of the most central and widely utilized cross-coupling methods in organic synthesis enabling for the assembly of key structural motifs in pharmaceuticals, agrochemicals and natural products.[1-9] This class of reactions takes advantage of transition-metal-catalysts that operate through well-defined catalytic cycle and enable C(sp^2)–N cross-coupling in a highly predictable manner with excellent functional group tolerance.[10-16]

Recently, tremendous progress has been achieved in transition-metal-catalyzed activation of amide bonds (Figure 1).[17-33] Although, traditionally, amide N–C(O) bonds are inert to oxidative addition to transition metals due to high resonance energy of the amide bond, by exploiting ground-state-destabilization concept oxidative addition of amides occurs readily, enabling for the powerful manipulation of amides by well-defined transition-metal-catalyzed cycles.[28-36] In this context, acyl-Buchwald-Hartwig reaction of amides is especially valuable as a method to achieve C–N to C–N' cross-coupling interconversion of typically inert amide bonds and resulting in a net transamidation process of historically challenging amide bonds.[37-47]

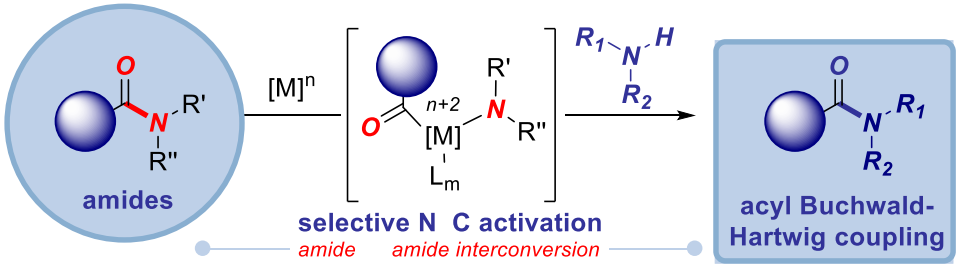


Figure 1. Acyl Buchwald-Hartwig cross-coupling of amides.

The selection of solvents is critical as a reaction milieu in organic processes. The environmental and health impact of common solvents in the synthesis of APIs (API = active pharmaceutical ingredient), where solvents constitute up to 90% of the nonaqueous waste, has led to the evolution of solvent

selection guides to reduce the impact of solvents on human health and environment.[48-57] One of the key areas in green chemistry is the replacement of toxic solvents that pose environmental and health issues with non-toxic and sustainable alternatives.[48-61] The use of green solvents reduces environmental waste, facilitates downstream processing and decreases overall energy cost, while at the same time prevents health and safety concerns of conventional solvents.[58-65]

However, the most common solvent for the Pd-catalyzed acyl-Buchwald-Hartwig cross-coupling of amides is dimethoxyethane (DME),[40-42,66,67] which is classified as hazardous and undesirable at best by the recent solvent selection guides.[48-57] To exploit the full potential of acyl-Buchwald-Hartwig cross-coupling of amides, a process that is analogous to the traditional Buchwald-Hartwig amination, but leads to a powerful amide interconversion (transamidation),[37-47] it is critical that safer alternatives to DME are identified. To address this urgent need in the biorelevant amide C–N to C–N' interconversion, we present the first solvent selection guide for the acyl Buchwald-Hartwig cross-coupling of amides. We show that out of the solvents considered, MTBE[68-71] (MTBE = methyl *tert*-butyl ether) and 2-MeTHF[72-74] (2-MeTHF = 2-methyltetrahydrofuran) are the preferred alternative solvents for this cross-coupling using a selection of robust Pd(II)–NHC (NHC = N-heterocyclic carbene) precatalysts.[75-78] We show that 2-MeTHF in particular is the preferred solvent in terms of safety, health, biodegradability and environmental score,[48-57,72-74] while providing superior reactivity in terms of kinetics and scope studies to the conventionally used DME in the acyl-Buchwald-Hartwig cross-coupling of amides.[40-42,66,67] Furthermore, MTBE is the common industrial solvent that features excellent solvating properties, while diminishing the formation of peroxides, and is also superior to the classically used DME in this cross-coupling manifold.[68-71]

Following breakthrough studies by Garg and co-workers on Ni-catalyzed transamidation of N-Boc-activated amides (RE, resonance energy, $PhCO_2NRBoc$, 9.7 kcal/mol, R = Ph),[79,80] Pd(II)–NHCs have been identified as highly active catalysts for acyl-Buchwald-Hartwig cross-coupling of amides.[40-42] This manifold exploits site-selective N-*tert*-butoxycarbonylation of secondary amide bonds to decrease the

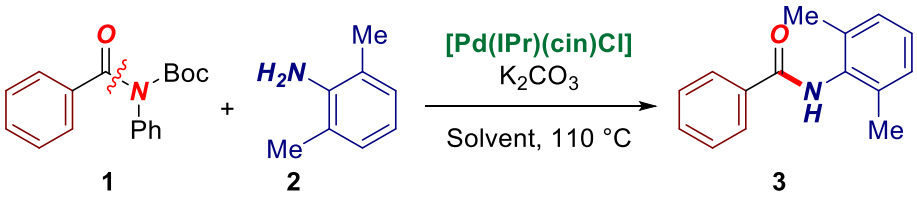
kinetic and thermodynamic barrier for the process.[81-83] The exceptional activity of Pd–NHCs results from the electronic properties of the ancillary NHC ligand with strong σ-donation enabling facile oxidative addition of the amide N–C(O) bond to the monoligated Pd(0)–NHC,[16,75-77] while the use of well-defined Pd(II)-NHC precatalysts permits air- and moisture-stability of the precatalysts without resorting to glovebox techniques as is often the case with Ni(0) systems.[40-42,79,80] The latter is important difference between Ni(0) and Pd(II) catalysts for acyl-Buchwald-Hartwig of amides, which is critical for the wide utilization of this cross-coupling manifold, although several elegant solutions including Ni capsules have been developed.[79,80]

RESULTS AND DISCUSSION

For the initial screen, we selected 14 solvents as shown in Table 1. The selection was based on environmental and health impact as outlined by the recent solvent selection guides[48-57] and compatibility with Pd(II)–NHC systems.[75-78,84] As a crucial selection criterium solvents should also be readily available to the end-users in both industrial and academic settings, while their removal from the post-reaction mixtures should be facile. Neolyst CX31, [Pd(IPr)(cin)Cl], IPr = 1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene, was selected as the Pd(II)–NHC catalyst for the initial screen due to its robustness, commercial-availability and the high activity in the amide cross-coupling.[85,86] DME has been included for comparison as benchmark.

We were pleased to find that several recommended solvents performed well in the cross-coupling under the Pd(II)–NHC conditions using 2,6-dimethylaniline (2 equiv), and K_2CO_3 (3 equiv) as a base in the presence of [Pd(IPr)(cin)Cl] (3 mol%) as the catalyst. The initial screen (Table 1, entries 1-14) identified 2-MeTHF (2-methyltetrahydrofuran) (entry 1), CPME (cyclopentyl methyl ether) (entry 2), *i*-PrOAc (isopropyl acetate) (entry 3), *p*-cymene (entry 4), DEC (diethyl carbonate) (entry 5) and MTBE (methyl *tert*-butyl ether) (entry 6) as the best solvents for the cross-coupling, affording the desired transamidation product in 63-98% yields; however, it should be noted that EA (ethyl acetate) (entry 7)

Table 1. Selection of Green Solvents[a,b]



1 2 3

entry	solvent	yield (%)
1	2-MeTHF	98
2	CPME	63
3	*i*-PrOAc	77
4	*p*-cymene	87
5	DEC	90
6	MTBE	92
7	EA	72
8	anisole	16
9	1,8-cineole	40
10	DMC	79
11	GVL	25
12	ethyl levulinate	32
13	PC	22
14	DME	86

[a]Amide (1.0 equiv), Ar-NH_2 (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), solvent (0.25 M), 110 °C, 15 h. [b]GC/^{1}H NMR yields. 2-MeTHF = 2-methyltetrahydrofuran; CPME = cyclopentyl methyl ether; *i*-PrOAc = isopropyl acetate; *p*-cymene = 1-methyl-4-(propan-2-yl)benzene; DEC = diethyl carbonate; MTBE = methyl *tert*-butyl ether; EA = ethyl acetate; 1,8-cineole = 1,3,3-trimethyl-2-oxabicyclo[2.2.2]octane; DMC = dimethyl carbonate; GVL = γ-valerolactone; ethyl levulinate = ethyl 4-oxopentanoate; PC = propylene carbonate; DME = 1,2-dimethoxyethane.

and DMC (dimethyl carbonate) (entry 10) are also effective solvents. These results compare favorably with the benchmark DME (86% yield) (entry 14). It is worth noting that anisole (entry 8), 1,8-cineole

(eucalyptol) (entry 9), γ-valerolactone (GVL) (entry 11), ethyl levulinate (entry 12) and PC (propylene carbonate) (entry 13) were generally less effective. Furthermore, out of the carbonate solvents[48-57] examined both DEC (diethyl carbonate) (entry 5) and DMC (dimethyl carbonate) (entry 10) proved effective, while DEC showed better reactivity and was selected for further study (*vide infra*). Similarly, out of the ester solvents[48-57] examined, both *i*-PrOAc (entry 3) and EA (entry 7) were effective, while *i*-PrOAc showed better reactivity and was selected for further evaluation. It is also worth noting that alcohols and ketones are not suitable solvents for amide bond cross-coupling by C–N activation due to esterification and aldol type reactions of the resonance activated amide bonds.[84] On the basis of the initial screening, we have selected six solvents for further evaluation.

We have also conducted an additional round of screening using the six identified solvents that showed the highest reactivity (Table S1, SI). For this round, we focused on evaluating the effect of using (1) the less sterically demanding Neolyst CX21, [Pd(IPr)(allyl)Cl], that undergoes faster activation;[85,86] (2) the use of electron-rich imidazolinylidene Pd-PEPPSI-SIPr that promotes faster oxidative addition;[66,67,87] (3) the addition of water to promote ligand exchange/catalyst activation.[88] In this additional screen, 2-MeTHF and MTBE showed the highest overall reactivity (average of 80%); however, we note that promising results have also been achieved using *i*-PrOAc, which is one of the top recommended green solvents by solvent selection guides (*vide infra*).[48-57]

Next, we have further conducted a detailed investigation using different Pd(II)–NHC precatalysts as promoters for the coupling using 2-MeTHF and MTBE as the identified solvents (Table 2). This comprehensive selection of catalysts (Figure 2) was based on their activity in the cross-coupling reactions, stability of Pd(II)–NHC precatalysts, robustness to undergo activation to Pd(0) and diversity of the ancillary and throw-away ligands. The selected catalysts included those with the privileged IPr imidazolylidene scaffold and various throw-away ligands (cinnamyl, allyl, *t*-Bu-indenyl, 3-Cl-Py), such as [Pd(IPr)(cin)Cl] (**4**),[85,86] [Pd(IPr)(allyl)Cl] (**5**),[85,86] [Pd(IPr)(*t*-Bu-ind)Cl] (**6**),[89] [Pd(IPr)(3-Cl-py)Cl] (**7**),[90] less sterically-demanding IMes imidazolylidene, such as [Pd(IMes)(allyl)Cl] (**8**),[91] saturated and

more σ-donating imidazolinylidene SIPr, such as [Pd(SIPr)(3-Cl-py)Cl] (**9**)[92] and [Pd(SIPr)(cin)Cl] (**10**),[85,86] and extremely sterically-hindered IPr* ligand, such as [Pd(IPr*)(3-Cl-py)Cl] (**11**).[93] Two other

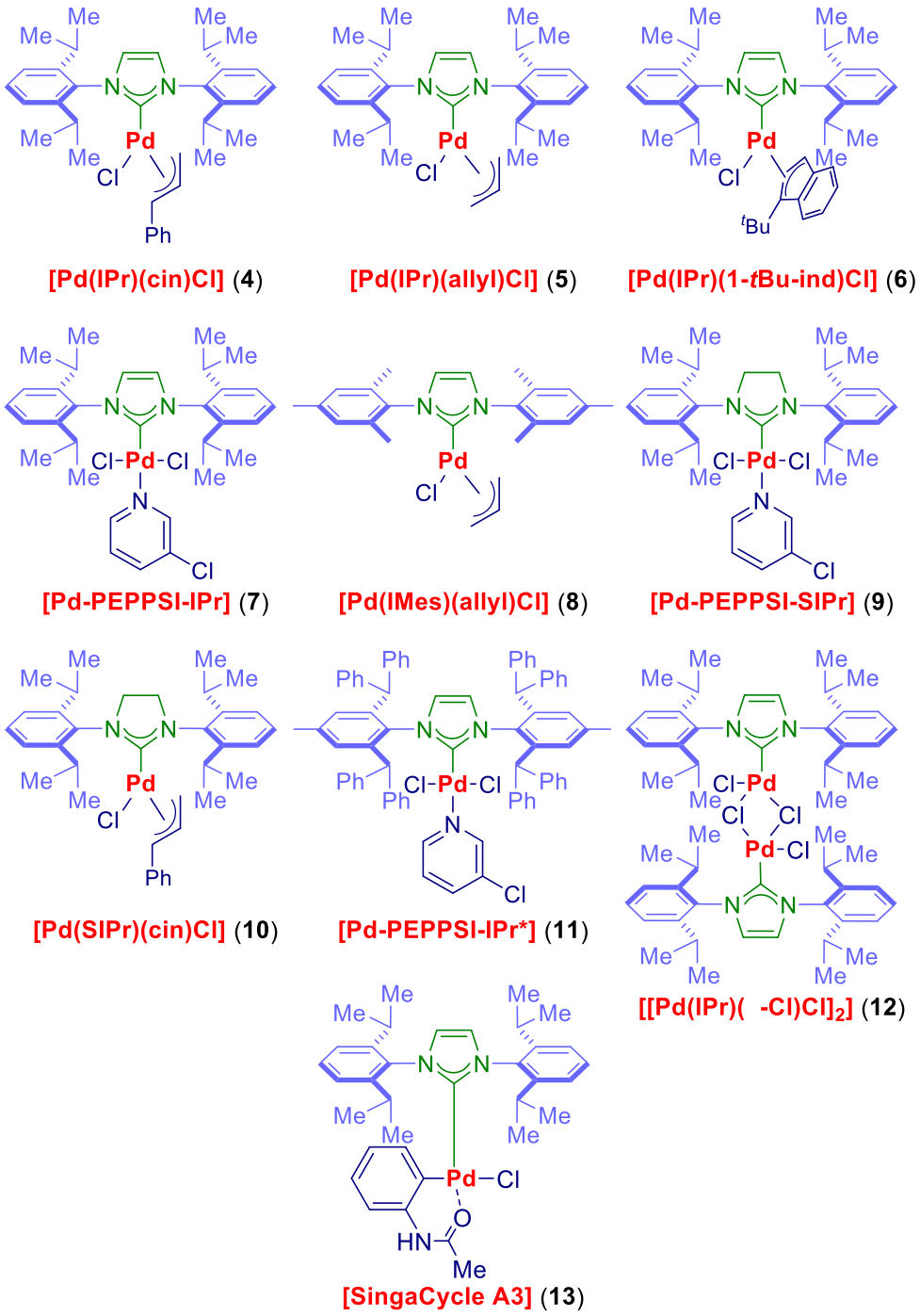
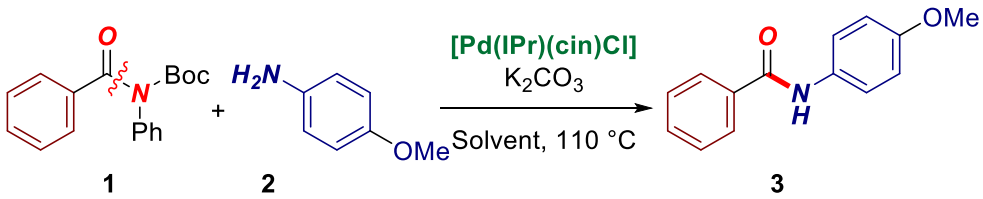


Figure 2. Structures of Pd(II)-NHC precatalysts in the acyl Buchwald-Hartwig cross-coupling of amides.

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



1 2 3

entry	catalyst	MTBE yield (%)	2-MeTHF yield (%)
1	[Pd(IPr)(cin)Cl] (**4**)	95	93
2	[Pd(IPr)(allyl)Cl] (**5**)	94	90
3	[Pd(IPr)(*t*-Bu-ind)Cl] (**6**)	93	98
4	[Pd(IPr)(3-Cl-py)Cl] (**7**)	96	84
5	[Pd(IMes)(allyl)Cl] (**8**)	95	97
6	[Pd(SIPr)(3-Cl-py)Cl] (**9**)	77	62
7	[Pd(SIPr)(cin)Cl] (**10**)	94	98
8	[Pd(IPr*)(3-Cl-py)Cl] (**11**)	49	32
9	[Pd(IPr)(μ-Cl)Cl]$_2$ (**12**)	91	98
10	SingaCycle A3 (**13**)	83	98

[a]Amide (1.0 equiv), Ar-NH_2 (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), solvent (0.25 M), 110 °C, 15 h. [b]GC/^{1}H NMR yields.

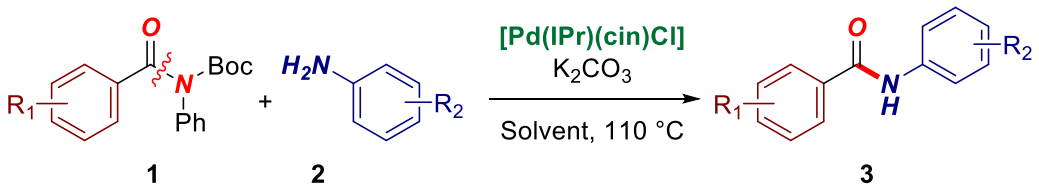
catalysts were selected with different throw-away ligands, namely chloro dimers [Pd(IPr)(μ-Cl)Cl]$_2$ (**12**)[85,86,92] and palladacycles (SingaCycle A3) (**13**)[94] due to recent reports on their high activity in the cross-coupling.

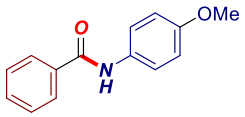
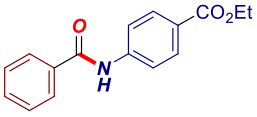
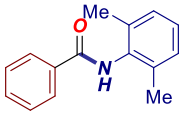
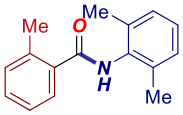
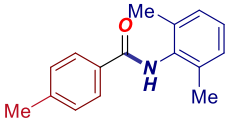
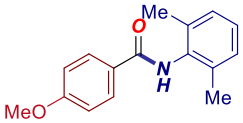
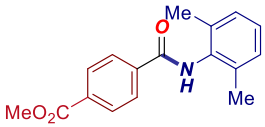
We were pleased to find that with the exception of the SIPr-PEPPSI-based catalyst (**9**) (Table 2, entry 6) and sterically-demanding IPr* ligand (**11**) (entry 8), all evaluated Pd(II)–NHCs shows excellent reactivity in both solvents identified. For subsequent screening, we selected Neolyst CX31 (**4**) (entry 1)

due to its ready availability and robustness in the coupling;[85,86] however, it should be noted that several other catalysts, including [Pd(IPr)(*t*-Bu-ind)Cl] (**6**) (entry 3), [Pd(IPr)(allyl)Cl] (**5**) (entry 2), [Pd(SIPr)(cin)Cl] (**10**) (entry 7) and [Pd(IMes)(allyl)Cl] (**8**) (entry 5) showed excellent reactivity in the coupling, which could be useful for specific reaction optimization of the acyl-Buchwald-Hartwig cross-coupling of amides in green recommended solvents.

Having conducted initial optimizations, we next performed evaluation of scope with respect to representative anilines and amide variation across the six solvents that showed the highest reactivity in the initial screen, namely 2-MeTHF (2-methyltetrahydrofuran), CPME (cyclopentyl methyl ether), *i*-PrOAc (isopropyl acetate), *p*-cymene, DEC (diethyl carbonate) and MTBE (methyl *tert*-butyl ether) (Table 3). Reaction time has not been optimized. 15 h has been selected as a benchmark based on previous studies on Pd-catalyzed transamidations.[40-42] In terms of anilines, we selected electron-rich (entry 1), electron-deficient (entry 2) and sterically-hindered anilines (entry 3). With respect to the amide component, we selected sterically-hindered (entry 4), sterically- and electronically-unbiased (entry 5), deactivated electron-rich (entry 6) and electron-deficient amide (entry 7). In this screen, 2-MeTHF and MTBE showed the highest performance across all substrates examined with an average yield of >90%. As expected, substitution with sterically-hindered groups (entry 4) and the sensitive ester group (entry 2 and 7) proved to be the most challenging substrate combinations. Nevertheless, it is worthwhile to note that several other solvents examined, namely CPME, *i*-PrOAc and DEC gave satisfactory to high yields in the majority of the examples examined (average of 69-77%). This broad compatibility with recommended solvents could be useful for further implementation of green protocols for acyl-Buchwald-Hartwig cross-coupling of amides. Furthermore, the selectivity of the coupling of the amide N–C bond in the presence of ester bond should be noted. This functional group tolerance is inherent to Pd-catalyzed cross-coupling and not compatible with recent transition-metal-free protocols for amide bond interconversion.[44]

Table 3. Scope of the Acyl Buchwald-Hartwig Cross-Coupling of Representative Anilines and Amide in Green Solvents[a,b,c]



entry	product	2-MeTHF yield (%)	CPME yield (%)	*i*-PrOAc yield (%)	*p*-Cymene yield (%)	DEC yield (%)	MTBE yield (%)
1		93	78	76	57	72	95
2		98	24	92	77	78	90
3		98	63	77	87	90	92
4		98	64	41	28	51	91
5		98	98	96	41	98	93
6		92	98	98	98	92	98
7		90	98	64	98	<5	92

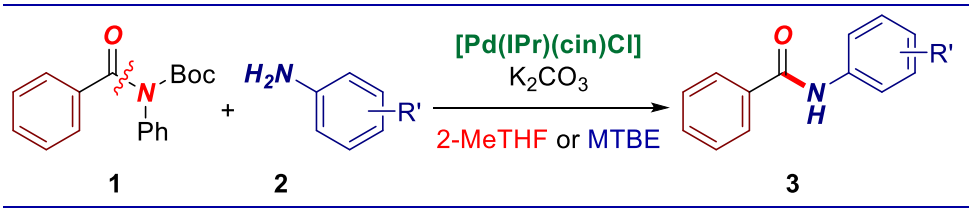
[a]Amide (1.0 equiv), Ar-NH_2 (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), solvent (0.25 M), 110 °C, 15 h. [b]Isolated yields. [c]Key: red, yield <50%; yellow, yield 50−89%; green, yield ≥90%.

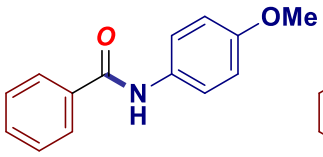
With the insight from the solvent evaluation, we next probed the versatility of the acyl-Buchwald-Hartwig cross-coupling of amides in 2-MeTHF and MTBE as the identified solvents (Tables 4-5). As shown, the reaction showed broad scope and excellent functional group tolerance with respect to the

aniline component (Table 4). As such, electronic variation on the aniline is well-tolerated, which includes the challenging deactivating ester group (**3a-3d**). Furthermore, steric-hindrance, including even extremely sterically-hindered 2,6-diisopropylaniline afforded the products in high yields (**3e-3h**). Moreover, meta-substitution (**3i-3j**) as well as fluoro-containing anilines that give valuable fluoro-containing benzamides (**3j-3k**) were successfully employed in the coupling. Interestingly, even secondary anilines such as N-methylaniline and tetrahydroquinoline could be used to furnish the products in high yields (**3l-3m**). Interestingly, the reaction tolerates nitro-groups, which strongly deactivate the aniline towards cross-coupling (**3n**).[66,67,79,80] Finally, biorelevant amines, such as 3-amino-9-ethylcarbazole can also be used in this cross-coupling (**3o**), highlighting the potential in medicinal chemistry settings.[40,44] It should be noted that in some cases (**3k**, **3n**) the yield is lower due to side-reactions, including non-specific decomposition.

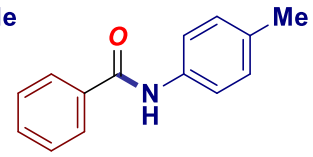
The scope with respect of this acyl-Buchwald-Hartwig cross-coupling to the amide component is also very broad (Table 5). As shown, sterically-hindered (**3p**) and electronically-differentiated amides (**3q-3s**), including with ester functional group (**3s**) gave the coupling products in high yields and with full N–C vs. O–C coupling selectivity. Furthermore, fluorinated amides that might be problematic due to the strong-electron withdrawing effect enhancing the N–C(O) resonance are easily accommodated (**3t-3u**).[40-47] Similarly, heterocycles, such as electronically deactivating 2-furylamide (**3v**) as well as alkyl amides (**3w**) are well tolerated. It is worth noting that comparable efficiency has been observed across all substrates using both 2-MeTHF and MTBE as the two solvents identified, which could be useful for the selection of a most suitable solvent for the coupling.

Table 4. Scope of the Acyl Buchwald-Hartwig Cross-Coupling of Amides in Green Solvents: Scope of Anilines[a,b]

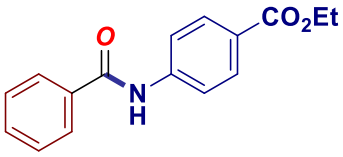




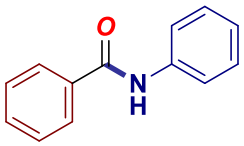
3a: 93% yield/95% yield



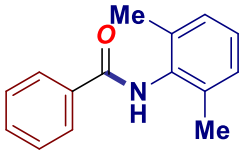
3b: 98% yield/98% yield



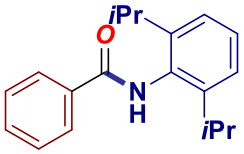
3c: 98% yield/90% yield



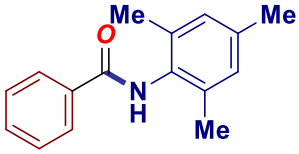
3d: 95% yield/93% yield



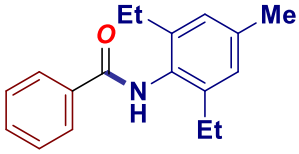
3e: 98% yield/92% yield



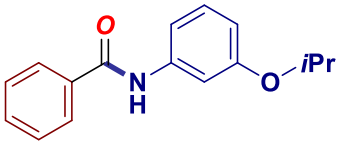
3f: 89% yield/85% yield



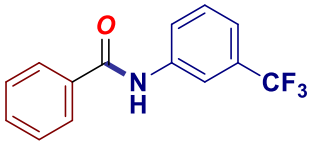
3g: 94% yield/93% yield



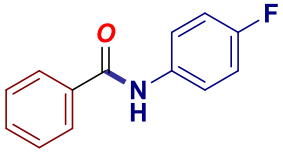
3h: 95% yield/96% yield



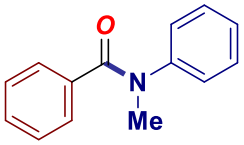
3i: 92% yield/93% yield



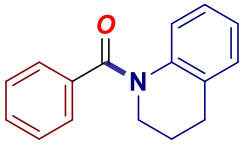
3j: 96% yield/80% yield



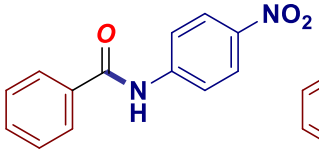
3k: 72% yield/96% yield[c]



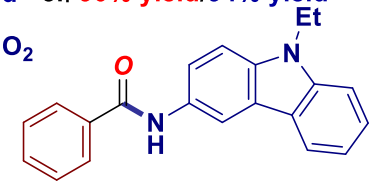
3l: 90% yield/94% yield



3m: 90% yield/88% yield



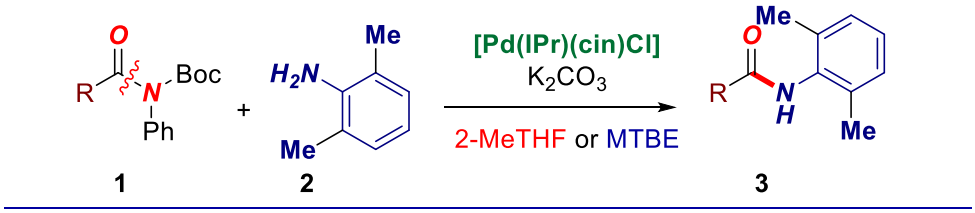
3n: 43% yield/48% yield

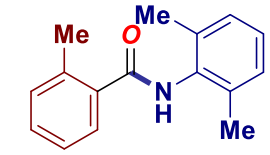


3o: 73% yield/91% yield

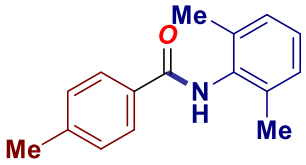
[a]Amide (1.0 equiv), Ar-NH_2 (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), **2-MeTHF** or **MTBE** (0.25 M), 110 °C, 15 h. [b]Isolated yields in **2-MeTHF** / **MTBE**. [c][Pd] (6 mol%).

Table 5. Scope of the Acyl Buchwald-Hartwig Cross-Coupling of Amides in Green Solvents: Scope of Amides[a,b]

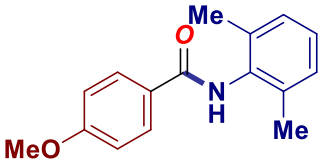




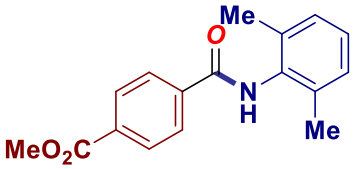
3p: 98% yield/91% yield



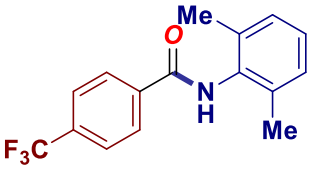
3q: 98% yield/93% yield



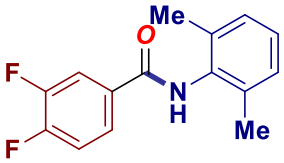
3r: 92% yield/98% yield



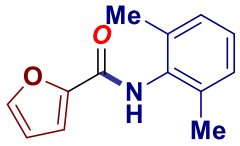
3s: 90% yield/92% yield



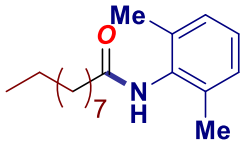
3t: 91% yield/90% yield



3u: 98% yield/97% yield



3v: 98% yield/97% yield

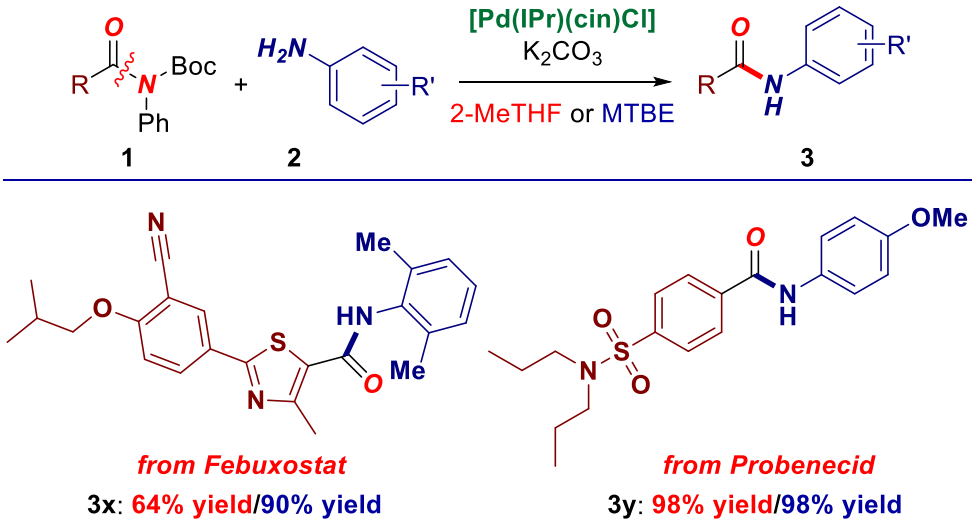


3w: 98% yield/83% yield

[a]Amide (1.0 equiv), Ar-NH_2 (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), **2-MeTHF** or **MTBE** (0.25 M), 110 °C, 15 h. [b]Isolated yields in **2-MeTHF** / **MTBE**.

Prompted by the high efficiency of this acyl-Buchwald-Hartwig cross-coupling, we demonstrated the utility of this reaction in the late-stage functionalization of APIs (Table 6). As shown, direct cross-coupling of amides of *Febuxostat* (antigout)[95,96] and *Probenecid* (antihyperuricemic)[97] using 2-MeTHF or MTBE as solvents, provided the transamidation products in high yields, demonstrating the potential of this reaction in medicinal chemistry research. These reactions benefit from the functional group tolerance to heterocycles, nitriles and sulfonamides of the Pd-catalyzed acyl Buchwald-Hartwig cross-coupling of amides.[40-47]

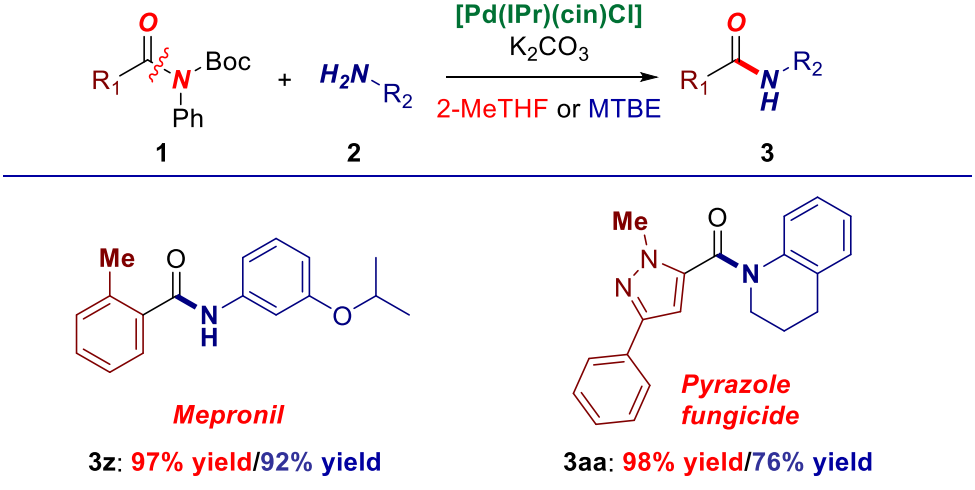
Table 6. Late-Stage Functionalization of Pharmaceuticals[a,b]



[a]Amide (1.0 equiv), Ar-NH_2 (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), **2-MeTHF** or **MTBE** (0.25 M), 110 °C, 15 h. [b]Isolated yields in **2-MeTHF** / **MTBE**.

Particularly noteworthy is the ability of this acyl-Buchwald-Hartwig cross-coupling to be directly employed in the synthesis of bioactive chemicals, such as *Mepronil*[98,99] and pyrazole fungicides[100] (Table 7). These reactions highlight the potential of amides as unconventional C–N to C–N' electrophiles in organic synthesis.

Table 7. Synthesis of Agrochemicals[a,b]



[a]Amide (1.0 equiv), Ar-NH_2 (2.0 equiv), [Pd] (3 mol%), K_2CO_3 (3.0 equiv), **2-MeTHF** or **MTBE** (0.25 M), 110 °C, 15 h. [b]Isolated yields in **2-MeTHF** / **MTBE**.

Finally, we conducted kinetic studies to gain preliminary insight into the high efficiency of 2-MeTHF and MTBE as the preferred solvents for the acyl-Buchwald-Hartwig cross-coupling of amides (Figure 3). As shown, the kinetic studies indicate that green and sustainable 2-MeTHF is a superior solvent to the toxic DME in the coupling, while the use of MTBE also provides improved kinetic profile. It is interesting to note that with 2-MeTHF the conversion occurs at the beginning of the reaction. We believe that 2-MeTHF might coordinate to Pd and facilitate catalyst activation. These observations highlight the importance of using alternative solvents in the amide bond activation methods.

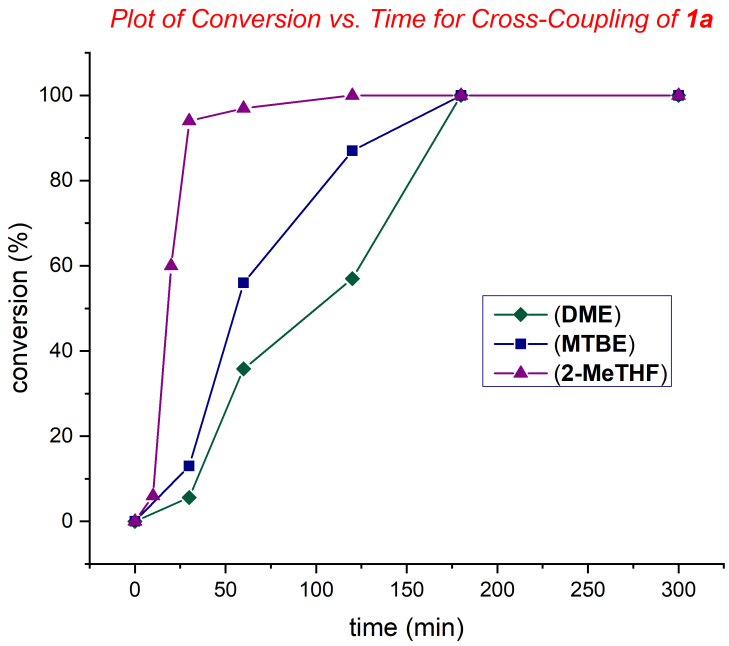


Figure 3. Kinetic profile in the acyl-Buchwald-Hartwig cross-coupling of amides. **1a** (1.0 equiv), Ph-NH_2 (2.0 equiv), Pd(IPr)(cin)Cl (3 mol%), K_2CO_3 (3.0 equiv), solvent (0.25 M), 110 °C, 0-300 min.

CONCLUSIONS

In summary, we have presented the first green solvent selection for the powerful platform of acyl Buchwald-Hartwig cross-coupling of amides. This reaction proceeds by selective amide N–C bond cleavage and results in a net transamidation of the historically challenging secondary amide bonds. The present study identified 2-MeTHF and MTBE as the recommended solvents for the Buchwald-Hartwig cross-coupling of amides. In particular, 2-MeTHF is a recommended solvent by several recent solvent

selection guides in terms of health, safety, sustainability and environmental impact,[48-57,72-74] while MTBE has found broad industrial applications as an alternative to ethers.[68-71] Furthermore, several other alternative solvents, such as CPME, *i*-PrOAc and DEC have also been identified for the cross-coupling and can be employed in select cross-coupling cases. The unique versatility of the method has been demonstrated by broad scope, excellent functional group tolerance, applications to the late-stage functionalization of APIs and synthesis of bioactive compounds. The green solvent selection enables enhanced reactivity in the biorelevant C–N to C–N' cross-coupling manifold of amides, while significantly improving health, environmental and safety factors. Finally, it should be noted that even though green solvents, such as ethers or THF derivatives are vastly preferred over not environmental solvents, such as chlorinated solvents, there is still path to improvement to work with alcohols or water. In this context, future studies on amide bond activation should incorporate green solvent selection guides to expand the existing arsenal of amide bond interconversion methods.

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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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) de Figueiredo, R. M.; Suppo, J.-S.; Campagne, J.-M. Nonclassical Routes for Amide Bond Formation. *Chem. Rev.* **2016**, *116*, 12029−12122. DOI: 10.1021/acs.chemrev.6b00237.

(2) Hartwig, J. F. Carbon–heteroatom Bond Formation Catalysed by Organometallic Complexes. *Nature* **2008**, *455*, 314−322. DOI:10.1038/nature07369.

(3) Dorel, R.; Grugel, C. P.; Haydl, A. M. The Buchwald-Hartwig Amination After 25 Years. *Angew. Chem., Int. Ed.* **2019**, *58*, 17118−17129. DOI: 10.1002/anie.201904795.

(4) Forero-Cortes, P. A.; Haydl, A. M. The 25th Anniversary of the Buchwald-Hartwig Amination: Development, Applications, and Outlook. *Org. Process Res. Dev.* **2019**, *23*, 1478−1483. DOI: 10.1021/acs.oprd.9b00161.

(5) Heravi, M. M.; Kheilkordi, Z.; Zadsirjan, V.; Heydari, M.; Malmir, M. Buchwald-Hartwig reaction:

An overview. *J. Organomet. Chem.* **2018**, *861*, 17−104. DOI: 10.1016/j.jorganchem.2018.02.023.

(6) Seifinoferest, B.; Tanbakouchian, A.; Larijani, B.; Mahdavi, M. Ullmann-Goldberg and Buchwald-Hartwig C-N Cross Couplings: Synthetic Methods to Pharmaceutically Potential N-Heterocycles. *Asian J. Org. Chem.* **2021**, *10*, 1319−1344. DOI: 10.1002/ajoc.202100072.

(7) West, M. J.; Fyfe, J. W. B.; Vantourout, J. C.; Watson, A. J . B. Mechanistic Development and Recent Applications of the Chan−Lam Amination. *Chem. Rev.* **2019**, *119*, 12491−12523. DOI: 10.1021/acs.chemrev.9b00491.

(8) Inoue, F.; Kashihara, M.; Yadav, M. R.; Nakao, Y. Buchwald-Hartwig Amination of Nitroarenes. *Angew. Chem., Int. Ed.* **2017**, *56*, 13307−13309. DOI: 10.1002/anie.201706982.

(9) Konya, K.; Pajtas, D.; Kiss-Szikszai, A.; Patonay, T. Buchwald-Hartwig Reactions of Monohaloflavones. *Eur. J. Org. Chem.* **2015**, *4*, 828−839. DOI: 10.1002/ejoc.201403108.

(10) Loomis, W. D.; Stumpf, P. K. Transamination and Transamidation in *Der Stickstoffumsatz / Nitrogen Metabolism*. ed. Allen, E. K. Springer, **1958**, 249−261. DOI: 10.1007/978-3-642-94733-9_12.

(11) Galat, A.; Elion, G. The interaction of amides with amines: A general method of acylation. *J. Am. Chem. Soc.* **1943**, *65*, 1566–1567. DOI: 10.1021/ja01248a033.

(12) Pettit, G.; Kalnins, M.; Liu, T.; Thomas, E.; Parent, K. Notes-potential cancerocidal agents. III. Formanilides. *J. Org. Chem.* **1961**, *26*, 2563–2566. DOI: 10.1021/jo01351a623.

(13) Kraus, M. A. The formylation of aliphatic amines by dimethylformamide. *Synthesis* **1973**, 361–362. DOI: 10.1002/chin.197342194.

(14) Bon, E.; Bigg, D. C. H.; Bertrand, G. Aluminum chloride-promoted transamidation reactions. *J. Org. Chem.* **1994**, *59*, 4035–4036. DOI: 10.1021/jo00094a004.

(15) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Stahl, S. S. Mechanism of Al(III)-catalyzed transamidation of unactivated secondary carboxamides. *J. Am. Chem. Soc.* **2006**, *128*, 5177–5183. DOI: 10.1021/ja060331x.

(16) Martin, A. R. The Buchwald-Hartwig Reaction in *Science of Synthesis: N-Heterocyclic Carbenes in Catalytic Organic Synthesis*. ed. Nolan, S. P.; Cazin, C. S. J. Thieme, **2018**, 161–182. DOI: 10.1055/sos-SD-223-00066.

(17) Liu, C.; Szostak, M. Decarbonylative Cross-Coupling of Amides. *Org. Biomol. Chem.* **2018**, *16*, 7998−8010. DOI: 10.1039/c8ob01832d.

(18) Chaudhari, M. B.; Gnanaprakasam, B. Recent Advances in the Metal−Catalyzed Activation of Amide Bonds. *Chem. Asian J.* **2019**, *14*, 76−93. DOI: 10.1002/asia.201801317.

(19) Li, G.; Ma, S.; Szostak, M. Amide Bond Activation: The Power of Resonance. *Trends Chem.* **2020**, *2*, 914−928. DOI: 10.1016/j.trechm.2020.08.001.

(20) Chen, Y.; Turlik, A.; Newhouse, T. Amide α,β-Dehydrogenation Using Allyl-Palladium Catalysis and a Hindered Monodentate Anilide. *J. Am. Chem. Soc.* **2016**, *138*, 1166−1169. DOI: 10.1021/jacs.5b12924.

(21) Caldwell, N.; Jamieson, C.; Simpson, I.; Watson, A. J. B. Catalytic Amidation of Unactivated Ester Derivatives Mediated by Trifluoroethanol. *Chem. Commun.* **2015**, *51*, 9495−9498. DOI: 10.1039/C5CC02895G.

(22) Zhu, R. Y.; Farmer, M. E.; Chen, Y. Q.; Yu, J. Q. A Simple and Versatile Amide Directing Group for C−H Functionalizations. *Angew. Chem., Int. Ed.* **2016**, *55*, 10578−10599. DOI: 10.1002/anie.201600791.

(23) Zultanski, S. L.; Zhao, J.; Stahl, S. S. Practical Synthesis of Amides via Copper/ABNO-

Catalyzed Aerobic Oxidative Coupling of Alcohols and Amines. *J. Am. Chem. Soc.* **2016**, *138*, 6416−6419. DOI: 10.1021/jacs.6b03931.

(24) Bechara, W. S.; Pelletier, G.; Charette, A. B. Chemoselective Synthesis of Ketones and Ketimines by Addition of Organometallic Reagents to Secondary Amides. *Nat. Chem.* **2012**, *4*, 228−234. DOI: 10.1038/nchem.1268.

(25) Das, S.; Addis, D.; Zhou, S.; Junge, K.; Beller, M. Zinc-catalyzed Reduction of Amides: Unprecedented Selectivity and Functional Group Tolerance. *J. Am. Chem. Soc.* **2010**, *132*, 1770−1771. DOI: 10.1021/ja910083q.

(26) de la Torre, A.; Kaiser, D.; Maulide, N. Flexible and Chemoselective Oxidation of Amides to α-Keto Amides and α-Hydroxy Amides. *J. Am. Chem. Soc.* **2017**, *139*, 6578−6581. DOI: 10.1021/jacs.7b02983.

(27) Vantourout, J. C.; Miras, H. N.; Isidro-Llobet, A.; Sproules, S.; Watson, A. J. B. Spectroscopic Studies of the Chan-Lam Amination: A Mechanism-Inspired Solution to Boronic Ester Reactivity. *J. Am. Chem. Soc.* **2017**, *139*, 4769−4779. DOI: 10.1021/jacs.6b12800.

(28) Ojeda-Porras, A.; Gamba-Sánchez, D. Recent Developments in Amide Synthesis Using Nonactivated Starting Materials. *J. Org. Chem.* **2016**, *81*, 11548−11555. DOI: 10.1021/acs.joc.6b02358.

(29) Shi, S.; Nolan, S. P.; Szostak, M. Well-Defined Palladium(II)-NHC (NHC = N-Heterocyclic Carbene) Precatalysts for Cross-Coupling Reactions of Amides and Esters by Selective Acyl CO–X (X = N, O) Cleavage. *Acc. Chem. Res.* **2018**, *51*, 2589−2599. DOI: 10.1021/acs.accounts.8b00410.

(30) Meng, G.; Szostak, M. N-Acyl-Glutarimides: Privileged Scaffolds in Amide N–C Bond Cross-Coupling. *Eur. J. Org. Chem.* **2018**, *20-21*, 2352−2365. DOI: 10.1002/ejoc.201800109.

(31) Takise, R.; Muto, K.; Yamaguchi, J. Cross-Coupling of Aromatic Esters and Amides. *Chem. Soc.*

Rev. **2017**, *46*, 5864−5888. DOI: 10.1039/c7cs00182g.

(32) Kaiser, D.; Bauer, A.; Lemmerer, M.; Maulide, N. Amide Activation: An Emerging Tool for Chemoselective Synthesis. *Chem. Soc. Rev.* **2018**, *47*, 7899−7925. DOI: 10.1039/c8cs00335a.

(33) Liu, C.; Szostak, M. Twisted Amides: From Obscurity to Broadly Useful Transition-Metal-Catalyzed Reactions by N−C Amide Bond Activation. *Chem. Eur. J.* **2017**, *23*, 7157−7173. DOI: 10.1002/chem.201783061.

(34) Szostak, R.; Shi, S.; Meng, G.; Lalancette, R.; Szostak, M. Ground-State Distortion in *N*-Acyl-*tert*-butyl-carbamates (Boc) and *N*-Acyl-tosylamides (Ts): Twisted Amides of Relevance to Amide N–C Cross-Coupling. *J. Org. Chem.* **2016**, *81*, 8091−8094. DOI: 10.1021/acs.joc.6b01560.

(35) Meng, G.; Shi, S.; Lalancette, R.; Szostak, R.; Szostak, M. Reversible Twisting of Primary Amides via Ground State N–C(O) Destabilization: Highly Twisted Rotationally Inverted Acyclic Amides. *J. Am. Chem. Soc.* **2018**, *140*, 727−734. DOI: 10.1021/jacs.7b11309.

(36) Liu, C.; Shi, S.; Liu, Y.; Liu, R.; Lalancette, R.; Szostak, R.; Szostak, M. The Most Twisted Acyclic Amides: Structure and Reactivity. *Org. Lett.* **2018**, *20*, 7771−7774. DOI: 10.1021/acs.orglett.8b03175.

(37) Acosta-Guzmán, P.; Mateus-Gómez, A.; Gamba-Sánchez, D. Direct Transamidation Reactions: Mechanism and Recent Advances. *Molecules* **2018**, *23*, 2382. DOI: 10.3390/molecules23092382.

(38) Lanigan, R. M.; Sheppard, T. D. Recent Developments in Amide Synthesis: Direct Amidation of Carboxylic Acids and Transamidation Reactions. *Eur. J. Org. Chem.* **2013**, *33*, 7453−7465. DOI: 10.1002/ejoc.201300573.

(39) Li, G. C.; Szostak, M. Non-Classical Amide Bond Formation: Transamidation and Amidation of Activated Amides and Esters by Selective N–C/O–C Cleavage. *Synthesis* **2020**, *52*, 2579−2599. DOI:

10.1055/s-0040-1707101.

(40) Meng, G.; Lei, P.; Szostak, M. A General Method for Two-Step Transamidation of Secondary Amides Using Commercially Available, Air- and Moisture-Stable Palladium/NHC (N-Heterocyclic Carbene) Complexes. *Org. Lett.* **2017**, *19*, 2158−2161. DOI: 10.1021/acs.orglett.7b00796.

(41) Shi, S.; Szostak, M. Pd–PEPPSI: a general Pd–NHC precatalyst for Buchwald–Hartwig cross-coupling of esters and amides (transamidation) under the same reaction conditions. *Chem. Commun.* **2017**, *53*, 10584−10587. DOI: 10.1039/c7cc06186b.

(42) Zhou, T.; Li, G.; Nolan, D. P.; Szostak, M. [Pd(NHC)(acac)Cl]: Well-Defined, Air-Stable, and Readily Available Precatalysts for Suzuki and Buchwald-Hartwig Cross-coupling (Transamidation) of Amides and Esters by N−C/O−C Activation. *Org. Lett.* **2019**, *21*, 3304−3309. DOI: 10.1021/acs.orglett.9b01053.

(43) Li, G.; Szostak, M. Highly Selective Transition-metal-free Transamidation of Amides and Amidation of Esters at Room Temperature. *Nat. Commun.* **2018**, *9*, 4165. DOI: 10.1038/s41467-018-06623-1.

(44) Li, G.; Ji, C. L.; Hong, X.; Szostak, M. Highly Chemoselective, Transition-Metal-Free Transamidation of Unactivated Amides and Direct Amidation of Alkyl Esters by N−C/O−C Cleavage. *J. Am. Chem. Soc.* **2019**, *141*, 11161−11172. DOI: 10.1021/jacs.9b04136.

(45) Rahman, M. M.; Li, G.; Szostak, M. Metal-Free Transamidation of Secondary Amides by N−C Cleavage. *J. Org. Chem.* **2019**, *84*, 12091−12100. DOI: 10.1021/acs.joc.9b02013.

(46) Liu, Y.; Shi, S.; Achtenhagen, M.; Liu, R.; Szostak, M. Metal-Free Transamidation of Secondary Amides via Selective N–C Cleavage under Mild Conditions. *Org. Lett.* **2017**, *19*, 1614−1617. DOI: 10.1021/acs.orglett.7b00429.

(47) Liu, Y.; Achtenhagen, M.; Liu, R.; Szostak, M. Transamidation of N-Acyl-Glutarimides with Amines. *Org. Biomol. Chem.* **2018**, *16*, 1322−1329. DOI: 10.1039/C7OB02874A.

(48) Allen, D. T.; Gathergood, N.; Licence, P.; Subramaniam, B. Expectations for Manuscripts Contributing to the Field of Solvents in ACS Sustainable Chemistry & Engineering. *ACS Sustain. Chem. Eng.* **2020**, *8*, 14627–14629. DOI: 10.1021/acssuschemeng.0c06901.

(49) Prat, D.; Hayler, J.; Wells, A. A survey of solvent selection guides. *Green Chem.* **2014**, *16*, 4546−4551. DOI: 10.1039/c4gc01149j.

(50) Alder, C. M.; Hayler, J. D.; Henderson, R. K.; Redman, A. M.; Shukla, L.; Shuster, L. E.; Sneddon, H. F. Updating and further expanding GSK's solvent sustainability guide. *Green Chem.* **2016**, *18*, 3879−3890. DOI: 10.1039/c6gc00611f.

(51) Prat, D.; Wells, A.; Hayler, J.; Sneddon, H.; McElroy, C. R.; Abou-Shehada, S.; Dunne, P. J. CHEM21 selection guide of classical- and less classical-solvents. *Green Chem.* **2016**, *18*, 288−296. DOI: 10.1039/c5gc01008j.

(52) Tobiszewski, M.; Tsakovski, S.; Simeonov, V.; Namieśnik, J.; Pena-Pereira, F. A solvent selection guide based on chemometrics and multicriteria decision analysis. *Green Chem.* **2015**, *17*, 4773−4785. DOI: 10.1039/c5gc01615k.

(53) Dioraziom, L. J.; Hose, D. R. J.; Adlington, N. K. Toward a More Holistic Framework for Solvent Selection. *Org. Process Res. Dev.* **2016**, *20*, 760−773. DOI: 10.1021/acs.oprd.6b00015.

(54) Sheldon, R. A. The *E* factor 25 years on: the rise of green chemistry and sustainability. *Green Chem.* **2017**, *19*, 18−43. DOI: 10.1039/c6gc02157c.

(55) Erythropel, H. C.; Zimmerman, J. B.; Winter, T. M.; Petitjean, L.; Melnikov, F.; Lam, C. H.; Lounsbury, A. W.; Mellor, K. E.; Janković, N. Z.; Tu, Q.; Pincus, L. N.; Falinski, M. M.; Shi, W.; Coish,

P.; Plata, D. L.; Anastas, P. T. The Green ChemisTREE: 20 years after taking root with the 12 principles. *Green Chem.* **2018**, *20*, 1929−1961. DOI: 10.1039/c8gc00482j.

(56) Bryan, M. C.; Dillon, B.; Hamann, L. G.; Hughes, G. J.; Kopach, M. E.; Peterson, E. A.; Pourasharf, M.; Raheem, I.; Richardson, P.; Richter, D.; Sneddon, H. F. Sustainable Practices in Medicinal Chemistry: Current State and Future Directions. *J. Med. Chem.* **2013**, *56*, 6007−6021. DOI: 10.1021/jm400250p.

(57) Slater, C. S.; Savelski, M. J.; Carole, W. A.; Constable, D. J. C. Solvent Use and Waste Issues in *Green Chemistry in the Pharmaceutical Industry*. ed. Dunn, P. J.; Wells, A. S.; Williams, M. T. Wiley: Weinheim, **2010**, 49−82. DOI: 10.1002/9783527629688.ch3.

(58) Pace, V.; Castoldi, L.; Monticelli, S.; Safranek, S.; Roller, A.; Langer, T.; Holzer, W. A Robust, Eco-Friendly Access to Secondary Thioamides through the Addition of Organolithium Reagents to Isothiocyanates in Cyclopentyl Methyl Ether (CPME). *Chem. Eur. J.* **2015**, *21*, 18966−18970. DOI: 10.1002/chem.201504247.

(59) Jessop, P. G. Searching for green solvents. *Green Chem.* **2011**, *13*, 1391−1398. DOI: 10.1039/c0gc00797h.

(60) Welton, T. Solvents and sustainable chemistry. *Proc. R. Soc. A* **2015**, *471*, 502. DOI: 10.1098/rspa.2015.0502.

(61) Byrne, F. P.; Jin, S.; Paggiola, G.; Petchey, T. H. M.; Clark, J. H.; Farmer, T. J.; Hunt, A. J.; McElroy, C. R.; Sherwood, J. Tools and techniques for solvent selection: green solvent selection guides. *Sustain. Chem. Process* **2016**, *4*, 7. DOI: 10.1186/s40508-016-0051-z.

(62) Sheldon, R. A.; Arends, I. W. C. E.; Hanefeld, U. Introduction: Green Chemistry and Catalysis in *Green Chemistry and Catalysis*. ed. Sheldon, R. A.; Arends, I. W. C. E.; Hanefeld, U. Wiley:

Weinheim, **2007**, 1−47. DOI: 10.1002/9783527611003.ch1.

(63) Li, C. J.; Trost, B. M. Green Chemistry for Chemical Synthesis. *Proc. Natl. Acad. Sci.* **2008**, *105*, 13197−13202. DOI: 10.1073/pnas.0804348105.

(64) Anastas, P.; Eghbali, N. Green Chemistry: Principles and Practice. *Chem. Soc. Rev.* **2010**, *39*, 301−312. DOI: 10.1039/b918763b.

(65) Sheldon, R. A. Fundamentals of green chemistry: efficiency in reaction design. *Chem. Soc. Rev.* **2012**, *41*, 1437−1451. DOI: 10.1039/c1cs15219j.

(66) Li, G.; Zhou, T.; Poater, A.; Cavallo, L.; Nolan, S. P.; Szostak, M. Buchwald–Hartwig cross-coupling of amides (transamidation) by selective N–C(O) cleavage mediated by air- and moisture-stable [Pd(NHC)(allyl)Cl] precatalysts: catalyst evaluation and mechanism. *Catal. Sci. Technol.* **2020**, *10*, 710−716. DOI: 10.1039/c9cy02080b.

(67) Li, G.; Lei, P.; Szostak, M.; Casals, E.; Poater, A.; Cavallo, L.; Nolan, S. P. Mechanistic Study of Suzuki-Miyaura Cross-Coupling Reactions of Amides Mediated by [Pd(NHC)(allyl)Cl] Precatalysts. *ChemCatChem* **2018**, *10*, 3096–3106. DOI: 10.1002/cctc.201800511.

(68) Zuhse, R.; Leggewie, C.; Hollmann, F.; Kara, S. Scaling-Up of "Smart Cosubstrate" 1,4-Butanediol Promoted Asymmetric Reduction of Ethyl-4,4,4-trifluoroacetoacetate in Organic Media. *Org. Process Res. Dev.* **2015**, *19*, 369−372. DOI: 10.1021/op500374x.

(69) Magnus, N. A.; Campagna, S.; Confalone, P. N.; Savage, S.; Meloni, D. J.; Waltermire, R. E.; Wethman, R. G.; Yates, M. Quaternary Chiral Center via Diastereoselective Enolate Amination Enables the Synthesis of an Anti-inflammatory Agent. *Org. Process Res. Dev.* **2010**, *14*, 159−167. DOI: 10.1021/op900255k.

(70) Fleckenstein, C. A.; Kadyrov, R.; Plenio, H. Efficient Large-Scale Synthesis of 9-Alkylfluorenyl

Phosphines for Pd-Catalyzed Cross-Coupling Reactions. *Org. Process Res. Dev.* **2008**, *12*, 475−479. DOI: 10.1021/op7001479.

(71) Mallesha, N.; Rao, S. P.; Suhas, R.; Gowda, D. C. An efficient synthesis of *tert*-butyl ethers/esters of alcohols/amino acids using methyl *tert*-butyl ether. *Tetrahedron Lett.* **2012**, *53*, 641–645. DOI: 10.1016/j.tetlet.2011.11.108.

(72) Pace, V.; Hoyos, P.; Castoldi, L.; María, P. D.; Alcántara, A. R. 2-Methyltetrahydrofuran (2-MeTHF): A Biomass-Derived Solvent with Broad Application in Organic Chemistry. *ChemSusChem* **2012**, *5*, 1369−1379. DOI: 10.1002/cssc.201100780.

(73) Monticelli, S.; Castoldi, L.; Murgia, I.; Senatore, R.; Mazzeo, E.; Wackerlig, J.; Urban, E.; Langer, T.; Pace, V. Recent advancements on the use of 2-methyltetrahydrofuran in organometallic chemistry. *Monatsh Chem.* **2017**, *148*, 37−48. DOI: 10.1007/s00706-016-1879-3.

(74) Bisz, E.; Szostak, M. 2-Methyltetrahydrofuran: A Green Solvent for Iron-Catalyzed Cross-Coupling Reactions. *ChemSusChem* **2018**, *11*, 1290−1294. DOI: 10.1002/cssc.201800142.

(75) Froese, R. D. J.; Lombard, C.; Pompeo, M.; Rucker, R. P.; Organ, M. G. Designing Pd–N-Heterocyclic Carbene Complexes for High Reactivity and Selectivity for Cross-Coupling Applications. *Accounts Chem. Res.* **2017**, *50*, 2244−2253. DOI: 10.1021/acs.accounts.7b00249.

(76) Hussaini, S. Y.; Haque, R. A.; Razali, M. R. Recent progress in silver(I)-, gold(I)/(III)- and palladium(II)-N-heterocyclic carbene complexes: A review towards biological perspectives. *J. Organomet. Chem.* **2019**, *882*, 96−111. DOI: 10.1016/j.jorganchem.2019.01.003.

(77) Fortman, G. C.; Nolan, S. P. *N*-Heterocyclic carbene (NHC) ligands and palladium in homogeneous cross-coupling catalysis: a perfect union. *Chem. Soc. Rev.* **2011**, *40*, 5151−5169. DOI: 10.1039/c1cs15088j.

(78) Kantchev, E. A. B.; O'Brien, C. J.; Organ, M. G. Pd-N-heterocyclic carbene (NHC) catalysts for cross-coupling reactions. *Aldrichim. ACTA* **2006**, *39*, 97−111.

(79) Baker, E. L.; Yamano, M. M.; Zhou, Y.; Anthony, S. M.; Garg, N. K. A two-step approach to achieve secondary amide transamidation enabled by nickel catalysis. *Nat. Commun.* **2016**, *7*, 11554. DOI: 10.1038/ncomms11554.

(80) Dander, J. E.; Baker, E. L.; Garg, N. K. Nickel-catalyzed transamidation of aliphatic amide derivatives. *Chem. Sci.* **2017**, *8*, 6433−6438. DOI: 10.1039/C7SC01980G.

(81) Liebman, J.; Greenberg, A. The origin of rotational barriers in amides and esters. *Biophys. Chem.* **1974**, *1*, 222−226. DOI: 10.1016/0301-4622(74)80008-6.

(82) Hoerter, J. M.; Otte, K. M.; Gellman, S. H.; Cui, Q.; Stahl, S. S. Discovery and mechanistic study of Al(III)-catalyzed transamidation of tertiary amides. *J. Am. Chem. Soc.* **2008**, *130*, 647−654. DOI: 10.1021/ja0762994.

(83) Stephenson, N. A.; Zhu, J.; Gellman, S. H.; Stahl, S. S. Catalytic transamidation reactions compatible with tertiary amide metathesis under ambient conditions. *J. Am. Chem. Soc.* **2009**, *131*, 10003−10008. DOI: 10.1021/ja8094262.

(84) Lei, P.; Mu, Y.; Wang, Y.; Wang, Y.; Ma, Z.; Feng, J.; Liu, X.; Szostak, M. Green Solvent Selection for Suzuki−Miyaura Coupling of Amides. *ACS Sustainable Chem. Eng.* **2021**, *9*, 552−559. DOI: 10.1021/acssuschemeng.0c08044.

(85) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. Modified (NHC)Pd(allyl)Cl (NHC = N-heterocyclic carbene) complexes for room-temperature Suzuki-Miyaura and Buchwald-Hartwig reactions. *J. Am. Chem. Soc.* **2006**, *128*, 4101−4111. DOI: 10.1021/ja057704z.

(86) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. Rapid Room Temperature Buchwald–Hartwig and

Suzuki–Miyaura Couplings of Heteroaromatic Compounds Employing Low Catalyst Loadings. *Chem. Eur. J.* **2006**, *12*, 5142−5148. DOI: 10.1002/chem.200600283.

(87) Stauffer, S. R.; Lee, S.; Stambuli, J. P.; Hauck, S. I.; Hartwig, J. F. High Turnover Number and Rapid, Room-Temperature Amination of Chloroarenes Using Saturated Carbene Ligands. *Org. Lett.* **2000**, *2*, 1423−1426. DOI: 10.1021/ol005751k.

(88) Lei, P.; Meng, G.; Ling, Y.; An, J.; Nolan, S. P.; Szostak, M. General Method for the Suzuki−Miyaura Cross-Coupling of Primary Amide-Derived Electrophiles Enabled by [Pd(NHC)(cin)Cl] at Room Temperature. *Org. Lett.* **2017**, *19*, 6510−6513. DOI: 10.1021/acs.orglett.7b03191.

(89) Melvin, P. R.; Nova, A.; Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.; Shah, H. P.; Tudge, M. T. Design of a Versatile and Improved Precatalyst Scaffold for Palladium-Catalyzed Cross-Coupling: $(\eta^3\text{-}1\text{-}^t\text{Bu-indenyl})_2(\mu\text{-Cl})_2\text{Pd}_2$. *ACS Catal.* **2015**, *5*, 3680−3688. DOI: 10.1021/acscatal.5b00878.

(90) O'Brien, C. J.; Kantchev, E. A. B.; Valente, C.; Hadei, N.; Chass, G. A.; Lough, A.; Hopkinson, A. C.; Organ, M. C. Easily Prepared Air- and Moisture-Stable Pd–NHC (NHC=N-Heterocyclic Carbene) Complexes: A Reliable, User-Friendly, Highly Active Palladium Precatalyst for the Suzuki–Miyaura Reaction. *Chem. Eur. J.* **2006**, *12*, 4743−4748. DOI: 10.1002/chem.200600251.

(91) Navarro, O.; Kaur, H.; Mahjoor, P.; Nolan, S. P. Cross-Coupling and Dehalogenation Reactions Catalyzed by (*N*-Heterocyclic carbene)Pd(allyl)Cl Complexes. *J. Org. Chem.* **2004**, *69*, 3173−3180. DOI: 10.1021/jo035834p.

(92) Zhou, T.; Ma, S.; Nahra, F.; Obled, A. M. C.; Poater, A.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P.; Szostak, M. $[\text{Pd(NHC)}(\mu\text{-Cl})\text{Cl}]_2$: Versatile and Highly Reactive Complexes for Cross-Coupling Reactions that Avoid Formation of Inactive Pd(I) Off-Cycle Products. *iScience* **2020**, *23*, 101377. DOI:

10.1016/j.isci.2020.101377.

(93) Chartoire, A.; Frogneux, X.; Boreux, A.; Slawin, A. M. Z.; Nolan, S. P. [Pd(IPr*)(3-Cl-pyridinyl)Cl_2]: A Novel and Efficient PEPPSI Precatalyst. *Organometallics* **2012**, *31*, 6947−6951. DOI: 10.1021/om300725f.

(94) Peh, G.-R.; Kantchev, E. A. B.; Er, J.-C.; Ying, J. Y. Rational Exploration of N-Heterocyclic Carbene (NHC) Palladacycle Diversity: A Highly Active and Versatile Precatalyst for Suzuki-Miyaura Coupling Reactions of Deactivated Aryl and Alkyl Substrates. *Chem. Eur. J.* **2010**, *14*, 4010−4017. DOI: 10.1002/chem.200902842.

(95) Becker, M. A.; Schumacher, H. R.; Wortmann, R. L.; MacDonald, P. A.; Eustace, D.; Palo, W. A.; Streit, J.; Joseph-Ridge, N. Febuxostat compared with allopurinol in patients with hyperuricemia and gout. *New Engl. J. Med.* **2005**, *353*, 2450−2461. DOI: 10.1056/NEJMoa050373.

(96) Schumacher, H. R.; Becker, M. A.; Lloyd, E.; MacDonald, P. A.; Lademacher, C. Febuxostat in the treatment of gout: 5-yr findings of the FOCUS efficacy and safety study. *Rheumatology* **2009**, *48*, 188−194. DOI: 10.1093/rheumatology/ken457.

(97) Perwitasari, O.; Yan, X.; Johnson, S.; White, C.; Brooks, P.; Tompkins, S. M.; Tripp, R. A. Targeting Organic Anion Transporter 3 with Probenecid as a Novel Anti-Influenza A Virus Strategy. *Antimicrob. Agents Chemother.* **2013**, *57*, 475−483. DOI: 10.1128/AAC.01532-12.

(98) Shimizu, T.; Nakao, T.; Suda, Y.; Abe, H. Mechanism of Action and Selectivity of a Fungicide, Mepronil. *J. Pestic. Sci.* **1992**, *17*, 39−46. DOI: 10.1584/jpestics.17.39.

(99) Zhang, C. Q.; Liu, Y. H.; Ma, X. Y.; Feng, Z.; Ma, Z. H. Characterization of sensitivity of *Rhizoctonia solani*, causing rice sheath blight, to mepronil and boscalid. *Crop Prot.* **2009**, *28*, 381−386. DOI: 10.1016/j.cropro.2008.12.004.

(100) Lei, P.; Zhang, X.; Xu, Y.; Xu, G.; Liu, X.; Yang, X.; Zhang, X.; Ling, Y. Synthesis and fungicidal activity of pyrazole derivatives containing 1,2,3,4‐tetrahydroquinoline. *Chem. Cent. J.* **2016**, *10*, 40. DOI: 10.1186/s13065-016-0186-8.

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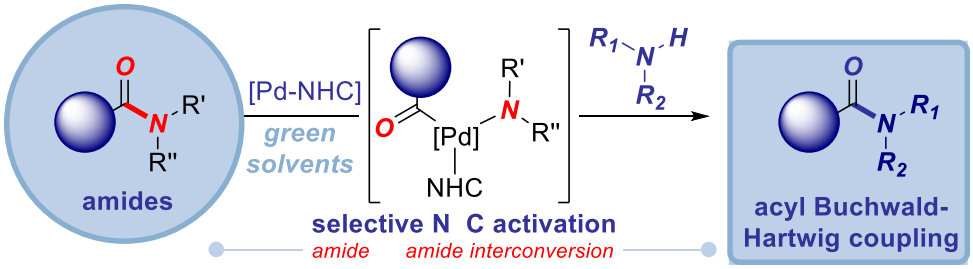

green solvent selection for acyl Buchwald-Hartwig cross-coupling of amides
practical, readily available & air-stable Pd(II)-NHC precatalysts
green solvent selection leads to improved catalyst systems

Synopsis: Evaluation of green solvents for acyl Buchwald-Hartwig cross-coupling of amides (transamidation) to provide environmental solvent selection for this powerful C–N to C–N' interconversion is reported.