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A Cross-Coupling Approach to Amide Bond Formation from Esters

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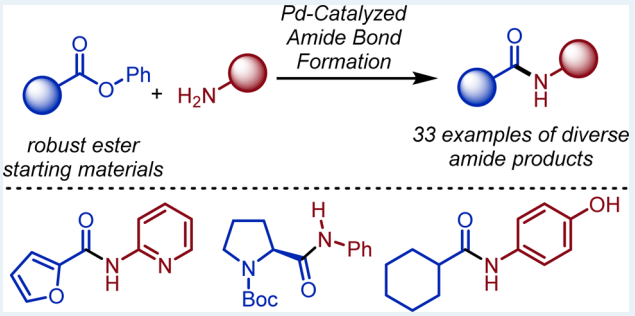
Supporting Information

ABSTRACT: A palladium-catalyzed cross-coupling between aryl esters and anilines is reported, enabling access to diverse amides. The reaction takes place via activation of the C−O bond by oxidative addition with a Pd−NHC complex, which enables the use of relatively non-nucleophilic anilines that otherwise require stoichiometric activation with strong bases in order to react. High yields of aromatic, aliphatic, and heterocyclic products are obtained. A range of activated esters are evaluated in the presence and absence of catalyst, demonstrating that the catalytic methodology substantially increases the types of electrophiles that can be utilized for amide bond formation in the absence of harsh bases.



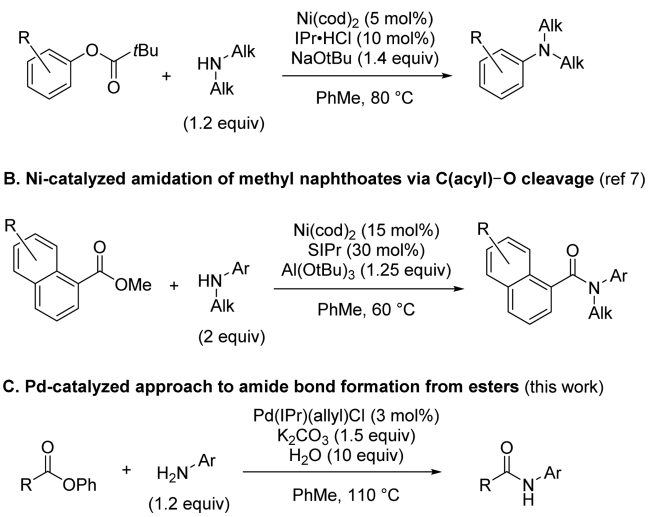
KEYWORDS: *cross-coupling, amides, palladium catalysis, C−O bond activation, C−N coupling*

The field of palladium catalysis has greatly increased the accessibility of important heteroatom-containing molecules, with the coupling of N−H bonds and aryl halides (Buchwald−Hartwig reaction) being particularly important.[1] The key strength of this transformation lies in the ability of the catalyst to activate two coupling partners that would otherwise be inert toward each other. Expanding the types of electrophiles that react via this pathway is thus an ongoing goal in organic synthesis. The use of esters as coupling partners in catalytic amination reactions has recently been explored using nickel catalysis. Chatani and co-workers reported the first example in 2010, coupling alkyl amines with aryl pivalates to prepare aniline derivatives via selective cleavage of the C(aryl)−O bond in the key oxidative addition step (Scheme 1A).[2] This bond cleavage mode has been further exploited with a variety of nucleophilic coupling partners.[3]

Although cross-coupling reactions that proceed via cleavage of C(acyl)−O bonds or other activated carboxylic acid derivatives are also well-known,[4] amination reactions proceeding by this pathway are exceedingly rare.[5] This is at least partially because of the "natural" reactivity of amines and carboxylic acid derivatives such as acid chlorides and anhydrides, which do not require a catalyst for activation. However, for less-activated coupling components such as simple esters and aryl amines, a catalyst or aggressive base may be necessary.[6] The first mild, cross-coupling approach to this reaction was recently reported by the Garg lab using a Ni-NHC catalyst system with methyl naphthoate substrates activated by $Al(OtBu)_3$ (Scheme 1B).[7]

Given the prevalence of amides in bioactive molecules and the inefficiency of many of the most commonly used methods for their synthesis,[8] alternative synthetic routes are important to explore. Catalytic transformations are particularly promising.[9] In comparison to the coupling of acids,[10] conversion of esters to amides is relatively less well-developed.[11] It has recently been reported that some Ni and Pd catalysts can oxidatively add to robust phenyl esters, generating an acyl-metal intermediate.[12] We sought to explore if this species could react with a nitrogen

Scheme 1. Cross-Coupling Reactions of Amines and Esters



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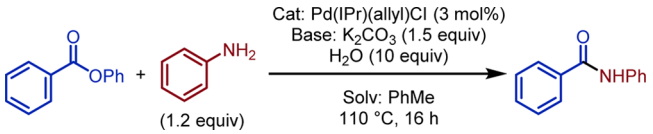
nucleophile. Herein, we present how ester activation via oxidative addition can be utilized to form diverse amides from relatively non-nucleophilic nitrogen species which do not react in the absence of catalyst (Scheme 1C). To the best of our knowledge, this represents the first example of Pd-catalyzed amide bond formation directly from esters and anilines, and it is a promising step toward more direct, efficient amidation reactions wherein simple esters can be considered simultaneous activating and protecting groups for carboxylic acids.

At the outset of our studies, the coupling of phenyl benzoate and aniline was investigated. The optimal conditions identified utilized 1.2 equiv of aniline, the Pd-NHC precatalyst Pd(IPr)(allyl)Cl (3 mol %), K_2CO_3 (1.5 equiv) as the base, water as an additive (10 equiv), and toluene as the solvent at 110 °C, providing 99% yield of the desired amide product (Table 1, entry 1). The use of a preassembled NHC-ligated catalyst was important, with separated components giving reduced yields (entry 2). Phosphine ligands proved generally ineffective for the transformation, (entries 3−5), and mild inorganic bases were found to be optimal (entries 6−8). The inclusion of at least 1 equiv of water was necessary for high conversion (entries 9 and 10). The reaction temperature could be reduced (entry 11) and 1:1 stoichiometry of coupling components (entry 12) could be used with a modest decrease in yield.

Table 1. Optimization of the Pd-Catalyzed Amidation Reaction[a]



entry	deviation from optimal reaction conditions	% yield[b]
1	no deviation	99
2	cat. = 3 mol % [$Pd(OAc)_2$ + IPr·HCl]	50
3	cat. = 3 mol % [$Pd(OAc)_2$ + P(*o*-tol)$_3$]	20
4	cat. = 3 mol % [$Pd(OAc)_2$ + SPhos]	12
5	cat. = 3 mol % [$Pd(OAc)_2$ + PPh, PBu_3, or dppb]	trace
6	no base	trace
7	base = K_3PO_4	79
8	base = NEt_3	28
9	no H_2O	trace
10	1 equiv of H_2O	78
11	T = 90 °C	65
12	1 equiv of ester, 1 equiv of aniline	86
13	no cat.	0
14	cat. = 3 mol % IPr (no Pd)	0
15	no cat. base = KO*t*Bu	6
16	no cat. base = KOH, NaOH, Cs_2CO_3, or NEt_3	trace
17	no cat. solv = DMF, DMSO, dioxane, or DME	0
18[c]	no cat. 1 equiv of $AlMe_3$, 0 °C	63
19[d]	no cat. 2 equiv of BuLi, 0 °C	60

[a]Reactions run at 0.2 M concentration on 0.1 mmol scale under an argon atmosphere. [b]Yield determined by ^{1}H NMR of the crude mixture with 1,3,5-trimethoxybenzene as internal standard. [c]Reaction performed in DCM according to ref 16. [d]Reaction performed in THF according to ref 17.

Given the established reactivity between esters and nucleophilic aliphatic amines,[13] we felt it was particularly important to determine how difficult the uncatalyzed variant of this reaction is. Using the optimized conditions without catalyst (entry 13) or with just ligand[14] (entry 14) provided no detectable product. KO*t*Bu as a stronger base gave 6% yield (entry 15), whereas other bases (entry 16) and solvents (entry 17) were ineffective.[15] The only high-yielding reactions we found were using traditional stoichiometric conditions for the direct synthesis of amides from anilines and esters. For example, pretreatment of the aniline with the flammable organometallic reagents $AlMe_3$ (entry 18)[16] or BuLi (entry 19)[17] prior to addition of the ester gave appreciable yields. Given the prevalence of amides in complex, functional group-rich molecules, reactions with such harsh reagents are often undesirable. Further optimization and control experiments are provided in the Supporting Information.

To evaluate the scope of the reaction, a diverse range of ester and aniline starting materials were explored (Table 2). Benzanilide was isolated in 91% yield (**3a**). Incorporation of electron-donating (**3b**−**3d**), naphthyl (**3e**, **3f**), electron-withdrawing (**3g**−**3l**), or sterically hindered (**3m**, **3n**) groups on either the nucleophilic or electrophilic coupling partners were tolerated. Chemoselectivity for phenyl esters is particularly notable (**3j**, **3k**). Various heterocyclic species could also be utilized (**3o**−**3u**). Amides bearing methyl (**3v**), primary (**3w**, **3x**), secondary (**3y**), and tertiary (**3z**) alkyl groups adjacent to the carbonyl could be obtained in good yields, demonstrating a relative insensitivity to sterics. This contrasts significantly with previous catalytic reactions that feature ester bond cleavage, which generally cannot tolerate aliphatic substituents.[12] Cleavage of the C(acyl)−O bond of phenyl pivalate to provide **3z** is also interesting because the same substrate was used by Chatani and co-workers with a Ni/IPr catalyst system to provide the product of C(aryl)−O cleavage (Scheme 1A). Finally, various aminophenols could be coupled (**3aa**−**3ae**). Complete chemoselectivity for amide formation over ester formation with aminophenols is particularly notable, given the precedence of ligand-controlled selectivity in aminocarbonylation and alkyoxycarbonylation reactions.[18] The ability to obtain high yields regardless of the electronics of the amine nucleophile is a significant advantage of this methodology.

The main benefit of utilizing ester starting materials for amide bond formation rather than more-activated derivatives such as acid chlorides or anhydrides is the enhanced stability while maintaining sufficient reactivity. For example, many pentafluorophenyl and *N*-hydroxysuccinimide-derived esters are commercially available for applications in the synthesis of peptides[10,11] or polymers.[19] These bench-stable species are resistant to undesired side reactions that may occur with more reactive acid chlorides, while being sufficiently activated to directly react with nitrogen-centered nucleophiles to form amide bonds (Scheme 2). Alkyl amines work best, though anilines, which react ∼4 orders of magnitude slower, can also be used with these highly activated electrophiles.[20] Simple phenyl esters are considerably less electrophilic than *N*-hydroxysuccinimide or pentafluorophenyl esters, and they are thus expected to be much more resistant to both desired substitution chemistry and undesired side reactions.

To get a better understanding about the practical applications of this amide bond forming reaction, we surveyed the reactivity of several esters with aniline under catalytic and noncatalytic conditions (Table 3). While activated pentafluorophenyl and *N*-hydroxy succinimide esters are known to react with aniline in the presence of mild base, noncatalytic reactions with more robust esters are rarely reported. We thus carried out a screen with a selection of solvents (DMF, MeCN, DME) and mild bases (NEt_3, K_2CO_3) at 100 °C. Esters derived from

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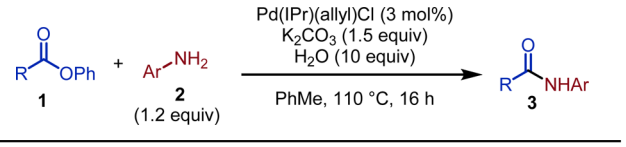
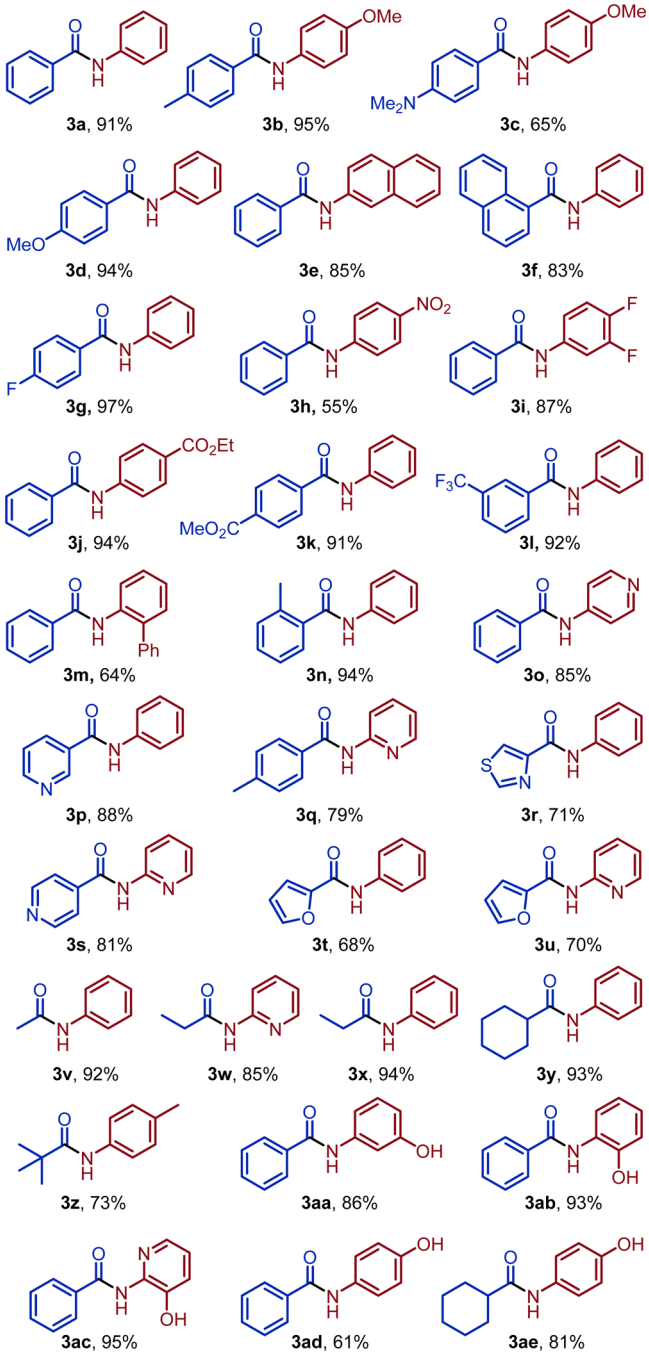
Table 2. Scope of Coupling Partners[a]

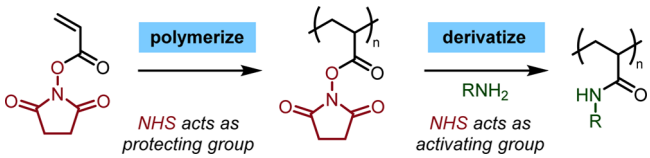




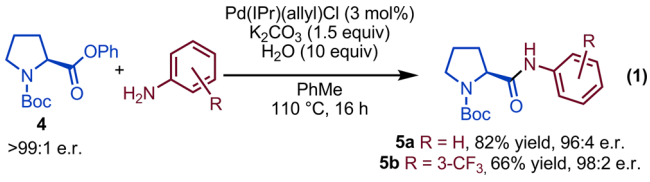
[a]General reaction conditions: Ester (0.2 mmol), aniline (0.24 mmol), Pd(IPr)(allyl)Cl (0.006 mmol), K_2CO_3 (0.3 mmol), H_2O (2 mmol), toluene (1 mL) at 110 °C for 16 h under argon. Isolated yields are reported. See Supporting Information for full experimental details.

electron-withdrawing *p*-trifluoromethylphenol and hexafluoroisopropanol[21] were found to be moderately reactive, while less electrophilic esters were essentially inert.[22] Because the reactivity and stability of C(acyl)−X species can be crudely approximated by the pK_a of their leaving groups, we can thus identify a rough point, pK_a ∼ 15, wherein catalytic substrate activation may become beneficial. Using our Pd-catalyzed conditions on substrates above this point gave substantial yield improvements in all cases. Benzanilide was formed in 94% yield from 4-trifluoromethylphenyl benzoate, 65% yield from trifluoroisopropylbenzoate, and 74% yield from 4-methoxyphenylbenzoate. The extension of efficient couplings to include these robust esters will be of particular importance in multistep chemical synthesis, where more easily hydrolyzed functional groups would not be tolerated. It also provides promising progress toward the ability to couple functional groups that would be typically considered protected acids, such as methyl, *t*-butyl, and benzyl esters, which often need to be deprotected prior to amidation of the free acid.[23] The C(acyl)−O bond of these aliphatic esters are considerably more robust, so even better catalytic systems need to be identified to enable their cleavage.

Scheme 2. N-Hydroxysuccinimide (NHS) Esters Act as Both Protecting and Activating Groups of Carboxylic Acids for Polymer Synthesis



One of the main advantages of using pentafluorophenyl, *N*-hydroxysuccinimide, and related activated esters as starting materials for peptide synthesis is their clean reaction with amine nucleophiles with minimal racemization of the sensitive chiral center, as can be the case when more-electron-withdrawing groups are used. We were thus curious if amino acids could be directly coupled as their ester derivative. Reaction of enantiopure proline-derived **4** provided anilides **5a** and **5b** in good yields, and HPLC analysis showed that the stereocenter remained intact, with minimal loss of enantiopurity (eq 1). The extension of this process to more diverse amino acid derivatives, particularly those bearing acidic and reactive free N−H groups, is underway.



While thorough investigation is still needed to fully elucidate the mechanism of this amide bond formation, the coupling reactions of esters to form ketones and biaryls have been studied experimentally and by DFT calculations.[12a−c,24] From this precedent, oxidative addition of both Pd(0) and Ni(0) catalysts into C(acyl)−O bond to generate acyl−metal intermediates are both established elementary steps. Such complexes are known to react with amines to produce amides, as occurs in well-established aminocarbonylation reactions of aryl halides, either by direct attack on the carbonyl or complexation with the metal followed by reductive elimination.[25] A plausible mechanism would thus involve oxidative addition of a Pd(0)-NHC active catalyst into the ester C−O bond, followed by reaction of the intermediate Pd(II) complex with aniline. The bulky NHC ligand is critical for donating

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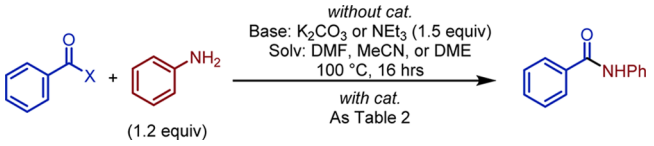
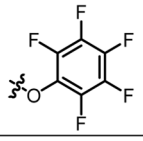
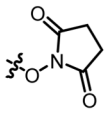
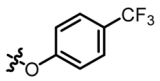
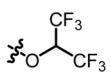
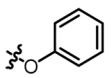
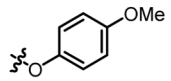
Table 3. Evaluation of Esters of Varying Degree of Activation



X =						
pKa of X–H	5.4 (H_2O)	7.8 (H_2O) 14 (DMSO)	15.3 (DMSO)	17.2 (DMSO)	18 (DMSO)	19.1 (DMSO)
without cat.	✓	✓	~ (44%)	~ (36%)	✖ (trace)	✖ (trace)
with cat.	n/a	n/a	✓ (94%)	✓ (65%)	✓ (99%)	✓ (74%)

sufficient electron density to the catalyst to enable oxidative addition, while preventing decarbonylation and increasing the rate of reductive elimination from Pd(II) via its steric bulk.

The reaction of amines with esters to form amides is of fundamental importance in organic synthesis. In noncatalytic reactions, this can occur when a highly reactive ester is used, or the nucleophile is activated by harsh stoichiometric base. The current work demonstrates that, through the use of a Pd catalyst, moderately activated aryl esters can react with a diverse range of aniline derivatives, including electron-deficient aminopyridines and bifunctional aminophenols. Analysis of various ester derivatives demonstrates that this catalytic methodology pushes the boundary on the robustness of the ester starting materials that can be used for amide bond formation. Application to the synthesis of proline derivatives without destruction of stereochemical information demonstrates the generality and mildness of this strategy. Most importantly, this first report that Pd can activate esters toward C–N bond formation provides a new direction by which much needed low-waste amidation reactions may be explored.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acscatal.7b00245.

Experimental procedures, characterization of organic molecules, and optimization tables (PDF)

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Notes

The authors declare no competing financial interest.

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