Chemical Communications

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Pd-PEPPSI: A General Pd-NHC Precatalyst for Buchwald-Hartwig Cross-Coupling of Esters and Amides (Transamidation) under the Same Reaction Conditions

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Amides are of fundamental interest in many fields of chemistry involving organic synthesis, chemical biology and biochemistry. Here, we report the first catalytic Buchwald-Hartwig coupling of both common esters and amides by highly selective C(acyl)–X (X = O, N) cleavage to rapidly access aryl amide functionality via cross-coupling strategy. Reactions are promoted by versatile, easily prepared, well-defined Pd-PEPPSI type precatalysts, proceed in good to excellent yields and with excellent chemoselectivity for the acyl bond cleavage. The method is user friendly because it employs commercially-available, moisture- and air-stable precatalysts. Notably, for the first time we demonstrate selective C(acyl)–N and C(acyl)–O cleavage/Buchwald-Hartwig amination under the same reaction conditions, which allows for streamlining amide synthesis by avoiding restriction to a particular acyl metal precursor. Of broad interest, this study opens the door to using a family of well-defined Pd(II)-NHC precatalysts bearing pyridine "throw-away" ligands for the selective C(acyl)–amination of bench-stable carboxylic acid derivatives.

The development of new reactions for the synthesis of amides has become an important goal in organic synthesis.[1,2] The ubiquitous presence of amides in pharmaceuticals, polymers and natural products means that the amide coupling reaction is the most commonly performed transformation in organic chemistry laboratories.[3,4] However, many of the most common amidation methods are either inefficient or suffer from serious drawbacks, such as low atom economy and the use of toxic stoichiometric coupling reagents.[1,2] As a consequence, (1) the development of new methods for the synthesis of amides has been identified as the key green chemistry research area;[5] (2) the discovery of new alternative catalytic methods can be of tremendous impact in many fields of chemistry involving organic synthesis, chemical biology and biochemistry.[1–4]

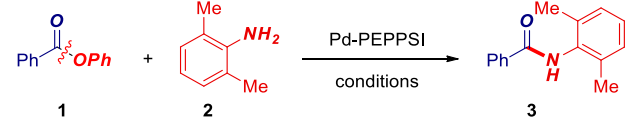The recent years have witnessed the emergence of extremely efficient Pd-catalyzed cross-coupling reactions of amines with aryl halides and pseudohalides to form C–N bonds (Buchwald-Hartwig cross-coupling).[6–9] With these Pd-catalyzed reactions, it is now possible to rapidly access diverse aromatic amines for numerous academic and industrial applications. The generality of this C(sp²)–amination manifold hinges upon identification of suitable supporting ligands and precatalysts to enable broad catalytic activity.[10] However, this pathway is ultimately limited to the formation of *aryl amines*.

Here, we translate the general Buchwald-Hartwig amination manifold of aryl halides to both common esters[11] and amides[12] by highly chemoselective C(acyl)–X (X = O, N) cleavage to rapidly access diverse *aryl amides* by unconventional cross-coupling strategy.[13] This new cross-coupling method employs readily available, unactivated simple esters and amides, non-nucleophilic amines and an air-stable, well-defined precatalyst. Notable features of our study include: (1) unprecedented robust Pd-catalyzed C(acyl)–amination with non-nucleophilic anilines; (2) for the first time we demonstrate selective C(acyl)–N and C(acyl)–O cleavage/Buchwald-Hartwig amination under the same reaction conditions. This allows for a streamlined amide synthesis and avoids restriction to a particular acyl metal precursor; (3) in contrast to recently reported transformations, significantly improved access to Pd-precatalysts (synthesis in a single, operationally-trivial step), which is critical for the future identification of ancillary ligands with broad utility and could lead to the widespread application of the C(acyl)–X Buchwald-Hartwig amination in many fields of chemical research. There are two instant advantages of using PEPPSI-type precatalysts: (i) one-step synthesis in a single operationally-simple step; (ii) a variety of PEPPSI complexes is readily accessible by modifications of the NHC scaffold, which may result in the development of even more active catalysts.[15]

The activation of inert acyl C–O and C–N bonds in common esters and amides relies on the oxidative addition of a transition metal into the traditionally inert acyl C–X bond (for example, planar amides barrier to rotation 15-20 kcal/mol).[14] Rapid developments in this area involve NHC (N-heterocyclic carbene) ligands[15] that render oxidative addition facile owing to

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Table 1 Optimization of the Pd-Catalyzed Amination of Esters[a]
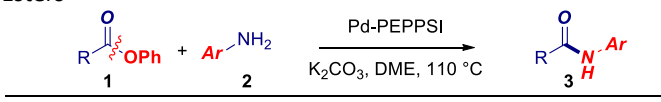
Entry	Catalyst	Base	Solvent	T (°C)	Yield (%)[b]
1	**4a**	K_2CO_3	DME	110	>98
2	**4a**	KOt-Bu	DME	110	57
3	**4a**	Cs_2CO_3	DME	110	45
4	**4a**	K_3PO_4	DME	110	36
5	**4a**	Na_2CO_3	DME	110	<5
6	**4a**	NaOt-Bu	DME	110	<5
7	**4a**	K_2CO_3	THF	110	<5
8	**4a**	K_2CO_3	dioxane	110	<5
9	**4a**	K_2CO_3	toluene	110	<5
10[c]	**4a**	K_2CO_3	DME	110	43
11	**4b**	K_2CO_3	DME	110	96
12	**4c**	K_2CO_3	DME	110	77
13	**4d**	K_2CO_3	DME	110	59
14	**4e**	K_2CO_3	DME	110	26
15[d]	**4a**	K_2CO_3	DME	110	88
16[e]	**4a**	K_2CO_3	DME	110	72

[a]Conditions: ester (1.0 equiv), aniline (2.0 equiv), base (3.0 equiv), [Pd] (3 mol%), solvent (0.25 M), T, 16 h. [b]Determined by ^{1}H NMR and GC. [c]H_2O (10 equiv). [d]Aniline (1.2 equiv). [e]Aniline (1.2 equiv), K_2CO_3 (1.2 equiv). See ESI for details.

4a: R = 3-Cl-py
4b: R = py
4c: R = 1-Me-im
4d
4e
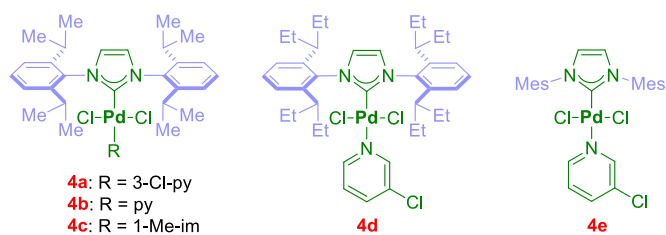
Fig. 1 Pd-PEPPSI catalysts prepared in a single step (this study).

the stronger σ-donation than phosphines.[16,17] Meanwhile, variable steric bulk around the metal facilitates reductive elimination. However, the synthesis of these Pd-NHCs is often challenging, requires multiple steps and typically strict glovebox techniques. With this in mind, we recently hypothesized that Pd-PEPPSI type precatalysts[18] would allow direct access to acyl-Pd intermediates from common esters and amides using simple and readily available reagents and reaction protocols. Notably, these complexes are easily synthesized on a gram scale in a single, operationally-simple step involving $PdCl_2$, NHC, and "throw-away" pyridine ligand.[19] During the cycle, the "throw-away" ligand dissociates to form the active catalyst. Furthermore, in these versatile complexes, Pd and ligand are introduced in the optimal 1:1 ratio, which obviates the use of an excess of the often expensive ancillary ligand and significantly simplifies the reaction setup.[10c] Finally, these highly-reactive, air-stable Pd-NHC complexes are modular in nature,[18] which allows for the rational design of other types of Pd-PEPPSI type complexes bearing diverse pyridine-type "throw-away" ligands.

The proposed Buchwald-Hartwig acyl C–O/amination was first surveyed in the model reaction between phenyl benzoate

Table 2 Pd-PEPPSI-Catalyzed Buchwald-Hartwig Amination of Esters[a,b]

3a: 96% yield
3b: 91% yield
3c: 71% yield[c]
3d: 97% yield
3e: 74% yield
3f: 50% yield[c]
3g: 75% yield
3h: 78% yield
3i: 84% yield
3j: 85% yield
3k: 75% yield
3l: 91% yield
3m: 96% yield
3n: 90% yield[c]
3o: 95% yield

[a]Conditions: ester (1.0 equiv), aniline (2.0 equiv), K_2CO_3 (3.0 equiv), [**4a**] (3 mol%), DME (0.25 M), 110 °C, 16 h. [b]Isolated yields. [c][**4a**] (6 mol%). See ESI for details.

and the challenging, extremely sterically-hindered 2,6-dimethylaniline (Table 1). The optimized catalyst system uses Pd-PEPPSI-IPr (3 mol%), 2,6-dimethylaniline (2.0 equiv), K_2CO_3 (3.0 equiv), DME, 110 °C, affording the desired product in quantitative yield. Importantly, K_2CO_3 proved to be the most efficient base, with Cs_2CO_3 and K_3PO_4 also providing promising results for mildly basic reaction conditions (entries 1-6).[18] The reaction showed strong dependence on the solvent used with DME providing the best results (entries 7-9). The reaction was sensitive to the presence of excess of water (entry 10).[15e] As anticipated, the reaction showed a strong dependence on the PEPPSI type scaffold (entries 11-14). Interestingly, the pyridine "throw-away" ligand (**4b**) cleanly produced the coupling product (entry 11), while 1-methylimidazole ligand (**4c**) resulted in the less efficient cross-coupling (entry 12). Intriguingly, the use of more bulky PEPPSI-IPent (**4d**)[18c] and less sterically-demanding PEPPSI-IMes (**4e**) gave less efficient coupling (entries 13-14). Finally, we determined that the use of close to stoichiometric amount of base and aniline leads to efficient coupling, providing an entry point for further development (entries 15-16). Collectively, these findings suggest that (1) PEPPSI-IPr may serve as the privileged NHC scaffold for the C–O acyl/amination with challenging sterically-hindered anilines; (2) modification of the NHC backbone and "throw-away" ligand within the PEPPSI framework may lead to discovering even more active catalysts.

With the optimized conditions in hand, the generality of the Pd-PEPPSI amination of esters was examined (Table 2). As

shown, the reaction exhibits broad scope with respect to both the ester and the aryl amine components. Various neutral, electron-rich (**3a-c**), sterically-hindered (**3d**), polyaromatic (**3e**) and electron-withdrawing (**3f**) ester substrates are compatible with this coupling, providing rapid access to diverse amides. Moreover, electron-rich heterocycles conjugated at the deactivating 2-position (**3g**) and aliphatic esters (**3h**) can be selectively cross-coupled. Of particular note is the chemoselectivity for the coupling of phenyl esters in the presence of alkyl counterparts (**3f**, **3j**).

Having developed an efficient protocol for the acyl C–O amination, we hypothesized that the high activity of Pd-PEPPSI precatalysts might enable C–N amination of common amides (transamidation) under the same reaction conditions.[2a,b] If successful, this process would represent a significant strategic advantage as it would avoid restriction to a particular acyl metal precursor in the synthesis of aryl amides by a mild cross-coupling approach.[15f] Indeed, classic studies by Greenberg demonstrated that rotational barrier in esters is similar to that in resonance destabilized amides (Er = ca. 10 kcal/mol).[20,15f]

We were delighted to find that Pd-PEPPSI-IPr promoted the desired coupling under the same reaction conditions (Table 3), *thus providing compelling evidence for a common acyl C–X (X = O, N) Buchwald-Hartwig reactivity manifold.* Intriguingly, a survey of different PEPPSI-type scaffolds indicated that catalyst (**4b**) bearing pyridine "throw-away" ligand improved the yield (entry 2), which may be due to Pd center being more nucleophilic in this complex to facilitate oxidative addition.[18c] Furthermore, promising results were obtained using 1-methylimidazole-containing catalyst (**4c**) (entry 3) and more bulky PEPPSI-IPent (**4d**) (entry 4), while less sterically-demanding PEPPSI-IMes (**4e**) (entry 5) gave inferior results. Clearly, modifications of the catalyst backbone will result in further enhancement in the catalytic activity. Note that no reaction is observed using free NHC ligand for both ester and amide (>95% recovery of starting material).

Next, the scope of this coupling was briefly investigated (Table 4). Furthermore, the developed reaction conditions could be directly applied to the coupling of various N-activated amides, including alkyl and aryl N-Boc-carbamates and alkyl and aryl N-sulfonamides (Table 4B). Considering that these N-Boc or N-Ts amides are readily prepared from common secondary amides,[12] the capacity of this catalytic regime to couple various amides complements classic transamidation techniques of secondary amides, which is traditionally a challenging process on its own.[2a,b]

Kinetic studies were performed to investigate the effect of leaving group on the coupling (Fig. 2). The model reactions using ester (**1a**) and amide (**5a**) follow almost identical kinetic profile, consistent with electronic destabilization of the amide and aryl ester bond.[14,15f] As expected, an induction period is observed for both ester and amide.[19b] Thus, common acyl cross-coupling manifold of esters and amides may be much more widely implicated than previously considered in the acyl cross-coupling chemistry. A TON of 350 and 320 was obtained in the coupling of ester (**1a**) and amide (**5a**) with aniline, respectively, consistent with highly efficient catalysis, and by

far exceeding any Pd-phosphine catalyzed acyl-cross-coupling.

Table 3 Optimization of the Pd-Catalyzed Amination of Amides[a]

Entry	Catalyst	Base	Solvent	T (°C)	Yield (%)[b]
1	**4a**	K$_2$CO$_3$	DME	110	71 (>98)
2	**4b**	K$_2$CO$_3$	DME	110	82 (96)
3	**4c**	K$_2$CO$_3$	DME	110	45 (77)
4	**4d**	K$_2$CO$_3$	DME	110	56 (59)
5	**4e**	K$_2$CO$_3$	DME	110	21 (26)

[a]Conditions: amide (1.0 equiv), aniline (2.0 equiv), base (3.0 equiv), [Pd] (3 mol%), DME (0.25 M), T, 16 h. [b]Determined by ^{1}H NMR and GC. Yield in brackets indicates yield obtained with ester **1a** under identical reaction conditions. See ESI for details.

Table 4 Pd-PEPPSI-Catalyzed Buchwald-Hartwig Amination of Amides[a,b]

[a]Conditions: amide (1.0 equiv), aniline (2.0 equiv), K$_2$CO$_3$ (3.0 equiv), [**4b**] (3 mol%), DME (0.25 M), 110 °C, 16 h. [b]Isolated yields. [c][**4b**] (6 mol%).

Fig. 2 Kinetic profile of **1a** (PhCO$_2$Ph) and **5a** (PhCONBocPh). Conditions: Ph-NH$_2$ (2.0 equiv), [**4a**] (3 mol%), K$_2$CO$_3$ (3.0 equiv), DME, 110 °C.

In summary, we have developed the first catalytic Buchwald-Hartwig coupling of both common esters and amides by highly selective C(acyl)–X (X = O, N) cleavage by exploiting well-defined, versatile Pd-PEPPSI precatalysts. This method complements the classic techniques for amide bond formation and is distinguished by high catalytic reactivity via alternative cross-coupling pathway. Pd-PEPPSI precatalysts represent a new general class of catalysts for Buchwald-Hartwig amination of common acyl electrophiles. These well-defined, air- and moisture-stable catalysts are easily prepared in a single, operationally-simple step, providing a modular access to highly reactive catalysts for C–O and C–N acyl amination. Mechanistic studies have provided evidence supporting common catalytic manifold of esters and amides for catalytic acyl C–X amination. Efforts toward expanding the scope and synthesis of improved Pd-NHC catalysts are currently ongoing and will be reported in due course. Further evaluation of well-defined Pd-NHC precatalysts will lay a foundation for general applications of acyl Buchwald-Hartwig cross-coupling in the synthesis of amides.

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