

Protocol for Palladium/N-Heterocyclic Carbene-Catalyzed Suzuki– Miyaura Cross-Coupling of Amides by N–C(O) Activation

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Abstract Amides are among the most important and ubiquitous functional groups in organic chemistry and process development. In this Practical Synthetic Procedure, a protocol for the Suzuki-Miyaura cross-coupling of amides by selective N-C(O) bond activation catalyzed by commercially available, air- and moisture-stable palladium/N-heterocyclic carbene (NHC) complexes is described. The procedure described involves [Pd(IPr)(cin)Cl] [IPr = 2,6-(diisopropylphenyl)imidazol-2-ylidene, cin = cinnamyl] at 0.10 mol% at room temperature and is performed on decagram scale. Furthermore, a procedure for the synthesis of amide starting materials is accomplished via selective N-tertbutoxycarbonylation, which is the preferred method over N-acylation. The present protocol carries advantages of operational simplicity, commercial availability of catalysts, and excellent conversions at low catalyst loadings. The method is generally useful for activation of N-C(O) amide bonds in a broad spectrum of amide precursors. The protocol should facilitate the implementation of amide cross-coupling reactions.

Key words amides, N–C(O) activation, N-heterocyclic carbenes (NHCs), Suzuki–Miyaura cross-coupling, Pd(II)–NHCs, [Pd(IPr)(cin)Cl]

The amide bond is an essential subunit of peptides and proteins and is one of the most prevalent functional groups in organic synthesis.¹ Although traditional amide bonds are difficult to cleave due to amidic resonance $(n_N \rightarrow \pi^*_{C=0} \text{ conjugation of 15-20 kcal/mol in planar amides})$, recent studies have established the utility of highly selective direct metal insertion into the N–C(O) moiety.² This novel reactivity manifold of amide bonds offers the advantage of accessing acyl metals directly from amides and exploits these versatile intermediates in well-controlled elementary reac-



tions.³ A remarkable feature of the strategy of activating acyclic amides by ground-state-destabilization is the capacity to deliver N-activated amides for a wide array of previously elusive transformations of amide bonds by selective fine-tuning of amidic resonance (Scheme 1).⁴





The amide bond activation manifold has a major potential to enable new transformations for synthetic chemists working in various fields of chemistry, including the synthesis of pharmaceuticals, agrochemicals, polymers as well as commodity chemicals.⁵

In the past 5 years, numerous classes of amide bond cross-coupling reactions have been developed, ranging from the discovery of palladium-catalyzed acyl cross-couplings to the development of methods based on decarbonylative mechanism of the amide bond^{2–4} as well as acyl substitution mechanism that could be also accomplished in the

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absence of transition metals (Scheme 1).⁶ To facilitate the implementation of amide cross-coupling reactions and enable transfer to larger scales, it is critical that proven and tested protocols are available to a range of interested synthesis practitioners.

In this Practical Synthetic Procedure, we describe a protocol for the Suzuki-Miyaura cross-coupling of amides by selective N-C(O) bond activation catalyzed by commercially available, air- and moisture-stable palladium/N-heterocyclic carbene (NHC) complexes. The procedure described involves [Pd(IPr)(cin)Cl] [IPr = 2,6-(diisopropylphenyl)imidazol-2-vlidene, cin = cinnamvll (Figure 1) at 0.10 mol% at room temperature and is performed on a 10 g scale. Furthermore, we describe a procedure for the synthesis of amide starting materials accomplished via selective N-tertbutoxycarbonylation, which is preferred over N-acylation. The present protocol has advantages of operational-simplicity, commercial-availability of catalysts, and excellent conversions at low catalyst loadings. The method is generally useful for the activation of N-C(O) amide bonds in a broad spectrum of amide precursors.



The viability of amide bond cross-coupling is usually evaluated considering two factors: (1) accessibility of the starting materials from common amides and (2) efficiency of the cross-coupling.^{2,3} The acyl Suzuki–Miyaura crosscoupling is a benchmark method to evaluate the efficiency of amide bond precursors and catalysts.³ To date, no catalyst class has been demonstrated to be more efficient in the cross-coupling of amides than well-defined Pd(II)–NHCs.⁷ Importantly, the acyl Suzuki–Miyaura cross-coupling of amides provides a high-value alternative strategy to access ketones via a catalytic mechanism advantageous over the use of Weinreb amides.⁸

N-Boc amides have been well established as electronically-activated twisted amides [RE (resonance energy) = 7.2 kcal/mol; τ = 29.1°; χ_N = 8.4°] for N–C(O) bond cross-coupling.⁴ The synthesis of *N*-Boc amide starting materials is presented in Scheme 2. The amides can be accessed either via N-acylation or N-*tert*-butoxycarbonylation. The latter route enables the direct utilization of common amides as cross-coupling precursors. However, we note that the *N*acyl substitution route is also useful in cases when amides provide advantages in cross-coupling reactions over other acyl electrophiles in terms of efficiency, stability, or selectivity.





In our experience, the synthesis of *N*-Boc amides by *N*-*tert*-butoxylation is vastly preferred because it obviates issues of over-acylation of amine in the N-acylation route; the N-acylation route almost always leads to mixtures of RNHBoc, RNH₂, and RNBoc₂ when making the RNHBoc precursor. A 10 g scale synthesis is representative (Scheme 2): Reaction of *N*-phenylbenzamide (**1a'**; 10.60 g, 53.8 mmol, 1.0 equiv) with di-*tert*-butyl dicarbonate (12.33 g, 56.5 mmol, 1.05 equiv) in the presence of NEt₃ (5.44 g, 53.8 mmol, 1.0 equiv) and DMAP (0.066 g, 0.54 mmol, 1 mol%) in acetonitrile (0.5 M) gives 15.2 g of the desired *N*-Boc-*N*-phenylbenzamide (95% yield) after recrystallization from ethyl acetate/hexanes. No special precautions are necessary for the N-*tert*-butoxylation step.

We have previously shown that Pd(II)-NHCs are vastly preferred catalysts in generating acyl metals from amides.⁹ Now, we have examined the efficiency in large scale crosscoupling (Scheme 3). A decagram-scale reaction using 0.10 mol% of [Pd(IPr)(cin)Cl]¹⁰ is representative: To a mixture of tert-butyl benzoyl(phenyl)carbamate (10.0 g, 33.63 mmol, 1.0 equiv), K₂CO₃ (5.58 g, 40.36 mmol, 1.2 equiv), p-tolylboronic acid (5.49 g, 40.36 mmol, 1.2 equiv), [Pd(IPr)(cin)Cl] (21.8 mg, 0.10 mol%), and water (3.0 g, 166.8 mmol, 5.0 equiv) is added 2-MeTHF (22.4 mL, 1.5 M) on the benchtop in the absence of air. The reaction is stirred at room temperature for 15 hours. Insoluble salts are removed by filtration using EtOAc. The crude mixture is purified by chromatography on silica gel to give 6.20 g of the ketone product (94% yield). The purity was determined by ¹H NMR (500 MHz, CDCl₃) to be >98%.



Several points are worth noting:

1) While it is critical that the cross-coupling is conducted in the absence of air, benchtop setup using standard Schlenk techniques or inert gas sparging makes the reaction operationally simple and generally available [i.e., the method is not restricted to the glove box access as is the case with $Ni(cod)_2$].

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2) The use of a green and renewable solvent, 2-MeTHF, is greatly preferred due to environmental advantages and better solubility of inorganic bases.¹¹ However, several other solvents can also be used, such as THF, DME, toluene, or 1,4-dioxane.

3) Water facilitates the cross-coupling.¹² However, when the cross-coupling is performed at higher temperatures, the addition of water has a negative effect on the reaction efficiency.

4) It is critical that preformed Pd(II)–NHC precatalysts be used.⁹ Much lower conversions are typically observed using in situ prepared Pd–NHC catalysts. Note that this feature is advantageous from the experimental standpoint.¹³

5) Several classes of Pd(II)–NHCs can be used, including [Pd(NHC)(allyl)Cl] type complexes, such as [Pd(NHC)-(allyl)Cl] and [Pd(NHC)(cin)Cl],¹⁰ and [Pd–PEPPSI] type complexes^{14a} as well as [Pd(NHC)(ind)Cl] complexes,^{14b} and NHC–Pd(II) chloro-dimers, [Pd(NHC)(μ -Cl)Cl]₂.^{14c} In our experience, the commercially-available [Pd(IPr)(cin)Cl] (Neolyst CX31) and fast-activating, allyl-free [Pd(IPr)-(μ -Cl)Cl]₂ are the first choice for testing the amide bond N–C(O) cross-coupling due to high reactivity.^{10a-c}

6) The same cross-coupling procedure can be employed in the Suzuki–Miyaura cross-coupling of esters by C(acyl)– O activation.¹⁵ This provides complementarity in the crosscoupling manifolds by a common ground-state-activation mechanism of bench-stable acyl electrophiles.

7) The presented synthesis of amides by N-*tert*-butoxylation can be applied to the synthesis of *N*-Boc₂ amides directly from primary amides.⁴ This in turn enables common 1° amides to serve as convenient precursors to acyl metals.

8) The amide bond ground-state-activation concept can be further applied to transition-metal-free reactions; the best examples are practical transamidations and esterifications of the amide bond in the absence of transition metals.¹⁶

9) This mode of activation of amides using Pd(II)–NHCs can be also systematically applied to other cross-coupling reactions, including alkylation¹⁷ or Buchwald–Hartwig type C(acyl)–N or C(acyl)–O amidation.¹⁸

10) An important point concerns the use of *N*-alkyl versus *N*-aryl Boc-activated amides. In our experience, there is little difference in acyl-type reactivity using various *N*-Boc derivatives. This is supported by the respective resonance energies of the amide bond (e.g., *N*-Boc/Me, RE: 6.2 kcal/mol; *N*-Boc/Ph, RE: 7.2 kcal/mol).⁴ However, the reader should be cautioned that there is often a significant difference between various *N*-Boc amides in decarbonylative pathway due to stability of these amides.^{2b} In these cases, we recommend testing *N*-Boc amides with various N-substituents, including *N*-Me, *N*-Bn, *N*-*n*-alkyl as well as screening the reaction temperature.^{2,6}

A representative substrate scope using the conditions employed for the large-scale reaction is shown in Scheme 4. These reactions employ [Pd(IPr)(cin)Cl] at 0.10 mol% load**PSP**

ing at room temperature, while slightly elevated temperatures (60 $^{\circ}$ C) or higher catalyst loading (0.25 mol%) are used in cases that result in lower conversions.



 $\begin{array}{l} \textbf{Scheme 4} & \text{Representative cross-coupling at low catalyst loading.} \\ \textit{Reagents and conditions: amide (0.50 mmol), ArB(OH)_2 (1.2 equiv), \\ [Pd] (0.10 mol%), K_2CO_3 (1.2 equiv), H_2O (5.0 equiv), 2-Me-THF (1.5 M), \\ 23 ^{\circ}C, 15 h. ^{a} [Pd] (0.25 mol%) was used. ^{b} Reaction temp: 60 ^{\circ}C. \\ \end{array}$

In conclusion, we have presented a detailed procedure for the Suzuki–Miyaura cross-coupling of amides by selective N–C(O) bond activation. The method employs commercially available, bench-stable Pd(II)–NHC precatalysts, does not require special equipment, and is readily conducted on decagram scale at low catalyst loading using environmentally friendly solvent. Considering the key presence of amides in organic chemistry and process development, we anticipate a wide range of industrial applications of this general activation concept. Further studies focusing on developing amide cross-coupling and related methods are presently underway in our laboratories.

All compounds reported here have been previously described in the literature, unless stated otherwise. All experiments were performed using standard Schlenk techniques under argon or N_2 atmosphere, unless stated otherwise. All solvents were purchased at the highest commercial grade and used as received or after purification by passing through activated alumina columns or distillation from sodium/ benzophenone under N_2 . All other chemicals were purchased at the highest commercial grade and used as received. All other general methods have been published.^{6b}

tert-Butyl Benzoyl(phenyl)carbamate (1a) (54 mmol Scale)

To an oven-dried round-bottomed 500 mL flask equipped with a stir bar were added *N*-phenylbenzamide (**1a'**; 10.60 g, 53.8 mmol, 1.0 equiv), NEt₃ (5.44 g, 53.8 mmol, 1.0 equiv), and DMAP (0.066 g, 0.54 mmol, 1.0 mol%). MeCN (108 mL, 0.50 M) was added, followed by a slow addition of di-*tert*-butyl dicarbonate (12.33 g, 56.5 mmol, 1.05 equiv), and the resulting reaction mixture was stirred for 15 h at RT. After the indicated time, the solvent was removed under high pressure, the organic layer was dissolved in EtOAc (500 mL), washed with aq 1 N HCl (3×200 mL) and brine (200 mL), dried (Na₂SO₄), filtered, and concentrated to give the crude product. The crude product was

dissolved in EtOAc (20 mL) and slowly heated up to 70 °C with vigorous stirring until all solid had dissolved. If needed, additional EtOAc should be added, if it appears that the remaining solid could not dissolve. Hexene was slowly added at 70 °C with vigorous stirring until trace solid precipitated from the solution. Stirring was stopped and the reaction mixture was allowed to cool down to RT overnight or until no further crystals were formed. The desired product was obtained after filtration and drying under vacuum as a white solid; yield: 15.2 g (95%); >98% purity by ¹H NMR analysis.

Characterization data are included in the section below.

Phenyl(p-tolyl)methanone (3a) (33 mmol Scale)

An oven-dried round-bottomed 100 mL flask equipped with a stir bar was charged with *tert*-butyl benzoyl(phenyl)carbamate (**1a**; 10.00 g, 33.63 mmol, 1.0 equiv), K_2CO_3 (5.58 g, 40.36 mmol, 1.2 equiv), *p*-tolyl-boronic acid (5.49 g, 40.36 mmol, 1.2 equiv), [Pd(IPr)(cin)Cl] (Neolyst CX31, 21.8 mg, 0.10 mol%), and H₂O (3.00 g, 166.80 mmol, 5.0 equiv). The flask containing the reaction mixture was placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 2-MeTHF (22.4 mL, 1.5 M) was added with vigorous stirring at RT and the mixture was stirred for 15 h at RT. After the indicated time, the mixture was diluted with EtOAc (100 mL), filtered, and concentrated. Purification by chromatography on silica gel (EtOAc/hexanes 1:10) afforded the title product as a white solid; yield: 6.20 g (94%); >98% purity by ¹H NMR analysis.

Characterization data are included in the section below.

Synthesis of Starting Materials (5 mmol Scale); General Procedure

To an oven-dried round-bottomed 100 mL flask equipped with a stir bar were added an *N*-arylbenzamide substrate (5 mmol, 1.0 equiv), Et₃N (5 mmol, 1.0 equiv), and DMAP (0.05 mmol, 1.0 mol%). MeCN (10 mL, 0.50 M) was added, followed by a slow addition of di-*tert*butyl dicarbonate (5.25 mmol, 1.05 equiv), and the resulting reaction mixture was stirred for 15 h at RT. After the indicated time, the solvent was removed under high pressure, the organic layer was dissolved in EtOAc (20 mL), washed with aq 1 N HCl (3 × 20 mL) and brine (20 mL), dried (Na₂SO₄), filtered, and concentrated to give the crude product. Purification by recrystallization from EtOAc/hexanes afforded the title products.

Characterization data are included in the section below. The starting materials **1a–d** are known compounds and their spectral data match those reported in the literature.^{9b}

Suzuki–Miyaura Cross-Coupling (0.5 mmol Scale); General Procedure

An oven-dried vial equipped with a stir bar was charged with an *N*-Boc-amide substrate **1** (0.50 mmol, 1.0 equiv), K_2CO_3 (0.60 mmol, 1.2 equiv), the respective arylboronic acid (0.60 mmol, 1.2 equiv), [Pd(IPr)(cin)CI] (Neolyst CX31, 0.10 mol%), and H₂O (2.5 mmol, 5.0 equiv). The flask containing the reaction mixture was placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. 2-MeTHF (1.5 M) was added with vigorous stirring at RT and the mixture was stirred for the indicated time. After the indicated time, the reaction mixture was diluted with EtOAc (10 mL), filtered, and concentrated. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title products.

Characterization data are included in the section below. The crosscoupling products **3a–d** are known compounds and their spectral data match those reported in the literature.^{9b}

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Characterization Data of Starting Materials

tert-Butyl Benzoyl(phenyl)carbamate (1a)

White solid (EtOAc/hexanes 1:4); yield: 15.80 g (95%).

¹H NMR (500 MHz, $CDCl_3$): δ = 7.75–7.73 (m, 2 H), 7.53 (t, *J* = 7.4 Hz, 1 H), 7.44 (dd, *J* = 14.1, 7.7 Hz, 4 H), 7.34 (t, *J* = 7.4 Hz, 1 H), 7.28 (dd, *J* = 10.3, 2.9 Hz, 2 H), 1.24 (s, 9 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 172.8, 153.3, 139.1, 137.0, 131.7, 129.2, 128.3, 128.2, 128.0, 127.8, 83.5, 27.5.

tert-Butyl (2-Methylbenzoyl)(phenyl)carbamate (1b)

White solid (EtOAc/hexanes 1:4); yield: 1.48 g (93%).

¹H NMR (500 MHz, CDCl₃): δ = 7.48 (dd, J = 14.3, 7.2 Hz, 3 H), 7.41-7.35 (m, 2 H), 7.32 (d, J = 7.9 Hz, 2 H), 7.28-7.25 (m, 2 H), 2.52 (s, 3 H), 1.19 (s, 9 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 172.6, 152.9, 138.6, 137.9, 135.7, 130.7, 129.9, 129.2, 128.1, 128.0, 126.4, 125.5, 83.6, 27.4, 19.5.

tert-Butyl (4-Methoxybenzoyl)(phenyl)carbamate (1c)

White solid (EtOAc/hexanes 1:4); yield: 1.33 g (81%).

¹H NMR (500 MHz, CDCl₃): δ = 7.75 (d, *J* = 7.6 Hz, 2 H), 7.40 (t, *J* = 7.2 Hz, 2 H), 7.31 (t, *J* = 7.3 Hz, 1 H), 7.25 (d, *J* = 7.9 Hz, 2 H), 6.93 (d, *J* = 7.7 Hz, 2 H), 3.86 (s, 3 H), 1.30 (s, 9 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 172.1, 162.8, 153.6, 139.5, 130.9, 129.1, 128.7, 127.8, 127.5, 113.6, 83.1, 55.5, 27.7.

tert-Butyl [4-(Methoxycarbonyl)benzoyl](phenyl)carbamate (1d)

White solid (EtOAc/hexanes 1:4); yield: 1.39 g (78%).

¹H NMR (500 MHz, CDCl₃): δ = 8.14 (d, *J* = 8.1 Hz, 2 H), 7.78 (d, *J* = 8.1 Hz, 2 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 7.38 (t, *J* = 7.3 Hz, 1 H), 7.28 (d, *J* = 7.8 Hz, 2 H), 3.97 (s, 3 H), 1.26 (s, 9 H).

 ^{13}C NMR (125 MHz, CDCl_3): δ = 171.8, 166.2, 153.0, 141.0, 138.6, 132.5, 129.5, 129.3, 128.1, 128.0, 127.8, 84.0, 52.4, 27.5.

Characterization Data of Cross-Coupling Products

Phenyl(p-tolyl)methanone (3a)

White solid (EtOAc/hexanes 1:10); yield: 6.20 g (94%).

¹H NMR (500 MHz, CDCl₃): δ = 7.79 (d, *J* = 7.9 Hz, 2 H), 7.73 (d, *J* = 8.0 Hz, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.47 (t, *J* = 7.6 Hz, 2 H), 7.27 (t, *J* = 6.4 Hz, 2 H), 2.44 (s, 3 H).

¹³C NMR (125 MHz, CDCl₃): δ = 196.5, 143.3, 138.0, 134.9, 132.2, 130.3, 130.0, 129.0, 128.2, 21.7.

Phenyl(o-tolyl)methanone (3b)

Colorless oil (EtOAc/hexanes 1:20); yield: 86.5 mg (88%)

¹H NMR (500 MHz, $CDCl_3$): δ = 7.81 (d, *J* = 7.7 Hz, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 1 H), 7.30 (dd, *J* = 12.4, 7.6 Hz, 2 H), 7.25 (t, *J* = 7.4 Hz, 1 H), 2.34 (s, 3 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 198.6, 138.7, 137.8, 136.8, 133.2, 131.0, 130.3, 130.2, 128.5, 128.5, 125.2, 20.0.

(4-Methoxyphenyl)(phenyl)methanone (3c)

White solid (EtOAc/hexanes 1:10); yield: 103.7 mg (98%).

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¹H NMR (500 MHz, CDCl₃): δ = 7.82 (d, J = 8.9 Hz, 2 H), 7.75 (d, J = 7.0 Hz, 2 H), 7.55 (t, J = 7.4 Hz, 1 H), 7.46 (t, J = 7.6 Hz, 2 H), 6.95 (d, J = 8.9 Hz, 2 H), 3.87 (s, 3 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 195.6, 163.3, 138.3, 132.6, 131.9, 130.2, 129.7, 128.2, 113.6, 55.5.

Methyl 4-Benzoylbenzoate (3d)

White solid (EtOAc/hexanes 1:20); yield: 96.4 mg (80%).

¹H NMR (500 MHz, CDCl₃): δ = 8.14 (d, *J* = 8.2 Hz, 2 H), 7.84 (d, *J* = 8.2 Hz, 2 H), 7.80 (d, *J* = 7.5 Hz, 2 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 3.96 (s, 3 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 196.0, 166.3, 141.3, 137.0, 133.2, 133.0, 130.1, 129.8, 129.5, 128.5, 52.5.

Phenyl(o-tolyl)methanone (3b')

Colorless oil (EtOAc/hexanes 1:20); yield: 60.9 mg (62%)

¹H NMR (500 MHz, CDCl₃): δ = 7.81 (d, *J* = 7.7 Hz, 2 H), 7.57 (t, *J* = 7.4 Hz, 1 H), 7.45 (t, *J* = 7.6 Hz, 2 H), 7.39 (t, *J* = 7.5 Hz, 1 H), 7.30 (dd, *J* = 12.4, 7.6 Hz, 2 H), 7.25 (t, *J* = 7.4 Hz, 1 H), 2.34 (s, 3 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 198.6, 138.7, 137.8, 136.8, 133.2, 131.0, 130.3, 130.2, 128.5, 128.5, 125.2, 20.0.

(4-Methoxyphenyl)(phenyl)methanone (3c')

White solid (EtOAc/hexanes 1:20); yield: 91.5 mg (86%).

¹H NMR (500 MHz, CDCl₃): δ = 7.82 (d, *J* = 8.9 Hz, 2 H), 7.75 (d, *J* = 7.0 Hz, 2 H), 7.55 (t, *J* = 7.4 Hz, 1 H), 7.46 (t, *J* = 7.6 Hz, 2 H), 6.95 (d, *J* = 8.9 Hz, 2 H), 3.87 (s, 3 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 195.6, 163.3, 138.3, 132.6, 131.9, 130.2, 129.7, 128.2, 113.6, 55.5.

Methyl 4-Benzoylbenzoate (3d')

White solid (EtOAc/hexanes 1:20); yield: 90.2 mg (75%).

¹H NMR (500 MHz, CDCl₃): δ = 8.14 (d, *J* = 8.2 Hz, 2 H), 7.84 (d, *J* = 8.2 Hz, 2 H), 7.80 (d, *J* = 7.5 Hz, 2 H), 7.61 (t, *J* = 7.4 Hz, 1 H), 7.50 (t, *J* = 7.7 Hz, 2 H), 3.96 (s, 3 H).

 ^{13}C NMR (125 MHz, CDCl₃): δ = 196.0, 166.3, 141.3, 137.0, 133.2, 133.0, 130.1, 129.8, 129.5, 128.5, 52.5.

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Supporting Information

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References

- (1) Greenberg, A.; Breneman, C. M.; Liebman, J. F. *The Amide Link-age: Structural Significance in Chemistry, Biochemistry and Materials Science*; Wiley-VCH: New York, **2003**.
- (2) For selected reviews on amide N–C(O) bond activation, see:
 (a) Meng, G.; Szostak, M. *Eur. J. Org. Chem.* **2018**, 2352. (b) Liu, C.; Szostak, M. Org. *Biomol. Chem.* **2018**, 16, 7998. (c) Dander, J. E.; Garg, N. K. *ACS Catal.* **2017**, 7, 1413. (d) Takise, R.; Muto, K.; Yamaguchi, J. *Chem. Soc. Rev.* **2017**, 46, 5864. (e) Bourne Branchu, Y.; Gosmini, C.; Danoun, G. *Chem. Eur. J.* **2019**, 25, 2663. (f) Chaudhari, M. B.; Gnanaprakasam, B. *Chem. Asian J.* **2019**, 14, 76.
- (3) For a review on acyl-cross-coupling, see: Buchspies, J.; Szostak, M. *Catalysts* **2019**, *9*, 53.
- (4) For studies on amide bond destabilization, see: Liu, C.; Shi, S.; Liu, Y.; Liu, R.; Lalancette, R.; Szostak, R.; Szostak, M. Org. Lett. 2018, 20, 7771.
- (5) For lead references on amide bonds in drug discovery and polymer chemistry, see: (a) Roughley, S. D.; Jordan, A. M. J. Med. Chem. 2011, 54, 3451. (b) Kaspar, A. A.; Reichert, J. M. Drug Discov. Today 2013, 18, 807. (c) Marchildon, K. Macromol. React. Eng. 2011, 5, 22. (d) Brunton, L.; Chabner, B.; Knollman, B. Goodman and Gilman's The Pharmacological Basis of Therapeutics; MacGraw-Hill: New York, 2010. For selected recent examples of amide bonds in synthetic chemistry, see: (e) Barger, C. J.; Dicken, R. D.; Weidner, V. L.; Motta, A.; Lohr, T. L.; Marks, T. J. J. Am. Chem. Soc. 2020, 142, 8019. (f) Wei, T.; Lu, S.; Sun, J.; Xu, Z.; Yang, X.; Wang, F.; Ma, Y.; Shi, Y. S.; Chen, X. J. Am. Chem. Soc. 2020, 142, 3806. (g) Gonçalves, C. R.; Lemmerer, M.; Teskey, C. J.; Adler, P.; Kaiser, D.; Maryasin, B.; González, L.; Maulide, N. J. Am. Chem. Soc. 2019, 141, 18437. (h) Derosa, J.; Kleinmans, R.; Tran, V. T.; Karunananda, M. K.; Wisniewski, S. R.; Eastgate, M. D.; Engle, K. M. J. Am. Chem. Soc. 2018, 140, 17878. (i) Chen, J.; Xia, Y.; Lee, S. Org. Lett. 2020, 22, 3504. (j) Sharma, S.; Buchbinder, N. W.; Braje, W. M.; Handa, S. Org. Lett. 2020, 22, 5737.
- (6) For selected studies on amide N-C(O) cross-coupling, see:
 (a) Hie, L.; Nathel, N. F. F.; Shah, T. K.; Baker, E. L.; Hong, X.; Yang, Y. F.; Liu, P.; Houk, K. N.; Garg, N. K. *Nature* 2015, *524*, 79.
 (b) Meng, G.; Szostak, M. Org. Lett. 2015, *17*, 4364. (c) Meng, G.; Szostak, M. Angew. Chem. Int. Ed. 2015, *54*, 14518. (d) Ni, S.; Zhang, W.; Mei, H.; Han, J.; Pan, Y. Org. Lett. 2017, *19*, 2536.
 (e) Yue, H.; Guo, L.; Liao, H. H.; Cai, Y.; Zhu, C.; Rueping, M. Angew. Chem. Int. Ed. 2017, *56*, 4282. (f) For a comprehensive list, refs. 2 and 3.
- (7) For reviews on Pd–NHCs in amide N–C(O) activation, see:
 (a) Shi, S.; Nolan, S. P.; Szostak, M. Acc. Chem. Res. 2018, 51, 2589.
 (b) Vemula, S. R.; Chhoun, M. R.; Cook, G. R. Molecules 2019, 24, 215.
- (8) For excellent reviews on the impact of synthetic chemistry on medicinal chemistry, see: (a) Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. Chem. Soc. Rev. 2016, 45, 546. (b) Blakemore, D. C.; Castro, L.; Churcher, I.; Rees, D. C.; Thomas, A. W.; Wilson, D. M.; Wood, A. Nat. Chem. 2018, 10, 383.
- (9) For studies using different classes of [Pd-NHCs], see:
 (a) [Pd(NHC)(allyl)Cl] complexes: Lei, P.; Meng, G.; Szostak, M. ACS Catal. 2017, 7, 1960. (b) [Pd(NHC)(ind)Cl] complexes: Lei, P.; Meng, G.; Shi, S.; Ling, Y.; An, J.; Szostak, R.; Szostak, M. Chem. Sci. 2017, 8, 6525. (c) [Pd–PEPPSI] complexes: Lei, P.;

PSP

Meng, G.; Ling, Y.; An, J.; Szostak, M. *J. Org. Chem.* **2017**, *82*, 6638. (d) [Pd(NHC)(acac)Cl] complexes: Zhou, T.; Li, G.; Nolan, S. P.; Szostak, M. Org. Lett. **2019**, *21*, 3304.

- (10) (a) Marion, N.; Navarro, O.; Mei, J.; Stevens, E. D.; Scott, N. M.; Nolan, S. P. *J. Am. Chem. Soc.* **2006**, *128*, 4101. (b) Navarro, O.; Marion, N.; Mei, J.; Nolan, S. P. *Chem. Eur. J.* **2006**, *12*, 5142.
 (c) Marion, N.; Nolan, S. P. *Acc. Chem. Res.* **2008**, *41*, 1440.
- (11) Lei, P.; Ling, Y.; An, J.; Nolan, S. P.; Szostak, M. Adv. Synth. Catal. **2019**, 361, 5654.
- (12) For a mechanism of the Suzuki–Miyaura N–C(O) cross-coupling of amides, see: Li, G.; Lei, P.; Szostak, M.; Casals, E.; Poater, A.; Cavallo, L; Nolan, S. P. *ChemCatChem* **2018**, *10*, 3096.
- (13) For general reviews, see: (a) Li, H.; Johansson-Seechurn, C. C. C.; Colacot, T. J. ACS Catal. 2012, 2, 1147. (b) Science of Synthesis: Cross-Coupling and Heck-Type Reactions, 1st ed; Molander, G. A.; Wolfe, J. P.; Larhed, M., Ed.; Thieme: Stuttgart, 2013. (c) New Trends in Cross-Coupling, 1st ed; Colacot, T. J., Ed.; The Royal Society of Chemistry: Cambridge, 2015.
- (14) (a) [Pd–PEPPSI] complexes: Froese, R. D. J.; Lombardi, C.;
 Pompeo, M.; Rucker, R. P.; Organ, M. G. Acc. Chem. Res. 2017, 50, 2244. (b) [Pd(NHC)(ind)Cl] complexes: Melvin, P. R.; Nova, A.;

Balcells, D.; Dai, W.; Hazari, N.; Hruszkewycz, D. P.; Shah, H. P.; Tudge, M. T. *ACS Catal.* **2015**, *5*, 5596. (c) $[Pd(NHC)(\mu-Cl)Cl]_2$ complexes: Zhou, T.; Ma, S.; Nahra, F.; Obled, A. M. C.; Poater, A.; Cavallo, L.; Cazin, C. S. J.; Nolan, S. P.; Szostak, M. *iScience* **2020**, *23*, 101377.

- (15) For studies on ester C(acyl)–O activation, see: Li, G.; Shi, S.; Lei, P.; Szostak, M. *Adv. Synth. Catal.* **2018**, *360*, 1538.
- (16) For representative studies, see: (a) Li, G.; Szostak, M. Nat. Commun. 2018, 9, 4165. (b) Li, G.; Ji, C. L.; Hong, X.; Szostak, M. J. Am. Chem. Soc. 2019, 141, 11161. (c) Li, G.; Lei, P.; Szostak, M. Org. Lett. 2018, 20, 5622. (d) For a study using Co-catalysis, see: Bourne-Branchu, Y.; Gosmini, C.; Danoun, G. Chem. Eur. J. 2017, 23, 10043. (e) For a study using Ni catalysis, see ref. 6a (f) For a transition-metal-free study, see: Verho, O.; Lati, M. P.; Oschmann, M. J. Org. Chem. 2018, 83, 4464.
- (17) Meng, G.; Szostak, M. Org. Lett. 2018, 20, 6789.
- (18) Li, G.; Zhou, T.; Poater, A.; Cavallo, L.; Nolan, S. P.; Szostak, M. *Catal. Sci. Technol.* **2020**, *10*, 710.