Pd–PEPPSI: A General Pd–NHC Precatalyst for Suzuki-Miyaura Cross-Coupling of Esters by C–O Cleavage

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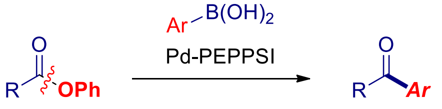
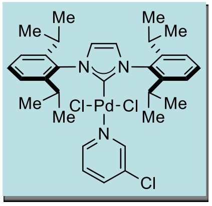
Supporting Information



- catalytic C–O cleavage
- reactivity scale: amide ≈ ester
- easily prepared, modular catalysts



ABSTRACT: The Suzuki-Miyaura cross-coupling of aryl esters by selective C–O bond cleavage represents a powerful methodology in organic synthesis. Here, we report that versatile, easily prepared, well-defined Pd-PEPPSI type precatalysts serve as highly reactive catalysts for the direct Suzuki-Miyaura cross-coupling of esters. Sterically and electronically diverse aryl esters couple with arylboronic acids in good to excellent yields using a single, operationally-simple protocol. Kinetic studies demonstrate that the cross-coupling of aryl esters proceeds with similar rates to the cross-coupling of amides. This study strongly supports the use of well-defined Pd(II)-NHC precatalysts bearing pyridine "throw-away" ligands for the selective C(acyl)–cleavage of bench-stable carboxylic acid derivatives. Considering the modular scaffold of Pd-NHC precatalysts we envision that the method will be of general interest for the development of new catalysts for C–O cleavage reactions.

Oxidative addition of a metal to acyl electrophile represents a fundamental step in catalysis.[1] Historically, the use of aryl esters in the cross-coupling manifolds has been difficult due to low reactivity of the C–O bond towards metal insertion as a result of $n_O \rightarrow \pi^*_{C=O}$ conjugation.[2,3] A recent advance has been the development of an array of decarbonylative cross-couplings of common aryl esters fuelled by the design of new electron-rich, chelating phosphine ligands for Ni and Pd to trigger oxidative addition.[4,5] Intriguingly, the ability to promote previously inaccessible catalytic pathways engaging ubiquitous C–O bonds offers a unique potential to develop valuable bond forming reactions in chemicals synthesis.

Recently, our laboratory introduced a new amide bond activation manifold that allows the activation and subsequent cross-coupling of the C–N acyl amide bond via ground-state destabilization.[6–8] Expanding upon this theme, we recently demonstrated that this amide activation platform could be extended to the cross-coupling of aryl esters.[9] This catalytic manifold hinges on the decreased rotational barrier in aryl esters (E_R = 9.3 kcal/mol) and ground-state-destabilized amides (E_R < 10 kcal/mol)[10] to enable selective metal insertion into the acyl bond using synthetically-attractive bench-stable carboxylic acid derivatives.[11,12] The prevalence of aryl esters in organic synthesis provides new avenues for modular cross-coupling processes of common electrophiles.

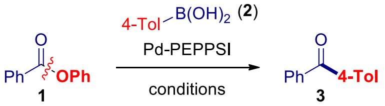
To realize the full potential of the acyl cross-coupling manifold it is critical that it be possible to employ new general catalyst systems that operate under operationally-simple conditions.

In this communication, we report that versatile, easily prepared, well-defined Pd-PEPPSI type precatalysts[13–15] serve as highly reactive catalysts for the direct Suzuki-Miyaura cross-coupling[16] of esters. Moreover, we demonstrate that the cross-coupling of aryl esters proceeds with similar rates to the cross-coupling of amides. Considering the modular scaffold of Pd(II)-NHC precatalysts bearing pyridine "throw-away" ligand,[17] we envision that the method will be of general interest for the development of new catalysts for acyl C–O cleavage reactions.[18]

The use of Pd-PEPPSI catalysts in the acyl C–O coupling manifold involves two immediate advantages: (i) PEPPSI type complexes are prepared in a single operationally-straightforward step, which is not the case with other Pd-NHC type complexes. This may facilitate a general use of Pd-NHC catalysts in ester C–O cross-couplings. (ii) A variety of PEPPSI type complexes can be easily accessed by appending alkyl or halide groups on the NHC scaffold, which may result in the development of even more active catalysts for the acyl C–O cross-coupling. We also report for the first time that, in terms of steric demand, IPr may be the preferred NHC scaffold for achieving high efficiency in the acyl cross-coupling, consistent with steric properties of acyl-Pd complexes.[2a]

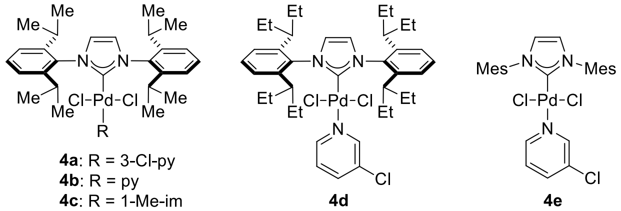
Our motivation for studying Pd-PEPPSI type precatalysts for the Suzuki-Miyaura cross-coupling of esters stems from their unique catalytic properties: (1) Pd-PEPPSI complexes are among the most active catalysts for palladium-catalyzed cross-coupling reactions.[14] (2) PEPPSI type of Pd-NHC complexes represent a modular class of Pd-NHC catalysts, which is crucial for the rational design of catalysts through changes in the ancillary and throw-away ligand.[18] (3) PEPPSI type complexes are easy and inexpensive to prepare,[14,15] which may spearhead the widespread use of acyl cross-couplings in organic synthesis.

Table 1. Optimization of the Reaction Conditions[a]



entry	catalyst	base	solvent	T (°C)	yield (%)[b]
1	**4a**	K_2CO_3	THF	80	84
2	**4a**	K_2CO_3	toluene	80	80
3	**4a**	K_2CO_3	dioxane	80	83
4	**4a**	K_2CO_3	DME	80	48
5	**4a**	K_3PO_4	THF	80	69
6	**4a**	KOH	THF	80	32
7	**4a**	Cs_2CO_3	THF	80	13
8	**4a**	Na_2CO_3	THF	80	<5
9	**4a**	K_2CO_3	THF	60	76
10	**4a**	K_2CO_3	THF	40	39
11	**4a**	K_2CO_3	THF	110	88
12	**4b**	K_2CO_3	THF	80	75
13	**4c**	K_2CO_3	THF	80	53
14	**4d**	K_2CO_3	THF	80	42
15	**4e**	K_2CO_3	THF	80	45
16[c]	**4a**	K_2CO_3	THF	80	72
17[d]	**4a**	K_2CO_3	THF	80	75
18[e]	**4a**	K_2CO_3	THF	80	71

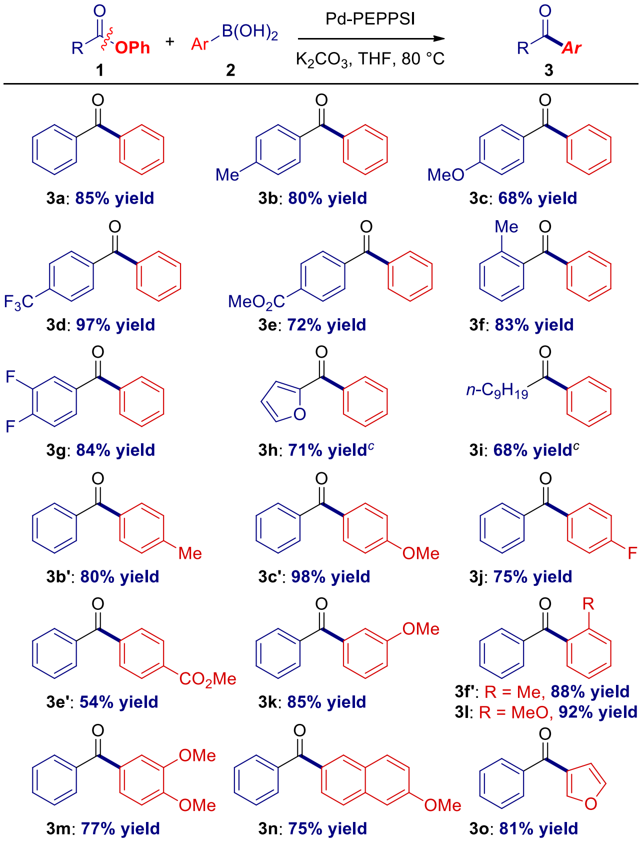
[a] **1** (1.0 equiv), R-B(OH)$_2$ (3.0 equiv), [Pd] (3 mol %), K_2CO_3 (4.5 equiv), THF (0.80 mL), T, 16 h. [b] GC/^{1}H NMR yields. [c] K_2CO_3 (1.0 equiv). [d] R-B(OH)$_2$ (1.2 equiv). [e] K_2CO_3 (1.0 equiv), R-B(OH)$_2$ (1.2 equiv).



4a: R = 3-Cl-py
4b: R = py
4c: R = 1-Me-im
4d
4e

Various PEPPSI type catalysts were screened under different conditions for the model reaction between phenyl benzoate (**1a**) and 4-tolylboronic acid (**2b**) (Table 1). The optimized catalyst system uses Pd-PEPPSI-IPr (3 mol%), 4-Tol-B(OH)$_2$ (3.0 equiv), K_2CO_3 (4.5 equiv), sTHF, 80 °C, affording the desired product in 84% yield. Selected optimization results are summarized in Table 1. THF, toluene and dioxane proved to be the most effective solvents (entries 1-4). The reaction showed strong dependence on the base used with K_2CO_3 and K_3PO_4 providing the best results (entries 5-8). The reaction showed good efficiency at temperatures as low as 40 °C (entries 9-10). Increasing the temperature to 110 °C did not significantly affect the reaction (entry 11). The reaction was inefficient at room temperature. As anticipated, the reaction showed a profound dependence on the PEPPSI type scaffold (entries 11-14). The pyridine "throw-away" ligand (**4b**) cleanly produced the coupling product (entry 11). 1-Methylimidazole ligand (**4c**) at the palladium also resulted in the efficient cross-coupling (entry 12), with no observable side-products. Intriguingly, the use of more bulky PEPPSI-IPent (**4d**)[14b] and less sterically-demanding PEPPSI-IMes (**4e**) gave inferior results (entries 13-14). Overall, these findings suggest that (1) PEPPSI-IPr may serve as the privileged NHC scaffold for the C–O acyl cross-coupling; (2) changes in the "throw-away" ligand attached to the palladium center may lead to the development of more active catalysts for the cross-coupling.[18] Finally, the use of close to stoichiometric amount of base and boronic acid leads to efficient coupling, providing an entry point for further development (entries 15-18).

Table 2. Pd-PEPPSI-Catalyzed Suzuki-Miyaura Cross-Coupling of Esters[a,b]



[a] Conditions: ester, Ar-B(OH)$_2$ (3.0 equiv), [**4a**] (3 mol%), K_2CO_3 (4.5 equiv), THF (0.80 mL), 80 °C, 16 h. [b] Isolated yields. [c] [**4a**] (6 mol%).

The scope of this cross-coupling was next investigated (Table 2). As shown, the reaction accommodates a broad range of ester and boronic acid cross-coupling partners. Electronically-diverse ester electrophiles are well-tolerated in this coupling (**3a-3d**), including deactivated electron-rich arenes (**3d**). Sensitive electrophilic functional groups such as esters (**3e**) are readily accommodated. Sterically-demanding esters (**3f**) and even sensitive substrates such as polyfluorinated (**3g**), heterocyclic (**3h**) and aliphatic esters (**3i**) were smoothly converted into the desired products. The scope of the boronic acid component is also broad. In general, high to excellent yields of the cross-coupling products were obtained for electron-neutral (**3b'**), electron-rich (**3c'**), electron-deficient (**3j**, **3e'**) and sterically-demanding (**3f'**, **3l**) arylboronic acids. Moreover, polyaromatic (**3n**) and heterocyclic boronic acids (**3o**) are suitable substrates for this transformation. Of note, the product biaryl ketones are prevalent motifs in biologically-active compounds, organic materials and agrochemicals.[12] Boronic acid is typically used in excess. Transmetallation is generally considered as the rate-determining step in Suzuki-Miyaura couplings using Pd-NHC.[13a] Turnover number (TON) of 230 was determined for the coupling of ester **1a** (Pd-PEPPSI-IPr, 0.10 mol%, 110 °C). Side products, such as decarbonylation and unselective cleavage of the O–Ph bond, have not been observed.

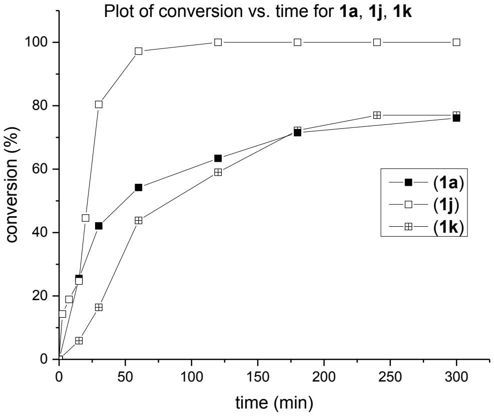


Figure 1. Kinetic profile of **1a**. Kinetic profile of **1j** (PhCONBocPh) and **1k** (PhCONTsPh) is shown for comparison. Conditions: **1**, 4-Tol-B(OH)$_2$ (2.0 equiv), **4a** (3 mol%), K_2CO_3 (3.0 equiv), THF, 60 °C.

To further demonstrate the high activity of Pd-PEPPSI-IPr in the cross-coupling, for comparison, we have conducted representative reactions catalyzed by Pd(IPr)(cinnamyl)(Cl) (8 representative examples, see SI). The obtained results clearly demonstrate that under the same reaction conditions Pd-PEPPSI-IPr shows comparable or higher reactivity than Pd(IPr)(cinnamyl)(Cl).

Kinetic studies were employed to investigate the effect of ester electronic destabilization[9] on the coupling (Figure 1). Generally speaking, these acyl activation reactions are subclassified as either C–N or C–O depending on the bond that undergoes the cross-coupling.[2a] Our study demonstrates that the cross-coupling of aryl esters proceeds with similar rates to the cross-coupling of amides (**1j**: PhCONBoc/Ph; **1k**: PhCONTs/Ph).[19] The generality of this acyl activation platform should enable the productive engagement in modular cross-coupling reactions without restriction to a particular acylmetal precursor.

Preliminary studies into the activation of PEPPSI-IPr and (IPr)Pd(cinnamyl)Cl[20] show more facile activation of PEPPSI-IPr under the developed conditions (PEPPSI: 30 min, 70% yield; 60 min, 77% yield; (IPr)Pd(cinnamyl)Cl: 30 min, 41% yield; 60 min, 48% yield), which opens the door for the development of even more active catalysts. In agreement with these findings, kinetic studies revealed higher catalytic activity of Pd-PEPPSI-IPr than (IPr)Pd(cinnamyl)Cl (see SI). Further studies on catalytic properties of Pd-NHC catalysts in the acyl cross-coupling manifold are ongoing.

In summary, we report that versatile Pd-PEPPSI type precatalysts serve as highly reactive catalysts for the direct Suzuki-Miyaura cross-coupling of esters. This reaction features modular, easily prepared Pd-NHC precatalysts, which operate under operationally-convenient conditions. We have further shown that the cross-coupling of esters proceeds at similar rates to the cross-coupling of amides. Evidently, the strong σ-donation of the NHC ligand facilitates oxidative addition, leading to a modular approach to the historically challenging C–O cross-coupling. Studies to address the design of catalysts in the catalytic C–O cross-coupling will be forthcoming.

EXPERIMENTAL SECTION

General. All starting materials reported in the manuscript have been previously described in literature and prepared by the method reported previously. Esters were prepared by standard methods.[4b,9,11] All experiments were performed using standard Schlenk techniques under nitrogen or argon unless stated otherwise. All products have been previously reported. General methods have been published.[7a] All products have been previously reported. The purity has been established by ^{1}H NMR analysis ($CDCl_3$, 500 MHz). All compounds are estimated to be >95% pure as determined by ^{1}H NMR.

General Procedure for the Suzuki-Miyaura Cross-Coupling of Esters. An oven-dried vial equipped with a stir bar was charged with an ester substrate (neat, 1.0 equiv), potassium carbonate (typically, 4.5 equiv), boronic acid (typically, 3.0 equiv), PEPPSI-IPr ([1,3-bis(2,6-diisopropylphenyl) imidazol-2-ylidene](3-chloropyridyl) palladium(II) dichloride, typically, 3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. THF (typically, 0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath and stirred for the indicated time. Note: All reactions have been carried out in microwave vials with heavy-wall, Type I, Class A borosilicate. These vials are designed to withstand pressures up to 300 PSI (20 bars) and are equivalent to Fisher-Porter tube. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product.

Representative Cross-Coupling Procedure. An oven-dried vial equipped with a stir bar was charged with phenyl benzoate (neat, 1.0 mmol, 198.0 mg, 1.0 equiv), potassium carbonate (4.5 mmol, 621.9 mg, 4.5 equiv), *p*-tolylboronic acid (3.0 mmol, 407.9 mg, 3.0 equiv), PEPPSI-IPr (3 mol%, 20.4 mg), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. THF (0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 80 °C and stirred for 16 h at 80 °C. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (20 mL), filtered, and concentrated. Purification by chromatography on silica gel (EtOAc/hexanes) afforded the title product. Yield 80% (157.2 mg). White solid. Characterization data are included in the section below.

Synthesis of Pd-NHC Complexes. Pd-PEPPSI complexes **4a** and **4d** are commercially available. Complexes **4b**, **4c** and **4e** were prepared by procedures reported in the literature.[14d,21]

Benzophenone (Table 2, **3a**). According to the general procedure, the reaction of phenyl benzoate (0.20 mmol, 1.0 equiv), phenylboronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 85% yield (30.9 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 7.7 Hz, 4 H), 7.59 (t, J = 7.5 Hz, 2 H), 7.49 (t, J = 7.6 Hz, 4 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.84, 137.77, 132.52, 130.18, 128.40. Spectroscopic data matched literature values.[7a]

Phenyl(p-tolyl)methanone (Table 2, **3b**). According to the general procedure, the reaction of phenyl 4-methylbenzoate (0.20 mmol, 1.0 equiv), phenylboronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 80% yield (31.4 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2 H), 7.74 (d, J = 8.2 Hz, 2 H), 7.59 (t, J = 7.3 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 2 H), 7.29 (d, J = 7.9 Hz, 2 H), 2.45 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.64, 143.36, 138.08, 135.00, 132.28, 130.43, 130.06, 129.10, 128.33, 21.79. Spectroscopic data matched literature values.[7a]

Phenyl(4-(trifluoromethyl)phenyl)methanone (Table 2, **3c**). According to the general procedure, the reaction of phenyl 4-methoxybenzoate (0.20 mmol, 1.0 equiv), phenylboronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 68% yield (28.8 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 2 H), 7.77 (d, J = 7.6 Hz, 2 H), 7.57 (t, J = 7.3 Hz, 1 H), 7.48 (t, J = 7.4 Hz, 2 H), 6.98 (d, J = 8.0 Hz, 2 H), 3.90 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.69, 163.34, 138.41, 132.68, 132.01, 130.28, 129.85, 128.31, 113.67, 55.62. Spectroscopic data matched literature values.[7a]

Phenyl(4-(trifluoromethyl)phenyl)methanone (Table 2, **3d**). According to the general procedure, the reaction of phenyl 4-(trifluoromethyl)benzoate (0.20 mmol, 1.0 equiv), phenylboronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 97% yield (48.5 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 2 H), 7.82 (dd, J = 7.1 Hz, 2 H), 7.77 (d, J = 8.1 Hz, 2 H), 7.67-7.62 (m, 1 H), 7.51 (t, J = 7.7 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.67, 140.86, 136.86, 133.86 (q, J^F = 32.5 Hz), 133.23, 130.27, 130.24, 128.67, 125.48 (q, J = 3.8 Hz), 123.81 (q, J^F = 271.3 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -63.02. Spectroscopic data matched literature values.[7a]

Methyl 4-benzoylbenzoate (Table 2, **3e**). According to the general procedure, the reaction of methyl phenyl terephthalate (0.20 mmol, 1.0 equiv), phenylboronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 72% yield (34.6 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 2 H), 7.85 (d, J = 8.0 Hz, 2 H), 7.81 (d, J = 8.0 Hz, 2 H), 7.63 (t, J = 7.5 Hz, 1 H), 7.51 (t, J = 7.5 Hz, 2 H), 3.98 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.17, 166.45, 141.45, 137.08, 133.35, 133.08, 130.24, 129.91, 129.63, 128.60, 52.61. Spectroscopic data matched literature values.[7a]

Phenyl(o-tolyl)methanone (Table 2, **3f**). According to the general procedure, the reaction of phenyl 2-methylbenzoate (0.20 mmol, 1.0 equiv), phenylboronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 83% yield (32.5 mg). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2 H), 7.64-7.59 (m, 1 H), 7.49 (t, J = 7.7 Hz, 2 H), 7.43 (td, J = 7.5, 1.5 Hz, 1 H), 7.37-7.31 (m, 2 H), 7.31-7.28 (m, 1 H), 2.37 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.77, 138.75, 137.87, 136.87, 133.25, 131.12, 130.36, 130.25, 128.64, 128.58, 125.32, 20.12. Spectroscopic data matched literature values.[7a]

(3,4-Difluorophenyl)(phenyl)methanone (Table 2, **3g**). According to the general procedure, the reaction of phenyl 3,4-difluorobenzoate (0.20 mmol, 1.0 equiv), phenylboronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 84% yield (36.6 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.77 (d, J = 7.5 Hz, 2 H), 7.69 (t, J = 9.0 Hz, 1 H), 7.61 (t, J = 13.2 Hz, 2 H), 7.51 (t, J = 8.0 Hz, 2 H), 7.27 (q, J = 8.0 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 194.21, 154.41 (dd, J^F = 254.8, 12.3 Hz), 150.32 (dd, J^F = 255.0, 12.4 Hz), 137.00, 134.57 (t, J^F = 3.7 Hz), 132.93, 129.97, 128.62, 127.25 (q, J^F = 3.8 Hz), 119.45 (dd, J^F =17.5, 1.3 Hz), 117.40 (d, J^F = 17.5 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -130.60 (d, J = 21.2 Hz), -136.18 (d, J = 21.2 Hz). Spectroscopic data matched literature values.[9]

Furan-2-yl(phenyl)methanone (Table 2, **3h**). According to the general procedure, the reaction of phenyl furan-2-carboxylate (0.20 mmol, 1.0 equiv), phenylboronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (6 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 71% yield (24.4 mg). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) 7.98 (d, J = 7.0 Hz, 2 H), 7.73 (s, 1 H), 7.61 (t, J = 7.5 Hz, 1 H), 7.51 (t, J = 7.5 Hz, 2 H), 7.25 (d, J = 3.5 Hz, 1 H), 6.61 (dd, J = 3.5, 1.5 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 182.71, 152.44, 147.23, 137.41, 132.71, 129.43, 128.56, 120.69, 112.34. Spectroscopic data matched literature values.[11a]

1-Phenyldecan-1-one (Table 2, **3i**). According to the general procedure, the reaction of phenyl decanoate (0.20 mmol, 1.0 equiv), phenylboronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (6 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 68% yield (31.6 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 7.5 Hz, 2 H), 7.55 (t, J = 7.5 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 2 H), 2.96 (t, J = 7.0 Hz, 2 H), 1.73 (p, J = 7.0, 6.5 Hz, 2 H), 1.40-1.25 (m, 12 H), 0.88 (t, J = 6.0 Hz, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 200.76, 137.25, 132.98, 128.67, 128.19, 38.79, 32.02, 29.63, 29.62, 29.53, 29.43, 24.54, 22.81, 14.25. Spectroscopic data matched literature values.[7a]

Phenyl(p-tolyl)methanone (Table 2, **3b'**). According to the general procedure, the reaction of phenyl benzoate (1.0 mmol, 1.0 equiv), *p*-tolylboronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 80% yield (157.2 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 8.2 Hz, 2 H), 7.74 (d, J = 8.2 Hz, 2 H), 7.59 (t, J = 7.3 Hz, 1 H), 7.48 (t, J = 7.5 Hz, 2 H), 7.29 (d, J = 7.9 Hz, 2 H), 2.45 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.64, 143.36, 138.08, 135.00, 132.28, 130.43, 130.06, 129.10, 128.33, 21.79. Spectroscopic data matched literature values.[7a]

(4-Methoxyphenyl)(phenyl)methanone (Table 2, **3c'**). According to the general procedure, the reaction of phenyl benzoate (0.20 mmol, 1.0 equiv), (4-methoxyphenyl)boronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 98% yield (41.6 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 2 H), 7.77 (d, J = 7.6 Hz, 2 H), 7.57 (t, J = 7.3 Hz, 1 H), 7.48 (t, J = 7.4 Hz, 2 H), 6.98 (d, J = 8.0 Hz, 2 H), 3.90 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.69, 163.34, 138.41, 132.68, 132.01, 130.28, 129.85, 128.31, 113.67, 55.62. Spectroscopic data matched literature values.[7a]

(4-Fluorophenyl)(phenyl)methanone (Table 2, **3j**). According to the general procedure, the reaction of phenyl benzoate (0.20 mmol, 1.0 equiv), (4-fluorophenyl)boronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 75% yield (30.0 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, J = 8.5, 5.5 Hz, 2 H), 7.77 (d, J = 8.0 Hz, 2 H), 7.59 (t, J = 7.5 Hz, 1 H), 7.49 (t, J = 7.5 Hz, 2 H), 7.16 (t, J = 8.5 Hz, 2 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.37, 165.54 (d, J^F = 252.5 Hz), 137.68, 133.97 (d, J^F = 3.8 Hz), 132.80 (d, J^F = 8.8 Hz), 132.59, 130.00, 128.49, 115.59 (d, J^F = 21.2 Hz). ^{19}F NMR (471 MHz, $CDCl_3$) δ -106.06. Spectroscopic data matched literature values.[7a]

Methyl 4-benzoylbenzoate (Table 2, **3e'**). According to the general procedure, the reaction of phenyl benzoate (0.20 mmol, 1.0 equiv), (4-(methoxycarbonyl)phenyl)boronic acid (3.0 equiv), K_2CO_3 (4.5 equiv), H_2O (5.0 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 54% yield (25.9 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, J = 8.0 Hz, 2 H), 7.85 (d, J = 8.0 Hz, 2 H), 7.81 (d, J = 8.0 Hz, 2 H), 7.63 (t, J = 7.5 Hz, 1 H), 7.51 (t, J = 7.5 Hz, 2 H), 3.98 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.17, 166.45, 141.45, 137.08, 133.35, 133.08, 130.24, 129.91, 129.63, 128.60, 52.61. Spectroscopic data matched literature values.[7a]

(3-Methoxyphenyl)(phenyl)methanone (Table 2, **3k**). According to the general procedure, the reaction of phenyl benzoate (0.20 mmol, 1.0 equiv), (3-methoxyphenyl)boronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 85% yield (36.0 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 7.7 Hz, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.49 (t, J = 7.4 Hz, 2 H), 7.41-7.34 (m, 3 H), 7.14 (d, J = 8.6 Hz, 1 H), 3.87 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.66, 159.70, 139.03, 132.55, 130.17, 129.34, 128.39, 123.01, 119.00, 114.44, 55.61. Spectroscopic data matched literature values.[22]

Phenyl(o-tolyl)methanone (Table 2, **3f'**). According to the general procedure, the reaction of phenyl benzoate (0.20 mmol, 1.0 equiv), *o*-tolylboronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 88% yield (34.5 mg). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2 H), 7.64-7.59 (m, 1 H), 7.49 (t, J = 7.7 Hz, 2 H), 7.43 (td, J = 7.5, 1.5 Hz, 1 H), 7.37-7.31 (m, 2 H), 7.31-7.28 (m, 1 H), 2.37 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 198.77, 138.75, 137.87, 136.87, 133.25, 131.12, 130.36, 130.25, 128.64, 128.58, 125.32, 20.12. Spectroscopic data matched literature values.[7a]

(2-Methoxyphenyl)(phenyl)methanone (Table 2, **3l**). According to the general procedure, the reaction of phenyl benzoate (0.20 mmol, 1.0 equiv), (2-methoxyphenyl)boronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 92% yield (39.0 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 7.8 Hz, 2 H), 7.56 (t, J = 7.1 Hz, 1 H), 7.49 (d, J = 7.7 Hz, 1 H), 7.44 (t, J = 7.5 Hz, 2 H), 7.37 (d, J = 7.4 Hz, 1 H), 7.05 (t, J = 7.4 Hz, 1 H), 7.00 (d, J = 8.3 Hz, 1 H), 3.73 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.58, 157.46, 137.93, 133.03, 131.99, 129.94, 129.70, 128.97, 128.33, 120.60, 111.57, 55.72. Spectroscopic data matched literature values.[11a]

(3,4-Dimethoxyphenyl)(phenyl)methanone (Table 2, **3m**). According to the general procedure, the reaction of phenyl benzoate (0.20 mmol, 1.0 equiv), (3,4-dimethoxyphenyl) boronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 77% yield (37.3 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 8.1 Hz, 2 H), 7.57 (t, J = 7.0 Hz, 1 H), 7.51-7.44 (m, 3 H), 7.38 (d, J = 8.3 Hz, 1 H), 6.89 (d, J = 8.3 Hz, 1 H), 3.96 (s, 3 H), 3.95 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 195.71, 153.13, 149.14, 138.42, 132.01, 130.35, 129.85, 128.30, 125.64, 112.24, 109.85, 56.24, 56.19. Spectroscopic data matched literature values.[11a]

(6-Methoxynaphthalen-2-yl)(phenyl)methanone (Table 2, **3n**). According to the general procedure, the reaction of phenyl benzoate (0.20 mmol, 1.0 equiv), (6-methoxynaphthalen-2-yl)boronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 75% yield (39.3 mg). White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.21 (d, J = 1.7 Hz, 1 H), 7.94 (dd, J = 8.6, 1.7 Hz, 1 H), 7.88-7.79 (m, 4 H), 7.65-7.58 (m, 1 H), 7.51 (dd, J = 8.4, 7.0 Hz, 2 H), 7.24-7.17 (m, 2 H), 3.96 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 196.70, 159.81, 138.33, 137.13, 132.81, 132.24, 132.11, 131.15, 130.10, 128.41, 127.72, 127.13, 126.68, 119.85, 105.88, 55.57. Spectroscopic data matched literature values.[22]

Furan-3-yl(phenyl)methanone (Table 2, **3o**). According to the general procedure, the reaction of phenyl benzoate (0.20 mmol, 1.0 equiv), furan-3-yl boronic acid (3.0 equiv), K_2CO_3 (4.5 equiv) and PEPPSI-IPr (3 mol%) in THF (0.25 M) for 15 h at 80 °C, afforded after filtration and chromatography the title compound in 81% yield (27.9 mg). Colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (s, 1 H), 7.86 (d, J = 8.3 Hz, 2 H), 7.59 (t, J = 7.4 Hz, 1 H), 7.53-7.46 (m, 3 H), 6.91 (d, J = 1.8 Hz, 1 H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 189.56, 148.69, 144.09, 138.96, 132.61, 128.96, 128.68, 126.65, 110.35. Spectroscopic data matched literature values.[7a]

Determination of Relative Reaction Rates. An oven-dried vial equipped with a stir bar was charged with an ester substrate (neat, 0.20 mmol, 1.0 equiv), potassium carbonate (3.0 equiv), boronic acid (2.0 equiv) and PEPPSI-IPr (3 mol%), placed under a positive pressure of argon, and subjected to three evacuation/backfilling cycles under high vacuum. THF (0.25 M) was added with vigorous stirring at room temperature, the reaction mixture was placed in a preheated oil bath at 60 °C and stirred at 60 °C for the indicated time. After the indicated time, the reaction mixture was cooled down to room temperature, diluted with CH_2Cl_2 (10 mL), filtered, and concentrated. The sample was analyzed by ^{1}H NMR ($CDCl_3$, 500 MHz) and/or GC-MS to obtain conversion, selectivity and yield using internal standard and comparison with authentic samples.

ASSOCIATED CONTENT

Supporting Information

NMR data, comparison of reactivity of Pd-PEPPSI-IPr and (IPr)Pd(cin)Cl, kinetic profile of (IPr)Pd(cin)Cl. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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