Highly Selective and Divergent Acyl and Aryl Cross-Coupling of Amides via Ir-Catalyzed C–H Borylation/N–C(O) Activation

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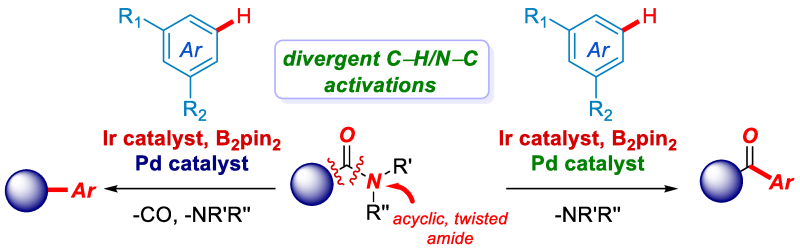
Supporting Information



ABSTRACT: Herein, we demonstrate that amides can be readily coupled with non-activated arenes via sequential Ir-catalyzed C–H borylation/N–C(O) activation. This methodology provides facile access to biaryl ketones and biaryls by the sterically-controlled Ir-catalyzed C–H borylation and divergent acyl and decarbonylative amide N–C(O) and C–C activation. The methodology diverts the traditional acylation and arylation regioselectivity, allowing to directly utilize readily available arenes and amides to produce valuable ketone and biaryl motifs.

Non-directed activation of C–H bonds is among the most important tools for transforming functional groups in organic synthesis.[1] The value of non-directed C–H functionalizations lies in the fact that these transformations enable the construction of complex fragments by exploiting readily available arenes (Figure 1A).[2] One of the most promising applications of these methods are Ir-catalyzed C–H borylations, wherein the development of sterically- and ligand-controlled C–H functionalizations enables transformative fragment couplings by exploiting new routes to organoboron building blocks of broad relevance to pharmaceuticals, functional materials and the synthesis of fine chemicals.[2–5]

Simultaneously, the recent years have witnessed the development of powerful strategies for activation of amide N–C(O) bonds,[6] whereby the traditional amidic resonance ($n_N \rightarrow \pi^*C{=}O$ delocalization)[7,8] is diverted into facile oxidative addition of the N–C(O) amide bond by ground-state-destabilization and diminution of amidic resonance.[9–12] The value of amide cross-coupling lies in the fact that amides are among the most ubiquitous functional groups in organic synthesis, serve as essential scaffolds in polymers, and, most importantly, constitute key linkages in peptides and proteins.[6–8] A prominent feature of amide bond cross-coupling is that the acyl-metal intermediate formed after metal insertion can undergo CO extrusion, resulting in an overall N–C(O)/C–C bond activation to afford an aryl-metal, which allows for the direct installation of arenes by de-amidative cleavage.[13]

Recently, we became interested in establishing the synergistic merger of non-directed C–H activation with amide N–C(O) cross-coupling (Figure 1B). The utilization of readily available arenes[1–5] as an abundant source of coupling partners together with the selective breaking of nitrogen–carbon bonds in amides[6–8] holds significant promise to define new paradigms in transformation of functional groups crucial to many synthetic and biological processes.[14]

Herein, we detail the successful development of highly selective and divergent acyl and aryl cross-coupling of amides with non-activated arenes via C–H/N–C(O) activation. This methodology connects the classic sterically-hindered Ir-catalyzed C–H borylation[2,3] with the biorelevant manifold of amide bond activation[6–8] to provide straightforward access to biaryl ketones and biaryls by two inert bond activation events and diverting the traditional acylation and arylation regioselectivity. The method shows excellent functional group tolerance, chemo- and regioselectivity. We demonstrate the synthetic utility by late-stage derivatization of pharmaceuticals and conjugative cross- coupling of bioactive molecules. The synergistic merger with non-activated arenes opens the door to routinely utilize amides as acyl and aryl cross-coupling electrophiles in a wide range of chemical processes.[1–14]

The arylation of N,N-Boc-benzamide, which is readily prepared in single step from benzamide,[7a] with 4-tol-Bpin was selected as the starting point of our study to identify conditions for the cross-coupling of boronic esters with amides (Table S1, Supporting Information). Encouragingly, we found that the

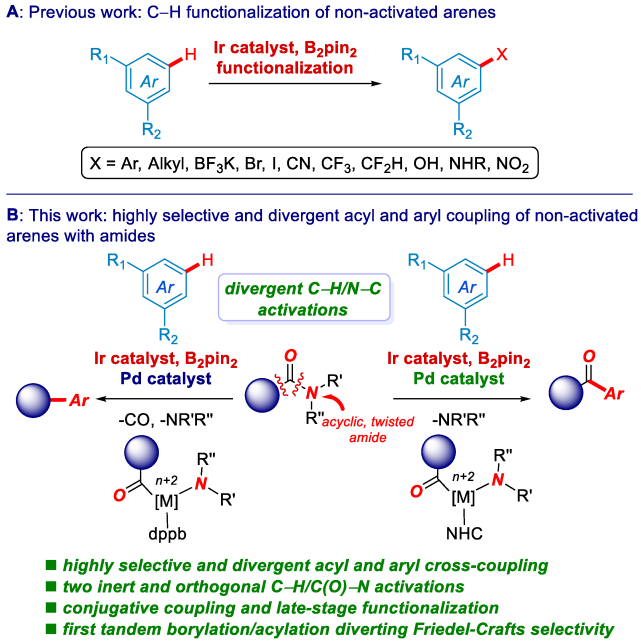


Figure 1. (A) Meta-borylation in organic synthesis. (B) Present work.

broadly applicable, air- and moisture-stable [Pd(IPr)(cin)Cl] (Neolyst CX31, cin = cinnamyl)[15] serves as an efficient catalyst for this coupling to give the model biaryl ketone product in 98% yield (entry 13). Notably, this cross-coupling with boronic esters was found to be sensitive to the amount of water and temperature, controlling the release of aryl boronic acid,[16] with best results obtained in THF:H_2O (9:1) at 23 °C (cf. Table S2 for arylation). The key difference between the two Pd catalytic systems (Table S1 vs. Table S2) is that Pd–NHCs facilitate oxidative addition/reductive elimination steps due to strong σ-donation and flexible bulk,[9a] respectively, while Pd-phosphine systems in the presence of weak base favour decarbonylation due to slowing down transmetallation relative to CO de-insertion step.[13] Note that the substrates are presented on schemes to reflect how the reactions were carried out. [Pd(IPr)(cin)Cl] is the catalyst of choice for amide bond Suzuki cross-coupling.[9a,15]

With the identified conditions in hand, we explored the scope of the sequential C–H/N–C(O) activation (Scheme 1). The borylation was conducted with 0.75 equiv of B_2pin_2 in the presence of 0.50 mol% of $[Ir(cod)(OMe)]_2$ and 1.0 mol% of dtbpy.[2a,b] Arylboronate esters were subjected to the C(O)–N amide cross-coupling after removing of volatiles and addition of amide derivatives. 1,3-Dimethoxybenzne was used for the borylation reaction as the model arene substrate.[2a,b] As shown in Scheme 1, the scope of the reaction with respect to amide precursors is very broad and encompasses a wide variety of functional groups. Electron-rich (**3a**, **3c**, **3e**, **3t**), sterically-hindered (**3b**, **3o**, **3p**), and electron-deficient (**3d**, **3f**, **3g**, **3h**) groups were well-tolerated. Electrophilic functional groups, such as ester (**3f**), carbonate (**3j**, **3p**), cyano (**3k**), nitro (**3l**), which would be problematic with classical Weinreb amides, gave the desired ketone products in high yields. Furthermore, heterocyclic amides, including thiophene (**3i**), pyrazine (**3q**) and pyridine (**3r**) readily undergo coupling. Of note, the latter example (**3r**) represents a direct activation of vitamin B3 (nicotinamide), while 4-hydroxybenzamide (**3j**) is a common amide pharmaceutical intermediate, demonstrating potential pharmaceutical applications (*vide infra*). Notably, in all cases, the meta-substituted product was formed with exquisite selectivity, which is in sharp contrast to the traditional acylation with arenes giving ortho products.

The scope of the arene was also extensively studied (Scheme 2). Pleasingly, we found that this C–H/N–C(O) acylation is compatible with a broad range of 1,3-disubstitued arenes giving the cross-coupling products in good to excellent yields. Acylation of challenging electron-deficient organoboranes substituted with ester groups (**3u**, **3x**, **3y**) is well-tolerated. Pivalates (**3v**), alkyl groups (**3w**), ethers (**3z**, **3aa**), ketones (**3ab**), heterocycles (**3ac**, **3ad**), amides (**3af**), amines (**3ag**) and fluorinated arenes (**3ah**, **3ai**) afford the desired ketone products in high yields, in all cases featuring exclusive arylation regioselectivity. The divergent chemoselectivity for the activated amide is noteworthy (**3af**). Notably, this method could be employed for the direct derivatization of esters of natural products and pharmaceuticals with complex architecture as illustrated by the esters of fructose (**3aj**), menthol (**3ak**), *trans*-androsterone (**3al**), cholesterol (**3am**) as well as adapalene (**3an**), and febuxostat (**3ao**).

The applicability to various amides was explored (Figure S1). This C–H/N–C(O) activation works with N-acylglutarimides (**1w**), N-acyl amides (**1x**), N-Ts-sulfonamides (**1y**) and N-Boc-carbamates (**1z**), which expands the scope of amide component to N-cyclic and N-acyclic amides.[6–9]

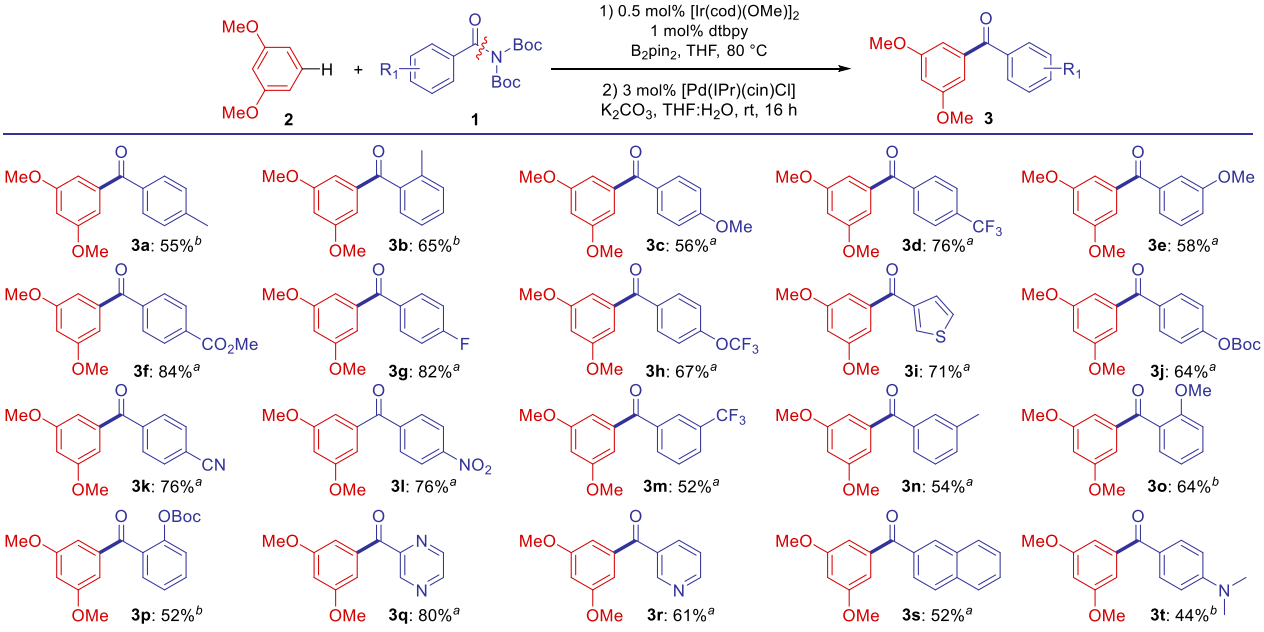
Encouraged by the success of C–H/N–C(O) acylative coupling, we considered the possibility of developing divergent aryl coupling by triple C–H/N–C(O)/C–C bond activation (Scheme 3). For this type of cross-coupling, critical is the control of the rate of boronic acid release to match with decarbonylation of the acyl-metal.[13] Although initial results gave no or little conversion to the biaryl product, we discovered that the use of $MeB(OH)_2$ additive facilitates the organoboronate release under these conditions,[16a] leading to the efficient coupling (Table S2).

We examined the generality of the C–H/N–C(O)/C–C biaryl coupling (Scheme 3). This method is compatible with diverse substituents on both reaction components, including esters (**4a**, **4d**, **4e**, **4g**), heterocycles (**4b**), electronically-deactivated substrates (**4c**), halides (**4f**), tosylates (**4h**), ketones (**4j**), and sterically-hindered substrates (**4m**), delivering the biaryl products in good to high yields. Notably, this method delivers functional handles for further derivatization, including electrophilic groups.

Most crucially, the synthetic potential of this biaryl C–H/N–C(O)/C–C coupling was demonstrated in the rapid late-stage modification of esters of natural products, such as, menthol (**4q**), fructose (**4r**), and *trans*-androsterone (**4s**), thus underscoring the synthetic potential of this activation platform.

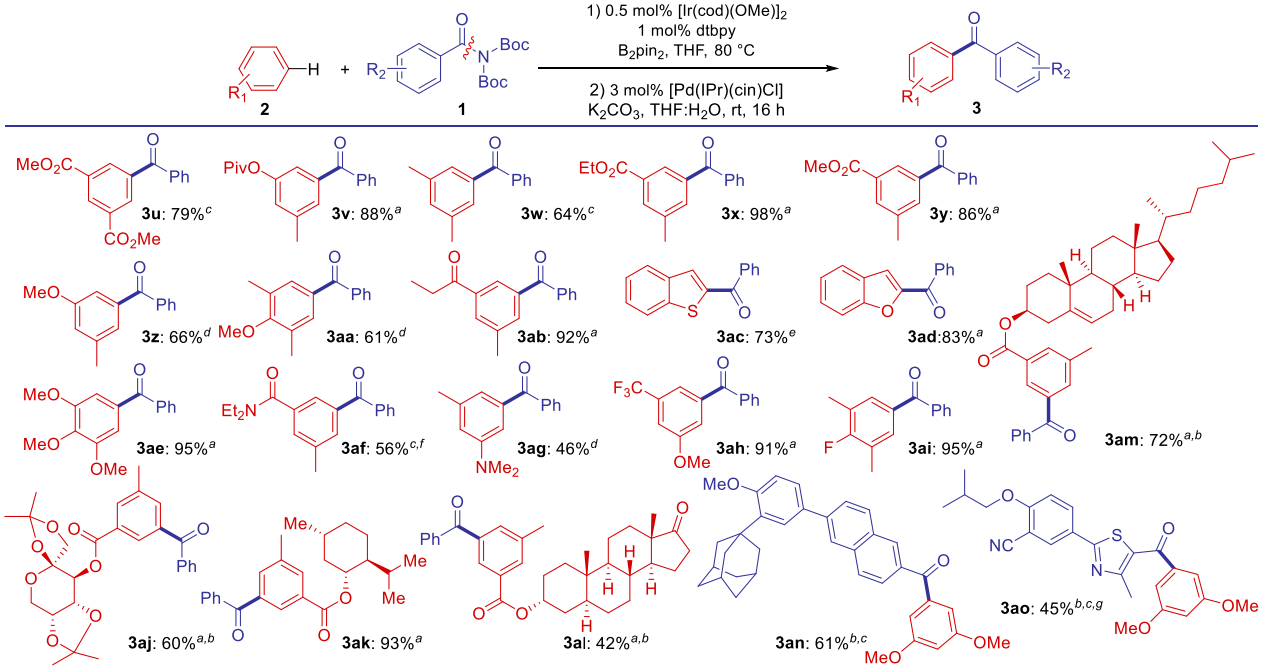
An assessment of various amides in the biaryl coupling was performed (Figure S2, Supporting Information). Pleasingly, N-cyclic (**1w**) as well as N-acyclic amides, such as N-acyl (**1x**), N-Ts-sulfonamide (**1y**) and N-Ms-sulfonamide (**1ak**) can be utilized in this coupling protocol to deliver biaryls from arenes and amides in good yields.

Scheme 1. Acylation of arylboronate esters with amides by sequential C–H/N–C(O) activation: amide scope[a]



[a]Conditions: **2** (2.0 equiv), B_2pin_2 (0.75 equiv), $[Ir(cod)(OMe)]_2$ (0.5 mol%), dtbpy (1 mol%), THF, 80 °C, 24 h, **1** (1.0 equiv), [Pd(IPr)(cin)Cl] (3 mol%), K_2CO_3 (3.0 equiv), THF:H_2O = 9:1 (0.20 M), 23 °C, 16 h. [b]Cs_2CO_3 (3.0 equiv), 60 °C.

Scheme 2. Acylation of arylboronate esters with amides by sequential C–H/N–C(O) activation: arene scope[a]

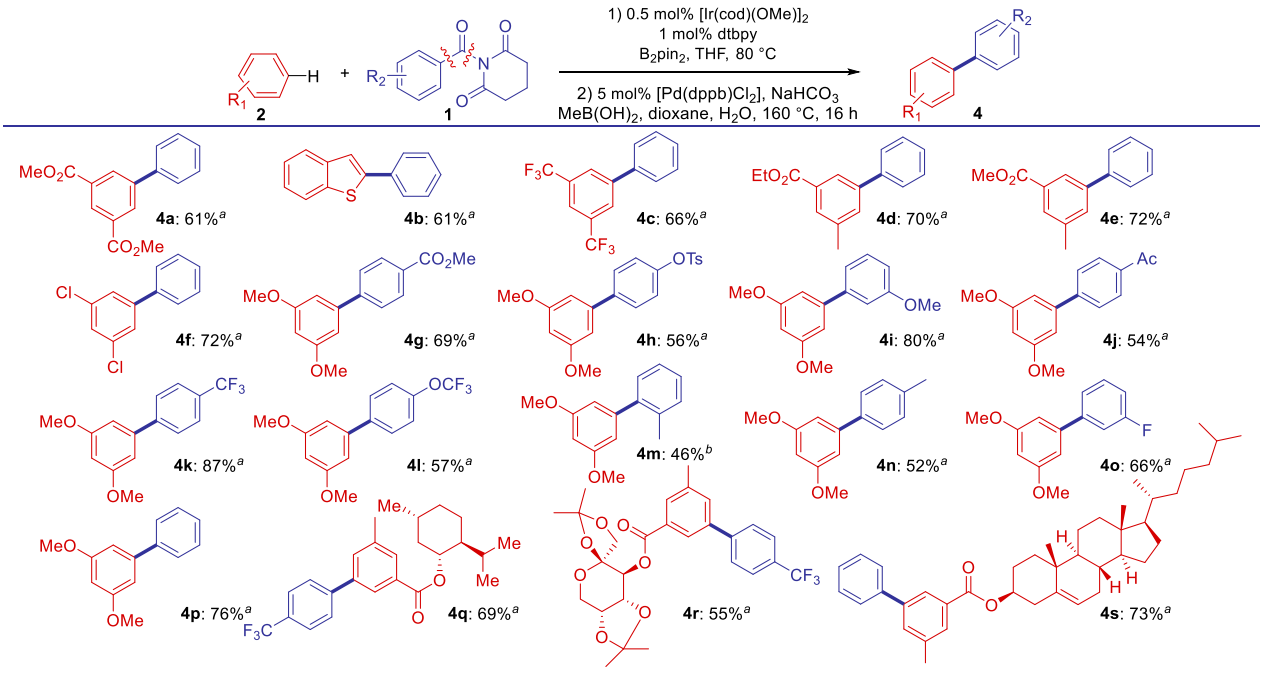


[a]Conditions: see Scheme 1. [b][Pd(IPr)(cin)Cl] (5 mol%). [c]Cs_2CO_3, 60 °C. [d]KOH, 60 °C. [e]Cs_2CO_3, THF, 80 °C. [f]Step 1: hexane. [g]N-Ms-N-phenylbenzamide.

Finally, we applied our C–H/N–C(O) activation technology to conjugative coupling of bioactive molecules (Scheme 4). Thus, the direct derivatization of complex arenes and amides is readily accomplished to deliver conjugates between complex bioactive molecules and amides under standard conditions (**3aq-3ar**).[1b]

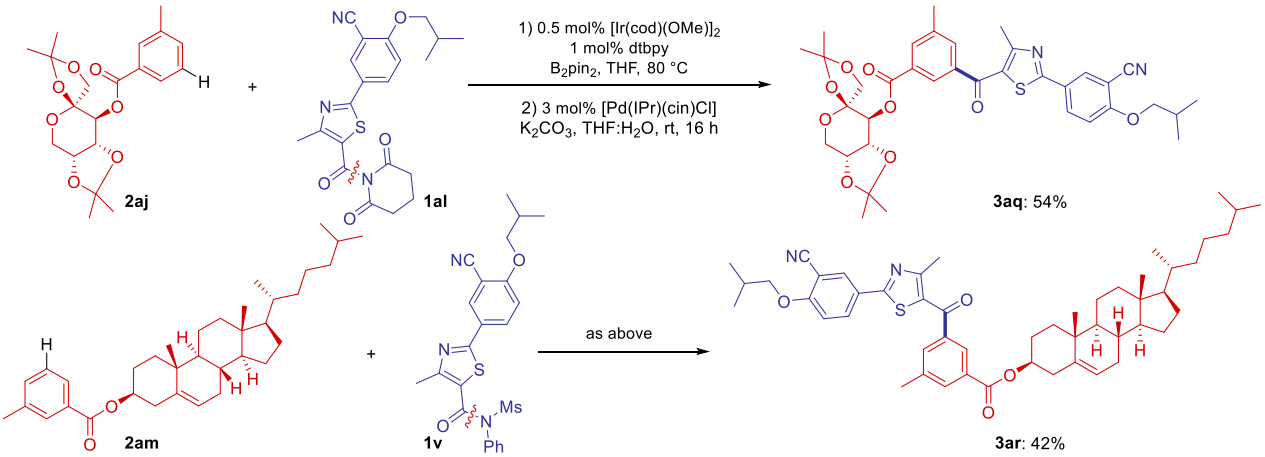
In conclusion, an expedient method for the cross-coupling of non-activated arenes with amides via sequential Ir-catalyzed C–H borylation/N–C(O) activation has been developed. This reaction provides facile access to biaryl ketones and biaryls by exploiting regioselective C–H activation with the divergent reactivity of the amide bond by acyl and decarbonylative pathways. This methodology tolerates a wide variety of functional groups, including various amides and direct derivatization of natural products and pharmaceuticals with intricate architectures. Based on this methodology, we demonstrated conjugative coupling between complex biomolecules. This study opens the door for arene-amide coupling in a wide variety of chemical processes.

Scheme 3. Arylation of arylboronate esters with amides by sequential C–H/N–C(O)/C–C activation: scope[a]



[a]Conditions: **2** (2.0 equiv), B_2pin_2 (0.6 equiv), $[Ir(cod)(OMe)]_2$ (0.5 mol%), dtbpy (1 mol%), THF, 80 °C, 24 h, **1** (1.0 equiv), $[Pd(dppb)Cl_2]$ (5 mol%), $NaHCO_3$ (4 equiv), $MeB(OH)_2$ (1.5 equiv), dioxane (0.125 M), H_2O, 160 °C, 16 h. [b]2-Methyl-N-Ms-N-phenylbenzamide. See SI for details.

Scheme 4. Coupling of arenes with amides by C–H/N–C(O) activation: complex arenes and amides[a]



[a]Conditions: **2** (2.0 equiv), B_2pin_2 (0.75 equiv), $[Ir(cod)(OMe)]_2$ (0.5 mol%), dtbpy (1 mol%), THF, 80 °C, 24 h, **1** (1.0 equiv), [Pd(IPr)(cin)Cl] (3 mol%), K_2CO_3 (3.0 equiv), THF:H_2O = 9:1 (0.20 M), 23 °C, 16 h.

ASSOCIATED CONTENT

Supporting Information

Procedures and analytical data. This material is available free of charge via the Internet at http://pubs.acs.org.

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