

Ligand-Accelerated *ortho*-C–H Alkylation of Arylcarboxylic Acids using Alkyl Boron Reagents

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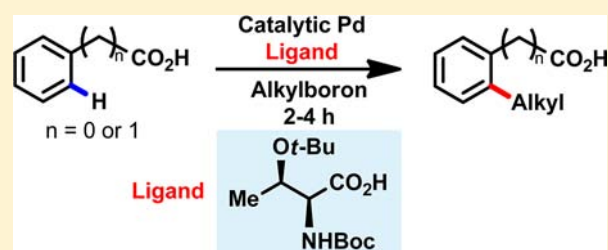
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Supporting Information

ABSTRACT: A protocol for the Pd(II)-catalyzed *ortho*-C–H alkylation of phenylacetic and benzoic acids using alkylboron reagents is disclosed. Monoprotected amino acid ligands (MPAA) were found to significantly promote reactivity. Both potassium alkyltrifluoroborates and alkylboronic acids were compatible coupling partners. The possibility of a radical alkyl transfer to Pd(II) was also investigated.

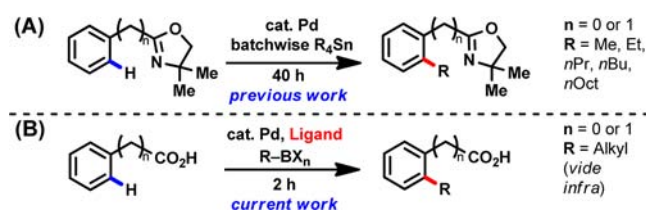


1. INTRODUCTION

The importance of the aryl–alkyl motif is exemplified by its abundance in natural products¹ and pharmaceuticals,² and many methods for its construction have been described.^{3,4} A complementary approach that is rapidly gaining traction utilizes C–H bonds as coupling partners.^{5,6} Notable progress has been made on this front despite the propensity for intermediate metal–alkyl fragments to undergo undesired β -hydride elimination and homocoupling side reactions. Our early efforts focused on the development of C(sp²)–H alkylation reactions using model substrates containing strongly coordinating pyridine and oxazoline⁵ directing groups (Scheme 1A) with

acids to similar ends.⁸ Herein, we report the ligand-accelerated C(sp²)–H alkylation of phenylacetic and benzoic acids using Pd(II) as a catalyst (Scheme 1B). This protocol provides a one-step route to *ortho*-alkylated benzoic⁹ and phenylacetic acids, which are useful building blocks for the preparation of medicinally relevant compounds. Furthermore, we demonstrate the utility of this protocol by using it to install a “magic methyl”¹⁰ group onto a biaryl scaffold generating lead compound BMS-98947–055–01.

Scheme 1. Development of C(sp²)–H Alkylation



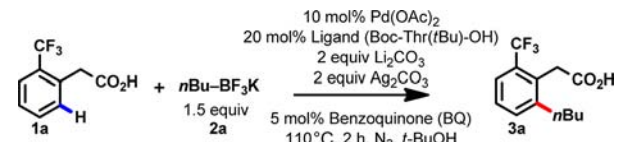
the long-term goal of imparting reactivity on more synthetically useful substrates.⁶ Thus far, we have achieved C–H alkylation using removable amide^{6h} and *O*-methylhydroxamic acid⁷ directing groups which are capable of outcompeting unproductive side reactions. We have also reported a single example of electron-rich benzoic acid C(sp²)–H methylation;^{6a} however, the *ortho*-alkylation of arylcarboxylic acids using other alkylboron reagents is, in general, hampered by the β -hydride elimination pathway. Inspired by Fu’s successful development of tailored ligands for alkyl–alkyl cross-coupling,^{4a–d} we sought to utilize the accelerated C–H cleavage reactivity imparted by mono-*N*-protected amino

2. RESULTS AND DISCUSSION

2.1. Initial Discovery and Optimizations. Initial studies were guided by conditions optimized from our previous C–H arylation work using aryltrifluoroborates as coupling partners.^{8d} For alkyltrifluoroborate coupling, three key modifications were essential for providing alkylated **3a** in good yields: (1) Exchanging KHCO₃ for Li₂CO₃ (Table 1, entry 14), (2) conducting reactions under an O₂ free atmosphere (entries 4, 5), and (3) employing an optimized ligand (Boc-Thr(*t*Bu)–OH). Examination of various inorganic salts indicated that both Li⁺ and CO₃^{2–} are beneficial for this reaction. In addition to promoting C–H insertion,^{6a} salt additives were previously shown to impact the transmetalation step (entries 13–18).¹¹ Alkylated **3a** was observed with or without Ag₂CO₃ but the inclusion of Ag₂CO₃ increased yields significantly. O₂ was found to decrease yields (entries 4,5). An optimized ligand, Boc-Thr(*t*Bu)–OH, was identified from an extensive screen of commercially available mono-*N*-protected amino acids (see Supporting Information S6–S7). Although sterically demanding ligands can discourage β -hydride elimination in alkylation reactions,⁴ substrate–ligand matching may also be important for

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Table 1. Standard Conditions and Deviations^a


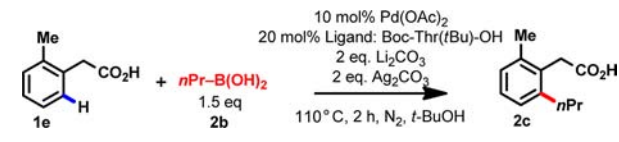
entry	deviation	conv. (%) ^b	isolated yield (%)	material balance (%) ^c
1	no deviation	84	69	83
2	1 h	70	64	91
3	4 h	82	72	87
4	1 atm air	50	41	84
5	1 atm O ₂	13	13	88
6	no Pd(OAc) ₂	0	0	94
7	no Ag ₂ CO ₃	3	3	94
8	no ligand	13	13	85
9	no BQ	88	79	89
10	20 mol % BQ	27	25	91
11	no BQ, 1 equiv DMF (dimethylformamide)	82	73	89
12	no Li ₂ CO ₃	0	0	91
13	Li carboxylate, no Li ₂ CO ₃	0	0	91
14	2 equiv KHCQ ₃ instead of Li ₂ CQ ₃	7	6	93
15	Li carboxylate, 2 equiv KHCO ₃ instead of Li ₂ CO ₃	58	52	82
16	K carboxylate, 2 equiv Li ₂ CO ₃	60	45	79
17	2 equiv LiCl instead of Li ₂ CO ₃	52	47	93
18	4 equiv LiCl instead of Li ₂ CO ₃	9	8	92

^aReaction conditions: carboxylic acid substrate (0.5 mmol), alkyl trifluoroborate (0.75 mmol), Li₂CO₃ (1.0 mmol), Ag₂CO₃ (1.0 mmol), BQ (0.025 mmol), ligand (0.1 mmol), Pd(OAc)₂ (0.05 mmol), *t*-BuOH (2.5 mL). ^bDetermined by ¹H NMR. ^cMaterial balance determined based on isolated 3a and recovered starting material (1a).

promoting C–H activation. During the ligand screen using model substrates 1a and 1e, non-*N*-protected amino acids and amino acids with strongly coordinating side chains such as methionine, histidine, or tryptophan were found to generally inhibit this reaction (see Supporting Information, SI: S6–S7 for ligand screen).

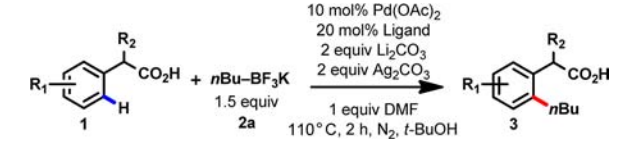
Further optimization studies based upon these three modifications yielded two sets of standard conditions: one utilizing catalytic benzoquinone (Std-BQ, Table 1, entry 1) and the other utilizing dimethylformamide (Std-DMF, Table 1, entry 11). Differences in conversion were observed depending on the additive employed, but in general, these additives increased the reproducibility of reaction outcomes; the effects of these additives were also studied in detail (see Supporting Information S22–S24) and the observations were consistent with many previously reported cross-coupling reactions.^{12–14} Importantly, with a simple inorganic base modification, alkyl boronic acids were found to be compatible coupling partners under the reported protocol (Table 2, also see Supporting Information S10–S11).

2.2. Substrate Scope. Substrate scope was investigated using the Std-DMF conditions. Electron-poor (Table 3, 3a–d) and electron-rich (Table 3, 3e–l) phenylacetic acids were generally well tolerated. Ligand enhancement effects were consistently pronounced for electron-poor arenes (3a–d). With respect to electron-rich arenes, yields varied depending on ring-substitution: 3i (72%), 3j (13%), and 3k (70%), and

Table 2. Alkylboronic Acid Compatibility^a


entry	deviation	% conv (% yield)
1	no deviation	6% (6%)
2	K ₂ CO ₃ instead of Li ₂ CO ₃	95% (68%)
3	K ₂ CO ₃ instead of Li ₂ CO ₃ and 1 atm O ₂	32%

^aReaction Conditions: carboxylic acid substrate (0.5 mmol), *n*Pr–B(OH)₂ (0.75 mmol), Li₂CO₃ (1.0 mmol), Ag₂CO₃ (1.0 mmol), ligand (0.1 mmol), Pd(OAc)₂ (0.05 mmol), *t*-BuOH (2.5 mL).

Table 3. Phenylacetic Acid Substrate Scope^a


3a, 73% ^b 15% ^c	3b, 86% ^b 15% ^c	3c, 60% ^b 8% ^c	3d, 66% ^b 5% ^c
3e, 80% ^b 31% ^c	3f-mono/3f'-di 67% 3f, 6% 3f' ^b 61% 3f' ^c	3g, 64% ^d 15% ^c	3h, 70% ^b 32% ^c
3i, 72% ^b 25% ^c	3j, 13% ^b 15% ^c	3k, 70% ^b 46% ^c	3l, 52%, >98% ^{eee} 32%, >98% ^{eee} 44%, >98% ^{eee}
racemic - 3m, 13% ^b 9% ^c	3n-mono/3n'-di 39% 3n, 22% 3n' ^b 4% 3n, 68% 3n' ^{b, f}	racemic - 3o, 54% ^b 21% ^c	

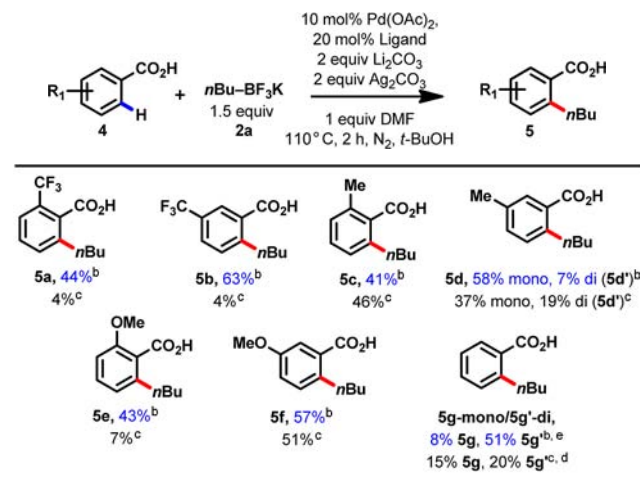
^aReaction conditions (Std-DMF): carboxylic acid substrate (0.5 mmol), alkyl trifluoroborate (0.75 mmol), Li₂CO₃ (1.0 mmol), Ag₂CO₃ (1.0 mmol), DMF (0.5 mmol), ligand (0.1 mmol), Pd(OAc)₂ (0.05 mmol), *t*-BuOH (2.5 mL). Quantification: isolated yields. ^bLigand = Boc-(L)-Thr(*t*Bu)-OH. ^cNo ligand. ^dLigand = Boc-Leu-OH. ^eLigand = Boc-(D)-Thr(*t*Bu)-OH. ^f2 equiv *n*Bu–BF₃K, 3 equiv Ag₂CO₃.

importantly, *ortho*-substituents appear to have a positive effect. We also note that ligand optimization may still be necessary for particular substrates. For example, when Boc-Leu-OH was applied in place of Boc-Thr(*t*Bu)-OH for the coupling of 1g, the yield nearly tripled from 22 to 64% (3g). Notably, over-the-counter NSAID drugs naproxen (11) and ketoprofen (1o) were compatible substrates and the alkylation of enantiopure 11 proceeded without erosion of stereochemistry at the adjacent acidic α -carbon. The presence of large α -substituents hampered this reaction (3m). In general, mono:di selectivities of phenyl acetic acids were poor in the absence of *ortho*- or *meta*-substitution (3n-mono:3n'-di 1:0.6). However, the use of

excess alkyltrifluoroborate and Ag_2CO_3 led to the predominant formation of di product (3n -mono: $3\text{n}'$ -di 1:17).

With respect to benzoic acids, we rescreened ligands and found Ac-Val-OH to be most effective. It is also interesting to note that electron-poor substrates (Table 4, 5a and 5b)

Table 4. Benzoic Acid Substrate Scope^a

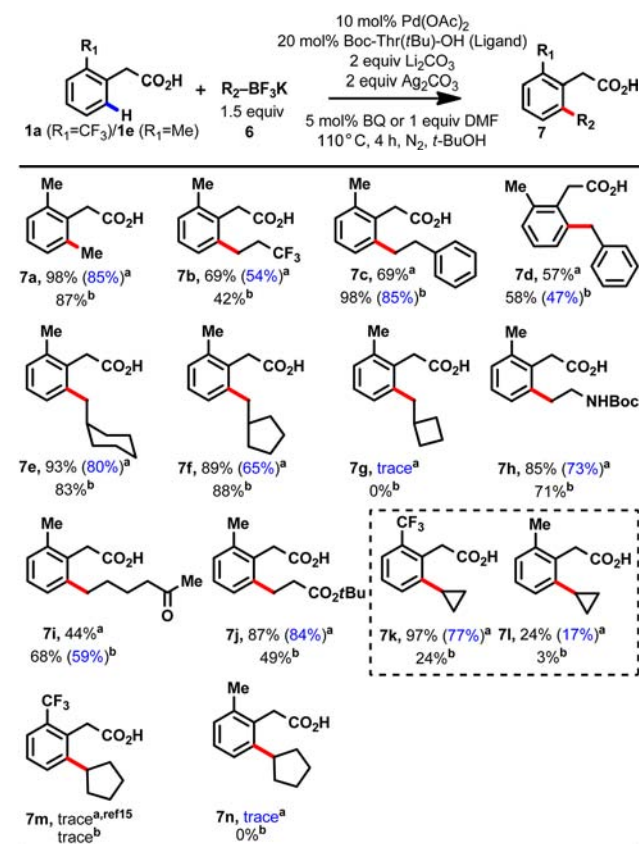


^aReaction conditions (Std-DMF): carboxylic acid substrate (0.5 mmol), alkyl trifluoroborate (0.75 mmol), Li_2CO_3 (1.0 mmol), Ag_2CO_3 (1.0 mmol), DMF (0.5 mmol), ligand (0.1 mmol), Pd(OAc)_2 (0.05 mmol), *t*-BuOH (2.5 mL); Quantification: ^bLigand = Ac-Val-OH, isolated yield. ^cNo ligand, ¹H NMR conversion. ^d5 mol % BQ, no DMF. ^e3 equiv *n*Bu-BF₃K, 3 equiv Ag_2CO_3 .

benefited most from the application of ligands where alkylation of electron-rich substrates varied depending on arene substitution pattern (5c–f). Notably, monoselectivity increased for 5d with the application of a ligand (mono:di from 1.9:1 to 7.7:1). For unsubstituted benzoic acid, the di product (5g') was formed as the major product in the presence of ligands. Efforts to suppress the di alkylation of benzoic acid to selectively form mono alkylated product were unsuccessful (see Supporting Information S25–S26).

An exploration of potassium alkyltrifluoroborate scope was undertaken using both Std-DMF and Std-BQ conditions (Table 5). Noncoordinating primary alkyltrifluoroborates (methyl, trifluoropropyl, phenethyl) were compatible coupling partners (7a–c) along with benzyl (7d), methylcyclohexyl (7e), and methylcyclopentyl (7f). However, the coupling of 1e with methylcyclobutyl boron gave only trace amounts of desired product (7g) and methylcyclopropyl did not couple at all. There is a possibility that the alkyl intermediates underwent β -carbon scission instead of reductive elimination. Alkyltrifluoroborates containing functional handles (protected amine, ketone, ester) were also compatible coupling partners (7h–j). Unfortunately, alkyltrifluoroborates containing α -heteroatoms, olefins, or alkynes did not yield desired coupled products. It was also found that with the exception of cyclopropyltrifluoroborate (7k and 7l) and cyclopentyltrifluoroborate (7m¹⁵ and 7n), reactions with secondary alkylborons were problematic.¹⁶ We anticipate that extensive ligand development could provide a solution to this problem in the future. A GC/MS sampling of organic phase extracted from reactions using cyclohexyltrifluoroborate yielded cyclohexene and bicyclohexyl suggesting that β -hydride elimination¹⁷ and homocoupling could be competing pathways.

Table 5. Potassium Alkyltrifluoroborate Scope^a

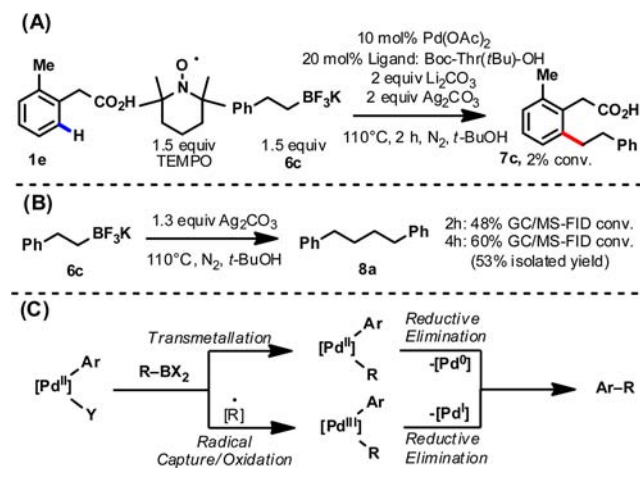


^aReaction conditions. Std-BQ: carboxylic acid substrate (0.5 mmol), alkyl trifluoroborate (0.75 mmol), Li_2CO_3 (1.0 mmol), Ag_2CO_3 (1.0 mmol), BQ (0.025 mmol), Ligand (0.1 mmol), Pd(OAc)_2 (0.05 mmol), *t*-BuOH (2.5 mL), 4 h reaction time. ^bReaction conditions. Std-DMF: carboxylic acid substrate (0.5 mmol), alkyl trifluoroborate (0.75 mmol), Li_2CO_3 (1.0 mmol), Ag_2CO_3 (1.0 mmol), DMF (0.5 mmol), Ligand (0.1 mmol), Pd(OAc)_2 (0.05 mmol), *t*-BuOH (2.5 mL), 4 h reaction time. Quantification: Conv. determined by ¹H NMR, isolated yields in parentheses.

2.3. Mechanistic Considerations. The ineffective coupling of methylcyclobutyl and methylcyclopropyl borons, and the need for an O_2 free atmosphere prompted us to investigate the possibility of alkyl radical formation.¹⁸ First, nearly complete inhibition of this reaction by TEMPO was observed (Scheme 2A) and without substrate 1e, phenethylTEMPO adduct was obtained in 67% GC yield (see Supporting Information S12–S14). A control experiment revealed that only Ag_2CO_3 was necessary to generate alkyl radicals as evidenced by the formation of phenethylTEMPO adduct (see Supporting Information S12–S14).¹⁹ Second, homocoupling product (6c) was formed by treating phenethyltrifluoroborate (6c) with Ag_2CO_3 in the absence of TEMPO (Scheme 2B). The incompatibility of methylcyclopropyl boron could stem from a radical ring-opening/isomerization to the terminal radical olefin species which could then unproductively polymerize.

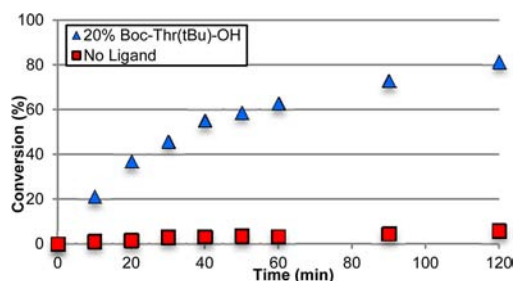
Radical alkyl intermediacy poses an interesting mechanistic dilemma.^{6n,20} Following C–H cleavage, a transmetalation event could occur to give R–Pd(II)–Ar species. Alternatively, alkyl radical capture by Ar–Pd(II)–Y (where Y may be any anionic species present in solution such as OAc^- or OtBu^-) may provide intermediate R–Pd(III)–Ar which could then

Scheme 2. (A) Reaction Inhibition by TEMPO, (B) Alkyltrifluoroborate Homocoupling, and (C) Putative Reaction Pathways



reductively eliminate to give the alkylated products (Scheme 2, C). While evidence for the latter sequence is scarce, the possibility cannot be ruled out at this time. The coupling of α -stereogenic alkyl borons could provide more definitive evidence.^{18,21,22} Unfortunately, they are incompatible under the reported conditions (see Supporting Information).

With the application of amino acid ligands, significant acceleration effects were observed in contrast to reactions where ligands were not applied (Figure 1). Additives BQ and

Figure 1. Ligand effect: rate profile for conversion of **1a** to **3a**.

DMF were not used in order to isolate the effects of the amino acid ligands on this C–H alkylation reaction. Reactivity was probed using a set of electronically diverse substrates (Table 6). A ligand loading survey revealed unusual trends where for electron-poor substrates (**1a**, **1b**), a Ligand: Pd ratio of 0.5:1 was as effective as a ratio of 2:1. In contrast, for electron-rich substrates (**1e** and **1f**), conversion correlatively increased with increased ligand loading. To understand the origin of the substrate-dependent ligand effects, we attempted to identify the rate-determining steps for the *n*butylation of **1a** and **1e**. KIE (kinetic isotope effect) values for the *n*butylation of electron-poor **1a** were found to be 1.5 and 3.4 when 20 mol % and 2.5 mol % ligand were used, respectively. These results suggest that for electron-poor **1a**, C–H cleavage is slow (relative to other elementary steps) at low ligand loading, and with sufficient amounts of ligand, C–H cleavage is significantly accelerated to the extent that C–H cleavage is no longer rate-limiting. In contrast, KIE values of electron-rich **1e** were small under both conditions (20 mol % ligand: 1.4; 2.5 mol % ligand: 0.9) suggesting that C–H cleavage may not be involved in rate

Table 6. Effects of Ligand Loading^a

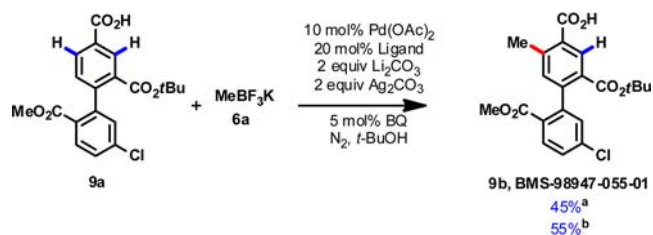
Reaction scheme: **1** + **2a** (1.5 equiv) $\xrightarrow[110^\circ\text{C}, 2\text{ h, N}_2, \text{t-BuOH}]{10\text{ mol}\% \text{ Pd(OAc)}_2, 20\text{ mol}\% \text{ Ligand: Boc-Thr(tBu)-OH}, 2\text{ equiv Li}_2\text{CO}_3, 2\text{ equiv Ag}_2\text{CO}_3}$ **3**

ligand loading	¹ H NMR Conversion (%)			
	<i>ortho</i> -CF ₃ 1a	<i>ortho</i> -Me 1e	<i>meta</i> -CF ₃ 1b	<i>meta</i> -Me 1f
20 mol %	83%	86%	>99%	87%
5 mol %	85%	48%	>99%	68%
0 mol %	13%	27%	12%	33%

^aReaction conditions: carboxylic acid substrate (0.5 mmol), alkyl trifluoroborate (0.75 mmol), Li₂CO₃ (1.0 mmol), Ag₂CO₃ (1.0 mmol), ligand (0.1 mmol), Pd(OAc)₂ (0.05 mmol), *t*-BuOH (2.5 mL). ^bDetermined by ¹H NMR. ^cMaterial balance determined based on isolated **3a** and recovered starting material (**1a**).

limiting step in either case with this substrate. However, the alkylation of electron-rich **1e** and **1f** are enhanced by the application of ligand thus suggesting that ligands may play an additional role in catalysis beyond accelerating the C–H cleavage step. For a more extensive treatment, see Supporting Information S15–S24.

2.4. Application in Medicinal Chemistry. Finally, with practicality in mind, we sought to apply this protocol in a medicinal chemistry setting. From the perspective of small molecule therapeutics, the installation of methyl groups has long been recognized as a method for significantly attenuating the biological activity of a molecule while minimally perturbing its sterics and electronics. For example, the addition of a single methyl group to the piperidine ring of Merck's orexin-1/2 (OX₁R/OX₂R) antagonist was found to increase potency by >480 fold.²³ In this case, methylation was thought to induce a critical conformational change in the antagonist, but in general, this may not be true as the origin of these effects require case-by-case examination. Colloquially, these beneficial methyl additions have been termed “magic methyl” effects and to fully understand their origins, a diverse and robust repertoire of methylation methods is required.¹⁰ Here we apply this alkylation protocol to rapidly and selectively *ortho*-methylate a biaryl carboxylic acid generating a medically relevant compound **BMS-98947-055-01** (**9b**) in 45% yield (Scheme 3). The use of Boc-Phe-OH as a ligand, lower temperature (90 °C), and an extended reaction time (12 h) improved yield (55%) over our standard condition (STD-BQ) for this particular substrate.

Scheme 3. Selective C–H Methylation of Biaryl **9a** Generates **9b**, BMS-98947-055-01^{a,b}

^aReaction Conditions. Std-BQ: 1.5 equiv MeBF₃K, Ligand = Boc-Thr(*t*Bu)-OH, 110 °C, 2 h. ^bThree equiv MeBF₃K, Ligand = Boc-Phe-OH, 90 °C, 12 h.

3. CONCLUSION

In summary, a ligand-accelerated C–H alkylation of phenylacetic and benzoic acids is disclosed. Both electron-rich and electron-poor substrates are reactive. Alkyl trifluoroborates and alkyl boronic acids are compatible coupling partners. A variety of primary alkyl boron coupling partners are compatible, including fragments possessing trifluoromethyl, phenyl, Boc-amine, ester, or ketone functional groups. Unusual ligand acceleration effects were noted. Despite these advances, coupling with α -secondary or α -tertiary alkylborons remains a challenge, and achievement of this goal will enable a more conclusive investigation of alkyl radical intermediacy within the context of this C–H functionalization manifold.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and analytical data for all new compounds. 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 interest.

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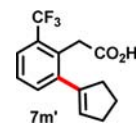
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