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

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ABSTRACT: A protocol for the Pd(II)-catalyzed *ortho*-C–H alkylation of phenylacetic and benzoic acids using alkylboron reagents is disclosed. Mono-protected 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 products[1] 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(sp^2)–H alkylation reactions using model substrates containing strongly coordinating pyridine and oxazoline[5] directing groups (Scheme 1, A) with 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 acid[7] directing groups which are capable of outcompeting unproductive side reactions. We have also reported a single example of electron-rich benzoic acid C(sp^2)–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 acids to similar ends.[8] Herein, we report the ligand-accelerated C(sp^2)–H alkylation of phenylacetic and benzoic acids using Pd(II) as a catalyst (Scheme 1, B). This protocol provides a one-step route to *ortho*-alkylated benzoic[9] 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(sp^2)–H Alkylation

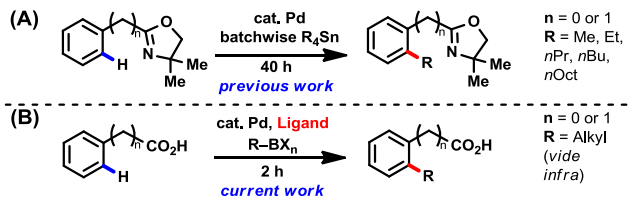
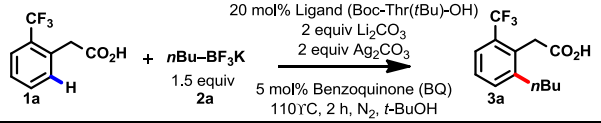


Table 1. Standard Conditions and Deviations



Entry	Deviation	Conv. (%)[a]	Isolated Yield (%)	Material Balance (%)[b]
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_2CO_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_2CO_3	0	0	91
13	Li Carboxylate, no Li_2CO_3	0	0	91
14	2 equiv $KHCO_3$ instead of Li_2CO_3	7	6	93
15	Li Carboxylate, 2 equiv $KHCO_3$ instead of Li_2CO_3	58	52	82
16	K Carboxylate, 2 equiv Li_2CO_3	60	45	79
17	2 equiv LiCl instead of Li_2CO_3	52	47	93
18	4 equiv LiCl instead of Li_2CO_3	9	8	92

Reaction Conditions: 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). [a]determined by ^{1}H-NMR. [b]material balance determined based on isolated **3a** and recovered starting material (**1a**).

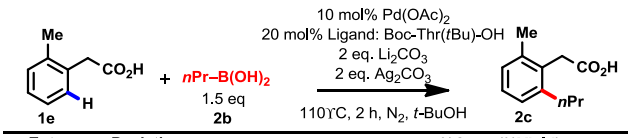
2.Results and Discussion

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 $KHCO_3$ for Li_2CO_3 (Table 1, entry 14), (2) conducting reactions under an O_2 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 CO_3^{2-} are beneficial for this reaction. In addition to promoting C–H insertion,[6a] salt additives were previously shown to impact the transmetallation step (entries 13-18).[11] Alkylated **3a** was observed with or without Ag_2CO_3 but the inclusion of Ag_2CO_3 in-

creased yields significantly. O_2 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, SI: S6-S7). Although sterically demanding ligands can discourage β-hydride elimination in alkylation reactions,[4] substrate-ligand matching may also be important for 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).

Table 2. Alkylboronic Acid Compatibility



Entry	Deviation	%Conv (%Yield)
1	No Deviation	6% (6%)
2	K_2CO_3 instead of Li_2CO_3	95% (68%)
3	K_2CO_3 instead of Li_2CO_3 and 1 atm O_2	32%

Reaction Conditions: carboxylic acid substrate (0.5 mmol), *n*Pr–B $(OH)_2$ (0.75 mmol), Li_2CO_3 (1.0 mmol), Ag_2CO_3 (1.0 mmol), Ligand (0.1 mmol), $Pd(OAc)_2$ (0.05 mmol), *t*-BuOH (2.5 mL).

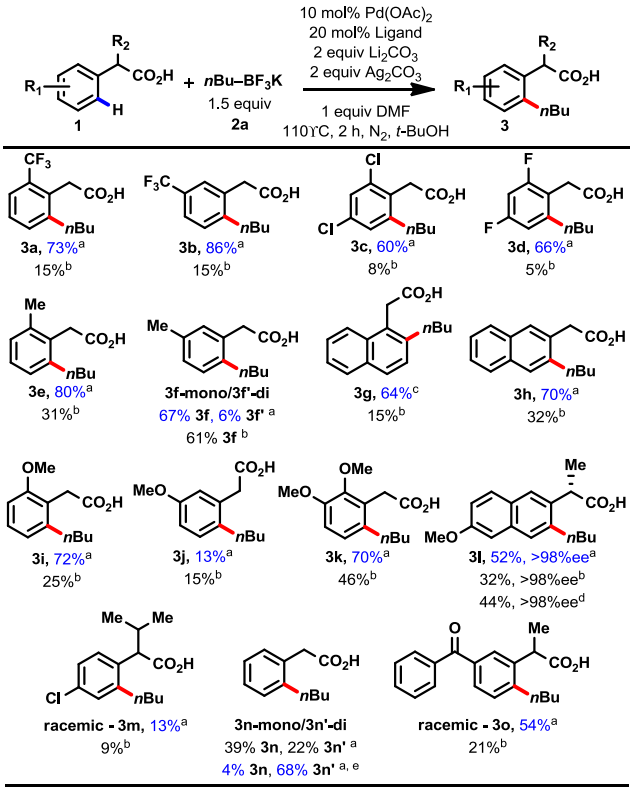
Further optimization studies based upon these three modifications yielded two sets of standard conditions: one utilizing catalytic benzoquinone (Std-BQ, Table 1, entry 1) and the other utilizing dimethylformamide (Std-DMF, Table 1, entry 11). Differences in conversion were observed depending on the additive employed, but in general, these additives increased the reproducibility of reaction outcomes; the effects of these additives were also studied in detail (see SI: 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 SI: 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 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 (**1l**) and ketoprofen (**1o**) were compatible substrates and the alkylation of enantiopure **1l** 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:**3n'**-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**) 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 SI: S25-S26).

Table 3. Phenylacetic Acid Substrate Scope



Reaction 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: Isolated yields; [a]: Ligand = Boc-(L)-Thr(*t*Bu)-OH; [b]: No Ligand; [c]: Ligand = Boc-Leu-OH; [d]: Ligand = Boc-(D)-Thr(*t*Bu)-OH; [e]: 2 equiv *n*Bu–BF_3K, 3 equiv Ag_2CO_3.

Table 4. Benzoic Acid Substrate Scope

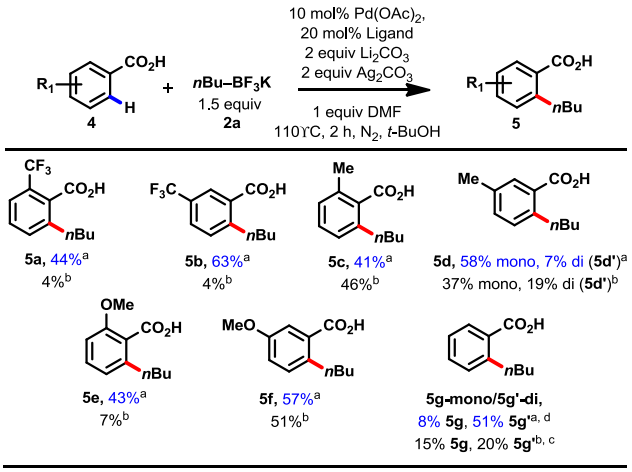
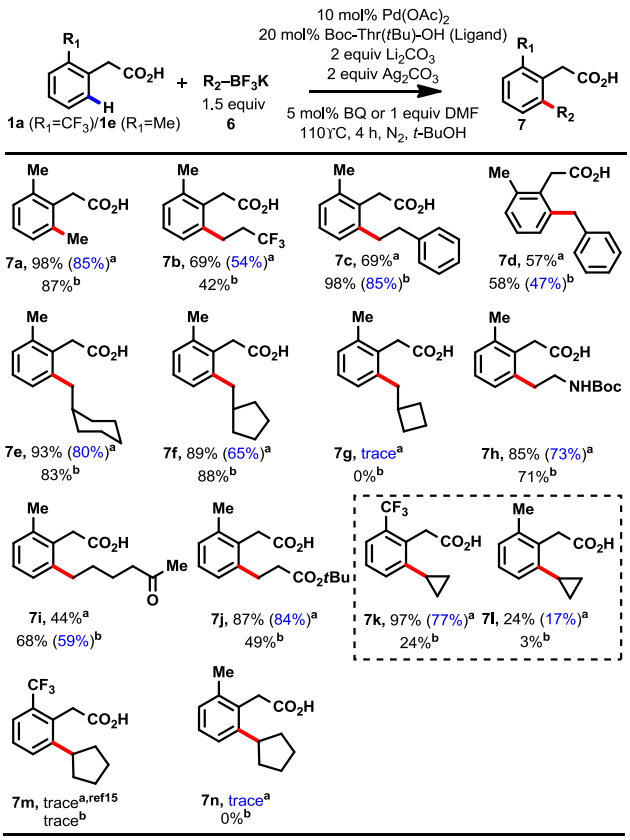


Table 5. Potassium Alkyltrifluoroborate Scope



Reaction 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: [a]: Ligand = Ac-Val-OH, Isolated yield; [b]:No Ligand, ^{1}H-NMR conversion; [c]: 5 mol% BQ, no DMF; [d]: 3 equiv *n*Bu–BF_3K, 3 equiv Ag_2CO_3.

An exploration of potassium alkyltrifluoroborate scope was undertaken using both Std-DMF and Std-BQ conditions (Table 5). Non-coordinating 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. Alkyltrifluoborates 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 (**7m'**[15] 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 elimination[17] and homocoupling could be competing pathways.

Reaction Conditions: [a]**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 or [b]**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 ^{1}H-NMR, isolated yields in parenthesis.

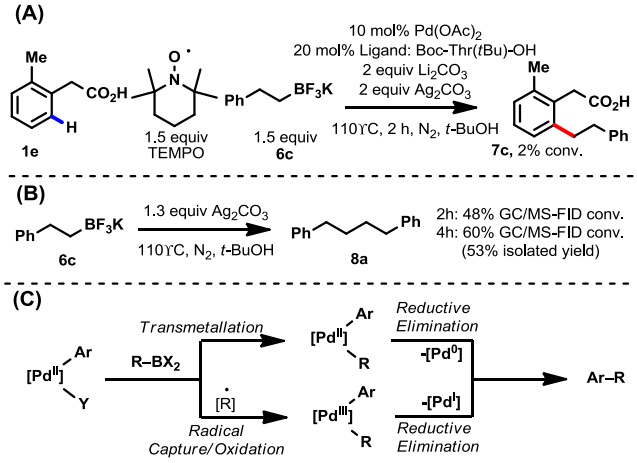
2.3 Mechanistic Considerations

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 2, A) and without substrate **1e**, phenethylTEMPO adduct was obtained in 67% GC yield (see SI: 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 SI: S12-S14).[19] Second, homocoupling product **8a** was formed by treating phenethyltrifluoroborate (**6c**) with Ag_2CO_3 in the absence of TEMPO (Scheme 2, B). 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 transmetallation 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 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 SI).

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



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 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 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 SI S15-S24.

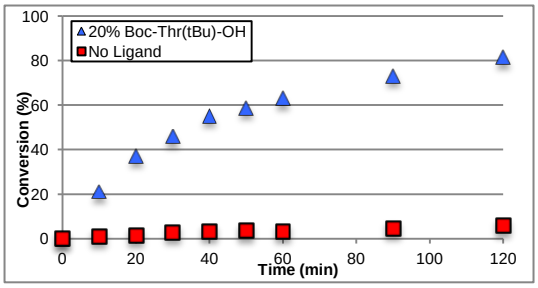
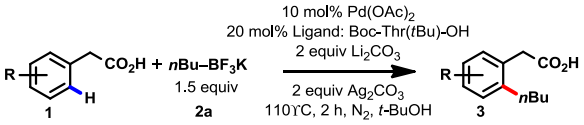


Figure 1. Ligand Effect: Rate Profile for Conversion of **1a** to **3a.**

Table 6. Effects of Ligand Loading



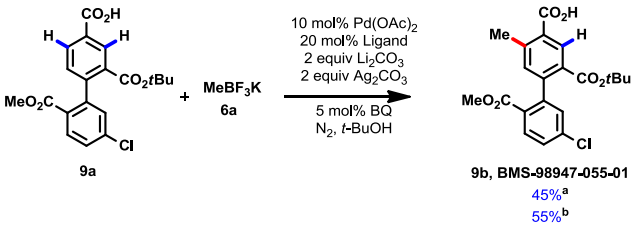
Ligand Loading	*ortho*-CF_3 1a	*ortho*-Me 1e	*meta*-CF_3 1b	*meta*-Me 1f
	^{1}H-NMR Conversion (%)			
20 mol%	83%	86%	>99%	87%
5 mol%	85%	48%	>99%	68%
0 mol%	13%	27%	12%	33%

Reaction Conditions: carboxylic acid substrate (0.5 mmol), alkyl trifluoroborate (0.75 mmol), Li_2CO_3 (1.0 mmol), Ag_2CO_3 (1.0 mmol), Ligand (0.1 mmol), $Pd(OAc)_2$ (0.05 mmol), *t*-BuOH (2.5 mL). [a]determined by ^{1}H-NMR. [b]material balance determined based on isolated 3a and recovered starting material (1a).

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 (OX_1R/OX_2R) 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 medicinally 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.



Reaction Conditions: [a]**Std-BQ:** 1.5 equiv $MeBF_3K$, Ligand = Boc-Thr(*t*Bu)-OH, 110 °C, 2 h; [b]3 equiv $MeBF_3K$, 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 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 interests.

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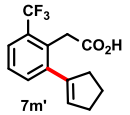
(13) Excess BQ reduced conversion (Table 1, entry 10) presumably through coordinative saturation of Pd and due to an undesired side reaction. A GC/MS analysis of crude reaction mixtures revealed masses correlating to variably alkylated benzoquinones.

(14) Crude **3h** reaction mixtures separated by preparative TLC revealed α-acetoxylated **1h** and the butylesters of **1h** and **3h**.

(15) From table 5: **7m'** was likely the β-hydride elimination product of a second C–H activation event centered on the newly installed benzylic methine carbon of **7m**.



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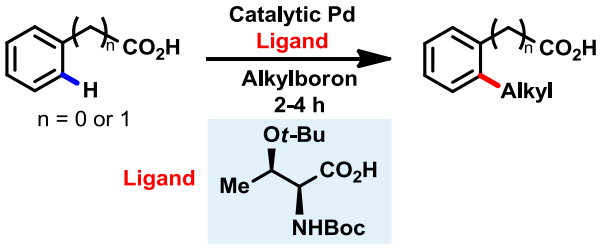
Catalytic Pd
Ligand
Alkylboron
2-4 h
CO2H
H
n = 0 or 1
Alkyl
Ligand
Ot-Bu
Me
CO2H
NHBoc