Communication

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Iron-Catalyzed *ortho* C–H Methylation of Aromatics Bearing a Simple Carbonyl Group with Methylaluminum and Tridentate Phosphine Ligand

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Supporting Information Placeholder

ABSTRACT: Iron-catalyzed C–H functionalization of aromatics has attracted widespread attention from chemists in recent years, while the requirement of an elaborate directing group on the substrate has so far hampered the use of simple aromatic carbonyl compounds such as benzoic acid and ketones, much reducing its synthetic utility. We describe here a combination of a mildly reactive methylaluminum reagent and a new tridentate phosphine ligand for metal catalysis, 4-(bis(2-(diphenylphosphanyl)phenyl)phosphanyl)-*N*,*N*-dimethylaniline (Me_2N-TP), that allows us to convert an *ortho* C–H bond to a C–CH_3 bond in aromatics and heteroaromatics bearing simple carbonyl groups under mild oxidative conditions. The reaction is powerful enough to methylate all four *ortho* C–H bonds in benzophenone. The reaction tolerates a variety of functional groups, such as boronic ester, halide, sulfide, heterocycles and enolizable ketones.

Two decades ago Murai demonstrated the feasibility of C–C bond formation via catalytic C–H activation of aryl ketones as reaction substrates.[1] However, the focus of subsequent studies has diverged from simple carbonyl groups to strongly coordinating nitrogen directing groups,[2,3,4] such as an amide of 8-aminoquinoline (8Q, Figure 1a).[3a-d,3h,4b-d] The popularity of such directing groups has originated partly from the difficulty of direct functionalization of free carboxylic acids,[2b] and partly from an assumption that strong metal coordination to the substrate increases the efficacy of the catalytic reaction, although this idea has frequently been challenged.[5] In the iron catalysis using an 8Q amide substrate,[4b-d,6] the substrate acts as a tridentate ligand while the remaining three coordination sites are occupied by a bidentate ligand (e.g., dppen) and an incoming organic group (INT-A, Figure 1a). We therefore conjectured that a strongly binding tridentate phosphine[7] may eliminate the need for the use of the 8Q ligand, allowing us to utilize simple aromatic carbonyl compounds (INT-B, Figure 1b). We report here an iron-catalyzed *ortho* C–H methylation of a wide variety of aromatics and heteroaromatics bearing a simple carbonyl group—a transformation found to be useful for probing the profound methyl effects in pharmacology[8] through late-stage synthetic elaboration. This transformation was enabled by a new tridentate phosphine ligand for metal catalysis, 4-(bis(2-(diphenylphosphanyl)phenyl)phosphanyl)-*N*,*N*-dimethylaniline (Me_2N-TP), combined with a mildly reactive and readily available $AlMe_3$ as the methyl donor and 2,3-dichlorobutane (2,3-DCB) as the oxidant.

Figure 1b illustrates a gram-scale mono-*ortho*-methylation of 2-naphthoic acid without affecting the boronate moiety. Of the two equivalents of $AlMe_3$ used, one equivalent was consumed for acid deprotonation. Ketones also serve as good substrates, as illustrated in Figure 1c for a gram-scale exclusive 5-methylation of 7,8-benzoflavone—a potent aromatase inhibitor.[9]

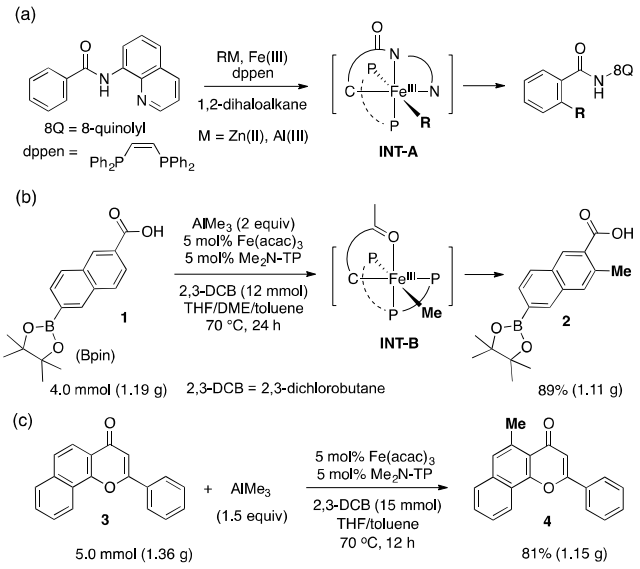
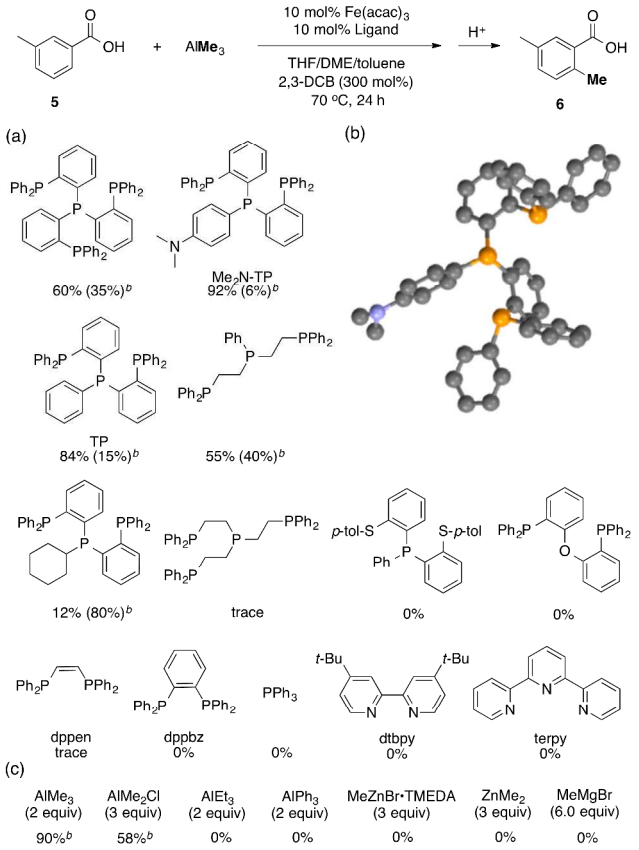


Figure 1. Iron-catalyzed C–H functionalization: the contrast between an 8Q directing group vs. simple carbonyl groups. (a) Previous work: C–H activation of an 8Q amide via INT-A. (b) This work: gram-scale C–H methylation of a boron-substituted 2-naphthoic acid 1. (c) This work: gram-scale C–H methylation of 7,8-benzoflavone 3.

This catalytic system does not need any extraneous directing group that has often impaired the simplicity of the C–H functionalization strategy and limited the applicability. The reaction conditions are mildly oxidative and Lewis acidic, and the reaction tolerates functional groups sensitive to base and reductant, such as boronic ester (Figure 1b), halide, sulfide, heterocycles and enolizable ketones, enabling late-stage structural modification of molecules of biological and materials interest by the use of a nontoxic metal.[10] Inexpensive $AlMe_3$ is the methyl group source of choice, while the easy-to-handle bis-(trimethylaluminum)-1,4-diazabicyclo[2.2.2]octane adduct (DABAL-Me_3; Table 1, **11**) can be used at the expense of lower reactivity.



[a]The reaction was performed on a 0.2 mmol scale. Recovery of the starting material is shown in parentheses. [b]The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

Figure 2. Effects of ligands and organometallic reagents on methylation of *m*-toluic acid. (a) Ligand effects on yield. (b) X-ray structure of **NMe$_2$-TP**. Thermal ellipsoids correspond to 30% probability. Hydrogen atoms are omitted for clarity. (c) Organometallic reagent effects on yield.

We describe the reaction conditions for the methylation of 6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-naphthoic acid (**1**), illustrating retention of the boronate moiety—a commonly used donor of aromatic groups under palladium-catalyzed C–H functionalization.[11] A toluene solution of $AlMe_3$ (2.0 equiv) was added dropwise to a mixture of **1** (1.19 g, 4.0 mmol), $Fe(acac)_3$ (5.0 mol %) and Me_2N-TP (5.0 mol %) in 10:1 anhydrous THF/1,2-dimethoxyethane (DME) under nitrogen at room temperature. After methane formation subsided, 2,3-DCB (3.0 equiv) was added and the mixture was stirred at 70 °C for 24 h to achieve full conversion of **1** without any by-products detected by ^{1}H NMR. Aqueous acid workup afforded **1** in 89% isolated yield after recrystallization. DME is beneficial for solubilization of aluminum carboxylate intermediates. Catalyst loading can be reduced to 3 mol% at the expense of reaction rate. 2,3-DCB is the reagent of choice for its efficacy and low cost.

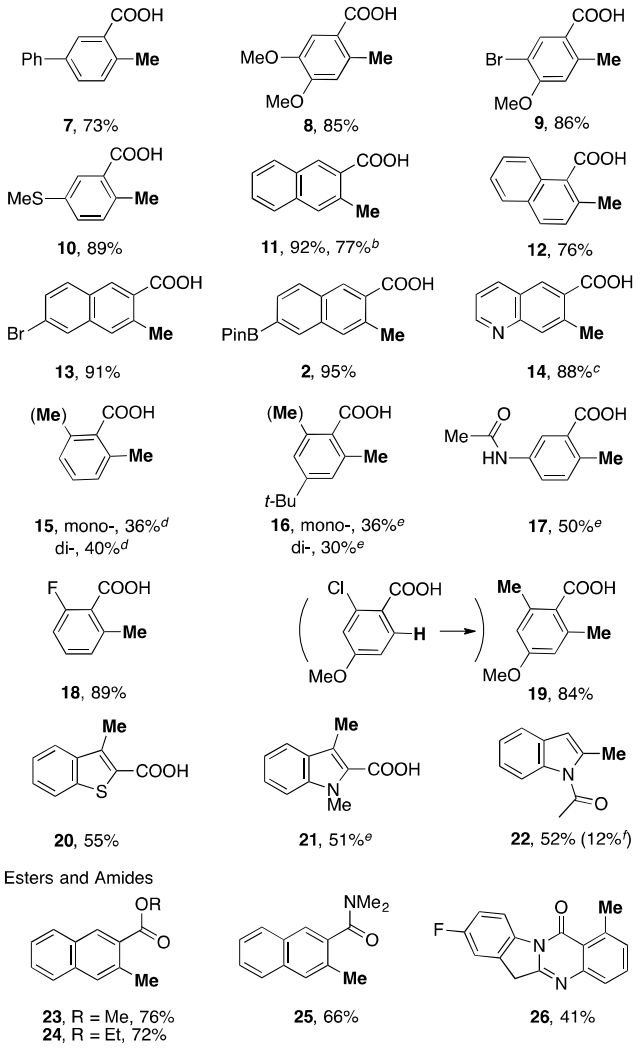
We found a marked correlation between the ligand structure and the reaction outcome, as summarized in Figure 2a: effective ligands need at least three phosphine groups, among which the central one bears a phenyl group. Of these, Me_2N-TP was found to be the best. The beneficial effect of the Me_2N- group here (cf. TP) was also found in an iron-catalyzed C–H activation reported by us previously.[4b,12] As seen in a crystal structure of Me_2N-TP (Figure 2b) and of a recently reported Fe(II)/TP complex,[7] the three phosphine groups are so oriented as to be suitable for tridentate coordination. Interestingly, the reaction with Me_2N-TP was modestly or poorly effective for 8Q amide derivatives, suggesting that the ligand and the directing group compete for the coordination sites on the metal center (see supplementary information (SI)). Bipyridine ligands that are effective in some iron catalysis were ineffective (bottom row of Figure 2a).[13]

The reaction is also highly sensitive to the organometallic sources of the methyl group (Figure 2c). Trimethylaluminum was the most effective among all of the reagents examined, while dimethylaluminum chloride is modestly reactive. Triethyl- and triphenylaluminum produced no desired product. Organozinc and -magnesium reagents failed entirely, although they serve as good donors for substrates bearing a strongly coordinating directing group.[4d,6b] We ascribe the unique efficacy of the methyl aluminum reagent to its weak reducing ability and facile transmetallation to iron, undisturbed by β-H elimination that readily proceeds for higher alkyl groups (Figure 1d).

We illustrate the synthetic utility of the new catalytic system for *ortho*-functionalization of aromatic and heteroaromatic carboxylic acids and derivatives in Table 1. The reaction produced only the desired methylated products, and the recovery of the starting material accounted largely for the rest of the material. Being sensitive to steric hindrance, *ortho*-methylation of *meta*-substituted benzoic acids and 2-naphthoic acids occurred only on the less hindered site in high yield (**7**–**11**). The reaction of **11** with DABAL-Me_3[14] (1 equiv) afforded the desired methylation product in 77% yield. However, without steric hindrance, a second *ortho*-methylation quickly followed the first methylation to give a dimethylation product (**15**, **16**). Even when a less than stoichiometric amount of $AlMe_3$ was used, the reaction still afforded a mixture of mono- and dimethylated products with recovery of the starting acid, suggesting therefore that a methyl-group-bearing catalytic intermediate stays on the monomethylated molecule and undergoes the second methylation before it migrates to another molecule.[5c] The secondary 4-acetamide group on a benzoic acid (**17**) did not activate the nearby C–H bond, and the reaction proceeded selectively at the C–H nearby the carboxylate group. The tertiary acetamide moiety in *N*-acetylindole promoted methylation of the nearby C_2–H bond (**22**).

Table 1. Methylation of Aromatic Carboxylic Acids, Esters and Amides[a]

Carboxylic Acids



Esters and Amides

[a]The methyl groups in bold indicate those introduced by the reaction. The reaction was performed on a 0.8 mmol scale using $Fe(acac)_3$/NMe_2-TP (5–10 mol%) and $AlMe_3$ (200 mol%) following the procedure described in the text for a gram-scale experiment. Yields of isolated products are shown. See the SI for details. [b]DABAL-Me_3 was used as the methyl source. [c]Isolated as methyl ester by treatment with $SOCl_2$/Et_3N/MeOH. [d]^1H NMR yield using 1,1,2,2-tetrachloroethane as an internal standard. [e]Isolated as the methyl ester by treating with $TMSCH_2N_2$/Et_2O/MeOH. [f]Yield of 2-methyl indole.

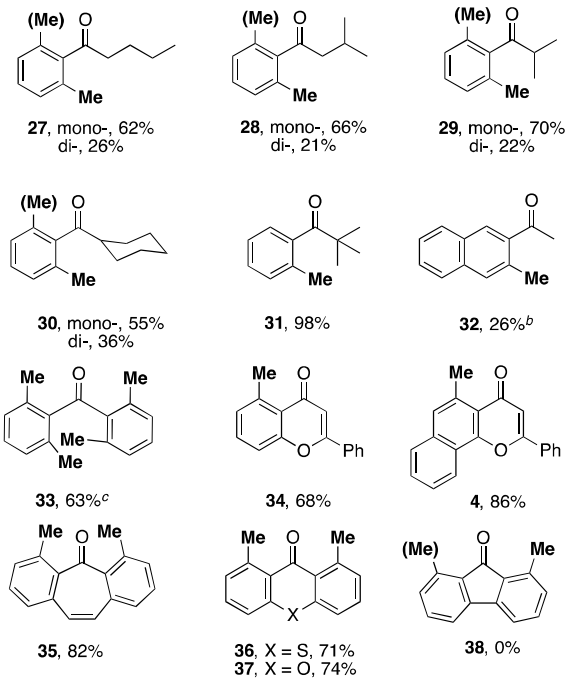
Functional group tolerance is noteworthy, as already pointed out in Figure 1b (boronate group). The sulfide group (**10**) as well as a remote bromide (**9**, **13**) and *ortho*-fluoride (**18**) are tolerated, while *ortho*-chloride was substituted by a methyl group (**19**). Heterocycles in **14**, **20**, **21** and an indoleamine 2,3-dioxygenase-1 inhibitor[15] **26** as well as sulfide in **10** did not disturb the catalytic cycle, showing that our iron catalytic system is resistant to the heterocycle- and sulfur-poisoning effects.[16] Ester and amide groups also act as good directing groups (**23**, **24** and **25**).

Alkyl aryl ketones are very good substrates (**27**–**30**, Table 2 top two rows; full conversions of reactants were observed in most of the cases), and underwent *ortho*-methylation without any carbonyl addition side reaction (except for a methyl ketone, **32**). Exclusive monomethylation of *tert*-butyl phenyl ketone (**31**) suggests that steric interaction between the *tert*-butyl and the newly introduced *ortho*-methyl groups hinders the necessary rotation of the carbonyl group and prevents the second C–H activation. We did not detect any C(sp^3)–H methylation on the *tert*-butyl group. A KIE experiment for parallel reactions using this substrate gave a k_H/k_D value of 1.23, suggesting that either the C–H cleavage step occurs via a transition state of low symmetry, or that it is not directly involved in the turnover-limiting step. A sterically unencumbered methyl ketone gave **32** in low yield because of a carbonyl addition side reaction to give the corresponding alcohol.

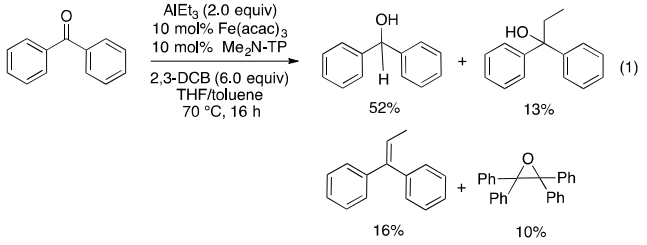
Benzophenone, where four *ortho* C–H bonds are available, underwent remarkably smooth tetramethylation in 63% yield (**33**). A contrasting result shown in eq. 1 for $AlEt_3$ is remarkable—occurrence of carbonyl reduction, addition and dimerization products suggestive of the concurrent occurrence of catalytic cycles including reduced iron species and a ketyl radical, when the desired C–H activation is a slow reaction.

Flavone (**34**) and α-naphthoflavone (**4**) underwent exclusive methylation at the 5-position, which was confirmed by the single-crystal structure (see SI). Xanthone and thioxanthone afforded dimethylated products **36** and **37** exclusively, and so did dibenzosuberenone (**35**). On the other hand, fluorenone (**38**) gave none of the desired methylation product, probably because the large bond angle of CH–C–CO prevented the formation of a ferracycle intermediate (cf. the small atomic radius of iron).[4b] The reactions of the diaryl ketones **33**, **35–38** underwent full conversion of the starting material, but were accompanied by dimerization products (cf. eq. 1).

Table 2. Methylation of Aryl Ketones[a]



[a]The methyl groups in bold indicate those introduced by the reaction. The reaction was performed on a 0.8 mmol scale using $Fe(acac)_3$/NMe_2-TP (5 mol%) and $AlMe_3$ (150 mol%) following the procedure described in the text for a gram-scale experiment. Yields of isolated products are shown. See the SI for details. [b]$Fe(acac)_3$/NMe_2-TP (10 mol%) and $AlMe_3$ (110 mol%) were used. [c]$Fe(acac)_3$/NMe_2-TP (10 mol%), $AlMe_3$ (300 mol%) and 2,3-DCB (600 mol%) were used.



In summary, a new tridentate phosphine ligand, **NMe_2-TP**, was found to be very effective for iron-catalyzed C–H methylation of simple aromatic carbonyl compounds without recourse to additional directing groups, which enhances the utility of the C–H activation synthetic strategy. Wide substrate generality, functional group tolerance and resistance to catalytic poisons are additional attractive features of the new catalytic system, together with the economical and environmental merits of iron catalysis.[10] Although an iron(II) complex of **TP** was recently reported in the literature,[7] tridentate phosphines such as **TP** and **NMe_2-TP** have not, to our knowledge, been utilized for metal catalysis, and we expect that their potential in catalysis is worthy of careful investigations in the future.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and physical properties of the compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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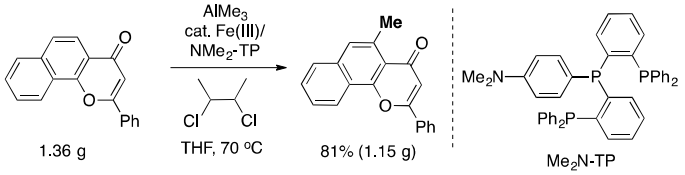
AlMe3
cat. Fe(III)/
NMe2-TP
Cl
Cl
THF, 70 °C
Me
O
O
Ph
1.36 g
81% (1.15 g)
Me2N
P
PPh2
Ph2P
Me2N-TP