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Iron-Catalyzed Directed C(sp^2)–H and C(sp^3)–H Functionalization with Trimethylaluminum

Rui Shang, Laurean Ilies,* and Eiichi Nakamura*

Department of Chemistry, School of Science, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-0033, Japan

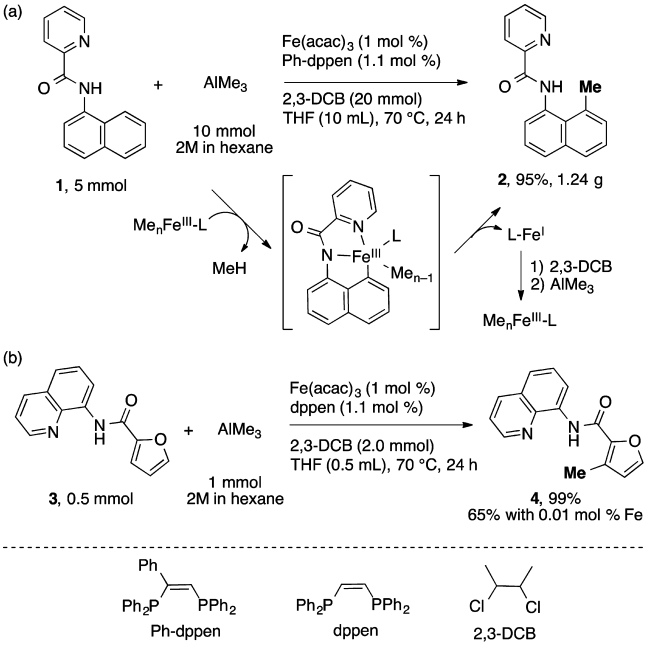
Supporting Information

ABSTRACT: Conversion of a C(sp^2)–H or C(sp^3)–H bond to the corresponding C–Me bond can be achieved by using $AlMe_3$ or its air-stable diamine complex in the presence of catalytic amounts of an inorganic iron(III) salt and a diphosphine along with 2,3-dichlorobutane as a stoichiometric oxidant. The reaction is applicable to a variety of amide substrates bearing a picolinoyl or 8-aminoquinolyl directing group, enabling methylation of a variety of (hetero)aryl, alkenyl, and alkyl amides. The use of the mild aluminum reagent prevents undesired reduction of iron and allows the reaction to proceed with catalyst turnover numbers as high as 6500.

While methyl groups on arenes and olefins play significant roles in the regulation of protein–ligand binding and drug design,[1] the synthetic repertoire for direct methylation of a C–H bond has found a limited number of literature examples, which involve the use of methyl organometallics (magnesium,[2] tin,[3] boron,[4] zinc reagents[5]) and electrophiles.[6] At this juncture, we focused on organoaluminum reagents, which to date have been neglected in C–H activation chemistry, and we report here that readily available $AlMe_3$ and its air-stable derivative, the bis(trimethylaluminum)·1,4-diazabicyclo-[2.2.2]octane adduct (DABCO·2$AlMe_3$),[7] act as an effective methyl donor in iron-catalyzed activation of C(sp^2)–H and C(sp^3)–H bonds (cf. Scheme 1). (*Z*)-1,2-Bis(diphenylphosphino)ethene (dppen) and (*Z*)-1-phenyl-1,2-bis(diphenylphosphino)ethene (Ph-dppen)[8] were the ligands of choice, and 2,3-dichlorobutane (2,3-DCB) was used as mild oxidant to regenerate the reactive iron species.[9] The catalytic system showed catalyst turnover numbers (TONs) as high as 6500, a value rarely achieved in C–H functionalization.[10] The reaction is effective for the methylation of an aromatic C(sp^2)–H bond in naphthylamine- and benzylamine-type compounds activated by a picolinoylamide (PA) group[11] (Scheme 1a) as well as in benzamide- and pivalamide-type compounds bearing an 8-aminoquinoline (NH-Q) group[12] (Scheme 1b). The reaction bears mechanistic similarity to our previously reported C–H activation reaction with a borate reagent.[13]

We recently reported[13] that an organoborate anion is capable of C–H bond cleavage and subsequent C–R bond formation via an R–Fe(III) intermediate that participates in the reaction without significant interference of homocoupling reactions.[14] This led us to consider that a mildly reactive organoaluminum reagent may also act as a selective alkyl donor to Fe(III).[15] To this end, we first examined a C–H methylation reaction with

Scheme 1. Iron(III)-Catalyzed Methylation of (a) *N*-(Naphthalen-1-yl)picolinamide and (b) *N*-(Quinolin-8-yl)furan-2-carboxamide and a Mechanistic Hypothesis



$AlMe_3$ using a stoichiometric amount of $Fe(acac)_3$. Mixing $Fe(acac)_3$, a diphosphine ligand, *N*-(naphthalen-1-yl)-picolinamide (**1**), and $AlMe_3$ at 70 °C in a molar ratio of 1:1:2 resulted in the formation of the desired methylation product **2** in 85% yield (Table 1, entry 1). The high-yield conversion of this stoichiometric reaction suggests that a methyliron reactive intermediate stabilized by the bidentate directing group and the diphosphine ligand was generated and underwent C–H cleavage[16] and C–Me bond formation to generate an iron(I) species as an end product, as has also been shown for the borate reaction.[13] The use of 6.0 equiv of MeMgBr instead of 2.0 equiv of $AlMe_3$ as the methyl source in the stoichiometric experiment in entry 1 gave the desired methylation product in less than 10% yield, likely because of premature reduction of the reactive iron species by the highly reductive MeMgBr.[14] The reaction intrinsically requires 3 equiv of the methyl nucleophile for removal of H atoms from the amide and arene and for C–Me bond formation (see the next

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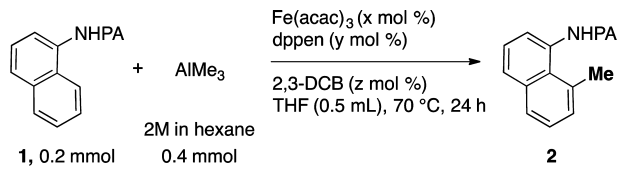
Table 1. Directed C−H Methylation with Stoichiometric and Catalytic Amounts of Iron[a]



1, 0.2 mmol 0.4 mmol 2

entry	$Fe(acac)_3$ (x mol %)	dppen (y mol %)	2,3-DCB (z mol %)	yield of **2** (%)
1	100	100	0	85[b]
2	10	11	400	99[b]
3	1	1.1	400	91[c]
4	0.1	0.11	400	44[c]
5	0	5.5	400	0[c]
6	5	0	400	24[c]

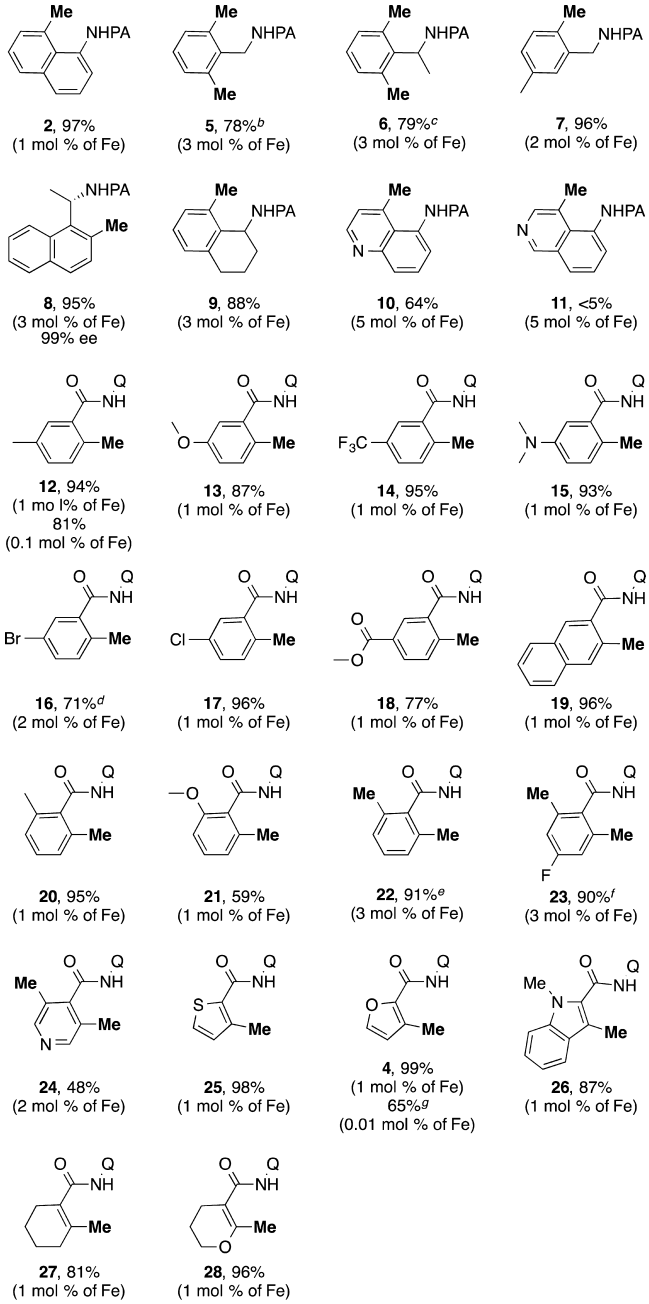
[a]The reaction was performed on a 0.2 mmol scale following the procedure described in the text. PA = picolinoyl. [b]The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. [c]The yield was estimated by GC using tridecane as an internal standard.

paragraph for discussion). As shown in Scheme 1a, the putative Fe(I) end product can be reoxidized to Fe(III) with 2,3-DCB,[9] allowing catalytic activation of the C−H bond. As shown in entries 2 and 3, the catalytic cycle operates in excellent yield with 1−10% catalyst loading. The iron catalyst (entry 5) and the ligand (entry 6) are mandatory for the reaction (for an investigation of ligands, see the Supporting Information (SI)). As we previously suggested,[13] the dppen or Ph-dppen ligands may stabilize the intrinsically unstable Fe(I) catalytic end product by metal-to-ligand charge transfer (MLCT).[17]

A typical synthetic procedure is described for the catalytic reaction in Scheme 1a. A solution of $Fe(acac)_3$ (1.0 mol %) and Ph-dppen (1.1 mol %) in THF was added to an anhydrous THF solution of **1** (1.24 g, 5 mmol), which was followed by slow injection of a commercially available solution of $AlMe_3$ in hexane (2.0 equiv) at room temperature. The reaction mixture changed from light orange to dark green after addition of the $AlMe_3$ solution. After gas evolution (methane) ceased in 10 min, 2,3-DCB (4.0 equiv) was added, and the mixture was stirred at 70 °C for 24 h. Aqueous workup followed by column chromatography gave the desired product **2** in 95% yield (1.24 g). The methylation took place exclusively at the 8-position of the naphthyl ring. The use of 1 equiv of $AlMe_3$ resulted in a 34% yield. The use of the related diphosphine ligand dppen instead of Ph-dppen gave a slightly lower yield (91%). The same conditions can also be applied to methylation of furancarboxamide **4** with high TON (Scheme 1b).

The scope of the methylation reaction is illustrated in Table 2. In addition to **1**, *N*-benzylpicolinamide also took part in the reaction in good yield but gave ortho-dimethylated product **5** as the major product. A meta substituent on the phenyl ring (cf. **7**) suppresses the methylation at the neighboring ortho position and gives exclusive monomethylation at the less congested ortho position. An α-substituent at the benzyl position is tolerated, as shown for **6** and **8**. The enantiopurity of the chiral center at the benzylic position can be retained in >99% ee (**8**). 1,2,3,4-Tetrahydronaphthalen-1-amine-derived amide can also be methylated in high yield (**9**). 5-Quinolylamide underwent methylation at the 4-position in 64% yield (**10**), while 5-isoquinolylamide did not (**11**),

Table 2. Products of the Iron-Catalyzed C−H Methylation[a]



[a]The reaction was performed on a 0.5 mmol scale following the procedure described in the text for a gram-scale experiment. For dimethylation, 3 equiv of $AlMe_3$ was used. Yields of isolated products are shown. PA = picolinoyl; Q = 8-quinolyl. See the SI for details. [b]The monomethylated product was obtained in 5% yield. [c]The monomethylated product was obtained in 11% yield. [d]A 5% yield of debromination byproduct was observed. [e]The monomethylated product was obtained in 6% yield. [f]The monomethylated product was obtained in 7% yield. [g]The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard.

suggesting that this C−H functionalization is very sensitive to the electronic property of the reactive center.

In the 8-quinolylamide series of compounds (cf. Scheme 1b), ortho-dimethylated products were obtained as major products for unsubstituted or para-substituted benzamides. Similar to the benzylamide series described above, a meta substituent on the phenyl ring (cf. **12**−**19**) suppresses the methylation at the

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neighboring ortho position and gives exclusive monomethylation at the ortho position opposite to the meta group.

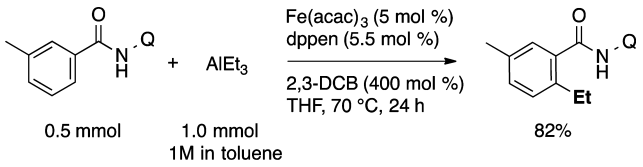
Functional groups such as ether, trifluoromethyl, tertiary amine, ester, fluoro, and chloro are well-tolerated (compounds **13**–**18**, **23**). A bromo-substituted benzamide was also methylated (**16**), accompanied by a small amount of debrominated product (5% yield). Ortho-substituted benzamides took part in the reaction smoothly, producing ortho-dimethylated products in good yields (cf. **20** and **21**). Heteroaryl benzamides such as pyridine- (**24**), thiophene- (**25**), furan- (**4**) and indolecarboxamide (**26**) gave the expected methylated products in moderate to excellent yields.

Alkenyl amides also serve as suitable substrates, as illustrated for cyclohexene- (**27**) and pyrancarboxamide (**28**). For acyclic alkenecarboxamides such as (*E*)-2,3-diphenylacrylamide and (*E*)-2-methylbut-2-enamide, *Z*-to-*E* isomerization of the starting materials and of the initial products took place to generate a mixture of isomers. Simple *N*-methylbenzamide and benzoquinoline gave less than 5% yields of the methylation products, indicating the importance of bidentate chelation for the stability of the iron intermediate.[13,16]

The present iron-catalyzed reaction with $AlMe_3$ showed a very high TON compared with those reported for a variety of C–H functionalizations, which are typically less than 100.[10,18] Thus, 1 mol % catalyst was generally enough to obtain high yields, and 0.1 mol % often gave a satisfactory yield (e.g., 81% for **12**), where the TON was 810. For 2-furancarboxamide, 0.01 mol % iron catalyst still gave a 65% yield of the desired product, where the TON reached 6500.

For reasons yet unclear, the trialkylaluminum reagent is more sensitive to the size of the alkyl substituents than organozinc reagents.[5a] Thus, ethylation using $AlEt_3$ took place as smoothly as methylation with $AlMe_3$ (Scheme 2), yet the reactions of **1** with isobutyl- and trioctylaluminum did not give the desired product at all (see the SI).

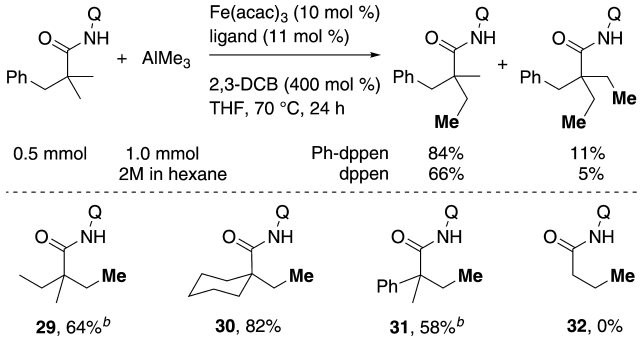
Scheme 2. Ethylation with Triethylaluminum



Direct methylation of a C(sp^3)–H bond can also be achieved with the $AlMe_3$/Fe(III) system.[19] Thus, a 2,2-disubstituted propionamide bearing an 8-aminoquinolyl group (Table 3) can be methylated under essentially the same conditions as those employed in Table 1 but at higher catalyst loading (10 mol %). Ph-dppen enables higher conversion than dppen, likely because of spin delocalization of the putative low-valent iron intermediate.[13,17] Propionamide derivatives disubstituted at the α-position react smoothly to produce **29**–**31** in good yields, whereas the α-unsubstituted propionamide expected to produce **32** is unreactive. Notably, the α-phenyl-substituted butyramide leading to **31** was unreactive under the previous conditions using an arylzinc reagent[19] but is reactive toward $AlMe_3$. The catalyst activated only the C–H bond of a methyl group to produce **31**, without activating any of the C–H bonds on the phenyl ring.

Finally, we describe the reaction of the bis-(trimethylaluminum)·1,4-diazabicyclo[2.2.2]octane adduct, a solid, air-stable, and commercially available methyl source[7]

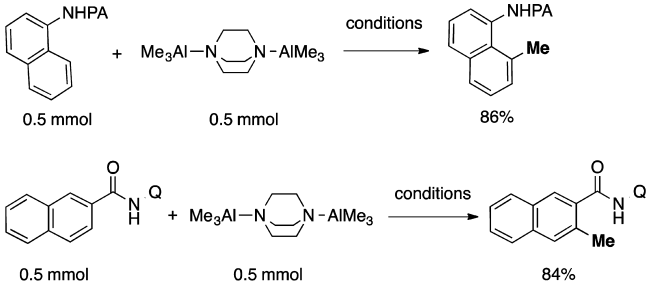
Table 3. Methylation of a C(sp^3)–H Bond[a]



[a]The reaction was performed on a 0.5 mmol scale following the procedure described in the text for a gram-scale experiment using 10 mol % catalyst and Ph-dppen as a ligand. Yields of isolated products are shown. Q = 8-quinolyl. See the SI for details. [b]The dimethylated product was obtained in <5% yield.

(Scheme 3). The reaction is slower than that with $AlMe_3$, and 5 mol % Fe(III) catalyst is necessary to complete the reaction in 24 h.

Scheme 3. Methylation Using Air-Stable Bis(trimethylaluminum)·1,4-diazabicyclo[2.2.2]octane



Conditions: $Fe(acac)_3$ (5.0 mol %), dppen (5.5 mol %), 2,3-DCB (400 mol %), THF, 70 °C, 24h

In conclusion, we have achieved a directed C–H methylation reaction of anilides and carboxamides bearing a picolinoyl or 8-aminoquinolyl group with trimethylaluminum or air-stable bis(trimethylaluminum)·1,4-diazabicyclo-[2.2.2.]octane adduct as the methylating reagent using an iron/diphospine catalyst and inexpensive 2,3-dichlorobutane as an oxidant. The mildly reactive aluminum reagent prevents premature reduction of an organoiron reactive species and realizes a robust catalytic cycle that shows much higher TONs than previously reported iron-catalyzed C–H functionalization[20] and related catalysis by noble metals.[10,18]

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and physical properties of the compounds. The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b04818.

■ AUTHOR INFORMATION

Corresponding Authors

*laur@chem.s.u-tokyo.ac.jp
*nakamura@chem.s.u-tokyo.ac.jp

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Notes

The authors declare no competing financial interest.

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