Doctorate Dissertation (Censored)

博士論文（要約）

Directed C–H Functionalization Catalyzed by Manganese or Chromium

(マンガンまたはクロム触媒による炭素－水素結合の直接官能基化)

A Dissertation Submitted for Degree of Doctor of Philosophy

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Abstract

The present thesis describes the development of novel catalytic systems for C–H functionalization reactions using manganese or chromium in the presence of appropriate organometallic reagents.

Chapter 1 describes the importance and issues of transition-metal-catalyzed C–H functionalization reactions. The significance of C–H functionalizations catalyzed by 3d transition metals was also described. The development of manganese- or chromium-catalyzed C–H functionalizations using novel reactive species is the main topic of this thesis.

Chapter 2 describes manganese-catalyzed directed C–H methylation with a Grignard reagent. The reaction proceeded under 25 °C with high catalyst efficiency in the absence of any external ligands, and substrates possessing various monodentate directing groups were methylated.

Chapter 3 describes chromium-catalyzed directed C–H functionalization in the presence of an organoaluminum reagent. Several C–H functionalization reactions took place with several electrophiles or an oxidant.

Finally, Chapter 4 gives the summary of the present studies and a future outlook.

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List of publication

1. “Manganese-Catalyzed Directed Methylation of C(sp^2)−H Bonds at 25 °C with High Catalytic Turnover”, Sato, T.; Yoshida, T.; Al Mamari, H. H.; Ilies, L.; Nakamura, E. *Org. Lett.* **2017**, *19*, 5458–5461. (Chapter 2)

Publication not included in this thesis

1. “Diporphyrin Magnesium Complex with Long-Wavelength Light Absorption for Organic Solar Cells”, Sato, T.; Nakagawa, T.; Okada, H.; Matsuo, Y. *J. Porphyrins and Phthalocyanines*, **2015**, *19*, 451–458.

Abbreviations

Ac: acetyl

acac: acetylacetonate

APCI: atmospheric pressure chemical ionization

ATR: attenuated total reflectance

Bu: butyl

CPME: cyclopentyl methyl ether

Cy: cyclohexyl

DCM: dichloromethane

DG: directing group

DME: 1,2-dimethoxyethane

DMF: *N*,*N*-dimethylformamide

DMPU: *N*,*N*'-dimethylpropyleneurea

DMSO: dimethyl sulfoxide

Et: ethyl

FG: functional group

GC: gas chromatography

GC-MS: gas chromatography-mass spectrometry

GPC: gel permeation chromatography

h: hour(s)

HRMS: high-resolution mass spectrometry

Hz: Hertz

IR: infrared spectroscopy

KIE: kinetic isotope effect

Me: methyl

min: minute(s)

MS: mass spectroscopy

MW: molecular weight

n.d.: not detected

NMP: *N*-methylpyrrolidone

NMR: nuclear magnetic resonance

NOE: nuclear Overhauser effect

Ph: phenyl

PMB: *p*-methoxybenzyl

ppm: parts per million

TES: triethylsilyl

TIPS:triisopropylsilyl

TON: turnover number

TM: transtion metal

TMS: trimethylsilyl

THF: tetrahydrofuran

THP: tetrahydropyran

TMEDA: *N,N,N′,N′*-tetramethylethylenediamine

Chapter 1

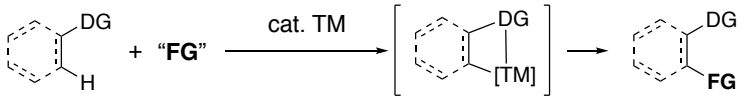
General Introduction

1.1. Transition-Metal-Catalyzed C–H Functionalization

Organic synthesis is an important field because it creates useful organic compounds such as organic devices, drugs, and agricultural chemicals. To synthesize them, many useful organic reactions such as transition-metal-catalyzed cross-coupling reactions have been developed.[1] Nowadays, to synthesize target compounds more efficiently, an atom- and step-economical synthetic method with high selectivity such as regioselectivity is desirable.

Transition-metal-catalyzed directed C–H functionalization is the most straightforward method for the regioselective transformation of molecules (Scheme 1). This type of reaction has been developed after the pioneering work by Murai group,[2] mainly using precious 4d and 5d transition metals.[3] In the view of sustainable chemistry, the use of abundant and inexpensive transtion metals as catalysts is desirable.

Scheme 1. Tansition-Metal-Catalyzed Directed C–H Functionalization

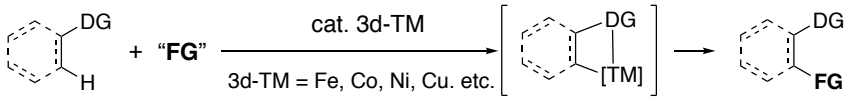


1.2. 3d Transition-Metal-Catalyzed C–H Functionalization

3d transition metals are abundant and inxepensive, thus their use for catalysis is attractive.[4] Recently, 3d transition-metal-catalyzed C–H functionalization has been developed (Scheme 2). However, this field is still underdeveloped; the need for special directing groups or engineered ligands hinders the application of these reactions to organic synthesis.[5] To solve these issues, uncovering novel reactivity of 3d transition

metals for C–H activation is desirable.

Scheme 2. 3d Tansition-Metal-Catalyzed C–H Functionalization

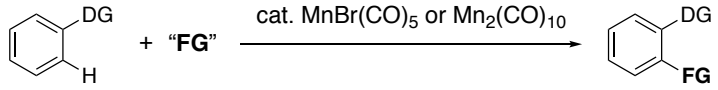


1.3. Manganese and Chromium as Catalysts for C–H Functionalization

1.3.1. Manganese

Manganese is an abundant 3d transtion metal and has low toxicity.[6] Therefore, the use of it as catalyst for C–H activation is attractive. Recently, manganese-catalyzed C–H functionalization reactions have been developed.[7] However, for these reactions an expensive manganese carbonyl complex and harsh reaction conditions were necessary (Scheme 3). Only recently reactions catalyzed by manganese(II) chloride were reported.[8]

Scheme 3. Manganese-Catalyzed C–H Functionalization

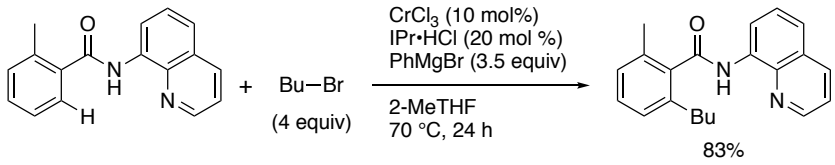


1.3.2. Chromium

Chromium is also a 3d transition metal, and it is abundant and inexpensive.[4] Moreover, chromium(III) has low toxicity, different from chromium(VI), which is highly toxic.[9] Therefore, the use of chromium(III) as a catalyst is also desirable.

Despite this, maybe because of misconception regarding the toxicity of chromium(III), chromium-catalyzed C–H functionalization reactions have been less investigated.[10,11] In these reactions, a Grignard reagent was necessary to generate reactive low-valent chromium species, and the scope of the substrate was limited (Scheme 4).

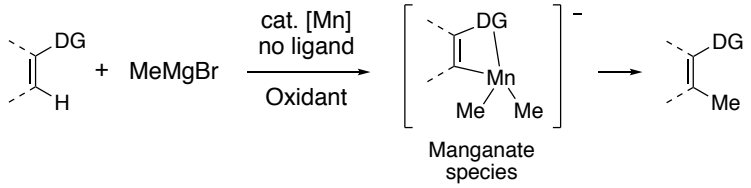
Scheme 4. A Selected Example of Chromium-Catalyzed C–H Functionalization[11e]



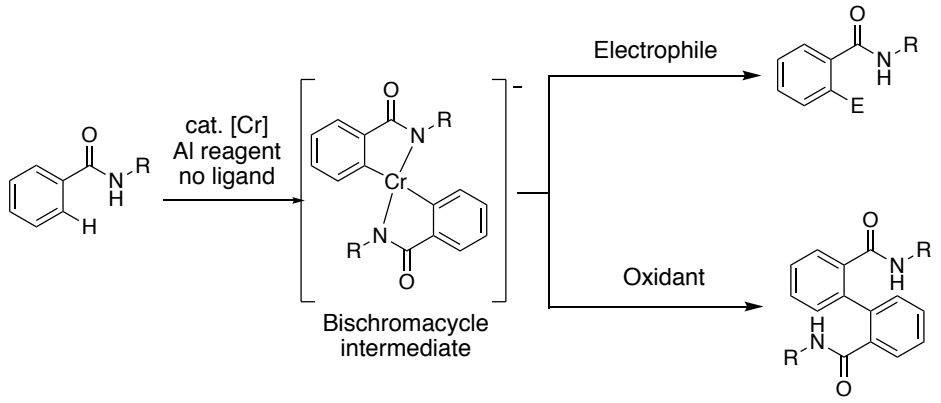
1.4. Thesis Outline

In this thesis, the author has developed a novel reactivity of manganese and chromium for C–H activation reactions in the presence of appropriate organometallic reagents. In Chapter 2, the reactivity of organomanganese ate species that was formed from a manganese salt and methyl Grignard reagent was described. Using this species, catalytic methylation has been achieved in the presence of an oxidant without any external ligands under mild reaction conditions (Scheme 5). In Chapter 3, chromium-catalyzed C–H functionalization in the presence of an organoaluminum reagent was described. In this system, bischromacycle was a plausible key intermediate, and catalytic C–H functionalization with electrophiles and C–H dimerization in the presence of an oxidant has been achieved (Scheme 6).

Scheme 5. Manganese-Catalyzed C–H Methylation Described in Chapter 2



Scheme 6. Chromium-Catalyzed C–H Functionalization Described in Chapter 3



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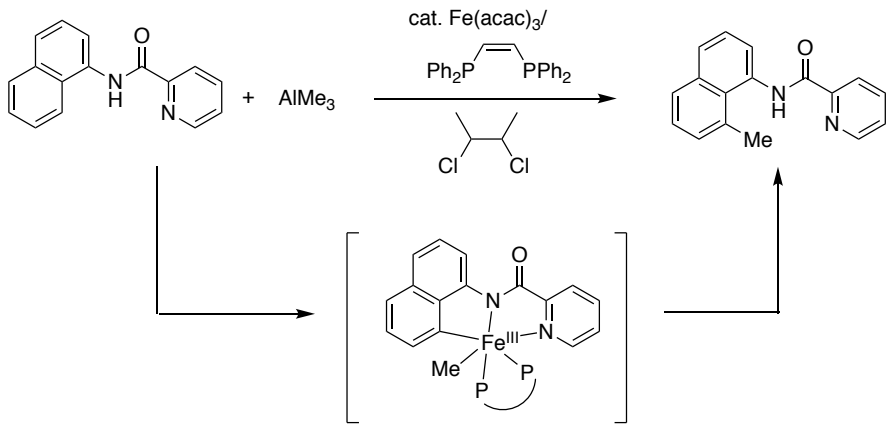
Chapter 2

Manganese-Catalyzed Directed C(sp^2)–H Methylation

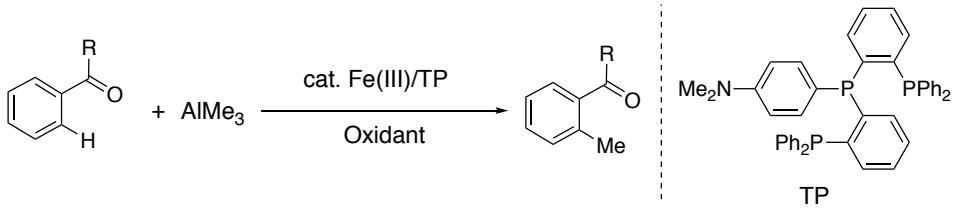
2.1. Introduction

Previously, Nakamura group has developed C–H functionalization reactions catalyzed by iron as an abundant 3d transition metal.[1] Recently, because of the importance of the methylation for medicinal chemistry,[2,3] the same group was also developed iron-catalyzed C–H methylation reactions.[4] However, these reactions required a bidentate directing group and an expensive diposphine ligand, or an engineered triphosphine ligand in order to stabilize the highly reactive organoiron intermediate (Schemes 1 and 2). I envisioned that by using an intrinsically more stable organometallic catalytic species, the bidentate directing group and external ligands may not be necessary. Based on this hypothesis, I focused my attention on manganese, because it is known that organomanganese species is relatively stable among other first row transition organometallics.[5] In this Chapter, manganese-catalyzed directed C–H functionalization with Grignard reagent is described.

Scheme 1. Iron-Catalyzed C–H Methylation of a Substrate Possessing a Bidentate Group Using a Diphosphine Ligand[4a]



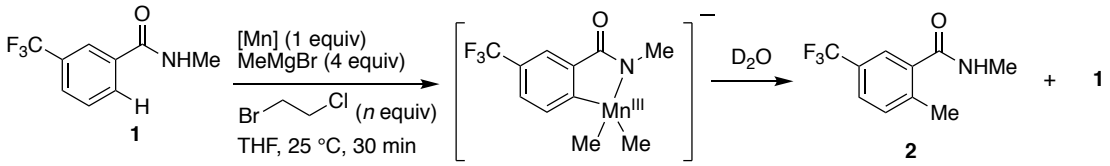
Scheme 2. Iron-Catalyzed C–H Methylation Using a Triphosphine Ligand[4b]



2.2. Stoichiometric Reaction

In order to explore the reactivity of organomanganese towards a C–H bond, I investigated the reaction of *N*-methyl-3-(trifluoromethyl)benzamide as a substrate possessing a monodentate directing group with methylmagnesium bromide as a methyl source and base in the presence of a stoichiometric amount of manganese salt (Table 1). When manganese(II) acetylacetonate was used as the manganese source, the methylated product was not obtained (entry 1). However, when manganese(III) acetylacetonate was used, a small amount of methylated product was obtained (entry 3), suggesting that high-valent organomanganese species may be effective for C–H activation. Accordingly, when manganese(II) acetylacetonate or manganese(III) acetylacetonate was used together with 1-bromo-2-chloroethane as a mild oxidant, the methylated product was obtained in moderate yield (entries 3 and 4). The reactions were quenched by deuterium oxide, but deuterium was not incorporated at all, suggesting that the C–C bond forming step is fast. The need of an oxidant and the presence of an excess of MeMgBr suggests that a high-valent organomanganese ate species may be the active species involved in the C–H bond cleavage step.[6]

Table 1. Stoichiometric Reaction for C–H Activation



entry	[Mn]	*n*	yield (%)[a]	
			2	**1**
1	$Mn(acac)_2$	0	0	100 (0% D)
2	$Mn(acac)_3$	0	17	82 (0% D)
3	$Mn(acac)_2$	2	55	40 (0% D)
4	$Mn(acac)_3$	2	41	54 (0% D)

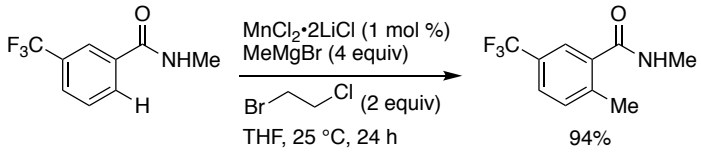
[a]Yield was determined by ^{1}H NMR in the presence of 1,1,2,2-dichloroethane as an internal standard.

2.3. Catalytic Reaction

Based on the result of the stoichiometric reaction, next I investigated the reaction using a catalytic amount of manganese.[7] An ate complex, $MnCl_2$•2LiCl, was used as the manganese source because it is soluble in THF and can be used conveniently as a stock solution. Gratifyingly, the catalytic reaction proceeded and the methylated product was obtained in excellent yield under mild reaction conditions without any external ligands and sophisticated directing group such as bidentate directing group (Scheme 3). Theoretically, for this reaction, 3 equivalent of MeMgBr, that is 1 equivalent of methyl source and 2 equlvalent of base, is necessary. Therefore the reaction proceeded with small excess amount of Grignard reagent. When non-substituted *N*-methylbenzamide was used as a substrate with 5.5 equivalent of MeMgBr and 3 equivalent of 1-bromo-2-chloroethane, the dimethylated product was obtained selectively (Scheme 4). For dimethylation, 5 equivalent of MeMgBr is

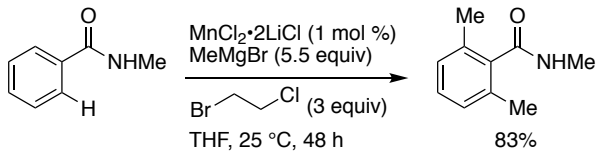
required theoretically. Therefore, also in this case, small excess amount of Grignard reagent was needed. Based on this result, next I investigated the parameters that affect the reactivity of the catalytic organomanganese species.

Scheme 3. Catalytic Methylation of *N*-Methyl-3-(trifluoromethyl)benzamide



(Yield was determined by ^{1}H NMR in the presence of 1,1,2,2-dichloroethane as an internal standard.)

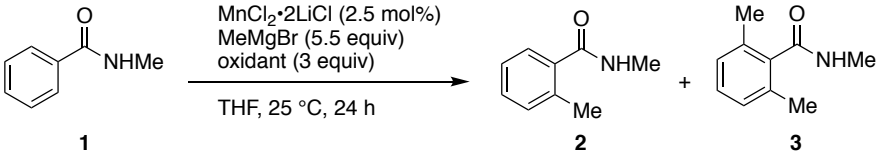
Scheme 4. Catalytic Methylation of *N*-Methylbenzamide



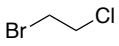
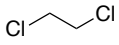
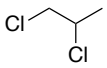
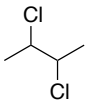
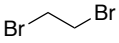
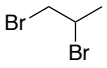
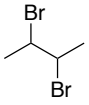
2.4. Effect of Oxidant

If indeed a high-valent organomanganese species is the active species, the nature of the oxidant must be important. Therefore, first I investigated the oxidant, focusing especially on mild dihalogenated alkane oxidants (Table 2).[8] Among these, 1-bromo-2-chloroethane gave the best result (entry 1). A dichlorinated alkane was not effective maybe because of weak ability of oxidation via single electron transfer (entries 2–4).[9] A dibrominated alkane was a less effective oxidant maybe because of a fast elimination reaction to form a haloalkene as a side reaction (entries 5–7). Without oxidant, methylation did not proceed (entry 8).

Table 2. Effect of Oxidant



1 **2** **3**

entry	oxidant	yield (%)[a]		
		2	**3**	**1**
1		<5	86	<5
2		n.d.	n.d.	85
3		n.d.	n.d.	91
4		n.d.	n.d.	80
5		19	26	<5
6		15	25	<5
7		32	18	<5
8	none	n.d.	n.d.	82

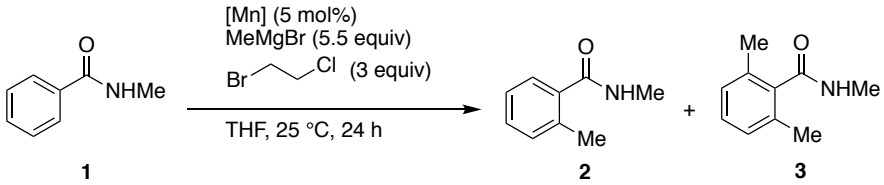
[a]Yield was determined by GC in the presence of tridecane as an internal standard.

2.5. Effect of Manganese Salt

I investigated several manganese salts as the catalyst precursor (Table 3). The methylation proceeded even when simple manganese(II) chloride or manganese(II) bromide was used as well as $MnCl_2$•2LiCl (entries 1–3). Manganese(II) acetylacetonate, manganese(III) acetylacetonate, manganese(II) acetate, and manganese(III) acetate showed similar reactivity compared to $MnCl_2$•2LiCl, probably because the same active

species was formed *in situ* (entries 4–7). Poorly soluble manganese(II) fluoride and manganese(III) fluoride gave lower yields (entries 8 and 9). The methylation did not proceed without a manganese catalyst (entriy 10).

Table 3. Effect of Manganese Salt



1 **2** **3**

entry	[Mn]	yield (%)[a]		
		2	**3**	**1**
1	$MnCl_2$•2LiCl	<5	77	<5
2	$MnCl_2$	<5	74	<5
3	$MnBr_2$	<5	73	<5
4	$Mn(acac)_2$	<5	70	<5
5	$Mn(acac)_3$	<5	79	<5
6	$Mn(OAc)_2$	<5	77	<5
7	$Mn(OAc)_3$•$2H_2O$	<5	78	<5
8	MnF_2	38	n.d.	60
9	MnF_3	32	n.d.	44
10	none	n.d.	n.d.	80

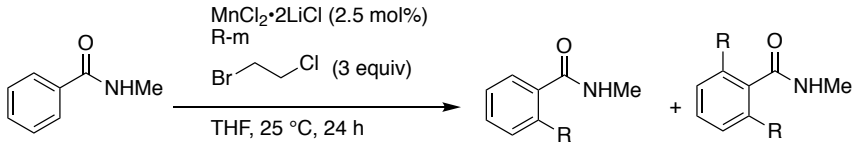
[a]Yield was determined by GC in the presence of tridecane as an internal standard.

2.6. Effect of Organometallic Reagent

I investigated other organometallic reagents (Table 4). When mono- or dimethylzinc prepared *in situ* was used, methylation did not proceed likely because of slow transmetalation (entries 2 and 3). Methyllithium was less effective maybe because its strong reduction ability prevented the formation of active species, or because magnesium was crucial for the generation of active species (entry 4). When

octylmagnesium bromide or phenylmagnesium bromide was used, octylation or phenylation did not proceed because of β-hydrogen elimination[10] or homocoupling reaction[11] as a side reaction (entries 5 and 6).

Table 4. Effect of Organometallic Reagent



entry	R-m	yield (%)[a] 2	3	1	other products
1	MeMgBr (5.5 equiv)	<5	86	<5	
2	MeMgBr (5.5 equiv) + $ZnCl_2$•TMEDA (4.5 equiv)	n.d.	n.d.	96	
3	MeMgBr (10 equiv) + $ZnCl_2$•TMEDA (4.5 equiv)	n.d.	n.d.	91	
4	MeLi (5.5 equiv)	8	n.d.	58	
5	OctylMgBr (5.5 equiv)	n.d.	n.d.	64	octene (173%[b]), octane (276%[b])
6	PhMgBr (5.5 equiv)	n.d.	n.d.	64	Ph-Ph (280%[b])

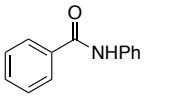
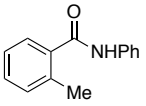
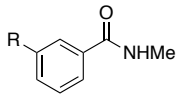
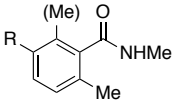
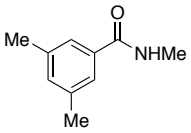
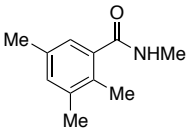
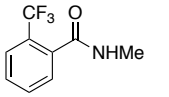
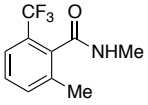
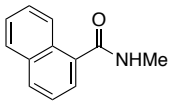
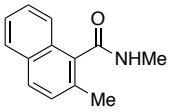
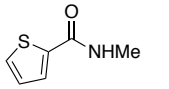
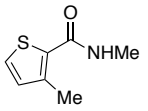
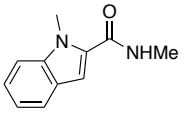
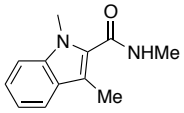
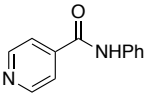
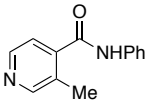
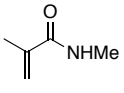
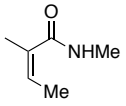
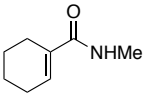
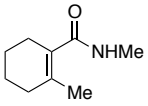
[a]Yield was determined by GC in the presence of tridecane as an internal standard.
[b]Yield was based on substrate.

2.7. Scope of Substrate

Next, the scope of the substrate was investigated (Table 5). Arene and alkene substrates possessing various directing groups reacted well. When *N*-phenylbenzamide was used as the substrate, the monomethylated product was obtained selectively due to steric effect (entry 1). When *N*-methylbenzamide was used as a substrate, the di- or monomethylated product was obtained with good selectivity by changing the amount of

reagents. When 5.5 equivalent of MeMgBr was used, dimethylated product was obtained selectively (entry 2). On the other hand, when 3.1 equivalent of MeMgBr was used, monomethylation proceeded with good selectlvity (entry 3). When a *meta*-methyl substrate was used, monomethylated product was selectively obtained because of steric hindrance (entry 4). When *m*-trifluoromethyl-substituted substrate was used, methylation proceeded with perfect monoselectivity (entry 5). This reaction took place well in the presence of 0.1 mol% of catalyst. Fluoro and bromo group was tolerated. When *m*-fluoro-substituted substrate was used, dimethylation proceeded (entry 6). Even when *m*-bromobenzamide was used, dimethylation took place despite the large size of bromo group (entry 7). When *m*-methoxy substrate was used, an almost 1:1 mixture of mono- and dimethylated product was obtained (entry 8). When 3,5-dimethylbenzamide was used, methylation proceeded even at the sterically hindered position (entry 9). *Ortho*-trifluoromethyl substrate reacted well (entry 10). *N*-Methyl-1-naphthaleneamide took part in the reaction and *ortho*-methylated product was obtained (entry 11). A heteroaromatic carboxamide such as thiophene-, indole-, and pyridinecarboxamide also reacted (entries 12–14). An acyclic and cyclic alkeneamide was methylated well (entries 15 and 16).

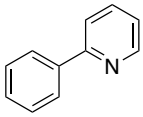
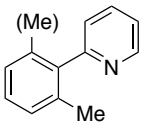
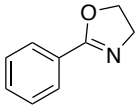
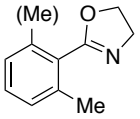
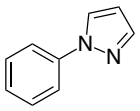
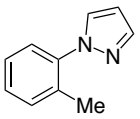
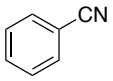
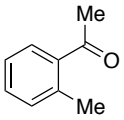
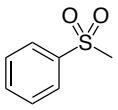
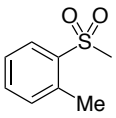
Table 5. Manganese-Catalyzed Methylation of Secondary Carboxamides[a]

entry	substrate	product		yield (%)[b] mono-	yield (%)[b] di-
1[c]				98	–
2[d]			R = H	–	83
3[e]			R = H	60	13
4			R = Me	69	6
5[f]			R = CF_3	75 (90)	–
6[d]			R = F	–	73
7[d]			R = Br	16	64
8[d]			R = OMe	36	48
9				84 (90)	
10[c]				81 (92)	
11				78 (89)	
12				60 (68)	
13				61 (70)	
14				79 (89)	
15				65 (80)	
16				88 (93)	

[a]Reaction conditions: the reaction was performed on a 0.5 mmol scale using $MnCl_2$•2LiCl (1 mol %), MeMgBr (4 equiv; unless otherwise noted below), and 1-bromo-2-chloroethane (2 equiv) at 25 °C for 24 h. [b]Yield of the isolated product. The yield shown in parentheses was determined by ^{1}H NMR using 1,1,2,2,-tetrachloroethane as an internal standard. [c]48 h. [d]MeMgBr (5.5 equiv) and 1-bromo-2-chloroethane (3 equiv), 48 h. [e]MeMgBr (3.1 equiv). [f]$MnCl_2$•2LiCl (0.1 mol %).

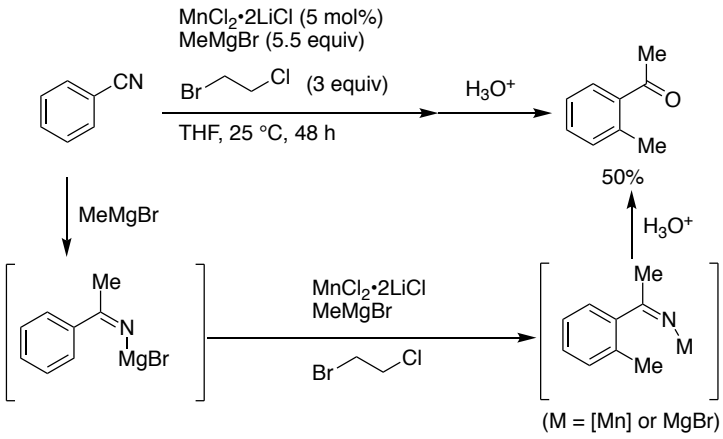
Other directing groups were also effective for this reaction (Table 6). Not only an amide group, but also several heteroaromatic groups such as pyridine, oxazoline, and pyrazole could be used as the directing group (entries 1–3). In these cases, larger amount of catalyst was necessary probably because of the weaker coordination of neutral directing groups. When benzonitrile was used as the substrate, addition followed by sequential methylation occurred, and *ortho*-methylacetophenone was obtained after acidic workup of the corresponding imine (entry 4 and Scheme 5).[12] A methylsulfone group, largely unexplored for C–H activation,[13] acted as the directing group (entry 5). Notably, diphenyl sulfone did not react and the starting material was recovered, suggesting that the deprotonated methyl sulfone acts as a directing group, in contrast with the previous report where the sulfone group coordinated the metal species.

Table 6. Manganese-Catalyzed Methylation of substrates possessing other directing groups[a]

entry	substrate	product	yield (%)[b] mono-	yield (%)[b] di-
1			64 (80)	8 (10)
2[c]			14 (19)	26 (41)
3[c]			32 (47)	
4[d]			50 (67)	
5[d,e]			22 (34)	

[a]Reaction conditions: the reaction was performed on a 0.5 mmol scale using $MnCl_2$•2LiCl (5 mol %), MeMgBr (4.5 equiv) and 1-bromo-2-chloroethane (3 equiv) at 25 °C for 48 h. [b]Yield of the isolated product. The yield shown in parentheses was determined by ^1H NMR using 1,1,2,2,-tetrachloroethane as an internal standard. [c]40 °C. [d]MeMgBr (5.5 equiv). [e]2,3-dibromobutane was used instead of 1-bromo-2-chloroethane.

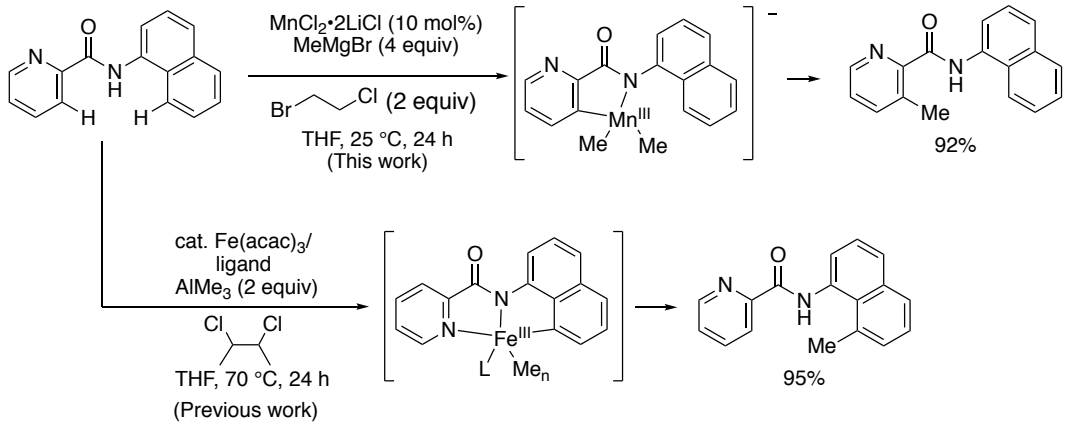
Scheme 5. Sequential Methylation of Benzonitrile



2.8. Different Regioselectivity between Manganese and Iron

The manganese-catalyzed methylation proceeded with different regioselectivity compared to the previously reported iron-catalyzed methylation[4a] (Scheme 6). When *N*-(1-naphthyl)-2-picolinamide was used as a substrate, the iron-catalyzed methylation took place at the naphthalene ring because of bidentate chelation (Scheme 6, bottom). On the other hand, in the manganese case, methylation proceeded at the pyridine ring (Scheme 6, top).[14] Even when the amount of MeMgBr increased to 6 equivalent, methylation at the naphthalene ring did not take place. This is probably because the intermediate is the ate complex and there is no room for the chelation of nitrogen at pyridine ring.[6b,15]

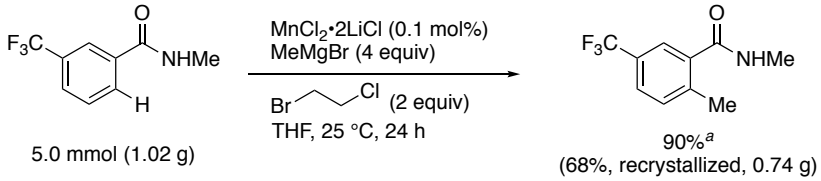
Scheme 6. Different Regioselectivity between Manganese and Iron[4a]



2.9. Gram Scale Reaction

Gram scale methylation proceeded well (Scheme 7). When 1.02 g of *N*-methyl-3-(trifluoromethyl)benzamide was used in the presence of 0.1 mol% of $MnCl_2$•2LiCl, methylation proceeded well, and the desired product was easily isolated in 68% yield just by recrystallization. This is an important feature of this reaction system for synthetic application because main side products are gas such as methane and ethylene, and manganese can be easily removed by washing with water, and as a result, a symple purification method can be utilized.

Scheme 7. Gram Scale Reaction

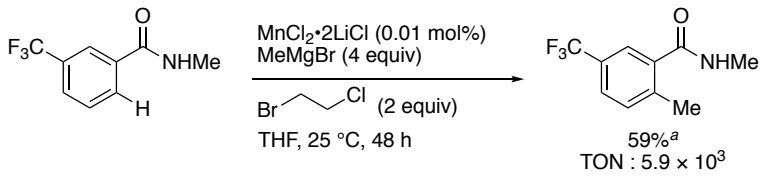


([a]Yield was determined by ^{1}H NMR in the presence of 1,1,2,2-dichloroethane as an internal standard.)

2.10. High Catalyst Efficiency

The manganese-catalyzed methylation reaction proceeded with high catalyst efficiency (Scheme 8). When 0.01 mol% of manganese catalyst was used, the methylated product was obtained in 59% yield translating to a catalyst turnover number (TON) of 5.9×10^3. The high turnover of the catalyst may be ascribed to the relatively high stability of organomanganese species.

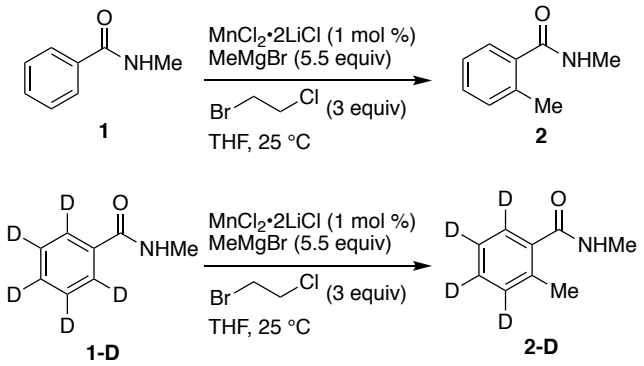
Scheme 8. Catalytic Methylation with High Catalyst Efficiency



[a]Yield was determined by ^{1}H NMR in the presence of 1,1,2,2-dichloroethane as an internal standard.

2.11. Mechanistic Insight

To obtain mechanistic information, I conducted parallel KIE experiment (Figure 1). The KIE value was 2.0, suggesting that the C–H bond cleavage step is the turnover-limiting step.



time (h)	1.5	2	2.5	3
yield of **2** (%)	9	14	20	25
yield of **2-D** (%)	5	7	9	12

=> $k_H/k_D = 2.0 \pm 0.1$

Figure 1. Parallel KIE Experiment

2.12. A Possible Catalytic Cycle

A possible catalytic cycle is shown in Figure 2. After oxidation of manganese and transmetalation, manganese(III) ate species **A** is formed. This species cleaves C–H bond to form manganacycle **B**. The KIE experiment suggests that this step is the turnover-limiting step. The methylated species **C** is obtained after reductive elimination. This step is fast according to the result of stoichiometric reactions. Manganese is reoxidized and ligand exchange occurs to regenerate the complex **A**, and then catalytic cycle proceeds.

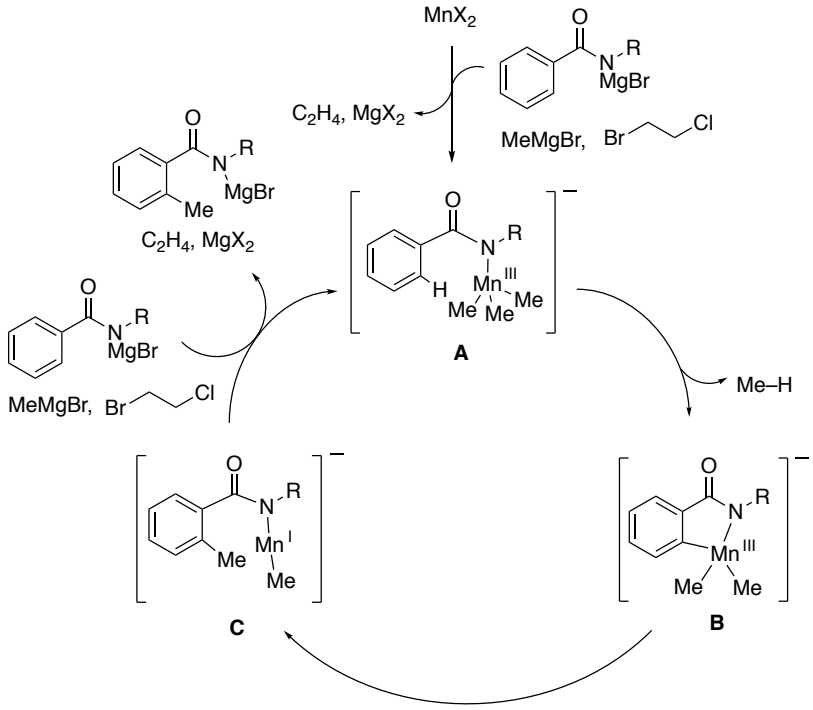


Figure 2. A Possible Catalytic Cycle

2.13. Summary

In summary, a manganese-catalyzed directed methylation of C(sp^2)–H bonds has been developed. This reaction proceeded under mild reaction conditions for various substrates possessing simple monodentate directing groups without the need of an external ligand. In some cases, the reaction took place with different regioselectivity compared to other transition metal-catalyzed reactions. High catalyst efficiency was achieved, likely because of the stability of organomanganese species. Reactions using a stoichiometric amount of manganese suggested that a high-valent organomanganese ate species is the active species.

2.14. Experimental Section

General. All reactions dealing with air- or moisture-sensitive compounds were carried out in a dry reaction vessel under an atmosphere of nitrogen. Gas-liquid chromatographic (GC) analysis was performed on a Shimadzu GC-2025 machine equipped with glass capillary column HR-1 (0.25-mm i.d. × 25 m). Flash silica gel column chromatography was performed on silica gel 60N (Kanto, spherical and neutral, 140–325 mesh) as described by Still.[16] Gel permeation column chromatography was performed on a Japan Analytical Industry LC-92XX II (eluent: chloroform) with JAIGEL 1H and 2H polystyrene columns. Melting points were determined by MEL-TEMP II. IR spectra were recorded on JACSO FT/IR-6100 equipped with an attenuated total reflection (ATR) and are reported as wavenumber (ν) cm^{-1}. NMR spectra were measured on JEOL ECZ-500 spectrometer and reported in parts per million from tetramethylsilane or DMSO. ^{1}H NMR spectra in $CDCl_3$ or DMSO were referenced internally to tetramethylsilane (0.0 ppm) or DMSO (2.49 ppm) as a standard, respectively. ^{13}C NMR spectra in $CDCl_3$ or DMSO were referenced to $CDCl_3$ (77.0 ppm) or DMSO (39.5 ppm) as a standard, respectively. ^{19}F NMR spectra were referenced to C_6F_6 (–164.9 ppm) as a standard. Mass spectra (GC-MS) are taken at SHIMADZU Parvum 2 gas chromatograph mass spectrometer. High resolution mass spectra were acquired by atmospheric pressure ionization (APCI) using a time-of-flight mass analyzer on Bruker micrOTF II with a calibration standard of polyethylene glycol (MW 600) or JEOL JMS-T100LC (AccuTOF) spectrometer with a calibration standard of Reserpine (MW 609).

Materials. Unless otherwise noted, materials were purchased from Tokyo Kasei Co.,

Aldrich Inc., and other commercial suppliers and used without further purification. Anhydrous ethereal solvents (stabilizer-free) were purchased from WAKO Pure Chemical and purified by a solvent purification system (GlassContour)[17] equipped with columns of activated alumina and supported copper catalyst (Q-5) prior to use. The water content was determined with a Karl-Fischer moisture titrator (MKC-210, Kyoto Electronics Company) to be less than 30 ppm. Manganese(II) chloride (99.99%) was purchased from Alfa Aesar. Manganese ate complex ($MnCl_2$•2LiCl) was prepared from manganese(II) chloride and anhydrous lithium chloride in THF.[18] Methylmagnesium bromide in THF was purchased from TCI and titrated prior to use.

Preparation of Substrates

The following compounds were prepared according to the literature procedures. The spectral data showed good agreement with the literature data.

N,3-dimethylbenzamide[19]

N-methyl-3-(trifluoromethyl)benzamide[19]

3-fluoro-*N*-methylbenzamide[19]

3-bromo-*N*-methylbenzamide[20]

3-methoxy-*N*-methylbenzamide[21]

N-methyl-1-naphthamide[19]

N-methyl-2-thiophenecarboxamide[21]

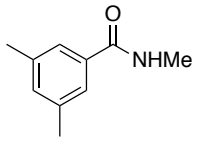
N,1-dimethyl-1*H*-indole-2-carboxamide[21]

N-(1-naphthyl)picolinamide[22]

N-methyl-1-cyclohexene-1-carboxamide[23]

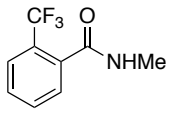
N-methyl-2,3,4,5,6-pentadeuteriobenzamide[19]

_N_,3,5-Trimethylbenzamide:



To a solution of 3,5-dimethylbenzoyl chloride (0.74 mL, 5.0 mmol) and $MeNH_2$•HCl (0.51 g, 7.5 mmol) in THF (10 mL) was added Et_3N (2.8 mL, 20 mmol). The mixture was stirred at 25 °C overnight, diluted with EtOAc (20 mL) and washed with H_2O (3 × 10 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by recrystallization from CH_2Cl_2/hexane to afford the desired product as white needles (0.50 g, 61%). Melting Point: 80–81 °C (CH_2Cl_2/hexane); IR (ATR): 3297, 3001, 2952, 2924, 2857, 1637, 1601, 1541, 1457, 1396, 1328 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.36 (s, 2H), 7.12 (s, 1H), 6.10 (br, 1H), 3.00 (d, J = 4.8 Hz, 3H), 2.35 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.6, 138.1, 134.6, 132.9, 124.6, 26.7, 21.2; HRMS (APCI) Calcd for $C_{10}H_{14}NO^+$ $[M + H]^+$ 164.1075, found, 164.1072.

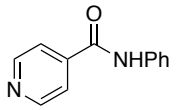
_N_-Methyl-2-(trifluoromethyl)benzamide:



To a solution of 2-(trifluoromethyl)benzoyl chloride (1.5 mL, 10 mmol) and $MeNH_2$•HCl (1.0 g, 15 mmol) in CH_2Cl_2 (15 mL) was added Et_3N (5.6 mL, 40 mmol). The mixture was stirred at 25 °C for 30 min, diluted with CH_2Cl_2 (30 mL) and washed with H_2O (3 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4. The

solvent was evaporated and the crude product was purified by recrystallization from CH_2Cl_2/hexane to afford the desired product as white needles (1.1 g, 53%). Melting Point: 114–115 °C (CH_2Cl_2/hexane); IR (ATR): 3284, 3083, 1636, 1558, 1315, 1138, 775 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.67 (d, J = 7.7 Hz, 1H), 7.57–7.47 (m, 3H), 6.03 (s, 1H), 2.96–2.95 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 135.8 (q, $J_{C–F}$ = 1.8 Hz), 131.9, 129.7, 128.5, 127.1 (q, $J_{C–F}$ = 31.8 Hz), 126.2 (q, $J_{C–F}$ = 5.4 Hz), 123.5 (q, $J_{C–F}$ = 271.8 Hz), 26.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ –62.3; HRMS (APCI) Calcd for $C_9H_9F_3NO^+$ $[M + H]^+$ 204.0636, found, 204.0632.

_N_-Phenyl-4-pyridinecarboxamide:



To a solution of isonicotinoyl chloride hydrochloride (1.8 g, 10 mmol) and aniline (1.0 mL, 11 mmol) in THF (30 mL) was added Et_3N (4.2 mL, 30 mmol). The mixture was stirred at 25 °C overnight, diluted with EtOAc (20 mL) and washed with H_2O (3 × 15 mL). The organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated and the crude product was purified by recrystallization from CH_2Cl_2/hexane to afford the desired product as a white granular solid (1.3 g, 60%). Melting Point: 169–170 °C (CH_2Cl_2/hexane); IR (ATR): 3337, 2989, 2955, 1653, 1600, 1542, 746, 687 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.77 (dd, J = 4.6, 1.4 Hz, 2H), 8.06 (br, 1H), 7.70 (d, J = 6.0 Hz, 2H), 7.64 (d, J = 7.7 Hz, 2H), 7.39 (t, J = 7.7 Hz, 2H), 7.20 (t, J = 7.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 150.7, 142.1, 137.2, 129.2, 125.3, 120.9, 120.4; HRMS (APCI) Calcd for $C_{12}H_{11}N_2O^+$ $[M + H]^+$ 199.0871, found, 199.0876.

Stoichiometric Reaction

In an oven-dried Schlenk tube were placed *N*-methyl-3-(trifluoromethyl)benzamide (41 mg, 0.20 mmol) and a manganese salt (0.20 mmol). MeMgBr in THF (0.84 mL, 0.95 M, 0.80 mmol) was added. 1-Bromo-2-chloroethane (33 μL, 0.40 mmol) was added if necessary. The reaction mixture was stirred at 25 °C for 30 min, and then it was quenched by the addition of D_2O (1 mL). After extraction with EtOAc (3 × 3 mL), the combined organic layers were passed over a silica gel pad with ethyl acetate, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^{1}H NMR in the presence of 1,1,2,2-tetrachloroethane as an internal standard. Deuterium was not incorporated in all cases.

Reaction of *N*-Methyl-3-(trifluoromethyl)benzamide with 1 mol % of Catalyst

In an oven-dried Schlenk tube were placed *N*-methyl-3-(trifluoromethyl)benzamide (41 mg, 0.20 mmol) and a solution of $MnCl_2$•2LiCl in THF (20 μL, 0.10 M, 0.0020 mmol). MeMgBr in THF (0.80 mL, 1.00 M, 0.80 mmol) and 1-bromo-2-chloroethane (33 μL, 0.40 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (1 mL) and small amount of water. After extraction with EtOAc (3 × 3 mL), the combined organic layers were passed over a silica gel pad with EtOAc, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^{1}H NMR in the presence of 1,1,2,2-tetrachloroethane as an internal standard (product: 94%, recovery: 6%).

Investigation of Oxidant

In an oven-dried Schlenk tube were placed *N*-methylbenzamide (27 mg, 0.20 mmol) and a solution of $MnCl_2$•2LiCl in THF (50 μL, 0.10 M, 0.0050 mmol). MeMgBr in THF (1.1 mL, 1.00 M, 1.1 mmol) and 1-bromo-2-chloroethane (50 μL, 0.60 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (1 mL) and small amount of water. The crude mixture was analyzed by GC in the presence of tridecane as an internal standard.

Investigation of Manganese Catalyst

In an oven-dried Schlenk tube were placed *N*-methylbenzamide (27 mg, 0.20 mmol) and the manganese catalyst (0.010 mmol). MeMgBr in THF (1.1 mL, 1.00 M, 1.1 mmol) and 1-bromo-2-chloroethane (50 μL, 0.60 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (1 mL) and small amount of water. The crude mixture was analyzed by GC in the presence of tridecane as an internal standard.

Investigation of Organometallic Reagent

In an oven-dried Schlenk tube were placed *N*-methylbenzamide (27 mg, 0.20 mmol) and the organometallic reagent was added. The solvent was removed in *vacuo*, and then THF (1.1 mL) was added if necessary. A solution of $MnCl_2$•2LiCl in THF (50 μL, 0.10 M, 0.0050 mmol) and 1-bromo-2-chloroethane (50 μL, 0.60 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by

the addition of a saturated aqueous solution of NH_4Cl (1 mL) and small amount of water. The crude mixture was analyzed by GC in the presence of tridecane as an internal standard.

General Procedure of Manganese-Catalyzed Directed Methylation

General Procedure A (Table 5)**:**

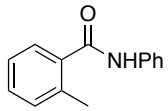
In an oven-dried Schlenk tube were placed the substrate (0.50 mmol) and a solution of $MnCl_2$•2LiCl in THF (50 μL, 0.10 M, 0.0050 mmol). MeMgBr in THF (2.00 mL, 1.00 M, 2.00 mmol) and 1-bromo-2-chloroethane (83 μL, 1.0 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (3 mL) and small amount of water. After extraction with EtOAc (3 × 5 mL), the combined organic layers were passed over a silica gel pad with EtOAc, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^1H NMR in the presence of 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by gel permeation column chromatography (eluent: $CHCl_3$) to afford the desired product.

General Procedure B (Table 6)**:**

In an oven-dried Schlenk tube were placed the substrate (0.50 mmol) and a solution of $MnCl_2$•2LiCl in THF (50 μL, 0.50 M, 0.025 mmol). MeMgBr in THF (2.25 mL, 1.00 M, 2.25 mmol) and 1-bromo-2-chloroethane (124 μL, 1.50 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 48 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (3 mL) and small amount of water. After extraction with EtOAc (3 × 5 mL), the combined organic layers were passed over

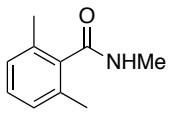
a silica gel pad with EtOAc, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^{1}H NMR in the presence of 1,1,2,2-tetrachloroethane as an internal standard. The crude product was purified by gel permeation column chromatography (eluent: $CHCl_3$) to afford the desired product.

2-Methyl-*N*-phenylbenzamide (Table 5, entry 1):



The general procedure A was applied to *N*-phenylbenzamide (99 mg, 0.50 mmol) for 48 h. The title compound was obtained (104 mg, 98%) (^{1}H NMR yield: 99%). The analytically pure product was obtained after a short pass over a silica gel column. The title compound was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 126–127 °C (CH_2Cl_2/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.78 (br, 1H), 7.58 (d, *J* = 7.7 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.33–7.30 (m, 3H), 7.21–7.16 (m, 2H), 7.12 (t, *J* = 7.4 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 138.0, 136.3, 136.2, 131.1, 130.1, 128.9, 126.6, 125.7, 124.4, 119.9, 19.7; HRMS (APCI) Calcd for $C_{14}H_{14}NO^{+}$ $[M + H]^{+}$ 212.1070, found, 212.1072. The compound data was in good agreement with the literature data.[24]

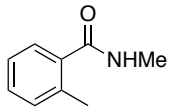
***N*,2,6-Trimethylbenzamide (Table 5, entry 2):**



The general procedure A was applied to *N*-methylbenzamide (68 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol) and 1-bromo-2-chloroethane (124 μL,

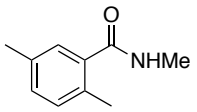
1.50 mmol) for 48 h. The title compound was obtained (62 mg, 83%) (^{1}H NMR yield: 89%). The product was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 146–147 °C (CH_2Cl_2/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 7.4 Hz, 2H), 5.81 (br, 1H), 2.97 (d, *J* = 5.0 Hz, 3H), 2.28 (s, 6H) ; ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.1, 137.6, 134.1, 128.6, 127.3, 26.2, 19.1; HRMS (APCI) Calcd for $C_{10}H_{14}NO^+$ $[M + H]^+$ 164.1070, found, 164.1077. The compound data was in good agreement with the literature data.[25]

***N*,2-Dimethylbenzamide (Table 5, entry 3):**



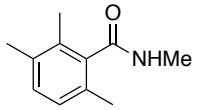
The general procedure A was applied to *N*-methylbenzamide (68 mg, 0.50 mmol) using MeMgBr in THF (1.55 mL, 1.00 M, 1.55 mmol). The title compound was obtained (45 mg, 60%) (^{1}H NMR yield: 69%). A dimethylated product was also obtained (11 mg, 13%) (^{1}H NMR yield: 16%). The title compound was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 63–64 °C (CH_2Cl_2/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28–7.25 (m, 2H), 7.18–7.12 (m, 2H), 6.14 (br, 1H), 2.91 (dd, *J* = 5.1, 1.4 Hz, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 136.4, 135.8, 130.8, 129.6, 126.6, 125.5, 26.4, 19.6; HRMS (APCI) Calcd for $C_9H_{12}NO^+$ $[M + H]^+$ 150.0913, found, 150.0918. The compound data was in good agreement with the literature data.[21]

***N*,2,5-Trimethylbenzamide (Table 5, entry 4):**



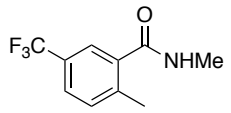
The general procedure A was applied to *N*,3-dimethylbenzamide (75 mg, 0.50 mmol). The title compound was obtained (56 mg, 69%) (^{1}H NMR yield: 81%). Dimethylated product was also obtained (5.3 mg, 6%) (^{1}H NMR yield: 9%). The title compound was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 122–123 °C (CH_2Cl_2/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (s, 1H), 7.09–7.05 (m, 2H), 6.05 (s, 1H), 2.92 (dd, *J* = 4.8, 1.1 Hz, 3H), 2.34 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 136.2, 135.0, 132.6, 130.7, 130.3, 127.4, 26.4, 20.7, 19.1; HRMS (APCI) Calcd for $C_{10}H_{14}NO^+$ $[M + H]^+$ 164.1070, found, 164.1077. The compound data was in good agreement with the literature data.[26]

***N*,2,3,6-Tetramethylbenzamide (Table 5, entry 4):**



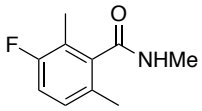
The title compound was further purified by recrystallization from CH_2Cl_2/hexane as a white amorphous solid. Melting Point: 139–140 °C (CH_2Cl_2/hexane); IR (ATR): 3254, 3086, 2924, 2852, 1634, 1568, 1559, 1508, 1457, 1316, 816 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.04 (d, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.7 Hz, 1H), 5.65 (br, 1H), 3.01 (d, J = 4.9 Hz, 3H), 2.26 (s, 3H), 2.22 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 137.9, 134.3, 132.5, 131.6, 130.0, 127.3, 26.4, 19.8, 19.0, 16.4; HRMS (APCI) Calcd for $C_{11}H_{16}NO^+$ $[M + H]^+$ 178.1232, found, 178.1225.

_N_,2-Dimethyl-5-(trifluoromethyl)benzamide (Table 5, entry 5):



The general procedure A was applied to *N*-methyl-3-(trifluoromethyl)benzamide (102 mg, 0.50 mmol) using $MnCl_2$•2LiCl in THF (5.0 μL, 0.10 M, 0.00050 mmol). The title compound was obtained (82 mg, 75%) (^{1}H NMR yield: 90%). The product was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 122–123 °C (CH_2Cl_2/hexane); IR (ATR): 3292, 3095, 2925, 2875, 1643, 1556, 1541, 1408, 1342, 1111, 712 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52–7.50 (m, 2H), 7.27 (d, J = 7.7 Hz, 1H), 6.46 (br, 1H), 2.91 (d, J = 4.9 Hz, 3H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.4, 140.2, 136.9, 131.3, 128.0 (q, $J_{C–F}$ = 32.4 Hz), 126.2 (q, $J_{C–F}$ = 4.2 Hz), 123.8 (q, $J_{C–F}$ = 270.0 Hz), 123.6 (q, $J_{C–F}$ = 3.6 Hz), 26.5, 19.6; ^{19}F NMR (470 MHz, $CDCl_3$) δ –65.7; HRMS (APCI) Calcd for $C_{10}H_{11}F_3NO^+$ $[M + H]^+$ 218.0793, found, 218.0793.

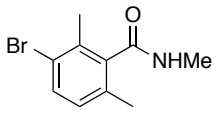
3-Fluoro-_N_,2,6-trimethylbenzamide (Table 5, entry 6):



The general procedure A was applied to 3-fluoro-*N*-methylbenzamide (77 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol) and 1-bromo-2-chloroethane (124 μL, 1.50 mmol) for 48 h. The title compound was obtained (66 mg, 73%) (^{1}H NMR yield: 79%). The product was further purified by

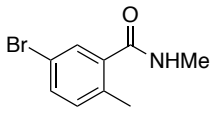
recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 133–134 °C (CH_2Cl_2/hexane); IR (ATR): 3280, 2989, 2957, 1652, 1636, 1558, 1542, 1409, 1320, 1242, 820 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.94–6.86 (m, 2H), 6.04 (br, 1H), 2.94 (d, J = 4.9 Hz, 3H), 2.20 (s, 3H), 2.14 (d, J = 2.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8 (d, $J_{C–F}$ = 3.0 Hz), 159.2 (d, $J_{C–F}$ = 241.8 Hz), 139.2 (d, $J_{C–F}$ = 3.6 Hz), 129.5 (d, $J_{C–F}$ = 4.2 Hz), 128.5 (d, $J_{C–F}$ = 7.8 Hz), 121.3 (d, $J_{C–F}$ = 18.0 Hz), 115.1 (d, $J_{C–F}$ = 22.2 Hz), 26.2, 18.5, 11.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ –123.3; HRMS (APCI) Calcd for $C_{10}H_{13}FNO^+$ $[M + H]^+$ 182.0981, found, 182.0973.

3-Bromo-*N*,2,6-trimethylbenzamide (Table 5, entry 7):



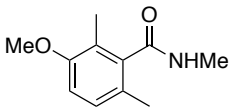
The general procedure A was applied to 3-bromo-*N*-methylbenzamide (107 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol) and 1-bromo-2-chloroethane (124 μL, 1.50 mmol) for 48 h. The title compound was obtained (77 mg, 64%) (^1H NMR yield: 70%). Monomethylated product was also obtained (19 mg, 16%) (^1H NMR yield: 21%). The title compound was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 174–175 °C (CH_2Cl_2/hexane); IR (ATR): 3283, 2998, 2954, 2922, 1653, 1557, 1542, 1412, 1311, 822 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.39 (d, J = 8.0 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.05 (br, 1H), 2.94 (d, J = 5.1 Hz, 3H), 2.29 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.1, 139.1, 133.7, 133.5, 132.5, 128.9, 122.6, 26.3, 19.9, 18.8; HRMS (APCI) Calcd for $C_{10}H_{13}{}^{79}BrNO^+$ $[M + H]^+$ 242.0175, found, 242.0170.

5-Bromo-*N*,2-dimethylbenzamide (Table 5, entry 7):



The title compound was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 139–140 °C (CH_2Cl_2/hexane); IR (ATR): 3284, 3001, 2953, 2924, 1645, 1550, 1542, 1404, 1319, 1038, 819 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 2.2 Hz, 1H), 7.41 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.09 (d, *J* = 8.0 Hz, 1H), 5.81 (br, 1H), 2.98 (d, *J* = 4.1 Hz, 3H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 138.2, 135.1, 132.7, 132.6, 129.6, 119.1, 26.7, 19.3; HRMS (APCI) Calcd for $C_9H_{11}{}^{79}BrNO^+$ $[M + H]^+$ 228.0024, found, 228.0023.

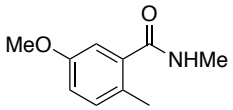
3-Methoxy-*N*,2,6-trimethylbenzamide (Table 5, entry 8):



The general procedure A was applied to 3-methoxy-*N*-methylbenzamide (83 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol) and 1-bromo-2-chloroethane (124 μL, 1.50 mmol) for 48 h. After purification, a mixture of di- and monomethylated product was obtained (78 mg; di-: 48%, mono-: 37%). The title compound was isolated after further purification by using gel permeation column chromatography (^1H NMR yield: 49%). The product was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 133–134 °C (CH_2Cl_2/hexane); IR (ATR): 3245, 2955, 2924, 2838, 1635, 1588, 1558, 1457, 1403, 1316, 1099, 811 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.98 (d, *J* = 8.3 Hz, 1H), 6.74 (d,

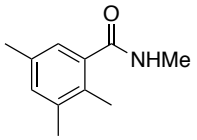
J = 8.3 Hz, 1H), 5.63 (br, 1H), 3.80 (s, 3H), 3.01 (d, *J* = 4.8 Hz, 3H), 2.24 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.9, 155.7, 138.8, 128.0, 125.8, 123.0, 110.5, 55.6, 26.4, 18.4, 12.8; HRMS (APCI) Calcd for $C_{11}H_{16}NO_2^+$ $[M + H]^+$ 194.1181, found, 194.1181.

5-Methoxy-*N*,2-dimethylbenzamide (Table 5, entry 8):



The title compound was isolated after further purification by using gel permeation column chromatography as a white amorphous solid (^{1}H NMR yield: 37%). The product was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 99–100 °C (CH_2Cl_2/hexane); IR (ATR): 3274, 2958, 2922, 2835, 1636, 1596, 1557, 1457, 1397, 1317, 1033, 824 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.08 (d, *J* = 8.3 Hz, 1H), 6.85 (d, *J* = 2.5 Hz, 1H), 6.82 (dd, *J* = 8.3, 2.8 Hz, 1H), 6.05 (br, 1H), 3.76 (s, 3H), 2.93 (d, *J* = 4.8 Hz, 3H), 2.31 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 157.3, 137.2, 131.8, 127.4, 115.3, 112.1, 55.3, 26.5, 18.7; HRMS (APCI) Calcd for $C_{10}H_{14}NO_2^+$ $[M + H]^+$ 180.1025, found, 180.1018.

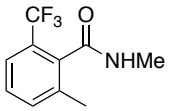
***N*,2,3,5-Tetramethylbenzamide (Table 5, entry 9):**



The general procedure A was applied to *N*,3,5-trimethylbenzamide (82 mg, 0.50 mmol). The title compound was obtained (74 mg, 84%) (^{1}H NMR yield: 90%). The product

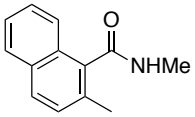
was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 142–143 °C (CH_2Cl_2/hexane); IR (ATR): 3307, 3010, 2950, 2924, 2857, 1635, 1604, 1541, 1457, 1324 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 6.98 (s, 1H), 6.93 (s, 1H), 5.97 (br, 1H), 2.92 (d, J = 4.8 Hz, 3H), 2.25–2.21 (m, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 137.5, 137.2, 134.7, 131.7, 130.6, 124.7, 26.4, 20.6, 20.0, 15.7; HRMS (APCI) Calcd for $C_{11}H_{16}NO^+$ $[M + H]^+$ 178.1232, found, 178.1225.

***N*,6-Dimethyl-2-(trifluoromethyl)benzamide (Table 5, entry 10):**



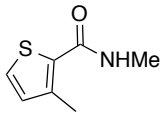
The general procedure A was applied to *N*-methyl-2-(trifluoromethyl)benzamide (102 mg, 0.50 mmol) for 48 h. The title compound was obtained in (87 mg, 81%) (^1H NMR yield: 92%). The product was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 148–149 °C (CH_2Cl_2/hexane); IR (ATR): 3272, 3090, 2918, 2858, 1646, 1557, 1542, 1318, 1116, 801 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.45–7.42 (m, 1H), 7.36–7.34 (m, 1H), 6.13 (s, 1H), 2.93 (d, J = 5.1 Hz, 3H), 2.30 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 136.5, 135.2 (d, $J_{C–F}$ = 2.4 Hz), 133.7, 128.8, 126.9 (q, $J_{C–F}$ = 30.6 Hz), 123.7 (q, $J_{C–F}$ = 272.4 Hz), 123.3 (q, $J_{C–F}$ = 10.2 Hz), 26.4, 18.9; ^{19}F NMR (470 MHz, $CDCl_3$) δ –62.4; HRMS (APCI) Calcd for $C_{10}H_{11}F_3NO^+$ $[M + H]^+$ 218.0793, found, 218.0797.

_N_,2-Dimethyl-1-naphthalenecarboxamide (Table 5, entry 11):



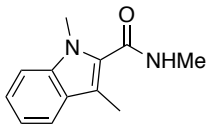
The general procedure A was applied to *N*-methyl-1-naphthalenecarboxamide (93 mg, 0.50 mmol). The title compound was obtained (78 mg, 78%) (^{1}H NMR yield: 89%). The product was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 188–189 °C (CH_2Cl_2/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 7.7 Hz, 1H), 7.70 (t, J = 9.1 Hz, 2H), 7.44–7.38 (m, 2H), 7.21 (d, J = 8.3 Hz, 1H), 6.07 (br, 1H), 2.95 (d, J = 4.8 Hz, 3H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.5, 133.8, 131.9, 131.5, 130.0, 128.6, 128.2, 127.8, 126.6, 125.2, 124.4, 26.3, 19.4; HRMS (APCI) Calcd for $C_{13}H_{14}NO^+$ $[M + H]^+$ 200.1070, found, 200.1072. The compound data was in good agreement with the literature data.[26]

_N_,3-Dimethyl-2-thiophenecarboxamide (Table 5, entry 12):



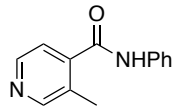
The general procedure A was applied to *N*-methyl-2-thiophenecarboxamide (71 mg, 0.50 mmol). The title compound was obtained (46 mg, 60%) as a yellow oil (^{1}H NMR yield: 68%). IR (ATR): 3307, 3102, 2935, 1626, 1543, 1518, 1408, 1287 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 (d, J = 5.1 Hz, 1H), 6.87 (d, J = 4.9 Hz, 1H), 6.02 (br, 1H), 2.95 (d, J = 4.8 Hz, 3H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 140.7, 131.8, 130.9, 126.1, 26.6, 15.5; HRMS (APCI) Calcd for $C_7H_{10}NOS^+$ $[M + H]^+$ 156.0478, found, 156.0484.

_N_,1,3-Trimethyl-1_H_-indole-2-carboxamide (Table 5, entry 13):



The general procedure A was applied to *N*,1-dimethyl-1*H*-indole-2-carboxamide (93 mg, 0.50 mmol). The title compound was obtained (61 mg, 61%) (^{1}H NMR yield: 70%). The product was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 188–189 °C (CH_2Cl_2/hexane); IR (ATR): 3306, 3003, 2924, 2853, 1608, 1541, 1457, 1360, 738 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.31–7.26 (m, 2H), 7.14–7.10 (m, 1H), 5.97 (br, 1H), 3.81 (s, 3H), 3.02 (d, *J* = 4.8 Hz, 3H), 2.42 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.7, 137.7, 130.3, 127.1, 123.8, 119.8, 119.4, 111.6, 109.7, 31.1, 26.4, 10.0; HRMS (APCI) Calcd for $C_{12}H_{14}N_2O^+$ $[M]^+$ 202.1101, found, 202.1110.

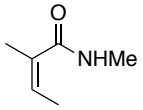
3-Methyl-_N_-phenyl-4-pyridinecarboxamide (Table 5, entry 14):



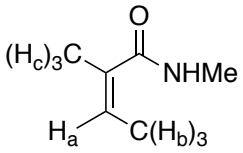
The general procedure A was applied to *N*-phenyl-4-pyridinecarboxamide (99 mg, 0.50 mmol). The title compound was obtained (84 mg, 79%) (^{1}H NMR yield: 89%). The product was further purified by recrystallization from CH_2Cl_2/hexane as yellow needles. Melting Point: 108–109 °C (CH_2Cl_2/hexane); IR (ATR): 3293, 2989, 2955, 1654, 1558, 1542, 1406, 1321, 747, 689 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 10.5 (br, 1H), 8.56 (br, 2H), 7.71 (d, *J* = 7.7 Hz, 2H), 7.44 (d, *J* = 4.6 Hz, 1H), 7.35 (t, *J* = 7.7 Hz, 2H),

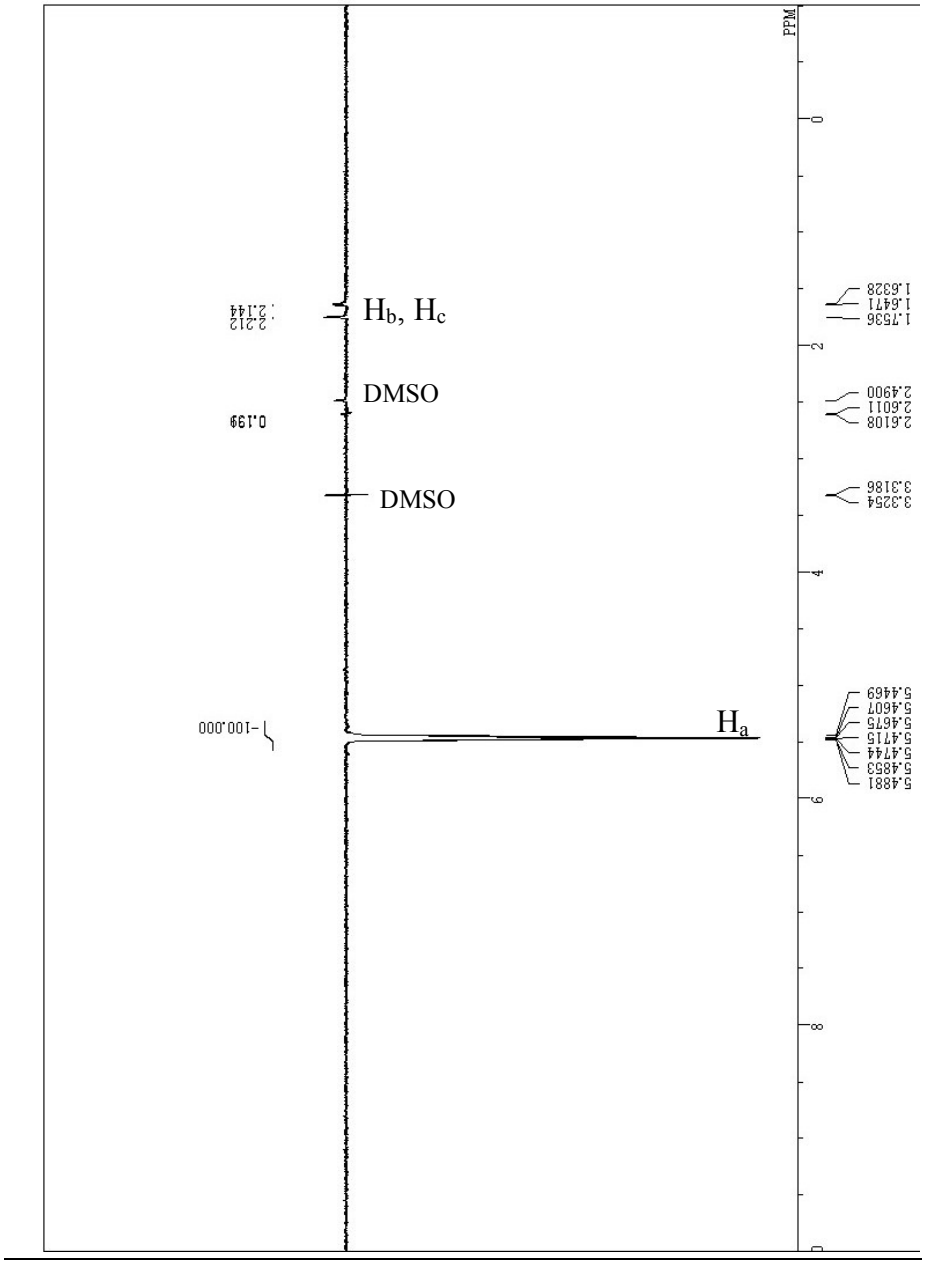
7.11 (t, *J* = 7.1 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.7, 151.9, 147.4, 143.3, 137.5, 130.7, 129.2, 125.1, 120.4, 120.1, 16.5; HRMS (APCI) Calcd for $C_{13}H_{13}N_2O^+$ $[M + H]^+$ 213.1028, found, 213.1031.

(*Z*)-*N*,2-Dimethyl-2-butenamide (Table 5, entry 15):

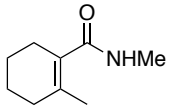


The general procedure A was applied to *N*-methylmethacrylamide (50 mg, 0.50 mmol). The title compound was obtained (37 mg, 65%) as a colorless oil (^{1}H NMR yield: 80%). IR (ATR): 3291, 3079, 2945, 1626, 1523, 1456, 1407, 829 cm^{-1}; ^{1}H NMR (500 MHz, DMSO): δ 7.65 (br, 1H), 5.47 (qd, *J* = 6.9, 1.4 Hz, 1H), 2.61 (dd, *J* = 4.5, 1.1 Hz, 3H), 1.76 (d, *J* = 1.4 Hz, 3H), 1.64 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.8, 132.7, 127.4, 25.9, 20.7, 15.0; HRMS (APCI) Calcd for $C_6H_{12}NO^+$ $[M + H]^+$ 114.0919, found, 114.0915. The stereochemistry of the compound was determined by NOE experiments, using $CDCl_3$ as a solvent. When signal Ha at δ = 5.47 (qd, *J* = 6.9, 1.4 Hz, 1H) was irradiated, the two methyl signals H_b and H_c at δ = 1.76 (d, *J* = 1.4 Hz, 3H) and δ =1.64 (d, *J* = 6.9 Hz, 3H) exhibited an enhancement by 2.1% and 2.2%.





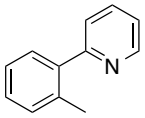
***N*,2-Dimethyl-1-cyclohexene-1-carboxamide (Table 5, entry 16):**



The general procedure A was applied to *N*-methyl-1-cyclohexene-1-carboxamide (70 mg, 0.50 mmol). The title compound was obtained (68 mg, 88%) (^{1}H NMR yield: 93%).

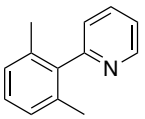
The product was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 63–64 °C (CH_2Cl_2/hexane); IR (ATR): 3299, 2929, 2856, 1616, 1522, 1473, 1457, 1397 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 5.82 (br, 1H), 2.85 (d, *J* = 4.8 Hz, 3H), 2.20–2.19 (m, 2H), 1.99–1.97 (br, 2H), 1.75 (s, 3H), 1.61–1.60 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6, 134.0, 129.3, 31.1, 26.8, 25.9, 22.3, 22.1, 20.7; HRMS (APCI) Calcd for $C_9H_{16}NO^+$ $[M + H]^+$ 154.1226, found, 154.1232.

2-(2-Methylphenyl)pyridine (Table 6, entry 1):



The general procedure B was applied to 2-phenylpyridine (78 mg, 0.50 mmol). The title compound was obtained (54 mg, 64%) as a yellow oil (^1H NMR yield: 80%). A dimethylated product was also obtained (7.4 mg, 8%) as a yellow oil (^1H NMR yield: 10%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.69 (d, *J* = 4.6 Hz, 1H), 7.73 (td, *J* = 7.2, 1.7 Hz, 1H), 7.39 (d, *J* = 6.8 Hz, 2H), 7.31–7.21 (m, 4H), 2.36(s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 149.1, 140.3, 136.1, 135.6, 130.6, 129.5, 128.2, 125.8, 124.0, 121.5, 20.2; HRMS (APCI) Calcd for $C_{12}H_{12}N^+$ $[M + H]^+$ 170.0964, found, 170.0964. The compound data was in good agreement with the literature data.[27]

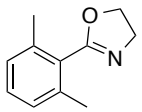
2-(2,6-Dimethylphenyl)pyridine (Table 6, entry 1):



^1H NMR (500 MHz, $CDCl_3$): δ 8.72 (d, *J* = 4.8 Hz, 1H), 7.76 (td, *J* = 7.7, 1.7 Hz, 1H),

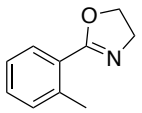
7.27–7.09 (m, 3H), 7.10 (d, J = 7.7 Hz, 2H), 2.04 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.9, 149.7, 140.5, 136.2, 135.7, 127.8, 127.5, 124.4, 121.6, 20.2; HRMS (APCI) Calcd for $C_{13}H_{14}N^+$ $[M + H]^+$ 184.1126, found, 184.1134. The compound data was in good agreement with the literature data.[28]

2-(2,6-Dimethylphenyl)-4,5-dihydrooxazole (Table 6, entry 2):



The general procedure B was applied to 2-phenyl-4,5-dihydrooxazole (74 mg, 0.50 mmol) at 40 °C. The title compound was obtained (23 mg, 26%) as a yellow oil (^{1}H NMR yield: 41%). A dimethylated product was also obtained (11 mg, 14%) as a yellow oil (^{1}H NMR yield: 19%). IR (ATR): 2965, 1660, 1465, 1349, 1239, 1047, 774 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (t, J = 7.4 Hz, 1H), 7.03 (d, J = 7.7 Hz, 2H), 4.41 (t, J = 9.4 Hz, 2H), 4.09 (t, J = 9.7 Hz, 2H), 2.32 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 136.9, 129.3, 128.9, 127.3, 67.1, 55.1, 19.7; HRMS (APCI) Calcd for $C_{11}H_{14}NO^+$ $[M + H]^+$ 176.1070, found, 176.1070.

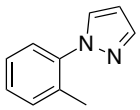
2-(2-Methylphenyl)-4,5-dihydrooxazole (Table 6, entry 2):



^{1}H NMR (500 MHz, $CDCl_3$): δ 7.80 (dd, J = 7.4, 0.8 Hz, 1H), 7.33 (td, J = 7.4, 1.1 Hz, 1H), 7.24–7.20 (m, 2H), 4.38 (t, J = 9.7 Hz, 2H), 4.10 (t, J = 9.7 Hz, 2H), 2.59 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 138.7, 131.1, 130.5, 129.8, 127.1, 125.5, 66.8,

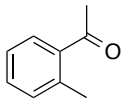
55.4, 21.7; HRMS (APCI) Calcd for $C_{10}H_{12}NO^+$ $[M + H]^+$ 162.0919, found, 162.0916. The compound data was in good agreement with the literature data.[28]

1-(2-Methylphenyl)pyrazole (Table 6, entry 3):



The general procedure B was applied to 1-phenylpyrazole (72 mg, 0.50 mmol) at 40 °C. The title compound was obtained (25 mg, 32%) as a yellow oil (^{1}H NMR yield: 47%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 1.7 Hz, 1H), 7.60 (d, *J* = 2.3 Hz, 1H), 7.33–7.26 (m, 4H), 6.44 (t, *J* = 2.0 Hz, 1H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.2, 134.0, 133.7, 131.2, 130.5, 128.3, 126.5, 126.1, 106.1, 18.0; HRMS (APCI) Calcd for $C_{10}H_{11}N_2^+$ $[M + H]^+$ 159.0917, found, 159.0918. The compound data was in good agreement with the literature data.[29]

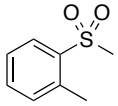
1-(2-Methylphenyl)ethanone (Table 6, entry 4):



The general procedure B was applied to benzonitrile (52 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol). The reaction was quenched by the addition of a saturated aqueous solution of NH_4Cl (1 mL) and a 3M aqueous solution of HCl (2 mL). The resulting mixture was stirred for 1 h. After extraction, the combined organic layers were passed over a Florisil pad. The title compound was obtained (33 mg, 50%) as a yellow oil (^{1}H NMR yield: 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.69 (d, *J* = 7.7 Hz, 1H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.28–7.24 (m, 2H), 2.58 (s, 3H), 2.53 (s, 3H);

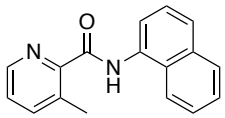
^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 138.1, 137.3, 131.7, 131.2, 129.1, 125.4, 29.3, 21.3; HRMS (APCI) Calcd for $C_9H_{11}O^+$ $[M + H]^+$ 135.0804, found, 135.0798. The compound data was in good agreement with the literature data.[30]

1-Methyl-2-(methylsulfonyl)benzene (Table 6, entry 5):



The general procedure B was applied to methyl phenyl sulfone (78 mg, 0.50 mmol) using MeMgBr in THF (2.75 mL, 1.00 M, 2.75 mmol) and 2,3-dibromobutane (184 μL, 1.50 mmol) instead of 1-bromo-2-chloroethane. The title compound was obtained (19 mg, 22%) as a yellow oil (^{1}H NMR yield: 34%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (dd, *J* = 7.7, 0.9 Hz, 1H), 7.53 (td, *J* = 7.4, 1.1 Hz, 1H), 7.04–7.34 (m, 2H), 3.08 (s, 1H), 2.72 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6, 137.5, 133.7, 132.7, 129.2, 126.7, 43.6, 20.3; HRMS (APCI) Calcd for $C_8H_{11}O_2S^+$ $[M + H]^+$ 171.0474, found, 171.0482. The compound data was in good agreement with the literature data.[31]

3-Methyl-*N*-(naphthalen-1-yl)picolinamide (Scheme 4):



In an oven-dried Schlenk tube were placed *N*-(1-naphthyl)picolinamide (50 mg, 0.20 mmol) and a solution of $MnCl_2$•2LiCl in THF (40 μL, 0.50 M, 0.020 mmol). MeMgBr in THF (0.77 mL, 1.04 M, 0.80 mmol) and 1-bromo-2-chloroethane (33 μL, 0.4 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 24 h, and then it

was quenched by the addition of a saturated aqueous solution of NH_4Cl (1 mL) and small amount of water. After extraction with EtOAc (3 × 3 mL), the combined organic layers were passed over a silica gel pad with ethyl acetate, and the resulting solution was concentrated under reduced pressure. The crude product was purified by silica gel column chromatography (hexane/EtOAc = 5:1) to afford the title compound (49 mg, 92%). The product was further purified by recrystallization from CH_2Cl_2/hexane as white needles. Melting Point: 143–144 °C (CH_2Cl_2/hexane); IR (ATR): 3328, 3011, 2924, 2853, 1688, 1525, 1497, 1340, 792, 772 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 11.0 (br, 1H), 8.56 (dd, J = 4.3, 0.8 Hz, 1H), 8.36 (d, J = 7.4 Hz, 1H), 8.09 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 8.0 Hz, 1H), 7.70–7.69 (m, 2H), 7.60–7.51 (m, 3H), 7.42 (dd, J = 7.7, 4.6 Hz, 1H), 2.87 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 147.0, 145.5, 141.4, 136.3, 134.1, 132.7, 128.8, 126.6, 126.1 (2C), 126.0, 125.9, 124.8, 120.7, 118.6, 20.9; HRMS (APCI) Calcd for $C_{17}H_{15}N_2O^+$ $[M + H]^+$ 263.1184, found, 263.1186.

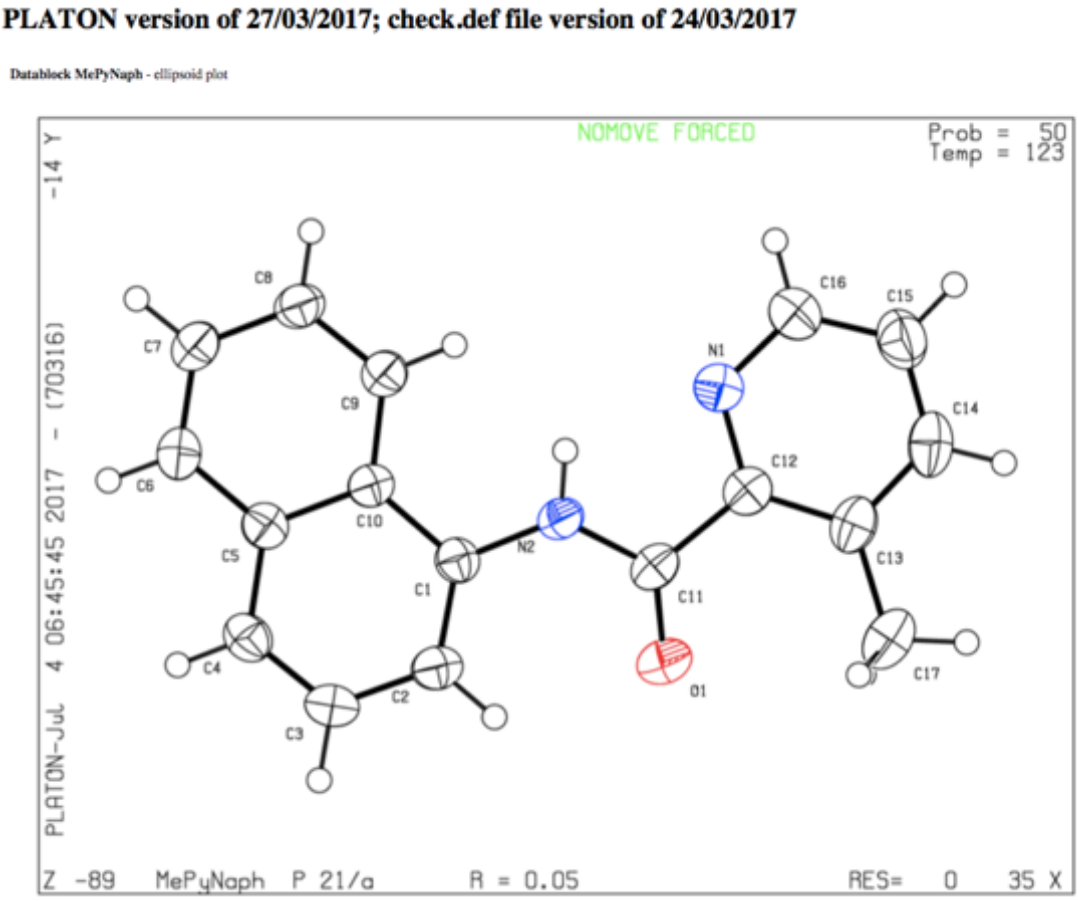
• X-ray crystallographic analysis

The diffraction images for X-ray crystallographic analysis were collected on a Rigaku Rapid II diffractometer equipped with an imaging plate (IP) using Cu Kα (λ = 1.5419 Å) radiation. The positional and thermal parameters were refined by the full-matrix least-squares method using SHELXL-2014/7 program.[32] The Yadokari-XG software was used for refinement of the structure.[33]

CCDC 1560075 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Crystal data for 3-methyl-*N*-(naphthalen-1-yl)picolinamide (CCDC 1560075)

Formula	$C_{17}H_{14}N_2O$
Formula weight	262.30
Measurement temperature	123(2) K
Crystal system	monoclinic
Space group	P 21/a
Lattice parameters	a = 14.4154(6) Å
	b = 6.0240(2) Å
	c = 15.0935(6) Å
	α = 90°
	β = 94.616(7)°
	γ = 90°
Volume	1306.44(9) Å^3
Z value	4
Density (calculated)	1.334 g/cm^3
F(000)	552.0
Number of reflections measured	13222
Number of unique reflections	2385
R_{int}	0.0514
Number of observed reflections ($I > 2\sigma(I)$)	1615
Goodness of fit indicator	1.040
Final R_1 indices [$I > 2\sigma(I)$] (R_{obs}, wR_{obs})	0.0517, 0.1215
R indices [all data] (R_{all}, wR_{all})	0.0846, 0.1370
Largest diff peak and hole	0.171/-0.197 e·Å^{-3}



Reaction on Gram Scale

In a 100 mL oven-dried two-necked round bottom flask were placed *N*-methyl-3-(trifluoromethyl)benzamide (1.02 g, 5.0 mmol) and MeMgBr in THF (20 mL, 1.00 M, 20 mmol) was added at 0 °C. A solution of $MnCl_2$•2LiCl in THF (10 µL, 0.50 M, 0.0050 mmol) and 1-bromo-2-chloroethane (0.83 mL, 10 mmol) were sequentially added at 25 °C. The reaction mixture was stirred at 25 °C for 24 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (30 mL) and a small amount of water. After extraction with EtOAc (3 × 50 mL), the combined organic layers were passed over a silica gel pad with EtOAc, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^{1}H NMR

in the presence of 1,1,2,2-tetrachloroethane as an internal standard (product: 90%, recovery: 10%). The crude product was purified by recrystallization from CH_2Cl_2/hexane to afford the desired product as a white solid (0.74 g, 68%).

Reaction with High Catalyst Efficiency

In an oven-dried Schlenk tube were placed *N*-methyl-3-(trifluoromethyl)benzamide (102 mg, 0.50 mmol) and a solution of $MnCl_2$•2LiCl in THF (5.0 μL, 0.10 M, 0.00050 mmol). MeMgBr in THF (2.00 mL, 1.00 M, 2.00 mmol) and 1-bromo-2-chloroethane (83 μL, 1.0 mmol) were sequentially added. The reaction mixture was stirred at 25 °C for 48 h, and then it was quenched by the addition of a saturated aqueous solution of NH_4Cl (3 mL) and small amount of water. After extraction with EtOAc (3 × 5 mL), the combined organic layers were passed over a silica gel pad with EtOAc, and the resulting solution was concentrated under reduced pressure. The crude mixture was analyzed by ^1H NMR in the presence of 1,1,2,2-tetrachloroethane as an internal standard (product: 59%, recovery: 41%).

KIE Experiment

In two oven-dried Schlenk tubes were placed *N*-methylbenzamide (27 mg, 0.20 mmol) and *N*-methyl-2,3,4,5,6-pentadeueriobenzamide (28 mg, 0.20 mmol), respectively. A solution of $MnCl_2$•2LiCl in THF (20 μL, 0.10 M, 0.0020 mmol), tridecane (36 mg, 0.20 mmol), MeMgBr in THF (1.1 mL, 1.00 M, 1.1 mmol), and 1-bromo-2-chloroethane (50 μL, 0.60 mmol) were sequentially added to each reaction tube. The two reaction mixtures were stirred at 25 °C and sampled after 1.5 h, 2 h, 2.5 h, and 3 h. The samples were analyzed by GC analysis in the presence of tridecane as an internal standard.

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Chapter 3

Chromium-Catalyzed Directed C–H Functionalization in the Presence of Organoaluminum Reagent

本章については，５年以内に雑誌等で刊行予定のため，非公開.

Chapter 4

Summary and Outlook

Transition-metal-catalyzed directed C–H functionalization is an attractive method for straightforward and regioselective transformations of organic compounds. However, for most of these reactions precious transition metals, a bidentate directing group, an engineered ligand, or harsh reaction conditions are required. During my Ph.D. course studies, I have developed practical manganese or chromium catalyzed C–H functionalization reactions using simple catalytic system without recourse of sophisticated ligands.

In Chapter 2, manganese-catalyzed C–H methylation with Grignard reagent was described. The catalytic methylation of substrates possessing various monodentate directing groups proceeded under mild reaction conditions with high catalytic efficiency without any external ligands. Stoichiometric reactions suggested that a high-valent organomanganese species is the active species for C–H bond activation.

In Chapter 3, chromium-catalyzed C–H functionalization with various electrophiles and C–H dimerization of carboxamides in the presence of an organoaluminum reagent were described. These reactions took place in the absence of an external ligand, a complicated substrate such as a substrate possessing preinstalled bidentate directing group, or an expensive reagent. Several experiments suggested that a bischromacycle is formed as a key intermediate.

In these studies, the observed distinct reactivity between manganese and chromium catalysts in the presence of methyl organometallic reagents suggested that these two metals form different metallacycle intermediates.

The ubiquitous nature and low cost of these elements in combination with simplicity of the catalyst system make them ideal catalyst for step efficient organic synthesis. These catalytic systems would provide a practical functionalization,

especially late-stage functionalization for drug compounds.