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Author(s)	王, 晨安
Citation	大阪大学, 2021, 博士論文
Version Type	VoR
URL	https://doi.org/10.18910/82205
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Osaka University

Doctoral Dissertation

Studies on Ruthenium(II)-Catalyzed C-H Bond Functionalization Utilizing *N*-Monodentate or *N*,*N*′-Bidentate Directing Group Assistance

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January 2021

Graduate School of Engineering,

Osaka University

Preface and Acknowledgements

The research presented in this dissertation were carried out under the direction of Professor Naoto Chatani of the Department of Applied Chemistry, Faculty of Engineering, Osaka University between April 2018 and March 2021. The dissertation is concerned with the development of the ruthenium(II)-catalyzed C-H functionalization utilizing *N*-monodentate or *N*,*N*'-bidentate directing group.

This dissertation would not have been able to complete without help and support from many people. Here, I would like to express my sincerest appreciation to all of them.

First of all, special acknowledgment is given to Professor Naoto Chatani. I would like to present my thanks to him for giving me precious chance to study in his laboratory, with his patient instruction and constructive suggestions.

I would like to thanks Dr. Yoshiya Fukumoto and Dr. Yusuke Ano for their instructive suggestions and discussions, which helped me a lot.

I wish to thanks Ms. Junko Ohmagari for her kindly help and support.

I would like to express my sincere thanks to the members of the Chatani Group. Since I joined Chatani lab in 2018, I have been supported by a lot of people: Mr. Yoshihiro Masuya, Mr. Takuya Igarashi, Mr.Yasuaki Iyori, Mr. Akira Haito, Mr. He Qiyuan, Mr. Masaya Higashino, Mr. Nao Matsubara, Mr. Yuki Amano, Ms. Akane Sasagawa, Mr. Ken Yamazaki, Mr. Kenjiro Takahashi, Mr. Shunsuke Ando, Mr. Yasuhiro Takami, Ms. Rina Ueno, Mr. Hisayasu Ishibashi, Mr. Shizuki monda, Mr. Itsuki Nohira, Mr. Kazuki Azumagawa, Mr. Natsuki Kawai, Ms. Nozomi Ohara, Mr Keiki Enomoto, Yuki Yamada, Ms Haruka Kawakami, Ms Aoi Morishige, Mr. Daichi Takahashi, Mr Hikaru Noguchi, Mr Akihisa Matsuura, Mr

Tianhao Zhang, Mr Ryosuke Nagamune, Mr Kunpei Nishimura, Mr Tatsuya Hirano, Mr Haruki Hirosawa.

Furthermore, I express my appreciation to Dr. Yadagiri Komagara, Dr. Aymen Skhiri, Dr. Shrikant Kahake Manmathappa, Dr. Sanjit Kumar Mahato, Ms. Amrita DAS, Ms. Meria Ronge who performed research in the Chatani laboratory as visiting fellows or as postdoctoral fellows.

Finally, I would like to express my deepest gratitude to my parents, Mr. Hanwei Wang and Ms. Chang Chen, and my beautiful wife, Ms. Ziyin He.

Suita, Osaka

January 2021

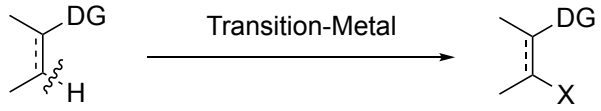
Chenan
Wang

Contents

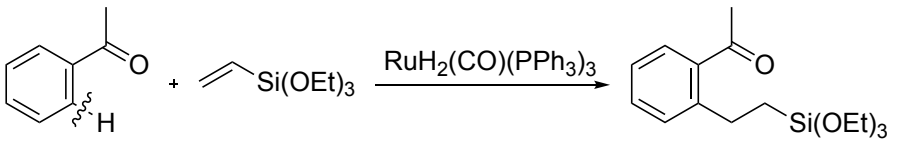
General Introduction

Transition-metal-catalyzed C-H functionalization reactions that proceed via chelation assistance have attracted considerable attention, since they are a successful strategy for the construction of C–C, C-N, C-O, and C-halogen bonds with excellent reactivity and regioselectivity (Scheme 1).[1] In this context, direct C-H functionalization reactions have been recognized as one of successful strategies for the preparation of organic compounds due to their high efficiency and atom economy.

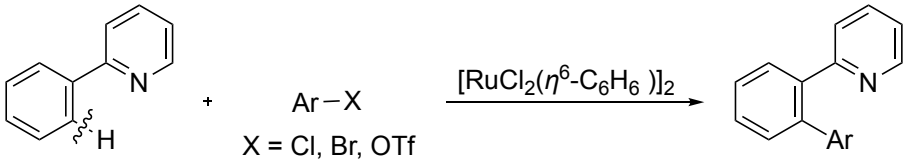
Scheme 1. Transition-metal-catalyzed C-H functionalization reactions



In 1993, Murai reported on the first synthetically useful example of the chelation-assisted alkylation of *ortho* C-H bonds in aromatic ketones with alkenes, which was catalyzed by a low-valent ruthenium complex, $RuH_2(CO)(PPh_3)_3$ (eq 1).[2] Following this pioneering work, Murai reported on a series of Ru-catalyzed C-H alkylations of aromatic compounds bearing various directing groups.[3] The formation of five-membered metallacycle was proposed as a key intermediate in this reaction. Transition-metal-catalyzed chelation-assisted C-H functionalization reactions of aromatic compounds have been widely explored since then. In 2001, Oi and Inoue reported on the first example of the Ru(II)-catalyzed C-H arylation of 2-arylpyridines with aryl halides (eq 2).[4] Ru(II)-catalyzed C-H functionalizations have been extensively studied since then.[1] In the Ru(0) catalytic system, the activation of C-H bonds is proposed to proceed through the oxidative addition of a C-H bond. On the other hand, in the Ru(II) catalytic system, concerted metalation deprotonation (CMD) or base-assisted internal electrophilic substitution (BIES) is proposed for the activation of a C-H bond.



(1)

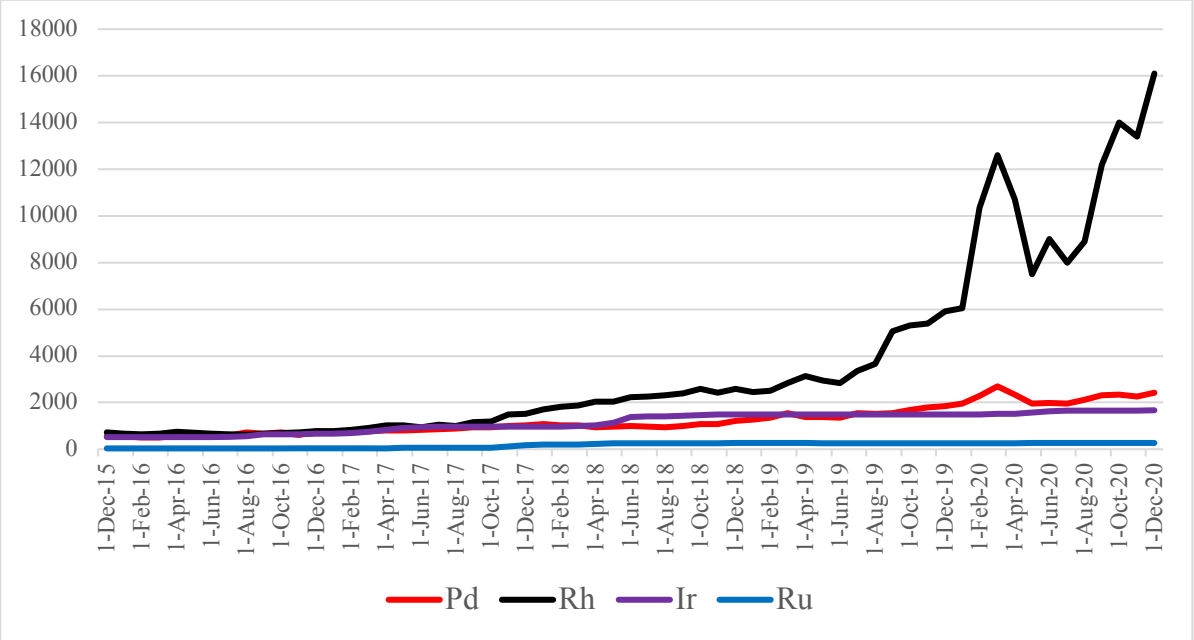


(2)

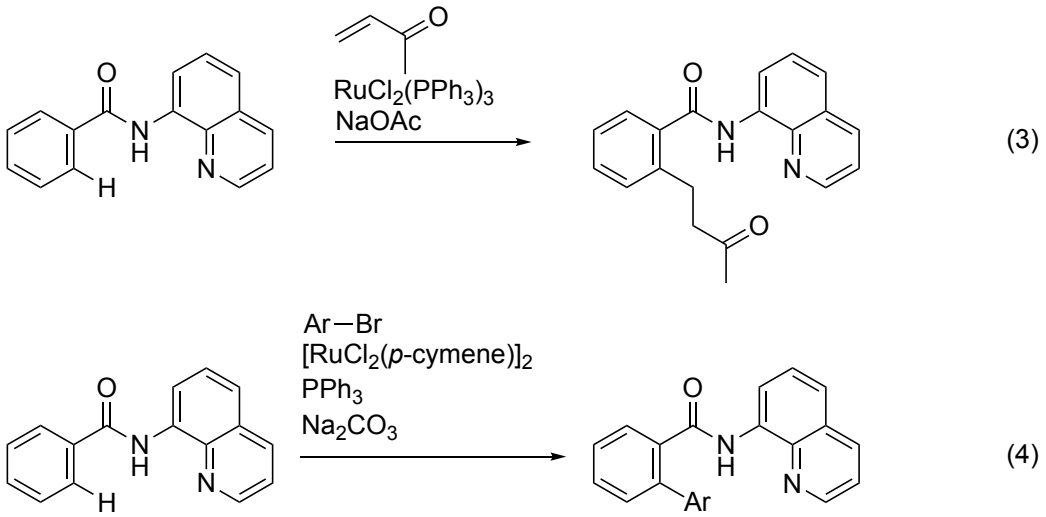
Various metals, such as palladium, rhodium, iridium, and ruthenium have been widely used as catalysts in C-H functionalization reactions. Among them, ruthenium ($270/Oz) is approximately 9 times less expensive than palladium ($2,420/Oz), 60 times less expensive than

rhodium ($16,100/Oz), and 6 times less expensive than iridium ($1,670/Oz) (Fig. 1).[5] Ruthenium catalysts are one of the less expensive metal complexes among noble metal complexes which have been used for the synthesis of useful and complex molecules from structurally simple compounds via C-H activation.

Figure 1. Monthly prices of Pd, Rh, Ir, Ru between 01 Dec 2015 ~01 Dec 2020



In 2013, our group reported on the first example of the Ru(II)-catalyzed alkylation of aromatic amides with *α,β*-unsaturated ketones with the aid of an 8-aminoquinoline as an *N,N* bidentate directing group (eq 3).[6] In the same year, our group also reported on the first example of the Ru(II)-catalyzed arylation of aromatic amides with aryl halides, by taking advantage of an 8-aminoquinoline directing group (eq 4).[7]

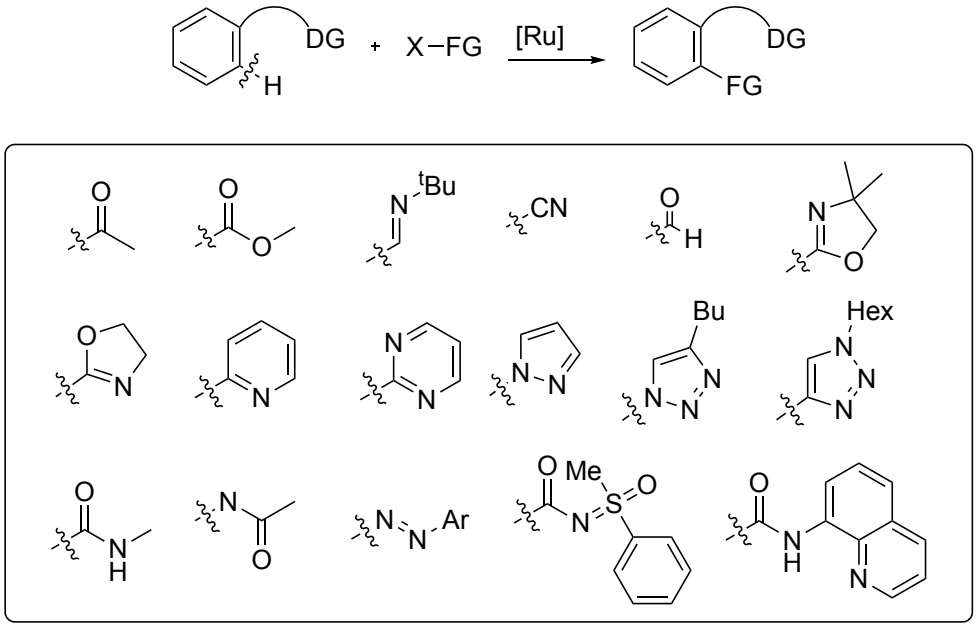


(3)

(4)

Various directing groups have been designed and used for the Ru-catalyzed C-H functionalization of aromatic compounds. Significant progress was made by Murai,[2] Chatani,[2] Kakiuchi,[1b] Oi,[1n] Dixneuf,[1a] Ackermann,[1i,o] Jeganmohan,[1m] as well as others (Scheme 2). Nevertheless, much less work has been done on the Ru-catalyzed C-H functionalization of aromatic compounds, compared with other noble metals, while ruthenium catalysts show a high potential, low-cost, stability, excellent reactivities, and selectivities. In addition, ruthenium complexes can exist in diverse oxidation states, which provides opportunities to design new types of transformations. Therefore, the development of Ru-catalyzed C-H activation continues to be an attractive area of research in transition-metal-catalyzed C-H functionalization reactions. The most pressing need in this area is the design new chelation systems that can be applied to the development of new Ru-catalyzed C-H functionalization reactions.

Scheme 2. Representative monodentate and bidentate directing groups



From this viewpoint, the objective of this study was to develop a series of ruthenium (II)-catalyzed C-H functionalization reactions utilizing a new *N*-monodentate as well as an 8-aminoquinoline (*N*,*N*′-bidentate) directing group. 2-Acylimidazole derivatives have been extensively used in organic synthesis, including in enantioselective transformations because they are useful molecular building blocks for accessing a variety of bioactive compounds.[8] In addition, it is also known that the imidazole moiety can be easily installed and converted into the corresponding acid, esters, amides, in a simple operation after the reaction.[9] However, 2-acylimidazole derivatives have not been used in C-H functionalization before our group reported on the Ir-catalyzed C-H alkynylation of 2-acylimidazoles.[10] This dissertation contains three parts.

Chapter 1 discusses the ruthenium(II)-catalyzed *ortho*-C-H alkylation of C(sp^2)-H bonds in aromatic amides containing an 8-aminoquinline moiety as a bidentate directing group with vinylsilanes.

Chapter 2 discusses the ruthenium(II)-catalyzed *ortho*-C-H alkylation of C(sp^2)-H bonds 2-aroyl-imidazoles with carboxylic acids. In these reactions, an imidazole moiety functions as an efficient *N*-monodentate directing group.

Chapter 3 discusses the ruthenium(II)-catalyzed *ortho*-C-H alkylation of C(sp^2)-H bonds 2-aroyl-imidazoles with aryl halides.

Finally, the findings are summarized in the conclusion section of the dissertation.

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Chapter 1

Ruthenium(II)-Catalyzed Alkylation of C-H Bonds in Aromatic Amides Containing an 8-Aminoquinoline Moiety as the *N*,*N*′-Directing Group

1.1 Introduction

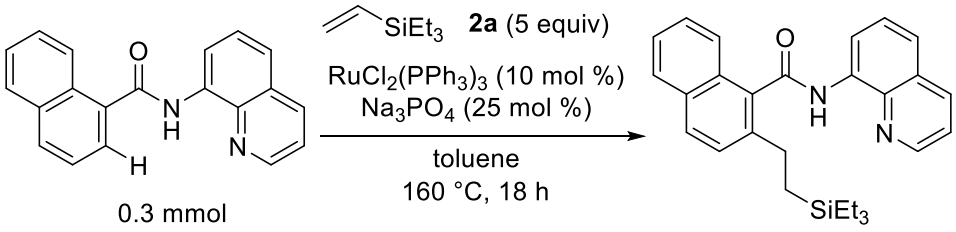
C-H alkylation reactions have attracted considerable attention as a successful strategy for preparing alkyl-substituted aromatic compounds, because of the atom economy. Since 1993, Murai and co-workers reported a low-valent ruthenium complex catalyzes the C-H alkylation of aromatic compounds with unactivated alkenes bearing various directing groups.[1] Following this report, Darses and Genet reported that a low-valent Ru complexes can be generated from $[RuCl_2(p\text{-cymene})]_2$, sodium formate, and PPh_3, which also shows a high catalytic activity.[2] Significant practical progress was achieved by Ackermann reported the Ru(II)-catalyzed C-H alkylation with alkenes bearing various *N*-heterocycles.[3] However, the Ru catalysts was used in C-H alkylation of aromatic amides with unactivated alkenes only less reports. Murai reportd Ru-catalyzed C-H silylation of aromatic amides with vinylsilanes. No alkylated product was obtained when an amide was used as a directing group. Recently, significant progress was made by Chatani[4], Ackermann[5] and Jeganmoha[6]. Therefore, I initiated research Ru(II)-catalyzed C-H alkylation reactions with alkenes.

Chapter 1 describes the Ru(II)-catalyzed *ortho*-C–H alkylation of aromatic amides that have an 8-aminoquinolinyl directing group with vinylsilanes. This reaction provides a new opportunity for introducing a silyl group into an organic compound.

1.2 Results and Discussion

Motivated by previous works in general introduction, Ruthenium(II)-catalyzed C-H alkylation of aromatic amides with vinylsilanes bearing a various type of bidentate directing groups were examined. The reaction of aromatic amide **1a** (0.3 mmol) with vinylsilane **2a** (1.5 mmol) with $RuCl_2(PPh_3)_3$ (0.03 mmol) as the catalyst and Na_3PO_4 (0.075 mmol) as the base in toluene (0.75 mL) at 160 °C for 18 h gave the alkylation product **3a** in 78% isolated yield (entry 1 in Table 1). The use of other bases did not improve the product yield (entries 2−5). The use of a PPh_3 ligand had not improved the yield.

Table 1. The Ru-Catalyzed C−H alkylation of **1a** with tirethylvinylsilane (**2a**).



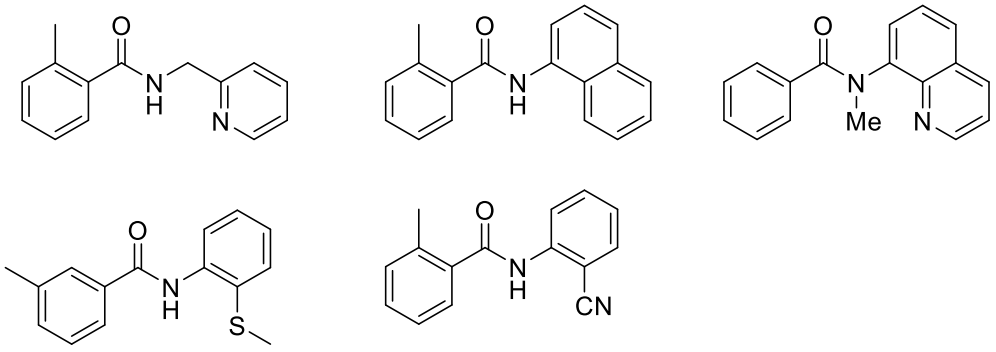
0.3 mmol **1a** → **3a**

entry	Deviation from the standard reaction conditions	yields/%[a]	
		3a	**1a**
1	None	80 (78)	0
2	NaOAc (0.075 mmol)	38	30
3	NaOPiv (0.075 mmol)	60	20
4	NaO_2CMes (0.075 mmol)	19	61
5	AgOAc (0.075 mmol)	0	51
6	NaOAc (0.075mmol), PPh_3 (0.09 mmol)	39	30

[a] NMR yields. The number in parenthesis is the isolated yield of **3a**.

The effect of the various directing groups were examined. No deign product was produced when others directing group were used, such as 2-pyridinylmethylamine, 2-naphthylamine, N-methyl-N-(quinolin-8-yl)benzamide, 2-methylthioaniline, or 2-cyanoaniline (Scheme 1). It therefore appears that both a quinoline nitrogen and an amide NH are essential for this reaction.

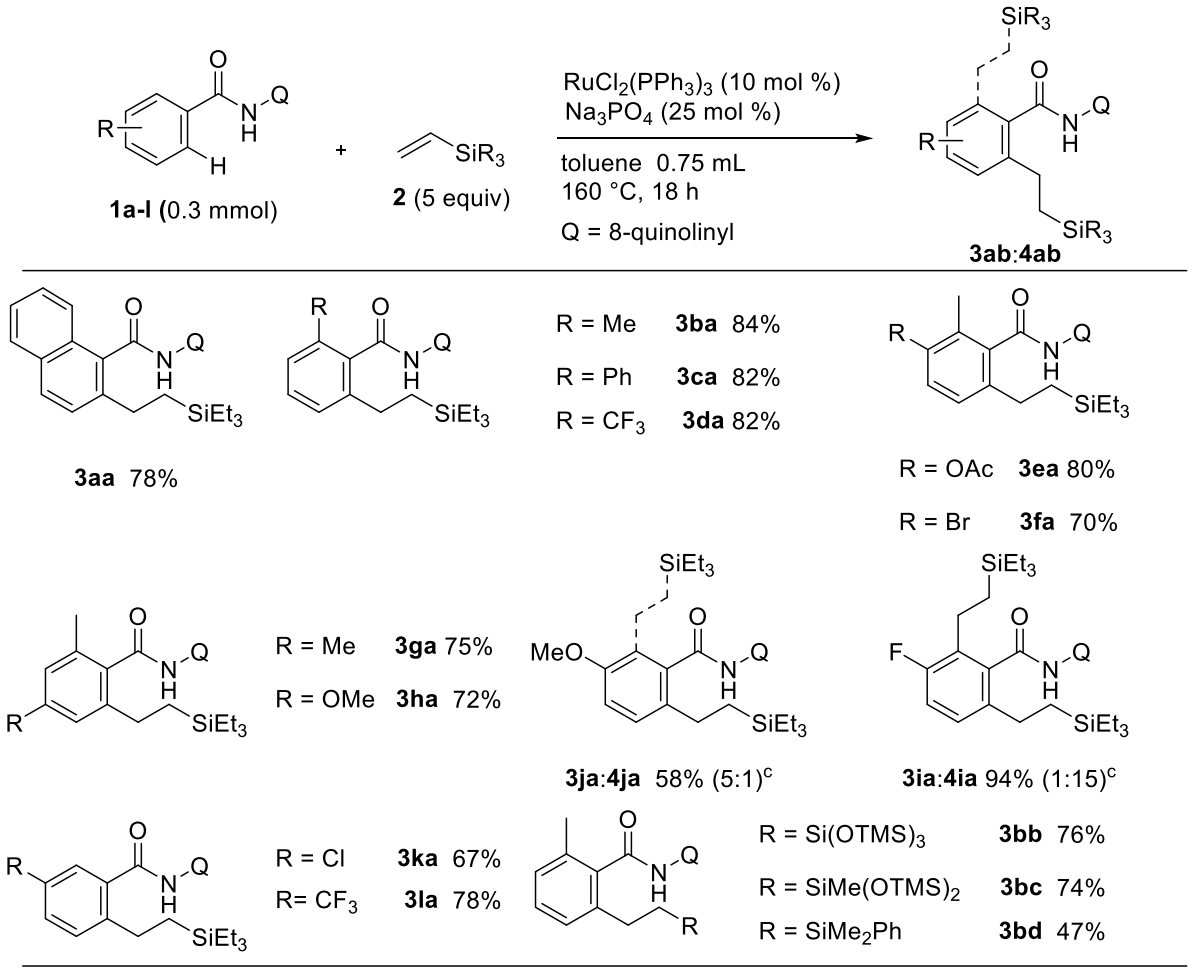
Scheme 1. Ineffective directing groups



Under the optimized reaction conditions, the scope of various aromatic amides with vinylsilanes were examined in Table 2. A wide range of functional groups were tolerated under the reaction conditions to give the corresponding products in good yields (**3ba**-**3ha**). For *m*-OMe-substituted aromatic amide **1j**, a 5:1 mixture of mono-alkylation product **3ja** and and di-alkylation products **4ja** were formed. For *m*-F-substituted aromatic amide **1i,** di-alkylation products **4ia** were formed as the major product. In sharp contrast, for *m*-substituted aromatic amide containing Cl and CF_3 groups, only less hindered C-H bonds reactivated afforded mono-

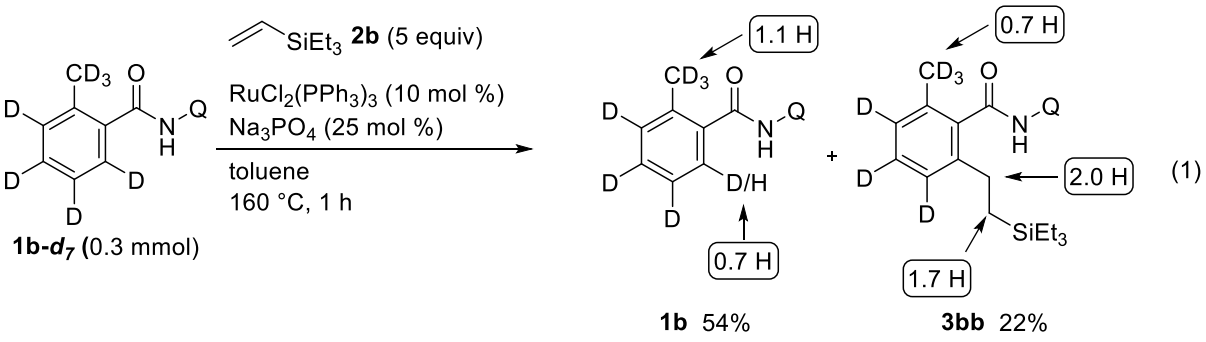
alkylation products in good yields. Various of vinylsilane, such as Tris(trimethylsiloxy)vinylsilane (**2b**), Di(trimethylsiloxy)methylvinylsilane (**2c**), and dimethylphenylvinylsilane (**2d**) were also carried out under the reaction condition gave the corresponding products in good yields (**3bb**-**3bd**).

Table 2. The Ru-Catalyzed C−H alkylation of aromatic amide with vinylsilane[a,b]



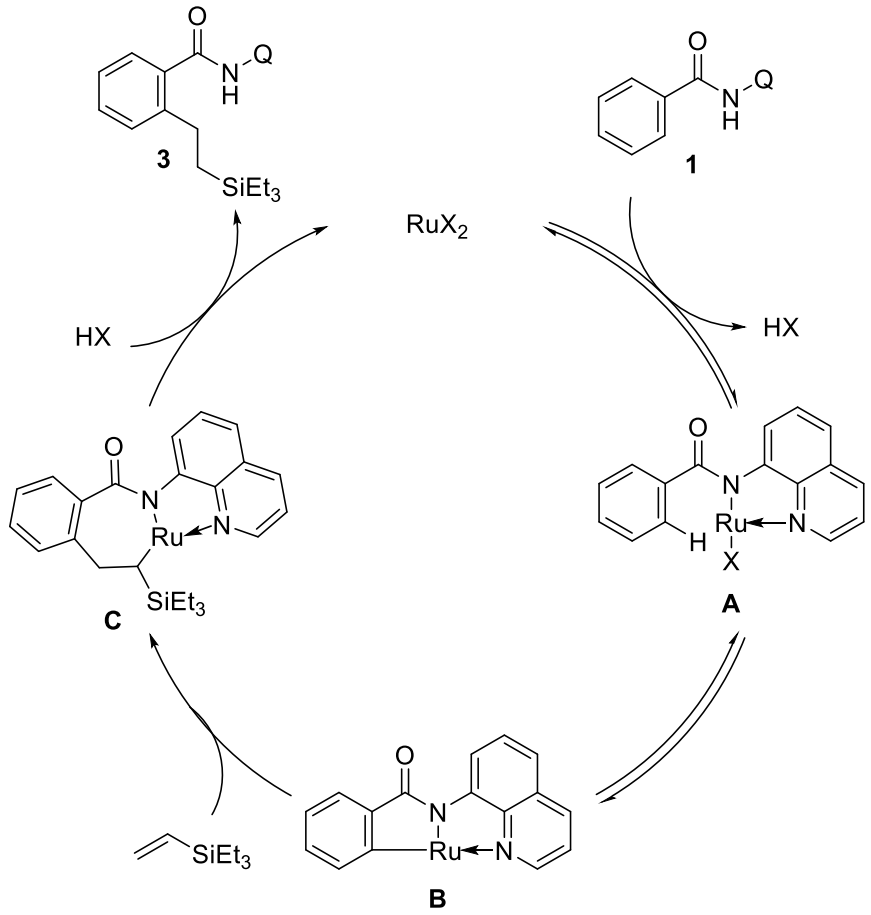
[a] reaction of aromatic amide **1a** (0.3 mmol) with vinylsilane **2a** (1.5 mmol) with $RuCl_2(PPh_3)_3$ (0.03 mmol) as the catalyst and Na_3PO_4 (0.075 mmol) as the base in toluene (0.75 mL) at 160 °C for 18 h isolated yield of **3a**. [b] isolated yields. [c] The number in parentheses refers the ratio of mono-alkylated product 3 and di-alkylated product 4.

The deuterium labeling experiments using **1a**-d_7 with vinylsilanes (**2a**) were carried out under the optimal conditions (eq 1). a significant amount of H/D took place at the *ortho*-position in the recovered **1a**-d_7, indicating that the C–H activation step was reversible. No deuterium atom was observed at the α-position of **3a**. Importantly, a deuterium atom (0.3 D) was observed only at the β-position of **3a**. In sharp contrast, compared with our previous Ru-catalyzed reaction with α,β-unsaturated ketones. As a result, using different alkene might be operating different mechanism for the Ru-catalyzed reactions.



A proposed mechanism for the alkylation is shown in Scheme 2. The coordination of the amide **1** to Ru complex by ligand exchange with the concomitant generation of HX gives the ruthenium complex **A**. Then, complex **A** undergoes reversible cyclometalation to give complex **B** probably via a concerted metalation deprotonation (CMD) mechanism, which is accelerated by sodium phosphate.[7] Insertion of a vinylsilane into a C-Ru bond in **B** gives the seven-membered ruthenacycle **C**, which is then protonated to gives the alkylated product **3** with the regeneration of the Ru(II) complex. The proposed mechanism involving the generation of the ruthenium complex **C** is consistent with the deuterium labeling results shown in Scheme 2.

Scheme 2. A proposed mechanism.



1.3 Conclusion

In summary, we have reported the development of a new catalytic system that takes advantage of chelation assistance by an 8-aminoquinoline moiety. The Ru(II)-catalyzed *ortho*-alkylation of C(sp^2)-H bonds of aromatic amides with vinylsilanes by using a 8-aminoquinoline moiety as *N*,*N*′-bidentate chelation system. Using an 8-aminoquinoline moiety as the directing group is indispensable for the reaction to proceed. Various groups, such as acetoxy, bromo, chloro, fluoro, methoxy and trifuoromethyl were tolerated under the reaction conditions. The use of an 8-aminoquinoline moiety as the directing group is indispensable for the success of this reaction. Compared with our previous Rh(I)-catalyzed alkylation of aromatic amides with alkenes. In sharp contrast, this reaction probably via a carbometalation mechanism.

1.4 Experimental Section

General Information

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. In some cases, some peaks in the ^{13}C NMR spectra cannot be analyzed because of overlapping peaks. Mass spectra and high resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO_2 (Silicycle SiliaFlash F60 (230-400 mesh)). Some compounds were purified by LC-908 HPLC (GPC).

Materials.

8-Aminoquinoline (CAS: 578-66-5), Triethylvinylsilane (CAS: 1112-54-5), Tris(trimethylsiloxy)vinylsilane (CAS: 5356-84-3) were purchased from Tokyo Chemical Industry Co., Ltd. Dimethylphenylvinylsilane (CAS: 1125-26-4), Methylbis(trimethylsilyloxy)vinylsilane CAS: (CAS: 5356-85-4), Sodium phosphate (CAS: 7601-54-9), Tris(triphenylphosphine) ruthenium(II) dichloride (CAS: 15529-49-4) was purchased from Sigma-Aldrich Co.

Synthesis of Starting Materials.

All amides bearing an 8-aminoquinoline moiety were prepared by reacting the corresponding acid or the corresponding acid chlorides with 8-aminoquinoline.[4]

General Procedure for the Preparation of Stating Amides.

(1) Synthesis of amides from acid chlorides.

The acid chloride (15 mmol) was dissolved in CH_2Cl_2 (20 mL). After cooling the reaction mixture to 0 °C, a solution of 8-aminoquinoline (15 mmol) and triethylamine (36 mmol) in 10 mL of CH_2Cl_2 was added dropwise. The resulting mixture was allowed to warm to rt and was then stirred overnight. The crude mixture was then washed with saturated aqueous $NaHCO_3$ (20 mL), and CH_2Cl_2 (3x20 mL). The combined organic layers were washed with 1 M HCl aq. (20 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solution taken to dryness. The resulting crude amide was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 5/1).

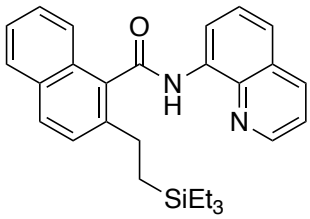
(2) Synthesis of amides from carboxylic acid.

To a stirred solution of carboxylic acid (15 mmol) and DMF (5 drops) in CH_2Cl_2 (10 mL), $(COCl)_2$ (1.5 mL, 18 mmol) was added dropwise. The solution was magnetically stirred at room temperature for 2 h. The solvent was then eliminated under reduced pressure, and the resulting residue was dissolved in CH_2Cl_2 (15 mL). After cooling the reaction mixture to 0 °C, a solution of 8-Aminoquinoline (15 mmol) and triethylamine (36 mmol) in 10 mL of the same solvent were added dropwise. The resulting mixture was allowed to warm to rt and stirred overnight. The crude product was washed with saturated aqueous $NaHCO_3$ (20 mL), and CH_2Cl_2 (3x20 mL). The organic phase was washed with 1 M HCl aq. (20 mL). The organic phase was dried over anhydrous Na_2SO_4 and the solvent removed by evaporation of the solvent. The resulting crude amide was purified by flash chromatography on silica gel (eluent: hexanes/EtOAc = 5/1).

General procedure for the Ruthenium-catalyzed alkylation of aromatic amides with Vinylsilane.

To an oven-dried 5 mL screw-capped vial, *N*-(quinolin-8-yl)-1-naphthamide (89.5mg, 0.3 mmol), Triethylvinylsilane (213.47mg, 1.5 mmol), $RuCl_2PPh_3$ (28.76mg, 0.03 mmol), Na_3PO_4 (12.3 mg, 0.075 mmol) and toluene (0.75 mL) were added. The mixture was stirred for 18 hours at 160°C and then cooled to room temperature. The resulting mixture was filtered through a celite pad and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 20/1 to 10/1) to afford the alkylation product **3aa** (102.9 mg, 78%) as a white powder.

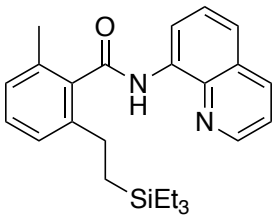
3-(2-(triethylsilyl)ethyl)-*N*-(quinolin-8-yl)-1-naphthamide (3aa)



102.9 mg, 78% yield, R_f 0.31 (hexane/EtOAc = 10:1). white solid, m.p. 73.5-73.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.37 (q, *J* = 8.0 Hz, 6H), 0.74 (t, *J* = 7.9 Hz, 9H), 1.06-1.02 (m, 2H), 2.84

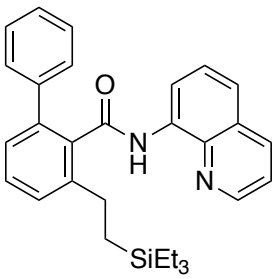
(t, *J* = 9.0 Hz, 2H), 7.48-7.39 (m, 4H), 7.58 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 1H), 7.89-7.84 (m, 2H), 8.01-7.98 (m, 1H), 8.17 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.65 (dd, *J* = 4.1, 1.6 Hz, 1H), 9.12 (d, *J* = 7.5 Hz, 1H), 10.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.13, 7.34, 15.13, 28.46, 116.97, 121.74, 122.13, 125.05, 125.65, 127.11, 127.39, 127.58, 128.07, 129.62, 130.43, 131.88, 133.18, 134.62, 136.43, 138.58, 140.31, 148.31, 168.55; MS *m/z* (relative intensity, %) 440 (24, M^+), 411(97), 309 (36), 296 (74), 267 (89), 177 (11), 171 (23), 168 (10), 165 (27), 154 (12), 144 (29), 115 (59), 87 (100), 59 (28); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{28}H_{32}N_2OSi$: 440.2284; Found: 440.2287.

2-methyl-6-(2-(triethylsilyl)ethyl)-N-(quinolin-8-yl)benzamide (**3ba**)



102.0 mg, 84% yield, R_f 0.40 (hexane/EtOAc = 10:1). white solid, m.p. 51.2-51.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.35 (q, *J* = 7.9 Hz, 6H), 0.74 (t, *J* = 7.9 Hz, 9H), 0.94-0.98 (m, 2H), 2.44 (s, 3H), 2.66-2.71 (m, 2H), 7.10 (d, *J* = 7.5 Hz, 1H), 7.15 (d, *J* = 7.8 Hz, 1H), 7.26-7.31 (m, 1H), 7.44 (q, *J* = 4.1 Hz, 1H), 7.55-7.63(m, 2H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.73 (dd, *J* = 4.3, 1.6 Hz, 1H), 9.00 (d, *J* = 7.5 Hz, 1H), 9.96 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.09, 7.30, 15.12, 19.55, 28.00, 116.86, 121.69, 121.95, 126.39, 127.50, 127.62, 128.04, 129.27, 134.49, 134.63, 136.40, 137.23, 138.59, 142.65, 148.28, 168.94; MS *m/z* (relative intensity, %) 404 (26, M^+), 375 (100), 273 (42), 260 (17), 245 (13), 232 (15), 229 (14), 171 (14), 159 (17), 144 (38), 129 (13), 115 (41), 87 (50), 59 (16); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{25}H_{32}N_2OSi$: 404.2284; Found: 440.2287.

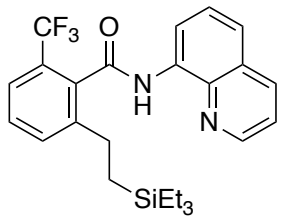
3-(2-(triethylsilyl)ethyl)-*N*-(quinolin-8-yl)biphenyl-2-carboxamide (**3ca**)



114.6 mg, 82% yield, R_f 0.26 (hexane/EtOAc = 10:1). white solid, m.p. 96.5-96.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.39-0.45 (m, 6H), 0.78-0.82 (m, 9H), 0.99-1.04 (m, 2H), 2.80-2.84 (m, 2H), 7.09-7.13 (m, 1H), 7.21-7.25 (m, 2H), 7.30-7.37 (m, 3H), 7.44-7.57 (m, 5H), 8.07 (dd, *J* = 8.5, 1.6 Hz, 1H), 8.61 (dd, J = 4.1, 1.6 Hz, 1H), 8.78 (dd, *J* = 7.5, 1.1 Hz, 1H), 9.70 (s, 1H); 13C NMR (100 MHz, $CDCl_3$) δ 3.14, 7.37, 15.12, 28.11, 116.63, 121.48, 121.67, 127.30, 127.36, 127.58, 127.81, 128.19, 128.22, 128.84, 129.46, 134.46, 136.18, 138.44, 139.75,

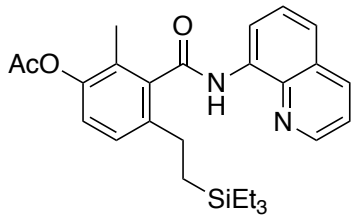
140.59, 143.84, 147.99, 168.27. MS m/z (relative intensity, %) 466 (34, M^+), 437 (100), 335 (18), 323 (55), 293 (68), 265 (25), 218 (19), 195 (38), 191 (52), 181 (20), 171 (19), 165 (10), 144 (54), 115 (61), 87 (95), 75 (10), 59 (27); HRMS (EI) m/z: [M]+ Calcd for $C_{30}H_{34}N_2OSi$: 466.2440; Found: 466.2436.

2-methyl-*N*-(quinolin-8-yl)-6-(trifluoromethyl)-benzamide (**3da**)



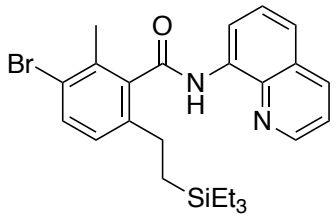
112.6 mg, 82% yield, R_f 0.37 (hexane/EtOAc = 10:1). white solid, m.p. 114.5-114.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.31-0.37 (m, 6H), 0.71-0.74 (m, 9H), 0.90-1.00 (m, 2H), 2.70-2.75 (m, 2H), 7.44 (q, *J* = 4.1 Hz, 1H), 7.50-7.55 (m, 2H), 7.56-7.63 (m, 3H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1H), 8.73 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.95 (dd, *J* = 7.1, 1.8 Hz, 1H), 10.01 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.06, 7.29, 15.23, 27.91, 117.11, 121.78, 122.32, 123.69 (q, *J* = 4.8 Hz), 124.01 (q, *J* = 272.2 Hz), 127.0 (q, *J* = 302.9 Hz), 127.55, 128.07, 129.57, 133.02, 134.26, 134.62, 136.47, 138.57, 144.76, 148.42, 165.83; MS *m/z* (relative intensity, %) 458 (14, M^+), 429 (100), 343 (20), 287 (13), 199 (11), 181 (12), 171 (11), 144 (20), 87 (14); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{25}H_{29}F_3N_2OSi$: 458.2001; Found: 458.1995.

2-methyl-4-(2-(triethylsilyl)ethyl)-3-(quinolin-8-ylcarbamoyl)phenyl acetate (**3ea**)



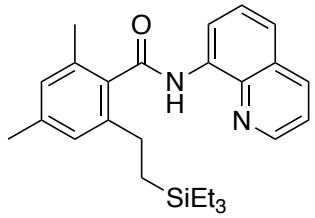
111.6 mg, 80% yield, R_f 0.09 (hexane/EtOAc = 10:1). white solid, m.p. 96.3-96.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.33 (q, *J* = 7.9 Hz, 6H), 0.72 (t, *J* = 8.0 Hz, 9H), 0.91-0.96 (m, 2H), 2.25 (s, 3H), 2.34 (s, 3H), 2.63-2.68 (m, 2H), 7.06 (d, J = 8.2 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.44 (q, *J* = 4.1 Hz, 1H), 7.58 (dd, *J* = 12.0, 7.7 Hz, 2H), 8.16-8.18 (m, 1H), 8.74-8.75 (m, 1H), 8.96 (d, *J* = 7.1 Hz, 1H), 9.99 (s, 1H)^{13}C NMR (100 MHz, $CDCl_3$) δ 3.06, 3.32, 7.29, 13.34, 14.94, 20.98, 27.72, 116.95, 121.78, 122.16, 122.97, 126.88, 127.44, 127.50, 128.03, 134.33, 136.40, 138.58, 140.43, 147.28, 148.40, 167.87, 169.61; MS *m/z* (relative intensity, %) 462 (21, M^+), 433 (100), 331 (20), 289 (10), 276 (19), 229 (12), 171 (13), 161 (12), 144 (31), 115 (27), 87 (47), 59 (15); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{27}H_{34}N_2O_3Si$: 462.2339; Found: 462.2340.

3-bromo-2-methyl-6-(2-(triethylsilyl)ethyl)-*N*-(quinolin-8-yl)benzamide (**3fa**)



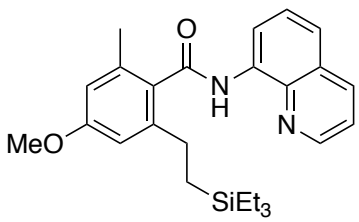
101.4 mg, 70% yield, R_f 0.46 (hexane/EtOAc = 10:1). white solid, m.p. 119.8-112.0 °C; ^{1}H NMR (400 MHz, CDCl3) δ 0.31-0.37 (m, 6H), 0.69-0.74 (m, 9H), 0.89-0.94 (m, 2H), 2.48 (s, 3H), 2.60-2.64 (m, 2H), 7.04 (d, *J* = 8.5 Hz, 1H), 7.46 (q, *J* = 4.1 Hz, 1H), 7.55-7.64 (m, 3H), 8.19 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.96 (dd, *J* = 7.2, 1.7 Hz, 1H), 9.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.09, 7.30, 15.05, 20.36, 27.83, 117.08, 121.82, 122.29, 122.82, 127.54, 128.08, 133.33, 134.22, 136.56, 138.53, 138.75, 142.06, 148.40, 167.94; MS *m/z* (relative intensity, %) 482 (16, M^+), 455 (100), 351 (37), 325 (10), 295 (11), 229 (22), 171 (25), 144 (50), 115 (37), 87 (48), 75 (13), 59 (17); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{25}H_{31}BrN_2OSi$: 482.1389; Found: 482.1387.

2,4-dimethyl-6-(2-(triethylsilyl)ethyl)-*N*-(quinolin-8-yl)benzamide (3ga)



94.2 mg, 75% yield, R_f 0.40 (hexane/EtOAc = 10:1). white solid, m.p. 74.2-74.5°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.34 (q, *J* = 7.9 Hz, 6H), 0.71-0.75 (m, 9H), 0.75-0.96 (m, 2H), 2.35 (s, 3H), 2.40 (s, 3H), 2.64-2.67 (m, 2H), 6.94 (d, *J* = 13.3 Hz, 2H), 7.42 (q, *J* = 4.1 Hz, 1H), 7.53-7.62 (m, 2H), 8.16 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.71 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.98 (dd, *J* = 7.5, 1.4 Hz, 1H), 9.94 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.11, 7.33, 15.19, 19.52, 21.39, 27.96, 116.81, 121.68, 121.85, 127.03, 127.56, 128.06, 128.44, 134.64, 136.40, 138.64, 139.04, 142.72, 148.27, 169.22; MS *m/z* (relative intensity, %) 418 (19, M^+), 389 (89), 287 (41), 275 (68), 259 (18), 246 (19), 229 (16), 171 (21), 166 (20), 159 (20), 115 (71), 87 (100), 59 (26); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{26}H_{34}N_2OSi$: 418.2440; Found: 418.2446.

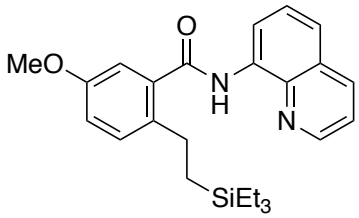
4-methoxy-2-methyl-(2-(triethylsilyl)ethyl)-*N*-(quinolin-8-yl)benzamide (3ha)



93.9 mg, 72% yield, R_f 0.20 (hexane/EtOAc = 10:1). white solid, m.p. 88.5-88.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.32-0.38 (m, 6H), 0.72-0.76 (m, 9H), 0.94-0.98 (m, 2H), 2.43 (s, 3H),

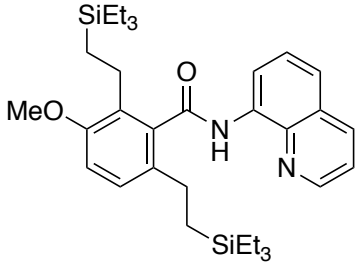
2.66-2.70 (m, 2H), 3.85 (d, *J* = 2.5 Hz, 3H), 6.67 (d, *J* = 15.1 Hz, 2H), 7.41-7.45 (m, 1H), 7.54-7.62 (m, 2H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.73 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.89-9.00 (m, 1H), 9.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.08, 7.30, 14.94, 19.91, 28.25, 55.31, 111.70, 112.87, 116.73, 121.66, 121.83, 127.51, 128.04, 130.37, 134.61, 136.39, 136.61, 138.59, 144.65, 148.26, 159.99, 168.99; MS *m/z* (relative intensity, %) 434 (11, M^+), 405 (26), 303 (11), 291 (100), 115 (33), 87 (52), 59 (12); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{26}H_{34}N_2O_2Si$: 434.2390; Found: 434.2394.

5-methoxy-2-(triethylsilyl)ethyl)-*N*-(quinolin-8-yl)benzamide (3ja)



61.7 mg, 49% yield, R_f 0.14 (hexane/EtOAc = 10:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.43 (q, *J* = 7.9 Hz, 6H), 0.79-0.83 (m, 9H), 0.81-0.96 (m, 2H), 2.81-2.85 (m, 2H), 3.85 (s, 3H), 6.98 (dd, J = 8.5, 2.7 Hz, 1H), 7.16 (d, *J* = 2.7 Hz, 1H), 7.26 (d, J = 8.4 Hz, 1H), 7.45 (q, *J* = 4.2 Hz, 1H), 7.54-7.60 (m, 2H), 8.18 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.76 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.95 (d, *J* = 6.9 Hz, 1H), 10.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.18, 7.40, 14.84, 27.04, 55.59, 112.56, 116.24, 116.66, 121.72, 121.85, 127.53, 128.06, 130.88, 134.78, 136.06, 136.43, 137.19, 138.65, 148.31, 157.57, 168.32. MS *m/z* (relative intensity, %) 420 (58, M^+), 391 (100), 305 (21), 276 (68), 261 (19), 248 (22), 245 (12), 229 (15), 171 (20), 167 (94), 153 (13), 115 (44), 103 (41), 87 (70), 75 (18), 59 (27); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{25}H_{32}N_2O_2Si$: 420.2233; Found:420.2231.

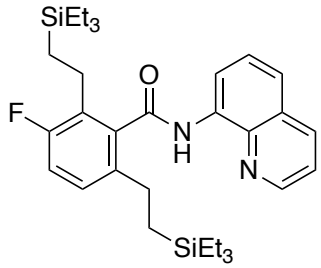
3-methoxy-2,6-bis(2-triethylsilyl)ethyl)-*N*-(quinolin-8-yl)benzamide (3ja)



17.1 mg, 9% yield, R_f 0.40 (hexane/EtOAc = 10:1). white solid, m.p. 90.6-90.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.30-0.38 (m, 12H), 0.71-0.75 (m, 18H), 0.90-0.94 (m, 4H), 0.71-0.73(m, 4H), 3.84 (s, 3H), 6.88 (d, *J* = 8.2 Hz, 1H), 7.10 (d, *J* = 8.5 Hz, 1H), 7.42 (q, *J* = 4.1 Hz, 1H), 7.53-7.59 (m, 2H), 8.17 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.70 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.96 (dd, *J* = 7.5, 1.4 Hz, 1H), 9.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.15, 7.27, 7.36, 13.09, 15.12, 22.43, 27.28, 55.69, 111.41, 116.94, 121.60, 121.81, 126.79, 127.57, 128.03, 131.13, 134.37, 134.56, 136.38, 137.52, 138.64, 148.20, 155.36, 168.61; MS *m/z* (relative intensity, %) 562 (18,

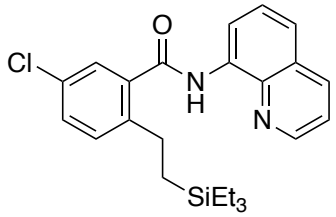
M^+), 533 (87), 418 (37), 303 (100), 275 (24), 229 (13), 171 (15), 144 (24), 115 (36), 87 (81), 59 (22); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{33}H_{50}N_2O_2Si_2$: 562.3411; Found: 562.3411.

3-fluoro-2,6-bis(2-triethylsilyl)ethyl-*N*-(quinolin-8-yl)benzamide (**4ia**)



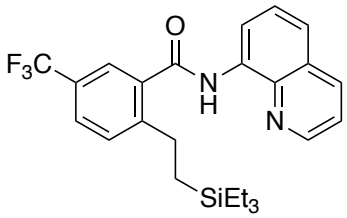
145.1 mg, 88% yield, R_f 0.23(hexane/EtOAc = 10:1). white solid, m.p. 70.9-71.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.32-0.38 (m, 12H), 0.71-0.76 (m, 18H), 0.90-0.95 (m, 4H), 2.62-2.66 (m, 4H), 7.03 (t, *J* = 9.0 Hz, 1H), 7.09 (d, *J* = 5.0 Hz, 1H), 7.44 (q, *J* = 4.2 Hz, 1H), 7.55-7.62 (m, 2H), 8.18 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.73 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.95 (dd, *J* = 7.3, 1.6 Hz, 1H), 9.97 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 116.18 (d, *J*= 22 Hz),117.03, 121.72, 122.11, 127.54, 127.54 (*J*= 7.7Hz), 128.04, 129.77, (d, *J*= 17.2 Hz), 134.26, 136.49, 137.87 (d, *J*= 3.9 Hz), 138.22 (d, *J*= 3.8 Hz), 138.57, 148.32, 159.18 (d, *J*= 242 Hz), 167.49 (d, *J*= 2.8); MS *m/z* (relative intensity, %) 550 (7, M^+), 521 (100), 291 (27), 144 (29), 115 (27), 87 (47), 59 (14); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{32}H_{47}FN_2OSi_2$: 550.3211; Found: 550.3201.

5-methoxy-2-(triethylsilyl)ethyl-*N*-(quinolin-8-yl)benzamide (**3ka**)



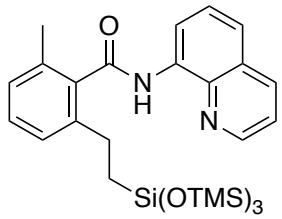
85.8 mg, 67% yield, R_f 0.37 (hexane/EtOAc = 10:1). white solid, m.p. 95.9-96.2°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.41-0.47 (m, 6H), 0.80-0.84 (m, 9H), 0.89-0.94(m, 2H), 2.82-2.86 (m, 2H), 7.28 (d, *J* = 8.5 Hz, 1H), 7.38 (dd, *J* = 8.3, 2.2 Hz, 1H), 7.46 (q, *J* = 4.1 Hz, 1H), 7.55-7.62 (m, 3H), 8.18 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.78 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.91 (dd, *J* = 7.2, 1.5 Hz, 1H), 10.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.16, 7.42, 14.69, 27.43, 116.80, 121.84, 122.15, 127.28, 127.52, 128.07, 130.37, 131.26, 131.52, 134.54, 136.52, 137.80, 138.61, 142.76, 148.45, 167.03; MS *m/z* (relative intensity, %) 426 (20, M^+), 395 (100), 293 (40), 252 (21), 169 (40), 165 (16), 155 (11), 144 (51), 115 (37), 103 (20), 87 (30), 75 (18), 59 (15); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{24}H_{29}ClN_2OSi$: 424.1738; Found: 424.1737.

5-trifluoromethyl-2-(triethylsilyl)ethyl-*N*-(quinolin-8-yl)benzamide (**3la**)



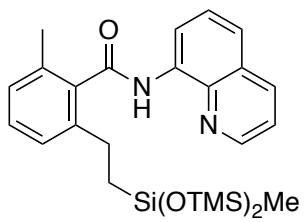
107.0 mg, 78% yield, R_f0.40 (hexane/EtOAc = 10:1). colorless oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.42-0.48 (m, 6H), 0.80-0.85 (m, 9H), 0.96 (m, 2H), 2.90-2.95 (m, 2H), 7.47 (q, H = 4.1 Hz, 2H), 7.57-7.68 (m, 3H), 7.86 (s, 1H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.79 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.93 (dd, *J* = 7.1, 1.6 Hz, 1H), 10.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.16, 7.39, 14.70, 28.02, 116.93, 121.88, 122.29, 124.08 (q, *J*= 270 Hz), 124.38 (q, *J*= 3.8 Hz), 127.03 (q, *J*= 3.8 Hz), 127.53, 128.10, 128.40 (q, *J*= 33.6 Hz), 130.36, 134.46, 136.56, 136.97, 138.62, 148.34, 148.50, 167.10; MS *m/z* (relative intensity, %) 458 (33, M^+), 429 (100), 343 (43), 286 (13), 277 (15), 199 (20), 171 (13), 144 (32), 115 (16), 87 (16), 75 (11); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{25}H_{29}F_3N_2OSi$: 458.2001; Found: 458.1997.

2-methyl-6-(2-(1,1,1,5,5,5-hexamethyl-3-((trimethylsilyl)oxy)trisiloxan-3-yl)ethyl)-*N*-(quinolin-8-yl)benzamide (3bb)



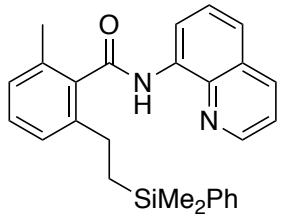
129.9 mg, 76% yield, R_f0.37 (hexane/EtOAc = 10:1). colorlss oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.15 (t, *J* = 3.3 Hz, 27H), 1.09 (dt, *J* = 9.5, 4.2 Hz, 2H), 2.64 (s, 3H), 2.96 (t, *J* = 8.9 Hz, 2H), 7.32 (d, *J* = 7.3 Hz, 1H), 7.38 (d, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 7.8 Hz, 1H), 7.64 (q, *J* = 4.2 Hz, 1H), 7.81-7.75 (m, 2H), 8.38 (dd, *J* = 8.3, 1.7 Hz, 1H), 8.93 (dd, *J* = 4.3, 1.7 Hz, 1H), 9.23 (dd, *J* = 7.3, 1.6 Hz, 1H), 10.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$)δ 1.70, 17.06, 19.57, 27.36, 117.08, 121.68, 121.91, 126.18, 127.55, 127.72, 128.13, 129.25, 134.61, 136.43, 137.54, 138.64, 141.89, 148.30, 168.88; MS *m/z* (relative intensity, %) 584 (14, M^+), 569 (47), 440 (78), 295 (13), 273 (12), 207 (100), 144 (13), 73 (51); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{28}H_{44}N_2O_4Si_4$: 584.2378; Found: 584.2368.

2-methyl-6-(2-(1,1,1,3,5,5,5-heptamethyltrisiloxan-3-yl)ethyl)-*N*-(quinolin-8-yl)benzamide (3bc)



113.5 mg, 74% yield, R_f 0.29 (hexane/EtOAc = 10:1). yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.06 (s, 3H), 0.15-0.18 (m, 18H), 1.10-1.14 (m, 2H), 2.66 (s, 3H), 2.94-2.98 (m, 2H), 7.33 (d, *J* = 7.5 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.47-7.53 (m, 1H), 7.65 (q, *J* = 4.1 Hz, 1H), 7.76-7.84 (m, 2H), 8.39 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.94 (dd, *J* = 4.2, 1.7 Hz, 1H), 9.24 (d, *J* = 7.5 Hz, 1H), 10.17 (s, 1H); ^{13}C NMR (100 MHz, CDCl3) δ 0.57, 1.79, 19.58, 20.38, 27.07, 117.00, 121.70, 121.95, 126.26, 127.56, 127.69, 128.11, 129.25, 134.56, 134.63, 136.46, 137.44, 138.60, 142.01, 148.30, 168.91; MS *m/z* (relative intensity, %) 510 (12, M^+), 495 (14), 366 (43), 221 (100), 144 (16), 73 (31); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{26}H_{38}N_2O_3Si_3$: 510.2190; Found: 510.2186.

2-methyl-6-(2-(methyldiphenylsilyl)ethyl)-*N*-(quinolin-8-yl)benzamide (3bc)



60.2 mg, 47% yield, R_f 0.23 (hexane/EtOAc = 10:1). white solid, m.p. 71.0-71.3°C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.11-0.12 (m, 6H), 1.20-1.25 (m, 2H), 2.46 (s, 3H), 2.46-2.74 (m, 2H), 7.09-7.19 (m, 5H), 7.26-7.34 (m, 3H), 7.45 (q, *J* = 4.2 Hz, 1H), 7.59-7.67 (m, 2H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.71 (t, *J* = 2.1 Hz, 1H), 9.00-9.01 (m, 1H), 9.95 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.33, 19.21, 19.56, 28.04, 76.83, 121.75, 122.00, 126.45, 127.60, 127.74, 128.11, 128.75, 129.28, 133.49, 134.29, 134.48, 134.72, 136.44, 137.30, 138.59, 138.74, 142.12, 148.32, 168.88; MS *m/z* (relative intensity, %) 424 (29, M^+), 409 (12), 289 (10), 280 (39), 206 (21), 144 (40), 135 (100), 75 (13); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{32}H_{30}N_2OSi$: 424.1971; Found: 424.1968.

Deuterium Labeling Experiments.

To an oven-dried 5 mL screw-capped vial, 2-methyl-*N*-(8-quinolinyl)benzamide **1b-d$_7$** (80.8 mg, 0.3 mmol), Triethylvinylsilane (213.47mg, 1.5 mmol), $RuCl_2PPh_3$ (28.76mg, 0.03 mmol), Na_3PO_4 (12.3 mg, 0.075 mmol) and toluene (0.75 mL) were added. The mixture was stirred for 1 hours at 160°C and then cooled to room temperature. The resulting mixture was filtered through a celite pad and then concentrated in vacuo. The residue was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 20/1 to 10/1) to afford the alkylation product **3bb** 22% and 2-methyl-*N*-(8-quinolinyl)benzamide **1b-d$_7$** was recovered 54%. The ratio of deuterium was determined by ^{1}H-NMR.

1.5 References and notes

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Chapter 2

Ruthenium(II)-Catalyzed Acyloxylation of C-H Bonds 2-Aroyl-Imidazoles with Carboxylic Acids via *N*-Monodentate Chelation Assistance

2.1 Introduction

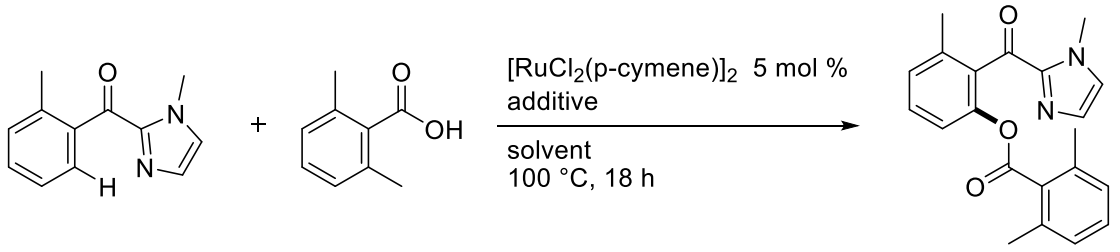
As delineated in general introduction and Chapter 1, transition-metal-catalyzed C–H functionalization has emerged as one of powerful strategies for the preparing useful molecules from structurally simple compounds. The acyloxylation of C-H bonds have attracted considerable attention as a successful method for introducing an oxygen-containing functionality into an organic compound. Recently, acyloxylation reactions with carboxylic acids has been achieved by many groups.[1] Since 2013, Jeganmohan reported the Ru(II)-catalyzed C-H acyloxylation of acetanilides [2a] and *N*-alkyl benzamides[2b] with carboxylic acids, respectively. Following this report, the use of various substrates in Ru(II)-catalyzed C-H acyloxylation were achieved.[3] To the best of our knowledge, aromatic esters C-H bonds acyloxylation with carboxylic acids are still limited.

Chapter 2 describes the Ru(II)-catalyzed *or*tho-C-H acyloxylation of 2-aroyl-imidazoles that have an imidazole directing group with carboxylic acids. The imidazole moiety has been used in C-H functionalization only one reported, which was reported by our group.[4] It is known the imidazole moiety could be converted into the corresponding esters, amide via a simple procedure.[5]

2.2 Result and Discussion

The reaction of the 2-aroyl-imidazoles (**1a**) (0.3 mmol) with 2,6-dimethylbenzoic acid (**2a**) (0.45 mmol) with $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol) as the catalyst and Ag_2CO_3 (0.45 mmol) as an oxidant in PhCl (1 mL) at 100 °C for 18 h gave the acyloxylation product **3aa** in 75% NMR yield (entry 1 in Table 1). The use of other solvent did not improve the product yield (entries 1-4). The use of other oxidants did not improve failed to improve the product yield (entries 5−8). The use of 2 equivalents of **2a** gives **3aa** in 80% isolated yield (entry 9). Finally, increase temperature to 100 °C could give **3aa** in 85% isolated yield (entry 10).

Table 1. The Ru-Catalyzed C−H acyloxylation of 2-aroyl-imidazoles **1a** with carboxylic acids (**2a**).[a]



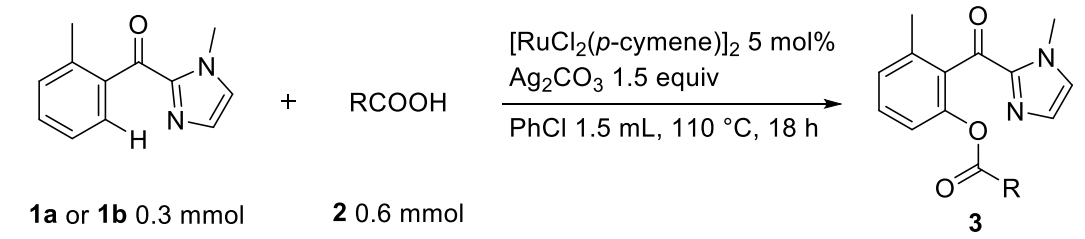
1a **2a** 1.5 equiv **3aa**

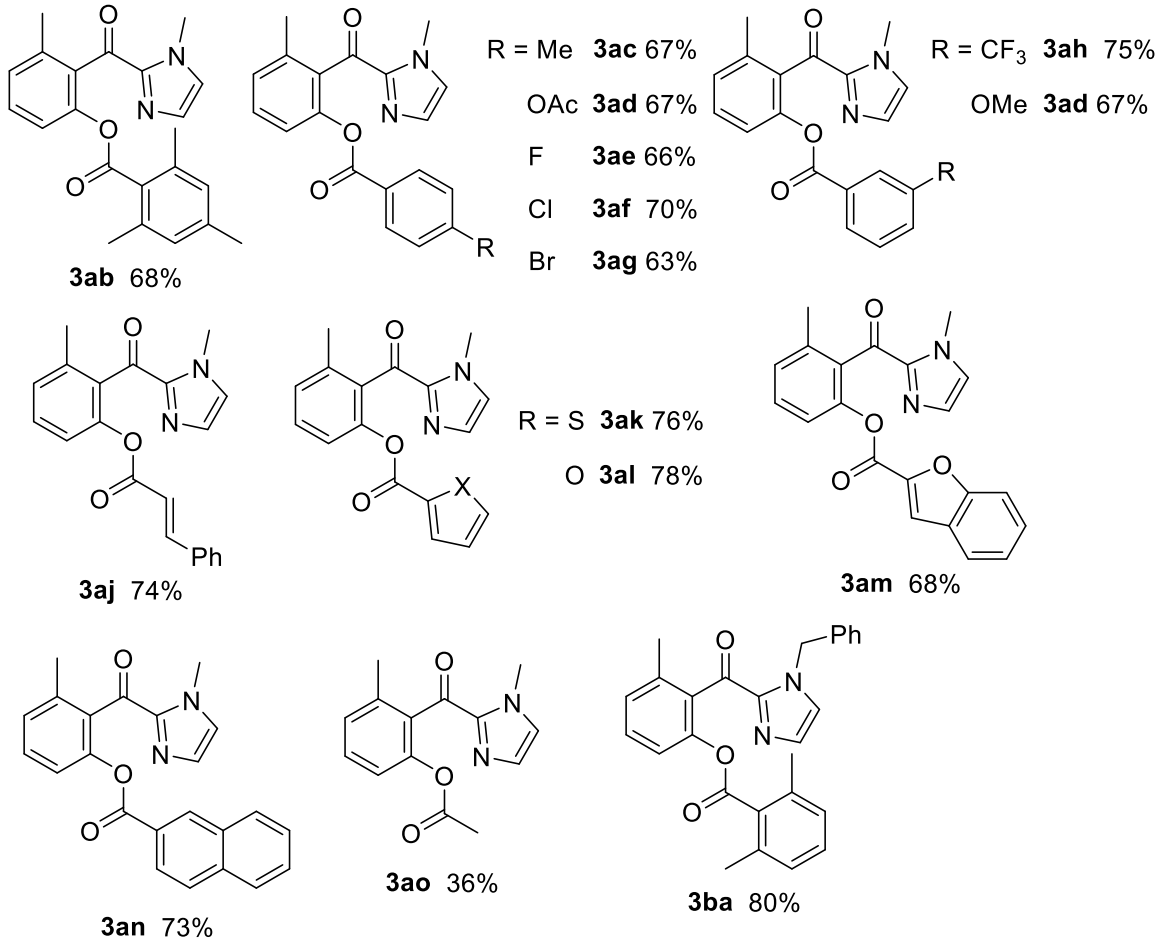
entry	additive (equiv)	solvent (ml)	yields/%[a]	
			3a	**1a**
1	Ag_2CO_3 (1.5)	PhCl (1)	75	5
2	Ag_2CO_3 (1.5)	toluene (1)	70	10
3	Ag_2CO_3 (1.5)	DCE (1)	12	65
4	Ag_2CO_3 (1.5)	1,4-dioxane (1)	38	38
5	AgOAc (1.5)	PhCl (1)	57	Nd
6	Ag_2O (1.2)	PhCl (1)	55	29
7	$AgNO_3$ (1.5)	PhCl (1)	Nd	Nd
8	MnO_2 (1.2)	PhCl (1)	(64)	Nd
9[b]	Ag_2CO_3 (1.5)	PhCl (1.5)	(80)	Nd
10[b,c]	Ag_2CO_3 (1.5)	PhCl (1.5)	(85)	Nd

[a] NMR yields. The number in parenthesis is the isolated yield of **3a**. Nd refers to not detected. [b].2,6-Dimethoxybenzoic acid (2 equiv) was used. [c] At 110 °C.

Under the optimized reaction conditions, the scope of 2-aroyl-imidazoles with carboxylic acids were examined in Table 2. A wide range of functional groups, such as Me, OMe, OAc, F, Cl Br and CF_3 were tolerated under the reaction conditions to give the corresponding acyolxylation products in good yields (**3ab**-**3ai**). The heteroaromatic carboxylic acids such as thiophene, furan, and benzofuran rings gave the corresponding acyolxylated products (**3ak**-**3am**). In addition, cinnamic acid, naphthalenecarboxylic acid and acetic acid were also tolerated under the reaction conditions (**3aj**, **3an**, **3ao**). Furthermore, the use of *N*-benzylimidazole also tolerated under the reaction conditions (**3ba**).

Table 2. The Ru-Catalyzed C−H acyloxylation of 2-aroyl-imidazoles with various carboxylic acids[a,b]



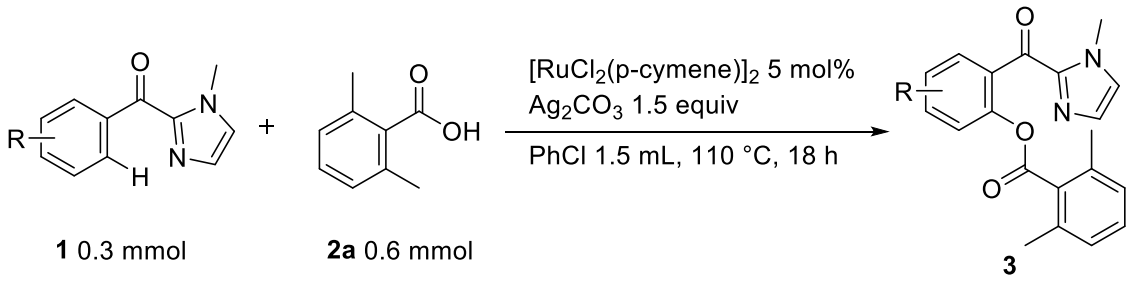


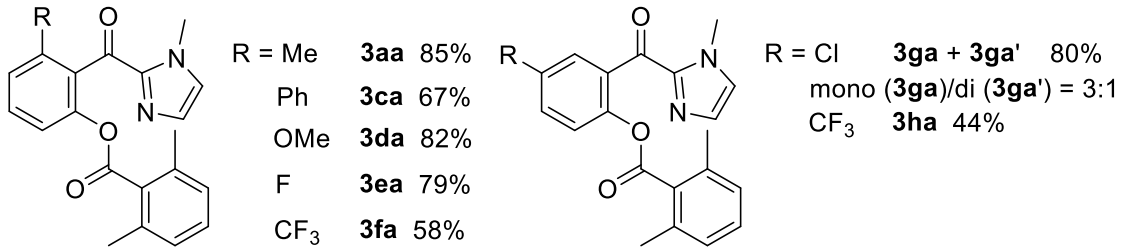
[a] The reaction of the 2-aroyl-imidazoles (**1a**) (0.3 mmol) with carboxylic acid (**2a**) (0.6 mmol) with $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol) as the catalyst and Ag_2CO_3 (0.45 mmol) as an oxidant in PhCl (1.5 mL) at 100 °C for 18 h. [b] isolated yields.

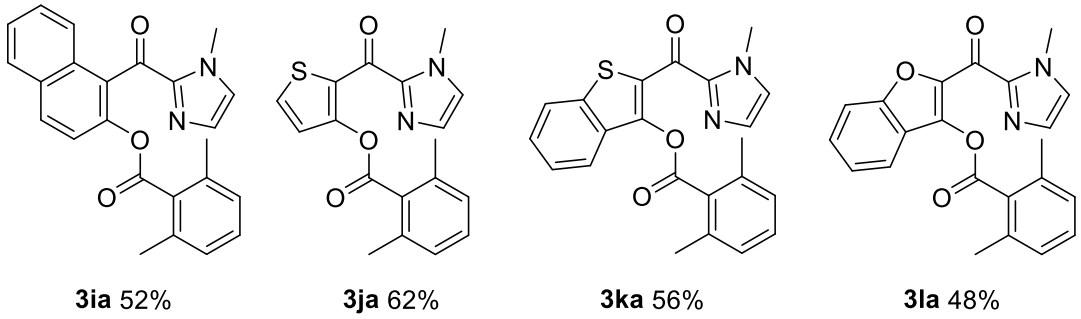
The substrates scope of 2-aroyl-imidazoles under the optimized reaction conditions in Table 3. A wide range of functional groups, such as Ph, OMe, F and CF_3 were tolerated under the reaction conditions to give the corresponding acyloxylated products in good yields (**3aa-3fa**). For *m*-Cl-substituted 2-aroyl-imidazoles **1g**, a 3:1 mixture of mono-acyloxylation product **3ga** and and di-acyloxylation products **3ga`** were formed. In sharp contrast, for *m*-CF_3-substituted 2-aroyl-imidazoles containing, only less hindered C-H bonds reactivated afforded mono-acyloxylation products in good yields (**3ha**). The use of 2-(2-naphthanoyl)-imidazole (**1i**) also

give the acyloxylation product **3ia**. The 2-heteroaromatic-imidazoles were tolerated under the reaction conditions to afforded the corresponding acyloxylation products (**3ja**-**3la**).

Table 3. The Ru-Catalyzed C−H acyloxylation of various 2-aroyl-imidazoles with carboxylic acids[a,b]

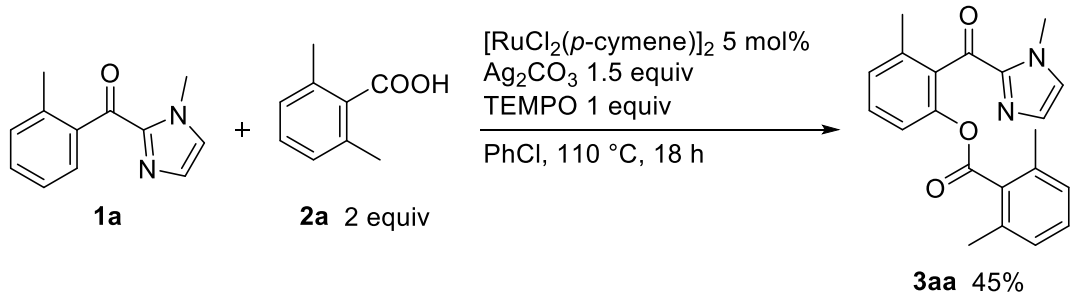






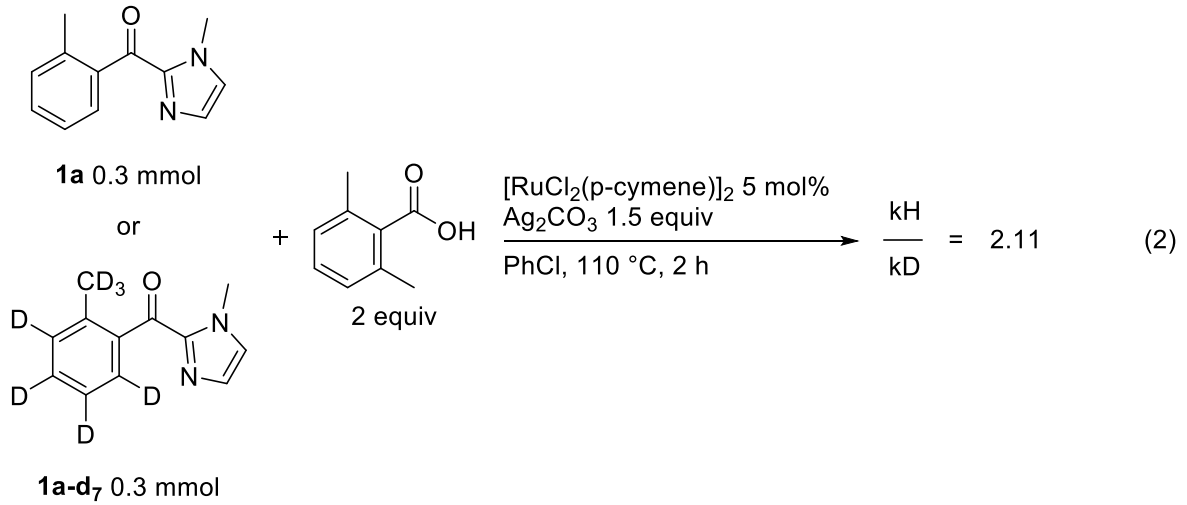
[a] The reaction of the various 2-aroyl-imidazoles (**1**) (0.3 mmol) with 2,6-dimethylbenzoic acid (**2a**) (0.6 mmol) with $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol) as the catalyst and Ag_2CO_3 (0.45 mmol) as an oxidant in PhCl (1.5 mL) at 100 °C for 18 h. [b] isolated yields.

The radical scavenger experiment was examined. When 1 equivalents TEMPO was added to the reaction mixture, acyloxylation product was obtained in 45% isolated yields (eq 1). It indicated that free radicals are not involved in the present reaction.

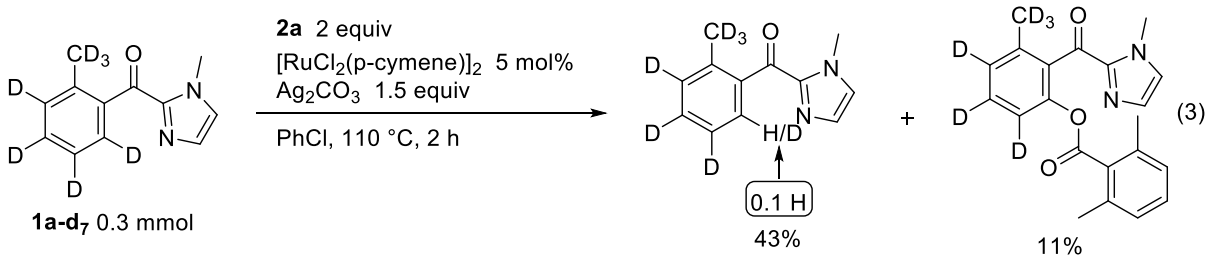


(1)

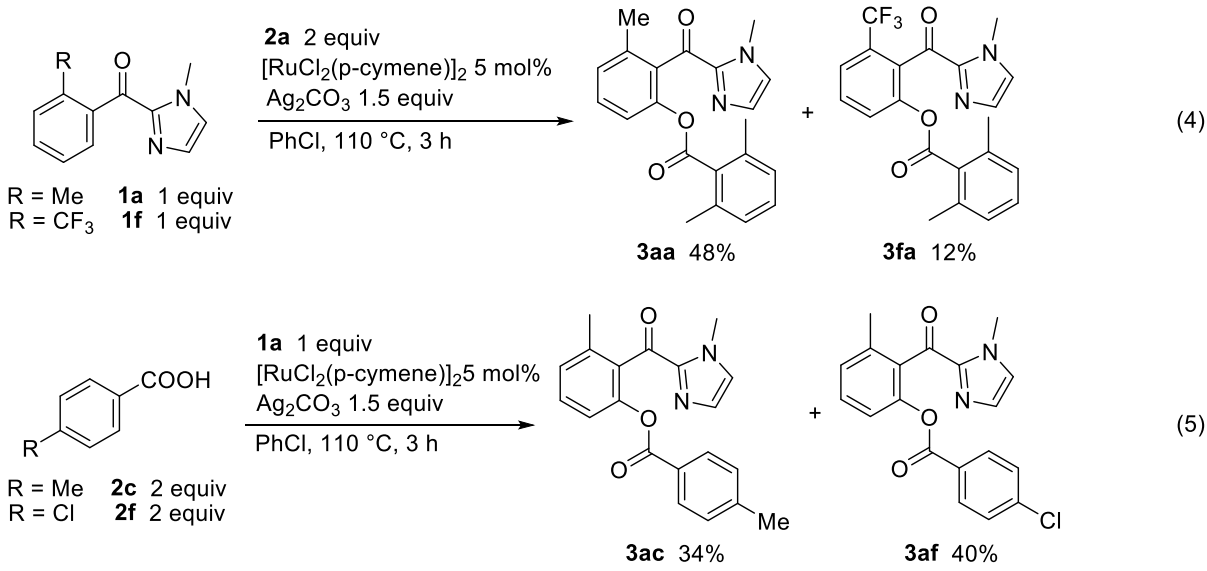
We then performed two parallel experiments between **1a** and deuterated **1a-*d*$_7$** under the optimal conditions. The kinetic isotope effect (KIE) was determined to be 2.11 (eq 2).



It indicated that that the C-H activation step is rate limiting step. The deuterium labeling experiments using **1a-*d*$_7$** were carried out under the optimal conditions. H/D exchange was observed only at the *ortho*-position in the recovered **1a-*d*$_7$** (eq 3). It indicates that the cleavage of the *ortho* C-H bond was reversible.

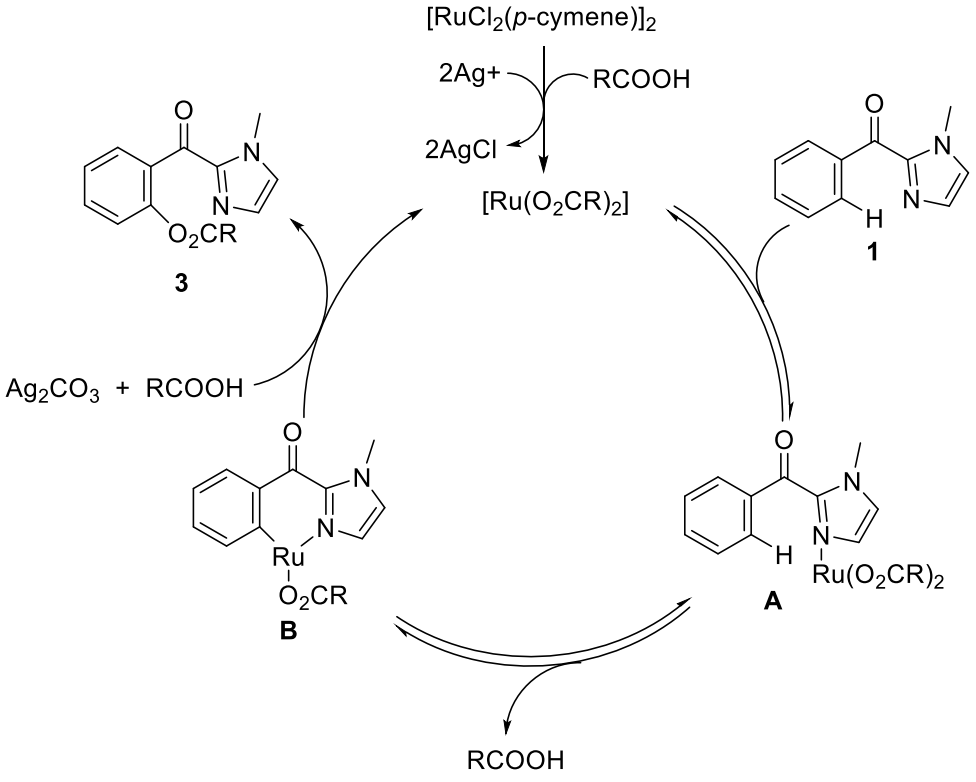


We next performed an intermolecular competition experiment using a 1:1 mixture **1a** and **1f** with 2,6-dimethylbenzoic acid (eq 4). The electron-rich substrate 1a reacted to give **3aa** as the major product, suggesting that the C-H bond activation step probable via a base-assisted internal electrophilic-type substitution (BIES).[6] Intermolecular competition experiments using a 1:1 mixture carboxylic acids (eq 5). As a result, a subtle electronic effect was observed.

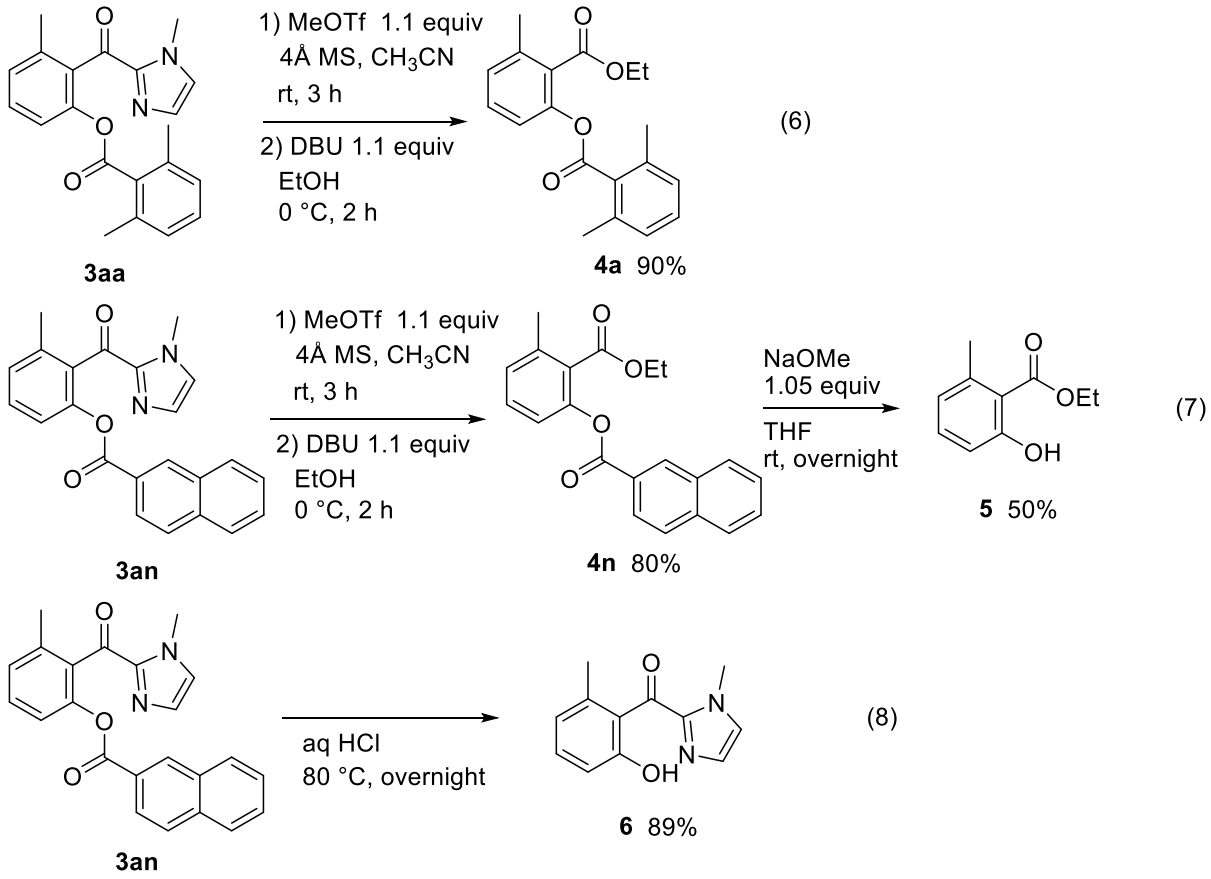


A proposed mechanism for the acyloxylation is shown in Scheme 1. A Ru(II) biscarboxylate complex or its cationic complex were obtained by ligand exchange. The coordination of an 2-aroyl-imidazole **1** to Ru(II) biscarboxylate complex gives the ruthenium complex **A**. Then, complex **A** undergoes reversible C-H metalation to give the six-membered ruthenacycle **B**, which is then oxidized by the Ag salt followed by reductive elimination give the acyloxylation product **3** with the regeneration of the Ru(II) catalyst.

Scheme 1. A proposed mechanism.



The synthetic application was shown. The corresponding esters could by converted from acyloxylation products via a simple operation. We could successfully remove the imidazole directing group under the mild condition, afford corresponding esters **4a** and **4b** in good yields, respectively (eq 6,7). The hydrolysis of **4b** and **3an** also gave the corresponding phenol derivatives (eq 7,8).



2.3 Conclusion

In summary, we have reported the development of a new catalytic system that takes advantage of chelation assistance by an imidazole moiety. The Ru(II)-catalyzed *ortho*-acyloxylation of C(sp^2)-H bonds of 2-aroyl-imidazoles with carboxylic acids by using an imidazoles moiety as *N*-monodentate chelation system. An imidazole moiety functions as an efficient *N*-monodentate directing group. Various groups, such as acetoxy, bromo, chloro, fluoro, methoxy and trifuoromethyl were tolerated under the reaction conditions. The acyloxylation products can be converted into the corresponding ester via a simple procedure.

2.4 Experimental Section

General Information.

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. In some cases, it was not possible to assign some of the peaks in the ^{13}C NMR spectra because of overlapping. Infrared spectra (IR) were recorded on a JASCO FT/IR-4000 spectrometer using the ATR method. Absorption data are reported in reciprocal centimeters from 800 to 3500 cm^{-1} with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra and high resolution mass spectra (HRMS) were obtained using a JEOL JMS-700 or JMS-T100LP spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO_2 (Silicycle SiliaFlash F60 (230-400 mesh). Some of the compounds that were prepared were purified by LC-908 HPLC (GPC). Medium-pressure liquid chromatography (MPLC) was performed with Biotage Isolera® equipped with Biotage® SNAP Ultra flash chromatography cartridges.

Materials.

Ruthenium source: $[Ru(p\text{-cymene})Cl_2]_2$ (Sigma-Aldrich Co.)

Additives: Ag_2CO_3 (Wako Pure Chemicals Industries, Ltd), AgOAc (Wako Pure Chemicals Industries, Ltd), Ag_2O (Wako Pure Chemicals Industries, Ltd), Na_3PO_4 (Sigma-Aldrich Co.), $AgSbF_6$ (Tokyo Chemical Industry Co., Ltd), $AgNO_3$, (Nacalai Tesque, Inc.), MnO_2 (Wako Pure Chemicals Industries, Ltd)

Benzoic acid:

2,6-dimethylbenzoic acid, 4-methylbenzoic acid, 4-acetoxybenzoic acid, 4-fluorobenzoic acid, 4-chlorobenzoic acid, 3-(trifluoromethyl) benzoic acid, trans-cinnamic acid, 2-thiophenecarboxylic acid, 2-furoic acid, benzofuran-2-carboxylic acid, 2-naphthoic acid (Tokyo Chemical Industry Co., Ltd)

2,4,6-trimethylbenzoic acid (Sigma-Aldrich Co.)

4-bromobenzoic acid, 3-methoxybenzoic acid (Kanto Chemical Co., Inc.), acetic acid (Nacalai Tesque, Inc.)

Synthesis of Starting Materials.

General Procedure for the Preparation of Stating 2-aroyl-imidazoles derivatives.

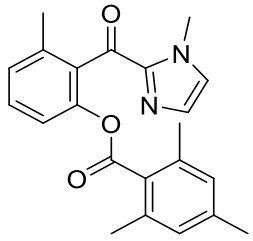
All of the 2-acyl imidazole derivatives were prepared by reacting the corresponding acids or the corresponding acid chlorides with 1-methylimidazole.[4]

To a stirred solution of 1-methylimidazole (30 mmol) in CH_3CN (120 mL) at 0 °C, a solution of acid chlorides (45 mmol) and triethylamine (36 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature and then stirred overnight. The crude product was washed with saturated aqueous $NaHCO_3$ (20 mL), brine (50 mL), and EtOAc (3x50 mL). The organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed by evaporation under reduced pressure. The residue was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 3/1).

General procedure for the Ruthenium-Catalyzed acyloxylation of 2-aroyl-imidazoles with carboxylic acids.

To an oven-dried 5 mL screw-capped vial, (1-methyl-1H-imidazol-2-yl)(2-methylphenyl)methanone (**1a**, 60.1 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015 mmol),2,6-dimethylbenzoic acid (90.1mg, 0.6 mmol), Ag_2CO_3 (124.1 mg, 0.45mmol), and PhCl (1.5 mL) were added. The mixture was stirred for 18 h at 110 °C and then allowed to cool to room temperature. The resulting mixture was filtered through a celite pad and the filtrate concentrated in vacuo. The residue was purified by MPLC (rate: 36 mL/min., eluent: hexane/EtOAc = 3/1 to 1/1) to afford the acyloxylation product **3aa** (88.6 mg, 85%) as a white powder.

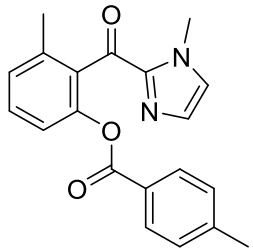
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 2,4,6-trimethylbenzoate



3ab

73.4 mg, 68% yield, R_f 0.43 (hexane/EtOAc = 1:1). white solid, m.p. 180.6-180.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (m, 12H), 4.03 (s, 3H), 6.80-6.81 (m, 2H), 7.03 (s, 1H), 7.14-7.21 (m, 3H), 7.39 (t, J = 7.9 Hz, 1H); 13C NMR (100 MHz, $CDCl_3$) δ 19.5, 19.8, 21.2, 36.2, 120.0, 127.4, 127.8, 128.6, 129.8, 130.0, 130.8, 132.9, 135.9, 136.9, 139.9, 143.4, 147.6, 168.0, 186.7; IR (ATR): 3109 w, 2958 w, 2922 w, 2863 w, 2363 w, 1746 s, 1655 s, 1609 m, 1576 w, 1507 w, 1460 m, 1429 w, 1395 s, 1293 w, 1254 m, 1218 s, 1161 s, 1053 s, 1011 w, 936 s, 900 m, 851 w, 773 w, 733 w, 699 w; MS m/z (relative intensity, %) 362 (4, M^+), 148 (11), 147 (100), 119 (11); HRMS (EI) m/z: [M]+ Calcd for $C_{22}H_{22}N_2O_3$: 362.1630; Found: 362.1628.

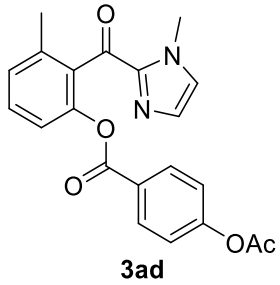
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 4-methylbenzoate



3ac

67.1 mg, 67% yield, R_f 0.35 (hexane/EtOAc = 10:1). white solid, m.p. 108.8-109.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 2.39 (s, 3H), 3.95 (s, 3H), 6.95 (s, 1H), 7.12 (s, 1H), 7.15-7.21 (m, 4H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.69-7.71 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 21.8, 35.9, 120.2, 126.5, 127.0, 128.0, 129.1, 130.0, 130.3, 130.5, 132.3, 137.4, 143.8, 144.3, 148.2, 164.2, 186.6; IR (ATR) 3016 w, 2968 w, 1740 s, 1657 m, 1610 m, 1397 s, 1263 w, 1225 s, 1073 w, 1019 w, 936 w, 901 w, 836 w, 775 w, 746 w; MS *m/z* (relative intensity, %) 334 (4, M^+), 200 (11), 199 (76), 119 (100), 91 (23); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{18}N_2O_3$: 334.1314; Found: 334.1317.

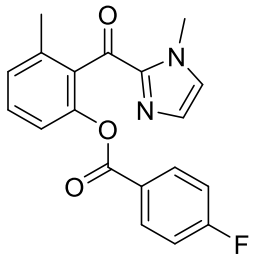
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 4-acetoxybenzoate



3ad

76.2 mg, 67% yield, R_f 0.24 (hexane/EtOAc = 1:1). white solid, m.p. 108.5-108.7 °C; 1H NMR (400 MHz, CDCl3) δ 2.33 (s, 3H), 2.34 (s, 3H), 3.96 (s, 3H), 6.96 (s, 1H), 7.09-7.13 (m, 3H), 7.18-7.21 (m, 2H), 7.41 (t, J = 7.9 Hz, 1H), 7.87 (dt, J = 9.0, 2.3 Hz, 2H); 13C NMR (100 MHz, CDCl3) δ 19.5, 21.3, 36.0, 120.2, 121.7, 126.9, 127.2, 128.2, 130.3, 130.6, 131.6, 132.4, 137.5, 143.7, 148.0, 154.7, 163.4, 169.0, 186.5; IR (ATR) 3399 w, 2925 w, 2361 w, 1741 s, 1655 m, 1604 w, 1578 w, 1504 w, 1462 w, 1397 s, 1371 w, 1261 m, 1222 s, 1195 s, 1160s, 1053 m, 1024 m, 1008 m, 935 w, 901 w, 857 w, 825 w, 769 w, 732 w, 700 w, 680 w, 663 w; MS m/z (relative intensity, %) 378 (4, M+), 215 (10), 200 (14), 199 (98), 163 (13), 121 (100); HRMS (EI) m/z: [M]+ Calcd for C21H18N2O5: 378.1216; Found: 378.1212.

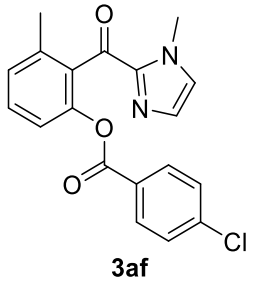
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 4-fluorobenzoate



3ae

66.9 mg, 66% yield, R_f 0.38 (hexane/EtOAc = 1:1). white solid, m.p. 112.2-112.4 °C; ^{1}HNMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.97 (s, 3H), 6.96 (s, 1H), 7.02-7.06 (m, 2H), 7.12 (d, *J* = 0.9 Hz, 1H), 7.17-7.21 (m, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.83-7.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.49, 35.97, 115.64 (d, *J* = 22.04 Hz), 120.145, 125.52 (d, *J* = 2.82 Hz), 127.09, 128.1881, 130.34, 130.55, 132.25, 132.52 (d, *J* = 9.59 Hz), 137.48, 143.66. 147.95, 163.23, 166.04 (d, *J* = 254.0 Hz); IR (ATR) 3468 w, 3111 w, 3073 w, 3006 w, 2962 w,1741 s, 1603 s. 1579 w, 1506 w, 1462 w, 1397 s, 1262 m,1224 s, 1154 m, 1073 m, 1013w, 934 w, 900 w, 855w, 762 w, 732 w, 685 w; MS *m/z* (relative intensity, %) 337 (1, M^+), 215 (12), 200 (14), 199 (100), 123 (72), 95 (20); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{19}H_{15}FN_2O_3$: 338.1067; Found: 338.1069.

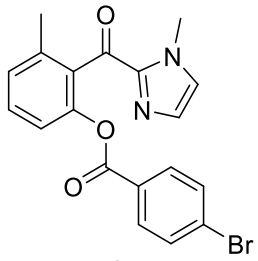
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 4-chlorobenzoate



3af

74.0 mg, 70% yield, R_f 0.43 (hexane/EtOAc = 1:1). white solid, m.p. 98.3-98.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.97 (s, 3H), 6.97 (s, 1H), 7.12 (s, 1H), 7.19 (dd, *J* = 7.8, 5.0 Hz, 2H), 7.33-7.36 (m, 2H), 7.40 (t, *J* = 7.9 Hz, 1H), 7.75-7.78 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 36.0, 120.1, 127.1, 127.8, 128.3, 128.8, 130.4, 130.5, 131.3, 132.2, 137.5, 140.0, 143.6, 147.9, 163.4, 186.3; IR (ATR) 3461 w, 3107 w, 2959 w, 2926 w, 1741s, 1655 m, 1594 m, 1462m, 1397 s, 1261 s, 1224 s, 1172 w, 1151 w, 1087 w, 1013 w, 935 w, 900 w, 851 w, 777 w, 753 w, 724 w, 700 w, 681 w, 665 w; MS *m/z* (relative intensity, %) 354 (1, M^+), 215 (12), 200 (13), 199 (100), 141 (18), 139 (59), 111 (16); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{19}H_{15}ClN_2O_3$: 354.0771; Found: 354.0775.

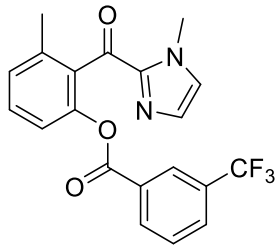
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 4-bromobenzoate



3ag

75.6 mg, 63% yield, R_f 0.45(hexane/EtOAc = 1:1). white solid, m.p. 120.6-120.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.97 (s, 3H), 6.98 (s, 1H), 7.12 (s, 1H), 7.18-7.21 (m, 2H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.51-7.53 (m, 2H), 7.69 (dd, *J* = 6.8, 1.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 36.1, 120.1, 127.1, 128.2, 128.3, 128.8, 130.4, 131.4, 131.8, 132.1, 137.6, 143.6, 147.9, 163.5, 186.3; IR (ATR) 3470 w, 3105 w, 3035 w, 2959 w, 2924 w, 1739 s, 1711 w, 1653 s, 1604 w, 1589 w, 1507 w, 1482 w, 1461 m, 1395 s, 1260 s, 1222 s, 1173 m, 1149 w, 1071 s, 1009 m, 934 w, 899 m, 847 w, 776 w, 748 m, 715 w, 699 w, 678 w, 664 w; MS *m/z* (relative intensity, %) 398 (1, M^+), 215 (11), 200 (13), 199 (100), 185 (32), 183 (33); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{19}H_{15}BrN_2O_3$: 398.0266; Found: 398.0261.

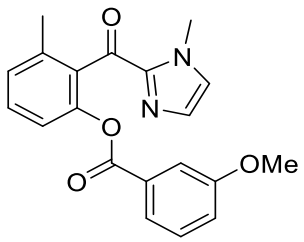
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 3-(trifluoromethyl)benzoate



3ah

87.1 mg, 75% yield, R_f 0.46 (hexane/EtOAc = 1:1). white solid, m.p. 133.0-133.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.99 (s, 3H), 6.97 (s, 1H), 7.10 (s, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.26-7.28 (m, 1H), 7.43 (t, *J* = 7.9 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.7 Hz, 1H), 7.91 (s, 1H), 8.10 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.52, 36.06, 119.99, 123.60 (q, *J* = 271.2 Hz); 126.46 (q, *J* = 3.83 Hz), 127.31, 128.42, 129.25, 129.97 (q, *J* = 3.83 Hz), 130.32, 130.40, 130.57, 131.04 (q, *J* = 32.6 Hz), 132.01, 133.32, 137.68, 143.53, 147.79, 162.83, 186.23; IR (ATR) 3107 w, 2962 w, 2927 w, 2868 w, 1745 m, 1654 m, 1609 w, 1577 w, 1508 w, 1462 w, 1443 w, 1396 m, 1334 m, 1294 w, 1240 m, 1218 s, 1169 m, 1127 m, 1070 m, 1003 w, 934 w, 899 m, 868 w, 810 w, 771w, 747 w, 696 w, 665 w; MS *m/z* (relative intensity, %) 388 (1, M^+), 215 (11), 200 (14), 199 (100), 173 (35), 145 (28); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{15}F_3N_2O_3$: 388.1035; Found: 388.1030.

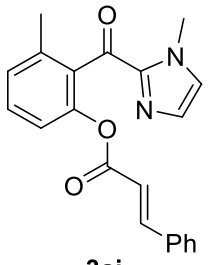
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 3-methoxybenzoate



3ai

66.3 mg, 63% yield, R_f 0.34 (hexane/EtOAc = 1:1). white solid, m.p. 104.5-104.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 3.79 (s, 3H), 3.96 (s, 3H), 6.96 (s, 1H), 7.08 (dd, *J* = 8.1, 2.6 Hz, 1H), 7.12 (s, 1H), 7.19 (dd, *J* = 11.7, 7.8 Hz, 2H), 7.26 (t, *J* = 7.9 Hz, 1H), 7.36-7.42 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 35.9, 55.5, 114.2, 120.1, 122.3, 127.1, 128.1, 129.4, 130.3, 130.5, 132.3, 137.4, 143.7, 148.1, 159.6, 164.1, 186.5; IR (ATR) 3107 w, 3006 w, 2958 w, 2837 w, 1738 m, 1654 m, 1602 w, 1586 w, 1485 w, 1460 w, 1432 w, 1396 s, 1333 w, 1274 s, 1212 s, 1175 m, 1150 w, 1130 w, 1091 w, 1065 w, 1039 w, 995 w, 934 w, 899 w, 829 w, 772 w, 747 w, 699 w, 680 w, 665 w; MS *m/z* (relative intensity, %) 350 (4, M^+), 215 (12), 200 (14), 199 (100), 135 (97), 107 (20), 77 (10); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{18}N_2O_4$: 350.1267; Found: 350.1266.

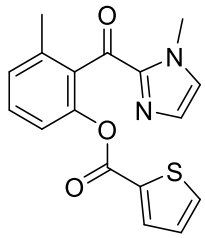
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl cinnamate



3aj

76.3 mg, 74% yield, R_f 0.32 (hexane/EtOAc = 1:1). white solid, m.p. 137.7-137.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 3H), 4.04 (s, 3H), 6.35 (d, *J* = 15.9 Hz, 1H), 7.03 (s, 1H), 7.12-7.16 (m, 2H), 7.17 (d, *J* = 0.8 Hz, 1H), 7.35-7.39 (m, 4H), 7.45 (dd, *J* = 4.6, 3.0 Hz, 2H), 7.54 (d, *J* = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 36.1, 116.9, 120.1, 127.2, 127.9, 128.2, 129.0, 130.2, 130.5, 130.7, 132.4, 134.1, 137.2, 143.6, 146.2, 147.8, 164.5, 186.5; IR (ATR) 3299 w, 3106 w, 3062 w, 3027 w, 2959 w, 2924 w, 2362 w, 1733 m, 1654 m, 1635 w, 1605 w, 1576 w, 1461 w, 1396 s, 1330 w, 1308 w, 1257 w, 1220 s, 1199 m, 1173 w, 1133 s, 1076 w, 1028 w, 979 w, 936 w, 900 w, 863 w, 766 w, 703 w, 683 w, 665 w; MS *m/z* (relative intensity, %) 347 (4, M^++1), 346 (16, M^+), 216 (37), 215 (17), 199 (45), 188 (15), 187 (14), 132 (10), 131 (100), 105 (10), 103 (40), 77 (18); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{21}H_{18}N_2O_3$: 346.1317; Found: 346.1315.

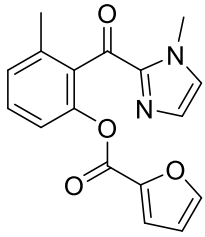
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl thiophene-2-carboxylate



3ak

74.5 mg, 76% yield, R_f 0.29 (hexane/EtOAc = 1:1). white solid, m.p. 98.2-98.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 3H), 4.02 (s, 3H), 6.97 (d, *J* = 0.5 Hz, 1H), 7.05 (dd, *J* = 4.9, 3.8 Hz, 1H), 7.11 (d, *J* = 0.9 Hz, 1H), 7.17 (dt, *J* = 7.7, 0.9 Hz, 1H), 7.27-7.28 (m, 1H), 7.39 (t, *J* = 7.9 Hz, 1H), 7.53 (dd, *J* = 5.0, 1.1 Hz, 1H), 7.68 (dd, *J* = 3.8, 1.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.4, 36.0, 120.0, 127.0, 127.9, 128.1, 130.2, 130.5, 132.1, 132.5, 133.4, 134.5, 137.4, 143.6, 147.7, 159.4, 186.3; IR (ATR) 3105 w, 2956 w, 2925 w, 2868 w, 1730 s, 1653 s, 1606 w, 1579 w, 1521 w, 1461 w, 1396 s, 1358 w, 1335 w, 1252 m, 1221 s, 1173 w, 1150 w, 1083 w, 1062 w, 1008 w, 936 w, 900 m, 861 w, 838 w, 773 w, 735 m, 700 w, 663 w; MS m/z (relative intensity, %) 326 (1, M+), 215 (11), 200 (14), 199 (100), 111 (70); HRMS (EI) m/z: [M]+ Calcd for C17H14N2O3S: 326.0725; Found: 326.0729.

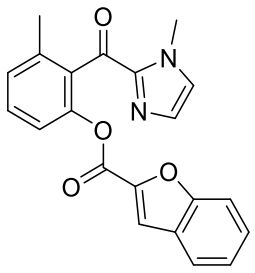
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl furan-2-carboxylate



3al

72.9 mg, 78% yield, R_f 0.24 (hexane/EtOAc = 1:1). yellow solid, m.p. 108.4-108.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.31 (s, 3H), 4.03 (s, 3H), 6.44-6.46 (m, 1H), 6.93-6.94 (m, 1H), 7.00 (s, 1H), 7.11 (d, *J* = 0.9 Hz, 1H), 7.16-7.22 (m, 2H), 7.39 (t, *J* = 8.0 Hz, 1H), 7.55-7.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 36.0, 112.0, 118.9, 120.1, 127.0, 128.2, 130.3, 130.5, 132.2, 137.5, 143.7, 143.7, 147.1, 147.4, 155.9, 186.2; IR (ATR) 3455 w, 3133 w, 2959 w, 2926 w, 2857 w, 2334 w, 1742s, 1654 s, 1607 w, 1569 w,1463 w, 1396 s, 1336 w, 1293 w, 1256 w, 1225 s, 2282 m, 1097 s, 1012 w, 935 w, 900 w, 842 w, 769 w, 730 w, 699 w, 665 w; MS *m/z* (relative intensity, %) 310 (0, M^+), 200 (15), 199 (100), 95 (32); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{17}H_{14}N_2O_4$: 310.0954; Found: 310.0950.

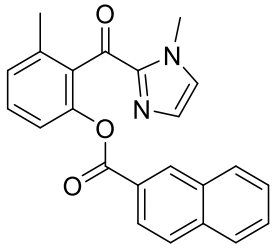
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl benzofuran-2-carboxylate



3am

73.1 mg, 68% yield, R_f 0.31 (hexane/EtOAc = 1:1). white solid, m.p.139.2-139.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 3.94 (s, 3H), 6.86 (s, 1H), 7.03 (d, *J* = 0.9 Hz, 1H), 7.12 (*d*, *J* = 7.8 Hz, 1H), 7.17-7.24 (m, 3H), 7.31-7.39 (m, 2H), 7.45-7.48 (m, 1H), 7.56-7.57 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 36.0, 112.4, 114.9, 120.0, 123.0, 124.0, 126.8, 127.1, 128.1, 128.4, 130.4, 130.5, 132.2, 137.7, 143.7, 144.6, 147.5, 156.0, 156.9, 186.1; IR (ATR) 3299 w, 3105 w, 3067 w, 3026 w, 2957 w, 2925 w, 2358 w, 1745 s, 1654 s, 1609 w, 1562 w, 1508 w, 1461 w, 1397 s, 1349 w, 1330 s, 1294m, 1257 w, 1224 m, 1167 s, 1143 m, 1081 w, 958 w, 936 w, 900 w, 846 w, 749 w, 699 w, 664 w; MS *m/z* (relative intensity, %) 360 (1, M^+), 304, 200 (13), 199 (100), 145 (35), 89 (11); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{21}H_{16}N_2O_4$: 360.1110; Found: 360.1114.

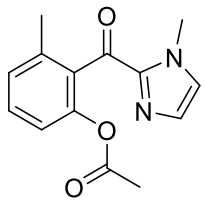
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 2-naphthoate



3an

80.6 mg, 73% yield, R_f 0.38 (hexane/EtOAc = 1:1). white solid, m.p.115.8-116.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 3.89 (s, 3H), 6.89 (s, 1H), 7.14 (s, 1H), 7.19 (d, *J* = 7.8 Hz, 1H), 7.26 (d, *J* = 7.1 Hz, 1H), 7.42 (t, *J* = 7.9 Hz, 1H), 7.51-7.60 (m, 2H), 7.79-7.86 (m, 4H), 8.33 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 35.9, 120.2, 125.2, 126.5, 126.9, 127.0, 127.9, 128.1, 128.2, 128.6, 129.4, 130.3, 130.5, 131.6, 132.3, 132.4, 135.7, 137.5, 143.8, 148.2, 164.3, 186.5; IR (ATR) 3458w, 3108 w, 3061 w, 2959 w, 1736 s, 1654 m, 1605 w, 1461 m, 1396 s, 1356 w, 1279 m, 1261 m, 1219 s, 1188 s, 1149 w, 1128 m, 1070 m, 957 w, 936 w, 900 m, 868 w, 828 w, 774 m, 763 m, 729 m; MS *m/z* (relative intensity, %) 370 (6, M^+), 199 (57), 156 (12) 155 (100), 127 (43); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{18}N_2O_3$: 370.1317; Found: 370.1317.

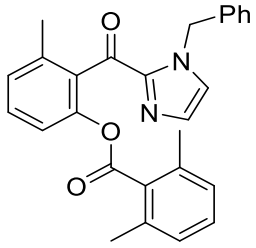
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl acetate



3ao

27.6 mg, 36% yield, R_f 0.22 (hexane/EtOAc = 1:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.99 (s, 3H), 2.25 (s, 3H), 4.12 (s, 3H), 7.06 (d, *J* = 8.2 Hz, 1H), 7.11-7.14 (m, 2H), 7.18 (d, *J* = 0.7 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.6, 20.8, 36.3, 120.3, 127.3, 128.0, 130.2, 130.7, 132.2, 137.3, 143.6, 147.8, 168.7, 186.6; IR (ATR) 3110 w, 3023 w, 2960 w, 2362 w, 2334 w, 1770 m, 1655 s, 1606 w, 1577 w, 1508 w, 1462 w, 1397 s, 1369 w, 1292 w, 1257 w, 1217 s, 1197 w, 1148 w, 1178 w, 1031 w, 901 w, 868 w, 792 w, 777 w, 702 w, 663 w; MS *m/z* (relative intensity, %) 258 (2, M^+), 216 (26), 200 (14), 199 (100), 188 (29), 187 (57), 105 (56); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{14}H_{14}N_2O_3$: 258.1004; Found: 258.1007.

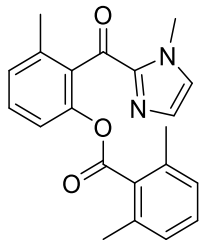
2-(1-benzyl-1*H*-imidazole-2-carbonyl)-3-methylphenyl 2,6-dimethylbenzoate



3ba

101.3 mg, 80% yield, R_f 0.62 (hexane/EtOAc = 1:1). white solid, m.p. 115.8-116.2 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.13 (s, 3H), 2.24 (s, 6H), 5.64 (s, 2H), 6.97 (d, *J* = 7.5 Hz, 2H), 7.06-7.25 (m, 10H), 7.38 (t, *J* = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 19.8, 51.7, 119.8, 126.5, 127.5, 127.8, 128.1, 128.8, 129.7, 129.9, 131.2, 132.5, 132.8, 135.8, 136.2, 136.8, 142.9, 147.5, 167.7, 186.6; IR (ATR) 3030 w, 2959 w, 2924 w, 1745 s, 1657 s, 1607 w, 1578 w, 1496 w, 1461 m, 1430 w, 1399 s, 1381m, 1296 w, 1259 w, 1240 w, 1217 s, 1162 w, 1135 w, 1103 m,1052 s, 1013 w, 930 w, 899 m, 858 w, 776 m, 715 m, 695 w, 668 w; MS *m/z* (relative intensity, %) 424 (10, M^+), 275 (12), 134 (10), 133 (100), 105 (14), 91 (12); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{27}H_{24}N_2O_3$: 424.1787; Found: 424.1786.

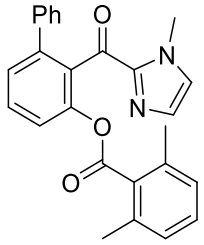
3-methyl-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 2,6-dimethylbenzoate



3aa

88.6 mg, 85% yield, R_f 0.31 (hexane/EtOAc = 1:1). white solid, m.p. 150.8-160.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 3H), 2.28 (s, 6H), 4.03 (s, 3H), 6.99 (d, *J* = 7.5 Hz, 2H), 7.03 (s, 1H), 7.14-7.18 (m, 3H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.40 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.5, 19.7, 36.1, 119.9, 127.5, 127.7, 127.9, 129.8, 130.0, 130.9, 132.8, 132.9, 135.6, 136.9, 143.4, 147.5, 167.8, 186.7; IR (ATR) 3107 w, 3067 w, 2959 w, 2925 w, 1746 m, 1655 m, 1607 w, 1577 w, 1506 w, 1461 w, 1424 w, 1395 s, 1292 w, 1258 m, 1240 w, 1216 s, 1174 w, 1149 w, 1103 m, 1052 s, 1014 w, 935 w, 900 m, 858 w, 776 m, 720 w, 700 w, 667 w; MS *m/z* (relative intensity, %) 348 (6, M^+), 134 (10), 133 (100), 105 (16); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{21}H_{20}N_2O_3$: 348.1474; Found: 348.1479.

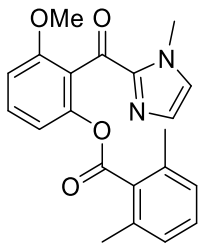
2-(1-methyl-1*H*-imidazole-2-carbonyl)-[1,1'-biphenyl]-3-yl 2,6-dimethylbenzoate



3ca

82.3 mg, 67% yield, R_f 0.46 (hexane/EtOAc = 1:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 6H), 3.77 (s, 3H), 6.77 (d, *J* = 0.5 Hz, 1H), 6.94 (d, *J* = 0.7 Hz, 1H), 6.99-7.01 (m, 2H), 7.15-7.24 (m, 4H), 7.28-7.33 (m, 3H), 7.42 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.55-7.59 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 35.6, 121.6, 126.5, 127.5, 127.8, 128.0, 129.1, 129.9, 130.2, 130.3, 132.2, 132.6, 135.8, 139.7, 142.3, 143.9, 147.8, 167.9, 185.9; IR (ATR) 3303 w, 3105 w, 3063 w, 3027 w, 2965 w, 1746 s, 1658 m, 1599 w, 1566 w, 1460 m, 1397 s, 1256 w, 1237 m, 1217 s, 1166 w, 1103 m, 1046 m, 937 w, 902 w, 861 w, 769 w, 702 w, 667 w; MS *m/z* (relative intensity, %) 410 (5, M^+), 134 (10), 133 (100), 105 (14); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{25}H_{22}N_2O_3$: 410.1630; Found: 410.1623.

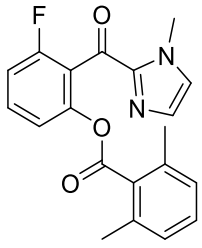
3-methoxy-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 2,6-dimethylbenzoate



3da

89.1 mg, 82% yield, R_f 0.34 (hexane/EtOAc = 1:1). white solid, m.p. 203.8-204.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.29 (s, 6H), 3.78 (s, 3H), 4.05 (s, 3H), 6.90 (d, *J* = 8.6 Hz, 1H), 6.98-7.03 (m, 4H), 7.14-7.19 (m, 2H), 7.46 (t, *J* = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 36.2, 56.4, 109.1, 115.1, 122.9, 127.2, 127.7, 129.8, 130.6, 130.8, 132.7, 135.6, 143.7, 148.3, 158.0, 167.7, 184.1; IR (ATR) 3106 w, 3069 w, 3007 w, 2963 w, 1748 w, 1658 s, 1606 m, 1585 w, 1467 m, 1436 w, 1398 s, 1268 m, 1257 m, 1240 m, 1220 s, 1169 w, 1103 m, 1077 s, 1047 w, 937 w, 901 m, 780 w, 749 w; MS *m/z* (relative intensity, %) 364 (4, M^+), 213 (11), 133 (100), 105 (16); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{21}H_{20}N_2O_4$: 364.1423; Found: 364.1426.

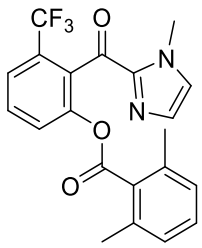
3-fluoro-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 2,6-dimethylbenzoate



3ea

83.1 mg, 79% yield, R_f 0.4 (hexane/EtOAc = 1:1). white solid, m.p. 114.5-114.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.35 (s, 6H), 4.03 (s, 3H), 7.01 (d, *J* = 7.5 Hz, 2H), 7.07-7.11 (m, 2H), 7.17-7.21 (m, 3H), 7.47-7.53 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.86, 36.14, 133.41, 133.62, 118.74 (d, *J* = 3.84 Hz), 122.06 (d, *J* = 21.08 Hz),127.49, 127.84, 130.06, 130.85, 131.37 (d, *J* = 9.58 Hz), 132.31, 135.78, 143.10, 148.57, 148.64, 159.93 (d, *J* = 248.2 Hz), 167.47, 180.50; IR (ATR) 3449 w, 3107 w, 3066 w, 2965 w, 2927 w, 2361 w, 1752 w, 1660 m, 1617 w, 1585 w, 1507 w, 1461 m, 1398 s, 1293 w, 1256 m, 1218 s, 1174 w, 1153 w, 1102 w, 1049 s, 979 w, 936 w, 901 m, 856 w, 777 w, 718 w, 698 w, 665 w; MS *m/z* (relative intensity, %) 352 (1, M^+), 134 (10), 133 (100), 105 (19); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{17}FN_2O_3$: 352.1223; Found: 352.1217.

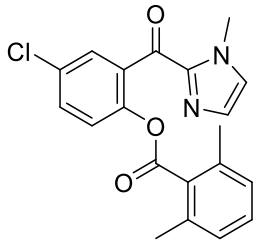
2-(1-methyl-1*H*-imidazole-2-carbonyl)-3-(trifluoromethyl)phenyl 2,6-dimethylbenzoate



3fa

70 mg, 58% yield, R_f 0.51 (hexane/EtOAc = 1:1). white solid, m.p. 137.0-137.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.25 (s, 6H), 4.02 (s, 3H), 6.99-7.00 (m, 2H), 7.05 (s, 1H), 7.14 (d, *J* = 0.9 Hz, 1H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.64 (t, *J* = 1.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.82, 35.97, 123.41 (q, *J* = 273.1 Hz), 123.97 (q, *J* = 4.8 Hz), 126.50, 127.63, 127.90, 129.28 (q, *J* = 31.58 Hz), 130.16, 130.38, 131.39, 132.01, 135.82, 143.23, 148.10, 167.30, 183.11; IR (ATR) 3108 w, 3067 w, 2965 w, 2928 w, 2356 w, 1752 s, 1666 w, 1592 w, 1508 w, 1463 w, 1399 s,1319 s, 1294 w, 1255 w,1221 s, 1167 m, 1131m, 1077 w, 1035 m, 938 w, 901 w, 860 w, 777 w, 737 ,w 701 ,w 682 ,w 669 w; MS *m/z* (relative intensity, %) 402 (4, M^+), 258 (12), 134 (13), 133 (100), 118 (72), 117 (12), 105 (22), 91 (15), 57 (21); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{21}H_{17}F_3N_2O_3$: 402.1191; Found: 402.1198.

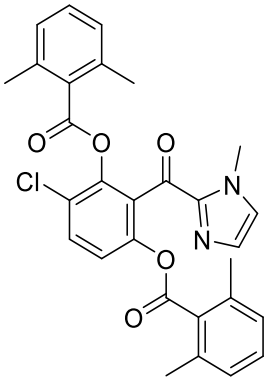
4-chloro-2-(1-methyl-1*H*-imidazole-2-carbonyl)phenyl 2,6-dimethylbenzoate



3ga

66.5 mg, 60 % yield, R_f 0.54 (hexane/EtOAc = 1:1). white solid, m.p. 102.5-102.7 °C; ^{1}H NMR(400 MHz, $CDCl_3$) δ 2.32 (s, 6H), 3.96 (s, 3H), 6.95-6.97 (m, 2H), 7.00 (s, 1H), 7.11-7.15 (m, 2H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.44 (dd, *J* = 8.7, 2.5 Hz, 1H), 7.71 (d, *J* = 2.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.1, 36.4, 124.4, 127.8, 128.0, 130.2, 130.5, 130.9, 131.1, 131.8, 132.0, 133.3, 136.2, 142.6, 147.1, 167.6, 182.3; IR (ATR) 3107 w, 3069 w, 3025 w, 2962 w, 2927 w, 1746 s, 1713 w, 1657 s, 1595 w, 1506 w, 1466 m, 1396 s, 1280 w, 1255 s, 1280 w, 1255 m, 1236 m, 1198 s, 1170 w, 1152 w, 1117 m, 1105 w, 1045 s, 948 w, 910 w, 875 w, 828 w, 808 w, 775 s, 718 w, 689 w, 654 w; MS *m/z* (relative intensity, %) 368 (2, M^+), 134 (10) 133 (100), 105 (15); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{20}H_{17}ClN_2O_3$: 368.0928; Found: 368.0927.

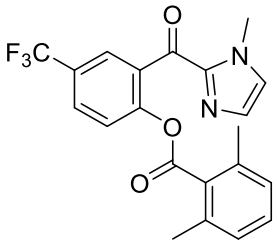
4-chloro-2-(1-methyl-1*H*-imidazole-2-carbonyl)-1,3-phenylene



3ga`

31.1 mg, 20% yield, R_f 0.49 (hexane/EtOAc = 1:1). white solid, m.p. 190.0-190.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.16 (s, 6H), 2.29 (s, 6H), 3.86 (s, 3H), 6.90-6.95 (m, 5H), 7.08-7.14 (m, 3H), 7.32 (d, *J* = 8.9 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ19.8, 20.9, 36.0, 121.4, 125.3, 127.9, 127.9, 128.4, 128.9, 130.1, 130.6, 130.7, 131.2, 131.3, 132.1, 135.8, 137.6, 142.9, 145.0, 146.9, 165.4, 166.9, 181.3; IR (ATR) 3068 w, 2966 w, 2928 w, 1752 s, 1659 s, 1596 w, 1463 w, 1396 s, 1254 w, 1222 m, 1206 m, 1172 w, 1102 w, 1046 m, 973 w, 950 w, 903 w, 870 w, 777 w, 719 w, 659 w; MS *m/z* (relative intensity, %) 516 (3, M^+), 134 (10), 133 (100), 105 (16); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{29}H_{25}ClN_2O_5$: 516.1452; Found: 516.1442.

2-(1-methyl-1*H*-imidazole-2-carbonyl)-4-(trifluoromethyl)phenyl 2,6-dimethylbenzoate

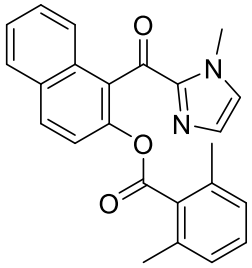


3ha

52.8 mg, 44 % yield, R_f 0.62 (hexane/EtOAc = 1:1). white solid, m.p. 115.5-115.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 6H), 4.06 (s, 3H), 7.04-7.06 (m, 2H), 7.10 (s, 1H), 7.21-7.25 (m, 2H), 7.50 (d, *J* = 8.6 Hz, 1H), 7.83 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.06-8.07 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.14, 36.43, 123.61(q, *J* = 271.19 Hz), 123.76, 127.61 (q, *J* = 32.58 Hz), 127.88, 128.10, 128.38 (q, *J* = 3.84 Hz), 128.90 (q, *J* = 3.84 Hz), 130.36, 130.48, 131.67, 132.50, 136.30, 142.40, 151.04, 167.24, 182.27; IR (ATR) 3111 w, 3070 w, 2965 w, 2931 w, 1748 m, 1657 m, 1616 w, 1593 w, 1465 w, 1396 s, 1332 s, 1299 w, 1250 m, 1238 m, 1203 s, 1167 s, 1120 s, 1079 w, 1034 m, 952 w, 909 w, 878 w, 835 w, 776 w, 726 w, 685 w; MS *m/z* (relative

intensity, %) 402 (0.4, M^+), 213 (11), 133 (100), 132 (10) 105 (15); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{21}H_{17}F_3N_2O_3$: 402.1191; Found: 402.1194.

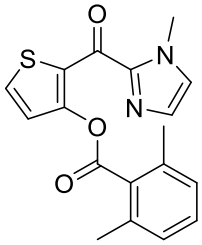
1-(1-methyl-1*H*-imidazole-2-carbonyl)naphthalen-2-yl 2,6-dimethylbenzoate



3ia

59.5 mg, 52% yield, R_f 0.33 (hexane/EtOAc = 1:1). white solid, m.p. 237.5-237.9 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 6H), 4.15 (s, 3H), 7.01-7.03 (m, 2H), 7.08-7.12 (m, 2H), 7.20 (t, *J* = 7.7 Hz, 1H), 7.43-7.53 (m, 3H), 7.62-7.65 (m, 1H), 7.91 (dd, *J* = 7.3, 2.1 Hz, 1H), 8.01 (d, *J* = 8.9 Hz, 1H); 13C NMR (100 MHz, $CDCl_3$) δ 19.9, 36.4, 121.4, 125.1, 126.1, 127.4, 127.7, 127.8, 128.5, 128.6, 129.9, 131.0, 131.1, 131.5, 131.6, 132.7, 135.7, 143.9, 145.4, 167.9, 186.3; IR (ATR) 3108 w, 3065 w, 2959 w, 2925 w, 1745 s ,1655 s, 1604 w, 1509 w, 1463 w, 1432 w, 1400 w, 1400 s, 1333 w, 1293 w, 1258 w, 1222 m, 1205 m, 1168 w, 1137 w, 1101 w, 1073 w, 1050 m, 935 w, 899 w, 809 w, 772 w, 701 w; MS m/z (relative intensity, %) 384 (5, M^+), 235 (24), 134 (10), 133 (100), 105 (20); HRMS (EI) m/z: [M]+ Calcd for $C_{24}H_{20}N_2O_3$: 384.1474; Found: 384.1471.

2-(1-methyl-1*H*-imidazole-2-carbonyl)thiophen-3-yl 2,6-dimethylbenzoate

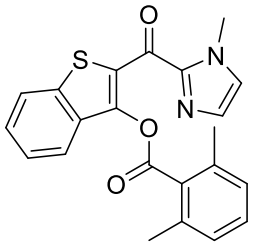


3ja

63.4 mg, 62% yield, R_f 0.60 (hexane/EtOAc = 1:1). white solid, m.p. 156.4-156.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 6H), 4.02 (s, 3H), 7.05-7.11 (m, 4H), 7.19 (d, *J* = 0.8 Hz, 1H), 7.25 (t, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.5, 36.5, 122.8, 124.3, 127.4, 128.2, 129.0, 130.3, 131.9, 133.3, 136.8, 142.6, 151.9, 167.1, 174.0; IR (ATR) 3108 w, 3019 w, 2959 w, 2926 w, 1747 m, 1633 m, 1593 w, 1516 w, 1465 w, 1413 s, 1292 w, 1259 w, 1237 m, 1216 m, 1165 w, 1142 w, 1103 w, 1052 m, 988 w, 926 w, 887 m, 858 w, 833 w, 777 w, 728 w, 681 w, 665 w; MS *m/z* (relative intensity, %) 340 (4, M^+), 213

(10), 133 (100), 105 (21); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{18}H_{16}N_2O_3S$: 340.0882; Found: 340.0887.

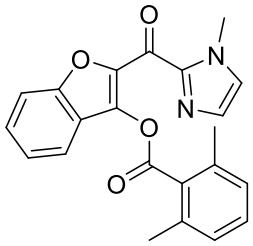
2-(1-methyl-1*H*-imidazole-2-carbonyl)benzo[*b*]thiophen-3-yl 2,6-dimethylbenzoate



3ka

65.4 mg, 56% yield, R_f 0.65 (hexane/EtOAc = 1:1). yellow solid, m.p. 171.2-171.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.69 (s, 6H), 4.02 (s, 3H), 7.06 (s, 1H), 7.16 (d, *J* = 7.7 Hz, 2H), 7.24 (d, *J* = 0.9 Hz, 1H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.42-7.44 (m, 1H), 7.48-7.50 (m, 1H), 7.84-7.89 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 36.5, 122.6, 123.0, 124.1, 125.1, 127.7, 128.2, 128.6, 129.2, 130.6, 131.2, 132.3, 137.8, 140.7, 142.8, 146.1, 166.4, 175.2; IR (ATR) 3467 w, 3114 w, 3019 w, 2968 w, 2361 m, 2338 w, 1742 s, 1640 m, 1596 w, 1563 w, 1501 w, 1463 w, 1401 m 1365 m, 1263 w, 1224 s, 1167 w, 1105 w, 1053 w, 1000 w, 972 w, 938 w, 900 w, 831 w, 767 w, 708 w, 658 w; MS *m/z* (relative intensity, %) 390 (14, M^+), 134 (10), 133 (100), 105 (19); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{18}N_2O_3S$: 390.1038; Found: 390.1040.

2-(1-methyl-1*H*-imidazole-2-carbonyl)benzofuran-3-yl 2,6-dimethylbenzoate



3la

53.3 mg, 48% yield, R_f 0.29 (hexane/EtOAc = 1:1). yellow solid, m.p. 113.5-113.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.57 (s, 6H), 4.05 (s, 3H), 7.09 (s, 1H), 7.11-7.13 (m, 2H), 7.23 (d, *J* = 0.9 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.33-7.38, 1H), 7.50-7.54 (m, 1H), 7.69 (dd, *J* = 8.2, 0.9 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 20.8, 36.2, 113.4, 120.8, 122.4, 124.1, 127.3, 128.3, 128.8, 130.3, 130.6, 131.3, 137.1, 138.7, 141.3, 142.5, 153.6, 165.7, 173.2; IR (ATR) 3108 w, 3067 w, 2967 w, 2928 w, 1756 m, 1639 s, 1593 w, 1563 w, 1449 w, 1415 m, 1366 w, 1345 w, 1283 w, 1260 w, 1230 s, 1189w, 1155 s, 1138 m, 1109 w, 1018 s, 993 m, 972 m, 916 w, 868 w, 868 m, 791 w, 772 w, 749 m, 698 w, 674 w; MS *m/z* (relative intensity, %) 374 (12, M^+), 134 (10), 133 (100), 105 (15); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{18}N_2O_4$: 374.1267; Found: 374.1263.

Experiment with TEMPO

To an oven-dried 5 mL screw-capped vial, (1-methyl-1H-imidazol-2-yl)(2-methylphenyl)methanone (**1a**, 60.1 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015mmol), 2,6-dimethylbenzoic acid (90.1mg, 0.6 mmol), Ag_2CO_3 (124.1 mg, 0.45 mmol), TEMPO (46.9 mg, 0.3 mmol), and PhCl (1.5 mL) were added. The mixture was stirred for 18 hours at 110 °C and then allowed to cool to room temperature. The resulting mixture was filtered through a celite pad and the filtrate concentrated in vacuo. The residue was purified by MPLC (rate: 36 mL/min., eluent: hexane/EtOAc = 3/1 to 1/1) to afford the acyloxylation product **3aa** (47 mg, 45%) as a white powder.

KIE Experiments

Two parallel reactions using 1a and 1a-d7 were carried out in two different oven-dried 5 mL screw-capped vial. In the vial, 1a or 1a-d7 (0.3 mmol), [Ru(p-cymene)Cl2]2 (9.2 mg, 0.015 mmol), 2,6-dimethylbenzoic acid (90.1mg, 0.6 mmol), Ag2CO3 (124.1 mg, 0.45 mmol), and PhCl (1.5 mL) were added. The mixture was stirred for 2 hours at 110 °C and then allowed to cool to room temperature. The resulting mixture was filtered through a celite pad and the filtrate concentrated in vacuo. The residue was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 3/1 to 1/1) to afford the acyloxylation product 3aa (24.4 mg, 23%) or 3aa-d6 (11.3 mg, 11%) as white powder. The KIE value was determined to be 2.11, suggesting that the C–H activation step is a rate limiting step.

Deuterium Scrambling Experiments

To an oven-dried 5 mL screw-capped vial, (1-methyl-1H-imidazol-2-yl)(2-methylphenyl)methanone **1b-d$_7$** (62.2 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015 mmol),2,6-dimethylbenzoic acid (90.1mg, 0.6 mmol), Ag_2CO_3 (124.1 mg, 0.45mmol), and PhCl (1.5 mL) were added. The mixture was stirred for 18 h at 110 °C and then allowed to cool to room temperature. The resulting mixture was filtered through a celite pad and the filtrate concentrated in vacuo. The residue was purified by MPLC (rate: 36 mL/min., eluent: hexane/EtOAc = 3/1 to 1/1) to afford the acyloxylation product **3aa** 43%and 1-methyl-1H-imidazol-2-yl)(2-methylphenyl)methanone **1b-d$_7$** was recovered 11%. The ratio of deuterium was determined by 1H-NMR.

Competition Experiments

To an oven-dried 5 mL screw-capped vial, (1-methyl-1H-imidazol-2-yl)(2-methylphenyl)methanone (**1a**, 60.1 mg, 0.3 mmol), (1-methyl-1H-imidazol-2-yl)(2-(trifluoromethyl)phenyl)methanone (**1f,** 76.3 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015mmol), 2,6-dimethylbenzoic acid (90.1mg, 0.6 mmol), Ag_2CO_3 (124.1 mg, 0.45 mmol), and PhCl (1.5 mL) were added. The mixture was stirred for 3 hours at 110 °C and then allowed

to cool to room temperature. The resulting mixture was filtered through a celite pad and the filtrate concentrated in vacuo. The conversion of **1a** and **1f** and the yields of **3aa** and **3fa** were determined by ^{1}H NMR spectroscopy with respect to the internal standard (1,1,2,2-tetrachloroethane). The reaction gave **3aa** and **3fa** in 48% and 12% NMR yields, along with **1a** (47%) and **1f** (84%) recovered, respectively.

To an oven-dried 5 mL screw-capped vial, (1-methyl-1H-imidazol-2-yl)(2-methylphenyl)methanone (**1a**, 60.1 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015mmol), 4-methylbenzoic acid (**2a**, 93.9 mg, 0.6 mmol), 4-chlorobenzoic acid (**2f,** 81.7 mg, 0.6 mmol), Ag_2CO_3 (124.1 mg, 0.45 mmol), and PhCl (1.5 mL) were added. The mixture was stirred for 3 hours at 110 °C and then allowed to cool to room temperature. The resulting mixture was filtered through a celite pad and the filtrate concentrated in vacuo. The yields of **3ac** and **3af** were determined by ^{1}H NMR spectroscopy with respect to the internal standard (1,1,2,2-tetrachloroethane). The reaction gave **3ac** and **3af** in 34% and 40% NMR, respectively.

Synthetic application

In a 25ml J-Young Schlenk, 4Å MS (200 mg; 100 mg/0.1 mmol) was heated under a vacuum for 30 minutes and was then allow to cool to room temperature under a nitrogen atmosphere. To the Schlenk tube, **3aa** (69.5 mg, 0.2 mmol) and anhydrous CH_3CN (2 mL) were added. The resulting suspension was stirred for 3 h at room temperature under a nitrogen atmosphere. Methyl trifluoromethanesulfonate (34.8 mg, 0.22 mmol) was then slowly added at room temperature and the reaction mixture was stirred for 3 h. After stirring for 3 h, the reaction mixture was allowed to cool to 0 °C and ethanol (2 mL) and DBU (33.5 mg, 0.22 mmol) were added. The reaction was then stirred for an additional 2 h at 0 °C and the progress of the reaction was monitored by TLC (10% ethyl acetate -hexane). The crude product was washed with brine (25 mL) and EtOAc (3x25 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed by evaporation. The residue was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 10/1) to afford the ester **4n** (56.4 mg, 90%) as a white powder.

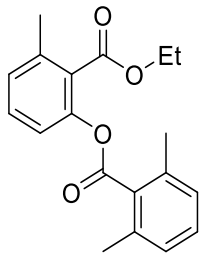
In a 25ml J-Young Schlenk, 4Å MS (400 mg; 100 mg/0.1 mmol) was heated under a vacuum for 30 minutes and was then allow to cool to room temperature under a nitrogen atmosphere. To the Schlenk tube, **3an** (148 mg, 0.4 mmol) and anhydrous CH_3CN (4 mL) were added. The resulting suspension was stirred for 3 h at room temperature under a nitrogen atmosphere. Methyl trifluoromethanesulfonate (72 mg, 0.44 mmol) was then slowly added at room temperature and the reaction mixture was stirred for 3 h. After stirring for 3 h, the reaction mixture was allowed to cool to 0 °C and ethanol (2 mL) and DBU (67 mg, 0.44 mmol) were added. The reaction was then stirred for an additional 2 h at 0 °C and the progress of the reaction was monitored by TLC (10% ethyl acetate -hexane). The crude product was washed with brine (50 mL) and EtOAc (3x50 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed by evaporation. The residue was purified by MPLC (rate:

40 mL/min., eluent: hexane/EtOAc = 10/1) to afford the ester **4n** (106.5 mg, 80%) as a white powder.

To an oven-dried 5 mL screw-capped vial, **4n** (37.5 mg, 0.1 mmol,), NaOMe (5.7 mg, 0.0105 mmol), THF (1 mL), and MeOH (0.02 ml) were added. The mixture was then stirred for overnight at room temperature. The resulting mixture was filtered through a celite pad and then concentrated in vacuo. The residue was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 10/1) to afford ethyl 2-hydroxy-6-methylbenzoate (**5**) (9.1 mg, 50%) as a white powder.

To an oven-dried 5 mL screw-capped vial, **3an** (37.5 mg, 0.1 mmol), 12 N HCI (1 mL) was added. The mixture was then stirred overnight at 80 °C. The crude product was washed with brine (20 mL) and extracted with EtOAc (3x20 mL). The combined organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed by evaporation. The residue was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 2/1) to afford **6** (19.2 mg, 89%) as a white powder.

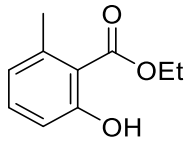
2-(ethoxycarbonyl)-3-methylphenyl 2,6-dimethylbenzoate



4a

56.4 mg, 90% yield. R_f 0.50 (hexane/EtOAc = 5:1). white solid, m.p. 82.8-83.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.26-1.30 (m, 3H), 2.41 (s, 3H), 2.48 (s, 6H), 4.32 (q, *J* = 7.1 Hz, 2H), 7.08 (d, *J* = 7.7 Hz, 2H), 7.13-7.17 (m, 2H), 7.24 (t, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.2, 19.9, 20.3, 61.5, 120.2, 127.6, 128.1, 128.1, 130.2, 130.5, 132.4, 136.1, 137.6, 147.9, 166.8, 168.0; IR (ATR) 3069 w, 2980 w, 2931 w, 2359 w, 2337 w, 1730 s, 1661 w, 1608 w, 1582 w, 1464 m, 1426 w, 1384 w, 1366 w, 1333 w, 1267 s, 1240 m, 1219 s, 1167 w, 1105 m, 1076 m, 1047 s, 938 w, 900 w, 857 w, 775 w, 735 w, 714 w; MS *m/z* (relative intensity, %) 312 (1, M^+), 134 (10), 133 (100), 105 (13); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{19}H_{20}O_4$: 312.1362; Found:312.1361.

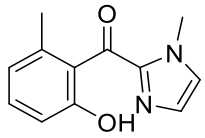
2-(ethoxycarbonyl)-3-methylphenyl 2-naphthoate



5

106.5 mg, 80% yield. R_f 0.44 (hexane/EtOAc = 5:1). white solid, m.p. 61.0-61.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.07 (t, *J* = 7.1 Hz, 3H), 2.46 (s, 3H), 4.20 (q, *J* = 7.1 Hz, 2H), 7.16 (t, *J* = 7.4 Hz, 2H), 7.40 (t, *J* = 8.0 Hz, 1H), 7.56-7.65 (m, 2H), 7.90-8.00 (m, 3H), 8.17 (dd, *J* = 8.6, 1.7 Hz, 1H), 8.76 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 20.1, 61.5, 120.7, 125.6, 126.6, 126.9, 127.0, 128.0, 128.4, 128.6, 128.8, 129.6, 130.8, 132.1, 132.6, 136.0, 138.4, 148.7, 165.1, 166.7; IR (ATR) 3460 w, 3062 w, 2981 w, 2932 w, 1737 s, 1630 w, 1607 w, 1462 w, 1395 w, 1365 w, 1272 s, 1247 m, 1220 s, 1188 s, 1082 w, 1063 w, 1017 w, 957 w, 868 w, 829 w, 774 w, 763 w; MS *m/z* (relative intensity, %) 334 (10, M^+), 156 (12), 155 (100), 127 (28); HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{21}H_{18}O_4$: 334.1205; Found: 334.1202.

(2-hydroxy-6-methylphenyl)(1-methyl-1H-imidazol-2-yl)methanone



6

19.2 mg, 89% yield. R_f0.35 (hexane/EtOAc = 1:1). white solid, m.p. 151.8-152.2 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.03 (s, 3H), 4.01 (s, 3H), 6.65-6.68 (m, 2H), 7.03 (d, *J* = 0.9 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.51 (s, 1H), 9.44 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 36.4, 117.4, 123.6, 127.0, 127.5, 128.4, 132.5, 139.7, 144.7, 155.9, 186.9; IR (ATR) 3312 w, 3108 w, 3072 w, 3024 w, 2965 w, 2857 w, 1754 w, 1740 w, 1725 w, 1710 w, 1658 m, 1602 w, 1586 w, 1550 w, 1463 m, 1400 s, 1367 w, 1289 w, 1261 w, 1224 w, 1172 w, 1150 w, 1084 w, 1029 w, 938 w, 907 s, 873 w, 785 w, 731 w, 703 w, 662 w; HRMS (DART) *m/z*: $[M+H]^+$ Calcd for $C_{12}H_{13}N_2O_2$ ($[M+H]^+$): 217.09715. Found: 217.09975.

2.5 References and notes

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Chapter 3

Ruthenium(II)-Catalyzed Arylation of C-H Bonds 2-Aroyl-Imidazoles with Aryl Halides via *N*-Monodentate Chelation Assistance

3.1 Introduction

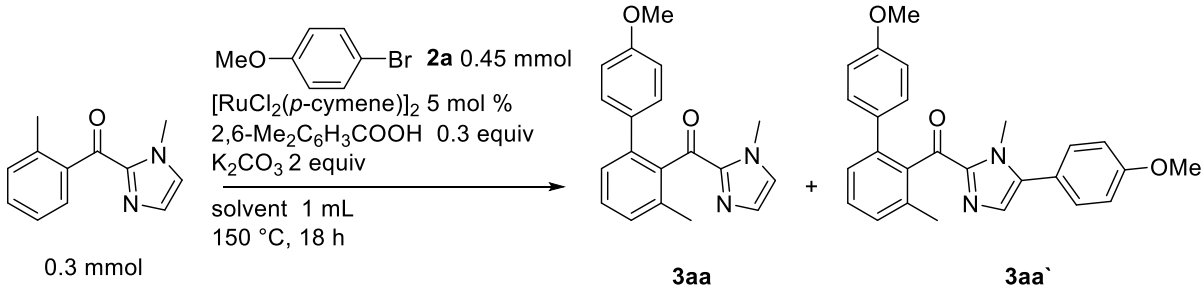
As delineated in the general introduction, Chapter 1, Chapter 2, transition-metal-catalyzed C–H functionalization has emerged as one of powerful strategies for construction of C–C, C–N, C–O, and C–halogen bonds. The arylation of C-H bonds have attracted considerable attention as a successful method for the preparation of biaryl derivatives. Since 2001, Oi and Inoue reported Ru(II)-catalyzed C-H arylation in 2-phenylpyridines with various aryl halides.[1] Following this report, the use of various substrates, such as 2-phenylpyridines, imines, oxazolines, pyrazoles, *N*-aryl triazoles, phenol, 2-phenylpyridines, aromatic amides, benzoic acids in Ru(II)-catalyzed C-H arylation were reported.[2-5] Acyloxylation reactions with carboxylic acids has been achieved by many groups. As above, a wide range of potential directing groups have been used for Ru(II)-catalyzed C-H arylation reactions. [6] To the best of our knowledge, aromatic esters C-H bonds arylation with aryl halides are still limited.[7]

Chapter 3 describes the Ru(II)-catalyzed *or*tho-C-H arylation of 2-aroyl-imidazoles that have an imidazole directing group with aryl halides. The imidazole moiety could be converted into the corresponding esters, amide via a simple procedure.

3.2 Results and Discussion

Ruthenium(II)-catalyzed C-H arylation of 2-aroyl-imidazoles with aryl halides were examined. The reaction of 2-aroyl-imidazoles (**1a**) (0.3 mmol) with 4-bromoanisole (**2a**) (0.45 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol) as the catalyst, 2,6-dimethylbenzoic acid (0.09 mmol) as an additive, and K_2CO_3 (0.6 mmol) as a base in toluene (1 mL) at 150 °C for 18 h gave the **3aa** and **3aa'** arylation products in 39% and 4% NMR yields, respectively (entry 1 in Table 1).The solvent effect were examined, NMP was found to be the best solvent (entry 1-5). The use of 1.2 equivalents **2a** and 3 equivalents of K_2CO_3 did not improve the product yield (entry 6-7).

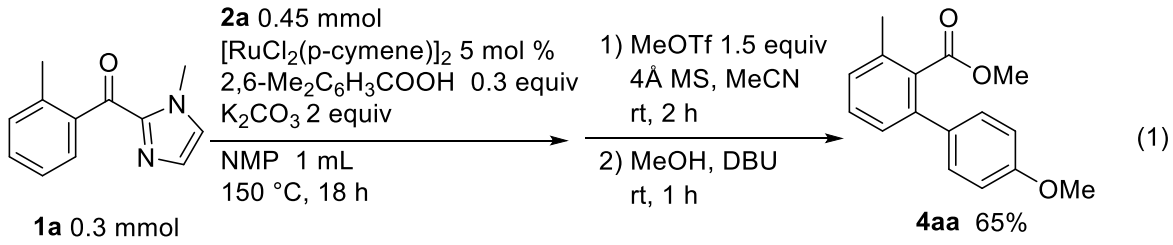
Table 1. The Ru-Catalyzed C−H arylation of **1a** with 4-bromoanisole (**2a**)[a,b]



entry	solvent	yields/%[a]	
		3aa:3aa`	**1a**
1	toluene (1)	39:4	20
2[b]	DCE (1)	Nd	56
3	1,4-dioxane (1)	29:7	29
4	*t*-amylOH (1)	13:5	23
5	NMP (1)	67:20 (50):(20)	Nd
6[c]	NMP (1)	64:18	Nd
7[c,d]	NMP (1)	62:17	Nd

[a] NMR yields. The number in parenthesis is the isolated yield. Nd refers to not detected. [b] At 120 °C. [c] **2a** (1.2 equiv) was used. [d] K_2CO_3 (3 equiv) was used.

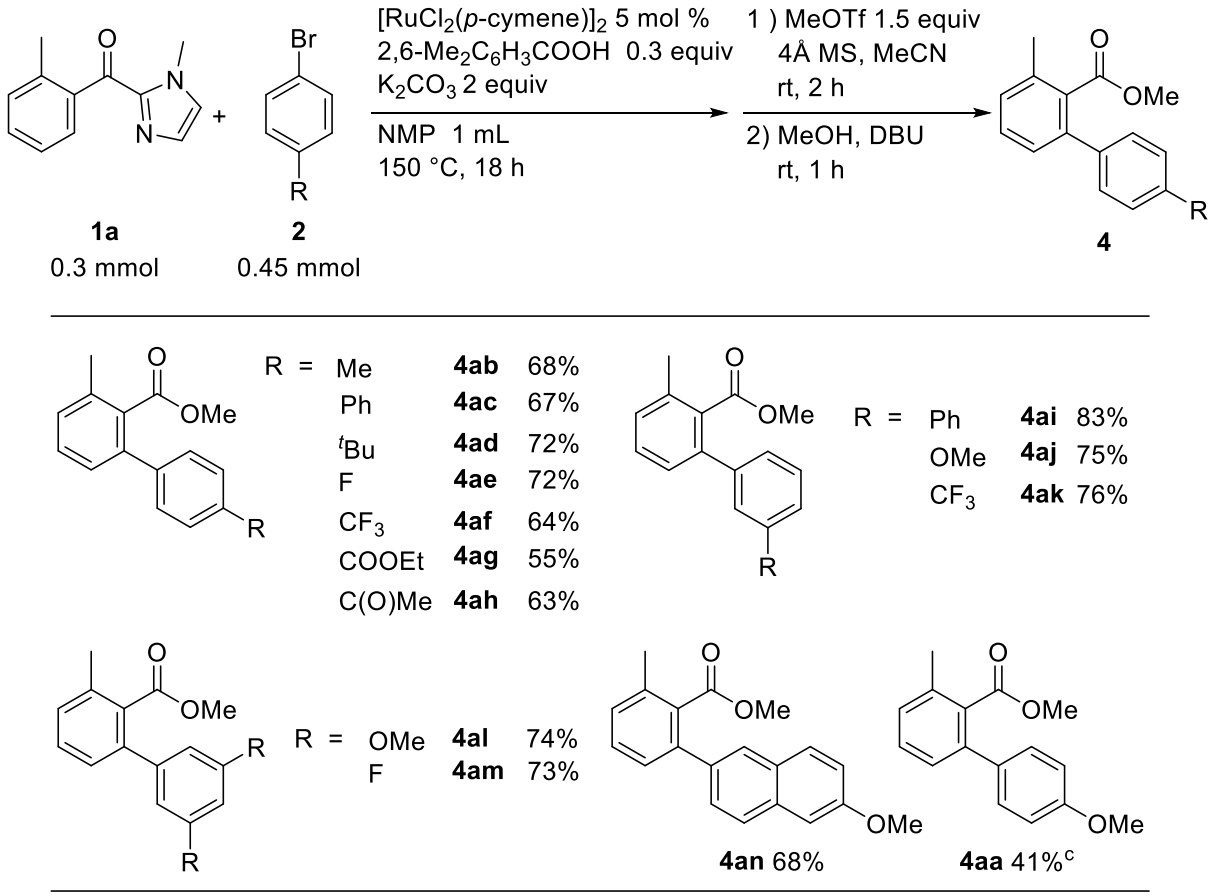
Products **3aa** and **3aa`** could be easily separated by column chromatography. However, we isolated the product after conversion to methyl ester. The mixture of arylation products **3aa** and **3aa`** was isolated by a simple column and then treated with Methyl triflate followed by MeOH and DBU, converted into the corresponding methyl ester in 65 % isolated yield.



(1)

Under the optimized reaction conditions, the scope of 2-aroyl-imidazoles with aryl halides were examined in Table 2. A wide range of functional groups, such as Ph, OMe, F, CF_3 easter and ketone were tolerated under the reaction conditions to give the corresponding arylation products in good yields (**4ab**-**4am**). The use of naphthalene bromide derivative also give the arylation product **4ah**. Remarkably, an electron-rich aryl chloride also gave the corresponding arylated product **4aa.**

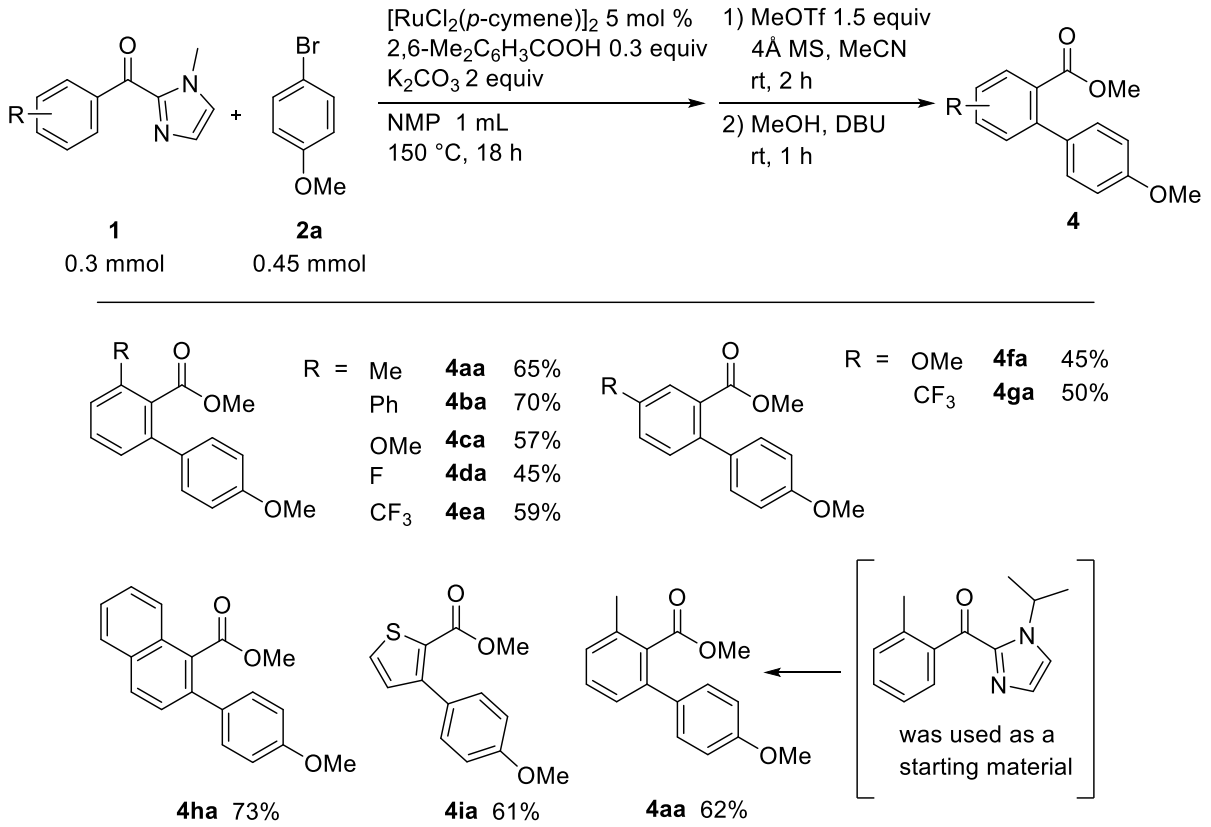
Table 2. The Ru-Catalyzed C−H arylation of 2-aroyl-imidazoles with various aryl halides[a,b]



[a] The reaction of 2-aroyl-imidazoles (**1a**) (0.3 mmol) with aryl halides (0.45 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol) as the catalyst, 2,6-dimethylbenzoic acid (0.09 mmol) as an additive, and K_2CO_3 (0.6 mmol) as a base in NMP (1 mL) at 150 °C for 18 h. [b] isolated yields. [c] 1-chloro-4-methoxybenzene was used.

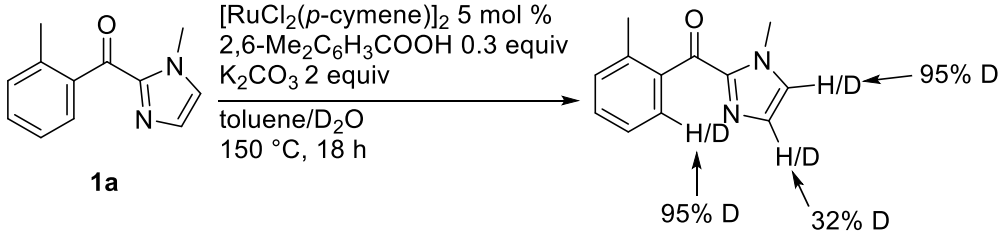
The substrates scope of 2-aroyl-imidazoles under the optimized reaction conditions in Table 3. A wide range of functional groups, such as Ph, OMe, F and CF_3 were tolerated under the reaction conditions to give the corresponding arylated products in good yields (**4aa**-**4ea**). For *m*-substituted 2-aroyl-imidazoles, such as OMe and CF_3 only less hindered C-H bonds reactivated afforded mono-arylation products in good yields (**4fa,4ga**). The use of 2-(2-naphthanoyl)-imidazole (**1h**) also gave the arylation product **4ha** in good yield. The 2-heteroaromatic-imidazoles, such as thiophene were tolerated under the reaction conditions to afforded the corresponding arylation products (**4ia**). When *N*-isopropyl-imidazole was used, the corresponding arylation product **4aa** obtained in good yields.

Table 3. The Ru-Catalyzed C−H arylation of various 2-aroyl-imidazoles with 4-bromoanisole[a,b]



[a] The reaction of various 2-aroyl-imidazoles (**1**) (0.3 mmol) with4-bromoanisole (0.45 mmol) in the presence of $[RuCl_2(p\text{-cymene})]_2$ (0.015 mmol) as the catalyst, 2,6-dimethylbenzoic acid (0.09 mmol) as an additive, and K_2CO_3 (0.6 mmol) as a base in NMP (1 mL) at 150 °C for 18 h. [b] isolated yields.

When toluene and D_2O was used as a co-solvent (4/1) under opination conditions. A significant H/D exchange in both at the *ortho*-C-H bond and at an imidazole ring in the recovered 2-aroyl-imidazoles (eq 2). The deuterium labeling experiments using **1a-*d*$_7$** were carried out under the optimal conditions (eq 3). A similar result was observed. It indicates that the cleavage of the *ortho* C-H bond was reversible.

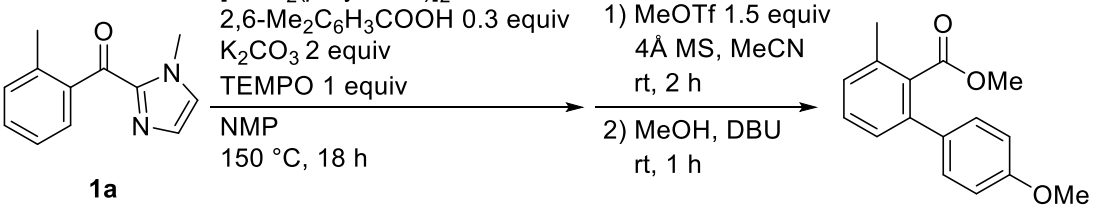


(2)

1a-d$_7$ 0.3 mmol

(3)

The radical scavenger experiment was examined. When 1 equivalents TEMPO was added to the reaction mixture, no arylation product was processed (eq 4). It indicates that oxidative addition of an aryl bromide to a Ru(II) catalyst probable via single-electron transfer (SET)-type processes, which was reported by Ackermann.[8]

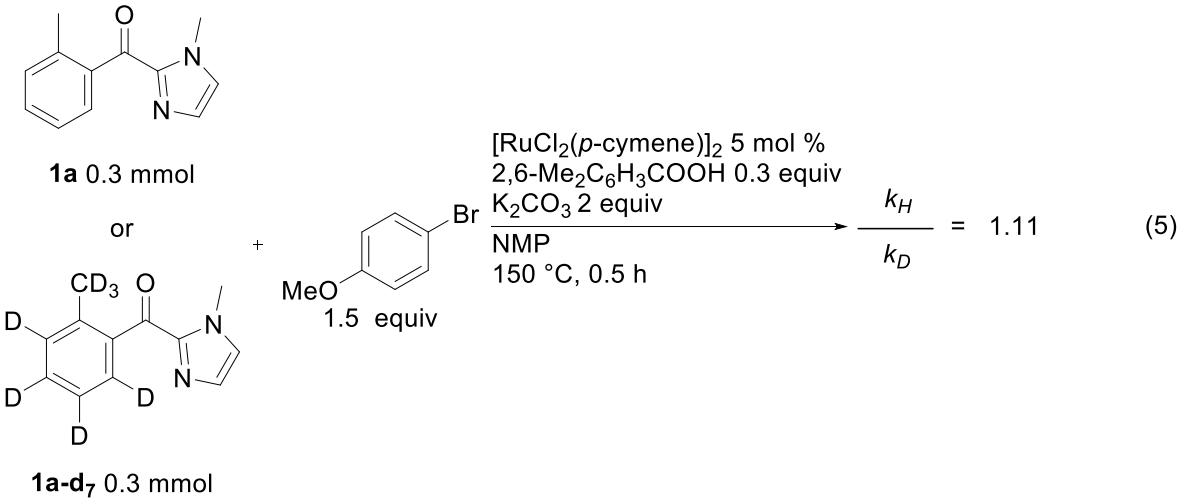


1a

3aa trace

(4)

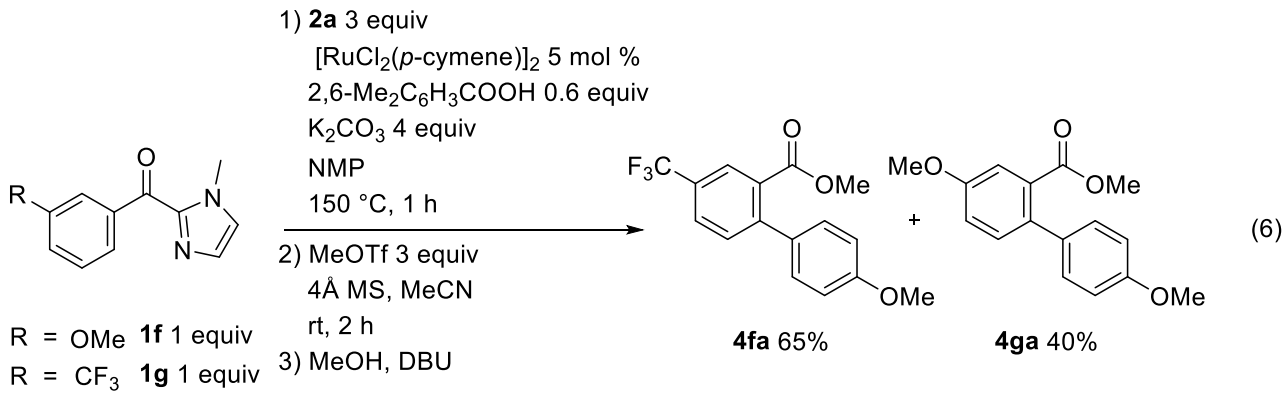
We then performed two parallel experiments between **1a** and deuterated **1a-*d*$_7$** under the optimal conditions (eq 5). The kinetic isotope effect (KIE) was determined to be 1.11. It indicated that that the C-H activation step is not rate limiting step.



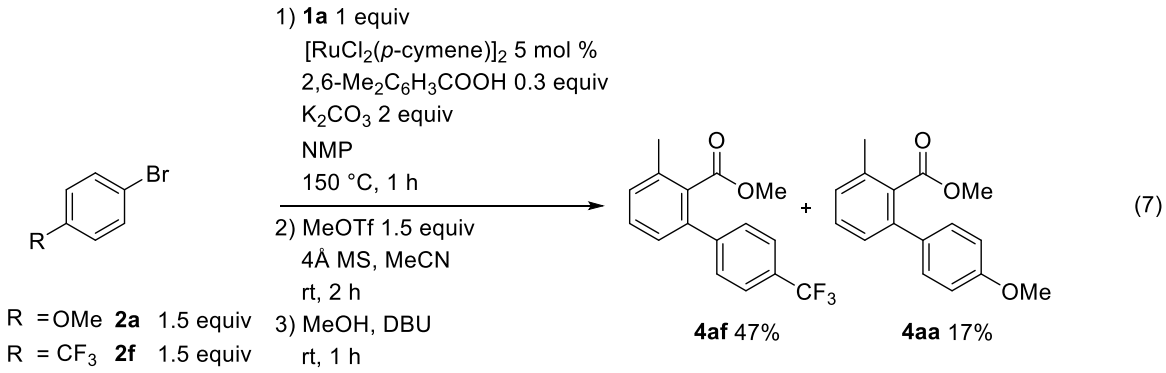
1a-d$_7$ 0.3 mmol

(5)

We next performed an intermolecular competition experiment using a 1:1 mixture **1f** and **1g** with 4-bromoanisole (eq 6). The electron-deficient substrate **1g** reacted to give **4ga** as the major product. Intermolecular competition experiments using a 1:1 mixture aryl bromides (eq 7). As a result, the electron-deficient substrate **2f** reacted to give **4af** as the major product.



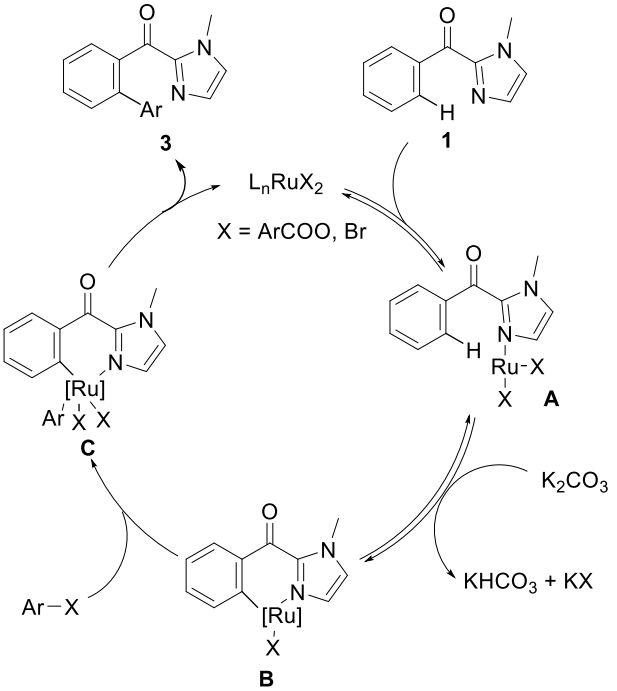
(6)



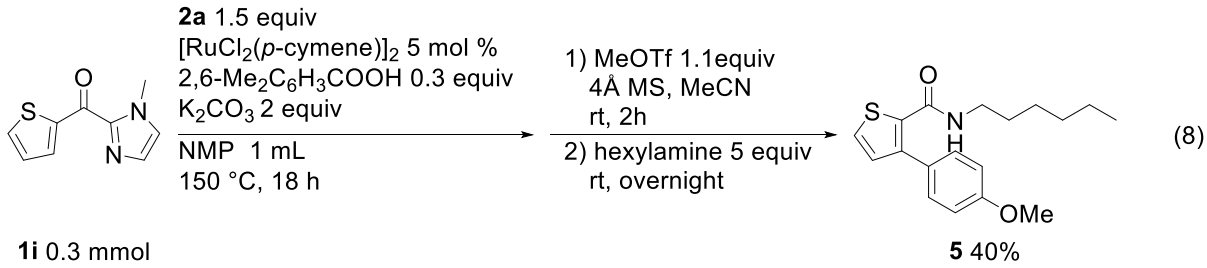
(7)

A proposed mechanism for the arylation is shown in Scheme 3. A Ru(II) biscarboxylate complex were obtained by ligand exchange.[2e] The coordination of an 2-aroyl-imidazole **1** to Ru(II) biscarboxylate complex gives the ruthenium complex **A**. Then, complex **A** undergoes reversible C-H metalation to give the six-membered ruthenacycle **B**. The oxidative addition of an aryl bromide gives the complex **C** probable via a SET-type mechanism. Reductive elimination give the arylation product **3** with the regeneration of the Ru(II) catalyst.

Scheme 3. A proposed mechanism.



The synthetic application was shown (eq 8). The corresponding amide could by converted from arylation products via a simple operation. We could successfully remove the imidazole directing group under the mild condition, afford corresponding amide **5** in 50% isolated yields.



(8)

3.3 Conclusion

In summary, we have reported the development of a new catalytic system that takes advantage of chelation assistance by an imidazole moiety. The Ru(II)-catalyzed *ortho*-arylation of C(sp^2)-H bonds of 2-aroyl-imidazoles with aryl halides by using an imidazoles moiety as *N*-monodentate chelation system. An imidazole moiety functions as an efficient *N*-monodentate directing group. Various groups, such as fluoro, methoxy, trifuoromethyl easter and ketone were tolerated under the reaction conditions. The arylation products can be converted into the corresponding ester and amide via a simple procedure.

3.4 Experimental Section

General Information.

^{1}H NMR and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, brs = broad singlet, and m = multiplet), coupling constant (Hz), and integration. In some cases, it was not possible to assign some of the peaks in the ^{13}C NMR spectra because of overlapping. Mass spectra and high resolution mass spectra (HRMS) were obtained using a JEOL JMS-T100LP spectrometer. Melting points were determined using a Yamato melting point apparatus. Column chromatography was performed with SiO_2 (Silicycle SiliaFlash F60 (230-400 mesh). Some of the compounds that were prepared were purified by LC-908 HPLC (GPC). Medium-pressure liquid chromatography (MPLC) was performed with Biotage Isolera® equipped with Biotage® SNAP Ultra flash chromatography cartridges.

Materials

Ruthenium source: [Ru(*p*-cymene)Cl_2]$_2$ (Sigma-Aldrich Co.)

Additives: K_2CO_3 (Wako Pure Chemicals Industries, Ltd), 2,6-dimethylbenzoic acid (Tokyo Chemical Industry Co., Ltd).

Aryl Halides: ethyl 4-bromobenzoate (Sigma-Aldrich Co.)

4-bromobiphenyl, 2-bromo-6-methoxynaphthalene (Wako Pure Chemicals Industries, Ltd) 1-bromo-4-methylbenzene, 1-bromo-4-methoxybenzene, 1-bromo-4-(tert-butyl)benzene, 1-bromo-4-fluorobenzene, 1-bromo-4-(trifluoromethyl)benzene, 4`-Bromoacetophenone, 3-Bromobiphenyl, 1-bromo-3-methoxybenzene, 1-bromo-3-(trifluoromethyl)benzene, 1-bromo-3,5-difluorobenzene, 1-bromo-3,5-dimethoxybenzene, 1-chloro-4-methoxybenzene (Tokyo Chemical Industry Co., Ltd)

Synthesis of Starting Materials.

All of the 2-acyl imidazole derivatives used in this study were prepared by reacting the corresponding acid or the corresponding acid chloride with 1-methylimidazole.[9]

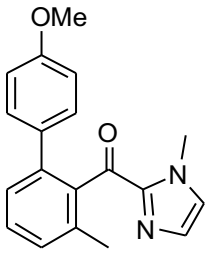
To a stirred solution of 1-methylimidazole (30 mmol) in CH_3CN (120 mL) at 0 °C, a solution of an acid chloride (45 mmol) and triethylamine (36 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature and then stirred overnight. The crude product was washed with saturated aqueous $NaHCO_3$ (20 mL), brine (50 mL), and EtOAc (3x50 mL). The organic phases were dried over anhydrous Na_2SO_4 and the solvent was removed by evaporation under reduced pressure. The residue was purified by MPLC (rate: 120 mL/min., eluent: hexane/EtOAc = 3/1).

General Procedure for the Ruthenium(II)-Catalyzed Arylation of ortho-C–H Bonds in 2-Aroyl-Imidazoles with Aryl Halides.

To an oven-dried 5 mL J-Young Schlenk tube, (1-methyl-1H-imidazol-2-yl)(2-methylphenyl)methanone (**1a**, 60.1 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015mmol), 2,6-dimethylbenzoic acid (13.5 mg, 0.09 mmol), K_2CO_3 (83 mg, 0.6 mmol) were added. The tube was evacuated and purged three times with N_2, and 1-bromo-4-methoxybenzene (**2a**, 84.2 mg, 0.45 mmol) and NMP (1 mL) were then added. The mixture was stirred at 150 °C for 18 h and then allowed to cool to room temperature. The resulting mixture was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 2/1) and the filtrate concentrated in vacuo. The mixture of products **3aa** and **3aa**' were used in the next step without further purification.

In a 10 ml two-necked flask, 4Å MS (300mg; 100 mg/0.1 mmol) was heated under a vacuum for 5 minutes and was then allow to cool to room temperature under a nitrogen atmosphere. To the Schlenk tube, **3aa** and **3aa'** (0.3 mmol) dissolved in anhydrous CH_3CN (3 mL) was added and methyl trifluoromethanesulfonate (74 mg, 0.45 mmol) was then slowly added. The mixture was stirred at room temperature for 2 h and MeOH (3 mL) and DBU (50 mg, 0.33 mmol) were then added. The reaction was then stirred for an additional 1 h at room temperature. The resulting mixture was filtered through a pad of celite and the filtrate concentrated to dryness. The residue was purified by MPLC (rate: 46 mL/min., eluent: hexane/EtOAc = 9/1) to afford the corresponding ester **4aa** (49.9 mg, 65%) as a colorless oil.

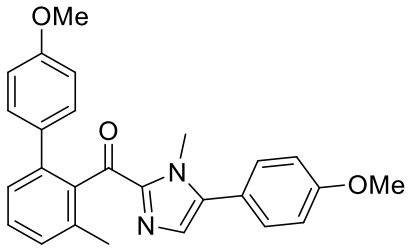
(4'-methoxy-3-methyl-[1,1'-biphenyl]-2-yl)(1-methyl-1H-imidazol-2-yl)methanone



3aa

46.6 mg, 51% yield, R_f 0.16 (hexane/EtOAc = 2:1). white solid, m.p. 135.7-136.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.30 (s, 3H), 3.75 (s, 3H), 3.87 (s, 3H), 6.73-6.77 (m, 2H), 6.84 (d, *J* = 0.5 Hz, 1H), 6.98 (d, *J* = 0.9 Hz, 1H), 7.14-7.18 (m, 3H), 7.21-7.24 (m, 1H), 7.36 (t, *J* = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 35.8, 55.3, 113.3, 126.4, 127.4, 129.1, 129.3, 130.0, 130.2, 133.5, 135.0, 138.9, 139.9, 144.4, 158.6, 190.8; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{19}H_{19}N_2O_2$ ($[M+H]^+$): 307.14410, Found: 307.14418.

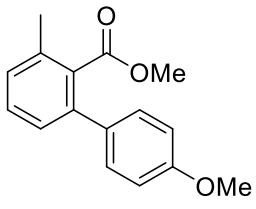
(4'-methoxy-3-methyl-[1,1'-biphenyl]-2-yl)(5-(4-methoxyphenyl)-1-methyl-1H-imidazol-2-yl)methanone



3aa'

24.2 mg, 20% yield, R_f 0.26 (hexane/EtOAc = 2:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.36 (s, 3H), 3.74 (s, 3H), 3.77 (s, 3H), 3.85 (s, 3H), 6.75-6.78 (m, 2H), 6.96-6.98 (m, 2H), 7.01 (s, 1H), 7.18-7.26 (m, 6H), 7.37 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 33.8, 55.3, 55.5, 113.3, 114.4, 120.8, 127.4, 129.2, 129.3, 129.4, 130.3, 130.5, 133.7, 135.1, 138.4, 139.4, 140.0, 145.2, 158.7, 160.2, 190.7; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{26}H_{25}N_2O_3$ ($[M+H]^+$): 413.18597, Found: 413.18762.

methyl 4'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxylatee(1097018-19-3)

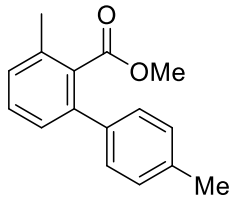


4aa

49.9 mg, 65% yield, R_f 0.37 (hexane/EtOAc = 9:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.63 (s, 3H), 3.84 (s, 3H), 6.93 (m, 7.18-7.21, 2H), 7.18-7.20 (m, 2H), 7.29-7.35

(m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 52.0, 55.3, 113.9, 127.3, 128.8, 129.4, 129.5, 133.3, 133.4, 135.4, 139.7, 159.1, 170.6; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{16}H_{17}O_3$ ($[M+H]^+$): 257.11722, Found: 257.11596

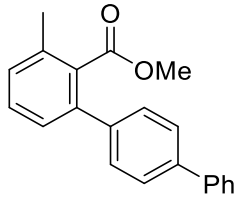
methyl 3,4'-dimethyl-[1,1'-biphenyl]-2-carboxylate (1097018-21-7)



4ab

49.1 mg, 68% yield, R_f 0.51 (hexane/EtOAc = 9:1). yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (s, 3H), 2.38 (s, 3H), 3.61 (s, 3H), 7.18-7.21 (m, 4H), 7.24-7.27 (m, 2H), 7.33 (t, J = 7.5 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 21.3, 52.0, 127.4, 128.2, 129.0, 129.2, 129.5, 133.3, 135.5, 137.2, 138.1, 140.2, 170.6; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{16}H_{17}O_2$ ($[M+H]^+$): 241.12231, Found: 241.12122

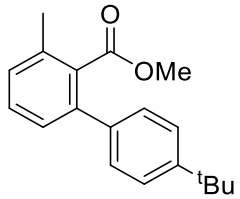
methyl 3-methyl-[1,1':4',1''-terphenyl]-2-carboxylate (1809272-56-7)



4ac

60.4 mg, 67% yield, R_f 0.43 (hexane/EtOAc = 9:1). white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.62 (s, 3H), 7.21-7.27 (m, 2H), 7.33-7.38 (m, 2H), 7.43-7.47 (m, 4H), 7.61-7.64 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 52.1, 127.1, 127.2, 127.3, 127.5, 128.7, 128.9, 129.3, 129.6, 133.2, 135.6, 139.8, 140.0, 140.2, 140.7, 170.5; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{21}H_{19}O_2$ ($[M+H]^+$): 303.13796, Found: 303.13671.

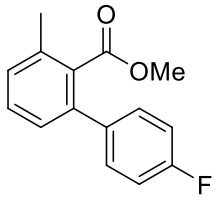
methyl 4'-(*tert*-butyl)-3-methyl-[1,1'-biphenyl]-2-carboxylate (1809272-57-8)



4ad

61.3 mg, 72% yield, R_f 0.51 (hexane/EtOAc = 9:1). yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.34 (s, 9H), 2.39 (s, 3H), 3.59 (s, 3H), 7.18-7.23 (m, 2H), 7.28-7.35 (m, 3H), 7.38-7.41 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 31.5, 34.7, 51.9, 125.3, 127.4, 128.0, 129.0, 129.5, 133.3, 135.4, 138.0, 140.1, 150.3, 170.6; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{19}H_{23}O_2$ ($[M+H]^+$): 283.16926, Found:283.16990.

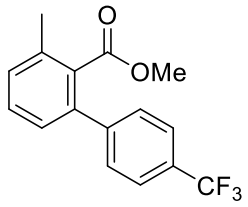
methyl 4'-fluoro-3-methyl-[1,1'-biphenyl]-2-carboxylate (1809272-60-3)



4ae

52.6 mg, 72% yield, R_f 0.46 (hexane/EtOAc = 9:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.60 (s, 3H), 7.05-7.09 (m, 2H), 7.16-7.22 (m, 2H), 7.30-7.36 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 52.0, 115.2, 115.5, 127.3, 129.5 (d, J = 21.1 Hz), 130.0(d, J = 7.6 Hz), 133.3, 135.6, 137.0 (d, J =2.9 Hz), 139.1, 162.4 (d, J = 245.3 Hz) 170.3; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{15}H_{14}FO_2$ ($[M+H]^+$): 245.09723, Found: 245.09795.

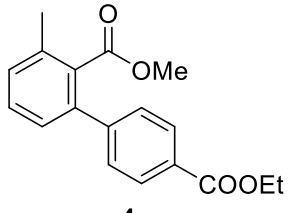
methyl 3-methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylate (486437-71-2)



4af

56.8 mg, 64% yield, R_f 0.47 (hexane/EtOAc = 9:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.59 (s, 3H), 7.18-7.20 (m, 1H), 7.26 (d, J = 8.7 Hz, 1H), 7.38 (t, J = 7.7 Hz, 1H), 7.47 (d, J = 8.0 Hz, 2H), 7.65 (d, J = 8.0 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 52.1, 124.3 (q, J = 270.2 Hz), 125.4 (q, J =3.8 Hz), 127.2, 128.7, 129.7 (q, J = 32.6 Hz), 129.8, 130.1, 133.2, 136.0, 138.9, 144.7, 170.0; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{16}H_{14}F_3O_2$ ($[M+H]^+$): 295.09404, Found: 295.09356.

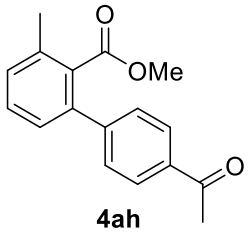
4'-ethyl 2-methyl 3-methyl-[1,1'-biphenyl]-2,4'-dicarboxylate (2040483-22-3)



4ag

49.5 mg, 55% yield, R_f 0.31 (hexane/EtOAc = 9:1). white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 3H), 2.41 (s, 3H), 3.58 (s, 3H), 4.40 (q, J = 7.1 Hz, 2H), 7.21-7.27 (m, 2H), 7.38 (t, J = 7.7 Hz, 1H), 7.44-7.45 (dt, J = 8.5, 1.9 Hz, 2H), 8.06-8.09 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.5, 19.9, 52.1, 61.1, 127.2, 128.3, 129.5, 129.7, 129.9, 133.1, 135.9, 139.3, 145.6, 166.6, 170.1; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{18}H_{19}O_4$ ($[M+H]^+$): 299.12779, Found: 299.12546.

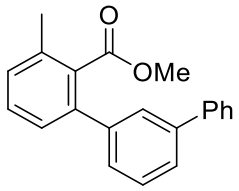
methyl 4'-acetyl-3-methyl-[1,1'-biphenyl]-2-carboxylate (1809272-58-9)



4ah

51 mg, 63% yield, R_f 0.17 (hexane/EtOAc = 9:1). white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 2.63 (s, 3H), 3.60 (s, 3H), 7.21-7.27 (m, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.44-7.48 (m, 2H), 7.98-8.00 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.9, 26.8, 52.1, 127.2, 128.5, 128.6, 129.7, 130.0, 133.1, 136.0, 136.0, 139.1, 145.9, 170.0, 197.9; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{17}H_{17}O_3$ ($[M+H]^+$): 269.11722, Found: 269.11703.

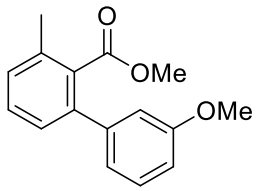
methyl 3-methyl-[1,1':3',1''-terphenyl]-2-carboxylate



4ai

75.4 mg, 83% yield, R_f 0.46 (hexane/EtOAc = 9:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.57 (s, 3H), 7.21-7.27 (m, 2H), 7.31-7.37 (m, 3H), 7.40-7.47 (m, 3H), 7.57-7.58 (m, 1H), 7.60-7.63 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 52.0, 126.2, 127.2, 127.2, 127.3, 127.5, 128.9, 128.9, 129.4, 129.6, 133.3, 135.6, 140.2, 140.9, 141.2, 141.5, 170.5; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{21}H_{19}O_2$($[M+H]^+$): 303.13796, Found: 303.13540.

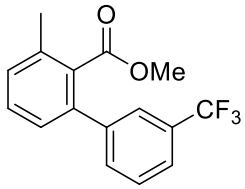
methyl 3'-methoxy-3-methyl-[1,1'-biphenyl]-2-carboxylate (2040483-23-4)



4aj

57.4 mg, 75% yield, R_f 0.35 (hexane/EtOAc = 9:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.60 (s, 3H), 3.80 (s, 3H), 6.86-6.95 (m, 3H), 7.21 (t, *J* = 6.9 Hz, 2H), 7.26-7.35 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 52.0, 55.3, 113.4, 113.6, 120.7, 127.2, 129.3, 129.4, 129.5, 133.2, 135.5, 140.0, 142.4, 159.6, 170.4; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{16}H_{17}O_3$($[M+H]^+$): 257.11722, Found: 257.11491.

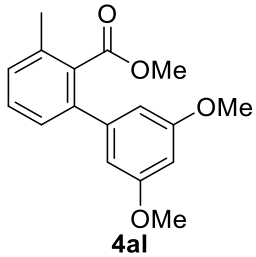
methyl 3-methyl-3'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylate (2022197-28-8)



4ak

66.9 mg, 76% yield, R_f 0.49 (hexane/EtOAc = 9:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.61 (s, 3H), 7.20-7.27 (m, 2H), 7.38 (t, *J* = 7.7 Hz, 1H), 7.49-7.56 (m, 2H), 7.59-7.61 (m, 1H), 7.64 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ19.9, 52.0, 124.2 (*J* = 271.2 Hz), 124.2 (*J* = 3.8 Hz), 125.2 (*J* = 3.8 Hz), 127.2, 128.9, 129.8, 130.8 (*J* = 32.5 Hz), 131.3, 131.7, 133.3, 136.0, 138.7, 141.8, 170.0; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{16}H_{14}F_2O_3$($[M+H]^+$): 295.09404, Found: 295.09262.

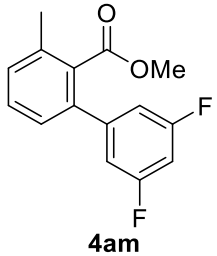
methyl 3',5'-dimethoxy-3-methyl-[1,1'-biphenyl]-2-carboxylate (2022197-29-9)



4al

63.4 mg, 74% yield, R_f 0.26 (hexane/EtOAc = 9:1). white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.39 (s, 3H), 3.64 (s, 3H), 3.79 (s, 6H), 6.44 (t, *J* = 2.3 Hz, 1H), 6.53 (d, *J* = 2.3 Hz, 2H), 7.19-7.23 (m, 2H), 7.33 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 52.1, 55.4, 99.9, 106.4, 127.1, 129.4, 129.5, 133.2, 135.5, 140.1, 143.0, 160.7, 170.4; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{17}H_{19}O_4$($[M+H]^+$): 287.12779, Found: 287.12680

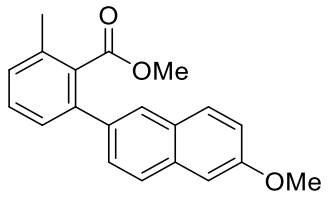
methyl 3',5'-difluoro-3-methyl-[1,1'-biphenyl]-2-carboxylate (2040483-25-6)



4am

57.7 mg, 73% yield, R_f 0.49 (hexane/EtOAc = 9:1). white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (s, 3H), 3.67 (s, 3H), 6.77-6.82 (m, 1H), 6.88-6.90 (m, 2H), 7.16-7.18 (m, 1H), 7.24-7.27 (m, 1H), 7.36 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.8, 52.2, 103.0 (t, *J* = 24.9 Hz), 111.5 (dd, *J* = 18.7, 6.7 Hz), 127.0, 129.8, 130.2, 133.1, 136.0, 138.0, 144.3 (t, *J* =9.5 Hz), 162.9 (dd, *J* = 274.4, 12.5 Hz), 169.8; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{15}H_{13}F_2O_2$($[M+H]^+$): 263.08731, Found: 263.08727.

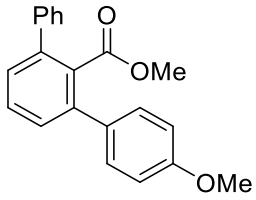
methyl 2-(6-methoxynaphthalen-2-yl)-6-methylbenzoate



4an

62.5 mg, 68% yield, R_f 0.31 (hexane/EtOAc = 9:1). white solid, m.p. 105.4-106.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.53 (s, 3H), 3.91 (s, 3H), 7.14-7.17 (m, 2H), 7.20-7.23 (m, 1H), 7.28-7.30 (m, 1H), 7.36 (t, *J* = 7.5 Hz, 1H), 7.46 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.73-7.76 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 13C-NMR (101 MHz, CHLOROFORM-D) δ 19.8, 52.0, 55.4, 105.6, 119.3, 126.9, 127.0, 127.1, 127.6, 128.9, 129.1, 129.6, 129.8, 133.4, 133.8, 135.6, 136.2, 140.2, 158.0, 170.6; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{20}H_{19}O_3$($[M+H]^+$): 307.13287, Found: 307.13287.

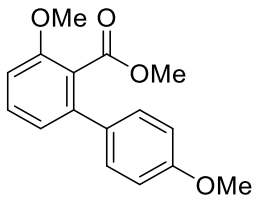
methyl 4-methoxy-[1,1':3',1''-terphenyl]-2'-carboxylate (1809272-30-7)



4ba

66.5 mg, 70% yield, R_f 0.23 (hexane/EtOAc = 9:1). white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.40 (s, 3H), 3.82 (s, 3H), 6.91-6.95 (m, 2H), 7.31-7.41 (m, 9H), 7.47 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.9, 55.3, 113.9, 127.6, 128.4, 128.5, 128.6, 129.0, 129.4, 129.6, 132.9, 132.9, 140.0, 140.4, 140.7, 159.2, 170.1; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{21}H_{19}O_3$($[M+H]^+$): 319.13287, Found: 319.13233.

methyl 3,4'-dimethoxy-[1,1'-biphenyl]-2-carboxylate (1809272-29-4)

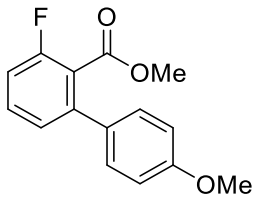


4ca

46.3 mg, 57% yield, R_f 0.14 (hexane/EtOAc = 9:1). white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.82 (s, 3H), 3.86 (s, 3H), 6.89-6.93 (m, 3H), 6.95-6.97 (m, 1H), 7.31-7.34 (m, 2H), 7.36-7.40 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.3, 55.3, 56.1, 109.5, 113.9, 122.1,

123.1, 129.4, 130.5, 132.5, 140.9, 156.5, 159.3, 168.9; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{16}H_{17}O_4$($[M+H]^+$): 273.11214, Found: 273.11086.

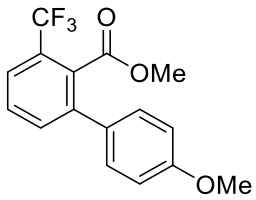
methyl 3-fluoro-4'-methoxy-[1,1'-biphenyl]-2-carboxylate (1809272-33-0)



4da

35.3 mg, 45% yield, R_f 0.23 (hexane/EtOAc = 9:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.84 (s, 3H), 6.92-6.96 (m, 2H), 7.06-7.10 (m, 1H), 7.16-7.18 (m, 1H), 7.28-7.32 (m, 2H), 7.39-7.44 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.6, 55.4, 114.1 (d, J = 21 Hz), 114.3, 121.5 (d, J = 16.3 Hz), 125.5 (d, J = 2.8 Hz), 129.4, 131.3 (d, J = 9.6 Hz), 131.8, 142.2, 159.6, 159.8 (d, J = 249.2 Hz),166.6; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{15}H_{14}FO_3$($[M+H]^+$): 261.09215, Found: 261.09131.

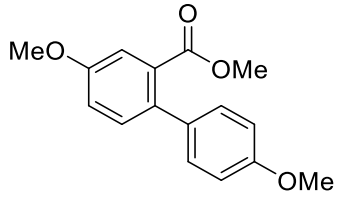
methyl 4'-methoxy-3-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylate (1809272-37-4)



4ea

55.0 mg, 59% yield, R_f 0.26 (hexane/EtOAc = 9:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67 (s, 3H), 3.85 (s, 3H), 6.92-6.96 (m, 2H), 7.27-7.31 (m, 2H), 7.53-7.58 (m, 2H), 7.65-7.67 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.7, 55.4, 114.0, 123.6 (q, J = 273.1 Hz), 124.7 (d, J = 3.8 Hz), 127.7 (q, J = 31.6 Hz), 129.6, 129.7, 131.4, 131.5, 133.7, 141.1, 159.7, 168.1; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{16}H_{14}F_3O_3$($[M+H]^+$): 311.08896, Found: 311.08819.

methyl 4,4'-dimethoxy-[1,1'-biphenyl]-2-carboxylate (185992-69-2)

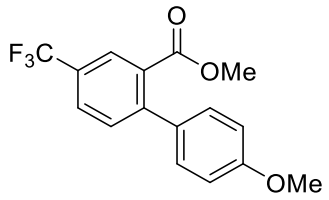


4fa

36.8 mg, 45% yield, R_f0.18 (hexane/EtOAc = 9:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 6.90-6.93 (m, 2H), 7.05 (dd, J = 8.5, 2.7 Hz, 1H),

7.19-7.22 (m, 2H), 7.27 (d, *J* = 8.5 Hz, 1H), 7.31 (d, *J* = 2.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.2, 55.4, 55.7, 113.6, 114.4, 117.6, 129.6, 131.7, 132.0, 133.5, 134.6, 158.4, 158.8, 169.3; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{16}H_{17}O_4([M+H]^+)$: 273.11214, Found: 273.11160.

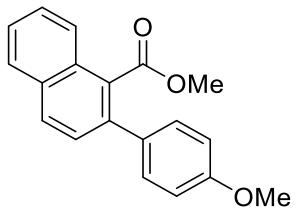
methyl 4'-methoxy-4-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylate (1809272-44-3)



4ga

46.7 mg, 50% yield, R_f 0.31 (hexane/EtOAc = 9:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (s, 3H), 3.85 (s, 3H), 6.94-6.98 (m, 2H), 7.23-7.27 (m, 2H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.73-7.76 (m, 1H), 8.05-8.06 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.5, 55.4, 113.9, 123.9 (q, *J* =271.2 Hz) ,127.0 (q, *J* = 3.9 Hz), 127.8 (q, *J* = 3.8 Hz), 129.3 (q, *J* = 33.5 Hz), 129.6, 131.4, 131.5, 132.2, 145.7, 159.7, 168.2; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{16}H_{14}F_3O_3([M+H]^+)$: 311.08896, Found: 311.08765.

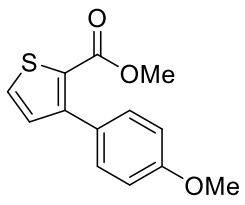
methyl 2-(4-methoxyphenyl)-1-naphthoate (1415046-18-2)



4ha

64.3 mg, 73% yield, R_f 0.26 (hexane/EtOAc = 9:1). white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (s, 3H), 3.84 (s, 3H), 6.95-6.99 (m, 2H), 7.40-7.43 (m, 2H), 7.48-7.57 (m, 3H), 7.87 (dd, *J* = 8.3, 1.0 Hz, 1H), 7.91-7.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.4, 55.4, 114.1, 125.0, 126.3, 127.5, 127.7, 128.2, 129.8, 130.0, 130.1, 132.2, 133.3, 137.7, 159.3, 170.4; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{19}H_{17}O_3([M+H]^+)$: 293.11722, Found: 293.11595.

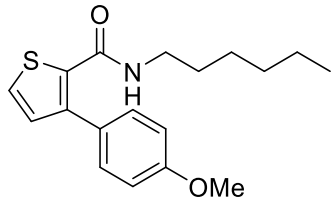
methyl 3-(4-methoxyphenyl)thiophene-2-carboxylate (91903-31-0)



4ia

45.2 mg, 61% yield, R_f 0.29 (hexane/EtOAc = 9:1). white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.78 (s, 3H), 3.84 (s, 3H), 6.92-6.96 (m, 2H), 7.06 (d, *J* = 5.3 Hz, 1H), 7.40-7.44 (m, 2H), 7.48 (d, *J* = 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 52.0, 55.4, 113.4, 126.1, 128.0, 130.3, 130.7, 131.7, 148.6, 159.5, 162.7; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{13}H_{13}O_3S([M+H]^+)$: 249.05799, Found: 249.05727.

***N*-hexyl-3-(4-methoxyphenyl)thiophene-2-carboxamide**



5

38.2 mg, 40% yield, R_f 0.37 (hexane/EtOAc = 3:1). colorless oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.86 (t, *J* = 7.1 Hz, 3H), 1.05-1.34 (m, 8H), 3.19-3.24 (m, 2H), 3.86-3.87 (m, 3H), 5.64 (s, 1H), 6.96-7.01 (m, 3H), 7.34-7.37 (m, 2H), 7.42 (d, J = 5.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.1, 22.6, 26.6, 29.2, 31.5, 39.7, 55.5, 114.5, 127.8, 128.4, 130.5, 131.0, 134.9, 141.4, 159.9, 162.3; HRMS (DART) m/z: $[M+H]^+$ Calcd for $C_{18}H_{24}NO_2S([M+H]^+)$: 318.15223, Found: 318.15139.

H/D Exchange

To an oven-dried 5 mL J-Young Schlenk tube, (1-methyl-1H-imidazol-2-yl)(2-methylphenyl)methanone (**1a**, 60.1 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015mmol), 2,6-dimethylbenzoic acid (13.5 mg, 0.09 mmol), K_2CO_3 (83 mg, 0.6 mmol) were added. The tube was evacuated and purged three times with N_2, and toluene (0.8 mL), and D_2O (0.2 ml) were then added. The mixture was stirred at 150 °C for 18 h and then allowed to cool to room temperature. The resulting mixture was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 2/1) and the filtrate concentrated to dryness in vacuo. The starting material **1a** was recovered (22.3 mg, 37%) as a white powder and the deuterium content was determined by ^{1}H NMR.

Deuterium Scrambling Experiments

To an oven-dried 5 mL J-Young Schlenk tube, **1a-*d*$_7$** (62.2 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015mmol), 2,6-dimethylbenzoic acid (13.5 mg, 0.09 mmol), K_2CO_3 (83 mg, 0.6 mmol) were added. The tube was evacuated and purged three times with N_2, and NMP (1 ml) were then added. The mixture was stirred at 150 °C for 1 h and then allowed to cool to room temperature. The resulting mixture was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 2/1) and the filtrate concentrated in vacuo. The starting material **1a-*d*$_6$**

(61.6 mg, 99%) was recovered as a white powder and the deuterium content was determined by ^{1}H NMR.

Experiment with TEMPO

To an oven-dried 5 mL J-Young Schlenk tube, (1-methyl-1H-imidazol-2-yl)(2-methylphenyl)methanone (**1a**, 60.1 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015mmol), 2,6-dimethylbenzoic acid (13.5 mg, 0.09 mmol), K_2CO_3 (83 mg, 0.6 mmol), TEMPO (46.9 mg, 0.3 mmol) were added. The tube was evacuated and purged three times with N_2, and 1-bromo-4-methoxybenzene (**2a**, 84.2 mg, 0.45 mmol) and NMP (1 mL) were then added. The mixture was stirred at 150 °C for 18 h and then allowed to cool to room temperature. The resulting mixture was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 2/1) and the filtrate concentrated to dryness in vacuo. The mixture of products **3aa** and **3aa'** were used in the next step without further purification.

In a 10 mL two-necked flask, 4Å MS (300mg; 100 mg/0.1 mmol) was heated under a vacuum for 5 minutes and was then allow to cool to room temperature under a nitrogen atmosphere. To the Schlenk tube, **3aa** and **3aa'** (0.3 mmol) dissolved in anhydrous CH_3CN (3 mL) was added and methyl trifluoromethanesulfonate (74 mg, 0.45 mmol) was then slowly added. The mixture was stirred at room temperature for 2 h and MeOH (3 mL) and DBU (50 mg, 0.33 mmol) were then added. The reaction was then stirred for an additional 1 h at room temperature. The resulting mixture was filtered through a pad of celite and the filtrate concentrated to dryness. The residue was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 9/1) to afford the recovered **1a** and the product **4aa** in trace.

KIE Experiments

Two parallel reactions using **1a** and **1a-*d*$_7$** were carried out in two different oven-dried 5 mL J-Young Schlenk tube. To the tube, **1a** or **1a-*d*$_7$** (0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015 mmol), 2,6-dimethylbenzoic acid (13.5 mg, 0.09 mmol), K_2CO_3 (83 mg, 0.6 mmol) were added. The tube was evacuated and purged three times with N_2, and 1-bromo-4-methoxybenzene (**2a**, 84.2 mg, 0.45 mmol) and NMP (1 mL) were then added. The mixture was stirred at 150 °C for 0.5 h and then allowed to cool to room temperature. The resulting mixture was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 2/1) and the filtrate concentrated in vacuo. The mixture of products **3aa** and **3aa**' were used in the next step without further purification.

In a 10 mL two-necked flask, 4Å MS (300mg; 100 mg/0.1 mmol) was heated under a vacuum for 5 minutes and was then allow to cool to room temperature under a nitrogen atmosphere. To the Schlenk tube, **3aa** and **3aa'** (0.3 mmol) dissolved in anhydrous CH_3CN (3 mL) was added and methyl trifluoromethanesulfonate (74 mg, 0.45 mmol) was then slowly added. The mixture was stirred at room temperature for 2 h and MeOH (3 mL) and DBU (50 mg, 0.33 mmol) were then added. The reaction was then stirred for an additional 1 h at room temperature. The resulting mixture was filtered through a pad of celite and the filtrate concentrated to dryness.

The residue was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 9/1) to afford the recovered **1a** (8.5 mg, 14%) and **1a-*d*$_7$** (14.3 mg, 23%) as a white power. The KIE value was determined to be 1.11, suggesting that the C–H activation step is not the rate limiting step.

Competition Experiments (Scheme 4e and 4f)

To an oven-dried 5 mL J-Young Schlenk tube, (3-methoxyphenyl)(1-methyl-1H-imidazol-2-yl)methanone (**1f**, 64.9 mg, 0.3 mmol), (1-methyl-1H-imidazol-2-yl)(3-(trifluoromethyl)phenyl)methanone (**1g**, 76.3 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015 mmol), 2,6-dimethylbenzoic acid (27.0 mg, 0.18 mmol), K_2CO_3 (166 mg, 1.2 mmol) were added. The tube was evacuated and purged three times with N_2, and 1-bromo-4-methoxybenzene (**2a**, 168.4 mg, 0.9 mmol) and NMP (2 mL) were then added. The mixture was stirred at 150 °C for 1 h and then allowed to cool to room temperature. The resulting mixture was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 2/1) and the filtrate concentrated in vacuo. The products were used in the next step without further purification.

In a 10 mL two-necked flask, 4Å MS (300mg) was heated under a vacuum for 5 minutes and was then allow to cool to room temperature under a nitrogen atmosphere. To the Schlenk tube, the mixture dissolved in anhydrous CH_3CN (6 mL) was added and methyl trifluoromethanesulfonate (148 mg, 0.45 mmol) was then slowly added. The mixture was stirred at room temperature for 2 h and MeOH (6 mL) and DBU (100 mg, 0.66 mmol) were then added. The reaction was then stirred for an additional 1 h at room temperature. The resulting mixture was filtered through a pad of celite and the filtrate concentrated to dryness. The residue was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 9/1) to afford a mixture of the corresponding esters. The yields of **4fa** and **4ga** were determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as the internal standard. The reaction gave **4ga** and **4fa** in 65% and 40% NMR yield, respectively.

To an oven-dried 5 mL J-Young Schlenk tube, (1-methyl-1H-imidazol-2-yl)(2-methylphenyl)methanone (**1a**, 60.1 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015mmol), 2,6-dimethylbenzoic acid (13.5 mg, 0.09 mmol), K_2CO_3 (83 mg, 0.6 mmol) were added. The tube was evacuated and purged three times with N_2, and 1-bromo-4-methoxybenzene (**2a**, 84.2 mg, 0.45 mmol), 1-bromo-4-(trifluoromethyl)benzene (**2f,** 101.25 mg, 0.45 mmol), and NMP (1 mL) were then added. The mixture was stirred at 150 °C for 1 h and then allowed to cool to room temperature. The resulting mixture was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 2/1) and the filtrate concentrated in vacuo. The mixture of products was used in the next step without further purification.

In a 10 mL two-necked flask, 4Å MS (300mg; 100 mg/0.1 mmol) was heated under a vacuum for 5 minutes and was then allow to cool to room temperature under a nitrogen atmosphere. To the Schlenk tube, the mixture dissolved in anhydrous CH_3CN (3 mL) was added and methyl trifluoromethanesulfonate (74 mg, 0.45 mmol) was then slowly added. The mixture was stirred at room temperature for 2 h and MeOH (3 mL) and DBU (50 mg, 0.33 mmol) were then added.

The reaction was then stirred for an additional 1 h at room temperature. The resulting mixture was filtered through a pad of celite and the filtrate concentrated to dryness. The residue was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 9/1) to afford a mixture of the corresponding ester. The yields of **4af** and **4aa** were determined by ^{1}H NMR spectroscopy with 1,1,2,2-tetrachloroethane as the internal standard. The reaction gave **4af** and **4aa** in 47% and 17% NMR yield, respectively.

Synthetic application

To an oven-dried 5 mL J-Young Schlenk tube, (1-methyl-1H-imidazol-2-yl)(thiophen-2-yl)methanone (**1i**, 57.7 mg, 0.3 mmol), [Ru(*p*-cymene)Cl_2]$_2$ (9.2 mg, 0.015mmol), 2,6-dimethylbenzoic acid (13.5 mg, 0.09 mmol), K_2CO_3 (83 mg, 0.6 mmol) were added. The tube was evacuated and purged three times with N_2, and 1-bromo-4-methoxybenzene (**2a**, 84.2 mg, 0.45 mmol) and NMP (1 mL) were then added. The mixture was stirred at 150 °C for 18 h and then allowed to cool to room temperature. The resulting mixture was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 2/1) and the filtrate concentrated in vacuo. The arylated products were used in the next step without further purification.

In a 10 mL two-necked flask, 4Å MS (300mg; 100 mg/0.1 mmol) was heated under a vacuum for 5 minutes and was then allow to cool to room temperature under a nitrogen atmosphere. To the Schlenk tube, the arylated products dissolved in anhydrous CH_3CN (3 mL) was added and methyl trifluoromethanesulfonate (74 mg, 0.45 mmol) was then slowly added. The mixture was stirred at room temperature for 2 h and hexylamine (152 mg, 1.5 mmol) were then added. The reaction was then stirred for overnight at room temperature. The resulting mixture was filtered through a pad of celite and the filtrate concentrated to dryness. The residue was purified by MPLC (rate: 40 mL/min., eluent: hexane/EtOAc = 3/1) to afford the corresponding amide **5** (38.2 mg, 40%) as a colorless oil.

3.5 References and notes

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Conclusion

In this study, a series of ruthenium-catalyzed C-H functionalization reactions in which *N*-monodentate or *N,N'*-bidentate directing groups are used was investigated.

The Ru(II)-catalyzed C-H alkylation of *ortho*-C-H bonds in aromatic amides with vinylsilanes is reported in Chapter 1. The use of an 8-aminoquinoline moiety as the directing group is indispensable for the success of this reaction. The reaction appears to proceed through a carbometalation mechanism, on the basis of deuterium-labeling experiments. The reaction provides a new opportunity for introducing silyl group into an organic compound.

The Ru(II)-catalyzed direct acyloxylation of *ortho*-C-H bonds in 2-aroyl-imidazoles with carboxylic acids is reported in Chapter 2. Deuterium labeling experiments indicate that the cleavage of the C-H bond is the rate determining step. The reaction appears to proceed through a Base-Assisted Internal Electrophilic Substitution (BIES) mechanism based on the electronic effects of substituents on the aromatic ring in the substrates. An imidazole moiety was converted into the corresponding esters via a simple, straightforward procedure.

The Ru(II)-catalyzed direct C-H arylation of *ortho*-C-H bonds in 2-aroyl-imidazoles with aryl bromides is reported in Chapter 3. Deuterium labeling experiments indicated that the cleavage of the C-H bond is not the rate determining step. Curiously, the reaction was inhibited when TEMPO was added to the reaction mixture, indicating that the reaction appears to proceed through a SET-type mechanism. The imidazole moiety can be easily converted into the corresponding esters and amides under mild reaction conditions.

In summary, a series of Ru(II)-catalyzed C-H functionalization reactions utilizing *N*-monodentate or *N,N'*-bidentate directing group are reported in this dissertation. The reactions that are reported in this dissertation provides new opportunities for introducing a silyl group, an oxygen functionality, and an aryl group into an organic compound. The results indicate that an imidazole moiety functioned as a potential directing group for C-H functionalization as well as masked esters and amides. The reactions provided other examples of C-H functionalization using 2-acylimidazoles. The findings reported in this dissertation indicate that an imidazole moiety has the potential for functioning as a new type of directing group, which would provide a new system for Ru(II)-catalyzed C-H functionalization reactions.

List of Publications

(1) Ruthenium(II)-Catalyzed Alkylation of C-H Bonds in Aromatic Amides with Vinylsilanes

Chen-an Wang, Supriya Rej and Naoto Chatani.

Chem. Lett. **2019**, *48*, 1185–1187.

(2) Ru(II)-Catalyzed Acyloxylation of the ortho-C-H Bond in 2-Aroyl-imidazoles with Carboxylic Acids

Chen-an Wang and Naoto Chatani.

Org. Chem. Front. **2020**, *7*, 2955-2959.

(3) Ru(II)-Catalyzed Arylation of the ortho-C-H Bonds in 2-Aroyl-Imidazoles with Aryl Halides

Chen-an Wang and Naoto Chatani

Chem. Lett. **2020**, https://doi.org/10.1246/cl.200886.