Studies on Reactions Promoted by Photo-generated Bromine Radical

Tairin Kawasaki

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Preface

The studies in this thesis have been carried out under the direction of Professor Masahiro Murakami at Kyoto University form April 2016 to March 2022. The studies are concerned with reactions prompted by photoinduced formal homolysis of Ni(II)–Br bonds.

The author would like to express his sincerest gratitude to Supervisor, Professor Masahiro Murakami for his continuous guidance, encouragement, and stimulating discussions throughout this study. All the works in this thesis could be achieved with his constant supervisions.

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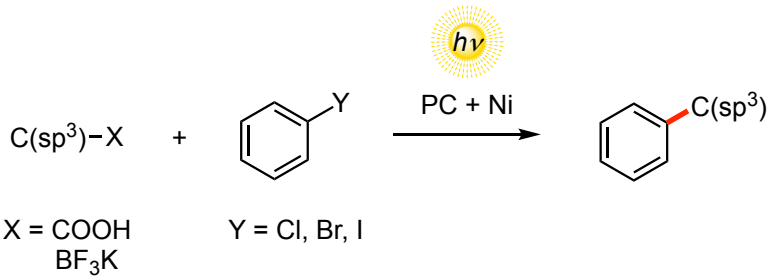
General Introduction

Rise of Reactions Combining Photoredox Catalysis with Transition-Metal Catalysis

The first appearance of combination of photoredox and transition-metal catalysis was the decarboxylative coupling of carboxylic acids with aryl halides forming alkylarenes,[1] and the coupling of alkyltrifluoroborates with aryl bromides forming alkylarenes[2] in 2014 (Scheme GI-1). Both reactions are catalyzed by an iridium photoredox catalyst and a nickel catalyst. Photoredox reactions catalyzed by iridium complexes had been developed for transformation of organic compounds in a radical mechanism.[3] Iridium polypyridyl complexes absorb visible light to get the excited state that induces single-electron transfer (SET). On the other hand, nickel polypyridyl complexes often catalyze coupling reactions in radical mechanisms under thermal conditions.[4] The radical-based reaction successfully merged the two deferent strategies that had been developed independently so far.

Scheme GI-1. Photoredox/Transition-Metal Dual Catalysis

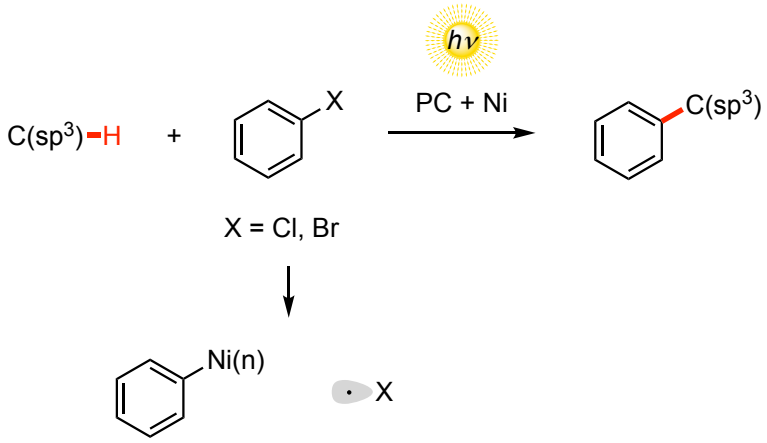


Photoinduced C(sp^3)–H Bonds Arylation with Aryl Halides

In 2016, Doyle[5] and Molander[6] independently reported a direct arylation of C(sp^3)–H bonds with aryl halides (Scheme GI-2). It was a breakthrough to use easily available aryl halides as a source of halogen radical that abstracts a hydrogen atom from

a C(sp^3)–H bond. The halogen radical is proposed to be generated from an aryl nickel intermediate there. After these reports, a number of photoinduced functionalization of C(sp^3)–H bonds with halogenated compounds have been developed.[7] Although those reactions are powerful tools to directly transform a C(sp^3)–H bond, those have a limitation to use essentially halogenated reagents that require to be prepared. The use of halogenated reagents also requires an additional base to neutralize the hydrogen halide generated through the reactions.

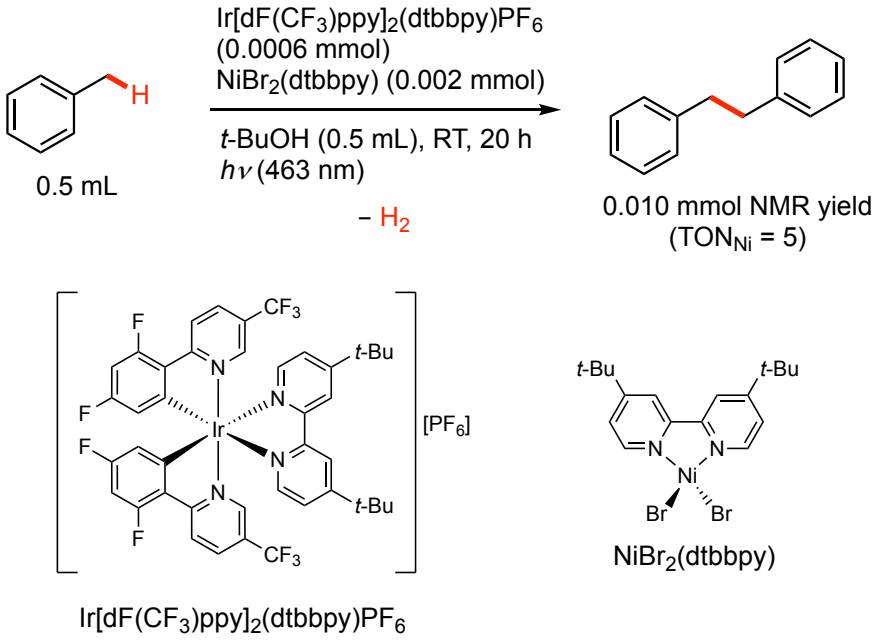
Scheme GI-2. Photoinduced C(sp^3)–H Bonds Arylation with Aryl Halides



Initial Findings Related to the Studies in This Thesis

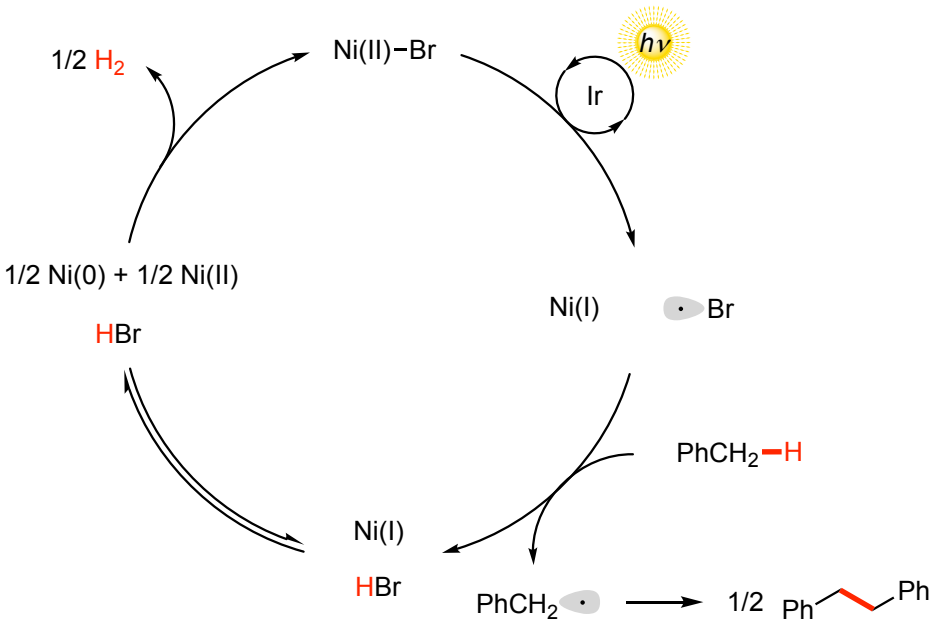
The studies in this thesis originates from the author's preliminary finding in his master course study (Scheme GI-3). When Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.0006 mmol) and $NiBr_2$(dtbbpy) (0.002 mmol) in toluene (0.5 mL) and *t*-BuOH (0.5 mL) was irradiated with visible light at room temperature, 0.010 mmol of bibenzyl was obtained (5 equiv to Ni). This result was interesting because the C(sp^3)–H bond was cleaved forming the new C–C bond, and additionally because no oxidant was required in such an oxidative transformation, presumably involving molecular dihydrogen.

Scheme GI-3. Photoinduced Dehydrogenative Homo-Coupling of Toluene



The hypothetical mechanism of the reaction the author found was assumed as shown in Scheme GI-4. At first, a Ni(II)–Br bond is homolytically cleaved by the action of the iridium photocatalyst to generate a nickel(I) species and a bromine radical. The bromine radical abstracts a hydrogen atom from toluene to generate a hydrogen bromide and a benzyl radical[8] from which dimerization reaction takes place to furnish bibenzyl. The nickel(I) species can disproportionate to a nickel(II) species and a nickel(0) species.[9] The nickel(0) species reduces two equivalent of proton to regenerate the nickel(II) species with hydrogen evolution.[10]

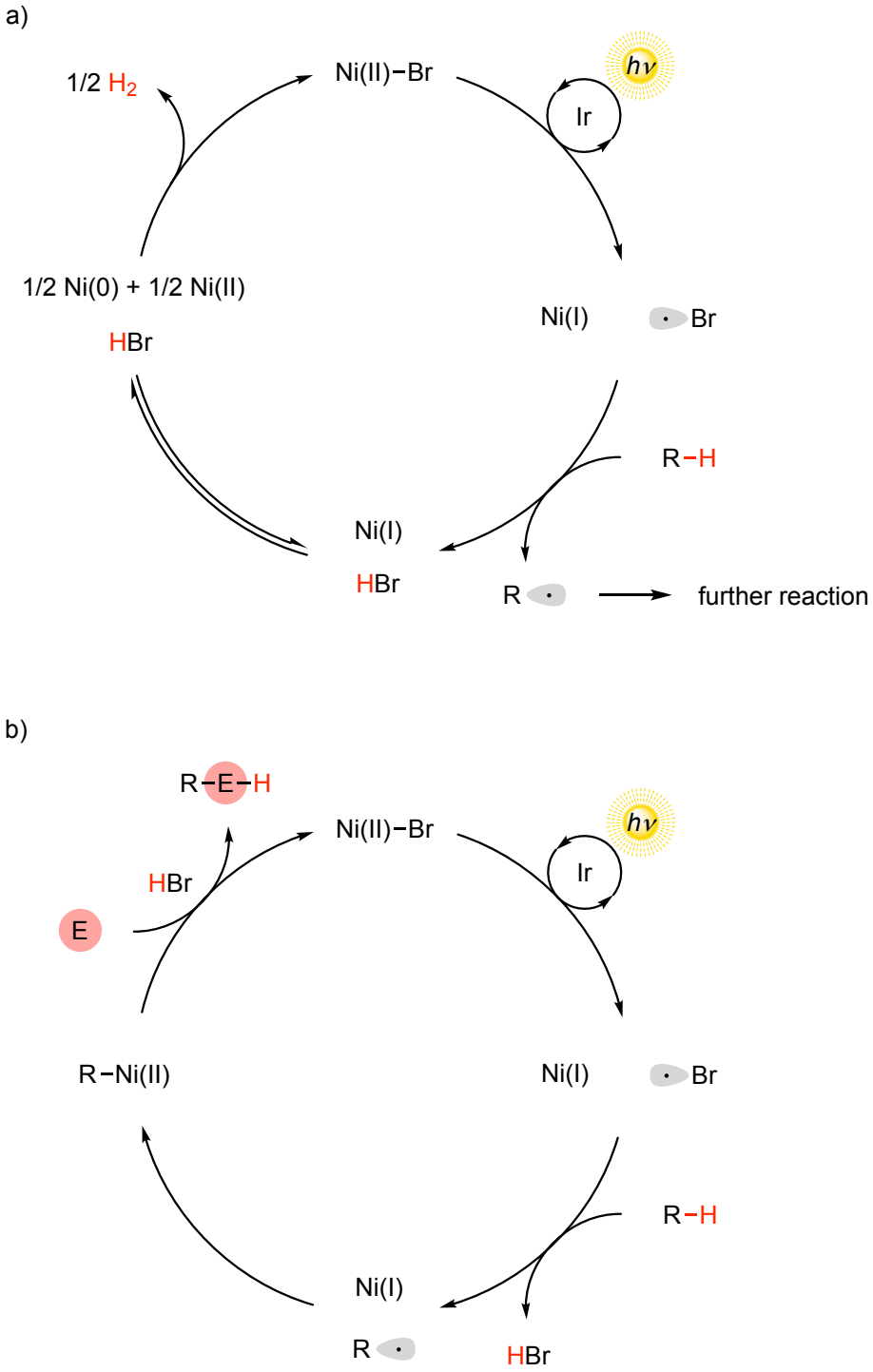
Scheme GI-4. Hypothetical Mechanism of Homo-Coupling of Toluene



Working Hypothesis

Based on the interpretation of the dehydrogenative homo-coupling of toluene, following two working hypotheses were formulated for development of further new reactions. One is a reaction mechanism for a dehydrogenative transformation (Scheme GI-5a). A hydrogen atom of an R–H bond is abstracted by the bromine radical to generate a hydrogen bromide and a carbon-centered radical that is functionalized in further reactions. The proton is reduced to molecular hydrogen by a low valent nickel species. The other is a reaction mechanism for an addition of an R–H bond to an electrophile (Scheme GI-5b). The generated nickel(I) species and carbon-centered radical couple to form an alkyl nickel(II) species, which has a nucleophilic reactivity. Thus, the alkyl nickel species reacts with an electrophile to furnish a functionalized product with reproduction of the nickel catalyst.

Scheme GI-5. Working Hypothesis

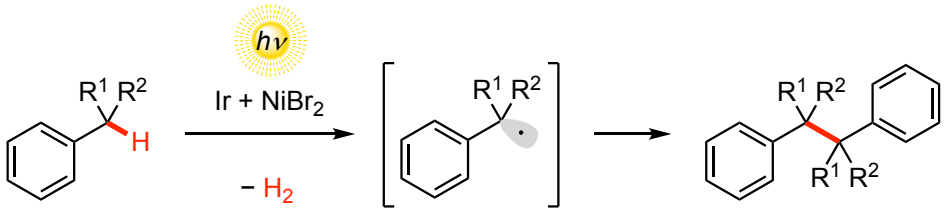


The reactions developed in Chapter 1, 2, 3, and 4 are based on the former hypothesis, and those developed in Chapter 5 and 6 are based on the latter one. The photoinduced formal homolysis of a Ni(II)–Br bond to a Ni(I) species and a bromine radical had never been reported although each hypothesis includes it.[11] The detailed mechanistic studies for this step are examined in Chapter 2. Followings are overview of the present thesis.

Chapter 1. Photo-Driven Dehydrogenative Homo-Coupling of Benzylic C–H Bonds Forming Strained C–C Bonds

Making a C–C bond in which carbon centers having bulky substituents are linked together is still a challenging task in organic chemistry. In Chapter 1 is described a photoinduced dehydrogenative homo-coupling of benzylic C–H bonds forming strained C–C bonds (Scheme GI-6). The author's preliminary result suggested the homo-coupling of toluene was promoted by an iridium photocatalyst and a nickel dibromide catalyst with low efficiency. This study reveals an analogous reaction between two tertiary C–H bonds efficiently takes place furnishing a sterically hindered C–C bond with gaseous hydrogen as a sole side product. A bibenzyl derivative is obtained via a radical-radical coupling of two benzyl radicals stabilized by substituents at the benzylic position.

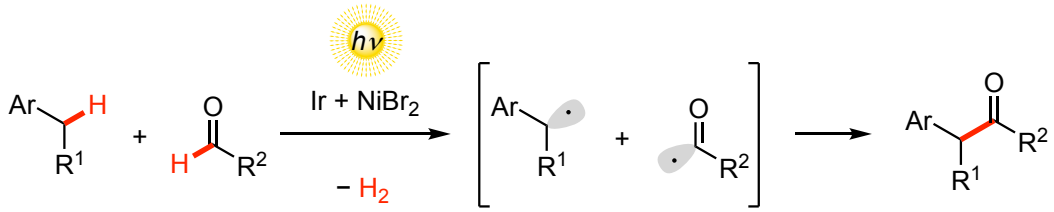
SchemeGI-6. Photo-Driven Dehydrogenative Homo-Coupling of Benzylic C–H Bonds Forming Strained C–C Bonds



Chapter 2. Dehydrogenative Coupling of Benzylic and Aldehydic C–H Bonds

A cross-selective σ-bond metathesis between two deferent C–H bonds is a formidable goal because it requires to overcome a kinetic difficulty in the cleavage of a C-H bond, a thermodynamically unfavorable balance, and undesired homo-selectivity, at the same time.[12] In Chapter 2 is described a photoinduced dehydrogenative cross-coupling of benzylic and aldehydic C–H bonds forming α-aryl ketones, dispensing with any oxidant (Scheme GI-7). The detailed mechanistic studies imply both of a benzyl radical and an acyl radical are generated during the reaction. The analogous reaction using an *N*-alkyl amide instead of an alkylarene produces an α-aminoketone.

Scheme GI-7. Dehydrogenative Coupling of Benzylic and Aldehydic C–H Bonds

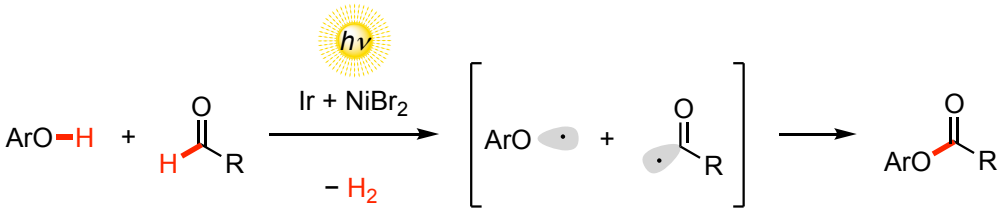


Chapter 3. Photoinduced Specific Acylation of Phenolic Hydroxy Groups with Aldehydes

In Chapter 3 is described a photoinduced dehydrogenative acylation of phenolic hydroxy groups with aldehydes forming aryl carboxylates (Scheme GI-8). This study originates from the unexpected finding; The dehydrogenative coupling of *p*-cresol (4-hydroxytoluene) with an aldehyde gave the mixture of the α-(4-hydroxyphenyl) ketone and the *p*-tolyl ester in the study in Chapter 2. The mechanistic investigation suggests the reaction mechanism includes hydrogen atom abstraction from a phenolic O–H bond to form a phenoxy radical. This unique mechanism of the acylation distinguishes a phenolic O–H bond from aliphatic ones having much larger bond dissociation energies (BDEs). β-Arbutin, a natural-occurring phenolic glycoside, is acylated selectively at the

phenolic O–H bond.

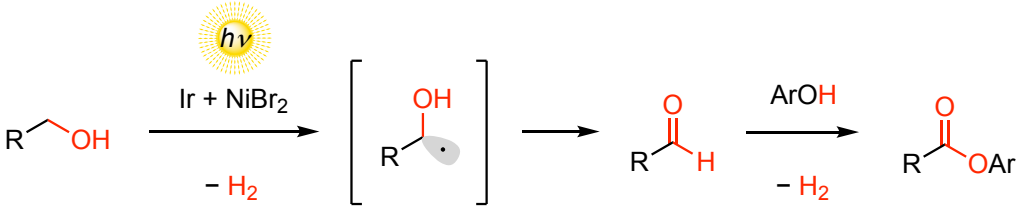
Scheme GI-8. Photoinduced Specific Acylation of Phenolic Hydroxy Groups with Aldehydes



Chapter 4. Visible Light-Driven Dehydrogenative Coupling of Primary Alcohols with Phenols Forming Aryl Carboxylates

In Chapter 4 is described a photoinduced dehydrogenative coupling of primary alcohols with phenols forming aryl carboxylates (Scheme GI-9). 2,4-Difluorophenol is the best coupling partner for efficient esterification of primary alcohols. The present reaction takes place at room temperature, dispensing with heating that the methods reported so far typically require.[13] The unique radical pathway of the esterification completely suppresses the homo-esterification of a primary alcohol, which becomes a trouble in the typical dehydrogenative cross-esterification with another deferent alcohol.[14] The resulting 2,4-difluorophenyl ester moiety is successfully transformed into various carbonyl compounds.

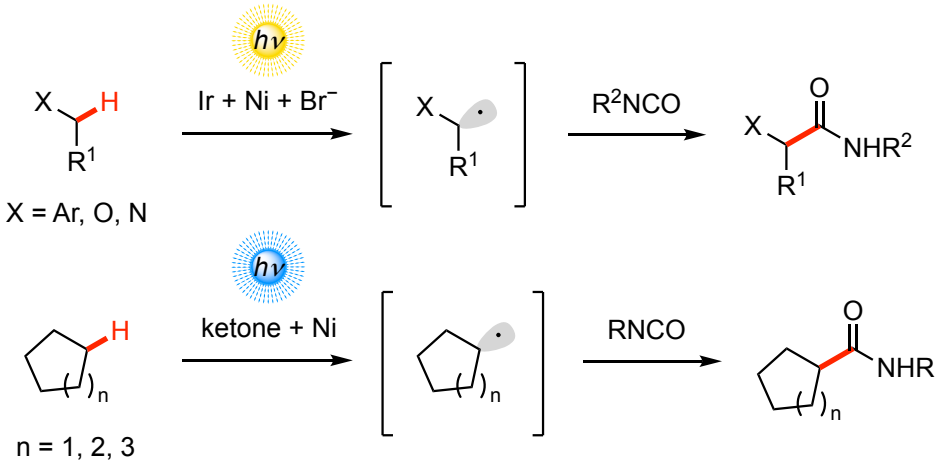
Scheme GI-9. Visible Light-Driven Dehydrogenative Coupling of Primary Alcohols with Phenols Forming Aryl Carboxylates



Chapter 5. Photoinduced Carbamoylation of C(sp^3)–H Bonds with Isocyanates

In Chapter 5 is described a photoinduced carbamoylation of C(sp^3)–H bonds with isocyanates (Scheme GI-10). A C-N double bond of an isocyanate inserts into benzylic C–H bond, an α-C–H bond of amide, and that of ether to form the corresponding amides under the visible light/iridium/nickel/bromide system. The asymmetric reaction of ethylbenzene using a suitable chiral ligand gives an enantioenriched α-aryl amide. A C–H bond of a simple hydrocarbon is also carbamoylated under an ultraviolet/ketone/nickel system in which an excited ketone species abstracts a hydrogen atom from the simple alkane to generate the carbon radical species.[15]

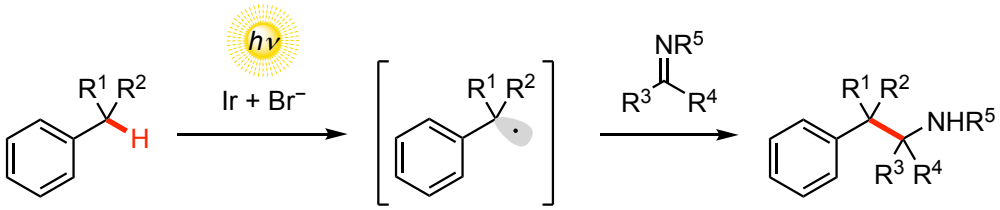
Scheme GI-10. Photoinduced Carbamoylation of C(sp^3)–H Bonds with Isocyanates



Chapter 6. Photoinduced Direct Addition of Alkylarenes to Imines

A phenethylamine moiety is included in numerous bioactive compounds. It is significant to develop a direct synthetic method for phenethylamines using simple starting materials. In Chapter 6 is described a photoinduced aminoalkylation of benzylic C–H bonds with imines, catalyzed by an iridium photoredox catalyst and a bromide anion catalyst, dispensing with a nickel catalyst (Scheme GI-11). More substituted benzylic C–H bond preferentially reacts with an imine to construct a more strained C–C bond, which is a unique selectivity deferent from the benzylic C–H bond addition promoted by strong bases.[16] This method allows to get phenethylamines having a number of substituents on the ethylene linkage.

Scheme GI-11. Photoinduced Direct Addition of Alkylarenes to Imines



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Chapter 1

Photo-Driven Dehydrogenative Homo-Coupling of Benzylic C–H Bonds Forming Strained C–C Bonds

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Abstract: A photoinduced dehydrogenative homo-coupling reaction of alkylarenes is reported. Gaseous hydrogen is evolved as the sole byproduct and neither oxidants nor hydrogen acceptors are required. The present reaction offers an environmentally benign and atom-economical means for forming sterically strained C–C single bonds, and also shows a striking example of photo-driven reactions overcoming a considerable rise in energy.

1.1 Introduction

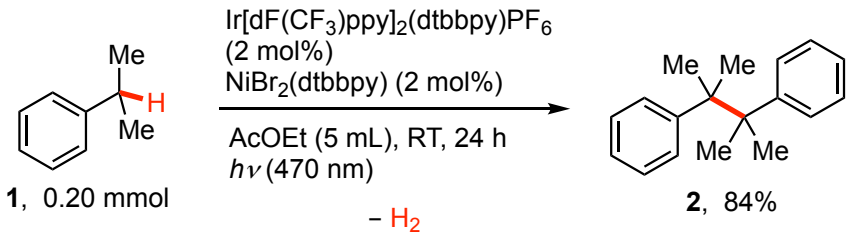
It is a central issue in organic synthesis how to form C–C bonds. Although a numerous number of C–C bond-forming reactions are available, there still is a paucity of efficient methods to make a bond between two tertiary carbon atoms in the face of arising significant steric repulsion. In particular, it presents a formidable task to couple different two tertiary carbon atoms by way of organometallic intermediates. On the other hand, there are a few classical methods to couple two same tertiary carbon atoms through a radical pathway. The most typical conventional method is reductive homo-coupling of *tert*-alkyl halides (or pseudohalides) using metallic reductants such as lithium, magnesium, and a combination of titanium and lithium aluminum hydride.[1] Decarboxylative dimerization of α,α-disubstituted carboxylic acids,[2] denitrogenation of azo compounds,[3] photodecarbonylation of ketones,[4] and oxidative coupling of hydrocarbons using peroxides as the sacrificial oxidants[5] are alternatively available for homo-coupling of two tertiary carbon atoms. Described herein is a more environmentally benign and atom-economical method, a photoinduced dehydrogenative homo-coupling reaction of alkylarenes. Gaseous hydrogen is generated as the sole byproduct, and neither metallic reductants, oxidants, hydrogen acceptors, nor explosive reagents are required.

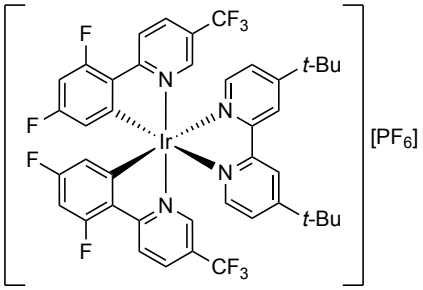
1.2 Results and Discussion

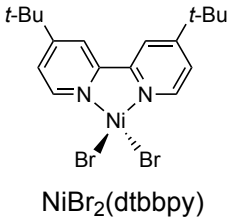
*1.2.1 Dehydrogenative Homo-Coupling of Cumene **1***

The present study was initiated based on the author's preliminary discovery that a combination of an iridium complex, and a nickel dibromide complex photochemically induced a dehydrogenative homo-coupling of toluene to form bibenzyl in low efficiency (Scheme GI3). The result led the author examine a homo-coupling of isopropylbenzene, whose geminal methyl groups can stabilize the benzyl radical generated via hydrogen atom abstraction. Thus, a solution containing **1** (0.20 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)]PF_6$ (2 mol%), $NiBr_2(dtbbpy)$ (2 mol%) in ethyl acetate was irradiated with blue LEDs (Scheme 1-1). After 24 h, the resulting mixture was evaporated under reduced pressure and the residue was subjected to preparative thin-layer chromatography (PTLC) on silica gel to afford the dimer **2**, which contained two quaternary carbons in juxtaposition, in 84% yield. Gas chromatographic analysis of the headspace of the reaction vessel confirmed the evolution of gaseous hydrogen, which indicated that the benzylic C–H bond of **1** underwent dehydrogenative homo-coupling. Control experiments suggested that visible light, the iridium, and the nickel complexes were all indispensable for this reaction.

Scheme 1-1. Dehydrogenative Homo-Coupling of Cumene **1**





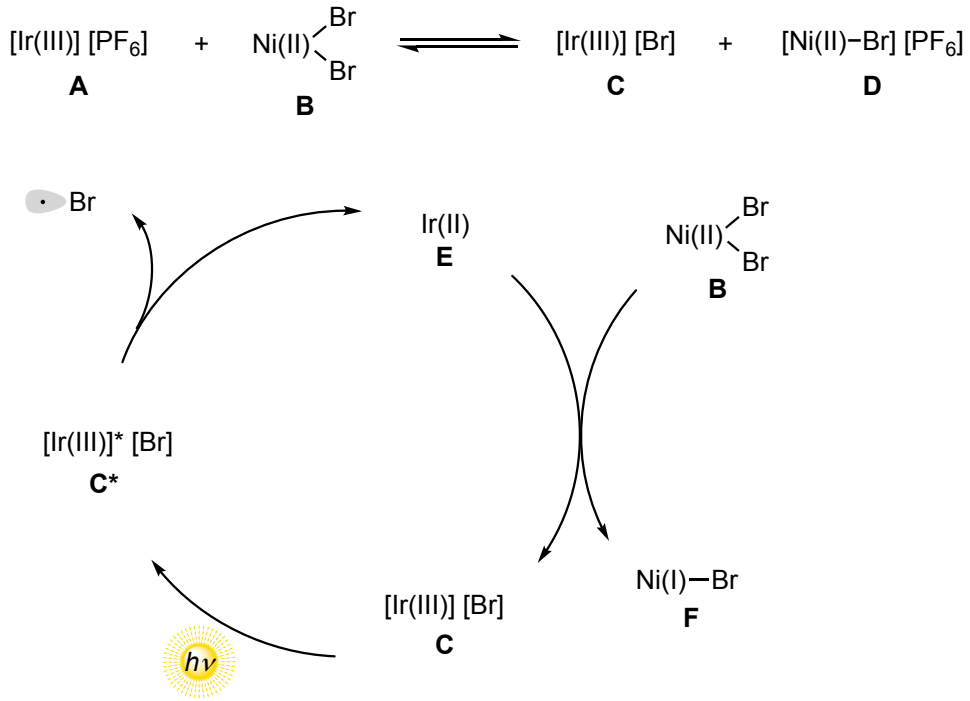


1.2.2 Proposed Mechanism

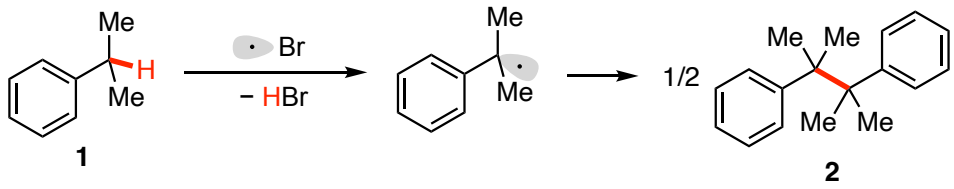
Shown in Scheme 1-2 is a reaction pathway for the homo-coupling. It consists of two stages. Stage 1: Ion exchange occurs between iridium(III) phosphate **A** and nickel(II) bromide **B** to generate iridium(III) bromide **C** and nickel(II) phosphate **D**.[6] A bromine radical is generated through the following steps and goes into Stage 2. Iridium(III) **C** absorbs light to get excited, and an ensuing single electron transfer from the bromide anion to the excited iridium(III) **C*** gives iridium(II) species **E** and a bromine radical.[7] The iridium(II) **E** ($E_{1/2}$[Ir(III)/Ir(II)] = −1.37 V vs SCE)[8] reduces the nickel(II) species **B** ($E_{1/2}$[Ni(II)/Ni(0)] = −1.2 V vs SCE)[9] to nickel(I) **F** and the iridium(III) bromide **C** is regenerated. Stage 2: The bromine radical abstracts the benzylic hydrogen from **1** to produce a benzylic radical with elimination of HBr. The benzylic radical undergoes homo-coupling to afford the dimer **2**. HBr reacts with nickel(I) species **F** to generate gaseous dihydrogen along with the nickel(II) species **B**.[11]

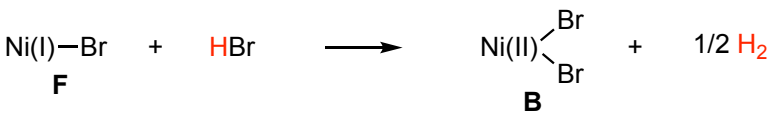
Scheme 1-2. Proposed Mechanism

Stage 1. Generation of Bromine Radical and Ni(I)



Stage 2. Homo-Coupling of 1 and Hydrogen Evolution

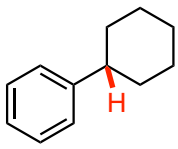
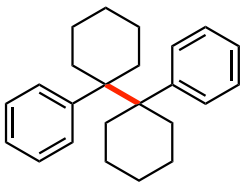
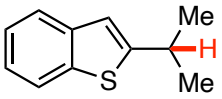
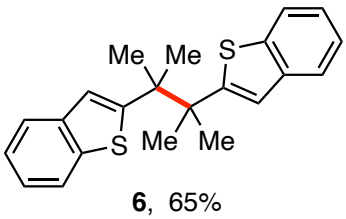


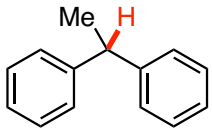
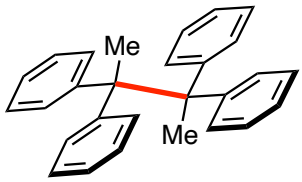
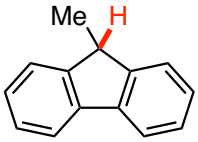
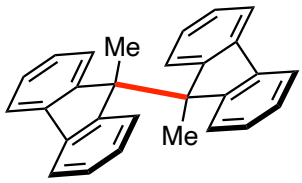
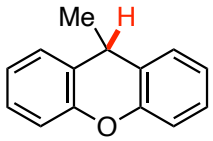
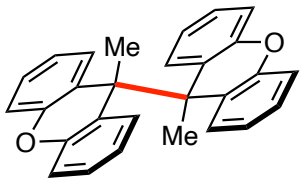
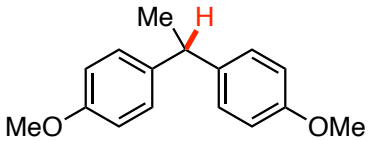
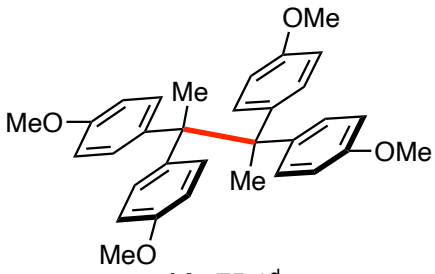
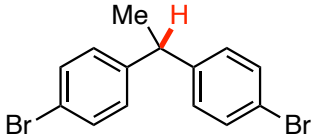
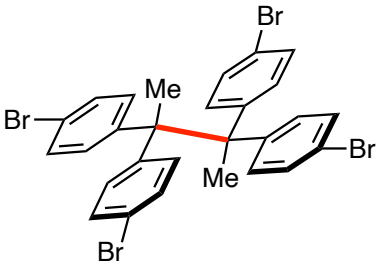


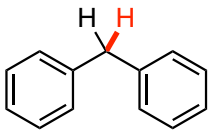
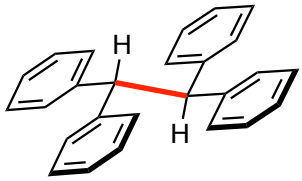
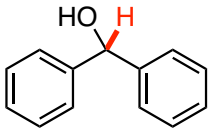
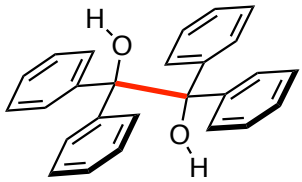
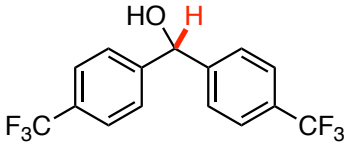
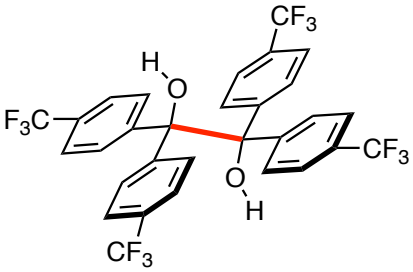
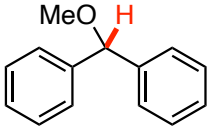
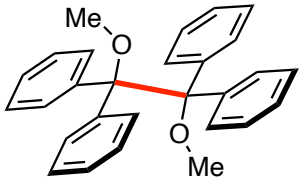
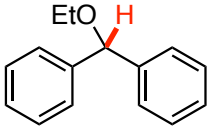
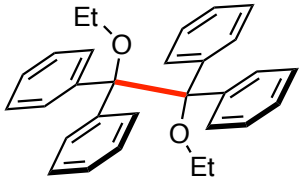
1.2.3 Substrate Scope

Next, the scope of the substrates was examined (Table 1-1). Phenylcyclohexane **3** and 2-isopropylbenzothiophene **5** afforded the corresponding dimeric products **4** and **6**, respectively (entries 1 and 2). 1,1-Diphenylethane **3** underwent the homo-coupling as well to give the dimer **4** in 80% yield (entry 3). Cyclic diarylethanes **9** and **11** were also viable substrates (entries 4 and 5). Functional groups such as methoxy and bromo groups were allowed on the benzene ring (entries 6 and 7). Diphenylmethane **17** underwent selective dimerization at the methylene carbon to afford **18**, and no further dehydrogenative coupling at the methine carbon occurred, presumably due to steric reasons (entry 8). On the other hand, ethylbenzene provided the corresponding dimer in less than 10% yield because the benzylic radical intermediate is less stable. Thus, the coupling carbon of suitable substrates should possess two aryl groups or two alkyl plus one aryl groups in order to generate the intermediary radical species with enough stability. Benzhydrol derivatives **19**, **21**, **23**, and **25** also underwent dehydrogenative coupling to give the corresponding dehydrogenated dimers, respectively (entries 9-12).

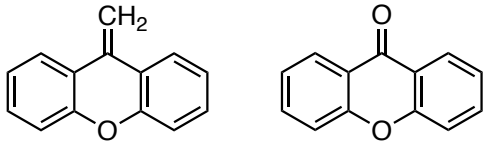
Table 1-1. Scope[a]

entry	substrates	products[b]
1	 **3**	 **4**, 64%
2	 **5**	 **6**, 65%

3	 **7**	 **8**, 80%
4	 **9**	 **10**, 93%[c]
5	 **11**	 **12**, 72%[c,d,e]
6	 **13**	 **14**, 75%[d]
7	 **15**	 **16**, 81%[d]

8	 **17**	 **18**, 87%
9	 **19**	 **20**, 92%[f]
10	 **21**	 **22**, 96%
11	 **23**	 **24**, 92%[c]
12	 **25**	 **26**, 80%[c]

[a] Reaction conditions: substrate (0.20 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)]PF_6$ (2 mol%), $NiBr_2(dtbbpy)$ (2 mol%), ethyl acetate (5.0 mL), blue LEDs (470 nm), 24 h. [b] Isolated yields. Purified by PTLC otherwise noted. [c] $NiBr_2(dtbbpy)$ (1 mol%). [d] Purified by gel-permeation chromatography. [e] Obtained together with a small amount of olefin **27** (3%) and xanthone **28** (2%). It was difficult to separate 12 from them because it gradually decomposed to **27** and **28** under air. [f] $NiBr_2(dtbbpy)$ (0.1 mol%).



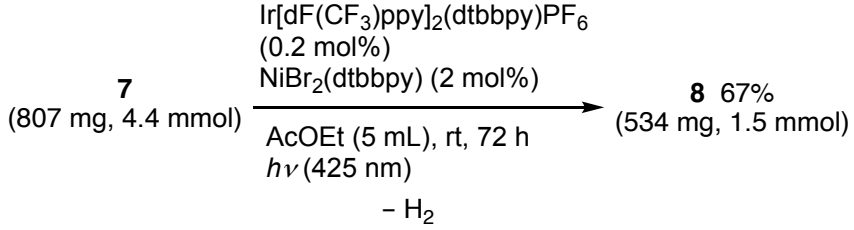
27 **28**

Figure 1-1. Structures of Side-Products **27**, **28**

1.2.4 Large Scale Reaction

Finally, the reaction of 4.4 mmol of 1,1-diphenylethane **7** (807 mg) using 0.2 mol% of $Ir[dF(CF_3)ppy]_2(dtbbpy)]PF_6$ was examined to demonstrate the feasibility on a preparative scale (Scheme 1-3). The substrates and catalysts were placed in an ordinary Pyrex flask. The flask was then evacuated and refilled with an argon gas, to which ethyl acetate (5.0 mL) was added. The resulting mixture was irradiated with blue LEDs (425 nm, 18 W) for 72 h. White solids precipitated out of the solution during the reaction. The resulting mixture was directly subjected to column chromatography on silica gel to give the dimeric product **8** (534 mg, 1.5 mmol) in 67% yield.

Scheme 1-3. Large Scale Reaction



1.3 Summary

In conclusion, a photoinduced homo-coupling reaction of alkylarenes was developed. The reaction generates gaseous hydrogen as the byproduct and requires neither metallic reductants, oxidants, hydrogen acceptors, nor explosive reagents. It offers an environmentally benign and atom-economical method of constructing C(tertiary)–C(tertiary) bonds. It should be noted that the present reaction is highly uphill in energy because significant steric strain develops with the products. In the case of the homo-coupling reaction of **7**, the free energy difference (ΔG) is estimated as much as 37 kcal/mol at 298 K in gas phase.[12] Light provides the energy to achieve such an energetically uphill reaction. Although several photocatalytic uphill reactions have been reported,[13] the energy difference is typically less than 10 kcal/mol, and it still remains a challenge of fundamental interest to develop energetically uphill reactions. The present reaction shows a striking example of photo-driven reactions overcoming a considerable rise in energy.

1.4 Experimental Section

1.4.1 General Method and Materials

General Method

All reactions were carried out using a flame-dried glassware under a nitrogen atmosphere. Photoreactions were carried out with blue LEDs (Large Scale Reaction: Hepatochem, HCK1012-01-012, 18 W; Small Scale Reaction: Kessil, A160WE, 40 W). The evolved dihydrogen was detected by analyzing the gas phase of the reaction vessel using SHIMADZU GAS CHROMATOGRAPH GC-2014s. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECZ400S/L1 (^{1}H at 400.44 MHz, ^{13}C at 100.69 MHz) spectrometer. $CDCl_3$ was used as a solvent. Chemical shifts were recorded in δ ppm referenced to a residual $CDCl_3$ (δ = 7.26 for ^{1}H, δ = 77.0 for ^{13}C). IR measurements were performed on FTIR SHIMADZU Affinity-1S spectrometer fitted with a Pike Technologies MIRacle Single Reflection ATR adapter. High-resolution mass spectra were recorded on JEOL JMS-700 (EI), Thermo Fisher Scientific Exactive Plus (ESI, APCI, DART). Preparative thin-layer chromatography (PTLC) was performed on silica gel plates with PF254 indicator (Merck). Flash column chromatography was performed with silica gel 60N (Kanto). Gel permeation chromatography (GPC) was performed using Japan Analytical Industry LaboACE LC-5060 equipped with columns of JAIGEL-1HR and -2HR.

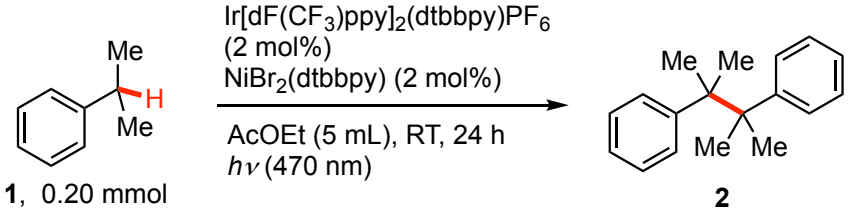
Materials

$NiBr_2$(dtbbpy),[14] $Ir[dF(CF_3)ppy]_2$(dtbbpy)PF_6,[15] 9-methylfluorene **9**,[16] 1,1'-diphenylmethyl methyl ether **23**,[17] and diphenylmethyl ethyl ether **25**[18] were synthesized following the method reported in the literatures. 2-Isopropyl-1-benzothiophene **5** was synthesized from benzo[b]thiophen-2-ylboronic acid and 2-iodopropane following the method reported in ref [19]. 9-Methyl-9H-xanthene **11** and 1,1-bis(4-methoxyphenyl)ethane **13** were synthesized following the method reported for the synthesis of **9**.[16] 1,1-Diphenylethane **7** was synthesized by hydrogenation of 1,1-diphenylethylene using Pd/C and H_2 gas. 1,1-Bis(4-bromophenyl)ethane **15** was synthesized from 4,4'-dibromobenzophenone via addition of methylmagnesium bromide following the method reported in ref [16] and a deoxygenation reaction using boron

trifluoride-diethyl ether complex and triethylsilane following the method reported in ref [20]. 4,4'-Bis(trifluoromethyl)benzhydrol **21** was synthesized from 4,4'-bis(trifluoromethyl)benzophenone[21] by reduction following the method reported in ref [22]. Other chemicals were purchased from commercial suppliers and used as received.

1.4.2 Control Experiments

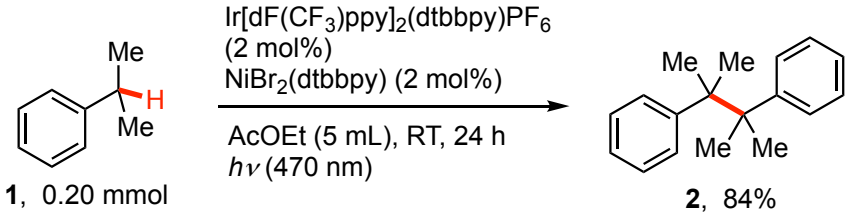
Table 1-2. Control Experiments



entry	deviation from standard condition	NMR yield of **2**
1	None	92%
2	w/o Ir cat.	0%
3	w/o Ni cat.	0%
4	w/o blue light	0%
5	$Ni(OAc)_2•4H_2O$ (2 mol%), dtbbpy (2 mol%) instead of $NiBr_2$(dtbbpy)	<5%
6	$Ni(OAc)_2•4H_2O$ (2 mol%), dtbbpy (2 mol%) (nBu)$_4$NBr (4 mol%) instead of $NiBr_2$(dtbbpy)	39%
7	$NiCl_2$(dtbbpy) instead of $NiBr_2$(dtbbpy)	<5%

1.4.3 Dehydrogenative Coupling of 1: A Typical Procedure

Scheme 1-4. Typical Procedure of the Dehydrogenative Homo-Coupling



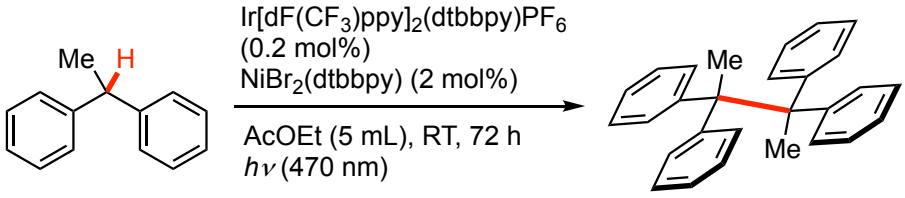
1, 0.20 mmol

2, 84%

To an oven-dried 5 mL Schlenk tube were added cumene **1** (24.3 mg, 0.20 mmol), Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (4.5 mg, 0.004 mmol), NiBr$_2$(dtbbpy) (2.0 mg, 0.004 mmol), and ethyl acetate (5.0 mL) under a nitrogen atmosphere. The tube was capped with rubber septa, and the solution was stirred and irradiated with blue LEDs at room temperature for 24 hours. Then, the resulting mixture was filtrated through a short column of silica gel and washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by PTLC (eluent: hexane:dichloromethane = 5:1) to give (2,3-dimethylbutane-2,3-diyl)dibenzene **2** (20.2 mg, 0.085 mmol, 84 %) as white solids.

1.4.4 Dehydrogenative Coupling of 7 on a Preparative Scale

Scheme 1-5. Dehydrogenative Coupling of **7** on a Preparative Scale



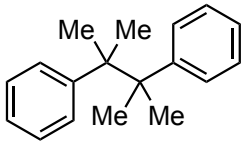
7, 4.4 mmol
807 mg

8, 67%
(534 mg, 1.5 mmol)

To an oven-dried 50-mL two-neck flask were added 1,1'-diphenylethane **7** (807 mg, 4.4 mmol), Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (8.8 mg, 0.008 mmol), NiBr$_2$(dtbbpy) (37.1 mg, 0.08 mmol), and ethyl acetate (5.0 mL) under a nitrogen atmosphere. The flask was capped with rubber septa, and the solution was stirred and irradiated with blue LEDs at room temperature for 72 hours. Then, the resulting mixture was filtrated through a short column of silica gel and washed with ethyl acetate. The filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel

(eluent: hexane:dichloromethane = 20:1) to give 2,2,3,3-tetraphenylbutane **8** (534 mg, 1.5 mmol, 67 %) as white solids.

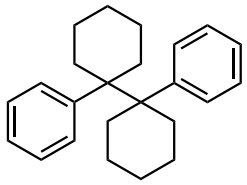
1.4.5 Spectroscopic Data of the Products



2

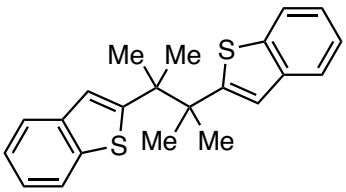
White solids (20.2 mg, 0.085 mmol, 84%), R_f = 0.5 (hexane/dichloromethane 5:1) ^{1}H NMR: δ = 7.15-7.24 (m, 6H), 7.03-7.12 (m, 4H), 1.32 (s, 12H); ^{13}C NMR: δ = 146.8, 128.6, 126.6, 125.5, 43.6, 25.2.

These NMR data were in agreement with the reported one.[23]



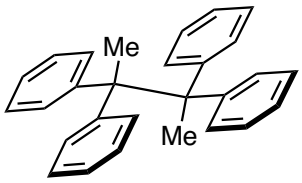
4

White solids (20.5 mg, 0.064 mmol, 64%), R_f = 0.8 (hexane/dichloromethane 3:1) ^{1}H NMR: δ = 7.08-7.24 (m, 6H), 6.89-7.02 (m, 4H), 2.31 (d, J = 13.0 Hz, 4H), 1.34-1.52 (m, 10H), 0.93-1.18 (m, 6H); ^{13}C NMR: δ = 141.3, 130.8, 126.6, 125.1, 49.4, 30.2, 26.6, 22.6; IR (neat): ν = 3090, 3057, 3019, 2924, 2851, 1599, 1580, 1499, 1472, 1456, 1445, 727, 702 cm^{-1}; HRMS(EI) *m/z*: $[M]^+$ Calcd for $C_{24}H_{30}$ 318.2348; Found 318.2345.



6

White solids (23.0 mg, 0.066 mmol, 65%), R_f = 0.4 (hexane/dichloromethane 10:1); ^{1}H NMR: δ = 7.72-7.77 (m, 2H), 7.64-7.68 (m, 2H), 7.23-7.33 (m, 4H), 7.01 (d, *J* = 0.6 Hz, 2H), 1.55 (s, 12H); ^{13}C NMR: δ = 153.3, 139.5, 139.0, 123.9, 123.5, 122.9, 122.2, 121.7, 44.3, 26.9; IR (neat): ν = 3059, 2976, 2874, 1454, 1431, 1371, 745, 725 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{22}S_2$ 350.1163; Found: 350.1164.

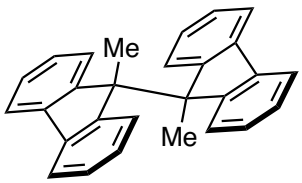


8

White solids (29.3 mg, 0.081 mmol, 80%), R_f = 0.3 (hexane/dichloromethane 5:1)

^{1}H NMR: δ = 6.92-7.17 (m, 20H), 2.04 (s, 6H); ^{13}C NMR: δ = 148.5, 131.8, 126.3, 125.5, 55.1, 28.0.

These NMR data were in agreement with the reported one.[24]

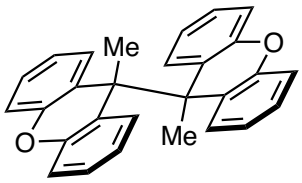


10

White solids (33.5 mg, 0.093 mmol, 93%), R_f = 0.3 (hexane/dichloromethane 5:1)

^{1}H NMR: δ = 7.41 (d, *J* = 7.2 Hz, 4H), 7.18 (dt, *J* = 1.0 Hz, 7.2 Hz, 4H), 7.02 (t, *J* = 7.2 Hz, 4H), 6.80 (d, *J* = 7.2 Hz, 4H), 1.91 (s, 6H); ^{13}C NMR: δ = 149.7, 140.7, 127.0, 125.9, 124.1, 119.1, 55.8, 21.0.

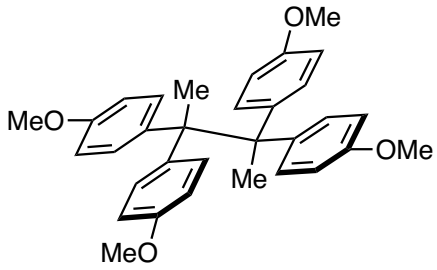
These NMR data were in agreement with the reported one.[25]



12

The residue was purified by GPC using chloroform as the eluent. Since **12** was inherently unstable under air to gradually decompose to **28** and **29**, the obtained white solids (30.1 mg) included **12** (0.072 mmol, 72%), **28** (0.0062 mmol, 3%), and **29** (0.0041 mmol, 2%) according to ^{1}H NMR analysis.

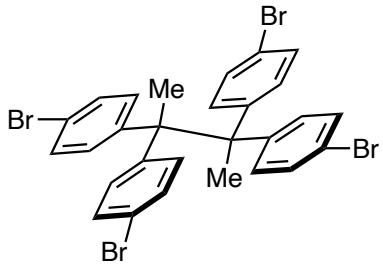
^{1}H NMR: δ = 7.19-7.25 (m, 4H), 6.81-6.96 (m, 8H), 6.65-6.74 (m, 4H), 1.69 (s, 6H); ^{13}C NMR: δ = 153.3, 128.8, 128.0, 125.2, 121.6, 115.6, 48.5, 20.9; IR (neat): ν = 3076, 3003, 1595, 1570, 1476, 1454, 1435, 1375, 1242, 748 cm^{-1}; HRMS (DART) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{23}O_2$ 391.1698; Found: 391.1700.



14

The residue was purified by GPC using chloroform as the eluent. White solids (36.4 mg, 0.075 mmol, 75%)

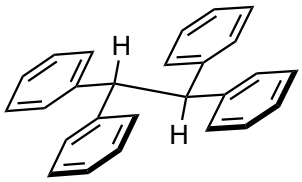
^{1}H NMR: δ = 6.90 (d, *J* = 8.0 Hz, 8H), 6.64 (d, *J* = 8.0 Hz, 8H), 3.78 (s, 12H), 1.91 (s, 6H); ^{13}C NMR: δ = 157.1, 140.8, 132.8, 111.5, 55.1, 53.9, 28.0; IR (neat): ν = 3011, 2949, 2832, 1604, 1578, 1502, 1460, 1246, 1030, 831 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{32}H_{34}O_4Na$ 505.2355; Found 505.2353.



16

The residue was purified by GPC using chloroform as the eluent. White solids (55.2 mg, 0.081 mmol, 81%)

^{1}H NMR: δ = 7.25 (d, *J* = 7.8 Hz, 8H), 6.81 (d, *J* = 7.8 Hz, 8H), 1.93 (s, 6H); ^{13}C NMR: δ = 146.4, 133.4, 129.8, 120.3, 54.4, 27.6; IR (neat): ν = 3057, 2997, 2955, 1485, 1396, 816 cm^{-1}; HRMS (APCI) *m/z*: [M + Cl]$^-$ Calcd for $C_{28}H_{22}C_{11}Br_4Cl$ 708.8144; Found 708.8170.

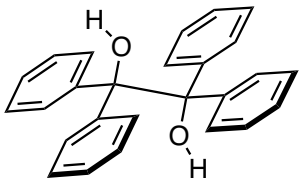


18

White solids (30.6 mg, 0.091 mmol, 91%), R_f = 0.5 (hexane/dichloromethane 3:1)

^{1}H NMR: δ = 7.14-7.20 (m, 8H), 7.07-7.14 (m, 8H), 6.97-7.06 (m, 4H), 4.77 (s, 2H); ^{13}C NMR: δ = 143.5, 128.5, 128.1, 125.8, 56.3.

These NMR data were in agreement with the reported one.[26]

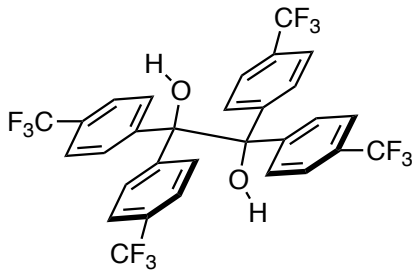


20

White solids (33.2 mg, 0.091 mmol, 91%), R_f = 0.7 (hexane/dichloromethane 1:3)

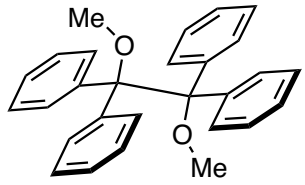
^{1}H NMR: δ = 7.28-7.32 (m, 8H), 7.15-7.20 (m, 12H), 3.03 (s, 2H); ^{13}C NMR: δ = 144.2, 128.6, 127.3, 126.9, 83.0.

These NMR data were in agreement with the reported one.[27]



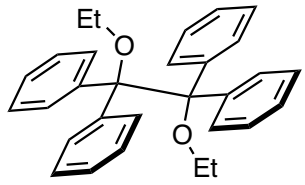
22

White solids (61.4 mg, 0.096 mmol, 96%), R_f = 0.3 (hexane/dichloromethane 2:1) ^{1}H NMR: δ = 7.48 (d, *J* = 8.6 Hz, 8H), 7.42 (d, *J* = 8.6 Hz, 8H), 3.01 (s, 2H); ^{13}C NMR: δ = 146.9, 130.0 (q, *J* = 32.6 Hz), 128.8, 124.7, 123.8 (q, *J* = 270.2 Hz), 82.8; IR (neat): ν = 3617, 3576, 1618, 1410, 1321, 1161, 1111 cm^{-1}; HRMS (ESI) *m/z*: [M + Cl]$^-$ Calcd for $C_{30}H_{18}$ $C_{11}F_{12}O_2Cl$ 673.0804; Found 673.0814.



24

White solids (36.2 mg, 0.092 mmol, 92%), R_f = 0.6 (hexane/dichloromethane 1:1) ^{1}H NMR: δ = 7.07-7.24 (m, 20H), 3.00 (s, 6H); ^{13}C NMR: δ = 139.8, 131.9, 126.9, 126.3, 91.8, 52.8; IR (neat): ν = 3055, 2970, 2827, 1597, 1489, 1445, 1075, 732, 700 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{28}H_{26}O_2Na$ 417.1830; Found 417.1828.



26

White solids (33.6 mg, 0.080 mmol, 80%), R_f = 0.7 (hexane/dichloromethane 1:1) ^{1}H NMR: δ = 7.04-7.18 (m, 20H), 3.27 (q, *J* = 6.9 Hz, 4H), 1.13 (t, *J* = 6.9 Hz, 6H); ^{13}C NMR: δ = 141.9, 131.9, 126.4, 125.8, 90.6, 59.8, 15.3; IR (neat): ν = 3053, 2972, 2926, 2870, 1597, 1489, 1443, 1385, 734, 700 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{30}H_{30}O_2Na$ 445.2143; Found 445.2139.

1.4.6 Computational Study

All calculations were performed with Gaussian 16, revision C.01 program.[28] Structures were optimized by DFT method[29] with the ωB97XD functional[30] in conjunction with the 6-31+G(d)[31] basis set without any symmetry or geometric constraint in gas phase. Single point energy calculations were performed with the optimized structures at the same level. Zero-point energy, enthalpy, and free energy were estimated at 298.15 K and 1 atm. Harmonic vibration frequency calculations at the same level were performed to verify all stationary points as local minima (with no imaginary frequency). Calculated energies of 1,1-diphenylethane **7**, 2,2,3,3-tetraphenylbutane **8**, and H_2 are summarized in Table 1-3.

Table 1-3. Calculated energies

	E (au)	H (au)	G (au)
1,1-diphenylethane **7**	-541.762019	-541.508609	-541.56035
2,2,3,3-tetraphenylbutane **8**	-1082.303753	-1081.81695	-1081.891355
H_2	-1.17193	-1.158459	-1.173248

Cartesian coordiates

1,1-diphenylethane **7**

C	0.023500	1.188700	-0.537800
C	-1.265100	0.411900	-0.296400
C	-1.527200	-0.713400	-1.088000
C	-2.192100	0.756600	0.687700
C	-2.678300	-1.470100	-0.904100
C	-3.349000	-0.001800	0.879000
H	-2.023200	1.624700	1.317800
C	-3.596900	-1.116300	0.085200
H	-2.860200	-2.338300	-1.531700
H	-4.056700	0.285300	1.652100
H	-4.497600	-1.705500	0.232700
C	1.251400	0.357000	-0.189200

C	1.326200	-0.345100	1.017600
C	2.348100	0.318400	-1.052400
C	2.470500	-1.062300	1.354100
C	3.496100	-0.400500	-0.400500
H	2.304500	0.856900	-1.997200
C	3.560900	-1.093000	0.485100
H	2.509400	-1.604400	2.295000
H	4.337500	-0.421100	-1.408400
H	4.452300	-1.656600	0.745600
H	0.474000	-0.340300	1.693500
H	0.069200	1.392500	-1.616200
C	0.08980	2.543900	0.179100
H	1.003200	3.071400	-0.11300
H	-0.769300	3.17300	-0.079000
H	0.11800	2.420500	1.267600

2,2,3,3-tetraphenylbutane **8**

C	0.668700	0.100000	-0.458000
C	1.640200	1.296000	-0.255800
C	1.428800	2.412800	0.556200
C	2.853100	1.254600	-0.965400
C	2.374200	3.435800	0.656900
C	3.797300	2.269000	-0.874400
H	3.081300	0.392400	-1.585300
C	3.563800	3.373400	-0.056300
H	2.164300	4.286500	1.299500
H	4.721900	2.191200	-1.439800
H	4.299200	4.168900	0.022400
C	1.474200	-1.186100	-0.137900
C	2.419500	-1.204000	0.896600
C	1.285100	-2.372900	-0.852800
C	3.128300	-2.357500	1.217500

C	1.997100	-3.530200	-0.543400
H	0.556500	-2.420500	-1.654200
C	2.920000	-3.531700	0.497100
H	3.852100	-2.333000	2.027600
H	1.818400	-4.434800	-1.118000
H	3.475300	-4.433200	0.740400
C	-0.669000	0.098900	0.458100
C	-1.642400	1.293400	0.255700
C	-1.472400	-1.188400	0.138100
C	-2.855300	1.250000	0.965100
C	-1.432400	2.410700	-0.556000
C	-2.417600	-1.207800	-0.896400
C	-1.281100	-2.374900	0.852800
C	-3.801100	2.262800	0.874000
C	-2.379400	3.432200	-0.656700
H	-0.512700	2.52920	-1.111400
C	-3.124500	-3.124500	-1.217500
C	-1.991300	-1.991300	0.543200
H	-0.552500	-2.421600	1.654100
C	-3.569200	3.367700	0.056100
H	-4.725700	2.183600	1.439100
H	-2.170800	4.283300	-1.299200
C	-2.914200	-3.536400	-0.497200
H	-1.811000	-4.437900	1.117700
H	-4.305800	4.162000	-0.022700
H	-3.468000	-4.438800	-0.740600
H	0.509200	2.529800	1.112100
H	2.617900	-0.295000	1.456900
H	-2.617600	-0.299100	-1.456600
H	-3.082200	0.387300	1.585000
C	-0.302600	0.085400	1.966400
H	0.11090	1.037700	2.296200

H	-1.193500	-0.110700	2.568000
H	0.429300	-0.685300	2.207200
C	0.302100	0.085700	-1.966200
H	1.193200	-0.108800	-2.568000
H	-0.428400	-0.686400	-2.206800
H	-0.113300	1.037200	-2.295900

H_2

H	0.000000	0.000000	0.370700
H	0.000000	0.000000	-0.370700

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Chapter 2

Dehydrogenative Coupling of Benzylic and Aldehydic C–H Bonds

Table of Contents

Abstract: A photoinduced dehydrogenative coupling reaction between benzylic and aldehydic C–H bonds is reported. When a solution of an alkylbenzene and an aldehyde in ethyl acetate is irradiated with visible light in the presence of iridium and nickel catalysts, a coupled α-aryl ketone is formed with evolution of dihydrogen. An analogous C–C bond forming reaction occurs between a C–H bond next to nitrogen of an *N*-methylamide and an aldehydic C–H bond to produce an α-amino ketone. These reactions provide a straightforward pathway from readily available materials leading to valued structural motifs of pharmacological relevance.

2.1 Introduction

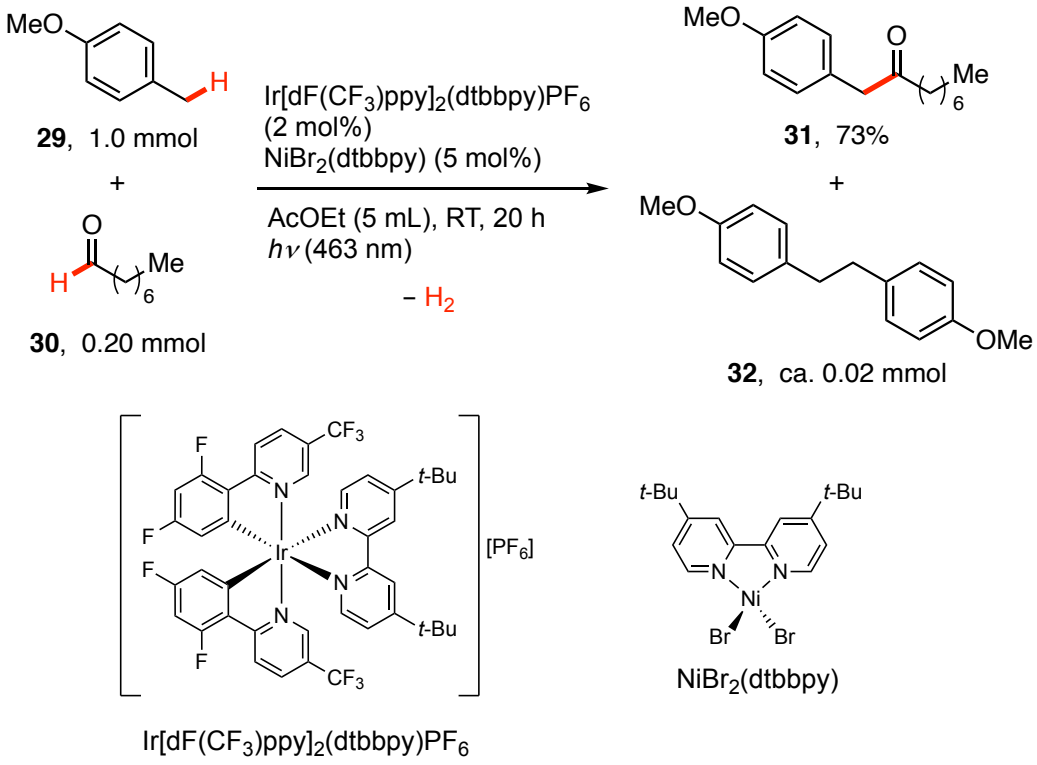
It would offer a straightforward method to con-struct organic skeletons if two different C–H bonds are site-selectively cleaved and dihydrogen is removed to form a new C–C bond.[1] Such a process of σ-bond metathesis is kinetically difficult to execute due to the inertness of C–H bonds. Furthermore, it is often unfavorable in terms of thermodynamic balances based on bond dissociation energies; generalized bond energies of C–H, C–C, and H–H bonds are ca. 98,2 81,[2] and 104 kcal/mol,[3] respectively. It is also formidable to facilitate cross-coupling in preference to homo-coupling. The examples of such dehydrogenative C–H/C–H cross-coupling reported so far are limited to (1) those using phenols and tetrahydroisoquinolines, which possess low oxidation potentials,[4] and (2) reactions using benzene derivatives substituted by heteroatom functional groups that direct metals to approach to a specific aromatic C–H bond.[5] Herein reported is a dehydrogenative C–H/C–H cross-coupling reaction of alkylbenzenes with aldehydes to form α-aryl ketones, which is promoted by collaboration of light, iridium, and nickel. An analogous C–H/C–H cross-coupling reaction of *N*-methylamides with aldehydes furnishes α-amino ketones. The present study offers a direct access from readily available substances to α-substituted ketones, which are valued structural motifs found in a number of biologically active molecules and their synthetic intermediates.

2.2 Results and Discussion

*2.2.1 Dehydrogenative Cross-Coupling of 4-Methoxytoluene **29** with Octanal **30***

It has been reported that C(sp^3)–H bonds undergo direct arylation,[6] acylation,[7] alkoxycarbonylation,[8] alkenylation,[9] alkylation,[10] and carboxylation[11] reactions by cooperative actions of a nickel catalyst and a photocatalyst under photoirradiation. Aldehydes was examined to use as the reaction partner of C(sp^3)–H bonds. After a number of trials, conditions suitable for a dehydrogenative C–H/C–H coupling reaction between toluene derivatives and aldehydes producing α-aryl ketones was found. A solution containing 4-methoxytoluene (**29**, 1.0 mmol, 5.0 equiv), octanal (**30**, 0.20 mmol, 1.0 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.004 mmol, 2 mol%), and $NiBr_2(dtbbpy)$ (0.01 mmol, 5 mol%) in ethyl acetate (4.9 mL) was irradiated with blue LEDs (40W, λ_{max} = 463 nm) at ambient temperature for 20 h (Scheme 2-1). The ketone **31** was formed as the major product and only a small amount of bibenzyl **32** (ca. 0.02 mmol) was detected. The excess amount of **29** remained unreacted. The formation of H_2 was confirmed by GC analysis of the gas phase in the headspace of the reaction vessel. Purification of the reaction mixture by silica gel chromatography afforded analytically pure ketone **31** in 73% yield based on **30**.

Scheme 2-1. Dehydrogenative Cross-Coupling of **29** with **30**

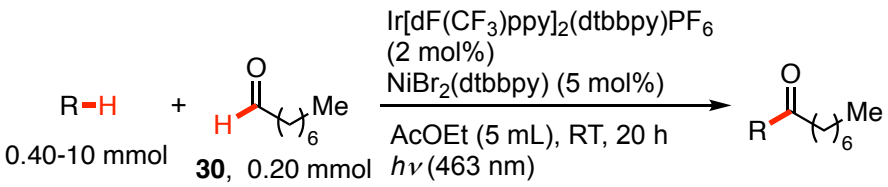


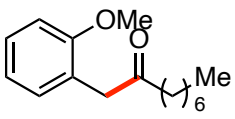
2.2.2 Scope of Alkylarenes

A variety of substituted alkylarenes underwent the dehydrogenative coupling reaction with octanal **30** under analogous conditions to give the corresponding ketones **33**-**51** (Table 2-1). In the cases of methyl-substituted arenes (**33**-**50**), only small amounts (typically less than 0.02 mmol) of bibenzyl-type side-products were observed. When 3,4-dimethylanisole was employed as the toluene derivative, the benzylic C–H bond para to the methoxy group preferentially participated in the acylation reaction to give **38** as the major product (para:meta = 89:11). Whereas electron-donating groups such as *tert*-butyl (**39**) and siloxy (**40**) groups were eligible substituents on the benzene ring, electron-withdrawing substituents such as alkoxycarbonyl, acyl, and cyano groups gave no cross-coupling products. This electronic contrast suggests that the benzylic hydrogen is abstracted in an electrophilic fashion. The reaction of *p*-cresol afforded benzyl ketone **41**, *i.e.*, *C*-acylated product in 32% yield along with the formation of the

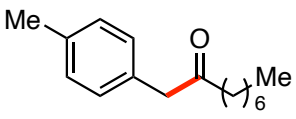
O-acylated product (27% yield). The toluene substrate having an ester moiety not on the benzene ring but on the alkoxy side chain afforded the product **42** in 58% yield. On the other hand, an analogous substrate having a nitrile in place of an ester gave **43** in 27% yield, probably because of the coordination of the nitrile moiety to nickel. The reactions of halo-substituted toluenes were sluggish under the standard reaction conditions (5.0 equiv). When 50 equiv of toluene derivatives were used, however, the corresponding ketones **44**-**46** were obtained in yields ranging from 51 to 66%. Of note was that the chloro and even the bromo substituents remained intact in the products. In addition to toluene derivatives, 2-methylthiophene proved to be an eligible substrate, giving the product **48** in 62% yield. The reactions of 2,5-dimethylfuran and *N*-acetyl-2-methylindole also gave the corresponding cross-coupling products **49** and **50**, respectively, albeit less efficiently. In the case of ethylbenzene, the secondary benzylic C–H bond was site-selectively abstracted to furnish the substituted ketone **51** in 46% yield together with a small amount of bibenzyl-type byproduct (2,3-diphenylbutane, 0.033 mmol as a diastereomer mixture). The lower yield of the cross-coupling product **51** can be ascribed to the steric reasons. Accordingly, sterically more congested isopropylbenzene **1** failed to undergo the dehydrogenative cross-coupling reaction, and instead, the corresponding bibenzyl (**2**, 2,3-dimethyl-2,3-diphenylbutane, 0.22 mmol, 44%) was formed as the major product.

Table 2-1. Scope of Alkylarenes[a]

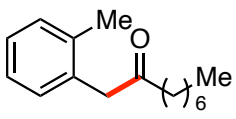




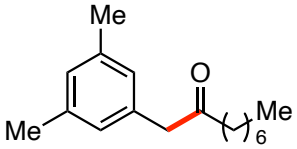
33, 78%[b]



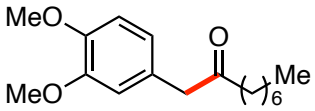
34, 77%[b]



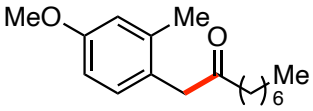
35, 71%[c]



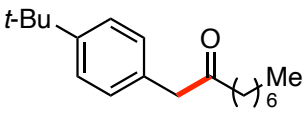
36, 66%



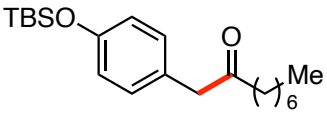
37, 53%[d]



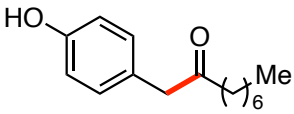
38, 58% (*p*:*m* = 89:11)



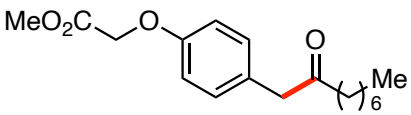
39, 57%[b]



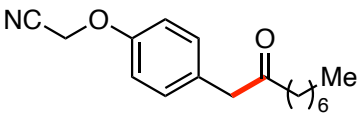
40, 44%



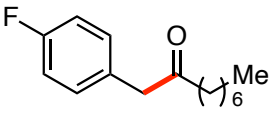
41, 32%



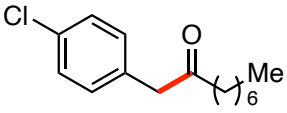
42, 58%



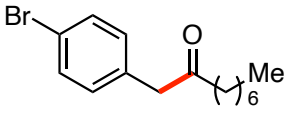
43, 27%



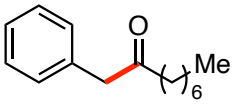
44, 66%[e]



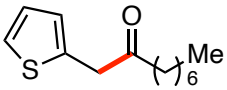
45, 51%[e]



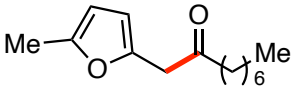
46, 52%[e]



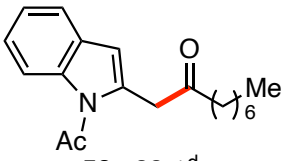
47, 66%[e]



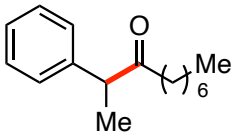
48, 62%



49, 30%[d,f]



50, 22%[d]



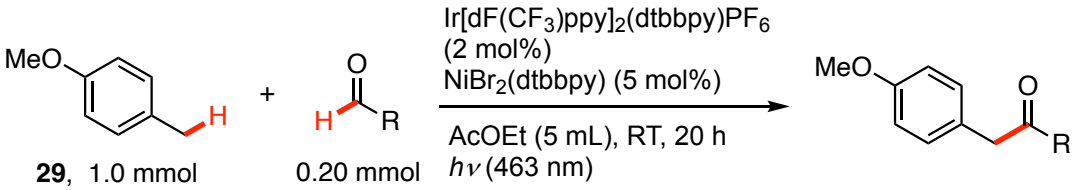
51, 46%

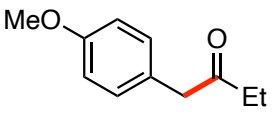
[a] Reaction conditions: alkylarenes (1.0 mmol, 5.0 equiv), octanal (**30**, 0.2 mmol, 1.0 equiv), $NiBr_2$(dtbbpy) (0.01 mmol, 5 mol%), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.004 mmol, 2 mol%), AcOEt (4.9 mL), blue LEDs (40W, λ_{max} = 463 nm), ambient temperature, 20 h. [b] Alkylarenes (1.4 mmol, 7.0 equiv). [c] Alkylarenes (1.6 mmol, 8.0 equiv). [d] Alkylarenes (0.40 mmol, 2.0 equiv). [e] Alkylarenes (10 mmol, 50 equiv). [f] 72 h.

2.2.3 *Scope of Aldehydes*

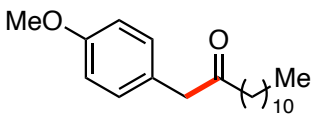
Shown in Table 2-2 are the results using various aliphatic aldehydes, which successfully underwent the dehydrogenative cross-coupling reaction with **29** to give the corresponding ketones **52**-**62**. Both linear (**52**-**54**) and α-branched (**55**-**57**) aldehydes could be employed. Acetal (**60**), hydroxy (**61**), and carbamate (**62**) functionalities remained intact under the present reaction conditions. The reaction of benzaldehyde was sluggish and the dibenzyl **32** was formed as the major product, suggesting the abstraction of aldehydic hydrogen is slow due to the electron-withdrawing nature of the phenyl group.

Table 2-2. Scope of Aldehydes[a]

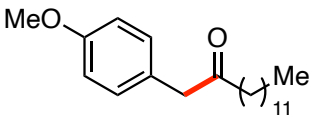




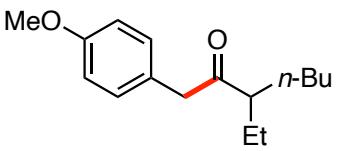
52, 65%



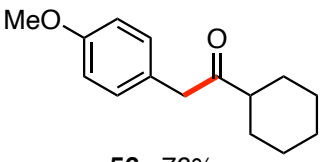
53, 67%



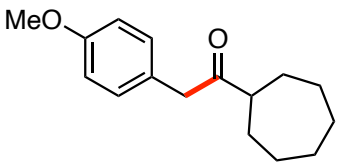
54, 72%



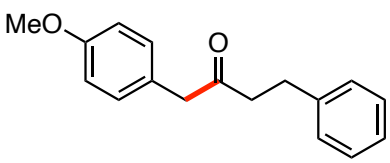
55, 80%



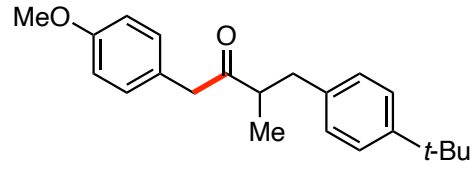
56, 76%



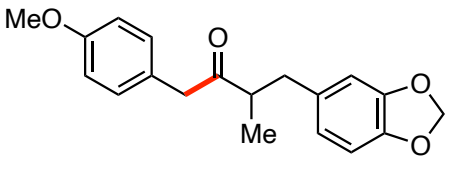
57, 78%



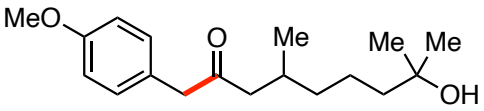
58, 62%



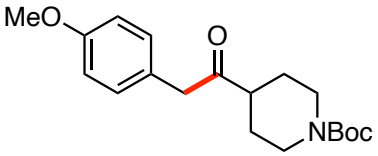
59, 77%



60, 56%



61, 61%



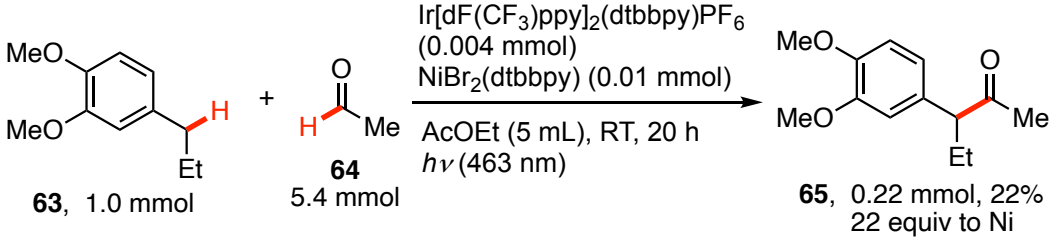
62, 60%

[a] Reaction conditions: *p*-methoxytoluene (**29**, 1.0 mmol, 5.0 equiv), aldehydes (0.2 mmol, 1.0 equiv), $NiBr_2$(dtbbpy) (0.01 mmol, 5 mol%), $Ir[dF(CF_3)ppy]_2$(dtbbpy)PF_6 (0.004 mmol, 2 mol%), AcOEt (4.9 mL), blue LEDs (40W, λ_{max} = 463 nm), ambient temperature, 20 h.

*2.2.4 Synthesis of α-Arylketone **65***

α-Aryl ketones often serve as the key intermediates for the synthesis of various pharmaceuticals. For example, ketone **65** (Scheme 2-2) is the intermediate in the synthesis of Tofisopam,[12] which is an anxiolytic agent marketed in several countries. The present method offers a straightforward access to **65** starting from acetaldehyde **64** and methyl eugenol, an abundant naturally-occurring compound. First, hydrogenation of methyl eugenol quantitatively gave **63**. It successfully underwent the dehydrogenative C–H/C–H cross-coupling reaction with acetaldehyde **64** at the benzylic position to furnish **65** (0.22 mmol, 22%, 22 equiv to Ni).

Scheme 2-2. Synthesis of Ketone **65**



63, 1.0 mmol

64
5.4 mmol

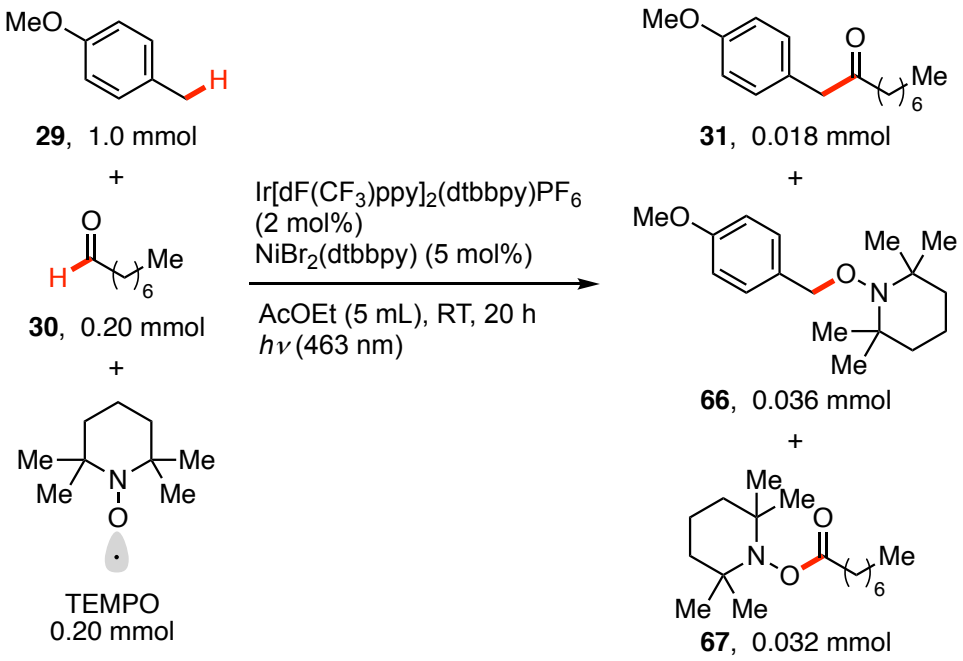
65, 0.22 mmol, 22%
22 equiv to Ni

2.2.5 Mechanistic Studies

Constructive mechanistic information was obtained by the following experiments. When $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ was treated with $NiBr_2(dtbbpy)$ in $CDCl_3$, the hexafluorophosphate anion was replaced with a bromo ligand to form $Ir[dF(CF_3)ppy]_2(dtbbpy)Br$, which was supported by ^1H NMR spectroscopy.[13] It has been reported that photoirradiation of $Ir[dF(CF_3)ppy]_2(dtbbpy)Br$ induces single electron transfer from the bromide anion to iridium,[14] and that the resulting bromine radical abstracts hydrogen from alkanes and aldehydes. No coupling product **31** was formed from toluene **29** and aldehyde **30** when $NiBr_2(dtbbpy)$ was replaced with a catalyst formed in situ from $Ni(OAc)_2$ and dtbbpy.[15] The product formation resumed upon addition of $(n\text{-}Bu)_4NBr$ to the $Ni(OAc)_2$/dtbbpy catalyst. Replacement of $NiBr_2(dtbbpy)$ with its chloride counterpart, $NiCl_2(dtbbpy)$, decreased the yield of **31** to 9%, presumably because of the higher oxidation potential of a chloride anion than that of a bromide anion.[16] All the experimental results mentioned above are consistent with the mechanism which involves an oxidation of a bromide anion to a bromine radical.

We also performed the reaction of **29** with **30** in the presence of TEMPO under the conditions that were otherwise identical to those shown in Scheme 2-1 (Scheme 2-3). The TEMPO adducts **66** and **67** were produced, corroborating the intermediacy of both benzylic and acyl radical species.

Scheme2-3. Radical Trapping Experiment



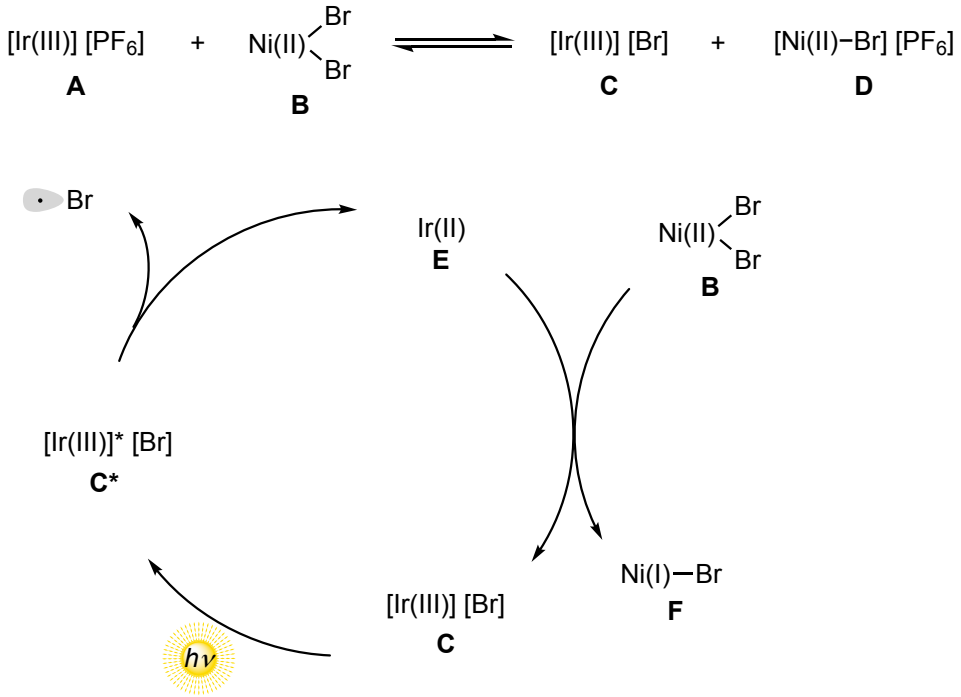
2.2.6 Proposed Mechanism

Depicted in Scheme 2-4 is one of the possible mechanistic scenarios for the formation of the cross-coupling product. It consists of two stages. Stage 1: Anion exchange between cationic iridium(III) hexafluorophosphate **A** and nickel(II) bromide **B** forms iridium(III) bromide complex **C**. When **C** absorbs light to get excited, single electron transfers from the bromide anion to iridium(III) to produce iridium(II) species **E** and a bromine radical.[13],[14] The iridium(II) **E** ($E_{1/2}$[Ir(III)/Ir(II)] = −1.37 V vs SCE)[17] donates single electron to Ni(II) species **B** ($E_{1/2}$[Ni(II)/Ni(0)] = −1.2 V vs SCE),[18] giving rise to Ni(I) species **F** and the iridium(III)bromide **C**. Stage 2: The bromine radical generated in the Stage 1 abstracts hydrogen atoms from benzylic and aldehydic C–H bonds to furnish benzylic and acyl radical species[13],[19] along with HBr. The acyl and benzylic radical species sequentially add to the nickel(I) species **F** to produce nickel(III) complex **G**. The following reductive elimination gives the ketone **31** and the nickel(I) species **F**.[20],[21] The nickel(I) species **F** reacts with HBr to generate H_2 and the

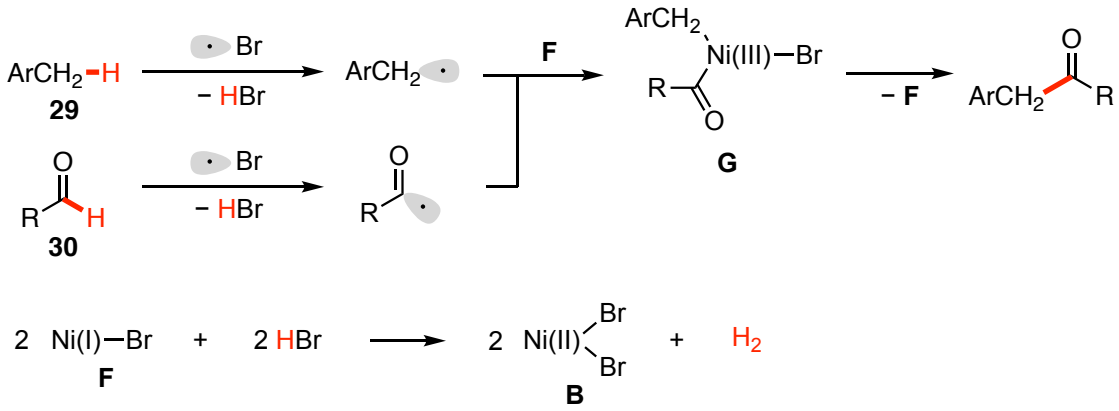
Ni(II)Br_2 species **B**, which re-enters the catalytic cycle of Stage 1.

Scheme 2-4. Proposed Mechanism

Stage 1. Generation of Bromine Radical and Ni(I)



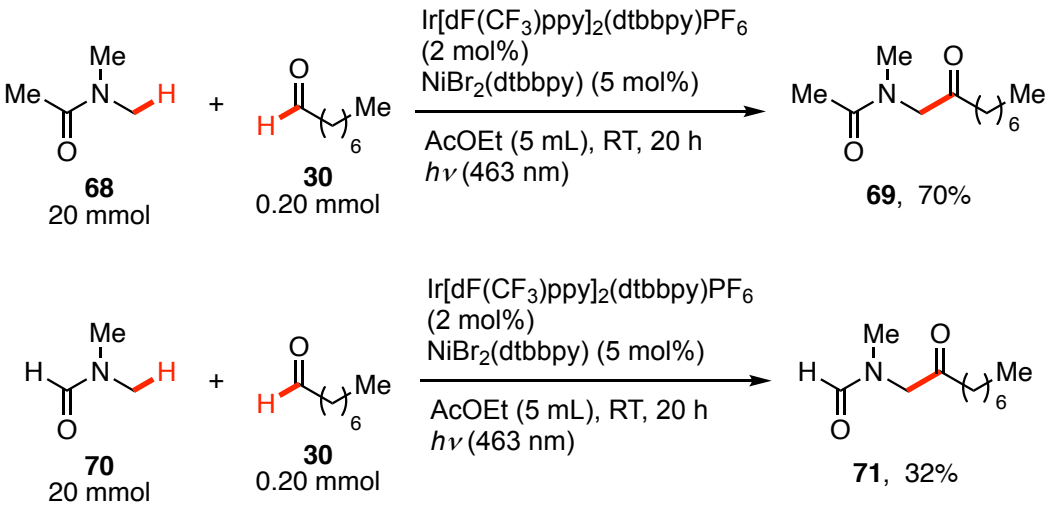
Stage 2. Formation of Ketone and Hydrogen Evolution



2.2.7 *Synthesis of α-Aminoketones*

Aromatic groups participate in the stabilization of benzylic radicals. Similarly, a nitrogen atom also stabilizes its bound carbon radical species. The author briefly examined whether C–H bonds next to nitrogen atoms could take part in the dehydrogenative coupling with aldehydic C–H bond, and suitable reaction conditions were found by modifying the conditions for alkylarenes (Scheme 2-5). When a solution containing a large excess of *N*,*N*-dimethylacetamide (**68**, 20 mmol, 100 equiv) was subjected to the reaction with octanal **30** under the conditions shown in Scheme 2-1, α-amino ketone **69** was produced in 70% yield based on **30**. *N*,*N*-Dimethylformamide **70** also underwent the dehydrogenative coupling reaction with **30** under the same conditions.

Scheme 2-5. Synthesis of α-Aminoketones



2.3 Summary

In summary, the photoinduced dehydrogenative C–H/C–H cross-coupling reaction between alkylbenzenes and aldehydes was developed. It offers a convenient and straightforward synthetic method of α-aryl ketones, which are valued structural motif relevant to pharmaceuticals. α-Amino ketones are also synthesized from *N*-methylamides through an analogous C–C bond forming reaction with aldehydes.

2.4 Experimental Section

2.4.1 General Method and Materials

General Method

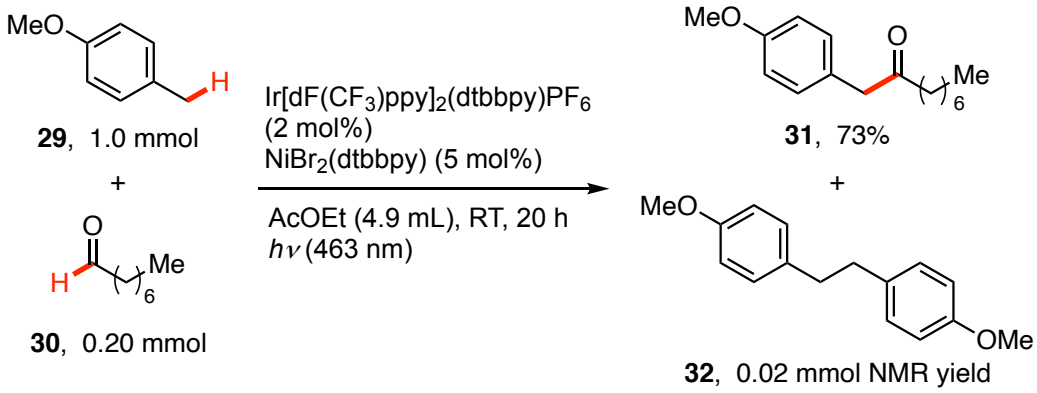
All reactions were carried out under a nitrogen atmosphere using flame-dried glassware. Photoreactions were carried out with blue LEDs (Kessil, A160WE, 40 W). The spectrum is shown below. The evolution of dihydrogen gas was detected by SHIMADZU GASCHROMATOGRAPH GC-8A. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECZ400S/L1 (^{1}H at 400.44 MHz, ^{13}C at 100.69 MHz) spectrometer. $CDCl_3$ was used as a solvent. Chemical shifts are recorded in δ ppm referenced to a residual $CDCl_3$ (δ = 7.26 for ^{1}H, δ = 77.0 for ^{13}C). IR measurements were performed on FTIR SHIMADZU Affinity-1S spectrometer fitted with a Pike Technologies MIRacle Single Reflection ATR adapter. High-resolution mass spectra were recorded on JEOL JMS-700 (EI), Thermo Fisher Scientific Exactive (ESI, APCI). Preparative thin-layer chromatography (PTLC) was performed on silica gel plates with PF254 indicator (Merck). Flash column chromatography was performed with silica gel 60N (Kanto).

Materials

$NiBr_2$(dtbbpy),[23] $NiCl_2$(dtbbpy),[24] Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6,[25] 4-(*t*-butyldimethylsiloxy)toluene,[26] methyl 2-(*p*-tolyloxy)acetate,[27] (*p*-tolyloxy)acetonitrile,[28] and *N*-acetyl-2-methylindole[29] were prepared according to the literature procedures. Other chemicals were purchased from commercial suppliers. Alkylarenes were degassed by freeze-pump-thaw cycling three times prior to use, and other purchased chemicals were used as received.

2.4.2 A Typical Procedure of the Dehydrogenative Coupling of Alkylbenzenes with Aldehydes

Scheme 2-6. A Typical Procedure of the Dehydrogenative Coupling of Alkylarenes with Aldehydes



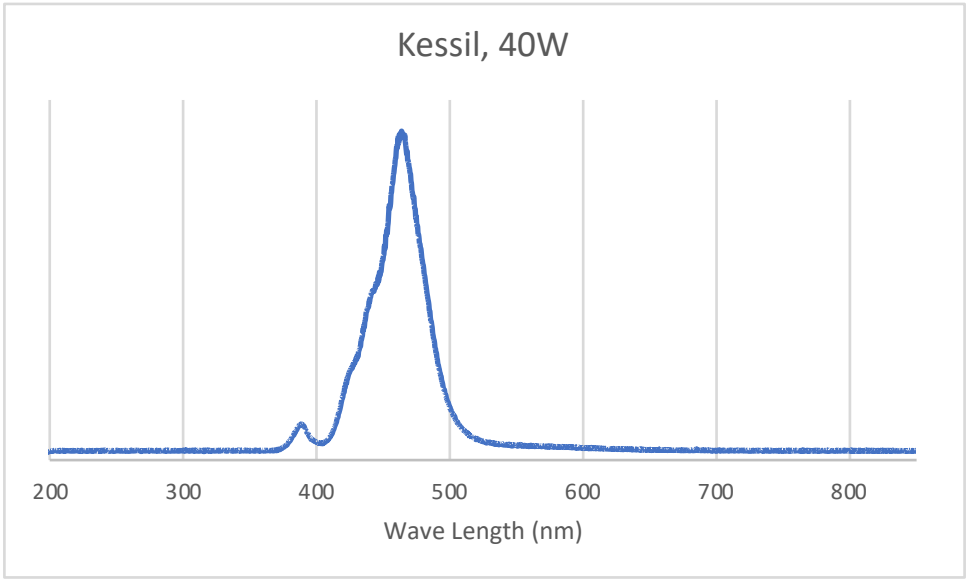


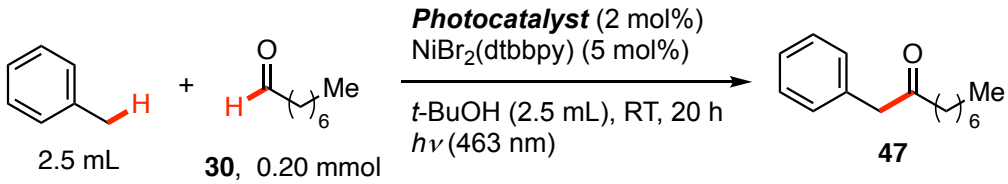
Chart 2-1. Spectrum of the Blue LED

To a Schlenk tube containing Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (4.49 mg, 0.004 mmol, 2 mol%) and NiBr$_2$(dtbbpy) (4.87 mg, 0.010 mmol, 5 mol%) were added 4-methoxytoluene **29** (126 μL, 1.0 mmol, 5.0 equiv), octanal **30** (25.6 mg, 0.20 mmol, 1.0 equiv) and ethyl acetate (4.9 mL) in the glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs (40W), with being cooled by a fan. After 20 hours, the reaction mixture was passed through a short pad of Florisil® with ethyl acetate as an eluent. The filtrate was

concentrated under reduced pressure to afford a mixture containing ketone **31** (72%, NMR yield) and bibenzyl **32** (0.02 mmol). The residue was purified by preparative thin-layer chromatography (PTLC) (Hexane:Et_2O = 7:1, R_f = 0.30) to give ketone **31** (36.3 mg, 0.146 mmol, 73%) as a viscos colorless oil.

2.4.3 Optimization Studies

Table 2-3. Screening of Photocatalysts



entry	photocatalyst	NMR yield of **47**
1	none	0%
2	Eosin Y	<5%
3	Mes-Acr-Me•ClO_4	11%
4	4CzIPN	<5%
5	$Ru(bpy)_3$•$2BF_4$	0%
6	$Ir(ppy)_3$	0%
7	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	62%

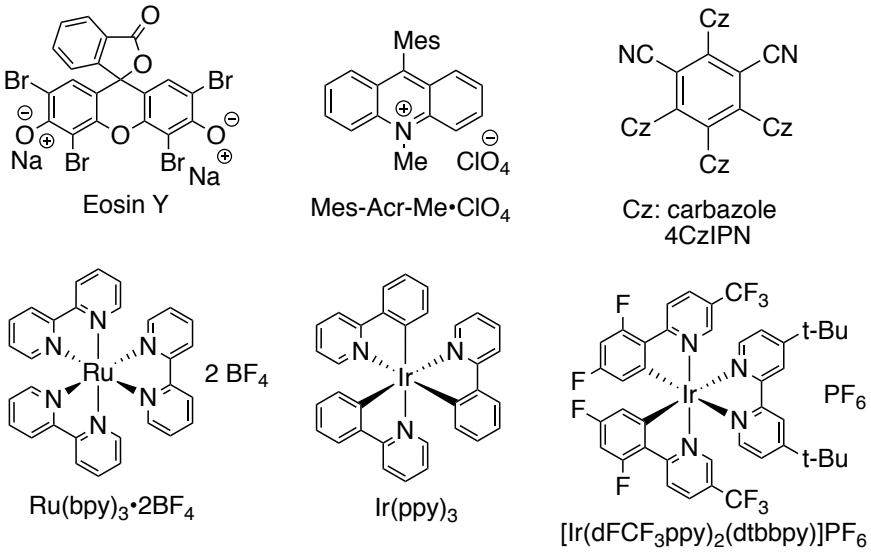
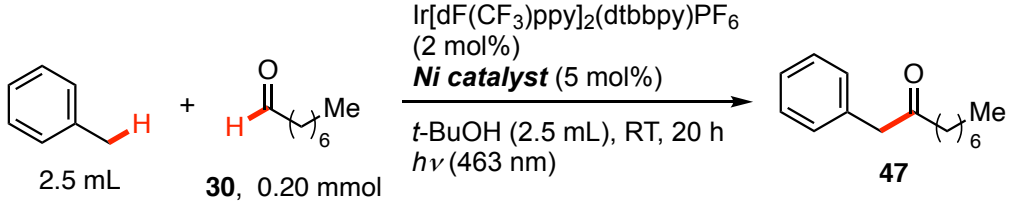


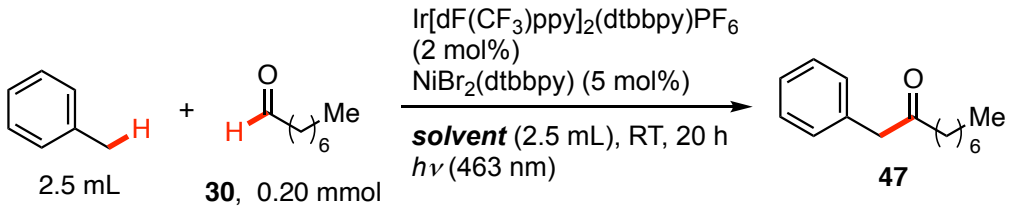
Figure 2-1. Structures of the Photocatalysts

Table 2-4. Screening of Nickel Catalysts



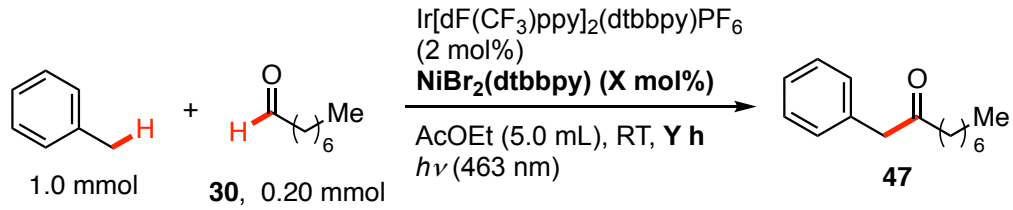
entry	Ni catalyst	NMR yield of **47**
1	$NiBr_2$(dtbbpy)	62%
2	$NiBr_2$(bpy)	14%
3	$NiCl_2$(dtbbpy)	17%
4	$NiBr_2$(dme)	<5%

Table 2-5. Screening of Solvents



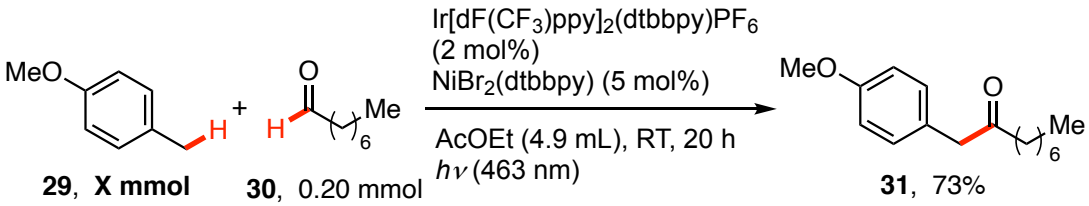
entry	solvent	NMR yield of **47**
1	none (toluene: 5.0 mL)	<5%
2	*t*-BuOH	62%
3	*i*-PrOH	9%%
4	EtOH	0%
5	MeOH	<5%
6	THF	29%
7	MeCN	20%
8	DMF	9%
9	acetone	69%
10	AcOEt	72%

Table 2-6. Screening of Amount of $NiBr_2$(dtbbpy) and Reaction Time



entry	$NiBr_2$(dtbbpy)	time	NMR yield of **47**
1	10 mol%	20 h	25%
2	5 mol%	40 h	26%
3	10 mol%	40 h	25%

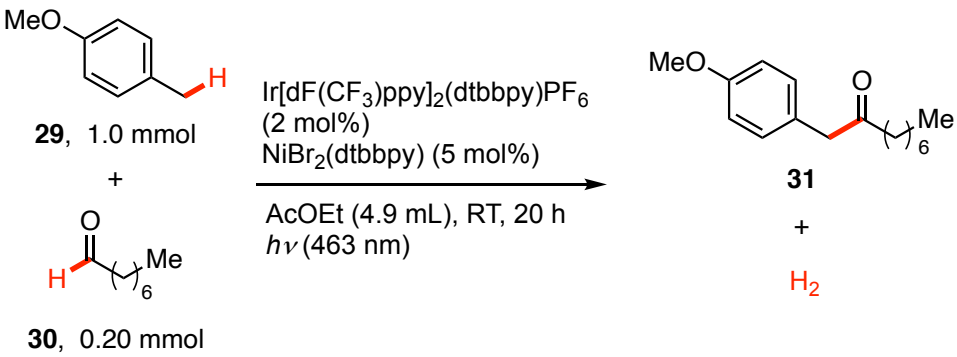
Table 2-7. Screening of Amounts of Alkylarene in the Reaction of **29**



entry	**29**	NMR yield of **47**
1	2.0 mmol	69%
2	1.0 mmol	72% (73% isolated yield)
3	0.40 mmol	60%

2.4.4 *Qualitative Analysis of Evolved Molecular Hydrogen*

Scheme 2-7. Detection of Gaseous Hydrogen



The gas phase in the headspace of the reaction vessel was analyzed by gas chromatography. A gas-tight syringe was used to take a sample (0.20 mL) from the vessel. Before each sampling, the gas in the syringe was replaced with the gas in the reaction vessel; 0.20 mL of gas in the headspace of the vessel was once taken and discharged. Then, 0.20 mL of gas in the vessel was newly taken and injected into a gas chromatograph.

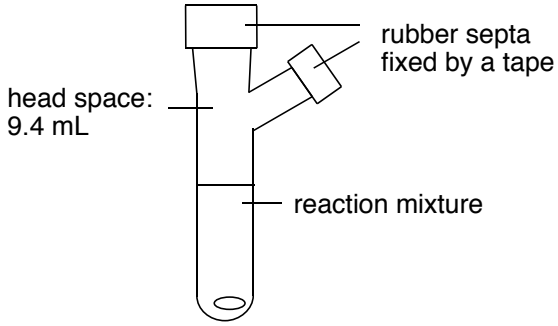


Figure 2-2. Illustration of the Reaction Set Up

2.4.5 Stern-Volmer Quenching Experiment

Samples for Stern-Volmer studies were prepared using varying amount of quenchers and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 in ethyl acetate. The solution was degassed by freeze-pump-thaw cycling three times and poured into quartz cuvettes in the glove box. The solution was irradiated at 435 nm and the emission intensity was observed at 500 nm. The results are given below.

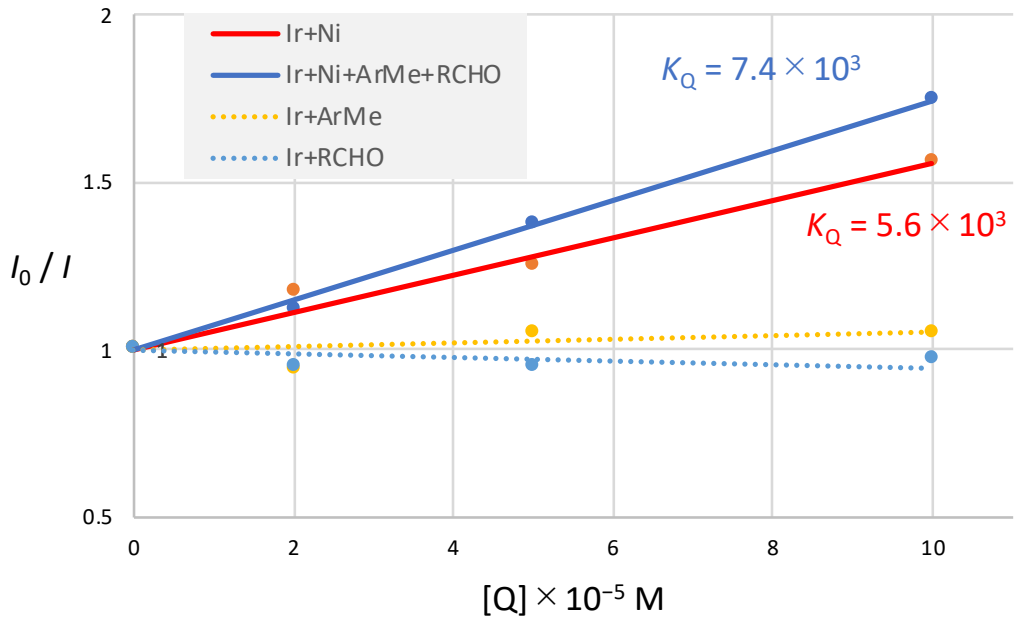
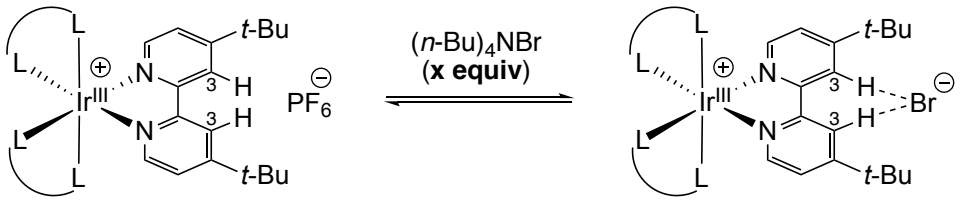


Chart 2-2. Stern-Volmer Plots

The Stern-Volmer plots revealed that $NiBr_2$(dtbbpy) quenched the excited state of the iridium complex.

2.4.6 Studies of Anion Exchange of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$

Scheme 2-8. Interaction Between Ir Catalyst and Br^-



3 mM in $CDCl_3$

To a $CDCl_3$ solution of $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (3 mM) was added (n-Bu)$_4$NBr (0.2, 0.5, 1.0, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0 and 8.0 equiv to Ir) and the mixture was analyzed by ^{1}H NMR spectroscopy. The spectra are shown below. Spectra at each equivalent are overlaid.

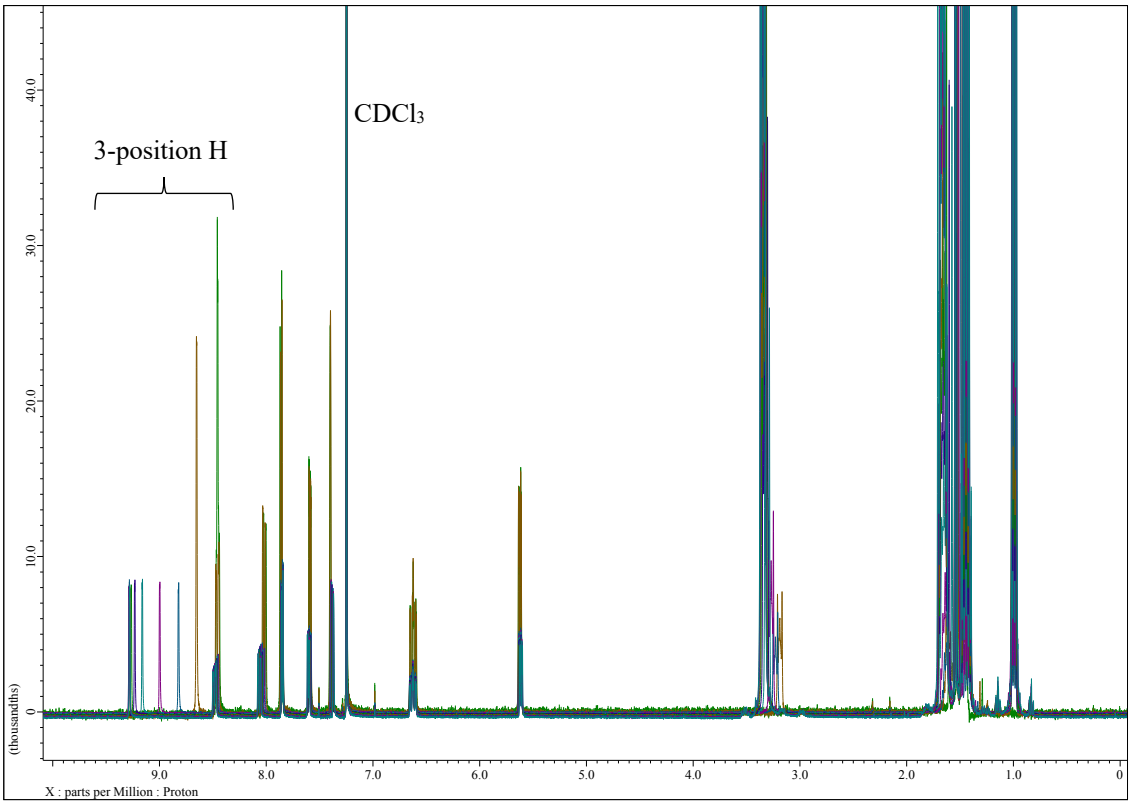


Chart 2-3. ^{1}H NMR Spectra of the Mixture Containing $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ and (n-Bu)$_4$NBr (0-10 ppm)

A signal assigned as the proton at the 3-position of the bipyridine ligand on iridium

shifted downfield significantly upon addition of $(n\text{-Bu})_4NBr$. Other signals remained as such. The enlarged spectra in the region ranging from 8.3-9.4 ppm is shown in Chart 2-4.

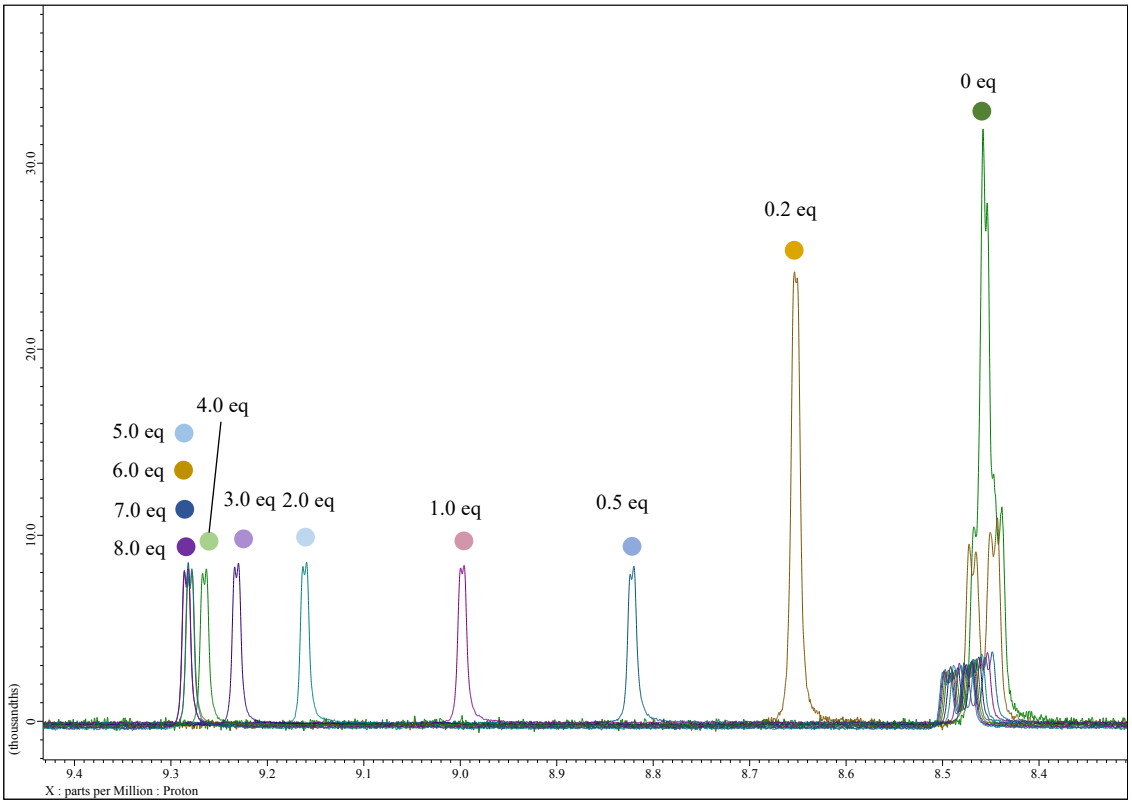
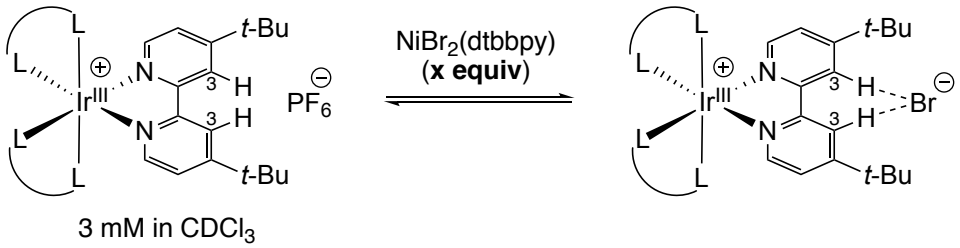


Chart 2-4. Enlarged Spectra (8.3-9.4 ppm)

The downfield shift of the signal reached at 9.3 ppm when 5.0 equiv of $(n\text{-Bu})_4NBr$ was added. No change was observed upon further addition. The downfield shift indicates that hexafluorophosphate anion is exchanged with the bromide anion, which interacts with the proton at the 3-position of the bipyridine ligand on iridium. See ref [30] for such hydrogen bonding, and ref [31] for the ^1H NMR spectrum of $Ir[dF(CF_3)ppy]_2(dtbbpy)Br$.

Scheme 2-9. Anion Exchange Between Ir Catalyst and $NiBr_2$(dtbbpy)



To a $CDCl_3$ solution of Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (3 mM) was added $NiBr_2$(dtbbpy) (0.1, 0.25, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5 5.0, 5.5 6.0, 6.5, 7.0 and 7.5 equiv to Ir) and the mixture was analyzed by ^{1}H NMR. The signal assigned as the proton at the 3-position of the bipyridine ligand on iridium shifted downfield in a way similar to that in the presence of (n-Bu)$_4$NBr. The signal was broadened because the nickel complex was paramagnetic.

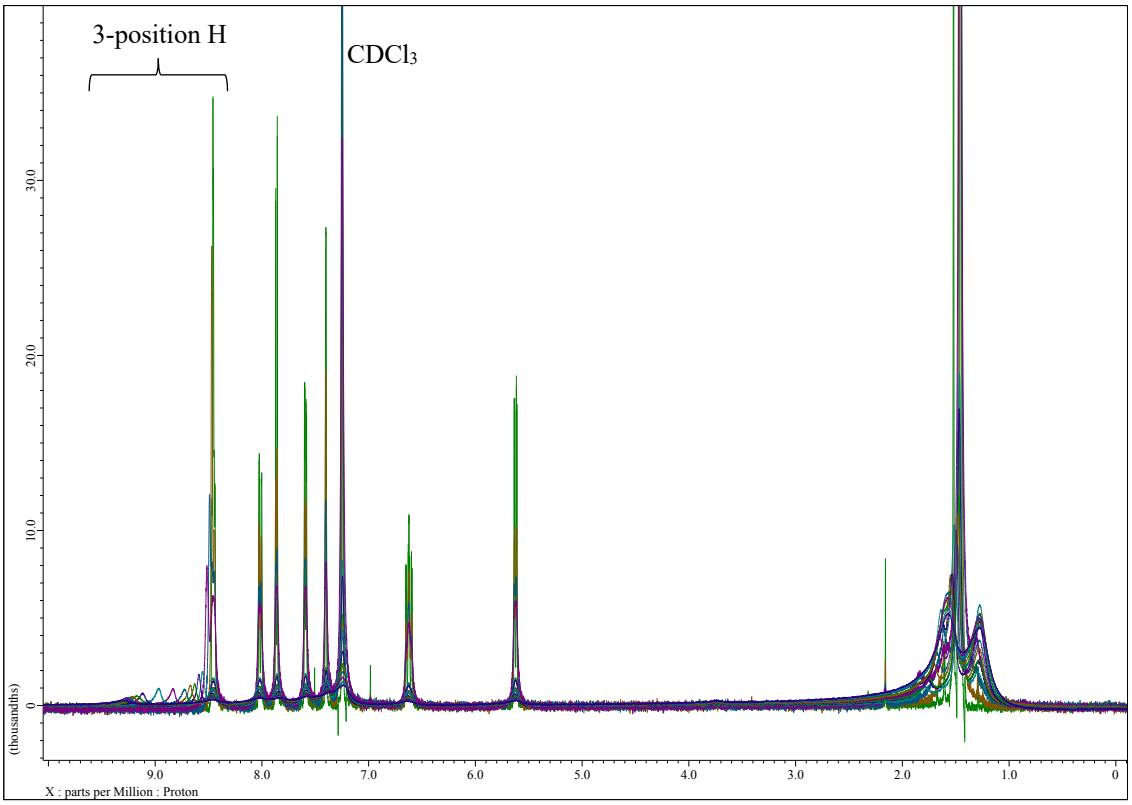


Chart 2-5. ^{1}H NMR Spectra of the Mixture Containing Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 and $NiBr_2$(dtbbpy) (0-10 ppm)

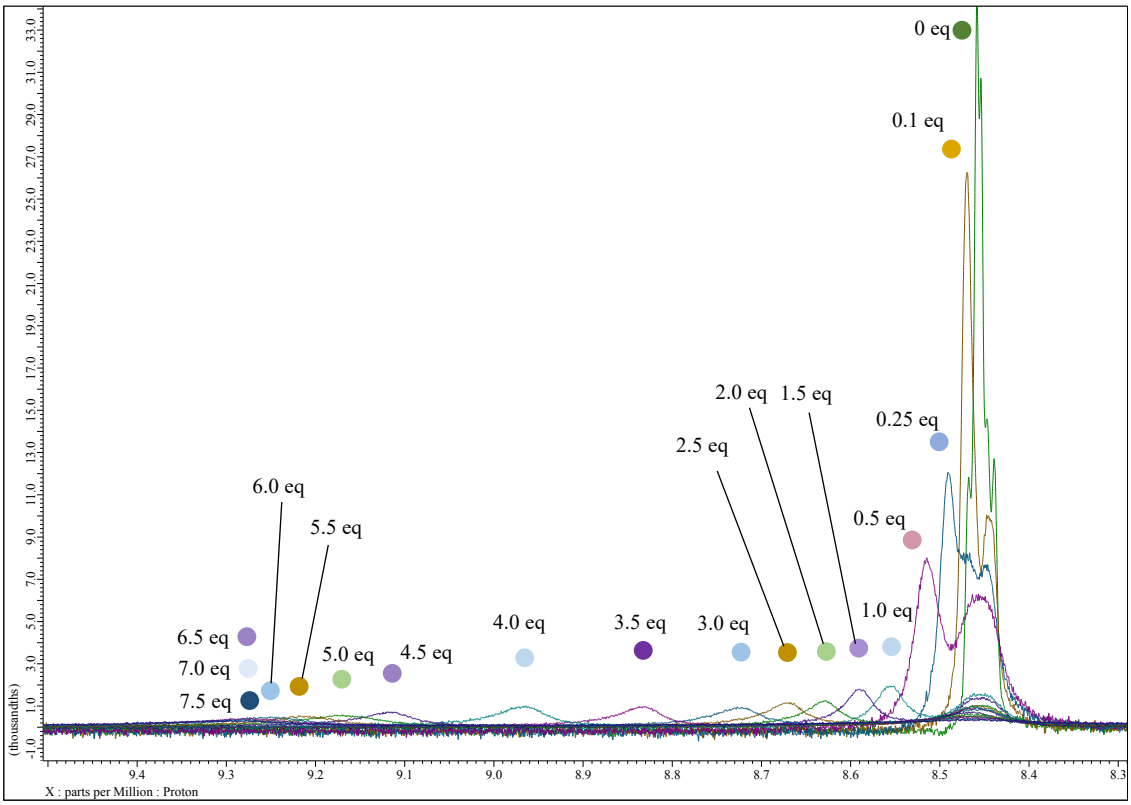
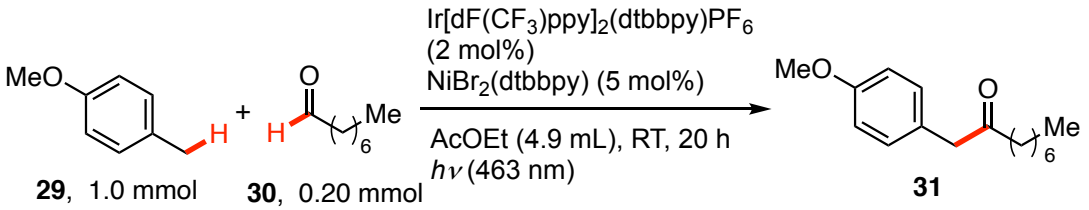


Chart 2-6. Enlarged Spectra (8.3-9.4 ppm)

2.4.7 Control Experiments

Table 2-8. Control Experiments

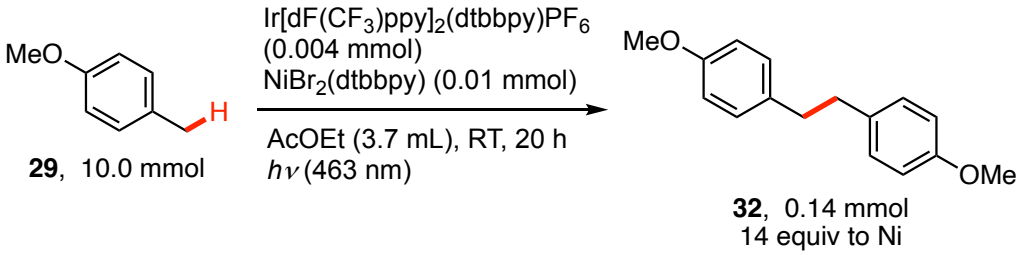


29, 1.0 mmol **30**, 0.20 mmol **31**

entry	deviation from standard condition	yield of **31**
1	none	73%
2	w/o $NiBr_2$(dtbbpy)	0%
3	Ni(cod)(dtbbpy) (5 mol%) instead of $NiBr_2$(dtbbpy)	0%
4	$Ni(OAc)_2$•$4H_2O$ (5 mol%), dtbbpy (5 mol%) instead of $NiBr_2$(dtbbpy)	0%
5	$Ni(OAc)_2$•$4H_2O$ (5 mol%), dtbbpy (5 mol%), (n-Bu)$_4$NBr (10 mol%) instead of $NiBr_2$(dtbbpy)	9%
6	(n-Bu)$_4$NBr (10 mol%) instead of $NiBr_2$(dtbbpy)	0%
7	dtbbpy (5 mol%), (n-Bu)$_4$NBr (10 mol%) instead of $NiBr_2$(dtbbpy)	0%

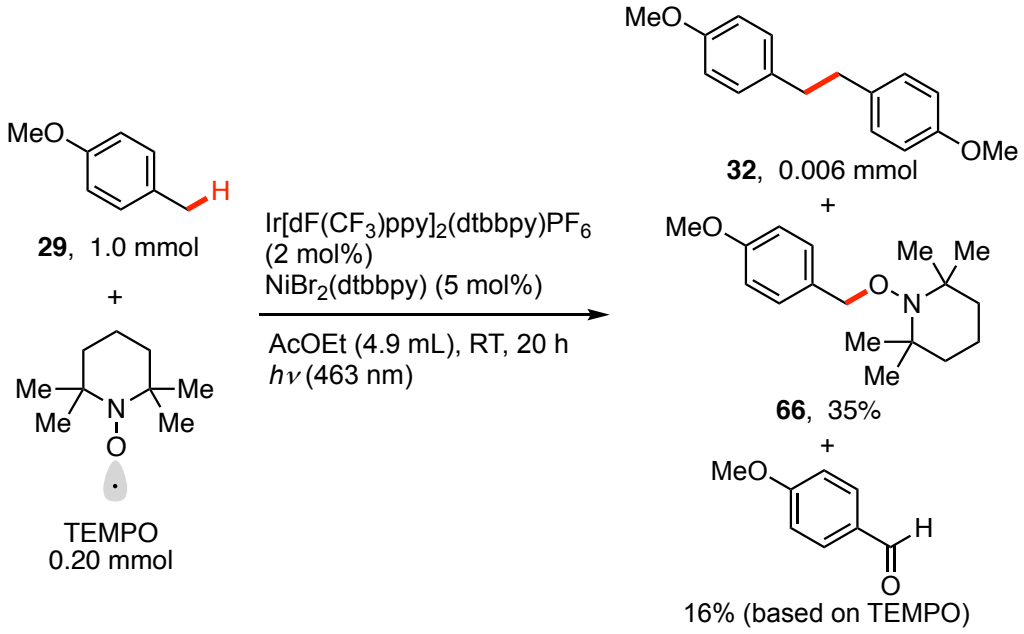
2.4.8 Radical Trapping Experiments

Scheme 2-10. Homo-Dimerization of **29**



To a Schlenk tube containing Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (4.49 mg, 0.004 mmol) and NiBr$_2$(dtbbpy) (4.87 mg, 0.010 mmol) were added 4-methoxytoluene **29** (1260 μL, 10.0 mmol) and ethyl acetate (3.7 mL) in the glove box. The reaction mixture was stirred and irradiated with blue LEDs (40W), with being cooled by a fan. After 20 hours, the reaction mixture was passed through a short pad of Florisil® with ethyl acetate as an eluent. The filtrate was concentrated under reduced pressure to afford bibenzyl **32**. The residue was purified by preparative thin-layer chromatography (PTLC) (Hexane:Et$_2$O = 7:1, R_f = 0.50) to give bibenzyl **32** (34.3 mg, 0.142 mmol, 14 equiv to Ni) as a pale yellow solid.

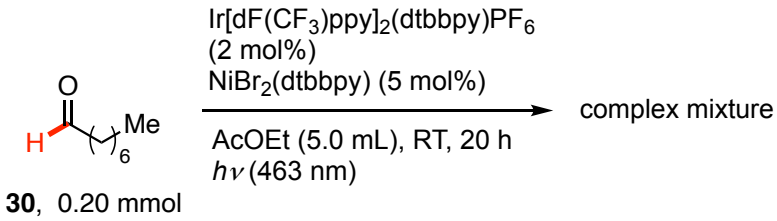
Scheme 2-11. Benzyl Radical Trapping Experiment from **29**



To a Schlenk tube containing Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (4.49 mg, 0.004 mmol, 2 mol%) and NiBr$_2$(dtbbpy) (4.87 mg, 0.010 mmol, 5 mol%) were added 4-

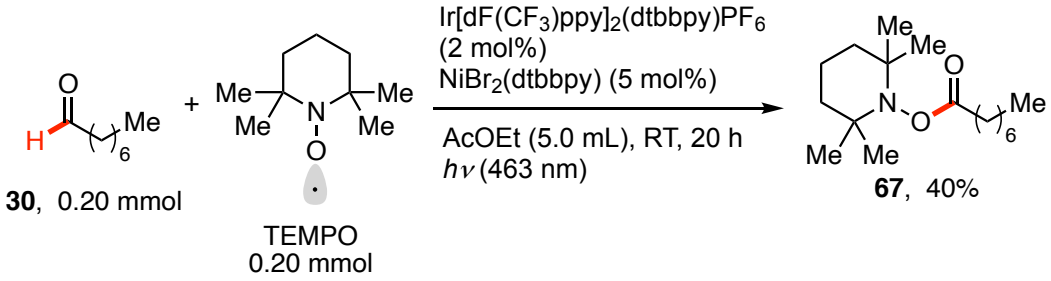
methoxytoluene **29** (126 μL, 1.0 mmol, 5.0 equiv), 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO, 31.3 mg, 1.0 equiv) and ethyl acetate (4.9 mL) in the glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs (40W), with being cooled by a fan. After 20 hours, the reaction mixture was passed through a short pad of silica gel with ethyl acetate as an eluent. The filtrate was concentrated under reduced pressure to afford a mixture containing **66** (35%, NMR yield), 4-methoxybenzaldehyde (16%, NMR yield based on TEMPO) and bibenzyl **32** (0.006 mmol).

Scheme 2-12. Decomposition of **30**



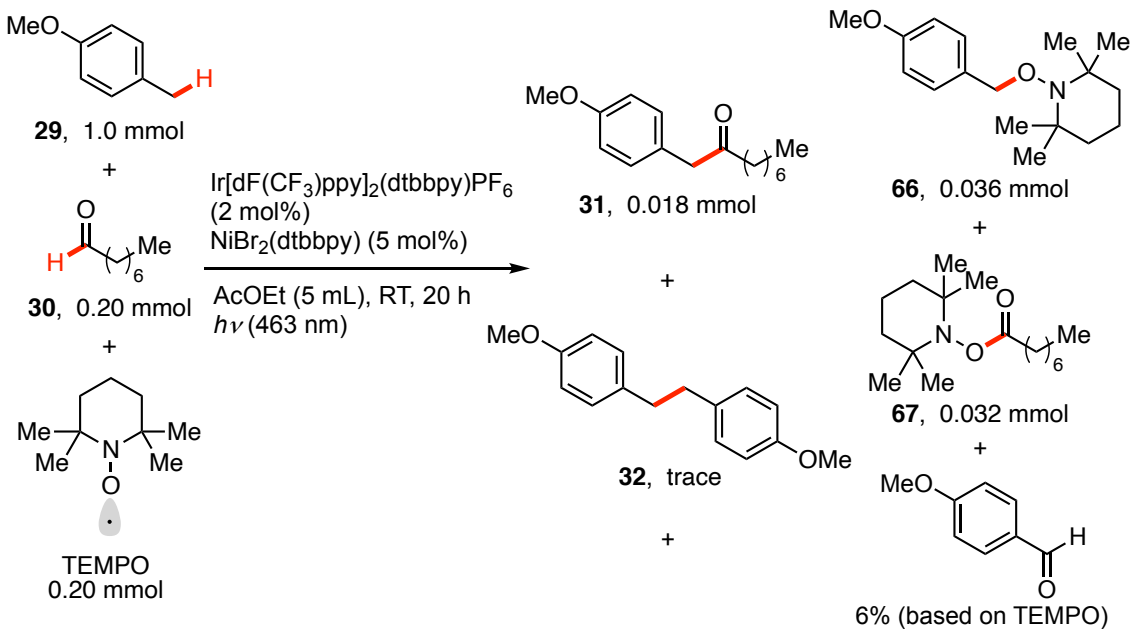
To a Schlenk tube containing Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (4.49 mg, 0.004 mmol, 2 mol%) and NiBr$_2$(dtbbpy) (4.87 mg, 0.010 mmol, 5 mol%) were added octanal **30** (25.6 mg, 0.20 mmol, 1.0 equiv) and ethyl acetate (5.0 mL) in the glove box. The reaction mixture was stirred and irradiated with blue LEDs (40W), with being cooled by a fan. After 20 hours, the reaction mixture was passed through a short pad of Florisil® with ethyl acetate as an eluent. The filtrate was concentrated under reduced pressure. Since the residue was a complex mixture, it was difficult to identify the products by ^{1}H NMR analysis. GC-MS analysis indicated the mixture contained tetradecan-7,8-dione (homo-dimer of the acyl radical intermediate), tridecan-7-one (product derived from the acyl radical intermediate and its decarbonylated intermediate), and other oligomeric products.

Scheme 2-13. Acyl Radical Trapping Experiment



To a Schlenk tube containing Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (4.49 mg, 0.004 mmol, 2 mol%) and $NiBr_2$(dtbbpy) (4.87 mg, 0.010 mmol, 5 mol%) were added octanal **30** (25.6 mg, 0.20 mmol, 1.0 equiv), 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO, 31.3 mg, 1.0 equiv) and ethyl acetate (5.0 mL) in the glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs (40W), with being cooled by a fan. After 20 hours, the reaction mixture was passed through a short pad of silica gel with ethyl acetate as an eluent. The filtrate was concentrated under reduced pressure to afford a mixture containing **67** (40%, NMR yield).

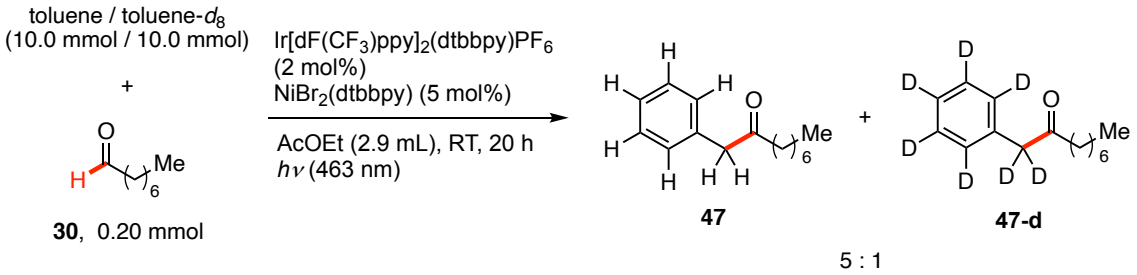
Scheme 2-14. Radical Trapping Experiment



To a Schlenk tube containing Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (4.49 mg, 0.004 mmol, 2 mol%) and NiBr$_2$(dtbbpy) (4.87 mg, 0.010 mmol, 5 mol%) were added 4-methoxytoluene **29** (126 μL, 1.0 mmol, 5.0 equiv), octanal **30** (25.6 mg, 0.20 mmol, 1.0 equiv), 2,2,6,6-tetramethylpiperidine 1-oxyl free radical (TEMPO, 31.3 mg, 1.0 equiv) and ethyl acetate (4.9 mL) in the glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs (40W), with being cooled by a fan. After 20 hours, the reaction mixture was passed through a short pad of silica gel with ethyl acetate as an eluent. The filtrate was concentrated under reduced pressure to afford a mixture containing **66** (18%, NMR yield), **67** (16%, NMR yield), ketone **3** (8%, NMR yield), 4-methoxybenzaldehyde (6%, NMR yield based on TEMPO) and **32** (trace). The residue was purified by preparative thin-layer chromatography (PTLC) (Hexane:AcOEt = 10:1) to give **66** (10.5 mg, 0.038 mmol, 18%, R_f = 0.50, viscos colorless oil) and **67** (7.6 mg, 0.027 mmol, 13%, R_f = 0.30, viscos colorless oil).

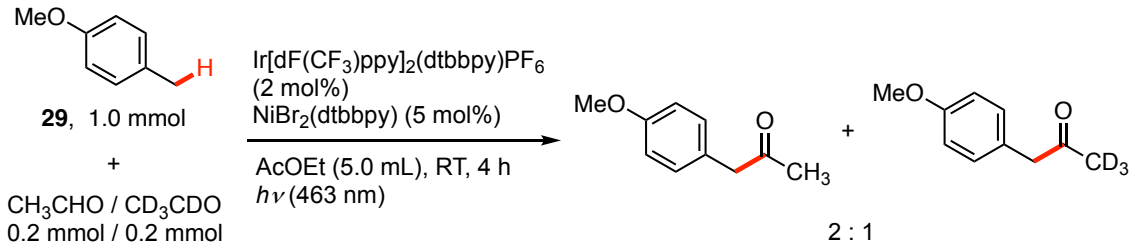
2.4.9 Kinetic Isotope Effect (KIE) Studies

Scheme 2-15. Intermolecular Competition Between Toluene and Toluene-d_8



To a Schlenk tube containing Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (4.49 mg, 0.004 mmol, 2 mol%) and NiBr$_2$(dtbbpy) (4.87 mg, 0.010 mmol, 5 mol%) were added toluene (1.06 mL, 10 mmol, 50 equiv), toluene-d_8 (1.07 mL, 10 mmol, 50 equiv), octanal **30** (25.6 mg, 0.20 mmol, 1.0 equiv) and ethyl acetate (2.9 mL) in the glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs (40W), with being cooled by a fan. After 20 hours, the reaction mixture was passed through a short pad of Florisil® with ethyl acetate as an eluent. The filtrate was concentrated under reduced pressure to afford a mixture containing ketone **47** and **47-d** (5:1).

Scheme 2-16. Intermolecular Competition Between CH_3CHO and CD_3CDO

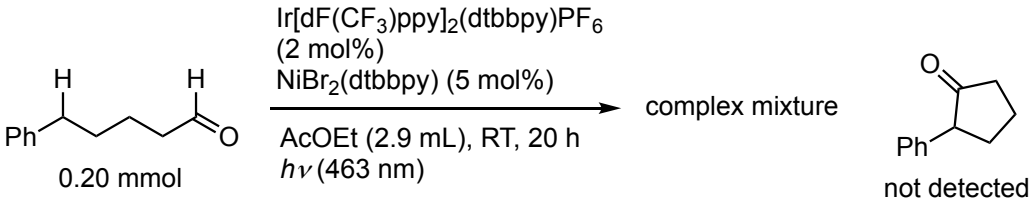


To a Schlenk tube containing Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (4.49 mg, 0.004 mmol, 2 mol%) and NiBr$_2$(dtbbpy) (4.87 mg, 0.010 mmol, 5 mol%) were added 4-methoxytoluene (126 μL, 1.0 mmol, 5.0 equiv), acetaldehyde (0.1 M in AcOEt, 2.0 mL, 0.20 mmol, 1.0 equiv), acetaldehyde-d_4 (0.1 M in AcOEt, 2.0 mL, 0.20 mmol, 1.0 equiv) and ethyl acetate (1.0 mL) in the glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs (40W), with being cooled by a fan. After 4 hours, the reaction mixture was passed through a short pad of Florisil® with ethyl acetate as an eluent. The filtrate was concentrated under

reduced pressure to afford a mixture containing 4-methoxyphenylacetone and deuterated 4-methoxyphenylacetone (2:1).

2.4.10 Attempt of Intramolecular Reaction

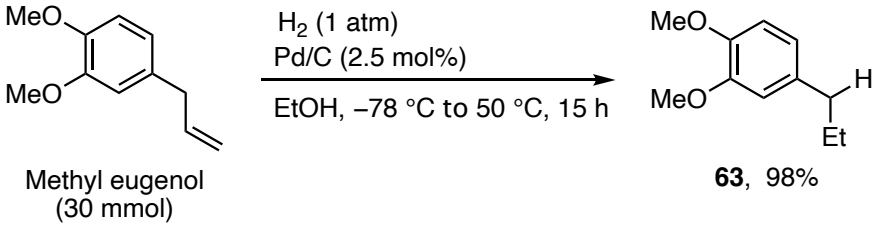
Scheme 2-17. Attempt of Intramolecular Reaction



To a Schlenk tube containing $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (4.49 mg, 0.004 mmol, 2 mol%) and $NiBr_2(dtbbpy)$ (4.87 mg, 0.010 mmol, 5 mol%) were added 5-phenylpentanal (32.4 mg, 0.20 mmol) and ethyl acetate (5.0 mL) in the glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs (40W), with being cooled by a fan. After 20 hours, the reaction mixture was passed through a short pad of Florisil® with ethyl acetate as an eluent. The filtrate was concentrated under reduced pressure. A complex mixture was obtained. No 2-phenylcyclopentanone was formed, which was confirmed by ^1H NMR analysis of the crude reaction mixture.

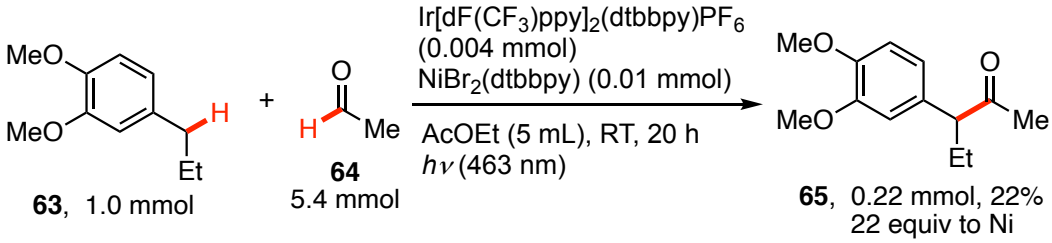
2.4.11 Synthesis of Ketone **37**

Scheme 2-18. Hydrogenation of *O*-Methyl Eugenol



To a two-necked 100 mL round bottom flask equipped with a magnetic stir bar and condenser was added 5% Pd/C (250 mg, 0.75 mmol, 2.5 mol%). The flask was replaced with argon and then added EtOH (20 mL). After the reaction mixture was cooled to −75 ℃, the flask was connected to hydrogen balloon. To the reaction mixture was added methyl eugenol (5.35 g, 30.0 mmol) at −75 ℃, and the resulting mixture was warmed up to room temperature. Then, the reaction was heated at 50 ℃. After 15 hours, the reaction mixture was passed through a short pad of celite with Et_2O as an eluent. The residue was concentrated under reduced pressure to remove solvent. Analytically pure 3,4-dimethoxy-*n*-propylbenzene **63** was obtained without additional purification (5.30 g, 29.4 mmol, 98%) as a viscos colorless oil.

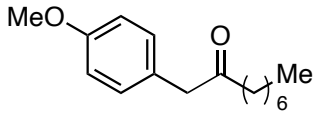
Scheme 2-19. Dehydrogenative Coupling of **63** with acetaldehyde **64**



To a Schlenk tube containing $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (4.49 mg, 0.004 mmol) and $NiBr_2(dtbbpy)$ (4.87 mg, 0.010 mmol) was added **63** (180.3 mg, 1.0 mmol), ethyl acetate (4.6 mL) and degassed acetaldehyde **64** (300 μL, 5.4 mmol) in the glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs (40W), with being cooled by a fan. After 20 hours, the reaction mixture was passed through a short pad of Florisil® with ethyl acetate as an eluent. The filtrate was concentrated under reduced pressure to afford ketone **65**. The residue was purified by preparative thin-layer chromatography (Hexane:Et_2O = 4:1,

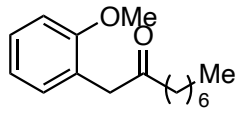
R_f = 0.20) to give ketone **65** (49.2 mg, 0.221 mmol, 22 equiv to Ni) as a viscos colorless oil.

2.4.12 Spectroscopic Data of Products



31

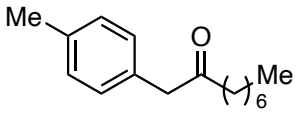
^{1}H NMR: δ = 7.11 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.61 (s, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.54 (quint, *J* = 7.2 Hz, 2H), 1.32-1.16 (m, 8H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 209.1, 158.6, 130.4, 126.4, 114.1, 55.2, 49.2, 41.8, 31.6, 29.1, 29.0, 23.8, 22.6, 14.0; IR (neat): 2928, 2855, 1711, 1510, 1246, 1177, 1036, 731 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{25}O_2$ 249.1849; Found 249.1849.



33

The reaction was conducted with 1.4 mmol of 2-methoxytoluene. The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.30) to give **33** (38.9 mg, 0.157 mmol, 62%) as a viscos colorless oil.

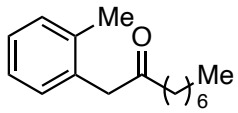
^{1}H NMR: δ = 7.25 (t, *J* = 7.8 Hz, 1H), 7.12 (d, *J* = 7.4 Hz, 1H), 6.92 (t, *J* = 7.4 Hz, 1H), 6.87 (d, *J* = 8.2 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.56 (quint, *J* = 7.2 Hz, 2H), 1.34-1.17 (m, 8H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR: δ = 209.1, 157.3, 131.1, 128.3, 123.7, 120.6, 110.4, 55.2, 44.6, 41.9, 31.6, 29.1, 29.0, 23.8, 22.6, 14.0; IR (neat): 2926, 2855, 1715, 1495, 1464, 1246, 1117, 1049, 1030, 750 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{25}O_2$ 249.1849; Found 249.1850.



34

The reaction was conducted with 1.4 mmol of *p*-xylene. The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.50) to give **34** (35.8 mg, 0.154 mmol, 77%) as a viscos colorless oil.

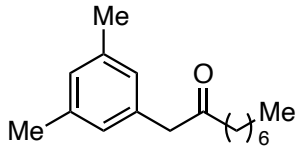
^{1}H NMR: δ = 7.14 (d, *J* = 7.9 Hz, 2H), 7.09 (d, *J* = 8.1 Hz, 2H), 3.64 (s, 2H), 2.43 (t, *J* = 7.4 Hz, 2H), 2.34 (s, 3H), 1.55 (quint, *J* = 7.2 Hz, 2H), 1.33-1.17 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 208.8, 136.5, 131.3, 129.3, 129.2, 49.7, 41.8, 31.6, 29.02, 28.97, 23.7, 22.5, 21.0, 14.0; IR (neat): 2926, 2857, 1713, 1514, 1456, 910, 731 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{25}O$ 233.1900; Found 233.1899.



35

The reaction was conducted with 1.6 mmol of *o*-xylene. The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.50) to give **35** (32.8 mg, 0.141 mmol, 71%) as a viscos colorless oil.

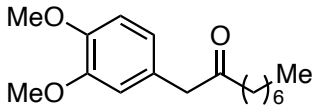
^{1}H NMR: δ = 7.21-7.08 (m, 4H), 3.70 (s, 2H), 2.41 (t, *J* = 7.4 Hz, 2H), 2.24 (s, 3H), 1.56 (quint, *J* = 7.3 Hz, 2H), 1.34-1.16 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 208.6, 136.8, 133.3, 130.41, 130.36, 127.2, 126.2, 48.3, 41.9, 31.6, 29.1, 29.0, 23.8, 22.6, 19.7, 14.0; IR (neat): 2926, 2855, 1713, 1458, 1375, 1128, 1069, 741 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{25}O$ 233.1900; Found 233.1899.



36

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.50) to give **36** (33.4 mg, 0.134 mmol, 66%) as a viscos colorless oil.

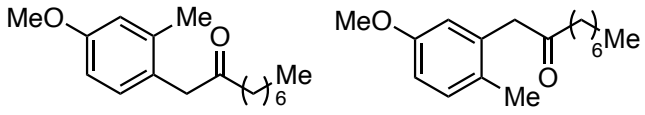
^{1}H NMR: δ = 6.90 (s, 1H), 6.82 (s, 2H), 3.60 (s, 2H), 2.43 (t, *J* = 7.4 Hz, 2H), 2.30 (s, 6H), 1.55 (quint, *J* = 7.2 Hz, 2H), 1.34-1.14 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 209.0, 138.2, 134.2, 128.6, 127.2, 50.0, 41.9, 31.6, 29.04, 29.01, 23.7, 22.6, 21.2, 14.0; IR (neat): 2924, 2855, 1713, 1605, 1464, 1375, 1072, 849, 700 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{27}O$ 247.2056; Found 247.2056.



37

The reaction was conducted with 0.40 mmol of 3,4-dimethoxytoluene. The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 4:1, R_f = 0.20) to give **37** (29.9 mg, 0.107 mmol, 53%) as a viscos colorless oil.

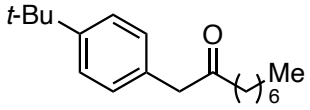
^{1}H NMR: δ = 6.82 (d, *J* = 8.1 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.71 (s, 1H), 3.86 (pseudo s, 6H), 3.60 (s, 2H), 2.43 (t, *J* = 7.4 Hz, 2H), 1.54 (quint, *J* = 7.0 Hz, 2H), 1.32-1.15 (m, 8H), 0.86 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR: δ = 209.0, 149.0, 148.0, 126.9, 121.5, 112.3, 111.3, 55.9, 55.8, 49.7, 41.8, 31.6, 29.1, 29.0, 23.7, 22.6, 14.0; IR (neat): 2928, 2855, 1709, 1514, 1464, 1260, 1236, 1155, 1140, 1028, 766 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{27}O_3$ 279.1955; Found 279.1955.



38 **38'**

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.30) to give a mixture of **38** and **38'** (30.5 mg, 0.116 mmol, 58%, **38**:**38'** = 89:11) as a viscos colorless oil.

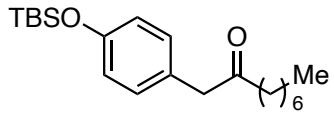
^{1}H NMR: (**38**) δ = 7.03 (d, *J* = 8.3 Hz, 1H), 6.75-6.68 (m, 2H), 3.78 (s, 3H), 3.62 (s, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 2.21 (s, 3H), 1.55 (quint, *J* = 7.0 Hz, 2H), 1.32-1.17 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H); (**38'**) δ = 7.09 (d, *J* = 8.3 Hz, 1H), 6.75-6.68 (m, 2H), 3.78 (s, 3H), 3.65 (s, 2H), 2.39 (t, *J* = 7.4 Hz, 2H), 2.17 (s, 3H), 1.55 (quint, *J* = 7.0 Hz, 2H), 1.32-1.17 (m, 8H), 0.87 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR: (**38**) δ = 209.0, 158.6, 138.1, 131.3, 125.5, 116.0, 111.3, 55.1, 47.5, 41.7, 31.6, 29.1, 29.0, 23.8, 22.6, 20.0, 14.0; (**38'**) δ = 208.4, 157.9, 134.3, 131.2, 128.7, 113.8, 112.3, 55.2, 48.5, 41.9, 31.6, 29.1, 29.0, 23.8, 22.6, 18.7, 14.0; IR (neat): 2926, 2855, 1711, 1609, 1503, 1456, 1256, 1161, 1047, 864, 808 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{27}O_2$ 263.2006; Found 263.2004.



39

The reaction was conducted with 1.4 mmol of 4-*tert*-butyltoluene. The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.50) to give **39** (31.2 mg, 0.113 mmol, 57%) as a viscos colorless oil.

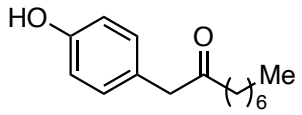
^{1}H NMR: δ = 7.35 (d, *J* = 8.5 Hz, 2H), 7.14 (d, *J* = 8.6 Hz, 2H), 3.65 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.55 (quint, *J* = 7.3 Hz, 2H), 1.37-1.13 (m, 17H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 208.9, 149.8, 131.3, 129.0, 125.6, 49.6, 42.0, 34.4, 31.6, 31.3, 29.05, 29.01, 23.7, 22.6, 14.0; IR (neat): 2957, 2926, 2857, 1713, 1464, 1364, 1269, 1020, 826 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{31}O$ 275.2369; Found 275.2371.



40

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.50) to give **40** (31.2 mg, 0.090 mmol, 44%) as a viscos colorless oil.

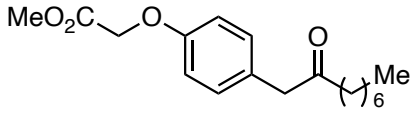
^{1}H NMR: δ = 7.05 (d, *J* = 8.4 Hz, 2H), 6.79 (d, *J* = 8.4 Hz, 2H), 3.59 (s, 2H), 2.41 (t, *J* = 7.4 Hz, 2H), 1.52 (quint, *J* = 7.2 Hz, 2H), 1.34-1.14 (m, 8H), 0.98 (s, 9H), 0.86 (t, *J* = 6.8 Hz, 3H), 0.19 (s, 6H); ^{13}C NMR: δ = 209.1, 154.6, 130.3, 127.1, 120.2, 49.4, 41.7, 31.6, 29.05, 29.00, 25.6, 23.7, 22.6, 18.2, 14.0, −4.5; IR (neat): 2928, 2857, 1713, 1609, 1508, 1254, 912, 837, 779 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{37}O_2Si$ 349.2557; Found 349.2561.



41

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 3:1, R_f = 0.10) to give **41** (15.2 mg, 0.065 mmol, 32%) as a white solid.

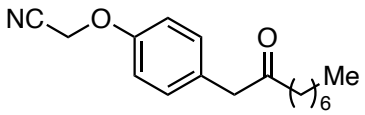
^{1}H NMR: δ = 7.04 (d, *J* = 8.1 Hz, 2H), 6.77 (d, *J* = 8.6 Hz, 2H), 5.42 (br s, 1H), 3.61 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.54 (quint, *J* = 7.1 Hz, 2H), 1.35-1.13 (m, 8H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 210.1, 154.8, 130.5, 126.2, 115.6, 49.2, 41.9, 31.6, 29.05, 28.98, 23.8, 22.6, 14.0; IR (neat): 3406, 2926, 2855, 1703, 1516, 1269, 1219, 822, 621 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{23}O_2$ 235.1693; Found 235.1692.



42

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 2:1, R_f = 0.30) to give **42** (35.9 mg, 0.117 mmol, 58%) as a viscos colorless oil.

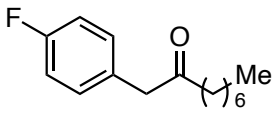
^{1}H NMR: δ = 7.12 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.62 (s, 2H), 3.80 (s, 3H), 3.61 (s, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.53 (quint, *J* = 7.2 Hz, 2H), 1.34-1.14 (m, 8H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 208.8, 169.3, 156.8, 130.5, 127.7, 114.8, 65.4, 52.2, 49.1, 41.9, 31.6, 29.04, 28.99, 23.7, 22.5, 14.0; IR (neat): 2924, 2855, 1761, 1711, 1510, 1437, 1204, 1177, 1084, 824 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{27}O_4$ 307.1904; Found 307.1904.



43

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 5:3, R_f = 0.10) to give **43** (15.0 mg, 0.055 mmol, 27%) as a viscos colorless oil.

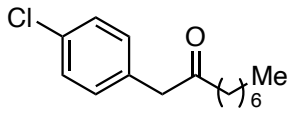
^{1}H NMR: δ = 7.18 (d, *J* = 8.7 Hz, 2H), 6.95 (d, *J* = 8.8 Hz, 2H), 4.75 (s, 2H), 3.65 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.55 (quint, *J* = 7.2 Hz, 2H), 1.34-1.18 (m, 8H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 208.4, 155.6, 130.8, 129.1, 115.2, 115.1, 53.7, 49.0, 42.1, 31.6, 29.1, 29.0, 23.7, 22.6, 14.0; IR (neat): 2926, 2855, 2085, 1709, 1508, 1215, 1049, 826 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{24}NO_2$ 274.1802; Found 274.1800.



44

The reaction was conducted with 10 mmol of 4-fluorotoluene. The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 12:1, R_f = 0.30) to give ketone **44** (31.2 mg, 0.132 mmol, 66%) as a viscos colorless oil.

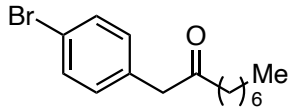
^{1}H NMR: δ = 7.16-7.14 (m, 2H), 7.03-6.99 (m, 2H), 3.65 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.55 (quint, *J* = 6.8 Hz, 2H), 1.33-1.17 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 208.3, 161.9 (d, *J* = 245.6 Hz), 130.9 (d, *J* = 7.7 Hz), 130.0 (d, *J* = 3.9 Hz), 115.5 (d, *J* = 21.2 Hz), 49.0, 42.1, 31.6, 29.05, 28.99, 23.7, 22.6, 14.0; ^{19}F NMR: -115.9 (tt, *J* = 8.9, 5.2 Hz); IR (neat): 2928, 2857, 1713, 1508, 1223, 1157, 826 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}OF$ 237.1649; Found 237.1651.



45

The reaction was conducted with 10 mmol of 4-chlorotoluene. The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 12:1, R_f = 0.30) to give ketone **45** (26.0 mg, 0.103 mmol, 51%) as a viscos colorless oil.

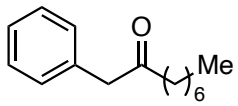
^{1}H NMR: δ = 7.29 (d, *J* = 8.5 Hz, 2H), 7.13 (d, *J* = 8.7 Hz, 2H), 3.65 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.55 (quint, *J* = 7.2 Hz, 2H), 1.34-1.17 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 208.0, 132.9, 132.7, 130.8, 128.8, 49.2, 42.2, 31.6, 29.04, 28.99, 23.7, 22.6, 14.0; IR (neat): 2926, 2855, 1711, 1491, 1408, 1092, 1016, 802, 725 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}OCl$ 253.1354; Found 153.1354.



46

The reaction was conducted with 10 mmol of 4-bromotoluene. The crude mixture was purified by preparative thin-layer chromatography (PTLC) (Hexane:Et_2O = 12:1, R_f = 0.30) to give ketone **46** (31.1 mg, 0.105 mmol, 52%) as a white solid.

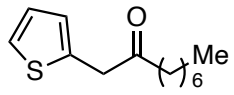
^{1}H NMR: δ = 7.45 (d, *J* = 8.5 Hz, 2H), 7.07 (d, *J* = 8.6 Hz, 2H), 3.63 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.55 (quint, *J* = 7.3 Hz, 2H), 1.33-1.16 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 207.9, 133.3, 131.7, 131.1, 121.0, 49.2, 42.2, 31.6, 29.04, 28.99, 23.7, 22.6, 14.0; IR (neat): 2926, 2855, 1715, 1489, 1406, 1070, 1013, 797, 723 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{21}OBr$ 297.0849; Found 297.0851.



47

The reaction was conducted with 10 mmol of toluene. The crude mixture was purified by preparative thin-layer chromatography (PTLC) (Hexane:Et_2O = 7:1, R_f = 0.50) to give ketone **47** (28.9 mg, 0.132 mmol, 66%) as a viscos colorless oil.

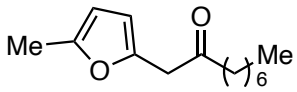
^{1}H NMR: δ = 7.33 (t, *J* = 7.4 Hz, 2H), 7.26 (t, *J* = 7.2 Hz, 1H), 7.20 (d, *J* = 7.2 Hz, 2H), 3.68 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.55 (quint, *J* = 7.0 Hz, 2H), 1.34-1.17 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 208.6, 134.4, 129.4, 128.7, 126.9, 50.1, 42.0, 31.6, 29.03, 28.99, 23.7, 22.6, 14.0; IR (neat): 2926, 2855, 1713, 1497, 1454, 733, 698 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{22}O$ 219.1743; Found 219.1743.



48

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 10:1, R_f = 0.40) to give **48** (28.0 mg, 0.125 mmol, 62%) as a viscos brown oil.

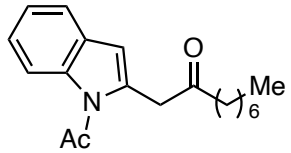
^{1}H NMR: δ = 7.22-7.20 (m, 1H), 6.98-6.96 (m, 1H), 6.89-6.87 (m, 1H), 3.88 (s, 2H), 2.49 (t, *J* = 7.4 Hz, 2H), 1.57 (quint, *J* = 7.2 Hz, 2H), 1.33-1.18 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 207.0, 135.4, 127.0, 126.7, 125.0, 43.6, 41.7, 31.6, 29.03, 28.99, 23.7, 22.6, 14.0; IR (neat): 2926, 2855, 1711, 1417, 1213, 853, 696 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{20}OS$ 225.1308; Found 225.1307.



49

The reaction was conducted with 0.40 mmol of 2,5-dimethylfuran for 72 hours. The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 10:1, R_f = 0.30) to give **49** (13.4 mg, 0.060 mmol, 30%) as a viscos colorless oil.

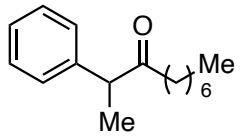
^{1}H NMR: δ = 6.05 (d, *J* = 3.0 Hz, 1H), 5.91 (d, *J* = 3.0 Hz, 1H), 3.63 (s, 2H), 2.44 (t, *J* = 7.4 Hz, 2H), 1.56 (quint, *J* = 7.2 Hz, 2H), 1.35-1.18 (m, 8H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 206.8, 151.7, 146.5, 108.8, 106.5, 42.6, 41.7, 31.6, 29.05, 29.00, 23.7, 22.6, 14.0, 13.5; IR (neat): 2924, 2855, 1717, 1566, 1456, 1217, 1020, 783 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{23}O_2$ 223.1693; Found 223.1691.



50

The reaction was conducted with 0.40 mmol of *N*-acetyl-2-methylindole. The crude mixture was purified by preparative thin-layer chromatography (CH_2Cl_2, R_f = 0.30) to give **50** (13.3 mg, 0.044 mmol, 22%) as a viscos colorless oil.

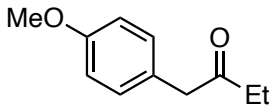
^{1}H NMR: δ = 7.62 (d, *J* = 8.4 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.31-7.22 (m, 2H), 6.48 (s, 1H), 4.09 (s, 2H), 2.77 (s, 3H), 2.57 (t, *J* = 7.3 Hz, 2H), 1.63 (quint, *J* = 7.3 Hz, 2H), 1.35-1.20 (m, 8H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR: δ = 206.8, 170.3, 135.8, 135.4, 129.9, 123.8, 123.0, 121.0, 114.1, 111.8, 44.4, 42.5, 31.7, 29.2, 29.1, 27.4, 23.6, 22.6, 14.1; IR (neat): 2928, 2855, 1701, 1460, 1377, 1308, 1211, 743 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{25}NO_2Na$ 322.1778; Found 322.1780.



51

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.50) to give **51** (21.8 mg, 0.094 mmol, 46%) as a viscos colorless oil.

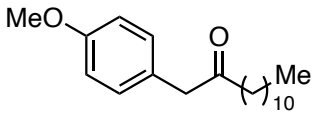
^{1}H NMR: δ = 7.32 (t, *J* = 7.3 Hz, 2H), 7.26 (t, *J* = 7.4 Hz, 1H), 7.21 (d, *J* = 6.9 Hz, 2H), 3.75 (q, *J* = 7.0 Hz, 1H), 2.34 (t, *J* = 7.5 Hz, 2H), 1.54-1.41 (m, 2H), 1.39 (d, *J* = 7.0 Hz, 3H), 1.33-1.10 (m, 8H), 0.85 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR: δ = 211.0, 140.7, 128.8, 127.8, 127.0, 52.9, 41.0, 31.6, 29.0, 28.9, 23.8, 22.5, 17.4, 14.0; IR (neat): 2928, 2855, 1713, 1493, 1452, 1373, 1072, 910, 733, 700 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{25}O$ 233.1900; Found 233.1899.



52

The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 7:1, R_f = 0.20) to give **52** (23.2 mg, 0.130 mmol, 65%) as a viscos colorless oil.

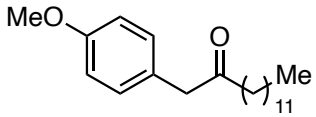
^{1}H NMR: δ = 7.12 (d, *J* = 8.3 Hz, 2H), 6.86 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.62 (s, 2H), 2.46 (q, *J* = 7.3 Hz, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR: δ = 209.4, 158.6, 130.3, 126.5, 114.1, 55.2, 48.9, 35.0, 7.8; IR (neat): 2936, 2835, 1713, 1510, 1244, 1177, 1034, 804 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{11}H_{15}O_2$ 179.1067; Found 179.1065.



53

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.30) to give **53** (40.8 mg, 0.134 mmol, 67%) as a white solid.

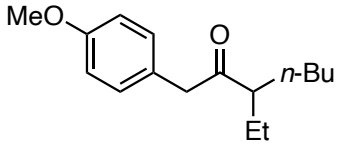
^{1}H NMR: δ = 7.11 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.53 (quint, *J* = 7.2 Hz, 2H), 1.34-1.16 (m, 16H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 209.0, 158.5, 130.3, 126.4, 114.1, 55.2, 49.2, 41.8, 31.9, 29.6 (2C), 29.4, 29.33, 29.30, 29.1, 23.7, 22.6, 14.1; IR (neat): 2924, 2851, 1705, 1512, 1464, 1248, 1175, 1032, 812 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{33}O_2$ 305.2475; Found 305.2477.



54

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.30) to give **54** (46.0 mg, 0.144 mmol, 72%) as a white solid.

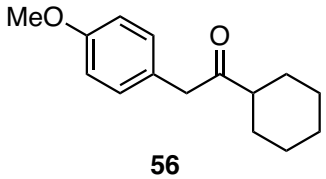
^{1}H NMR: δ = 7.11 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.79 (s, 3H), 3.61 (s, 2H), 2.42 (t, *J* = 7.4 Hz, 2H), 1.54 (quint, *J* = 7.2 Hz, 2H), 1.36-1.15 (m, 18H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 209.0, 158.5, 130.3, 126.4, 114.1, 55.2, 49.2, 41.8, 31.9, 29.59 (2C), 29.56, 29.4, 29.3 (2C), 29.1, 23.7, 22.7, 14.1; IR (neat): 2914, 2847, 1705, 1614, 1516, 1472, 1250, 1177, 1032, 812 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{35}O_2$ 319.2632; Found 319.2634.



55

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.30) to give **55** (39.8 mg, 0.160 mmol, 80%) as a viscos colorless oil.

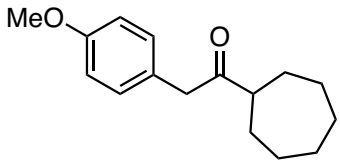
^{1}H NMR: δ = 7.11 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.63 (s, 2H), 2.51 (tt, *J* = 7.9, 5.6 Hz, 1H), 1.67-1.55 (m, 2H), 1.49-1.33 (m, 2H), 1.28-1.20 (m, 2H), 1.19-1.09 (m, 2H), 0.84 (t, *J* = 7.2 Hz, 3H), 0.79 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 212.1, 158.5, 130.6, 126.1, 114.0, 55.2, 52.7, 48.7, 31.0, 29.5, 24.6, 22.7, 13.9, 11.8; IR (neat): 2959, 2932, 2872, 1705, 1510, 1464, 1246, 1177, 1036, 820 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{25}O_2$ 249.1849; Found 249.1849.



56

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.30) to give **56** (35.6 mg, 0.153 mmol, 76%) as a viscos colorless oil.

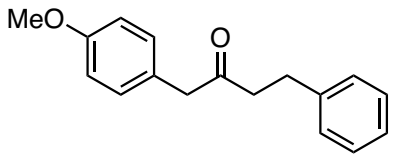
^{1}H NMR: δ = 7.10 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.66 (s, 2H), 2.45 (tt, *J* = 11.3, 3.3 Hz, 1H), 1.85-1.73 (m, 4H), 1.67-1.63 (m, 1H), 1.39-1.14 (m, 5H); ^{13}C NMR: δ = 211.6, 158.4, 130.4, 126.4, 114.0, 55.2, 49.9, 46.9, 28.5, 25.8, 25.6; IR (neat): 2928, 2853, 1703, 1512, 1456, 1246, 1028, 814 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{21}O_2$ 233.1536; Found 233.1535.



57

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.30) to give **57** (38.5 mg, 0.156 mmol, 78%) as a colorless crystal.

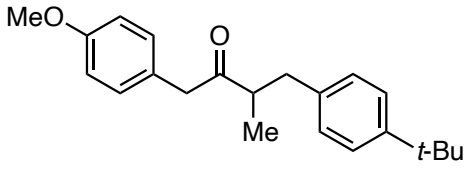
^{1}H NMR: δ = 7.11 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.66 (s, 2H), 2.64 (tt, *J* = 9.4, 4.2 Hz, 1H), 1.85-1.78 (m, 2H), 1.75-1.67 (m, 2H), 1.62-1.38 (m, 8H); ^{13}C NMR: δ = 211.9, 158.5, 130.4, 126.6, 114.0, 55.2, 51.3, 47.1, 29.9, 28.3, 26.6; IR (neat): 2924, 2853, 1701, 1510, 1456, 1246, 1036, 829, 619 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{23}O_2$ 247.1693; Found 247.1694.



58

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.20) to give **58** (31.7 mg, 0.125 mmol, 62%) as a colorless crystal.

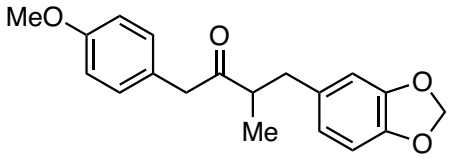
^{1}H NMR: δ = 7.26 (t, *J* = 7.2 Hz, 2H), 7.19 (t, *J* = 7.4 Hz, 1H), 7.14 (d, *J* = 6.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.60 (s, 2H), 2.87 (t, *J* = 7.3 Hz, 2H), 2.76 (t, *J* = 7.1 Hz, 2H); ^{13}C NMR: δ = 207.8, 158.6, 140.9, 130.4, 128.4, 128.3, 126.1, 126.0, 114.1, 55.2, 49.5, 43.3, 29.8; IR (neat): 2926, 2855, 1717, 1510, 1456, 1248, 1034, 700, 619 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{19}O_2$ 255.1380; Found 255.1380.



59

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 7:1, R_f = 0.20) to give **59** (50.6 mg, 0.156 mmol, 77%) as a viscos colorless oil.

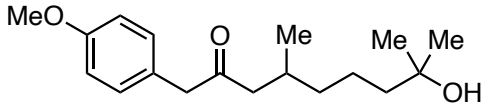
^{1}H NMR: δ = 7.29 (d, *J* = 7.6 Hz, 2H), 7.04 (d, *J* = 8.1 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.1 Hz, 2H), 3.80 (s, 3H), 3.54 (s, 1H), 3.01-2.89 (m, 2H), 2.56 (dd, *J* = 12.8, 6.6 Hz, 1H), 1.32 (s, 9H), 1.08 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR: δ = 211.9, 158.5, 149.0, 136.5, 130.5, 128.6, 126.0, 125.2, 114.0, 55.2, 48.5, 46.9, 38.8, 34.3, 31.4, 16.7; IR (neat): 2963, 2905, 2870, 1709, 1510, 1456, 1246, 1177, 1036, 806, 733 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{29}O_2$ 325.2162; Found 325.2164.



60

The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 4:1, R_f = 0.30) to give **60** (35.1 mg, 0.112 mmol, 56%) as a viscos colorless oil.

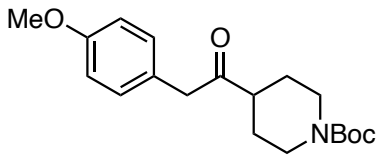
^{1}H NMR: δ = 6.99 (d, *J* = 8.6 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.68 (d, *J* = 7.7 Hz, 1H), 6.54-6.52 (m, 2H), 5.91 (s, 2H), 3.79 (s, 3H), 3.53 (s, 2H), 2.95-2.82 (m, 2H), 2.47 (dd, *J* = 13.1, 6.5 Hz, 1H), 1.06 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR: δ = 211.7, 158.5, 147.5, 145.9, 133.3, 130.4, 125.7, 121.8, 114.0, 109.2, 108.0, 100.8, 55.2, 48.7, 47.0, 39.0, 16.7; IR (neat): 2907, 1707, 1510, 1489, 1441, 1244, 1179, 1034, 928, 808 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{20}O_4Na$ 335.1254; Found 335.1257.



61

The crude mixture was purified by preparative thin-layer chromatography (Hexane:Et_2O = 3:1, R_f = 0.05) to give **61** (36.1 mg, 0.123 mmol, 61%) as a viscos colorless oil.

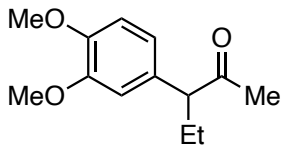
^{1}H NMR: δ = 7.11 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 3.79 (s, 3H), 3.59 (s, 2H), 2.41 (dd, *J* = 16.2, 5.9 Hz, 1H), 2.25 (dd, *J* = 16.2, 7.8 Hz, 1H), 2.01 (pseudo oct, *J* = 6.7 Hz, 1H), 1.52-1.05 (m, 13H), 0.85 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR: δ = 208.6, 158.6, 130.4, 126.3, 114.1, 70.9, 55.2, 49.7, 49.1, 43.9, 37.2, 29.3, 29.2, 29.0, 21.6, 19.8; IR (neat): 3362, 2965, 2936, 1711, 1514, 1244, 1177, 1051, 1026, 816 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{18}H_{28}O_3Na$ 315.1931; Found 315.1935.



62

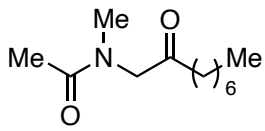
The crude mixture was purified by flash column chromatography (Hexane:AcOEt = 2:1) to give **62** (40.1 mg, 0.120 mmol, 60%) as a white solid.

^{1}H NMR: δ = 7.09 (d, *J* = 8.4 Hz, 2H), 6.86 (d, *J* = 8.7 Hz, 2H), 4.07 (br s, 2H), 3.79 (s, 3H), 3.67 (s, 2H), 2.73 (t, *J* = 12.0 Hz, 2H), 2.57 (tt, *J* = 11.3, 3.7 Hz, 1H), 1.73 (br s, 2H), 1.53 (dq, *J* = 12.0, 4.3 Hz, 2H), 1.44 (s, 9H); ^{13}C NMR: δ = 209.8, 158.6, 154.6, 130.4, 125.8, 114.1, 79.6, 55.2, 47.6, 47.0, 43.0, 28.4, 27.6; IR (neat): 2974, 2934, 1686, 1512, 1422, 1366, 1246, 1161, 1130, 1030, 731 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{27}NO_4Na_1$ 356.1832; Found 356.1838.



65

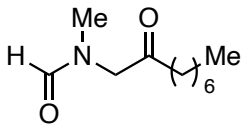
^{1}H NMR: δ = 6.82 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 8.2 Hz, 1H), 6.68 (s, 1H), 3.86 (pseudo s, 6H), 3.44 (t, *J* = 7.3 Hz, 1H), 2.09-1.96 (m, 4H), 1.68 (dquint, *J* = 15.1, 7.3 Hz, 1H), 0.82 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 208.9, 149.2, 148.2, 131.4, 120.6, 111.3, 110.8, 61.0, 55.9, 55.8, 28.9, 24.9, 12.0; IR (neat): 2963, 2874, 2835, 1709, 1514, 1464, 1418, 1260, 1238, 1142, 1026, 806, 729, 642 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{19}O_3$ 223.1329; Found 223.1327.



69

The reaction was conducted with 20 mmol of *N*,*N*-dimethylacetamide **68**. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 1:4, R_f = 0.20) to give ketone **69** (30.1 mg, 0.141 mmol, 70%) as a viscos pale yellow oil.

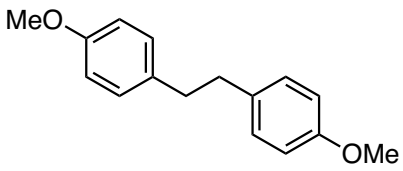
^{1}H NMR: (major rotamer) δ = 4.15 (s, 2H), 3.02 (s, 3H), 2.38 (t, *J* = 7.2 Hz, 2H), 2.12 (s, 3H), 1.65-1.52 (m, 2H), 1.33-1.18 (m, 8H), 0.90-0.81 (m, 3H); (minor rotamer) δ = 4.07 (s, 2H), 2.90 (s, 3H), 2.38 (t, *J* = 7.2 Hz, 2H), 1.94 (s, 3H), 1.65-1.52 (m, 2H), 1.33-1.18 (m, 8H), 0.90-0.81 (m, 3H); ^{13}C NMR: (major rotamer) δ = 205.8, 171.1, 56.8, 39.9, 37.4, 31.6, 29.1, 29.0, 23.5, 22.5, 21.2, 14.0; (minor rotamer) δ = 205.2, 170.9, 59.9, 39.8, 34.9, 31.6, 29.1 28.9, 23.5, 22.5, 21.1, 14.0; IR (neat): 2926, 2857, 1726, 1647, 1466, 1406, 1011, 731 cm^{-1}; HRMS (APCI) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{24}NO_2$214.1802; Found 214.1799.



71

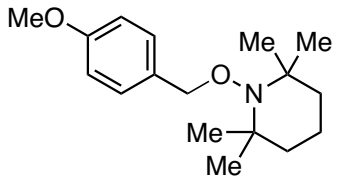
The reaction was conducted with 20 mmol of *N*,*N*-dimethylformamide **70**. The reaction was conducted with 10 mmol of toluene. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 1:4, R_f = 0.20) to give ketone **71** (13.0 mg, 0.065 mmol, 32%) as a viscos pale yellow oil..

^{1}H NMR: (major rotamer) δ = 8.11 (s, 1H), 4.12 (s, 2H), 2.98 (s, 3H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.65-1.55 (m, 2H), 1.35-1.18 (m, 8H), 0.88 (t, *J* = 6.3 Hz, 3H); (minor rotamer) δ = 7.96 (s, 1H), 4.00 (s, 2H), 2.87 (s, 3H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.65-1.55 (m, 2H), 1.35-1.18 (m, 8H), 0.87 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR: (major rotamer) δ = 204.6, 162.7, 53.2, 40.1, 35.4, 31.6, 29.1, 29.0, 23.5, 22.6, 14.0; (minor rotamer) δ = 205.2, 163.1, 58.0, 39.9, 35.4, 31.0, 29.1, 29.0, 23.5, 22.6, 14.0; IR (neat): 2924, 2855, 1728, 1670, 1389, 1070, 845 cm^{-1}; HRMS (APCI) *m/z*: [M + H]$^+$ Calcd for $C_{11}H_{22}NO_2$ 200.1645; Found 200.1643.



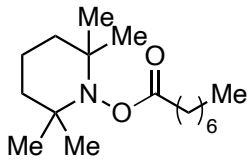
32

^{1}H NMR: δ = 7.08 (d, *J* = 8.6 Hz, 4H), 6.82 (d, *J* = 8.8 Hz, 4H), 3.79 (s, 6H), 2.83 (s, 4H); ^{13}C NMR: δ = 157.8, 134.0, 129.4, 113.7, 55.2, 37.3; IR (neat): 2928, 2853, 1506, 1244, 1173, 1028, 829 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{16}H_{18}O_2$ 242.1307; Found 242.1307.



66

^{1}H NMR: δ = 7.29 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 4.74 (s, 2H), 3.81 (s, 3H), 1.72-1.42 (m, 5H), 1.36-1.33 (m, 1H), 1.26 (s, 6H), 1.13 (s, 6H); ^{13}C NMR: δ = 159.0, 130.5, 129.1, 113.6, 59.9, 55.2, 39.7, 33.1, 20.3, 17.1; IR (neat): 2974, 2930, 1612, 1512, 1358, 1246, 1173, 1036, 822, 602 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{28}NO_2$ 278.2115; Found 278.2115.



67

^{1}H NMR: δ = 2.34 (t, *J* = 7.6 Hz, 2H), 1.74-1.46 (m, 8H), 1.38-1.25 (m, 8H), 1.15 (s, 6H), 1.05 (s, 6H), 0.88 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 173.4, 59.9, 39.0, 32.0, 31.7, 29.3, 28.9, 25.3, 22.6, 20.5, 17.0, 14.0; IR (neat): 2928, 2855, 1767, 1466, 1364, 1132, 1096, 930 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{34}N_1O_2$ 284.2584; Found 284.2585.

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Chapter 3

Photoinduced Specific Acylation of Phenolic Hydroxy Groups with Aldehydes

Table of Contents

Abstract: Herein reported is a convenient method to specifically acylate phenolic hydroxyl groups through a radical pathway. When a mixture of an aldehyde and a phenol in ethyl acetate is irradiated with blue light in the presence of iridium and nickel bromide catalysts at ambient temperature, phenoxy and acyl radicals are transiently generated in situ, and cross-couple to furnish an ester. Aliphatic hydroxy groups remain untouched under the present reaction conditions.

3.1 Introduction

Organic radicals are generally “hyperactive”, being capable of random abstraction of a hydrogen atom from nearby C–H bonds or quenching by non-selective radical/radical coupling. It is conceived challenging to cross-couple two specific radical species. However, such reactions can offer unconventional synthetic maneuvers to gain increasing attention recently.[1]

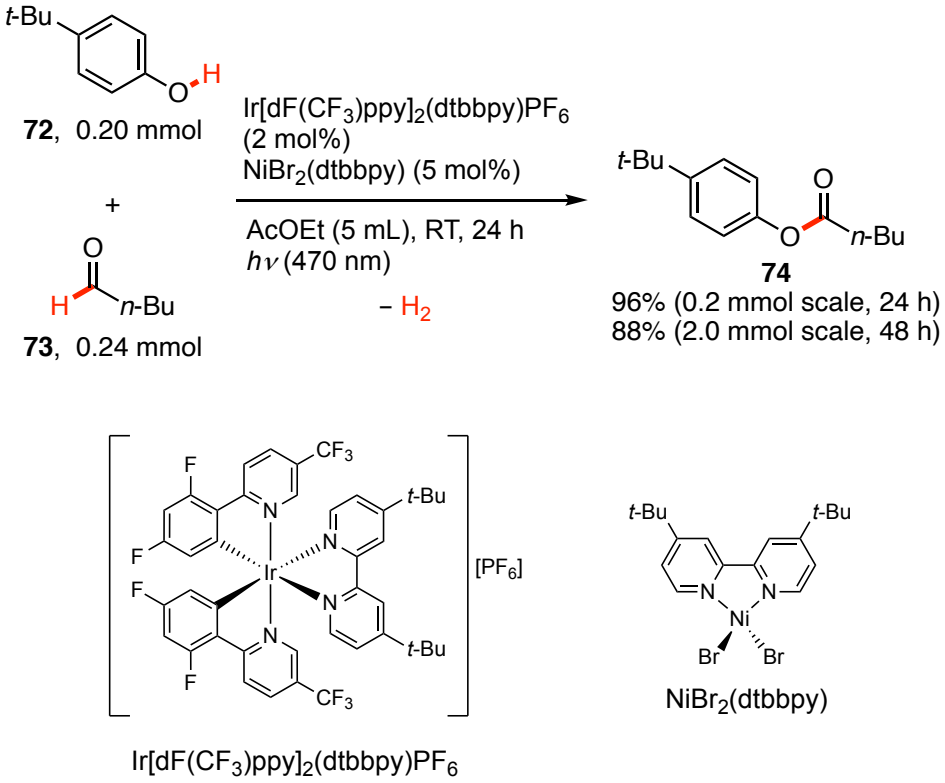
Phenols are readily subject to hydrogen atom abstraction to generate phenoxy radicals, which undergo homo-coupling reactions forming C–C and C–O bonds at the ortho/para carbons as well as at the oxygen.[2] It is also a facile process for aldehydes to generate acyl radicals by hydrogen atom abstraction.[3] There has been reported only a single example for a C–O bond forming cross-coupling reaction of a phenoxy radical with an acyl radical;[4] when 2 equiv of 2,4-di-*tert*-butyl-6-phenylphenoxyl radical, which is a persistent phenoxy radical protected by steric shielding, reacts with 1 equiv of benzaldehyde, one phenoxy radical abstracts the aldehydic hydrogen atom and the resulting acyl radical undergoes radical/radical coupling with the other phenoxy radical to form the corresponding ester. The bulky substituents located at the 2,4,6-positions sterically shield the phenoxy radical from undesired side-reactions on the benzene core.[5] Here the author reports a photoinduced acylation reaction of phenols with aldehydes. Phenoxy radicals, including those sterically unprotected ones, and acyl radicals cross-couple in an intermolecular fashion. The present reaction is unique in that phenolic hydroxyl groups are specifically acylated in the presence of aliphatic ones, being contrast to the conventional acylation reactions.[6]

3.2 Results and Discussion

*3.2.1 Dehydrogenative Coupling of 4-tert-Butylphenol **74** with Valeraldehyde **73***

A cooperative action of light/iridium/bromide anion/nickel induces a dehydrogenative C–H/C–H cross-coupling reaction of alkylarenes with aldehydes to furnish α-aryl ketones.[7] The mechanism involving benzylic and aldehydic radicals which cross-couple on nickel is proposed in Chapter 2. The bond dissociation energies (BDEs) of phenolic O–H bonds (360-365 kJ/mol) are only slightly smaller than those of benzylic C–H bonds (370-380 kJ/mol),[8] and a phenoxy radical is isoelectronic to a benzylic radical. When *p*-cresol was used as the alkylarene in study in Chapter 2, acylation of the phenolic O–H bond was observed in addition to that of the benzylic C–H bond. This led the author to investigate an acylation reaction of phenols with aldehydes in more detail, and it was found that 4-*tert*-butylphenol **72** was successfully acylated with valeraldehyde **73** under the slightly modified conditions to give the *O*-acylated product in high yield; a solution of **72** (0.20 mmol), valeraldehyde (**73**, 0.24 mmol, 1.2 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.004 mmol, 2 mol%), and $NiBr_2(dtbbpy)$ (0.01 mmol, 5 mol%) in ethyl acetate (5.0 mL) was irradiated with blue LEDs (λ_{max} = 467 nm) at ambient temperature for 24 h.[9] Purification of the reaction mixture by preparative thin-layer chromatography afforded analytically pure ester **74** in 96% yield based on **72**. Generation of dihydrogen gas was confirmed by GC analysis of the headspace of the reaction vessel. It was possible to perform the reaction on a 2.0 mmol scale. It required 48 h irradiation for completion, and subsequent purification using column chromatography on silica gel afforded the ester **74** in 88% isolated yield. No significant amounts of other by-product were observed.

Scheme 3-1. Dehydrogenative Acylation of **72** with **73**



3.2.2 Mechanistic Studies

Mechanistic insights of the present reaction were obtained from the following experiments. A nickel(II) salt lacking a bromide ligand, *i.e.*, $Ni(OAc)_2$ and dtbbpy were used in place of $NiBr_2$(dtbbpy) in the reaction shown in Scheme 3-1, and no reaction occurred.[10] Interestingly, addition of $(n\text{-Bu})_4NBr$ to the mixture restored the reactivity, suggesting that a bromide anion was essential. It is known that photoirradiation of a mixture of $[Ir[dF(CF_3)ppy]_2(dtbbpy)]^+$ and a bromide anion induces single electron transfer from the bromide anion to iridium(III) to produce a bromine radical, which abstracts a hydrogen atom from aliphatic and aldehydic C–H bonds.[11] The ion exchange in which $NiBr_2$(dtbbpy) reacts with $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ to generate a [Ir(III)]Br complex is observed in Chapter 2 (Scheme 2-9). It is likely that the bromide anion binds to the 3- and 3'-positions of the bipyridine ligand through hydrogen bonding.[12] Stern-Volmer quenching experiments indicated that the photoexcited

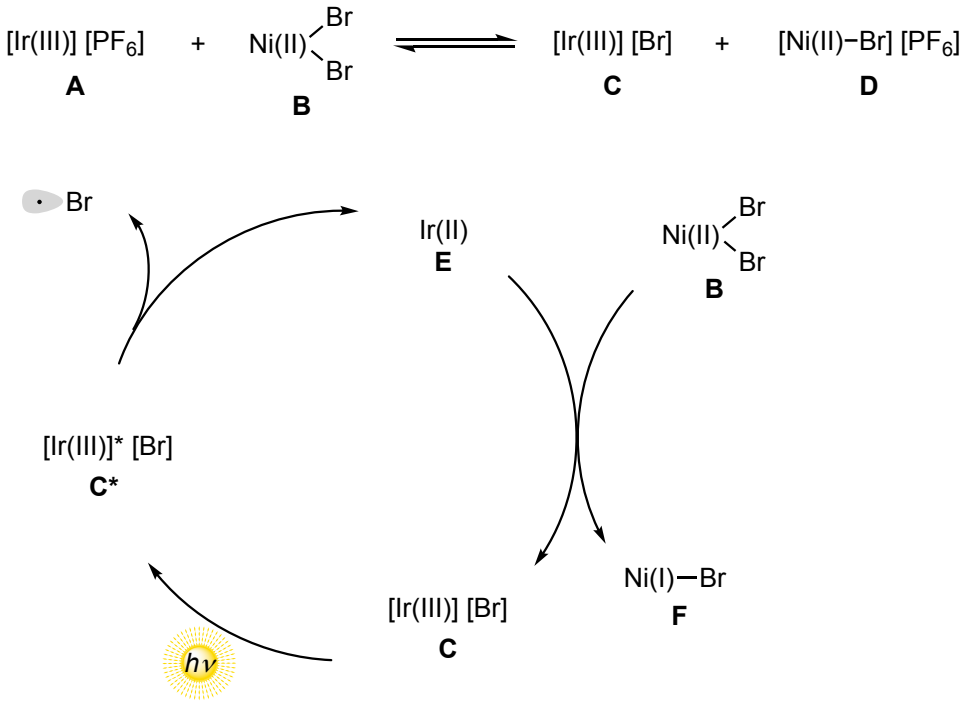
iridium(III) complex was quenched by $NiBr_2$(dtbbpy), but not by the phenol **72** or the aldehyde **73**. A radical trapping experiment using TEMPO was next carried out. Under the conditions that were otherwise identical to those described in Scheme 3-1, an acylated TEMPO was isolated,[10] being indicative of generation of an acyl radical species. Decrease of the reactivity of phenols was observed as the BDEs of their O–H bonds increased by installation of electron-withdrawing substituents on the benzene rings.[13] This electronic trend is suggestive of generation of a phenoxy radical from a phenol.

3.2.3 Proposed Mechanism

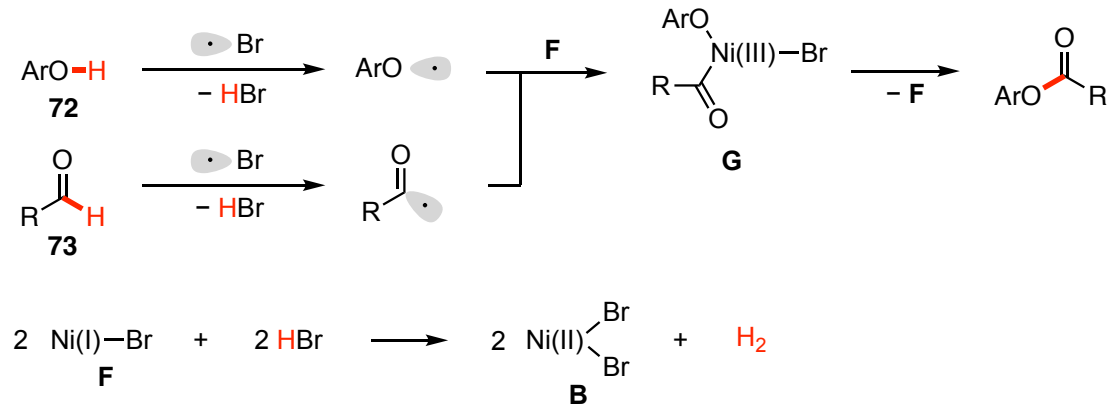
On these bases, the postulated mechanistic pathway is depicted in Scheme 3-2. It consists of two stages. Stage 1; the hexafluorophosphate anion of the cationic iridium(III) complex exchanges with a bromide anion. The iridium(III) bromide complex **C** gets excited by light to induce single electron transfer from the bromide anion to iridium(III). Thus, a bromine radical and iridium(II) species **E** are generated.[11] The iridium(II) **E** ($E_{1/2}$[Ir(III)/Ir(II)] = −1.37 V vs SCE)[14] reacts with Ni(II) species **B** ($E_{1/2}$[Ni(II)/Ni(0)] = −1.2 V vs SCE)[15] to regenerate the Ni(I) species **F** and the iridium(III) bromide **C**.[16] Stage 2; the bromine radical takes away a hydrogen atom from the phenol **72** in preference to the aldehyde **73**.[17] Although slower than the phenol **72**, the aldehyde **73** also undergoes hydrogen atom abstraction to generate an acyl radical. the resulting phenoxyl radical and acyl radical add to the nickel(I) species **F** to form nickel(III) species **G**, which undergoes reductive elimination to form an ester linkage. The nickel(I) species **F** reacts with HBr to evolve dihydrogen and the Ni(II)Br_2 species.[19]

Scheme 3-2. Proposed Mechanism

Stage 1. Generation of Bromine Radical and Ni(I)



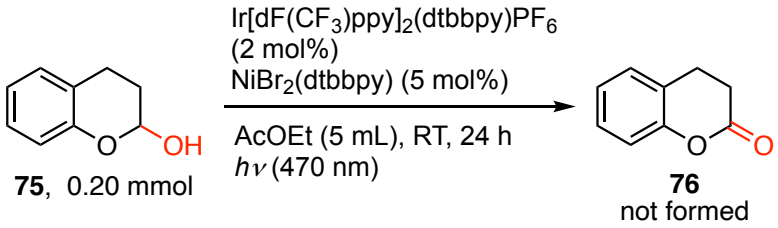
Stage 2. Formation of Ester and Hydrogen Evolution



3.2.4 Reaction of Hemi-Acetal 75

A different mechanistic scenario is also conceivable; nucleophilic addition of a phenol to an aldehyde gives rise to a hemi-acetal, and the subsequent dehydrogenation affords an ester.[6] Thus, the six-membered cyclic hemi-acetal **75** was subjected to the reaction conditions in order to see if dehydrogenation occurred (Scheme 3-3). However, no formation of the dehydrogenated lactone **76** was observed and the starting material remained intact, making the mechanism mentioned above unlikely.

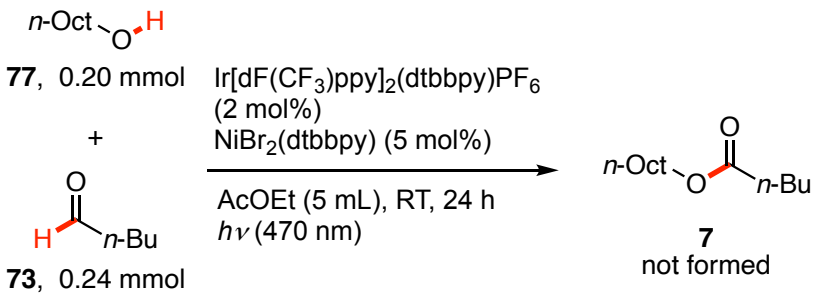
Scheme 3-3. Reaction of Hemi-Acetal **75**



3.2.5 Reaction of 1-Octanol 77

1-Octanol **77** instead of the phenol **72** was used in the reaction with the aldehyde **73** to examine the eligibility of aliphatic alcohols (Scheme 3-4). 1-Octanol **77** remained intact and the aldehyde **73** gradually decomposed.[20] The ineligibility of the aliphatic alcohol can be ascribed to its much larger BDE (430-440 kJ/mol)[8] than that of the phenol **72**.

Scheme 3-4. Reaction of 1-Octanol **77**

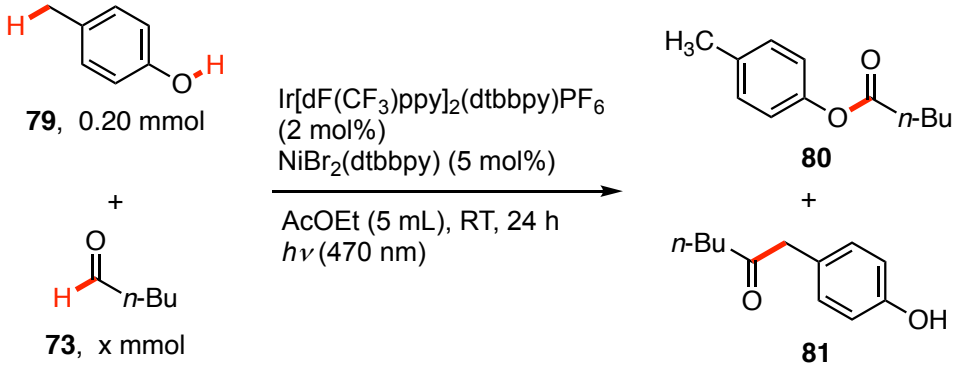


This unique chemo-specificity of the present method is noteworthy. Although a number of acylation reactions of hydroxy groups with aldehydes have been developed,[6] they mostly proceed through either (A) oxidation of the hemiacetal intermediate or (B) oxidation of the Breslow intermediates followed by nucleophilic addition of a hydroxy group. Those methods would acylate both aliphatic and phenolic hydroxy groups.

*3.2.6 Reaction of p-Cresol **79***

The acylation reaction of *p*-cresol **79** was reinvestigated (Scheme 3-5). As described in Chapter 2,[7] a mixture of the C–O bond forming product **80** and the C–C bond forming product **81** was produced under the standard reaction conditions (the ratio of **73**/**79** = 1/1). Interestingly, the C–O bond forming product **80** was produced almost exclusively with **73**/**79** = 5/1. Albeit uncertain, this unexpected shift in site-selectivity is possibly explained by considering abundance of the radical species. A bromine radical abstracts a hydrogen atom from the O–H bond in preference to the benzylic and aldehydic C–H bonds, reflecting their BDEs.[8] With the ratio of **73**/**79** = 1/1, the dominant generation of the phenoxy radical is probably moderately offset by its sluggishness to couple with the acyl radical, resulting in the production of similar amounts of **80** and **81**. With the ratio of **73**/**79** = 5/1, however, the abundance of the aldehyde steers a bromine radical to the aldehydic C–H bonds rather than to the benzylic C–H bond. As a result, the generation of the benzylic radical is minimized to produce **80** selectively.

Scheme 3-5. Reaction of *p*-Cresol **79**

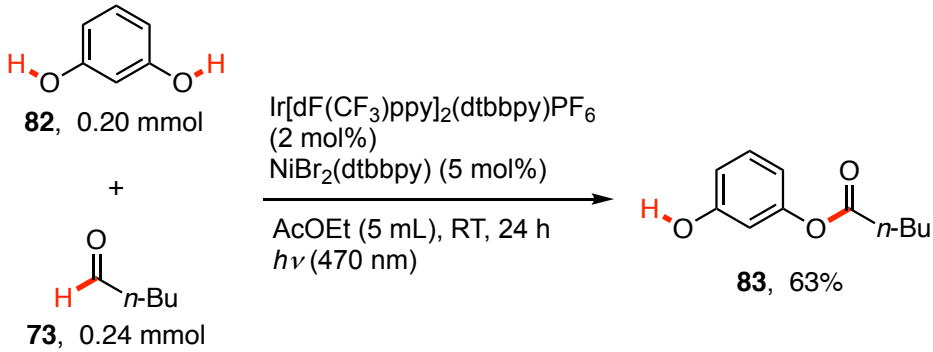


x	73/79	80	81
0.20	1	38%	33%
1.0	5	87%	0%

*3.2.7 Reaction of meta-Dihydroxybenzene **82***

The reaction of *m*-dihydroxybenzene **82** with **73** (1.2 equiv) afforded mono-ester **83** selectively, and the corresponding diester was not formed (Scheme 3-6). This is because the phenolic O–H bond becomes stronger as the electron density of the benzene ring decreases upon introduction of the acyl group.[13]

Scheme 3-6. Reaction of *meta*-Dihydroxybenzene **82**



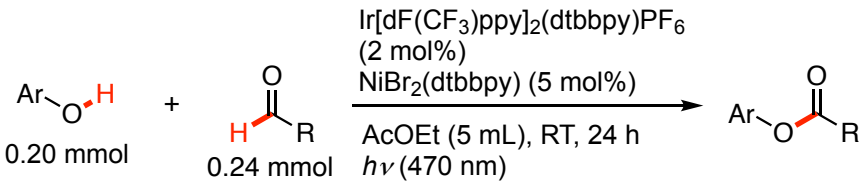
3.2.8 Substrate Scope

Various phenols underwent the dehydrogenative C–O bond forming reaction with the aldehyde **73** (Table 3-1). Excellent yields were obtained with phenols having

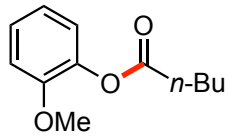
electron-donating substituents (**84**-**87**), 4-phenylphenol (**88**), and 2-naphthol (**89**). The BDE of their O–H bonds are smaller than that of simple phenol.[13] In the case of simple phenol **90**, the initial hydrogen atom abstraction step generating a phenoxy radical was slower, and the counterpart acyl radical gradually decomposed meanwhile to lower the yield.[20] The yield was improved when the aldehyde **73** was added in five portions over 120 h. The reaction of phenols having strongly electron-withdrawing groups such as a methoxycarbonyl group was sluggish, and the corresponding ester was produced in less than 20%. The substituent effect observed with phenols is in accordance with the mechanism involving generation of a phenoxy radical from a phenol. Even phenols whose hydroxy groups were sterically hindered by ortho substituents were eligible substrates (**91**-**93**). Fluoro (**94**) and chloro substituents (**95**) were tolerated on the benzene ring.

The reaction showed a wide scope also with regard to aldehydes. Simple aliphatic aldehydes (**96**-**100**) and those having carbamate (**101**), ester (**102**), acetal (**103**), and hydroxy (**104**) groups all reacted well with the phenol **72**. The reaction of aromatic aldehydes was slower,[21] and necessitated irradiation with more intense light for a longer period of time in order to attain reasonable yields (**105**-**108**). The lower reactivity of aromatic aldehydes is possibly ascribed to the inductive effect of the aromatic group which would make the aldehydic hydrogen less electron-rich. Since the bromine radical is electrophilic, the process of hydrogen atom abstraction from aromatic aldehydes would be slower. This postulation accords with the results that the higher yields were observed with *p*-tolualdehyde and *p*-anisaldehyde than with benzaldehyde.[22]

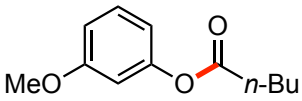
Table 3-1. Scope[a]



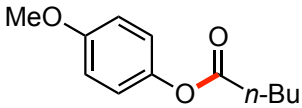
Scope of Phenols



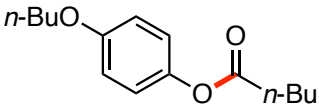
84, 88%[b]



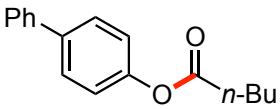
85, 84%



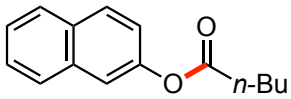
86, 89%[c]



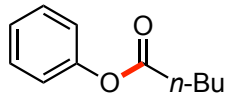
87, 71%[c]



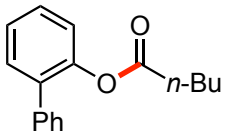
88, 93%



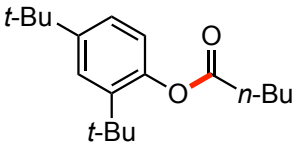
89, 99%[c]



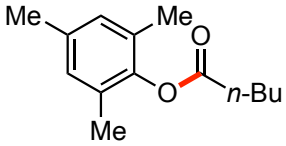
90, 54%[d]



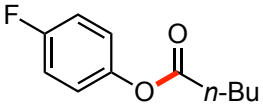
91, 64%



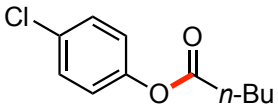
92, 71%



93, 62%[e]

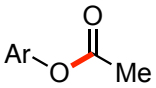


94, 76%[d]

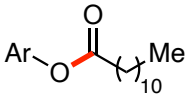


95, 66%[d]

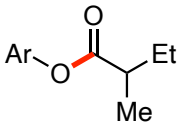
Scope of Aldehydes (Ar = 4-*tert*-butylphenyl)



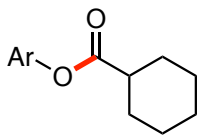
96, 80%[e]



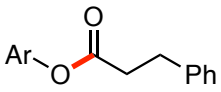
97, 94%



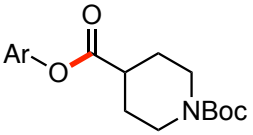
98, 77%



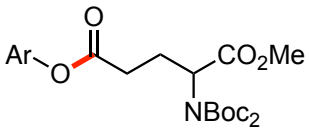
99, 90%



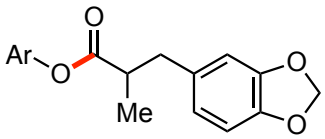
100, 64%



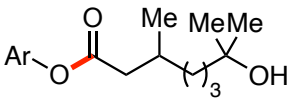
101, 72%



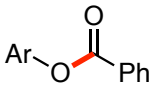
102, 46%



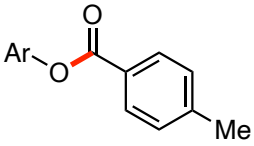
103, 62%



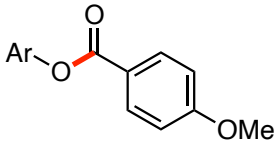
104, 97%



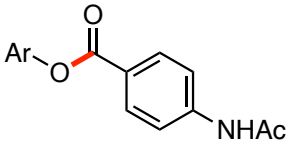
105, 59%[f]



106, 68%[f]



107, 78%[f]



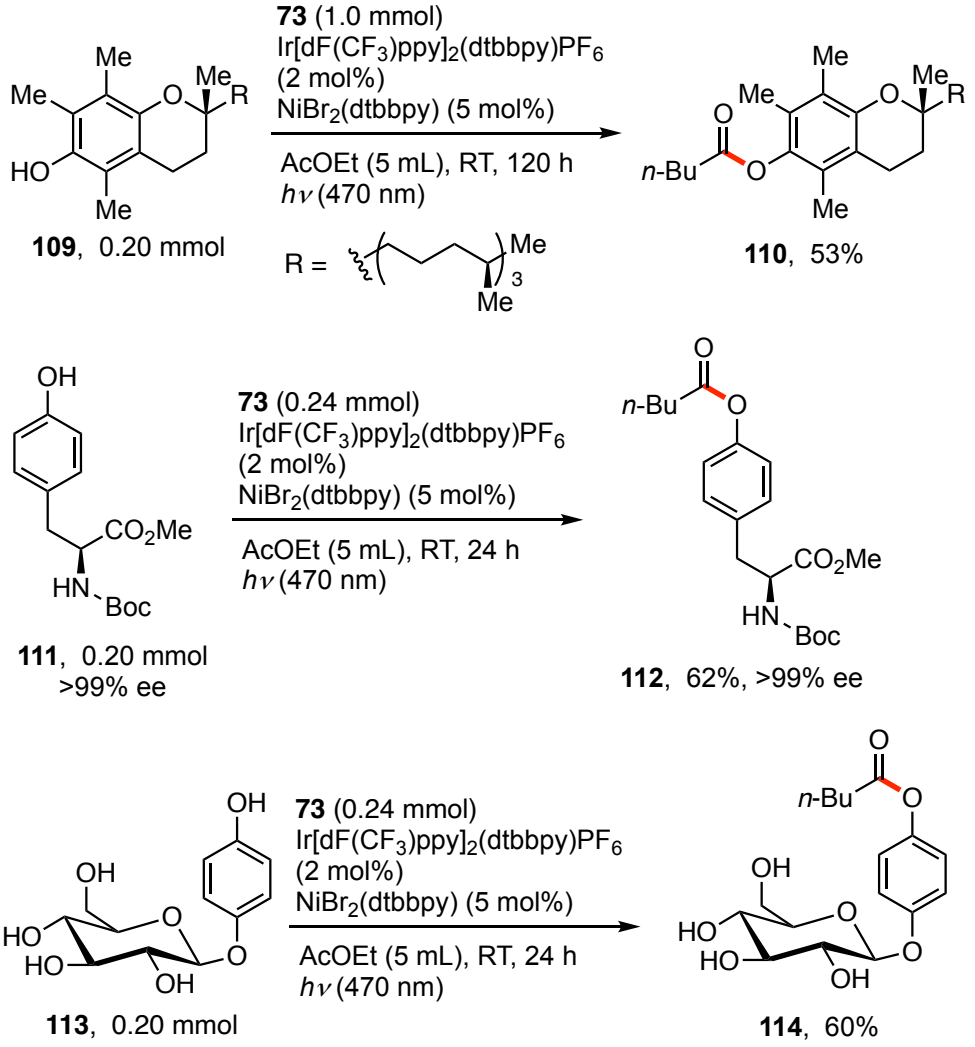
108, 49%[f]

[a] Reaction conditions: phenol derivatives (0.20 mmol, 1.0 equiv), aldehydes (0.24 mmol, 1.2 equiv), $NiBr_2$(dtbbpy) (0.01 mmol, 5 mol%), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.004 mmol, 2 mol%), AcOEt (5 mL), blue LEDs (23 W, λmax = 467 nm), ambient temperature, 24 hours otherwise noted. [b] 72 h. [c] 120 h. [d] Aldehydes were added in five portions (0.20 mmol each) over 120 h. [e] 5.0 Equiv of aldehydes. [f] 72 h. High power blue LEDs (40 W, λ_{max} = 463 nm).

3.2.9 Dehydrogenative Acylation of Natural-Occurring Phenols

The synthetic utility of the present method was highlighted by the reaction of naturally-occurring phenols (Scheme 3-7). α-Tocopherol **109** successfully engaged in the reaction with the use of 5.0 equiv of the aldehyde **73** in spite of the fact that its hydroxy group was significantly encumbered by the two ortho methyl groups. Optically pure α-amino acid **110** efficiently reacted with 1.2 equiv of aldehyde **73** with the stereochemical integrity of the α-carbon retained. Of particular note was that phenolic glycoside **113** (β-arbutin) was acylated selectively at the phenolic hydroxy group with the other aliphatic ones in the glycosyl unit remaining untouched. No epimerization occurred at the anomeric center nor at other chiral centers. A conventional synthesis of *O*-acylated phenolic glycosides necessitates protection/deprotection of aliphatic hydroxy groups.[23] The present acylating method provides a synthetic advantage that *O*-acylated phenolic glycoside can be synthesized starting from plant-origin phenolic glycosides without the need for protection/deprotection of the glycosyl unit.

Scheme 3-7. Dehydrogenative Acylation of Natural-Occurring Phenols



3.3 Summary

In summary, a dehydrogenative acylation reaction of phenols with aldehydes forming the corresponding esters was developed. It presents a unique example in which phenoxy radicals lacking steric shielding are intermolecularly trapped by acyl radicals. It is noteworthy that only phenolic O–H bonds are acylated and aliphatic ones remain intact. This feature stands in contrast to the results of a standard reaction to acylate a nucleophilic hydroxy group with activated acylating agents such as acyl chlorides. The present method provides a general and straightforward method to synthesize esters even from naturally-occurring phenol derivatives.

3.4 Experimental Section

3.4.1 General Method and Materials

General Method

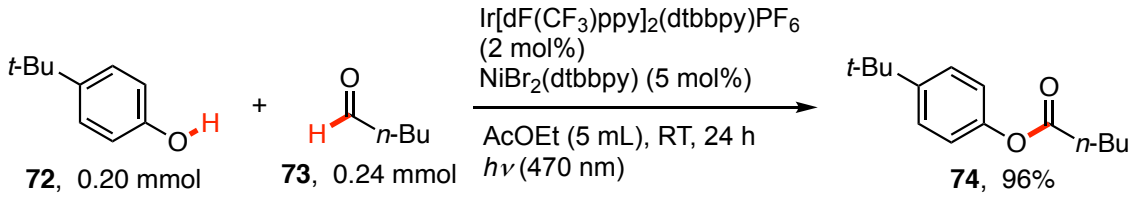
All reactions were carried out using a flame-dried glassware under a nitrogen atmosphere. Photoreactions were carried out with blue LEDs (Reaction using alkyl aldehydes: CCS LDL2-146X30BL2, λ_{max} = 470 nm, 23 W; Reaction using aryl aldehydes: Kessil, A160WE, λ_{max} = 463 nm, 40 W; the spectra are shown below). The evolved dihydrogen was detected by analyzing the gas phase of the reaction vessel using SHIMADZU GASCHROMATOGRAPH GC-8A. ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECZ400S/L1 (^{1}H at 400.44 MHz, ^{13}C at 100.69 MHz), and a JEOL JNM-ECA600 (^{1}H at 600.17 MHz and ^{13}C at 150.92 MHz) spectrometer. $CDCl_3$, acetone-d_6, and DMSO-d_6 were used as a solvent. Chemical shifts were recorded in δ ppm referenced to a residual $CDCl_3$ (δ = 7.26 for ^{1}H, δ = 77.0 for ^{13}C), acetone-d_6 (δ = 2.05 for ^{1}H), and DMSO-d_6 (δ = 7.26 for ^{1}H). IR measurements were performed on FTIR SHIMADZU Affinity-1S spectrometer fitted with a Pike Technologies MIRacle Single Reflection ATR adapter. High-resolution mass spectra were recorded on JEOL JMS-700 (EI), Thermo Fisher Scientific Exactive (ESI, APCI). Preparative thin-layer chromatography (PTLC) was performed on silica gel plates with PF254 indicator (Merck). Flash column chromatography was performed with silica gel 60N (Kanto).

Materials

$NiBr_2$(dtbbpy),[24] and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6,[25] 2-chromanol,[26] and 2-[*N*,*N*-di-(*tert*-butoxycarbonyl)amino]-5-oxopentanoate[27-29] were prepared according to the method previously reported. Other chemicals were purchased from commercial suppliers and used as received.

3.4.2 *Typical Procedures for the Synthesis of Esters from Phenols and Aldehydes*

Scheme 3-8. Typical Procedure of the Acylation of Phenols with Aldehyde (Procedure A)



To a Schlenk tube containing $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (4.5 mg, 0.004 mmol, 2 mol%), $NiBr_2(dtbbpy)$ (4.9 mg, 0.010 mmol, 5 mol%) and 4-*tert*-butylphenol **72** (30.0 mg, 0.20 mmol, 1.0 equiv) were added valeraldehyde **73** (17.2 mg, 0.24 mmol, 1.2 equiv) and anhydrous ethyl acetate (5 mL) in a nitrogen-filled glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs, with the vessel being cooled by a fan. After 24 hours, the reaction mixture was passed through a short pad of silica gel using ethyl acetate as an eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing ester **74** (quant. NMR yield). The mixture was subjected to preparative thin-layer chromatography (PTLC) (Hexane:AcOEt = 10:1, $R_f = 0.5$) to isolate ester **74** (45.4 mg, 0.194 mmol, 96%) as a colorless oil.

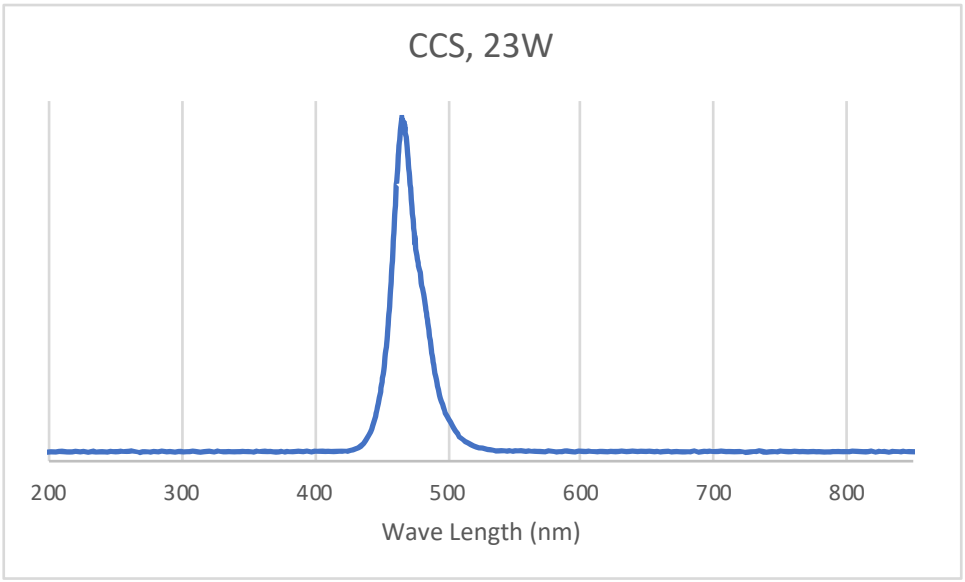
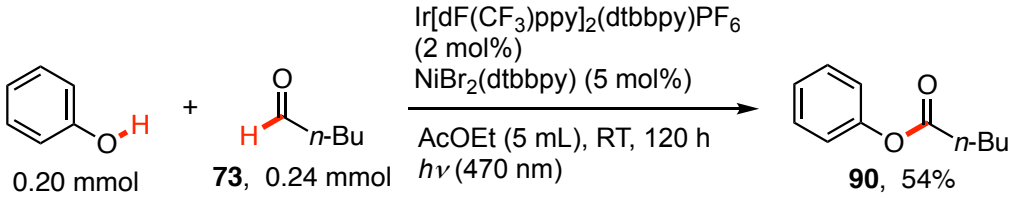


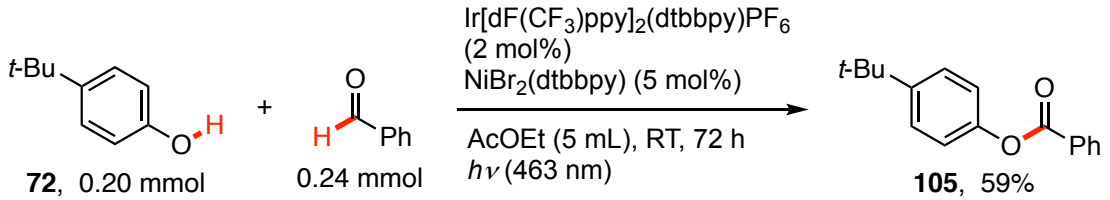
Chart 3-1. Spectrum of Blue LEDs

Scheme 3-9. Typical Procedure of the Acylation of Phenols with Aldehyde (Procedure B)



To a Schlenk tube containing Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (4.5 mg, 0.004 mmol, 2 mol%), $NiBr_2$(dtbbpy) (4.9 mg, 0.010 mmol, 5 mol%) and phenol (18.8 mg, 0.20 mmol, 1.0 equiv) were added valeraldehyde **73** (17.2 mg, 0.20 mmol, 1.0 equiv) and anhydrous ethyl acetate (5 mL) in a nitrogen-filled glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs, with the vessel being cooled by a fan. Every 24 hours, 0.20 mmol of valeraldehyde (17.2 mg, 1.0 equiv) was added. After 120 hours, the reaction mixture was concentrated under reduced pressure and the mixture was subjected to preparative thin-layer chromatography (PTLC) (Hexane:AcOEt = 10:1, R_f = 0.5) to isolate **90** (19.4 mg, 0.109 mmol, 54%) as a colorless oil.

Scheme 3-10. Typical Procedure of the Acylation of Phenols with Aldehyde (Procedure C)



To a Schlenk tube containing Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (4.5 mg, 0.004 mmol, 2 mol%), $NiBr_2$(dtbbpy) (4.9 mg, 0.010 mmol, 5 mol%) and 4-*tert*-butylphenol **72** (30.0 mg, 0.20 mmol, 1.0 equiv) were added benzaldehyde (20.2 mg, 0.24 mmol, 1.2 equiv) and anhydrous ethyl acetate (5 mL) in the glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs, with the vessel being cooled by a fan. After 72 hours, the reaction mixture was passed through a short pad of silica gel using ethyl acetate as the eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing ester **105** (64%, NMR yield). The mixture was subjected to preparative thin-layer chromatography (PTLC) (Hexane:AcOEt = 10:1, R_f = 0.5) to give **106** (30.3 mg, 0.119 mmol, 59%) as white solids.

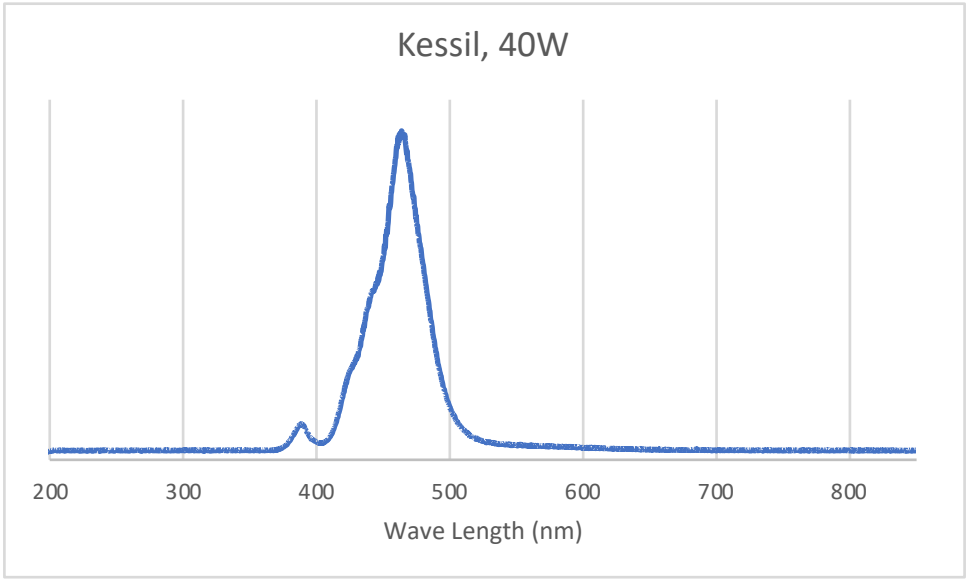


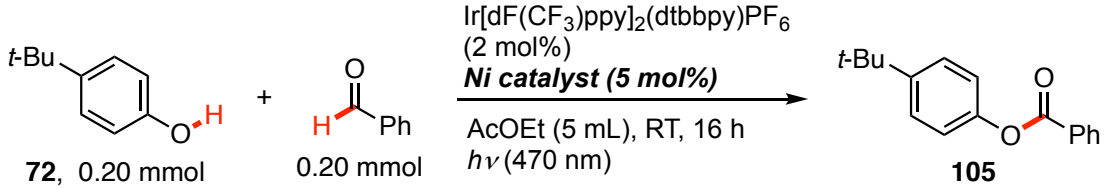
Chart 3-2. Spectrum of Blue LEDs

3.4.3 Detection of Evolved Molecular Hydrogen

The dehydrogenative esterification of 4-*tert*-butylphenol **72** with valeraldehyde **73** was performed according to the procedure A. The gas phase in the headspace of the reaction vessel was analyzed by gas chromatography. A gas-tight syringe was used to take a sample. The gas in the syringe was replaced with the gas in the reaction vessel prior to sampling; 0.20 mL of gas in the headspace of the vessel was once taken and discharged. Then, 0.20 mL of gas in the vessel was newly taken and injected into a gas chromatograph. The formation of dihydrogen was confirmed by comparison with an authentic sample.

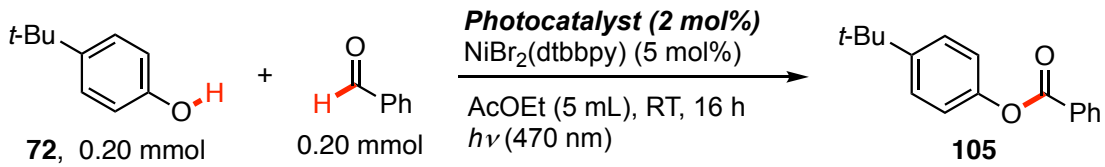
3.4.4 Optimization Studies

Table 3-2. Screening of Nickel Catalysts in the Reaction of **72** with Benzaldehyde



entry	Ni catalyst	NMR yield of **105**
1	$NiBr_2$(dme) (5 mol%)	<5%
2	$NiBr_2$(dme) (5 mol%), phen (5 mol%)	<5%
3	$NiBr_2$(dme) (5 mol%), bpy (5 mol%)	<5%
4	$NiBr_2$(dme) (5 mol%), dtbbpy (5 mol%)	8%
5	$NiBr_2$(dtbbpy) (5 mol%)	17%

Table 3-3. Screening of Photocatalysts in the Reaction of **72** with Benzaldehyde



72, 0.20 mmol　　0.20 mmol　　**105**

entry	photocatalyst	NMR yield of **105**
1	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	17%
2	$Ir(ppy)_3$	0%
3	4CzIPN	0%
4	Eosin Y	0%
5	$Ru(bpy)_3•2BF_4$	0%
6	Mes-Acr-Me•ClO_4	0%
7	None	0%

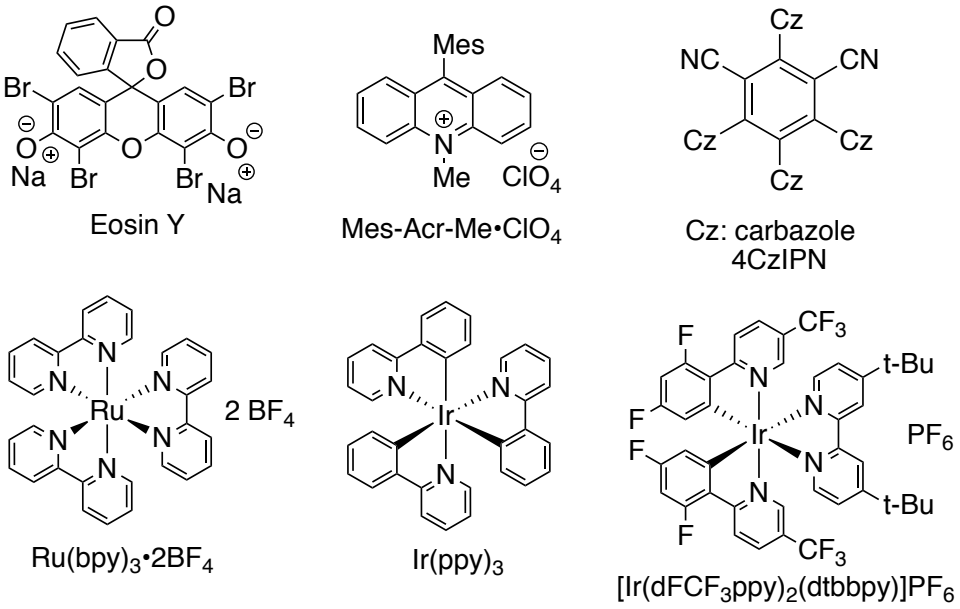
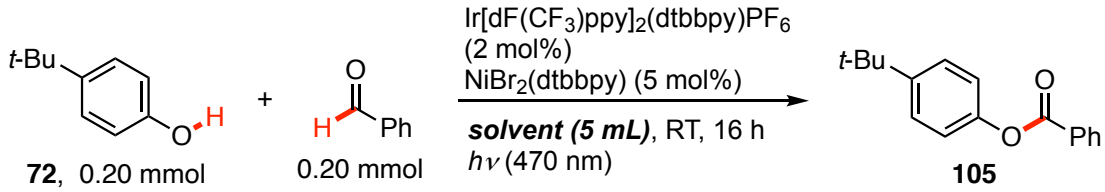


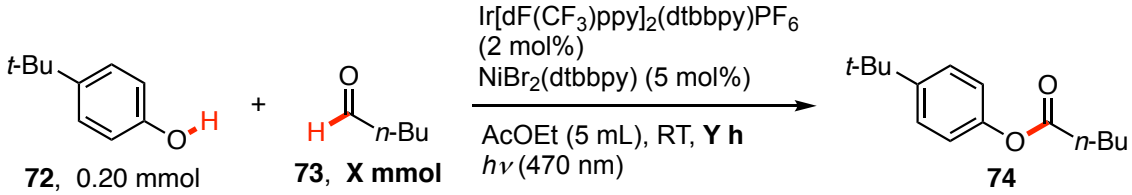
Figure 3-1. Structures of the Photocatalysts

Table 3-4. Screening of Solvents in the Reaction of **72** with Benzaldehyde



entry	solvent	NMR yield of **105**
1	AcOEt	17%
2	MeCN	0%
3	acetone	<5%
4	THF	0%
5	toluene	0%
6	DMF	<5%
7	CH_2Cl_2	<5%

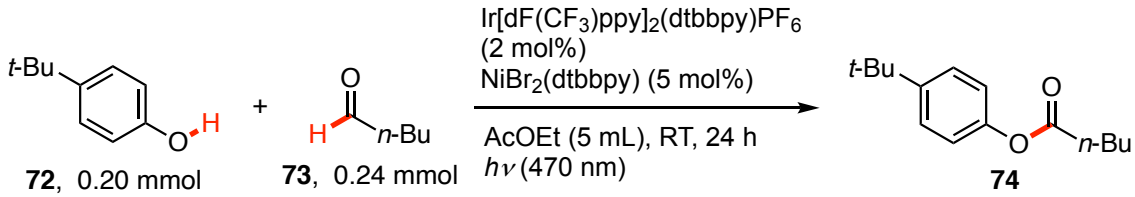
Table 3-5. Further Optimization in the Reaction of **72** and Valeraldehyde **73**



entry	valeraldehyde **73**	time	NMR yield of 74
1	0.20 mmol	16 h	66%
2	0.30 mmol	16 h	83%
3	0.20 mmol	24 h	82%
4	0.30 mmol	24 h	100% (94% isolated yield)
5	0.24 mmol	24 h	100% (96% isolated yield)

3.4.5 Control Experiments

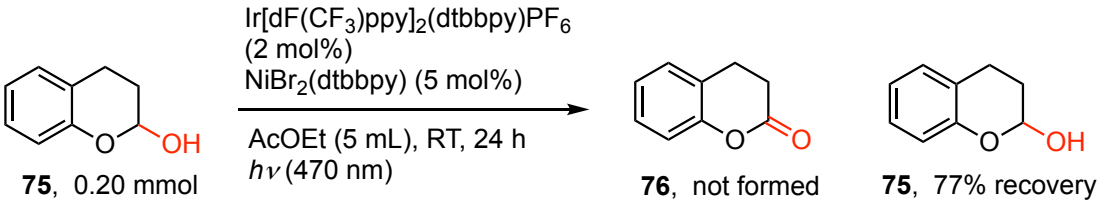
Table 3-6. Control Experiments



entry	deviation from standard condition	NMR yield of 74
1	None	100%
2	w/o Ir catalyst	0%
3	w/o Ni catalyst	0%
4	w/o light	0%
5	$Ni(OAc)_2•4H_2O$ (5 mol%), dtbbpy (5 mol%) instead of $NiBr_2$(dtbbpy)	0%
6	$Ni(OAc)_2•4H_2O$ (5 mol%), dtbbpy (5 mol%), (n-Bu)$_4$NBr (10 mol%) instead of $NiBr_2$(dtbbpy)	9%
7	$NiCl_2$(dtbbpy) instead of $NiBr_2$(dtbbpy)	<5%
	$NiCl_2$(dtbbpy) instead of NiI_2(dtbbpy)	0%

3.4.6 Attempt of Dehydrogenation of Hemi-Acetal 75

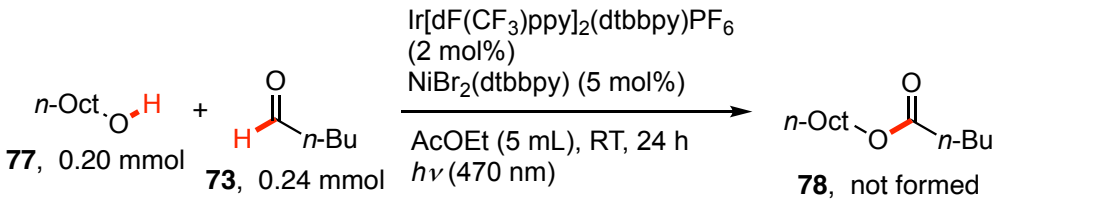
Scheme 3-11. Attempt of Dehydrogenation of Hemi-Acetal **75**



To a Schlenk tube containing Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (4.5 mg, 0.004 mmol, 2 mol%), NiBr$_2$(dtbbpy) (4.9 mg, 0.010 mmol, 5 mol%) and 2-chromanol **75** (30.0 mg, 0.20 mmol, 1.0 equiv) was added anhydrous ethyl acetate (5 mL) in a nitrogen-filled glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with Blue LEDs, with the vessel being cooled by a fan. After 24 hours, the reaction mixture was passed through a short pad of silica gel using ethyl acetate as the eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing the starting material **75** (77% recovery). The lactone **76** was not formed.

3.4.7 Attempt of Dehydrogenative Esterification of 1-Octanol 77

Scheme 3-12. Attempt of Dehydrogenative Coupling of 1-Octanol **77** with **73**



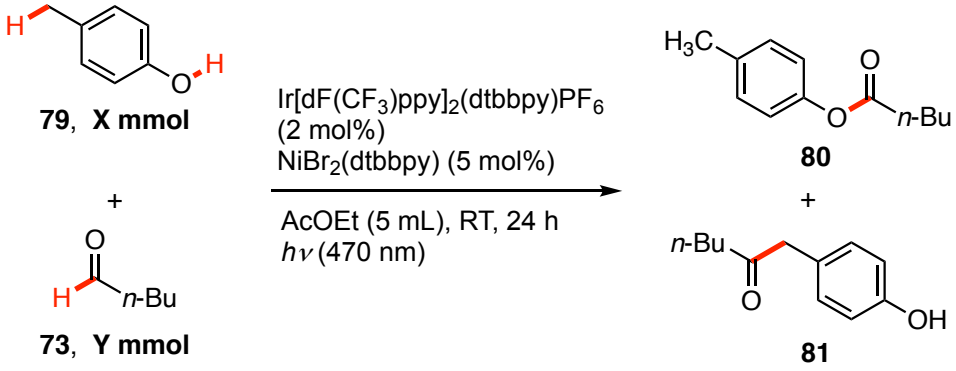
77: quantitative recovery (NMR yield)

To a Schlenk tube containing Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (4.5 mg, 0.004 mmol, 2 mol%) and NiBr$_2$(dtbbpy) (4.9 mg, 0.010 mmol, 5 mol%) were added *n*-octanol **77** (26.0 mg, 0.20 mmol, 1.0 equiv), valeraldehyde **73** (17.2 mg, 0.24 mmol, 1.2 equiv) and anhydrous ethyl acetate (5 mL) in a nitrogen-filled glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with Blue LEDs, with the vessel being cooled by a fan. After 24 hours, the reaction mixture was passed through a short pad of silica gel using ethyl acetate as the eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing **77**

(quant. NMR yield). The ester **78** was not formed. Aldehyde **73** was fully consumed and an intractable mixture was generated.

3.4.8 Competition Experiments in the Reaction of p-Cresol 79

Table 3-7. Competition Experiments



entry	**79** X mmol	**73** Y mmol	**79** : **73**	NMR yield **80**	NMR yield **81**
1	1.0	0.20	5 : 1	9%	23%
2	0.20	0.20	1 : 1	38%	33%
3	0.20	1.0	1 : 5	97%	0%

3.4.9 *Stern-Volmer Quenching Experiments*

Samples for Stern-Volmer studies were prepared using varying amounts of 4-*tert*-butylphenol **72** and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 in ethyl acetate. The solution was degassed by freeze-pump-thaw cycling three times and poured into quartz cuvettes in the glove box. The solution was irradiated at 435 nm and the emission intensity was observed at 500 nm. The results are given below. The results using NiBr$_2$(dtbbpy) and valeraldehyde **73** are also shown for comparison.

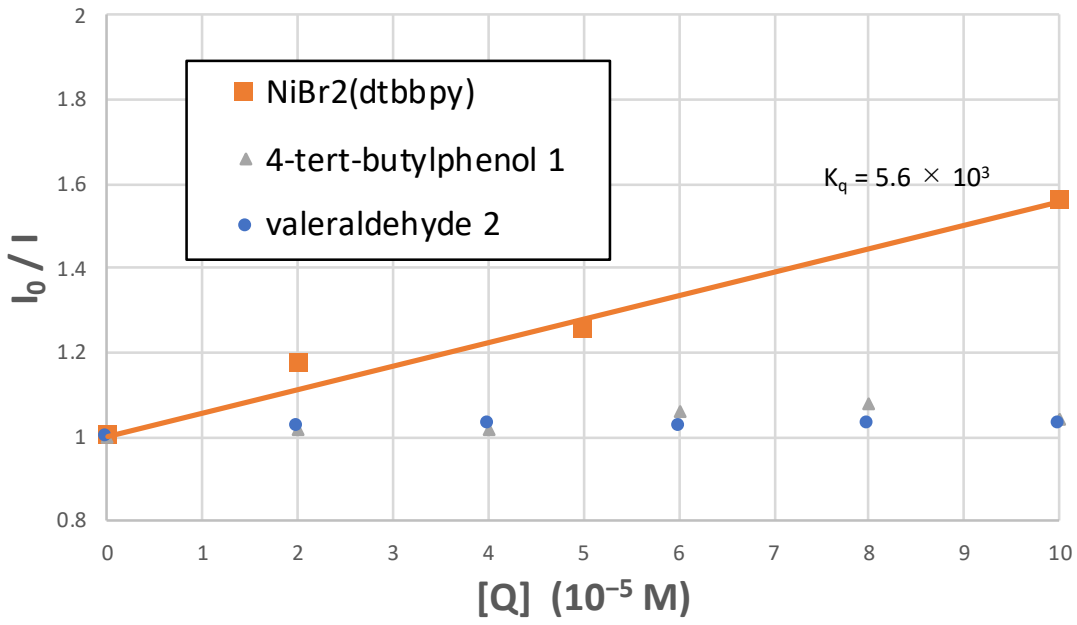
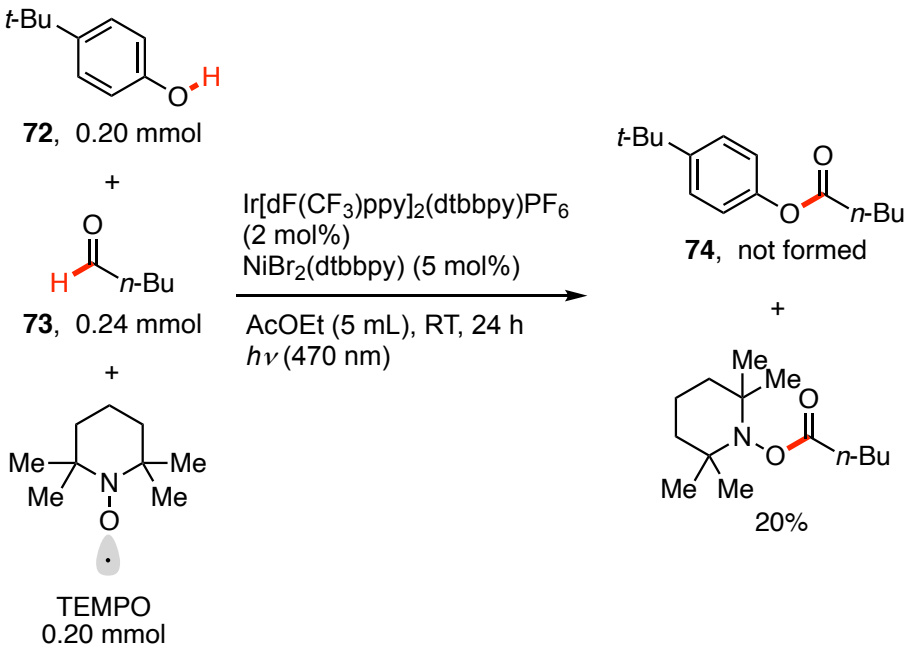


Chart 3-3. Stern-Volmer Plots

Whereas NiBr$_2$(dtbbpy) quenched the excited state of the iridium complex (K_q = 5.6 * 10^3), 4-*tert*-butylphenol **72** and valeraldehyde **73** exhibited no significant quenching within the margin of the experimental error.

3.4.10 Radical Trapping Experiment

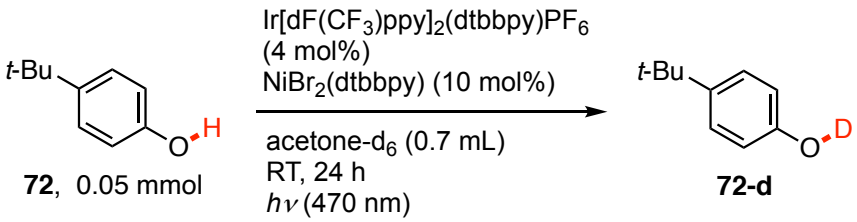
Scheme 3-13. Radical Trapping Experiment



To a Schlenk tube containing Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (4.5 mg, 0.004 mmol, 2 mol%), $NiBr_2$(dtbbpy) (4.9 mg, 0.010 mmol, 5 mol%) and 4-*tert*-butylphenol **72** (30.0 mg, 0.20 mmol, 1.0 equiv) were added valeraldehyde **73** (17.2 mg, 0.24 mmol, 1.2 equiv), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 31.3 mg, 0.20 mmol, 1.0 equiv) and anhydrous ethyl acetate (5 mL) in a nitrogen-filled glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with Blue LEDs, with the vessel being cooled by a fan. After 24 hours, the reaction mixture was passed through a short pad of silica gel using ethyl acetate as the eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing ester (20%, NMR yield). Ester **74** was not detected in the reaction mixture.

3.4.11 H/D Exchange of Phenolic O–H Bond

Table 3-8. H/D Exchange Experiment



entry	deviation from the condition	NMR yield of **72-d**
1	None	quant.
2	w/o Ir catalyst	0%
3	w/o Ni catalyst	0%
4	w/o light	0%

To a screw-caped NMR tube containing $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.3 mg, 0.002 mmol, 4 mol%), $NiBr_2(dtbbpy)$ (2.4 mg, 0.005 mmol, 10 mol%) and 4-*tert*-butylphenol **72** (7.5 mg, 0.050 mmol, 1.0 equiv) was added acetone-d_6 (0.7 mL) in a nitrogen-filled glove box. The reaction mixture was irradiated with Blue LEDs, with the tube being cooled by a fan. After 24 hours, the reaction mixture was analyzed by ^{1}H NMR spectroscopy. The ^{1}H NMR spectra at 0 and 24 hours are shown in Figure S4.

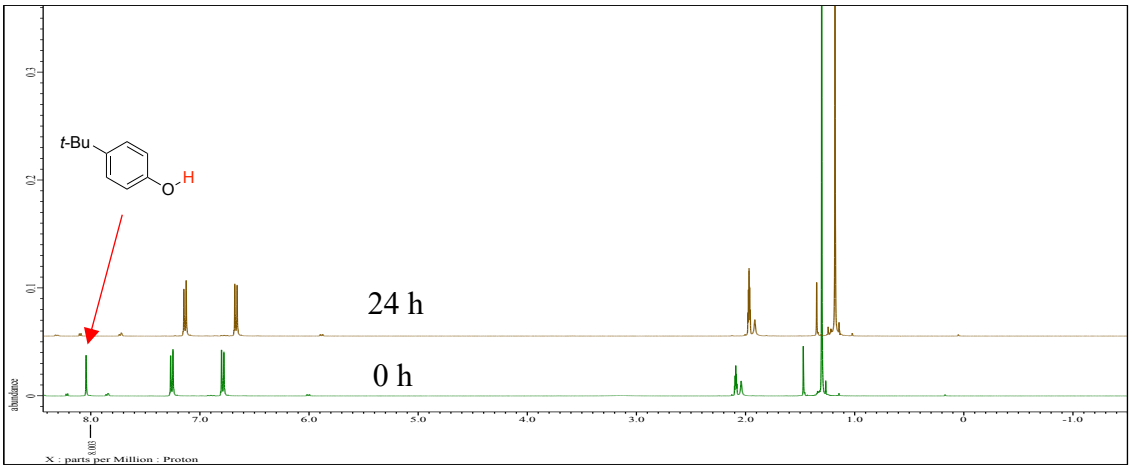


Chart 3-4. ^{1}H NMR Spectra of Entry 1 in Table 3-8

The signal of the hydroxylic proton of **72** (8.00 ppm) disappeared after 24 hours

of irradiation. The ratio of the residual proton present in acetone-d_6 and aromatic protons of **72** increased from 1:2 to 1:1.

Next, acetone-d_6 was removed under a reduced pressure, and the residue was analyzed by ^{2}H NMR spectroscopy using non-deuterated acetone as the solvent. A singlet signal appeared at 8.43 ppm (Chart 3-3).

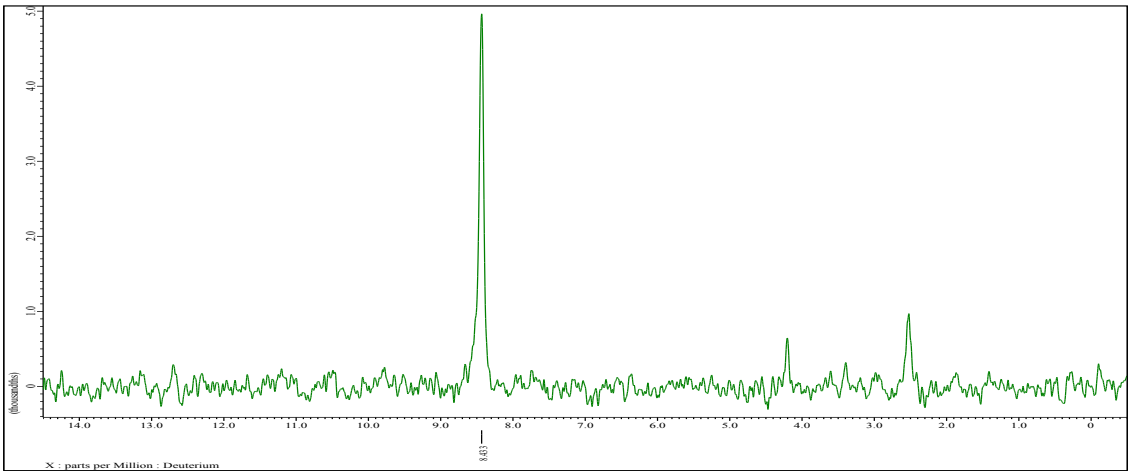
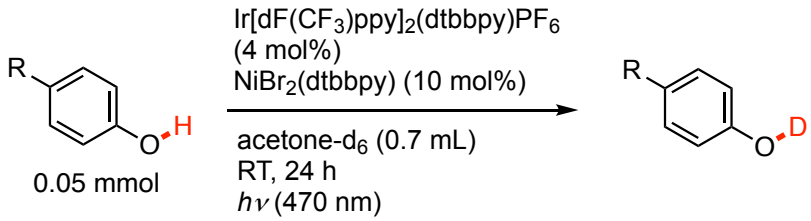


Chart 3-5. ^{2}H NMR Spectrum of Entry 1 in Table 3-8

Thus, the hydroxylic proton of **72** exchanged with deuterium derived from acetone-d_6. Iridium, nickel, and light were all essential for the H/D exchange (Table S6, entries 2-4), suggesting that cooperative action of light/iridium/nickel is responsible for the cleavage of the O–H bonds.

We next examined H/D exchange of 4-substituted phenols (Table 3-9 and Chart 3-4 – 3-6). The H/D exchange of 4-methoxyphenol was much faster than that of 4-*tert*-butylphenol, and that of methyl 4-hydroxybenzoate was sluggish. Thus, the rate of the O–H bond cleavage is likely to be correlated with the bond dissociation energy of the phenolic O–H bonds rather than their acidity. These results are alternative supports for our mechanistic assumption shown in Scheme 3-2.

Table 3-9. Comparison of Phenol Derivatives in H/D Exchange



entry	R	ratio of the residual hydroxylic proton (%)					
		0 h	2 h	4 h	8 h	12 h	24 h
1	OMe	100	<5	0	-	-	-
2	*t*-Bu	100	92	88	80	40	0
3	CO_2Me	100	100	96	93	93	93

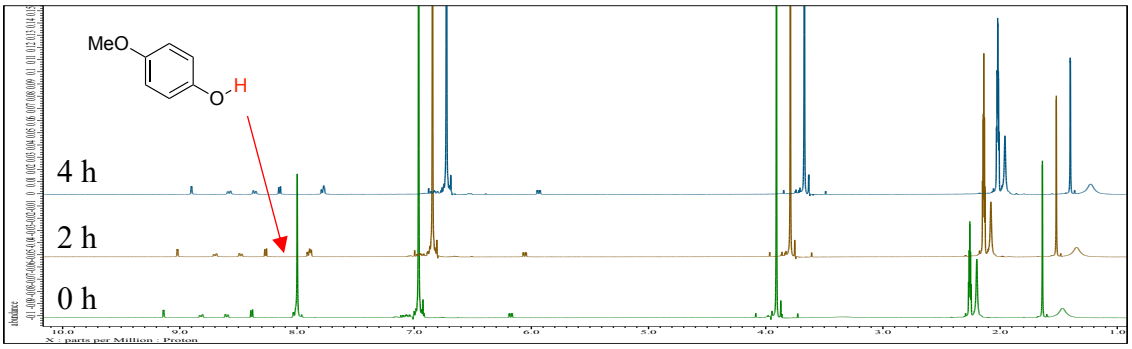


Chart 3-6. ^{1}H NMR Spectra of H/D Exchange of 4-Methoxyphenol

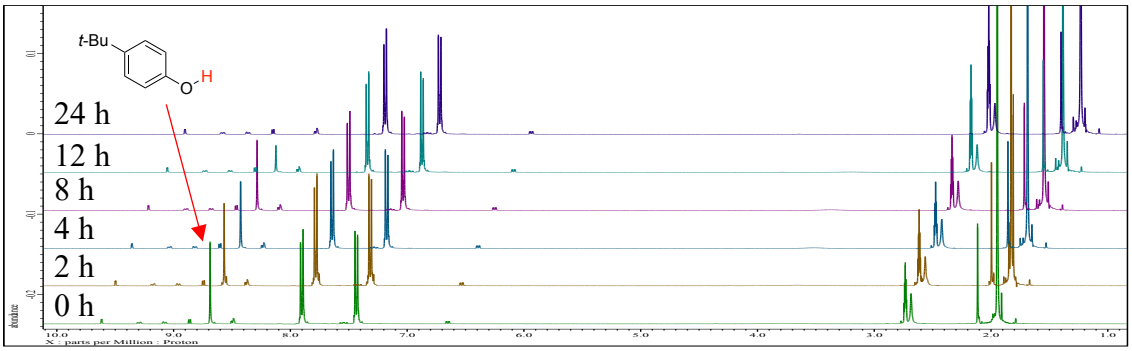


Chart 3-7. ^{1}H NMR Spectra of H/D Exchange of 4-*tert*-Butylphenol

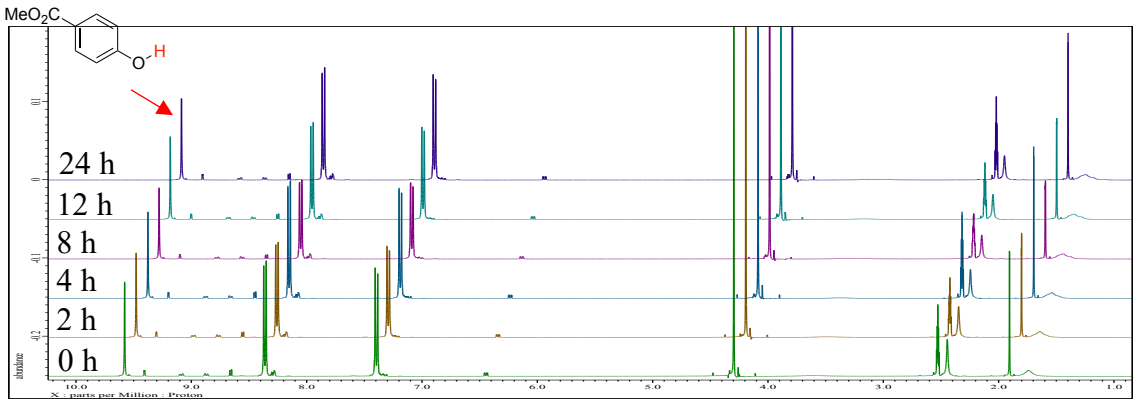
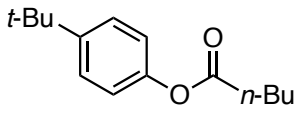


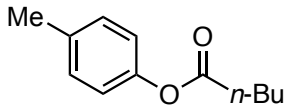
Chart 3-8. ^{1}H NMR Spectra of H/D Exchange of Methyl 4-Hydroxybenzoate

3.4.12 Spectroscopic Data of the Products



74

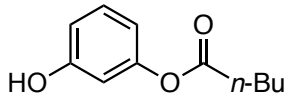
^{1}H NMR: δ = 7.38 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.74 (quint, *J* = 7.5 Hz, 2H), 1.45 (sext, *J* = 7.4 Hz, 2H), 1.31 (s, 9H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.5, 148.5, 148.4, 126.3, 120.8, 34.4, 34.1, 31.4, 27.0, 22.3, 13.7; IR (neat): 2961, 2872, 1757, 1508, 1207, 1171, 1143, 1098, 1016, 918, 837, 731 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{15}H_{22}O_2$ 234.1620; Found 234.1619.



80

The reaction was conducted by procedure A. 1.0 mmol of valeraldehyde. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **80** (33.6 mg, 0.175 mmol, 87%) as a colorless oil.

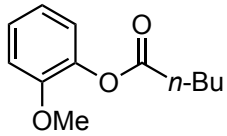
^{1}H NMR: δ = 7.16 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.5 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 2.34 (s, 3H), 1.74 (quint, *J* = 7.5 Hz, 2H), 1.45 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.5, 148.5, 135.3, 129.9, 121.2, 34.1, 27.0, 22.2, 20.8, 13.7; IR (neat): 2959, 2872, 1757, 1508, 1200, 1165, 1142, 1101, 916, 808 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{17}O_2$ 193.1223; Found 193.1220.



83

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 3:1, R_f = 0.3) to give **83** (24.6 mg, 0.127 mmol, 63%) as a colorless oil.

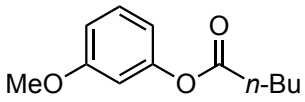
^{1}H NMR: δ = 7.22 (t, *J* = 8.2 Hz, 1H), 6.70-6.64 (m, 2H), 6.59 (s, 1H), 4.90 (s, 1H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.74 (quint, *J* = 7.5 Hz, 2H), 1.44 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.3, 156.3, 151.8, 130.1, 113.9, 112.9, 109.2, 34.1, 27.0, 22.2, 13.7; IR (neat): 3422, 2959, 2872, 1732, 1601, 1485, 1225, 1159, 1128, 957, 762, 683 cm^{-1}; HRMS (APCI) *m/z*: [M + H]$^+$ Calcd for $C_{11}H_{15}O_3$ 195.1016; Found 195.1014.



84

The reaction was conducted by procedure A. 72 Hours. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 11:1, R_f = 0.3) to give **84** (37.0 mg, 0.178 mmol, 88%) as a colorless oil.

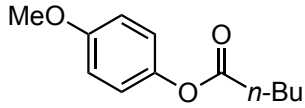
^{1}H NMR: δ = 7.19 (t, *J* = 7.8 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 6.98-6.92 (m, 2H), 3.82 (s, 3H), 2.59 (t, *J* = 7.5 Hz, 2H), 1.76 (quint, *J* = 7.5 Hz, 2H), 1.47 (sext, 7.5 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 171.9, 151.1, 139.8, 126.7, 122.8, 120.7, 112.4, 55.8, 33.7, 27.1, 22.2, 13.7; IR (neat): 2959, 2872, 1759, 1605, 1501, 1279, 1256, 1171, 1140, 1111, 1042, 912, 746 cm^{-1}; HRMS (APCI) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{17}O_3$ 209.1172; Found 209.1169.



85

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane: AcOEt = 10:1, R_f = 0.) to give **85** (35.0 mg, 0.168 mmol, 84%) as a colorless oil.

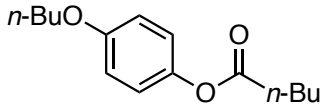
^{1}H NMR: δ = 7.27 (t, *J* = 8.2 Hz, 1H), 6.77 (d, *J* = 8.4 Hz, 1H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.63 (t, *J* = 2.3 Hz, 1H), 3.80 (s, 3H), 2.55 (t, *J* = 7.4 Hz, 2H), 1.74 (quint, *J* = 7.4 Hz, 2H), 1.45 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.2, 160.4, 151.7, 129.8, 113.8, 111.5, 107.6, 55.4, 34.1, 27.0, 22.2, 13.7; IR (neat): 2959, 2872, 1757, 1607, 1489, 1258, 1182, 1042, 941, 775, 685 cm^{-1}; HRMS (APCI) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{17}O_3$ 209.1172; Found 209.1169.



86

The reaction was conducted by procedure A. 120 Hours. The crude mixture was purified by preparative thin-layer chromatography (Hexane: AcOEt = 11:1, R_f = 0.3) to give **86** (37.4 mg, 0.179 mmol, 89%) as a colorless oil.

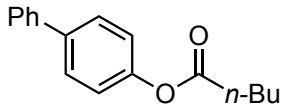
^{1}H NMR: δ = 6.99 (d, *J* = 9.2 Hz, 2H), 6.88 (d, *J* = 9.2 Hz, 2H), 3.80 (s, 3H), 2.54 (t, *J* = 7.5 Hz, 2H), 1.74 (quint, *J* = 7.5 Hz, 2H), 1.44 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.7, 157.4, 144.2, 122.3, 114.4, 55.6, 34.1, 27.0, 22.2, 13.7; IR (neat): 2959, 2872, 1753, 1504, 1248, 1194, 1140, 1101, 1032, 912, 820, 770 cm^{-1}; HRMS (APCI) *m/z*: [M + H]$^+$ Calcd for $C_{12}H_{17}O_3$ 209.1172; Found 209.1169.



87

The reaction was conducted by procedure A for 120 hours. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 11:1, R_f = 0.3) to give **87** (36.0 mg, 0.144 mmol, 71%) as a colorless oil.

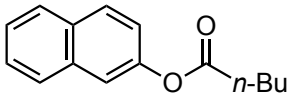
^{1}H NMR: δ = 6.97 (d, *J* = 9.2 Hz, 2H), 6.87 (d, *J* = 9.2 Hz, 2H), 3.94 (t, *J* = 6.5 Hz, 2H), 2.53 (t, *J* = 7.5 Hz, 2H), 1.79-1.70 (m, 4H), 1.53-1.40 (m, 4H) 0.99-0.93 (m, 6H); ^{13}C NMR: δ = 172.7, 156.3, 144.1, 122.2, 115.0, 68.1, 34.1, 31.3, 27.0, 22.2, 19.2, 13.8, 13.7; IR (neat): 2959, 2872, 1755, 1504, 1470, 1246, 1192, 1165, 1142, 1101, 820 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{23}O_3$ 251.1642; Found 251.1642.



88

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **88** (47.7 mg, 0.187 mmol, 93%) as white solids.

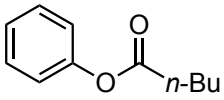
^{1}H NMR: δ = 7.61-7.53 (m, 4H), 7.44 (t, *J* = 7.5 Hz, 2H), 7.35 (t, *J* = 7.3 Hz, 1H), 7.15 (d, *J* = 7.3 Hz, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 1.77 (quint, *J* = 7.5 Hz, 2H), 1.47 (sext, *J* = 7.4 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.4, 150.2, 140.4, 138.9, 128.8, 128.1, 127.3, 127.1, 121.8, 34.1, 27.0, 22.3, 13.7; IR (neat): 2959, 2936, 1753, 1487, 1169, 1136, 1101, 849, 767, 739, 731, 691 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{19}O_2$ 255.1380; Found 255.1378.



89

The reaction was conducted by procedure A. 120 Hours. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 15:1, R_f = 0.4) to give a mixture of **89** (45.6 mg, 0.199 mmol, 99%) as a colorless oil.

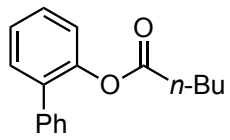
^{1}H NMR: δ = 7.86-7.79 (m, 3H), 7.55 (s, 1H), 7.51-7.44 (m, 2H), 7.12 (d, *J* = 8.9 Hz, 1H), 2.63 (t, *J* = 7.6 Hz, 2H), 1.80 (quint, *J* = 7.5 Hz, 2H) , 1.49 (sext, *J* = 7.4 Hz, 2H), 1.00 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.5, 148.4, 133.8, 131.4, 129.3, 127.7, 127.6, 126.5, 125.6, 121.2, 118.5, 34.2, 27.0, 22.3, 13.8; IR (neat): 2959, 2872, 1753, 1510, 1356, 1207, 1136, 1096, 961, 891, 810, 745 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{17}O_2$ 229.1223; Found 229.1221.



90

The reaction was conducted by procedure B. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **90** (19.4 mg, 0.109 mmol, 54%) as a colorless oil.

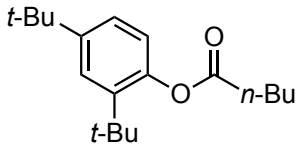
^{1}H NMR: δ = 7.38 (t, *J* = 7.8 Hz, 2H), 7.22 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 8.0 Hz, 2H), 2.56 (t, *J* = 7.5 Hz, 2H), 1.75 (quint, *J* = 7.5 Hz, 2H), 1.45 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.3, 150.7, 129.4, 125.7, 121.6, 34.1, 27.0, 22.2, 13.7; IR (neat): 2959, 2872, 1755, 1493, 1196, 1142, 1101, 926, 814, 745, 689 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{11}H_{14}O_2$ 178.0994; Found 178.0993.



91

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **91** (32.9 mg, 0.129 mmol, 64%) as a colorless oil.

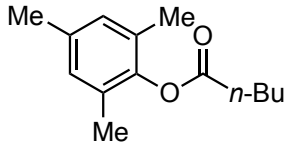
^{1}H NMR: δ = 7.42-7.28 (m, 8H), 7.12 (d, *J* = 7.9 Hz, 1H), 2.35 (t, *J* = 7.5 Hz, 2H), 1.51 (quint, *J* = 7.4 Hz, 2H), 1.22 (sext, *J* = 7.4 Hz, 2H), 0.85 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.2, 147.8, 137.6, 135.0, 130.8, 129.0, 128.5, 128.2, 127.4, 126.2, 122.8, 33.9, 26.7, 22.0, 13.6; IR (neat): 2957, 2872, 1755, 1477, 1190, 1138, 1109, 918, 743, 698 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{19}O_2$ 255.1380; Found 255.1378.



92

The reaction was conducted by procedure A. 72 Hours. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **21** (47.6 mg, 0.164 mmol, 81%) as white solids.

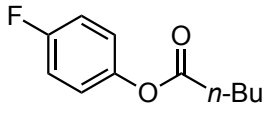
^{1}H NMR: δ = 7.39 (d, *J* = 2.4 Hz, 1H), 7.21 (dd, *J* = 8.4, 2.4 Hz, 1H), 6.89 (d, *J* = 8.4 Hz, 1H), 2.59 (t, *J* = 7.6 Hz, 2H), 1.77 (quint, *J* = 7.6 Hz, 2H), 1.47 (sext, *J* = 7.4 Hz, 2H), 1.35 (s, 9H), 1.31 (s, 9H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.5, 147.9, 146.8, 139.9, 124.1, 123.7, 123.2, 34.7, 34.6 (2C), 31.5 (3C), 30.2 (3C), 26.9, 22.3, 13.7; IR (neat): 2872, 2957, 1755, 1493, 1362, 1263, 1211, 1157, 1103, 889, 831, 731, 646 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{31}O_2$ 291.2319; Found 291.2318.



93

The reaction was conducted by procedure A. 1.0 mmol (5.0 equiv) of valeraldehyde. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **93** (27.6 mg, 0.125 mmol, 62%) as a colorless oil.

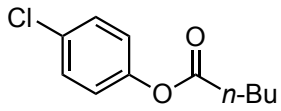
^{1}H NMR: δ = 6.86 (s, 2H), 2.59 (t, *J* = 7.6 Hz, 2H), 2.26 (s, 3H), 2.10 (s, 6H), 1.78 (quint, *J* = 7.6 Hz, 2H), 1.47 (sext, *J* = 7.5 Hz, 2H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 171.7, 145.9, 135.2, 129.6, 129.2, 33.8, 27.2, 22.4, 20.7, 16.3, 13.7; IR (neat): 2957, 2928, 1753, 1483, 1196, 1136, 1101, 1086, 920, 851 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{21}O_2$ 221.1536; Found 221.1533.



94

The reaction was conducted by procedure B. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **94** (29.9 mg, 0.152 mmol, 76%) as a colorless oil.

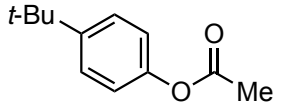
^{1}H NMR: δ = 7.09-6.99 (m, 4H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.74 (quint, *J* = 7.5 Hz, 2H), 1.44 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR: δ = 172.3, 160.1 (d, *J* = 243.7 Hz), 146.5 (d, *J* = 2.9 Hz), 122.9 (d, *J* = 8.7 Hz), 116.0 (d, *J* = 24.1 Hz), 34.0, 26.9, 22.2, 13.7; ^{19}F NMR: -117.2 (tt, *J* = 7.2, 5.5 Hz); IR (neat): 2961, 2874, 1759, 1503, 1186, 1152, 1138, 1099, 1090, 916, 827, 766 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{11}H_{13}O_2F$ 196.0900; Found 196.0899.



95

The reaction was conducted by procedure B. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **95** (28.2 mg, 0.133 mmol, 66%) as a colorless oil.

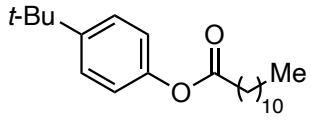
^{1}H NMR: δ = 7.33 (d, *J* = 9.0 Hz, 2H), 7.02 (d, *J* = 9.0 Hz, 2H), 2.55 (t, *J* = 7.5 Hz, 2H), 1.73 (quint, *J* = 7.5 Hz, 2H), 1.44 (sext, *J* = 7.4 Hz, 2H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.1, 149.2, 131.0, 129.4, 122.9, 43.0, 26.9, 22.2, 13.7; IR (neat): 2959, 2872, 1757, 1487, 1202, 1180, 1163, 1138, 1086, 1015, 916, 843 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{11}H_{13}O_2Cl$ 212.0604; Found 212.0600.



96

The reaction was conducted by procedure A. 1.0 mmol of acetaldehyde. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **96** (31.0 mg, 0.161 mmol, 80%) as a colorless oil.

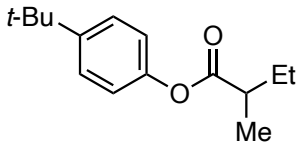
^{1}H NMR: δ = 7.38 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 2.29 (s, 3H), 1.32 (s, 9H); ^{13}C NMR: δ = 169.7, 148.6, 148.3, 126.3, 120.8, 34.5, 31.4, 21.2; IR (neat): 2963, 2868, 1763, 1510, 1368, 1196, 1169, 910, 837, 610 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{17}O_2$ 193.1223; Found 193.1220.



97

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **97** (62.8 mg, 0.189 mmol, 94%) as a colorless oil.

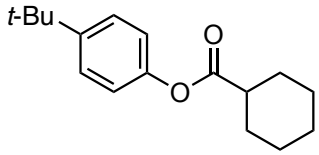
^{1}H NMR: δ = 7.38 (d, *J* = 8.9 Hz, 2H), 7.00 (d, *J* = 8.9 Hz, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 1.75 (quint, *J* = 7.4 Hz, 2H), 1.46-1.22 (m, 25H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 172.5, 148.5, 148.4, 126.3 (2C), 120.9 (2C), 34.4 (2C), 31.9, 31.4 (3C), 29.6 (2C), 29.5, 29.33, 29.26, 29.1, 25.0, 22.7, 14.1; IR (neat): 2924, 2853, 1759, 1510, 1207, 1171, 1140, 1103, 837, 721 cm^{-1}; HRMS (APCI) *m/z*: [M + H]$^+$ Calcd for $C_{22}H_{37}O_2$ 333.2788; Found 333.2790.



98

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **98** (36.4 mg, 0.155 mmol, 77%) as a colorless oil.

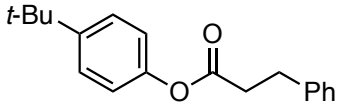
^{1}H NMR: δ = 7.38 (d, *J* = 8.8 Hz, 2H), 7.00 (d, *J* = 8.8 Hz, 2H), 2.62 (sext, *J* = 6.9 Hz, 1H), 1.83 (dq, *J* = 13.7, 6.9 Hz, 1H), 1.62 (dq, *J* = 13.7, 7.2 Hz, 1H), 1.34-1.27 (m, 12H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 175.3, 148.5, 148.4, 126.2, 120.8, 41.1, 34.4, 31.4, 26.8, 16.6, 11.6; IR (neat): 2965, 2878, 1753, 1510, 1207, 1169, 1126, 1101, 1090, 1016, 900, 858, 824 cm^{-1}; HRMS (APCI) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{23}O_2$ 235.1693; Found 235.1691.



99

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **99** (47.0 mg, 0.181 mmol, 90%) as a colorless oil.

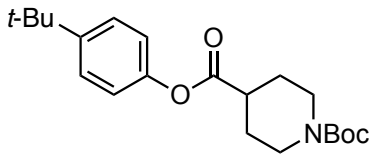
^{1}H NMR: δ = 7.37 (d, *J* = 8.9 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 2.55 (tt, *J* = 11.2, 3.7 Hz, 1H), 2.09-2.02 (m, 2H), 1.85-1.78 (m, 2H), 1.72-1.53 (m, 3H), 1.42-1.23 (m, 12H); ^{13}C NMR: δ = 174.7, 148.5, 148.4, 126.2, 120.8, 43.2, 34.4, 31.4, 29.0, 25.7, 25.4; IR (neat): 2934, 2857, 1751, 1508, 1207, 1171, 1152, 1123, 1016, 837, 733 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{25}O_2$ 261.1849; Found 261.1848.



100

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **100** (36.6 mg, 0.130 mmol, 64%) as a colorless oil.

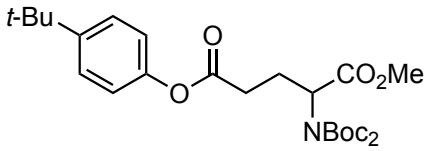
^{1}H NMR: δ = 7.38-7.22 (m, 7H), 6.93 (d, *J* = 8.8 Hz, 2H), 3.08 (t, *J* = 7.7 Hz, 2H), 2.88 (t, *J* = 7.9 Hz, 2H), 1.31 (s, 9H); ^{13}C NMR: δ = 171.6, 148.6, 148.3, 140.2, 128.6, 128.4, 126.4, 126.3, 120.8, 36.0, 34.4, 31.4, 31.0; IR (neat): 3028, 2961, 2868, 1755, 1508, 1206, 1171, 1107, 698 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{23}O_2$ 283.1693; Found 283.1691.



101

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (CH_2Cl_2, R_f = 0.6) to give **101** (52.1 mg, 0.144 mmol, 72%) as a colorless oil.

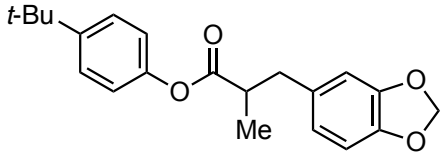
^{1}H NMR: δ = 7.38 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.17-3.97 (m, 2H), 2.98-2.86 (m, 2H), 2.69 (tt, *J* = 10.9, 3.9 Hz, 1H), 2.08-1.96 (m, 2H), 1.78 (dq, *J* = 12.2, 4.1 Hz, 2H), 1.47 (s, 9H), 1.31 (s, 9H); ^{13}C NMR: δ = 173.2, 154.7, 148.7, 148.2, 126.3, 120.7, 79.7, 43.0, 41.2, 34.5, 31.4, 28.4, 27.9; IR (neat): 2965, 2864, 1751, 1694, 1422, 1366, 1146, 1026, 731 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{31}NO_4Na$ 284.2145; Found 384.2152.



102

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (CH_2Cl_2, R_f = 0.4) to give **102** (45.4 mg, 0.092 mmol, 46%) as a colorless oil.

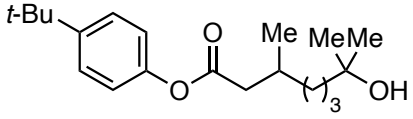
^{1}H NMR: δ = 7.37 (d, *J* = 8.8 Hz, 2H), 7.02 (d, *J* = 8.8 Hz, 2H), 5.03 (dd, J = 9.6, 4.4 Hz, 1H), 3.73 (s, 3H), 2.72-2.54 (m, 3H), 2.38-2.24 (m, 1H), 1.50 (s, 18H), 1.31 (s, 9H); ^{13}C NMR: δ = 171.4, 170.8, 152.0, 148.5, 148.3, 126.2, 120.9, 83.4, 57.3, 52.3, 34.4, 31.4, 30.9, 28.0, 25.1; IR (neat): 2978, 2907, 1748, 1701, 1368, 1171, 1134, 1111, 912, 853, 731 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{26}H_{39}NO_8Na$ 516.2568; Found 516.2572.



103

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 5:1, R_f = 0.5) to give **103** (42.3 mg, 0.124 mmol, 62%) as a white solid.

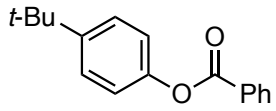
^{1}H NMR: δ = 7.36 (d, *J* = 8.9 Hz, 2H), 6.89 (d, *J* = 8.9 Hz, 2H), 6.77-6.74 (m, 2H), 6.69, (d, *J* = 7.8 Hz, 1H), 5.94 (s, 2H), 3.05 (dd, *J* = 13.4, 7.6 Hz, 1H), 2.92 (sext, *J* = 7.1 Hz, 1H), 2.74 (dd, *J* = 13.4, 7.0 Hz, 1H), 1.32-1.28 (m, 12H); ^{13}C NMR: δ = 174.7, 148.5, 148.3, 147.6, 146.1, 132.8, 126.3, 122.0, 120.7, 109.4, 108.2, 100.9, 41.9, 39.5, 34.4, 31.4, 16.9; IR (neat): 2963, 2874, 1751, 1504, 1489, 1246, 1203, 1171, 1140, 1098, 1038, 930, 806 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{21}H_{24}O_4Na$ 363.1567; Found 363.1574.



104

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 3:1, R_f = 0.4) to give **104** (62.5 mg, 0.195 mmol, 97%) as a colorless oil.

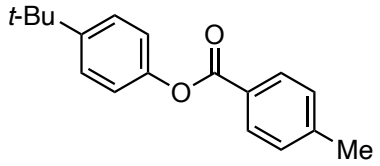
^{1}H NMR: δ = 7.38 (d, *J* = 8.3 Hz, 2H), 6.99 (d, *J* = 8.3 Hz, 2H), 2.55 (dd, *J* = 14.8, 6.2 Hz, 1H), 2.36 (dd, *J* = 14.8, 8.0 Hz, 1H), 2.11 (oct, *J* = 6.5 Hz, 1H), 1.54-1.18 (m, 21H), 1.05 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR: δ = 171.9, 148.5, 148.3, 126.3, 120.9, 71.0, 43.9, 41.8, 37.1, 34.4, 31.4, 30.5, 29.3, 29.2, 21.7, 19.7; IR (neat): 3402, 2963, 2870, 2748, 1508, 1364, 1207, 1171, 1126, 1107, 908, 837, 733 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{20}H_{32}O_3Na$ 343.2244; Found 343.2250.



105

The reaction was conducted by procedure C. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **105** (30.3 mg, 0.119 mmol, 59%) as white solids.

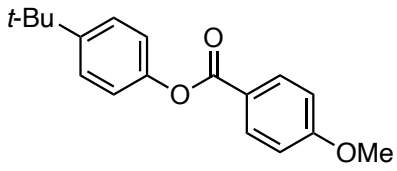
^{1}H NMR: δ = 8.21 (d, *J* = 8.3 Hz, 2H), 7.64 (t, *J* = 7.4 Hz, 1H), 7.51 (t, *J* = 7.7 Hz, 2H), 7.44 (d, *J* = 8.8 Hz, 2H), 7.14 (d, *J* = 8.8 Hz, 2H), 1.35 (s, 9H); ^{13}C NMR: δ = 165.3, 148.7, 148.6, 133.5, 130.1, 129.7, 128.5, 126.4, 121.0, 34.5, 31.4; IR (neat): 2963, 1732, 1263, 1204, 1171, 1061, 872, 704 cm^{-1}; HRMS (APCI) *m/z*: Calcd for $C_{17}H_{19}O_2$ $[M + H]^+$ 255.1380; Found 255.1379.



106

The reaction was conducted by procedure C. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 10:1, R_f = 0.5) to give **106** (42.3 mg, 0.158 mmol, 68%) as white solids.

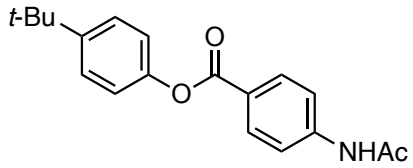
^{1}H NMR: δ = 8.09 (d, *J* = 8.2 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.31 (d, *J* = 8.0 Hz, 2H), 7.13 (d, *J* = 8.8 Hz, 2H), 2.45 (s, 3H), 1.34 (s, 9H); ^{13}C NMR: δ = 165.4, 148.63, 148.55, 144.3, 130.2, 129.2, 126.9, 126.3, 121.0, 34.5, 31.4, 21.7; IR (neat): 2961, 2868, 1736, 1263, 1202, 1171, 1059, 1016, 810, 744 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{21}O_2$ 269.1536; Found 269.1536.



107

The reaction was conducted by procedure C. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 9:1, R_f = 0.3) to give **107** (44.4 mg, 0.156 mmol, 78%) as white solids.

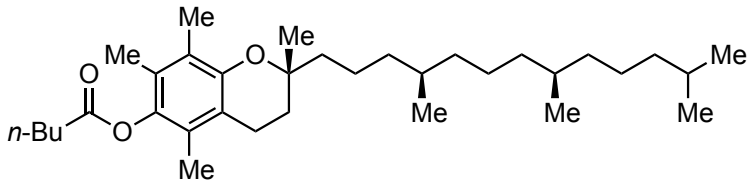
^{1}H NMR: δ = 8.12 (d, *J* = 9.0 Hz, 2H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.12 (d, *J* = 8.8 Hz, 2H), 6.98 (d, *J* = 9.0 Hz, 2H), 3.90 (s, 3H), 1.34 (s, 9H); ^{13}C NMR: δ = 165.1, 163.8, 148.7, 148.5, 132.3, 126.3, 122.0, 121.1, 113.8, 55.5, 34.5, 31.4; IR (neat): 2957, 2868, 1730, 1258, 1209, 1167, 1072, 766, 611 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{21}O_3$ 285.1485; Found 285.1487.



108

The reaction was conducted by procedure C. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 1:1, R_f = 0.3) to give **108** (30.9 mg, 0.099 mmol, 49%) as white solids.

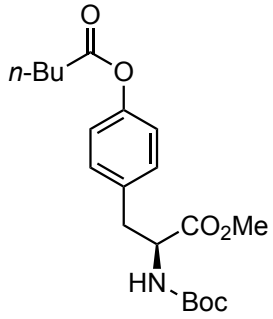
^{1}H NMR: δ = 8.16 (d, *J* = 8.5 Hz, 2H), 7.65 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.6 Hz, 2H), 7.12 (d, *J* = 8.5 Hz, 2H), 2.23 (s, 3H), 1.34 (s, 9H); ^{13}C NMR: δ = 168.4, 164.8, 148.7, 148.6, 142.6, 131.4, 126.4, 125.0, 121.0, 118.8, 34.4, 31.4, 24.8; IR (neat): 3372, 2963, 2862, 1717, 1674, 1595, 1533, 1258, 1173, 1063, 764, 631 cm^{-1}; HRMS (APCI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{22}NO_3$ 312.1594; Found 312.1596.



110

The reaction was conducted by procedure A. 1.0 mmol of valeraldehyde. 120 Hours. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 15:1, R_f = 0.5) to give **110** (55.1 mg, 0.107 mmol, 53%) as a colorless oil.

^{1}H NMR: δ = 2.63-2.55 (m, 4H), 2.09 (s, 3H), 2.01 (s, 3H), 1.97 (s, 3H), 1.85-1.70 (m, 4H), 1.60-0.93 (m, 29H), 0.90-0.81 (m, 12H); ^{13}C NMR: δ = 172.4, 149.3, 140.5, 126.7, 124.9, 123.0, 117.3, 75.0, 39.4, 37.4 (3C), 37.3, 33.9, 32.8, 32.7, 31.1, 28.0 (2C), 27.2 (2C), 24.8, 24.4, 22.7, 22.6, 22.5, 21.0, 20.6, 19.7, 19.6, 13.7, 12.9, 12.1, 11.8; IR (neat): 2926, 2868, 1751, 1460, 1377, 1152, 1103, 908, 732cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{34}H_{58}O_3Na$ 537.4278; Found 537.4279.

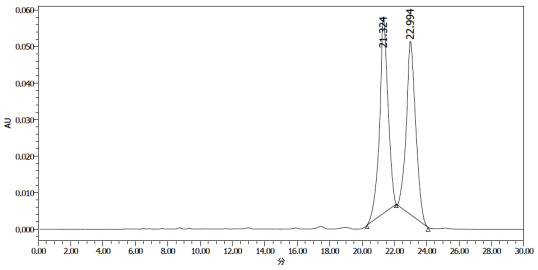


112

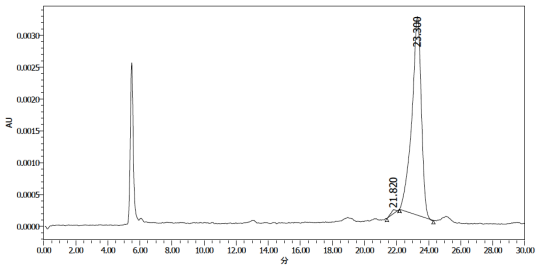
The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 3:1, R_f = 0.4) to give **112** (47.6 mg, 0.124 mmol, 62%) as white solids.

^{1}H NMR: δ = 7.13 (d, *J* = 8.4 Hz, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 4.97 (br d, *J* = 8.0 Hz, 1H), 4.57 (dd, *J* = 13.3, 6.0 Hz, 1H), 3.71 (s, 3H), 3.15-3.00 (m, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 1.73 (quint, *J* = 7.5 Hz, 2H), 1.49-1.33 (m, 11H), 0.97 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 172.24, 172.19, 155.0, 149.8, 133.5, 130.2, 121.6, 80.0, 54.3, 52.2, 37.7, 34.1, 28.3, 27.0, 22.2, 13.7; IR (neat): 3356, 2953, 2868, 1748, 1738, 1690, 1524, 1148, 1103, 993, 835, 635 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{20}H_{29}NO_6Na$ 402.1887; Found 402.1893. HPLC (Daicel Chiralpak IA, hexane/isopropyl alcohol = 96/4,

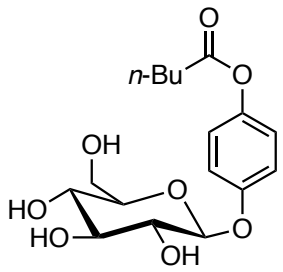
flow rate 0.6 mL/min, λ = 254 nm), t^1 = 21.3 min (minor), t^2 = 23.0 min (major).



	保持時間 (分)	面積 (μV秒)	%面積	高さ (μV)
1	21.324	1955830	50.52	53705
2	22.994	1915738	49.48	47354



	保持時間 (分)	面積 (μV秒)	%面積	高さ (μV)
1	21.820	1199	0.93	60
2	23.300	128362	99.07	3113



114

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (CH_2Cl_2:MeOH = 9:1, R_f = 0.2) to give **114** (43.1 mg, 0.120 mmol, 60%) as white solids.

D_2O was used as the solvent for NMR spectroscopy. ^{1}H NMR: δ = 7.18 (d, *J* = 9.0 Hz, 2H), 7.11 (d, *J* = 9.0 Hz, 2H), 5.11 (d, *J* = 7.5 Hz, 1H), 3.94 (dd, *J* = 12.4, 2.1 Hz, 1H), 3.77 (dd, *J* = 12.4, 5.7 Hz, 1H), 3.68-3.46 (m, 4H), 2.65 (t, *J* = 7.4 Hz, 2H), 1.71 (quint, *J* = 7.4 Hz, 2H), 1.42 (sext, *J* = 7.4 Hz, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 176.7, 154.6, 145.4, 122.8, 117.7, 100.5, 76.2, 75.5, 72.9, 69.4, 60.5, 33.5, 26.4, 21.6, 13.0; IR (neat): 3364, 2914, 2880, 1728, 1504, 1190, 1070, 1013, 897, 824, 660 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{24}O_8Na$ 379.1363; Found 379.1371.

3.5 References and Notes

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[16] For the detailed mechanistic studies on the iridium/nickel-catalyzed cross-coupling reactions, see: a) B. J. Shields, G. D. Scholes, A. G. Doyle, *J. Am. Chem. Soc.* **2018**, *140*, 3035-3039; b) R. Sun, Y. Qin. S. Ruccolo, C. Schnedermann, C. Costentin, D. G. Nocera, *J. Am. Chem. Soc.* **2019**, *141*, 89-93.

[17] BDEs of aldehydic C–H bonds (372 kJ/mol for varelaldehyde) are larger than those of O–H bonds of phenols.

[18] Diphenoxylnickel(III) species would be reversibly formed from phenoxynickel(II) species and the phenoxyl radical. However, reductive elimination producing a peroxide would be unfavorable.

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[20] When octanal was subjected to the reaction conditions in the absence of a phenol, a complex mixture containing hexadecan-8,9-dione (homo-coupling product of an acyl radical) and pentadecan-8-one (coupling of the acyl radical with a decarbonylated alkyl radical) was produced.

[21] A similar deviation in reactivities was observed in benzylic C–H acylation reaction. See ref 7.

[22] The reason of the lower yield of **108** than those of **105-107** is unclear.

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111.

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Chapter 4

Visible Light-Driven Dehydrogenative Coupling of Primary Alcohols with Phenols Forming Aryl Carboxylates

Table of Contents

Abstract: A preparative method of aryl esters from aliphatic primary alcohols and phenols was developed. The reaction proceeds under irradiation of visible light at ambient temperature, dispensing with any oxidant or hydrogen acceptor. Primary alcohols having a variety of functional groups are successfully esterified with phenols. The produced esters can be utilized as the precursor of various carbonyl compounds.

4.1 Introduction

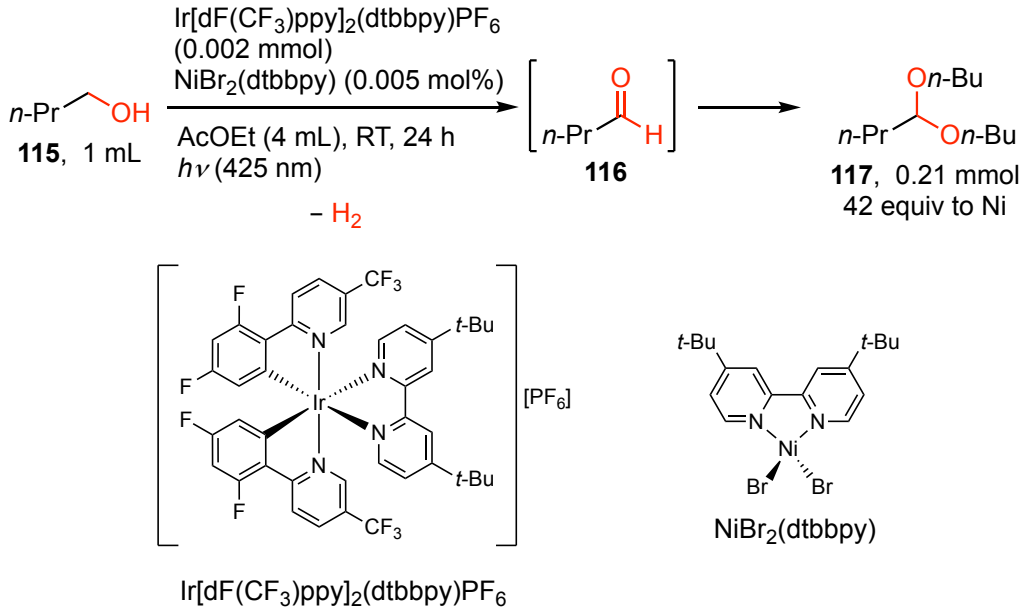
An oxidative transformation of primary alcohols into carboxylic acid derivatives presents one of the most fundamental maneuvers in synthesizing pharmaceuticals and functional materials because carboxylic acid derivatives serve as versatile intermediates.[1] Traditionally, such a transformation was executed through two steps consisting of (1) oxidation to carboxylic acids using a stoichiometric amount of a strong oxidant such as chromium salts,[2] and (2) a substitution reaction of the resulting carboxylic acids using an activator.[3] Because the conventional two-step method accompanies the generation of much waste, the development of environmentally more benign alternatives has been a subject of intensive research.[4] Among the methods developed, oxidant-free direct reactions from primary alcohols to carboxylic acid derivatives, evolving gaseous dihydrogen, are highly attractive.[5] Such examples include (a) reactions with aliphatic alcohols forming alkyl esters,[6] (b) reactions with amines forming amides,[7] and (c) reactions with aliphatic thiols forming alkyl thioesters.[8] High temperature is generally required in order to facilitate the elimination of hydrogen, and therewith, to promote the reaction forward. Herein reported is an oxidation reaction of primary alcohols to aryl esters which proceeds at ambient temperature through dehydrogenation. The present reaction requires only irradiation of visible light, dispensing with any oxidant.[9] The produced aryl esters are readily displaced with various nucleophiles such as alcohols and amines, serving as versatile synthetic platforms for various carbonyl compounds.

4.2 Results and Discussion

*4.2.1 Dehydrogenative Coupling of 1-Octanol **77** with 2,4-Difluorophenol **120***

The present study was prompted by the following experimental finding. When 1-butanol **115** (1 mL) in ethyl acetate (4 mL) was irradiated with blue LEDs (18 W, λ_{max} = 425 nm) in the presence of Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.002 mmol) and $NiBr_2$(dtbbpy) (0.005 mmol) at ambient temperature for 24 h, 1,1-dibutoxybutane **117** was formed (0.21 mmol, 42 equiv to Ni), suggesting that 1-butanol **115** was dehydrogenated to give butanal **116** (Scheme 4-1). Generation of dihydrogen gas was confirmed by a GC analysis of the headspace of the reaction vessel. A photoinduced selective acylation reaction of phenols with aldehydes is described in Chapter 3.[10] Whether a similar acylation reaction took place was examined when a primary alcohol was dehydrogenated in the presence of phenol. Thus, a mixture of 1-octanol **77** (0.20 mmol), phenol **118** (0.20 mmol), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.002 mmol, 1 mol%), and $NiBr_2$(dtbbpy) (0.005 mmol, 2.5 mol%) in ethyl acetate (2 mL) was irradiated with blue LEDs at ambient temperature for 48 h (Scheme 4-2). Chromatographic isolation with silica gel afforded phenyl octanoate **119** in 64% yield. The production of **119** suggested that octanal was generated from **77** through dehydrogenation and that the generated octanal underwent the dehydrogenative cross-coupling with **118**.[10] The effect of substituents of phenols was examined in the reaction of equimolar amounts of **77** and a phenol derivative (Table 3-1). 2,4-Difluorophenol **120** gave the best result (73% isolated yield) among others.[11]

Scheme 4-1. Dehydrogenation of 1-Butanol **115**



Scheme 4-2. Dehydrogenative Coupling of 1-Octanol **77** with Phenol **118**

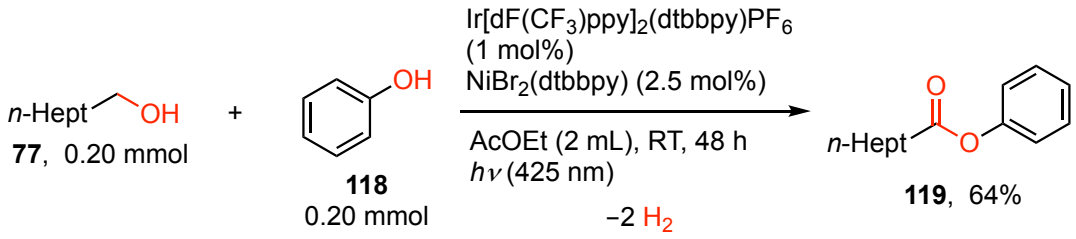
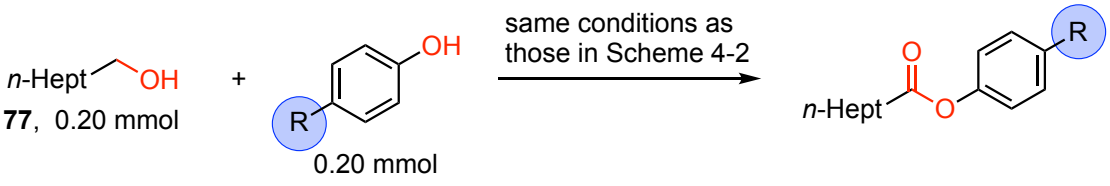


Table 4-1. Screening of Phenols



R	MeO	*t*-Bu	F	Cl	2,4-di-F **120**	Ac	CF_3
Aryl octanoate (%)	<5	22	56	85	88 (73)[b]	57	18

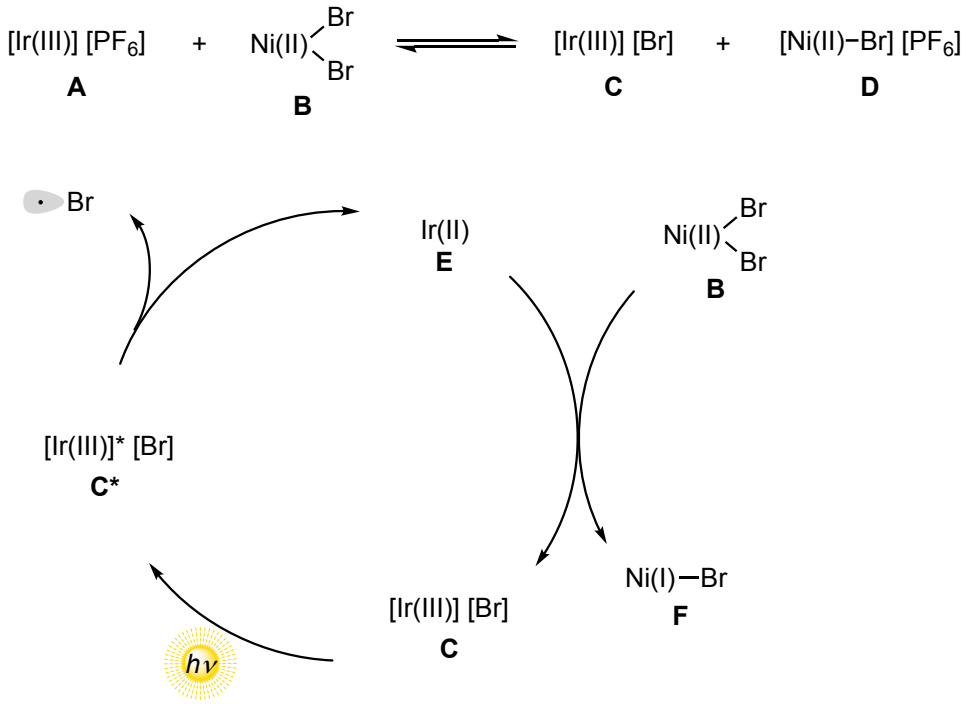
[a] Yields are determined by ^{1}H NMR analyses. [b] Isolated yield.

4.2.2 Proposed Mechanism

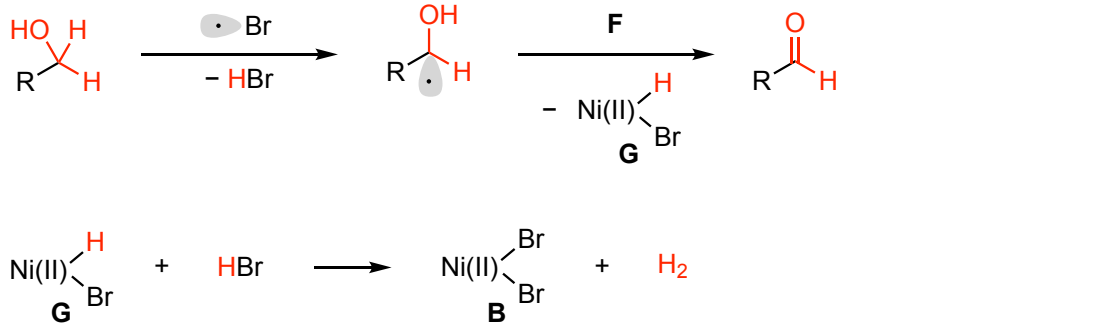
The plausible mechanism is shown in Scheme 4-3, although there are many other possibilities for it. It is explained by assuming 3 stages. Stage 1, which was assumed also in Chapter 2 on the dehydrogenative coupling of alkylbenzenes with aldehydes;[12] anion exchange between iridium(III) hexafluorophosphate A and nickel(II) dibromide B forms iridium(III) bromide complex C. When C absorbs light to get excited, a single electron transfers from the bromide anion to iridium(III) to generate iridium(II) species E and a bromine radical.[13] The iridium(II) E ($E_{1/2}$[Ir(III)/Ir(II)] = −1.37 V vs. SCE)[14] donates a single electron to Ni(II)Br_2 species B ($E_{1/2}$[Ni(II)/Ni(0)] = −1.2 V vs. SCE),[15] giving rise to nickel(I) bromide F and the iridium(III) bromide C. Stage 2; the bromine radical abstracts a hydrogen atom from the α-C–H bond of 1-octanol **77** to furnish an α-hydroxy radical species along with HBr. The nickel(I) bromide F abstracts a hydrogen atom from the α-hydroxy radical species to give nickel(II) species G and an aldehyde.[16] The nickel(II) species G reacts with HBr to afford nickel(II) dibromide B and hydrogen.[17] Stage 3, which was assumed also in Chapter 3 on the dehydrogenative acylation of phenols with aldehydes;[10] a bromine radical abstracts a hydrogen atom from the phenol and the aldehyde to generate an acyl radical and an aryloxy radical, respectively. The two radical species add to the nickel(I) species F. The resulting nickel(III) species H undergoes reductive elimination to form an ester linkage with elimination of F. The nickel(I) species F reacts with HBr to evolve dihydrogen and the $NiBr_2$ species.[17]

Scheme 4-3. Proposed Mechanism

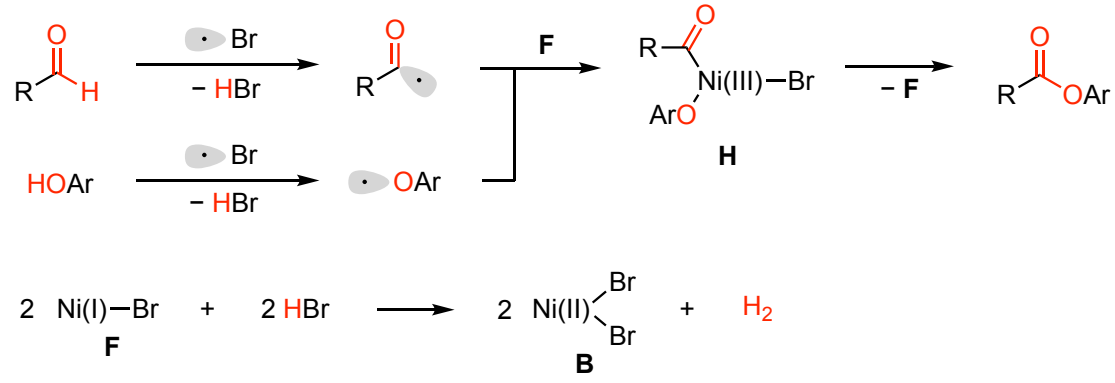
Stage 1. Generation of Bromine Radical and Ni(I)



Stage 2. Formation of Aldehyde and Hydrogen Evolution



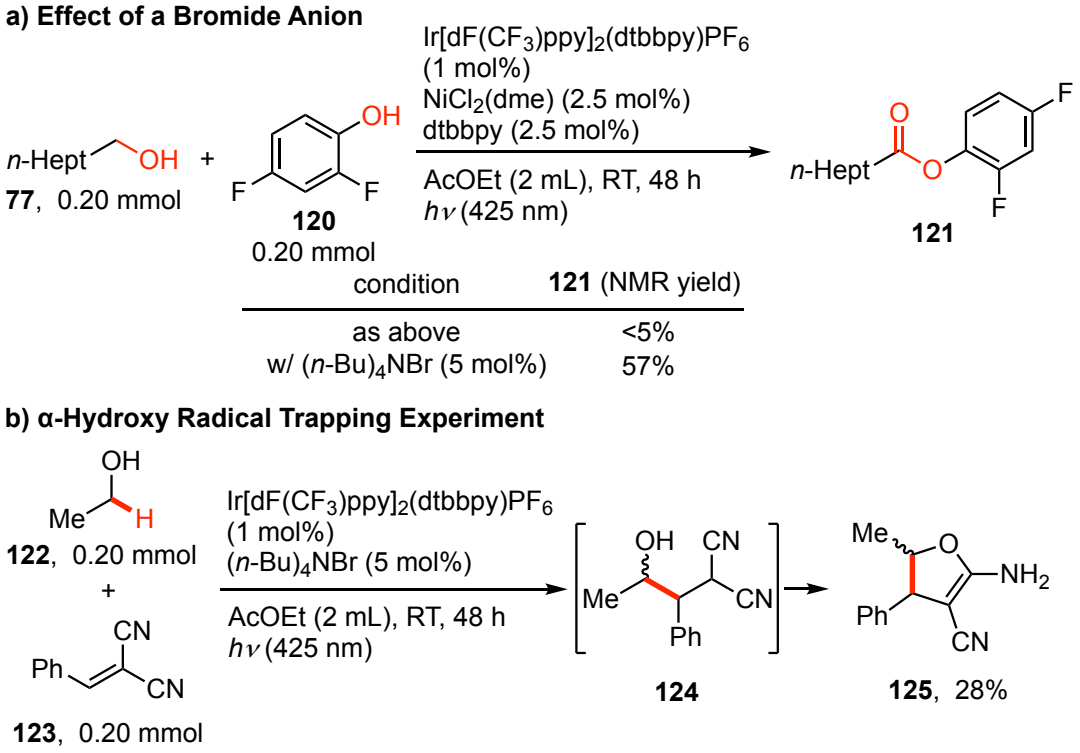
Stage 3. Formation of Ester and Hydrogen Evolution



4.2.3 Mechanistic Studies

When a nickel catalyst prepared in situ from $NiCl_2$(dme) and dtbbpy was used, the ester was scarcely produced (<5%). In contrast, the ester **121** was obtained in 57% yield when (n-Bu)$_4$NBr was added to the catalyst generated in situ from $NiCl_2$(dme) and dtbbpy. These contrasting results were consistent with the proposed mechanism involving hydrogen abstraction by a bromine radical.[18] When ethanol **122** was irradiated under the reaction conditions in the presence of benzalmalononitrile **123** and (n-Bu)$_4$NBr as a bromide source instead of the phenol and the $NiBr_2$ catalyst, the adduct **125** was produced in 28% yield. The formation of **125** was explained by assuming that an α-hydroxy radical was generated from ethanol via hydrogen abstraction by a bromine radical and that it underwent conjugated addition to **123**, which was followed by intramolecular cyclization.[19] The results shown in Scheme 4-4 corroborate the mechanism shown in Scheme 4-3.

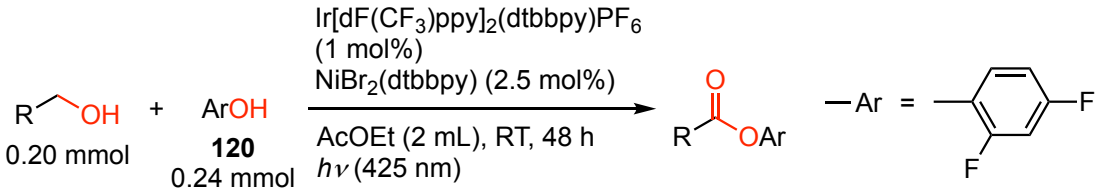
Scheme 4-4. Mechanistic Studies

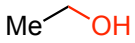
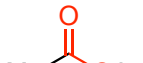
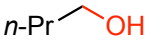
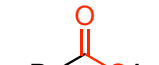
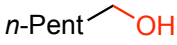
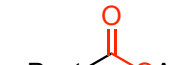
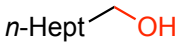
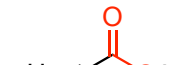
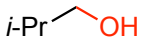
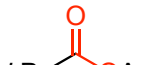
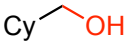
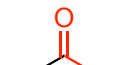


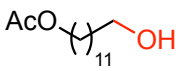
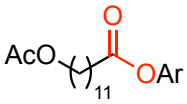
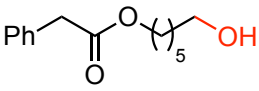
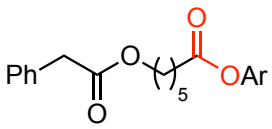
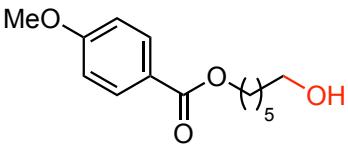
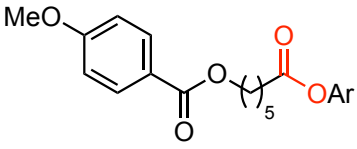
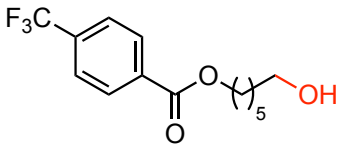
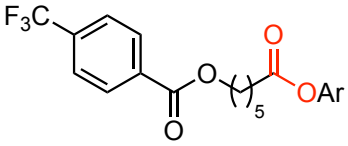
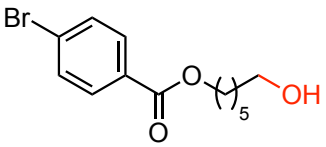
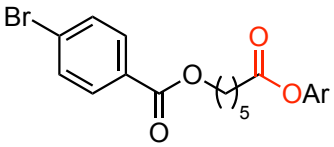
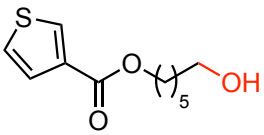
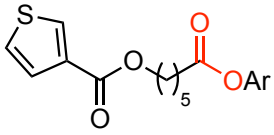
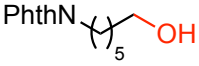
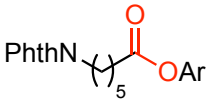
4.2.4 Scope of Primary Alcohols

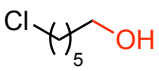
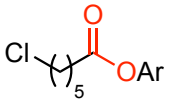
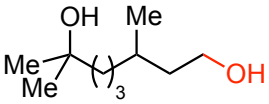
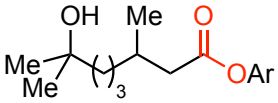
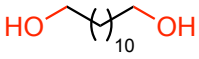
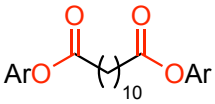
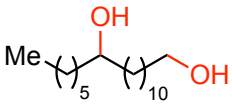
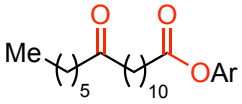
Standard reaction conditions for examination of the reaction scope with regard to primary alcohols were established by a slight modification of those shown in Table 4-2; a solution containing a primary alcohol (0.20 mmol), 2,4-difluorophenol (**120**, 0.24 mmol, 1.2 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.002 mmol, 1 mol%) and $NiBr_2(dtbbpy)$ (0.005 mmol, 2.5 mol%) in AcOEt (2 mL) was irradiated with blue LEDs (18 W, λ_{max} = 425 nm) at ambient temperature for 48 h. The resulting reaction mixture was purified by silica gel chromatography. Various esters were obtained from linear and branched alcohols (entries 1-6). It was possible to perform the reaction on a 4.0 mmol scale (entry 4). Neopentyl alcohol was unreactive, probably due to steric reasons. Primary alcohols having benzylic C–H bonds such as 3-phenyl-1-propanol failed to react with phenols, probably because those C–H bonds competed with alcoholic C–H bonds in hydrogen abstraction.[20] Primary alcohols having an ester moiety gave corresponding aryl esters with the ester moiety intact (entries 7-12). The tolerance of the ester functionality stands in contrast to the reported dehydrogenative esterification of alcohols, which can also trigger hydrogenation reaction of an ester moiety under the thermal condition.[21] Functionalities such as phthalimide, alkyl chloride and tertiary alcohol were all compatible with the reaction conditions, and the corresponding aryl esters were obtained in good yields (entries 13-15). 1,12-Dodecanediol **152** possessing two hydroxy groups in both ends of the alkyl chain gave the diaryl diester **153** in 77% yield (**120**: 2.4 equiv). 1,12-Octadecanediol **154**, which has both primary and secondary alcohols, gave ketoester **155**.

Table 4-2. Scope of Primary Alcohols



entry	primary alcohol	aryl ester
1	 **122**	 **126**, 64%
2	 **115**	 **127**, 75%
3	 **128**	 **129**, 78%
4	 **77**	 **121**, 78%, 61%[c]
5	 **130**	 **131**, 59%
6	 **132**	 **133**, 81%

7	 **134**	 **135**, 77%
8	 **136**	 **137**, 81%
9	 **138**	 **139**, 91%
10	 **140**	 **141**, 86%
11	 **142**	 **143**, 46%
12	 **144**	 **145**, 90%
13	 **146**	 **147**, 80%

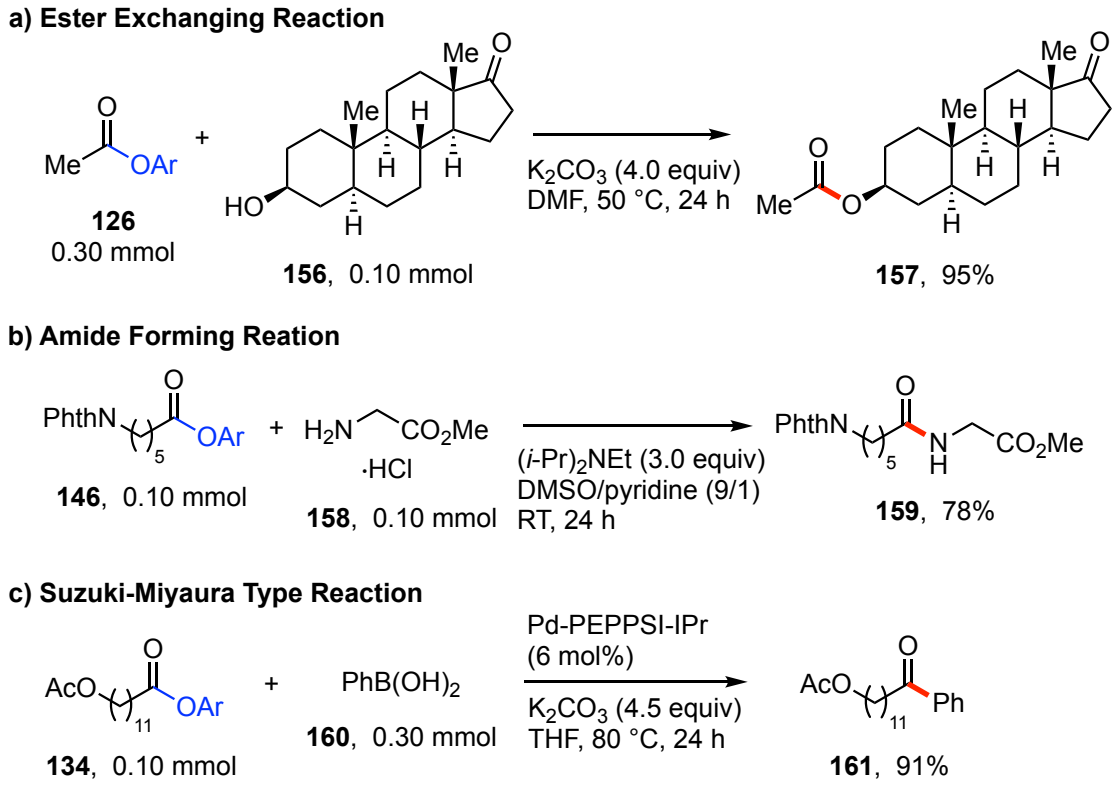
14	 **148**	 **149**, 76%
15	 **150**	 **151**, 87%
16	 **152**	 **153**, 77%[d]
17	 **154**	 **155**, 64%[e]

[a] Isolated yields. [b] Reaction conditions: primary alcohol (0.20 mmol, 1.0 equiv), 2,4-difluorophenol (**120**, 0.24 mmol, 1.2 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.002 mmol, 1 mol%), $NiBr_2(dtbbpy)$ (0.005 mmol, 2.5 mol%), AcOEt (2 mL), blue LEDs 18 W, λ_{max} = 425 nm), ambient temperature, 48 h. [c] **77** (4.0 mmol, 1.0 equiv), **120** (4.8 mmol, 1.2 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.02 mmol, 0.5 mol%), $NiBr_2(dtbbpy)$ (0.05 mmol, 1.25 mol%), AcOEt (20 mL), 96 h. [d] **152** (0.10 mmol, 1.0 equiv), **120** (0.24 mmol, 2.4 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.002 mmol, 2 mol%), $NiBr_2(dtbbpy)$ (0.005 mmol, 5 mol%). [e] **154** (0.10 mmol, 1.0 equiv), **120** (0.12 mmol, 1.2 equiv), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.002 mmol, 2 mol%), $NiBr_2(dtbbpy)$ (0.005 mmol, 5 mol%).

4.2.5 *Transformation of Aryl Ester Moiety*

An aryloxy group is a good leaving group, and aryl esters offer an access to a variety of carbonyl compounds, as exemplified in Scheme 4-5. Hydroxy and amino groups were readily acylated with aryl esters to afford the corresponding ester **157** and amides **159**,[22] respectively. The aryl ester successfully cross-coupled with phenylboronic acid **160**.[23]

Scheme 4-5. Transformation of Aryl Ester Moiety



4.3 Summary

In summary, a method to directly prepare aryl esters from aliphatic primary alcohols was developed. The reaction proceeds under ambient temperature and visible light irradiation, dispensing with any oxidant or hydrogen acceptor. The produced aryl esters provide versatile synthetic platforms for various carbonyl compounds.

4.4 Experimental Section

4.4.1 General Method and Materials

General Method

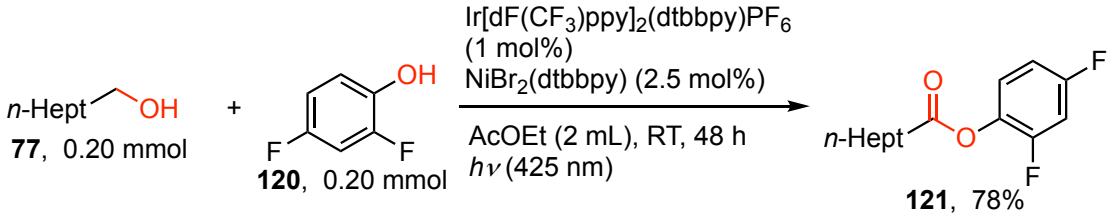
All reactions were carried out using a flame-dried glassware under a nitrogen atmosphere. Photoreactions were carried out with blue LED (HepatoChem, EvoluChem 425 PF, HCK1012-01-012, 18 W; the spectrum is shown below). ^{1}H,^{13}C, and ^{19}F NMR spectra were recorded on a JEOL JNM-ECZ400S/L1 (^{1}H at 400.44 MHz, ^{13}C at 100.69 MHz) spectrometer. $CDCl_3$ was used as a solvent. Chemical shifts were recorded in δ ppm referenced to a residual $CDCl_3$ (δ = 7.26 for ^{1}H, δ = 77.0 for ^{13}C). Gas chromatography of gas phase was measured on SHIMADZU GAS CHROMATOGRAPH GC-2014s. IR measurements were performed on FTIR SHIMADZU Affinity-1S spectrometer fitted with a Pike Technologies MIRacle Single Reflection ATR adapter. High-resolution mass spectra were recorded on JEOL JMS-SX102A (EI) with a magnetic sector mass spectrometer, Thermo Fisher Scientific Exactive Plus / Thermo Fisher Scientific UltiMate 3000 (ESI) with a Fourier-transform (orbitrap) mass spectrometer. Preparative thin-layer chromatography (PTLC) was performed on silica gel plates with PF254 indicator (Merck). Flash column chromatography was performed with silica gel 60N (Kanto).

Materials

$NiBr_2$(dtbbpy),[24] and Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6,[25] were prepared according to the method previously reported. Other chemicals were purchased from commercial suppliers and used as received.

4.4.2 A Typical Procedure for the Oxidation of Primary Alcohols with 2,4-Difluorophenol

Scheme 4-6. Typical Procedure of the Dehydrogenative Coupling of Primary Alcohols with **120**



To a 4 mL screw cap vial were added Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (2.2 mg, 0.002 mmol, 1 mol%), $NiBr_2$(dtbbpy) (2.4 mg, 0.005 mmol, 2.5 mol%), 1-octanol **77** (26.0 mg, 0.20 mmol, 1.0 equiv), 2,4-difluorophenol **120** (31.2 mg, 0.24 mmol, 1.2 equiv) and anhydrous ethyl acetate (2 mL) in a nitrogen-filled glove box. The reaction mixture was stirred and irradiated with blue LEDs (λ_{max} = 425 nm, 18 W, distance from the light source: 2 cm), with the vessel being cooled by a fan. After 48 hours, the screw cap was carefully opened and the reaction mixture was passed through a short pad of silica gel using ethyl acetate as an eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing ester **121** (91%. NMR yield). The mixture was subjected to preparative thin-layer chromatography (PTLC) (Hexane:AcOEt = 9:1, R_f = 0.5) to isolate ester **121** (40.1 mg, 0.156 mmol, 78%) as a colorless oil.

Caution: *The present reaction evolves gaseous hydrogen to increase the internal pressure of the vessel. The reaction must be performed using a pressure-resistant vessel or a pressure release valve*.

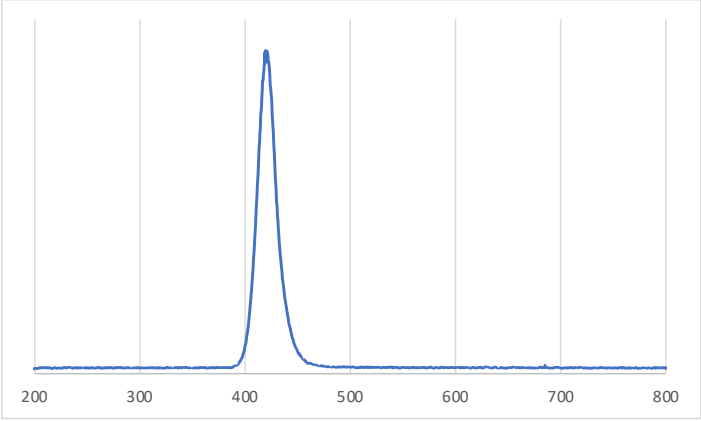
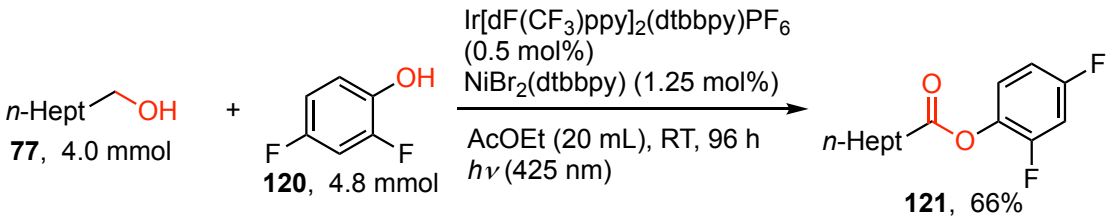


Chart 4-1. Spectrum of blue LED

4.2.3 Large-Scale Reaction

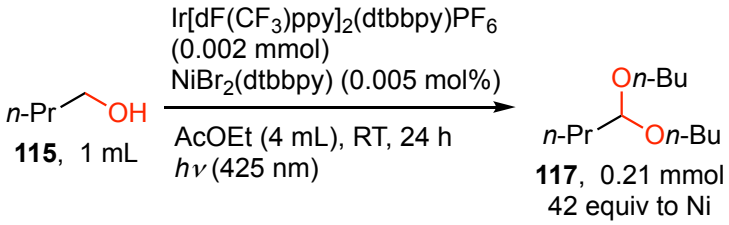
Scheme 4-7. Large-Scale Reaction



To a 20 mL Schlenk tube were added Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (22.4 mg, 0.02 mmol, 0.5 mol%), $NiBr_2$(dtbbpy) (24.3 mg, 0.05 mmol, 1.25 mol%), 1-octanol **77** (520.9 mg, 4.0 mmol, 1.0 equiv), 2,4-difluorophenol **120** (624.4 mg, 4.8 mmol, 1.2 equiv) and anhydrous ethyl acetate (20 mL) in a nitrogen-filled glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs (λ_{max} = 425 nm, 18 W, distance from the light source: 2 cm), with the vessel being cooled by a fan. The generated gaseous hydrogen was released in a fume hood through a bubbler tube. After 96 hours, the reaction mixture was concentrated under a reduced pressure and subjected to silica gel column chromatography (Hexane:DCM = 4:1) to isolate ester **121** (626.6 mg, 2.44 mmol, 61%) as a colorless oil.

4.2.4 *Dehydrogenation of 1-Butanol **115***

Scheme 4-8. Dehydrogenation of 1-Butanol **115**



To a 5 mL Schlenk tube were added Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.2 mg, 0.002 mmol), NiBr$_2$(dtbbpy) (2.4 mg, 0.005 mmol), 1-butanol (1 mL), and anhydrous ethyl acetate (4 mL) in a nitrogen-filled glove box. The tube was capped with rubber septa, which were fixed with a tape. The reaction mixture was stirred and irradiated with blue LEDs (λ_{max} = 425 nm, 18 W, distance from the light source: 2 cm), with the vessel being cooled by a fan. After 24 hours, the headspace of reaction vessel was analyzed by gas chromatography. The reaction mixture was passed through a short pad of silica gel using ethyl acetate as an eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing acetal **3** (0.21 mmol, 42 equiv to Ni, NMR yield).

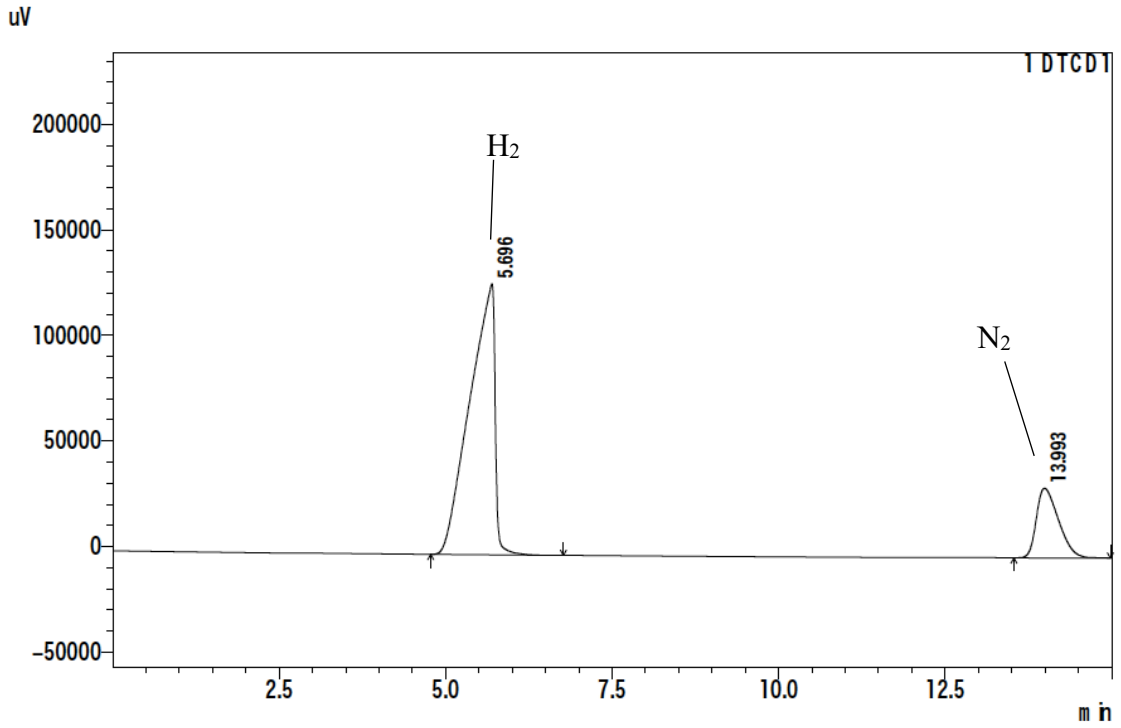
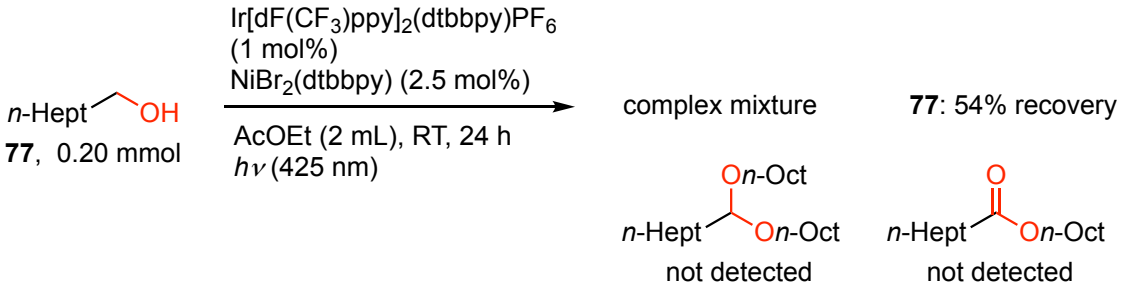


Chart 4-2. Chart of Gas Chromatography of Headspace of the Reaction Vessel After Irradiation

4.2.5 Dehydrogenation of 0.20 mmol of 1-Octanol 77

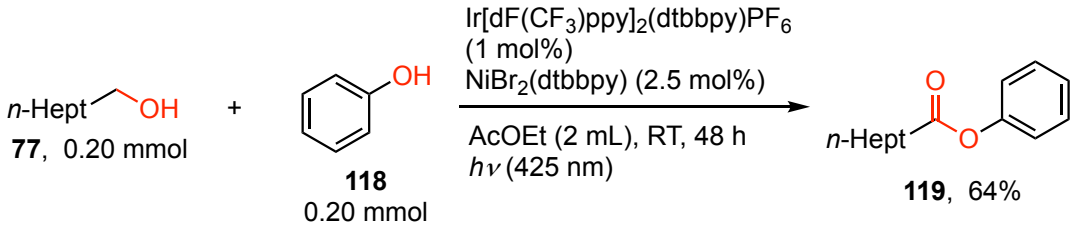
Scheme 4-9. Dehydrogenation of 0.20 mmol of 1-Butanol **77**



When 0.20 mmol of 1-octanol **77** was subjected to the dehydrogenation condition, neither acetal nor ester was formed and **77** decomposed. This result can be explained by assuming that the aldehyde intermediate decomposed through decarbonylation or aldol reaction.

4.2.6 Dehydrogenative Coupling of 1-Octanol with Phenol ***118***

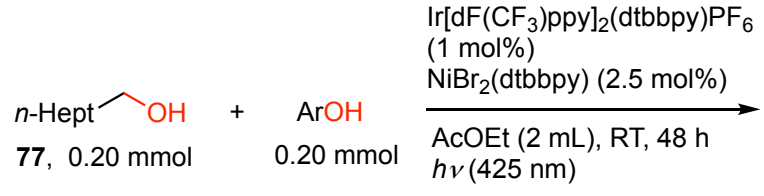
Scheme 4-10. Dehydrogenative Coupling of **77** with **118**

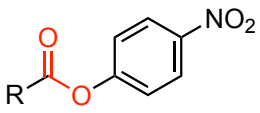


To a 4 mL screw cap vial were added Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (2.2 mg, 0.002 mmol, 1 mol%), NiBr$_2$(dtbbpy) (2.4 mg, 0.005 mmol, 2.5 mol%), 1-octanol **77** (26.0 mg, 0.20 mmol, 1.0 equiv), phenol **118** (18.8 mg, 0.20 mmol, 1.0 equiv), and anhydrous ethyl acetate (2 mL) in a nitrogen-filled glove box. The reaction mixture was stirred and irradiated with blue LEDs (λ_{max} = 425 nm, 18 W, distance from the light source: 2 cm), with the vessel being cooled by a fan. After 48 hours, the screw cap was carefully opened and the reaction mixture was passed through a short pad of silica gel using ethyl acetate as an eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing ester **119** (67%. NMR yield). The mixture was subjected to preparative thin-layer chromatography (PTLC) (Hexane:AcOEt = 9:1, R_f = 0.5) to isolate ester **119** (28.2 mg, 0.128 mmol, 64%) as a colorless oil.

4.4.7 Optimization Studies

Table 4-3. Screening of Phenols in the Dehydrogenative Coupling of 1-Octanol **77**





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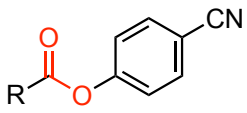

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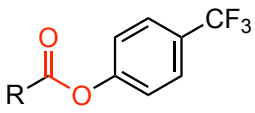
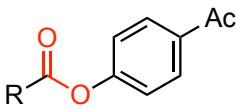
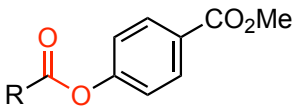


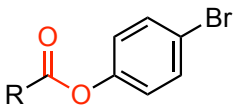
18%



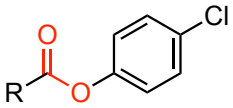
57%



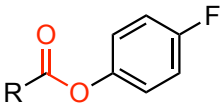
51%



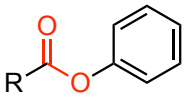
31%



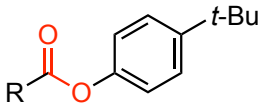
85%



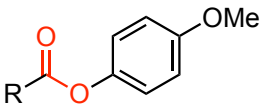
56%



67% (64%)

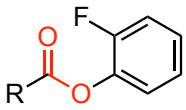


22%

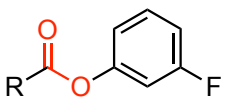


<5%

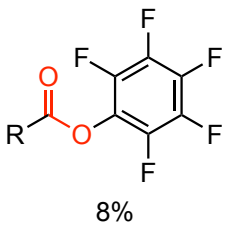
not detected



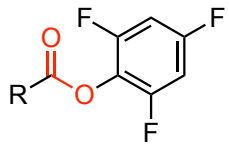
70%



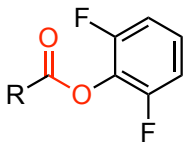
83%



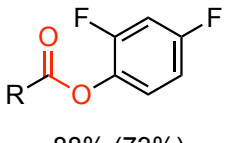
8%



50%



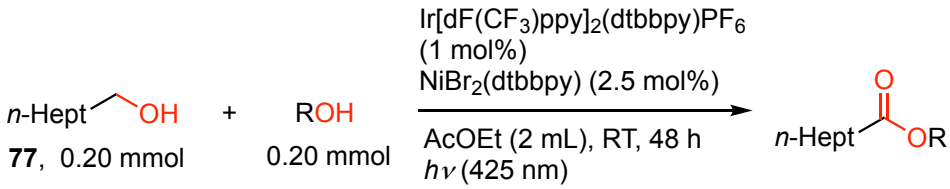
50%



88% (73%)

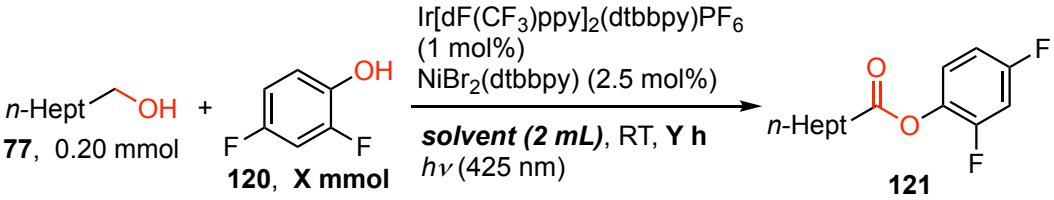
Isolated yields in parentheses.

Table 4-4. Screening of Other Alcohol Partners



entry	ROH	octanoate	NMR yield of **77**
1	H_2O	not detected	52%
2	MeOH	not detected	37%
3	CF_3CH_2OH	not detected	23%
4	CCl_3CH_2OH	not detected	<5%

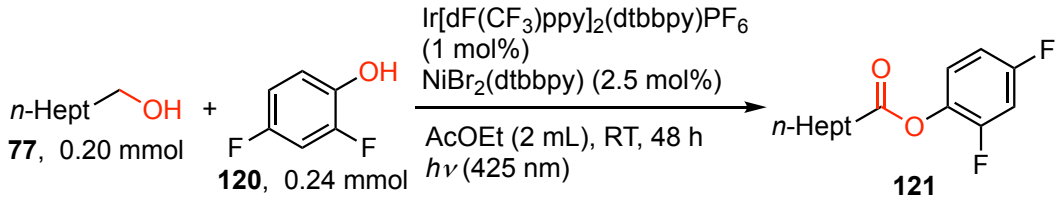
Table 4-5. Optimization for the Reaction of 1-Octanol **77** with 2,4-Difluorophenol **120**



entry	**120**	solvent	time	NMR yield of **121**	NMR yield of **77**
1	0.20 mmol	AcOEt	48 h	88%	11%
2	0.20 mmol	AcOEt	24 h	69%	27%
3	0.20 mmol	AcO*n*-Bu	48 h	63%	28%
4	0.20 mmol	acetone	48 h	5%	85%
5	0.20 mmol	*t*-BuOH	48 h	7%	99%
6	0.30 mmol	AcOEt	48 h	90%	6%
7	0.24 mmol	AcOEt	48 h	92% (78%)	7%

4.4.8 Control Experiments

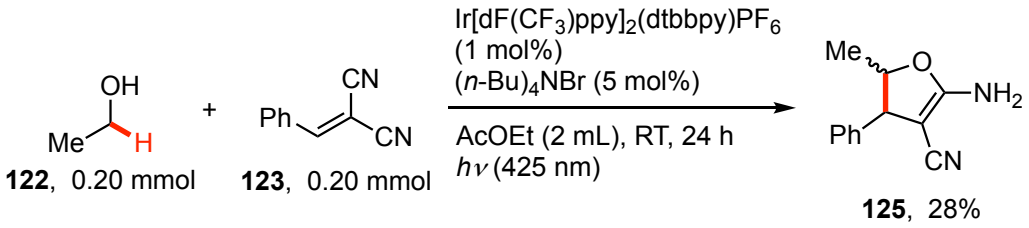
Table 4-6. Control Experiments



entry	deviation from standard condition	NMR yield of **121**	NMR yield of **77**
1	None	92%	7%
2	w/o Ir catalyst	0%	99%
3	w/o Ni catalyst	0%	69%
4	w/o light	0%	100%
5	(n-Bu)$_4$NBr (5 mol%) instead of NiBr$_2$(dtbbpy)	0%	100%
6	NiCl$_2$(dme) (2.5 mol%), dtbbpy (2.5 mol%) instead of NiBr$_2$(dtbbpy)	<5%	82%
7	NiCl$_2$(dme) (2.5 mol%), dtbbpy (2.5 mol%), (n-Bu)$_4$NBr (5 mol%) instead of NiBr$_2$(dtbbpy)	57%	49%

4.4.9 Radical Trapping Experiments

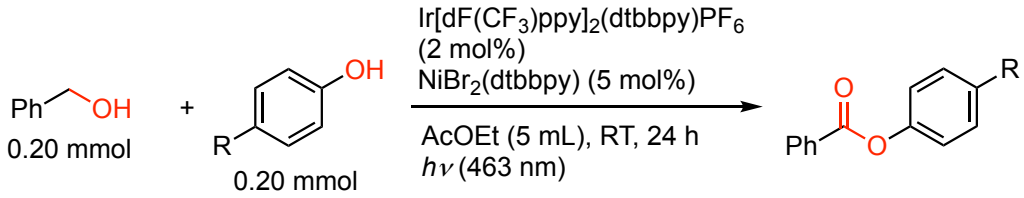
Scheme 4-11. A-Hydroxy Radical Trapping Experiment



To a 4 mL screw cap vial were added $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2.2 mg, 0.002 mmol, 1 mol%), $(n\text{-}Bu)_4NBr$ (3.2 mg, 0.01 mmol, 5 mol%), benzalmalononitrile (30.8 mg, 0.20 mmol, 1.0 equiv), ethanol (11.7 μL, 0.20 mmol, 1.0 equiv) and anhydrous ethyl acetate (2 mL) in a nitrogen-filled glove box. The reaction mixture was stirred and irradiated with blue LEDs, with the vessel being cooled by a fan. After 24 hours, the reaction mixture was concentrated under a reduced pressure. The mixture was subjected to PTLC (DCM, $R_f = 0.2$) to isolate the adduct **125** (11.4 mg, 0.057 mmol, 28%) as a pale yellow solid.

4.4.10 Optimization Studies in the Dehydrogenative Coupling of Benzyl Alcohol

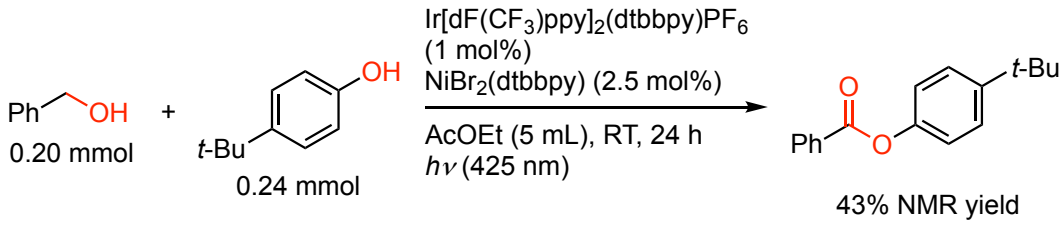
Table 4-7. Screening of Phenols in the Reaction of Benzyl Alcohol



entry	R	NMR yield		
		aryl benzoate	benzaldehyde	benzyl alcohol
1	OMe	0%	25%	59%
2	*t*-Bu	16%	31%	0%
3	F	0%	15%	0%
4	2,4-di-F	0%	10%	0%

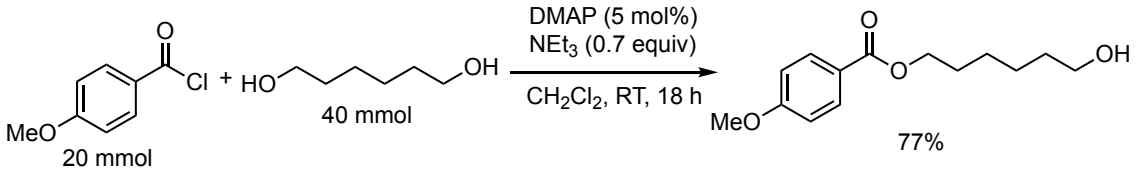
Light source: λ_{max} = 463 nm, 40W.

Scheme 4-12. Dehydrogenative Coupling of Benzyl Alcohol with 4-*tert*-Butylphenol



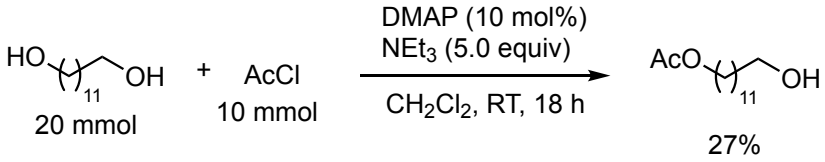
4.4.11 Preparation for Starting Materials

Scheme 4-13. Preparation of 6-Acyloxy-1-hexanol[26]



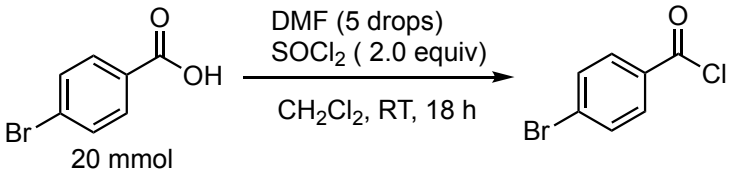
To a 100 mL two-necked flask were added 1,6-hexanediol (4.7 g, 40 mmol, 2 equiv) and *N*,*N*-dimethyl-4-aminopyridine (122 mg, 1 mmol, 5 mol%). The flask was capped with a rubber septum and purged with argon, to which dichloromethane (80 mL) and triethylamine (1.9 mL, 14 mmol, 0.7 equiv) were added. The resulting mixture was stirred at ambient temperature. Then, 4-methoxybenzoyl chloride (1.7 g, 10 mmol, 1 equiv) was added dropwise, and the mixture was kept stirred. After 18 hours, the reaction mixture was concentrated under a reduced pressure. The residue was subjected to silica gel column chromatography (Hexane:AcOEt = 7:3) to isolate 6-(4-methoxybenzoyloxy)-1-hexanol **138** (3.9 g, 15.3 mmol, 77%) as a colorless oil.

Scheme 4-14. Preparation of 12-Acetoxy-1-dodecanol **134**



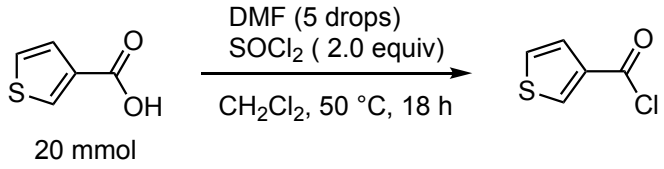
To a 300 mL three-necked flask were added 1,12-dodecanediol (4.05 g, 20 mmol, 2.0 equiv) and *N*,*N*-dimethyl-4-aminopyridine (122 mg, 1.0 mmol, 1 mol%). The flask was capped with a rubber septum and purged with argon, to which dichloromethane (200 mL) and triethylamine (6.9 mL, 50 mmol, 5.0 equiv) were added. The resulting mixture was stirred at ambient temperature. Then, acetyl chloride (0.71 mL, 10 mmol, 1.0 equiv) was added dropwise, and the mixture was kept stirred. After 18 hours, the reaction mixture was concentrated under a reduced pressure. The residue was subjected to silica gel column chromatography (Hexane:AcOEt = 7:3) to isolate 12-acetoxy-1-dodecanol **134** (657.9 mg, 2.69 mmol, 27%) as a white solid.

Scheme 4-15. Preparation of 4-Bromobenzoyl Chloride



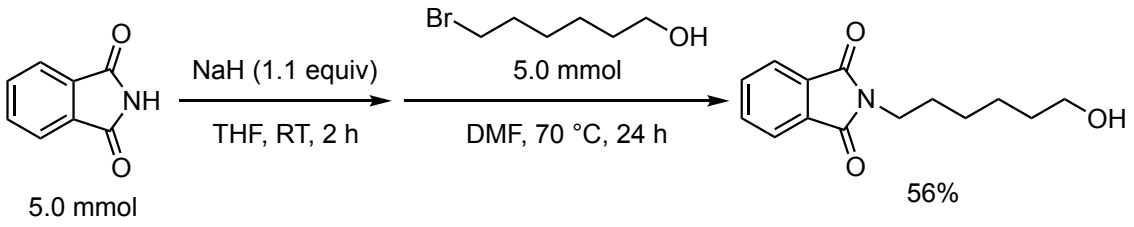
To a 50 mL two-necked flask was added 4-bromobenzoic acid (4.0 g, 20 mmol, 1 equiv). The flask was capped with a rubber septum and purged with argon, to which dichloromathane (20 mL) was added. The resulting solution was stirred at ambient temperature. Thionyl chloride (2.9 mL, 40 mmol, 2 equiv) and *N*,*N*-dimethylformamide (5 drops) were added sequentially to the solution, and then the mixture was kept stirred. After 18 hours, the reaction mixture was concentrated under a reduced pressure. The resulting 4-bromobenzoyl chloride was used in the next step without further purification.

Scheme 4-16. Preparation of 3-Thiophenecarbonyl Chloride



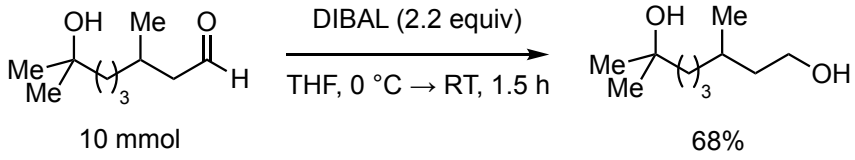
To a 50 mL two-necked flask connected with a condenser was added 3-thiophenecarboxylic acid (2.6 g, 20 mmol, 1 equiv). The flask was capped with a rubber septum and purged with argon, to which dichloromathane (20 mL), thionyl chloride (2.9 mL, 40 mmol, 2 equiv), and *N*,*N*-dimethylformamide (5 drops) were added. The reaction mixture was stirred and heated at 50 °C in an oil bath. After 18 hours, the reaction mixture was concentrated under a reduced pressure. The resulting 3-thiophenecarbonyl chloride was used in the next step without further purification.

Scheme 4-17. Preparation of 6-Phthalimidyl-1-hexanol **146**



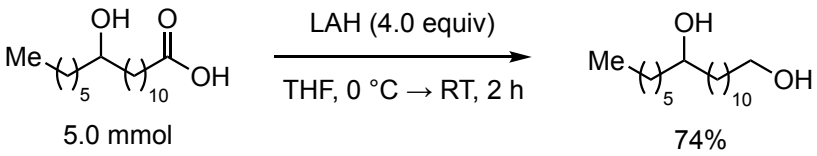
To a 50 mL two-necked flask was added phthalimide (0.74 g, 5 mmol, 1 equiv). The flask was capped with a rubber septum and purged with argon, to which tetrahydrofuran (10 mL) and sodium hydride (60% oil dispersion, 220 mg, 5.5 mmol, 1.1 equiv) was added. The reaction mixture was stirred at ambient temperature for 2 hours and concentrated under a reduced pressure. The flask was purged with argon, and *N*,*N*-dimethylformamide (10 mL) and 6-bromo-1-hexanol (0.68 mL, 5 mmol, 1 equiv) were added therein. The reaction mixture was stirred at 70 ℃ in an oil bath. After 24 hours, the reaction mixture was concentrated under a reduced pressure. The mixture was subjected to silica gel column chromatography (Hexane:AcOEt = 1:1) to isolate 6-phthalimidyl-1-hexanol **146** (0.69 g, 2.8 mmol, 56%) as a colorless oil.

Scheme 4-18. Preparation of 3,7-Dimethyl-1,7-octanediol **150**



To a 50 mL two-necked flask was added hydroxycitronellal (1.7 g, 10 mmol, 1 equiv). The flask was capped with a rubber septum and purged with argon, to which tetrahydrofuran (20 mL) was added. The resulting solution was stirred and cooled at 0 ℃. Diisobutylaluminium hydride (1 M in hexane, 22 mL, 22 mmol, 2.2 equiv) was added dropwise at that temperature, and then the reaction mixture was kept stirred at ambient temperature. After 1.5 hours, methanol and ice-cold water were slowly added to quench the reaction. The mixture was extracted with diethyl ether (20 mL × 3) and the organic phase was washed with water (40 mL × 2) and brine (40 mL). The organic phase was dried over Na_2SO_4. Solids were removed by filtration and the filtrate was concentrated under a reduced pressure to obtain 3,7-dimethyl-1,7-octanediol **150** (1.2 g, 6.8 mmol, 68%) as a colorless oil.

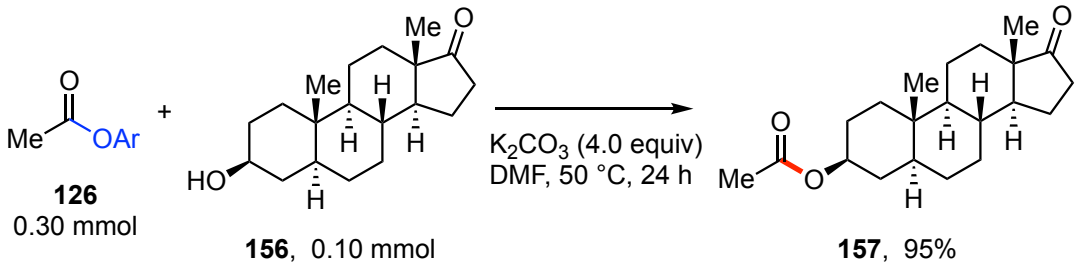
Scheme 4-19. Preparation of 1,12-Octadecanediol **154**



To a 50 mL two-necked flask was added 12-hydroxystearic acid (1.5 g, 5 mmol, 1 equiv). The flask was capped with a rubber septum and purged with argon, to which tetrahydrofuran (20 mL) was added. The resulting solution was stirred and cooled at 0 ℃. A solution of lithium aluminum hydride in Et_2O (1 M, 20 mmol, 2 equiv) was added dropwise at that temperature, and then the reaction mixture was kept stirred at ambient temperature for 2 hours. The reaction was quenched by additing ethyl acetate, methanol and ice-cold water sequentially. After being stirred overnight, the white precipitates were removed by filtration through a celite pad. The filtrate was extracted with diethyl ether (20 mL × 3) and the combined organic phase was washed with water (40 mL × 2) and brine (40 mL), and dried over Na_2SO_4. Solids were removed by filtration. The filtrate was concentrated under a reduced pressure to afford 1,12-octadecanediol **154** (1.1 g, 3.7 mmol, 74%) as a white solid.

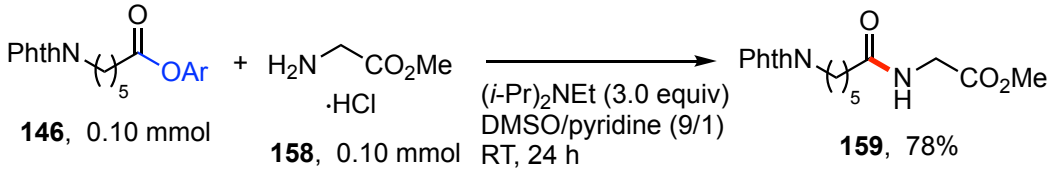
4.4.12 Transformations of the Aryl Ester Moiety

Scheme 4-20. *O*-Acylation of Epiandrosterone **156** with Aryl Ester **122**



To a 4 mL screw cap vial were added **122** (51.6 mg, 0.30 mmol, 3.0 equiv), epiandrosterone (29.0 mg, 0.20 mmol, 1.0 equiv), potassium carbonate (55.3 mg, 0.40 mmol, 4.0 equiv) and *N*,*N*-dimethylformamide (0.5 mL). The reaction mixture was stirred and heated at 50 °C using a thermo mighty stirrer equipped with a heating block. After 24 hours, water (10 mL) was added, and organic products were extracted with ethyl acetate (10 mL × 3). The combined organic phase was washed with water (10 mL × 2) and brine (10 mL), and dried over Na_2SO_4. Solids were removed by filtration and the filtrate was concentrated under a reduced pressure. The mixture was subjected to preparative thin-layer chromatography (Hexane:AcOEt = 9:1, R_f = 0.2) to isolate *O*-acetyl epiandsterone **157** (31.7 mg, 0.095 mmol, 95%) as a white solid.

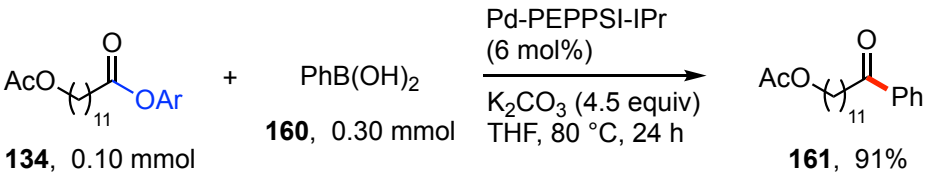
Scheme 4-21. *N*-Acylation of Glycine Methyl Ester **158** with Aryl Ester **146**



To a 4 mL screw cap vial were added **146** (37.3 mg, 0.10 mmol, 1.0 equiv), glycine methyl ester hydrochloride (12.6 mg, 0.10 mmol, 1.0 equiv), dimethylsulfoxide (0.9 mL), pyridine (0.1 mL), and *N*,*N*-diisopropylethylamine (51.0 µL, 0.30 mmol, 3.0 equiv). The reaction mixture was stirred at ambient temperature. After 24 hours, water (10 mL) was added, and organic products were extracted with ethyl acetate (10 mL × 3). The combined organic layer washed with water (10 mL × 2) and brine (10 mL), and dried over Na_2SO_4. Solids were removed by filtration and the filtrate was concentrated under a reduced pressure. The mixture was subjected to preparative thin-layer chromatography

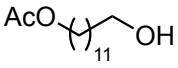
(Hexane:AcOEt = 3:7, R_f = 0.3) to isolate the amide **159** (25.9 mg, 0.78 mmol, 78%) as a white solid.

Scheme 4-22. Suzuki-Miyaura Coupling of Phenyl Boronic Acid **160** with Aryl Ester **134**



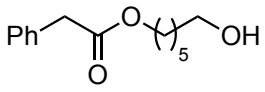
To a 4 mL screw cap vial were added **134** (37.0 mg, 0.10 mmol, 1.0 equiv), phenylboronic acid (36.6 mg, 0.60 mmol, 3.0 equiv), potassium carbonate (62.2 mg, 0.45 mmol, 4.5 equiv), Pd PEPPSI (IPr) (4.1 mg, 0.006 mmol, 6 mol%), and tetrahydrofuran (0.4 mL). The reaction mixture was stirred at 80 ℃ for 24 hours using a thermo mighty stirrer equipped with a heating block. The resulting mixture was subjected to a short pad of silica gel to remove the palladium catalyst and base. The filtrate was concentrated under a reduced pressure. The residue was subjected to preparative thin-layer chromatography (Hexane:AcOEt = 4:1, R_f = 0.4) to isolate the ketone **161** (28.9 mg, 0.91 mmol, 91%) as a white solid.

4.4.13 Spectroscopic Data of the Products



134

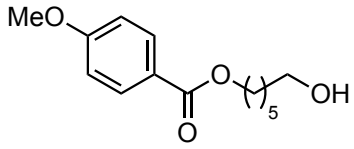
^{1}H NMR: δ = 4.05 (t, *J* = 6.8 Hz, 2H), 3.63 (t, *J* = 6.6 Hz, 2H), 2.04 (s, 3H), 1.68-1.50 (m, 4H), 1.41-1.20 (m, 17H); ^{13}C NMR: δ =171.2, 64.4, 63.1, 32.8, 29.6, 29.51(2H), 29.47, 29.4, 29.2, 28.6, 25.9, 25.7, 21.0; IR (neat): 3281, 2913, 2851, 1740, 1476, 1234, 1040, 718 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{14}H_{28}O_3Na$ 267.1931; Found 267.1931.



136

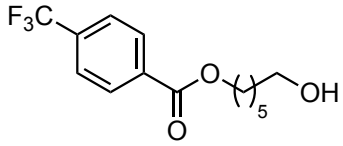
The reaction was conducted by General Procedure B in 5 mmol scale. The crude mixture was purified by silica gel column chromatography (Hexane:AcOEt = 7:3) to give **136** (0.74 g, 3.1 mmol, 62%) as a colorless oil.

^{1}H NMR: δ = 7.37-7.23 (m, 5H), 3.65-3.57 (m, 4H), 1.90 (brs, 1H), 1.69-1.47 (m, 4H), 1.41-1.24 (m, 4H); ^{13}C NMR: δ = 171.7, 134.2, 129.2, 128.5, 127.0, 64.8, 62.7, 41.5, 32.5, 28.5, 25.6, 25.3; IR (neat): 3377, 2934, 2860, 1730, 1454, 1252, 1057, 1030, 991, 696 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^{+}$ Calcd for $C_{14}H_{20}O_3Na$ 259.1305; Found 259.1304.



138

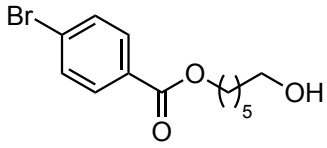
^{1}H NMR: δ = 7.98 (d, *J* = 8.4 Hz, 2H), 6.90 (d, *J* = 8.4 Hz, 2H), 4.27 (t, *J* = 6.7 Hz, 2H), 3.84 (s, 3H), 3.63 (t, *J* = 6.6 Hz, 2H), 1.97 (brs, 1H), 1.75 (quint, *J* = 6.8 Hz, 2H), 1.58 (quint, *J* = 6.6 Hz, 2H), 1.52-1.35 (m, 4H); ^{13}C NMR: δ = 166.4, 163.2, 131.5, 122.8, 113.5, 64.6, 62.7, 55.4, 32.6, 28.7, 25.8, 25.4; IR (neat): 3408, 2934, 2859, 1707, 1605, 1510, 1252, 1165, 1026, 847, 770 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^{+}$ Calcd for $C_{14}H_{20}O_4Na$ 275.1254; Found 275.1254.



140

The reaction was conducted by General Procedure B. The crude mixture was purified by silica gel column chromatography (Hexane:AcOEt = 7:3) to give **140** (1.5 g, 5.6 mmol, 28%) as a colorless oil.

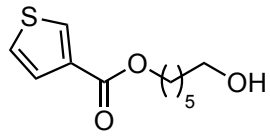
^{1}H NMR: δ = 8.14 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 4.35 (t, *J* = 6.7 Hz, 2H), 3.66 (t, *J* = 6.5 Hz, 2H), 1.80 (quint, *J* = 6.9 Hz, 2H), 1.72 (brs, 1H), 1.60 (quint, *J* = 6.7 Hz, 2H), 1.53-1.40 (m, 4H); ^{13}C NMR: δ = 165.4, 134.4 (q, *J* = 32.4 Hz), 133.7, 129.9, 125.4 (q, *J* = 3.5 Hz), 123.6 (q, *J* = 272.6 Hz), 65.5, 62.7, 32.6, 28.6, 25.8, 25.4; ^{19}F NMR: δ = −63.0; IR (neat): 3348, 2936, 2862, 1721, 1323, 1273, 1125, 1099, 1065, 1016, 862, 775, 704 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^{+}$ Calcd for $C_{14}H_{17}F_3O_3Na$ 313.1022; Found 313.1022.



142

The reaction was conducted by General Procedure B. The crude mixture was purified by silica gel column chromatography (Hexane:AcOEt = 7:3) to give **142** (2.8 g, 9.5 mmol, 47%) as a colorless oil.

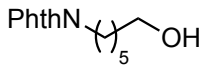
^{1}H NMR: δ = 7.89 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 4.31 (t, *J* = 6.6 Hz, 2H), 3.65 (t, *J* = 6.5 Hz, 2H), 1.77 (quint, *J* = 6.9 Hz, 2H), 1.59 (quint, *J* = 6.7 Hz, 2H), 1.52-1.35 (m, 5H); ^{13}C NMR: δ = 165.9, 131.7, 131.0, 129.3, 127.9, 65.2, 62.7, 32.6, 28.6, 25.8, 25.4; IR (neat): 3412, 2934, 2859, 1701, 1395, 1368, 1053, 718 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^{+}$ Calcd for $C_{13}H_{17}BrO_3Na$ 323.0253; Found 323.0256.



144

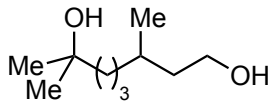
The reaction was conducted by General Procedure B. The crude mixture was purified by silica gel column chromatography (Hexane:AcOEt = 7:3) to give **144** (2.48 g, 10.9 mmol, 54%) as a colorless oil.

^{1}H NMR: δ = 8.10-8.07 (m, 1H), 7.53-7.49 (m, 1H), 7.31-7.27 (m, 1H), 4.27 (t, *J* = 6.7 Hz, 2H), 3.64 (t, *J* = 6.5 Hz, 2H), 1.84-1.68 (m, 3H), 1.58 (quint, *J* = 6.7 Hz, 2H), 1.51-1.35 (m, 4H); ^{13}C NMR: δ = 162.9, 133.9, 132.5, 127.8, 125.9, 64.6, 62.7, 32.5, 28.7, 25.8, 25.4; IR (neat): 3389, 2934, 2859, 1709, 1412, 1254, 1188, 1101, 746 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{11}H_{16}O_3SNa$ 251.0712; Found 251.0712.



146

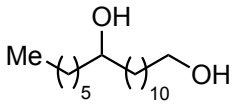
^{1}H NMR: δ = 7.86-7.80 (m, 2H), 7.73-7.67 (m, 2H), 3.68 (t, *J* = 7.2 Hz, 2H), 3.62 (t, *J* = 6.5 Hz, 2H), 1.69 (quint, *J* = 7.3 Hz, 2H), 1.62-1.29 (m, 7H); ^{13}C NMR: δ = 168.5, 133.8, 132.1, 123.1, 62.7, 37.8, 32.5, 28.5, 26.5, 25.2; IR (neat): 3412, 2934, 2859, 1701, 1395, 1053, 718 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{14}H_{17}NO_3Na$ 270.1101; Found 270.1101.



150

Identified by comparison with reported data.[27]

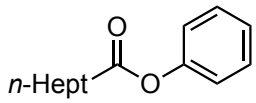
^{1}H NMR: δ = 3.74-3.58 (m, 2H), 1.74-1.05 (m, 17H), 0.89 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR: δ = 71.0, 61.0, 44.0, 39.8, 37.5, 29.4, 29.3, 29.1, 21.6, 19.6.



154

Identified by comparison with reported data.[28]

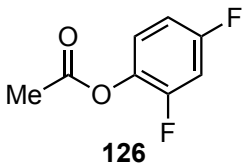
^{1}H NMR: δ = 3.66-3.53 (m, 3H), 1.63-1.17 (m, 32H), 0.88 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR: δ = 72.0, 63.1, 37.50, 37.48, 32.8, 31.8, 29.7, 29.6, 29.5 (3C), 29.39, 29.37, 25.7, 25.63, 25.61, 22.6, 14.1.



6

Identified by comparison with reported data.[29]

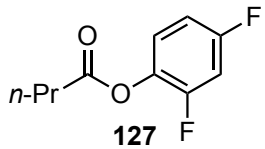
^{1}H NMR: δ = 7.38 (t, *J* = 8.0 Hz, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 2H), 2.56 (t, *J* = 7.5 Hz, 2H), 1.76 (quint, *J* = 7.5 Hz, 2H), 1.48-1.24 (m, 8H), 0.91 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 172.3, 150.8, 129.4, 125.7, 121.6, 34.4, 31.6, 29.1, 28.9, 25.0, 22.6, 14.0.



126

Purified by PTLC (Hexane:Et_2O = 9:1, R_f = 0.4) to give **126** (22.2 mg, 0.129 mmol, 64%) as a colorless oil.

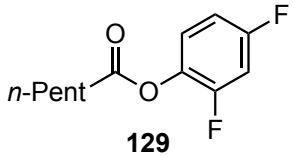
^{1}H NMR: δ = 7.09 (dt, *J* = 8.7, 5.5 Hz, 1H), 6.96-6.83 (m, 2H), 2.33 (s, 3H); ^{13}C NMR: δ = 168.3, 160.1 (dd, *J* = 247.1, 10.1 Hz), 154.0 (dd, *J* = 251.9, 12.0 Hz), 134.4 (dd, *J* = 13.0, 4.3 Hz), 124.2 (dd, *J* = 9.6, 1.9 Hz), 111.2 (dd, *J* = 23.1, 3.9 Hz), 160.1 (dd, *J* = 27.0, 22.2 Hz), 20.4; ^{19}F NMR: δ = −112.6 (tt, *J* = 8.1, 5.6 Hz), −123.5 (dddd, *J* = 10.0, 8.4, 5.7, 1.6 Hz); IR (neat): 2924, 2851, 1769, 1504, 1173, 1140, 964, 895, 849 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_8H_6F_2O_2$ 172.0330; Found 172.0330.



127

Purified by PTLC (Hexane:Et_2O = 9:1, R_f = 0.6) to give **127** (30.1 mg, 0.150 mmol, 75%) as a colorless oil.

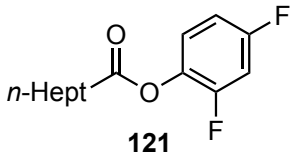
^{1}H NMR: δ = 7.08 (dt, *J* = 8.7, 5.5 Hz 1H), 6.95-6.83 (m, 2H), 2.57 (t, *J* = 7.4 Hz, 2H), 1.79 (sext, *J* = 7.4 Hz, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR: δ = 171.1, 160.1 (dd, *J* = 247.6, 10.6 Hz), 154.1 (dd, *J* = 251.4, 12.5 Hz), 134.5 (dd, *J* = 13.0, 4.3 Hz), 124.2 (dd, *J* = 9.6, 1.9 Hz), 111.2 (dd, *J* = 23.1, 3.9 Hz), 105.1 (dd, *J* = 27.0, 22.2 Hz), 35.6, 18.4, 13.5; ^{19}F NMR: δ = −112.8 (tt, *J* = 8.0, 5.4 Hz), −123.4 (dddd, *J* = 10.0, 8.3, 5.6, 1.5 Hz); IR (neat): 2970, 2880, 1769, 1506, 1175, 1138, 1092, 964, 849 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{10}H_{10}F_2O_2$ 200.0643; Found 200.0646.



129

Purified by PTLC (Hexane:AcOEt = 9:1, R_f = 0.5) to give **129** (35.7 mg, 0.156 mmol, 78%) as a colorless oil.

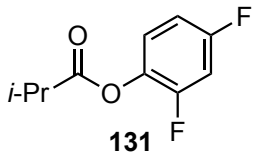
^{1}H NMR: δ = 7.08 (dt, *J* = 8.3, 5.5 Hz 1H), 6.95-6.83 (m, 2H), 2.54 (t, *J* = 7.5 Hz, 2H), 1.77 (quint, *J* = 7.4 Hz, 2H), 1.45-1.31 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ = 171.2, 160.1 (dd, *J* = 246.6, 10.6 Hz), 154.1 (dd, *J* = 251.4, 12.5 Hz), 134.5 (dd, *J* = 13.5, 3.9 Hz), 124.2 (dd, *J* = 10.6, 1.9 Hz), 111.1 (dd, *J* = 23.1, 3.9 Hz), 105.0 (dd, *J* = 26.5, 22.6 Hz), 33.8, 31.1, 24.5, 22.3, 13.9; ^{19}F NMR: δ = −112.8 (tt, *J* = 8.1, 5.6 Hz), −123.5 (dddd, *J* = 10.0, 8.4, 5.6, 1.5 Hz); IR (neat): 2934, 2874, 1769, 1506, 1188, 1140, 1094, 964, 849 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{12}H_{14}F_2O_2$ 228.0956; Found 228.0960.



121

Purified by PTLC (Hexane:AcOEt = 9:1, R_f = 0.5) to give **121** (40.1 mg, 0.156 mmol, 78%) as a colorless oil.

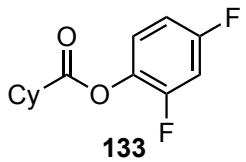
^{1}H NMR: δ = 7.08 (dt, *J* = 8.7, 5.5 Hz 1H), 6.95-6.82 (m, 2H), 2.59 (t, *J* = 7.5 Hz, 2H), 1.76 (quint, *J* = 7.5 Hz, 2H), 1.47-1.24 (m, 8H), 0.90 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR: δ = 171.2, 160.1 (dd, *J* = 246.6, 10.6 Hz), 154.1 (dd, *J* = 251.4, 12.5 Hz), 134.5 (dd, *J* = 12.5, 3.9 Hz), 124.2 (dd, *J* = 9.6, 1.9 Hz), 111.1 (dd, *J* = 23.1, 3.9 Hz), 105.0 (dd, *J* = 26.5, 22.6 Hz), 33.8, 31.6, 28.93, 28.86, 24.9, 22.6, 14.0; ^{19}F NMR: δ = −112.9 (dd, *J* = 8.1, 5.6 Hz), −123.5 (dddd, *J* = 10.0, 8.4, 5.6, 1.5 Hz); IR (neat): 2928, 2859, 1769, 1506, 1186, 1140, 1094, 964, 849 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{14}H_{18}F_2O_2$ 256.1269; Found 256.1270.



131

Purified by PTLC (Hexane:Et_2O = 9:1, R_f = 0.6) to give **131** (23.8 mg, 0.119 mmol, 59%) as a pale yellow oil.

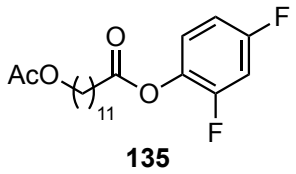
^{1}H NMR: δ = 7.08 (dt, *J* = 8.7, 5.5 Hz 1H), 6.95-6.83 (m, 2H), 2.85 (sept, *J* = 7.0 Hz, 1H), 1.33 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR: δ = 174.6, 160.0 (dd, *J* = 246.6, 10.6 Hz), 154.1 (dd, *J* = 251.4, 12.5 Hz), 134.6 (dd, *J* = 13.5, 3.9 Hz), 124.2 (dd, *J* = 9.6, 1.9 Hz), 111.1 (dd, *J* = 23.1, 3.9 Hz), 105.0 (dd, *J* = 27.0, 23.1 Hz), 33.9, 18.9; ^{19}F NMR: δ = −112.9 (tt, *J* = 8.1, 5.6 Hz), −123.8 (dddd, *J* = 10.0, 8.5, 5.6, 1.6 Hz); IR (neat): 2980, 2940, 1765, 1506, 1142, 1086, 964, 858 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{10}H_{10}F_2O_2$ 200.0643; Found 200.0645.



133

Purified by PTLC (Hexane:AcOEt = 9:1, R_f = 0.5) to give **133** (39.1 mg, 0.163 mmol, 81%) as a colorless oil.

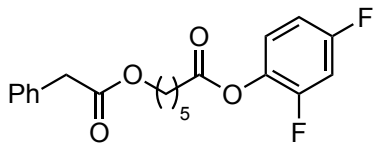
^{1}H NMR: δ = 7.07 (dt, *J* = 8.7, 5.6 Hz 1H), 6.94-6.82 (m, 2H), 2.61 (tt, *J* = 11.1, 3.7 Hz 1H), 2.12-2.00 (m, 2H), 1.88-1.74 (m, 2H), 1.73-1.51 (m, 3H), 1.44-1.21 (m, 3H); ^{13}C NMR: δ = 173.5, 160.0 (dd, *J* = 246.6, 10.6 Hz), 154.1 (dd, *J* = 252.4, 12.5 Hz), 134.6 (dd, *J* = 13.5, 3.9 Hz), 124.2 (dd, *J* = 9.6, 1.9 Hz), 111.1 (dd, *J* = 23.1, 3.9 Hz), 105.0 (dd, *J* = 26.5, 22.6 Hz), 42.8, 28.9, 25.6, 25.2; ^{19}F NMR: δ = −113.0 (tt, *J* = 8.1, 5.6 Hz), −123.7 (dddd, *J* = 10.0, 8.5, 5.6, 1.6 Hz); IR (neat): 2934, 2857, 1763, 1506, 1140, 1111, 1096, 964, 851 cm^{-1}; HRMS (EI) *m/z*: [M + Na]$^+$ Calcd for $C_{13}H_{14}F_2O_2Na$ 240.0956; Found 240.0959.



135

Purified by PTLC (Hexane:AcOEt = 9:1, R_f = 0.3) to give **135** (57.1 mg, 0.154 mmol, 77%) as a colorless oil.

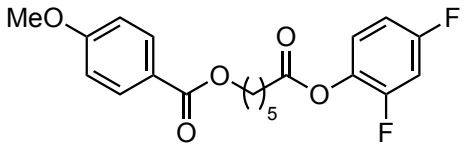
^{1}H NMR: δ = 7.08 (dt, *J* = 8.7, 5.5 Hz, 1H), 6.96-6.82 (m, 2H), 4.05 (t, *J* = 6.8 Hz, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.04 (s, 3H), 1.75 (quint, *J* = 7.4 Hz, 2H), 1.61 (quint, *J* = 7.0 Hz, 2H), 1.48-1.22 (m, 14H); ^{13}C NMR: δ = 171.2 (2C), 160.1 (dd, *J* = 247.6, 10.6 Hz), 154.1 (dd, *J* = 251.4, 12.5 Hz), 134.5 (dd, *J* = 12.5, 3.9 Hz), 124.2 (dd, *J* = 10.6, 1.9 Hz), 111.2 (dd, *J* = 23.1, 3.9 Hz), 105.0 (dd, *J* = 26.5, 22.6 Hz), 64.6, 33.8, 29.44 (2C), 29.36, 29.21, 29.16, 29.0, 28.6, 25.9, 24.8, 21.0; ^{19}F NMR: δ = −112.8 (tt, *J* = 8.1, 5.6 Hz), −123.4 (dddd, *J* = 10.0, 8.5, 5.6, 1.6 Hz); IR (neat): 2926, 2855, 1771, 1736, 15506, 1236, 1186, 1140, 1096, 964, 849 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^+$ Calcd for $C_{20}H_{28}F_2O_4Na$ 393.1848; Found 393.1856.



137

Purified by PTLC (Hexane:AcOEt = 9:1, R_f = 0.3) to give **137** (58.4 mg, 0.161 mmol, 81%) as a colorless oil.

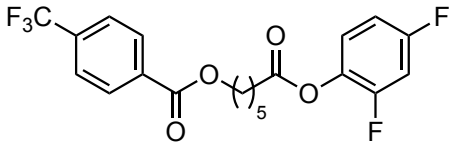
^{1}H NMR: δ = 7.39-7.21 (m, 5H), 7.08 (dt, *J* = 8.8, 5.5 Hz, 1H), 6.97-6.82 (m, 2H), 4.12 (t, *J* = 6.6 Hz, 2H), 3.62 (s, 2H), 2.57 (t, *J* = 7.4 Hz, 2H), 1.81-1.62 (m, 4H), 1.44 (quint, *J* = 7.7 Hz, 2H); ^{13}C NMR: δ = 171.6, 170.9, 160.1 (dd, *J* = 247.1, 10.1 Hz), 154.0 (dd, *J* = 251.4, 12.5 Hz), 134.4 (dd, *J* = 12.5, 3.9 Hz), 134.1, 129.2, 128.5, 127.0, 124.2 (dd, *J* = 10.6, 1.9 Hz), 111.2 (dd, *J* = 23.1, 3.9 Hz), 105.1 (dd, *J* = 27.0, 23.1 Hz), 64.5, 41.4, 33.6, 28.2, 25.3, 24.4; ^{19}F NMR: δ = −112.6 (tt, *J* = 8.1, 5.6 Hz), −123.5 (dddd, *J* = 10.2, 8.5, 5.7, 1.6 Hz); IR (neat): 2949, 2868, 1767, 1732, 1506, 1246, 1184, 1140, 964, 847, 725, 696 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{20}F_2O_4Na$ 385.1222; Found 385.1222.



139

Purified by PTLC (Hexane:AcOEt = 4:1, R_f = 0.3) to give **139** (68.7 mg, 0.82 mmol, 91%) as a colorless oil.

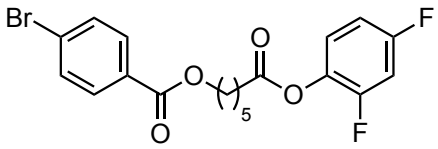
^{1}H NMR: δ = 7.99 (d, *J* = 9.0 Hz, 2H), 7.06 (tt, *J* = 8.7, 5.5 Hz, 1H), 6.96-6.80 (m, 4H), 4.32 (t, *J* = 6.5 Hz, 2H), 3.85 (s, 3H), 2.63 (t, *J* = 7.4 Hz, 2H), 1.89-1.78 (m, 4H), 1.58 (quint, *J* = 7.7 Hz, 2H); ^{13}C NMR: δ = 170.9, 166.4, 163.3, 160.1 (dd, *J* = 247.6, 10.6 Hz), 154.0 (dd, *J* = 252.4, 12.5 Hz), 134.4 (dd, *J* = 12.5, 3.9 Hz), 131.5, 124.2 (dd, *J* = 9.6, 1.9 Hz), 122.8, 113.6, 111.2 (dd, *J* = 23.1, 3.9 Hz), 105.0 (dd, *J* = 27.0, 22.2 Hz), 64.3, 55.4, 33.6, 28.4, 25.5, 24.5; ^{19}F NMR: δ = −112.7 (tt, *J* = 8.1, 5.6 Hz), −123.4 (dddd, *J* = 10.2, 8.5, 5.7, 1.6 Hz); IR (neat): 2941, 2868, 1767, 1707, 1605, 1506, 1252, 1167, 1096, 847, 770 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{20}F_2O_5Na$ 401.1171; Found 401.1171.



141

Purified by PTLC (Hexane:AcOEt = 9:1, R_f = 0.3) to give **141** (71.2 mg, 0.171 mmol, 86%) as a colorless oil.

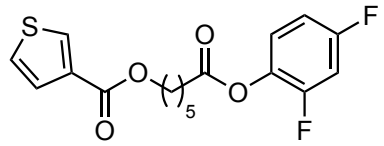
^{1}H NMR: δ = 8.15 (d, *J* = 8.1 Hz, 2H), 7.70 (d, *J* = 8.2 Hz, 2H), 7.06 (dt, *J* = 8.7, 5.5 Hz, 1H), 6.94-6.82 (m, 2H), 4.39 (t, *J* = 6.5 Hz, 2H), 2.64 (t, *J* = 7.4 Hz, 2H), 1.91-1.80 (m, 4H), 1.64-1.54 (m, 2H); ^{13}C NMR: δ = 170.9, 165.4, 160.1 (dd, *J* = 247.6, 10.6 Hz), 154.0 (dd, *J* = 251.4, 12.5 Hz), 134.40 (q, *J* = 32.4 Hz), 134.39 (dd, *J* = 13.5, 3.9 Hz), 133.5, 130.0, 125.4 (q, *J* = 3.5 Hz), 124.2 (dd, *J* = 10.6, 1.9 Hz), 123.6 (q, *J* = 272.9 Hz) 111.2 (dd, *J* = 23.1, 3.9 Hz), 105.1 (dd, *J* = 27.0, 22.2 Hz), 66.2, 33.6, 28.3, 25.5, 24.5; ^{19}F NMR: δ = −63.0, −112.5 (tt, *J* = 8.1, 5.7 Hz), −123.4 (dddd, *J* = 10.0, 8.3, 5.7, 1.5 Hz); IR (neat): 2945, 2868, 1769, 1721, 1506, 1325, 1275, 1123, 1098, 1065, 1016, 775, 704 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{17}F_5O_4Na$ 439.0939; Found 439.0950.



143

Purified by PTLC (DCM, R_f = 0.8) to give **143** (40.0 mg, 0.094 mmol, 47%) as a colorless oil.

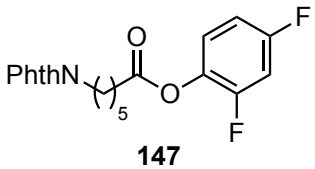
^{1}H NMR: δ = 7.90 (d, *J* = 8.8 Hz, 2H), 7.57 (d, *J* = 8.8 Hz, 2H), 7.06 (dt, *J* = 8.7, 5.5 Hz, 1H), 6.95-6.82 (m, 2H), 4.35 (t, *J* = 6.5 Hz, 2H), 2.63 (t, *J* = 7.4 Hz, 2H), 1.90-1.79 (m, 4H), 1.63-1.53 (m, 2H); ^{13}C NMR: δ = 170.9, 165.9, 160.1 (dd, *J* = 247.1, 10.1 Hz), 154.0 (dd, *J* = 251.9, 13.0 Hz), 134.4 (dd, *J* = 13.0, 4.3 Hz), 131.7, 131.1, 129.3, 128.0, 124.2 (dd, *J* = 10.6, 1.9 Hz), 111.2 (dd, *J* = 22.2, 3.9 Hz), 105.1 (dd, *J* = 26.5, 22.6 Hz), 64.9, 33.6, 28.3, 25.5, 24.5; ^{19}F NMR: δ = −112.6 (tt, *J* = 8.1, 5.6 Hz), −123.4 (dddd, *J* = 10.2, 8.5, 5.7, 1.6 Hz); IR (neat): 2953, 2868, 1767, 1717, 1506, 1269, 1098, 1011, 847, 756 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{19}H_{17}F_2O_4BrNa$ 449.0170; Found 449.0180.



145

Purified by PTLC (Hexane:AcOEt = 9:1, R_f = 0.3) to give **145** (63.9 mg, 0.180 mmol, 90%) as a colorless oil.

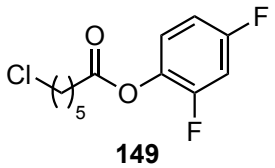
^{1}H NMR: δ = 8.10 (dd, *J* = 3.1, 1.2 Hz, 1H), 7.53 (dd, *J* = 5.1, 1.2 Hz, 1H), 7.30 (dd, *J* = 5.1, 3.1 Hz, 1H), 7.07 (dt, *J* = 8.7, 5.5 Hz, 1H), 6.94-6.82 (m, 2H), 4.31 (t, *J* = 6.5 Hz, 2H), 2.63 (t, *J* = 7.4 Hz, 2H), 1.90-1.76 (m, 4H), 1.57 (quint, *J* = 7.6 Hz, 2H); ^{13}C NMR: δ = 170.9, 162.8, 160.1 (dd, *J* = 247.6, 10.6 Hz), 154.0 (dd, *J* = 251.4, 12.5 Hz), 134.4 (dd, *J* = 12.5, 3.9 Hz), 133.8, 132.6, 127.9, 125.9, 124.2 (dd, *J* = 10.6, 1.9 Hz), 111.2 (dd, *J* = 23.1, 3.9 Hz), 105.1 (dd, *J* = 27.0, 22.2 Hz), 64.4, 33.6, 28.4, 25.5, 24.5; ^{19}F NMR: δ = −112.6 (tt, *J* = 8.1, 5.6 Hz), −123.4 (dddd, *J* = 10.0, 8.4, 5.7, 1.5 Hz); IR (neat): 2959, 2868, 1767, 1709, 1506, 1258, 1184, 1096, 964, 748 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{17}H_{16}F_2O_4SNa$ 377.0630; Found 377.0638.



147

Purified by PTLC (Hexane:AcOEt = 4:1, R_f = 0.2) to give **147** (59.4 mg, 0.159 mmol, 80%) as a colorless oil.

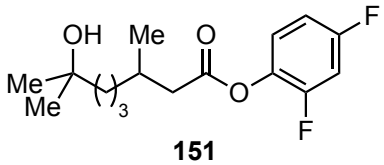
^{1}H NMR: δ = 7.87-7.80 (m, 2H), 7.74-7.67 (m, 2H), 7.06 (dt, *J* = 8.8, 5.5 Hz, 1H), 6.92-6.81 (m, 2H), 3.71 (t, *J* = 7.2 Hz, 2H), 2.59 (t, *J* = 7.4 Hz, 2H), 1.86-1.70 (m, 4H), 1.53-1.42 (m, 2H); ^{13}C NMR: δ = 170.9, 168.4, 160.0 (dd, *J* = 247.6, 10.6 Hz), 154.0 (dd, *J* = 251.4, 12.5 Hz), 134.4 (dd, *J* = 12.5, 3.9 Hz), 133.9, 132.1, 124.2 (dd, *J* = 9.6, 1.9 Hz), 123.2, 111.1 (dd, *J* = 23.1, 3.9 Hz), 105.1 (dd, *J* = 26.5, 22.6 Hz), 37.7, 33.5, 28.2, 26.1, 24.3; ^{19}F NMR: δ = −112.7 (tt, *J* = 8.3, 5.6 Hz), −123.8 (dddd, *J* = 9.9, 8.4, 5.7, 1.4 Hz); IR (neat): 2941, 2866, 1769, 1705, 1506, 1395, 1186, 1140, 1098, 718 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{20}H_{17}F_2NO_4Na$ 396.1018; Found 396.1026.



149

Purified by PTLC (Hexane:AcOEt = 9:1, R_f = 0.5) to give **149** (39.8 mg, 0.152 mmol, 76%) as a colorless oil.

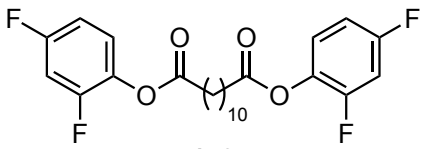
^{1}H NMR: δ = 7.08 (dt, *J* = 8.7, 5.5 Hz 1H), 6.96-6.83 (m, 2H), 3.56 (t, *J* = 6.6 Hz, 2H), 2.62 (t, *J* = 7.4 Hz, 2H), 1.89-1.74 (m, 4H), 1.63-1.53 (m, 2H); ^{13}C NMR: δ = 170.9, 160.1 (dd, *J* = 247.1, 10.1 Hz), 154.0 (dd, *J* = 251.4, 12.5 Hz), 134.4 (dd, *J* = 12.5, 3.9 Hz), 124.2 (dd, *J* = 9.6, 1.9 Hz), 111.2 (dd, *J* = 22.6, 3.4 Hz), 105.1 (dd, *J* = 27.0, 23.1 Hz), 44.7, 33.5, 32.1, 26.2, 24.1; ^{19}F NMR: δ = −112.6 (tt, *J* = 8.0, 5.4 Hz), −123.5 (dddd, *J* = 10.0, 8.5, 5.7, 1.6 Hz); IR (neat): 2943, 2868, 1767, 1506, 1184, 1140, 1113, 1098, 964, 851 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{12}H_{13}F_2O_2Cl$ 262.0567; Found 262.0571.



151

Purified by PTLC (Hexane:AcOEt = 3:1, R_f = 0.3) to give **151** (52.2 mg, 0.173 mmol, 87%) as a colorless oil.

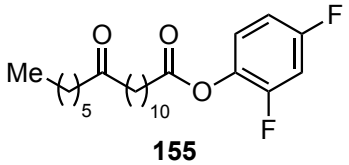
^{1}H NMR: δ = 7.07 (dt, *J* = 8.7, 5.6 Hz 1H), 6.95-6.82 (m, 2H), 2.59 (dd, *J* = 14.9, 6.1 Hz, 1H), 2.40 (dd, *J* = 14.9, 8.0 Hz, 1H), 2.18-2.02 (m, 1H), 1.52-1.18 (m, 13H), 1.05 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR: δ = 170.6, 160.1 (dd, *J* = 246.6, 10.6 Hz), 154.1 (dd, *J* = 251.4, 12.5 Hz), 134.4 (dd, *J* = 12.5, 3.9 Hz), 124.2 (dd, *J* = 10.6, 1.9 Hz), 111.2 (dd, *J* = 22.2, 3.9 Hz), 105.1 (dd, *J* = 27.0, 22.2 Hz), 70.9, 43.9, 41.2, 37.0, 30.5, 29.3, 29.2, 21.6, 19.6; ^{19}F NMR: δ = −112.7 (tt, *J* = 8.0, 5.4 Hz), −123.2 (dddd, *J* = 10.2, 8.5, 5.7, 1.6 Hz); IR (neat): 3393, 2967, 2938, 1765, 1506, 1246, 1140, 1096, 849 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{16}H_{22}F_2O_3Na$ 323.1429; Found 323.1435.



153

Purified by PTLC (Hexane:AcOEt = 17:3, R_f = 0.4) to give **153** (35.0 mg, 0.077 mmol, 77%) as a white solid.

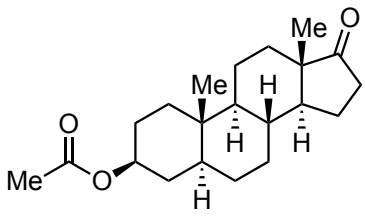
^{1}H NMR: δ = 7.08 (dt, *J* = 8.7, 5.5 Hz 2H), 6.96-6.83 (m, 4H), 2.59 (t, *J* = 7.5 Hz, 4H), 1.76 (quint, *J* = 7.5 Hz, 4H), 1.47-1.26 (m, 12H); ^{13}C NMR: δ = 171.2, 160.1 (dd, *J* = 246.7, 10.6 Hz), 154.1 (dd, *J* = 252.4, 12.5 Hz), 134.5 (dd, *J* = 13.0, 4.3 Hz), 124.2 (dd, *J* = 10.6, 1.9 Hz), 111.2 (dd, *J* = 23.1, 3.9 Hz), 105.1 (dd, *J* = 26.5, 22.6 Hz), 33.8, 29.3, 29.2, 29.0, 24.9; ^{19}F NMR: δ = −112.8 (dt, *J* = 8.0, 5.4 Hz), −123.4 (dddd, *J* = 10.0, 8.5, 5.6, 1.5 Hz); IR (neat): 2914, 2853, 1761, 1504, 1173, 1123, 1098, 964, 907, 847 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{26}F_4O_4Na$ 477.1659; Found 477.1667; Melting point: 55-57 °C.



155

Purified by PTLC (Hexane:AcOEt = 9:1, R_f = 0.3) to give **155** (26.3 mg, 0.064 mmol, 64%) as a white solid.

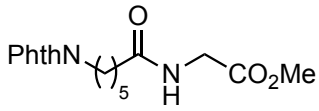
^{1}H NMR: δ = 7.08 (dt, *J* = 8.7, 5.5 Hz 1H), 6.96-6.82 (m, 2H), 2.58 (t, *J* = 7.5 Hz, 2H), 2.41-2.35 (m, 4H), 1.75 (quint, *J* = 7.5 Hz, 2H), 1.61-1.50 (m, 4H), 1.47-1.19 (m, 18H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR: δ = 211.7, 171.2, 160.1 (dd, *J* = 247.6, 10.6 Hz), 154.1 (dd, *J* = 252.4, 12.5 Hz), 134.5 (dd, *J* = 13.0, 4.3 Hz), 124.2 (dd, *J* = 10.6, 1.9 Hz), 111.2 (dd, *J* = 23.1, 3.9 Hz), 105.0 (dd, *J* = 27.0, 23.1 Hz), 42.82, 42.79, 33.8, 31.6, 29.3 (3C), 29.24, 29.15, 28.9 (2C), 24.8, 23.9 (2C), 22.5, 14.0; ^{19}F NMR: δ = −112.8 (tt, *J* = 8.1, 5.6 Hz), −123.4 (dddd, *J* = 10.0, 8.5, 5.6, 1.5 Hz); IR (neat): 2914, 2847, 1773, 1761, 1699, 1512, 1248, 1192, 1136, 1101, 966, 860 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{24}H_{36}F_2O_3Na$ 433.2525; Found 433.2531; Melting point: 47-49 °C.



157

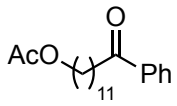
Identified by comparison with reported data.[30]

^{1}H NMR: δ = 4.74-4.62 (m, 1H), 2.42 (dd, *J* = 8.9, 19.2 Hz, 1H), 2.12-1.86 (m, 5H), 1.85-1.69 (m, 4H), 1.69-1.42 (m, 5H), 1.42-1.13 (m, 7H), 1.09-0.90 (m, 2H), 0.90-0.77 (m, 6H), 0.76-0.64 (m, 1H); ^{13}C NMR: δ = 222.1, 170.6, 73.5, 54.3, 51.4, 47.7, 44.6, 36.7, 35.8, 35.6, 35.0, 33.9, 31.5, 30.8, 28.2, 27.4, 21.7, 21.4, 20.4, 13.8, 12.2.



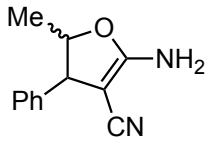
159

^{1}H NMR: δ = 7.85-7.79 (m, 2H), 7.72-7.67 (m, 2H), 6.01 (brs, 1H), 4.03 (d, *J* = 5.2 Hz, 2H), 3.73 (s, 3H), 3.67 (t, *J* = 7.2 Hz, 2H), 2.24 (t, *J* = 7.5 Hz, 2H), 1.76-1.64 (m, 4H), 1.39 (quint, *J* = 7.7 Hz, 2H); ^{13}C NMR: δ = 172.8, 170.5, 168.4, 133.8, 132.1, 123.1, 52.3, 41.1, 37.7, 36.0, 28.2, 26.3, 24.9; IR (neat): 3291, 2932, 2860, 1748, 1715, 1647, 1547, 1396, 1369, 1198, 1179, 1049, 723, 712 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^{+}$ Calcd for $C_{17}H_{20}N_2O_5Na$ 355.1264; Found 355.1265; Melting point: 115-117 °C.



161

^{1}H NMR: δ = 7.96 (d, *J* = 8.3 Hz, 2H), 7.55 (t, *J* = 7.4 Hz, 1H), 7.46 (t, *J* = 7.5 Hz, 2H), 4.05 (t, *J* = 6.8 Hz, 2H), 2.96 (t, *J* = 7.4 Hz, 2H), 2.04 (s, 3H), 1.73 (quint, *J* = 7.4 Hz, 2H), 1.61 (quint, *J* = 7.0 Hz, 2H), 1.44-1.22 (m, 14H); ^{13}C NMR: δ = 200.6, 171.2, 137.1, 132.8, 128.5, 128.0, 64.6, 38.6, 29.44 (4C), 29.36, 29.2, 28.6, 25.9, 24.4, 21.0; IR (neat): 2913, 2851, 1728, 1680, 1366, 1256, 1209, 1040, 966, 714, 691 cm^{-1}; HRMS (ESI) *m/z*: [M + Na]$^{+}$ Calcd for $C_{20}H_{30}O_3Na$ 341.2087; Found 341.2088; Melting point: 36-38 °C.



125

^{1}H NMR: (major diastereomer) δ = 7.39-7.10 (m, 5H), 5.72 (brs, 2H), 4.52 (quint, *J* = 6.4 Hz, 1H), 3.91 (d, *J* = 6.8 Hz, 1H), 1.47 (d, *J* = 6.2 Hz, 3H); (minor diastereomer) δ = 7.39-7.10 (m, 5H), 6.03 (quint, *J* = 7.1 Hz, 1H), 5.72 (brs, 2H), 4.25 (d, *J* = 8.8 Hz, 1H), 0.93 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR: (major diastereomer) δ = 167.0, 141.1, 128.9, 128.5, 127.3, 118.8, 88.6, 55.4, 20.3; (minor diastereomer) δ = 167.8, 137.9, 128.9, 128.6, 127.6, 118.9, 83.9, 51.2, 16.8.; IR (neat): 3424, 3343, 3281, 2980, 2928, 2172, 1678, 1647, 1591, 1439, 1038, 704 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{12}H_{12}N_2O$ 200.0944; Found 200.0948.

4.5 References and Notes

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[10] The acylation of phenolic O-H bonds with aldehydes is described in Chapter 3.

[11] According to the mechanism shown in Scheme 4-3, there are three steps in which a bromine radical abstracts hydrogen; from a phenol, a primary alcohol, and an aldehyde. The rates of these three steps of hydrogen abstraction should be balanced in order to gain good yields of the coupled ester. In the cases of phenols having less electron-withdrawing substituents, the BDEs of the phenolic O–H bonds become smaller, and accordingly, hydrogen abstraction becomes faster, suppressing that from a primary alcohol and an aldehyde. In the case of phenols having more electron-withdrawing substituents, the BDEs become larger, and accordingly, hydrogen abstraction from an aldehyde becomes faster than that of a phenolic O–H bond leading to decomposition of the aldehyde. For the effect of substituents on BDEs of phenols, see. F. B. Bordwell, J. Cheng, *J. Am. Chem. Soc.* **1991**, *113*, 1736-1743.

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[20] Although benzyl alcohol failed to react with 2,4-difluorophenol, its reaction with 4-*tert*-butylphenol afforded the corresponding ester in 43% yield.

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Chapter 5

Photoinduced Carbamoylation of C(sp^3)–H Bonds with Isocyanates

Table of Contents

Abstract: Alkylbenzenes coupled with isocyanates at the benzylic position upon irradiation with visible light in the presence of an iridium photoredox catalyst, a bromide anion, and a nickel catalyst, producing *N*-substituted α-aryl amides. An analogous carbamoylation reaction of aliphatic C–H bonds of alkanes took place when UV light and a diaryl ketone were used instead of visible light and the iridium complex. The present reaction offers a straightforward and atom-economical method for the synthesis of carboxamides starting from hydrocarbons with one-carbon extension.

5.1 Introduction

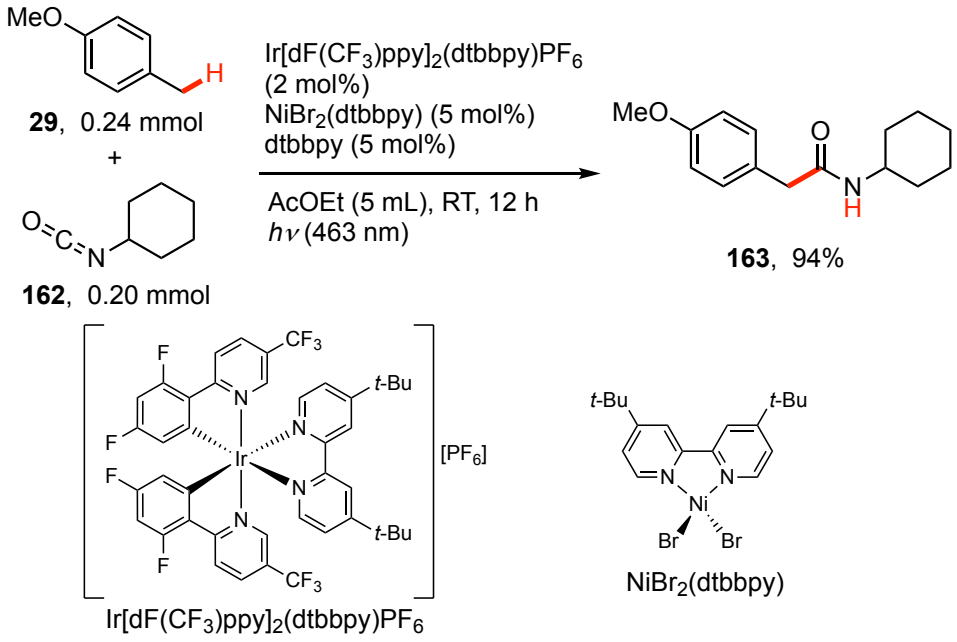
Direct C–C bond-forming reactions of readily available simple hydrocarbons would dramatically streamline synthetic pathways by dispensing with steps for prefunctionalization such as halogenation, metallation, and associated protection/deprotection. Especially valuable are those incorporating a carbonyl group, since carbonyl compounds are of great biological relevance and also one of the most important class of organic compounds from viewpoints of organic synthesis. Non-polar C–H bonds are inert in general and such direct transformations, with C–C bond formation in particular, are difficult to achieve in the absence of directing groups. Nonetheless, there have appeared a few reports for carbamoylation (aminocarbonylation) reactions of C(sp^3)–H bonds of simple hydrocarbons.[1] For example, alkylarenes are carbamoylated at the benzylic position with 10 atm of carbon monoxide and amines under oxidative reaction conditions using palladium as the catalyst.[1a] It is also possible to carbamoylate an α-C(sp^3)–H bond of ethers with perfluorophenyl isocyanate using photoexcited benzophenone,[1b] Direct carbamoylation of an *N*-methyl group of anilines was also reported.[1c] Herein reported is a new method using light, a photocatalyst, and a nickel complex, which directly carbamoylates benzylic and even aliphatic C–H bonds of simple hydrocarbons.

5.2 Results and Discussion

*5.2.1 Carbamoylation of Alkylbenzene **29***

In Chapter 2 is reported the photoinduced intermolecular dehydrogenative coupling reaction of alkylbenzenes with aldehydes.[2] The reaction was assumed to involve a generation of a benzylnickel intermediate via cleavage of the benzylic C–H bond. Since there are a few reports for coupling of an organonickel species with isocyanates,[3] a reaction of alkylbenzenes with isocyanates was examined. A solution containing 4-methoxytoluene (**29**, 0.24 mmol, 1.2 equiv), cyclohexyl isocyanate (**162**, 0.20 mmol, 1.0 equiv), Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$ (0.004 mmol, 2 mol%), NiBr$_2$(dtbbpy) (0.010 mmol, 5 mol%), and dtbbpy (0.010 mmol, 5 mol%) in AcOEt (5 mL) was irradiated with blue LEDs (40 W, λ_{max} = 463 nm) at ambient temperature for 12 hours. Removal of the volatiles under reduced pressure and subsequent purification of the residue by chromatography on silica gel afforded analytically pure amide **163** in 94% yield.

Scheme 5-1. Carbamoylation of Alkylbenzene **29**

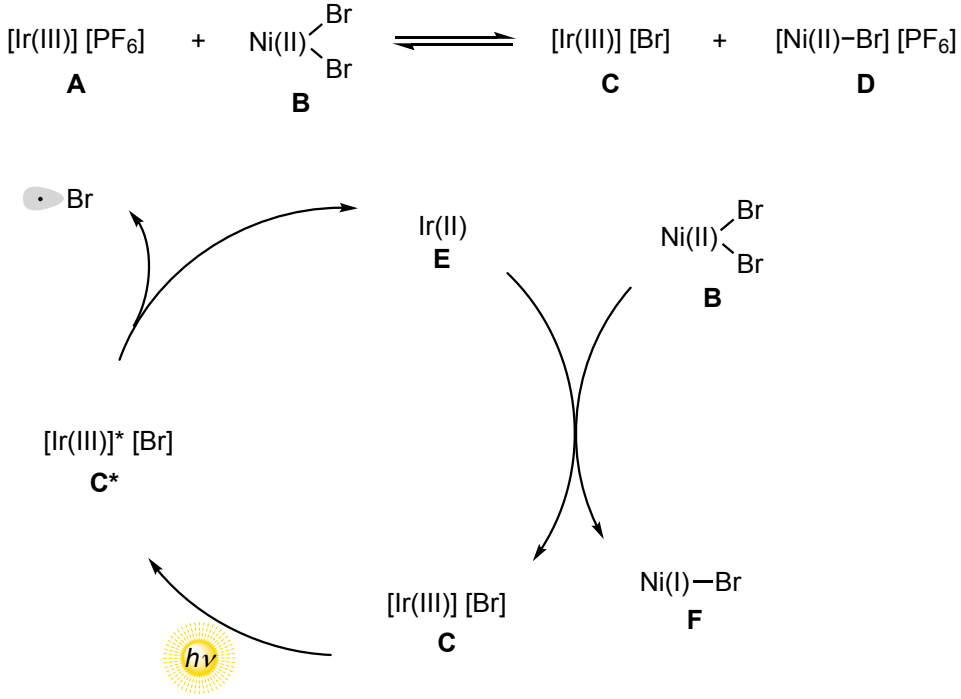


5.2.2 Proposed Mechanism

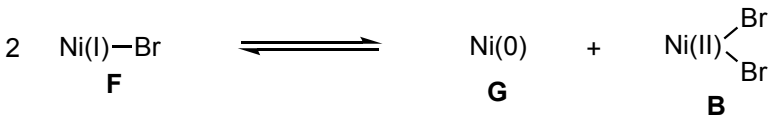
Shown in Scheme 5-2 is a schematic depiction of a mechanism we are assuming. It consists of two stages. Stage 1; Anion exchange between [Ir(III)]PF_6 and Ni(II)Br_2 generates [Ir(III)]Br together with [Ni(II)Br]PF_6. Excitation of [Ir(III)]Br with visible light induces a single electron transfer from the bromide anion to the iridium(III) center to form a bromine radical and iridium(II).[4] The iridium(II) species donates a single electron to nickel(II) dibromide **B** to form nickel(I) species **F** together with regeneration of [Ir(III)]Br. Stage 2; Disproportionation of two molecules of nickel(I) **F** takes place to generate nickel(0) species **G** with reproduction of **B**. Stage 3; The bromine radical abstracts hydrogen from the benzylic C–H bond of **29** to generate a benzylic radical and HBr. To the nickel(0) **G** coordinates isocyanate **162**, resulting in the formation of **H**.[3c] The benzylic radical subsequently adds to **H** to generate nickel(III) species **I**. Reductive elimination gives nickel(I) amide **J**, and the following protonation with HBr furnishes the amide product **163** and the nickel(I) bromide **F**.

Scheme 5-2. Proposed Mechanism

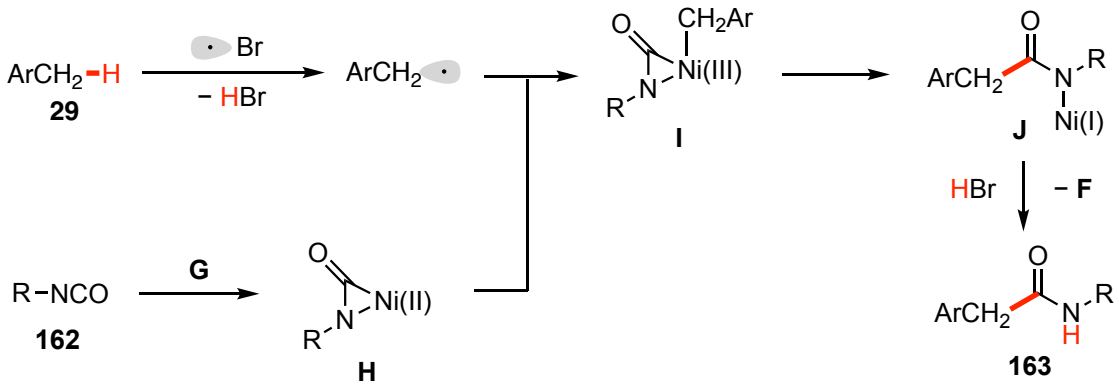
Stage 1. Generation of Bromine Radical and Ni(I)



Stage 2. Generation of Ni(0)



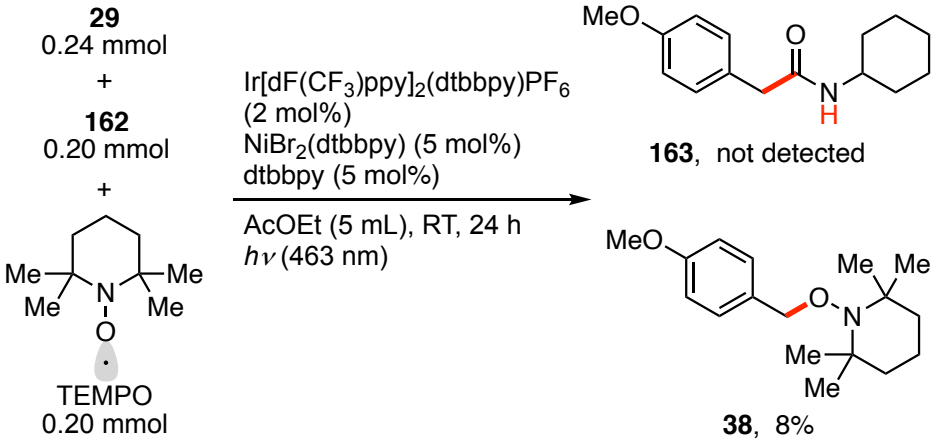
Stage 3. Formation of Amide



5.2.3 Mechanistic Studies

Control experiments revealed that light, the iridium photocatalyst, the bromide anion, and the nickel complex were all indispensable for the production of **163**. The presence of 2,2,6,6-tetramethylpiperidine *N*-oxy radical (TEMPO) in the reaction mixture prohibited the formation of **163** (Scheme 5-3). Instead, the formation of the benzylic radical–TEMPO adduct **38** was observed, supporting the mechanism involving the benzylic radical intermediate.

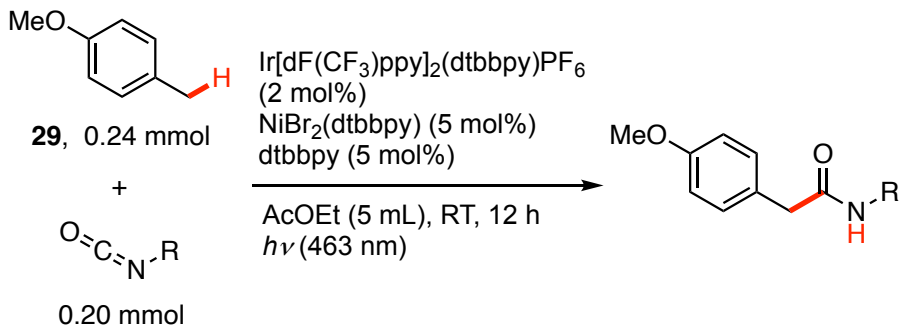
Scheme 5-3. Benzyl Radical Trapping Experiment

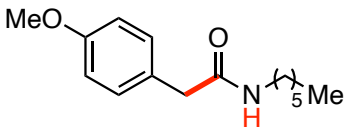


5.2.4 Scope of Isocyanates

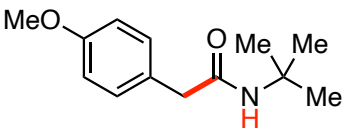
The scope of isocyanates using **29** as the hydrocarbon was next examined (Table 5-1). *N*-Hexyl and *tert*-butyl isocyanates were both successfully incorporated to give the corresponding amide **164** and **165** in moderate yields. Aromatic isocyanates were also viable substrates, and substituents including fluoro (**168**), chloro (**169**), and ethoxycarbonyl (**170**) groups were allowed on the benzene ring. The generality stands in sharp contrast to the limited scope of the previous report on a carbamoylation reaction of α-C–H bonds of ethers, which required the use of extremely electrophilic perfluorophenyl isocyanate.[1b]

Table 5-1. Scope of Isocyanates

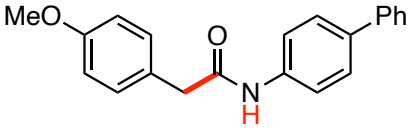




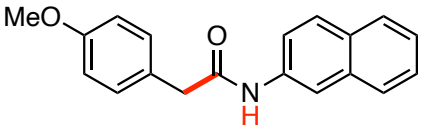
164, 65%



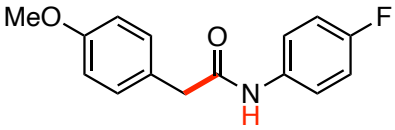
165, 72%



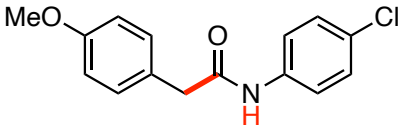
166, 62%



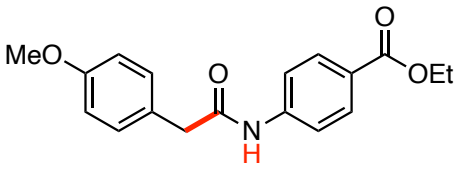
167, 48%



168, 54%



169, 56%[b]



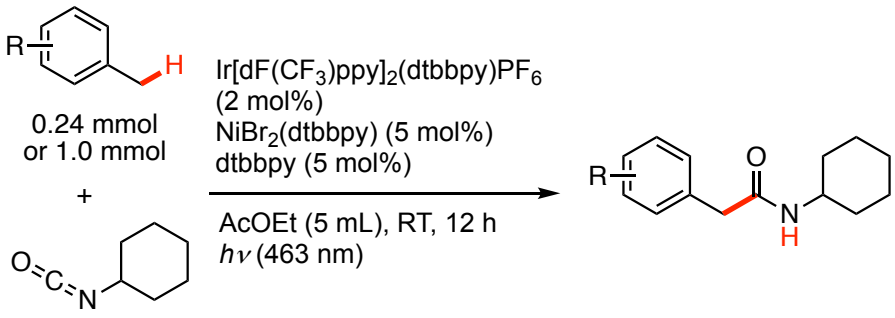
170, 57%

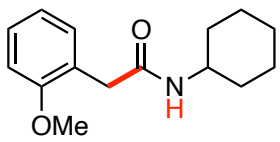
[a] Reaction conditions: *p*-methoxytoluene (**29**, 0.24 mmol, 1.2 equiv), isocyanates (0.20 mmol, 1.0 equiv), $NiBr_2$(dtbbpy) (0.01 mmol, 5 mol%), dtbbpy (0.01 mmol, 5 mol%), Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (0.004 mmol, 2 mol%), AcOEt (5 mL), blue LEDs (40 W, λ_{max} = 463 nm), room temperature, 12 h. [b] **29**: 1.0 mmol (5.0 equiv).

5.2.5 *Scope of Alkylbenezenes*

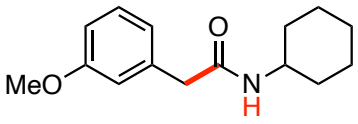
The scope of toluene derivatives was also examined using **162** as the isocyanate (Table 5-2). Under the standard conditions using 1.2 equiv of alkylbenzenes, those having an electron-donating alkoxy group at the *para* and *ortho* positions provided the amides in moderate to good yields (**171**, **173**, **174**). The modified conditions using K_3PO_4 instead of the dtbbpy gave better results for production of the amides **177** and **182**. On the other hand, alkylbenzenes lacking electron-donating substituents were less reactive, as was the case with the dehydrogenative toluene/aldehyde coupling reaction.[2a] This electronic trend is accounted for by assuming the mechanism involving electrophilic abstraction of a benzylic hydrogen by a bromine radical. In those cases, reasonable yields were obtained when 5.0 equiv (1.0 mmol) of alkylbenzenes was used (**172**, **175**, **176**, **178**, **179**, **181**).

Table 5-2. Scope of Alkylbenzenes

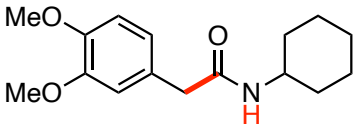




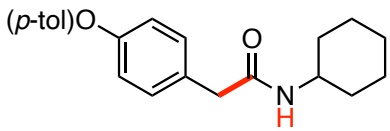
171, 69%



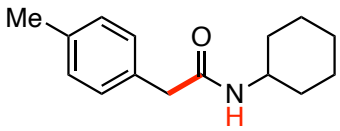
172, 60%[b]



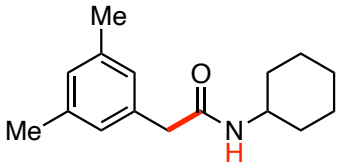
173, 67%



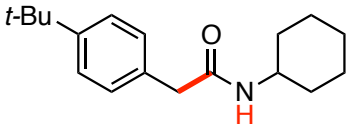
174, 61%



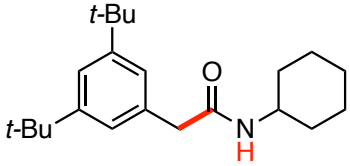
175, 98%[b]



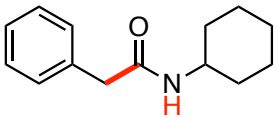
176, 89%[b]



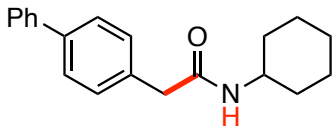
177, 64%[c]



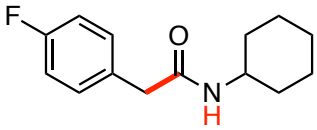
178, 88%[b]



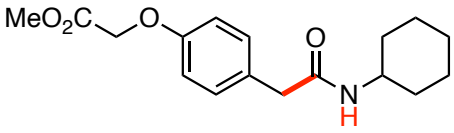
179, 75%[b]



180, 37%



181, 73%[b,c]



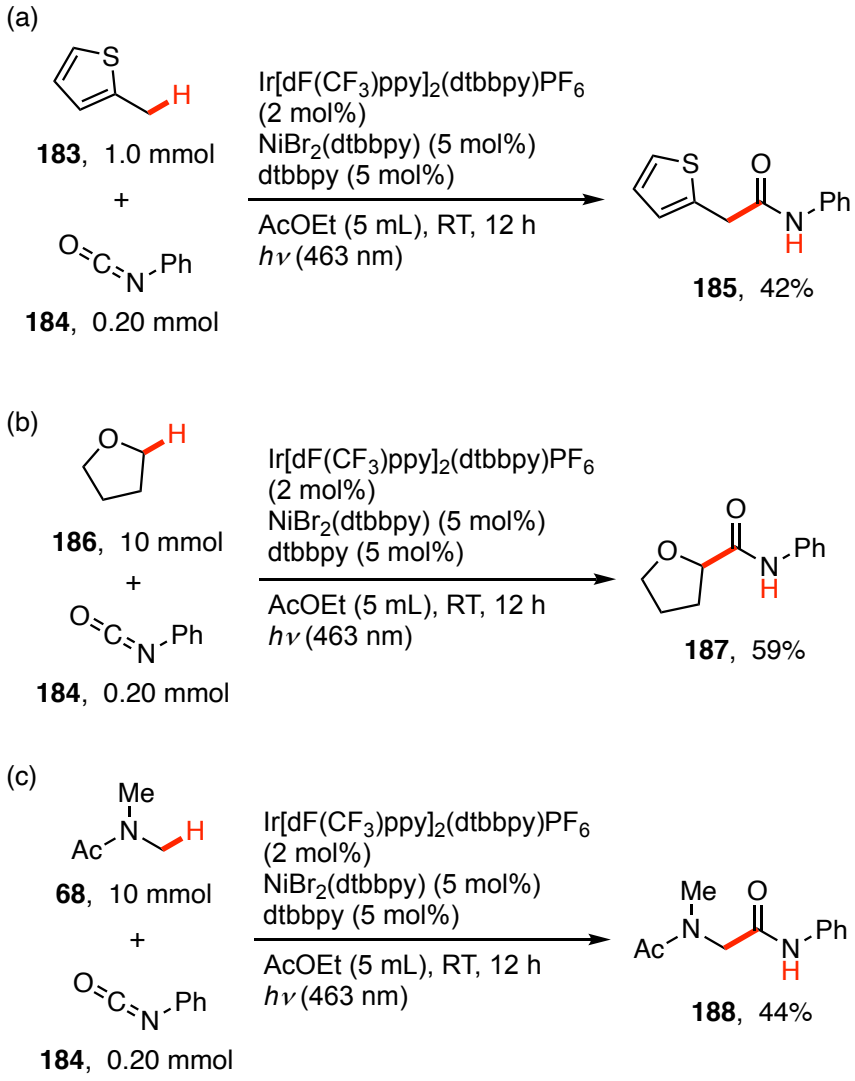
182, 71%[c]

[a] Reaction conditions: alkylarene (0.24 mmol, 1.2 equiv), cyclohexyl isocyanate (**162**, 0.20 mmol, 1.0 equiv), $NiBr_2$(dtbbpy) (0.01 mmol, 5 mol%), dtbbpy (0.01 mmol, 5 mol%), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.004 mmol, 2 mol%), AcOEt (5 mL), blue LEDs (40 W, λ_{max} = 463 nm), room temperature, 12 h. Isolated yields. [b] Alkylarenes: 1.0 mmol (5.0 equiv). [c] K_3PO_4 (15 mol%) was used instead of dtbbpy.

5.2.6 *Carbamoylation of Other Hetero C–H bonds*

Besides alkylbenzenes, 2-methylthiophene **183** underwent C–H carbamoylation without touching the thiophene ring (Scheme 5-4a). C–H bonds next to a heteroatom were also carbamoylated under similar reaction conditions. Tetrahydrofuran **186** gave the corresponding α-oxy amide **187** in 59% yield (Scheme 5-4b). Dimethylacetamide **68** afforded the α-amino carboxamide **188** in 44% yield (Scheme 5-4c).

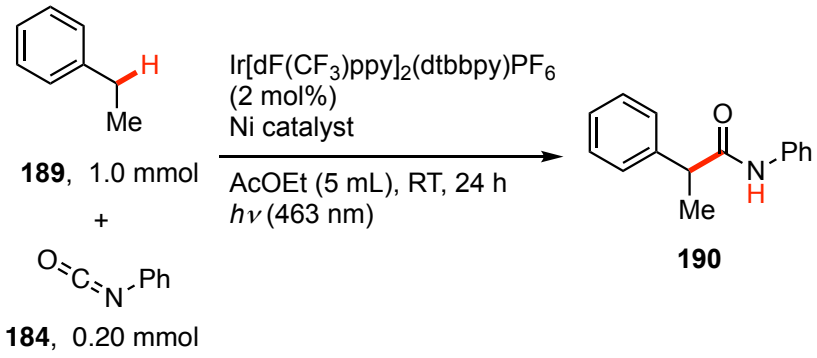
Scheme 5-4. Carbamoylation of **183**, **186**, and **68**

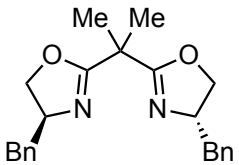


5.2.7 *Carbamoylation of Ethylbenzene **189***

The C–H carbamoylation reaction of ethylbenzene **189** occurred selectively at the benzylic position to give α-chiral phenylacetamide **190** in 66% yield (Scheme 5-5). Next, the present reaction was further applied to its asymmetric version, and chiral ligands for nickel were briefly screened.[5] It is generally difficult to induce enantioselectivity in C–H functionalization reactions of simple hydrocarbons because (1) high temperature is often required to activate inert C–H bonds, and (2) heteroatoms which would fix the conformation of the intermediate by coordination are lacking. Nonetheless, a promising enantiomeric ratio of 87:13 was observed when bisoxazoline ligand **191** was used in place of dtbbpy as the ligand for nickel, although the chemical yield decreased to 34% (Scheme 5-5).

Scheme 5-5. Carbamoylation of Ethylbenzene **189**





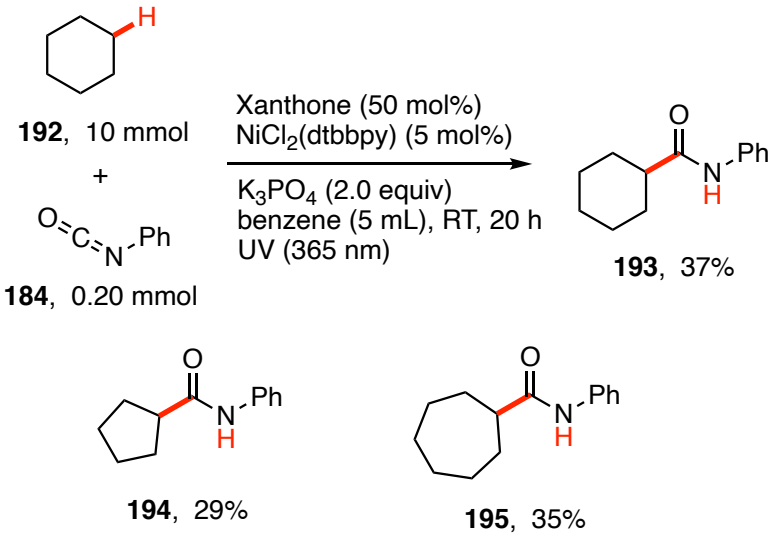
ligand **191**

Ni catalyst	**190**
$NiBr_2$(dtbbpy) (5 mol%) dtbbpy (5 mol%)	66%
$NiBr_2$(dme) (5 mol%) ligand **191** (15 mol%)	34% 87:13 er

5.2.8 *Carbamoylation of Simple Hydrocarbons*

Finally, carbamoylation of simple alkanes was examined. Their BDEs (*e.g.* 416 kJ/mol for cyclohexane)[6] are far greater than those of benzylic C–H bonds (376 kJ/mol for toluene),[6] and thus, alkanes are far less reactive than alkylarenes. When the visible light/iridium/bromide/nickel system was applied to cyclohexane, no carbamoylation reaction took place, probably because the transiently generated bromine radical failed to abstract hydrogen from the C–H bond. On the other hand, a UV light/xanthone/nickel system, which Murakami group developed for the C–H carboxylation reaction of alkanes with CO_2,[7] prompted the carbamoylation reaction to give the carboxamide **193**, albeit in 37% yield (Scheme 5-6). Cyclopentane and cycloheptane also gave the corresponding carboxamides **194** and **195** in comparable yields. Although pentane also underwent carbamoylation, the product mixture was complicated with the site-selectivity.

Scheme 5-6. Carbamoylation of Simple Alkanes



5.3 Summary

In summary, the photoinduced carbamoylation reaction of hydrocarbons with isocyanates was developed. Benzylic C(sp^3)–H bonds underwent the carbamoylation by the cooperative action of visible light, an iridium photocatalyst, a bromide anion, and a nickel catalyst. Aliphatic C(sp^3)–H bonds were carbamoylated using UV light and a ketone photocatalyst in place of visible light/iridium/bromide. The present reaction offers a straightforward and atom-economical access to carboxamides from hydrocarbons with one-carbon extension.

5.4 Experimental Section

5.4.1 General Method and Materials

General Method

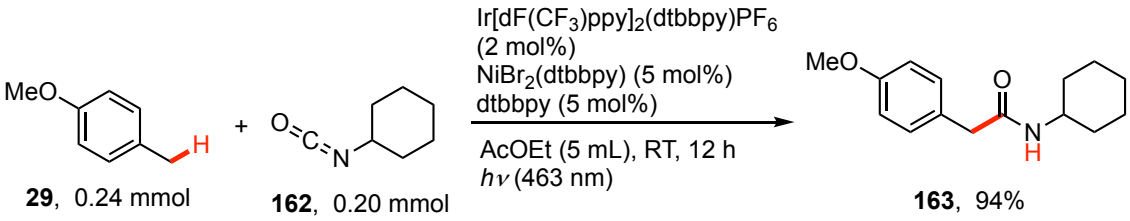
All reactions were carried out using a flame-dried glassware under a nitrogen atmosphere. Photoreactions were carried out with either blue LEDs (Kessil, A160WE, 40 W; the spectra are shown below) or ultraviolet LEDs (CCS, Controller: 8332A, Head: AC8361; the spectra are shown below). ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECZ400S/L1 (^{1}H at 400.44 MHz, ^{13}C at 100.69 MHz) spectrometer. $CDCl_3$ was used as a solvent. Chemical shifts were recorded in δ ppm referenced to a residual $CDCl_3$ (δ = 7.26 for ^{1}H, δ = 77.0 for ^{13}C). IR measurements were performed on FTIR SHIMADZU Affinity-1S spectrometer fitted with a Pike Technologies MIRacle Single Reflection ATR adapter. High-resolution mass spectra were recorded on either JEOL JMS-700 (EI) or Thermo Fisher Scientific Exactive (ESI, APCI). Preparative thin-layer chromatography (PTLC) was performed on silica gel plates with PF254 indicator (Merck). Flash column chromatography was performed with silica gel 60N (Kanto).

Materials

$NiBr_2$(dtbbpy),[8] $NiCl_2$(dtbbpy),[9] Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6,[10] and methyl 2-(*p*-tolyloxy)acetate[11] were prepared according to the method previously reported. Other chemicals were purchased from commercial suppliers and used as received.

5.4.2 *Typical Procedures for the Synthesis of Amides from Hydrocarbons and Isocyanates*

Scheme 5-7. A Typical Procedure of the Carbamoylation of Alkylarenes (Procedure A)



To a Schlenk tube containing $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (4.5 mg, 0.004 mmol, 2 mol%), $NiBr_2(dtbbpy)$ (4.9 mg, 0.010 mmol, 5 mol%) and dtbbpy (2.7 mg, 0.010 mmol, 5 mol%) were added 4-methoxytoluene **29** (29.3 mg, 0.24 mmol, 1.2 equiv), anhydrous ethyl acetate (5 mL) and cyclohexyl isocyanate **162** (25.0 mg, 0.20 mmol, 1.0 equiv) in a nitrogen-filled glove box. The tube was capped with rubber septa. The reaction mixture was stirred and irradiated with blue LEDs, with the vessel being cooled by a fan. After 12 hours, the reaction mixture was passed through a short pad of silica gel using ethyl acetate as an eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing amide **163** (96% NMR yield). The mixture was subjected to preparative thin-layer chromatography (PTLC) (Hexane:AcOEt = 3:2, R_f = 0.4) to isolate amide **163** (47.1 mg, 0.189 mmol, 94%) as a white solid.

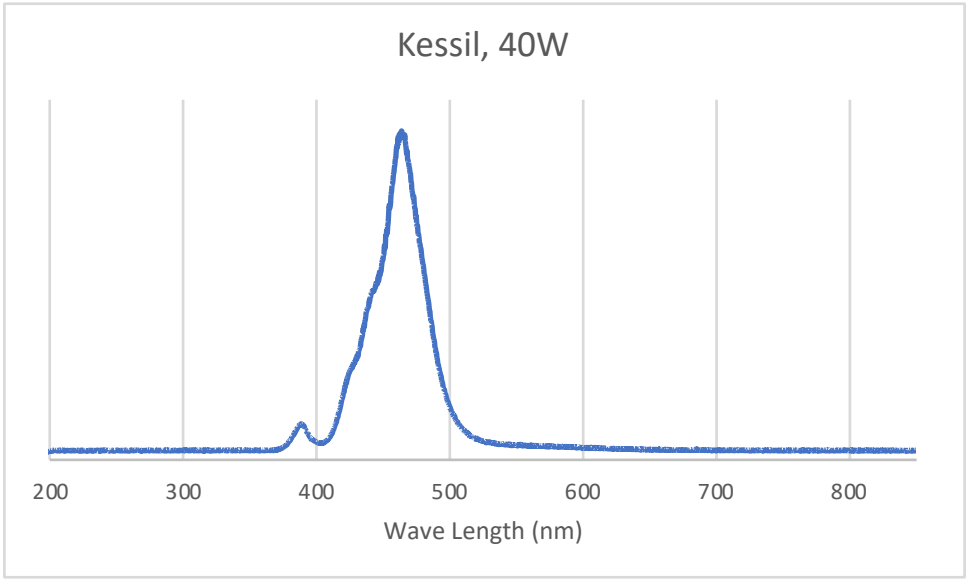
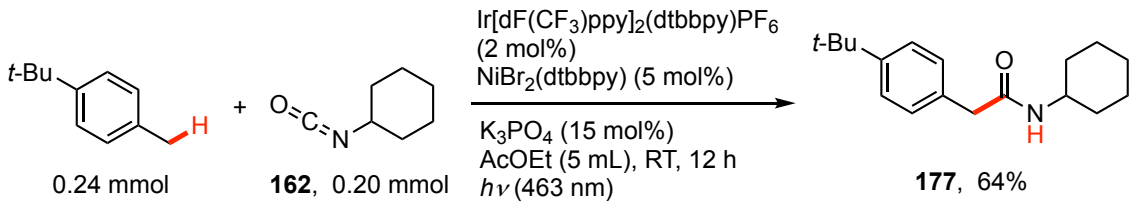


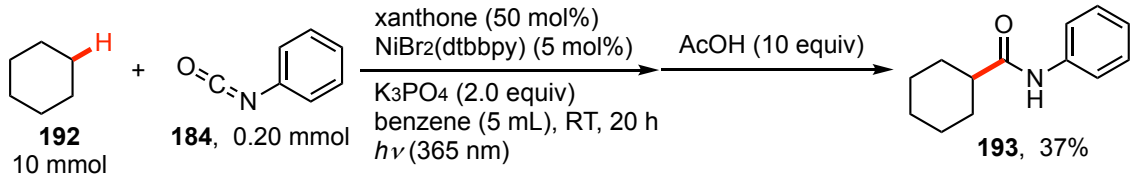
Figure 5-1. Spectrum of blue LEDs

Scheme 5-8. Typical Procedure of the Carbamoylation of Alkylarenes (Procedure B)



To a Schlenk tube containing Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (4.5 mg, 0.004 mmol, 2 mol%) and $NiBr_2$(dtbbpy) (4.9 mg, 0.010 mmol, 5 mol%) were added K_3PO_4 (6.4 mg, 0.03 mmol, 15 mol%), 4-*tert*-butyltoluene (35.6 mg, 0.24 mmol, 1.2 equiv), anhydrous ethyl acetate (5 mL) and cyclohexyl isocyanate **162** (25.0 mg, 0.20 mmol, 1.0 equiv) in a nitrogen-filled glove box. The tube was capped with rubber septa. The reaction mixture was stirred and irradiated with blue LEDs, with the vessel being cooled by a fan. After 12 hours, the reaction mixture was passed through a short pad of silica gel using ethyl acetate as an eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing amide **177** (66% NMR yield). The mixture was subjected to preparative thin-layer chromatography (PTLC) (Hexane:AcOEt = 3:2, R_f = 0.5) to isolate amide **177** (35.8 mg, 0.128 mmol, 64%) as a white solid.

Scheme 5-9. Typical Procedure of the Carbamoylation of Simple Hydrocarbons (Procedure C)



192
10 mmol

184, 0.20 mmol

193, 37%

To a Schlenk tube containing xanthone (19.6 mg, 0.10 mmol, 50 mol%) and $NiCl_2$(dtbbpy) (4.0 mg, 0.010 mmol, 5 mol%) were added K_3PO_4 (84.9 mg, 0.40 mmol, 2.0 equiv), cyclohexane (200 μL, 2.0 mmol, 10 equiv), anhydrous benzene (5 mL) and phenyl isocyanate **184** (23.8 mg, 0.20 mmol, 1.0 equiv) in a nitrogen-filled glove box. The tube was capped with rubber septa. The reaction mixture was stirred and irradiated with ultraviolet LEDs, with the vessel being cooled by a fan. After 20 hours, the reaction mixture was added acetic acid (114 μL, 2.0 mmol, 10 equiv), stirred for a few second and passed through a short pad of silica gel using ethyl acetate as an eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing amide **193** (42% NMR yield). The mixture was subjected to preparative thin-layer chromatography (PTLC) (Hexane:AcOEt = 4:1, R_f = 0.5 and DCM:AcOEt = 60:1) to isolate amide **193** (15.1 mg, 0.074 mmol, 37%) as a white solid.

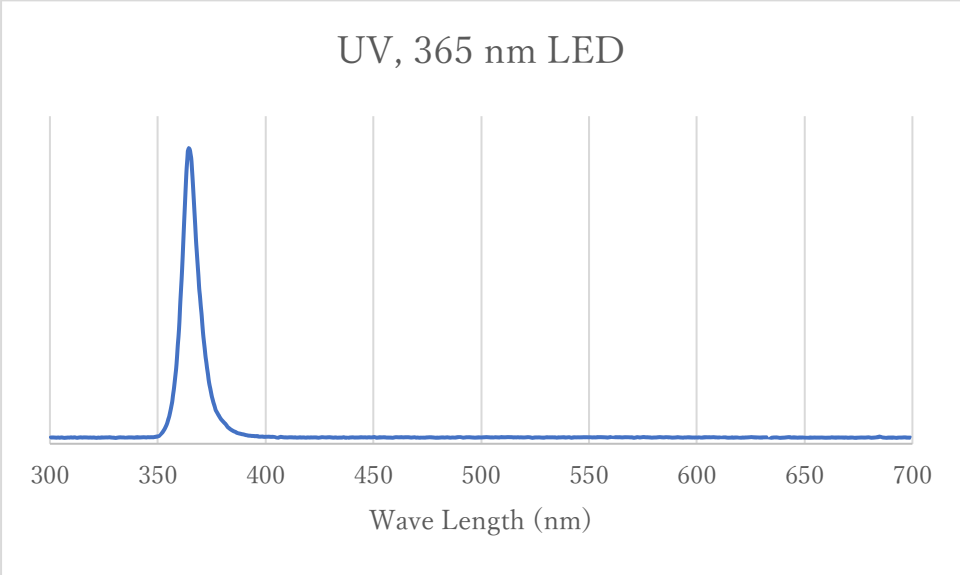
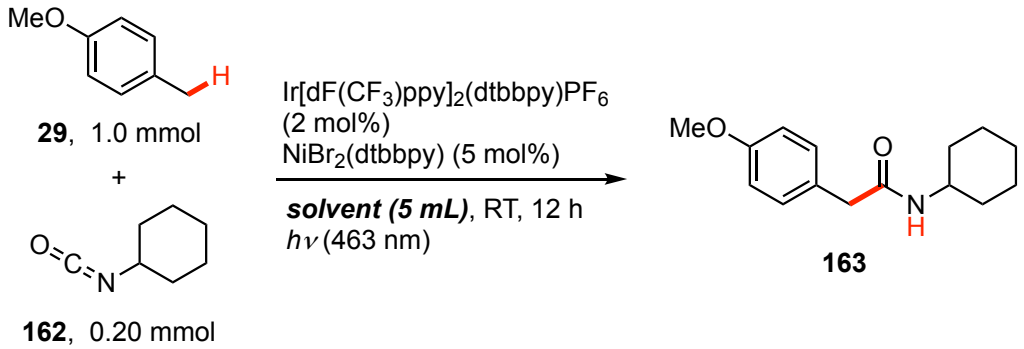


Figure 5-2. Spectrum of UV LEDs

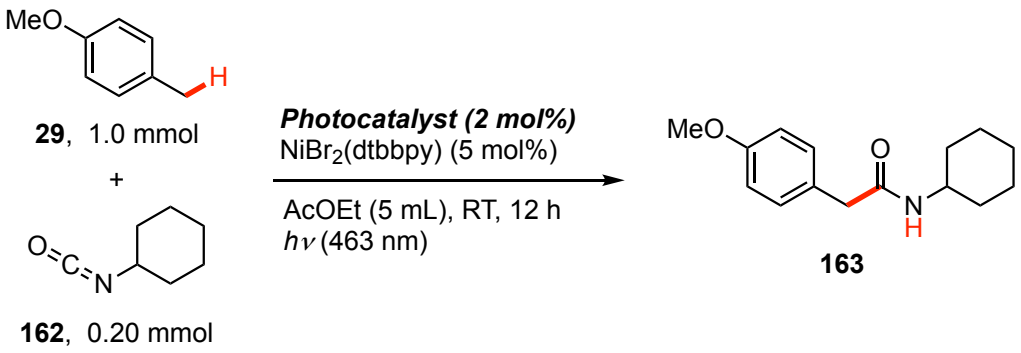
5.4.3 Optimization Studies

Table 5-3. Screening of Solvents in the Reaction of **29** (5.0 equiv) with **162**



entry	solvent	NMR yield of **163**
1	AcOEt	90%
2	Acetone	74%
3	MeCN	0%
4	DMSO	<5%
5	THF	<11%
6	Et_2O	25%
7	benzene	20%
8	CH_2Cl_2	0%

Table 5-4. Screening of Photocatalysts in the Reaction of **29** (5.0 equiv) with **162**



entry	photocatalyst	NMR yield of **163**
1	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	90%
2	4CzIPN	0%
3	acridinium catalyst	0%
4	pyrylium catalyst	0%
5	Methylene blue	0%
6	$Ir(ppy)_3$	0%
7	$Ru(bpy)_3PF_6$	0%
8	Eosin Y	0%

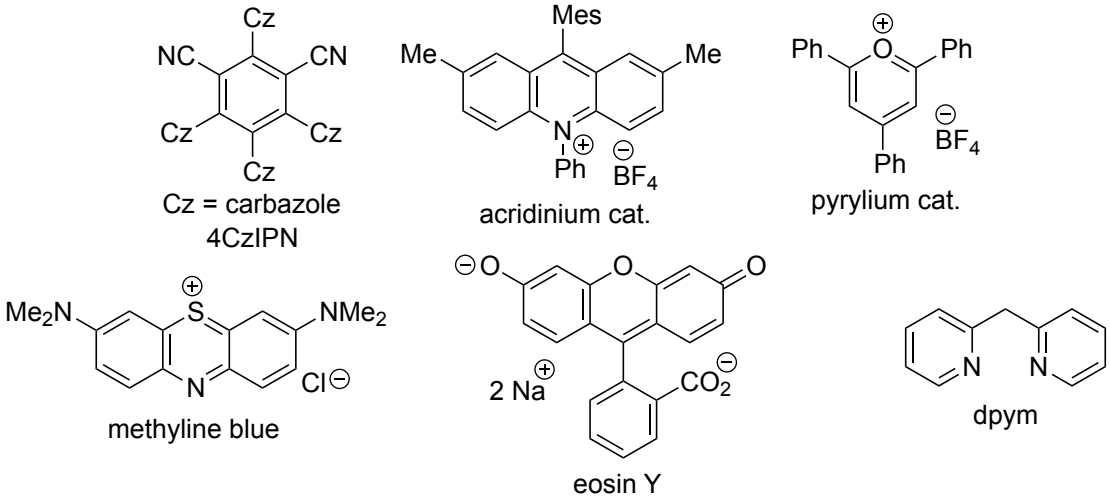
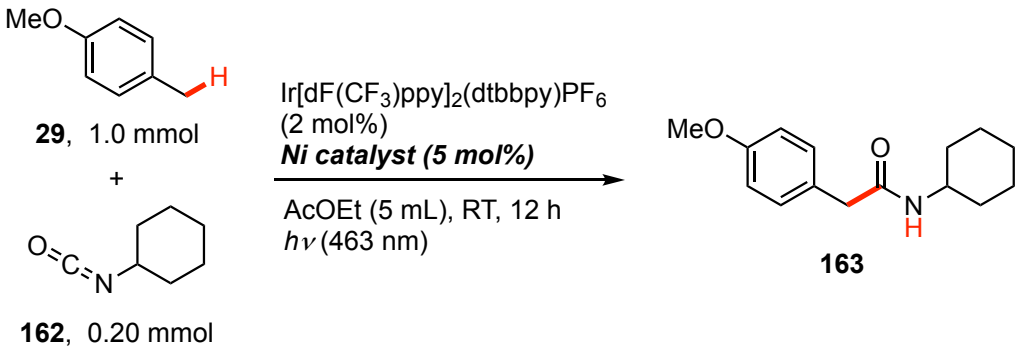


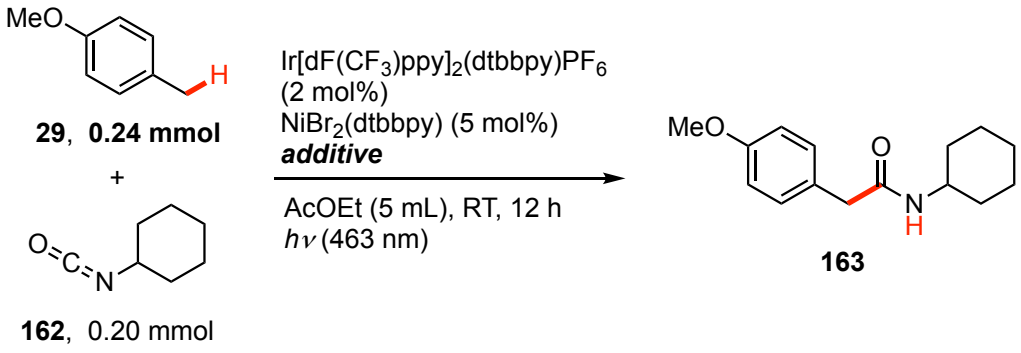
Figure 5-3. Structures of the Photocatalysts and dpym Ligand

Table 5-5. Screening of Nickel Catalysts in the Reaction of **29** (5.0 equiv) with **162**



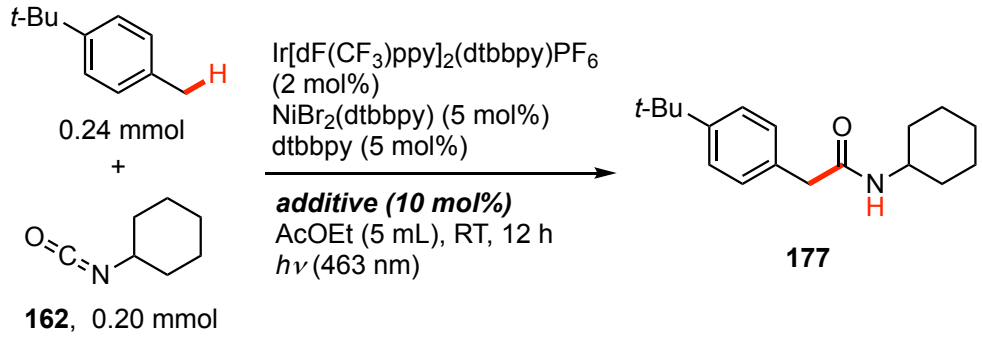
entry	Ni catalyst	NMR yield of **163**
1	$NiBr_2$(dtbbpy)	90%
2	$NiBr_2$(dme) (5 mol%), dtbbpy (10 mol%)	97%
3	$NiBr_2$(dme) (5 mol%), dpym (10 mol%)	0%
4	$NiBr_2$(dme) (5 mol%), dppf (10 mol%)	0%
5	$NiBr_2$(dme) (5 mol%), IPr(10 mol%)	<11%
6	$NiBr_2$(dme) (5 mol%), phen (10 mol%)	12%

Table 5-6. Effect of Additive in the Reaction of **29** (1.2 equiv) with **162**



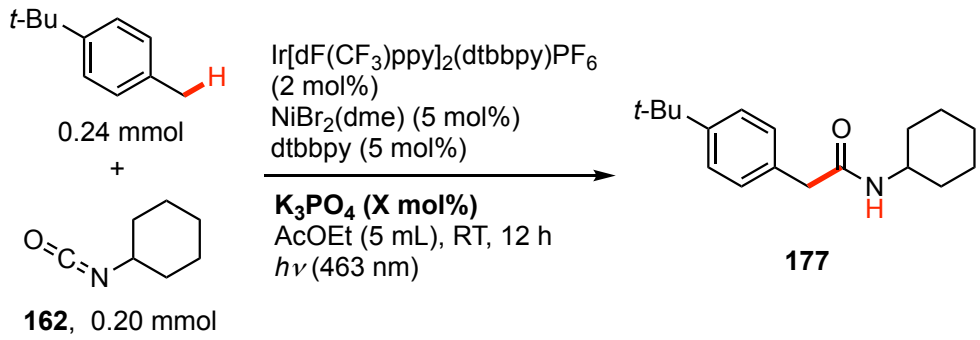
entry	additive	yield of **163**
1	None	18% NMR yield
2	dtbbpy (5 mol%)	94% isolated yield

Table 5-7. Screening of Additives in the Reaction of 4-*tert*-Butyltoluene with **162**



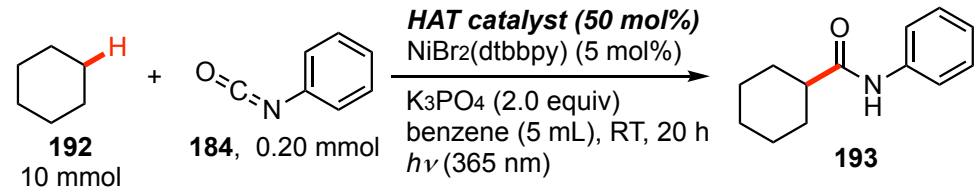
entry	additive	NMR yield of **177**
1	None	14%
2	pyridine	45%
3	2,6-lutidine	16%
4	K_2CO_3	42%
5	KOAc	25%
6	K_3PO_4	60%
7	Na_3PO_4	47%
8	K_2HPO_4	56%
9	DBU	12%
10	K*o*t-Bu	0%

Table 5-8. Screening of Amounts of K_3PO_4 in the Reaction of 4-*tert*-Butyltoluene with **162**



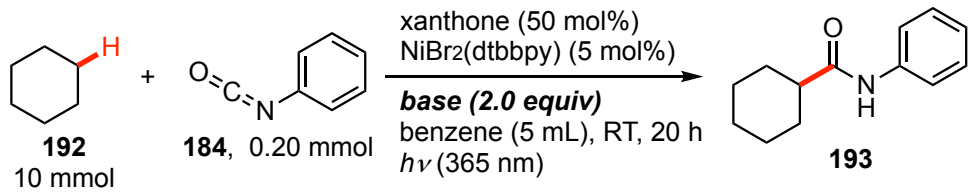
entry	K_3PO_4	NMR yield of **177**
1	0 mol%	14%
2	5 mol%	45%
3	10 mol%	60%
4	15 mol%	71%
5	17.5 mmol%	70%
6	20 mol%	44%

Table 5-9. Screening of HAT catalysts in the Reaction of **192** with **184**



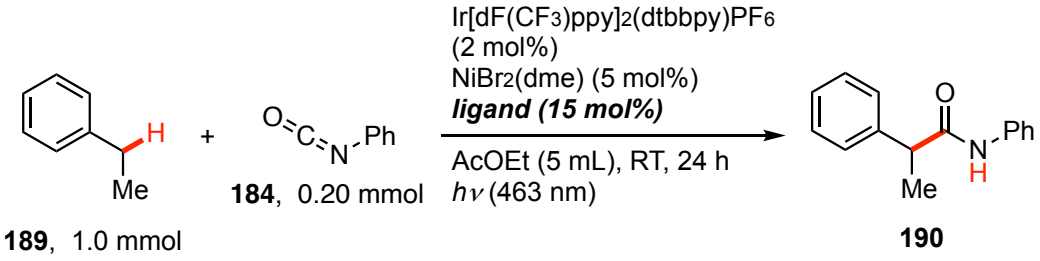
entry	HAT cat.	NMR yield	
		177	HAT cat.
1	benzophenone	36%	5%
2	4,4'-di-*tert*-butylbenzophenone	45%	0%
3	xanthone	43%	92%
4	$[(n\text{-Bu})_4N]_4W_{10}O_{32}$ (2 mol%)	0%	-

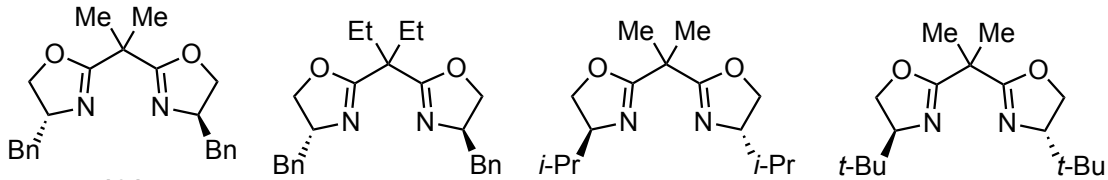
Table 5-10. Screening of bases in the Reaction of **192** with **184**

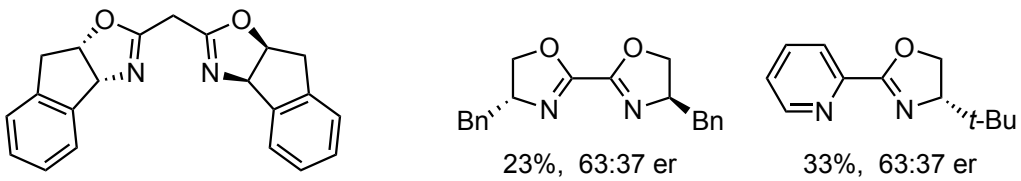


entry	base	NMR yield	
		177	HAT cat.
1	K_3PO_4	43%	92%
2	None	0%	14%
3	*i*-Pr_2NEt	0%	<5%
4	2,6-lutidine	0%	23%
5	DBU	0%	<5%
6	KOAc	32%	77%
7	K_2CO_3	31%	85%
8	Na_3PO_4	28%	81%
9	Li_3PO_4	30%	54%

Table 5-11. Screening for Chiral Ligands in the Reaction of **189** with **184**

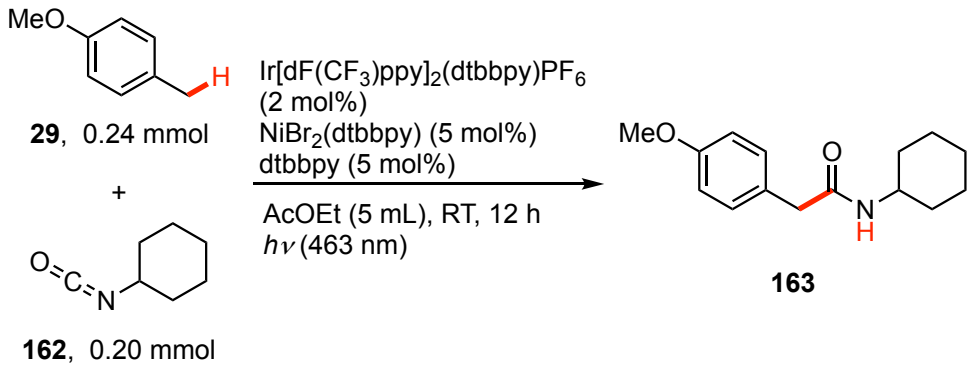






5.4.4 Control Experiments

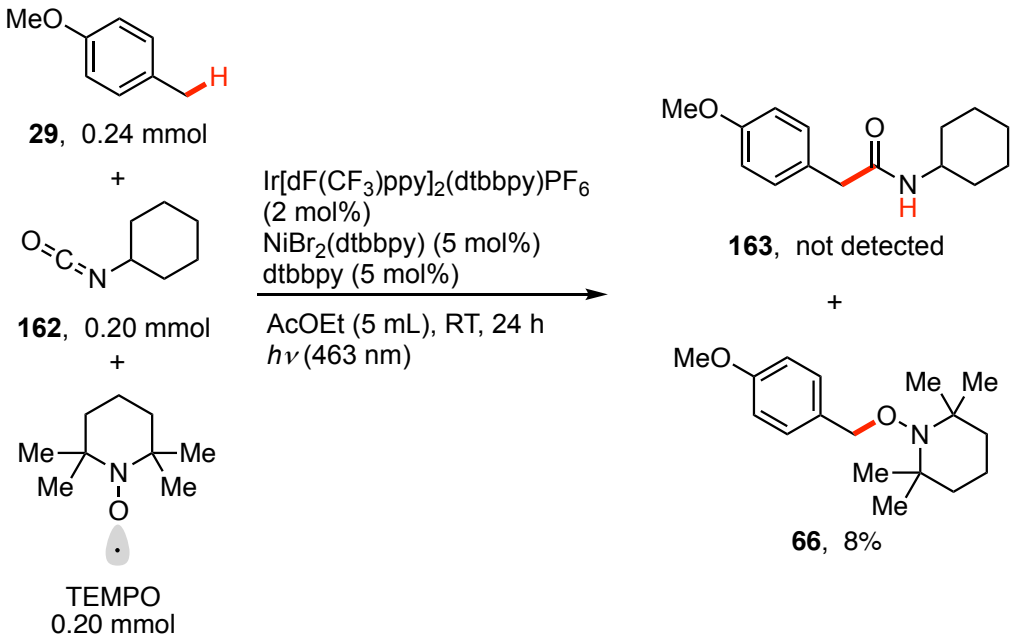
Table 5-12. Control Experiments



entry	deviation from standard condition	NMR yield of **163**
1	None	94% isolated yield
2	w/o light	0%
3	w/o $NiBr_2$(dtbbpy), dtbbpy	0%
4	w/o Ir catlyst	0%
5	365 nm light instead of 463 nm light, Ir catalyst	0%
6	$Ni(Oac)_2 4H_2O$ (5 mol%), dtbbpy (10 mol%) instead of $NiBr_2$(dtbbpy), dtbbpy	0%
7	$Ni(Oac)_2 4H_2O$ (5 mol%), dtbbpy (10 mol%), (*n*-Bu)$_4$NBr (10 mol%) instead of $NiBr_2$(dtbbpy), dtbbpy	58%
8	dtbbpy (10 mol%), (*n*-Bu)$_4$NBr (10 mol%) instead of $NiBr_2$(dtbbpy), dtbbpy	0%

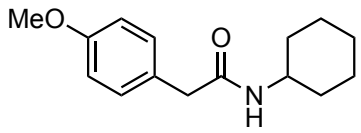
5.4.5 Radical Trapping Experiment

Scheme 5-10. Radical Trapping Experiment



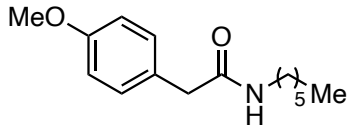
To a Schlenk tube containing Ir[dF(CF_3)ppy]$_2$(dtbbpy)PF_6 (4.5 mg, 0.004 mmol, 2 mol%) and $NiBr_2$(dtbbpy) (4.9 mg, 0.010 mmol, 5 mol%) were added 4-methoxytoluene **29** (29.3 mg, 0.24 mmol, 1.2 equiv), 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO, 31.3 mg, 0.20 mmol, 1.0 equiv), anhydrous ethyl acetate (5 mL) and cyclohexyl isocyanate (25.0 mg, 0.20 mmol, 1.0 equiv) in a nitrogen-filled glove box. The tube was capped with rubber septa. The reaction mixture was stirred and irradiated with blue LEDs, with the vessel being cooled by a fan. After 12 hours, the reaction mixture was passed through a short pad of silica gel using ethyl acetate as the eluent. The filtrate was concentrated under a reduced pressure to afford a mixture containing TEMPO adduct **66** (8%, NMR yield).[5] Amide **163** was not detected in the reaction mixture.

5.4.6 Spectroscopic Data of the Products



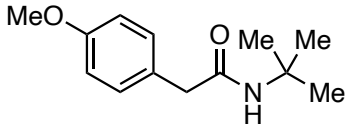
163

This product was identified by comparison with reported data.[13]



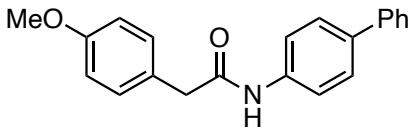
164

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.5) to give **164** (32.5 mg, 0.130 mmol, 65%) as a white solid. This product was identified by comparison with reported data.[14]



165

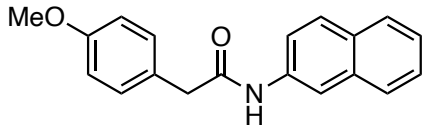
The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 3:2, R_f = 0.4) to give **165** (32.3 mg, 0.144 mmol, 72%) as a white solid. This product was identified by comparison with reported data.[15]



166

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 60:1, R_f = 0.5) to give **166** (39.3 mg, 0.124 mmol, 62%) as a white solid.

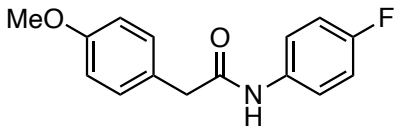
^{1}H NMR: δ = 7.57-7.46 (m, 6H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.35-7.24 (m, 3H), 7.16 (brs, 1H), 6.95 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 3H), 3.71 (s, 2H); ^{13}C NMR: δ = 169.5, 159.1, 140.4, 137.3, 136.9, 130.7, 128.7, 127.5, 127.1, 126.8, 126.2, 120.0, 114.7, 55.3, 44.0; IR (neat): 3294, 2994, 2837, 1659, 1510, 1246, 1033, 835, 760, 691 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{20}NO_2$ 318.1489; Found 318.1493.



167

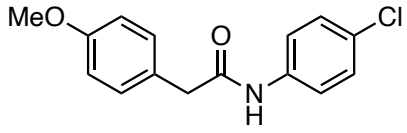
The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 60:1, R_f = 0.5) to give **167** (28.1 mg, 0.096 mmol, 48%) as a white solid.

^{1}H NMR: δ = 8.13 (s, 1H), 7.79-7.70 (m, 3H), 7.47-7.24 (m, 6H), 6.95 (d, *J* = 8.6 Hz, 2H), 3.84 (s, 3H), 3.74 (s, 2H); ^{13}C NMR: δ = 169.7, 159.1, 135.0, 133.7, 130.7, 130.6, 128.6, 127.6, 127.5, 126.5, 126.2, 125.0, 119.7, 116.5, 114.7, 55.3, 44.0; IR (neat): 3246, 3057, 2963, 1653, 1553, 1508, 1362, 1250, 1175, 1032, 826, 743 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{18}NO_2$ 292.1332; Found 292.1332.



168

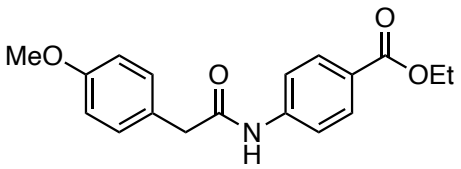
The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 2:1, R_f = 0.2) and (DCM:AcOEt = 10:1, R_f = 0.8) to give **168** (28.5 mg, 0.108 mmol, 54%) as a white solid. This product was identified by comparison with reported data.[16]



169

The reaction was conducted by procedure A with 5 equivalents of 4-chlorotoluene. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 3:2, R_f = 0.4) to give **169** (31.0 mg, 0.112 mmol, 56%) as a white solid.

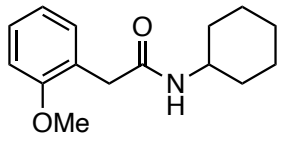
^{1}H NMR: δ = 7.36 (d, *J* = 8.8 Hz, 2H), 7.26-7.22 (m, 4H), 7.10 (brs, 1H), 6.93 (d, *J* = 8.5 Hz, 2H), 3.83 (s, 3H), 3.67 (s, 2H); ^{13}C NMR: δ = 169.5, 159.2, 136.2, 130.7, 129.4, 128.9, 126.0, 121.0, 114.7, 55.3, 43.9; IR (neat): 3246, 1653, 1607, 1541, 1510, 1589, 1398, 1250, 1032. 814 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{15}ClNO_2$ 276.0792; Found 276.0786.



170

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.7) to give **170** (36.2 mg, 0.114 mmol, 57%) as white solid.

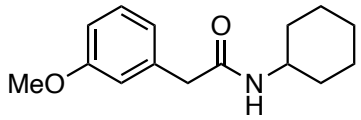
^{1}H NMR: δ = 7.95 (d, *J* = 8.8 Hz, 2H), 7.54-7.48 (m, 3H), 7.23 (d, *J* = 8.7 Hz, 2H), 6.91 (d, *J* = 8.7 Hz, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 3.81 (s, 3H), 3.68 (s, 2H), 1.37 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR: δ = 169.8, 166.1, 159.1, 141.8, 130.62, 130.60, 125.95, 125.85, 118.7, 114.6, 60.8, 55.3, 43.9, 14.3; IR (neat): 3306, 1709, 1662, 1599, 1512, 1279, 1244, 1105, 770, 735 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{20}NO_4$ 314.1394; Found 314.1387.



171

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.4) to give a mixture of **171** (34.5 mg, 0.138 mmol, 69%) as a white solid.

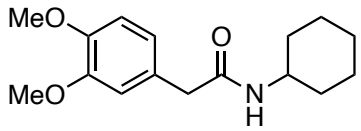
^{1}H NMR: δ = 7.26 (t, *J* = 7.6 Hz, 1H), 7.21 (d, *J* = 7.4 Hz, 1H), 6.93 (t, *J* = 7.4 Hz, 1H), 6.89 (t, *J* = 8.2 Hz, 1H), 5.57 (brd, *J* = 4.1 Hz, 1H), 3.84 (s, 3H), 3.77-3.67 (m, 1H), 3.51 (s, 2H), 1.85-1.75 (m, 2H), 1.63-1.50 (m, 3H), 1.38-1.24 (m, 2H), 1.18-0.96 (m, 3H); ^{13}C NMR: δ = 170.2, 157.1, 131.2, 128.6, 124.0, 121.0, 110.6, 55.3, 47.7, 39.0, 32.8, 25.5, 24.5; IR (neat): 3306, 1643, 1533, 1497, 1348, 1246, 1111, 1049, 1030 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{22}NO_2$ 248.1650; Found 248.1645.



172

The reaction was conducted by procedure A with 5 equivalents of 3-methoxytoluene. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.4) and (Hexane:AcOEt = 3:2, R_f = 0.3) to give **172** (30.3 mg, 0.120 mmol, 60%) as a white solid.

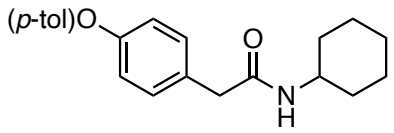
^{1}H NMR: δ = 7.25 (t, *J* = 7.9 Hz, 1H), 6.83-6.79 (m, 3H), 5.30 (brd, *J* = 4.0 Hz, 1H), 3.80 (s, 3H), 3.77-3.70 (m, 1H), 3.51 (s, 2H), 1.84-0.96 (m, 10H); ^{13}C NMR: δ = 169.8, 159.9, 136.6, 129.9, 121.6, 114.9, 112.7, 55.2, 48.1, 44.0, 32.8, 25.4, 24.7; IR (neat): 23287, 1636, 1551, 1491, 1248, 1169, 1038, 853, 766 cm^{-1}; HRMS (ESI) *m/z*: [M + H]$^+$ Calcd for $C_{15}H_{22}NO_2$ 248.1649; Found 248.1645.



173

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.3) and (Hexane:AcOEt = 4:3, R_f = 0.4) to give **173** (37.6 mg, 0.134 mmol, 67%) as a white solid.

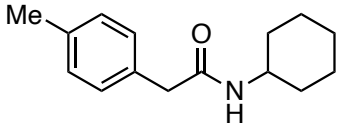
^{1}H NMR: δ = 6.82-6.80 (m, 1H), 6.76-6.74 (m, 2H), 6.34 (brd, *J* = 7.2 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.77-3.66 (m, 1H), 3.46 (s, 2H), 1.85-1.77 (m, 2H), 1.64-1.50 (m, 3H), 1.37-1.23 (m, 2H), 1.15-0.95 (m, 3H); ^{13}C NMR: δ = 170.3, 149.2, 148.2, 127.5, 121.5, 112.3, 111.4, 55.8 (2C), 48.1, 43.5, 32.9, 25.4, 24.6; IR (neat): 3283, 1631, 1545, 1514, 1261, 1229, 1153, 1030, 606 cm^{-1}; HRMS (ESI) *m/z*: [M + H]$^+$ Calcd for $C_{16}H_{24}NO_3$ 278.1765; Found 278.1751.



174

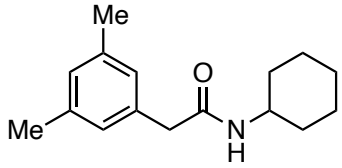
The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.4) to give **174** (40.2 mg, 0.122 mmol, 61%) as white solid.

^{1}H NMR: δ = 7.21-7.10 (m, 4H), 6.98-6.88 (m, 4H), 5.31 (brd, 1H), 3.81-3.70 (m, 1H), 3.49 (s, 2H), 2.33 (s, 3H), 1.88-1.77 (m, 2H), 1.66-1.53 (m, 3H), 1.40-1.24 (m, 2H), 1.17-0.97 (m, 3H); ^{13}C NMR: δ = 170.1, 157.0, 154.4, 133.1, 130.6, 130.2, 129.4, 119.1, 118.6, 48.2, 43.1, 32.9, 25.4, 24.7, 20.7; IR (neat): 3294, 2932, 2853, 1638, 1501, 1248, 1163, 878, 814 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{21}H_{26}NO_2$ 324.1958; Found 324.1961.



175

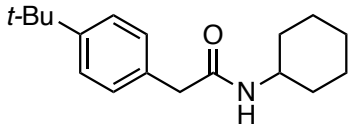
The reaction was conducted by procedure A with 5 equivalents of *p*-xylene. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.5) to give **175** (46.2 mg, 0.196 mmol, 98%) as a white solid. This product was identified by comparison with reported data.[17]



176

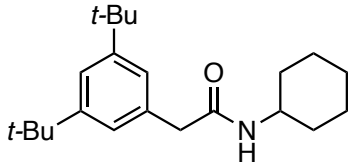
The reaction was conducted by procedure A with 5 equivalents of mesytylene. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 3:2, R_f = 0.4) to give **176** (44.4 mg, 0.178 mmol, 89%) as a white solid.

^{1}H NMR: δ = 6.90 (s, 1H), 6.85 (s, 2H), 5.33 (brd, 1H), 3.80-3.69 (m, 1H), 3.45 (s, 2H), 2.29 (s, 6H), 1.88-1.78 (m, 2H), 1.66-1.51 (m, 3H), 1.38-1.23 (m, 2H), 1.17-0.96 (m, 3H); ^{13}C NMR: δ = 170.2, 138.4, 134.9, 128.8, 127.1, 48.1, 43.8, 32.8, 25.4, 24.7, 21.2; IR (neat): 3283, 2922, 2851, 1639, 1551, 1350, 1248, 1171, 849, 687 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{23}NO$ 246.1852; Found 246.1852.



177

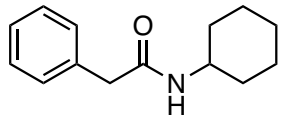
^{1}H NMR: δ = 7.36 (d, *J* = 8.4 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 5.31 (brd, *J* = 5.6 Hz, 1H), 3.79-3.71 (m, 1H), 3.50 (s, 2H), 1.88-1.80 (m, 2H), 1.66-1.51 (m, 3H), 1.40-1.24 (m, 11H), 1.16-0.96 (m, 3H); ^{13}C NMR: δ = 170.2, 150.1, 132.0, 129.0, 125.8, 48.1, 43.4, 34.4, 32.9, 31.2, 25.4, 24.7; IR (neat): 3273, 1636, 1549, 1449, 1339, 1267, 1155, 814 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{28}NO$ 274.2171; Found 274.2165.



178

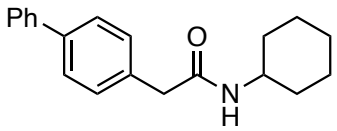
The reaction was conducted by procedure A with 5 equivalents of 3,5-di-*tert*-butyltoluene. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 10:1, R_f = 0.5) to give **178** (59.3 mg, 0.176 mmol, 88%) as a white solid.

^{1}H NMR: δ = 7.33 (s, 1H), 7.07 (s, 2H), 5.31 (brd, 1H), 3.84-3.73 (m, 1H), 3.54 (s, 2H), 1.86-1.76 (m, 2H), 1.61-1.47 (m, 3H), 1.39-1.21 (m, 20H), 1.17-0.95 (m, 3H); ^{13}C NMR: δ = 170.5, 151.5, 134.2, 123.6, 121.1, 47.8, 44.5, 34.8, 32.7, 31.4, 25.4, 24.4; IR (neat): 3271, 2932, 2853, 1636, 1547, 1362, 1250, 872, 710 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{36}NO$ 330.2791; Found 330.2793.



179

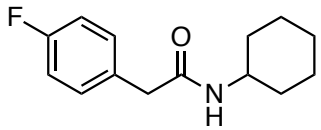
The reaction was conducted by procedure A with 5 equivalents of toluene. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.5) to give **179** (33.0 mg, 0.150 mmol, 75%) as a white solid. This product was identified by comparison with reported data.[18]



180

The reaction was conducted by procedure A. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 3:2, R_f = 0.3) and (DCM:AcOEt = 8:2, R_f = 0.5) to give **180** (21.9 mg, 0.074 mmol, 37%) as a white solid.

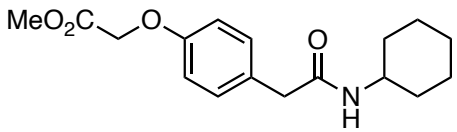
^{1}H NMR: δ = 7.62-7.56 (m, 4H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.38-7.30 (m, 3H), 5.31 (brd, 1H), 3.83-3.72 (m, 1H), 3.58 (s, 2H), 1.90-1.81 (m, 2H), 1.69-1.54 (m, 3H), 1.40-1.27 (m, 2H), 1.17-0.98 (m, 3H); ^{13}C NMR: δ = 169.9, 140.5, 140.1, 134.1, 129.8, 128.8, 127.6, 127.4, 127.0, 48.2, 43.6, 32.9, 25.4, 24.7; IR (neat): 3310, 2932, 2853, 1638, 1545, 1489, 1333, 1155, 822, 752 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{24}NO$ 294.1852; Found 294.1854.



181

The reaction was conducted by procedure B with 5 equivalents of 4-fluorotoluene. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.5) to give **181** (34.8 mg, 0.146 mmol, 73%) as a white solid.

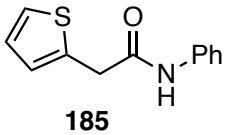
^{1}H NMR: δ = 7.24-7.12 (m, 2H), 7.05-6.99 (m, 2H), 5.30 (brd, *J* = 4.0 Hz, 1H), 3.78-3.70 (m, 1H), 3.49 (s, 2H), 1.88-1.80 (m, 2H), 1.67-1.53 (m, 3H), 1.39-1.25 (m, 2H), 1.16-0.97 (m, 3H); ^{13}C NMR: δ = 169.7, 162.0 (d, *J* = 245.6 Hz), 130.9, 130.8 (d, *J* = 7.7 Hz), 115.7 (d, *J* = 21.2 Hz), 48.2, 43.0, 32.9, 25.4, 24.7; ^{19}F NMR: δ = −115.2 (tt, *J* = 8.7, 5.3 Hz); IR (neat): 3238, 3071, 1634, 1558, 1506, 1223 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{19}FNO$ 236.1449; Found 236.1445.



182

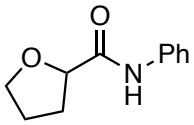
The reaction was conducted by procedure B. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.4) to give **182** (43.9 mg, 0.142 mmol, 71%) as a white solid.

^{1}H NMR: δ = 7.16 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.26 (brd, *J* = 5.8 Hz, 1H), 4.62 (s, 2H), 3.82-3.69 (m, 4H), 3.46 (s, 2H), 1.83-1.76 (m, 2H), 1.65-1.51 (m, 3H), 1.38-1.24 (m, 2H), 1.15-0.96 (m, 3H); ^{13}C NMR: δ = 170.1, 169.3, 156.9, 130.5, 128.4, 115.1, 65.3, 52.2, 48.1, 43.0, 32.9, 25.4, 24.7; IR (neat): 3304, 1736, 1645, 1531, 1510, 1308, 1288, 1231, 1204, 1180, 1082, 1024, 862 cm^{-1}; HRMS (ESI) *m/z*: $[M + H]^+$ Calcd for $C_{17}H_{24}NO_4$ 306.1707; Found 306.1700.



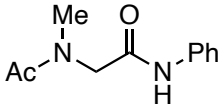
185

The reaction was conducted by procedure A with 5 equivalents of 2-methylthiophen. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 60:1, R_f = 0.5) to give **185** (18.7 mg, 0.084 mmol, 42%) as a white solid. This product was identified by comparison with reported data.[19]



187

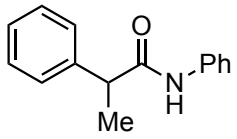
The reaction was conducted by procedure A with 50 equivalents of tetrahydrofuran. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 3:2, R_f = 0.3) to give **187** (22.8 mg, 0.119 mmol, 59%) as a white solid. This product was identified by comparison with reported data.[20]



188

The reaction was conducted by procedure A with 50 equivalents of *N,N*-dimethylacetamide. The crude mixture was purified by preparative thin-layer chromatography (MeOH:AcOEt = 1:9, R_f = 0.5) to give **188** (18.4 mg, 0.088 mmol, 44%) as a white solid.

^{1}H NMR: [major rotamer] δ = 8.68 (brs, 1H), 7.49 (d, *J* = 7.8 Hz, 2H), 7.28 (t, *J* = 7.6 Hz, 2H), 7.07 (t, *J* = 7.4 Hz, 1H), 4.11 (s, 2H), 3.16 (s, 3H), 2.17 (s, 3H); [minor rotamer] δ = 8.20 (brs, 1H), 7.55 (d, *J* = 8.0 Hz, 2H), 7.33 (t, *J* = 7.7 Hz, 2H), 7.14 (t, *J* = 7.4 Hz, 1H), 4.08 (s, 2H), 3.04 (s, 3H), 2.13 (s, 3H); ^{13}C NMR: [major rotamer] δ = 172.2, 167.2, 137.8, 128.9, 124.2, 119.7, 53.8, 37.9, 21.5; [minor rotamer] δ = 171.7, 166.1, 137.0, 129.0, 124.9, 120.3, 55.0, 35.0, 29.7; IR (neat): 3273, 1694, 1636, 1557, 1497, 1445, 1406, 1356, 1310, 1254, 1196, 991 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{11}H_{14}N_2O_2Na$ 229.0950; Found 229.0947.

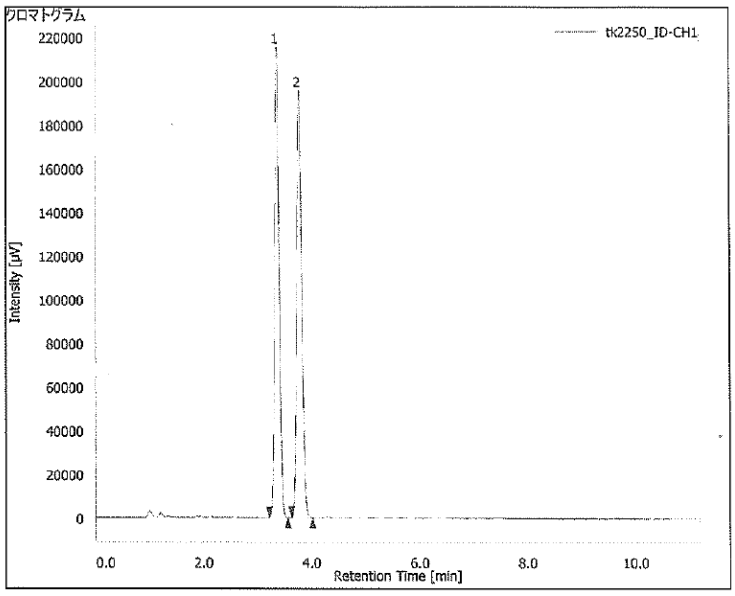


190

[racemic reaction] The reaction was conducted by procedure A with 5 equivalents of ethylbenzene. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.8) to give **190** (30.3 mg, 0.132 mmol, 66%) as a white solid. This product was identified by comparison with reported data.[21]

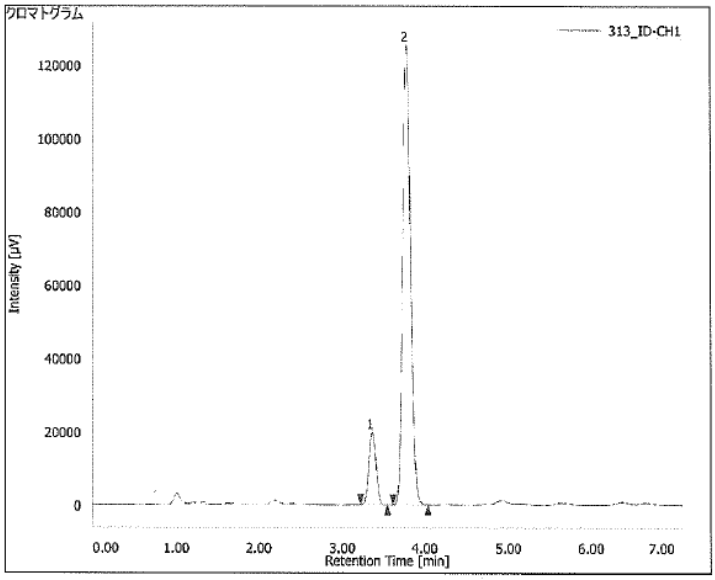
[enantioselective reaction] The reaction was conducted by procedure A with 5 equivalents of ethylbenzene and $NiBr_2$(dme) (5mol%) and ligand **191** (15 mol%) as Ni catalyst. The crude mixture was purified by preparative thin-layer chromatography (DCM:AcOEt = 9:1, R_f = 0.8) to give **190** (15.4 mg, 0.068 mmol, 34%) as a white solid. Enantiomeric ratio was determined to be 87:13 by a SFC analysis [column: Daicel Chiralpak ID (4.6 mm x 250 mm); eluent: CO_2:2-PrOH = 100:20; flow rate: 3.6 mL/min; detection wavelength: 220 nm; t_R = 3.4 (minor), 3.8 (major) min]

SFC chart of the racemic mixture

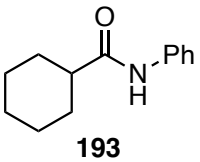


Peak	t_R [min]	Area [μV sec]	Area [%]
1	3.357	1272690	50.2
2	3.777	1263565	49.8

SFC chart of the enantio-enriched product

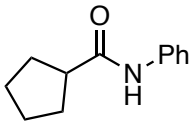


Peak	t_R [min]	Area [μV sec]	Area [%]
1	3.365	120429	12.7
2	3.787	125419	87.3



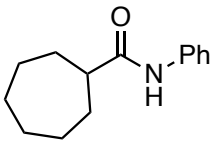
193

This product was identified by comparison with reported data.[22]



194

The reaction was conducted by procedure C. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 2:1, R_f = 0.5) and (DCM:MeOH = 60:1) to give **194** (11.1 mg, 0.058 mmol, 29%) as a white solid. This product was identified by comparison with reported data.[23]



195

The reaction was conducted by procedure C. The crude mixture was purified by preparative thin-layer chromatography (Hexane:AcOEt = 2:1, R_f = 0.5) and (DCM:MeOH = 60:1) to give **195** (15.1 mg, 0.069 mmol, 35%) as a white solid. This product was identified by comparison with reported data.[24]

5.5 References and Notes

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Chapter 6

Photoinduced Direct Addition of Alkylarenes to Imines

Table of Contents

Abstract: Herein reported is a direct addition reaction of simple alkylarenes to imines, which is driven by irradiation of the reactants with visible light in the presence of an iridium photoredox complex and a bromide anion. Phenethylamines including densely-substituted derivatives are synthesized in an atom-economical fashion.

6.1 Introduction

Phenethylamine presents a structural motif found in various bioactive molecules ranging from simple dopamine to densely-substituted ones such as BMS-795311 (Figure 6-1).[1] A direct addition reaction of simple alkylarenes to imines is potentially the most straightforward pathway leading to phenethylamine skeletons. For such straightforward pathways, there have been three catalytic reactions reported; (i) an anionic addition reaction of simple alkylbenzenes to *N*-*tert*-benzyl imines using a strong base as a catalyst,[2] (ii) a photoinduced addition reaction of benzyl ethers to *N*-aryl imines using an iridium photoredox catalyst together with a thiol catalyst for hydrogen atom transfer,[3] (iii) a photoinduced addition reaction of simple alkylbenzenes to α-carbonyl *N*-sulfonyl imines in the presence of a benzoquinone-type photocatalyst together with a copper Lewis acid.[4],[5] Herein reported is a new photoinduced addition reaction of simple alkylarenes to imines that is promoted by cooperative action of an iridium photoredox catalyst and a bromide anion.

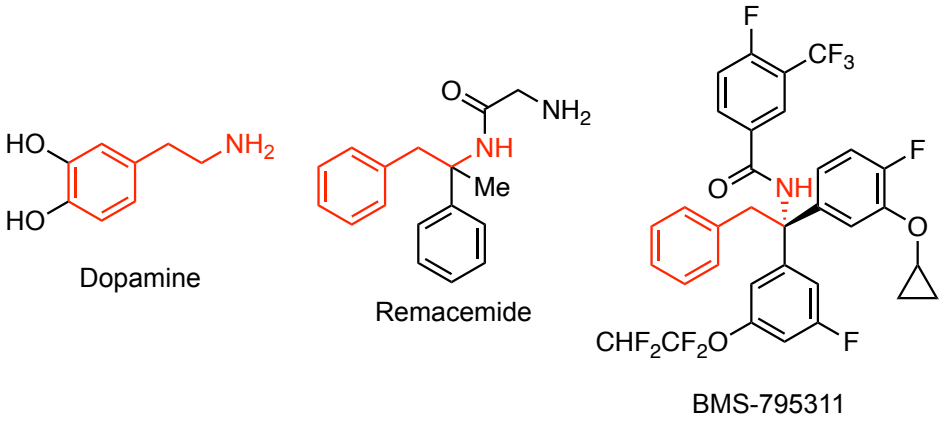


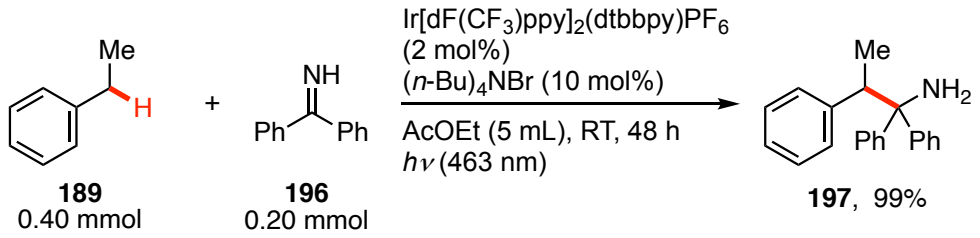
Figure 6-1. Phenethylamines in Pharmaceuticals

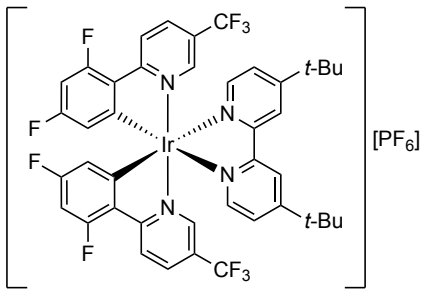
6.2 Results and Discussion

*6.2.1 Coupling of Ethylbenzene **189** with Benzophenone Imine **196***

Photoirradiation of a cationic iridium(III) complex in the presence of a bromide anion induces a single electron transfer from the bromide anion to iridium(III) to generate an iridium(II) species and a bromine radical.[6] The bromine radical abstracts hydrogen from a C–H bond next to oxygen, nitrogen, and an aromatic ring, furnishing the corresponding carbon radical. Such radical species have been exploited for synthetic purposes.[6b-d] In Chapter 2 and 5 were found a dehydrogenative cross-coupling reaction of benzylic and aldehydic C–H bonds[7] and a direct addition reaction of alkylarenes to isocyanates.[8] The continuing efforts to broaden the applicability of the iridium/bromide system to radical-mediated synthetic processes led the author to discover that imines acted as the suitable coupling partner of alkylbenzenes. As a representative reaction is shown in Scheme 6-1, a nickel catalyst is not essential.[9] A solution containing ethylbenzene **189** (0.40 mmol, 2.0 equiv), imine **196** (0.20 mmol), $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (2 mol%), and tetrabutylammonium bromide (10 mol%) in ethyl acetate (5 mL) was irradiated with blue LEDs (λ_{max} = 463 nm) at ambient temperature. After 48 h, the resulting mixture was evaporated under reduced pressure, and the residue was subjected to preparative thin-layer chromatography. Phenethylamine **197** was isolated in almost quantitative yield. Only a trace amount of homo-coupling product derived from **189** (2,3-diphenylbutane) was formed and there was essentially no homo-coupling product derived from **196**. No addition reaction occurred when either blue light, iridium, or bromide anion was absent, suggesting that each of them was indispensable.

Scheme 6-1. Coupling of Ethylbenzene **189** with Benzophenone Imine **196**





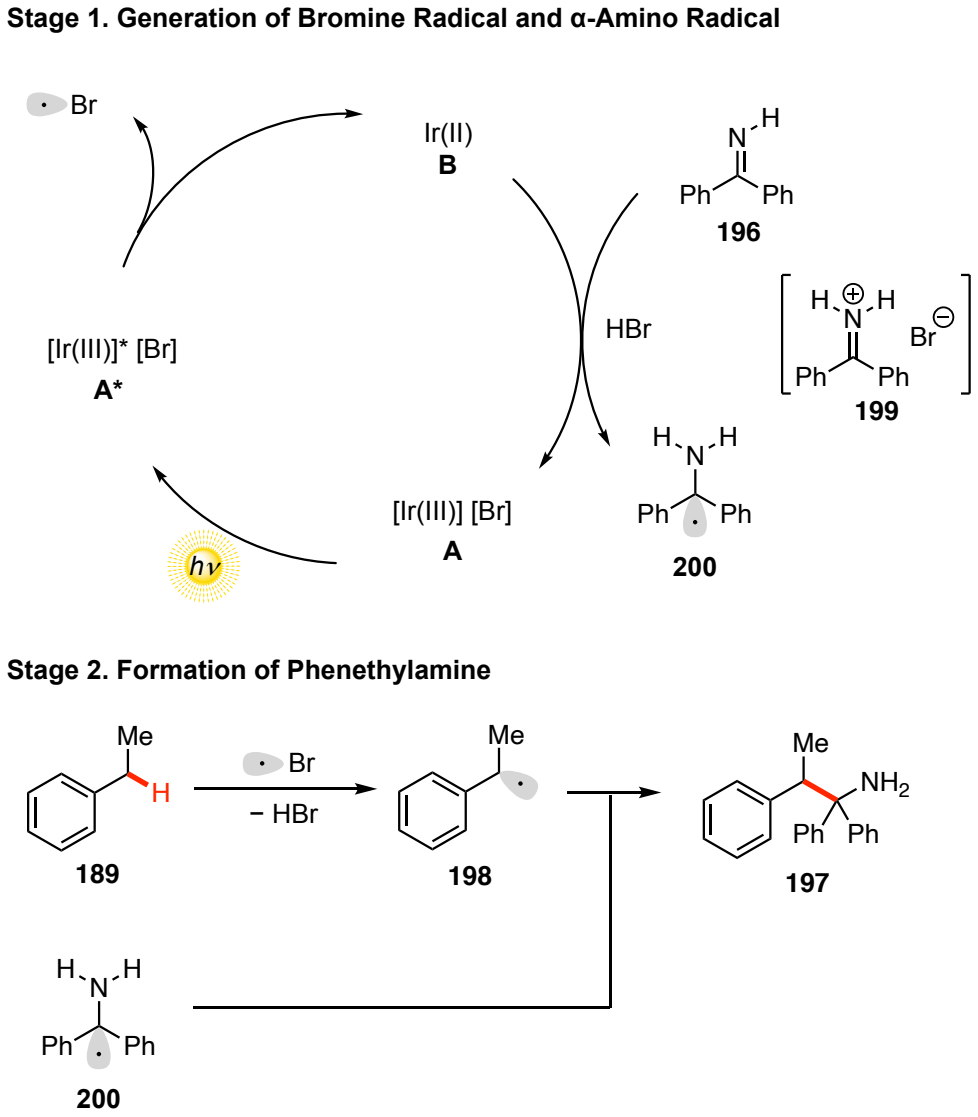
Ir[dF(CF$_3$)ppy]$_2$(dtbbpy)PF$_6$

6.2.2 Proposed Mechanism

Scheme 6-2 shows a mechanistic pathway that is plausible for the formation of phenethylamine **197**. It consists of two stages. Stage 1; A cationic iridium(III) species **A** absorbs light to get excited. A single electron transfers from the bromide anion to the excited state of the iridium(III) to generate an electronically neutral iridium(II) species together with a bromine radical.[6] The protonated imine is readily subject to reduction to α-amino radical **200** through a single electron transfer from the iridium(II) species. Stage 2; The bromine radical abstracts hydrogen from the benzylic C–H bond to furnish benzylic radical and hydrobromic acid, the latter of which protonates the imine **196**. Finally, the α-amino radical and benzylic radical undergo coupling to yield phenethylamine **197**. The persistent radical effect[10] explains the selective formation of the cross-coupling product. Whereas the benzylic radical **198** is a transient (short-lived) species that remains low in concentration, the α-amino radical **200** is a persistent (long-lived) species that can become abundant enough for radical-radical coupling. Since the bulky substituents around the radical center hinder the

homo-coupling of **200**, cross-coupling with **198** selectively takes place.

Scheme 6-2. Proposed Mechanism

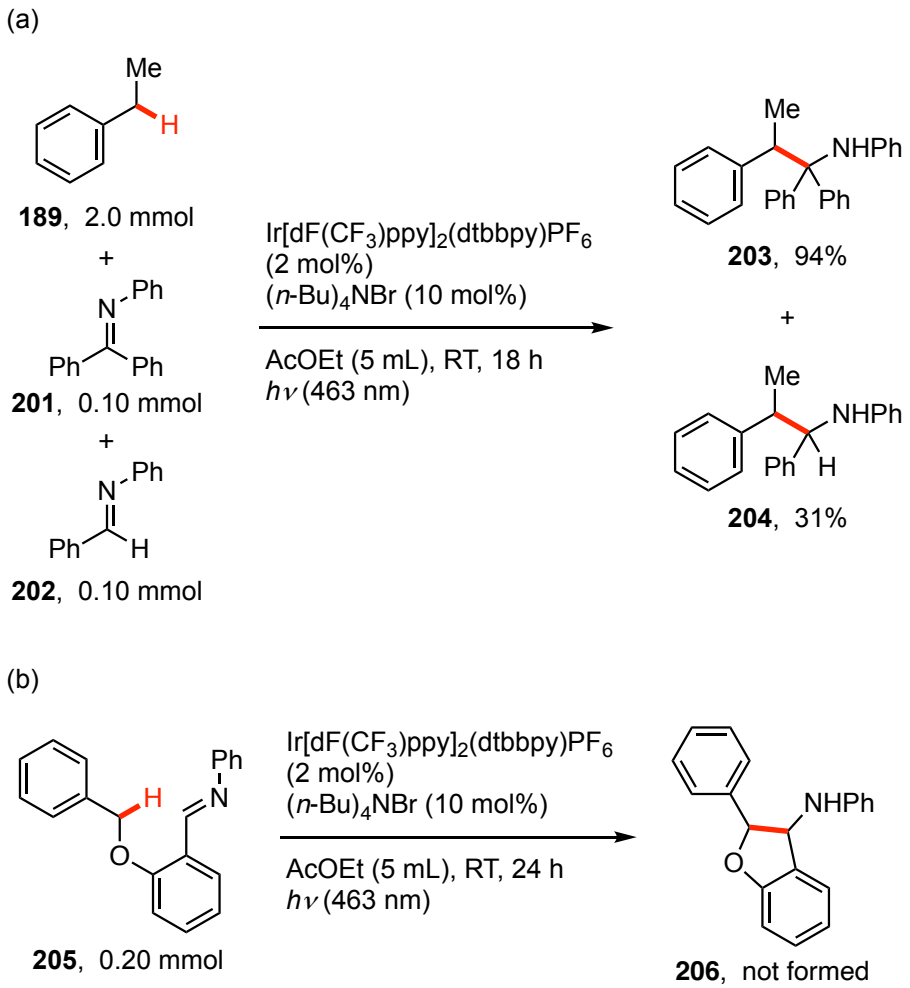


6.2.3 Mechanistic Studies

An alternative pathway through direct addition of benzylic radical **198** to the C–N double bond of imine **196** is also conceivable. However, the following experimental results suggested that it was less likely. When a mixture of benzophenone imine **201**

and benzaldimine **202** was subjected to the reaction with **189**, **189** preferentially coupled with **201** (Scheme 6-3a). This result indicates that the reaction rate depends on the reductive potential of the imine rather than the sterics around the imine carbon. In addition, imine **205** gave no cyclized product **206** and instead gave a mixture containing oligomeric products, suggesting that simple addition of a benzylic radical intermediate to the C–N double bond failed even in an intramolecular fashion (Scheme 6-3b).

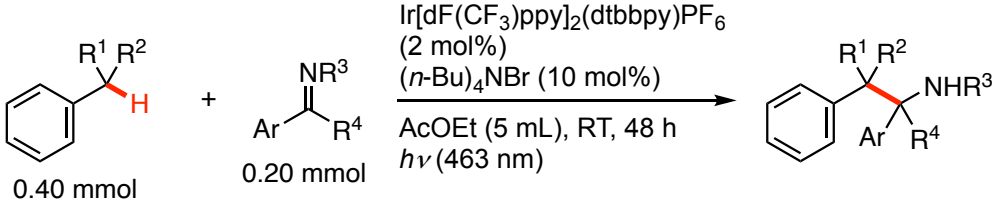
Scheme 6-3. Mechanistic Studies



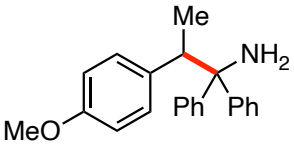
6.2.4 Substrate Scope

Various phenethylamines were synthesized from alkylarenes and imines, as listed in Table 6-1. Ethylbenzenes bearing a methoxy group at the para and ortho positions were successfully added to **196** to give the corresponding phenethylamines **207** and **208**. A phenolic hydroxy group was tolerated under the present reaction conditions, enabling the synthesis of tyramine derivative **209** without protection. A bromo group on the benzene ring, which would serve for further functionalization, survived to give the bromo- substituted phenethyl amine **210**. In addition to alkylbenzenes, 2-ethylthiophene was also a viable substrate (**211**). Substituents at the benzylic position were allowed as well. Benzyl amine and ether reacted to give 1,2-diamine **212** and 2-amino ether **213** in 75 and 85% yields, respectively. Isopropylbenzene was successfully coupled with **196** to synthesize densely-substituted phenethylamine **215** in 67% yield. Of note was that two tertiary carbons were readily connected. Synthesis of such a phenethylamine bearing a sterically crowded carbon–carbon bond is significantly limited, possibly because of the paucity of appropriate synthetic methods. Simple toluene, on the other hand, was less reactive due to the larger bond dissociation energy (BDE) of the C–H bond, and the yield of the phenethylamine was 28% even when 5 equiv of toluene was used. For the imines, aryl-substituted aldimines and ketimines participated in the reaction to give the corresponding phenethylamines (**203**, **204**, and **216-219**). On the other hand, imines derived from aliphatic ketones failed afford the coupling product.

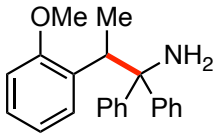
Table 6-1. Scope[a]



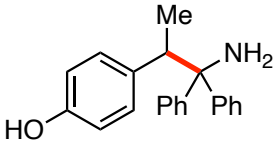
Scope of Alkylarenes



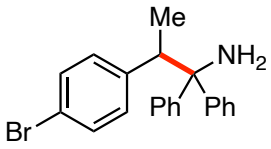
207, 96%



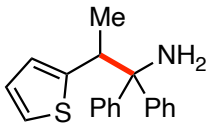
208, 45%



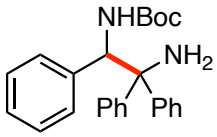
209, 56%



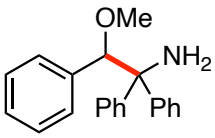
210, 70%



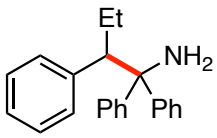
211, 83%



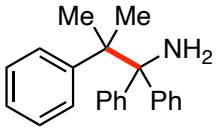
212, 75%



213, 85%

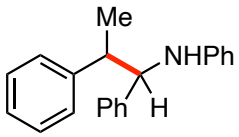


214, 73%

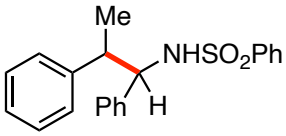


215, 67%

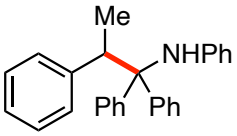
Scope of Imines



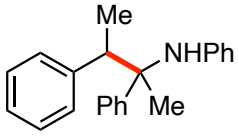
204, 62%



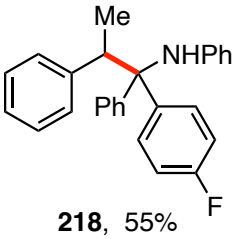
216, 44%



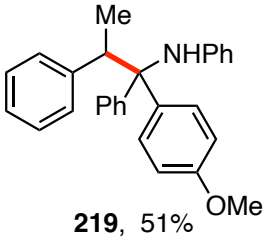
203, 60%



217, 63%[b]



218, 55%



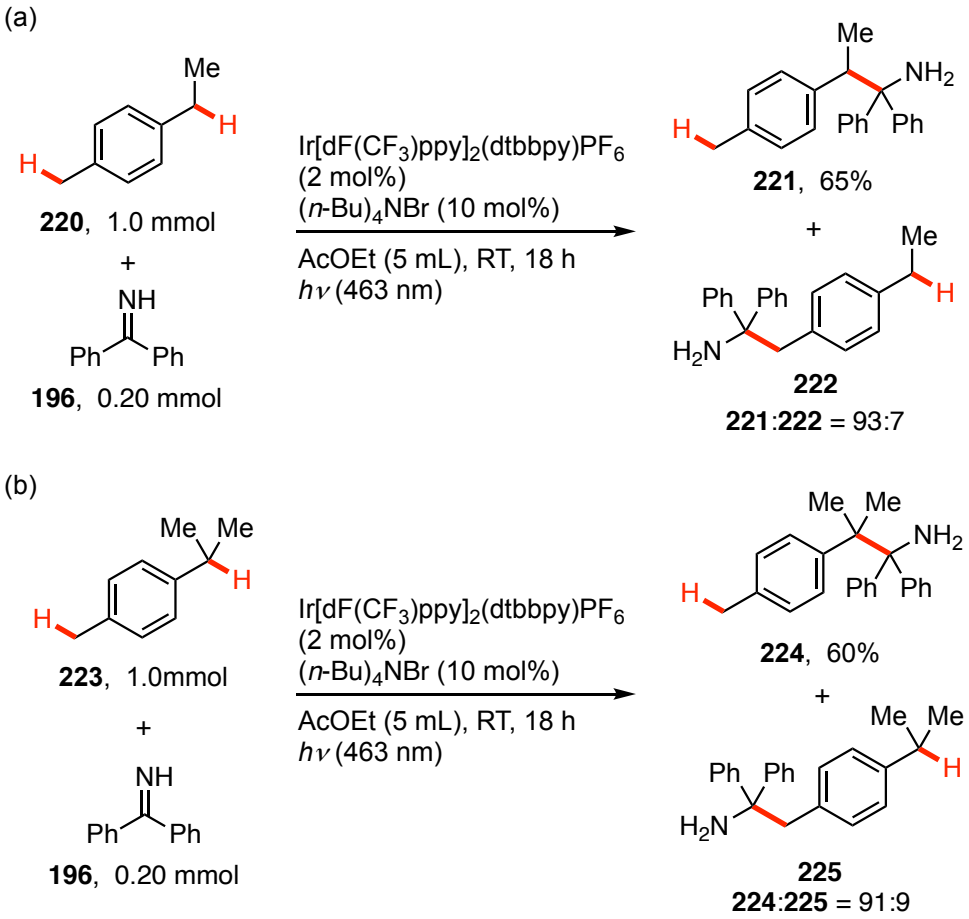
219, 51%

[a] Reaction conditions: alkylarene (0.40 mmol, 2.0 equiv), imine (0.20 mmol), Ir[dF(CF3)ppy]2(dtbbpy)PF6 (2 mol%), tetrabutylammonium bromide (10 mol%), ethyl acetate (5 mL), blue LEDs (λ_{max} = 463 nm), ambient temperature, 48 h. [b] Obtained as a diastereomer mixture (1:1~1:2). [c] **189** (5.0 equiv).

6.2.5 *Studies of Site-Selectivity*

The site-selectivity of the present radical-based method marked a sharp contrast with that of the anionic addition reaction.[2] It has been reported that 1-ethyl-4-methylbenzene **220** and 1-isopropyl-4-methylbenzene **223** couple with a benzaldimine selectively at the methyl group under the amide/alkoxide catalysis.[2a] On the other hand, **220** and **223** coupled with **196** at the ethyl and isopropyl groups, respectively, in preference to the methyl group with the present system (Scheme 6-4). The site-selectivity can be ascribed to the smaller BDEs of secondary and tertiary C–H bonds than that of the methyl C–H bond.[11]

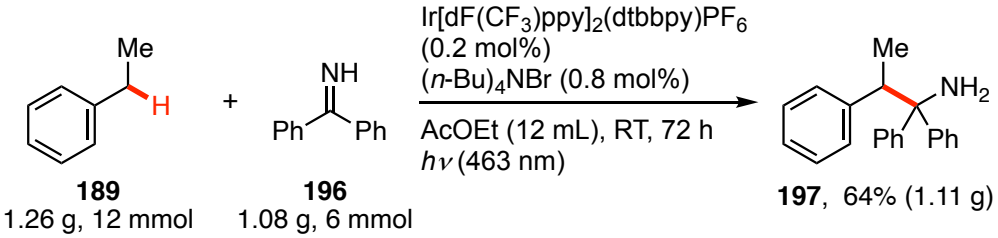
Scheme 6-4. Site-Selectivity



6.2.6 Gram-Scale Reaction

Finally, a reaction of ethylbenzene **189** with imine **196** in a gram scale using only 0.2 mol% of the iridium complex and 0.8 mol% of a bromide anion was performed (Scheme 6-5). After 72 h, the reaction mixture was purified by column chromatography on silica gel to afford 1.11 g (3.9 mmol, 64%) of phenethylamine **197**.

Scheme 6-5. Gram-Scale Reaction



189
1.26 g, 12 mmol

196
1.08 g, 6 mmol

197, 64% (1.11 g)

6.3 Summary

In conclusion, a new photoinduced direct addition reaction of alkylarenes to imines was developed. It provides the most straightforward and atom-economical pathway to phenethylamines including densely-substituted ones, which are otherwise difficult to prepare. The present synthetic method would serve to unveil unknown functions of phenethylamine derivatives such as physiological activities.

6.4 Experimental Section

6.4.1 General Method and Materials

General Methods

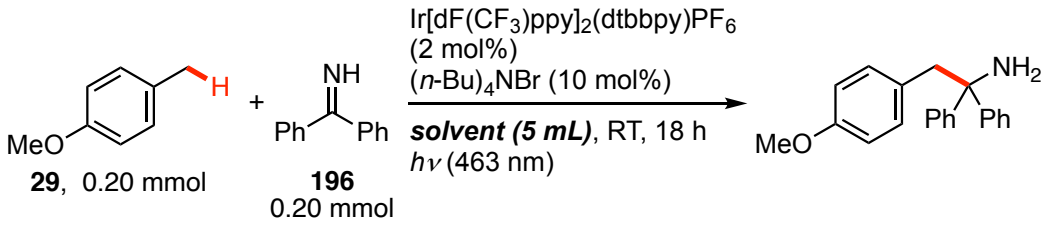
All reactions were carried out using flame-dried glassware under a nitrogen atmosphere. Photoreactions were carried out with blue LEDs (Kessil, A160WE, 40W). ^{1}H and ^{13}C NMR spectra were recorded on JEOL JNM-ECZ400S/L1(^{1}H at 400.44 MHz and ^{13}C at 100.69 MHz). NMR data were obtained in $CDCl_3$. Chemical shifts are recorded in δ ppm referenced to a residual $CDCl_3$ (δ = 7.26 for ^{1}H, δ = 77.0 for ^{13}C) Preparative thin-layer chromatography (PTLC) was performed on silica gel plated with PF254 indicator (Merck). IR measurements were performed on FTIR SHIMADZU Affinity-1S spectrometer fitted with a Pike Technologies MIRacle Single Reflection ATR adapter. High-resolution mass spectra were recorded on JEOL JMS-700 (EI), Thermo Fisher Scientific Exactive (ESI, APCI). Flash column chromatography was performed with silica gel 60N (Kanto).

Materials

N-Boc-benzylamine,[12] *N*-(phenylmethylene)benzenesulfonamide,[13] *N*-phenylbenzophenoneimine **201**,[14] *N*-phenylacetophenoneimine **202**,[15] *N*-phenyl-4-fluorobenzophenoneimine,[14] *N*-phenyl-4-methoxybenzophenoneimine,[14] and $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$[16] were prepared according to the literature procedure. Other materials were purchased from commercial suppliers and used as received.

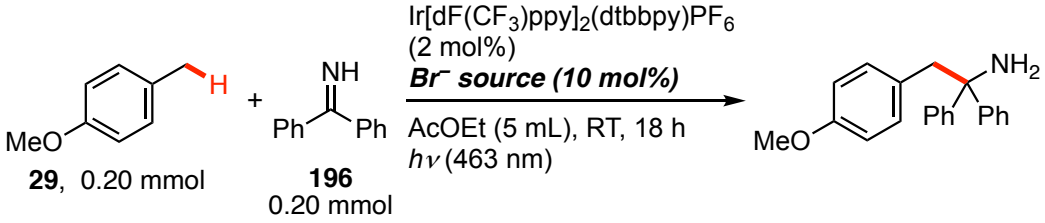
6.4.2 Optimization Studies

Table 6-2. Screening of Solvents



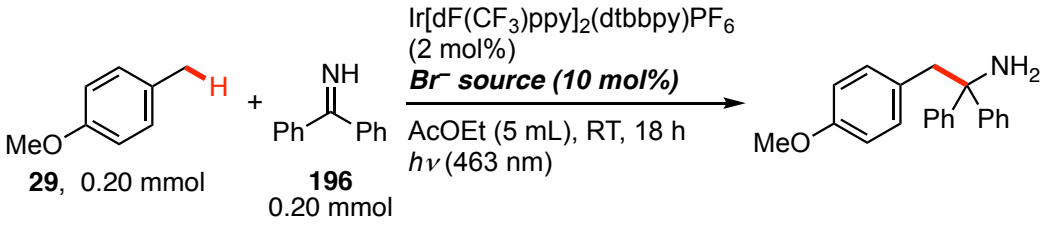
entry	solvent	NMR yield of product
1	AcOEt	30%
2	MeCN	<5%
3	EtOH	<5%
4	DMF	0%
5	acetone	18%
6	benzene	12%

Table 6-3. Screening of Bromide Sources



entry	Br^- source	NMR yield of product
1	$(n\text{-Bu})_4NBr$	30%
2	$ZnBr_2$	<5%
3	LiBr	22%
4	Ph_4PBr	24%

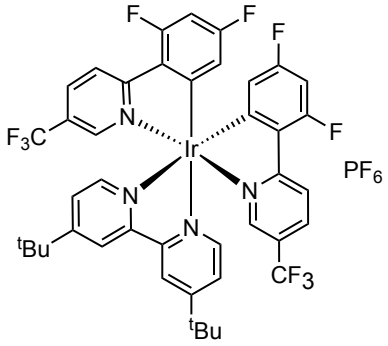
Table 6-4. Screening of Photocatalysts



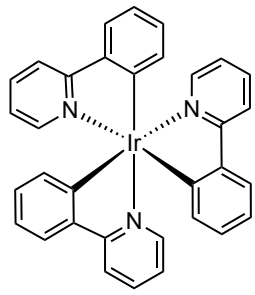
29, 0.20 mmol

196
0.20 mmol

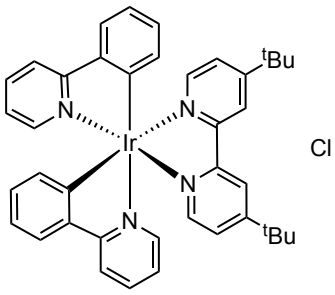
entry	photocatalyst	NMR yield of product
1	$Ir(dFCF_3ppy)_2(dtbbpy)PF_6$	30%
2	$Ir(ppy)_3$	0%
3	$Ir(ppy)_2(dtbbpy)Cl$	0%
4	Ph-Acr-Me•ClO_4	0%
5	Mes-Acr-Me•ClO_4	0%
6	phenoxazine catalyst	0%



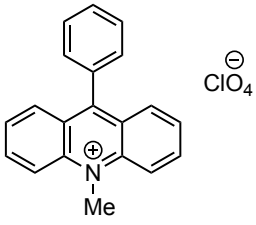
$Ir(dFCF_3ppy)_2(dtbbpy)PF_6$



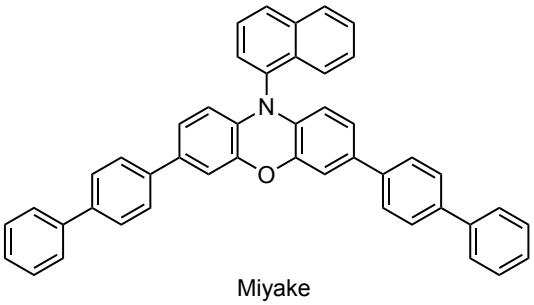
$Ir(ppy)_3$



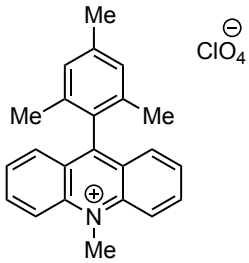
$[Ir(ppy)_2dtbbpy]Cl$



Ph-Acr-Me•ClO_4



Miyake

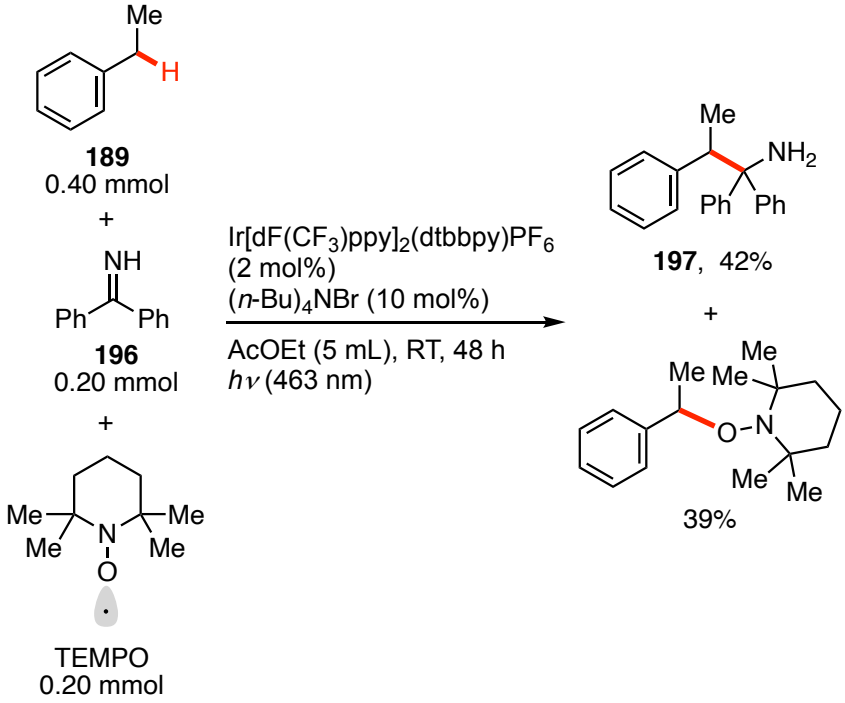


Mes-Acr-Me•ClO_4

Figure 6-2. Structures of the Photocatalysts

6.4.3 Radical Trapping Experiment

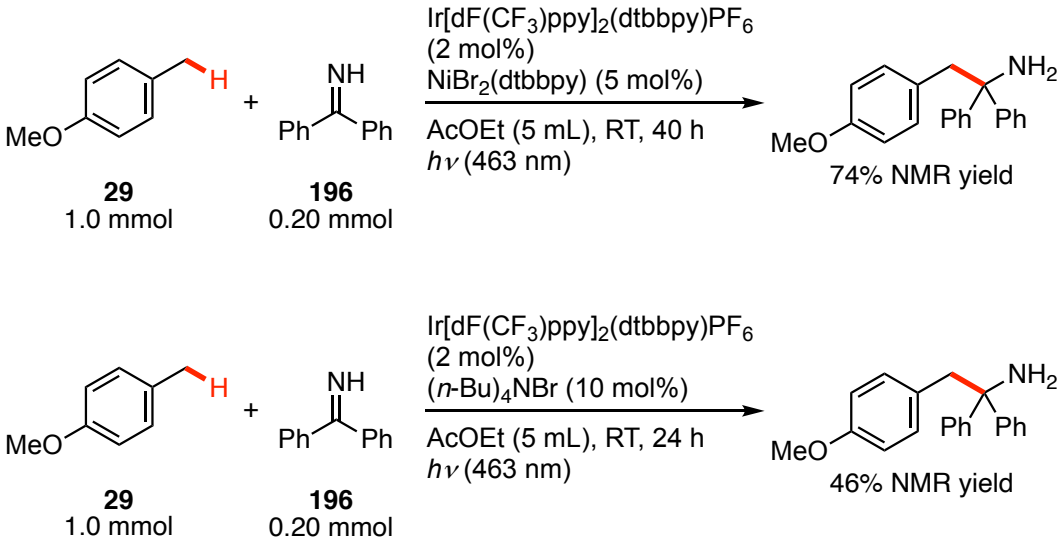
Scheme 6-6. Radical Trapping Experiment



To a 5 mL Schlenk flask, ethylbenzene **189** (2.0 equiv, 48.8 μL), benzophenone imine **196** (0.20 mmol, 36.2 mg), TEMPO (0.20 mmol, 31.3 mg), (*n*-Bu)$_4$NBr (10 mol%, 6.5 mg) and Ir(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$ (2 mol%, 4.5 mg) were dissolved in AcOEt (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred and irradiated with blue LEDs (λ_{max} = 463 nm, 150 W/m^2 at 5 cm from the light source), with being cooled by a fan. After 48 hours, the reaction mixture was concentrated under reduced pressure to afford a residue. The yields of products were determined by ^{1}H NMR.

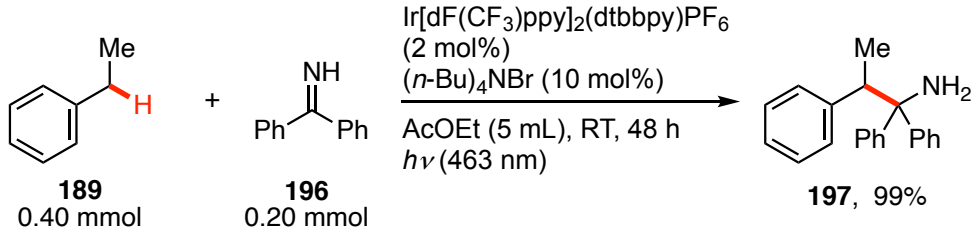
6.4.4 Reaction Using $NiBr_2(dtbbpy)$

Scheme 6-7. Reaction Using $NiBr_2(dtbbpy)$



6.4.5 A Typecal Procedure

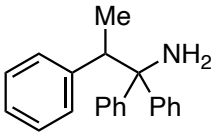
Scheme 6-8. A Typical Procedure of the Cross-Coupling



189 0.40 mmol + **196** 0.20 mmol → **197**, 99%

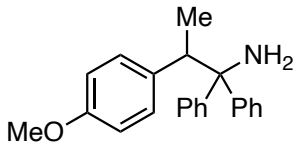
To a 5 mL Schlenk flask, ethylbenzene **189** (2.0 equiv, 48.8 μL), benzophenone imine **196** (0.20 mmol, 36.2 mg), (n-Bu)$_4$NBr (10 mol%, 6.5 mg) and Ir(dFCF$_3$ppy)$_2$(dtbbpy)PF$_6$ (2 mol%, 4.5 mg) were dissolved in AcOEt (5 mL) under a nitrogen atmosphere. The reaction mixture was stirred and irradiated with blue LEDs (λ_{max} = 463 nm, 150 W/m^2 at 5 cm from the light source), with being cooled by a fan. After 48 hours, the reaction mixture was concentrated under reduced pressure to afford a mixture containing amine. The residue was purified by preparative thin-layer chromatography (PTLC) (Hexane/AcOEt = 2/1) to give amine **197** (56.8 mg, 0.198 mmol, 99%) as a yellow oil.

6.4.6 Spectroscopic Data of the Products



197

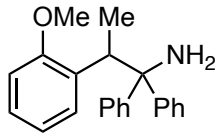
^{1}H NMR: δ = 7.51-7.49 (m, 2H), 7.32-7.30 (m, 2H), 7.27-7.23 (m, 1H), 7.21-7.16 (m, 2H), 7.14-7.02 (m, 6H), 6.89-6.82 (m, 2H), 3.97 (q, J = 7.1 Hz, 1H), 1.36 (d, J = 7.1 Hz, 3H); ^{13}C NMR: δ = 147.7, 146.2, 142.0, 129.7, 127.8, 127.7, 127.6, 127.3, 126.8, 126.4, 126.3, 125.9, 64.4, 47.7, 16.8; IR (neat): 3385, 3278, 1710, 1490, 1165, 945, 696 cm^{-1}; HRMS (EI) *m/z*: [M + H]$^+$ Calcd for C$_{21}$H$_{20}$N 286.1590; Found 286.1589.



207

Prepared according to the general procedure using 56.7 μL of *p*-ethylanisole (0.40 mmol). The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine **207** (60.6 mg, 0.19 mmol, 96%) as a yellow oil.

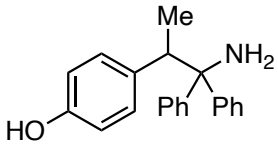
^{1}H NMR: δ = 7.51-7.45 (m, 2H), 7.34-7.29 (m, 2H), 7.27-7.20 (m, 3H), 7.17-7.12 (m, 2H), 7.11-7.05 (m, 1H), 6.79-6.71 (m, 2H), 6.66-6.59 (m, 2H), 3.94 (q, *J* = 7.2 Hz, 1H), 3.73 (s, 3H), 1.81 (br, 2H), 1.33 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ = 158.0, 147.7, 145.9, 133.8, 130.6, 127.8, 127.7, 127.6, 126.8, 126.3, 125.9, 112.7, 64.4, 55.1, 46.8, 16.9; IR (neat): 3383, 3318, 2908,1510, 1242, 696 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{22}H_{23}NONa$ 340.1672; Found 340.1679.



208

Prepared according to the general procedure using 56.8 μL of 2-ethylanisole (0.40 mmol). The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine **208** (28.8 mg, 0.091 mmol, 45%) as a yellow oil.

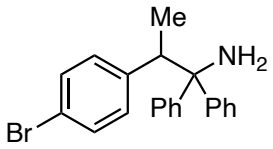
^{1}H NMR: δ = 7.51-7.43 (m, 2H), 7.35-7.22 (m, 3H), 7.17-7.02 (m, 6H), 6.91-6.87 (m, 1H), 6.82-6.76 (m, 1H), 6.68-6.62 (m, 1H), 4.66 (q, *J* = 7.2 Hz, 1H), 3.52 (s, 3H), 1.85 (br, 2H), 1,27 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR: δ = 157.1(1C), 148.6(1C), 146.1(1C), 131.1(1C), 129.4(1C), 128.4(2C), 127.4(2C), 127.13(3C), 127.08(2C), 126.3(1C), 125.7(1C), 119.7(1C), 109.7(1C), 64.9(1C), 55.0(1C), 37.1(1C), 17.3(1C); IR (neat): 3390, 3309, 2835, 1659, 1597, 1489, 1236, 1125, 1026, 696.3 cm^{-1}; HRMS (ESI) *m/z*: $[M - NH_2]^+$ Calcd for $C_{22}H_{21}O$ 301.1587; Found 301.1592.



209

Prepared according to the general procedure using 48.9 mg of 4-ethylphenol (0.40 mmol). The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine **209** (33.8 mg, 0.110 mmol, 56%) as a yellow oil.

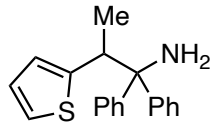
^{1}H NMR: δ = 7.49-7.43 (m, 2H), 7.37-7.28 (m, 2H), 7.26-7.24 (m, 1H), 7.22-7.20 (m, 2H), 7.16-7.13 (m, 2H), 7.10-7.04 (m, 1H), 6.72-6.63 (m, 2H), 6.57-6.46 (m, 2H), 3.91 (q, *J* = 7.2 Hz, 1H), 1.31 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ = 154.6, 147.3, 145.2, 133.0, 130.8, 128.0, 127.8, 127.5, 127.1, 126.5, 126.2, 114.5, 64.7, 46.7, 17.1; IR (neat): 3343, 3275, 1512, 1445, 829, 766, 698 cm^{-1}; HRMS (EI) *m/z*: $[M]^{+}$Calcd for $C_{21}H_{20}ON$ 302.1539; Found 302.1541.



210

Prepared according to the general procedure using 55.2 μL of 4-bromo-ethylbenzene (0.40 mmol). The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine **210** (51.5 mg, 0.142 mmol, 70%) as a yellow oil.

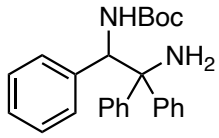
^{1}H NMR: δ = 7.51-7.46 (m, 2H), 7.35-7.30 (m, 2H), 7.27-7.22 (m, 2H), 7.19-7.04 (m, 6H), 6.77-6.71 (m, 2H), 3.91 (q, *J* = 7.1 Hz, 1H), 1.74 (br, 2H), 1,33 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ = 147.4, 146.0 141.2, 131.4, 130.3, 127.80, 127.78, 127.7, 126.6, 126.5, 126.1, 120.2, 64.2, 47.2, 16.8; IR (neat): 3388, 3375, 1489, 1442, 1076, 1031, 1002, 818, 748, 696 cm^{-1}; HRMS (ESI) *m/z*: $[M - NH_2]^{+}$ Calcd for $C_{21}H_{18}Br$ 349.0586; Found 349.0593.



211

Prepared according to the general procedure using 45.4 μL of 2-ethylthiophene (0.40 mmol). The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine **211** (48.5 mg, 0.17 mmol, 83%) as a colorless oil.

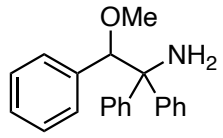
^{1}H NMR: δ = 7.62-7.53 (m, 2H), 7.40-7.28 (m, 4H), 7.26-7.14 (m, 3H), 7.12-7.06 (m, 1H), 7.04-6.98 (m, 1H), 6.81-6.75 (m, 1H), 6.58-6.52 (m, 1H), 4.39 (q, *J* = 7.0 Hz, 1H), 1.93 (br, 2H), 1.37 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR: δ = 147.3, 146.3, 145.6, 128.1, 127.8, 127.0, 126.4, 126.3, 126.1, 125.9, 125.8, 123.7, 64.0, 43.8, 18.2; IR (neat): 3649, 3568, 2982, 1489, 1447, 1197, 957, 831, 745 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{19}H_{18}NS$ 292.1154; Found 292.1155.



212

Prepared according to the general procedure using 82.9 mg of *N*-boc-benzylamine (0.40 mmol). The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine **212** (58.2 mg, 0.15 mmol, 75%) as a colorless oil.

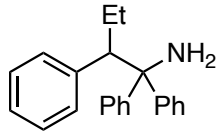
^{1}H NMR: δ = 7.46-7.40 (m, 2H), 7.37-7.31 (m, 2H), 7.27-7.21 (m, 1H), 7.15-7.00 (m, 8H), 6.88-6.78 (m, 2H), 6.00 (br, 1H), 5.72-5.53 (br, 1H), 1.96 (br, 2H), 1.37 (s, 9H); ^{13}C NMR: δ = 155.2(1C), 146.5(1C), 145.2(1C), 138.9(1C), 128.32(2C), 128.29(2C), 127.8(2C), 127.4(2C), 126.9(3C), 126.7(1C), 126.53(2C), 126.48(1C), 79.5(1C), 65.0(1C), 59.8(1C), 28.5(3C); IR (neat): 3385, 3279, 1711, 1514, 1368, 1165, 945, 698 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{25}H_{28}N_2O_2Na$ 411.2043; Found 411.2047.



213

Prepared according to the general procedure using 50.9 μL of benzylmethylether (0.40 mmol). The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine **213** (51.3 mg, 0.169 mmol, 85%) as a colorless oil.

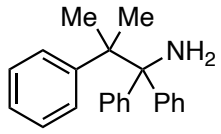
^{1}H NMR: δ = 7.52-7.46 (m, 2H), 7.35-7.28 (m, 2H), 7.26-7.21 (m, 1H), 7.19-7.02 (m, 8H), 6.87-6.83 (m, 2H), 5.09 (s, 1H), 3.31 (s, 3H); ^{13}C NMR: δ = 146.8, 145.4, 136.8, 128.8, 127.9, 127.8, 127.6, 127.4, 127.3, 127.0, 126.4, 126.3, 87.2, 65.2, 56.5; IR (neat): 3649, 3365, 1489, 1094, 1013, 696 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{21}NONa$ 326.1515; Found 326.1520.



214

Prepared according to the general procedure using 55.9 μL of *n*-propylbenzene (0.40 mmol). The residue was purified by preparative thin-layer chromatography (PTLC)(Hexane/AcOEt=2/1) to give amine **214** (43.9 mg, 0.15 mmol, 73%) as a yellow oil.

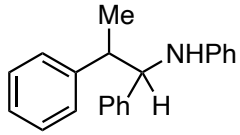
^{1}H NMR: δ= 7.43-7.41 (m, 2H), 7.33-7.30 (m, 2H), 7.26-7.23 (m, 1H), 7.13-7.05 (m, 8H), 6.86-.6.83 (m, 2H), 3.57 (dd, *J* = 2.0 Hz, *J* = 11.8 Hz, 1H), 1.95 (m, 1H), 1.70 (m, 3H), 0.77 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR: δ= 147.9, 146.4, 139.8, 130.3, 127.8, 127.65, 127.62, 127.4, 126.7, 126.4, 126.3, 125.9, 64.8, 56.6, 23.7, 12.7; IR (neat): 3379, 3318, 3026, 2960, 1445, 1493, 698 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{22}N$ 300.1747; Found 300.1748.



215

Prepared according to the general procedure using 55.9 μL of isopropylbenzene (0.40 mmol). The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine **215** (40.1 mg, 0.13 mmol, 67%) as a colorless oil.

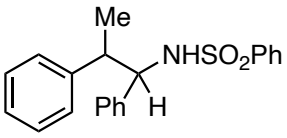
^{1}H NMR: δ = 7.41-7.34 (m, 4H), 7.22-7.01 (m, 11H), 1.56 (s, 6H); ^{13}C NMR: δ = 147.5, 147.0, 129.24, 129.16, 127.0, 126.9, 126.2, 125.8, 67.1, 46.8, 27.2; IR (neat): 3649, 3587, 1990, 1541, 1226, 870 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{22}N$ 300.1747; Found 300.1753.



204

Prepared according to the general procedure using 36.3 mg of benzylideneaniline (0.20 mmol). The residue was purified by PTLC (Hexane/AcOEt = 5/1) to give amine **204** (35.6 mg, 0.124 mmol, 62%) as a colorless oil consisting of two diastereomers (d.r. 1:1, as determined by ^{1}H NMR spectroscopy).

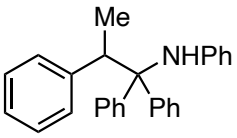
^{1}H NMR (mixture of diastereomers, both isomers quoted): δ = 7.35-7.28 (m, 6H), 7.24-7.16 (m, 10H), 7.14-6.92 (m, 8H), 6.70-6.50 (m, 2H), 6.46-6.43 (m, 2H), 6.38-6.33 (m, 2H), 4.56-4.48 (m, 1H), 4.36-4.30 (m, 1H), 4.17 (br, 1H), 4.00 (br, 1H), 3.27-3.20 (m, 1H), 3.04-2.96 (m, 1H), 1.33 (d, *J* = 7.2 Hz, 3H), 1.17 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR: δ = 147.5(1C), 147.2(1C), 143.2(1C), 142.8(1C), 142.7(1C), 141.4(1C), 129.0(2C), 128.9(2C), 128.7(2C), 128.3(2C), 128.2(2C), 128.1(2C), 128.0(2C), 127.7(2C), 127.5(2C), 127.4(2C), 127.1(1C), 127.0(1C), 126.8(1C), 126.6(1C), 117.2(2C), 113.5(4C), 63.8(1C), 63.0(1C), 47.4(1C), 45.8(1C), 19.6(1C), 16.2(1C); IR (neat): 3389, 3022, 1599, 1499, 1312, 1180, 1076, 868 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{21}H_{20}N$ 286.1590; Found 286.1594.



216

Prepared according to the general procedure using 49.1 mg of *N*-(Phenylmethylene)benzenesulfonamide (0.20 mmol). The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine **216** (30.9 mg, 0.088 mmol, 44%) as a yellow oil consisting of two diastereomers (d.r. 1:2, as determined by ^{1}H NMR spectroscopy).

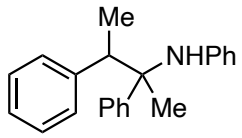
^{1}H NMR (mixture of diastereomers, both isomers quoted): δ = 7.50-7.46 (m, 2H), 7.41-7.36 (m, 6H), 7.36-7.32 (m, 2H), 7.27-7.18 (m, 12H), 7.17-7.10 (m, 8H), 7.05-6.96 (m, 12H), 6.93-6.87 (m, 2H), 6.72-6.67 (m, 2H), 4.84 (br, 1H), 4.61 (br, 2H), 4.45 (dd, *J* = 7.0 Hz, 8.4 Hz,1H), 4.33-4.27 (dd, *J* = 5.0 Hz, 8.6 Hz, 2H), 3.13 (dq, *J* = 7.1 Hz, 7.2 Hz, 1H), 2.91 (dq, *J* = 7.0 Hz, 8.6 Hz, 2H) 1.29 (d, *J* = 7.2 Hz, 3H), 1.04 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR: δ = 141.5, 141.2, 140.2, 139.9, 139.4, 138.5, 132.0, 129.4, 129.0, 128.6, 128.5, 128.21, 128.19, 128.1, 127.74, 127.70, 127.53, 127.50, 127.4, 127.2, 127.1, 127.0, 126.9, 126.8, 63.5, 63.3, 46.6, 45.8, 19.1, 17.3; IR (neat): 3281, 2970, 1541, 1090, 1319, 1155, 1089. 752, 698 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{21}NO_2SNa$ 374.1185; Found 374.1190.



203

Prepared according to the general procedure using 51.5 mg of *N*-Phenylbenzophenoneimine (0.20 mmol). The residue was purified by PTLC (Hexane/AcOEt = 5/1) to give amine **203** (38.6 mg, 0.11 mmol, 53%) as a colorless oil.

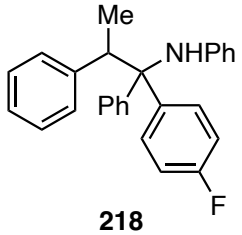
^{1}H NMR: δ = 7.65-7.58 (m, 2H), 7.46-7.37 (m, 2H), 7.34-7.30 (m, 3H), 7.27-7.22 (m, 2H), 7.20-7.15 (m, 2H), 7.14-7.07 (m, 2H), 6.85-6.77 (m, 2H), 6.68-6.60 (m, 2H), 6.49-6.40 (m, 1H), 6.21-6.12 (m, 2H) 4.73 (m, 1H), 3.74 (q, *J* = 7.3 Hz, 1H), 1.22 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR: δ = 145.6, 141.9, 141.2, 138.4, 130.6, 129.6, 129.1, 128.2, 127.73, 127.65, 127.2, 127.1, 126.9, 126.7, 116.8, 115.4, 68.6, 53.9, 17.7; IR (neat): 3587, 3417, 1599, 1497, 906.5, 698 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{27}H_{24}N$ 362.1903; Found 362.1903.



217

Prepared according to the general procedure using 39.1 mg of *N*-phenylacetophenone imine (0.20 mmol). The residue was purified by PTLC (Hexane/AcOEt = 9/1) to give amine **217** (37.9 mg, 0.13 mmol, 63%) as a yellow oil consisting of two diastereomers (d.r. 1:1, as determined by ^{1}H NMR spectroscopy).

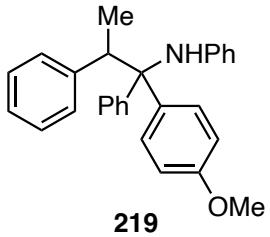
^{1}H NMR (mixture of diastereomers, both isomers quoted): δ = 7.50 (d, *J* = 7.4 Hz, 2H), 7.36-7.31 (m, 4H), 7.30-7.25 (m, 4H), 7.24-7.14 (m, 8H), 7.02-6.98 (m, 2H), 6.98-6.92 (m, 2H), 6.91-6.85 (m, 2H), 6.59-6.50 (m, 2H), 6.29-6.23 (m, 2H), 6.15-6.08 (m, 2H), 4.35-4.00 (br, 2H), 3.08-2.97 (m, 2H), 1.70 (s, 3H), 1.63 (s, 3H), 1.25 (d, *J* = 7.2 Hz, 3H), 1.12 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR: δ = 146.0(1C), 145.9(1C), 145.3(1C), 143.8(1C), 141.9(2C), 129.6(2C), 129.2(2C), 128.5(4C), 128.22(2C), 128.17(2C), 127.9(2C), 127.71(2C), 127.66(2C), 127.3(2C), 127.2(1C), 126.8(1C), 126.5(1C), 126.3(1C), 117.2(1C), 117.0(1C), 115.8(2C), 115.6(2C), 61.2(1C), 61.0(1C), 53.0(1C), 52.8(1C), 22.6(1C), 18.5(1C), 15.9(1C), 15.8(1C); IR (neat): 3540, 3401, 1490, 840.5, 700 cm^{-1}; HRMS(EI) *m/z*: $[M]^{+}$ Calcd for $C_{22}H_{22}N$ 300.1747; Found 300.1752.



218

Prepared according to the general procedure using 55.1 mg of *N*-phenyl-4-fluorobenzophenone imine (0.20 mmol). The residue was purified by PTLC (Hexane/AcOEt = 5/1) to give amine **218** (41.8 mg, 0.11 mmol, 55%) as a yellow green solid consisting of two diastereomers (d.r. 1:2, as determined by ^{1}H NMR spectroscopy).

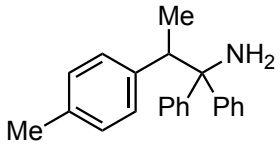
^{1}H NMR (mixture of diastereomers, both isomers quoted): δ = 7.60-7.45 (m, 4H), 7.44-7.36 (m, 4H), 7.35-7.31 (m, 4H), 7.28-7.22 (m, 2H), 7.21-7.09 (m, 6H), 7.04-6.96 (m, 2H), 6.94-6.88 (m, 2H), 6.85-6.78 (m, 4H), 6.69-6.59 (m, 4H), 6.53-6.43 (m, 2H), 6.16-6.14 (m, 4H), 4.76-4.66 (m, 2H), 3.74-3.63 (m, 2H), 1.29-1.11 (m, 6H); ^{13}C NMR: δ = 161.8 (d, *J* = 247 Hz), 161.4 (d, *J* = 247 Hz), 145.4, 145.3, 141.6, 141.0, 138.4, 137.4 (d, *J* = 3.9 Hz), 133.9 (d, *J* = 2.9 Hz), 132.3 (d, *J* = 7.7 Hz), 130.9 (d, *J* = 7.7 Hz), 130.4, 129.54, 129.49, 129.0, 128.3, 128.2, 127.85, 127.79, 127.3, 127.19, 127.17, 127.0, 126.9, 117.0, 115.5, 115.41, 115.36, 114.3 (d, *J* = 21.2 Hz), 114.0 (d, *J* = 21.2 Hz), 74.1, 68.3, 54.03, 53.95, 17.6, 17.5, two carbons are missing presumably due to overlapping; IR (neat): 3588, 2972, 2364, 1636, 1541, 872 cm^{-1}; HRMS (APCI) *m/z*: [M + Cl]$^{-}$ Calcd for $C_{27}H_{24}FNCl$ 416.1587; Found 416.1591.



219

Prepared according to the general procedure using 57.5 mg of *N*-phenyl-4-methoxybenzophenone imine (0.20 mmol). The residue was purified by PTLC (Hexane/AcOEt = 5/1) to give amine **219** (40.4 mg, 0.103 mmol, 51%) as a colorless oil consisting of two diastereomers (d.r. 1:1, as determined by ^{1}HNMR spectroscopy).

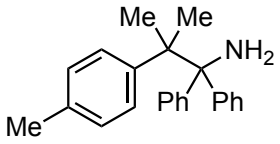
^{1}H NMR (mixture of diastereomers, both isomers quoted): δ = 7.65-7.57 (m, 2H), 7.55-7.46 (m, 2H), 7.42-7.38 (m, 2H), 7.36-7.21 (m, 8H), 7.20-7.06 (m, 6H), 6.90-6.74 (m, 8H), 6.70-6.63 (m, 4H), 6.48-6.42 (m, 2H), 6.20-6.13 (m, 2H), 3.83 (s, 3H), 3.77 (s, 3H), 3.73-3.64 (m, 2H), 1.22-1.17 (m, 6H); ^{13}C NMR: δ = 158.4(1C), 158.1(1C), 145.70(1C), 145.67(1C), 142.3(1C), 141.42(1C), 141.37(1C), 138.8(1C), 133.8(1C), 131.8(2C), 130.5(2C), 130.3(2C), 130.1(1C), 129.6(4C), 129.3(1C), 129.1(2C), 128.2(4C), 127.74(2C), 127.71(2C), 127.65(2C), 127.2(2C), 127.0(2C), 126.8(1C), 126.7(1C), 116.8(1C), 115.5(2C), 115.4(2C), 112.9(2C), 112.5(2C), 68.3(1C), 68.2(1C), 55.2(1C), 55.1(1C), 54.03(1C), 53.96(1C), 17.8(1C), 17.7(1C); IR (neat): 3690, 3076, 3053, 2833, 1605, 1506, 1441, 1287, 1242, 1173, 1032, 833, 696 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^{+}$ Calcd for $C_{28}H_{27}NONa$ 416.1985; Found 416.1989.



221

Prepared according to the general procedure using 55.9 μL of *p*-ethyltoluene (0.40 mmol) for 18 h. The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine **221** (30.1 mg, 0.100 mmol, 50%) as a yellow oil.

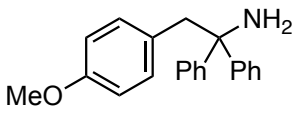
^{1}H NMR: d = 7.52-7.44 (m, 2H), 7.35-7.28 (m, 2H), 7.25-7.21 (m, 3H), 7.18-7.12 (m, 2H), 7.12-7.04 (m, 1H), 6.94-6.85 (m, 2H), 6.76-6.69 (m, 2H), 3.96 (q, *J* = 7.1 Hz, 1H), 2.42 (s, 3H), 1.76 (br, 2H), 1.33 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR: δ = 147.8, 146.1, 138.8, 135.8, 129.6, 128.1, 127.8, 127.7, 127.6, 126.8, 126.3, 125.9, 64.4, 47.3, 20.9, 16.9; IR (neat): 3383, 3086, 3055, 2972, 1597, 1445, 1188, 1032, 907, 814, 696 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{22}H_{22}N$ 300.1747; Found 300.1747.



224

Prepared according to the general procedure using 62.4 μL of *p*-cymene (0.40 mmol) for 18 h. The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine **224** (50.4 mg, 0.160 mmol, 80%) as a yellow oil.

^{1}H NMR: δ = 7.46-7.36 (m, 4H), 7.22-7.14 (m, 6H), 7.01-7.94 (m, 4H), 2.30 (s, 3H), 1.89 (br, 2H), 1.53 (s, 6H); ^{13}C NMR: δ = 147.0, 144.4, 135.3, 129.3, 129.1, 127.7, 127.0, 126.1, 67.1, 46.5, 27.2, 20.8; IR (neat): 3649, 3402, 3055, 1597, 1490, 1443, 1194, 1092, 1018, 818, 752, 700, 626 cm^{-1}; HRMS (EI) *m/z*: $[M]^+$ Calcd for $C_{23}H_{24}N$ 314.1903; Found 314.1909.



Prepared according to the general procedure using 51.0 μL of *p*-methylanisole **29** (0.40 mmol). The residue was purified by PTLC (Hexane/AcOEt = 2/1) to give amine (18.8 mg, 0.062 mmol, 31%) as a colorless oil.

^{1}H NMR: δ = 7.38-7.31 (m, 4H), 7.30-7.24 (m, 4H), 7.23-7.17 (m, 2H), 6.67-6.58 (m, 4H), 3.72 (s, 3H), 3.51 (s, 2H); ^{13}C NMR: δ = 158.2, 148.1, 131.7, 128.6, 127.9, 127.0, 126.4, 113.1, 61.3, 55.1, 48.0; IR (neat): 3481, 3421, 1670, 1361, 1062 cm^{-1}; HRMS (ESI) *m/z*: $[M + Na]^+$ Calcd for $C_{21}H_{21}NONa$ 326.1515; Found 326.1521.

6.4 References and Notes

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[7] The dehydrogenative coupling of alkylarenes with aldehydes is described in Chapter 2.

[8] The carbamoylation of C(sp^3)–H bonds is described in Chapter 5.

[9] Reaction using $NiBr_2$(dtbbpy) is described in Scheme 6-7.

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List of Publication

Chapter 1:
"Photodriven Dehydrogenative Homocoupling of Benzylic C–H Bonds Forming Strained C–C Bonds"
Naoki Ishida, Mingon Son, Tairin Kawasaki, Misato Ito, Masahiro Murakami
Synlett **2021**, *32*, 2067-2070.

Chapter 2:
"Dehydrogenative Coupling of Benzylic and Aldehydic C–H Bonds"
Tairin Kawasaki, Naoki Ishida, Masahiro Murakami
J. Am. Chem. Soc. **2020**, *142*, 3366-3370.

Chapter 3:
"Photoinduced Specific Acylation of Phenolic Hydroxy Groups with Aldehydes"
Tairin Kawasaki, Naoki Ishida, Masahiro Murakami
Angew. Chem. Int. Ed. **2020**, *59*, 18267-18271.

Chapter 4:
"Visible-Light-Driven Dehydrogenative Coupling of Primary Alcohols with Phenols Forming Aryl Carboxylates"
Tairin Kawasaki, Tomohiro Tosaki, Naoki Ishida, Masahiro Murakami
Org. Lett. **2021**, *23*, 7683-7687.

Chapter 5:
"Photoinduced Carbamoylation of C(sp^3)–H Bonds with Isocyanates"
Tairin Kawasaki, Katsushi Yamazaki, Ryota Tomono, Naoki Ishida, Masahiro Murakami
Chem. Lett. **2021**, *50*, 1684-1687.

Chapter 6:
"Photoinduced Direct Addition of Alkylarenes to Imines"
Ryota Tomono, Tairin Kawasaki, Naoki Ishida, Masahiro Murakami.
Chem. Lett. **2021**, *50*, 1972-1974.

Other Publications:

"Synthetic Approach to Benzocyclobutenones Using Visible Light and a Phosphonate Auxiliary"
Takaaki Yano, Tairin Kawasaki, Tatsuya Yuhki, Naoki Ishida, Masahiro Murakami
Org. Lett. **2018**, *20*, 1224-1227.

"2-Arylsilacyclobutane as a Latent Carbanion Reacting with CO_2"
Naoki Ishida, Shintaro Okumura, Tairin Kawasaki, Masahiro Murakami
Angew. Chem. Int. Ed. **2018**, *57*, 11399-11403.

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The following parts of the accepted materials were modified; (a) Parts of the introduction, conclusion, and expressions were modified according to the context of the thesis. (b) Subtitles were inserted to the section heads. (c) The label numbers of reagents were modified to be consistent throughout the thesis.

Chapter 1: N. Ishida, M. Son, T. Kawasaki, M. Ito, M. Murakami. Photodriven Dehydrogenative Homocoupling of Benzylic C–H Bonds Forming Strained C–C Bonds. Synlett. 2021, 32, 2067-2070. Copyright 2021 Thieme. DOI: 10.1055/a-1644-4876. To access the published article, see [https://www.thieme-connect.com/products/ejournals/abstract/10.1055/a-1644-4876].

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Chapter 3: T. Kawasaki, N. Ishida, M. Murakami. Photoinduced Specific Acylation of Phenolic Hydroxy Groups with Aldehydes. *Angew. Chem. Int. Ed*. **2020**, *59*, 18267-18271. DOI: 10.1002/anie.202008897.

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Chapter 5: T. Kawasaki, K. Yamazaki, R. Tomono, N. Ishida, M. Murakami. Photoinduced Carbamoylation of C(sp^3)–H Bonds with Isocyanates. *Chem. Lett.* **2021**, *50*, 1684-1687. DOI: 10.1246/cl.210333.

Chapter 6: R. Tomono, T. Kawasaki, N. Ishida, M. Murakami. Photoinduced Direct Addition of Alkylarenes to Imines. *Chem. Lett*. **2021**, *50*, 1972-1974. DOI: 10.1246/cl.210478.