博士論文

Development of Novel Synthetic Organic Reactions Directed Towards the Synthesis of Biologically Active Compounds

(生物活性化合物合成を志向した新規有機合成反応の開発)

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（Zhen Wang）

CONTENTS

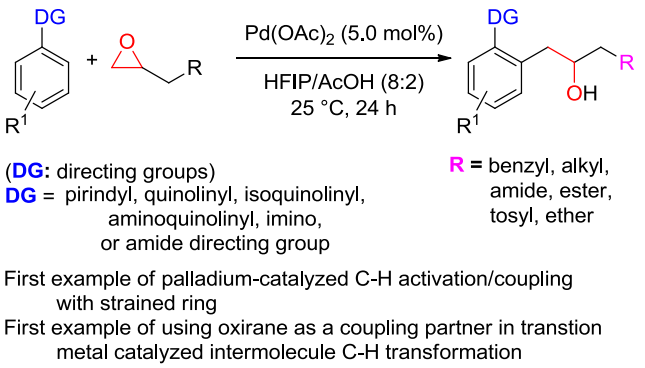
Abbreviations

Ac	acetyl
Boc	*tert*–butoxycarbonyl
brsm	base on recovered starting material
Cu	copper
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DCE	1,2-dichloroethane
DCM	dichloromethane
IBX	2-iodoxybenzoic acid
KIE	Kinetic Isotope Effect
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
Min	minute(s)
Mo	molybdenum
MPO	4-methoxypyridine *N*-oxide
NMP	*N*-methylpyrrolidone,
Pd	palladium
RT	room temperature
Rh	rhodium
TBS	*tert*-butyldimethylsilyl
TEA	triethylamine
THF	tetrahydrofuranyl
TLC	thin-layer chromatography
Ts	4-toluenesulfonyl

Abstract

1. Palladium–Catalyzed Oxirane–Opening Reaction with Arenes via C–H Bond Activation[1)]

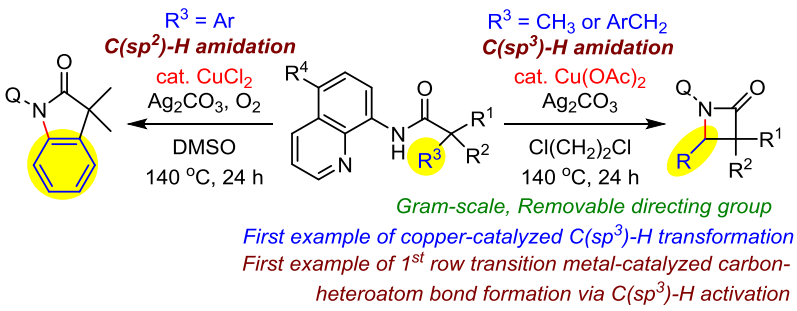
In the past several decades, palladium–catalyzed C–H bond transformations have been developed dramatically. For example, coupling reactions of aromatic compounds with organohalides and organometallic reagents, insertion reactions of unsaturated molecules, such as acrylates, into a C–H bond of aromatic substrates, and introduction of heteroatom functionalities into aromatic compounds were reported. There is no report, however, about palladium–catalyzed coupling reaction between aromatic substrates and strained compounds via C–H bond activation.



I focused on oxiranes as a coupling partner because, to the best of my knowledge, there is no report on transition metal–catalyzed intermolecular direct C–H bond transformations using oxiranes as substrates. As a result of investigations, I succeeded to develop palladium–catalyzed C−H activation/C−C coupling reaction between arenes and oxiranes. The reaction proceeded at room temperature with high functional group tolerance, and the products were obtained in good to excellent yields, even in gram scale. By using *N*–methoxybenzamide as a substrate, I obtained 3–substituted isochroman–1–ones. The coupling reaction proceeded with stereoretention. KIE experiments suggested that C–H bond activation is the rate–determining step.

2. Copper–Catalyzed Intramolecular C(sp^3)–H and C(sp^2)–H Amidation by Oxidative Cyclization[2)]

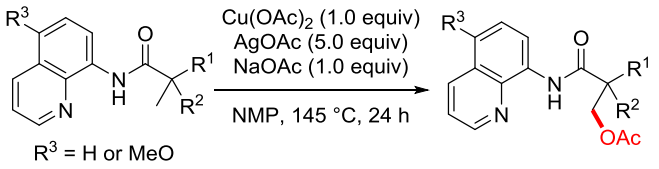
I developed the first example of copper–catalyzed intramolecular C(sp^3)–H and C(sp^2)–H amidation. The reaction is also the first example of first row transition metal–catalyzed carbon–heteroatom bond formation. The reaction has broad substrate scope, and



synthetically useful β–lactams were obtained from quinolyl amides in excellent yields, even in gram–scale. The reaction proceeded at a terminal methyl group as well as the internal benzylic position of an alkyl chain. By slightly modifying the reaction conditions, the reaction pathway switched to C(sp^2)–H amidation for a specific substrate, and 2–indolinone was selectively produced in high yield. Since the quinolyl directing group could be removed by oxidation, this reaction must become a useful method to synthesize β–lactams and 2–indolinones.

3. Copper–Mediated C(sp^3)–H and C(sp^2)–H Acetoxylation[3)]

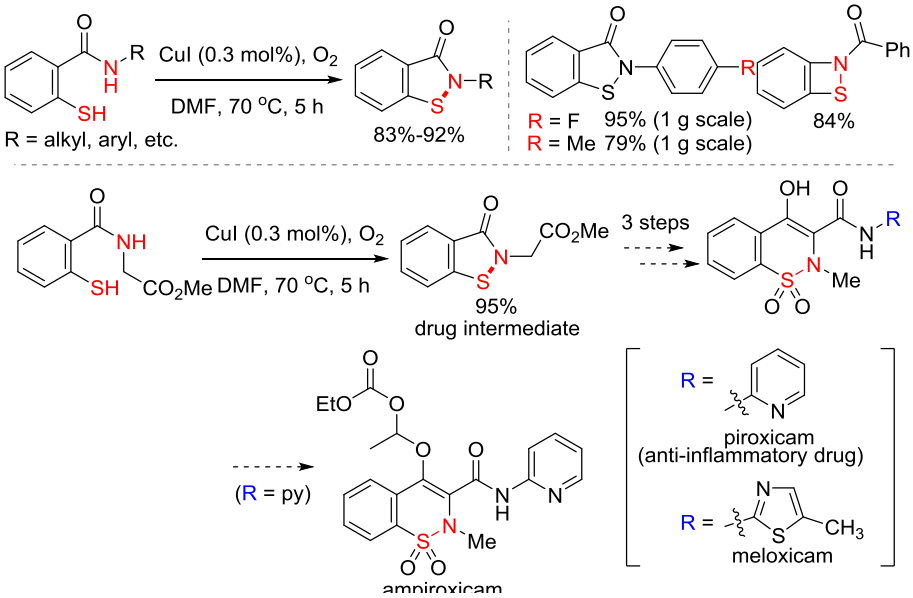
I developed the first example of a copper–mediated intermolecular acetoxylation via C(sp^3)–H activation. This reaction is also the first-row transition metal–mediated intermolecular carbon–heteroatom bond formation. The reaction absolutely proceeded at the β-methyl group. The seric effect played an important role in the distribution of the products. This reaction has high functional group tolerance, and the reaction proceeded in excellent yield, even in gram–scale, for a complicated compound. The directing group can be removed by oxidation using a 5–methoxyquinolyl group as a directing group. This acetoxylation can be applied to a complex molecule, which will lead to late–stage functionalization. Deuterium labeling experiments suggested that the C(sp^3)–H bond activation step is not the rate–determining step, which is different from copper–catalyzed intramolecular C(sp^3)–H amidation. Aromatic C(sp^2)–H acetoxylation also proceeded under the similar reaction conditions.



First Example of First Row Transition Metal-Mediated C(sp^3)-H Acetoxylation

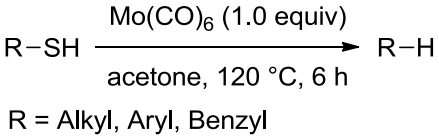
The reaction absolutely proceeded at the methyl group.

4. Copper–Catalyzed Intramolecular N–S Bond Formation[4)]



Copper–catalyzed synthesis of benzo[*d*]isothiazol–3(2*H*)–ones and *N*–acylbenzothiazetidine by intramolecular dehydrogenative cyclization is developed. The reaction proceeded under oxygen atmosphere with 0.3% CuI, and without any additives. In this reaction, a new nitrogen–sulfur (N–S) bond is formed by N–H/S–H coupling. The present reaction has high functional group tolerance and gives products in gram scale. This method promotes double cyclization, allowing for synthesis of a drug intermediate, which can be used to synthesize anti–inflammatory drugs.

5. Molybdenum–Mediated Desulfurization of Thiols and Disulfides[5)]



$Mo(CO)_6$–mediated desulfurization of thiols and disulfides was realized. In this reaction, the mercapto groups of aryl, benzyl, and primary and secondary alkyl thiols; and S–S single bonds of disulfides could be removed. This reaction has high functional group tolerance. In addition, the desulfurization reaction was not affected by steric hindrance. The results of the reactions in acetone–d_6 suggested that the hydrogen sources in thiol and disulfide desulfurization were the hydrogen atom(s) of an SH group and acetone (solvent), respectively, and the desulfurization reaction proceeded via the formation of an organomolybdenum species.

References:

1) Wang, Z.; Kuninobu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2015**, *137*, 6140.

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4) Wang, Z.; Kuninobu, Y.; Kanai, M. *J. Org. Chem.* **2013**, *78*, 7337.

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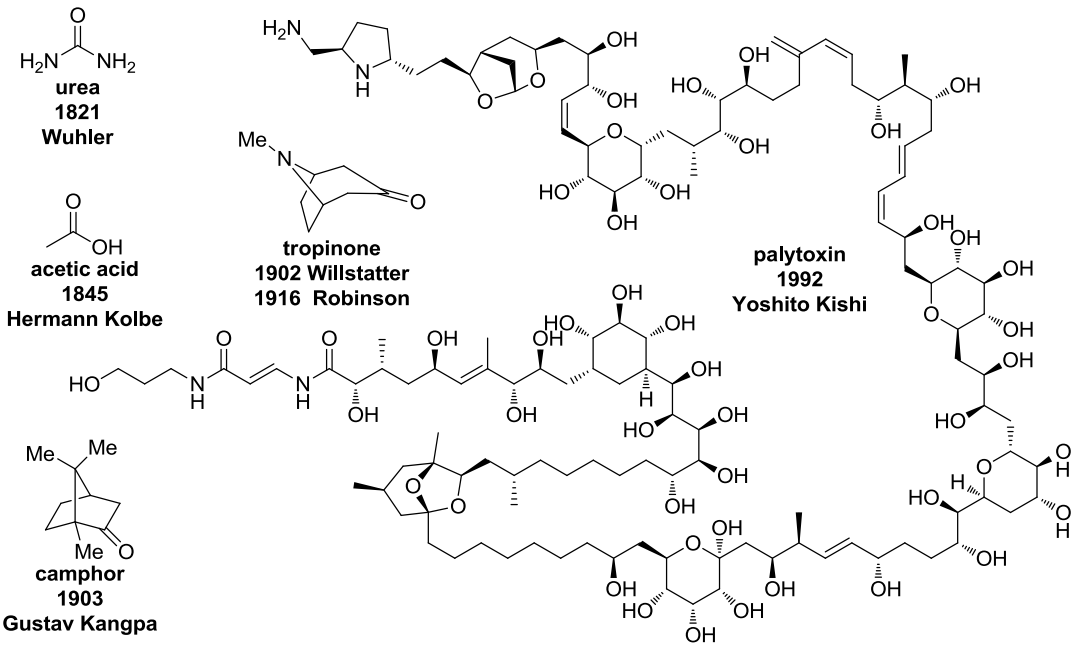
Introduction for Projects 1-3

Total synthesis of natural products is one of the most important research areas of organic chemistry, and is the fusion of science and art on the molecular level. Total synthesis of natural products has not only an important theoretical and practical significance for the development of chemistry itself, but also a positive strategic significance to improve the capability of an independent innovation in a drug development, to protect the ecological resource and environment, and to train professional organic chemists.

Figures 1. Several landmark molecules in the history of total synthesis



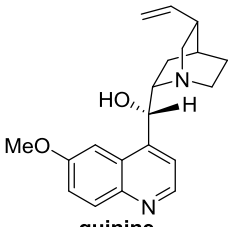
W. Smit, *et al. Org. Synth.*, The Science behind the Art. Cambridge: *The Royal Society of Chemistry* **1998**; R. Robinson. *et al. J. Chem. Soc.*, Transaction. **1917**, *111*, 762; Y. Kishi, *et al. J. Am. Chem. Soc.* **1994**, *116*, 11205.

Total synthesis of natural products has a long history. As showed in **Figure 1**, in 1821, Wöhler firstly synthesized urea from an inorganic substance (ammonium cyanate) in his labratory, therefore, it can be said that he created a new era of organic synthesis. In 1845, Kolbe synthesized acetic acid from inorganic compounds for the first time. In 1903, Gustav Kangpa synthesized camphor, which is the first example of industrialization. In 1902, the German chemist Willstätter synthesized tropine ketones, symbolizing the beginning of multi–step organic syntheses. In 1916, Robinson implemented and biomimetically synthesized tropine ketones, which was not only a big step in alkaloid chemistry but also showed that tandem reactions in a one–pot synthesis are capable of forming bicyclic molecules. In 1992, the Japanese chemist

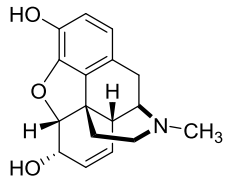
Yoshito Kishi synthesized palytoxins, which inspired synthetic chemists that all natural products could be synthesize in the labrotary, from then on.

There are also some famous naturally derived drugs, which were synthesized by some groups (**Figure 2**). In 1950, Woodward synthesized quinine, and at that time, he proposed the conception of total synthesis. Morphine was synthesized by Gates in 1956. As the development of synthetic strategy and methods, chemists spent a shorter time to finish the total synthesis of complex natural products. Total synthesis of quinine and morphine took for more than 100 years from the isolation, but only 30 years were needed for the total synthesis of palitaxol and penicillin. However, the way to obtain commercially available molecules is extraction of the compounds from natural sources rather than total synthesis of the molecules.

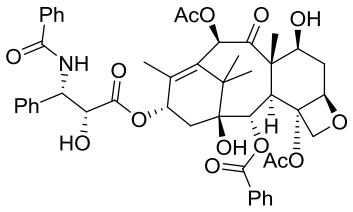
Figure 2. Some famous naturally derived drugs



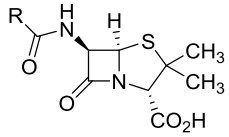
quinine
Isolated in **1820**
First total synthesis by Woodward in **1950**
J. Am. Chem. Soc. **1944**, *66*, 849



morphine
Isolated in **1804**
First total synthesis by M. Gates in **1956**
J. Am. Chem. Soc. **1956**, *78*, 1380



paclitaxel
Isolated in **1962**
was used as a drug in **1994**
first total synthesis by R. A. Holton in **1994**
J. Am. Chem. Soc. **1994**, *116,* 1597



penicillin
Isolated from microorganisms
Discovered in **1928** by A.Fleming
First total synthesis by J. C. Sheehan in **1957**
J. Am. Chem. Soc. **1957**, *79*, 1262

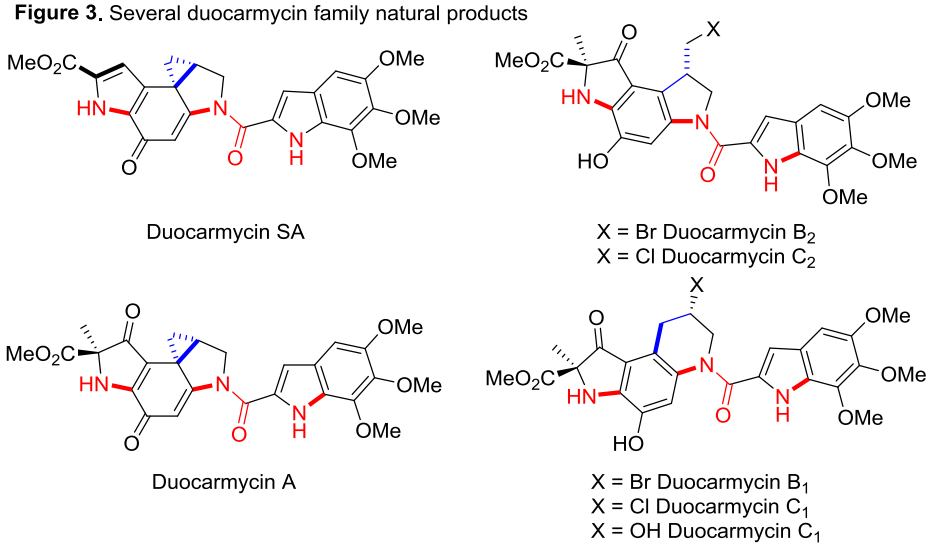
Nobel Prize winners
1928, A.Fleming, for discovery
1945, H. Florey, for mass production
1965, D. C. Hodgkin, for structure determination

At present, challenging the complexity of single molecule is not the mainstream of modern organic synthesis, but synthetic chemists move their attention to collective total synthesis and build a molecule library. On the other hand, discovering new reactions and strategies to improve the efficiency of total synthesis is another urgent task. After I joined Kanai's lab, I focus on

developing new methods and designing new strategies to efficiently synthesize duocarmycin family natural products.

Duocarmycin family natural products, alkaloids, were isolated from Streptomyces bacteria in 1988 (Figure 3).[1] These molecules can bind to the minor groove of DNA and alkylate the nucleobase adenine at the N3 position. The irreversible alkylation of DNA disrupts the nucleic acid architecture, which eventually leads to tumor cell death. A mechanism of the action of duocarmycins is different from that of tubulin binders, such as taxol and vinblastine. Boger and other groups created a better understanding of the pharmacophore and mechanism of action of duocarmycins.[2]

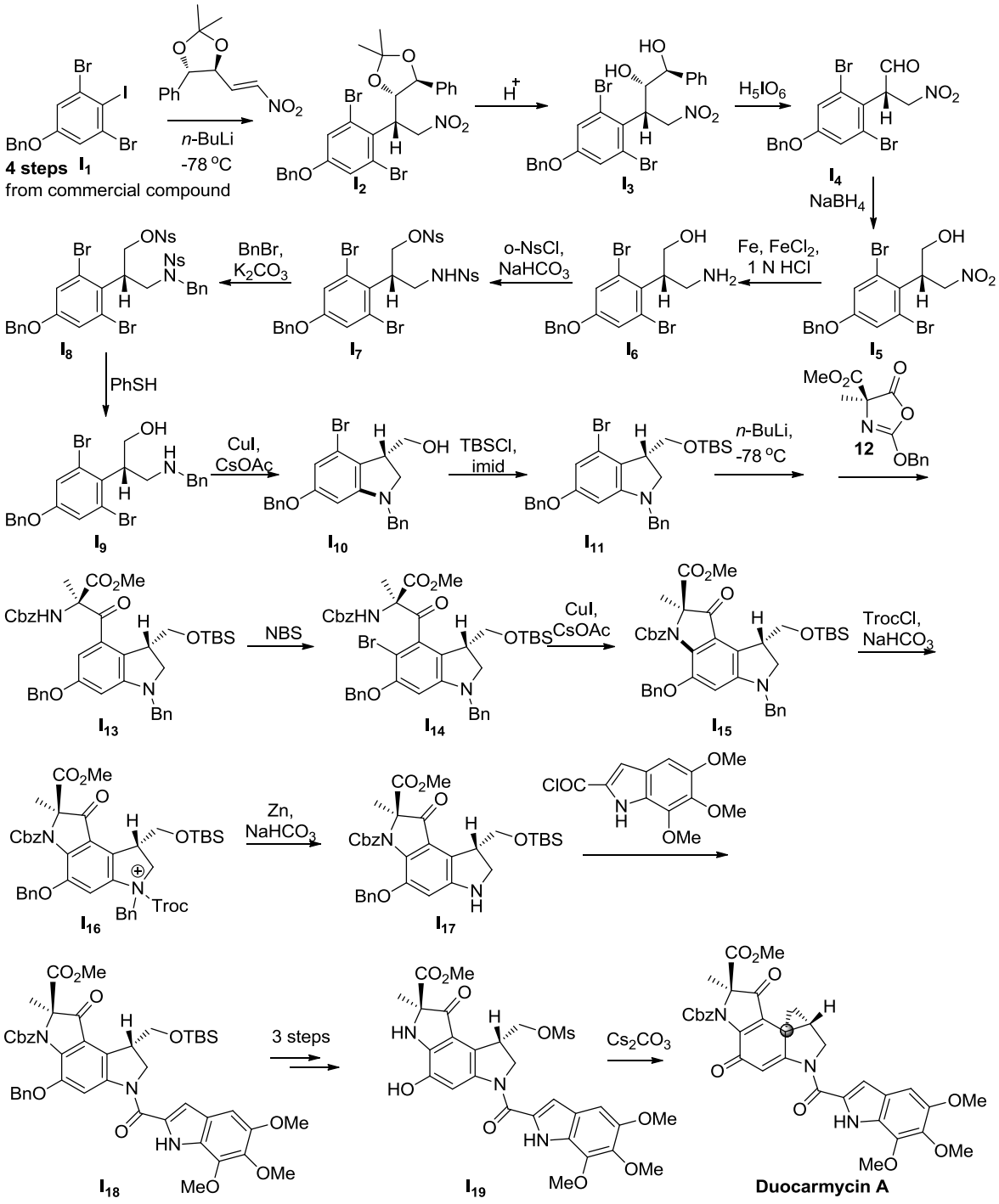
Figure 3. Several duocarmycin family natural products



At present, there are several reports on the total synthesis of duodarmycins. However, the routes for the synthesis of duocarmycin are long and inefficiently. Fukuyama used the longest linear 25 steps to complete the total synthesis of duocarmycin A from commercially available compounds.[3] As showed in Scheme 1, Fukuyama started his total synthesis from compound I_1 with 2 bromo atoms and 1 iodo atom, which can be prepared from commercially available compounds in 4 steps. Using 1,4–addition reaction, the first stereocenter was introduced and compound I_2 was obtained. Then the unnecessary chain was removed using 2 steps to give aldehyde I_4. A formyl group of coumound I_4 was reduced to produce alcohol I_5. A nitro group of I_5 was selectively reduced and protected in 4 steps, and *N*-benzylamine I_9 was obtained. The first

indolene structure of Duocarmycin was constructed by intramolecular Ullman coupling reaction, and successive protection of the hydroxy group of alcohol I_{10} to give dihydroindole I_{11}**.** Then I_{11} was coupled with oxazolone I_{12}, and the second sterocenter of Duocarmycin was introduced. Selective introduction of a bromo atom to the formed I_{13}, and the second indolene structure of Duocarmycin was constructed by successive Ullman coupling reaction to give tricyclo compound I_{15}. The *N*-benzyl protecting group of I_{15} was selectively removed in 2 steps, and compound I_{17} was prepared**.** Duocarmycin A was synthesized in 5 steps from compound I_{17}. In this route, the author took many steps to adjust the oxidation states, to selectively introduce functional groups, and to manipulate many protecting groups. These factors made this route inefficient.

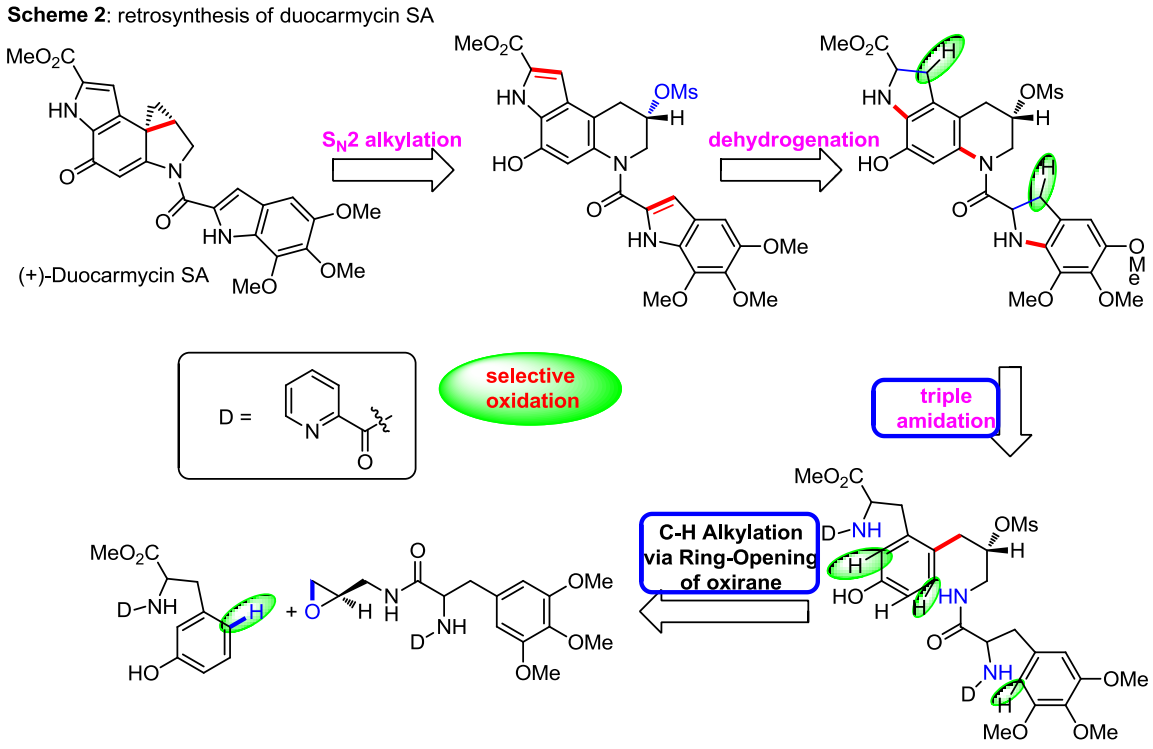
Scheme 1. Fukuyama's total synthesis of duocarmycin A



In order to develop an efficiently route for the synthesis of duocarmycin family natural products, I designed a new strategy based on developing new methods. The key reactions are catalytic triple intramolecular C–H amidation followed by dehydrogenation and transition–metal–

catalyzed oxirane–opening reaction with arenes via C–H activation (Scheme 2). The detailed background of each method will be summarized in the Introduction section of each project.

Scheme 2: retrosynthesis of duocarmycin SA



References:

1 (a) Yasuzawa, T.; Iida, T.; Muroi, K.; Ichimura, M.; Takahashi, K.; Sano, H. *Chem. Pharm. Bull.* **1988**, *36*, 3728. (b) Takahashi, I.; Takahashi, K.; Ichimura, M.; Morimoto, M.; Asano, K.; Kawamoto, I.; Tomita, F.; Nakano, H. *J. Antibiot.* **1988**, *41*. 1915.

2 (a) Tercel, M.; McManaway, S. P.; Leung, E.; Liyanage, H. D. S.; Lu, G.–L.; Pruijn, F. B. *Angew. Chem. Int. Ed*. **2013,** *52*, 5442. (b) Boger, D. L.; Johnson, D. S. *Proc. Nat. Acad. Sci. U. S. A.* **1995,** *92*, 3642. (c) Tietze, L. F.; Krewer, B. *Chem. Bio. Drug. Des*. **2009,** *74*, 205.

3 Yamada, K.; Kurokawa, T.; Tokuyama, H.; Fukuyama, T. *J. Am. Chem. Soc.* **2003**, *125*, 6630.

1. Palladium–Catalyzed Oxirane–Opening Reaction with Arenes via C–H Bond Activation

1.1. Introduction

Compared with classical coupling reactions, C-H transformations are environmentally benign reactions, which do not need to prefunctionalize the starting materials. In the last few decades, C–H bond transformations have attracted widespread attention as efficient and ideal reactions, and have been dramatically advanced.[1] Among the transition metal–catalyzed C–H transformations, there are several reports on transiton–metal–catalyzed C–H alkylation reactions of arenes[2], using alkyltin[3] and alkylboron[4] reagents, alkyl halides,[5] alkenes,[6] and alkanes as coupling partners (Figure 1-1).[7] Another possible alkylation reagent is oxiranes, and synthetically–useful substituted–phenethyl alcohols could be synthesized with high atom–economy if a C–C bond formation reaction via ring–opening of oxiranes with arenes is achieved. There are a lot of reports on transition metal catalyzed C–H activation and coupling with strained ring, such as aziridines, methylenecyclopropanes, cyclopropenes, cyclopropenones, and diazabicyclic olefins (Figure 1-2).[12] Rhodium catalysts show superiority in this field, which mainly attributed to the mild reaction conditions. To our knowledge, however, there is only one report of transition metal–catalyzed, intermolecular S_N2'–type reactions via C–H activation using vinyl oxiranes as coupling partners (Figure 1-3a).[8–12] The S_N2–type ring–opening reactions of oxiranes by carbon nucleophiles is

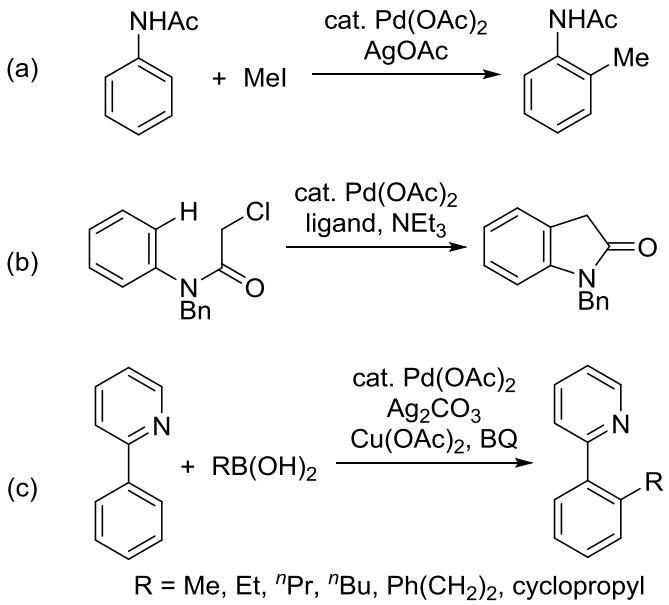


Figure 1-1. Common coupling partners in C-H alkylation

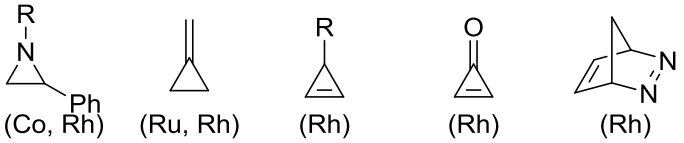


Figure 1-2. Several strained compounds in C-H transformations

difficult due to low reactivity of oxiranes. For example, it is necessary to activate oxiranes by BF_3•OEt_2 even when highly reactive organolithium reagents are used.[13] On the other hand, the coordination ability of oxygen atom in oxiranes is weak compared with the most used nitrogen atom. Here, I realized a palladium–catalyzed C–H activation/S_N2–type oxirane–opening reaction with broad substrate scope (Figure 1-3b). This is the first example of palladium–catalyzed C–H transformation via ring–opening of strained substrates.[11,12] The main reason for no example of palladium–catalyzed C–H transformation/coupling with strained compounds is that palladium–catalyzed C–H transformations generally proceed under harsh conditions, such as high temperature, long reaction time, and a lot of additives (oxidative reagents, base, or other transition metals), which causes decomposition of the strained rings. With these problems in mind, I began our research on a palladium–catalyzed C–H transformation using oxiranes as coupling partners.

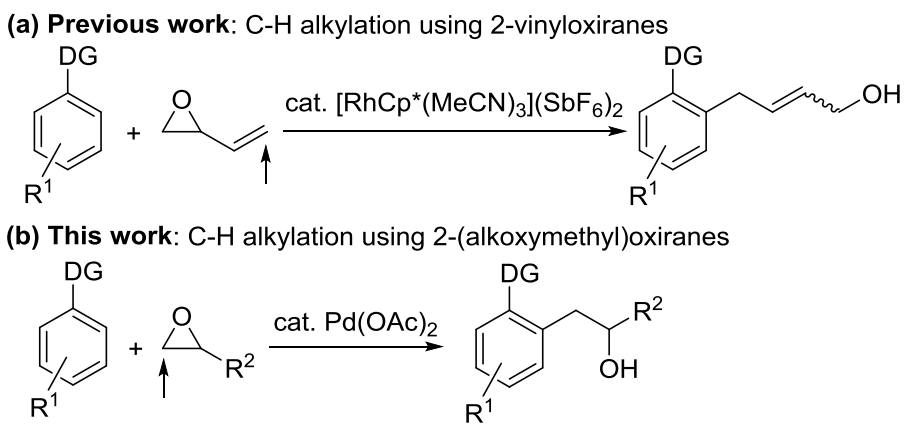


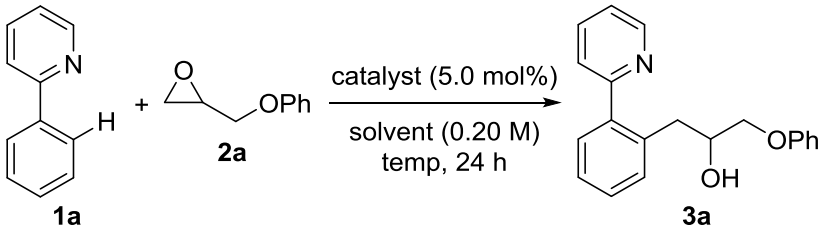
Figure 1-3. Examples of transition metal-catalyzed C-C bond formation via C-H activation using oxiranes

1.2. Optimization Studies

I initially investigated a reaction between 2–phenylpyridine (**1a**) and 2–ethyloxirane. Formation of the desired coupling product, however, was not achieved using various transition metal salts and complexes under different reaction conditions. A main reason is that the nitrogen atom coordination ability is stronger than oxygen atom of oxirane, which causes that the transition metal was surrounded by the pyridine substrate rather than oxirane. In addition, the basicity of the nitrogen atom caused decomposition of the oxirane. I thought that using oxiranes bearing additional heteroatoms, which act as an additional catalyst coordination sites, might solve

the weak coordination ability of oxiranes. Therefore, I investigated the reaction using 2–(phenoxymethyl)oxirane (**2a**), because the two oxygen atoms of **2a** should coordinate to a metal center by chelation. Acetic acid (AcOH) was selected as a solvent because acids should accelerate oxirane ring–opening reactions. Several metal salts were screened at 100 ^{o}C (Table 1-1, entries 1–5), but the desired coupling reaction only occurred when using $Pd(OAc)_2$. Alkylated product **3a** was formed in 11% yield (Table 1-1, entry 5). The low yield resulted mainly from the decomposition of oxirane **2a** due to the acidity of AcOH. Therefore, I used 1,1,1,3,3,3–hexafluoro–2–propanol (HFIP) as a mixed solvent because (1) HFIP is a highly polarized solvent, which dilutes the concentration AcOH rather than decrease the acidity of AcOH; and (2) the electron poor oxygen atom of HFIP weakly coordinates to a palladium catalyst and will not strongly affect the property of the palladium catalyst due to the electronic withdrawing effect and steric effect of fluoride atoms. Screening of various AcOH/HFIP ratios (Table 1-1, entries 6–9) revealed that an AcOH/HFIP ratio of 2:8 increased the yield of **3a** to 30% (Table 1-1, entry 7). Unfortunately, a large amount of **2a** decomposed under the reaction conditions. To improve the yield, I performed a reaction at lower temperature to suppress the decomposition of **2a** (Table 1-1, entries 10–13). The desired product **3a** was obtained quantitatively at room temperature (Table 1-1, entry 13). The yield of **3a** decreased to 76% when 1.5 equiv of oxirane **2a** was used (Table 1-1, entry 14). Therefore, 2.0 equiv of oxiranes was used in the subsequent experiments. This result is especially noteworthy because of the few examples of palladium–catalyzed C–H transformations that proceed at room temperature.[14] The reaction proceeds wihout any additives and byproducts.

Table 1-1. Optimization of Reaction Conditions[a]



1a **3a**

entry	Catalyst	solvent	temp [℃]	yield [%][b] (**3a**)
1	$Rh(OAc)_2$	AcOH	100	0
2	$ReCl(CO)_5$	AcOH	100	0

3	$Co(OAc)_2$	AcOH	100	0
4	$Mn(OAc)_3 \cdot 2H_2O$	AcOH	100	0
5	$Pd(OAc)_2$	AcOH	100	11
6	$Pd(OAc)_2$	AcOH/HFIP (1:9)	100	22
7	$Pd(OAc)_2$	AcOH/HFIP (2:8)	100	30
8	$Pd(OAc)_2$	AcOH/HFIP (3:7)	100	18
9	$Pd(OAc)_2$	HFIP	100	0
10	$Pd(OAc)_2$	AcOH/HFIP (2:8)	90	31
11	$Pd(OAc)_2$	AcOH/HFIP (2:8)	80	37
12	$Pd(OAc)_2$	AcOH/HFIP (2:8)	60	74
13	$Pd(OAc)_2$	AcOH/HFIP (2:8)	25	>99
14	$Pd(OAc)_2$[c]	AcOH/HFIP (2:8)	25	76

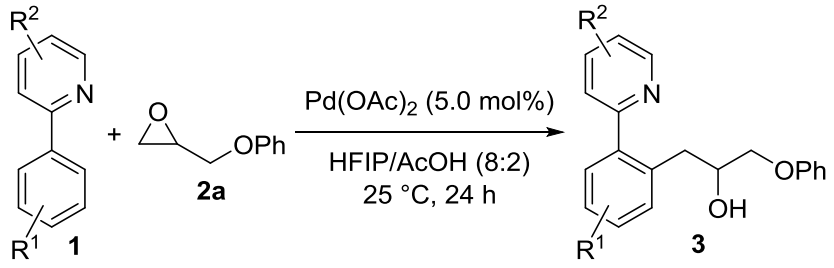
[a]Reactions conditions: **1a** (0.200 mmol), **2a** (0.400 mmol), solvent (1.0 mL). [b]Yield was determined by ^{1}H NMR using 1,1,2,2–tetrachloroethane as an internal standard. [c]**2a** (0.300 mmol, 1.5 equiv).

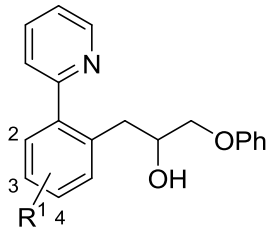
1.3. Substrate Scope and Mechanism Research

With the best conditions in hand, I next explored the scope and limitations of this system under the optimized reaction conditions (Table 1-2). At first, I investigated the arenes with different substituents. 2–Phenylpyridines bearing an electron–donating (MeO and Me) or –withdrawing (CO_2Et, Br, and F) group at the 4–position of the benzene ring coupled smoothly with oxirane **2a**, without loss of the functional groups. Although two possible regioisomers might be formed when a substituent exists at the 3–position of an aromatic ring of 2–phenylpyridines **1g** and **1h**, only single isomers **3g** and **3h** formed because the reaction occurred only at the less hindered site. The coupling reaction was not inhibited by steric hindrance from a substituent at the 2–position of **1i** and **1j**. The corresponding products **3k**, **3l**, and **3m**, derived from pyridylnaphthalenes **1k** and **1l**, and benzo[*h*]quinoline **1m**, were produced in high yields. An electron–donating or –withdrawing substituent on the pyridine ring of **1n** and **1o** was also

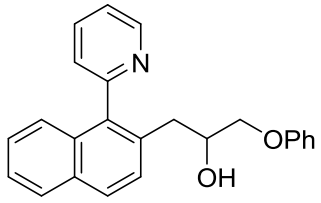
tolerated in this reaction. The yield of alkylated product **3p** was not obviously decreased by steric hindrance from a substituent at the 6–position of the pyridine ring. An isoquinolinyl or quinolinyl group also worked as a directing group, and the corresponding alkylated products **3q**[15] and **3r** were obtained in 87% and 97% yields, respectively.

Table 1-2. Investigation of 2-Phenylpyridine Derivatives[a]

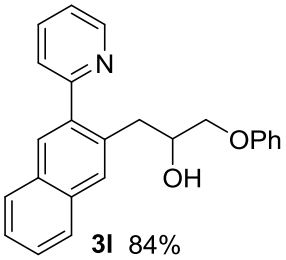




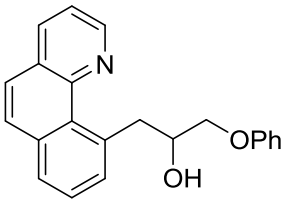
R^1 = H	**3a**	>99%	
4-MeO	**3b**	93%	
4-Me	**3c**	84%	
4-CO_2Me	**3d**	76%	
4-Br	**3e**	83%	
4-F	**3f**	78%	
3-MeO	**3g**	87%	
3-Ph	**3h**	94%	
2-MeO	**3i**	93%	
2-Ph	**3j**	79%	



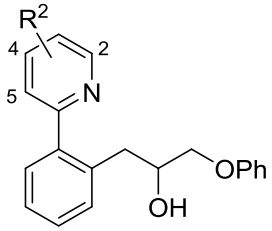
3k 86%



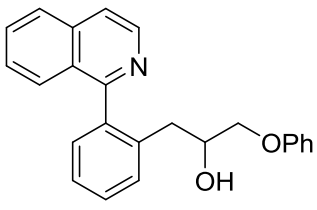
3l 84%



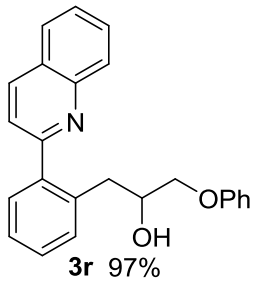
3m 88%



R^2 = 5-Me **3n** 84%
4-CF_3 **3o** 92%
2-Me **3p** 73%



3q 87%

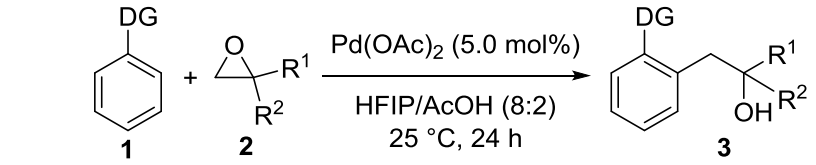


3r 97%

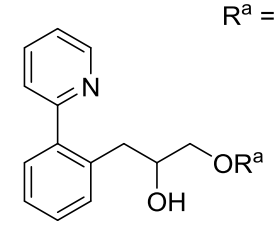
Next, I investigated coupling reactions between different type of oxiranes and arenes with

different directing groups (Table 1-3). I found that the β–oxygen atom of oxirane is necessary for coupling with 2–phenylpyridine. A substituent on the oxygen atom of 2–(phenoxymethyl)oxirane (**2a**) could be changed to several different types of substituents. 2–(Aryloxymethyl)oxiranes produced the corresponding coupling products **3s**–**3u** in 43%–81% yields. In the case of oxirane with a 4–(9*H*–carbazolyl) group, the desired reaction proceeded without NH group protection, the low yield mainly attributed to the low solubility of this oxirane. The corresponding coupling products **3v**–**3z**, **3A**–**3B**, **3I** were obtained in 58%–94% yields when oxiranes bearing an aliphatic substituent on the oxygen atom were used as substrates. The desired products were not produced, however, when the substituent on the oxygen atom was larger: namely, a trityl group. These results are likely due to inhibition of the coordination of an oxygen atom to a palladium center by steric hindrance, on the other hand, the solubity of oxirane with big substituents is low. By changing 2–phenylpyridines to other aromatic compounds with qunolinyl and isoquinolinyl, such as benzo[*h*]quinoline and 1–phenylisoquinoline, the coupling reaction proceeded in good to excellent yields using a variety of oxiranes other than 2–(alkoxymethyl)oxiranes. The coupling reaction proceeded using an oxirane without an oxygen atom at the β–position, and provided the coupling product **3C** in 83% yield. The coupling reaction had high functional group tolerance, and gave the desired product with the following functional groups, including C=C double bond (**3D**), isoindoline–1,3–dione (**3E**) and carbamate (**3F**) moieties, and ester (**3G**, **3H**, **3I**, **3K**, and **3M**) and tosyl (**3L**) groups. In the case of an oxirane with a double bond, the yield of **3D** was moderate, likely due to decomposition of the palladium catalyst with the formation of a palladium black. A coupling product **3I** was also produced using a 1,1–disubstituted oxirane. For the products **3J**, **3k**, and **3L**, attribute to the strong intromolecular hydrogen bond in $CDCl_3$, a rotamers can be observed. By using an aromatic compound with an aminoquinolinyl directing group which is a very common directing group in transition–metal–catalyzed C–H transforations, the desired product **3M** was obtained in 67% yield. A coupling product **3N** was obtained in 71% yield using acetophenone *O*–methyl oxime as a substrate without destroying the directing group. The desired reaction did not proceed, however, using 2–vinyloxirane and 1,2–disubstituted oxiranes (methyl 3–methyloxirane–2–carboxylate and dimethyl (2*S*,3*R*)–oxirane–2,3–dicarboxylate) under the same reaction conditions.

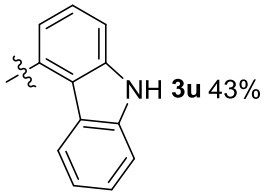
Table 1-3. Investigation of Aromatic Compounds **1** and Oxiranes **2a**



1 **2** **3**

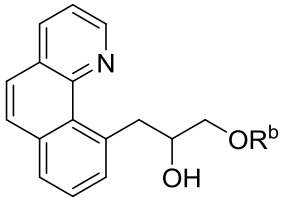


R^a = C_6H_4-2-OMe **3s** 74%
C_6H_4-4-OMe **3t** 81%

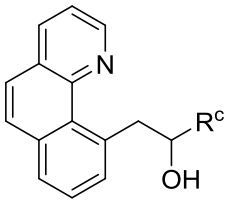


3u 43%

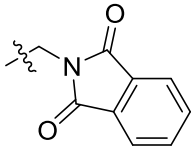
R^a = Me **3v** 81%
CH_2Ph **3w** 91%
$CH_2CH{=}CH_2$ **3x** 83%
$CH_2(CF_2)_2H$ **3y** 71%



R^b = Me **3z** 94%
^{n}Bu **3A** 71%[b]
2-ethylhexyl **3B** 58%[b]

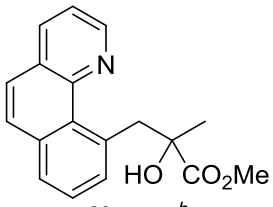


R^c = CH_2Ph **3C** 83%[b]
$(CH_2)_2CH{=}CH_2$ **3D** 49%

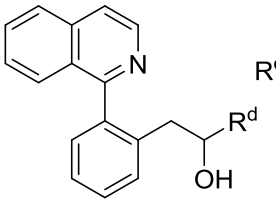


3E 66%[b]

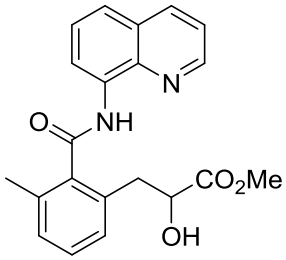
$CH_2NHCO_2{}^tBu$ **3F** 54%[b]
CH_2CO_2Et **3G** 88%[b]
CO_2Me **3H** 92%[b]



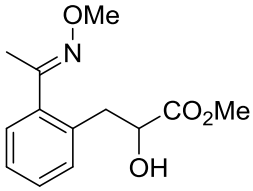
3I 86%[b]



R^d = CH_2OCH_2Ph **3J** 91%[c]
CO_2Me **3K** 78%[b,d]
OTs **3L** 54%[b]



3M 67%[e]



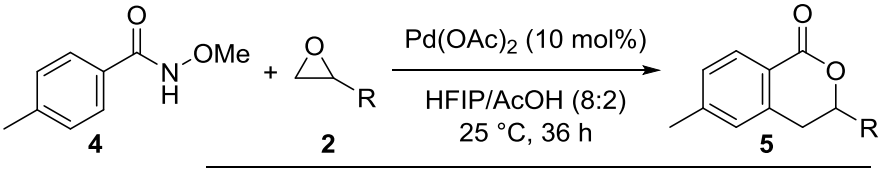
3N 71%[b]

[a] Reaction conditions: **1** (0.200 mmol), **2a** (0.400 mmol), solvent (1.0 mL). [b] $Pd(OAc)_2$ (10 mol%), 36 h. [c] Ratio of rotamers = 3:1 in $CDCl_3$. [d] Ratio of rotamers = 3:1 in $CDCl_3$ or 1:1 in CD_3OD. [e] $Pd(OAc)_2$ (20 mol%).

3–Substituted isochroman–1–ones are important frameworks in natural products and pharmaceutical compounds.[15] When *N*–methoxybenzamide and oxiranes were used as substrates,

coupling reaction and successive cyclization proceeded and 3–substituted isochroman–1–ones **5a**–**5d** were obtained in 58%–75% yields (Table 1-4). The desired product **5b** was obtained using an oxirane without an additional coordinating oxygen atom, but 2–hexyloxirane did not produce a coupling product at all. This result indicated that π–electrons of the phenyl group of the oxirane might coordinate to the palladium catalyst.

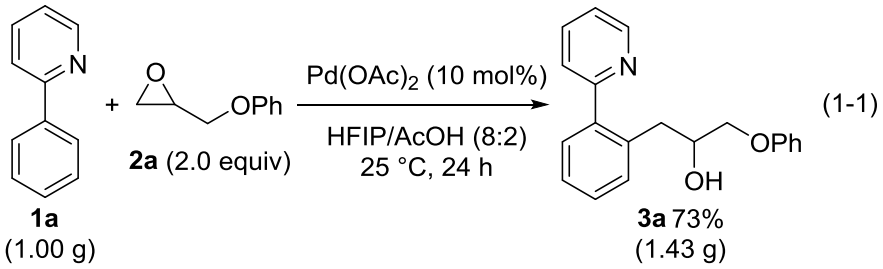
Table 1-4. Formation of 3-Substituted Isochroman-1-ones **5** from *N*-Methoxybenzamide **4** and Oxiranes **2**



4 + **2** → **5**

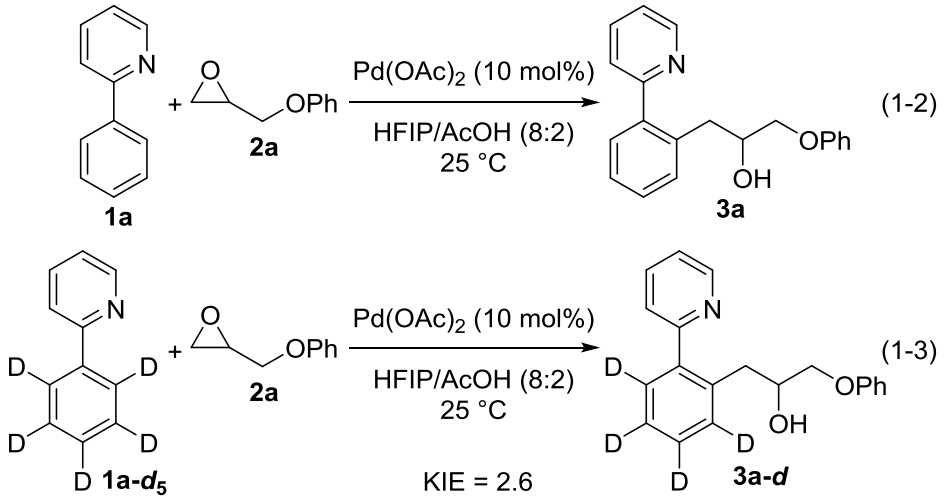
R =	CO_2Me	**5a**	68%	R =	**5d** 58%
	CH_2Ph	**5b**	72%		
	CH_2OPh	**5c**	75%		

The reaction could be performed on gram scale (eq 1-1). Treatment of 1.00 g of **1a** with 2.0 equiv of oxirane **2a** gave 1.42 g of **3a** in 73% yield.

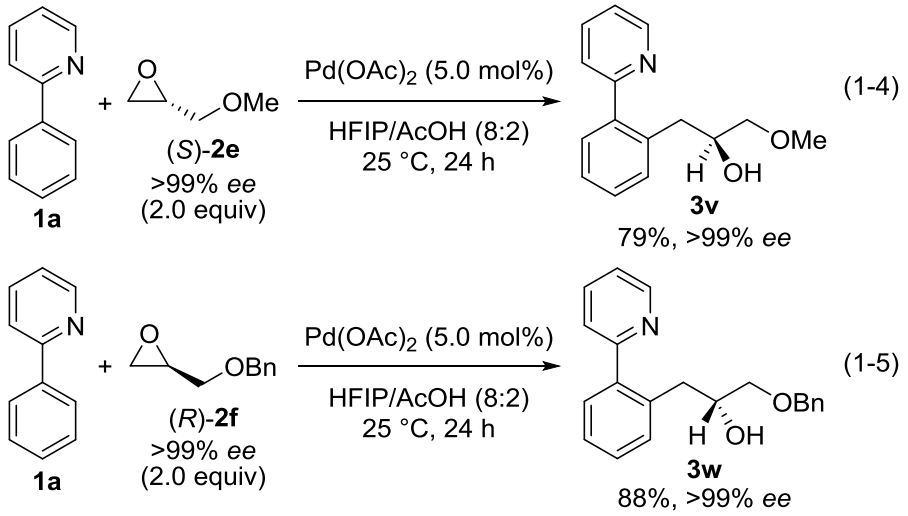


(1-1)

To determine the rate–determining step of the present reaction, a deuterium–labeling experiment was performed. Treatment of 2–phenylpyridine (**1a**) or deuterated 2–phenylpyridine (**1a**–d_5) with oxirane **2a** revealed a kinetic isotope effect value of 2.6. Although the value is a little smaller than the previously reported on palladium–catalyzed C–H transformation, this result suggested that C–H bond activation is the rate–determining step (eqs 1-2 and 1-3).

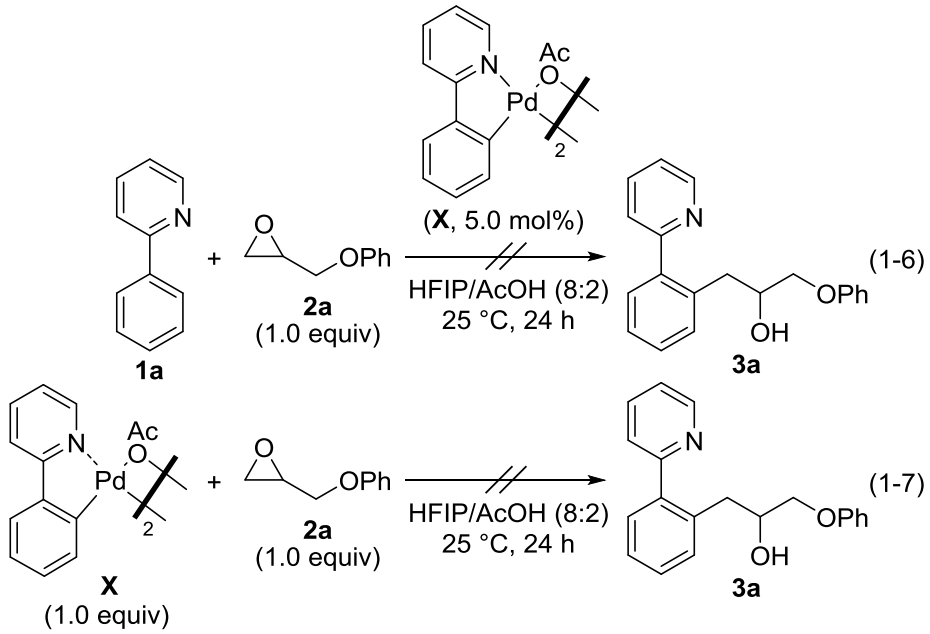


When an enantiomerically pure oxirane (*S*)–**2e** or (*R*)–**2f** was used, the coupling reactions proceeded with stereoretention and the corresponding products **3v** and **3w** were obtained in more than 99% *ee* (eqs 1-4 and 1-5). These findings suggested that oxiranes **2** were not racemized by ring–opening and reconstruction of the oxirane rings under the reaction conditions, in other words, the other C–O bond did not intend in this reaction.



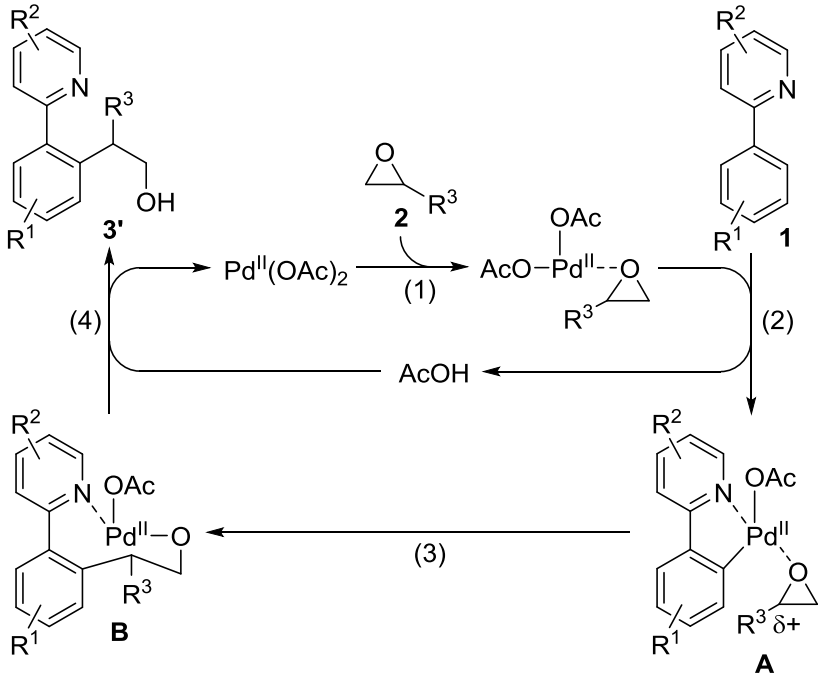
In previous reports, dinuclear palladium complex **X** (eqs 1-6 and 1-7) was demonstrated to be an active intermediate for Pd–catalyzed C–H bond transformations of 2–phenylpyridines.[18] Therefore, the complex was synthesized and the following two reactions were investigated: (1) a

reaction between 2– phenylpyridine (**1a**) and oxirane **2a** in the presence of a catalytic amount of **X** (eq 1-6); and (2) a reaction between a stoichiometric amount of palladium complex **X** and oxirane **2a** (eq 1-7). The desired coupling reaction, however, did not proceed at all even at an elevated temperature (80 ^{o}C). Based on these results, I concluded that dinuclear palladium(II) complex **X** was not a catalytic species in our reaction. The result implies that palladium(IV) species generated via oxidation by substrate oxiranes might be an active catalyst for this reaction.[17,18]



One possible pathway is similar to the proposed mechanism of rhodium(III)–catalyzed C–C coupling between 2–phenylpyridines and aziridines (Scheme 1-1).[19] Wherein the reaction mainly proceeded at internal carbon of oxirane **2** rather than terminal carbon of **2**. In this reaction, the C–C coupling reaction occurs at a more–substituted carbon atom of aziridines. On the other hand, the present reaction occurred at a less–substituted carbon atom of oxiranes. Therefore, the mechanisms of the two reactions may be different.

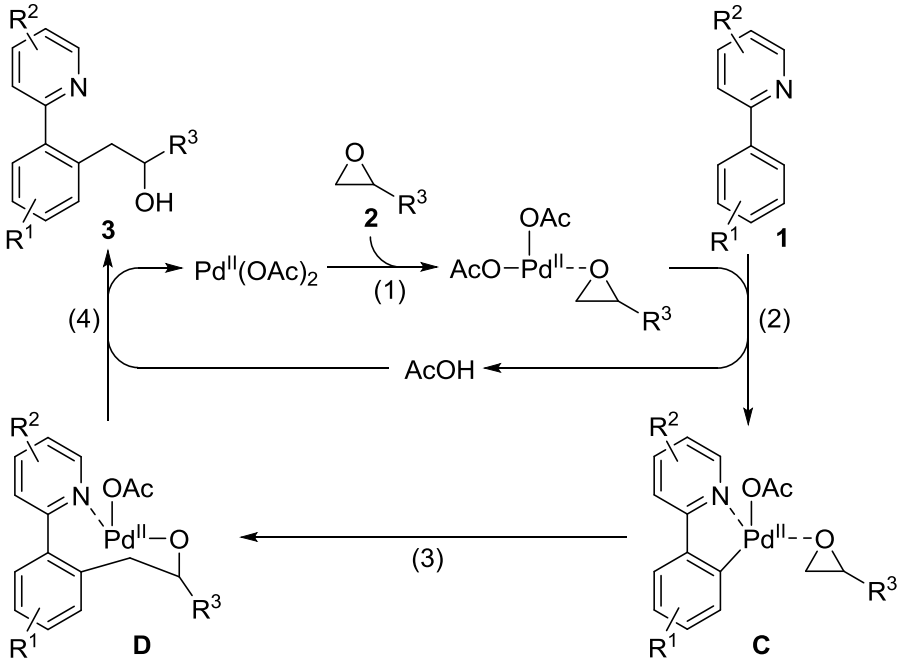
Scheme 1-1. A possible mechanism via Pd(II)-promoted C-C bond formation at a more-substituted carbon atom of oxiranes



Thus, I considered two possible mechanisms (Schemes 1-2 and 1-3) based on the previous reports and our experiments.[20]

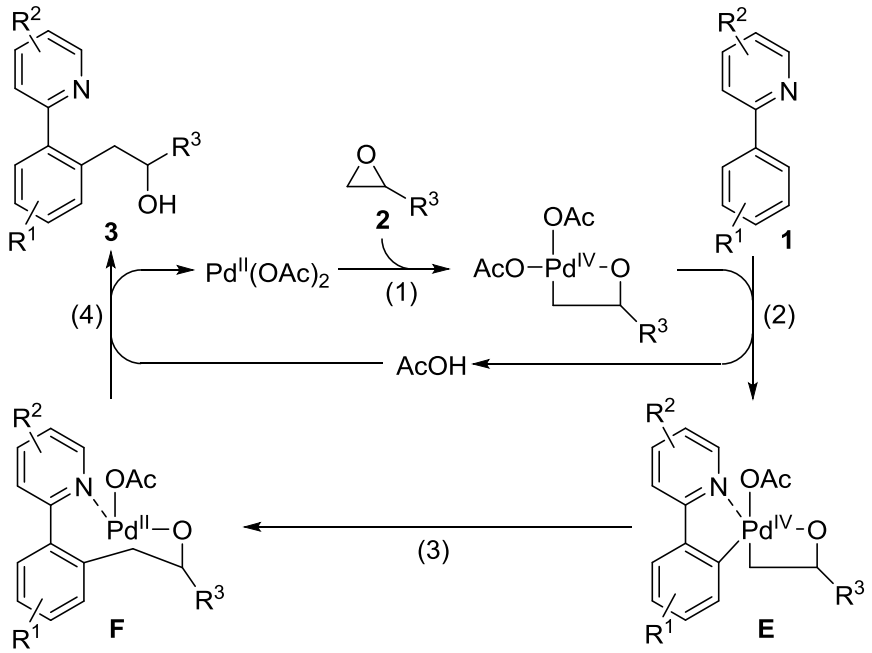
Scheme 1-2: (1) coordination of oxirane **2** to $Pd(OAc)_2$; (2) coordination of 2–phenylpyridine derivative **1** to the formed Pd(II) intermediate and C–H bond activation via elimination of acetic acid to give intermediate **C** via a CMD mechanism;[21] (3) insertion of oxirane **2** into the formed Pd(II)–carbon bond of **C** via ring–opening of oxirane **2** to give intermediate **D**;[22] and (4) protonation of intermediate **D** to give a coupling product **3** and regenerate $Pd(OAc)_2$. The key feature of this mechanism is that the C–H activation proceeded by palladium (II) via CMD mechanism and the palladium does not change the value in this reaction.

Scheme 1-2. A possible mechanism via Pd(II)-promoted C-C bond formation at a less-substituted carbon atom of oxiranes



Scheme 1-3: (1) oxidative addition of oxirane **2** to a Pd(II) catalyst to give a Pd(IV) intermediate; (2) coordination of 2–phenylpyridine derivative **1** to the Pd(IV) intermediate and C–H bond activation via the elimination of acetic acid to give intermediate **E**;[23] (3) reductive elimination to give intermediate **F** via the formation of a $C(sp^2)$–$C(sp^3)$ bond;[24] and (4) protonation of intermediate **F** to give a coupling product **3** and regenerate $Pd(OAc)_2$. The main point for this mechanism is that palladium (IV) promoted the C–H activation via a CMD mechaniam rather than palladium (II) in Scheme 2, and the reaction involves palladium(II)/palladium(IV) cycles. At present, the mechanism is not clear, but further detailed studies are ongoing in our lab. On the other hand, I began to apply it to the total synthesis of duocarmycin.

Scheme 1-3. A possible mechanism via Pd(IV) intermediate



1.4. Summary

In summary, a palladium–catalyzed coupling reaction between an *ortho*–C(sp^2) atom of arenes and a C(sp^3) atom of oxiranes was realized (Figure 1-4). This is first example of palladium–catalyzed C–H transformation using a strained compound as a coupling partner. This is also the first example of a transition metal–catalyzed intermolecular direct coupling reaction between a C–H bond of arenes and a carbon atom of oxirane rings via C–H bond activation. The reaction exhibited a wide substrate scope (arenes with 7 types of directing groups and 6 types of oxiranes) and proceed at room temperature in good to excellent yields without any additives, even in gram scale. This is an atom economical and environmental benign reaction. By using an *N*–methoxybenzamide as a substrate, 3–substituted isochroman–1–ones, which are a very important scaffold in natural produts and drug molecules, were obtained in one–pot procedure. Kinetic isotope effect experiments suggested that C–H bond activation was involved in a rate–determining step of the coupling reaction. These findings provide useful insights into synthetic organic chemistry, especially, C–H bond transformations. At present, we are trying to elucidate

the detailed mechanism and use it to the total synthesis of duocarmycin.

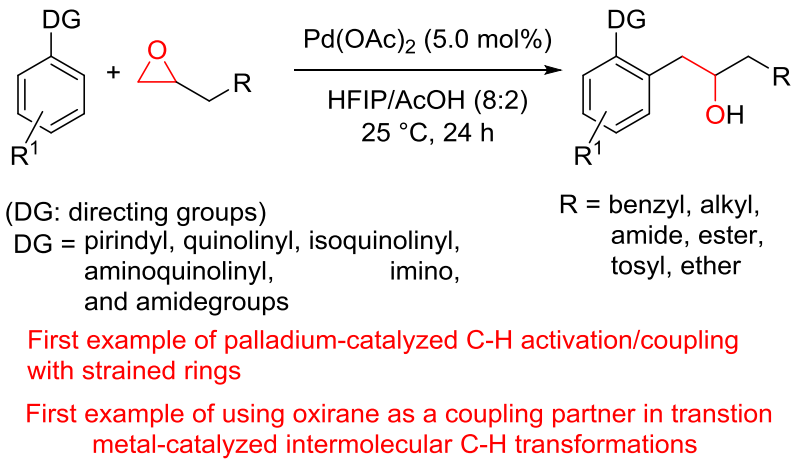


Figure 1-4. Summary

1.5. Rerences and Notes

(1) Recent reviews on C−H bond functionalizations: (a) C−H activation. In Topics in Current Chemistry; Yu, J.–Q.; Shi, Z.–J.; Eds.; *Springer: Berlin*, **2010**; Vol. *292*. (b) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev*. **2010**, *110*, 624. (c) Mkhalid, I. A. I.; Barnard, J. H.; Marder, T. B.; Murphy, J. M.; Hartwig, J. F. *Chem. Rev*. **2010**, *110*, 890. (d) Lyons, T. W.; Sanford, M. S. *Chem. Rev*. **2010**, *110*, 1147. (e) Ackermann, L. *Chem. Rev*. **2011**, *111*, 1315. (f) Kuninobu, Y.; Takai, K.; *Chem. Rev*. **2011**, *111*, 1938. (g) Wencel–Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev*. **2011**, *40*, 4740. (h) Cho, S. H.; Kim, J. Y.; Kwak, J.; Chang, S. *Chem. Soc. Rev*. **2011**, *40*, 5068. (i) Engle, K. M.; Mei, T. S.; Wasa, M.; Yu, J.–Q. *Acc. Chem. Res*. **2012**, *45*, 788. (j) Zhu, C.; Wang, R.; Falck, J. R. *Chem. Asian J*. **2012**, *7*, 1502. (k) Li, B. J.; Shi, Z.–J. *Chem. Soc. Rev.* **2012**, *41*, 5588. (l) Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev*. **2012**, *112*, 5879. (m) Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem., Int. Ed*. **2012**, *51*, 8960. (n) Kuhl, N.; Hopkinson, M. N.; Wencel–Delord, J.; Glorius, F. *Angew. Chem., Int. Ed*. **2012**, *51*, 10236. (o) Wencel–Delord, J.; Glorius, F. *Nature Chem*. **2013**, *5*, 369. (p) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed*. **2013**, ***52,*** 11726.

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(20) I can not deny the following pathway: (1) formation of a mononuclear Pd(II) species from arenes 1 and Pd(OAc)2 via the elimination of AcOH (C–H bond activation); and (2–1) coordination of oxiranes 2 to a Pd(II) center (formation of intermediate C); or (2–2) oxidative addition of oxiranes 2 to the formed Pd(II) species to give Pd(IV) species (formation of intermediate E)".

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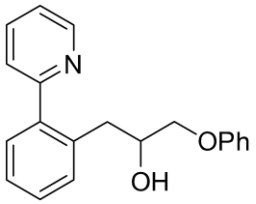
7330.

1.6. Experimental

General. All reactions were carried out in a dry solvent under argon atmosphere unless otherwise noted. [$Pd(OAc)_2$] (purity: 99.98%) was purchased from Aldrich Co. Methanol, hexafluoro–2–isopropanol (HFIP), and acetic acid were purchased from Wako Pure Chemical Industries, and were dried and degassed before use. NMR spectra were recorded on JEOL ECX500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) and JEOL ECS400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometer. Proton chemical shifts are reported relative to a residual solvent peak ($CDCl_3$ at 7.26 ppm, CD_3OD at 3.31 ppm, and $(CD_3)_2CO$ at 2.05 ppm). Carbon chemical shifts are reported relative to a residual solvent peak ($CDCl_3$ at 77.3 ppm, CD_3OD at 49.0 ppm, and $(CD_3)_2CO$ at 29.8 ppm). The following abbreviations were used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad. IR spectra were recorded on a JASCO FT/IR–410. High–resolution mass spectra (HRMS) were measured on a JEOL JMS–T100LC AccuTOF spectrometer (for HRMS).

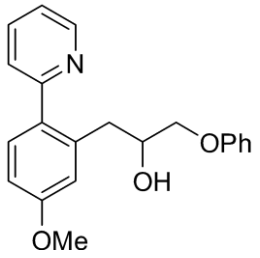
Typical Procedure for the Palladium–Catalyzed C(sp^2)–C(sp^3) Coupling Reaction between 2–Phenylpyridine (1a) and 2–(Phenoxymethyl)oxirane (2a). A mixture of 2–phenylpyridine (**1a**, 31.0 mg, 0.200 mmol), 2–(phenoxymethyl)oxirane (**2a**, 60.1 mg, 0.400 mmol), $Pd(OAc)_2$ (4.49 mg, 0.0200 mmol), HFIP (0.80 mL), and acetic acid (0.20 mL) was stirred at 25 ℃ for 24 h under Ar atmosphere. Then, the reaction mixture was quenched with saturated aq. Na_2CO_3 (5.0 mL), and the mixture was extracted with ethyl acetate (3 x 25 mL). The organic phase was dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on silica gel (hexane / EtOAc = 3:1) to give **3a** as a yellow oil (61.1 mg, >99%). [Note: When a mixture of $Pd(OAc)_2$ and 2–phenylpyridine (**1a**) was stayed for a long time (more than 20 min) before addition of 2–(phenoxymethyl)oxirane (**2a**), the yield of **3a** became lower (~10%).]

1–Phenoxy–3–(2–(2–pyridinyl)phenyl)–2–propanol (3a). 61.1 mg, >99%, yellow oil; ^{1}H NMR

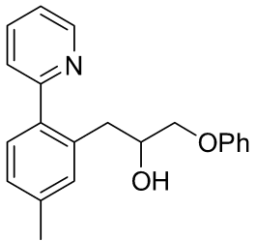


(400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 4.9 Hz, 1H), 8.05 (brs, 1H), 7.85 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.38–7.33 (m, 3H), 7.33–7.26 (m, 4H), 6.99–6.94 (m, 3H), 4.35–4.28 (m, 1H), 4.15 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.98 (dd, *J* = 9.1, 6.9 Hz, 1H), 3.12–2.95 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 160.3, 148.7, 141.3, 139.2, 138.0, 132.2, 131.03, 131.02, 130.4, 130.0, 127.7, 126.1, 123.7, 121.8, 115.6, 72.6, 72.3, 37.5; IR (KBr, ν / cm^{-1}) 3432, 2921, 2864, 1639, 1597, 1562, 1495, 1473, 1443, 1428, 1299, 1246, 1172, 1153, 1040, 1000, 918, 797, 753, 692, 631; HRMS (ESI+) Calcd for $C_{20}H_{19}NO_2$ ($M+Na^+$) 328.1308, Found 328.1308.

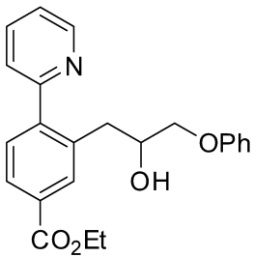
1–(5–Methoxy–2–(2–pyridinyl)phenyl)–3–phenoxy–2–propanol (3b).62.4 mg, 93%, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 5.2 Hz, 1H), 8.20 (brs, 1H), 7.82 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.36 (d, *J* = 8.5 Hz, 1H), 7.33–7.27 (m, 3H), 7.00–6.91 (m, 4H), 6.88 (dd, *J* = 8.5, 2.7 Hz, 1H), 4.39–4.24 (m, 1H), 4.15 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.95 (dd, *J* = 9.1, 7.2 Hz, 1H), 3.77 (s, 3H), 3.10–2.94 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 159.2, 158.6, 147.3, 139.1, 138.0, 132.7, 131.7, 129.7, 124.8, 121.9, 120.9, 116.2, 114.8, 113.0, 72.0, 71.3, 55.5, 37.1; IR (KBr, ν / cm^{-1}) 3423, 2959, 2931, 2858, 2719, 1643, 1561, 1496, 1469, 1430, 1321, 1287, 1247, 1172, 1154, 1115, 1042, 1018, 998, 819, 789, 691; HRMS (ESI^+) Calcd for $C_{21}H_{21}NO_3$ ($M+Na^+$) 358.1414, Found 358.1415.



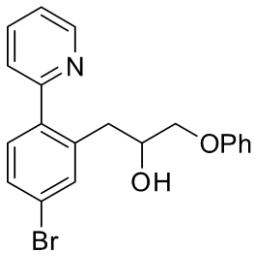
1–(5–Methyl–2–(2–pyridinyl)phenyl)–3–phenoxy–2–propanol (3c). 53.7 mg, 84%, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 4.9 Hz, 1H), 8.07 (brs, 1H), 7.84 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.55 (d, *J* = 8.0 Hz, 1H), 7.37–7.27 (m, 5H), 7.15 (d, *J* = 7.9 Hz, 1H), 7.01–6.91 (m, 3H), 4.20–4.38 (m, 1H), 4.15 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.96 (dd, *J* = 9.1, 7.0 Hz, 1H), 3.07–2.91 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.3, 159.0, 147.3, 139.3, 138.0, 137.3, 137.2, 132.2, 130.3, 129.6, 127.6, 124.9, 122.2, 120.9, 114.9, 72.3, 71.5, 36.9, 21.4; IR (KBr, ν / cm^{-1}) 3433, 2923, 2863, 2777, 1642, 1599, 1496, 1471, 1430, 1380, 1336, 1300, 1247, 1173, 1153, 1130, 1113, 1095, 1078, 1040, 1000, 938, 915, 883, 826, 788, 754, 736, 692, 666, 633; HRMS (ESI+) Calcd for $C_{21}H_{21}NO_2$ ($M+Na^+$) 342.1465, Found 342.1477.



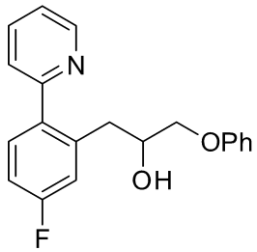
Ethyl 3–(2–hydroxy–3–phenoxypropyl)–4–(2–pyridinyl)benzoate (3d). 57.4 mg, 76%, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (d, *J* = 4.9 Hz, 1H), 8.13 (d, *J* = 1.6 Hz, 1H), 8.00 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.89 (ddd, *J* = 7.8, 7.8, 1.7 Hz, 1H), 7.72 (brs, 1H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.32–7.43 (m, 1.1 Hz, 1H), 7.34–7.25 (m, 2H), 7.01–6.87 (m, 3H), 4.39 (q, *J* = 7.1 Hz, 2H), 4.26–4.38 (m, 1H), 4.14 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.97 (dd, *J* = 9.1, 6.6 Hz, 1H), 3.13–2.98 (m, 2H), 1.38 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 159.2, 158.1, 147.7, 143.9, 138.2, 137.9, 132.6, 131.2, 130.4, 129.7, 127.9, 125.2, 123.0, 121.0, 114.8, 72.2, 71.4, 61.4, 36.8, 14.6; IR (KBr, ν / cm^{-1}) 3420, 2921, 2864, 1714, 1640, 1599, 1496, 1470, 1432, 1366, 1288, 1248, 1189, 1110, 1039, 1020, 894, 796, 754, 691, 667, 631; HRMS (ESI+) Calcd for $C_{23}H_{23}NO_4$ ($M+Na^+$) 400.1519, Found 400.1526.



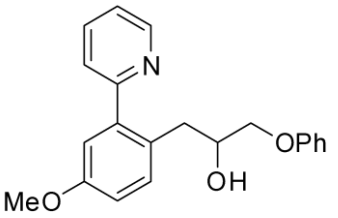
1–(5–Bromo–2–(2–pyridinyl)phenyl)–3–phenoxy–2–propanol (3e). 63.8 mg, 83%, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, *J* = 4.9 Hz, 1H), 7.81 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.76 (brs, 1H), 7.56 (d, *J* = 1.7 Hz, 1H), 7.48 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.42 (dd, *J* = 8.2, 1.9 Hz, 1H), 7.34–7.19 (m, 4H), 6.95–6.86 (m, 3H), 4.29–4.16 (m, 1H), 4.08 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.90 (dd, *J* = 9.1, 6.9 Hz, 1H), 3.00–2.87 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.1, 157.9, 147.7, 139.9, 138.8, 138.3, 134.3, 131.8, 130.0, 129.7, 124.9, 123.6, 122.7, 121.0, 114.8, 72.2, 71.4, 36.8; IR (KBr, / cm^{-1}) 3418, 2928, 2867, 1640, 1589, 1562, 1496, 1469, 1429, 1446, 1025, 918, 786，753，691; HRMS (ESI^+) Calcd for $C_{20}H_{18}BrNO_2$ ($M+Na^+$) 406.0413, Found 406.0418.



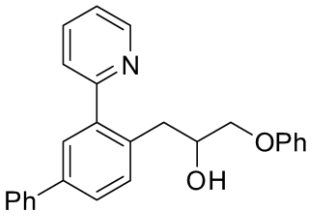
1–(5–Fluoro–2–(2–pyridinyl)phenyl)–3–phenoxy–2–propanol (3f). 50.4 mg, 78%, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.8 Hz, 1H), 7.96–7.81 (m, 2H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.44–7.23 (m, 4H), 7.16 (dd, *J* = 9.7, 2.4 Hz, 1H), 7.08–7.01 (m, 1H), 6.98–6.93 (m, 3H), 4.36–4.23 (m, 1H), 4.14 (dd, *J* = 9.1, 4.4 Hz, 1H), 3.95 (dd, *J* = 9.1, 7.0 Hz, 1H), 3.07–2.95 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.3 (d, *J* =250 Hz), 159.2, 158.1, 147.6, 140.8 (d, *J* = 8.5 Hz), 138.2, 136.2 (d, *J* = 2.2 Hz), 132.1 (d, *J* = 8.9 Hz), 129.7, 125.0, 122.5, 121.0, 118.0 (d, *J* = 20.4 Hz), 114.9, 114.0 (d, *J* = 21.0 Hz), 72.1, 71.3, 37.0; IR (KBr, ν / cm^{-1}) 3443, 2921, 2864, 1640,



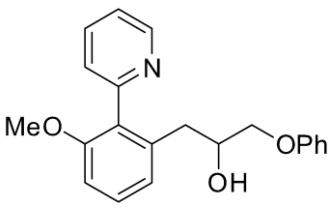
1597, 1562, 1496, 1470, 1432, 1377, 1288, 1247, 1173, 1153, 1119, 1073, 1038, 947, 788, 754, 690, 668; HRMS (ESI+) Calcd for $C_{20}H_{18}FNO_2$ (M+Na^+) 346.1214, Found 346.1204.

1–(4–Methoxy–2–(2–pyridinyl)phenyl)–3–phenoxy–2–propanol (3g). 

58.4 mg, 87%, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 4.6 Hz, 1H), 7.86 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.81 (brs, 1H), 7.56 (d, *J* = 7.7 Hz, 1H), 7.37–7.23 (m, 4H), 7.01–6.90 (m, 5H), 4.30–4.20 (m, 1H), 4.11 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.93 (dd, *J* = 9.1, 6.9 Hz, 1H), 3.84 (s, 3H), 2.99 (dd, *J* = 13.9, 3.9 Hz, 1H), 2.91 (dd, *J* = 13.9, 8.7 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 158.9, 158.2, 147.5, 140.9, 138.1, 132.6, 129.7, 129.4, 125.0, 122.5, 120.9, 115.8, 115.0, 114.8, 72.0, 71.4, 55.7, 35.9; IR (KBr, ν / cm^{-1}) 3475, 2921, 2864, 1643, 1597, 1562, 1496, 1476, 1429, 1428, 1297, 1246, 1226, 1173, 1095, 1034, 1000, 918, 814, 794, 756, 691, 676, 666; HRMS (ESI^+) Calcd for $C_{21}H_{21}NO_3$ (M+Na^+) 358.1414, Found 358.1420.

1–Phenoxy–3–(3–(2–pyridinyl)–[1,1'–biphenyl]–4–yl)–2–propanol (3h). 

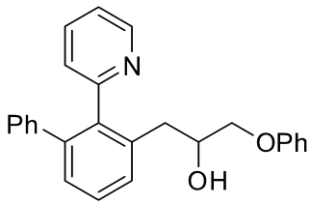
71.7 mg, 94%, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.1 Hz, 1H), 7.99 (brs, 1H), 7.88 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.72–7.59 (m, 5H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.46 (dd, *J* = 10.4, 4.8 Hz, 2H), 7.42–7.28 (m, 4H), 7.04–6.93 (m, 3H), 4.34 (brs, 1H), 4.17 (dd, *J* = 9.1, 4.5 Hz, 1H), 3.99 (dd, *J* = 9.1, 7.0 Hz, 1H), 3.18–3.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 158.9, 147.5, 140.8, 140.3, 139.9, 138.2, 136.5, 132.0, 129.7, 129.14, 129.06, 128.1, 127.6, 127.4, 125.1, 122.5, 120.9, 114.8, 72.1, 71.4, 36.5; IR (KBr, ν / cm^{-1}) 3443, 2931, 2864, 1644, 1496, 1473, 1429, 1391, 1289, 1251, 1172, 1153, 1139, 1115, 1096, 1077, 1038, 1020, 1003, 920, 892, 854, 833, 794, 727, 692, 648, 636, 613; HRMS (ESI^+) Calcd for $C_{26}H_{23}NO_2$ (M+Na^+) 404.1621, Found 404.1628.

1–(3–Methoxy–2–(2–pyridinyl)phenyl)–3–phenoxy–2–propanol (3i). 

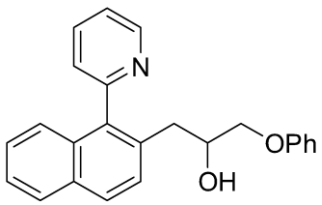
62.3 mg, 93%, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (dd, *J* = 4.9, 0.8 Hz, 1H), 7.72 (ddd, *J* = 7.8, 7.8, 1.4 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 8.0 Hz, 1H), 7.29–7.18 (m, 4H), 7.00 (d, *J* = 7.7 Hz, 1H), 6.87–6.92 (m, 4H), 4.14–4.20 (m, 1H), 4.01 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.83 (dd, *J* = 9.1, 6.7 Hz, 1H), 3.69 (s, 3H), 2.84 (dd, *J* = 13.5, 3.8 Hz, 1H), 2.60 (dd, *J* = 13.5, 9.4 Hz, 1H); ^{13}C

NMR (100 MHz, $CDCl_3$) δ 159.2, 157.1, 155.1, 147.9, 139.3, 136.4, 129.9, 129.6, 129.4, 128.0, 123.2, 122.3, 120.9, 114.8, 109.3, 72.1, 71.0, 55.9, 36.8; IR (KBr, ν / cm^{-1}) 3434, 2963, 2933, 2868, 1733, 1645, 1600, 1496, 1469, 1457, 1437, 1375, 1285, 1250, 1172, 1152, 1079, 1040, 998, 935, 882, 802, 784, 752, 692, 668; HRMS (ESI^+) Calcd for $C_{21}H_{21}NO_3$ ($M+Na^+$) 358.1414, Found 358.1407.

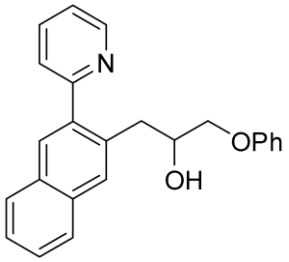
1–Phenoxy–3–(2–(2–pyridinyl)–[1,1'–biphenyl]–3–yl)–2–propanol (3j). 60.3 mg, 79%, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 4.1, 1.1 Hz, 1H), 7.56–7.30 (m, 5H), 7.29–7.20 (m, 2H), 7.17–7.06 (m, 4H), 7.01 (dd, *J* = 6.3, 2.8 Hz, 2H), 6.93–6.90 (m, 3H), 6.77 (d, *J* = 8.2 Hz, 1H), 4.16–4.28 (m, 1H), 4.10 (dd, *J* = 9.0, 4.2 Hz, 1H), 3.85 (dd, *J* = 9.0, 6.7 Hz, 1H), 2.80–3.05 (m, 1H), 2.45–2.73 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 158.2, 154.03,147.6, 142.0, 136.5, 130.7, 130.1, 129.7, 128.8, 128.1, 127.9, 127.8, 126.7, 122.0, 121.3, 121.0, 116.8, 114.8, 70.0, 63.5, 33.8; IR (KBr, ν / cm^{-1}) 3434, 2921, 2864, 1643, 1597, 1562, 1496, 1473, 1443, 1423, 1290, 1246, 1172, 1153, 1079, 1024, 918, 805, 789, 754, 702, 667; HRMS (ESI^+) Calcd for $C_{26}H_{23}NO_2$ ($M+Na^+$) 404.1621, Found 404.1614.



1–Phenoxy–3–(1–(2–pyridinyl)–2–naphthalenyl)–2–propanol (3k). 61.1 mg, 86%, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, *J* = 3.9 Hz, 1H), 7.96–7.81 (m, 3H), 7.59–7.52 (m, 2H), 7.50–7.35 (m, 4H), 7.32–7.25 (m, 3H), 7.02–6.89 (m, 3H), 4.16–4.32 (m, 1H), 4.11 (dd, *J* = 9.2, 4.4 Hz, 1H), 3.89 (dd, *J* = 9.2, 6.4 Hz, 1H), 3.09 (dd, *J* = 13.7, 3.4 Hz, 1H), 2.65 (dd, *J* = 13.7, 10.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.2, 157.3, 149.0, 136.9, 135.6, 132.7, 132.1, 129.73, 129.65, 129.5, 128.5, 128.2, 127.5, 126.8, 125.7, 125.6, 122.8, 121.0, 114.8, 72.8, 71.1, 38.1; IR (KBr, ν / cm^{-1}) 3433, 2921, 2864, 1644, 1597, 1562, 1495, 1473, 1443, 1385, 1299, 1246, 1172, 1153, 1040, 1000, 918, 797, 752, 692, 623; HRMS (ESI^+) Calcd for $C_{24}H_{21}NO_2$ ($M+Na^+$) 378.1465, Found 378.1476.

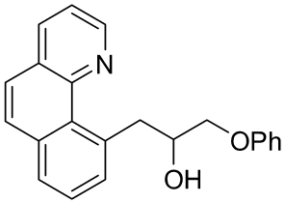


1–Phenoxy–3–(3–(2–pyridinyl)–2–naphthalenyl)–2–propanol (3l). 59.7 mg, 84%, yellow solid; ^1H NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 4.8 Hz, 1H), 7.99–7.74 (m, 6H), 7.70 (d, *J* = 8.0 Hz, 1H), 7.56–7.41 (m, 2H), 7.42–7.24 (m, 3H), 7.05–6.86 (m, 3H), 4.32–4.42 (m, 1H), 4.17 (dd, *J* = 9.1, 4.5

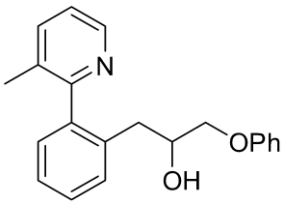


Hz, 1H), 4.01 (dd, *J* = 9.1, 6.9 Hz, 1H), 3.24 (dd, *J* = 13.7, 4.0 Hz, 1H), 3.14 (dd, *J* = 13.7, 9.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 159.2, 147.6, 138.4, 138.2, 135.1, 133.9, 132.2, 130.3, 130.0, 129.7, 128.1, 127.5, 127.0, 126.2, 125.4, 122.4, 121.0, 114.9, 72.1, 72.0, 36.8; IR (KBr, ν / cm^{-1}) 3434, 2953，2923, 2865, 1636, 1598, 1567, 1496, 1481, 1427, 1382, 1335, 1290, 1246, 1173, 1153, 1112, 1095, 1079, 1040, 1012, 954, 892, 859, 814, 790, 752, 691, 668, 634; HRMS (ESI^+) Calcd for $C_{24}H_{21}NO_2$ ($M+Na^+$) 378.1465, Found 378.1468.

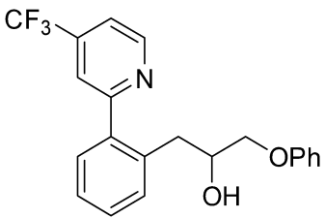
1–(Benzo[*h*]quinolin–10–yl)–3–phenoxy–2–propanol (3m). 58.0 mg, 88%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, *J* = 4.1 Hz, 1H), 8.23 (d, *J* = 7.9 Hz, 1H), 7.87–7.77 (m, 2H), 7.68–7.53 (m, 4H), 7.33 (t, *J* = 7.8 Hz, 2H), 7.04 (d, *J* = 8.0 Hz, 2H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.24 (d, *J* = 4.1 Hz, 1H), 4.68–4.57 (m, 1H), 4.29–4.18 (m, 3H), 3.96 (dd, *J* = 13.2, 3.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 147.4, 146.8, 138.5, 136.9, 135.8, 133.0, 132.8, 130.2, 129.9, 129.7, 128.0, 127.9, 125.4, 121.7, 121.0, 115.0, 73.0, 72.2, 40.2; IR (KBr, ν / cm^{-1}) 3433, 2965, 2921, 2864, 1716, 1645, 1597, 1562, 1496, 1470, 1443, 1394, 1377, 1288, 1248, 1172, 1124, 1074, 1038, 981, 923, 835, 754, 732, 691, 667; HRMS (ESI+) Calcd for $C_{22}H_{19}NO_2$ ($M+Na^+$) 352.1308, Found 352.1311.



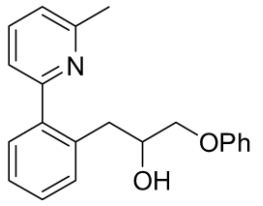
1–(2–(3–Methyl–2–pyridinyl)phenyl)–3–phenoxy–2–propanol (3n). 53.7 mg, 84%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.41 (d, *J* = 4.8 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.41 (brs, 1H), 7.35 (t, *J* = 6.6 Hz, 1H), 7.28–7.12 (m, 6H), 6.94–6.81 (m, 3H), 4.21–4.09 (m, 1H), 3.88–3.69 (m, 1H), 3.81 (dd, *J* = 9.1, 6.6 Hz, 1H), 2.88 (brs, 1H), 2.58 (brs, 1H), 2.19 (s, 3H); ^{13}C NMR (125 MHz, CD_3OD) δ 160.2, 146.7, 140.9, 140.5, 137.8, 134.0, 133.5, 132.0, 130.4, 130.3, 129.6, 127.5, 124.2, 121.8, 115.5, 72.2, 71.5, 38.0, 19.4; IR (KBr, ν / cm^{-1}) 3433, 2921, 2864, 1645, 1600, 1586, 1494, 1446, 1291, 1246, 1172, 1116, 1077, 1039, 1021, 972, 754, 691; HRMS (ESI+) Calcd for $C_{21}H_{21}NO_2$ ($M+Na^+$) 342.1465, Found 342.1479.



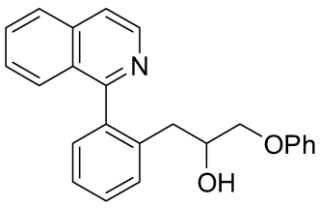
1–Phenoxy–3–(2–(4–(trifluoromethyl)–2–pyridinyl)phenyl)–2–propanol (3o). 68.7 mg, 92%,



yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.68 (d, *J* = 4.3 Hz, 1H), 7.80 (ddd, *J* = 7.7, 7.7, 1.6 Hz, 1H), 7.43–7.21 (m, 6H), 7.18 (d, *J* = 7.2 Hz, 1H), 6.93 (t, *J* = 7.2 Hz, 1H), 6.88 (d, *J* = 8.0 Hz, 2H), 6.55 (brs, 1H), 4.15 (brs, 1H), 4.01 (brs, 1H), 3.84 (brs, 1H), 2.90 (brs, 1H), 2.45 (brs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.1, 158.8, 149.3, 141.2, 136.8 (q, *J* = 32.5 Hz), 135.2, 131.4, 130.3, 129.6 (q, *J* = 4.6 Hz), 128.9, 128.6, 127.2, 124.4, 122.2 (q, *J* = 38.4 Hz), 121.0 (q, *J* = 24.9 Hz), 114.8, 73.1, 68.1, 34.2; IR (KBr, ν / cm^{-1}) 3429, 2963, 2931, 2864, 1673, 1645, 1562, 1496, 1470, 1443, 1394, 1377, 1288, 1235, 1172, 1124, 1074, 977, 923, 835, 797, 754, 691, 667, 647, 611; HRMS (ESI+) Calcd for $C_{21}H_{18}F_3NO_2$ ($M+Na^+$) 396.1182, Found 396.1179.

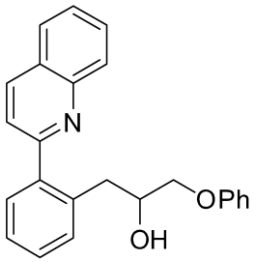


1–(2–(6–Methyl–2–pyridinyl)phenyl)–3–phenoxy–2–propanol (3p). 46.6 mg, 73%, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (brs, 1H), 7.74 (t, *J* = 7.7 Hz, 1H), 7.48–7.25 (m, 7H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.02–6.91 (m, 3H), 4.43–4.25 (m, 1H), 4.17 (dd, *J* = 9.1, 4.2 Hz, 1H), 3.99 (dd, *J* = 9.1, 6.9 Hz, 1H), 3.11–3.00 (m, 2H), 2.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.2, 158.3, 156.8, 140.2, 138.2, 137.4, 131.4, 130.2, 129.6, 129.2, 126.7, 121.98, 121.96, 120.9, 114.8, 72.2, 71.5, 36.8, 23.8; IR (KBr, ν / cm^{-1}) 3428, 2921, 2871, 2658, 1643, 1495, 1456, 1376, 1337, 1290, 1246, 1172, 1115, 1097, 1077, 1039, 1008, 948, 909, 881, 854, 805, 755; HRMS (ESI+) Calcd for $C_{21}H_{21}NO_2$ ($M+Na^+$) 342.1465, Found 342.1477.

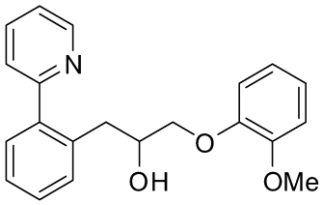


1–(2–(1–Isoquinolinyl)phenyl)–3–phenoxy–2–propanol (3q). 61.8 mg, 87%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, *J* = 5.8 Hz, 1H), 7.93 (dd, *J* = 13.5, 8.4 Hz, 2H), 7.77–7.70 (m, 2H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.57–7.48 (m, 2H), 7.46–7.34 (m, 3H), 7.33–7.23 (m, 3H), 6.96–6.86 (m, 2H), 4.32–4.21 (m, 1H), 4.08 (dd, *J* = 9.2, 4.5 Hz, 1H), 3.88 (dd, *J* = 16.0, 9.2 Hz, 1H), 3.02 (dd, *J* = 13.6, 3.4 Hz, 1H), 2.69 (dd, *J* = 13.6, 10.9 Hz, 1H); ^{13}C NMR (125 MHz, C_6D_{12}) δ 160.1, 159.2, 140.5, 138.8, 138.0, 137.5, 131.3, 131.1, 130.9, 129.7, 129.6, 129.5, 128.3, 127.7, 127.3, 125.8, 120.9, 120.8, 114.8, 72.8, 72.0, 37.4; IR (KBr, ν / cm^{-1}) 3444, 2921, 2867, 1836, 1771, 1637, 1558, 1495, 1455, 1418, 1386, 1359, 1320, 1290, 1246, 1172, 1103, 1078, 1042,

1020, 979, 909, 827, 806, 731, 692; HRMS (ESI^+) Calcd for $C_{24}H_{21}NO_2$ ($M+Na^+$) 378.1465, Found 378.1476.

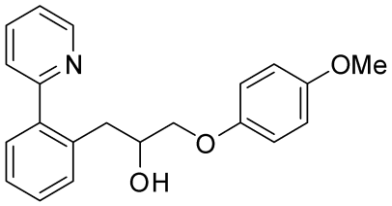


2–Phenoxy–1–(2–(2–quinolinyl)phenyl)ethanol (3r). 66.2 mg, 97%, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.40 (dd, *J* = 5.1, 1.6 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 7.90 (d, *J* = 8.1 Hz, 1H), 7.77 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.71 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.64–7.56 (m, 2H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.47 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.40 (t, *J* = 7.4 Hz, 1H), 7.31–7.24 (m, 2H), 6.97–6.89 (m, 3H), 4.45–4.35 (m, 1H), 4.21 (dd, *J* = 9.3, 5.2 Hz, 1H), 4.03 (dd, *J* = 9.3, 4.3 Hz, 1H), 3.18 (dd, *J* = 14.0, 9.9 Hz, 1H), 3.09 (dd, *J* = 14.0, 2.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.3, 158.7, 146.3, 140.1, 138.0, 131.7, 130.6, 129.61, 129.59, 129.5, 128.7, 127.7, 127.2, 126.91, 126.89, 126.86, 122.8, 120.9, 114.9, 72.2, 71.8, 37.0; IR (KBr, ν / cm^{-1}) 3431, 2921, 2864, 1637, 1620, 1601, 1558, 1496, 1467, 1425, 1378, 1340, 1317, 1290, 1246, 1173, 1117, 1079, 1045, 950, 920, 882, 836, 754, 739, 692, 631; HRMS (ESI+) Calcd for $C_{23}H_{19}NO_2$ ($M+Na^+$) 378.4183, Found 378.1476.

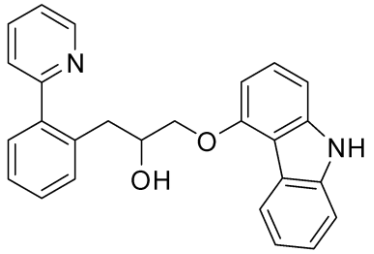


1–(2–Methoxyphenoxy)–3–(2–(2–pyridinyl)phenyl)–2–propanol (3s). 49.6 mg, 74%, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 4.2, 0.9 Hz, 1H), 7.84 (ddd, *J* = 7.7, 7.7, 1.7 Hz, 1H), 7.76 (brs, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.1 Hz, 1H), 7.41 (dd, *J* = 7.0, 7.0 Hz, 2H), 7.35–7.29 (m, 2H), 7.02–6.98 (m, 1H), 6.96–6.89 (m, 3H), 4.39–4.29 (m, 1H), 4.20 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.98 (dd, *J* = 9.5, 7.2 Hz, 1H), 3.85 (s, 3H), 3.10 (dd, *J* = 13.7, 3.8 Hz, 1H), 3.02 (dd, *J* = 13.7, 9.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 149.9, 148.9, 147.5, 140.0, 138.0, 137.6, 131.6, 130.3, 129.3, 126.7, 125.0, 122.3, 121.5, 121.2, 114.2, 112.4, 73.5, 71.3, 56.2, 36.9; IR (KBr, ν / cm^{-1}) 3429, 2951, 2874, 1644, 1506, 1473, 1456, 1428, 1374, 1329, 1254, 1226, 1178, 1124, 1026, 1010, 926, 787, 745, 678, 604; HRMS (ESI^+) Calcd for $C_{21}H_{21}NO_3$ ($M+Na^+$) 358.1414, Found 358.1415.

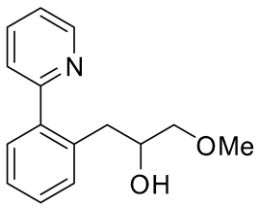
1–((4–Methoxybenzyl)oxy)–3–(2–(2–pyridinyl)phenyl)–2–propanol (3t).60.3 mg, 81%, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.3 Hz, 1H), 7.90 (brs, 1H), 7.85 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.37–7.46 (m, 3H), 7.33 (dd, *J* = 9.7, 3.9 Hz, 2H), 6.94–6.87 (m,



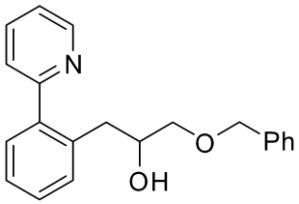
2H), 6.87–6.82 (m, 2H), 4.17–4.36 (m, 1H), 4.09 (dd, *J* = 9.1, 4.6 Hz, 1H), 3.92 (dd, *J* = 9.1, 6.4 Hz, 1H), 3.78 (s, 3H), 3.04 (dd, *J* = 13.6, 3.8 Hz, 1H), 2.98 (dd, *J* = 13.6, 9.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0, 154.0, 153.5, 147.4, 139.9, 138.0, 137.5, 131.5, 130.3, 129.3, 126.8, 125.0, 122.4, 115.7, 114.9, 72.9, 71.5, 56.0, 36.8; IR (KBr, ν / cm^{-1}) 3411, 2911, 2874, 1637, 1560, 1541, 1508, 1473, 1456, 1440, 1289, 1232, 1180, 1106, 1039, 823, 747, 709, 680, 668; HRMS (ESI^+) Calcd for $C_{21}H_{21}NO_3$ ($M+Na^+$) 358.1414, Found 358.1415.



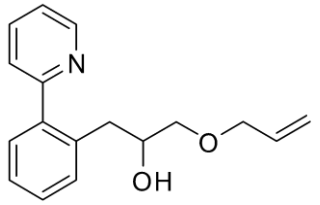
1–((9*H*–Carbazol–4–yl)oxy)–3–(2–(2–pyridinyl)phenyl)–2–propanol (3u). 33.9 mg, 43%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 3.7 Hz, 1H), 8.25 (d, *J* = 7.6 Hz, 1H), 8.07 (brs, 1H), 7.88 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.60 (d, *J* = 7.9 Hz, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.48–7.28 (m, 7H), 7.11 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.06 (d, *J* = 8.1 Hz, 1H), 6.75 (d, *J* = 7.9 Hz, 1H), 4.59–4.48 (m, 1H), 4.42 (dd, *J* = 7.5, 3.1 Hz, 1H), 4.26 (dd, *J* = 15.1, 7.5 Hz, 1H), 3.30–3.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 155.8, 147.5, 139.0, 138.2, 137.6, 131.7, 130.5, 129.5, 127.1, 127.0, 126.9, 125.12, 125.06, 122.4, 123.3, 123.0, 122.5, 119.8, 113.0, 110.2, 103.7, 101.6, 72.3, 72.0, 37.2; IR (KBr, ν / cm^{-1}) 3443, 2921, 2864, 2358, 2330, 1639, 1597, 1562, 1495, 1473, 1443, 1428, 1299, 1264, 1171, 1143, 1140, 938, 707, 631; HRMS (ESI+) Calcd for $C_{20}H_{15}D_4NO_2$ ($M+Na^+$) 332.1559, Found 417.1576.



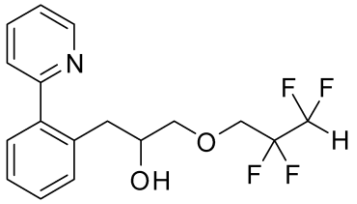
1–Methoxy–3–(2–(2–pyridinyl)phenyl)–2–propanol (3v). 39.4 mg, 81%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (d, *J* = 5.1 Hz, 1H), 7.84 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.50 (brs, 1H), 7.43–7.37 (m, 3H), 7.35–7.29 (m, 2H), 4.17–3.99 (m, 1H), 3.52 (dd, *J* = 9.4, 5.3 Hz, 1H), 3.44 (s, 3H), 3.41 (dd, *J* = 9.4, 6.3 Hz, 1H), 2.90 (dd, *J* = 13.6, 3.8 Hz, 1H), 2.84 (dd, *J* = 13.6, 9.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 147.6, 140.0, 137.9, 137.8, 131.54, 131.49, 130.3, 129.3, 126.7, 122.3, 77.8, 71.9, 59.4, 37.0; IR (KBr, ν / cm^{-1}) 3522, 2941, 2864, 1643, 1597, 1562, 1495, 1473, 1443, 1428, 1299, 1246, 1172, 1153, 1127, 1080, 1003, 818, 797, 753, 678, 669; HRMS (ESI+) Calcd for $C_{15}H_{17}NO_2$ ($M+Na^+$) 266.1151, Found 266.1149.



1–(Benzyloxy)–3–(2–(2–pyridinyl)phenyl)–2–propanol (3w). 58.1 mg, 91%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.44 (dd, *J* = 5.4, 1.4 Hz, 1H), 7.69 (ddd, *J* = 7.9, 7.9, 2.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.38 (brs, 1H), 7.28–7.11 (m, 10H), 4.52–4.45 (m, 2H), 4.02–3.93 (m, 1H), 3.50 (dd, *J* = 9.4, 4.8 Hz, 1H), 3.37 (dd, *J* = 9.4, 6.5 Hz, 1H), 2.81 (dd, *J* = 13.6, 3.9 Hz, 1H), 2.75 (dd, *J* = 13.6, 8.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 147.6, 134.0, 138.9, 137.90, 137.85, 131.5, 130.3, 129.2, 128.6, 127.9, 127.7, 126.7, 124.9, 122.3, 75.2, 73.6, 72.0, 37.0; IR (KBr, ν / cm^{-1}) 3367, 2921, 2859, 1644, 1496, 1474, 1453, 1442, 1427, 1362, 1302, 1267, 1206, 1180, 1119, 1020, 1026, 1000, 910, 835, 798, 732, 698, 664, 632; HRMS (ESI+) Calcd for $C_{21}H_{21}NO_2$ ($M+Na^+$) 342.1465, Found 342.1469.

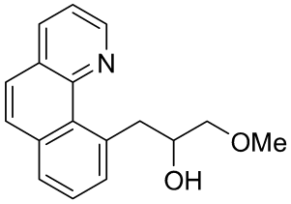


1–(Allyloxy)–3–(2–(2–pyridinyl)phenyl)–2–propanol (3x). 44.7 mg, 83%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 5.3, 1.3 Hz, 1H), 7.83 (ddd, *J* = 7.7, 7.7, 1.6 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 1H), 7.49 (brs, 1H), 7.45–7.28 (m, 5H), 6.00–5.89 (m, 1H), 5.33–5.27 (m, 1H), 5.21–5.14 (m, 1H), 4.13–4.03 (m, 3H), 3.59 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.45 (dd, *J* = 9.4, 6.6 Hz, 1H), 2.94 (dd, *J* = 13.6, 3.8 Hz, 1H), 2.86 (dd, *J* = 13.6, 9.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.1, 147.5, 139.9, 137.91, 137.86, 135.2, 131.5, 130.3, 129.2, 126.6, 124.9, 122.3, 117.0, 75.3, 72.5, 72.0, 37.0; IR (KBr, ν / cm^{-1}) 3434, 2921, 2864, 1645, 1597, 1562, 1495, 1473, 1443, 1427, 1299, 1238, 1172, 1153, 1094, 1024, 1000, 929, 797, 753, 667, 631; HRMS (ESI^+) Calcd for $C_{17}H_{19}NO_2$ ($M+Na^+$) 292.1308, Found 292.1300.

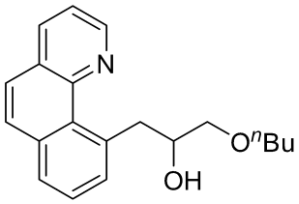


1–(2–(2–Pyridinyl)phenyl)–3–(2,2,3,3–tetrafluoropropoxy)–2–propanol (3y). 54.2 mg, 79%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.59 (d, *J* = 4.1 Hz, 1H), 7.86 (ddd, *J* = 7.8, 7.8, 1.9 Hz, 1H), 7.82 (brs, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.46–7.37 (m, 3H), 7.36–7.31 (m, 2H), 5.94 (tt, *J* = 53.3, 5.2 Hz, 1H), 4.08 (dd, *J* = 8.5, 4.4 Hz, 1H), 3.97 (tt, *J* = 12.6, 1.6 Hz, 2H), 3.70 (dd, *J* = 9.7, 4.7 Hz, 1H), 3.64 (dd, *J* = 9.7, 5.7 Hz, 1H), 2.95–2.78 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 147.4, 139.9, 138.1, 137.5, 131.4, 130.3, 129.4, 126.9, 125.0, 122.4, 115.3 (tt, *J* = 251, 26.3 Hz), 109.4 (tt, *J* = 250, 23.5 Hz), 77.5, 72.0, 68.9 (t, *J* = 28.4 Hz),

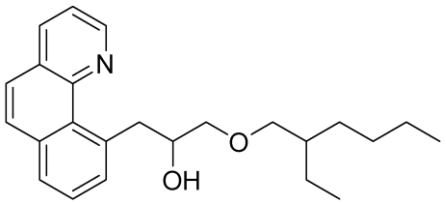
36.6; IR (KBr, ν / cm^{-1}) 3242, 2931, 2863, 1636, 1597, 1552, 1495, 1473, 1444, 1375, 1275, 1121, 1074, 915, 767; HRMS (ESI^+) Calcd for $C_{17}H_{17}F_4NO_2$ ($M+Na^+$) 366.1088, Found 366.1098.



1–(Benzo[*h*]quinolin–10–yl)–3–methoxy–2–propanol (3z). 50.3 mg, 94%, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.92 (dd, *J* = 4.5, 1.8 Hz, 1H), 8.20 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.88–7.77 (m, 2H), 7.68–7.59 (m, 3H), 7.53 (dd, *J* = 8.0, 4.5 Hz, 1H), 5.68 (brs, 1H), 4.46–4.34 (m, 1H), 4.09 (dd, *J* = 13.1, 8.1 Hz, 1H), 3.83 (dd, *J* = 13.1, 3.9 Hz, 1H), 3.73–3.59 (m, 2H), 3.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5, 146.8, 138.9, 136.8, 135.8, 132.6, 130.1, 129.6, 127.93, 127.91, 127.8, 125.4, 121.5, 77.6, 73.1, 59.4, 40.5; IR (KBr, ν / cm^{-1}) 3566, 3048, 2960, 2904, 2884, 1508, 1421, 1394, 1338, 1196, 1125, 964, 885, 763, 731; HRMS (ESI^+) Calcd for $C_{17}H_{17}NO_2$ ($M+Na^+$) 290.1151, Found 290.1162.



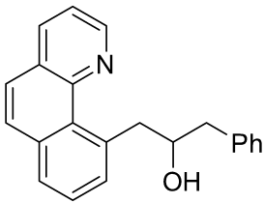
1–(Benzo[*h*]quinolin–10–yl)–3–butoxy–2–propanol (3A). 43.9 mg, 71%, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, *J* = 2.9 Hz, 1H), 8.22 (d, *J* = 7.8 Hz, 1H), 7.82 (dd, *J* = 8.8, 2.9 Hz, 2H), 7.64 (t, *J* = 6.7 Hz, 3H), 7.54 (dd, *J* = 7.8, 4.3 Hz, 1H), 5.61 (brs, 1H), 4.47–4.36 (m, 1H), 4.10 (dd, *J* = 13.0, 8.0 Hz, 1H), 3.86 (dd, *J* = 13.0, 4.0 Hz, 1H), 3.66 (d, *J* = 5.5 Hz, 2H), 3.57 (t, *J* = 6.6 Hz, 2H), 1.76–1.61 (m, 2H), 1.48–1.40 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 146.8, 139.0, 136.8, 135.8, 132.7, 130.1, 129.7, 127.94, 127.89, 127.7, 125.4, 121.5, 75.6, 73.2, 71.5, 40.6, 32.2, 19.7, 14.2; IR (KBr, ν / cm^{-1}) 3420, 3056, 2956, 2931, 2866, 1734, 1592, 1570, 1425, 1393, 1237, 1122, 835, 806, 731; HRMS (ESI^+) Calcd for $C_{20}H_{23}NO_2$ ($M+Na^+$) 332.1621, Found 332.1623.



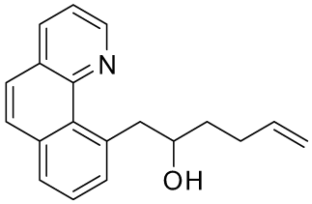
1–(Benzo[*h*]quinolin–10–yl)–3–((2–ethylhexyl)oxy)–2–propanol (3B). 42.4 mg, 58%, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, *J* = 3.6 Hz, 1H), 8.22 (d, *J* = 7.1 Hz, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.69–7.59 (m, 3H), 7.54 (dd, *J* = 7.9, 4.3 Hz, 1H), 5.64 (brs, 1H), 4.41–4.37 (m, 1H), 4.11 (dd, *J* = 13.1, 7.9 Hz, 1H), 3.87 (dd, *J* = 13.1, 3.9 Hz, 1H), 3.66–3.61 (m, 2H), 3.51–3.39 (m, 2H), 1.59 (dd, *J* = 15.2, 9.2 Hz, 2H), 1.52–1.19 (m, 7H), 0.93–0.86 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 146.8, 139.1, 136.7, 135.8,

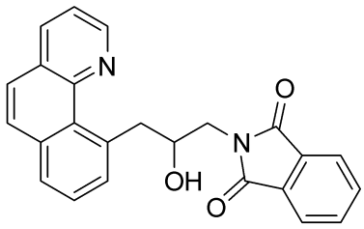
132.7, 130.2, 129.7, 127.9, 127.9, 127.7, 125.4, 121.5, 75.7, 74.6, 73.3, 40.6, 40.0, 30.9, 29.4, 24.2, 23.4, 14.4, 11.4; IR (KBr, ν / cm^{-1}) 3445, 3159, 3057, 2959, 2903, 2858, 1733, 1457, 1394, 1263, 1103, 835, 731; HRMS (ESI+) Calcd for $C_{24}H_{31}NO_2$ ($M+Na^+$) 388.2247, Found 388.2253.

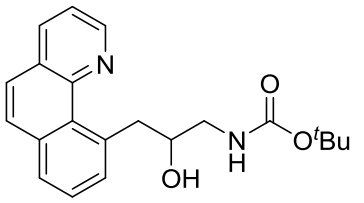
1–(Benzo[*h*]quinolin–10–yl)–3–phenyl–2–propanol (3C). 52.0 mg, 83%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 4.3, 1.6 Hz, 1H), 8.09 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.70 (dd, *J* = 8.1, 3.6 Hz, 2H), 7.55–7.49 (m, 2H), 7.45–7.37 (m, 2H), 7.32–7.25 (m, 4H), 7.21–7.15 (m, 1H), 5.58 (brs, 1H), 4.51–4.35 (m, 1H), 4.02 (dd, *J* = 13.0, 9.1 Hz, 1H), 3.64 (dd, *J* = 13.0, 3.3 Hz, 1H), 3.13–2.99 (m, 2H); ^{13}C NMR (125 MHz, CD_3OD) δ 148.6, 147.9, 140.9, 140.4, 137.4, 136.9, 133.7, 130.9, 130.6, 130.2, 129.2, 129.0, 128.6, 128.5, 127.0, 126.4, 122.3, 75.8, 45.9, 45.4; IR (KBr, ν / cm^{-1}) 3393, 3031, 3025, 2917, 2848, 1591, 1570, 1515, 1496, 1426, 1394, 1325, 1168, 1125, 1081, 1049, 976, 908, 834, 797, 749, 729, 701; HRMS (ESI+) Calcd for $C_{22}H_{19}NO$ ($M+Na^+$) 336.1359, Found 336.1364.

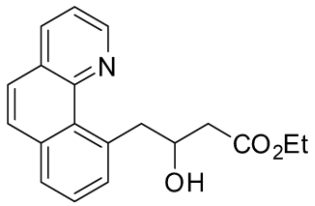


1–(Benzo[*h*]quinolin–10–yl)hex–5–en–2–ol (3D). 27.2 mg, 49%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (dd, *J* = 4.5, 1.8 Hz, 1H), 8.23 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.82 (d, *J* = 8.7 Hz, 2H), 7.67–7.61 (m, 2H), 7.60–7.57 (m, 1H), 7.55 (dd, *J* = 8.0, 4.5 Hz, 1H), 5.96 (ddt, *J* = 17.0, 10.2, 6.6 Hz, 1H), 5.65 (brs, 1H), 5.11 (dd, *J* = 17.0, 1.8 Hz, 1H), 5.00 (d, *J* = 10.2 Hz, 1H), 4.26–4.22 (m, 1H), 4.07 (dd, *J* = 13.0, 8.4 Hz, 1H), 3.79 (dd, *J* = 13.0, 3.6 Hz, 1H), 2.48–2.27 (m, 2H), 1.95–1.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.6, 146.8, 139.5, 136.9, 135.8, 132.6, 130.2, 129.7, 128.0, 127.9, 127.7, 126.9, 125.4, 121.6, 114.6, 74.3, 43.7, 38.1, 30.4; IR (KBr, ν / cm^{-1}) 3419, 2921, 2849, 1639, 1592, 1571, 1514, 1426, 1393, 1317, 1168, 1124, 1065, 908, 834, 808, 760, 731, 667; HRMS (ESI+) Calcd for $C_{19}H_{19}NO$ ($M+Na^+$) 300.1359, Found 300.1368.

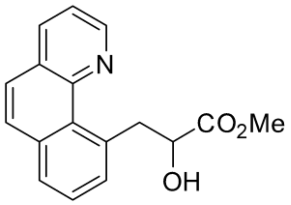


2–(3–(Benzo[*h*]quinolin–10–yl)–2–hydroxypropyl)isoindoline–1,3–dione (3E).  50.6 mg, 66%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.97 (d, *J* = 4.4 Hz, 1H), 8.22 (d, *J* = 8.0 Hz, 1H), 7.91–7.84 (m, 2H), 7.84–7.80 (m, 2H), 7.76–7.68 (m, 2H), 7.68–7.60 (m, 3H), 7.55 (dd, *J* = 8.0, 4.7 Hz, 1H), 5.67 (brs, 1H), 7.59–4.56 (m, 1H), 4.23–4.06 (m, 3H), 3.82 (dd, *J* = 13.1, 3.4 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.1, 147.4, 147.1, 138.3, 136.9, 135.8, 134.1, 132.52, 132.49, 131.9, 130.2, 129.6, 128.0, 127.9, 125.5, 123.5, 121.7, 72.3, 45.4, 41.7; IR (KBr, ν / cm^{-1}) 3508, 3049, 2933, 1770, 1709, 1467, 1427, 1393, 1011, 896, 837, 794, 763, 724, 714, 628; HRMS (ESI+) Calcd for $C_{24}H_{18}N_2O_3$ ($M+Na^+$) 405.1210, Found 405.1218.

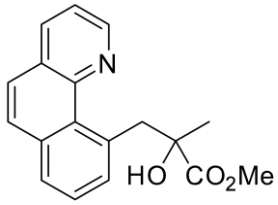
***tert*–Butyl (3–(benzo[*h*]quinolin–10–yl)–2–hydroxypropyl)carbamate (3F).**  38.1 mg, 54%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, *J* = 2.7 Hz, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.72–7.51 (m, 4H), 6.09 (brs, 1H), 5.22 (brs, 1H), 4.28 (brs, 1H), 4.18 (dd, *J* = 12.8, 9.1 Hz, 1H), 3.64 (dd, *J* = 12.8, 3.2 Hz, 2H), 3.41–3.29 (m, 1H), 1.47 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 147.4, 146.7, 138.7, 137.1, 135.8, 132.6, 130.0, 129.8, 128.12, 128.07, 127.9, 125.5, 121.7, 74.1, 47.7, 41.3, 30.0, 28.7; IR (KBr, ν / cm − 1) 3360, 3049, 2963, 2924, 2853, 1706, 1508, 1457, 1428, 1392, 1365, 1250, 1170, 1089, 894, 835, 763, 731; HRMS (ESI+) Calcd for $C_{21}H_{24}N_2O_3$ ($M+Na^+$) 375.1679, Found 375.1682.

Ethyl 4–(benzo[*h*]quinolin–10–yl)–3–hydroxybutanoate (3G).  54.5 mg, 88%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (dd, *J* = 4.4, 1.8 Hz, 1H), 8.22 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.83 (dd, *J* = 11.4, 5.2 Hz, 2H), 7.63 (ddd, *J* = 8.8, 8.3, 2.0 Hz, 3H), 7.55 (dd, *J* = 8.0, 4.4 Hz, 1H), 5.84 (brs, 1H), 4.72–4.68 (m, 1H), 4.20 (q, *J* = 7.0 Hz, 2H), 4.11 (dd, *J* = 13.1, 8.1 Hz, 1H), 3.91 (dd, *J* = 13.1, 4.0 Hz, 1H), 2.86–2.70 (m, 2H), 1.29 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.7, 147.5, 146.9, 138.5, 137.5, 136.8, 135.8, 132.8, 130.1, 129.6, 128.0, 127.9, 125.5, 121.6, 77.5, 71.3, 60.7, 43.2, 14.5; IR (KBr, ν / cm^{-1}) 3524, 3157, 2971, 2873, 1731, 1592, 1570, 1515,

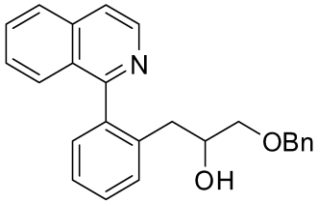
1425, 1394, 1372, 1271, 1151, 1032, 836, 732; HRMS (ESI+) Calcd for $C_{19}H_{19}NO_3$ ($M+Na^+$) 332.1257, Found 332.1249.

Methyl 3–(benzo[*h*]quinolin–10–yl)–2–hydroxypropanoate (3H). 

51.2 mg, 91%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.96 (dd, *J* = 4.5, 1.8 Hz, 1H), 8.25 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.88–7.81 (m, 2H), 7.70–7.61 (m, 3H), 7.58 (dd, *J* = 8.0, 4.5 Hz, 1H), 7.08 (brs, 1H), 4.96–4.87 (m, 1H), 4.36 (dd, *J* = 13.2, 9.2 Hz, 1H), 4.03 (dd, *J* = 13.2, 4.1 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.8, 147.3, 146.9, 137.3, 137.2, 135.8, 132.5, 130.2, 129.7, 128.2, 128.1, 128.0, 125.5, 121.9, 74.8, 52.3, 40.5; IR (KBr, ν / cm^{-1}) 3481, 3157, 2951, 2865, 1735, 1592, 1508, 1435, 1395, 1206, 1113, 1026, 837, 730; HRMS (ESI+) Calcd for $C_{17}H_{15}NO_3$ ($M+Na^+$) 304.0944, Found 304.0939.

Methyl 3–(benzo[*h*]quinolin–10–yl)–2–hydroxy–2–methylpropanoate (3I). 

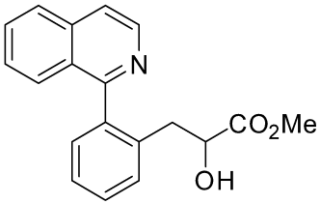
50.8 mg, 86%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$ δ 8.94 (dd, *J* = 4.5, 1.7 Hz, 1H), 8.26 (dd, *J* = 8.0, 1.7 Hz, 1H), 8.16 (brs, 1H), 7.91–7.78 (m, 2H), 7.71–7.52 (m, 4H), 4.46 (d, *J* = 13.5 Hz, 1H), 3.91 (d, *J* = 13.5 Hz, 1H), 3.78 (s, 3H), 1.71 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.8, 146.9, 146.7, 137.5, 136.0, 135.8, 133.9, 130.7, 129.9, 128.4, 128.1, 127.8, 125.3, 121.9, 52.4, 44.7, 26.7, 21.5; IR (KBr, ν / cm^{-1}) 3436, 2983, 2864, 1733, 1643, 1573, 1517, 1426, 1395, 1369, 1329, 1256, 1112, 982, 840, 743, 731, 668; HRMS (ESI+) Calcd for $C_{18}H_{17}NO_3$ ($M+Na^+$) 318.1101, Found 318.1111.

1–(Benzyloxy)–3–(2–(isoquinolin–1–yl)phenyl)–2–propanol (3J). 

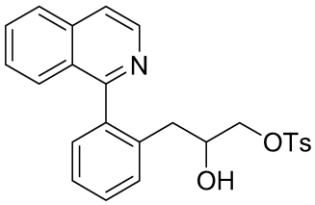
67.2 mg, 91% (dr = 3:1 in $CDCl_3$), yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.52–8.48 (m, 1.33H), 7.89–7.83 (m, 2.66H), 7.73 (d, *J* = 8.5 Hz, 0.33 H), 7.70–7.59 (m, 3H), 7.59–7.20 (m, 11H), 6.80 (brs, 1H), 5.42 (brs, 0.33H), 4.56–4.47 (m, 2.67H), 4.08–3.99 (m, 1.33H), 3.56 (dd, *J* = 9.5, 4.7 Hz, 1H), 3.44–3.30 (m, 1.67H), 2.90 (dd, *J* = 13.7, 3.5 Hz, 1.33H), 2.63 (dd, *J* = 14.0, 5.7 Hz, 0.33H), 2.54 (dd, *J* = 13.6, 10.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 160.2, 140.6, 139.0, 138.8, 138.1, 137.4, 131.8, 131.2, 131.1, 130.8, 129.4, 128.6, 128.5, 128.2, 128.0, 128.0, 127.8, 127.7, 127.2, 126.1, 125.7, 120.6, 75.7, 73.5, 73.4, 72.6, 72.5, 69.4, 37.5, 37.0; IR (KBr, ν / cm^{-1}) 3421, 3058, 3031,

2924, 2856, 1734, 1622, 1586, 1558, 1496, 1455, 1386, 1359, 1320, 1244, 1101, 1028, 978, 909, 876, 828, 747, 697, 681, 630; HRMS (ESI+) Calcd for $C_{25}H_{23}NO_2$ ($M+Na^+$) 392.1621, Found 392.1628.

Methyl 2–hydroxy–3–(2–(isoquinolin–1–yl)phenyl)propanoate (3K). 37.9 mg, 78% (dr = 3:1 in $CDCl_3$; dr = 1:1 in CD_3OD), yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (d, *J* = 5.8 Hz, 1H), 8.55 (d, *J* = 5.8 Hz, 0.33H), 8.25 (brs, 1H), 7.93 (dd, *J* = 13.8, 8.4 Hz, 2.33H), 7.86 (d, *J* = 8.5 Hz, 0.33H), 7.77–7.69 (m, 2.33H), 7.59 (d, *J* = 7.7 Hz, 1H), 7.57–7.49 (m, 2H), 7.46–7.32 (m, 3H), 4.67–4.56 (m, 0.33H), 4.47 (dd, *J* = 11.6, 3.7 Hz, 1H), 3.73 (s, 3.33H), 3.22 (dd, *J* = 14.2, 3.7 Hz, 0.33H), 3.10 (dd, *J* = 13.7, 3.7 Hz, 1H), 3.00 (dd, *J* = 14.2, 5.5 Hz, 0.33H), 2.80 (dd, *J* = 13.5, 11.8 Hz, 1H); ^{1}H NMR (500 MHz, CD_3OD) δ 8.53 (d, *J* = 5.8 Hz, 1H), 8.49 (d, *J* = 5.8 Hz, 1H), 8.02 (dd, *J* = 8.2, 2.1 Hz, 2H), 7.88 (dd, *J* = 5.7, 2.9 Hz, 2H), 7.83–7.74 (m, 3H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.62–7.46 (m, 6H), 7.45–7.39 (m, 2H), 7.38–7.34 (m, 1H), 7.32 (d, *J* = 7.5 Hz, 1H), 4.10 (ddd, *J* = 14.4, 8.8, 5.0 Hz, 2H), 3.54 (s, 3H), 3.47 (s, 3H), 3.07 (dd, *J* = 14.0, 4.7 Hz, 1H), 2.86 (dd, *J* = 14.1, 7.8 Hz, 1H), 2.77 (dd, *J* = 14.0, 5.0 Hz, 1H), 2.65 (dd, *J* = 14.0, 9.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.4, 159.4, 140.4, 138.0, 137.6, 137.3, 135.8, 131.6, 131.2, 131.0, 130.9, 129.7, 129.2, 128.2, 127.9, 127.8, 127.8, 127.3, 127.2, 126.4, 126.2, 121.0, 73.3, 52.2, 37.4, 37.0; IR (KBr, ν / cm^{-1}) 3159, 3057, 2951, 2863, 1748, 1622, 1587, 1558, 1490, 1443, 1385, 1359, 1322, 1270, 1208, 1173, 1114, 1018, 978, 876, 829, 806, 763, 734, 695, 680, 631; HRMS (ESI+) Calcd for $C_{19}H_{17}NO_3$ ($M+Na^+$) 330.1101, Found 330.1099.

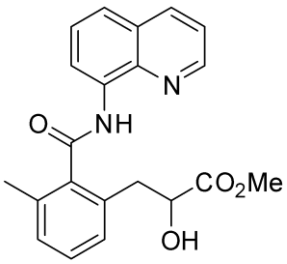


2–Hydroxy–3–(2–(isoquinolin–1–yl)phenyl)propyl 4–methylbenzenesulfonate (3L). 59.0 mg, 68%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.36–9.32 (m, 1H), 8.33–8.29 (m, 1H), 8.24–8.18 (m, 2H), 8.10 (dd, *J* = 7.2, 7.2 Hz, 1H), 7.92–7.83 (m, 1H), 7.80 (d, *J* = 7.8 Hz, 2H), 7.67 (d, *J* = 5.7 Hz, 1H), 7.64–7.58 (m, 2H), 7.54 (d, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 6.37 (brs, 1H), 5.56 (d, *J* = 13.2 Hz, 1H), 4.96–4.92 (m, 1H), 4.26 (d, *J* = 13.2 Hz, 1H), 3.22 (dd, *J* = 13.8, 7.2 Hz, 1H), 2.29 (s, 3H), 2.29–2.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.6, 146.1, 143.3, 139.9, 139.6, 139.1, 138.4, 136.1, 133.3, 132.2, 131.4, 130.6, 129.9, 128.9, 128.5, 127.8, 126.9, 126.3, 125.4, 75.0, 64.4, 37.8, 21.6; IR (KBr, ν / cm^{-1}) 3306, 3058, 2964, 2925, 2857, 1734,

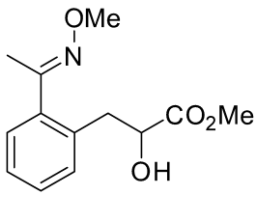


1628, 1603, 1561, 1511, 1454, 1431, 1401, 1379, 1334, 1264, 1222, 1179, 1121, 1089, 1033, 1011, 937, 917, 880, 816, 766, 734, 700, 681, 639, 623; HRMS (ESI+) Calcd for $C_{25}H_{23}NO_4S$ ($M+Na^+$) 456.1240, Found 456.1230.

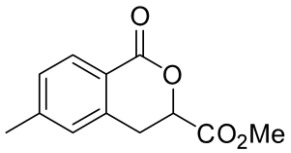
Methyl 2–hydroxy–3–(3–methyl–2–(quinolin–8–ylcarbamoyl)phenyl)propanoate (3M). 48.8 mg, 67%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.99 (s, 1H), 9.94–8.80 (m, 2H), 8.22 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.67–7.59 (m, 2H), 7.49 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.34 (t, *J* = 7.6 Hz, 1H), 7.21 (dd, *J* = 12.8, 7.6 Hz, 2H), 5.51 (brs, 1H), 4.51 (dd, *J* = 10.0, 3.5 Hz, 1H), 3.72 (s, 3H), 3.24 (dd, *J* = 14.1, 3.5 Hz, 1H), 3.03 (dd, *J* = 14.1, 10.0 Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 174.7, 169.0, 149.1, 139.3, 138.5, 137.0, 135.5, 134.6, 134.1, 129.8, 129.4, 128.6, 127.6, 127.4, 123.1, 122.0, 119.1, 72.8, 52.6, 38.6, 20.2; IR (KBr, ν / cm^{-1}) 3346, 3058, 2952, 1741, 1670, 1523, 1485, 1325, 1268, 1102, 827, 791, 668; HRMS (ESI+) Calcd for $C_{21}H_{20}N_2O_4$ ($M+Na^+$) 387.1315, Found 387.1305.

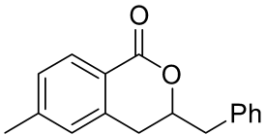


(*E*)–Methyl 2–hydroxy–3–(2–(1–(methoxyimino)ethyl)phenyl)propanoate (3N). 35.7 mg, 71%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36–7.27 (m, 4H), 5.43 (d, *J* = 7.1 Hz, 1H), 4.47–4.43 (m, 1H), 4.06 (s, 3H), 3.79 (s, 3H), 3.21–3.17 (m, 2H), 2.24 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.2, 156.1, 137.4, 135.1, 131.0, 129.3, 128.7, 127.3, 72.9, 62.3, 52.4, 37.6, 16.6; IR (KBr, ν / cm^{-1}) 3481, 3056, 2952, 2865, 2754, 1744, 1541, 1438, 1364, 1277, 1208, 1099, 1044, 887, 762, 638; HRMS (ESI+) Calcd for $C_{13}H_{17}NO_4$ ($M+Na^+$) 274.1050, Found 274.1059.

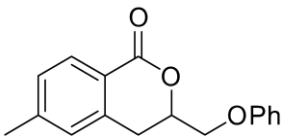


Methyl 6–methyl–1–oxoisochroman–3–carboxylate1 (5a). 30.0 mg, 68%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (d, *J* = 7.9 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.05 (s, 1H), 5.15 (dd, *J* = 5.8, 5.3 Hz, 1H), 3.74 (s, 3H), 3.38 (dd, *J* = 16.5, 5.3 Hz, 1H), 3.25 (dd, *J* = 16.5, 5.8 Hz, 1H), 2.40 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.8, 163.7, 145.4, 136.5, 130.7, 129.4, 128.3, 122.4, 75.2, 53.2, 30.4, 22.0; IR (KBr, ν / cm^{-1}) 3429, 2960, 1749, 1719, 1614, 1439, 1389, 1249, 1226, 1200, 1270, 1135, 1103, 1025, 950, 834, 769, 709, 688; HRMS (ESI+) Calcd for $C_{12}H_{12}O_4$ ($M+Na^+$) 243.0628, Found 243.0636.

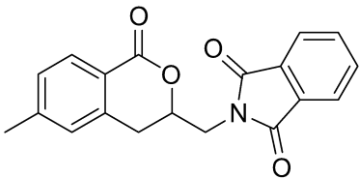


3–Benzyl–6–methylisochroman–1–one (5b). 36.3 mg, 72%, yellow solid; 

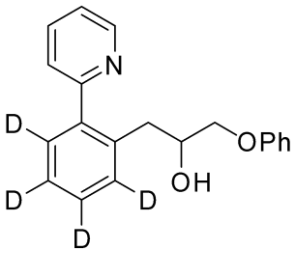
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.9 Hz, 1H), 7.38–7.24 (m, 5H), 7.17 (d, *J* = 7.9 Hz, 1H), 6.98 (s, 1H), 4.78–4.66 (m, 1H), 3.25 (dd, *J* = 13.7, 5.6 Hz, 1H), 3.01 (dd, *J* = 13.7, 7.7 Hz, 1H), 2.91 (dd, *J* = 16.2, 11.2 Hz, 1H), 2.79 (dd, *J* = 16.2, 3.0 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 144.9, 139.1, 136.4, 130.6, 129.8, 128.9, 128.8, 128.2, 127.2, 122.7, 79.3, 41.5, 32.5, 22.0; IR (KBr, ν / cm^{-1}) 3648, 3029, 2918, 1721, 1614, 1455, 1362, 1278, 1247, 1158, 1134, 1079, 1014, 911, 838, 752, 700; HRMS (ESI+) Calcd for $C_{17}H_{16}O_2$ ($M+Na^+$) 275.1043, Found 275.1045.

6–Methyl–3–(phenoxymethyl)isochroman–1–one (5c). 40.2 mg, 75%, yellow solid; 

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.9 Hz, 1H), 7.51–7.41 (m, 2H), 7.38 (d, *J* = 7.9 Hz, 1H), 7.30–7.24 (m, 1H), 7.15 (t, *J* = 7.3 Hz, 1H), 7.09 (d, *J* = 8.1 Hz, 2H), 5,13–5.02 (m, 1H), 4.46 (dd, *J* = 9.8, 4.6 Hz, 1H), 4.36 (dd, *J* = 9.8, 5.9 Hz, 1H), 3.39 (dd, *J* = 16.2, 11.3 Hz, 1H), 3.24 (dd, *J* = 16.3, 3.3 Hz, 1H), 2.58 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.1, 158.4, 145.3, 138.7, 130.7, 129.8, 129.0, 128.4, 122.5, 121.7, 114.8, 76.3, 68.9, 30.4, 22.0; IR (KBr, ν / cm^{-1}) 3445, 3061, 3040, 2924, 1721, 1614, 1600, 1541, 1497, 1456, 1377, 1281, 1243, 1140, 1118, 1081, 1039, 1172, 1081, 839, 775, 755, 691; HRMS (ESI+) Calcd for $C_{17}H_{16}O_3$ ($M+Na^+$) 291.0992, Found 291.0983.

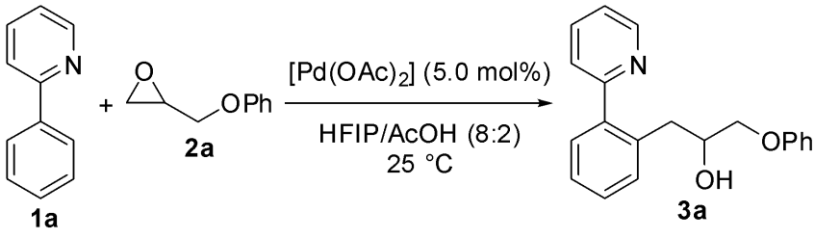
2–((6–Methyl–1–oxoisochroman–3–yl)methyl)isoindoline–1,3–dione (5d). 56.0 mg, 58%, yellow solid; 

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, *J* = 7.9 Hz, 1H), 7.87 (dd, *J* = 5.1, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.1, 3.1 Hz, 2H), 7.18 (d, *J* = 7.9 Hz, 1H), 7.04 (s, 1H), 4.96–4.83 (m, 1H), 4.18 (dd, *J* = 14.1, 7.5 Hz, 1H), 3.93 (dd, *J* = 14.1, 5.4 Hz, 1H), 3.12–2.97 (m, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 164.6, 145.2, 138.0, 134.5, 132.2, 130.7, 129.1, 128.3, 123.8, 122.5, 75.1, 41.4, 31.2, 22.0; IR (KBr, ν / cm^{-1}) 3424, 3051, 2925, 1773, 1716, 1614, 1428, 1396, 1273, 1238, 1125, 1078, 1018, 976, 911, 839, 774, 725, 715; HRMS (ESI+) Calcd for $C_{19}H_{15}NO_4$ ($M+Na^+$) 344.0893, Found 344.0882.



1–Phenoxy–3–(2–(2–pyridinyl)phenyl)–2–propanol–d_5 (3a–*d*). 57.5 mg, 93%, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.62 (dd, *J* = 4.2, 1.0 Hz, 1H), 7.96 (brs, 1H), 7.86 (ddd, *J* = 7.8, 7.8, 1.7 Hz, 1H), 7.57 (d, *J* = 7.9 Hz, 1H), 7.37–7.27 (m, 3H), 7.00–6.93 (m, 3H), 4.31 (s, 1H), 4.14 (dd, *J* = 9.2, 4.6 Hz, 1H), 3.97 (dd, *J* = 9.1, 6.9 Hz, 1H), 3.06 (dd, *J* = 13.7, 4.0 Hz, 1H), 3.01 (dd, *J* = 13.7, 8.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.9, 147.4, 139.8, 138.1, 137.3, 129.6, 125.0, 122.4, 121.2, 120.9, 114.9, 72.1, 71.4, 36.8; IR (KBr, ν / cm^{-1}) 3444, 2923, 2857, 2755, 1734, 1636, 1599, 1496, 1475, 1456, 1435, 1399, 1291, 1173, 1172, 1153, 1043, 1018, 997, 911, 880, 855, 814, 798, 754, 692, 631; HRMS (ESI+) Calcd for $C_{20}H_{15}D_4NO_2$ ($M+Na^+$) 332.1559，Found 332.1556.

KIE experiments. Coupling reactions were carried out under the reaction conditions which are described in Figures S1 and S2, stopped at arbitrary reaction times, and analyzed by ^{1}H NMR spectroscopy (Figures S1 and S2). As a result, the slope values of two graphs were 0.0013 mM/min and 0.0005 mM/min, respectively, and thus the KIE value was 2.6. The KIE value suggested that C–H bond activation step was the rate–determining step.



Entry	Time (min)	^{1}H NMR yield (%)	Product (mmol)
1	60	0.047	0.094
2	120	0.097	0.194
3	160	0.148	0.296
4	200	0.209	0.418
5	265	0.303	0.606
6	300	0.330	0.660
7	340	0.393	0.786

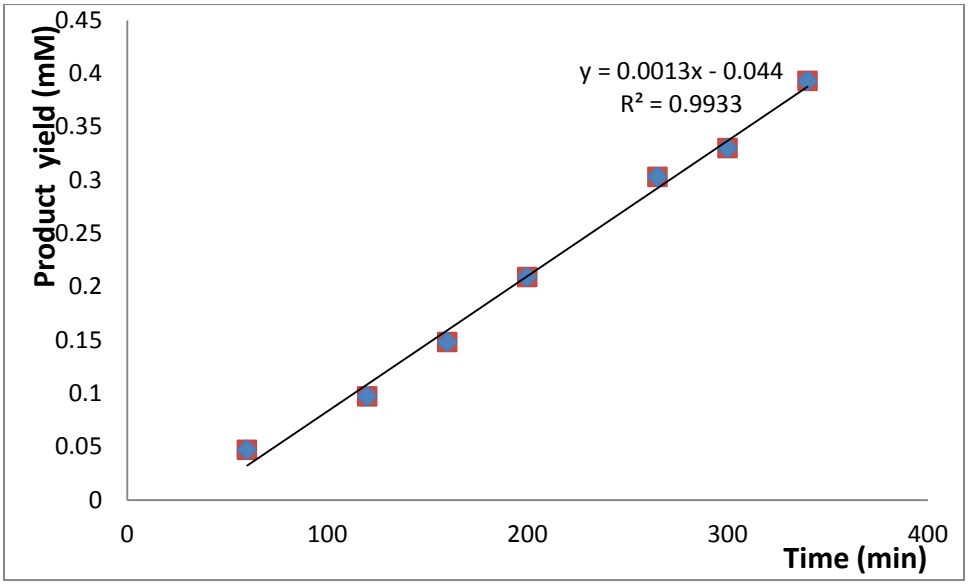
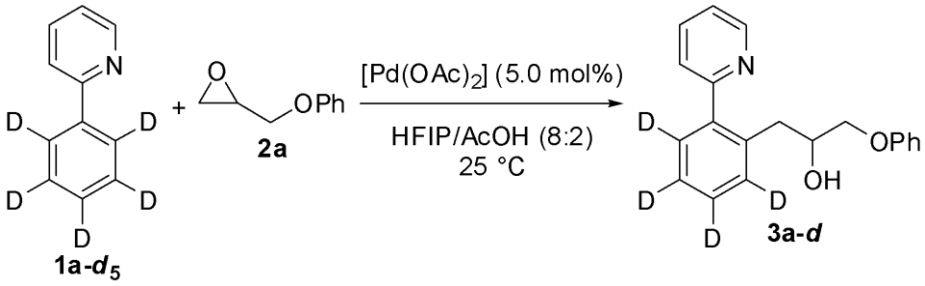


Figure S1-1. Determination of a reaction rate using **1a** as a substrate.



Entry	Time (min)	1H NMR yield (%)	Product (mmol)
1	60	0.035	0.070
2	120	0.070	0.140
3	160	0.095	0.190
4	200	0.108	0.216
5	265	0.134	0.268
6	300	0.156	0.312
7	340	0.186	0.372

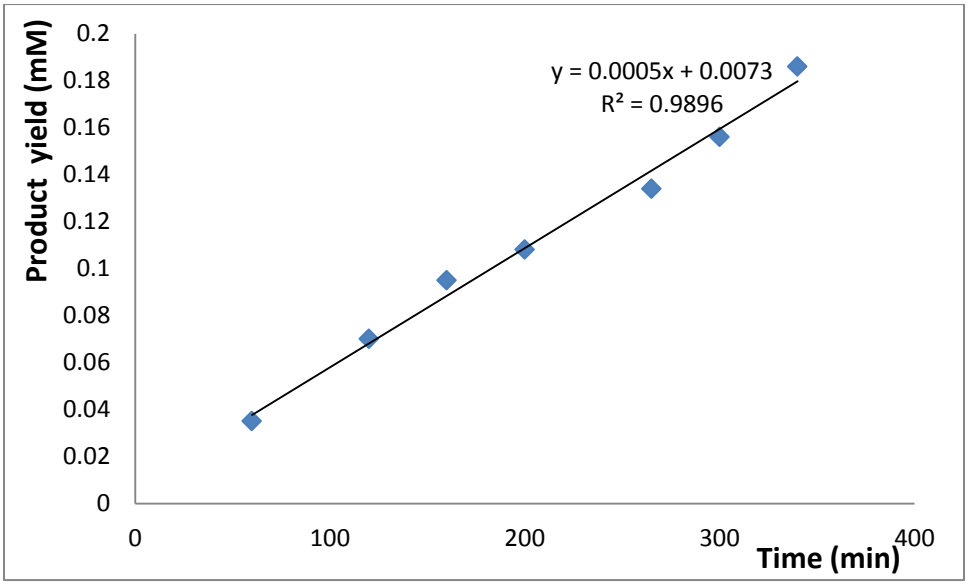
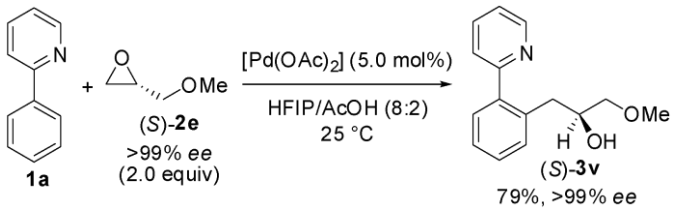


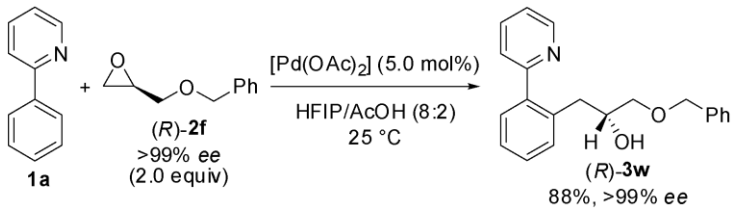
Figure S1-2. Determination of a reaction rate using **1a**–d_5 as a substrate.

Coupling Reactions Using Chiral Oxiranes. The enantiomeric excess of (*S*)–**3v** was determined by HPLC (chiral column: CHIRALPAK AD–H; solvent: hexane/2–propanol = 9/1; flow rate: 1.0 mL/min; detection: at 254 nm) analysis in comparision with authentic racemic material: Retention time = 19.9 min (*R*) and 28.0 min (*S*).



The enantiomeric excess of (*R*)–**3w** was determined by HPLC (chiral column: CHIRALPAK AD–H; Mobile phase: hexane/2–propanol = 9/1; flow rate: 1.0 mL/min; detection at 254 nm) analysis in comparision with authentic racemic material: Retention time = 12.8 min (*R*) and 21.1 min (S).

1. Palladium-Catalyzed Oxirane-Openning Reaction with Arenes via C-H Activation



1a

(*R*)-**2f**
>99% *ee*
(2.0 equiv)

(*R*)-**3w**
88%, >99% *ee*

2. Copper–Catalyzed Intramolecular C(sp^3)–H and C(sp^2)–H Amidation by Oxidative Cyclization

2.1. Introduction

β–Lactams (cyclic amides) and related compounds are important partial structures of natural products and drug molecules, such as penicillin and cephalosporin, ezetimibe,[1] and piperacillin[2] (β–lactam antibiotics) (Figure 2-1). There are a lot of classic methods that can be used to prepare β–lactams, such as, Beckmann rearrangement,[3] Schmidt reaction,[4] cyclization of amino acids,[5] and iodolactamization[6]. However, there are several drawbacks for these reactions, such as using highly activated intermediates, harsh reaction conditions, and production of a lot of side products. If we can develop a method catalyzed by the earth aboudance first row transition metals based on C–H activation, it is very useful for the preparation of β–lactams. I selected copper as a catalyst and a direct intramolecular C–H amidation as an alternative synthetic method. Although there are several reports of intramolecular C(sp^2)–H amidation,[7] however, these reactions used precious second or third row transition metals, such as rhodium or palladium. Examples of intramolecular C(sp^3)–H amidation are still rare. The few examples include: (a) rhodium–catalyzed C(sp^3)–H amidation at internal positions of alkyl chains, such as benzylic and tertiary positions (Figure 2-2a);[8] and (b) palladium–catalyzed allylic C(sp^3)–H amidation (Figure 2-2b);[9] and (c) palladium–catalyzed C(sp^3)–H amidation at terminal and internal positions (Figure 2-2c).[10] Intramolecular C(sp^3)–H amidation using first row transition metal catalysts, however, has not been reported. Actually, there is no reports on first row transition metal–catalyzed carbon–heteroatom bond formation via C(sp^3)–H activation, which mainly attribute to strong bonds between highly covalent first row transition metals and heteroatoms. I realized the first copper–catalyzed intramolecular C(sp^3)–H (and C(sp^2)–H) amidation uisng a bidentate directing group (aninoquinonyl group).[11] The amidation reaction proceeded at both terminal and internal C(sp^3)–H bonds with broad substrate generality.

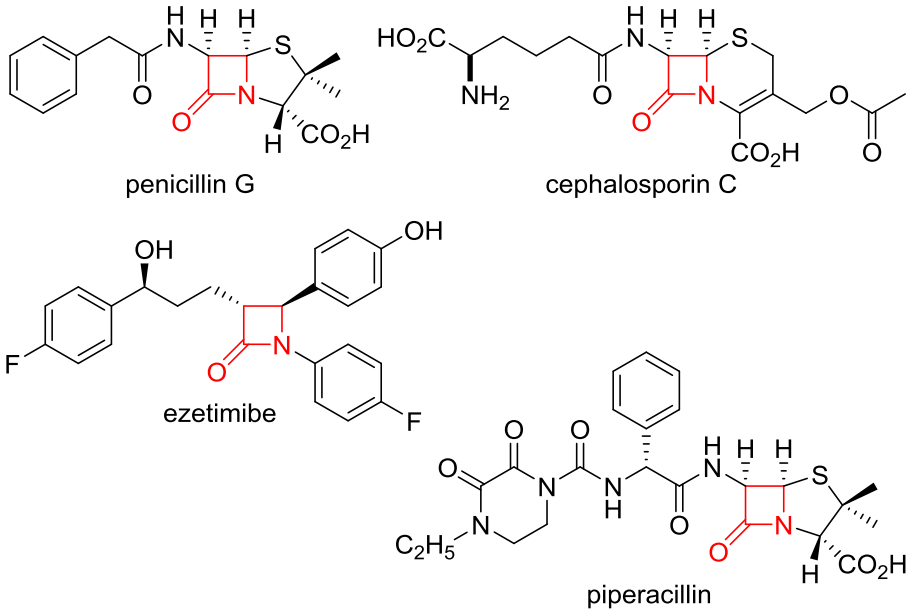


Figure 2-1. Examples of β-lactam antibiotics.

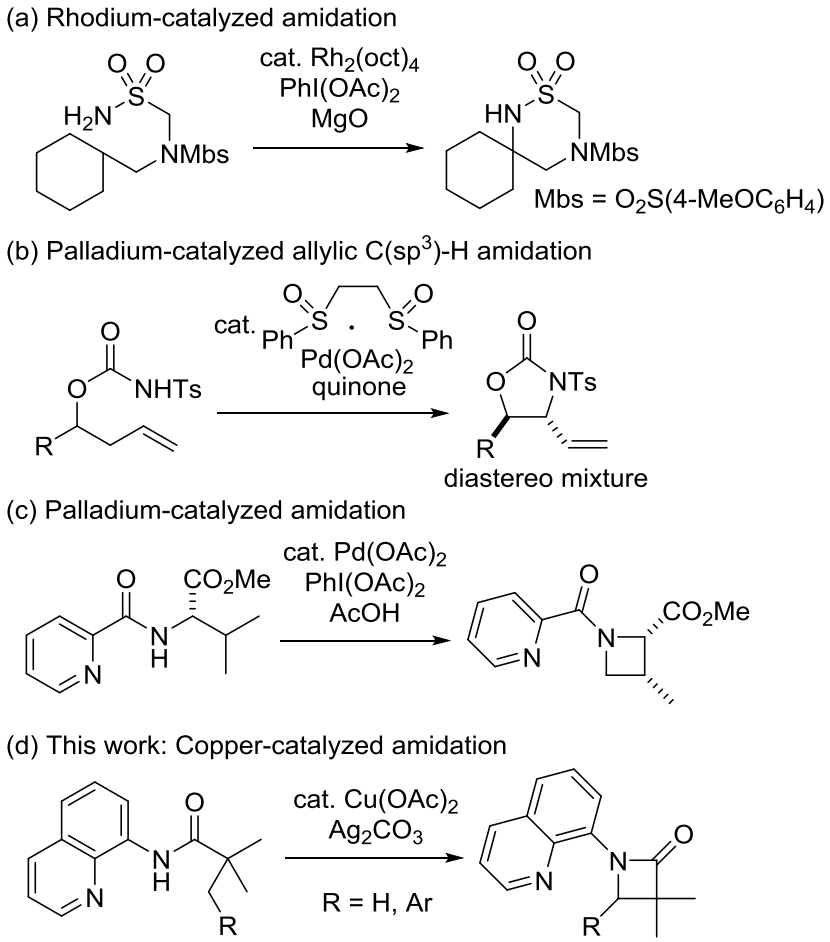


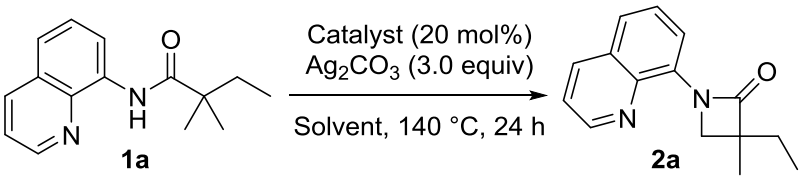
Figure 2-2. Examples of transition metal-catalyzed intramolecular C(sp^3)-H amidation.

2.2. Optimization Studies

Considering the small radius of a copper atom, I chose a quatenary amide as a starting material to investigate the desired reaction. Treatment of amide **1a** with a catalytic amount of CuCl and Ag_2CO_3 as an oxidant in dimethyl sulfoxide at 140 ℃ for 24 h gave β–lactam **2a** in only 17% yield (Table 2-1, entry 1). To improve the yield of **2a**, several solvents and catalysts were investigated (Table 2-1). I found that the reaction worked better in low polar solvents rather than high polar solvents (entries 1-10). This phenomenon manily attributed to the Cu(III) center was stabilized by the heteroatom of high polar solvent, in contrast, copper is unsaturated

coordination in low polar solvent which can accelerate the reductive elimination step (see the proposed reaction mechanism, Scheme 2-1). The best solvent and catalyst were 1,2–dichloroethane and CuSCN (or $Cu(OAc)_2$), respectively (entries 14 and 18). In this reaction, β–lactam formation through C–H amidation at the terminal methyl group was predominant, and β–lactam through internal methylene C–H amidation was not detected at all.

Table 2-1. Investigation of several solvents and copper catalysts.

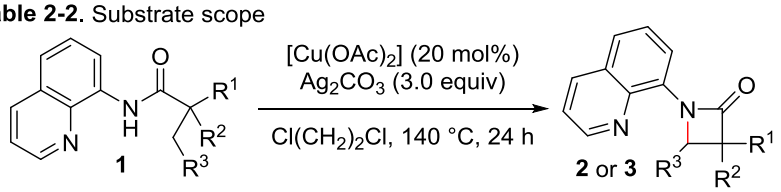


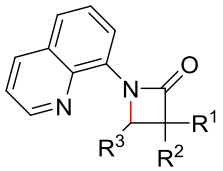
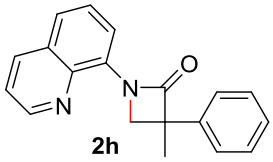
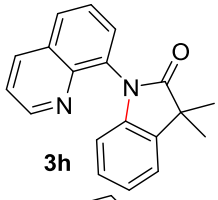
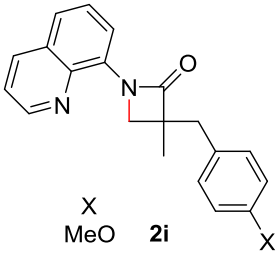
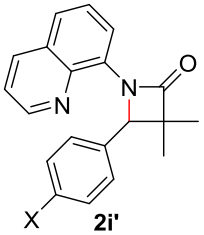
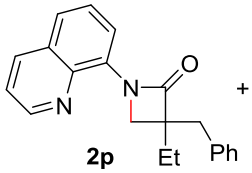
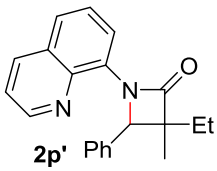
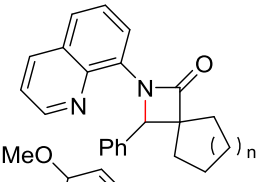
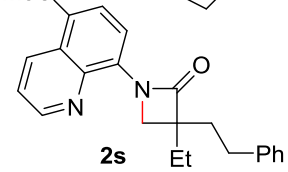
Entry	Solvent	Catalyst	Yield [%]
1	DMSO	CuCl	17
2	acetonitrile	CuCl	trace
3	DMF	CuCl	19
4	benzonitrile	CuCl	41
5	1,2-dichloroethane	CuCl	47
6	chlorobenzene	CuCl	42
7	*tert*-butyl methyl ether	CuCl	trace
8	toluene	CuCl	31
9	1,4-dioxone	CuCl	40
10	octane	CuCl	33
11	1,2-dichloroethane	CuBr	50
12	1,2-dichloroethane	CuI	38
13	1,2-dichloroethane	CuCN	52
14	1,2-dichloroethane	CuSCN	93
15	1,2-dichloroethane	CuF_2	43
16	1,2-dichloroethane	$CuCl_2$	55
17	1,2-dichloroethane	$CuBr_2$	45
18	1,2-dichloroethane	$Cu(OAc)_2$	82
19	1,2-dichloroethane	$Cu(OPiv)_2$	79

2.3. Substrate Scope and Mechanism Research

With the best reaction conditions in hand, I investigated the substrate scope. Although CuSCN was more reactive than $Cu(OAc)_2$ for amide **1a** (Table 2-1), its applicability to other substrates was unsatisfactory. Therefore, I investigated the substrate scope using $Cu(OAc)_2$ as the catalyst (Table 2-2). For substrates **1b**–**1g**, the amidation reaction proceeded selectively at a methyl group rather than methylene group (entries 1–6). For phenacyl amide substrate **1h**, which possesses competitive positions at methyl and phenyl groups, the reaction proceeded at both C(sp^3)–H and C(sp^2)–H bonds, affording a mixture of β–lactam **2h** and 2–indolinone **3h**, with **2h** as the preferred product (entry 7). The reaction also proceeded selectively at an internal benzylic C(sp^3)–H bond (entries 8–17). The selectivity between methyl C–H and benzyl C–H bonds was moderate and the product distribution was not affected by the substituents on the phenyl ring (ca. 1:2, entries 8–15). I concluded that the reaction was affected by the acidity of C–H bonds rather than the steric effect. When the benzylic and methylene positions were the competitive sites, benzylic C–H amidation was the predominant pathway affording strained bicyclic compounds (entries 16 and 17). One of disadvantages of animoquinolyl group-directed C–H transformations is removal of the directing group after the reactions. Therefore, I used a removable directing group, 5–methoxyquinolyl group,[17] and the reaction also proceeded using an amide with the directing group producing β–lactam **2s** in high yield (entry 18).

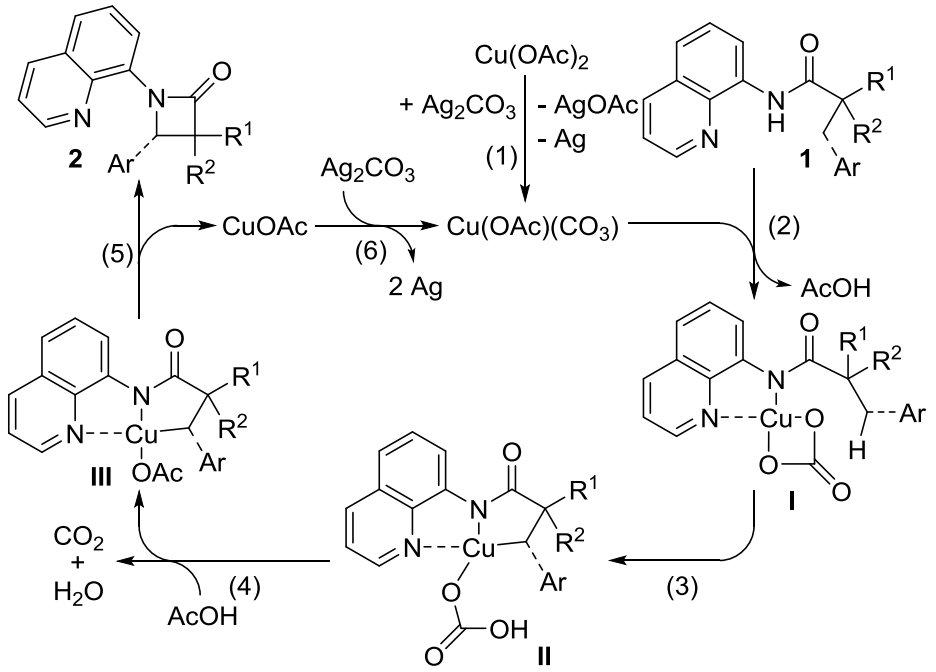
Table 2-2. Substrate scope



Entry	2							Yield [%]
		R^1	R^2					
1		Me	Me	**2b**				86
2		CF_3	Me	**2c**				89
3		$Ph(CH_2)_2$	Me	**2d**				86
4		^{t}Bu	Me	**2e**				93
5		$Ph(CH_2)_2$	Et	**2f**				90
6	R^3 = H	-$(CH_2)_5$-		**2g**				77
7	 **2h** +  **3h**				**2h**	65	**3h**	31
	 + 							
	X							
8	MeO	**2i**		**2i'**	**2i**	25	**2i'**	52
9	Me	**2j**		**2j'**	**2j**	38	**2j'**	51
10	H	**2k**		**2k'**	**2k**	25	**2k'**	64
11	Br	**2l**		**2l'**	**2l**	24	**2l'**	60
12	Cl	**2m**		**2m'**	**2m**	25	**2m'**	62
13	F	**2n**		**2n'**	**2n**	30	**2n'**	60
14	CF_3	**2o**		**2o'**	**2o**	21	**2o'**	58
15	 **2p** +  **2p'**				**2p**	30	**2p'**	60 [2.3:1][a]
16				n = 1 **2q'**				83
17				2 **2r'**				75
18	 **2s**							71

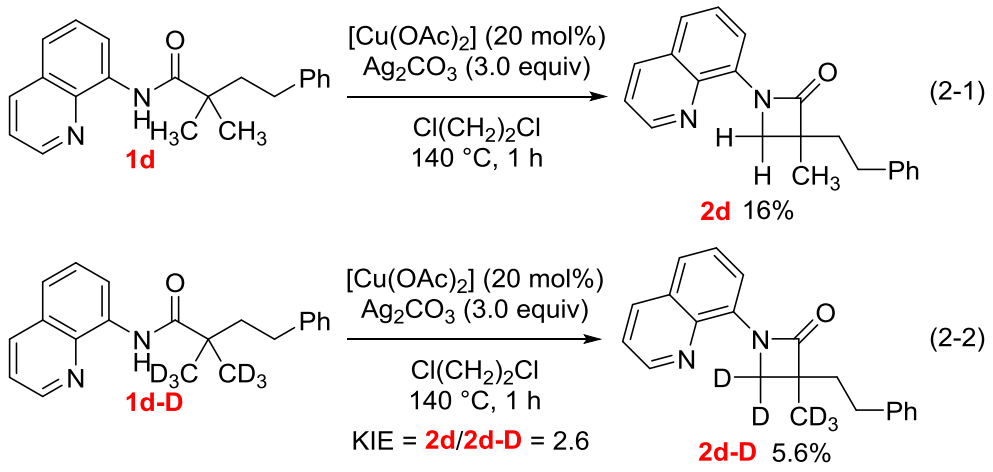
[a] Diastereomeric ratio.

Considering the beneficial effects of acetate anions on reactivity (Table 2-1), I propose the following mechanism for the formation of β–lactams (Scheme 2-1): (1) oxidation of a copper salt $Cu(OAc)_2$ with Ag_2CO_3;[12] (2) formation of a copper–amide intermediate **I** via elimination of acetic acid;[13] (3) formation of a metalacyclic intermediate **II** via a concerted metalation–deprotonation (CMD) pathway (C(sp^3)–H bond activation);[14] (4) reaction between the metalacyclic intermediate **II** and acetic acid to give an intermediate **III** by the elimination of CO_2 and H_2O; (5) reductive elimination to give a β–lactam **2** and copper species CuOAc; and (6) oxidation of the CuOAc species with Ag_2CO_3 to regenerate $Cu(OAc)(CO_3)$.[12] After the first cycle, the reaction proceeds via steps (2) to (6).

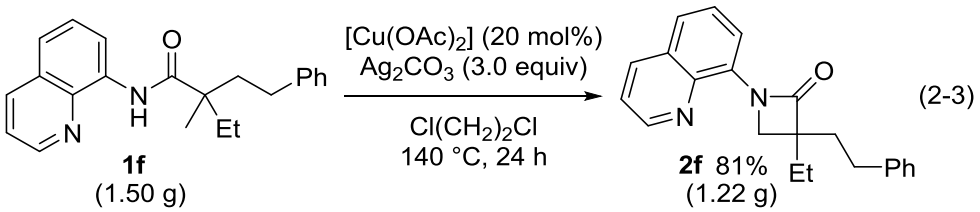


Scheme 2-1. A proposed mechanism for the intramolecular C(sp^3)-H amidation

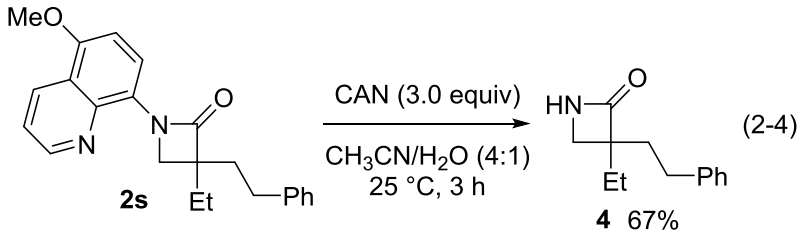
Next, I performed a deuterium–labeling experiment to gain insight into the rate–determining step for the formation of β–lactams. Treatment of amide **1d** or deuterated amide **1d–D** with a copper catalyst and oxidant gave the corresponding β–lactams **2d** and **2d–D** in 16% and 5.6% yields, respectively, after 1 h (eqs 2-1 and 2-2). The kinetic isotope effect value was 2.6, supporting our assumption that C–H bond activation is the rate–determining step.[15]



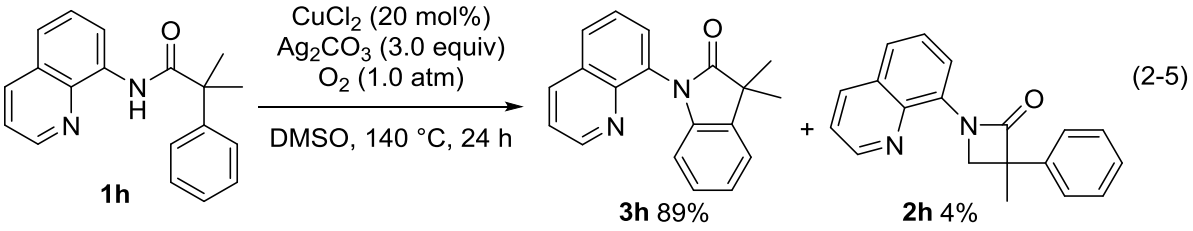
The reaction could be performed in gram–scale without significantly changing the efficiency (eq 2-3). Thus, treatment of 1.50 g of **1f** with $Cu(OAc)_2$ and Ag_2CO_3 gave 1.22 g of **2f** in 81% yield, comparable to the yield shown in Table 2-2, entry 5 (**1f**: 33.2 mg).



A residual directing group in the products decreases the practicality of the transformation. According to Chen's finding, the 5–methoxyquinolyl group can be cleaved under oxidative conditions (eq 2-4).[16] Treatment of β–lactam **2s** with ceric ammonium nitrate afforded deprotected β–lactam **4** in 67% yield without opening the sensitive β–lactam scaffold (eq 2-4).



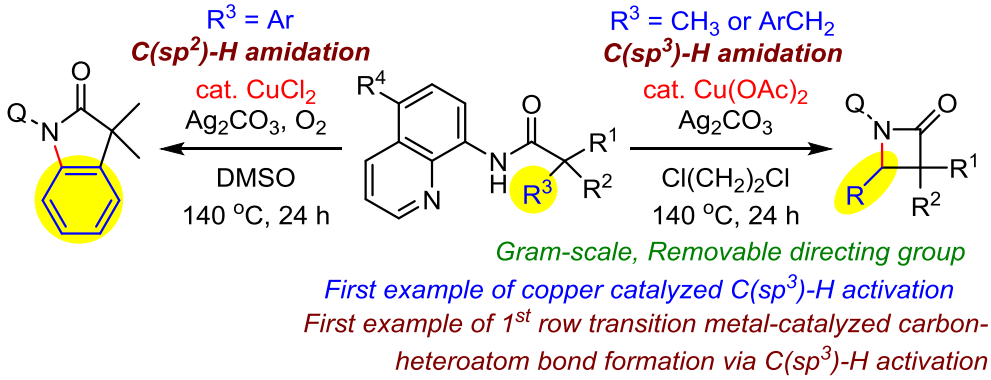
In my retrosynthesis of duocarmycin, the desired reaction is formation of 5–membered aromatic amides via C(sp^2)–H activation. So I tried to realize intramolecular C(sp^2)-H amidation even in the presence of both C(sp^2)–H and C(sp^3)–H bonds. Interestingly, the reaction of **1h** occurred at the C(sp^2)–H bond selectively when the reaction conditions were slightly modified (eq 2-5). Thus, treatment of **1h** in the presence of $CuCl_2$ catalyst and Ag_2CO_3 in dimethyl sulfoxide under an O_2 atmosphere at 140 ℃ for 24 h produced 2–indolinone **3h** and β–lactam **2h** in 89% and 4% yields, respectively. This result is in sharp contrast to the result shown in Table 2-2, entry 7, where C(sp^3)–H amidation was the preferred reaction pathway. This result may be due to that the copper(III) species can be stabilized by DMSO, but I think that the reaction must proceeded in a different mechanism under this conditions and SET will be the main mechanism for this reaction and the high polar transition state is stabilized by DMSO.



2.4. Summary

In summary, I succeeded in intramolecular C(sp^3)–H and C(sp^2)–H amidation under copper catalysis. Although there are a few examples of palladium–catalyzed intramolecular C–H amidation, this is the first example of copper–catalyzed C(sp^3)–H amidation, and this is the first example of first row transition–metal–catalyzed carbon–heteroatom bond formation. The reaction proceeded at a terminal methyl group, as well as at the internal benzylic position of an alkyl chain. If methyl and benzyl sites locate at competitive positions, the reaction mainly proceeded at the more acidic benzylic positions. The electronic effect determines the distribution of products rather than the steric effect. This reaction has broad substrate scope, and β–lactams were obtained in high yields, even in gram–scale. 2–Indolinone was also synthesized via C(sp^2)–H amidation by slightly modifying the optimized conditions for C(sp^3)–H amidation. Because the 5–

methoxyquinolyl directing group can be removed by oxidation, this reaction becomes a useful method for the synthesis of β–lactams and 2–indolinones. Attempts to improve the position selectivity and catalyst activity are ongoing in our group, On the other hand, I am trying to use this method to the synthesis of duocarmycim..



2.5. References and Notes

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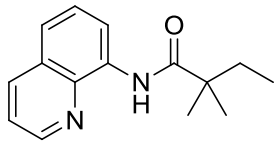
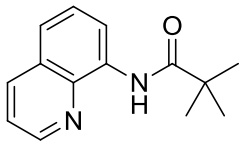
2.6. Experimental

General. All reactions were carried out in a dry solvent under argon atmosphere unless otherwise noted. $Cu(OAc)_2$ (99.999%) and Cu(SCN) (99%) were purchased from Aldrich. Methanol, *N*,*N*–dimethylformamide, dichloromethane (DCE), and THF were purchased from Wako Pure Chemical Industries, and were dried and degassed before use. Lithium diisopropylamide (LDA) was purchased from Aldrich. NMR spectra were recorded on JEOL ECX500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometer. Proton chemical shifts are reported relative to residual solvent peak ($CDCl_3$ at 7.26 ppm). Carbon chemical shifts are reported relative to residual solvent peak ($CDCl_3$ at 77.3 ppm). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad. IR spectra were recorded on a JASCO FT/IR–410. High–resolution mass spectra (HRMS) were measured on a JEOL JMS–T100LC AccuTOF spectrometer (for HRMS).

Preparation of amides 1a and 1b. To a solution of an acid chloride (11.0 mmol) in dichloromethane (40 mL), a solution of 8–aminoquinoline (1.44 g, 10.0 mmol) and NEt_3 (1.01 g, 11.0 mmol) in dichloromethane (10 mL) was added dropwise. The resulting mixture was stirred at 25 ℃ for 30 min. Then, the mixture was quenched with saturated aq. $NaHCO_3$ (50 mL), and was extracted with dichloromethane for three times (3 x 50 mL). The organic layer was dried over Na_2SO_4. After filtration and evaporation, an amide was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1).



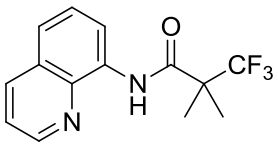
2,2–Dimethyl–*N*–(8–quinolinyl)butanamide (1a). 1.94 g, 91% yield, yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.91–8.72 (m, 2H), 8.14 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.53 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.48 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.44 (dd, *J* = 8.2, 4.2 Hz, 1H), 1.77 (q, *J* = 7.5 Hz, 2H), 1.39 (s, 6H), 0.96 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.9, 148.4, 138.9, 136.6, 134.9, 128.2, 127.7, 121.7, 121.4, 116.5, 44.3, 34.3, 25.3, 9.5; IR (KBr, ν / cm^{-1}) 3367, 2967, 2877, 2359, 1677, 1530, 1486, 1423, 1383, 1325, 1155, 826, 791, 756, 681, 617; HRMS (ESI^+) Calcd for $C_{15}H_{18}N_2O$ ($M+Na^+$) 265.1311, Found 265.1311.



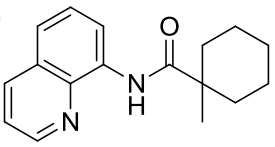
***N*–(8–quinolinyl)pivalamide (1b**). 1.90 g, 99% yield, yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.27 (s, 1H), 8.85–8.74 (m, 2H), 8.13 (dd, *J* = 8.0, 1.4 Hz, 1H), 7.52 (dd, *J* = 8.2, 8.2 Hz, 1H), 7.47 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.42 (dd, *J* = 8.2, 4.2 Hz, 1H), 1.43 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 148.4, 139.0, 136.5, 134.9, 128.1, 127.6, 121.7, 121.4, 116.4, 40.6, 28.0; IR (KBr, ν / cm^{-1}) 3365, 3047, 2962, 2869, 1681, 1528, 1486, 1424, 1383, 1366, 1325, 1159, 922, 826, 791, 754, 680, 620; HRMS (ESI^+) Calcd for $C_{14}H_{16}N_2O$ ($M+Na^+$) 251.1155, Found 251.1146.

Preparation of amides 1c, 1g, and 1h. To a solution of a carboxylic acid (11.0 mmol) in THF (20 mL), $SOCl_2$ (1.57 g, 13.2 mmol) was added dropwise. The resulting mixture was stirred at 25 ℃ for 1 h. The reaction mixture was concentrated in vacuo to give an acid chloride, which was used without purification. To a solution of the prepared acid chloride in dichloromethane (20 mL), a solution of 8–aminoquinoline (1.44 g, 10.0 mmol) and Et_3N (1.01 g, 11.0 mmol) in dichloromethane (10 mL) was added dropwise. The resulting mixture was stirred at 25 ℃ for 30 min, was quenched with saturated aq. $NaHCO_3$ (30 mL), and was extracted with dichloromethane (3 x 100 mL) for three times. The organic layer was dried over Na_2SO_4. After filtration and evaporation, the obtained amide was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1).

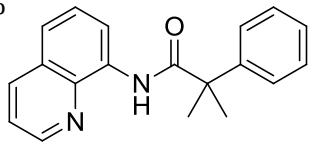
3,3,3–Trifluoro–2,2–dimethyl–*N*–(8–quinolinyl)propanamide (1c). 1.24 g, 82% yield, yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.54 (s, 1H), 8.95–8.67 (m, 2H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.53 (m, 2H), 7.45 (dd, *J* = 8.2, 4.2 Hz, 1H), 1.64 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.7,



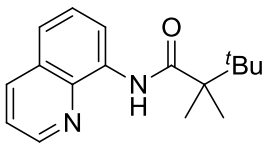
148.7, 139.0, 136.5, 134.3, 128.1, 127.5, 127.4 (q, J = 282 Hz), 122.3, 122.0, 116.9, 49.9 (q, J = 25.3 Hz), 20.2; IR (KBr, ν / cm^{-1}) 3348, 2989, 2877, 1696, 1652, 1539, 1488, 1327, 1289, 1206, 1124, 908, 825, 790, 754, 669; HRMS (ESI^+) Calcd for $C_{14}H_{13}F_3N_2O$ ($M+Na^+$) 305.0872, Found 305.0878.



1–Methyl–*N*–(8–quinolinyl)cyclohexanecarboxamide (1g). 2.21 g, 92% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 10.29 (s, 1H), 8.93–8.70 (m, 2H), 8.12 (dd, J = 8.4, 1.6 Hz, 1H), 7.65–7.37 (m, 3H), 2.26–2.14 (m, 2H), 1.71–1.47 (m, 7H), 1.44–1.37 (m, 1H), 1.35 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.8, 148.4, 139.0, 136.5, 135.0, 128.1, 127.6, 121.7, 121.3, 116.4, 44.6, 36.0, 26.8, 26.0, 23.2; IR (KBr, ν / cm^{-1}) 3363, 2927, 2856, 1681, 1527, 1486, 1470, 1423, 1384, 1324, 1262, 1160, 1131, 924, 825, 791, 754, 680; HRMS (ESI^+) Calcd for $C_{17}H_{20}N_2O$ ($M+Na^+$) 291.1468, Found 291.1458.



2–Methyl–2–phenyl–*N*–(8–quinolinyl)propanamide (1h). 5.24 g, 95% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 9.88 (s, 1H), 8.77 (d, J = 7.6 Hz, 1H), 8.60 (dd, J = 4.2, 1.4 Hz, 1H), 8.08 (dd, J = 8.3, 1.4 Hz, 1H), 7.65–7.19 (m, 8H), 1.79 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 148.3, 145.1, 138.9, 136.3, 134.9, 129.0, 128.0, 127.5, 127.2, 126.6, 121.6, 121.5, 116.2, 48.6, 27.2; IR (KBr, ν / cm^{-1}) 3566, 3345, 2970, 1682, 1525, 1488, 1472, 1456, 1428, 1388, 1328, 1218, 904, 774, 742, 770, 669; HRMS (ESI^+) Calcd for $C_{19}H_{18}N_2O$ ($M+Na^+$) 313.1311, Found 313.1310.



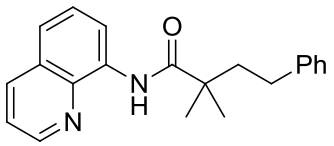
Preparation of 2,2,3,3–Tetramethyl–*N*–(8–quinolinyl)butanamide (1e). Methyl 2,2,3,3–tetramethylbutanoate was prepared by alkylation of ((1–methoxy–2–methyl–1–propen–1–yl)oxy)trimethylsilane. To a mixture of ((1–methoxy–2–methyl–1–propen–1–yl)oxy)trimethylsilane (4.30 g, 24.7 mmol) and *tert*–butyl chloride (6.85 g, 74.0 mmol) in dichloromethane (15 mL), zinc chloride (170 mg, 1.23 mmol) was added under nitrogen atmosphere at 0 ℃, and stirred at 25 ℃ for 24 h. The reaction mixture was diluted with dichloromethane (20 mL), and washed with 5% aq. $NaHCO_3$ (50 mL). The aqueous layer was back–extracted with dichloromethane (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, and concentrated in vacuo to give methyl 2,2,3,3–

tetramethylbutyrate (2.78 g, 71% yield). To a solution of 8–aminoquinoline (5.56 g, 38.5 mmol) in THF (100 mL), a hexane solution of *n*–BuLi (1.6 M, 24.1 mL, 38.6 mmol) was added dropwise at –78 ℃. The mixture was warmed to 25 ℃ and stirred for 1 h. The mixture was added to a THF (20.0 mL) solution of the prepared ester at –78 ℃, and the mixture was warmed to 25 ℃ and stirred for 12 h. After quenching with saturated aq. $NaHCO_3$ (200 mL) at 0 ℃, the mixture was extracted with ethyl acetate (3 x 100 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give the amide, which was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1). **1e:** 3.60 g, 76% yield, white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.26 (s, 1H), 8.81 (dd, *J* = 5.0, 5.0 Hz, 2H), 8.14 (d, *J* = 8.1 Hz, 1H), 7.59–7.41 (m, 3H), 1.40 (s, 6H), 1.07 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 148.5, 139.2, 136.5, 134.8, 128.2, 127.7, 121.7, 121.3, 116.3, 49.4, 35.8, 26.6, 21.8; IR (KBr, ν / cm^{-1}) 3563, 3370, 2971, 2863, 1669, 1528, 1485, 1423, 1384, 1324, 1139, 939, 901, 825, 792, 758, 669; HRMS (ESI^+) Calcd for $C_{17}H_{22}N_2O$ ($M+Na^+$) 293.1624, Found 293.1631.

Preparation of amides 1d, 1d–D, 1f, 1i, 1j, 1k, 1l, 1m, 1n, and 1o. To a solution of methyl isobutyrate (3.06 g, 30.0 mmol) in THF (100 mL), a THF solution of lithium diisopropylamide (1.5 M, 21.0 mL, 31.5 mmol) was added at –78 ℃ dropwise. The mixture was stirred at –78 ℃ for 1 h, and the corresponding alkyl halide (33.0 mmol) was added to the solution. The mixture was warmed to 25 ℃, and was stirred for 16 h. The reaction mixture was quenched with saturated aq. $NaHCO_3$ (100 mL) at 0 ℃, and was extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give an ester.

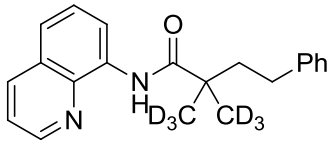
To a solution of 8–aminoquinoline (9.52 g, 66.0 mmol) in THF (200 mL), a hexane solution of *n*–BuLi (1.6 M, 41.3 mL, 66.0 mmol) was added dropwise at –78 ℃. The mixture was warmed to 25 ℃ and stirred for 1 h. The reaction mixture was added to a solution of the prepared ester in THF at –78 ℃, and the mixture was warmed to 25 ℃ and stirred for 12 h. After quenching with saturated aq. $NaHCO_3$ (150 mL) at 0 ℃, the mixture was extracted with ethyl acetate (3 x 150 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give an amide, which was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1).

2,2–Dimethyl–4–phenyl–*N*–(8–quinolinyl)butanamide (1d).



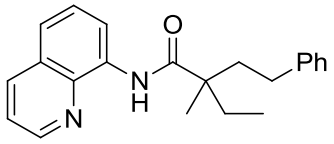
Synthesis of an ester from methyl 3–phenylpropanoate and methyl isobutyrate, 1.52 g, 65% yield, yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.83–8.68 (m, 2H), 8.07 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.57–7.35 (m, 3H), 7.22–7.02 (m, 5H), 2.69–2.44 (m, 2H), 2.04–1.89 (m, 2H), 1.40 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 148.5, 142.5, 139.1, 136.6, 134.8, 128.63, 128.55, 128.2, 127.7, 126.0, 121.8, 121.5, 116.5, 44.1, 44.0, 31.8, 26.0; IR (KBr, ν / cm^{-1}) 3564, 3363, 3025, 2961, 2863, 1681, 1526, 1486, 1455, 1423, 1384, 1325, 1057, 924, 826, 792, 753, 699; HRMS (ESI^+) Calcd for $C_{21}H_{22}N_2O$ ($M+Na^+$) 341.1624, Found 341.1621.

2,2–Dimethyl–4–phenyl–*N*–(8–quinolinyl)butanamide–d_6 (1d–D).



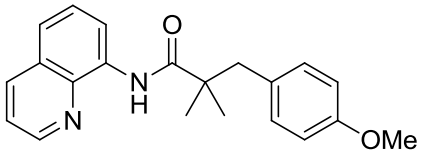
Synthesis of an ester from methyl 3–phenylpropanoate and CD_3I, 1.02 g, 61% yield, yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.95–8.80 (m, 2H), 8.17 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.61–7.43 (m, 3H), 7.35–7.13 (m, 5H), 2.76–2.65 (m, 2H), 2.17–1.98 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 148.5, 142.5, 139.0, 136.5, 134.8, 128.6, 128.5, 128.2, 127.7, 126.0, 121.8, 121.5, 116.5, 43.8, 43.7, 31.7 [A signal of CD_3 groups could not be observed. This is supposed to be heptet, which is too weak to observe in ^{13}C NMR.]; IR (KBr, ν / cm^{-1}) 3565, 3443, 3060, 1683, 1523, 1487, 1423, 1384, 1326, 1034, 895, 825, 791, 753, 668, 617; HRMS (ESI^+) Calcd for $C_{21}H_{16}D_6N_2O$ ($M+Na^+$) 347.2001, Found 347.1995.

2–Ethyl–2–methyl–4–phenyl–*N*–(8–quinolinyl)butanamide (1f).

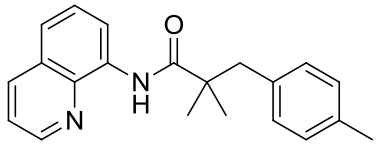


Synthesis of an ester from (2–iodoethyl)benzene and 2–methylbutanoate, 2.31 g, 71% yield, yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.84–8.69 (m, 2H), 8.06 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.51–7.34 (m, 3H), 7.25–7.01 (m, 5H), 2.69–2.43 (m, 2H), 2.16–2.05 (m, 1H), 1.94–1.71 (m, 2H), 1.62 (dt, *J* = 14.7, 7.4 Hz, 1H), 1.38 (s, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 148.5, 142.6, 139.0, 136.5, 134.8, 128.6, 128.5, 128.2, 127.7, 126.0, 121.8, 121.5, 116.5, 47.9, 42.4, 33.3, 31.5, 21.1, 9.2; IR (KBr, ν / cm^{-1}) 3566, 3362, 3061, 2965, 2826, 2863, 1682, 1525, 1486,

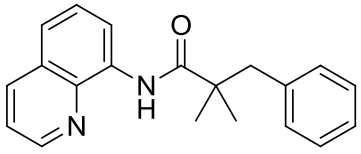
1473, 1456, 1422, 1386, 1324, 1259, 1163, 825, 791, 756, 698, 669; HRMS (ESI^+) Calcd for $C_{22}H_{24}N_2O$ ($M+Na^+$) 355.1781, Found 355.1774.

3–(4–Methoxyphenyl)–2,2–dimethyl–*N*–(8–quinolinyl)propanamide (1i). 

Synthesis of an ester from 1–(chloromethyl)–4–methoxybenzene and isobutyrate, 2.20 g, 61% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 10.15 (s, 1H), 8.83 (dd, *J* = 7.6, 1.5 Hz, 1H), 8.74 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.13 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.56–7.38 (m, 3H), 7.15–7.07 (m, 2H), 6.76–6.68 (m, 2H), 3.70 (s, 3H), 2.98 (s, 2H), 1.41 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.3, 158.4, 148.4, 139.0, 136.4, 134.7, 131.4, 130.2, 128.1, 127.6, 121.7, 121.5, 116.5, 113.6, 55.3, 46.3, 45.3, 25.4; IR (KBr, ν / cm^{-1}) 3362, 2962, 2877, 1682, 1651, 1525, 1487, 1324, 1246, 1178, 1034, 918, 827, 791, 756, 682; HRMS (ESI^+) Calcd for $C_{21}H_{22}N_2O_2$ ($M+Na^+$) 357.1573, Found 357.1571.

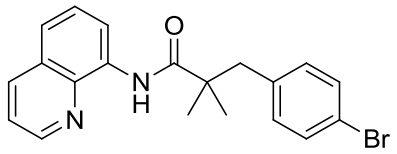
2,2–Dimethyl–*N*–(8–quinolinyl)–3–(*p*–tolyl)propanamide (1j). 

Synthesis of an ester from 1–(bromomethyl)–4–methylbenzene and isobutyrate, 1.20 g, 67% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 10.17 (s, 1H), 8.83 (d, *J* = 7.6 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.3 Hz, 1H), 8.14 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.59–7.39 (m, 3H), 7.08 (d, *J* = 7.8 Hz, 2H), 7.00 (d, *J* = 7.8 Hz, 2H), 3.01 (s, 2H), 2.24 (s, 3H), 1.40 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.4, 148.4, 139.0, 136.5, 136.0, 135.0, 134.8, 130.4, 128.9, 128.1, 127.7, 121.7, 121.5, 116.5, 46.7, 45.2, 25.5, 21.2; IR (KBr, /ν / cm^{-1}) 3564, 2355, 1682, 1539, 1523, 1487, 1472, 1386, 825, 792; HRMS (ESI^+) Calcd for $C_{21}H_{22}N_2O$ ($M+Na^+$) 341.1624, Found 341.1626.

2,2–Dimethyl–3–phenyl–*N*–(8–quinolinyl)propanamide (1k). 

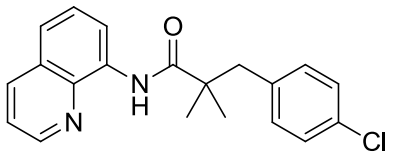
Synthesis of an ester from benzyl bromide and isobutyrate, 1.80 g, 77% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 10.18 (s, 1H), 8.85 (d, *J* = 7.7 Hz, 1H), 8.74 (d, *J* = 4.2 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.58–7.37 (m, 3H), 7.23–7.12 (m, 5H), 3.06 (s, 2H), 1.43 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.2, 148.4, 139.0, 138.2, 136.4, 134.7, 130.5, 128.2, 128.1, 127.6, 126.6, 121.7, 121.5, 116.5, 47.1, 45.2, 25.5; IR (KBr, ν / cm^{-1}) 3363, 3027, 2963, 1672, 1527, 1486, 1455, 1423, 1385, 1325, 1259, 1147, 917,

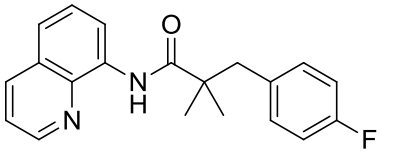
825, 791, 752, 721, 701; HRMS (ESI^+) Calcd for $C_{20}H_{20}N_2O$ ($M+Na^+$) 327.1468, Found 327.1465.

3–(4–Bromophenyl)–2,2–dimethyl–*N*–(8–quinolinyl)propanamide (1l). 

Synthesis of an ester from 1–bromo–4–(bromomethyl)benzene and isobutyrate, 1.43 g, 66% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.87–8.69 (m, 2H), 8.14 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.57–7.43 (m, 2H), 7.43 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.06 (d, *J* = 8.4 Hz, 2H), 2.98 (s, 2H), 1.41 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 148.5, 139.0, 137.2, 136.5, 134.6, 132.1, 131.3, 128.1, 127.6, 121.8, 121.7, 120.7, 116.5, 46.5, 45.1, 25.5; IR (KBr, ν / cm^{-1}) 3363, 3123, 1683, 1508, 1487, 1473, 1420, 1396, 1325, 1259, 1010, 917, 825, 791; HRMS (ESI^+) Calcd for $C_{20}H_{19}BrN_2O$ ($M+Na^+$) 405.0573, Found 405.0566.

3–(4–Chlorophenyl)–2,2–dimethyl–*N*–(8–quinolinyl)propanamide (1m). Synthesis of an ester from 1–chloro–4–(bromomethyl)benzene and isobutyrate, 1.53 g, 71% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.87–8.70 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.61–7.39 (m, 3H), 7.20–7.07 (m, 4H), 3.00 (s, 2H), 1.41 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.9, 148.5, 139.0, 136.7, 136.5, 134.6, 132.5, 131.8, 128.4, 128.2, 127.6, 121.8, 121.7, 116.6, 46.5, 45.2, 25.5; IR (KBr, ν / cm − 1) 3375, 3356, 2358, 1682, 1557, 1507, 1487, 1473, 1386, 1325, 1090, 826, 790; HRMS (ESI^+) Calcd for $C_{20}H_{19}ClN_2O$ ($M+Na^+$) 361.1078, Found 361.1078.

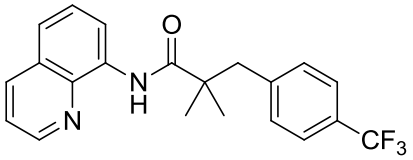


3–(4–Fluorophenyl)–2,2–dimethyl–*N*–(8–quinolinyl)propanamide (1n). 

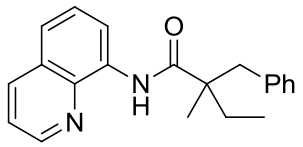
Synthesis of an ester from 1–(bromomethyl)–4–fluorobenzene and isobutyrate, 1.59 g, 61% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.86–8.71 (m, 2H), 8.13 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.58–7.39 (m, 3H), 7.18–7.10 (m, 2H), 6.93–6.81 (m, 2H), 3.01 (s, 2H), 1.41 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.0, 161.9 (d, *J* = 244 Hz), 148.4, 139.0, 136.5, 134.6, 133.6 (d, *J* = 3.4 Hz), 131.5 (d, *J* = 7.8 Hz), 128.1, 127.6, 121.8,

121.7, 116.5, 114.7 (d, *J* = 21.1 Hz), 46.3, 45.0 (d, *J* = 1.1 Hz), 25.5; IR (KBr, ν / cm − 1) 3358, 3048, 2968, 1682, 1526, 1508, 1487, 1423, 1386, 1325, 1221, 1158, 919, 825, 791, 758, 668; HRMS (ESI^+) Calcd for $C_{20}H_{19}FN_2O$ ($M+Na^+$) 345.1374, Found 345.1363.

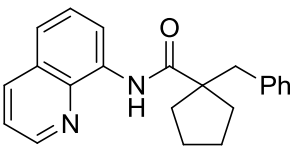
2,2–Dimethyl–*N*–(8–quinolinyl)–3–(4–(trifluoromethyl)phenyl)propanamide (1o). Synthesis of an ester from 1–(bromomethyl)–4–(trifluoromethyl)benzene and isobutyrate, 1.69 g, 63% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 10.12 (s, 1H), 8.89–8.67 (m, 2H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.59–7.49 (m, 2H), 7.43 (d, *J* = 8.0 Hz, 3H), 7.34–7.19 (m, 2H), 3.09 (s, 2H), 1.44 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.6, 148.5, 142.4, 139.0, 136.5, 134.5, 130.7, 128.9 (q, *J* = 32.4 Hz), 128.1, 127.6, 125.1 (q, *J* = 3.8 Hz), 125.1, 124.5 (q, *J* = 273 Hz), 121.8, 116.6, 46.9, 45.2, 25.6; IR (KBr, ν / cm − 1) 3359, 3027, 1682, 1557, 1552, 1456, 1419, 1386, 1325, 1163, 859, 825, 791, 669; HRMS (ESI^+) Calcd for $C_{21}H_{19}F_3N_2O$ ($M+Na^+$) 395.1342, Found 395.1335.



2–Benzyl–2–methyl–*N*–(8–quinolinyl)butanamide (1p). Synthesis of an ester from benzyl bromide and methyl 2–methylbutanoate, 1.09 g, 65% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 1H), 8.95–8.67 (m, 2H), 8.14 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.61–7.37 (m, 3H), 7.23–7.04 (m, 5H), 3.26 (d, *J* = 13.3 Hz, 1H), 2.83 (d, *J* = 13.3 Hz, 1H), 2.05 (m, 7.4 Hz, 1H), 1.71–1.52 (m, 1H), 1.35 (s, 3H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.5, 148.4, 139.0, 138.1, 136.4, 134.7, 130.5, 128.2, 128.1, 127.7, 126.5, 121.7, 121.5, 116.5, 49.2, 46.2, 33.0, 20.5, 9.4; IR (KBr, ν / cm–1) 3566, 3365, 2967, 2924, 1671, 1653, 1526, 1487, 1457, 1423, 1385, 1324, 1082, 915, 825, 791, 767, 719, 700; HRMS (ESI^+) HRMS (ESI^+) Calcd for $C_{21}H_{22}N_2O$ ($M+Na^+$) 341.1624, Found 341.1622.

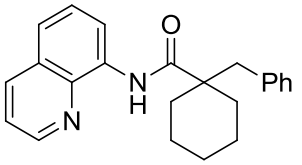


1–Benzyl–*N*–(8–quinolinyl)cyclopentanecarboxamide (1q). Synthesis of an ester from benzyl bromide and methyl cyclopentanecarboxylate, 1.79 g, 73% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 10.03 (s, 1H), 8.80 (d, *J* = 4.2 Hz, 1H), 8.72 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.12 (dd, *J*

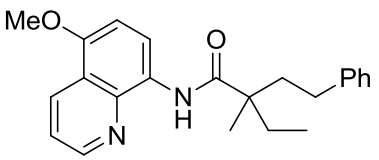


= 8.2, 1.6 Hz, 1H), 7.57–7.36 (m, 3H), 7.23–7.05 (m, 5H), 3.13 (s, 2H), 2.24–2.27 (m, 2H), 1.81–1.89 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 148.3, 138.9, 138.6, 136.4, 134.8, 129.9, 128.3, 128.1, 127.6, 126.5, 121.7, 121.4, 116.4, 57.8, 44.9, 35.6, 24.2; IR (KBr, ν / cm–1) 3566, 3356, 3027, 2954, 2871, 2359, 1671, 1524, 1485, 1455, 1423, 1384, 1324, 1239, 1164, 915, 825, 791, 742, 700; HRMS (ESI$^+$) Calcd for $C_{22}H_{22}N_2O$ (M+Na$^+$) 353.1624, Found 353.1613.

1–Benzyl–*N*–(8–quinolinyl)cyclohexanecarboxamide (1r). Synthesis of an ester from benzyl bromide and methyl cyclohexanecarboxylate, 0.99 g, 66% yield, yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.05 (s, 1H), 8.95–8.63 (m, 2H), 8.12 (dd, *J* = 8.1, 0.9 Hz, 1H), 7.63–7.37 (m, 3H), 7.19–7.02 (m, 5H), 2.98 (s, 2H), 2.26 (d, *J* = 10.3 Hz, 2H), 1.80–1.71 (m, 2H), 1.69–1.52 (m, 5H), 1.34 (s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.8, 148.3, 139.0, 137.4, 136.4, 134.7, 130.4, 128.1, 128.0, 127.7, 126.5, 121.6, 121.4, 116.5, 49.8, 47.5, 34.4, 26.2, 23.4; IR (KBr, ν / cm − 1) 3566, 2826, 2863, 1682, 1523, 1487, 1472, 1456, 1420, 1386, 1323, 1082, 912, 825, 791, 738, 701; HRMS (ESI$^+$) Calcd for $C_{23}H_{24}N_2O$ (M+Na$^+$) 367.1781, Found 367.1777.

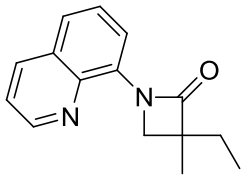


2–Ethyl–*N*–(5–methoxy–8–quinolinyl)–2–methyl–4–phenylbutanamide (1s). To a solution of methyl 2–methylbutanoate (3.00 g, 25.8 mmol) in THF, a THF solution of lithium diisopropylamide (1.5 M, 18.1 mL, 27.2 mmol) was added dropwise at –78 ℃, and the mixture was stirred at –78 ℃ for 1 h. (2–Iodoethyl)benzene (6.59 g, 28.4 mmol) was added to the solution, and the mixture was warmed to 25 ℃ and stirred for 16 h. After quenching with saturated aq. $NaHCO_3$ (100 mL) at 0 ℃, the mixture was extracted with ethyl acetate (3 x 150 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give methyl 2–ethyl–2–methyl–4–phenylbutanoate. To a solution of 5–methoxy–8–quinolinamine (9.89 g, 56.8 mmol) in THF (100 mL), a hexane solution of *n*–BuLi (1.6 M, 35.5 mL, 56.8 mmol) was added dropwise at –78 ℃. The mixture was warmed to 25 ℃ and stirred for 1 h. The reaction mixture was added to a solution of methyl 2–ethyl–2–methyl–4–phenylbutanoate (5.59 g, 27.1 mmol) in THF (20.0 mL) at –78 ℃, and the mixture was warmed to 25 ℃ and stirred for 12 h. After quenching with saturated aq. $NaHCO_3$ (150 mL) at 0 ℃, the mixture was extracted with

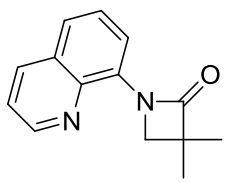


ethyl acetate (3 x 150 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give amide **1s**, which was purified by column chromatography on silica gel (hexane/ethyl acetate = 5:1). **1s:** 5.90 g, 63%, brown solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 8.72 (m, 2H), 8.50 (d, *J* = 8.4 Hz, 1H), 7.37 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.12 (m, 5H), 6.77 (d, *J* = 8.4 Hz, 1H), 3.91 (s, 3H), 2.58 (m, 2H), 2.08 (m, 1H), 1.97–1.73 (m, 2H), 1.70–1.53 (m, 1H), 1.38 (s, 3H), 0.90 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.3, 150.4, 148.9, 142.7, 139.7, 131.5, 128.7, 128.5, 128.3, 126.0, 120.9, 120.7, 116.6, 104.6, 56.0, 47.8, 42.5, 33.3, 31.5, 21.1, 9.2; IR (KBr, ν / cm⁻1) 3565, 3374, 2967, 2860, 1669, 1527, 1494, 1456, 1269, 1244, 1154, 1091, 820, 789, 742, 669; HRMS (ESI$^+$) Calcd for $C_{23}H_{26}N_2O_2$ (M+Na^+) 385.1883, Found 385.1881.

Typical procedure for Copper–Catalyzed Intramolecular C(sp^3)–H and C(sp^2)–H Amidation. A mixture of 2,2–dimethyl–*N*–(8–quinolinyl)butanamide (**1a**, 24.2 mg, 0.100 mmol), $Cu(OAc)_2$ (3.63 mg, 20.0 μmol), and 1,2–dichloroethane (1.0 mL) was stirred at 140 ℃ for 24 h under argon atmosphere. Then, the reaction mixture was cooled to room temperature, and was subjected to column chromatography on silica gel (hexane/ethyl acetate = 8:1) to give **2a**.



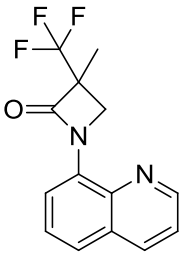
2a, 19.8 mg, 82% yield, yellow solid,; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 3.9, 2.2 Hz, 1H), 8.49 (dd, *J* = 6.1, 3.0 Hz, 1H), 8.10 (ddd, *J* = 8.0, 2.2, 2.2 Hz, 1H), 7.57–7.46 (m, 2H), 7.37 (ddd, *J* = 7.5, 3.9, 3.9 Hz, 1H), 4.40 (d, *J* = 7.3 Hz, 1H), 4.24 (d, *J* = 7.3 Hz, 1H), 1.93–1.72 (m, 2H), 1.44 (s, 3H), 1.07 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 148.7, 140.7, 136.1, 135.4, 129.2, 127.0, 122.9, 121.4, 119.7, 58.4, 56.1, 28.0, 19.4, 9.4; IR (KBr, ν / cm⁻1) 3651, 3567, 2969, 1735, 1685, 1506, 1474, 1457, 1398, 1348, 1188, 1149, 1105, 842, 790, 753; HRMS (ESI$^+$) Calcd for $C_{15}H_{16}N_2O$ (M+Na^+) 263.1155, Found 263.1153.



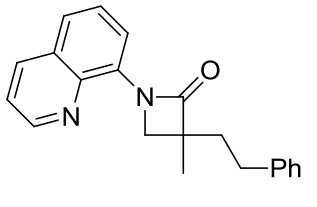
3,3–Dimethyl–1–(8–quinolinyl)–2–azetidinone (2b). 19.5 mg, 86% yield, yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.79 (dd, *J* = 4.0, 1.7 Hz, 1H), 8.49 (dd, *J* = 6.3, 2.6 Hz, 1H), 8.09 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.54–7.46 (m, 2H), 7.37 (dd, *J* = 8.5, 4.0 Hz, 1H), 4.34 (s, 2H), 1.45 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 148.7, 140.6, 136.1, 135.4, 129.2, 127.0, 123.0, 121.4, 119.7, 61.0, 51.7, 21.7;

IR (KBr, ν / cm − 1) 3460, 2962, 2926, 2890, 1737, 1505, 1474, 1426, 1402, 1365, 1349, 1194, 1151, 1106, 1041, 980, 825, 189, 758, 637; HRMS (ESI^+) Calcd for $C_{14}H_{14}N_2O$ ($M+Na^+$) 249.0998, Found 249.0992.

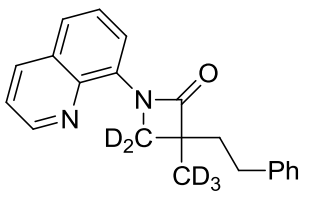
3–Methyl–1–(8–quinolinyl)–3–(trifluoromethyl)–2–azetidinone (2c). 24.9 mg, 89% yield, white solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 4.0, 4.0 Hz, 1H), 8.45 (d, *J* = 4.0 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.58 (d, *J* = 7.3 Hz, 1H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.1 Hz, 1H), 4.78 (d, *J* = 8.0 Hz, 1H), 4.48 (d, *J* = 8.0 Hz, 1H), 1.71 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 163.4, 149.1, 140.5, 136.3, 134.1, 128.0 (d, *J* = 284 Hz), 126.9, 126.7, 124.1, 121.7, 120.1, 59.0 (d, *J* = 28.9 Hz), 54.4, 14.3; IR (KBr, ν / cm − 1) 3455, 2972, 2883, 1760, 1636, 1506, 1477, 1409, 1370, 1320, 1199, 1177, 1146, 1112, 1033, 826, 790, 757, 635; HRMS (ESI^+) Calcd for $C_{14}H_{11}F_3N_2O$ ($M+Na^+$) 303.0716, Found 303.0718.



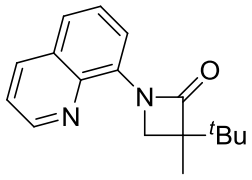
3–Methyl–3–phenethyl–1–(8–quinolinyl)–2–azetidinone (2d). 27.2 mg, 86% yield, yellow oil; ^1H NMR (500 MHz, $CDCl_3$) δ 8.84 (d, *J* = 4.0 Hz, 1H), 8.53 (d, *J* = 6.5 Hz, 1H), 8.13 (d, *J* = 8.3 Hz, 1H), 7.64–7.47 (m, 2H), 7.41 (dd, *J* = 8.3, 4.0 Hz, 1H), 7.34–7.07 (m, 5H), 4.49 (d, *J* = 7.3 Hz, 1H), 4.33 (d, *J* = 7.3 Hz, 1H), 3.06–2.64 (m, 2H), 2.21–1.93 (m, 2H), 1.56 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 148.7, 142.1, 140.7, 136.2, 135.3, 129.2, 128.7, 128.6, 127.0, 126.2, 123.1, 121.4, 119.8, 58.8, 55.5, 37.3, 31.5, 19.9; IR (KBr, ν / cm − 1) 3650, 2991, 1736, 1685, 1654, 1559, 1506, 1474, 1400, 1346, 1151, 1101, 824, 790, 752, 698; HRMS (ESI^+) Calcd for $C_{21}H_{20}N_2O$ ($M+Na^+$) 339.1468, Found 339.1459.



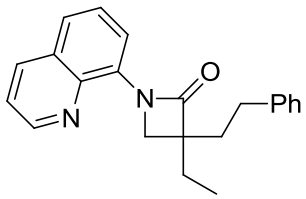
3–Methyl–3–phenethyl–1–(8–quinolinyl)–2–azetidinone–d_5 (2d–D). 29.3 mg, 91% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 4.0, 1.7 Hz, 1H), 8.51 (dd, *J* = 6.4, 2.4 Hz, 1H), 8.11 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.55–7.47 (m, 2H), 7.39 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.32–7.14 (m, 5H), 2.93–2.63 (m, 2H), 2.21–2.02 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 148.7, 142.1, 140.6, 136.2, 135.2, 129.2, 128.7, 128.6, 127.0, 126.2, 123.1, 121.4, 119.7, 55.1,



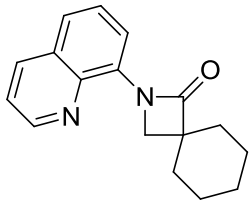
37.2, 31.5 [Signals of CD_3 and CD_2 groups could not be observed. They are supposed to be heptet and quintet, which are too weak to observe in ^{13}C NMR.]; IR (KBr,ν / cm–1) 3448, 1735, 1505, 1474, 1397, 1348, 1255, 1096, 826, 791, 756, 700, 668; HRMS (ESI^+) Calcd for $C_{21}H_{15}D_5N_2O$ ($M+Na^+$) 344.1782, Found 344.1791.



3–(*tert*–Butyl)–3–methyl–1–(8–quinolinyl)–2–azetidinone (2e). 23.2 mg, 93% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.50 (dd, *J* = 6.2, 2.8 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.49 (m, 2H), 7.37 (dd, *J* = 8.2, 4.1 Hz, 1H), 4.50 (d, *J* = 7.5 Hz, 1H), 4.10 (d, *J* = 7.5 Hz, 1H), 1.46 (s, 3H), 1.10 (s, 9H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 148.7, 140.7, 136.1, 135.2, 129.2, 127.0, 122.9, 121.4, 119.6, 62.3, 56.8, 33.3, 26.1, 16.8; IR (KBr,ν / cm–1) 3456, 2962, 2883, 1739, 1637, 1505, 1474, 1401, 1347, 1202, 1152, 825, 629; HRMS (ESI^+) Calcd for $C_{17}H_{20}N_2O$ ($M+Na^+$) 291.1468, Found 291.1464.

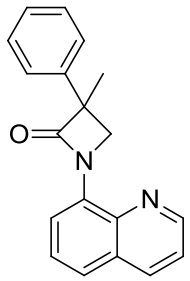


3–Ethyl–3–phenethyl–1–(8–quinolinyl)–2–azetidinone (2f). 29.7 mg, 90% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.74 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.43 (dd, *J* = 6.8, 2.3 Hz, 1H), 8.02 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.46–7.38 (m, 2H), 7.30 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.23–7.06 (m, 5H), 4.32 (d, *J* = 7.6 Hz, 1H), 4.29 (d, *J* = 7.6 Hz, 1H), 2.86–2.59 (m, 2H), 2.13–1.94 (m, 2H), 1.83 (m, 2H), 1.03 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.6, 148.7, 142.2, 140.7, 136.1, 135.1, 129.2, 128.7, 128.6, 127.0, 126.2, 123.1, 121.4, 119.7, 60.0, 55.9, 35.2, 31.3, 26.3, 9.2; IR (KBr,ν / cm–1) 3453, 2981, 2903, 1737, 1652, 1505, 1473, 1457, 1401, 1152, 826, 790, 699; HRMS (ESI^+) Calcd for $C_{22}H_{22}N_2O$ ($M+Na^+$) 353.1624, Found 353.1623.

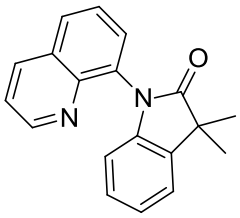


2–(8–Quinolinyl)–2–azaspiro[3.5]–1–nonanone (2g). 20.5 mg, 77% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.80 (dd, *J* = 4.0, 1.7 Hz, 1H), 8.50 (dd, *J* = 5.4, 3.6 Hz, 1H), 8.09 (dd, *J* = 8.1, 1.7 Hz, 1H), 7.51–7.45 (m, 2H), 7.36 (dd, *J* = 8.4, 4.1 Hz, 1H), 4.33 (s, 2H), 1.93–1.85 (m, 6H), 1.75–1.35 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 148.6, 140.5, 136.1, 135.5, 129.2, 127.0, 122.8, 121.4, 119.5, 59.5, 57.2, 31.4, 25.5, 23.6; IR (KBr,ν / cm–1) 3457, 2927, 2851, 1738, 1505,

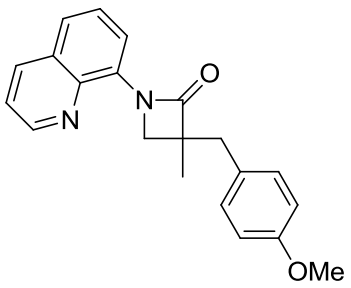
1474, 1401, 1369, 1342, 1202, 1152, 1133, 1107, 968, 825, 789, 755, 627; HRMS (ESI^+) Calcd for $C_{17}H_{18}N_2O$ ($M+Na^+$) 289.1311, Found 289.1302.



3–Methyl–3–phenyl–1–(8–quinolinyl)–2–azetidinone (2h). 18.7 mg, 65% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.81 (dd, *J* = 3.9, 1.3 Hz, 1H), 8.56 (dd, *J* = 6.5, 2.4 Hz, 1H), 8.10 (dd, *J* = 8.2, 1.3 Hz, 1H), 7.53 (m, 4H), 7.41–7.35 (m, 3H), 7.28 (d, *J* = 7.5 Hz, 1H), 4.83 (d, *J* = 7.2 Hz, 1H), 4.68 (d, *J* = 7.2 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 171.4, 148.8, 141.5, 140.7, 136.2, 135.2, 129.2, 128.9, 127.3, 127.0, 126.4, 123.2, 121.5, 119.9, 61.1, 59.4, 24.0; IR (KBr,ν / cm–1) 3455, 2961, 1737, 1647, 1540, 1505, 1474, 1402, 1349, 1154, 825, 789, 763, 700; HRMS (ESI^+) Calcd for $C_{19}H_{16}N_2O$ ($M+Na^+$) 311.1155, Found 311.1158.



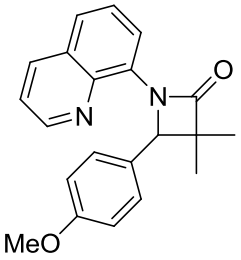
3,3–Dimethyl–1–(8–quinolinyl)–2–indolinone (3h). 8.9 mg, 31% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.82 (dd, *J* = 4.0, 1.3 Hz, 1H), 8.22 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.94 (d, *J* = 8.3 Hz, 1H), 7.78 (d, *J* = 7.1 Hz, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.42 (dd, *J* = 8.0, 4.0 Hz, 1H), 7.35–7.29 (m, 1H), 7.08 (m, 2H), 6.38 (d, *J* = 7.1 Hz, 1H), 1.65 (s, 3H), 1.58 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 182.1, 151.2, 144.6, 144.4, 136.3, 135.8, 132.9, 130.1, 129.9, 129.3, 127.6, 126.6, 122.7, 122.6, 122.1, 109.9, 44.9, 25.5, 24.7; IR (KBr,ν / cm–1) 3649, 2969, 2894, 1718, 1610, 1507, 1490, 1458, 1395, 1298, 1198, 1090, 830, 793, 758, 628; HRMS (ESI^+) Calcd for $C_{19}H_{16}N_2O$ ($M+Na^+$) 311.1155, Found 311.1151.



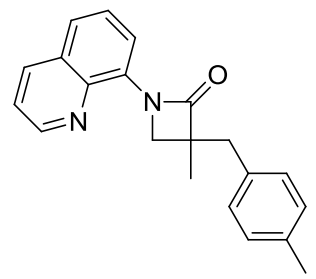
3–(4–Methoxybenzyl)–3–methyl–1–(8–quinolinyl)–2–azetidinone (2i). 8.3 mg, 25% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.41 (dd, *J* = 6.9, 2.1 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54–7.43 (m, 2H), 7.35 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.22 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.40 (d, *J* = 7.3 Hz, 1H), 4.29 (d, *J* = 7.3 Hz, 1H), 3.76 (s, 3H), 3.13 (d, *J* = 14.1 Hz, 1H), 2.89 (d, *J* = 14.1 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 158.6, 148.7, 140.7, 136.1, 135.1, 131.2, 129.6, 129.2, 126.9, 123.1, 121.4, 119.8, 114.0,

58.0, 56.3, 55.4, 40.2, 20.1; IR (KBr, ν / cm − 1) 3444, 2962, 2893, 1735, 1652, 1558, 1507, 1473, 1400, 1349, 1249, 1152, 1034, 825, 791; HRMS (ESI^+) Calcd for $C_{21}H_{20}N_2O_2$ ($M+Na^+$) 355.1417, Found 355.1408.

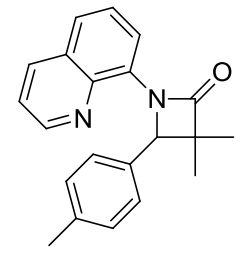
4–(4–Methoxyphenyl)–3,3–dimethyl–1–(8–quinolinyl)–2–azetidinone (2i′). 17.3 mg, 52% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.57 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.27 (dd, *J* = 6.4, 2.0 Hz, 1H), 7.92 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.51–7.40 (m, 2H), 7.17 (dd, *J* = 8.7, 4.2 Hz, 1H), 7.05 (d, *J* = 8.6Hz, 2H), 6.65 (d, *J* = 8.6 Hz, 2H), 5.93 (s, 1H), 3.61 (s, 3H), 1.56 (s, 3H), 0.85 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 158.9, 149.0, 141.4, 135.9, 133.7, 130.9, 129.2, 127.7, 126.8, 124.4, 122.4, 121.4, 113.8, 71.4, 56.3, 55.3, 23.6, 18.8; IR (KBr, ν / cm − 1) 3446, 2961, 1745, 1614, 1513, 1505, 1473, 1399, 1344, 1249, 1177, 1128, 1098, 1033, 829, 790, 636; HRMS (ESI^+) Calcd for $C_{21}H_{20}N_2O_2$ ($M+Na^+$) 355.1417, Found 355.1418.



3–Methyl–3–(4–methylbenzyl)–1–(8–quinolinyl)–2–azetidinone (2j). 12.1 mg, 38% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 5.4, 1.7 Hz, 1H), 8.43 (dd, *J* = 5.4, 2.2 Hz, 1H), 8.07 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.47 (m, 2H), 7.35 (d, *J* = 9.6, 4.0 Hz, 1H), 7.19 (d, *J* = 7.1 Hz, 2H), 7.10 (d, *J* = 7.1 Hz, 2H), 4.43 (d, *J* = 7.3 Hz, 1H), 4.29 (d, *J* = 7.3 Hz, 1H), 3.15 (d, *J* = 13.9 Hz, 1H), 2.92 (d, *J* = 13.9 Hz, 1H), 2.29 (s, 3H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 148.7, 140.7, 136.3, 136.1, 135.2, 134.4, 130.1, 129.3, 129.2, 126.9, 123.1, 121.4, 119.8, 58.2, 56.2, 40.6, 21.3, 20.1; IR (KBr,ν / cm–1) 3327, 2969, 2813, 1736, 1506, 1474, 1399, 1348, 824, 788; HRMS (ESI^+) Calcd for $C_{21}H_{20}N_2O$ ($M+Na^+$) 339.1468, Found 339.1457.

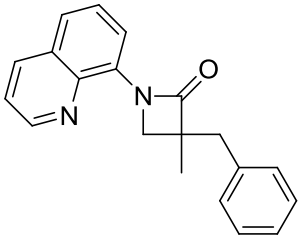


3,3–Dimethyl–1–(8–quinolinyl)–4–(*p*–tolyl)–2–azetidinone (2j′). 16.1 mg, 51% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.65 (d, *J* = 4.2 Hz, 1H), 8.36 (dd, *J* = 5.9, 3.1 Hz, 1H), 8.01 (d, *J* = 8.7 Hz, 1H), 7.64–7.48 (m, 2H), 7.25 (dd, *J* = 8.7, 4.2 Hz, 1H), 7.10 (d, *J* = 7.9 Hz, 2H), 7.00 (d, *J* =

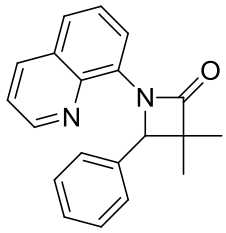


7.9 Hz, 2H), 6.04 (s, 1H), 2.23 (s, 3H), 1.65 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.8, 149.0, 141.4, 137.0, 135.9, 135.8, 133.8, 129.2, 129.1, 126.8, 126.4, 124.4, 122.4, 121.4, 71.6, 56.3, 23.6, 21.3, 18.8; IR (KBr,ν / cm–1) 3447, 2962, 2853, 1747, 1636, 1505, 1473, 1343, 1206, 1162, 1128, 1099, 1042, 788; HRMS (ESI^+) Calcd for $C_{21}H_{20}N_2O$ ($M+Na^+$) 339.1468, Found 339.1458.

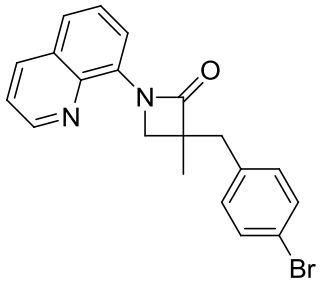
3–Benzyl–3–methyl–1–(8–quinolinyl)–2–azetidinone (2k). 7.56 mg, 25% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.70 (d, *J* = 4.0 Hz, 1H), 8.34 (d, *J* = 6.9 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.44–7.37 (m, 2H), 7.28 (dd, *J* = 8.2, 4.0 Hz, 1H), 7.26–7.19 (m, 4H), 7.16–7.09 (m, 1H), 4.36 (d, *J* = 7.3 Hz, 1H), 4.23 (d, *J* = 7.3 Hz, 1H), 3.12 (d, *J* = 13.9 Hz, 1H), 2.89 (d, *J* = 13.9 Hz, 1H), 1.39 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 148.7, 140.7, 137.6, 136.1, 135.1, 130.2, 129.2, 128.6, 126.9, 126.8, 123.1, 121.4, 119.9, 58.1, 56.2, 41.1, 20.1; IR (KBr,ν / cm–1) 3406, 2966, 2902, 1737, 1568, 1505, 1474, 1426, 1401, 1349, 1197, 1152, 1098, 1032, 825, 789, 700, 668; HRMS (ESI^+) Calcd for $C_{20}H_{18}N_2O$ ($M+Na^+$) 325.1311, Found 325.1304.



3,3–Dimethyl–4–phenyl–1–(8–quinolinyl)–2–azetidinone (2k′). 19.4 mg, 64% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (d, *J* = 5.5 Hz, 1H), 8.32 (dd, *J* = 5.7, 3.2 Hz, 1H), 7.94 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.51–7.44 (m, 2H), 7.20–7.04 (m, 6H), 6.01 (s, 1H), 1.58 (s, 3H), 0.84 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 148.9, 141.3, 139.0, 135.8, 133.8, 129.2, 128.4, 127.3, 126.8, 126.4, 124.4, 122.2, 121.4, 71.8, 56.4, 23.6, 18.8; IR (KBr,ν / cm–1) 3567, 2964, 2925, 1747, 1504, 1474, 1425, 1399, 1364, 1342, 1206, 978, 827, 789, 756, 701, 668, 637; HRMS (ESI^+) Calcd for $C_{20}H_{18}N_2O$ ($M+Na^+$) 325.1311, Found 325.1308.

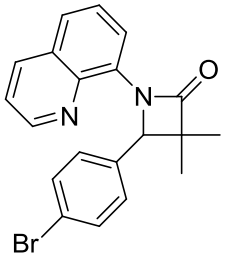


3–(4–Bromobenzyl)–3–methyl–1–(8–quinolinyl)azetidin–2–one (2l). 9.2 mg, 24% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.40 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.53–7.45 (m, 2H), 7.41 (d, *J* = 8.3 Hz, 2H), 7.36 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 4.38 (d, *J* = 7.3 Hz, 1H), 4.29 (d, *J* = 7.3 Hz, 1H), 3.13 (d, *J* = 14.0 Hz, 1H), 2.91 (d, *J* = 14.0 Hz, 1H), 1.45 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ

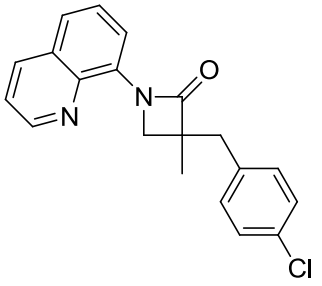


172.7, 148.8, 140.7, 136.5, 136.2, 134.9, 131.9, 131.7, 129.2, 126.9, 123.3, 121.4, 120.9, 119.9, 57.9, 55.9, 40.5, 20.2; IR (KBr,ν / cm–1) 3455, 2962, 1737, 1628, 1505, 1474, 1402, 1350, 1223, 1152, 1072, 663; HRMS (ESI^+) Calcd for $C_{20}H_{17}BrN_2O$ ($M+Na^+$) 403.0416, Found 403.0416.

4–(4–Bromophenyl)–3,3–dimethyl–1–(8–quinolinyl)–2–azetidinone (2l′). 22.9 mg, 60% yield, yellow solid;[1]H NMR (500 MHz, $CDCl_3$) δ 8.51 (dd, *J* = 3.9, 1.7 Hz, 1H), 8.34 (dd, *J* = 6.3, 2.7 Hz, 1H), 7.94 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.51–7.43 (m, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.18 (dd, *J* = 8.5, 3.9 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 2H), 5.96 (s, 1H), 1.56 (s, 3H), 0.84 (s, 3H); [13]C NMR (126 MHz, $CDCl_3$) δ 173.4, 148.9, 140.9, 138.2, 136.0, 133.5, 131.6, 129.2, 128.1, 126.9, 124.4, 121.8, 121.5, 121.2, 71.3, 56.5, 23.5, 18.9; IR (KBr,ν / cm–1) 3448, 2964, 2925, 1748, 1504, 1474, 1400, 1342, 1281, 1206, 1161, 1127, 1098, 1009, 827, 789, 756, 668, 635; HRMS (ESI^+) Calcd for $C_{20}H_{17}BrN_2O$ ($M+Na^+$) 403.0416, Found 403.0410.

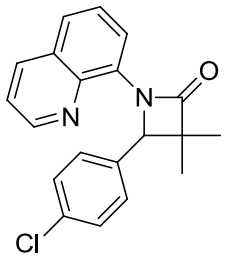


3–(4–Chlorobenzyl)–3–methyl–1–(8–quinolinyl)–2–azetidinone (2m). 8.4 mg, 25% yield, yellow solid; [1]H NMR (500 MHz, $CDCl_3$) δ 8.78 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.41 (dd, *J* = 7.3, 1.5 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.57–7.45 (m, 2H), 7.37 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.31–7.21 (m, 4H), 4.39 (d, *J* = 7.3 Hz, 1H), 4.30 (d, *J* = 7.3 Hz, 1H), 3.16 (d, *J* = 14.0 Hz, 1H), 2.94 (d, *J* = 14.0 Hz, 1H), 1.47 (s, 3H); [13]C NMR (126 MHz, $CDCl_3$) δ 172.4, 148.5, 140.4, 135.9, 135.7, 134.6, 132.5, 131.3, 128.9, 128.4, 126.6, 123.0, 121.2, 119.6, 57.6, 55.7, 40.2, 19.9; IR (KBr,ν / cm–1) 3649, 2982, 1735, 1685, 1654, 1559, 1398, 1348, 1091, 828, 639; HRMS (ESI^+) Calcd for $C_{20}H_{17}ClN_2O$ ($M+Na^+$) 359.0922, Found 359.0918.

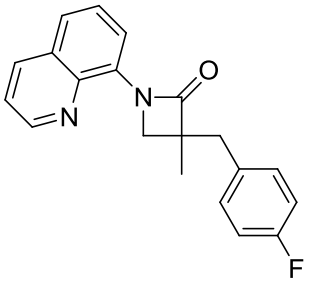


4–(4–Chlorophenyl)–3,3–dimethyl–1–(8–quinolinyl)–2–azetidinone (2m′). 20.9 mg, 62% yield, yellow solid; [1]H NMR (500 MHz, $CDCl_3$) δ 8.61 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.43 (dd, *J* = 5.5, 3.3 Hz, 1H), 8.04 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.59–7.54 (m, 2H), 7.28 (dd, *J* = 5.5, 3.3 Hz, 1H), 7.21–7.12 (m, 4H), 6.07 (s, 1H), 1.66 (s, 3H), 0.94 (s, 3H); [13]C NMR (126 MHz, $CDCl_3$) δ 173.4,

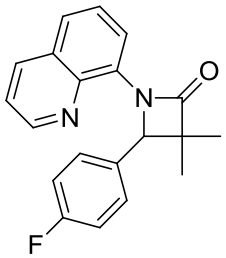
148.9, 140.9, 137.7, 136.0, 133.6, 133.1, 129.2, 128.7, 127.7, 126.9, 124.4, 121.9, 121.5, 71.3, 56.5, 23.5, 18.8; IR (KBr, ν / cm–1) 3649, 2965, 2925, 1748, 1636, 1504, 1493, 1473, 1399, 1342, 1206, 1097, 788, 701, 637; HRMS (ESI^+) Calcd for $C_{20}H_{17}ClN_2O$ ($M+Na^+$) 359.0922, Found 359.0911.



3–(4–Fluorobenzyl)–3–methyl–1–(8–quinolinyl)–2–azetidinone (2n). 9.6 mg, 30% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.39 (dd, *J* = 7.3, 1.7 Hz, 1H), 8.08 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.54–7.41 (m, 2H), 7.36 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.32–7.22 (m, 2H), 7.02–6.92 (m, 2H), 4.38 (d, *J* = 7.3 Hz, 1H), 4.29 (d, *J* = 7.3 Hz, 1H), 3.15 (d, *J* = 14.1 Hz, 1H), 2.93 (d, *J* = 14.1 Hz, 1H), 1.46 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 162.0 (d, *J* = 244 Hz), 148.7, 140.7, 136.1, 135.0, 133.2 (d, *J* = 3.5 Hz), 131.6 (d, *J* = 9.4 Hz), 129.2, 126.9, 123.2, 121.4, 119.9, 115.4 (d, *J* = 21.1 Hz), 57.8, 56.2, 40.3, 20.2; IR (KBr,ν / cm–1) 3649, 3421, 2991, 2903, 1735, 1652, 1558, 1540, 1507, 1473, 1401, 1349, 1221, 1154, 825, 789; HRMS (ESI^+) Calcd for $C_{20}H_{17}FN_2O$ ($M+Na^+$) 343.1217, Found 343.1211.

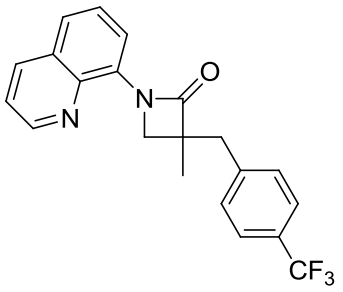


4–(4–Fluorophenyl)–3,3–dimethyl–1–(8–quinolinyl)–2–azetidinone (2n′). 19.2 mg, 60% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.63 (dd, *J* = 4.0, 1.7 Hz, 1H), 8.42 (dd, *J* = 6.3, 2.7 Hz, 1H), 8.04 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.61–7.50 (m, 2H), 7.27 (dd, *J* = 8.4, 4.0 Hz, 1H), 7.22–7.09 (m, 2H), 7.00–6.83 (m, 2H), 6.07 (s, 1H), 1.66 (s, 3H), 0.94 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.5, 162.2 (d, *J* = 246 Hz), 148.9, 141.1, 135.9, 134.8 (d, *J* = 3.4 Hz), 133.6, 129.2, 127.9 (d, *J* = 7.9 Hz), 126.8, 124.4, 122.0, 121.4, 115.4 (d, *J* = 22.0 Hz), 71.2, 56.4, 23.5, 18.8; IR (KBr,ν / cm–1) 3738, 2959, 2893, 1746, 1506, 1473, 1399, 1341, 1222, 1158, 1098, 1146, 816, 788, 759; HRMS (ESI^+) Calcd for $C_{20}H_{17}FN_2O$ ($M+Na^+$) 343.1217, Found 343.1205.

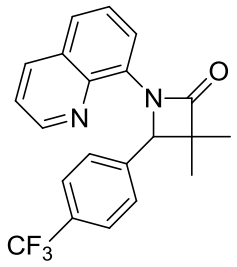


3–Methyl–1–(8–quinolinyl)–3–(4–(trifluoromethyl)benzyl)–2–azetidinone (2o). 7.8 mg, 21% yield, yellow solid; ^1H NMR (500 MHz, $CDCl_3$) δ 8.77 (d, *J* = 2.5 Hz, 1H), 8.38 (d, *J* = 7.1 Hz, 1H), 8.09 (d, *J* = 8.3 Hz, 1H), 7.60–7.41 (m, 6H), 7.37 (dd, *J* = 8.3, 4.0 Hz, 1H) , 4.42 (d, *J* = 7.3 Hz, 1H), 4.31 (d, *J* = 7.3 Hz, 1H), 3.23 (d, *J* = 13.9 Hz, 1H), 3.04 (d, *J* = 13.9 Hz, 1H), 1.56 (s,

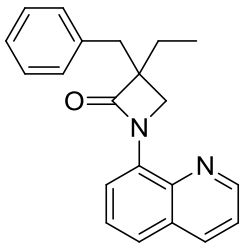
3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 148.8, 141.7, 136.2, 134.8, 130.5, 129.4 (q, *J* = 32.5 Hz), 129.2, 126.9, 125.5 (q, *J* = 274 Hz), 125.5 (q, *J* = 3.6 Hz), 123.4, 121.7, 121.5, 120.0, 58.0, 55.9, 40.9, 20.2; IR (KBr,ν / cm–1) 3629, 1735, 1700, 1685, 1541, 1507, 1474, 1457, 1324, 1122, 668; HRMS (ESI$^+$) Calcd for $C_{21}H_{17}F_3N_2O$ (M+Na$^+$) 393.1185, Found 393.1189.



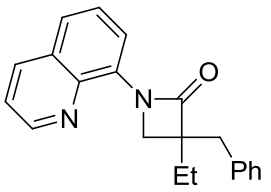
4–(4–(Trifluoromethyl)phenyl)–3,3–dimethyl–1–(8–quinolinyl)–2–azetidinone (2o′). 21.5 mg, 58% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.58 (dd, *J* = 4.9, 1.7 Hz, 1H), 8.47 (dd, *J* = 4.9, 3.3 Hz, 1H), 8.05 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.61–7.55 (m, 2H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 7.28 (d, *J* = 4.0 Hz, 1H), 6.17 (s, 1H), 1.68 (s, 3H), 0.93 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.2, 148.9, 143.4, 140.8, 136.0, 133.5, 130.5, 129.7, 129.3 (q, *J* = 32.5 Hz), 129.2, 126.9, 125.51 (q, *J* = 273 Hz), 125.46 (q, *J* = 3.6 Hz), 121.7, 121.5, 71.4, 56.8, 23.5, 18.9; IR (KBr,ν / cm–1) 3481, 2966, 1748, 1647, 1505, 1473, 1421, 1399, 1364, 1325, 1164, 1125, 1067, 1017, 852, 827, 789, 756, 637; HRMS (ESI$^+$) Calcd for $C_{21}H_{17}F_3N_2O$ (M+Na$^+$) 393.1185, Found 393.1178.



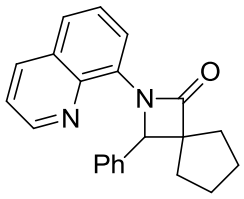
3–Benzyl–3–ethyl–1–(8–quinolinyl)–2–azetidinone (2p). 9.5 mg, 30% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (dd, *J* = 3.9, 1.7 Hz, 1H), 8.30 (dd, *J* = 7.0, 1.6 Hz, 1H), 8.02–7.93 (m, 1H), 7.38 (d, *J* = 3.9 Hz, 2H), 7.30–7.15 (m, 5H), 7.10 (dd, *J* = 10.8, 3.6 Hz, 1H), 4.31 (d, *J* = 7.4 Hz, 1H), 4.21 (d, *J* = 7.4 Hz, 1H), 3.13 (d, *J* = 14.0 Hz, 1H), 2.92 (d, *J* = 14.0 Hz, 1H), 1.85–1.65 (m, 2H), 1.04 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.4, 148.7, 140.8, 137.5, 136.1, 134.9, 130.3, 129.2, 128.5, 126.9, 126.8, 123.1, 121.4, 119.9, 60.7, 54.8, 39.5, 26.5, 9.3; IR (KBr,ν / cm–1) 3446, 2987, 1735, 1647, 1558, 1541, 1506, 1473, 1398, 1349, 1153, 790, 758, 636; HRMS (ESI$^+$) Calcd for $C_{21}H_{20}N_2O$ (M+Na$^+$) 339.1468, Found 339.1460.



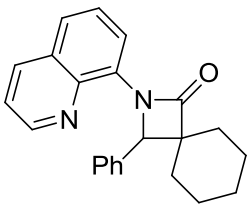
3–Ethyl–3–methyl–4–phenyl–1–(8–quinolinyl)–2–azetidinone (2p′). 19.0 mg, 60% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55–8.53 (m, 1H, major + minor), 8.35–8.31 (m, 1H,



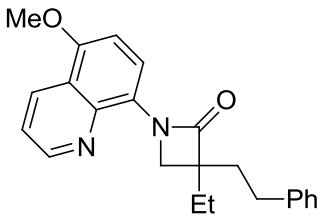
major), 8.31–8.27 (m, 1H, minor), 8.01–7.81 (m, 1H, major + minor), 7.53–7.38 (m, 2H, major + minor), 7.22–6.87 (m, 6H, major + minor), 6.08 (s, 1H, major), 5.98 (s, 1H, minor), 1.99–1.89 (m, 2H, major), 1.57 (s, 3H, minor), 1.49–1.45 (m, 2H, minor), 1.22–1.16 (m, 3H, minor), 1.13 (t, J = 7.4 Hz, 3H, major), 0.83 (s, 3H, major), 0.69 (t, J = 7.5 Hz, 3H, minor); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 148.89, 148.85, 141.3, 139.1, 138.7, 135.8, 133.8, 129.2, 128.4, 128.2, 127.4, 127.2, 126.9, 126.81, 126.78, 126.6, 124.4, 124.3, 122.4, 122.1, 121.4, 77.3, 72.0, 69.4, 60.6, 59.8, 29.8, 25.3, 20.0, 16.2, 9.5, 8.6; IR (KBr,ν / cm–1) 3363, 2956, 1745, 1680, 1527, 1486, 1423, 1386, 1326, 1079, 826, 791, 755, 700, 647, 638, 611; HRMS (ESI^+) Calcd for $C_{21}H_{20}N_2O$ ($M+Na^+$) 339.1468, Found 339.1458.



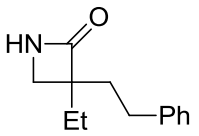
3–Phenyl–2–(8–quinolinyl)–2–azaspiro[3.4]–1–octanone (2q′). 27.3 mg, 83% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.55 (dd, J = 4.2, 1.7 Hz, 1H), 8.34 (dd, J = 5.9, 3.0 Hz, 1H), 7.90 (dd, J = 8.2, 1.7 Hz, 1H), 7.48–7.41 (m, 2H), 7.13 (m, 5H), 7.08–7.03 (m, 1H), 6.05 (s, 1H), 2.33–2.15 (m, 2H), 1.80–1.72 (m, 2H), 1.68–1.52 (m, 2H), 1.40–1.26 (m, 1H), 1.19–1.15 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 148.8, 141.1, 139.4, 135.8, 133.8, 129.2, 128.5, 127.4, 126.8, 126.7, 124.1, 121.9, 121.3, 72.7, 67.2, 35.5, 29.7, 25.9, 25.5; IR (KBr,ν / cm–1) 3651, 2982, 1742, 1636, 1542, 1504, 1398, 1348, 1319, 1153, 904, 826, 789, 761, 699; HRMS (ESI^+) Calcd for $C_{22}H_{20}N_2O$ ($M+Na^+$) 351.1468, Found 351.1464.



3–Phenyl–2–(8–quinolinyl)–2–azaspiro[3.5]–1–nonanone (2r′). 25.7 mg, 75% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.54 (dd, J = 4.1, 1.7 Hz, 1H), 8.37–8.29 (m, 1H), 7.90 (dd, J = 8.3, 1.7 Hz, 1H), 7.44 (dd, J = 6.8, 3.3 Hz, 2H), 7.24–6.95 (m, 6H), 5.97 (s, 1H), 2.14–2.09 (m, 1H), 2.03–1.95 (m, 1H), 1.90–1.76 (m, 1H), 1.69–1.20 (m, 6H), 1.02–0.88 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.6, 148.8, 141.2, 138.6, 135.8, 133.7, 129.2, 128.2, 127.4, 127.1, 126.8, 124.2, 122.1, 121.3, 71.6, 60.8, 34.1, 28.1, 25.6, 23.9, 22.3; IR (KBr,ν / cm–1) 3650, 3094, 2928, 2850, 1760, 1740, 1558, 1505, 1473, 1456, 1397, 1362, 1338, 1213, 1130, 826, 788, 763, 701; HRMS (ESI^+) Calcd for $C_{23}H_{22}N_2O$ ($M+Na^+$) 365.1624, Found 365.1615.

3–Ethyl–1–(5–methoxy–8–quinolinyl)–3–phenethyl–2–azetidinone (2s). 

25.6 mg, 71% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.83 (dd, *J* = 4.2, 1.8 Hz, 1H), 8.55 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.32 (d, *J* = 8.4 Hz, 1H), 7.38 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.27 (m, 4H), 7.21–7.15 (m, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 4.28 (d, *J* = 7.3 Hz, 1H), 4.26 (d, *J* = 7.3 Hz, 1H), 3.99 (s, 3H), 2.99–2.84 (m, 1H), 2.84–2.66 (m, 1H), 2.18–2.02 (m, 2H), 2.00–1.85 (m, 2H), 1.11 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 172.2, 151.7, 149.4, 142.4, 141.9, 130.9, 128.64, 128.59, 128.3, 126.1, 121.1, 120.63, 120.60, 104.4, 59.7, 56.1, 55.4, 35.2, 31.3, 26.3, 9.2; IR (KBr,ν / cm–1) 3649, 3567, 2968, 1733, 1507, 1480, 1457, 1409, 1373, 1276, 1158, 1096, 785, 700, 615; HRMS (ESI^+) Calcd for $C_{23}H_{24}N_2O_2$ ($M+Na^+$) 383.1730, Found 383.1729.

3–Ethyl–3–phenethyl–2–azetidinone (4). 

Amide **1s** (72.5 mg, 0.20 mmol) was dissolved in a mixture of CH_3CN and H_2O (5/1, 2.4 mL) at rt. CAN (329 mg, 0.60 mmol, 3.0 equiv) was added, and the reaction mixture was stirred at rt for 3 h. The reaction was quenched with sat. $NaHCO_3$ (20 mL), and extracted with ethyl acetate (3 x 30 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give amide **4** in 67% yield (27 mg) as yellow oil; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26–7.08 (m, 5H), 5.69 (s, 1H), 3.06 (d, *J* = 5.6 Hz, 1H), 3.04 (d, *J* = 5.6 Hz, 1H), 2.78–2.65 (m, 1H), 2.65–2.50 (m, 1H), 1.96–1.85 (m, 2H), 1.74–1.66 (m, 2H), 0.95 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 142.0, 128.7, 128.5, 126.2, 61.2, 46.0, 34.9, 31.1, 25.8, 9.0; IR (KBr,ν / cm–1) 3446, 2923, 2890, 1748, 1636, 1558, 1540, 1507, 1457, 1275, 700; HRMS (ESI^+) Calcd for $C_{13}H_{17}NO$ ($M+Na^+$) 226.1202, Found 226.1201.

3. Copper–Mediated C(sp^3)–H and C(sp^2)–H Acetoxylation

3.1. Introduction

Direct C–H bond transformations are highly efficient and ideal methods for synthesizing organic molecules. Second– and third–row transition metal complexes or salts are often used as catalysts or mediators to promote direct C–H transformations. The abundance and low cost of first–row transition metals compared with second– and third–row transition metals, and the few examples of first–row transition metal–catalyzed or –mediated C–H transformations have recently prompted researchers to concentrate their effort on developing direct C–H (especially C(sp^2)–H) transformations using first–row transition metals.[1]

To date, however, there are still only a few examples of first–row transition metal–catalyzed or –mediated unactivated C(sp^3)–H transformations: for example, Nakamura and co–workers reported iron–catalyzed arylation, alkenylation, and alkylation at C(sp^3)–H bonds adjacent to a nitrogen atom;[2] the Chatani[3] and Ge[4] groups independently reported nickel–catalyzed C(sp^3)–H arylation and alkylation; however, all these first row transition–metals–catalyzed C(sp^3)–H transformations focused on the carbon–carbon bond formation, we reported copper–catalyzed intramolecular C(sp^3)–H amidation;[5] and Ge's group subsequently reported a similar C(sp^3)–H amidation,[6] although these two reactions are intramolecular reaction, they are first examples on first row transition–metal–catalyzed carbon–heteroatom bond formation. So it is necessary to investigate an intermolecular carbon–heteroatom bond formation using a first row transition metal or catalyst. Considering there are a lot of acetate anion exists in copper–catalyzed C(sp^3)–H amidation, I chose copper–catalyzed intermolecular acetoxylation as my target reaction. On the other hand, organic molecules bearing acetoxy group(s) are important as natural products, drugs, and agricultural chemicals. For example, cytochalasin D[7] is a cell–permeable and potent inhibitor of actin polymerization, and decazolin[8] is herbicide (Figure 3-1).

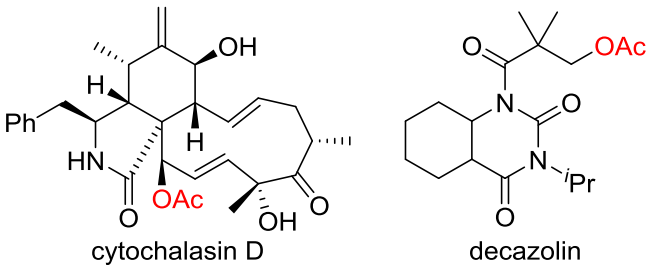


Figure 1. Bioactive compounds containing an acetate group.

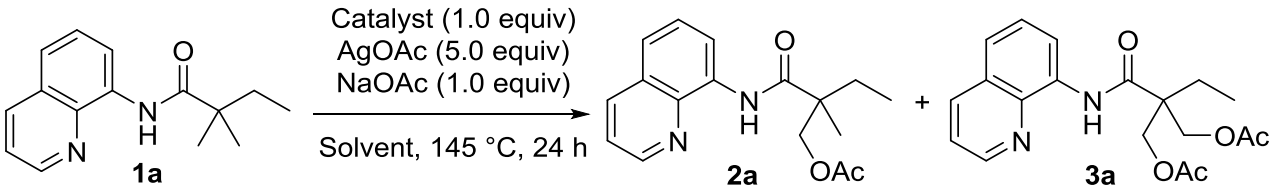
Several tranditional methods for introducing acetoxy groups into the desired site(s) of organic molecules have been developed, such as the Schotten–Baumann reaction,[9] the Tishchenko reaction,[10] the Baeyer–Villiger oxidation,[11] and the Pinner reaction.[12] C(sp^3)–H Acetoxylation is the most direct and efficient method for introducing acetoxy group(s), and acetoxylated products can be synthesized from simple substrates. Among them are the recently reported palladium–catalyzed oxidative C(sp^3)–H acetoxylations;[13–16] but there have been no report on C(sp^3)–H acetoxylation promoted by a first–row transition metal complex or salt.[17.18] I report herein copper–mediated unactivated C(sp^3)–H acetoxylation using a chelating directing group.[19] I also used this method to achieve C(sp^2)–H acetoxylation.

3.2. Optimization Studies

Considering the small radius of copper atom, I chose an amide which contains a quartery carbon as a starting material to investigate the desired reaction, since a quartery carbon makes the methyl closed to copper center. In addition, I selected high polarized solvents considering the solubility of various salts. Because several groups reported copper–mediated C–heteroatom bond formation reactions via C–H activation, which were inhibited by the products, 1 equivalent of a copper salt was used. Treatment of amide **1a** with a mixture of CuCl, AgOAc, and NaOAc in hexamethylphosphoric triamide (HMPA) at 145 ℃ for 24 h gave mono– and di–acetoxylated products **2a** and **3a** in 30% and 14% yield, respectively (Table 3-1, entry 1). In this reaction, acetoxylation occurred only at the terminal C(sp^3)–H bond, and internal C(sp^3)–H acetoxylation of the ethyl group, C(sp^2)–H acetoxylation of the quinolyl group,[20] and intramolecular C(sp^3)–H

amidation[5,6] did not proceed at all. This result shows that the steric effect is more important rather than electronic one in this reaction. Based on the screening of several copper salts (entries 2–8), $Cu(OAc)_2$ was revealed as the best catalyst, and **2a** and **3a** were obtained in 48% and 33% yields, respectively (entry 8). In this reaction, sodium acetate was not indispensable; however, the yields of **2a** and **3a** decreased slightly when sodium acetate was not used (entry 9). Because HMPA is a carcinogen, the solvent was replaced with another solvent (entries 10–13). As a result, *N*–methylpyrrolidone (NMP) exhibited the similar reactivity as HMPA (entry 13). Unfortunately, the yields of **2a** and **3a** were decreased by decreasing the amount of $Cu(OAc)_2$ (entry 14).[21] This phenomenon mainly attributed to the strong coordination ability of the products rather than the staring materials (the products are a tri– or tetradentate compounds and the starting materials are bidentate molecules).

Table 3-1. Optimization of Reaction Conditions



entry	catalyst	solvent	Yield (%)Mono–OAc (**2a**)	Di–OAc (**3a**)
1	CuCl	HMPA	30	14
2	$CuCl_2$	HMPA	22	15
3	CuBr	HMPA	35	32
4	$CuBr_2$	HMPA	26	27
5	CuCN	HMPA	21	5
6	$Cu(OH)_2$	HMPA	10	5
7	$Cu_2(OH)_2(CO_3)$	HMPA	37	3
8	$Cu(OAc)_2$	HMPA	48	33
9	$Cu(OAc)_2$	HMPA	36	18
10	$Cu(OAc)_2$	DMSO	28	trace
11	$Cu(OAc)_2$	DMA	34	22
12	$Cu(OAc)_2$	DMF	34	32

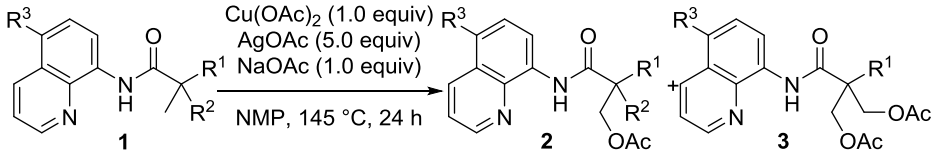
13	$Cu(OAc)_2$	NMP	46	32
14	$Cu(OAc)_2$[b]	NMP	31	18

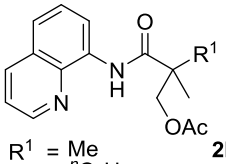
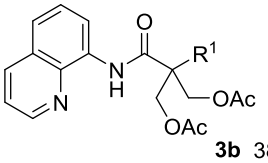
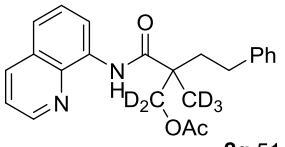
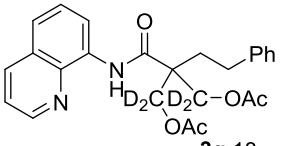
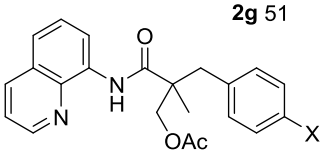
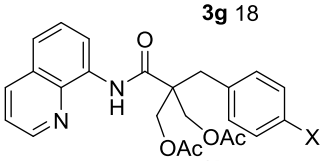
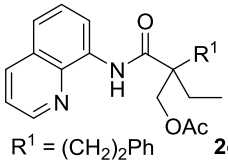
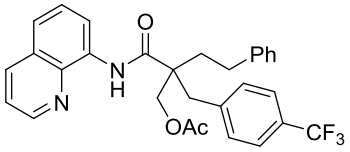
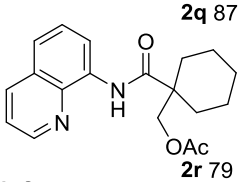
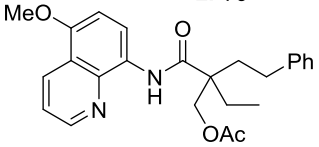
[a]NaOAc was not added. [b]0.50 equiv.

3.3. Substrate Scope and Mechanism Research

With the best reaction conditions in hand, I then investigated the substrate scope of the acetoxylation (Table 3-2). Amides with a tertiary alkyl group gave the corresponding mono– and di–acetoxylated products **2b**–**2e**, **2g** and **3b**–**3e**, **3g**, respectively (entries 1–4 and 6).[22] In the case of substrates **1d** and **1e**, acetoxylation did not occur at the more acidic benzylic C(sp^3)–H bonds (entries 3 and 4). This result indicated that the steric effect played a more important role than the electronic effect. In the case of tertiary alkyl amides **1f** and **1h**–**1n** bearing a trifluoromethyl or benzylic group, only mono–acetoxylated products **2f** and **2h**–**2n** were obtained in 62%–83% yields with high functional group tolerance (entries 5 and 7–13). The yields of the acetoxylated products increased with an increase of the electron–withdrawing ability of the functional group. The results of substrates **1o**–**1r** revealed that the reaction occurred preferentially at the methyl groups, and acetoxylation did not proceed at the terminal position of the ethyl groups, methylene moieties (internal position), or benzylic C(sp^3)–H bonds (entries 14–17). The corresponding acetoxylated product **2s** was obtained in 68% yield when an amide bearing a methoxy group on the quinolyl group was used as a substrate (entry 18). The regioselectivity of this reaction was different from intramolecule C(sp^3)-H amidation reaction (Chapter 2). I deduced that the main reason is that the copper center is occupied by a high polar solvent and reductive C-OAc bond formation is promoted in this reaction, whereas the copper center in intramolecule C(sp^3)-H amidation is unsaturated because of the use of a low polar solvent.

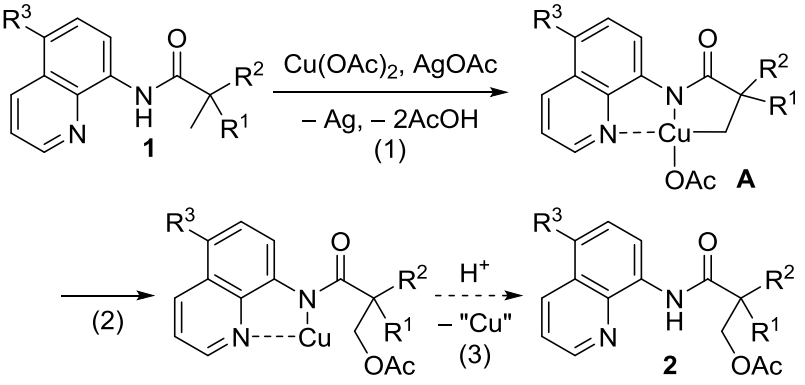
Table 3-2. Investigation of Substrate Scope



entry	**2**	Yield (%)	**3**	Yield (%)
				
1	R^1 = Me	**2b** 39		**3b** 38
2	$^nC_3H_7$	**2d** 55		**3c** 23
3	$(CH_2)_2Ph$	**2d** 55		**3d** 21
4	CH_2OCH_2Ph	**2e** 54		**3e** 22
5	CF_3	**2f** 73		**3f** <1
6		**2g** 51		**3g** 18
				
7	X = OMe	**2h** 67		**3h** <1
8	Me	**2i** 71		**3i** <1
9	H	**2j** 74		**3j** <1
10	Br	**2k** 62		**3k** <1
11	Cl	**2l** 78		**3l** <1
12	F	**2m** 81		**3m**<1
13	CF_3	**2n** 83		**3n** <1
				
14	R^1 = $(CH_2)_2Ph$	**2o** 78		
15	CH_2Ph	**2p** 86		
16		**2q** 87		
17		**2r** 79		
18		**2s** 68		

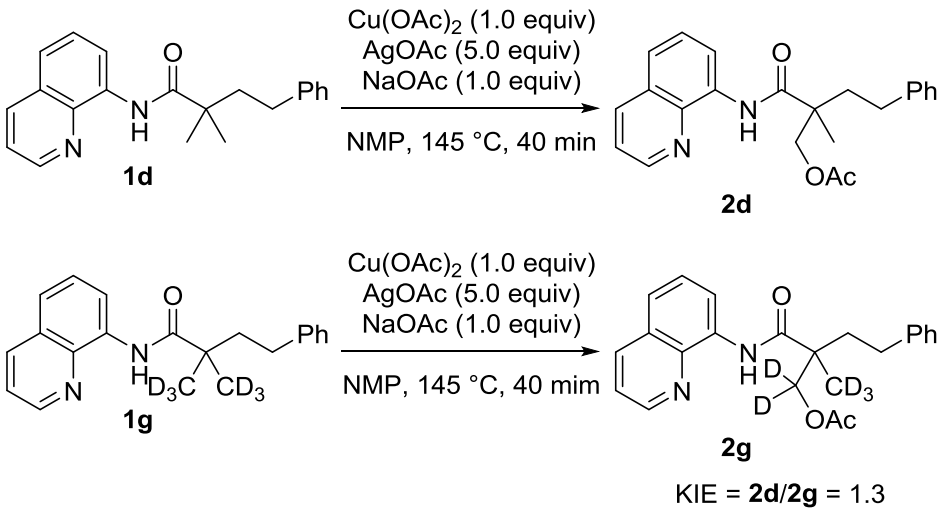
Based on the researches on copper–catalyzed intramolecular amidation(**project 2**) and copper–mediated acetoxylation, the proposed mechanism for the C(sp^3)–H acetoxylation is as follows (Scheme 3-1): (1) formation of a metallacyclic intermediate by the reaction of amide 1 with $Cu(OAc)_2$ and AgOAc via the elimination of 2 equivalents of acetic acid via a concerted metalation–deprotonation pathway (including C(sp^3)–H bond activation); (2) reductive elimination; and (3) protonation of the formed amide–copper intermediate to give the acetoxylated product.

Scheme 3-1. Proposed mechanism for C(sp^3)-H acetoxylation.

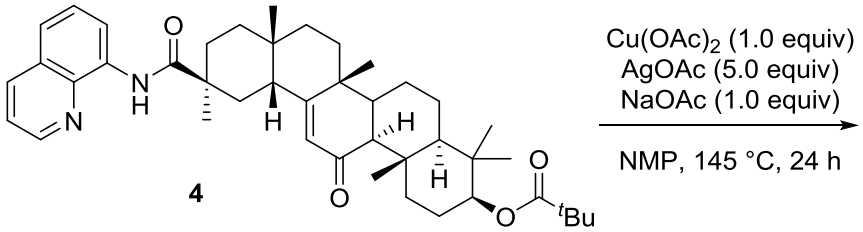


I then performed kinetic isotope experiments to elucidate the rate–determining step of the C(sp^3)–H acetoxylation (Scheme 3-2). Treatment of amide **1d** or its deuterated substrate **1g** with a mixture of $Cu(OAc)_2$, AgOAc, and NaOAc in NMP at 145 ℃. Based on these results, the kinetic isotope effect value was calculated to be 1.3, suggesting that C(sp^3)–H bond activation was not involved in the rate–determining step of the acetoxylation. This is sharply different with the copper–catalyzed C(sp^3)–H amidation, in which C(sp^3)–H bond activation is the rate–determine step. Two possible reasons were considered: the first one is that copper(III) was stablized by a high polar solvent; and the second one is that positive copper(III) cation forms a stronger copper–oxygen bond rather than copper–nitrogen bond, which caused the reductive elimination slower and became the reductive elimination the rate–determine step.

Scheme 3-2. Kinetic isotope experiments.



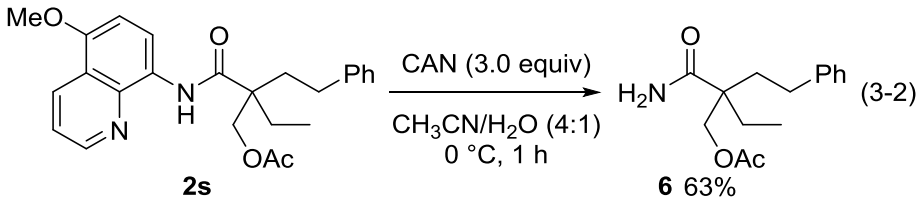
The acetoxylation also proceeded in excellent yield without the formation of regioisomers and loss the functional groups when a more complex molecule **4** was used as a substrate (Scheme 3-3). This finding suggests that the C(sp^3)–H acetoxylation is applicable to late–stage functionalization of complex molecules. The acetoxylation also proceeded in excellent yield without decreasing the yield of the product even in gram–scale (eq 3-1). By the reaction of amide **4** with a mixture of $Cu(OAc)_2$, AgOAc, and NaOAc, 1.10 g of acetoxylated product **5** was obtained in 53% yield. The yield of **5** on a large scale was comparable to that of **5** (42.9 mg, 58%) on a small scale.



4 → **5** (3-1)

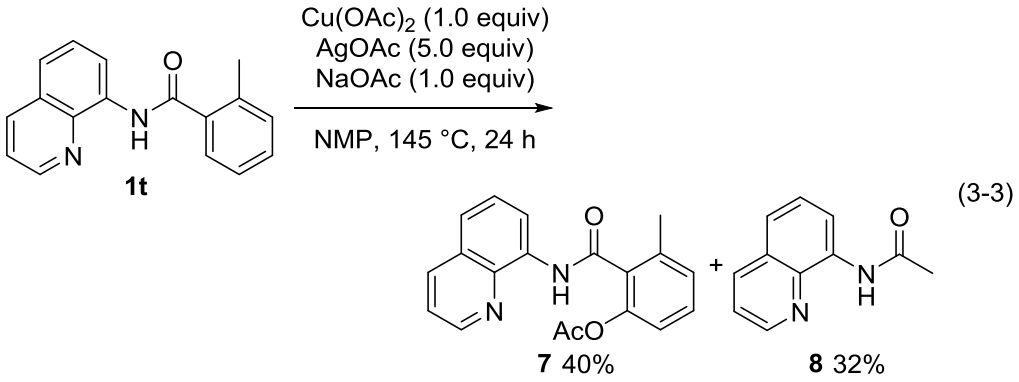
4	**5**	Yield (%)
66.7 mg	42.9 mg	58
1.92 g	1.10 g	53

When 5–methoxyquinolyl group was used as the directing group, the acetoxylation reaction proceeded well. The directing group could be removed by oxidation (eq 3-2).[23] Treatment of the acetoxylated product 2s with ceric ammonium nitrate afforded the deprotected compound 6 in 63% yield without the loss of an acetoxy group.



2s → **6** 63% (3-2)

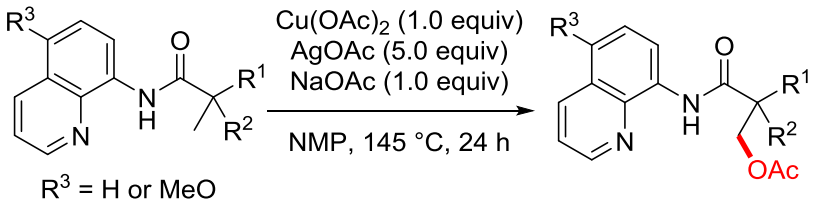
Acetoxylation also proceeded at an aromatic C(sp^2)–H bond. Treatment of aromatic amide 1t with a mixture of $Cu(OAc)_2$, AgOAc, and NaOAc in NMP at 145 ℃ for 24 h gave an ortho–acetoxylated product **7** and amide **8** in 40% and 32% yield, respectively (eq 3-3).[24–26]



(3-3)

3.4. Summary

In conclusion, a copper–mediated intermolecular C(sp^3)–H acetoxylation was realized (Figure 3-2). The reaction was difficult to be promoted by a catalytic amount of a copper salt. The main reason is that the products are tri– or tetra–dentate compounds, which can strongly coordinate to a small copper metal rather than bidentate starting materials. Because the reaction proceeded at the methyl site rather than a competitive benzylic and methylene sites, the steric effect played a very important role in this reaction rather than the electronic effect. The product distribution of this reaction was different from the copper-catalyzed intramolecular C(sp^3)-H amidation (Chapter 2), which mainly attributed to the polarity of the solvent, since the acetoxylation reaction, copper center is saturated, whereas copper center is unsaturated in amidation reaction. This reaction has high functional group tolerance, and the reaction proceeded in excellent yield, even in gram–scale. The directing group can be removed by oxidation when using a 5–methoxyquinolyl group as a directing group. This acetoxylation can be applied to a complex molecule, which will lead to late–stage functionalization. Deuterium labeling experiments suggested that the C(sp^3)–H bond activation step is not the rate–determining step, which is also different from copper–catalyzed intramolecular amaidation. Aromatic C(sp^2)–H acetoxylation also proceeded under similar reaction conditions. I believe that this reaction will provide useful insights into C–H bond transformations. For the detailed mechanism research is ongoing in our lab.



First Example of First Row Transition Metal-Catalyzed/Mediated C(sp^3)-H Acetoxylation

The reaction absolutely proceeded at methyl group.

Figure 3-2. Summary

3.5. References and Notes

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(20) Only a trace amount of 2a was formed without adding AgOAc. In addition, the desired reaction did not proceed in the absence of $Cu(OAc)_2$.

(21) N–(8–quinolinyl)isobutyramide (amide with a secondary alkyl group) did not give the desired acetoxylated product, and amide 8 (for the structure, see Scheme 5) was obtained in 21% yield.

(22) He, G.; Zhang, S.–Y.; Nack, W. A.; Li, Q.; and Chen, G. *Angew. Chem. Int. Ed*. **2013**, *52*, 11124. See also, ref. 10a.

(23) (a) Kalyani, D.; and Sanford, M. S. *Org. Lett.* **2005**, *7*, 4149; (b) Desai, L. V.; Malik. H. A.;

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(24) The mechanism for the formation of amide 8 is not clear yet.

(25) In the case when 2–methyl–2–phenyl–N–(8–quinolinyl)propanamide was used as a substrate, intramolecular C(sp^2)–H amidation proceeded and the corresponding 2–indolinone derivative was obtained in 61% yield. See, ref. 5.

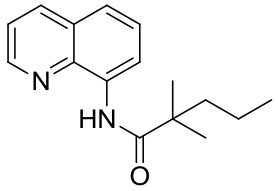
3.6. Experimental

General. All reactions were carried out in a dry solvent under argon atmosphere unless otherwise noted. $Cu(OAc)_2$ (99.999%) and AgOAc (≥99.0%) were purchased from Aldrich. Sodium acetate, *N*–methyl–2–pyrrolidone, and THF were purchased from Wako Pure Chemical Industries, and THF was dried and degassed before use. Lithium diisopropylamide (LDA) was purchased from Aldrich. NMR spectra were recorded on JEOL ECS400 (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometer. Proton chemical shifts are reported relative to residual solvent peaks ($CDCl_3$ at 7.26 ppm, acetone–d_6 at 2.09 ppm). Carbon chemical shifts are reported relative to residual solvent peaks ($CDCl_3$ at 77.3 ppm, acetone–d_6 at 206 and 30.6 ppm). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad. IR spectra were recorded on a JASCO FT/IR–410. High–resolution mass spectra (HRMS) were measured on a JEOL JMS–T100LC AccuTOF spectrometer (for HRMS).

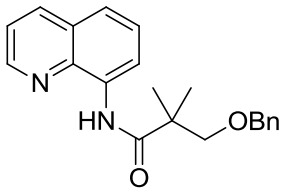
The spectra of amides **1a**, **1b**, **1d**, **1f**, **1g**, **1h**, **1i**, **1j**, **1k**, **1l**, **1m**, **1n**, **1o**, **1p**, **1r**, and **1s**, and 3,3–dimethyl–1–(8–quinolinyl)–2–indolinone (ref. 26) were determined by comparison with the reported data.[1]

Preparation of amide 1c (1e was also prepared using this mehod). To a solution of 2,2–dimethylpentanoic acid (0.969 g, 11.0 mmol) in THF (20 mL), $SOCl_2$ (1.57 g, 13.2 mmol) was added dropwise. After stirring at 25 ℃ for 1 h, the reaction mixture was concentrated in vacuo to

give an acid chloride, which was used without purification. To a solution of the prepared acid chloride in dichloromethane (20 mL), a solution of 8–aminoquinoline (1.44 g, 10.0 mmol) and Et_3N (1.01 g, 11.0 mmol) in dichloromethane (10 mL) was added dropwise within 30 min. The resulting mixture was stirred at 25 ℃ for 30 min, was quenched with saturated aq. $NaHCO_3$ (30 mL), and was extracted with dichloromethane (3 x 100 mL). The organic layer was dried over Na_2SO_4. After filtration and evaporation, the obtained amide was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1).



2,2–Dimethyl–*N*–(8–quinolinyl)pentanamide (1c). 2.68 g, 92% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.25 (s, 1H), 8.97 – 8.61 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.78 – 7.36 (m, 3H), 1.95 – 1.64 (m, 2H), 1.40 (s, 6H), 1.35 (m, 2H), 0.92 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.0, 148.4, 139.0, 136.5, 134.9, 128.2, 127.7, 121.7, 121.4, 116.4, 44.2, 44.1, 25.9, 18.5, 14.9; IR (KBr, ν/cm^{-1}) 3366, 2959, 2871, 1687, 1527, 1487, 1423, 1384, 1326, 1260, 1155, 1056, 929, 826, 792, 756, 681; HRMS (ESI$^+$) Calcd for $C_{16}H_{20}N_2O$ (M+Na$^+$) 279.1468, Found 279.1459.



3–(Benzyloxy)–2,2–dimethyl–*N*–(8–quinolinyl)propanamide (1e). 1.98 g, 93% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.05 (s, 1H), 8.83 (dt, *J* = 7.6, 1.3 Hz, 1H), 8.50 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.09 (dd, *J* = 8.3, 1.6 Hz, 4H), 7.55 – 7.40 (m, 4H), 7.38 – 7.23 (m, 1H), 4.73 (s, 2H), 3.62 (s, 2H), 1.39 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.9, 148.3, 139.2, 138.4, 136.3, 135.6, 128.5, 128.1, 127.7, 127.62, 127.59, 121.6, 121.4, 116.8, 77.0, 73.7, 44.6, 23.5; IR (KBr, ν/cm^{-1}) 3420, 2966, 2867, 1672, 1527, 1488, 1457, 1423, 1385, 1326, 1260, 1155, 1096, 1029, 923, 825, 792, 737, 697; HRMS (ESI$^+$) Calcd for $C_{21}H_{22}N_2O_2$ (M+Na$^+$) 357.1573, Found 357.1565.

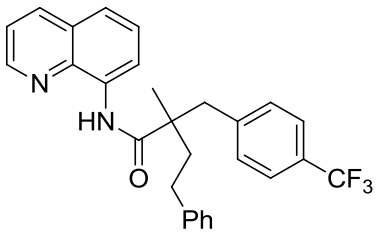
Preparation of amide 1q. To a solution of methyl 4–phenylbutanoate (5.35 g, 30.0 mmol) in THF (100 mL), a THF solution of lithium diisopropylamide (1.5 M, 21.0 mL, 31.5 mmol) was added at –78 ℃ dropwise. The mixture was stirred at –78 ℃ for 1 h, and 1–(bromomethyl)–4–(trifluoromethyl)benzene (7.89 g, 33.0 mmol) was added to the solution. The mixture was warmed to 25 ℃, and was stirred for 16 h. The reaction mixture was quenched with saturated aq.

$NaHCO_3$ (100 mL) at 0 ℃, and was extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give methyl 4–phenyl–2–(4–(trifluoromethyl)benzyl)butanoate.

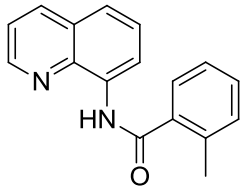
To a solution of the ester in THF (100 mL), a THF solution of lithium diisopropylamide (1.5 M, 21.0 mL, 31.5 mmol) was added at –78 ℃ dropwise. The mixture was stirred at –78 ℃ for 1 h, and the iodomethane (4.68 g, 33.0 mmol) was added to the solution. The mixture was warmed to 25 ℃, and was stirred for 16 h. The reaction mixture was quenched with saturated aq. $NaHCO_3$ (100 mL) at 0 ℃, and was extracted with ethyl acetate (3 x 100 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give methyl 2–methyl–4–phenyl–2–(4–(trifluoromethyl)benzyl)butanoate.

To a solution of 8–aminoquinoline (9.52 g, 66.0 mmol) in THF (200 mL), a hexane solution of *n*–BuLi (1.6 M, 41.3 mL, 66.0 mmol) was added dropwise at –78 ℃. The mixture was warmed to 25 ℃ and stirred for 1 h. The reaction mixture was added to a solution of the prepared ester in THF at –78 ℃, and the mixture was warmed to 25 ℃ and stirred for 12 h. After quenching with saturated aq. $NaHCO_3$ (150 mL) at 0 ℃, the mixture was extracted with ethyl acetate (3 x 150 mL). The combined organic layer was washed with brine, dried over $MgSO_4$, and evaporated in vacuo to give an amide, which was purified by column chromatography on silica gel (hexane/ethyl acetate = 10:1).

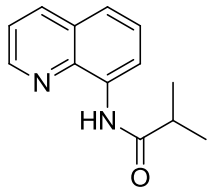
2–Methyl–4–phenyl–*N*–(8–quinolinyl)–2–(4–(trifluoromethyl)benzyl)butanamide (1q). 11.2 g, 81% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.08 (s, 1H), 8.75 (dd, *J* = 7.5, 1.3 Hz, 1H), 8.64 (dd, *J* = 4.2, 1.5 Hz, 1H), 8.06 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.54 – 7.29 (m, 5H), 7.24 – 7.04 (m, 7H), 3.28 (d, *J* = 13.2 Hz, 1H), 2.79 (d, *J* = 13.2 Hz, 1H), 2.63 (m, 2H), 2.35 – 2.16 (m, 1H), 1.85 – 1.70 (m, 1H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.5, 148.5, 142.1, 141.9, 138.9, 136.5, 134.3, 130.8, 129.3 (q, *J* = 32.4 Hz), 128.8, 128.7, 128.6, 128.1, 127.6, 126.2, 125.2 (q, *J* = 3.7 Hz), 124.4 (q, *J* = 276 Hz), 121.9, 116.6, 49.0, 46.6, 42.8, 31.5, 21.0; HRMS (ESI^+) Calcd for $C_{28}H_{25}F_3N_2O$ ($M+Na^+$) 485.1811, Found 485.1816.



Preparation of amide 1t. To a solution of 2–methylbenzoyl chloride (11.0 mmol) in dichloromethane (40 mL), a solution of 8–aminoquinoline (1.44 g, 10.0 mmol) and NEt_3 (1.01 g, 11.0 mmol) in dichloromethane (10 mL) was added dropwise within 30min. After stirring at 25 ℃ for 30 min, the mixture was quenched with saturated aq. $NaHCO_3$ (50 mL), and was extracted with dichloromethane (3 x 50 mL). The organic layer was dried over Na_2SO_4. After filtration and evaporation, an amide was purified by column chromatography on silica gel (hexane/ethyl acetate = 9:1).



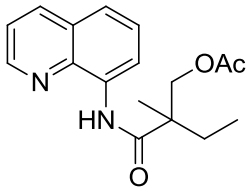
2–Methyl–*N*–(8–quinolinyl)benzamide (1t). 3.01 g, 96% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1H), 8.96 (d, *J* = 7.5 Hz, 1H), 8.88 – 8.63 (m, 1H), 8.17 (d, *J* = 7.0 Hz, 1H), 7.70 (d, *J* = 7.5 Hz, 1H), 7.57 (m, 2H), 7.48 – 7.37 (m, 2H), 7.33 (m, 2H), 2.62 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4, 148.5, 138.8, 136.9, 136.8, 136.6, 134.9, 131.6, 130.5, 128.2, 127.6, 127.5, 126.2, 122.0, 121.9, 116.7, 20.4; IR (KBr, ν/cm^{-1}) 3350, 3049, 3008, 2979, 2861, 1674, 1597, 1576, 1524, 1386, 1327, 1288, 1262, 1232, 1141, 1106, 1072, 1040, 899, 825, 791, 739, 683, 691; HRMS (ESI^+) Calcd for $C_{17}H_{14}N_2O$ (M+Na^+) 285.0998, Found 285.1011.



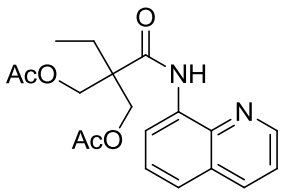
***N*–(8–Quinolinyl)isobutyramide.** Prepared by the same method as **1t** with using isobutyroyl chloride. 2.94 g, 98% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.90 (s, 1H), 8.81–8.65 (m, 2H), 8.15 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.64 – 7.32 (m, 3H), 2.99 – 2.51 (septet, *J* = 7.1 Hz, 1H), 1.35 (d, *J* = 7.1 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.0, 148.3, 138.7, 136.6, 134.9, 128.2, 127.7, 121.8, 121.5, 116.6, 37.4, 20.0; IR (KBr, ν/cm^{-1}) 3357, 2969, 2881, 1684, 1524, 1487, 1458, 1423, 1387, 1323, 1239, 1191, 1156, 937, 826, 791, 756, 687; HRMS (ESI^+) Calcd for $C_{13}H_{14}N_2O$ (M+Na^+) 237.0998, Found 237.0988.

Typical procedure for copper–mediated intermolecular C(sp^3)–H acetoxylation. A reaction tube was covered with aluminum foil, and a mixture of 2,2–dimethyl–*N*–(8–quinolinyl)butanamide (**1a**, 24.2 mg, 0.100 mmol), $Cu(OAc)_2$ (18.2 mg, 0.100 mmol), NaOAc (8.20 mg, 0.100 mmol), AgOAc (83.5 mg, 0.500 mmol), and *N*–methyl–2–pyrrolidone (1.0 mL) was stirred at 145 ℃ for 24 h under argon atmosphere. Then, the reaction mixture was cooled to

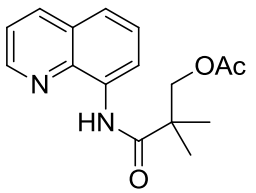
room temperature, and water (10 mL) was added to the reaction tube. The mixture was extracted with ethyl acetate (3 x 15 mL), and the organic phase was dried over Na_2SO_4 and was concentrated in vacuo. Then the mixture was subjected to column chromatography on silica gel (hexane/ethyl acetate = 3:1) to give the desired products (**2a**, 13.8 mg, 46%; **3a**, 11.5 mg, 32%).



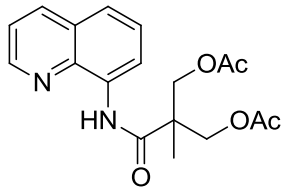
2–Methyl–2–(8–quinolinylcarbamoyl)butyl acetate (2a). 13.8 mg, 46% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.42 (s, 1H), 8.84 – 8.67 (m, 2H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.50 (m, 3H), 4.36 (d, *J* = 11.1 Hz, 1H), 4.21 (d, *J* = 11.1 Hz, 1H), 2.14 (s, 3H), 1.92 (dt, *J* = 14.8, 7.5 Hz, 1H), 1.70 (dt, *J* = 14.8, 7.5 Hz, 1H), 1.41 (s, 3H), 0.98 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.8, 171.1, 148.4, 139.0, 136.6, 134.8, 128.2, 127.7, 121.8, 121.7, 116.8, 69.4, 47.6, 29.6, 21.2, 19.5, 8.8; IR (KBr, ν/cm^{-1}) 3358, 2969, 2881, 1747, 1677, 1596, 1532, 1487, 1425, 1382, 1324, 1235, 1152, 1038, 986, 935, 906, 827, 791, 756, 691; HRMS (ESI$^+$) Calcd for $C_{17}H_{20}N_2NaO_3$ (M+Na$^+$) 323.1366, Found 323.1368.



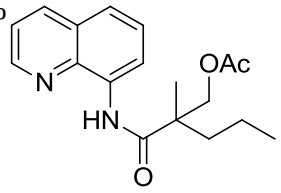
2–Ethyl–2–(8–quinolinylcarbamoyl)propane–1,3–diyl diacetate (3a). 11.5 mg, 32% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.93 – 8.67 (m, 2H), 8.18 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.50 (m, 3H), 4.49 (d, *J* = 11.8 Hz, 2H), 4.42 (d, *J* = 11.8 Hz, 2H), 2.16 (s, 6H), 1.91 (q, *J* = 7.5 Hz, 2H), 1.00 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, acetone–d_6) δ 172.1, 171.5, 150.4, 140.1, 138.3, 136.4, 129.8, 128.8, 123.7, 123.4, 117.9, 66.0, 51.9, 26.3, 21.6, 9.4; IR (KBr, ν/cm^{-1}) 3445, 2971, 2881, 1748, 1678, 1534, 1488, 1425, 1382, 1325, 1233, 1156, 1043, 903, 827, 793, 759, 712; HRMS (ESI$^+$) Calcd for $C_{19}H_{22}N_2O_5$ (M+Na$^+$) 381.1421, Found 381.1419.



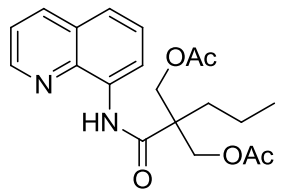
2,2–Dimethyl–3–oxo–3–(8–quinolinylamino)propyl acetate (2b). 11.2 mg, 39% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.93 – 8.69 (m, 2H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.69 – 7.36 (m, 3H), 4.26 (s, 2H), 2.15 (s, 3H), 1.44 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 171.1, 148.4, 139.0, 136.6, 134.9, 128.2, 127.7, 121.84, 121.79, 116.8, 70.6, 43.9, 23.1, 21.2; IR (KBr, ν/cm^{-1}) 3428, 2968, 2881, 1747, 1646, 1530, 1488, 1424, 1375, 1326, 1235, 1155, 1039, 826, 793, 698; HRMS (ESI$^+$) Calcd for $C_{16}H_{18}N_2O_3$ (M+Na$^+$) 309.1210, Found 309.1204.



2–Methyl–2–(8–quinolinylcarbamoyl)propane–1,3–diyl diacetate (3b). 13.1 mg, 38% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.60 (s, 1H), 8.93 – 8.67 (m, 2H), 8.18 (dt, *J* = 8.1, 1.6 Hz, 1H), 7.67 – 7.39 (m, 3H), 4.40 (s, 4H), 2.16 (s, 6H), 1.46 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.8, 148.4, 139.0, 136.7, 134.7, 128.2, 127.7, 122.1, 121.9, 117.1, 67.0, 47.3, 21.1, 18.5; IR (KBr, ν/cm^{-1}) 3444, 2968, 2861, 1748, 1683, 1654, 1532, 1489, 1424, 1375, 1327, 1235, 1040, 826, 793, 756; HRMS (ESI$^+$) Calcd for $C_{18}H_{20}N_2O_5$ (M+Na$^+$) 367.1264, Found 367.1280.

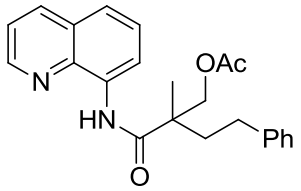


2–Methyl–2–(8–quinolinylcarbamoyl)pentyl acetate (2c). 17.3 mg, 55% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.43 (s, 1H), 8.81 (dd, *J* = 4.3, 1.5 Hz, 2H), 8.17 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.60 – 7.42 (m, 3H), 4.36 (d, *J* = 11.1 Hz, 1H), 4.20 (d, *J* = 11.1 Hz, 1H), 2.14 (s, 3H), 1.95 – 1.75 (m, 1H), 1.67 – 1.57 (m, 2H), 1.43 (s, 3H), 1.41 – 1.25 (m, 1H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 171.1, 148.4, 139.0, 136.6, 134.8, 128.2, 127.7, 121.8, 121.7, 116.7, 69.8, 47.4, 39.3, 21.2, 20.0, 17.8, 14.8; IR (KBr, ν/cm^{-1}) 3427, 2960, 2872, 1746, 1677, 1653, 1577, 1530, 1487, 1424, 1375, 1324, 1233, 1153, 1036, 927, 826, 792, 758, 688; HRMS (ESI$^+$) Calcd for $C_{18}H_{22}N_2O_3$ (M+Na$^+$) 337.1523, Found 337.1513.



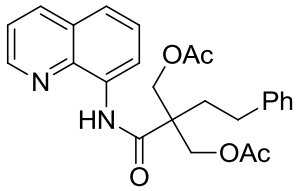
2–Propyl–2–(8–quinolinylcarbamoyl)propane–1,3–diyl diacetate (3c). 8.57 mg, 23% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.56 (s, 1H), 8.79 (dd, *J* = 6.0, 1.9 Hz, 2H), 8.18 (dd, *J* = 8.3, 1.5 Hz, 1H), 7.65 – 7.41 (m, 3H), 4.49 (d, *J* = 11.4 Hz, 2H), 4.41 (d, *J* = 11.4 Hz, 2H), 2.17 (s, 6H), 1.80 (dd, *J* = 10.6, 6.3 Hz, 2H), 1.47 – 1.34 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.0, 170.9, 148.4, 139.0, 136.7, 134.7, 128.2, 127.7, 122.0, 121.9, 117.1, 65.4, 50.4, 34.8, 21.2, 17.5, 14.8; IR (KBr,ν/cm^{-1}) 3420, 2961, 2851, 1747, 1682, 1654, 1532, 1488, 1425, 1381, 1326, 1230, 1148, 1048, 827, 793, 759; HRMS (ESI$^+$) Calcd for $C_{20}H_{24}N_2O_5$ (M+Na$^+$) 395.1577, Found 395.1561.

2–Methyl–4–phenyl–2–(8–quinolinylcarbamoyl)butyl acetate (2d).



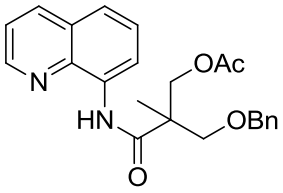
20.70 mg, 55% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.51 (s, 1H), 8.91 – 8.75 (m, 2H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.64 – 7.38 (m, 3H), 7.36 – 7.07 (m, 5H), 4.41 (d, *J* = 11.2 Hz, 1H), 4.28 (d, *J* = 11.2 Hz, 1H), 2.90 – 2.57 (m, 2H), 2.26 – 2.17 (m, 1H), 2.16 (s, 3H), 1.96 (m, 1H), 1.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 171.0, 148.4, 141.9, 139.0, 136.7, 134.7, 128.8, 128.7, 128.6, 128.2, 127.7, 126.2, 121.9, 116.9, 69.6, 47.4, 39.1, 31.0, 21.2, 20.2; IR (KBr, ν/cm–1) 3444, 3031, 2973, 2871, 1746, 1677, 1530, 1488, 1424, 1375, 1326, 1235, 1165, 1040, 924, 826, 793, 755, 700; HRMS (ESI$^+$) Calcd for $C_{23}H_{24}N_2O_3$ (M+Na$^+$) 399.1679, Found 399.1672.

2–Phenethyl–2–(8–quinolinylcarbamoyl)propane–1,3–diyl diacetate (3d).

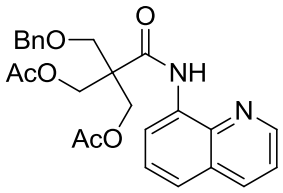


9.1 mg, 21% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.64 (s, 1H), 8.87 – 8.72 (m, 2H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.64 – 7.51 (m, 2H), 7.48 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.29 – 7.22 (m, 3H), 7.18 (d, *J* = 7.1 Hz, 2H), 4.55 (d, *J* = 11.6 Hz, 2H), 4.49 (d, *J* = 11.6 Hz, 2H), 2.71 (dd, *J* = 8.0, 4.7 Hz, 2H), 2.18 (s, 6H), 2.15 (dd, *J* = 8.0, 4.7 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 170.5, 148.4, 141.5, 139.0, 136.7, 134.6, 128.7, 128.6, 128.3, 127.7, 126.4, 122.2, 122.0, 117.2, 65.2, 50.4, 34.7, 30.6, 21.2; IR (KBr, ν/cm^{-1}) 3445, 2987, 2871, 1741, 1651, 1531, 1488, 1383, 1339, 1238, 1210, 1109, 1040, 826, 792, 756, 701; HRMS (ESI$^+$) Calcd for $C_{25}H_{26}N_2O_5$ (M+Na$^+$) 457.1734, Found 457.1738.

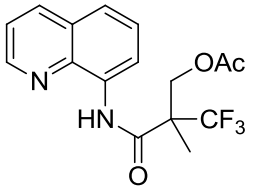
2–((Benzyloxy)methyl)–2–methyl–3–oxo–3–(8–quinolinylamino)propyl acetate (2e).



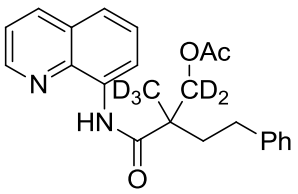
21.6 mg, 54% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.12 (s, 1H), 8.82 (dd, *J* = 7.2, 1.8 Hz, 1H), 8.53 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.57 – 7.47 (m, 2H), 7.45 – 7.37 (m, 3H), 7.36 – 7.28 (m, 3H), 4.76 (d, *J* = 12.2 Hz, 1H), 4.72 (d, *J* = 12.2 Hz, 1H), 4.47 (d, *J* = 11.1 Hz, 1H), 4.37 (d, *J* = 11.1 Hz, 1H), 3.83 (d, *J* = 9.4 Hz, 1H), 3.72 (d, *J* = 9.4 Hz, 1H), 2.07 (s, 3H), 1.42 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 171.0, 148.4, 139.2, 138.0, 136.4, 135.3, 128.6, 128.2, 127.9, 127.8, 127.6, 121.8, 121.7, 117.1, 73.9, 73.2, 67.7, 48.1, 21.2, 18.7; IR (KBr, ν/cm^{-1}) 3421, 2969, 2881, 1743, 1676, 1531, 1488, 1424, 1383, 1326, 1238, 1094, 1039, 826, 793, 738, 698; HRMS (ESI$^+$) Calcd for $C_{23}H_{24}N_2O_4$ (M+Na$^+$) 415.1628, Found 415.1633.



2–((Benzyloxy)methyl)–2–(8–quinolinylcarbamoyl)propane–1,3–diyl diacetate (3e). 9.9 mg, 22% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.15 (s, 1H), 8.79 (dd, *J* = 6.3, 2.7 Hz, 1H), 8.55 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 1H), 8.15 (dd, *J* = 8.2, 1.6 Hz, 2H), 7.58 – 7.50 (m, 3H), 7.35 (m, 3H), 4.71 (s, 2H), 4.58 (d, *J* = 11.4 Hz, 2H), 4.51 (d, *J* = 11.4 Hz, 2H), 3.88 (s, 2H), 2.07 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.8, 169.5, 148.4, 139.1, 137.7, 136.5, 135.0, 128.6, 128.2, 128.0, 127.9, 127.6, 122.1, 121.8, 117.3, 74.0, 69.4, 64.3, 51.5, 21.0; IR (KBr, ν/cm^{-1}) 3429, 2969, 1743, 1638, 1534, 1488, 1456, 1425, 1379, 1326, 1231, 1094, 1041, 887, 827, 698, 634; HRMS (ESI$^+$) Calcd for $C_{25}H_{26}N_2O_6$ (M+Na$^+$) 473.1683, Found 473.1678.

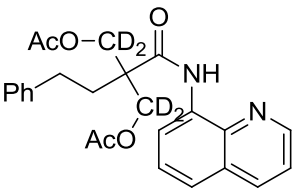


3,3,3–Trifluoro–2–methyl–2–(8–quinolinylcarbamoyl)propyl acetate (2f). 24.8 mg, 73% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.7 (s, 1H), 8.85 – 8.71 (m, 2H), 8.19 (dd, *J* = 8.2, 1.4 Hz, 1H), 7.61 – 7.43 (m, 3H), 4.68 (d, *J* = 11.6 Hz, 1H), 4.46 (d, *J* = 11.6 Hz, 1H), 2.17 (s, 3H), 1.66 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.4, 164.8, 148.7, 138.9, 136.64, 136.60 (q, *J* = 282 Hz), 134.2, 128.2, 127.6, 122.7, 122.1, 117.3, 64.3, 53.3 (q, *J* = 24.8 Hz), 21.0, 15.7; IR (KBr, ν/cm^{-1}) 3434, 2969, 1756, 1685, 1647, 1540, 1489, 1427, 1379, 1328, 1231, 1152, 1120, 1047, 902, 827, 792, 757, 670; HRMS (ESI$^+$) Calcd for $C_{16}H_{15}F_3N_2O_3$ (M+Na$^+$) 363.0927, Found 363.0938.

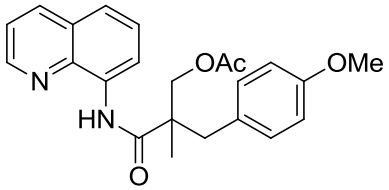


2–Methyl–4–phenyl–2–(8–quinolinylcarbamoyl)butyl acetate–*d*$_5$ (2g). 19.5 mg, 51% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.50 (s, 1H), 8.90 – 8.77 (m, 2H), 8.23 – 8.15 (m, 1H), 7.61 – 7.42 (m, 3H), 7.34 – 7.12 (m, 5H), 2.80 – 2.56 (m, 2H), 2.22 (m, 1H), 2.16 (s, 3H), 2.01 – 1.90 (m, 1H); ^{13}C NMR (100 MHz, acetone–d_6) δ 174.4, 171.6, 150.4, 143.7, 140.2, 138.3, 136.5, 130.0, 129.9, 129.8, 128.8, 127.4, 123.7, 123.2, 117.7, 48.4, 40.3, 32.1, 21.6 [signals of CD_3 and CD_2 groups could not be observed. These signals are supposed to be septet and quintet, respectively, and therefore, they are too weak to observe in ^{13}C NMR.]; IR (KBr, ν/cm^{-1}) 3446, 1748, 1717, 1683, 1526, 1508, 1488, 1457, 1373, 1326, 1259, 827, 791, 699; HRMS (ESI$^+$) Calcd for $C_{23}H_{19}D_5N_2O_3$ (M+Na$^+$) 404.1993, Found 404.1974.

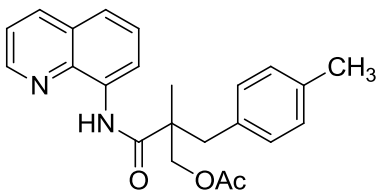
2–Phenethyl–2–(8–quinolinylcarbamoyl)propane–1,3–diyl diacetate–d_4 (3g). 7.89 mg, 18% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.63 (s, 1H), 8.88 – 8.67 (m, 2H), 8.20 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.60 – 7.44 (m, 3H), 7.28 – 7.22 (m, 3H), 7.20 – 7.13 (m, 2H), 2.86 – 2.66 (m, 2H), 2.18 (s, 6H), 2.17 – 2.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 170.5, 148.4, 141.5, 139.0, 136.7, 134.6, 128.7, 128.6, 128.3, 127.7, 126.4, 122.2, 122.0, 117.2, 50.1, 34.6, 30.6, 21.2 [A signal of CD_2 groups could not be observed. This is supposed to be quintet, which is too weak to observe in ^{13}C NMR.]; IR (KBr, ν /cm^{-1}) 3441, 2972, 1742, 1637, 1533, 1488, 1424, 1371, 1326, 1256, 1084, 1034, 899, 827, 791, 756, 691; HRMS (ESI$^+$) Calcd for $C_{25}H_{22}D_4N_2O_5$ (M+Na$^+$) 461.1985, Found 461.2000.



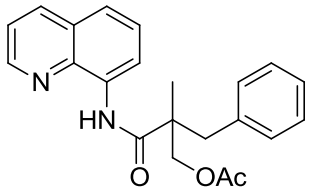
2–(4–Methoxybenzyl)–2–methyl–3–oxo–3–(8–quinolinylamino)propyl acetate (2h). 26.3 mg, 67% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.37 (s, 1H), 8.92 – 8.68 (m, 2H), 8.17 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.40 (m, 3H), 7.09 (d, *J* = 6.7 Hz, 2H), 6.74 (d, *J* = 6.7 Hz, 2H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.22 (d, *J* = 11.2 Hz, 1H), 3.71 (s, 3H), 3.13 (d, *J* = 13.4 Hz, 1H), 2.99 (d, *J* = 13.4 Hz, 1H), 2.17 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 171.0, 158.7, 148.4, 141.7, 139.0, 136.6, 134.7, 131.5, 128.4, 128.2, 127.7, 121.8, 116.9, 113.9, 69.1, 55.4, 48.4, 41.7, 21.2, 19.8; IR (KBr, ν /cm^{-1}) 3566, 2979, 1747, 1717, 1683, 1615, 1531, 1488, 1423, 1374, 1323, 1246, 1179, 1037, 827, 793, 737; HRMS (ESI$^+$) Calcd for $C_{23}H_{24}N_2O_4$ (M+Na$^+$) 415.1628, Found 415.1633.



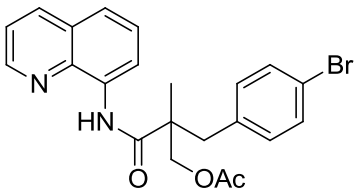
2–Methyl–2–(4–methylbenzyl)–3–oxo–3–(8–quinolinylamino)propyl acetate (2i). 26.7 mg, 71% yield, yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.95 – 8.66 (m, 2H), 8.16 (dd, *J* = 8.3, 1.6 Hz, 2H), 7.67 – 7.40 (m, 3H), 7.23 – 6.93 (m, 4H), 4.32 (d, *J* = 11.2 Hz, 1H), 4.22 (d, *J* = 11.2 Hz, 1H), 3.14 (d, *J* = 13.4 Hz, 1H), 3.02 (d, *J* = 13.4 Hz, 1H), 2.25 (s, 3H), 2.17 (s, 3H), 1.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.4, 171.0, 148.3, 139.0, 136.6, 136.5, 134.7, 133.3, 130.4, 129.2, 128.2, 127.7, 121.82, 121.79, 116.9, 69.1, 48.3,



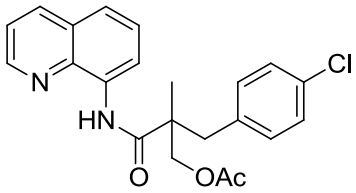
42.0, 22.3, 21.2, 19.9; IR (KBr, ν /cm^{-1}) 3432, 2965, 1747, 1717, 1531, 1487, 1424, 1374, 1324, 1231, 1167, 1038, 989, 917, 826, 792, 757, 699; HRMS (ESI^+) Calcd for $C_{23}H_{24}N_2O_3$ ($M+Na^+$) 399.1679, Found 399.1669.



2–Benzyl–2–methyl–3–oxo–3–(8–quinolinylamino)propyl acetate (2j). 26.8 mg, 74% yield, yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1H), 8.87 – 8.70 (m, 2H), 8.16 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.62 – 7.38 (m, 3H), 7.25 – 7.10 (m, 5H), 4.33 (d, *J* = 11.1 Hz, 1H), 4.24 (d, *J* = 11.1 Hz, 1H), 3.19 (d, *J* = 13.4 Hz, 1H), 3.05 (d, *J* = 13.4 Hz, 1H), 2.17 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.3, 171.0, 148.4, 139.0, 136.6, 136.5, 134.7, 132.8, 130.5, 128.5, 128.2, 127.7, 127.0, 121.8, 116.9, 69.1, 48.3, 42.5, 21.2, 19.9; IR (KBr, ν /cm^{-1}) 3444, 2970, 1747, 1647, 1532, 1488, 1424, 1375, 1325, 1231, 1038, 826, 793, 736, 702; HRMS (ESI^+) Calcd for $C_{22}H_{22}N_2O_3$ ($M+Na^+$) 385.1523, Found 385.1528.



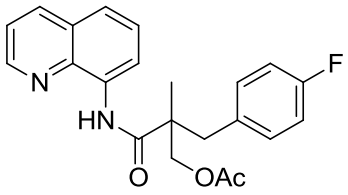
2–(4–Bromobenzyl)–2–methyl–3–oxo–3–(8–quinolinylamino)propyl acetate (2k). 27.4 mg, 62% yield, yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.86 – 8.67 (m, 2H), 8.21 – 8.11 (d, *J* = 8.3 Hz,, 1H), 7.63 – 7.40 (m, 3H), 7.31 (d, *J* = 8.3 Hz, 1H), 7.24 – 6.97 (m, 3H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.23 (d, *J* = 11.2 Hz, 1H), 3.15 (d, *J* = 13.5 Hz, 1H), 2.96 (d, *J* = 13.5 Hz, 1H), 2.17 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 170.9, 148.4, 139.0, 136.6, 132.2, 131.8, 131.6, 130.5, 128.6, 128.2, 127.7, 122.0, 121.9, 116.9, 69.1, 48.3, 41.9, 21.2, 19.9; IR (KBr, ν /cm^{-1}) 3433, 2981, 1736, 1668, 1529, 1487, 1425, 1383, 1337, 1243, 1210, 1130, 1038, 1011, 826, 792, 702; HRMS (ESI^+) Calcd for $C_{22}H_{21}BrN_2O_3$ ($M+Na^+$) 463.0628, Found 463.0619.



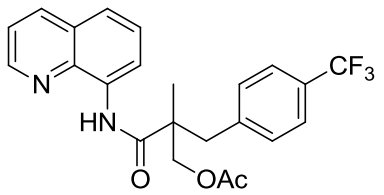
2–(4–Chlorobenzyl)–2–methyl–3–oxo–3–(8–quinolinylamino)propyl acetate (2l). 31.0 mg, 78% yield, yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.89 – 8.69 (m, 2H), 8.17 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.65 – 7.43 (m, 3H), 7.21 – 7.07 (m, 4H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.23 (d, *J* = 11.2 Hz, 1H), 3.17 (d, *J* = 13.4 Hz, 1H), 2.97 (d, *J* = 13.4 Hz, 1H),

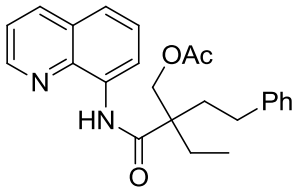
2.17 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 170.9, 148.4, 138.9, 136.6, 135.0, 134.5, 132.9, 131.8, 128.6, 128.2, 127.6, 122.0, 121.9, 116.9, 69.1, 48.3, 41.9, 21.2, 19.8; IR (KBr, ν /cm^{-1}) 3423, 2968, 1746, 1647, 1530, 1489, 1424, 1374, 1323, 1231, 1092, 1038, 1015, 826, 792, 758, 698; HRMS (ESI$^+$) Calcd for $C_{22}H_{21}ClN_2O_3$ (M+Na$^+$) 419.1133, Found 419.1122.

2–(4–Fluorobenzyl)–2–methyl–3–oxo–3–(8–quinolinylamino)propyl acetate (2m). 30.8 mg, 81% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.85 – 8.72 (m, 2H), 8.17 (d, *J* = 8.3 Hz, 1H), 7.62 – 7.50 (m, 2H), 7.45 (dd, *J* = 8.3, 4.3 Hz, 1H), 7.13 (dd, *J* = 8.0, 5.8 Hz, 2H), 6.88 (m, 2H), 4.33 (d, *J* = 11.2 Hz, 1H), 4.23 (d, *J* = 11.2 Hz, 1H), 3.17 (d, *J* = 13.5 Hz, 1H), 2.98 (d, *J* = 13.5 Hz, 1H), 2.17 (s, 3H), 1.39 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 170.9, 162.1 (d, *J* = 244 Hz), 148.4, 139.0, 136.6, 134.5, 132.2 (d, *J* = 3.0 Hz), 132.0 (d, *J* = 8.9 Hz), 128.2, 127.7, 122.0, 121.9, 116.9, 115.3 (d, *J* = 21.8 Hz), 69.1, 48.4, 41.7, 21.2, 19.8; IR (KBr, ν /cm^{-1}) 3434, 1747, 1645, 1530, 1509, 1486, 1425, 1375, 1323, 1223, 1159, 1038, 826, 791, 759; HRMS (ESI$^+$) Calcd for $C_{22}H_{21}FN_2O_3$ (M+Na$^+$) 403.1428, Found 403.1421.

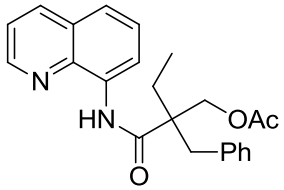


2–Methyl–3–oxo–3–(8–quinolinylamino)–2–(4–(trifluoromethyl)benzyl)propyl acetate (2n). 35.7 mg, 83% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 8.75 (m, 2H), 8.21 – 8.13 (dt, *J* = 8.0, 1.5 Hz,, 1H), 7.63 – 7.50 (m, 2H), 7.50 – 7.41 (m, 3H), 7.29 (d, *J* = 7.9 Hz, 2H), 4.35 (d, *J* = 11.2 Hz, 1H), 4.26 (d, *J* = 11.2 Hz, 1H), 3.26 (d, *J* = 13.4 Hz, 1H), 3.05 (d, *J* = 13.4 Hz, 1H), 2.17 (s, 3H), 1.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 170.9, 148.5, 140.8, 138.9, 136.6, 134.4, 130.8, 129.3 (q, *J* = 32.4 Hz), 127.6, 127.0 (q, *J* = 245 Hz), 125.4 (q, *J* = 3.7 Hz), 123.0, 122.1, 121.9, 116.9, 69.1, 48.4, 42.3, 21.2, 19.9; IR (KBr, ν /cm^{-1}) 3433, 1747, 1645, 1531, 1487, 1424, 1375, 1324, 1229, 1163, 1121, 1067, 1039, 1019, 918, 826, 791, 755, 691; HRMS (ESI$^+$) Calcd for $C_{23}H_{21}F_3N_2O_3$ (M+Na$^+$) 453.1396, Found 453.1382.

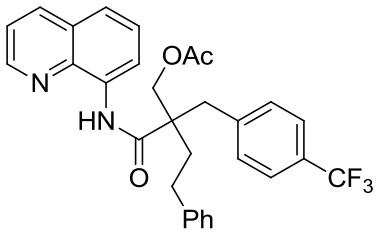


2–Ethyl–4–phenyl–2–(8–quinolinylcarbamoyl)butyl acetate (2o). 

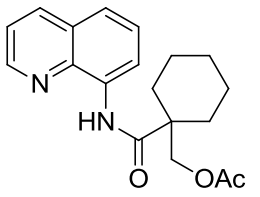
30.5 mg, 78% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.49 (s, 1H), 8.97 – 8.75 (m, 2H), 8.32 – 8.13 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.69 – 7.41 (m, 3H), 7.36 – 7.11 (m, 5H), 4.46 (s, 2H), 2.67 (dd, *J* = 9.7, 7.2 Hz, 2H), 2.19 (s, 3H), 2.13 – 2.04 (dd, *J* = 9.7, 7.2 Hz, 2H), 1.95 (q, *J* = 7.3 Hz, 2H), 1.02 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.1, 171.1, 148.4, 142.1, 139.0, 136.6, 134.7, 128.7, 128.6, 128.2, 127.7, 126.2, 121.9, 121.8, 116.9, 66.0, 50.6, 36.3, 30.8, 27.1, 21.2, 8.7; IR (KBr, ν /cm^{-1}) 3354, 2968, 2881, 1747, 1716, 1676, 1530, 1488, 1457, 1425, 1382, 1324, 1230, 1039, 826, 793, 757, 699; HRMS (ESI$^+$) Calcd for $C_{24}H_{26}N_2O_3$ (M+Na$^+$) 413.1836, Found 413.1856.

2–Benzyl–2–(8–quinolinylcarbamoyl)butyl acetate (2p). 

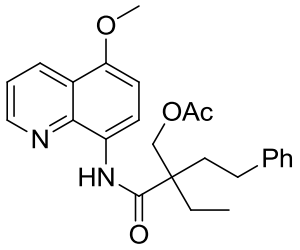
32.4 mg, 86% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.41 (s, 1H), 8.83 (dd, *J* = 7.2, 1.7 Hz, 1H), 8.76 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.17 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.59 – 7.51 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.24 – 7.13 (m, 5H), 4.35 (d, *J* = 11.6 Hz, 1H), 4.23 (d, *J* = 11.6 Hz, 1H), 3.26 (d, *J* = 13.6 Hz, 1H), 3.09 (d, *J* = 13.6 Hz, 1H), 2.20 (s, 3H), 1.89 (dt, *J* = 14.9, 7.4 Hz, 1H), 1.82 (dt, *J* = 14.9, 7.4 Hz, 1H), 1.04 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.9, 170.9, 148.4, 139.0, 136.7, 136.6, 134.7, 130.5, 128.5, 128.2, 127.7, 127.0, 121.8, 121.8, 116.9, 65.8, 51.7, 39.8, 27.0, 21.3, 8.9; IR (KBr, ν /cm^{-1}) 3444, 2967, 2863, 1745, 1645, 1531, 1488, 1457, 1424, 1384, 1324, 1229, 1035, 825, 791, 743, 701; HRMS (ESI$^+$) Calcd for $C_{23}H_{24}N_2O_3$ (M+Na$^+$) 399.1679, Found 399.1694.

4–Phenyl–2–(8–quinolinylcarbamoyl)–2–(4–(trifluoromethyl)benzyl)butyl acetate (2q). 45.3 mg, 87% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 8.81 (dd, *J* = 6.8, 2.1 Hz, 1H), 8.75 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.19 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.51 – 7.43 (m, 3H), 7.35 – 7.23 (m, 4H), 7.19 (m, 3H), 4.43 (d, *J* = 11.8 Hz, 1H), 4.37 (d, *J* = 11.8 Hz, 1H), 3.39 (d, *J* = 13.6 Hz, 1H), 3.16 (d, *J* = 13.6 Hz, 1H), 2.85 – 2.67 (m, 2H), 2.24 (s, 3H), 2.23 – 2.13 (m, 1H), 2.10 – 1.99 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.9, 170.8, 148.5, 141.6, 140.8, 139.0, 136.7, 134.4, 130.6 (q, *J* = 

36.3 Hz), 129.2, 128.8, 128.6, 128.3, 127.7, 126.4, 125.4 (q, *J* = 281 Hz), 125.2 (q, *J* = 3.7 Hz), 122.2, 122.0, 117.1, 65.6, 51.6, 40.9, 37.1, 30.9, 21.2; IR (KBr, ν/cm^{-1}) 3430, 2970, 1748, 1671, 1636, 1530, 1488, 1457, 1424, 1384, 1325, 1229, 1165, 1121, 1067, 1037, 1019, 826, 793, 754, 700; HRMS (ESI^+) Calcd for $C_{30}H_{27}F_3N_2O_3$ ($M+Na^+$) 543.1866, Found 543.1881.



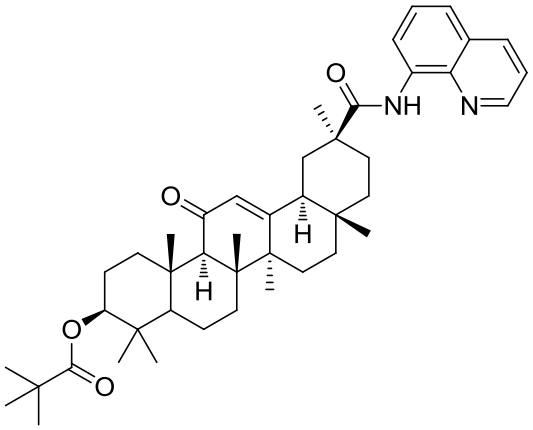
(1–(8–Quinolinylcarbamoyl)cyclohexyl)methyl acetate (2r). 25.8 mg, 79% yield, yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.45 (s, 1H), 8.89 – 8.71 (m, 2H), 8.17 (dd, *J* = 8.2, 1.7 Hz, 1H), 7.62 – 7.38 (m, 3H), 4.25 (s, 2H), 2.38 – 2.14 (m, 2H), 2.07 (s, 3H), 1.63 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.5, 171.1, 148.4, 139.0, 136.6, 134.9, 128.2, 127.7, 121.8, 121.7, 116.7, 69.7, 47.8, 31.5, 26.0, 22.6, 21.1; IR (KBr, ν/cm^{-1}) 3430, 2934, 2859, 1747, 1637, 1530, 1488, 1424, 1381, 1326, 1232, 1140, 1037, 826, 792, 757, 615; HRMS (ESI^+) Calcd for $C_{19}H_{22}N_2O_3$ ($M+Na^+$) 349.1523, Found 349.1511.



2–Ethyl–2–((5–methoxy–8–quinolinyl)carbamoyl)–4–phenylbutyl acetate (2s). 28.6 mg, 68% yield, yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.24 (s, 1H), 8.81 (dd, *J* = 4.2, 1.7 Hz, 1H), 8.75 (d, *J* = 8.5 Hz, 1H), 8.59 (dd, *J* = 8.5, 1.7 Hz, 1H), 7.46 (dd, *J* = 8.4, 4.2 Hz, 1H), 7.39 – 7.13 (m, 5H), 6.86 (d, *J* = 8.4 Hz, 1H), 4.45 (s, 2H), 4.00 (s, 3H), 2.74 – 2.62 (m, 2H), 2.18 (s, 3H), 2.12 – 2.03 (m, 2H), 1.94 (q, *J* = 7.5 Hz, 2H), 1.01 (t, *J* = 7.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.6, 171.1, 150.5, 148.9, 142.2, 139.7, 131.5, 128.6, 128.6, 128.2, 126.2, 121.0, 120.7, 117.0, 104.6, 66.1, 56.0, 50.4, 36.3, 30.8, 27.1, 21.3, 8.7; IR (KBr, ν/cm^{-1}) 3555, 3364, 2968, 2865, 1748, 1649, 1528, 1495, 1457, 1245, 1144, 989, 821, 789, 742, 671; HRMS (ESI^+) Calcd for $C_{25}H_{28}N_2O_4$ ($M+Na^+$) 443.1941, Found 443.1958.

Preparation of amide 4. To a solution of pivaloyl chloride (1.20 g, 9.97 mmol) in dichloromethane (40 mL), a solution of 18–β–glycyrrhetinic acid (2.04 g, 4.33 mmol) and NEt_3 (1.01 g, 9.97 mmol) in dichloromethane (10 mL) was added dropwise within 30min. After stirring at 25 ℃ for 30 min, the mixture was quenched with saturated aq. $NaHCO_3$ (50 mL), and was extracted with dichloromethane (3 x 50 mL). The organic layer was dried over Na_2SO_4. After filtration and evaporation, the obtained yellow compound was not purified. The compound was

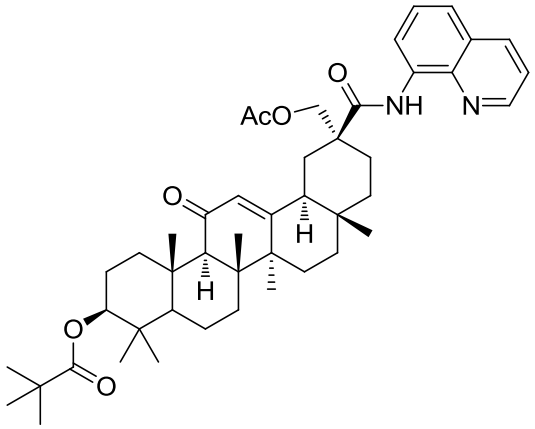
dissolved in THF (20 mL), and $SOCl_2$ (0.773 g, 6.50 mmol) was added dropwise. After stirring at 25 ℃ for 1 h, the reaction mixture was concentrated in vacuo to give an acid chloride, which was used without purification. To a solution of the prepared acid chloride in dichloromethane (20 mL), a solution of 8–aminoquinoline (0.749 g, 5.20 mmol) and Et_3N (0.526 g, 5.20 mmol) in dichloromethane (10 mL) was added dropwise within 30 min. The resulting mixture was stirred at 25 ℃ for 30 min, was quenched with saturated aq. $NaHCO_3$ (30 mL), and was extracted with dichloromethane (3 x 100 mL). The organic layer was dried over Na_2SO_4. After filtration and evaporation, the obtained amide was purified by column chromatography on silica gel (hexane/ethyl acetate = 12:1). 2.39 g, 81% yield, yellow foam; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.38 (s, 1H), 9.04 (dd, *J* = 4.1, 1.5 Hz, 1H), 8.82 – 8.68 (d, *J* = 7.1, 1H), 8.25 – 8.03 (d, *J* = 8.3, 1H), 7.67 – 7.41 (m, 3H), 6.24 (s, 1H), 4.50 (dd, *J* = 11.3, 4.6 Hz, 1H), 2.87 (d, *J* = 13.6 Hz, 1H), 2.47 (m, 2H), 2.31 (m, 1H), 2.20 – 1.98 (m, 3H), 1.91 – 1.79 (m, 1H), 1.65 (m, 5H), 1.48 (s, 3H), 1.46 – 1.36 (m, 4H) , 1.33 (s, 3H), 1.25 (m, 2H), 1.21 (s, 9H), 1.18 (s, 3H), 1.12 (s, 3H), 1.07 (m, 1H), 0.91 (s, 3H), 0.89 (s, 3H), 0.85 (m, 1H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 178.4, 174.7, 169.5, 149.1, 139.0, 136.5, 134.6, 129.3, 128.2, 127.5, 122.2, 121.7, 116.6, 80.2, 62.1, 55.3, 48.1, 45.8, 45.7, 43.5, 42.1, 39.2, 39.1, 38.5, 37.9, 37.3, 33.0, 32.2, 31.7, 29.9, 28.8, 28.3, 27.5, 26.7, 26.6, 23.8, 23.6, 18.9, 17.6, 17.0, 16.7; IR (KBr, ν/cm^{-1}) 3445, 2970, 2871, 1719, 1655, 1577, 1526, 1474, 1458, 1423, 1388, 1326, 1284, 1209, 1167, 1140, 1092, 1032, 981, 937, 892, 826, 793, 736; HRMS (ESI^+) Calcd for $C_{44}H_{60}N_2O_4$ ($M+Na^+$) 703.4445, Found 703.4429.



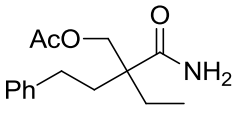
Gram–scale procedure for copper–mediated C(sp^3)–H acetoxylation of 4. A reaction tube was covered with aluminum foil, and a mixture of amide **4** (1.92 g, 2.82 mmol), $Cu(OAc)_2$ (512 mg, 2.82 mmol), AgOAc (2.35 g, 14.1 mmol), NaOAc (231 mg, 2.82 mmol), and *N*–methyl–2–pyrrolidone (28.0 mL) was stirred at 145 ℃ for 24 h under argon atmosphere. The reaction mixture was cooled to room temperature, was filtrated through celite, and the residue was washed with ethyl acetate (200 mL). Then, water (100 mL) was added to the filtrate, and the mixture was

extracted with ethyl acetate (3 x 150 mL). The organic phase was dried over Na_2SO_4 and was concentrated in vacuo. The crude mixture was subjected to column chromatography on silica gel (hexane/ethyl acetate = 3:1) to give the desired product (**5**, 1.10 g).

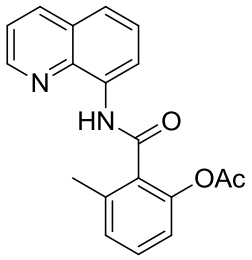
Acetoxylated product 5. 42.9 mg, 58% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.48 (s, 1H), 9.02 (dd, *J* = 4.2, 1.6 Hz, 1H), 8.78 (dd, *J* = 6.1, 2.9 Hz, 1H), 8.19 (dd, *J* = 8.2, 1.6 Hz, 1H), 7.84 – 7.54 (m, 3H), 6.21 (s, 1H), 4.50 (dd, *J* = 11.3, 5.0 Hz, 1H), 4.23 (d, *J* = 10.9 Hz, 1H), 4.05 (d, *J* = 10.9 Hz, 1H), 2.86 (d, *J* = 13.6 Hz, 1H), 2.56 – 2.40 (m, 2H), 2.30 – 2.02 (m, 4H), 1.99 (s, 3H), 1.88 (m, 1H), 1.78 – 1.54 (m, 9H), 1.46 (s, 3H), 1.40 (m, 2H), 1.33 – 1.23 (m, 2H). 1.21 (s, 9H), 1.18 (s, 3H), 1.13 (s, 3H), 0.91 (s, 3H), 0.89 (s, 3H), 0.81 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 200.6, 178.4, 171.3, 171.0, 167.0, 149.1, 139.0, 136.6, 134.3, 129.6, 128.2, 127.6, 122.3, 122.0, 116.7, 80.3, 72.1, 62.1, 55.3, 49.3, 47.2, 45.8, 43.5, 39.3, 39.1, 38.6, 37.3, 37.2, 36.8, 32.9, 32.6, 28.7, 28.3, 27.5, 27.0, 26.63, 26.57, 23.8, 23.6, 21.1, 19.0, 17.6, 17.0, 16.7; IR (KBr, ν/cm^{-1}) 3435, 2980, 2930, 2876, 1728, 1716, 1645, 1576, 1527, 1425, 1378, 1325, 1210, 1165, 1141, 1092, 1032, 982, 938, 827, 794; HRMS (ESI$^+$) Calcd for $C_{46}H_{62}N_2O_6$ (M+Na^+) 761.4500, Found 761.4489.



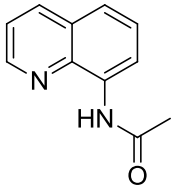
2–Carbamoyl–2–ethyl–4–phenylbutyl acetate (6). Amide **2s** (36.3 mg, 0.10 mmol) was dissolved in a mixture of CH_3CN and H_2O (5/1, 1.2 mL) at rt. CAN (165 mg, 0.300 mmol, 3.0 equiv) was added at 0 ^{o}C, and the reaction mixture was stirred at 0 ^{o}C for 2 h. The reaction was quenched with sat. $NaHCO_3$ (10 mL), and extracted with ethyl acetate (3 x 15 mL). The organic layer was dried over anhydrous Na_2SO_4, and concentrated in vacuo. The resulting residue was purified by column chromatography on silica gel (hexane/ethyl acetate = 4:1) to give amide **6**. 16.6 mg, 63% yield, yellow oil; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 2H), 7.19 (m, 3H), 5.81 (brs, 1H), 5.47 (brs, 1H), 4.28 (s, 2H), 2.66 – 2.49 (m, 2H), 2.10 (s, 3H), 1.97 – 1.80 (m, 2H), 1.79 – 1.61 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 176.7, 170.9, 142.0, 128.8, 128.5,



126.3, 65.6, 49.4, 35.7, 30.5, 26.5, 21.2, 8.5; IR (KBr,ν / cm–1) 3441, 2969, 2871, 1647, 1542, 1508, 1458, 1375, 1237, 795; HRMS (ESI^+) Calcd for $C_{15}H_{21}NO_3$ ($M+Na^+$) 286.1414, Found 286.1407.



3–Methyl–2–(8–quinolinylcarbamoyl)phenyl acetate (7). 12.8 mg, 40% yield, yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 10.02 (s, 1H), 8.93 (dd, *J* = 6.9, 2.0 Hz, 1H), 8.78 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.18 (dd, *J* = 8.3, 1.6 Hz, 1H), 7.65 – 7.53 (m, 2H), 7.45 (dd, *J* = 8.3, 4.2 Hz, 1H), 7.37 (dd, *J* = 7.9, 7.6 Hz, 1H), 7.19 (d, *J* = 7.6 Hz, 1H), 7.05 (d, *J* = 7.9 Hz, 1H), 2.49 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 165.1, 148.7, 147.7, 138.7, 137.8, 136.5, 134.5, 130.9, 130.3, 128.5, 128.2, 127.6, 122.3, 122.0, 120.5, 117.1, 21.1, 19.8; IR (KBr, ν/cm–1) 3482, 3411, 3331, 1771, 1677, 1618, 1524, 1484, 1326, 1196, 1028, 794, 756, 691; HRMS (ESI^+) Calcd for $C_{19}H_{16}N_2O_3$ ($M+Na^+$) 343.1053, Found 343.1045.

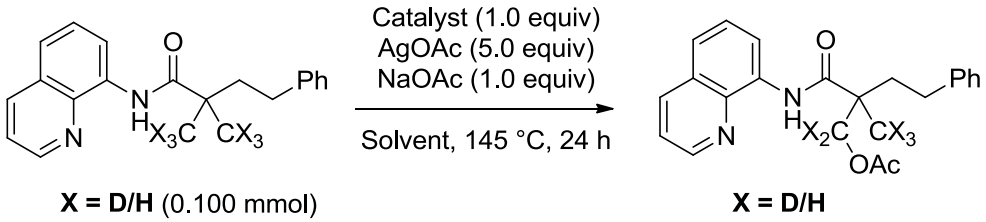


***N*–(8–Quinolinyl)acetamide (8).** 5.96 mg, 32% yield, yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 9.78 (s, 1H), 8.78 (m, 2H), 8.14 (dd, *J* = 8.3, 1.3 Hz, 1H), 7.62 – 7.32 (m, 3H), 2.34 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 148.3, 138.4, 136.6, 134.7, 128.1, 127.6, 121.8, 121.7, 116.7, 25.3; IR (KBr, ν/cm^{-1}) 3358, 3054, 1685, 1577, 1532, 1487, 1423, 1385, 1327, 1264, 1173, 1092, 1034, 1003, 949, 910, 826, 793, 735, 703, 637; HRMS (ESI^+) Calcd for $C_{11}H_{10}N_2O$ ($M+Na^+$) 209.0685, Found 209.0676.

Kinetic isotope effect experiments for intermolecular C(sp^3)–H acetoxylation

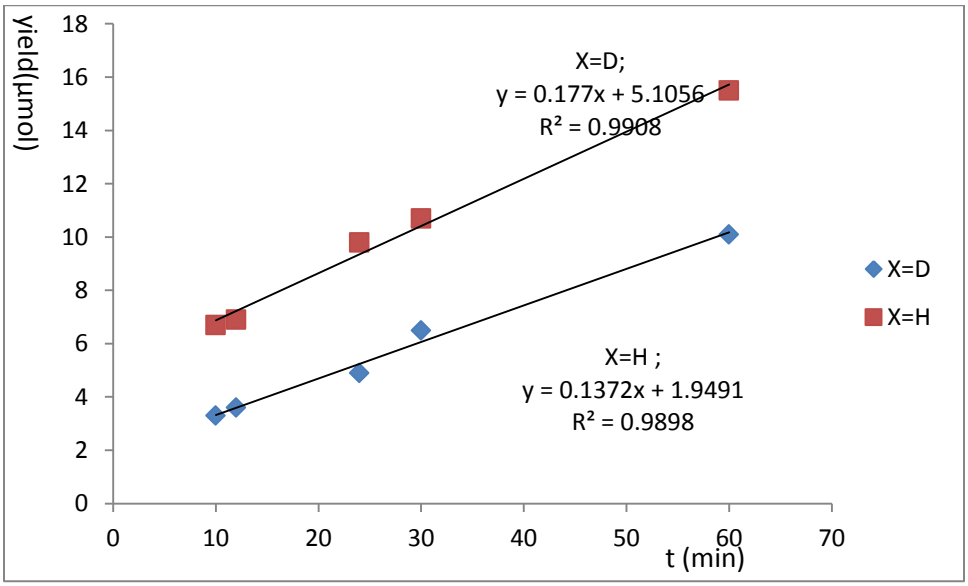
Experiment: A screw cap vial was charged with 2,2–dimethyl–4–phenyl–N–(quinolin–8–yl)butanamide (31.8 mg, 0.100 mmol) or 2,2–dimethyl–4–phenyl–N–(quinolin–8–yl)butanamide–d_6 (32.4 mg, 0.100 mmol), $Cu(OAc)_2$ (18.2 mg, 0.100 mol), NaOAc (8.20 mg, 0.100 mol), AgOAc (83.5 mg, 0.500 mol), and *N*–methyl–2–pyrrolidone (1.0 mL) under Ar atmosphere. The vial was sealed and stirred vigorously at 145 ˚C. The reaction was stopped by rapid cooling in the indicated reaction period, poured into water, and extracted with ethyl acetate (3 x 25 mL). The organic layer was dried, filtered, and concentrated in vacuo. The residue was analyzed by ^1H NMR using 1,1,2,2–tetrachloroethane as an internal standard.

Figure S3-1. KIE experiments for C(sp^3)-H acetoxylation



X = D/H (0.100 mmol) **X = D/H**

X	t (min)				
	10	12	24	30	60
X = D (μmol)	3.3	3.6	4.9	6.5	10.1
X = H (μmol)	6.7	6.9	9.8	10.7	15.5



Reference

1. Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem. Int. Ed.* **2014**, *53*, 3496.

4. Copper–Catalyzed Intramolecular N–S Bond Formation

4.1. Introduction

Cysteine and cystine broadly exist in the natural world, and they can convert each other via redox process. If we can interrupt this step, it is possible to modify the protein structure, such as formation of an N–S bond or using a reductive method removing the sulfur atom, On the other hand, organic compounds bearing heteroatom–heteroatom bond(s) are important as reagents, bioactive molecules,[1] and functional materials.[2] Among them, there are many natural products and drugs that contain heteroatom–heteroatom bond(s) between two different heteroatoms such as N–O,[3] N–S,[4] and S–O[5] bonds. One bioactive compound with an N–S bond is benzoisothiazolone which has effective antifungal, antibacterial, and antipsychotic properties (Figure 4-1).[6] As illustrated in Figure 4-2, several methods to construct benzoisothiazolone skeletons have been reported: (a) condensation of 2–(chlorocarbamoyl)phenyl hypochlorothioites with amines;[7] (b) a CuI/1,10–phenanthroline–mediated reaction using 2–halo–arylamides, sulfur powder, and potassium carbonate as a substrate, S source, and base, respectively;[8] and (c) a dehydrogenative N–H/S–H coupling reaction via the formation of an N–acylnitrenium ion using a hypervalent iodine reagent as an oxidant.[9] These synthetic methods require multi–step synthesis of the starting materials and/or highly reactive reagents, however, and produce some waste from the starting materials and reagents.[10] Considering the strong electronic effect of nitrogen and sulfur atoms, I hypothesized that transition–metal–catalyzed dehydrogenative cross–coupling reactions between N–H/S–H bonds might be the direct and efficient methods to produce benzoisothiazolones (Figure 4-2 (d)). My findings indicate that a small amount of a copper salt can promote an intramolecular dehydrogenative coupling reaction between N–H and S–H bonds to give N–S bonds using oxygen as an oxidant.

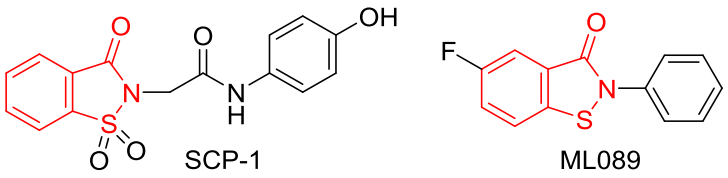


Figure 4-1. Bioactive molecules that contain benzo[*d*]isothiazol-3(2*H*)-one skeletons

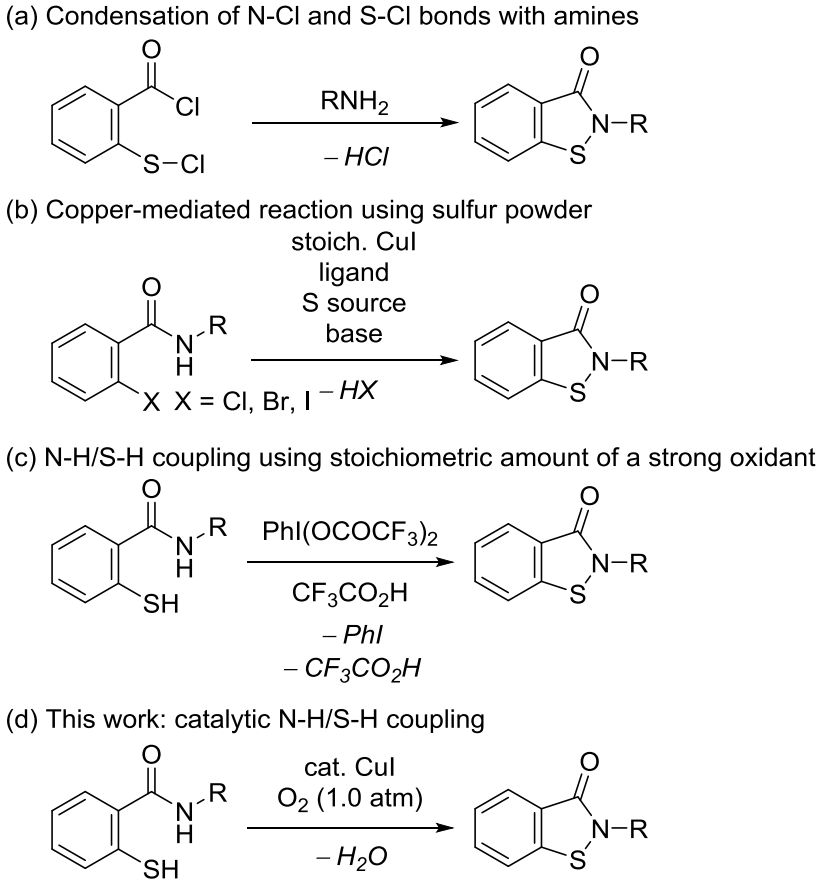
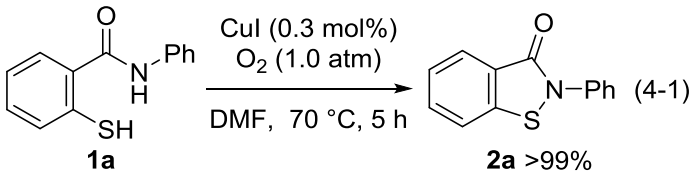


Figure 4-2. Previous and present methods for the synthesis of benzo[*d*]isothiazol-3(2*H*)-ones

4.2. Optimization Studies

Considering the environment, I chose aerobic oxygen as an oxidant. After modifying the reaction conditions, I found that treatment of 2–mercapto–*N*–phenylbenzamide (**1a**) with a catalytic amount of copper(I) iodide (CuI) in *N*,*N*–dimethylformamide (DMF) at 70 ℃ for 5 h under O_2 conditions gave 2–phenylbenzo[*d*]isothiazol–3(2*H*)–one (**2a**) in quantitative yield (eq 4-1).[11–18] This reaction did not proceed in the absence of O_2. The structure of **2a** was determined by single crystal X–ray structure analysis and revealed the formation of an N–S bond and construction of a five–membered heterocyclic skeleton.

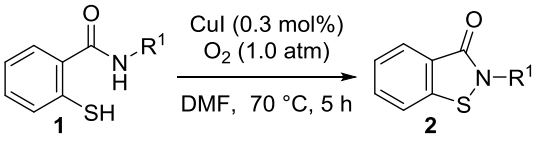


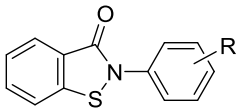
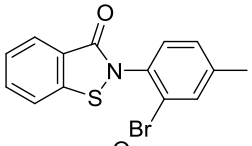
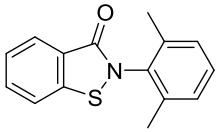
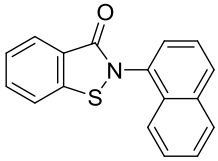
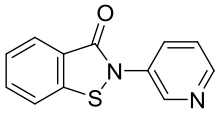
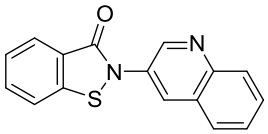
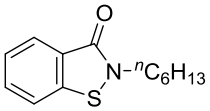
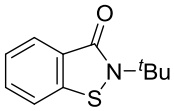
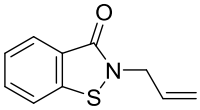
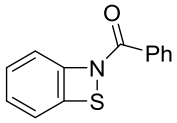
1a **2a** >99%

4.3. Substrate Scope and Mechanism Research

Next, the substrate scope was investigated (Table 4-1). *N*–Aryl 2–mercaptobenzamides **1b**–**1l** provided the corresponding 2–arylbenzo[*d*]isothiazol–3(2*H*)–ones **2b**–**2l** in excellent yields (entries 1–11). The reaction was not affected by electron–donating or –withdrawing groups (entries 1–4). In entries 5–7, the reaction proceeded without loss of the halogen atoms. The cyclization reaction was not inhibited by steric hindrance (entry 8). Pyridyl and quinolyl groups could be used as an aromatic ring on a nitrogen atom of the substrates **1k** and **1l** (entries 10 and 11). Alkyl–substituted 2–mercaptobenzamides **1m**–**1o** afforded the corresponding benzoisothiazolones **2m**–**2o** in excellent yield (entries 12–14). The 4–membered heterocyclic product **2p** was also obtained in 84% yield (entry 15).

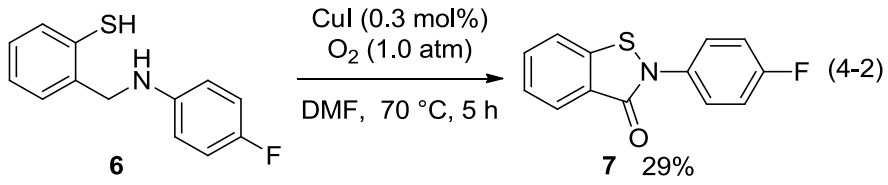
Table 4-1. Synthesis of Heterocyclic Compounds **2** via N-H and S-H Bond Activation of **1**.



entry	1			yield / %
1		R = 4-MeO	**1b**	**2b** 95
2		4-Me	**1c**	**2c** 95
3		4-F	**1d**	**2d** 95
4		4-CN	**1e**	**2e** 99
5		2-Br	**1f**	**2f** 98
6[a]		2-I	**1g**	**2g** 83
7			**1h**	**2h** 97
8			**1i**	**2i** 98
9			**1j**	**2j** 95
10			**1k**	**2k** 95
11[a]			**1l**	**2l** 90
12			**1m**	**2m** >99
13			**1n**	**2n** 92
14			**1o**	**2o** 95
15[a]			**1p**	**2p** 84

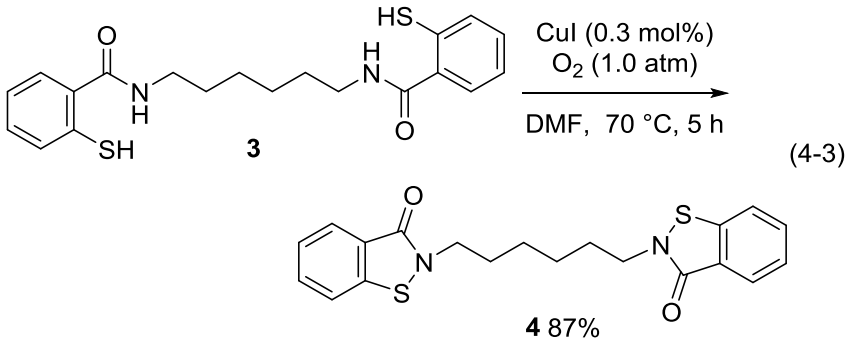
[a] Solvent: dimethylsulfoxide (DMSO).

In the case of 2–(((4–fluorophenyl)amino)methyl)benzenethiol, N–S bond formation proceeded; however, the reaction did not stop at this step and further oxidation of the benzylic position also occurred to give **2d** in 29% yield (eq 4-2).



(4-2)

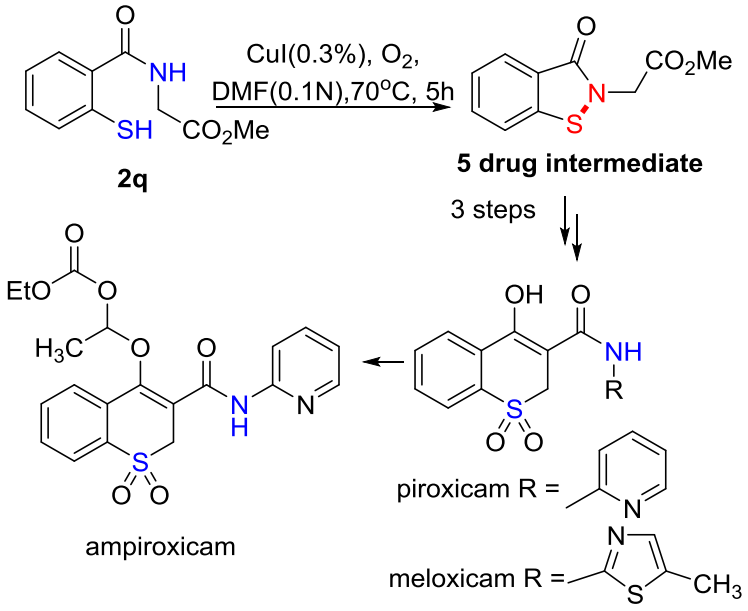
A double–cyclization reaction also proceeded and product **4** was obtained in 87% yield (eq 4-3). In this reaction, the yield of product **4** was comparable to that of single–cyclization products.



(4-3)

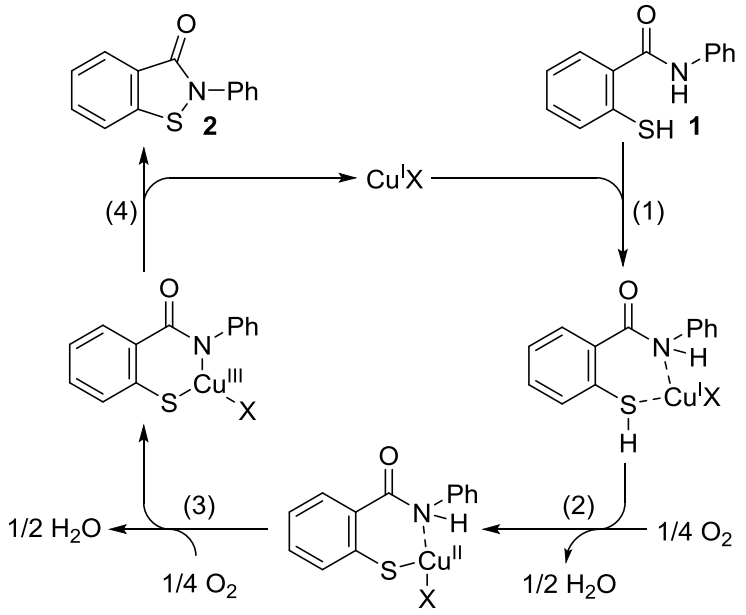
The present reaction was applied to the synthesis of a drug precursor, which named proxican. (Scheme 4-1). Piroxicam is a non–steroidal anti–inflammatory drug used to relieve the symptoms of rheumatoid and osteoarthritis, primary dysmenorrhea, and postoperative pain.[19,20] Benzoisothiazolone **2q** could be synthesized using the present method. Oxidation of **2q**[21] would give a precursor of piroxicam, **5**, and several successive transformations would lead to piroxicam following the reported method.[18a]

Scheme 4-1. Synthesis of Important Drug Molecule

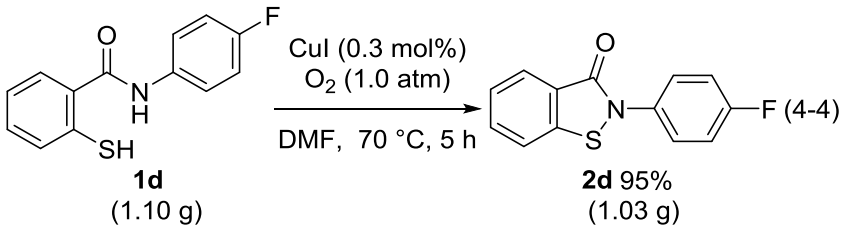


Benzoisothiazolone **2a** was not obtained from the corresponding disulfide, which may be formed by dehydrogenative homo–coupling of **1a**. This result indicated that cyclization did not proceed via formation of the disulfide. The proposed mechanism for the formation of benzoisothiazolone **2** is as follows (Scheme 4-2): (1) coordination of 2–mercaptobenzamide **1** to a copper atom; (2) oxidative formation of a Cu–S bond via the elimination of H_2O, (3) oxidative formation of a Cu–N bond via the elimination of H_2O [22] (or the order of steps 2 and 3 is reversed), and (4) reductive elimination[23] to give benzoisothiazolone **2** and regenerate the copper catalyst.

Scheme 4-2. Proposed Mechanism for the Formation of Benzoisothiazolone **2**



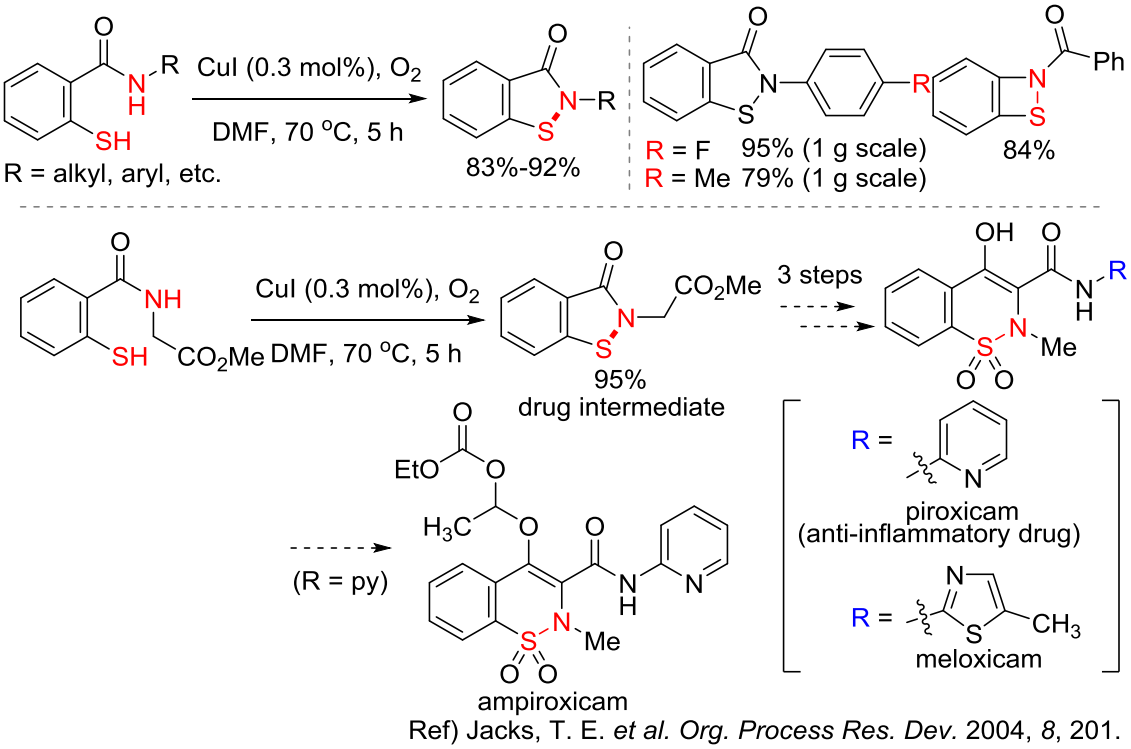
The reaction can be performed in gram scale. Treatment of 1.10 g of **1d** with a catalytic amount of CuI produced 1.03 g of **2d** in 95% yield (eq 4-4), which is comparable to the yield in eq 1 (46 mg scale).



4.4. Summary

In summary, I successfully achieved a copper–catalyzed synthesis of benzo[*d*]isothiazol–3(2*H*)–ones and *N*–acyl–benzothiazetidine by intramolecular dehydrogenative cyclization (Figure 4-3). This reaction proceeded using a small amount of the catalyst (0.3 mol%) and oxygen as an oxidant to form a new N–S bond by N–H/S–H coupling. Many natural products and drugs contain heteroatom–heteroatom bond(s) such as N–S bond(s), and it is therefore important to

develop novel and efficient methods to construct N–S bonds. There have been several reports on the construction of N–S bonds, but there is a room for improvement of the efficiency. On the other hand, the present reaction is more efficient because N–S bond–containing heterocyclic skeletons can be constructed catalytically by the direct formation of N–S bonds from NH and SH bonds. The present reaction affords products in gram scale. This method promotes double cyclization, allowing for the synthesis of a drug precursor. I believe that this reaction will be a useful method for the synthesis of heterocyclic compounds with an N–S bond.



Ref) Jacks, T. E. *et al. Org. Process Res. Dev.* 2004, *8*, 201.

Figure 4-3. Summary

4.5. References and Notes

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(11) Investigation of several catalysts (catalyst, 1.0 mol%; O_2, 1.0 atm; DMSO; 100 ℃; 6 h): none, 31%; KBr, 84%; $FeBr_3$, 35%; CuI, >99%. In other conditions (catalyst, 0.3 mol%; O_2, 1.0 atm; DMF; 70 ℃; 5 h): none, 11%; KBr, 0%; $MnBr_2$, 27%; $FeBr_3$, 38%; CoI_2, 24%; NiI_2, 26%; CuCl, 63%; CuBr, 83%; $CuBr_2$, 69%; $Cu(OAc)_2$, 80%; Cu_2O, 13%; CuO, 11%.

(12) Investigation of the amount of catalyst loading (CuI, O_2, 1.0 atm; DMF; 70 ℃; 6 h): 0.10 mol%, 87%; 0.30 mol%, 99%; 0.50 mol%, 99%.

(13) Investigation of several solvents (CuI, 1.0 mol%; O_2, 1.0 atm; 60 ℃; 6 h): 1,4–dioxane, 17%; toluene, 9%; 1,2–dichloroethane, 7%; isopropanol, 15%; methanol, 11%; NMP, 18%; DMA, 18%; DMF, 97%; acetonitrile, 22%; water, 11%.

(14) Investigation of several concentrations (CuI, 1.0 mol%; O_2, 1.0 atm; DMF; 70 ℃; 6 h): 0.01 M, 77%; 0.05 M, 84%; 0.20 M, 90%; 0.50 M, 86%; 1.0 M, 73%.

(15) Investigation of several temperatures (CuI, 1.0 mol%; O_2,1.0 atm; DMSO; 6 h): 25 ℃, 11%; 40 ℃, 37%; 60 ℃, 66%; 80 ℃, 90%. In the case of DMF as a solvent: (CuI, 1.0 mol%; O_2, 1.0 atm; DMF; 6 h): 25 ℃, 9%; 60 ℃, 92%; 70 ℃, >99%; 80 ℃, >99%.

(16) Investigation of several reaction times (CuI, 0.3 mol%; O_2, 1.0 atm; DMF; 70 ℃): 3 h, 74%; 4.5 h, 97%; 5 h, >99%.

(17) The product **2a** was obtained in 62% yield when the reaction was carried out under air conditions.

(18) The ^{1}H NMR and IR spectra of **2a** are consistent with the following report: Shimizu, M.; Sugano, Y.; Konakahara, T.; Gama, Y.; Shibuya, I. *Tetrahedron* **2002**, *58*, 3779.

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(20) Organic molecules which contain 2*H*–benzo[*e*][1,2]thiazine 1,1–dioxide skeleton have bioactivities. For an example, see: Jacks, T. E.; Belmont, D. T.; Briggs, C. A.; Horne, N. M.; Kanter, G. D.; Karrick, G. L.; Krikke, J. J.; McCabe, R. J.; Mustakis, J. G.; Nanninga, T. N.; Risedorph, G. S.; Seamans, R. E.; Skeean, R.; Winkle, D. D.; Zennie, T. M. *Org. Process Res. Dev.* **2004**, *8*, 201.

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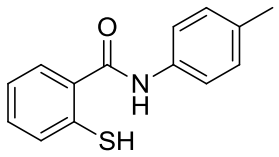
4.6. Experimental

General. All reactions were carried out in dry solvents under argon atmosphere unless otherwise noted. Methyl thiosalicylate was purchased and was used without further purification. CuI (99.999% purity) was purchased from Aldrich Co. and used as received. *N*,*N*–Dimethylformamide, methanol, dichloromethane, and dimethyl sulfoxide were purchased and were dried and degassed before use. **1q**[24,25] was synthesized following the reported method. NMR spectra were recorded on 500 MHz (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) and 400 MHz (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR) spectrometers. Proton chemical shifts are reported relative to residual solvent peak ($CDCl_3$ at 7.26 ppm, CD_3OD at 3.31 ppm, and DMSO–d_6 at 2.50 ppm). Carbon chemical shifts are reported relative to solvent peaks ($CDCl_3$ at 77.3 ppm, CD_3OD at 49.1 ppm, and DMSO–d_6 at 39.5 ppm). IR spectra were recorded on Fourier transform infrared spectrophotometer. High–resolution mass spectra (HRMS) were measured on a TOF spectrometer (for HRMS). The known starting materials **1b**, **1f**, **1g**, **1j**, and **1o**, were identified by comparing these spectroscopic data with those of reported data.[9]

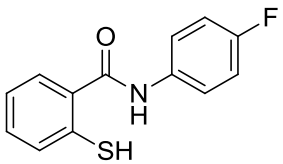
Typical procedure for the synthesis of 2–mercapto–*N*–phenylbenzamide (1a). To a cooled (0 ℃) solution of aniline (6.64 g, 71.3 mmol) in CH_2Cl_2 (150 mL) was added a solution of $AlMe_3$ in hexane (2.0 M, 35.7 mL, 71.3 mmol). The reaction mixture was warmed to room temperature and was continued to stir for 30 minutes until the gas evolution ceased. Then, methyl thiosalicylate (5.00 g, 29.7 mmol) was added and the solution was refluxed for 12 h. The reaction mixture was cooled in an ice bath and aq. HCl (10%, 60 mL) was added carefully. The solution was extracted

with CH_2Cl_2 (3 x 150 mL) and the combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (150 mL) and brine (150 mL) consequently. Then, the organic layer was dried over sodium sulfate. After filtration and removal of the solvent under vacuum, the residue was purified by crystallization from Et_2O to afford 2–mercapto–*N*–phenylbenzamide (**1a**) as a white solid (6.52 g, 95% yield). TLC (hexane/AcOEt = 3/1): R_f = 0.14, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (brs, 1H), 7.61 (d, *J* = 7.9 Hz, 2H), 7.57 (d, *J* = 7.7 Hz, 1H), 7.36 (dd, *J* = 11.0, 4.2 Hz, 3H), 7.33–7.24 (m, 1H), 7.23–7.12 (m, 2H), 4.55 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.8, 137.8, 133.7, 133.2, 131.6, 131.2, 129.3, 128.3, 125.7, 125.1, 120.5; IR (KBr, ν / cm–1) 3448, 1646, 1639, 1599, 1540, 1508, 1438, 1322, 1253, 1176, 1003, 889, 753, 690; HRMS (ESI^+) Calcd for $C_{13}H_{11}NOS$ ($M+Na^+$) 252.0454, Found 252.0454.

2–Mercapto–*N*–(4–methylphenyl)benzamide (1c). *p*–Toluidine (3.82 g, 35.7 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et_2O/hexane (1/1). 3.47 g, 96%, white solid. TLC (hexane/AcOEt = 3/1): R_f = 0.15, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (brs, 1H), 7.55 (d, *J* = 7.4 Hz, 1H), 7.49 (d, *J* = 7.5 Hz, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.28 (dd, *J* = 7.4, 7.4 Hz, 1H), 7.17 (m, 3H), 4.65 (brs, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.8, 135.2, 134.8, 133.7, 133.2, 131.5, 131.1, 129.8, 128.2, 125.6, 120.6, 21.2; IR (KBr, ν / cm^{-1}) 3435, 1644, 1514, 1403, 1321, 1300, 1253, 1113, 1060, 1038, 941, 894, 814, 785, 741, 652; HRMS (ESI^+) Calcd for $C_{17}H_{11}NOS$ ($M+Na^+$) 264.0454, Found 264.0456. HRMS (ESI^+) Calcd for $C_{14}H_{13}NOS$ ($M+Na^+$) 266.0610, Found 266.0610.

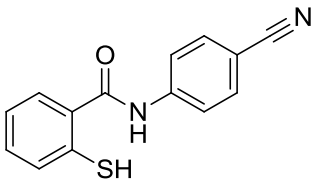


***N*–(4–Fluorophenyl)–2–mercaptobenzamide (1d).** 4–Fluoroaniline (6.51 mL, 71.3 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et_2O/hexane (3/1). 6.01 g, 82%, white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.39, ^{1}H NMR (500 MHz, DMSO) δ 10.44 (brs, 1H), 7.75 (dd, *J* = 8.9, 8.9 Hz, 2H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.50 (d, *J* = 7.7 Hz, 1H), 7.36 (td, *J* = 7.7, 1.2 Hz, 1H), 7.26 (d, *J* = 7.7 Hz, 1H), 7.24–7.14 (m, 2H), 5.28 (brs, 1H); ^{13}C NMR (100 MHz, DMSO) δ 166.4, 158.3 (*J* = 238 Hz), 135.4 (*J* = 2.4 Hz), 133.9, 133.2, 130.6, 128.6, 124.7, 121.7 (*J* = 8.4 Hz), 115.3 (*J* = 22.7 Hz); IR (KBr, ν / cm^{-1})

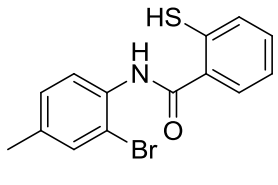


3333, 2955, 2928, 2856, 1634, 1540, 1457,1433, 1314, 1038, 742; HRMS (ESI^+) Calcd for $C_{13}H_{10}FNOS$ ($M+Na^+$) 270.0359, Found 270.0357.

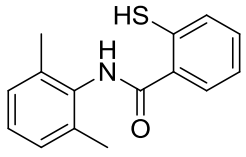
***N*–(4–Cyanophenyl)–2–mercaptobenzamide (1e)**. 4–aminobenzonitrile (3.37 g, 11.9 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et_2O/hexane (3/1). 1.84 g, 61%, light yellow solid, TLC (hexane/AcOEt = 2/1): R_f = 0.31, ^1H NMR (400 MHz, $CDCL_3$) δ 7.81–7.74 (m, 2H), 7.67–7.56 (m, 3H), 7.34 (m, 2H), 7.22 (t, *J* = 7.4 Hz, 1H), 4.35 (s, 1H). ^{13}C NMR (100 MHz, $CDCL_3$) δ 166.8, 142.0, 133.54, 133.49, 132.8, 132.0, 131.8, 128.4, 125.9, 120.2, 119.0, 107.8; IR (KBr, ν / cm^{-1}) 3446, 2887, 2778, 2359, 2342, 1637, 1541, 1275, 1104, 749, 668, 648; HRMS (ESI+) Calcd for $C_{14}H_{10}N_2OS$ ($M+Na^+$) 277.0406, Found 277.0415.



***N*–(2–Bromo–4–methylphenyl)–2–mercaptobenzamide (1h).** 2–Bromo–4–methylaniline (3.98 g, 21.4 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et_2O/hexane (2/1). 2.57 g, 90%, white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.25, ^1H NMR (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 8.22 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.44 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.36–7.32 (m, 1H), 7.27–7.22 (m, 1H), 6.86 (d, *J* = 8.0 Hz, 1H), 4.59 (d, *J* = 0.8 Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5, 139.0, 135.4, 134.6, 132.9, 132.1, 131.9, 131.5, 128.0, 126.8, 125.8, 122.8, 110.8, 21.6; IR (KBr, ν / cm^{-1}) 3257, 1643, 1526, 1474, 1303, 1029, 797, 740; HRMS (ESI^+) Calcd for $C_{14}H_{12}B_rNOS$ ($M+Na^+$) 343.9715, Found 343.9711.



***N*–(2,6–Dimethylphenyl)–2–mercaptobenzamide (1i).** 2,6–Dimethylaniline (2.59 g, 21.4 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et_2O/hexane (1/1). 2.08 g, 90%, yellow white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.11, ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (d, *J* = 7.7 Hz, 1H), 7.38 (d, *J* = 7.7 Hz, 2H), 7.32 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.23–7.04 (m, 4H), 4.84 (s, 1H), 2.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 135.8, 133.6, 133.5, 131.4, 131.1, 128.5, 128.2, 128.1, 127.9, 125.5, 18.8; IR



(KBr, ν / cm^{-1}) 3433, 2956, 2928, 2856, 1634, 1540, 1457, 1433, 1313, 1263, 1038, 1009, 742, 649; HRMS (ESI^+) Calcd for $C_{15}H_{15}NOS$ ($M+Na^+$) 280.0767, Found 280.0770.

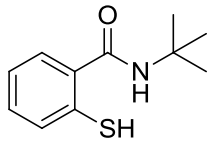
2–Mercapto–*N*–(3–pyridinyl)benzamide (1k). Pyridin–3–amine (2.01 g, 21.4 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et_2O. 1.78 g, 87%, white solid, TLC (hexane/AcOEt = 1/1): R_f = 0.42, ^1H NMR (500 MHz, CD_3OD) δ 8.86 (d, *J* = 2.3 Hz, 1H), 8.31 (dd, *J* = 4.5, 1.2 Hz, 1H), 8.25 (d, *J* = 7.9 Hz, 1H), 7.65 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.46 (t, *J* = 4.5 Hz, 1H), 7.45 (s, 1H), 7.35 (td, *J* = 7.9, 1.2 Hz, 1H), 7.25 (td, *J* = 7.9, 1.2 Hz, 1H); ^{13}C NMR (125 MHz, CD_3OD) δ 169.9, 145.5, 142.4, 137.7, 135.0, 134.8, 132.4, 132.2, 129.9, 129.7, 126.2, 125.5; IR (KBr, ν/cm^{-1}) 3442, 2721, 1637, 1558, 1540, 1456, 1419, 1330, 1302, 1129, 1005, 742, 630; HRMS (ESI^+) Calcd for $C_{12}H_{10}N_2OS$ ($M+Na^+$) 253.0406, Found 253.0407.

2–Mercapto–*N*–(3–quinolinyl)benzamide (1l). Quinolin–3–amine (3.08 g, 21.4 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et_2O. 2.11 g, 84%, brown white solid, TLC (hexane/AcOEt = 1/1): R_f = 0.45, ^1H NMR (400 MHz, $CDCl_3$) δ 8.95 (d, *J* = 2.3 Hz, 1H), 8.85 (d, *J* = 2.3 Hz, 1H), 8.26 (s, 1H), 8.07 (d, *J* = 7.8 Hz, 1H), 7.90–7.81 (m, 1H), 7.72–7.68 (m, 1H), 7.67–7.64 (m, 1H), 7.57 (ddd, *J* = 7.8, 7.8, 1.3 Hz, 1H), 7.41 (dd, *J* = 7.8, 1.3 Hz, 1H), 7.35 (td, *J* = 7.8, 1.3 Hz, 1H), 7.25 (td, *J* = 7.8, 1.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 145.5, 144.1, 133.6, 132.9, 131.9, 131.7, 131.6, 129.1, 128.9, 128.43, 128.39, 128.1, 127.7, 125.9, 124.8; IR (KBr, ν/cm^{-1}) 3438, 1637, 1542, 1508, 1489, 1466, 1420, 1366, 1300, 1144, 990, 782, 741; HRMS (ESI^+) Calcd for $C_{16}H_{12}N_2OS$ ($M+Na^+$) 303.0563, Found 303.0562.

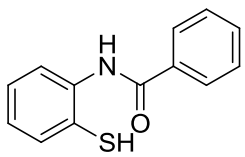
***N*–hexyl–2–mercaptobenzamide (1m).** Hexan–1–amine (3.64 g, 35.7 mmol), instead of aniline, was used following the general procedure. Purification: flash column chromatography with hexane/EtOAc (5/1). 3.26 g, 92%, blue white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.23, ^1H NMR (500 MHz, $CDCl_3$) δ 7.40 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.30 (dd, *J* = 7.6, 1.2 Hz, 1H), 7.23 (td, *J* = 7.6, 1.2 Hz, 1H), 7.11 (dd, *J* = 7.6, 7.6 Hz, 1H), 6.14 (s, 1H), 4.75 (s, 1H), 3.41 (m, 6.9 Hz,

2H), 1.64–1.53 (m, 2H), 1.42–1.24 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.8, 133.7, 133.0, 131.1, 130.7, 128.0, 125.3, 40.3, 31.7, 29.7, 26.9, 22.8, 14.2; IR (KBr, ν/cm^{-1}) 3433, 2955, 2928, 2855, 1634, 1620, 1540, 1457, 1433, 1313, 1263, 1162, 1038, 742; HRMS (ESI$^+$) Calcd for $C_{13}H_{19}NOS$ (M+Na$^+$) 260.1080, Found 260.1080.

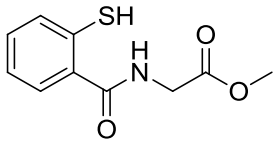
***N*–(*tert*–Butyl)–2–mercaptobenzamide (1n).** 2–Methylpropan–2–amine (2.27 mL, 21.4 mmol), instead of aniline, was used following the general procedure. Purification: crystallization from Et_2O/hexane (3/1). 1.76 g, 95%, brown white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.27, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.32–7.28 (m, 1H), 7.26–7.22 (m, 1H), 7.13 (m, 1H), 5.80 (s, 1H), 4.62 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4, 135.0, 132.3, 131.0, 130.4, 127.9, 125.4, 52.2, 29.0; IR (KBr, ν/cm^{-1}) 3298, 2977, 2890, 1632, 1587, 1536, 1470, 1446, 1361, 1319, 1272, 1221, 1044, 878, 742, 676; HRMS (ESI$^+$) Calcd for $C_{11}H_{15}NOS$ (M+Na$^+$) 232.0767, Found 232.0764.



***N*–(2–Mercaptophenyl)benzamide (1p).** 0.75 g, 75%, white solid, TLC (hexane/AcOEt = 1/2): R_f = 0.15, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.94 (s, 1H), 8.50 (d, *J* = 7.8 Hz, 1H), 7.73–7.66 (m, 2H), 7.56 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.50–7.41 (m, 3H), 7.31 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.95 (td, *J* = 7.8, 1.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.2, 140.2, 136.9, 134.6, 132.6, 132.3, 129.1, 127.3, 124.6, 123.7, 120.8; IR (KBr, ν/cm^{-1}) 3445, 3120, 2980, 2960, 1681, 1577, 1509, 1478, 1433, 1313, 1225, 963, 766, 729, 688, 623; HRMS (ESI$^+$) Calcd for $C_{13}H_{11}NOS$ (M+Na$^+$) 252.0454, Found 252.0451.

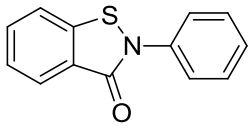


Methyl 2–(2–mercaptobenzamido)acetate (1q). 1.02 g, 76%, yellow oil, TLC (hexane/AcOEt = 1/2): R_f = 0.35, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 7.6 Hz, 1H), 7.45–7.35 (m, 1H), 7.29–7.19 (m, 1H), 6.64 (s, 1H), 4.23 (d, *J* = 5.1 Hz, 2H), 3.81 (s, 3H); ^{13}C NMR (125 MHz, $CDCL_3$) δ 170.5, 167.9, 137.7, 133.4, 131.9, 128.2, 127.9, 126.6, 52.8, 42.0; IR (KBr, ν/cm^{-1}) 3420, 2924, 2851, 1748, 1734, 1646, 1636, 1541, 1212, 1173, 1092, 801, 745, 635; HRMS (ESI$^+$) Calcd for $C_{10}H_{11}NO_3S$ (M+Na$^+$) 248.0352, Found 248.0350.

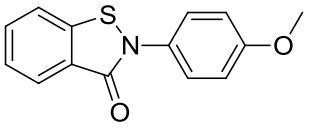


Typical procedure for copper–catalyzed intramolecular N–S bond formation: Synthesis of

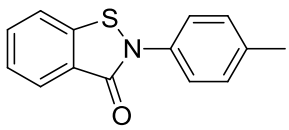
2–phenylbenzo[*d*]isothiazol–3(2*H*)–one (2a). A mixture of 2–mercapto–*N*–phenylbenzamide (**1a**, 45.9 mg, 0.20 mmol), CuI (0.11 mg, 0.60 mol), and DMF (2.0 mL) was stirred at 70 ℃ for 5 h under oxygen. Then, the reaction mixture was cooled to room temperature, diluted with water, and extracted with ethyl acetate. The organic layer was dried over sodium sulfate. After filtration and removal of the solvent in vacuo, the residue was subjected to the flash column chromatography on silica gel with hexane/AcOEt (3/1) as eluent to give 2–phenylbenzo[*d*]isothiazol–3(2*H*)–one (**2a**, white solid, 45.6 mg, >99% yield). TLC (hexane/AcOEt = 2/1): R_f = 0.43, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.7 Hz, 1H), 7.70 (d, *J* = 7.7 Hz, 2H), 7.63 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.55 (d, *J* = 7.7 Hz, 1H), 7.50–7.39 (m, 3H), 7.30 (t, *J* = 7.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.2, 140.0, 137.4, 132.5, 129.5, 127.3, 127.2, 125.9, 125.0, 124.7, 120.3; IR (KBr, ν/cm^{-1}) 3447, 1653, 1592, 1487, 1448, 1323, 1301, 1267, 1114, 1017, 753, 737, 688, 670, 609; HRMS (ESI$^+$) Calcd for $C_{13}H_9NOS$ (M+Na$^+$) 250.0297, Found 250.0299.



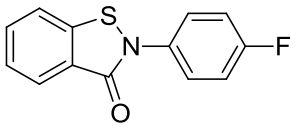
2–(4–Methoxyphenyl)benzo[*d*]isothiazol–3(2*H*)–one (2b). 48.6 mg, 95%, white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.29, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (d, *J* = 7.6 Hz, 1H), 7.64 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.57–7.53 (m, 3H), 7.43 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.02–6.90 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.5, 158.9, 140.2, 132.3, 129.9, 127.3, 127.0, 125.9, 124.8, 120.3, 114.8, 55.8; IR (KBr, ν/cm^{-1}) 3465, 2835, 1651, 1508, 1447, 1329, 1297, 1248, 1179, 1128, 1030, 972, 860, 826, 783, 738, 671; HRMS (ESI$^+$) Calcd for $C_{14}H_{11}NO_2S$ (M+Na$^+$) 280.0403, Found 280.0402.



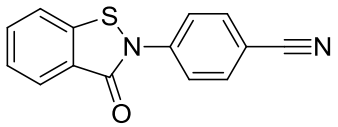
2–(*p*–Tolyl)benzo[*d*]isothiazol–3(2*H*)–one (2c). 45.8 mg, 95%, white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.54, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.40–7.32 (m, 1H), 7.27 (m, 3H), 7.18–7.10 (m, 1H), 6.98 (d, *J* = 8.0 Hz, 2H), 2.10 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.4, 140.2, 137.4, 134.8, 132.4, 130.1, 127.3, 125.9, 125.1, 124.9, 120.3, 21.3; IR (KBr, ν/cm^{-1}) 3458, 1644, 1505, 1447, 1330, 1313, 1269, 1127, 928, 883, 814, 786, 749, 676, 636; HRMS (ESI$^+$) Calcd for $C_{14}H_{11}NOS$ (M+Na$^+$) 264.0454, Found 264.0456.



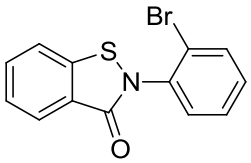
2–(4–Fluorophenyl)benzo[*d*]isothiazol–3(2*H*)–one (2d). 46.5 mg, 95%, white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.32, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.9 Hz, 1H), 7.69–7.59 (m, 3H), 7.55 (d, *J* = 7.9 Hz, 1H), 7.42 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.13 (dd, *J* = 7.9, 7.9 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 161.3 (*J* = 246 Hz), 139.9, 133.2, 132.6, 127.3, 126.9 (*J* = 8.4 Hz), 126.0, 124.6, 120.3, 116.4 (*J* = 22.7 Hz); IR (KBr, ν/cm^{-1}) 3450, 1657, 1599, 1505, 1460, 1447, 1417, 1333, 1310, 1298, 1233, 1159, 1127, 824, 802, 732, 669; HRMS (ESI$^+$) Calcd for $C_{13}H_8FNOS$ (M+Na$^+$) 268.0203, Found 268.0204.



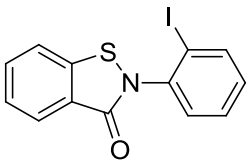
4–(3–Oxobenzo[*d*]isothiazol–2(3*H*)–yl)benzonitrile (2e). 50.2 mg, 99%, white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.30, ^{1}H NMR (500 MHz, $CDCL_3$) δ 8.10 (d, *J* = 7.8 Hz, 1H), 7.99–7.92 (m, 2H), 7.78–7.68 (m, 3H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.47 (dd, *J* = 11.3, 4.3 Hz, 1H). ^{13}C NMR (125 MHz, $CDCL_3$) δ 164.4, 141.8, 139.4, 133.5, 133.4, 127.7, 126.5, 124.8, 123.5, 120.4, 118.5, 109.7; IR (KBr, ν/cm^{-1}) 3446, 2887, 2778, 2359, 2342, 1637, 1541, 1275, 1104, 749, 668, 648; HRMS (ESI+) Calcd for $C_{14}H_8N_2OS$ (M+Na$^+$) 275.0255, Found 275.0261.



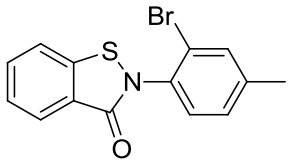
2–(2–Bromophenyl)benzo[*d*]isothiazol–3(2*H*)–one (2f). 59.8 mg, 98%, brown solid, TLC (hexane/AcOEt = 3/1): R_f = 0.36, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16–8.12 (m, 1H), 7.74 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.71–7.66 (m, 1H), 7.62–7.58 (m, 1H), 7.46 (m, 3H), 7.34 (ddd, *J* = 7.8, 7.8, 1.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.9, 141.5, 135.5, 134.1, 132.7, 131.5, 131.2, 128.7, 127.6, 126.0, 124.3, 123.6, 120.5; IR (KBr, ν/cm^{-1}) 3446, 3063, 1667, 1595, 1471, 1445, 1328, 1309, 1250, 1131, 1047, 782, 755, 739, 671, 656, 613; HRMS (ESI$^+$) Calcd for $C_{13}H_8BrNOS$ (M+Na$^+$) 327.9402, Found 327.9398.



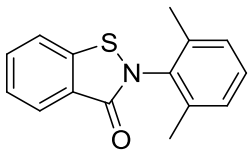
2–(2–Iodophenyl)benzo[*d*]isothiazol–3(2*H*)–one (2g). Reaction conditions: DMSO (2 mL), 100 ^{o}C, 5 h. Purification: silica gel column chromatography (hexane/AcOEt = 1/1), 58.6 mg, 83%, brown solid, TLC (hexane/AcOEt = 3/1): R_f = 0.28, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 8.0 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.71–7.66 (m, 1H), 7.62–7.58 (m, 1H), 7.50–7.41 (m,



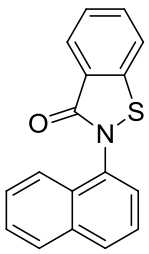
3H), 7.19–7.15 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.7, 141.4, 140.4, 139.1, 132.7, 131.3, 130.9, 129.7, 127.7, 126.0, 123.9, 120.6, 99.7; IR (KBr, ν/cm^{-1}) 3447, 2921, 1660, 1596, 1464, 1447, 1328, 1308, 1250, 1131, 1019, 908, 781, 755, 738, 670, 613; HRMS (ESI$^+$) Calcd for $C_{13}H_8INOS$ (M+Na$^+$) 375.9263, Found 375.9258.

2–(2–Bromo–4–methylphenyl)benzo[*d*]isothiazol–3(2*H*)–one (2h). 

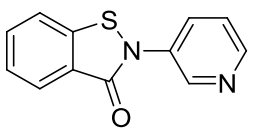
62.0 mg, 97%, white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.33, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (d, *J* = 8.0 Hz, 1H), 7.67 (td, *J* = 8.0, 1.5 Hz, 1H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.45 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.30 (d, *J* = 1.5 Hz, 1H), 7.14 (dd, *J* = 8.0, 1.5 Hz, 1H), 2.35 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.0, 141.5, 139.1, 135.1, 133.6, 132.6, 132.1, 132.0, 127.6, 125.9, 123.7, 120.7, 120.5, 21.0; IR (KBr, ν/cm^{-1}) 3446, 1645, 1474, 1444, 1400, 1324, 1308, 1249, 1113, 1038, 1017, 810, 785, 737, 670, 623; HRMS (ESI$^+$) Calcd for $C_{14}H_{10}B_rNOS$ (M+Na$^+$) 341.9559, Found 341.9557.

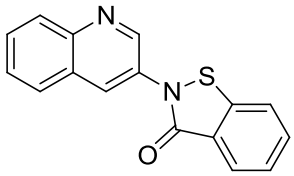
2–(2,6–Dimethylphenyl)benzo[*d*]isothiazol–3(2*H*)–one (2i). 

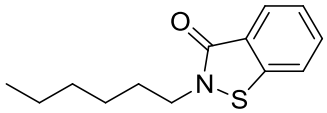
50.1 mg, 98%, white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.38, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.8 Hz, 1H), 7.72–7.64 (m, 1H), 7.61 (d, *J* = 8.0 Hz, 1H), 7.45 (m, 1H), 7.29–7.24 (m, 1H), 7.17 (d, *J* = 7.8 Hz, 2H), 2.20 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 141.6, 138.4, 133.6, 132.3, 129.9, 128.8, 127.6, 125.7, 124.4, 120.7, 18.2; IR (KBr, ν/cm^{-1}) 3444, 2951, 2919, 2854, 1653, 1598, 1471, 1445, 1325, 1307, 1245, 1129, 775, 740; HRMS (ESI$^+$) Calcd for $C_{15}H_{13}NOS$ (M+Na$^+$) 278.0610, Found 278.0607.

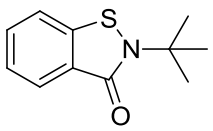
2–(1–Naphthalenyl)benzo[*d*]isothiazol–3(2*H*)–one (2j). 

52.8 mg, 95%, white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.30, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.8 Hz, 1H), 7.99–7.92 (m, 2H), 7.73 (d, *J* = 7.8 Hz, 1H), 7.70 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 2H), 7.59–7.47 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 141.7, 134.7, 132.8, 132.6, 130.9, 130.3, 128.7, 127.9, 127.6, 127.5, 127.0, 126.0, 125.6, 123.9, 123.2, 120.5; IR (KBr, ν/cm^{-1}) 3444, 1659, 1596, 1507, 1446, 1394, 1305, 1272, 1139, 908, 798, 770, 739, 672, 645, 613; HRMS (ESI$^+$) Calcd for $C_{17}H_{11}NOS$ (M+Na$^+$) 300.0454, Found 300.0449.

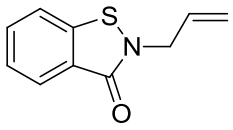
2–(3–Pyridinyl)benzo[*d*]isothiazol–3(2*H*)–one (2k).  43.8 mg, 95%, brown solid, TLC (hexane/AcOEt = 2/1): R_f = 0.43, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.93 (d, *J* = 2.2 Hz, 1H), 8.53 (d, *J* = 3.9 Hz, 1H), 8.16 (m, 1H), 8.09 (d, *J* = 8.0 Hz, 1H), 7.69–7.64 (m, 1H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.44 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.40 (dd, *J* = 8.0, 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.6, 147.7, 145.1, 139.9, 134.7, 133.1, 131.7, 127.5, 126.3, 124.3, 124.0, 120.5; IR (KBr, ν/cm^{-1}) 3688, 3647, 3472, 3098, 1670, 1652, 1574, 1481, 1446, 1424, 1322, 1301, 1133, 801, 781, 734, 699, 670, 633; HRMS (ESI$^+$) Calcd for $C_{12}H_8N_2OS$ (M+Na$^+$) 251.0250, Found 251.0240.

2–(3–Quinolinyl)benzo[*d*]isothiazol–3(2*H*)–one (2l).  Reaction conditions: DMSO (2.0 mL), 100 ^{o}C, 5 h. Purification: silica gel column chromatography (hexane/AcOEt = 1/1). 50.2 mg, 90%, brown solid, TLC (hexane/AcOEt = 3/1): R_f = 0.25, ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (d, *J* = 2.6 Hz, 1H), 8.54 (d, *J* = 2.4 Hz, 1H), 8.15 (d, *J* = 7.8 Hz, 2H), 7.88 (d, *J* = 7.8 Hz, 1H), 7.77–7.69 (m, 2H), 7.66–7.59 (m, 2H), 7.49 (dd, *J* = 7.8, 7.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.8, 146.8, 146.6, 140.1, 133.1, 131.4, 130.3, 130.1, 129.6, 128.1, 127.93, 127.87, 127.6, 126.4, 124.4, 120.6; IR (KBr, ν/cm^{-1}) 3442, 1664, 1630, 1597, 1426, 1344, 1320, 1296, 1423, 1107, 974, 781, 733, 670; HRMS (ESI$^+$) Calcd for $C_{16}H_{10}N2OS$ (M+Na$^+$) 301.0406, Found 301.0409.

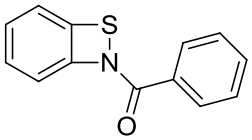
2–Hexylbenzo[*d*]isothiazol–3(2*H*)–one (2m).  46.8 mg, >99%, pale yellow solid, TLC (hexane/AcOEt = 3/1): R_f = 0.52, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 7.5 Hz, 1H), 7.62–7.57 (m, 1H), 7.57–7.52 (m, 1H), 7.39 (ddd, *J* = 7.5, 7.5, 1.3 Hz, 1H), 3.89 (td, *J* = 7.4, 2.6 Hz, 2H), 1.82–1.68 (m, 2H), 1.42–1.24 (m, 6H), 0.88 (t, *J* = 5.7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.5, 140.3, 131.8, 126.8, 125.6, 125.1, 120.5, 44.2, 31.6, 29.7, 26.5, 22.7, 14.2; IR (KBr, ν/cm^{-1}) 3457, 2955, 2928, 2857, 1649, 1598, 1447, 1339, 1303, 1248, 1189, 740, 673; HRMS (ESI$^+$) Calcd for $C_{13}H_{17}NOS$ (M+Na$^+$) 258.0923, Found 258.0918.



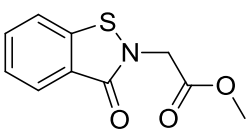
2–(*tert*–Butyl)benzo[*d*]isothiazol–3(2*H*)–one (2n). 38.2 mg, 92%, white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.55, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (d, *J* = 7.7 Hz, 1H), 7.55 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.34 (dd, *J* = 7.7, 7.7 Hz, 1H), 1.69 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.8, 139.6, 131.5, 127.1, 126.3, 125.3, 119.9, 58.9, 28.6; IR (KBr, ν/cm^{-1}) 3479, 3065, 2970, 2929, 1644, 1594, 1540, 1394, 1365, 1324, 1303, 1204, 1155, 786, 741, 675; HRMS (ESI$^+$) Calcd for $C_{11}H_{13}NOS$ (M+Na$^+$) 230.0616, Found 230.0608.



2–Allylbenzo[*d*]isothiazol–3(2*H*)–one (2o). 36.2 mg, 95%, yellow white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.35, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 8.2 Hz, 1H), 7.59 (m, 1H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.39 (dd, *J* = 7.6, 7.6 Hz, 1H), 5.93 (ddt, *J* = 17.8, 12.0, 7.4 Hz, 1H), 5.33 (ddt, *J* = 17.8, 1.1, 1.0 Hz, 1H), 5.30 (ddt, *J* = 12.0, 1.3, 1.1 Hz, 1H), 4.56 (ddd, *J* = 7.4, 1.3, 1.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.3, 140.6, 132.6, 132.0, 126.9, 125.7, 124.9, 120.6, 119.5, 46.4; IR (KBr, ν/cm^{-1}) 3447, 2918, 1644, 1447, 1334, 1314, 1284, 1240, 1192, 990, 932, 785, 740, 673; HRMS (ESI$^+$) Calcd for $C_{10}H_9NOS$ (M+Na$^+$) 214.0297, Found 214.0293.

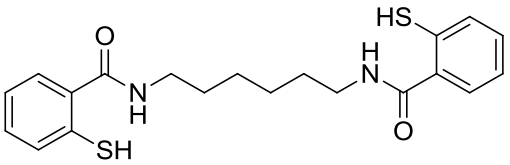


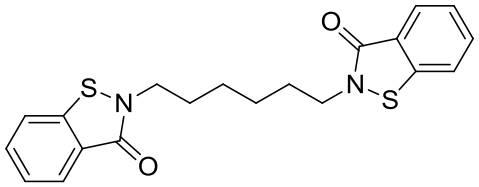
7–Thia–8–azabicyclo[4.2.0]octa–1,3,5–trien–8–yl(phenyl)methanone (2p). Reaction conditions: DMSO (2.0 mL), 100 ^{o}C, 5 h. Purification: silica gel column chromatography (hexane/AcOEt = 3/1). 38.0 mg, 84%, white solid, TLC (hexane/AcOEt = 3/1): R_f = 0.63, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.09 (m, 3H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.50 (m, 4H), 7.39 (dd, *J* = 7.6, 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.3, 154.4, 135.3, 133.9, 131.2, 129.3, 127.8, 126.6, 125.4, 123.5, 121.9; IR (KBr, ν/cm^{-1}) 3065, 3019, 1509, 1478, 1455, 1314, 1225, 1159, 1071, 963, 908, 764, 730, 688, 666, 622; HRMS (ESI$^+$) Calcd for $C_{13}H_9NOS$ (M+Na$^+$) 250.0297, Found 250.0298.



Methyl 2–(3–oxobenzo[*d*]isothiazol–2(3*H*)–yl)acetate (2q). 43.0 mg, 96%, yellow oil, TLC (hexane/AcOEt = 1/2): R_f = 0.34, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.56 (d, *J* = 7.8 Hz, 1H), 7.42 (dd, *J* = 7.8, 7.8 Hz, 1H), 4.62 (s, 2H), 3.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.3, 166.1, 141.0, 132.6, 127.1, 125.9, 123.5, 120.6, 52.9, 44.8; IR (KBr, ν/cm^{-1})

3446, 1749, 1647, 1636, 1339, 1316, 1213, 1088, 742; HRMS (ESI^+) Calcd for $C_{10}H_9NO_3S$ ($M+Na^+$) 246.0195, Found 246.0186.

***N*,*N*'–(Hexane–1,6–diyl)bis(2–mercaptobenzamide) (3).**  3.43 g, 93%, light green solid, TLC (hexane/AcOEt = 1/2): R_f = 0.18; ^1H NMR (400 MHz, DMSO) δ 8.51 (s, 2H), 7.47 (d, *J* = 7.5 Hz, 2H), 7.40 (d, *J* = 7.5 Hz, 2H), 7.27 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.15 (dd, *J* = 7.5, 7.5 Hz, 2H), 5.36 (s, 2H), 3.29–3.11 (m, 4H), 1.52 (m, 4H), 1.36 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.9, 133.7, 133.1, 131.2, 130.8, 128.1, 125.5, 39.8, 29.7, 26.4; IR (KBr, ν/cm^{-1}) 3455, 3010, 2920, 1702, 1637, 1540, 1424, 1368, 1317, 1236, 1093, 744; HRMS (ESI^+) Calcd for $C_{20}H_{24}N_2O_2S_2$ ($M+Na^+$) 411.1171, Found 411.1156.

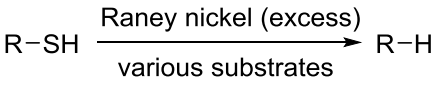
2,2'–(Hexane–1,6–diyl)bis(benzo[*d*]isothiazol–3(2*H*)–one) (**4**).  66.0 mg, 87%, white solid, TLC (hexane/AcOEt = 1/2): R_f = 0.34; ^1H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.5 Hz, 2H), 7.59 (dd, *J* = 7.5, 7.5 Hz, 2H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.40 (dd, *J* = 7.5, 7.5 Hz, 2H), 3.89 (t, *J* = 7.1 Hz, 4H), 1.81–1.73 (m, 4H), 1.50–1.41 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 140.3, 131.9, 126.9, 125.7, 125.0, 120.6, 44.0, 30.0, 26.4; IR (KBr, ν/cm^{-1}) 3453.9, 2929.3, 2856.1, 2799.2, 1638.2, 1459.9, 1446.4, 1187.9, 1160.0, 1100.2, 786.8, 741.5, 674.0; HRMS (ESI^+) Calcd for $C_{20}H_{20}N_2O_2S_2$ ($M+Na^+$) 407.0858, Found 407.0840.

5. Molybdenum–Mediated Desulfurization of Thiols and Disulfides

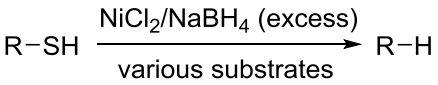
5.1. Introduction

I realized a copper–catalyzed N–S bond formation reaction in Project 4. I herein developed a molybdenum–catalyzed desulfurization reaction. Desulfurization reactions are important in organic syntheses,[1] production of non–polluting fuels,[2] and decomposition of sulfur–containing wastes to reduce the environmental burden of industrial processes. Desulfurization reactions have a long history and several methods have been developed. Reductive desulfurization using Raney nickel is one of the most important and practically useful methods (Figure 5-1a).[3] Despite its wide application, this method has several problems, such as catalyst instability (unstable to air and ignitable), poor functional group tolerance, and formation of toxic H_2S gas. Several other desulfurization methods are available that use the following compounds: nickel boride (Figure 5-1b);[4] sodium hydride containing Ni complex reducing reagents (Figure 5-1c);[5] $Fe_3(CO)_{12}$ or $Co_2(CO)_8$ under phase transfer catalysis (Figure 5-1d);[6] carbon monoxide and water in the presence of $Co_2(CO)_8$ at high temperature under high pressure (Figure 5-1e);[7] Co–Mo/Al_2O_3 catalyst at high temperature (Figure 5-1f);[8] molybdenum vapor (Figure 5-1g);[9] Mo(110);[10] and formic acid at high temperature (Figure 5-1h).[11] Only a few examples of desulfurization reactions with high functional group tolerance and high transformation, however, are reported. I realized molybdenum–mediated desulfurization of thiophenols, benzylic thiols, primary and secondary alkanethiols, and disulfides. This desulfurization reaction has wide substrate scope and high functional group tolerance. One of superiorities is that molybdenum salts are very stable in air or moisture, which are easy to be operated and measured.

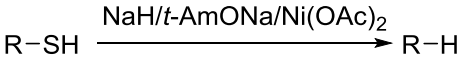
(a) Using Raney nickel



(b) Using Ni_2B

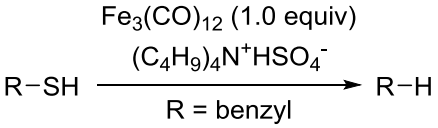


(c) Using nickel-containing reducing agents

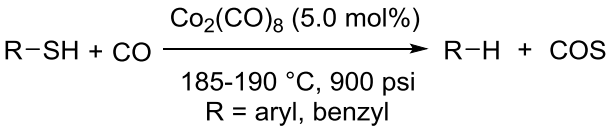


Substrates: Thiols, thioethers, dithioethers

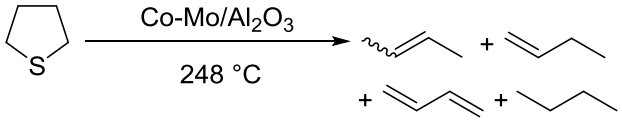
(d) Using $Fe_3(CO)_{12}$



(e) Using $Co_2(CO)_8$ and carbon monoxide

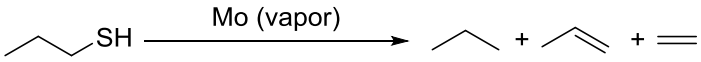


(f) Desulfurization of thiophenes using Co-Mo/Al_2O_3 catalysts



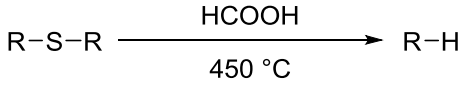
Substrates: Thiophene, tetrahydrothiophene, butanethiol
mixture of several products

(g) Using molybdenum vapor



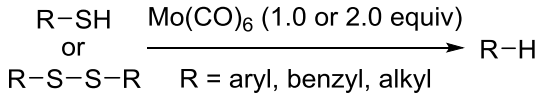
Substrates: 2-methylthiirane, thietane, 1-pronanethiol, diallyl sulfide
mixture of several products

(h) Using formic acid



mixture of several products

(i) This work



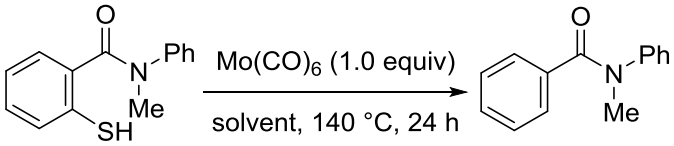
high functional group tolerance

Figure 5-1. Examples of desulfurization reactions

5.2. Optimization Studies

I used 2–mercapto–*N*–methyl–*N*–phenylbenzamide (**1a**) as a starting material. When I modified the reaction conditions, I found that the selection of a transition metal complex was quite important in this reaction, and a series of transition–metal carbonyl complexes were investigated. The desulfurization reaction only proceeded using molybdenum hexacarbonyl ($Mo(CO)_6$). However, only a trace amount of desulfurized product was formed in DMF when using the following other transition metal carbonyl complexes: $Cr(CO)_6$, $W(CO)_6$, $MnBr(CO)_5$, $Mn_2(CO)_{10}$, $Re_2(CO)_{10}$, $ReBr(CO)_5$, $[ReBr(CO)_3(thf)]_2$, $CpRe(CO)_3$, $Fe(CO)_5$, $Fe_2(CO)_9$, $Fe_3(CO)_{12}$, $Ru_3(CO)_{12}$, $[CpFe(CO)_2]_2$, $[CpRu(CO)_2]_2$, $RuHCl(CO)(PPh_3)_3$, $Co_2(CO)_8$, $[RhCl(CO)_4]_2$, $Ir_4(CO)_{12}$, and $IrH(CO)(PPh_3)_3$. The desulfurization reaction proceeded in many organic solvents using $Mo(CO)_6$ (Table 5-1, entries 1–17). When acetone was used as a solvent, the yield was improved by decreasing both the reaction temperature and the reaction time: treatment of 2–mercapto–*N*–methyl–*N*–phenylbenzamide (**1a**) with 1.0 equiv of $Mo(CO)_6$ in acetone at 120 ℃ for 6 h gave desulfurized product **2a** in 81% yield (entry 18).[12,13,14] In this reaction, the amide group remained unchanged and did not inhibit the desulfurization.

Table 5-1. Investigation of Several Solvents



1a **2a**

Entry	Solvent	Yield (%)
1	octane	40
2	dioxane	52
3	xylenes	39
4	toluene	45
5	tert-butyl methyl ether	51
6	chlorobenzene	44
7	trifluorobenzene	45
8	1,2-dichlorobenzene	67
9	THF	78
10	1,2-dichloroethane	39
11	benzonitrile	44
12	NMP	58
13	DMA	65
14	DMF	69
15	acetonitrile	62
16	DMSO	28
17	acetone	60
18[a]	acetone	81

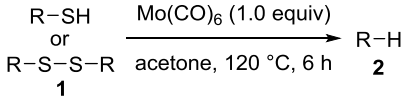
(a 120 ^{o}C, 6 h.)

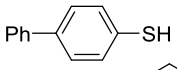
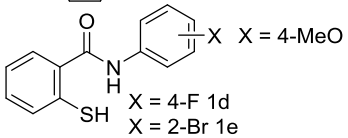
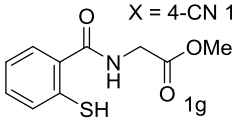
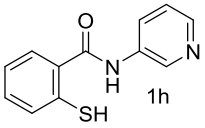
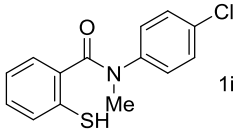
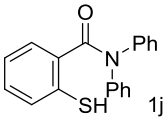
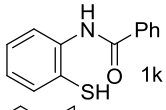
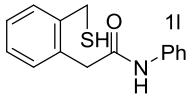
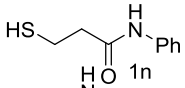
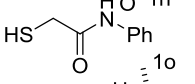
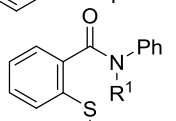
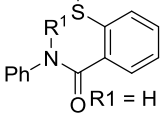
5.3. Substrate Scope and Mechanism Research

With the best reaction conditions in hand, I then investigated the substrate scope of the molybdenum–catalyzed desulfurization reaction (Table 5-2). The desulfurization reaction proceeded in good to excellent yields when thiophenol derivatives **2b**–**2k** were used as substrates (entries 1–10). The desulfurization reaction was not affected by the electronic effect (entries 2–5) and steric effect (entries 2–10). In addition, the functional groups, such as methoxy, fluoro, chloro, bromo, cyano, ester, amide, and pyridyl groups (entries 2–8), and C=C double bond (entry 15) were intact, whereas several functional groups, such as bromo[15] and cyano[16] groups and the C=C

double bond,[17] are unstable by using the Raney nickel method. Desulfurization of benzyl thiol **1l** as well as primary and secondary alkanethiols **1m**–**1p** also proceeded in 66%–85% yields (entries 11–15). Interestingly, the desulfurization reaction also proceeded using disulfides **1q** and **1r** as substrates (entries 16 and 17). A driving force behind the desulfurization reaction is the strong molybdenum–sulfur bond (ΔH_f = 659 kJ/mol).[18]

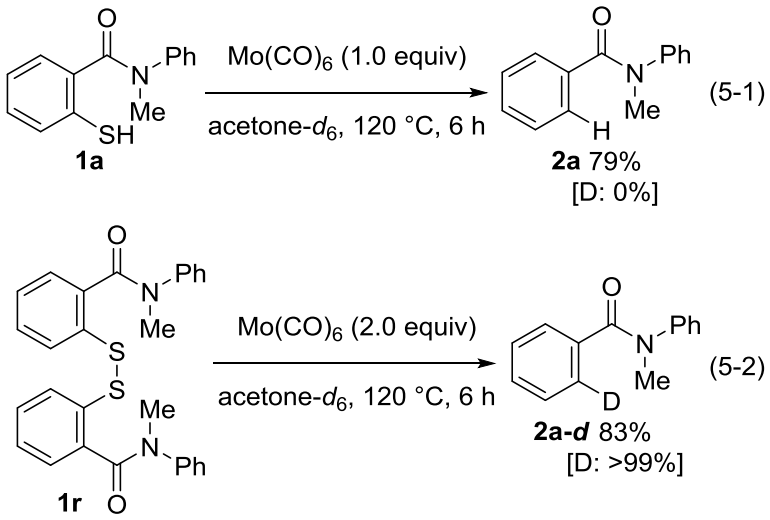
Table 5-2. Desulfurization of Several Thiocompounds



Entry	1	Yield (%)
1		2b 81
2	 X = 4-MeO	2c 79
3	X = 4-F 1d	2d 80
4	X = 2-Br 1e	2e 72
5	X = 4-CN 1f	2f 71
6	 1g	2g 74
7	 1h	2h 73
8	 1i	2i 71
9	 1j	2j 88
10	 1k	2k 67
11	 1l	2l 80
12	^{n}C18H37SH 1m	2m 85
13	 1n	2n 66
14	 1o	2o 74
15	1p	2p 81
16[a]		2q 75
17[a]	 R1 = H 1q R1 = Me 1r	2r 77

a Mo(CO)6 (2.0 equiv).

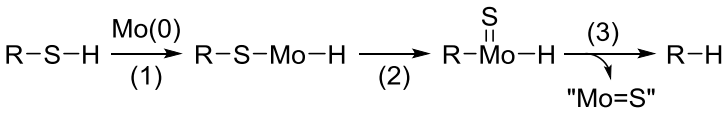
To elucidate the hydrogen source, I performed the reaction using thiophenol **1a** or disulfide **1r** with $Mo(CO)_6$ in acetone–d_6 (eq 5-1 and 5-2). Non–deuterated amide **2a** was formed from thiol **1a** in 79% yield (eq 5-1). In the case of disulfide **1r**, deuterated amide **2a**–***d*** was obtained in 83% yield [D: >99%] (eq 5-2). These results suggest that the hydrogen sources of **1a** and **1r** are the hydrogen atoms of an SH group and acetone (solvent), respectively.



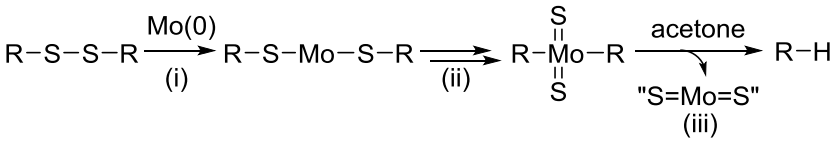
The proposed mechanism of the desulfurization reaction is as follows (Scheme 5-1): (1) oxidative addition of a thiol to a molybdenum center;[19] (2) formation of molybdenum–carbon bond via the formation of a Mo=S double bond;[19] and (3) reductive elimination to give a desulfurized product (Figure 5-1a). In the case of disulfides, the following mechanism is proposed: (i) oxidative addition of a disulfide to a molybdenum center; (ii) formation of molybdenum–carbon bond via the formation of Mo=S double bond(s);[20] and (iii) quench of the organomolybdenum intermediate with acetone (solvent) to give a desulfurized product (Scheme 1b).

Scheme 5-1. Possible Reaction Mechanisms

(a) Desulfurization of Thiols



(b) Desulfurization of Disulfides



5.4. Summary

In summary, I successfully achieved a molybdenum–mediated desulfurization reaction of thiophenols, alkanethiols (benzylic, primary, and secondary), and disulfides. This reaction has high functional group tolerance, and the desulfurization reaction proceeded with maintenance of the functional groups, such as amide, methoxy, cyano, ester, and pyridyl groups, halogen atoms (fluorine, chlorine, and bromine atoms), and the C=C double bond. The functional group maintenance is an advantage of this method compared with the widely used reductive Raney nickel method. In addition, the desulfurization reaction was not affected by steric hindrance. One of important features of this reaction is that molybdenum is stable against air and moisture, the operation of this reaction is easy to carry out. The present reaction is anticipated to become a choice reaction for desulfurization of thiophenols, alkanethiols, and disulfides.

5.5. References and Notes

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(12) Investigation of reaction temperatures: 140 ℃, 59%; 130 ℃, 63%; 120 ℃, 81%; 110 ℃, 55%; 100 ℃, 23%; 80 ℃, trace.

(13) Investigation of the amount of Mo(CO)6 (140 ℃): 1.0 equiv, 81%; 0.75 equiv, 71%; 0.50 equiv, 38%; 0.20 equiv, 11%; 0.10 equiv, <5%.

(14) Typical procedure for molybdenum–mediated desulfurization of thiols in 1 mmol scale. A mixture of 2–mercapto–N–methyl–N–phenylbenzamide (1a, 243 mg, 1.00 mmol), Mo(CO)6 (264 mg, 1.00 mmol), and acetone (10.0 mL) in a pressure–resistant glass tube was stirred at 120 ℃ for 6 h. Then, the reaction mixture was subjected to a short pad of Celite and the precipitate was washed with ethyl acetate (200 mL). The solvent was removed in vacuo, and the residue was subjected to column chromatography on silica gel (hexane/ethyl acetate = 3:1) to give 2a (154 mg, 73% yield). yellow solid, 1H NMR (500 MHz, CDCl3) δ 7.30–7.28 (m, 2H), 7.24–7.20 (m, 3H), 7.17–7.12 (m, 3H), 7.03 (d, J = 8.0 Hz, 2H), 3.50 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 170.9, 145.1, 136.1, 129.8, 129.4, 128.9, 127.9, 127.1, 126.7, 38.6.

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5.6. Supporting Information

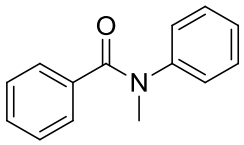
General. All reactions were carried out in a dry solvent under argon atmosphere unless otherwise noted. $Mo(CO)_6$ (99.9%) were purchased from Aldrich. THF were purchased from Wako Pure Chemical Industries, and were dried and degassed before use. NMR spectra were recorded on JEOL ECX500 (500 MHz for ^{1}H NMR and 125 MHz for ^{13}C NMR) spectrometer 400 MHz (400 MHz for 1H NMR and 100 MHz for ^{13}C NMR) spectrometers. Proton chemical shifts are reported relative to residual solvent peak ($CDCl_3$ at 7.26 ppm). Carbon chemical shifts are reported relative to residual solvent peak ($CDCl_3$ at 77.3 ppm). The following abbreviations are used to designate multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quint = quintet, m = multiplet, br = broad. IR spectra were recorded on a JASCO FT/IR–410. High–resolution mass spectra (HRMS) were measured on a JEOL JMS–T100LC AccuTOF spectrometer (for HRMS).

Compounds **2a**,[1] **2b**,[2] **2c**,[3] **2d**,[4] **2e**,[5] **2f**,[6] **2g**,[7] **2h**,[8] **2i**,[9] **2j**,[10] **2k**,[3] **2l**,[11] **2m**,[12] **2n**,[4] **2o**,[4] and **2p**,[13] were known and identified by comparison with the reported ^{1}H and/or ^{13}C NMR spectra.

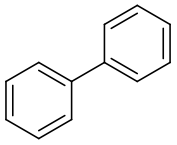
Typical procedure for Molybdenum–Mediated Desulfurization of Thiols and Disulfides: A

mixture of 2–mercapto–N–methyl–N–phenylbenzamide (**1a**, 24.2 mg, 0.100 mmol), $Mo(CO)_6$ (3.63 mg, 20.0 μmol), and THF (1.0 mL) was stirred at 140 ℃ for 24 h. Then, the reaction mixture was subjected to column chromatography on silica gel (hexane/ethyl acetate = 3:1) to give **2a**.

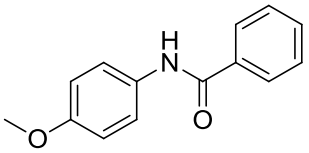
***N*–Methyl–*N*–phenylbenzamide (2a).** 17.5 mg, 83% yield, yellow solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30–7.28 (m, 2H), 7.24–7.20 (m, 3H), 7.17–7.12 (m, 3H), 7.03 (d, J = 8.0 Hz, 2H), 3.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 145.1, 136.1, 129.8, 129.4, 128.9, 127.9, 127.1, 126.7, 38.6.



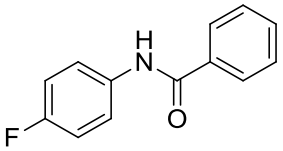
1,1'–Biphenyl (2b). 12.5 mg, 81% yield, yellow oil, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62–7.57 (m, 4H), 7.44 (dd, J = 7.5, 7.5 Hz, 4H), 17.35 (t, J = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.5, 129.0, 127.5, 127.4.



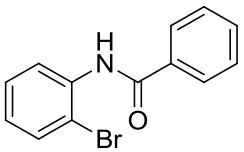
***N*–(4–Methoxyphenyl)benzamide (2c)**. 18.0 mg, 79% yield, white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89–7.82 (m, 3H), 7.55–7.51 (m, 3H), 7.44 (dd, J = 7.4, 7.4 Hz, 2H), 6.88 (d, J = 8.2 Hz, 2H), 3.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.8, 156.8, 135.3, 131.9, 131.2, 129.0, 127.2, 122.4, 114.5, 55.7.



***N*–(4–Fluorophenyl)benzamide (2d)** 17.2 mg, 80% yield, white solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, J = 8.4 Hz, 2H), 7.80 (s, 1H), 7.63–7.54 (m, 3H), 7.49 (dd, J = 7.6, 7.6 Hz, 2H), 7.07 (dd, J = 8.4, 8.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 165.9, 159.3 (d, J = 244 Hz), 135.0, 134.1 (d, J = 3.3 Hz), 132.2, 129.1, 127.2, 122.3 (J = 7.5 Hz), 116.0 (J = 22.7 Hz).

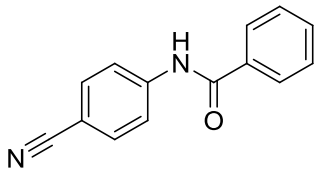


***N*–(2–Bromophenyl)benzamide (2e)**. 19.9 mg, 72% yield, white solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.56 (d, J = 7.9 Hz, 1H), 8.47 (s, 1H), 7.94 (d, J = 7.4 Hz, 2H), 7.59–7.51 (m, 4H), 7.38 (dd, J = 7.9, 7.9 Hz, 1H), 7.02 (dd, J = 7.3, 7.3 Hz, 1H); ^{13}CNMR (126 MHz, $CDCl_3$) δ 165.5, 136.1, 134.9,

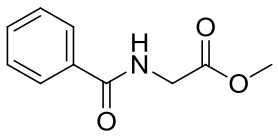


132.5, 132.4, 129.2, 128.8, 127.4, 125.5, 122.0, 114.0.

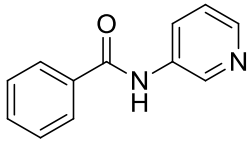
***N*–(4–Cyanophenyl)benzamide (2f)**. 15.8 mg, 71% yield, white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.90–7.83 (m, 2H), 7.83–7.74 (m, 2H), 7.68–7.54 (m, 3H), 7.55–7.43 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 142.3, 134.3, 133.5, 132.7, 129.2, 127.4, 120.2, 119.1, 107.5.



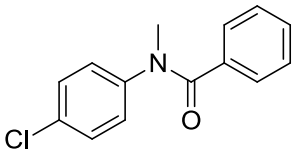
Methyl 2–benzamidoacetate (2g). 14.3 mg, 74% yield, white solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 8.3 Hz, 2H), 7.52 (t, J = 6.8 Hz, 1H), 7.44 (dd, J = 8.3, 6.8 Hz, 2H), 6.72 (s, 1H), 4.25 (d, J = 5.0 Hz, 2H), 3.80 (s, 3H); ^{13}CNMR (126 MHz, $CDCl_3$) δ 170.8, 167.7, 133.9, 132.1, 128.9, 127.3, 52.7, 42.0.



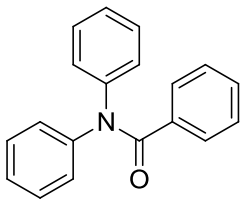
***N*–(Pyridin–3–yl)benzamide (2h)**. 14.5 mg, 73% yield, yellow solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.69 (s, 1H), 8.41 (s, 1H), 8.33 (d, J = 8.7 Hz, 1H), 7.95–7.88 (m, 3H), 7.61–7.50 (m, 3H), 7.34 (d, J = 7.5 Hz, 1H); 13C NMR (100 MHz, $CDCl_3$) δ 167.5, 145.5, 141.7, 138.5, 135,8, 132.6, 129.2, 128.77, 127.3, 124.0.



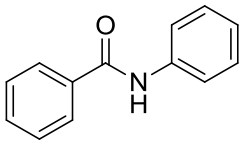
***N*–(4–Chlorophenyl)–*N*–methylbenzamide (2i).** 17.4 mg, 73% yield, white solid, ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.23 (m, 3H), 7.20–7.17 (m, 4H), 6.96 (d, J = 8.5 Hz, 2H), 3.46 (s, 3H); ^{13}C NMR (100MHz, $CDCl_3$) δ 170.8, 143.7, 135.8, 132.3, 130.1, 129.5, 128.9, 128.3, 128.2, 38.6.



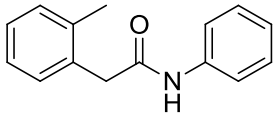
***N*,*N*–Diphenylbenzamide (2j)**. 24.1 mg, 88% yield, white solid, ^{1}HNMR (400 MHz, $CDCl_3$) δ 7.53–7.45 (m, 2H), 7.38–7.28 (m, 5H), 7.26 (m, 8H); 13C NMR (100 MHz, $CDCl_3$) δ 170.9, 144.1, 136.3, 130.4, 129.4, 129.3, 128.1, 127.7, 126.6.



***N*–Phenylbenzamide (2k)**. 13.2 mg, 67% yield, white solid, ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.87 (d, J = 8.1 Hz, 2H), 7.82 (s, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.56 (t, J = 6.8 Hz, 1H), 7.49 (dd, J = 8.1,6.8 Hz, 2H), 7.38 (dd, J = 8.1, 7.4 Hz, 2H), 7.16 (t, J = 7.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 166.1, 138.2, 135.2, 132.0, 129.3, 129.0, 127.3, 124.8, 120.5.



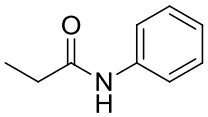
***N*–Phenyl–2–(*o*–tolyl)acetamide (2l)**. 18.0 mg, 80% yield, white solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (d, J = 8.3 Hz, 2H), 7.30–7.24 (m, 6H), 7.13 (s, 1H), 7.08 (dd, J = 7.4, 7.4 Hz, 1H), 3.74 (s, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.2, 137.8, 137.6, 133.2, 131.2, 130.8, 129.1, 128.4, 127.0, 124.7, 120.1, 43.1, 19.8.



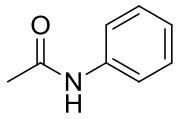
Octadecane (2m). 21.6 mg, 85% yield, white solid,

1H NMR (500 MHz, $CDCl_3$) δ 1.34–1.19 (m, 32H), 0.88 (t, J = 6.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 32.2, 30.0 (8C), 29.9, 29.6, 23.0, 14.4.

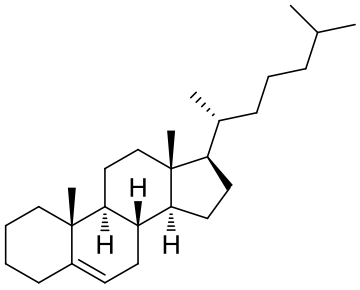
***N*–Phenylpropionamide (2n)**. 9.8 mg, 66% yield, white solid, ^{1}HNMR (500 MHz, $CDCl_3$) δ 7.52 (d, J = 7.5 Hz, 2H), 7.32 (dd, J = 7.5,7.5 Hz, 2H), 7.17 (s, 1H), 7.10 (t, J = 7.5 Hz, 1H), 2.40 (q, J = 7.4 Hz, 2H), 1.25 (t, J = 7.4 Hz, 3H); 13C NMR (126 MHz, $CDCl_3$) δ 172.2, 138.2, 129.2, 124.4, 120.0, 31.0, 9.9.



***N*–Phenylacetamide (2o).** 10.0 mg, 74% yield, white solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, J = 7.7 Hz, 2H), 7.45 (s, 1H), 7.31 (dd, J =7.7, 7.7 Hz, 2H), 7.10 (t, J = 7.7 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.7, 138.1, 129.2, 124.5, 120.2, 24.8.

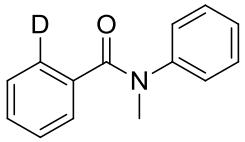


Cholest–5–ene (2p). 30.0 mg, 81% yield, white solid, ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.34–5.20(m, 1H), 2.34–2.17 (m, 1H), 2.05–1.92 (m, 3H), 1.88–1.78 (m, 2H), 1.72 (d, J = 12.4 Hz, 1H), 1.63–1.02 (m, 23H), 1.00 (s, 3H), 0.92 (d, J = 6.5 Hz, 3H), 0.87 (d, J =



2.2 Hz, 3H), 0.86 (d, J = 2.2 Hz, 3H), 0.68 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.9, 119.2, 57.1, 56.4, 50.8, 42.6, 40.14, 40.12, 39.8, 37.8, 36.5, 36.1, 33.2, 32.15, 32.14, 28.5, 28.32, 28.27, 24.5, 24.1, 23.1, 22.8, 21.0, 19.7, 19.0, 12.1.

Deuterated *N*–methyl–*N*–phenylbenzamide (2a–d). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, J = 7.9 Hz, 1H), 7.25–7.05 (m, 6H), 7.05–6.88 (m, 2H), 3.50 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 170.9, 145.2, 136.1, 129.8, 129.4, 129.0, 128.0, 127.8, 127.2, 126.7, 38.6 (A carbon signal which is connected to a deuterium atom was not observed.); HRMS (ESI+) Calcd for C14H12DNO (M+Na+) 235.0952, Found 235.0959.



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I am the luckiest man, because I can study and learn in Kanai's lab; I am the most unlucky person, because I could not talk and discuss science with Kanai sensei everyday. I could not forget the day when Kanai sensei gave me a telephone interviews, because that is the first time I talked English in day life. Although my English is very poor, kanai sensei still gave me a chance to learn in his lab, I really cherish this opportunity. In the past three years, Kanai sensei help me a lot on my living and research, he teached me how to study, how to finish a project, how to write proposal materials, and how to be a good and professional scientist. I really enjoy the biweekly discussion and research seminar time, since I can directly learn from him. The happiest thing in his lab is reading the documents which were revised by Kanai sensei, I not only can learn how to polish a document, but also can read sparks of wisdom of Kanai sensei. It seems that Kanai sensei ont only knows the knowledges but also really understand it, the knowledge flows in his blood and is a part of his body. He is not only an excellent scientist, but also possesses a great character. He is so nice that he never lost his temper. Three chinese words,"有教无类，大智若愚，古圣先贤", are suitable to him. Suddenly I notice that no any words can accurately describe his great and express my thanks. Please accept my appreciations from the bottom of my heart!

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Art is long, and time is fleeting. When I finish my Ph. D study, my son will begin run in his dream, I really wish that he can pursue truth in the future.

Thanks every people who ever and will appear in my life!

Wang Zhen (王 震)

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