博士学位論文

Studies on Nickel-Catalyzed C-O Bond Activation with the Assistance of Directing Group

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２０２１年１月

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Preface and acknowledgement

The researches described in this thesis were carried out under the direction of Professor Naoto Chatani in the Department of Applied Chemistry at the Faculty of Engineering of Osaka University from April 2015 to March 2021. The thesis is concerned with the activation of C-O bonds with the assistance of directing groups.

I cannot finish this thesis without the help and support from many kind people. Here, I really appreciate to all of those people who I have spent together during my laboratory life in Chatani group.

First, I would like to express my sincere gratitude to Professor Naoto Chatani for his guidance and support throughout this work. He allowed me freedom about research, so I could enjoy my research. During the discussion with him, I was always surprised at his unique idea. He also supported my job hunting by writing a recommendation.

I would like to give thanks to Professor Yoshiya Fukumoto. I was a member in Fukumoto team from April 2015 to summer in 2017. He taught me about the basic things for proceeding research, such as how to analysis the data, identification of organic compounds and how to write notebook.

I also thank Dr. Yusuke Ano. He came back to Chatani group as an assistant professor from April 2017. When I have a question about research, he answered kindly. He has also joined journal club (called '*rinko*' in japanese), which leads to raise our chemistry level.

I also wish to thank Professor Mamoru Tobisu. He was an associate professor in Chatani group from April 2015 to March 2017. He is a pioneer of the research area on C-O bond activation. I was so glad to discuss with him at the PhD defense.

I express special appreciation to the secretaries in our labolatory, including Ms. Yoshimi Shinomiya and Ms. Junko Ohmagari for their kind help.

I would like to express my heartfelt thanks to Dr. Kyoko Inoue (NMR), Dr. Hiroaki Tanaka (HRMS) for the assistance at the analytical instrumentation facility. I also wish to thank the Instrumental Analysis Center for assistance with the elemental analyses.

I would like to express my special thanks to the past members of the Chatani group. As described above, I started my research in Fukumoto team. Ms. Natsuki Okazaki was my first supervisor until entrance examination for graduate school. Even though she was master 1st students and busy for class, she taught me experiment kindly. After entrance examination, Mr. Yuto Tamura became my second supervisor. I learned many kinds of experiments and how to collect spectral data of organic compounds. I worked under him only for one month (September 2015), however, I felt very hard because almost all of experimental operations were the first time for me. After that, Dr. Masaya Hirano became my third supervisor. He taught me the chemistry of silylation, and supported my bachelor thesis. I also thank to Mr. Sodai Yamada. I enjoyed the discussion about the proposal of new reaction. I also wish to acknowledge the support from my respected seniors: Dr. Takeshi Uemura, Dr. Yoshinori Aihara, Dr. Keisuke Nakamura, Dr. Kaname Shibata, Dr. Takayuki Furukawa, Dr. Toshifumi Morioka, Dr. Takuya Igarashi, Dr. Yoshihiro Masuya, Dr. Teruhiko Kubo, Mr. Tsuyoshi Takahira, Mr. Jiangning Zhao (*cho-san*), Dr. Kosuke Yasui, Mr. Takuma Yamaguchi, Ms. Mao Yamaguchi.

I also express my thanks to my classmates of the Chatani group: Dr. Chenan Wang, Mr. Atsushi Obata (more than 1200 experiments), Dr. Shun Sakurai (Mechanical engineer and PhD student in Tobisu lab), Ms. Satoko Natsui (5 experiments per day), Mr. Akihiro Nishizawa (work on new year holidays) and Mr. Kousuke Yanagisawa. I enjoyed

working with them and drinking party.

I would also wish to express my gratitude to the junior members of the Chatani group: Mr. Yuki Amano (*Amanty*), Ms. Akane Sasagawa, Mr. Akira Haito, Mr. Masaya Higashino, Mr. Nao Matsubara, Mr. Qiyuan He (*Ka-kun*), Mr. Shunsuke Ando, Ms. Rina Ueno (co-author in Chapter 2, screening of conditions using carbamates and scope of carbamates), Mr. Kenjiro Takahashi (*Kenjiro* or *Jiroken*, co-author in Chapter 1, scope of substrates with oxazolyl group and the examination of the tolerance of functional groups), Mr. Yasuhiro Takami (*ra-men* buddy, my weight was increased because of Takami.), Mr. Ken Yamazaki (co-autor in Chapter 1, assistance with the proposal of mechanism using DFT calculation), Mr. Hisayasu Ishibashi, Mr. Kazuki Azumagawa, Ms. Nozomi Ohara, Mr. Natsuki Kawai (diet buddy, we cannot get any result.), Mr. Itsuki Nohira (drinking buddy, drink together almost once a week before corona), Mr. Shizuki Monda, Mr. Hiroki Enomoto, Ms. Haruka Kawakami, Mr. Daichi Takahashi, Mr. Hikaru Noguchi, Mr. Akihisa Matsuura, Ms. Aoi Morishige (co-author in Chapter 2, colleting spectrum of products from the reaction of carbamates), Mr. Ryosuke Nagamune, Mr. Kumpei Nishimura, Mr, Tatsuya Hirano and Mr. Haruki Hirosawa.

Furthermore, I express my appreciation to Dr. Luis Carlos Misal Castro, Dr. Akimichi Ohtsuki, Dr. Yadagiri Kommagalla (*Giri-san*), Dr. Aymen Skhiri, Dr. Supriya Rej, Dr. Shrikant Kahake Manmathappa (*Shri-san*), Dr. Sanjit Kumar Mahato, Dr. Bernard Parker, Dr. Mikhail Konev, Dr. Lu Lu, Mr. Alex Moerman, Dr. Meria Ronge and Dr. Daichi Koseki who worked in the Chatani group as postdoctoral fellows or visiting students.

Finally, I would also like to express my deepest gratitude to my parents, Mr. Yasushi Iyori and Ms. Misuzu Iyori and my brother Mr. Masahito Iyori. They provided consistent support for me.

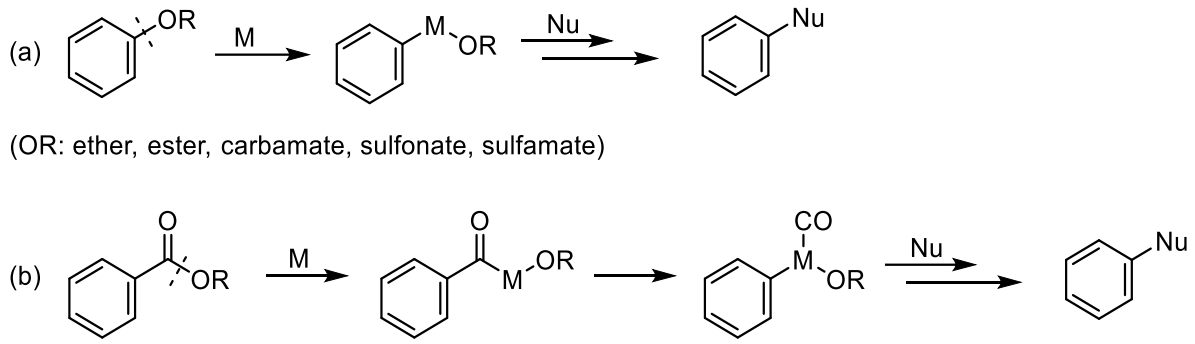
Suita, Osaka
January 2021

Yasuaki Iyori

Contents

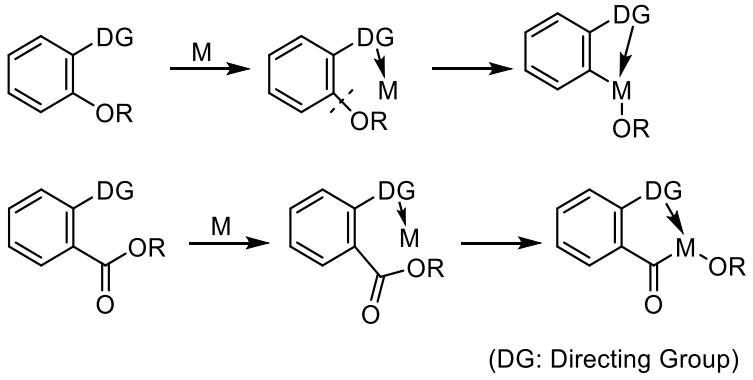
General Introduction

Cross-coupling reactions are now recognized as one of the efficient tools for the synthesis of organic molecules via the formation of new C-C bonds and C-heteroatom bonds. Although aromatic halides have generally been used as electrophilic coupling partners in cross-coupling reactions, these compounds are frequently toxic and halogen-containing waste are generated after the reaction is complete. Considerable interest has recently focused on the use of other types of electrophiles, such as phenol derivatives[1] or aromatic esters[2] in cross coupling reactions, since they are inexpensive and readily available. In both cases, the activation of a relatively inert C-O bond is the key step. Coupling reactions of phenol derivatives, such as ethers, esters, carbamates, sulfonates, and sulfamates proceeds through the oxidative addition of a C-O bond of the substrate to a catalyst followed by reaction with nucleophiles (Scheme 1a). In the case of aromatic esters, the oxidative addition of an acyl C-O bond to a catalyst followed by decarbonylation gives an aryl alkoxy metal intermediate which reacts with nucleophiles to give coupling products (Scheme 1b). The cleavage of a C-O bond has been achieved by using a combination of a low valent transition metal complex and a strong donor ligand because a C-O bond is stronger than a C-halogen bond.



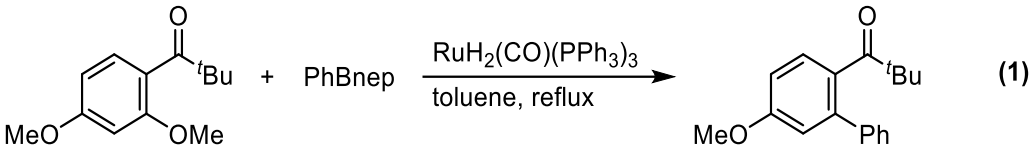
Scheme 1. Activation of C-O bonds in phenol derivatives and aromatic esters

In addition, C-O bond activation reactions assisted by a directing group have also been reported.[3] In this type of reaction, the directing group coordinates to the catalyst, and a C-O bond at the proximal position of the directing group is then cleaved (Scheme 2).



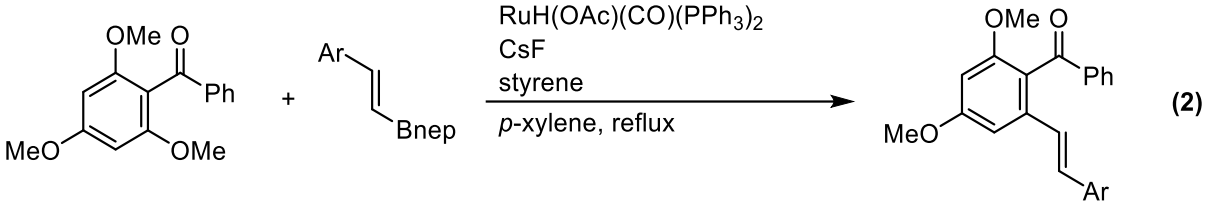
Scheme 2. C-O bond activation assisted by directing group

One of the pioneering studies on chelation-assisted C-O bond activation reactions of phenol derivatives was reported by our group in 2004 (eq 1).[4] Aromatic ketones bearing a methoxy group at the *ortho* position reacted with aryl boronic acid esters in the presence of a ruthenium complex. C-O bond activation occurred exclusively at the *ortho* position, even when the substrate contains two C-OMe bonds. Two years later, the oxidative addition complex was isolated by our group.[5] Snieckus recently reported on ester group-directed reactions[6] and amide group-directed reactions.[7]



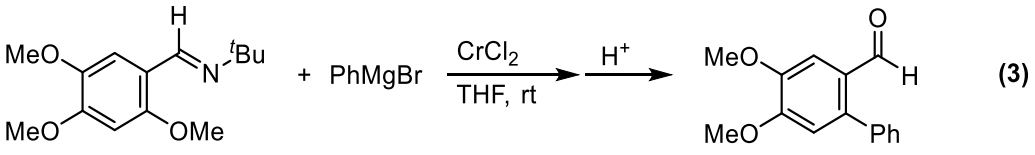
(1)

In 2015, Kakiuchi reported on the ruthenium-catalyzed mono-selective alkenylation of C-O bonds in 2,6-dimethoxyphenyl ketones with alkenyl boron compounds (eq 2).[8] When RuH(OAc)(CO)(P^iPr_3)$_2$ was used as a catalyst, aryl boronic acid esters were applicable to this system.[9]



(2)

Other transition metal catalysts were also found to promote C-O bond activation. In 2015, Zeng reported on the Kumada-Tamao-Corriu type cross-coupling reaction of *ortho*-alkoxy substituted imines in the presence of a chromium catalyst (eq 3).[10] In this reaction, an imine group functions as a directing group and the alkoxy group at the *ortho* position is specifically activated in a regioselective manner. As shown in eq 4, the reaction of carbonates with aryl boronic acid proceeded using a nickel-palladium co-catalyst system.[11] In this reaction, the formation of bimetallic nanocluster by nickel and palladium was proposed, which functions as catalytic active species.



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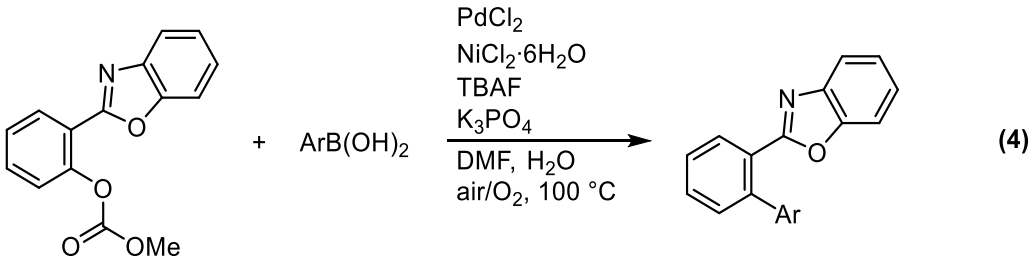
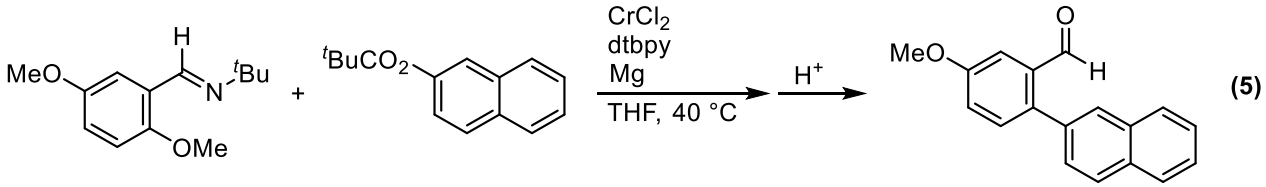


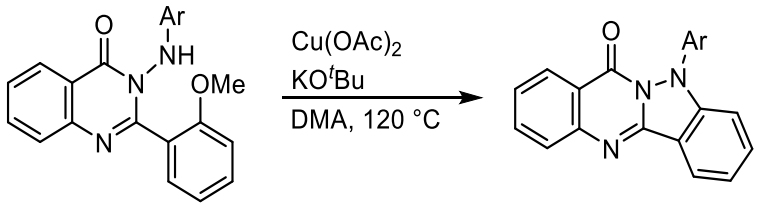
(4)

In 2020, Zeng reported that cross-electrophile coupling between two different phenol derivatives proceeds in the presence of a chromium catalyst (eq 5).[12] This reaction is the first example of the cross-electrophile coupling of C-O/C-O bonds.



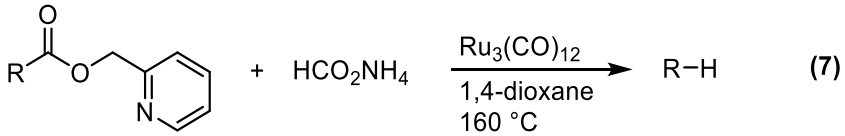
(5)

In 2017, Cheng and Wu reported on the copper-catalyzed intramolecular cyclization via the cleavage of C-O bonds (eq 6).[13] In this reaction, an amino group functions, not only as a directing group but also as a nucleophile that is eventually incorporated into the product.



(6)

Acyl C-O bond cleavage in esters has also been developed. In 2001, our group reported on the ruthenium-catalyzed reaction of an *O*-pyridylmethyl ester with $HCOONH_4$ (eq 7).[14] The nitrogen atom on a pyridine ring coordinates to a uthenium center, which promotes C-O bond activation. When aryl boronates were used as coupling partners, diaryl ketones were obtained (eq 8).[15] It was found that a palladium catalyst also promotes C-O bond activation of *O*-pyridyl ester. The use of aryl boronic acid[16] and hydrosilane[17] gave ketones and aldehydes, respectively (eq 9 and 10).



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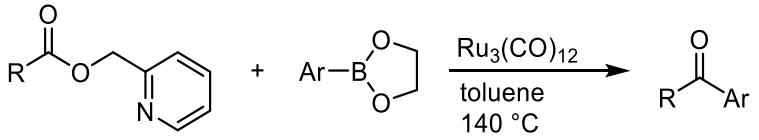

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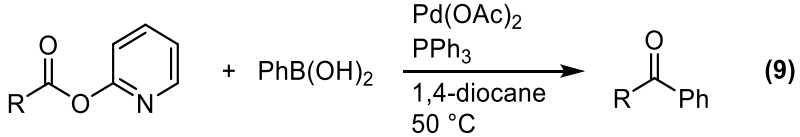

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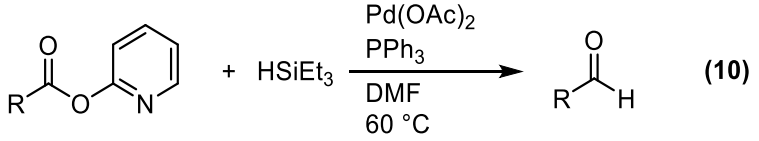
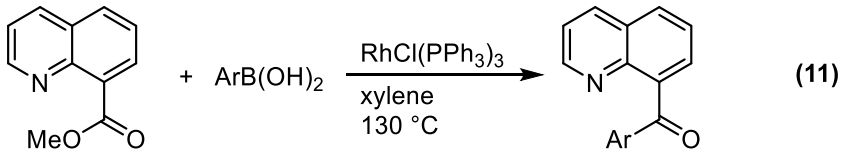


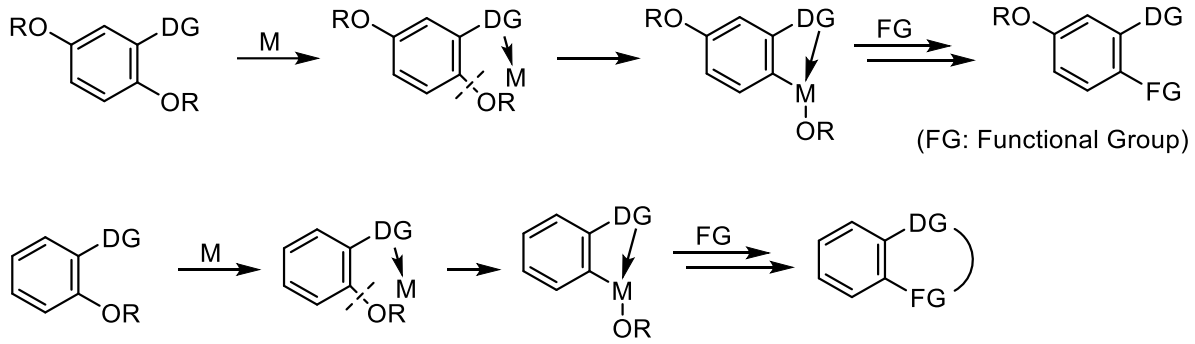
(10)

In 2013, Wang reported on the rhodium-catalyzed Suzuki-Miyaura type cross-coupling reaction of esters (eq 11).[18] The C-O bond activation of inert *O*-alkyl ester was achieved with the assistance of a quinoline ring as a directing group.



(11)

As described above, directing group-assisted reactions enable the regioselective transformation of C-O bonds to afford cross-coupling reactions. On the other hand, the synthesis of the cyclic compound that includes the directing group was also reported (Scheme 3). A directing group promotes the activation of the *ortho* C-O bond and the directing group is then incorporated into the products as a ring component.



Scheme 3. Regioselective C-O bond activation and synthesis of cyclic compounds

Inspired by the unique reactivity of the combination of a transition metal catalyst and a directing group, nickel-catalyzed C-O bond activation reactions wre explored in this research.

In Chapter 1, the nickel-catalyzed reductive removal of ester groups without an external reductant is discussed. In this reaction, the cleavage of inert acyl C-O bonds of *O*-alkyl esters is the key step.

In Chapter 2, the C-O/N-H annulation of amides with an alkoxy group at the *ortho* position with alkynes is discussed. In this reaction, the C-O bond at the *ortho* position is cleaved, even in the absence of a ligand. This methodology is applicable to C-S bond activation and C-CN bond activation.

In Chapter 3, the C-O/O-H annulation of salicylate esters with alkynes is discussed. In this reaction, an acyl C-O bond activation of salicylate esters occurs, which is promoted by a hydroxy group as a directing group. In Chapters 2 and 3, the synthesis of cyclic compounds including a directing group is reported.

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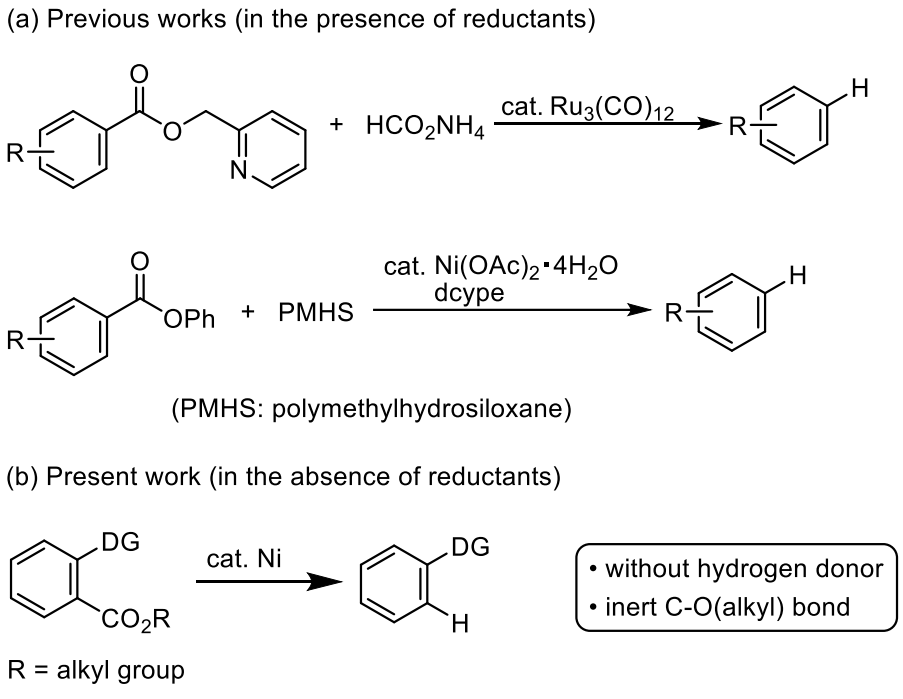
Chapter 1

Nickel-catalyzed reductive removal of ester groups without external reductant

1.1 Introduction

Defunctionalization reactions have not received much attention they deserve in organic synthesis because most of the attention has focused on the development of functionalization reactions involving the formation of new C-C and C-heteroatom bonds. However, defunctionalization reactions are related to the preparation of useful compounds from sustainable and readily available organic resources are currently of interest.[1] There are only two examples of the reductive cleavage of aromatic esters. In 2001, ruthenium-catalyzed reductive cleavage of *O*-pyridylmethyl esters with ammonium formate was reported by our group.[2] Recently, Rueping reported that nickel-catalyzed removal of ester groups from *O*-phenyl esters proceeded in the presence of hydrosilanes.[3] However, in these reports, the addition of a hydrogen donor was essential for the successful reaction. Herein, the author investigated the nickel-catalyzed reductive removal of ester groups in the absence of an external reductant, which involves inert acyl C–O bond activation of an *O*-alkyl ester.[4]



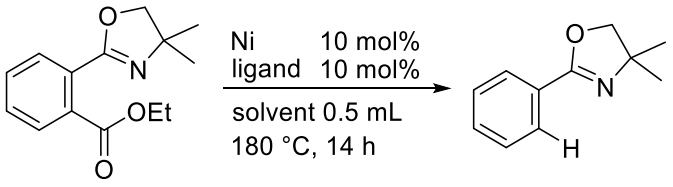
Scheme 1. Transition-metal-catalyzed reductive removal of ester groups from aromatic esters.

1.2 Results and Discussion

The author initiated this study by optimization of the conditions for the reaction of ethyl benzoate bearing an oxazolyl group at the *ortho* position, as in **1a** (Table 1). First, the effect of ligands was examined. The reaction using PCy_3 as a ligand gave the product **2** in 12% yield (entry 1). The use of dcype did not lead to any improvement in yield of **2** (entry 2). When IPr·HCl was used as ligand, the product yield was improved (entry 3). After screening of

other NHC ligands, free IMes were found to be the most effective ligand (entry 3-6). 1,4-Dioxane also can be used as a solvent (entry 7). However, when DMF and *m*-xylene were used, the reaction did not proceed efficiently (entry 8, 9). When the reaction temperature was decreased to 160 °C, the product yield was decreased to 44%, which indicates that high reaction temperature is essential to this reaction (entry 10). Ni (II) species were found to be less active under the standard reaction conditions (entry 11-13).

Table 1. Screening of conditions.[a]



1a **2**

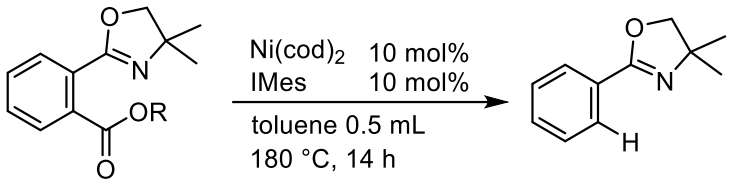
entry	Ni	ligand	solvent	GC yields[b] **2**	GC yields[b] **1a**
1	$Ni(cod)_2$	PCy_3	toluene	12%	78%
2	$Ni(cod)_2$	dcype	toluene	9%	61%
3[c]	$Ni(cod)_2$	IPr·HCl	toluene	68%	11%
4[c]	$Ni(cod)_2$	ICy·HCl	toluene	80%	3%
5[c]	$Ni(cod)_2$	IMes·HCl	toluene	78%	5%
6	**$Ni(cod)_2$**	**IMes**	**toluene**	**87%**	**3%**
7	$Ni(cod)_2$	IMes	1,4-dioxane	88%	9%
8	$Ni(cod)_2$	IMes	DMF	16%	69%
9	$Ni(cod)_2$	IMes	*m*-xylene	40%	44%
10[d]	$Ni(cod)_2$	IMes	toluene	44%	49%
11	$Ni(OAc)_2$	IMes	toluene	16%	51%
12	$NiCl_2$	IMes	toluene	trace	73%
13	$Ni(acac)_2$	IMes	toluene	5%	83%

[a] Reaction conditions: **1a** (0.2 mmol), $Ni(cod)_2$ (0.02 mmol), and ligand (0.02 mmol) in toluene (0.5 mL) at 180 ºC for 14 h. [b] Yields of **2** and **1a** were determined from GC with undecane as the internal standard. [c] NaO^{t}Bu (0.03 mmol) was added. [d] Run at 160 °C.

Next, the effect of an alkoxy group in the substrate was examined (Table 2). All esters with primary alkoxy groups (entry 1-3) and secondary alkoxy groups (entry 4) reacted efficiently to give the desired product **2** in good yields. However, the reaction of an ester with tertiary alkoxy group **1e** gave the desired product in low yield (entry 5).

The author next evaluated the effect of directing groups (Scheme 2). The reaction was applied to aromatic esters with an *N*-heteroaromatic ring, as in **3**, **4**, and **5**. Curiously, it was found that amide and ester groups also function as directing groups. Secondary amide group functioned as a directing group (**6**). When using diisopropyl phthalate **7**, isopropyl benzoate was obtained in 38% yield and the starting ester **7** was recovered in 62% GC yield.

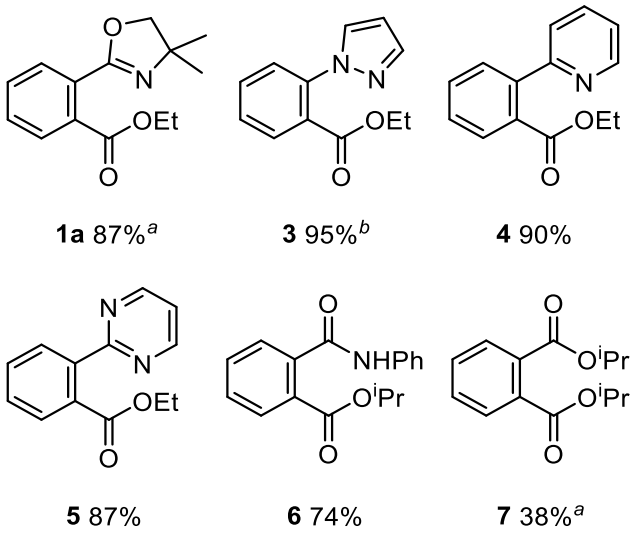
Table 2. Screening of substituents on an alkoxy group.[a]



1 0.2 mmol **2**

entry	R	GC yields[b] **2**	**1**
1	Me (**1b**)	79%	3%
2	Et (**1a**)	87%	3%
3	Bu (**1c**)	97%	trace
4	^{i}Pr (**1d**)	77%	5%
5	^{t}Bu (**1e**)	25%	43%

[a] Reaction conditions: **1** (0.2 mmol), $Ni(cod)_2$ (0.02 mmol), and IMes (0.02 mmol) in toluene (0.5 mL) at 180 ºC for 14 h. [b] Yields of **2** and **1** were determined from GC with undecane as the internal standard.



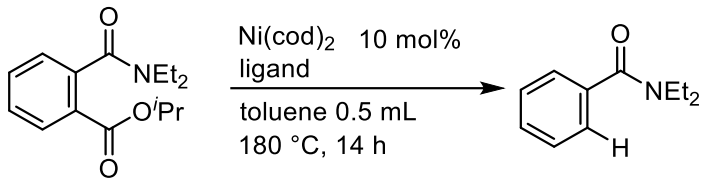
1a 87%[a] **3** 95%[b] **4** 90%

5 87% **6** 74% **7** 38%[a]

Scheme 2. Screening of directing groups. Reaction conditions: ester (0.2 mmol), Ni(cod)2 (0.02 mmol), IMes (0.02 mmol) in toluene (0.5 mL) at 180 °C for 14 h. Yields shown are isolated yields, unless otherwise noted. [a] GC yield. [b] NMR yield.

Tertiary amide **8** was also applicable to this reaction, which gave the product in 28% yield under the standard conditions (Table 3, entry 1). After screening of ligands, ICy was found to be the most effective ligand (entry 2-4). When the 20 mol% ICy was used, the product **8** was obtained in 57% isolated yield (entry 5).

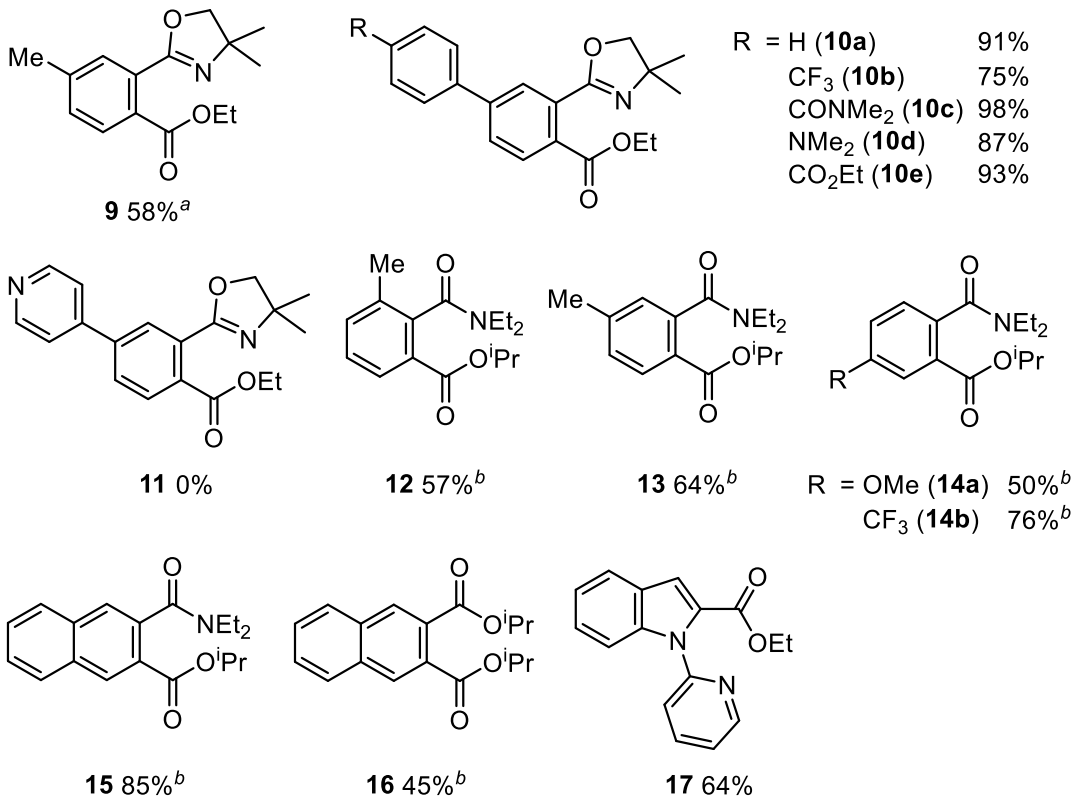
Table 3. Screening of conditions using **8**.[a]



8 **Pro**

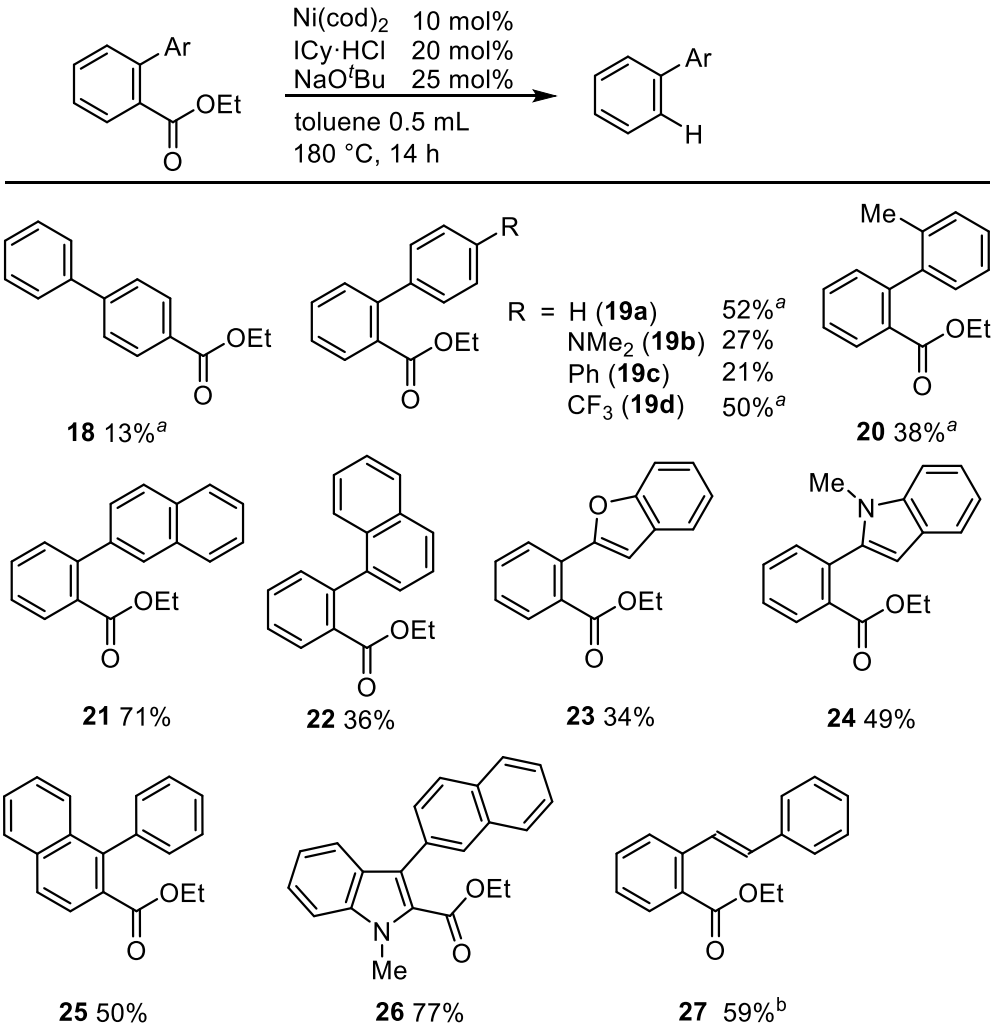
entry	ligand	NMR yields[b] Pro	8
1	IMes 10 mol%	28%	71%
2	IMes·HCl 10 mol% + NaO^{t}Bu 15 mol%	21%	75%
3	IPr·HCl 10 mol% + NaO^{t}Bu 15 mol%	9%	71%
4	ICy·HCl 10 mol% + NaO^{t}Bu 15 mol%	29%	57%
5	**ICy·HCl 20 mol% + NaO^{t}Bu 20 mol%**	**79% (57%)[c]**	**3%**

[a] Reaction conditions: **8** (0.2 mmol), Ni(cod)$_2$ (0.02 mmol), and ligand in toluene (0.5 mL) at 180 ºC for 14 h. [b] Yields of **Pro** and **8** were determined from NMR with 1,1,2,2-tetrachloroethane as the internal standard.



Scheme 3. Substrate scope. Reaction conditions: ester (0.2 mmol), Ni(cod)$_2$ (0.02 mmol) and IMes (0.02 mmol) in toluene (0.5 mL) for 14 h at 180 °C. Yields shown are isolated yields, unless otherwise noted. [a] GC yield. [b] ICy·HCl (0.04 mmol) and NaO^{t}Bu (0.04 mmol) were used instead of IMes.

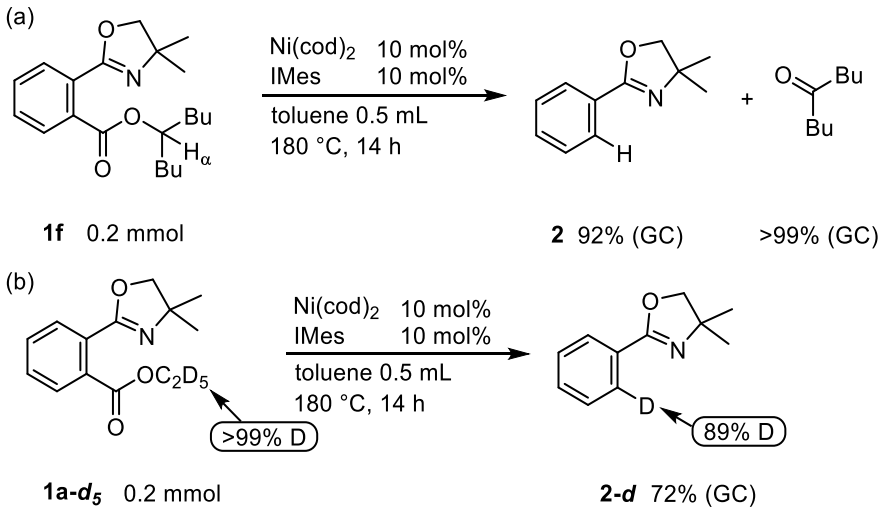
The scope of the reaction with respect to substrates was examined (Scheme 3). An oxazoyl group served as a good directing group, as in **9** and **10**. Various functional groups, such as CF_3 (**10b**), amide (**10c**), and NMe_2 (**10d**), were tolerated. In the case of a substrate with two ester groups, as in **10e**, reductive removal of an ester group occurred only at the *ortho*-position of an oxazolyl group and the other ester group remained intact. However, the reaction of a substrate bearing a 4-pyridyl group **11** gave no desired product and 91% of the starting material was recovered. An amide group also promoted the reductive defunctionalization, as in **12**, **13, 14** and **15**. In the case of an amide bearing a methoxy group, as in **14a**, the cleavage of C-OMe bond also occurred to give *N,N*-diethylbenzamide in 12% NMR yield. The reaction was also applicable to π-extended aromatic esters **16**, which gave the desired product in 45% yield, along with naphthalene being produced in 17% yield. The indole derivative **17** with pyridyl group as a directing group reacted successfully.



Scheme 4. Substrate scope. Reaction conditions: ester (0.2 mmol), $Ni(cod)_2$ (0.02 mmol), ICy·HCl (0.04 mmol) and NaO^{t}Bu (0.05 mmol) in toluene (0.5 mL) for 14 h at 180 °C. Yields shown are isolated yields, unless otherwise noted. [a] GC yield. [b] NaO^{t}Bu (0.06 mmol) was used.

It is noteworthy that an arene ring also functions as a directing group (Scheme 4). While the reaction of the ethyl benzoate bearing a phenyl group at the *para*-position (**18**) gave biphenyl only in 13% yield, ethyl [1,1'-biphenyl]-2-carboxylate (**19a**) reacted to give the biphenyl in 52% yield, indicating that a phenyl group at the *ortho*-position would coordinate to nickel, which would then accelerate the reaction.[5] After examination of the effect of a substituent on the arene ring (**19**), the author found that an electron-withdrawing group on the phenyl ring facilitates the reaction, as in **19d**. When *o*-tolyl group was used as a directing group (**20**), the product yield was decreased due to the steric hinderance. A naphthalene ring, as in **21** and **22**, and heteroaromatic rings, as in **23** and **24** were also found to function as a directing group. The reaction was also applicable to *p*-extended aromatic esters (**25**) and the indole derivative **26**. An alkene also serves as a directing group, as in **27**.

Mechanistic studies were conducted in an attempt to gain insights into the reaction mechanism (Scheme 5). The reaction of **1f** gave **2** in 92% yield along with 5-nonanone in quantitative yield, suggesting that the H_α atom is transferred to the *ortho* position (Scheme 5a). In fact, in the reaction of **1a-*d*$_5$**, a deuterium atom was introduced to the *ortho*-position, although some deuterium loss was observed (Scheme 5b).

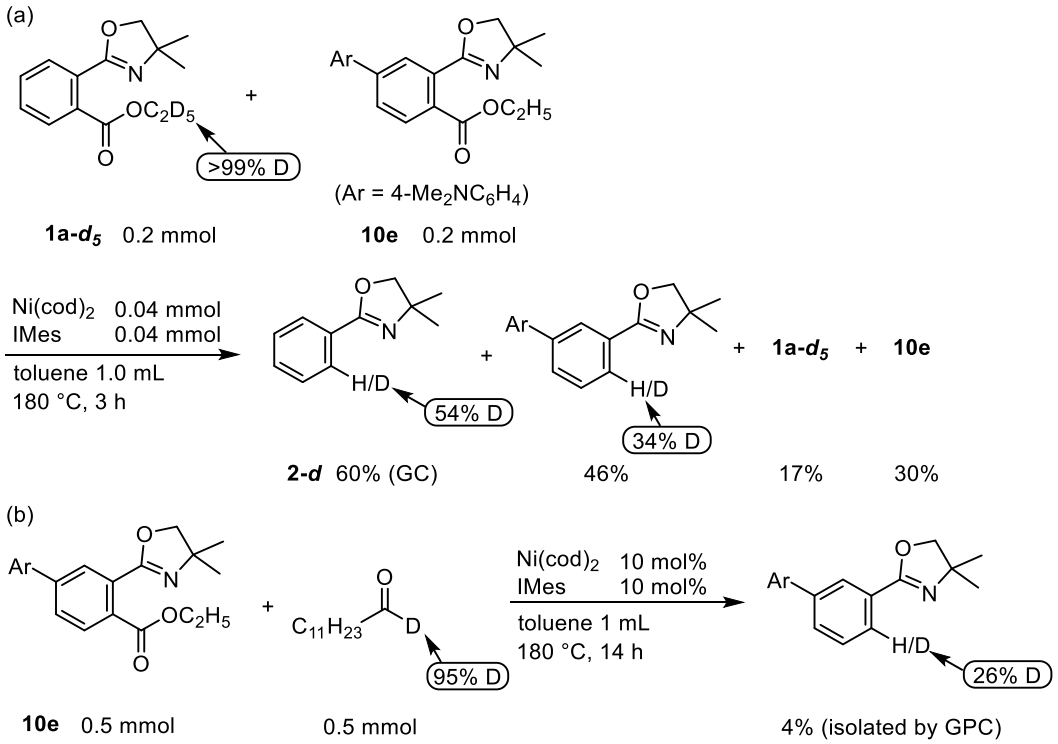


Scheme 5. Mechanistic studies.

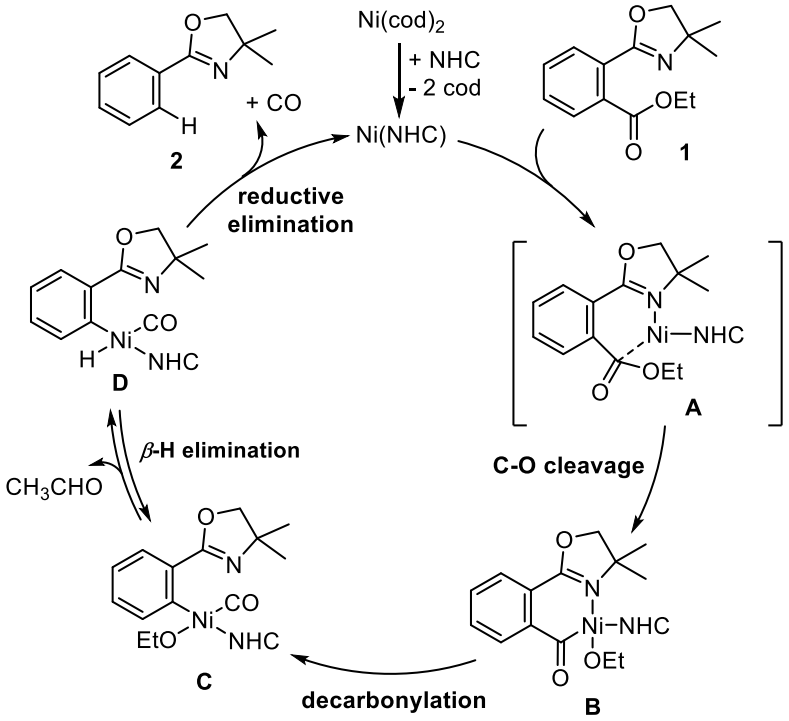
The author conducted a crossover experiment using **1a-*d*$_5$** and **10e** (Scheme 6a). Curiously, deuterium atoms were scrambled, although no H/D exchange was observed in the recovered starting materials. To gain additional insights into the reaction mechanism, **10e** reacted with a deuterium labeled aldehyde, which gave the desired product albeit in low yield and 26% of the atoms introduced in the ortho position of the product were deuterium atoms (Scheme 6b).

A proposed reaction mechanism is shown in Scheme 7. A nitrogen atom coordinates to a nickel center and the oxidative addition of this C-O bond of an ester to nickel takes place to give complex **B**[6] through **A**.[7] Decarbonylation proceeds to afford complex **C**,[8] which undergoes *β*-hydride elimination to form complex **D** with the generation of acetaldehyde.[9] Finally, reductive elimination gives **2** with the regeneration of the catalytic active Ni(0) species. In a crossover experiment (Scheme 6a), H/D exchange between the starting materials was not detected, suggesting that the cleavage of a C-O bond and/or decarbonylation is irreversible. The results obtained from a crossover experiment

(Scheme 6a), in which deuterium atom scrambling was observed in the products and the result obtained from Scheme 6b suggest that the β-hydride elimination step is reversible.

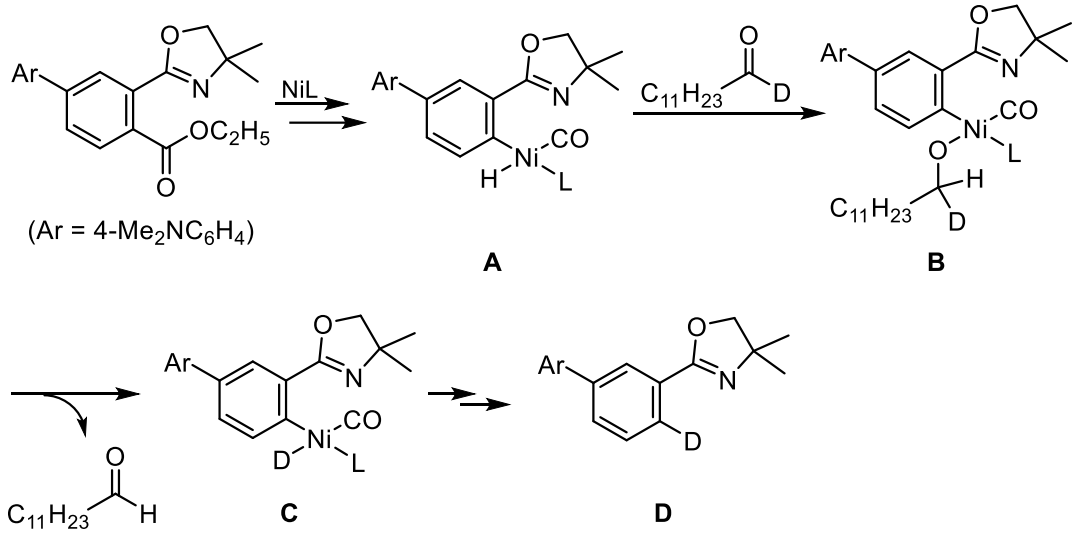


Scheme 6. Crossover experiments.

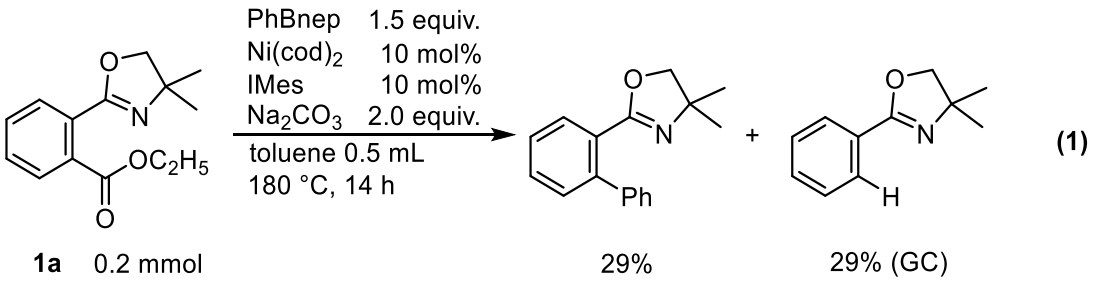


Scheme 7. Proposed mechanism.

Scheme 8 shows a plausible mechanism for the introduction of deuterium atom as shown in Scheme 6b. In the course of the reaction, nickel hydride complex **A** is generated. The insertion of deuterium labeled aldehyde to complex **A** gave complex **C**. After *β*-hydride elimination, nickel deuteride complex **C** was formed with the generation of non-deuterium labeled aldehyde. Finally, the reductive elimination gives **D**.



Scheme 8. A plausible mechanism for scrambling of deuterium atom.



The reaction of **1a** with a boronic ester was examined, which gave the coupling product in 29% yield (eq 1).[10] This result indicates that the present reaction proceeds via a similar pathway to that of previously reported coupling reactions of esters, suggesting that intermediate **C** as shown in Scheme 7 is generated during the course of the reaction.

1.3 Conclusion.

In conclusion, the nickel-catalyzed reductive removal of an ester group in the absence of an external reductant is described. This reaction proceeds via a mechanism involving the oxidative addition of the inert C–O bond of an *O*-alkyl ester, which was achieved by the assistance of a directing group. In the course of our investigations of the substrate scope, it was found that an aryl group also functioned as a directing group.

1.4 Experimental Section

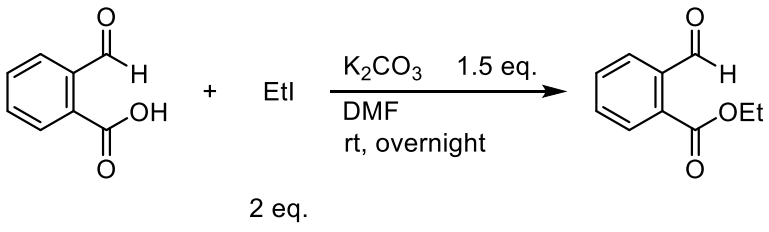
1.4.1 General Information

^{1}H, ^{2}H and ^{13}C NMR spectra were recorded on a JEOL ECS-400 spectrometer or a JEOL ECZ-400S spectrometer. The chemical shifts in ^{1}H NMR spectra were recorded relative to tetramethylsilane (δ: 0.0). The chemical shifts in ^{2}H NMR spectra were recorded relative to $CDCl_3$ (δ: 7.26). The chemical shifts in ^{13}C NMR spectra were recorded relative to $CDCl_3$ (δ: 77.0). Data are recorded as follows: chemical shifts in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad singlet, m = multiplet, c = complex), coupling constant (Hz), and integration. Infrared spectra (IR) were recorded on a JASCO FT/IR-4000 spectrometer using ATR method. Absorption data are reported in reciprocal centimeters from 800 to 3500 cm^{-1} with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained using a SHIMDZU QP-2010 spectrometer with a quadrupole mass analyzer at 70 eV. Data are recorded as follows: mass/charge ratio and relative intensity to base peak at 100 %. High-resolution mass spectra (HRMS) were obtained using a JEOL JMS-T100LP spectrometer with a time-of-flight mass analyzer. Elemental analyses were performed by the Elemental Analysis Section of Osaka University. Melting points were determined on a Stanford Research Systems MPA100 apparatus equipped with a digital thermometer and are uncorrected. Analytical gas chromatography (GC) was carried out on a SHIMADZU GC-2014 chromatograph equipped with a flame ionization detector. Preparative gel permeation chromatography (GPC) were carried out on a JAI LC-5060 equipped with two JAIGEL-2HR columns connected in series or two JAIGEL-2HR-40 columns connected in series. Medium-pressure liquid chromatography (MPLC) was performed with Biotage Isolera® equipped with Biotage® SNAP Ultra flash chromatography cartridges. Column chromatography was performed with SiO_2 (Silicycle Siliaflash F60 (230-400 mesh)).

1.4.2 Materials

Toluene (super dehydrated), 1,4-dioxane (super dehydrated), DMF (super dehydrated), $Ni(cod)_2$, PCy_3, dcype, ICy•HCl, IMes•HCl, IPr•HCl, IMes and NaO^{t}Bu were purchased and used as received. Diisopropyl phthalate (**7**) and *m*-xylene were purchased and distilled over CaH_2 before use. Ethyl [1,1'-biphenyl]-4-carboxylate (**18**) [CAS: 6301-56-0] and Ethyl [1,1'-biphenyl]-2-carboxylate (**19a**) [CAS: 19926-49-9] were prepared by Fischer esterification of the corresponding carboxylic acid and Ethanol in the presence of the catalytic amount of H_2SO_4. Ethyl 2-(naphthalen-2-yl)benzoate (**21**) [CAS: 1246739-14-9] and Ethyl 2-(naphthalen-1-yl)benzoate (**22**) [CAS: 954137-87-2] were prepared following procedure[11] described in the literature. Other starting materials were prepared as described below.

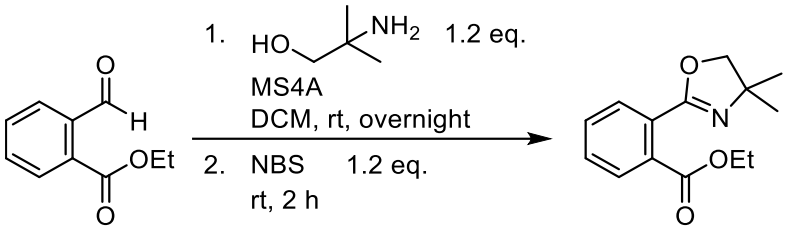
Ethyl 2-formylbenzoate (pre-1a) [CAS: 34046-43-0]



A mixture of phthalaldehydic acid (15.2 g, 101 mmol), K_2CO_3 (20.7 g, 149 mmol), DMF (120 mL), and EtI (33.1 g, 212 mmol) were stirred rt overnight. After the reaction, H_2O (200 mL) and Et_2O (100 mL) were added and the organic layer was separated. The organic layer was washed with H_2O (100 mL) and dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was purified by vacuum distillation (0.28 Torr, 78 °C) under CaH_2 to afford the desired **pre-1a** as a colorless oil (12.4 g, 69.3 mmol, 68%).

^{1}H NMR ($CDCl_3$) δ: 1.43 (t, *J* = 7.3 Hz, 3H), 4.45 (q, *J* = 7.3 Hz, 2H), 7.56-7.74 (c, 2H), 7.86-8.06 (c, 2H), 10.63 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.1, 61.9, 128.3, 130.2, 132.2, 132.4, 132.8, 136.9, 166.2, 192.0.

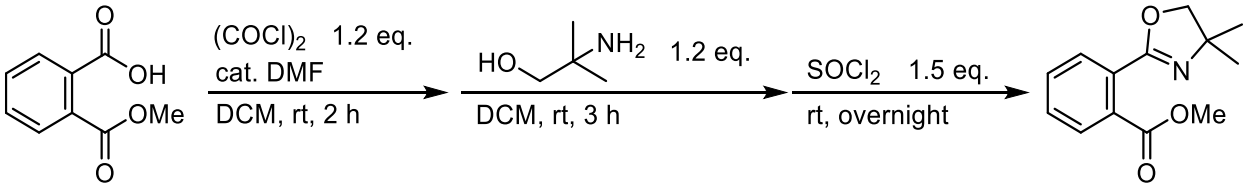
Ethyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (1a)



A mixture of **pre-1a** (6.51 g, 36.5 mmol), 2-amino-2-methyl-1-propanol (4.03 g, 45.2 mmol) and MS4A (15 g) in DCM (60 mL) was stirred overnight at room temperature under a N_2 atmosphere. NBS (8.00 g, 44.9 mmol) was then added to the reaction mixture which was then stirred for 1 h at room temperature. After the reaction, the mixture was filtered through a Celite pad and a saturated aqueous solution of $NaHCO_3$ (60 mL) was added. The organic layer was separated and the aqueous layer was extracted with DCM (100 mL). The combined organic layers were dried over Na_2SO_4. After removing volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 5/1 to 2/1, R_f = 0.20 in hexane/EtOAc = 2/1) to afford the desired **1a** as a pale yellow oil (3.60 g, 14.6 mmol, 40%). Further purification by vacuum distillation (0.29 mmHg, 94 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.37 (t, *J* = 7.2 Hz, 3H), 1.40 (s, 6H), 4.11 (s, 2H), 4.35 (q, *J* = 7.2 Hz, 2H), 7.46-7.54 (c, 2H), 7.70-7.77 (c, 2H). **^{13}C NMR** ($CDCl_3$) δ: 14.2, 28.1, 61.4, 67.9, 79.8, 128.3, 128.9, 129.8, 130.3, 130.9, 132.4, 162.3, 167.6. **IR** (ATR): 2970 w, 2930 w, 2895 w, 1726 s, 1657 m, 1287 s. **MS**: m/z (EI, relative intensity, %): 247 (2, M^+), 232 (65), 202 (11), 188 (58), 187 (13), 186 (100), 148 (30), 130 (60), 102 (19). **Anal.** Calcd for $C_{14}H_{17}NO_3$: C, 68.00; H, 6.93; N, 5.66. Found: C, 68.03; H, 6.97; N, 5.74.

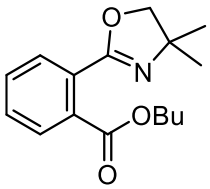
Methyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (1b)



Oxalyl chloride (2.0 mL, 23.3 mmol) was added dropwise to a solution of monomethyl phthalate (3.57 g, 19.8 mmol) and DMF (3 drops) in DCM (25 mL), at 0 °C. After stirring for 1 h at room temperature, the volatiles were removed under reduced pressure. The residue was suspended in DCM (10 mL) and slowly added to a suspension of 2-amino-2-methyl-1-propanol (2.23 g, 25.0 mmol) and NEt_3 (2.52 g, 24.9 mmol) in DCM (20 mL) at 0 °C. After stirring for 3 h at room temperature, 1N HCl (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (30 mL×2). The combined organic layers were transferred to a round bottom flask and cooled to 0 °C. $SOCl_2$ (2.2 mL, 30.5 mmol) was added slowly to the mixture, which was stirred at room temperature overnight. After adding a saturated aqueous solution of $NaHCO_3$ (100 mL), the organic layer was separated. The aqueous layer was extracted with DCM (50 mL×2) and the combined organic layers were dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 5/1 to 2/1, R_f = 0.14 in hexane/EtOAc = 2/1) to afford the desired **1b** as a pale yellow oil (3.60 g, 15.4 mmol, 78%). Further purification by vacuum distillation (0.11 mmHg, 92 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.40 (s, 6H), 3.88 (s, 3H), 4.11 (s, 2H), 7.41-7.61 (c, 2H), 7.68-7.77 (c, 2H). **^{13}C NMR** ($CDCl_3$) δ: 28.1, 52.4, 68.0, 79.8, 128.6, 129.0, 129.7, 130.3, 131.0, 131.9, 162.1, 168.0. **IR** (ATR): 2967 w, 2893 w, 1730 s, 1657 m, 1290 s. **MS**: *m*/*z* (EI, relative intensity, %): 233 (3, M^+), 219 (12), 218 (85), 188 (56), 187 (13), 186 (100), 160 (12), 148 (22), 130 (71), 104 (11), 102 (23), 76 (10). **Anal.** Calcd for $C_{13}H_{15}NO_3$: C, 66.94; H, 6.48; N, 6.00. Found: C, 66.81; H, 6.65; N, 6.07.

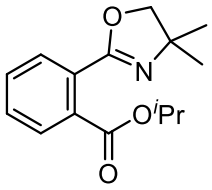
Butyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (1c)



The procedure for synthesis of **1b** was modified by using monobutyl phthalate (4.69 g, 23.5 mmol) in place of monomethyl phthalate. The product was isolated by flash column chromatography on silica-gel (eluent: Hexane/EtOAc = 5/1 to 2/1, R_f = 0.26 in Hexane/EtOAc = 2/1) and subsequent flash column chromatography on NH_2-modified silica-gel (R_f = 0.06 in hexane/EtOAc = 20/1) in 72% yield (4.69 g, 17.0 mmol). Further purification by vacuum distillation (0.47 mmHg, 117 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 0.96 (t, *J* = 7.3 Hz, 3H), 1.40 (s, 6H), 1.41-1.52 (m, 2H), 1.62-1.82 (m, 2H), 4.10 (s, 2H), 4.30 (t, *J* = 6.9 Hz, 2H), 7.42-7.59 (c, 2H), 7.65-7.82 (c, 2H). **^{13}C NMR** ($CDCl_3$) δ: 13.7, 19.1, 28.1, 30.5, 65.3, 67.8, 79.6, 128.3, 128.8, 129.8, 130.2, 130.8, 132.3, 162.1, 167.6. **IR** (ATR): 2962 m, 2931 w, 2872 w, 1728 s, 1657 m, 1286 s, 1259 s. **MS**: *m*/*z* (EI, relative intensity, %): 275 (2, M^+), 260 (41), 202 (11), 188 (59), 187 (13), 186 (100), 148 (23), 130 (48), 102 (13), 41 (10). **Anal.** Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.40; H, 7.72; N, 5.21.

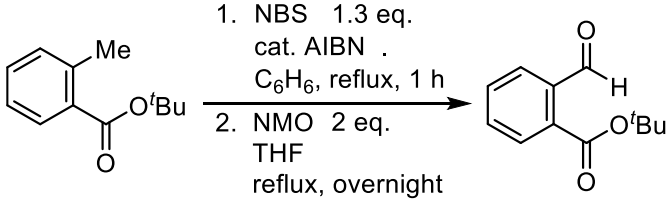
Isopropyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (1d)



The procedure for synthesis of **1b** was modified by using monoisopropyl phthalate[12](10.89 g, 52.3 mmol) in place of monomethyl phthalate. The product was isolated by bulb-to-bulb distillation (1.1 mmHg, 140 °C) in 73% yield (9.96 g, 38.1 mmol) as a white solid.

Mp = 62.7-64.2 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.36 (d, *J* = 6.4 Hz, 6H), 1.40 (s, 6H), 4.10 (s, 2H), 5.23 (qq, *J* = 6.4 Hz, 6.4 Hz, 1H), 7.37-7.58 (c, 2H), 7.64-7.71 (c, 1H), 7.72-7.79 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 21.8, 28.2, 67.9, 69.0, 79.6, 128.2, 128.8, 129.9, 130.3, 130.6, 132.9, 162.3, 167.1. **IR** (ATR): 2977 w, 2932 w, 2894 w, 1712 s, 1658 s, 1289 s, 1250 s. **MS**: *m*/*z* (EI, relative intensity, %): 261 (2, M^+), 247 (12), 246 (73), 204 (35), 202 (19), 188 (68), 187 (13), 186 (100), 160 (11), 148 (32), 130 (58), 102 (14). **HRMS (ESI)** Calcd for $C_{15}H_{20}NO_3$ ($[M+H]^+$): 262.14377. Found: 262.14425.

***tert*-Butyl 2-formylbenzoate (pre-1e)**

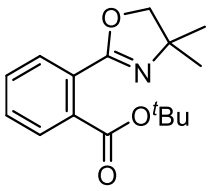


t-Butyl *o*-toluate[13] (11.4 g, 59.5 mmol), NBS (14.3 g, 80.1 mmol) and AIBN (0.99 g, 6.0 mmol) were heated to reflux in Benzene (50 mL) for 1 h. After the mixture was cooled to room temperature, H_2O (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (50 mL) and the combined organic layer was dried over Na_2SO_4. After the volatile was removed under reduced pressure, a pale yellow oil was obtained. The resulting crude mixture, *N*-methylmorpholine *N*-oxide (14.2 g, 121 mmol) were heated to reflux in THF (60 mL) overnight. After the mixture was cooled to room temperature, H_2O (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (50 mL×2) and the combined organic layer was dried over Na_2SO_4. The resulting crude mixture was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 100/1 to 20/1, R_f = 0.16 in hexane/EtOAc = 20/1) to afford the desired **pre-1e** as a pale yellow oil (3.45 g, 16.7 mmol, 28%).

^{1}H NMR ($CDCl_3$) δ: 1.63 (s, 9H), 7.60-7.64 (c, 2H), 7.88-7.91 (c, 2H), 10.60 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 28.0, 82.7, 128.0, 130.0, 131.7, 132.7, 134.0, 136.7, 165.4, 192.0. **IR** (ATR): 2979 w, 2934 w, 1701 s, 1293 s. **MS**: *m*/*z* (EI,

relative intensity, %): 150 (45), 149 (100, M^+-57), 133 (62), 122 (32), 105 (34), 77 (17), 57 (46). **HRMS (DART)** Calcd for $C_{12}H_{15}O_3$ ([M+H]$^+$): 207.10157. Found: 207.10234.

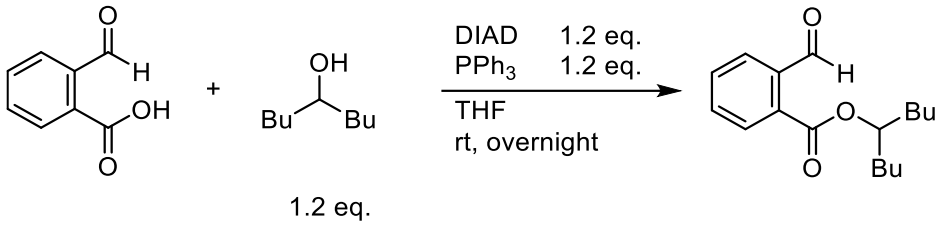
***tert*-Butyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (1e)**



The procedure for synthesis of **1a** was modified by using *t*-Butyl 2-formylbenzoate (3.45 g, 16.7 mmol) in place of **pre-1a**. The product was isolated by flash column chromatography on silica-gel (eluent: Hexane/EtOAc = 5/1 to 2/1, R_f = 0.31 in hexane/EtOAc = 2/1) in 80% yield (3.69 g, 13.4 mmol) as a pale yellow oil. Further purification by vacuum distillation (0.15 mmHg, 93 °C) under CaH_2 afforded the title compound as a pale yellow oil.

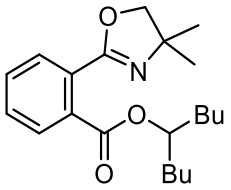
^{1}H NMR ($CDCl_3$) δ: 1.40 (s, 6H), 1.58 (s, 9H), 4.10 (s, 2H), 7.39-7.50 (c, 2H), 7.57-7.64 (m, 1H), 7.71-7.79 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 28.0, 28.2, 67.9, 79.5, 81.7, 127.6, 128.5, 129.8, 130.1, 130.3, 134.4, 162.3, 167.1. **IR** (ATR): 2974 w, 2931 w, 2893 w, 1720 s, 1655 m, 1300 s. **MS**: *m/z* (EI, relative intensity, %): 275 (1, M^+), 230 (11), 204 (67), 202 (23), 189 (21), 188 (32), 187 (13), 186 (100), 175 (36), 174 (16), 160 (27), 148 (30), 146 (25), 130 (62), 104 (11), 103 (10), 102 (18), 57 (29). **Anal.** Calcd for $C_{16}H_{21}NO_3$: C, 69.79; H, 7.69; N, 5.09. Found: C, 69.49; H, 7.58; N, 5.08.

Nonan-5-yl 2-formylbenzoate (pre-1f)



DIAD (5.02 g, 24.8 mmol) was added dropwise to a solution of phthalaldehydic acid (3.00 g, 20.0 mmol), 5-nonanol (3.32 g, 23.0 mmol), and PPh_3 (5.94 g, 22.6 mmol) in THF (40 mL) at 0 °C. After stirring overnight at rt, the volatiles were removed under reduced pressure. The resulting crude mixture was purified by column chromatography on silica gel (R_f = 0.06 in hexane/EtOAc = 20/1) to give the mixture that contained **pre-1f** and some impurities (2.28 g), which was used in the subsequent step without further purification.

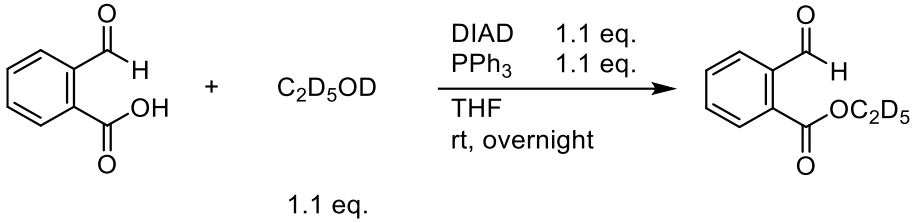
Nonan-5-yl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (1f)



The procedure for synthesis of **1a** was modified by using **pre-1f** (3.81 g, mixture with some impurities) in place of **pre-1a**. The product was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 10/1 to 2/1, R_f = 0.34 in hexane/EtOAc = 2/1) in 26% yield based on phthalaldehydic acid (two steps, 1.77 g, 5.1 mmol) as a pale yellow oil. Further purification by vacuum distillation (0.13 mmHg, 104 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ 0.81-1.00 (c, 6H), 1.22-1.48 (c, 14H), 1.51-1.79 (c, 4H), 4.09 (s, 2H), 5.10 (tt, *J* = 5.3 Hz, 7.3 Hz, 1H), 7.43-7.54 (c, 2H), 7.64-7.72 (m, 1H), 7.72-7.79 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.0, 22.6, 27.5, 28.1, 33.8, 67.9, 75.6, 79.6, 128.5, 128.7, 130.0, 130.2, 130.7, 132.9, 162.4, 167.1. **IR** (ATR): 2957 m, 2931 m, 2862 w, 1723 s, 1658 m, 1267 s. **MS**: *m*/*z* (EI, relative intensity, %): 330 (2, M^+-15), 221 (14), 220 (100), 205 (10), 204 (83), 203 (14), 202 (49), 189 (32), 188 (47), 187 (12), 186 (92), 175 (28), 174 (14), 160 (24), 148 (59), 146 (15), 130 (76), 102 (14). **Anal.** Calcd for $C_{21}H_{31}NO_3$: C, 73.01; H, 9.04; N, 4.05. Found: C, 72.70; H, 9.11; N, 4.14.

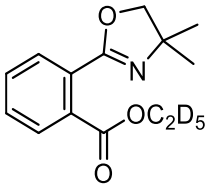
Ethyl-*d_5* 2-formylbenzoate (pre-1a-*d_5*)



To a solution of phthalaldehydic acid (6.70 g, 44.6 mmol), ethanol-*d_6* (2.52 g, 48.4 mmol), and PPh_3 (13.1 g, 50.0 mmol) in THF (60 mL), DIAD (10.1 g, 50.0 mmol) was added dropwise at 0 °C. After stirring overnight at rt, the volatiles were removed under reduced pressure. The resulting crude mixture was suspended with Et_2O (100 mL) and was filtered through Celite pad. After the volatiles were removed under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 10/1, R_f = 0.29 in hexane/EtOAc = 5/1) to afford the desired **pre-1a-*d_5*** as a pale yellow oil (6.29 g, 34.3 mmol, 77%).

^{1}H NMR ($CDCl_3$) δ: 7.57-7.74 (m, 2H), 7.86-8.07 (m, 2H), 10.63 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.7-13.5 (m), 60.7-61.6 (m), 128.3, 130.3, 132.2, 132.4, 132.9, 136.9, 166.3, 192.1. **MS**: *m*/*z* (EI, relative intensity, %): 183 (1, M^+), 155 (35), 154 (10), 150 (16), 149 (100), 133 (77), 132 (28), 121 (17), 111 (10), 110 (21), 107 (13), 106 (85), 105, (62), 104 (79), 93 (22), 78 (14), 77 (43), 76 (36), 65 (12), 51 (28), 50 (18). **HRMS (ESI)** Calcd for $C_{10}H_4O_3D_5$ ([M-H]$^+$): 182.08600. Found: 182.08647.

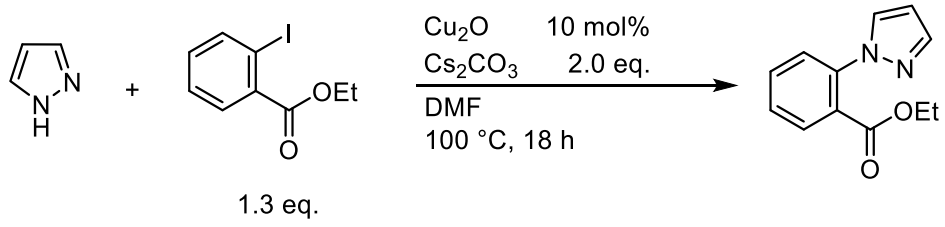
Ethyl-d_5 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (1a-d_5)



The procedure for synthesis of **1a** was modified by using **pre-1a-d_5** (6.29 g, 34.3 mmol) in place of **pre-1a**. The product was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 5/1 to 2/1, R_f = 0.20 in Hexane/EtOAc = 2/1) in 83% yield (7.18 g, 28.4 mmol) as a pale yellow oil. Further purification by vacuum distillation (0.22 mmHg, 94 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.39 (s, 6H), 4.10 (s, 2H), 7.47-7.52 (c, 2H), 7.71-7.75 (c, 2H). **^{2}H NMR** ($CHCl_3$) δ: 1.31, 4.31. **^{13}C NMR** ($CDCl_3$) δ: 12.9-13.5 (m), 28.1, 60.2-60.9 (m), 67.9, 79.7, 128.4, 128.9, 129.8, 130.3, 130.8, 132.4, 162.2, 167.6. **MS**: *m*/*z* (EI, relative intensity, %): 252 (2, M^+), 238 (10), 237 (68), 188 (58), 187 (14), 186 (100), 148 (25), 130 (60), 102 (16). **HRMS (DART)** Calcd for $C_{14}H_{13}NO_3D_5$ ($[M+H]^+$): 253.15950. Found: 253.16165.

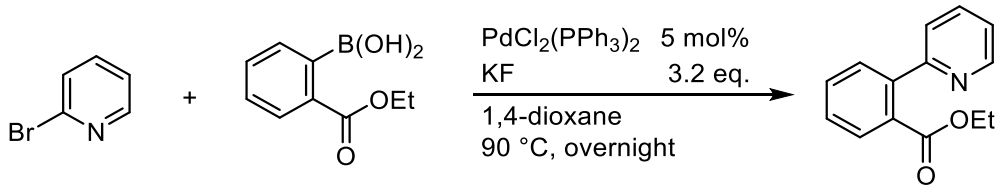
Ethyl 2-(1*H*-pyrazol-1-yl)benzoate (3)



The title compound was synthesized according to Bolm's procedure.[14] A three necked flask was flame-dried and purged with N_2. After the flask was cooled to room temperature, Cu_2O (0.283 g, 2.0 mmol), Cs_2CO_3 (13.1 g, 40.3 mmol), DMF (30 mL), ethyl 2-iodobenzoate (7.45 g, 27.0 mmol), and pyrazole (1.42 g, 20.9 mmol) were placed in the flask. The reaction mixture was stirred at 100 °C for 18 h. After the reaction mixture was cooled, the mixture was filtered through Celite pad. H_2O (50 mL) was added to the mixture. The organic layer was extracted with Et_2O (50 mL×2) and dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 10/1 to 5/1, R_f = 0.08 in hexane/EtOAc = 5/1) to afford the desired **3** as a yellow oil (2.85 g, 14.1 mmol, 67%). Further purification by vacuum distillation (0.14 mmHg, 89 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.14 (t, *J* = 7.2 Hz, 3H), 4.18 (q, *J* = 7.2 Hz, 2H), 6.45 (t, *J* = 2.3 Hz, 1H), 7.52-7.37 (m, 2H), 7.58 (td, *J* = 7.6, 1.2 Hz, 1H), 7.69 (d, *J* = 2.3 Hz, 1H), 7.70 (d, *J* = 2.3 Hz, 1H), 7.83 (dd, *J* = 7.8, 1.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 13.9, 61.4, 106.9, 125.4, 127.8, 128.1, 130.0, 130.4, 131.9, 139.4, 140.8, 166.8. **IR** (ATR): 2982 w, 2912 w, 1719 s, 1272 s, 752 s. **MS**: *m*/*z* (EI, relative intensity, %): 216 (53, M^+), 171 (100), 144 (83), 116 (19), 89 (16). **Anal.** Calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.55; H, 5.48; N, 12.93.

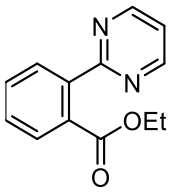
Ethyl 2-(pyridin-2-yl)benzoate (4)



A two necked flask was charged with 1,4-dioxane (70 mL), which was degassed three times and charged with N_2. 2-Bromopyridine (3.98 g, 25.2 mmol), 2-(ethoxycarbonyl)phenylboronic acid (5.00 g, 25.7 mmol), KF (4.71 g, 81.0 mmol) and $PdCl_2(PPh_3)_2$ (0.931 g, 1.33 mmol) were added to the mixture and the mixture was stirred at 90 ℃ overnight. After the mixture was cooled to room temperature, EtOAc (100 mL) was added. The organic layer was washed with 5% K_2CO_3 aq (100 mL×3) and was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 5/1, R_f = 0.17 in hexane/EtOAc = 5/1) to afford the desired **4** as a white solid (2.88 g, 12,7 mmol, 50%).

Mp = 71.3-71.8 ºC. **^{1}H NMR** ($CDCl_3$) δ 1.05 (t, *J* = 7.1 Hz, 3H), 4.14 (q, *J* = 7.1 Hz, 2H), 7.26 (ddd, *J* = 7.7, 5.0, 1.0 Hz, 1H), 7.38-7.52 (m, 2H), 7.52-7.64 (m, 2H), 7.74 (td, *J* = 7.7, 1.8 Hz, 1H), 7.80-7.91 (m, 1H), 8.64 (ddd, *J* = 5.0 Hz, 1.8 Hz, 1.0 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 13.8, 60.9, 121.9, 122.8, 128.2, 129.7×2, 131.0, 131.8, 136.1, 141.0, 149.0, 158.9, 168.7. **IR** (ATR): 2983 w, 1721 s, 1285 s, 751 s. **MS**: *m/z* (EI, relative intensity, %): 227 (1, M^+), 198 (13), 154 (13), 127 (23). **Anal.** Calcd for $C_{14}H_{13}NO_2$: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.05; H, 5.72; N, 6.17.

Ethyl 2-(pyrimidin-2-yl)benzoate (5)

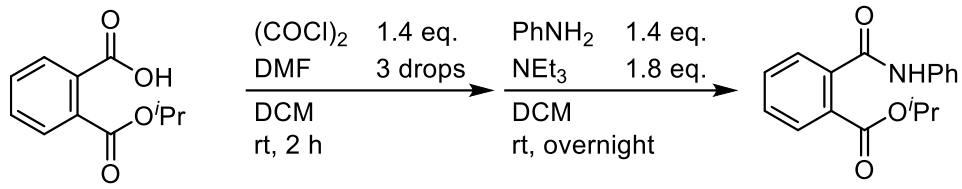


The procedure for synthesis of **4** was modified by using 2-Chloropyrimidine (2.83 g, 24.8 mmol) in place of 2-bromopyridine. The product was isolated by flash column chromatography on silica-gel (R_f = 0.06 in hexane/EtOAc = 5/1) in 84 % yield (4.74 g, 20.8 mmol) as a pale yellow oil. Further purification by vacuum distillation (0.16 mmHg, 110 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.15 (t, *J* = 7.3 Hz, 3H), 4.22 (q, *J* = 7.3 Hz, 2H), 7.24 (t, *J* = 5.0 Hz, 1H), 7.52 (td, J = 7.3, 1.2 Hz, 1H), 7.59 (td, *J* = 7.3, 1.4 Hz, 1H), 7.76 (dd, *J* = 7.3, 1.2 Hz, 1H), 7.99 (dd, *J* = 7.3, 1.4 Hz, 1H), 8.80 (d, *J* = 5.0 Hz, 2H). **^{13}C NMR** ($CDCl_3$) δ: 13.9, 61.0, 119.0, 129.1, 129.5, 129.9, 130.7, 132.9, 138.2, 156.8, 165.9, 169.2. **IR** (ATR): 2981 w, 1719 s, 1414 s, 1267 s, 752 s. **MS**: *m/z* (EI, relative intensity, %): 228 (7, M^+), 184 (23), 183 (100),

156 (22), 155 (12), 129 (16), 102 (14). **Anal.** Calcd for $C_{13}H_{12}N_2O_2$: C, 68.41; H, 5.30; N, 12.27. Found: C, 68.29; H, 5.13; N, 12.39.

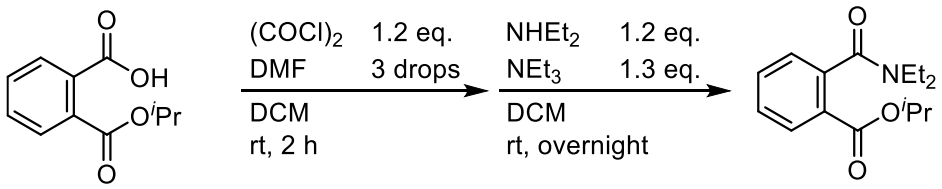
Isopropyl 2-(phenylcarbamoyl)benzoate (6)



Oxalyl chloride (2.2 mL, 25.6 mmol) was added dropwise to a solution of monoisopropyl phthalate (3.86 g, 18.5 mmol) and DMF (3 drops) in DCM (40 mL) at 0 °C. After stirring for 2 h at rt, the volatiles were removed under reduced pressure. The residue was suspended in DCM (40 mL) and slowly added to a suspension of aniline (3.0 mL, 32.8 mmol) and NEt_3 (3.7 mL, 26.7 mmol) in DCM (40 mL) at 0 °C. After stirring overnight at rt, 1N HCl (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (50 mL×2) and the combined organic layer was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was isolated by flash column chromatography on silica gel (eluent: hexane/EtOAc = 5/1 to EtOAc only, R_f = 0.09 in hexane/EtOAc = 5/1) and subsequent flash column chromatography on silica gel (eluent: DCM only to DCM/EtOAc = 10/1, R_f = 0.31 in DCM/EtOAc = 20/1) to afford the desired **6** as a white solid (3.52 g, 12.4 mmol, 67%).

Mp = 139.3-139.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.23 (d, *J* = 6.4 Hz, 6H), 5.19 (qq, *J* = 6.4 Hz, 6.4 Hz, 2H), 7.14 (t, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8, 2H), 7.49-7.55 (m, 1H), 7.57-7.58 (c, 2H), 7.64 (d, *J* = 7.8 Hz, 2H), 7.69 (br, 1H), 7.93 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 21.6, 69.4, 119.6, 124.2, 127.6, 128.9, 129.3, 129.7, 130.1, 131.9, 138.11, 138.14, 166.2, 167.3. **IR** (ATR): 3276 w, 3247 w, 2980 w, 2934 w, 1706 s, 1657 m, 1601 m, 1349 m, 1290 s. **MS**: *m/z* (EI, relative intensity, %): 283 (8, M^+), 224 (12), 191 (26), 150 (10), 149 (100), 93 (34). **Anal**. Calcd for $C_{17}H_{17}NO_3$: C, 72.07; H, 6.05; N, 4.94. Found: C, 72.01; H, 6.00; N, 5.04.

Isopropyl 2-(diethylcarbamoyl)benzoate (8)

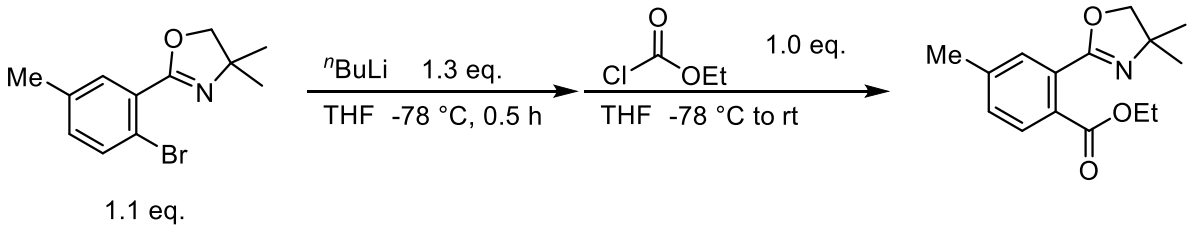


To a solution of monoisopropyl phthalate (11.7 g, 56.0 mmol) and DMF (3 drops) in DCM (50 mL), oxalyl chloride (8.63 g, 68.0 mmol) was added dropwise at 0 °C. After stirring for 2 h at rt, the volatiles were removed under reduced pressure. The residue was suspended in DCM (20 mL) and slowly added to a suspension of diethylamine (5.35 g, 73.1 mmol) and NEt_3 (6.85 g, 67.7 mmol) in DCM (50 mL) at 0 °C. After stirring overnight at rt, 1N HCl (30 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (30 mL) and the

combined organic layer was dried over $MgSO_4$. After the volatile was removed under reduced pressure, the resulting crude mixture was isolated by column chromatography on silica gel (eluent: hexane/EtOAc = 2/1, R_f = 0.16 in hexane/EtOAc = 2/1) to afford the desired **7** in 93% yield (13.7 g, 52.1 mmol) as a pale yellow oil. Further purification by vacuum distillation (0.11 mmHg, 98 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.04 (t, *J* = 7.1 Hz, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.33 (d, *J* = 6.4 Hz, 6H), 3.12 (q, *J* = 7.1 Hz, 2H), 3.59 (q, *J* = 7.1 Hz, 2H), 5.11-5.33 (m, 1H), 7.27 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.42 (td, *J* = 7.7, 1.2 Hz, 1H), 7.54 (td, *J* = 7.7, 1.2 Hz, 1H), 8.02 (dd, *J* = 7.7, 1.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.7, 13.6, 21.8, 38.9, 43.0, 68.7, 126.8, 127.8, 128.2, 130.5, 132.3, 139.2, 165.1, 170.2. **IR** (ATR): 2979 w, 2935 w, 1715 s, 1633 s, 1287 s, 1266 s. **MS**: *m*/*z* (EI, relative intensity, %): 263 (5, M^+), 262 (24), 220 (12), 204 (11), 149 (100), 72 (52). **HRMS (DART)** Calcd for $C_{15}H_{22}NO_3$ ($[M+H]^+$): 264.15942. Found: 264.16013.

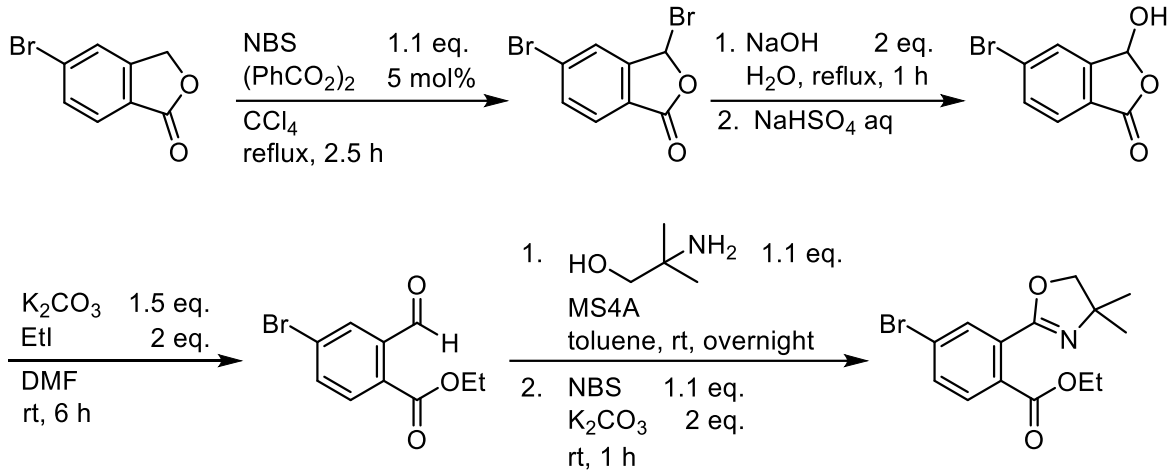
Ethyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-4-methylbenzoate (9)



2-(2-Bromo-5-methylphenyl)-4,4-dimethyl-4,5-dihydrooxazole was synthesized from 2-bromo-5-methylbenzoic acid and 2-amino-2-methyl-1-propanol by the same procedure that was used for the synthesis of **1b.** A three-necked flask was flame-dried and purged with N_2 and charged with 2-(2-bromo-5-methylphenyl)-4,4-dimethyl-4,5-dihydrooxazole (4.80 g, 17.9 mmol) and THF (20 mL). A 1.55 M solution of ^{n}BuLi (13.9 mL, 21.5 mmol) in hexane was slowly added to the solution at -78 °C. After stirring for 30 min at the same temperature, the resulting mixture was slowly added to a solution of ethyl chloroformate (1.73 g, 16.0 mmol) in THF (15 mL) at -78 °C. After warming the solution to room temperature, the reaction mixture was diluted with a saturated aqueous solution of NH_4Cl (50 mL), and extracted with EtOAc (50 mL×3). The organic layer was washed with brine (50 mL) dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 1/0 to 1/2, R_f = 0.09 in hexane/EtOAc = 5/1) and subsequent bulb-to-bulb distillation (6.0 mmHg, 170 °C) to afford the desired **9** as a pale yellow oil (2.91 g, 11.1 mmol, 69%).

^{1}H NMR ($CDCl_3$) δ 1.36 (t, *J* = 7.2 Hz, 3H), 1.41 (s, 6H), 2.40 (s, 3H), 4.11 (s, 2H), 4.33 (q, *J* = 7.2 Hz, 2H), 7.29 (dd, *J* = 8.1, 1.2 Hz, 1H), 7.54 (d, *J* = 1.2 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.2, 21.2, 28.1, 61.2, 67.8, 79.8, 128.6, 129.2, 129.3, 130.5, 130.9, 141.7, 162.8, 167.4. **IR** (ATR): 2979 w, 2934 w, 2901 w, 1738 s, 1243 s. **MS**: *m*/*z* (EI, relative intensity, %): 261 (3, M^+), 247 (10), 246 (59), 202 (51), 201 (14), 200 (100), 162 (20), 144 (43), 116 (13), 89 (11). **HRMS (DART)** Calcd for $C_{15}H_{20}NO_3$ ($[M+H]^+$): 262.14377. Found: 262.14434.

Ethyl 4-bromo-2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)benzoate (1-Br)



5-Bromophthalide (25 g, 123 mmol), NBS (23 g, 133 mmol) and $(PhCO_2)_2$ (1.4 g, 6.0 mmol) were heated to reflux in CCl_4 (150 mL) for 2.5 h under N_2 atmosphere. The mixture was cooled to room temperature and filtered through Celite pad with CH_2Cl_2. The solvent was evaporated and the resulting solid was dissolved in CH_2Cl_2 (100 mL). H_2O (100 mL) was added. The organic layer was separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL×3). Combined organic layer was washed with brine (50 mL×2) and dried over Na_2SO_4. The volatile was removed under reduced pressure to give the crude mixture of 3,5-dibromoisobenzofuran-1(3*H*)-one (36.5 g) as a pale yellow solid. This material was used in the subsequent step without further purification

3,5-Dibromoisobenzofuran-1(3*H*)-one (36.5 g, crude mixture) and NaOH (10.6 g, 266 mmol) were heated to reflux in H_2O (200 mL) for 1 h under air. The mixture was cooled to room temperature. After $NaHSO_4 \cdot H_2O$ (17.5 g, 127 mmol) was added, the pale yellow solid was formed and was collected. After EtOAc (20 mL) was added to water residue, the pale yellow solid was formed and was collected. The aqueous layer was extracted with EtOAc (20 mL×3) and the combined organic layer was dried over Na_2SO_4. The volatile was removed under reduced pressure to give a pale yellow solid. Combined solids were the crude mixture of 5-bromo-3-hydroxyisobenzofuran-1(3*H*)-one (28.3 g). This material was used in the subsequent step without further purification.

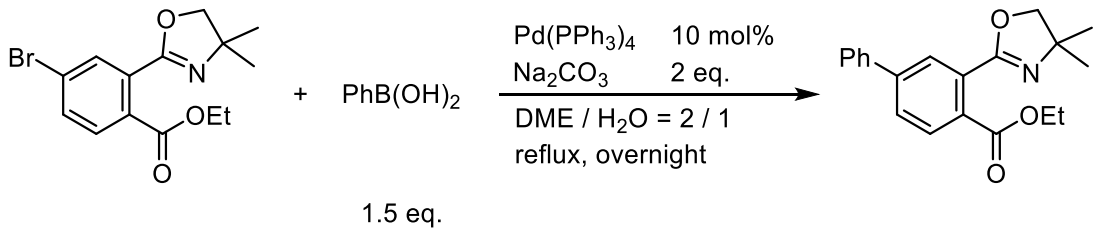
A solution of 5-Bromo-3-hydroxyisobenzofuran-1(3*H*)-one (28.3 g, crude mixture) and K_2CO_3 (26.0 g, 189 mmol) in DMF (200 mL) was stirred for 1 h at rt and EtI (38.5 g, 251 mmol) was slowly added to the mixture at rt. After the addition, the reaction mixture was stirred for 6 h at rt. The reaction mixture was filtered through Celite pad. The resulting mixture was divided into two fractions and each fraction was treated as described below. H_2O (100 mL) and hexane (15 mL) were added to the mixture and the aqueous layer was extracted with Et_2O (20 mL×3). The organic layer was washed with H_2O (100 mL) and brine (200 mL), and dried over Na_2SO_4. Each organic layer was combined in one flask and the volatile was removed under reduced pressure to give the crude mixture of ethyl 4-bromo-2-formylbenzoate (21.1 g) as a pale yellow oil. This material was used in the subsequent step without further purification.

A mixture of ethyl 4-bromo-2-formylbenzoate (21.1 g, crude mixture), 2-amino-2-methyl-1-propanol (9.06 g, 102 mmol) and MS4A (6.90 g) in toluene (160 mL) was stirred for overnight at rt under N_2 atmosphere. NBS and K_2CO_3

were added to the reaction mixture and the reaction mixture was stirred for 1 h at rt. After the reaction, the mixture was filtered through Celite pad and sat. NH_4Cl aq (100 mL) was added. The organic layer was separated and the aqueous layer was extracted with toluene (20 mL×3). The combined organic layer was washed with Brine (50 mL×2) and dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 1/0 to 10/1, R_f = 0.11 in hexane/EtOAc = 5/1) to afford the desired **1-Br** as a pale yellow oil (14.4 g, 44.1 mmol, 36% yield based on 5-bromophthalide).

^{1}H NMR ($CDCl_3$) δ: 1.36 (t, *J* = 6.9 Hz, 3H), 1.40 (s, 6H), 4.11 (s, 2H), 4.34 (q, *J* = 6.9 Hz, 2H), 7.59-7.64 (c, 2H), 7.90 (d, *J* = 1.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.2, 28.1, 61.7, 68.1, 80.0, 125.4, 130.3, 130.6, 131.1, 132.8, 133.4, 161.1, 166.7. **IR** (ATR): 2972 w, 2931 w, 2896 w, 1729 s, 1657 m, 1285 s. **MS**: *m/z* (EI, relative intensity, %): 327 (1, M^++1), 325 (1, M^+-1), 312 (38), 310 (39), 268 (39), 267 (13), 266 (100), 264 (61), 228 (15), 226 (15), 210 (23), 208 (23). **HRMS (DART)** Calcd for $C_{14}H_{17}NO_3Br$ ($[M+H]^+$): 326.03863. Found: 326.03689.

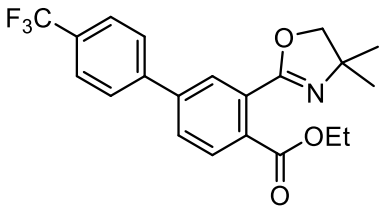
Ethyl 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-[1,1'-biphenyl]-4-carboxylate (10a)



A two necked flask was charged with **1-Br** (0.777 g, 2.38 mmol) and DME (12 mL). The mixture was degassed three times and the flask was charged with N_2. Phenyl boronic acid (0.435 g, 3.57 mmol), Na_2CO_3 (0.505 g, 4.76 mmol), H_2O (6 mL) and $Pd(PPh_3)_4$ (0.275 g, 0.238 mmol) were added to the mixture and the mixture was heated to reflux temperature overnight. After the mixture was cooled to room temperature, the reaction was quenched with sat. NH_4Cl aq. (15 mL). H_2O was added to the reaction mixture and the organic layer was separated and the aqueous layer was extracted with EtOAc (15 mL×3). The combined organic layer was washed with brine (30 mL) and dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was isolated by column chromatography on silica gel (eluent: hexane/EtOAc = 1/0 to 3/1, R_f = 0.24 in hexane/EtOAc = 3/1) to afford the desired **10a** as a yellow powder (0.603 g, 1.86 mmol, 78%).

Mp = 65.2-65.6 ºC **^{1}H NMR** ($CDCl_3$) δ 1.39 (t, *J* = 7.2 Hz, 3H), 1.43 (s, 6H), 4.13 (s, 2H), 4.37 (q, *J* = 7.2 Hz, 2H), 7.36-7.42 (m, 1H), 7.42-7.49 (m, 2H), 7.60-7.66 (m, 2H), 7.71 (dd, *J* = 8.2, 2.0 Hz, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 2.0 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.2, 28.2, 61.4, 68.0, 79.9, 127.3, 128.2, 128.6, 128.8, 128.9, 129.2, 129.8, 130.7, 139.2, 144.0, 162.6, 167.3. **IR** (ATR): 2972 w, 2931 w, 2896 w, 1727 s, 1658 m, 1288 s. **MS**: *m/z* (EI, relative intensity, %): 323 (9, M^+), 308 (41), 264 (49), 263 (19), 262 (100), 224 (14), 207 (41), 206 (40), 151 (12). **Anal.** Calcd for $C_{20}H_{21}NO_3$: C, 74.28; H, 6.55; N, 4.33. Found: C, 74.02; H, 6.50; N, 4.26.

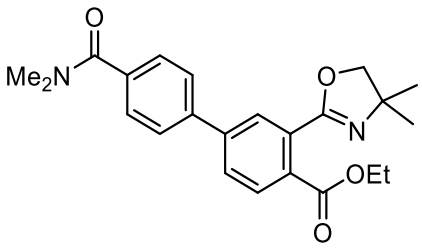
Ethyl 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-4'-(trifluoromethyl)-[1,1'-biphenyl]-4-carboxylate (10b)



10b was prepared from **1-Br** (2.00 g, 6.85 mmol) following the procedure for synthesis of **10a** by using 4-(trifluoromethyl)phenylboronic acid (1.75 g, 9.43 mmol) in place of Phenylboronic acid. The product was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 1/0 to 5/1, R_f = 0.14 in hexane/EtOAc = 5/1) in 68% yield (1.64 g, 4.19 mmol) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.39 (t, *J* = 7.1 Hz, 3H), 1.43 (s, 6H), 4.14 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 7.70-7.75 (c, 5H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.2, 28.1, 61.6, 68.1, 79.9, 124.1 (q, *J* = 271 Hz), 125.8 (q, *J* = 3.8 Hz), 127.6, 128.7, 128.9, 129.3, 129.9, 130.2 (q, *J* = 33 Hz), 131.7, 142.4, 142.7, 162.1, 167.2. **IR** (ATR): 2972 w, 2932 w, 2897 w, 1726 s, 1658 m, 1324 s, 1287 m, 1110 s. **MS**: *m/z* (EI, relative intensity, %): 391 (4, M^+), 377 (14), 376 (60), 333 (11), 332 (54), 331 (21), 330 (100), 292 (19), 274 (46), 177 (12). **HRMS (DART)** Calcd for $C_{21}H_{21}NO_3F_3$ ($[M+H]^+$): 392.14680. Found: 392.14465.

Ethyl 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-4'-(dimethylcarbamoyl)-[1,1'-biphenyl]-4-carboxylate (10c)

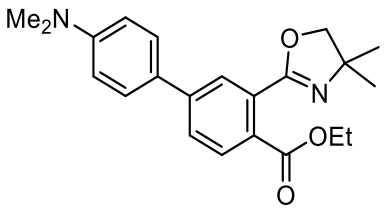


10c was prepared from **1-Br** (2.05 g, 6.27 mmol) following the procedure for synthesis of **10a** by using 4-(dimethylcarbamoyl)phenylboronic acid (1.83 g, 9.48 mmol) in place of phenylboronic acid. The product was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 1/0 to 0/1, R_f = 0.01 in hexane/EtOAc = 5/1) followed by GPC in 59% yield (1.45 g, 3.67 mmol) as a white solid. Further purification by recrystallization from hexane/EtOAc afforded the title compound as a white solid.

Mp = 126.4-127.3 ºC. **^{1}H NMR** ($CDCl_3$) δ 1.37 (t, *J* = 7.3 Hz, 3H), 1.43 (s, 6H), 3.02 (s, 3H), 3.14 (s, 3H), 4.15 (s, 2H), 4.38 (q, *J* = 7.3 Hz, 2H), 7.51-7.53 (m, 2H), 7.64-7.69 (m, 2H), 7.72 (dd, *J* = 8.1 Hz, 1.6 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.96 (d, *J* = 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.2, 28.1, 35.3, 39.5, 61.5, 68.0, 79.8, 127.2, 127.7, 128.6, 128.7, 129.2, 129.8, 131.2, 136.1, 140.3, 143.0, 162.3, 167.2, 171.1. **IR** (ATR): 2975 w, 2930 w, 2898 w, 1730 s, 1637 s, 1290 s, 1264 s. **MS**: *m/z* (EI, relative intensity, %): 395 (10), 394 (36, M^+), 380 (14), 379 (56), 351 (18),

350 (72). 349 (11), 336 (13), 335 (59), 334 (24), 333 (100), 295 (11), 278 (14), 277 (24), 261 (13), 205 (20), 166 (12), 144 (11). **HRMS (DART)** Calcd for $C_{23}H_{27}N_2O_4$ ([M+H]$^+$): 395.19653. Found: 395.19544.

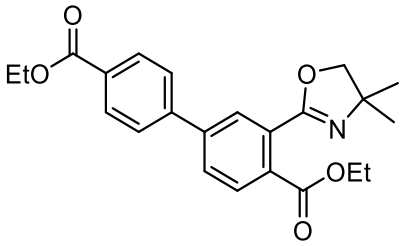
Ethyl 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-4'-(dimethylamino)-[1,1'-biphenyl]-4-carboxylate (10d)



10d was prepared from **1-Br** (2.51 g, 7.70 mmol) following the procedure for synthesis of **10a** by using 4-(dimethylamino)phenylboronic acid (1.92 g, 11.7 mmol) in place of phenylboronic acid. The product was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 1/0 to 1/1, R_f = 0.06 in Hexane/EtOAc = 5/1) followed by GPC in 66% yield (1.85 g, 5.05 mmol) as a green solid.

Mp = 154.2-154.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.38 (t, *J* = 7.2 Hz, 3H), 1.44 (s, 6H), 3.01 (s, 6H), 4.15 (s, 2H), 4.36 (q, *J* = 7.2 Hz, 2H), 6.79 (d, *J* = 8.7 Hz, 2H), 7.54-7.60 (m, 2H), 7.67 (dd, *J* = 8.0, 1.8 Hz, 1H), 7.82 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 1.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.3, 28.2, 40.4, 61.2, 67.9, 79.8, 112.5, 126.6, 127.3×2, 127.9, 128.8, 129.4, 130.0, 144.1, 150.5, 163.0, 167.3. **IR** (ATR): 2978 w, 2933 w, 1736 s, 1656 w, 1601 m, 1244 s. **MS**: *m*/*z* (EI, relative intensity, %): 367 (25), 366 (100, M$^+$), 307 (23), 306 (11), 305 (51), 266 (11), 249 (13), 152 (11), 124 (12). **HRMS (DART)** Calcd for $C_{22}H_{27}N_2O_3$ ([M+H]$^+$): 367.20162. Found: 367.20124.

Diethyl 3-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-[1,1'-biphenyl]-4,4'-dicarboxylate (10e)

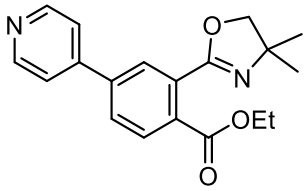


10e was prepared from **1-Br** (0.85 g, 2.61 mmol) following the procedure for synthesis of **10a** by using 4-(ethoxycarbonyl)phenylboronic acid (0.759 g, 3.91 mmol) in place of Phenylboronic acid. The product was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 1/0 to 1/1, R_f = 0.21 in Hexane/EtOAc = 3/1) in 78% yield (0.802 g, 2.03 mmol) as a colorless syrup.

^{1}H NMR ($CDCl_3$) δ 1.39 (t, *J* = 7.2 Hz, 3H), 1.42 (t, *J* = 7.2 Hz, 3H), 1.43 (s, 6H), 4.14 (s, 2H), 4.38 (q, *J* = 7.2 Hz, 2H), 4.41 (q, *J* = 7.2 Hz, 2H), 7.68-7.71 (m, 2H), 7.74 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 1.8 Hz, 1H), 8.11-8.14 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ: 14.2, 14.3, 28.1, 61.1, 61.5, 68.0, 79.9, 127.2, 128.7, 128.9, 129.2, 129.8, 130.1, 131.6, 142.8, 143.4, 162.2, 166.2, 167.2. One signal is obscured by overlap with other signals. **IR** (ATR): 2976 w, 2975 w, 2930 w, 1717 s, 1657 w, 1273 s. **MS**: *m*/*z* (EI, relative intensity, %): 395 (8, M$^+$), 381

(15), 380 (60), 350 (17), 337 (14), 336 (63), 335 (23), 334 (100), 306 (13), 296 (13), 278 (25), 250 (17), 145 (10). **Anal.** Calcd for $C_{23}H_{25}NO_5$: C, 69.86; H, 6.37; N, 3.54. Found: C, 69.78; H, 6.40; N, 3.55.

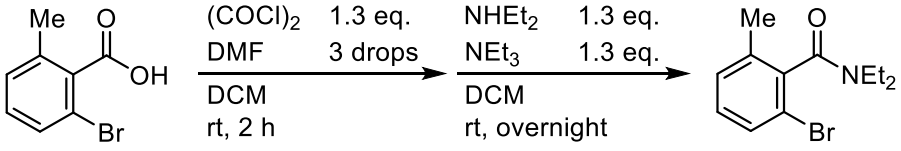
Ethyl 2-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-4-(pyridin-4-yl)benzoate (11)



11 was prepared from **1-Br** (2.04 g, 6.26 mmol) following the procedure for synthesis of **10a** by using 4-pyridylboronic acid (1.11 g, 9.08 mmol) in place of phenylboronic acid. The product was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 1/0 to 2/1, R_f = 0.09 in Hexane/EtOAc = 3/1) followed by flash column chromatography on NH_2-modified silica-gel (eluent: $CHCl_3$ only, R_f = 0.01 in Hexane/EtOAc = 3/1) in 66% yield (1.34 g, 4.13 mmol) as a colorless syrup.

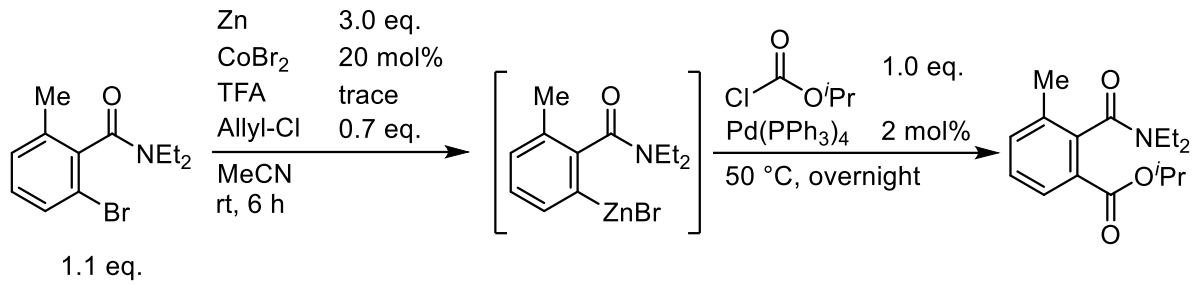
^{1}H NMR ($CDCl_3$) δ: 1.39 (t, *J* = 7.1 Hz, 3H), 1.43 (s, 6H), 4.14 (s, 2H), 4.39 (q, *J* = 7.1 Hz, 2H), 7.48-7.63 (m, 2H), 7.75 (dd, *J* = 8.1, 1.8 Hz, 1H), 7.86 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 1.8 Hz, 1H), 8.68-8.71 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ: 14.2, 28.2, 61.7, 68.1, 79.9, 121.7, 128.5, 128.7, 129.4, 129.9, 132.7, 140.8, 146.5, 150.4, 161.9, 167.1. **IR** (ATR): 2971 w, 2931 w, 2897 w, 1726 s, 1656 m, 1594 m, 1288 s, 1266 s. **MS**: *m/z* (EI, relative intensity, %): 324 (3, M^+), 310 (15), 309 (72), 266 (10), 265 (55), 264 (19), 263 (100), 225 (22), 207 (46), 179 (12), 83 (13). **HRMS (DART)** Calcd for $C_{19}H_{21}N_2O_3$ ($[M+H]^+$): 325.15467. Found: 325.15450.

2-Bromo-*N*,*N*-diethylbenzamide (pre-12)



To a solution of 2-Bromo-6-methylbenzoic acid (3.31 g, 15.4 mmol) and DMF (3 drops) in DCM (30 mL), Oxalyl chloride (2.42 g, 19.0 mmol) was added dropwise at 0 °C. After stirring for 2 h at rt, the volatiles were removed under reduced pressure. The residue was suspended in DCM (30 mL) and slowly added to a suspension of Diethylamine (1.51 g, 20.6 mmol) and NEt_3 (2.03 g, 20.1 mmol) in DCM (30 mL) at 0 °C. After stirring overnight at rt, 1N HCl (30 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (30 mL) and the combined organic layer was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was isolated by column chromatography on silica gel (eluent: hexane/EtOAc = 5/1 to 2/1, R_f = 0.25 in hexane/EtOAc = 2/1) to afford the desired **pre-12** as a white solid (3.77 g, 14.7 mmol, 96%). The spectroscopic data of this material was reported in the literature.[15]

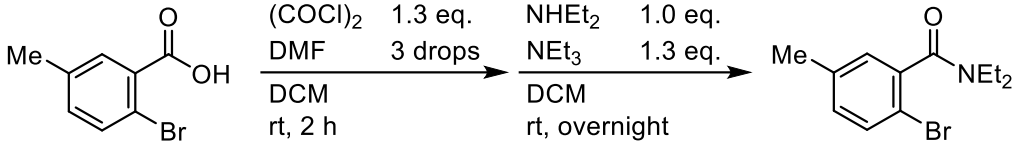
Isopropyl 2-(diethylcarbamoyl)-3-methylbenzoate (12)



The aryl zinc reagent was prepared by a modified procedure reported by Gosmini.[16] A two necked flask was flame-dried and purged with N_2. After cooling to room temperature, Zn (1.74 g, 26.6 mmol), $CoBr_2$ (0.287 g, 1.31 mmol), MeCN (8 mL), allyl chloride (0.373 g, 4.87 mmol) and TFA (60 μL) were placed in the flask. After the mixture was stirred for 3 min, 2-bromo-*N,N*-diethylbenzamide (2.02 g, 7.89 mmol) was added. After stirring for 6 h at rt, $Pd(PPh_3)_4$ (0.172 g, 0.149 mmol) and isopropyl chloroformate (0.856 g, 6.98 mmol) were added. The resulting mixture was stirred overnight at 50 °C. 1N HCl aq (15 mL) was added and the organic layer was separated. The aqueous layer was extracted with EtOAc (30 mL×2) and the combined organic layer was dried over $MgSO_4$. After the volatile was removed under reduced pressure, the resulting crude mixture was isolated by column chromatography on silica gel (eluent: hexane/EtOAc = 2/1, R_f = 0.16 in hexane/EtOAc = 2/1) followed by column chromatography on silica gel (eluent: hexane/EtOAc = 5/1 to 1/1, R_f = 0.16 in hexane/EtOAc = 2/1) to afford the desired **12** as a colirless oil (1.00 g, 3.61 mmol, 52%). Further purification by vacuum distillation (0.22 mmHg, 107 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.02 (t, *J* = 7.1 Hz, 3H), 1.29-1.34 (c, 9H), 2.31 (s, 3H), 2.99-3.16 (m, 2H), 3.34 (dq, *J* = 14.2 Hz, 7.1 Hz, 1H), 3.91 (dq, *J* = 14.2 Hz, 7.1 Hz, 1H), 5.20 (qq, *J* = 6.2 Hz, 6.2 Hz, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.37 (dd, *J* = 7.8 Hz, 0.7 Hz, 1H), 7.87 (dd, *J* = 7.8 Hz, 0.7 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 11.8, 12.5, 18.0, 21.0, 21.1, 37.7, 41.8, 67.7, 126.8, 127.2, 127.3, 133.7, 134.0, 137.6, 164.4, 168.6. **IR** (ATR): 2979 w, 2935 w, 1715 m, 1631 s, 1279 s. **MS**: *m/z* (EI, relative intensity, %): 262 (14, M^+-15), 218 (10), 164 (10), 163 (100), 72 (56). **Anal.** Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 69.21; H, 8.47; N, 5.10.

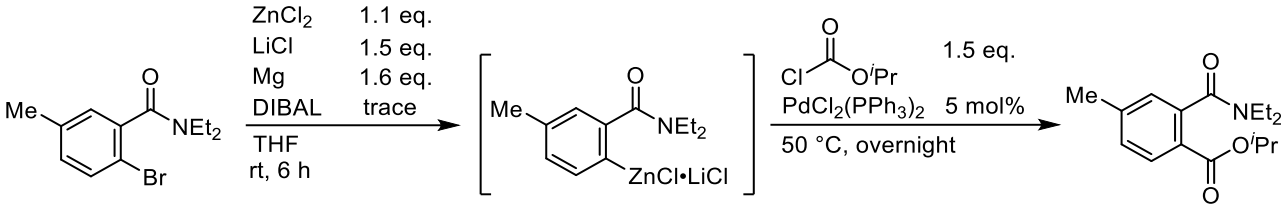
2-Bromo-*N,N*-diethyl-5-methylbenzamide (pre-13)



To a solution of 2-bromo-5-methylbenzoic acid (6.43 g, 29.9 mmol) and DMF (3 drops) in DCM (50 mL), Oxalyl chloride (3.5 mL, 40.8 mmol) was added dropwise at 0 °C. After stirring for 2 h at rt, the volatiles were removed under reduced pressure. The residue was suspended in DCM (10 mL) and slowly added to a suspension of

Diethylamine (2.23 g, 30.5 mmol) and NEt_3 (4.05 g, 40.0 mmol) in DCM (30 mL) at 0 °C. After stirring overnight at rt, 1N HCl (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (50 mL×2) and the combined organic layer was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was isolated by column chromatography on silica gel (eluent: hexane/EtOAc = 2/1, R_f = 0.24 in hexane/EtOAc = 2/1) to afford the desired **pre-13** as a yellow oil (7.07 g, 25.7 mmol, 86%). The spectroscopic data of this material was reported in the literature.[17]

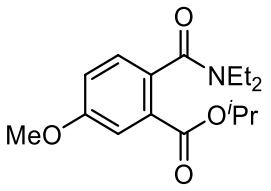
Isopropyl 2-(diethylcarbamoyl)-4-methylbenzoate (13)



The aryl zinc reagent was prepared according to modified procedure reported by Knochel.[18] A three necked flask was charged with LiCl anhydrous (1.87 g, 44.1 mmol) and $ZnCl_2$ (4.17 g, 30.6 mmol). The flask was flame-dried for 5 min. and purged with N_2. After cooling to room temperature, THF (40 mL), Mg (0.985 g, 40.6 mmol) and DIBAL (1 M in THF, 0.2 mL, 0.2 mmol) were placed in the flask. After the mixture was stirred for 5 min. at rt, 2-Bromo-*N,N*-diethyl-5-methylbenzamide (7.07 g, 26.2 mmol) was added. After stirring for 6 h at rt, the remaining zinc was allowed to settle and the resulting solution was transferred to new flame-dried flask. $PdCl_2(PPh_3)_2$ (1.06 g, 1.51 mmol) and Isopropyl chloroformate (5.05 g, 41.2 mmol) were added. The resulting mixture was stirred overnight at 50 °C. After the reaction, sat. NH_4Cl aq (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (50 mL×2) and the combined organic layer was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was isolated by column chromatography on silica gel (eluent: DCM only to DCM/Et_2O = 10/1, R_f = 0.22 in DCM/Et_2O = 10/1) followed by column chromatography on silica gel (eluent: hexane/EtOAc = 5/1 to 1/1, R_f = 0.19 in hexane/EtOAc = 2/1) followed by the isolation by GPC to afford the desired **13** as an yellow oil (3.34 g, 12.0 mmol, 46%). Further purification by vacuum distillation (0.28 mmHg, 128 °C) under CaH_2 afforded the title compound as a yellow oil.

^{1}H NMR ($CDCl_3$) δ: 1.03 (t, *J* = 7.1 Hz, 3H), 1.24-1.37 (c, 9H), 2.40 (s, 3H), 3.11 (q, *J* = 7.2 Hz, 2H), 3.58 (br, 2H), 5.20 (qq, *J* = 6.2 Hz, 6.2 Hz, 1H), 7.04-7.06 (m, 1H), 7.19-7.23 (m, 1H), 7.91 (d, *J* = 8.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.7, 13.6, 21.4, 21.8, 38.9, 43.0, 68.5, 124.9, 127.4, 128.9, 130.6, 139.2, 143.1, 165.1, 170.4. **IR** (ATR): 2979 w, 2934 w, 1713 s, 1634 s, 1286 s. **MS**: *m/z* (EI, relative intensity, %): 277 (5), 276 (24), 218 (10), 164 (10), 163 (100), 72 (57). **Anal.** Calcd for $C_{16}H_{23}NO_3$: C, 69.29; H, 8.36; N, 5.05. Found: C, 68.97; H, 8.25; N, 5.13.

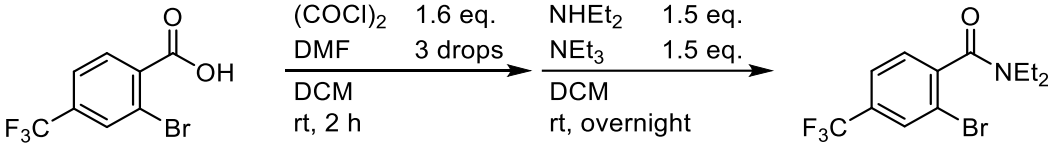
Isopropyl 2-(diethylcarbamoyl)-5-methoxybenzoate (14a)



The procedure for synthesis of **13** was modified by using *N,N*-diethyl-2-bromo-4-methoxy-benzamide[19] (3.37 g, 11.8 mmol) in place of **pre-13**. The product was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 5/1 to 2/1, R_f = 0.07 in hexane/EtOAc = 2/1) followed by GPC in 26% yield (0.85 g, 3.05 mmol). Further purification by vacuum distillation (0.19 mmHg, 122 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.03 (t, *J* = 7.1 Hz, 3H), 1.29 (t, *J* = 7.1 Hz, 3H), 1.33 (d, *J* = 6.4 Hz, 6H), 3.14 (q, *J* = 7.1 Hz, 2H), 3.57 (q, *J* = 7.1 Hz, 2H), 3.85 (s, 3H), 5.21 (qq, *J* = 6.4 Hz, 6.4 Hz, 1H), 7.06 (dd, *J* = 8.5 Hz, 2.8 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 1H), 7.51 (d, *J* = 2.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.4, 13.4, 21.5, 38.8, 42.9, 55.2, 68.6, 115.0, 117.8, 127.9, 129.2, 131.3, 159.0, 164.8, 170.0. **IR** (ATR): 2979 w, 2936 w, 1715 m, 1632 s, 1607 m, 1283 s. **MS**: *m/z* (EI, relative intensity, %): 293 (4, M^+), 292 (18), 180 (10), 179 (100), 72 (31). **HRMS (DART)** Calcd for $C_{16}H_{24}NO_4$ ($[M+H]^+$): 294.16998. Found: 294.16784.

2-Bromo-*N,N*-diethyl-4-(trifluoromethyl)benzamide (pre-14b)

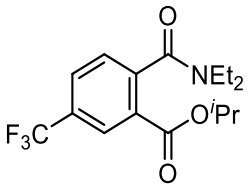


To a solution of 2-bromo-4-(trifluoromethyl) benzoic acid (4.61 g, 17.1 mmol) and DMF (3 drops) in DCM (30 mL), oxalyl chloride (2.4 mL, 27.9 mmol) was added dropwise at 0 °C. After stirring for 2 h at rt, the volatiles were removed under reduced pressure. The residue was suspended in DCM (10 mL) and slowly added to a suspension of diethylamine (1.81 g, 25.3 mmol) and NEt_3 (2.53 g, 25.0 mmol) in DCM (30 mL) at 0 °C. After stirring overnight at rt, 1N HCl aq (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with DCM (50 mL×2) and the combined organic layer was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was isolated by column chromatography on silica gel (eluent: hexane/EtOAc = 2/1, R_f = 0.28 in hexane/EtOAc = 2/1) to afford the desired **pre-14b** as a yellow oil (5.16 g, 15.9 mmol, 93%).

^{1}H NMR ($CDCl_3$) δ: 1.09 (t, *J* = 7.0 Hz, 3H), 1.29 (t, *J* = 7.0 Hz, 3H), 3.05-3.22 (m, 2H), 3.35 (dq, *J* = 13.9 Hz, 7.0 Hz, 1H), 3.84 (dq, *J* = 13.9 Hz, 7.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.61-7.63 (m, 1H), 7.85 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.4, 13.8, 39.0, 42.6, 119.6, 122.8 (q, *J* = 272.8 Hz), 124.5 (q, *J* = 3.7 Hz), 127.8, 129.8 (q, *J* = 3.8 Hz),

132.1 (q, *J* = 33 Hz), 142.2, 167.2. **MS**: *m/z* (EI, relative intensity, %): 325 (14, M^++1), 324 (48), 323 (14, M^+-1), 322 (49), 253 (96), 251 (100), 244 (44), 224 (17), 222 (18), 144 (20). **Anal.** Calcd for $C_{12}H_{13}BrF_3NO$: C, 44.47; H, 4.04; N, 4.32. Found: C, 44.10; H, 4.17; N, 4.27.

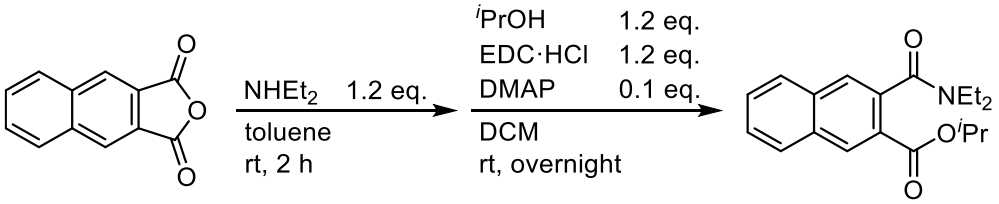
Isopropyl 2-(diethylcarbamoyl)-5-(trifluoromethyl)benzoate (14b)



The procedure for synthesis of **13** was modified by using **pre-14b** (5.16 g, 15.9 mmol) in place of **pre-13**. The product was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 5/1 to 2/1, R_f = 0.20 in hexane/EtOAc = 2/1) followed by GPC in 26% yield (1.35 g, 4.07 mmol). Further purification by vacuum distillation (0.23 mmHg, 107 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.07 (t, *J* = 7.1 Hz, 3H), 1.32 (t, *J* = 7.1 Hz, 3H), 1.37 (d, *J* = 6.0 Hz, 6H), 3.15 (q, *J* = 7.1 Hz, 2H), 3.61 (q, *J* = 7.1 Hz, 2H), 5.26 (qq, *J* = 6.0 Hz, 6.0 Hz, 1H), 7.47 (d, *J* = 7.8 Hz, 1H), 7.84 (dd, *J* = 7.8, 1.4 Hz, 1H), 8.2 (d, *J* = 1.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.4, 13.4, 21.5, 38.9, 42.9, 69.5, 123.2 (q, *J* = 270.8 Hz), 127.3-127.5 (c), 127.5, 128.7, 128.7-128.9 (c), 130.5 (q, *J* = 33 Hz), 142.4, 163.7, 168.7. **IR** (ATR): 2983 w, 2939 w, 1722 m, 1638 s, 1264 s. **MS**: *m/z* (EI, relative intensity, %): 331 (6, M^+), 330 (21), 288 (26), 272 (16), 270 (13), 244 (12), 218 (11), 217 (100), 72 (74), 58 (14). **Anal.** Calcd for $C_{16}H_{20}NO_3F_3$: C, 58.00; H, 6.08; N, 4.23. Found: C, 57.82; H, 6.27; N, 4.21.

Isopropyl 3-(diethylcarbamoyl)-2-naphthoate (15)

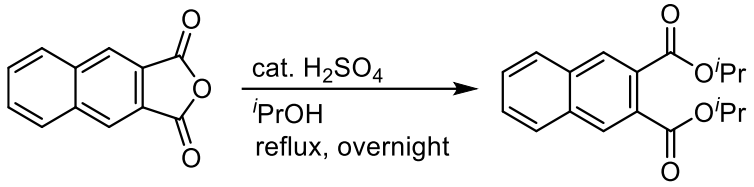


To a solution of 2,3-Naphthalenedicarboxylic anhydride (3.95 g, 19.9 mmol) in toluene (30 mL), $NHEt_2$ (1.98 g, 27.1 mmol) was added dropwise at rt. After stirring for 2 h at rt under air, the volatiles were removed under reduced pressure. The residue was suspended in DCM (30 mL). EDC·HCl (4.21 g, 22.0 mmol), DMAP (0.25 g, 2.1 mmol) and ^{i}PrOH (1.45 g, 24.1 mmol) were added. After stirring overnight at rt under air, H_2O (40 mL) was added and the mixture was extracted with DCM (50 mL×2) and the organic layer was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was isolated by column chromatography on silica gel

(eluent: hexane/EtOAc = 5/1 to 1/1, R_f = 0.25 in hexane/EtOAc = 1/1) to afford the desired **15** as a white solid (2.55 g, 8.13 mmol, 41%).

Mp = 65.2-65.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.05 (t, *J* = 7.2 Hz, 3H), 1.28-1.45 (c, 9H), 3.19 (q, *J* = 7.2 Hz, 2H), 3.58-3.68 (m, 2H), 5.29 (qq, *J* = 6.3 Hz, 6.3 Hz, 1H), 7.50-7.64 (c, 2H), 7.72 (s, 1H), 7.85 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.57 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.7, 13.6, 21.8, 39.0, 43.1, 68.7, 125.8, 126.1, 127.1, 127.6, 128.6, 128.9, 131.9, 132.0, 134.4, 135.1, 165.2, 170.3. **IR** (ATR): 2980 w, 2933 w, 2874 w, 1710 s, 1625 s, 1279 s. **MS**: *m*/*z* (EI, relative intensity, %): 313 (13, M^+), 312 (13), 270 (18), 252 (15), 200 (16), 199 (100), 127 (10), 115 (17), 72 (34). **Anal.** Calcd for $C_{19}H_{23}NO_3$: C, 72.82; H, 7.40; N, 4.47. Found: C, 72.75; H, 7.43; N, 4.46.

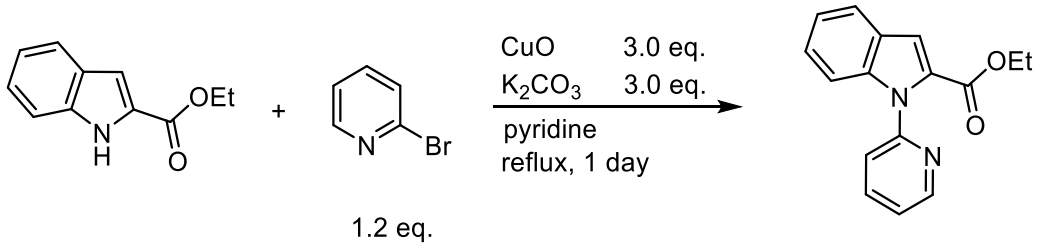
Isopropyl 3-(diethylcarbamoyl)-2-naphthoate (16)



A solution of 2,3-Naphthalenedicarboxylic anhydride (3.97 g, 20.0 mmol) and H_2SO_4 (1.0 mL) in ^{i}PrOH (30 mL) was heated to reflux overnight. After cooled to rt, the volatiles were removed under reduced pressure. sat. $NaHCO_3$ aq (100 mL) was added and the mixture was extracted with Et_2O (80 mL×2) and the organic layer was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was isolated by column chromatography on silica gel (R_f = 0.25 in hexane/EtOAc = 10/1) to afford the desired **15** as a colorless oil (4.46 g, 14.8 mmol, 74%).

^{1}H NMR ($CDCl_3$) δ: 1.41 (d, *J* = 6.4 Hz, 12H), 5.30 (qq, *J* = 6.4 Hz, 6.4 Hz, 2H), 7.57-7.61 (m, 2H), 7.89-7.92 (m, 2H), 8.20 (s, 2H). **^{13}C NMR** ($CDCl_3$) δ: 21.8, 69.1, 128.3, 128.5, 129.3, 129.7, 133.3, 167.1. **IR** (ATR): 3059 w, 2980 w, 2936 w, 2877 w, 1716 s, 1281 s. **MS**: *m*/*z* (EI, relative intensity, %): 300 (15, M^+), 200 (21), 199 (100), 172 (23), 155 (10), 127 (11), 126 (11), 115 (19). **HRMS (DART)** Calcd for $C_{18}H_{21}O_4$ ($[M+H]^+$): 301.14344. Found: 301.14399.

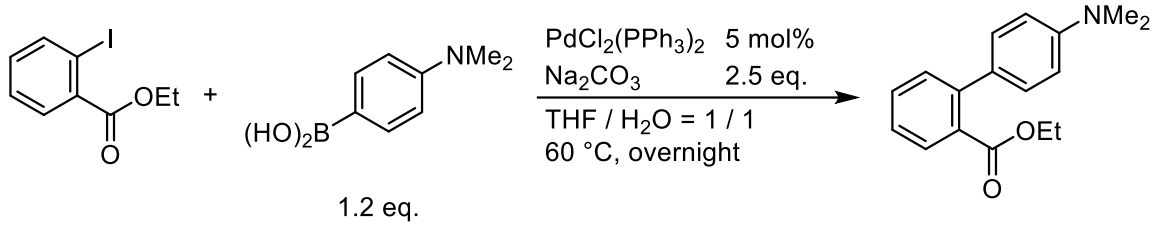
Ethyl 1-(pyridin-2-yl)-*1H*-indole-2-carboxylate (17)



The title compound was synthesized according to Lim's procedure.[20] A three necked flask was charged with Ethyl Indole-2-carboxylate (3.14 g, 16.6 mmol), CuO (4.17 g, 52.4 mmol) and K_2CO_3 (6.99 g, 49.9 mmol), and was purged with N_2. 2-Bromopyridine (2.1 mL) and pyridine (100 mL) were added and the mixture was heated to reflux for 1 day. After the reaction, the mixture was filtered through Celite pad and the volatile was removed. The resulting crude mixture was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 10/1 to 5/1, R_f = 0.13 in hexane/EtOAc = 5/1) to afford the desired **17** as a yellow syrup (4.09 g, 15.3 mmol, 91%).

^{1}H NMR ($CDCl_3$) δ: 1.24 (t, *J* = 7.2 Hz, 3H), 4.24 (q, *J* = 7.2 Hz, 2H), 7.12-7.24 (m, 1H), 7.28-7.36 (m, 2H), 7.36-7.44 (m, 2H), 7.47 (s, 1H), 7.73 (dd, *J* = 9.2, 0.9 Hz, 1H), 7.90 (td, *J* = 7.7, 2.1 Hz, 1H), 8.65 (dd, *J* = 4.8, 1.1 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.1, 60.7, 111.4, 112.6, 121.6, 122.0, 122.5, 122.8, 125.8, 126.5, 129.0, 137.9, 139.7, 149.2, 151.5, 161.3. **IR** (ATR): 3047 w, 2996 w, 2938 w, 1709 s, 1187 s. **MS**: *m/z* (EI, relative intensity, %): 267 (18), 266 (100, M^+), 265 (28), 221 (51), 219 (19), 194 (45), 193 (38), 192 (22). **HRMS (DART)** Calcd for $C_{16}H_{15}N_2O_2$ ($[M+H]^+$): 267.11280. Found: 267.11315.

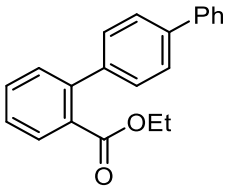
Ethyl 4'-(dimethylamino)-[1,1'-biphenyl]-2-carboxylate (19b)



A three necked flask was purged with N_2. The flask was charged with ethyl 2-iodobenzoate (4.14 g, 15.0 mmol), 4-(dimethylamino)phenylboronic acid (3.05 g, 18.5 mmol), THF (40 mL), 1N Na_2CO_3 aq (40 mmol) and $PdCl_2(PPh_3)_2$ (0.532 g, 0.76 mmol). The mixture was stirred at 60 ℃ overnight. After the mixture was cooled to room temperature, H_2O (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (50 mL×2) and the resulting mixture was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 100/1 to 10/1, R_f = 0.14 in hexane/EtOAc = 10/1) to afford the desired **19b** as a pale yellow solid (3.64 g, 13.5 mmol, 90%). Further purification by recrystallization from hexane/Et_2O afforded the title compound as a white solid.

Mp = 56.9-57.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.09 (t, *J* = 7.2 Hz, 3H), 2.98 (s, 6H), 4.15 (q, *J* = 7.2 Hz, 2H), 6.75 (dd, *J* = 6.7, 2.2 Hz, 2H), 7.19-7.24 (m, 2H), 7.32 (td, *J* = 7.7, 1.2 Hz, 1H), 7.37 (dd, *J* = 7.7, 1.2 Hz, 1H), 7.47 (td, *J* = 7.7, 1.2 Hz, 1H), 7.74 (dd, *J* = 7.7, 1.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 13.9, 40.6, 60.8, 112.1, 126.1, 129.1, 129.2, 129.4, 130.5, 130.9, 131.3, 142.2, 149.8, 169.5. **IR** (ATR): 2981 w, 2894 w, 1715 s. **MS**: *m/z* (EI, relative intensity, %): 270 (18), 269 (100, M^+), 268 (16), 241 (43), 240 (47), 224 (11), 152 (13), 111 (14). **Anal.** Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.79; H, 7.15; N, 5.13.

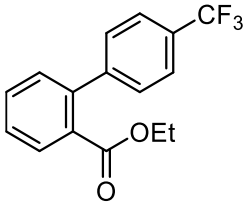
Ethyl [1,1':4',1''-terphenyl]-2-carboxylate (19c)



19c was prepared from ethyl 2-iodobenzoate (4.88g, 17.7 mmol) following the procedure for synthesis of **19b** by using 4-biphenylboronic acid (25.3 mmol) in place of 4-(dimethylamino)phenylboronic acid. The product was isolated by flash column chromatography on silica-gel (R_f = 0.23 in hexane/EtOAc = 20/1) in 88% yield (4.69 g, 15.5 mmol) as a white solid. Further purification by recrystallization from hexane/Et_2O afforded the title compound as a white solid.

Mp = 77.8-78.1 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.01 (t, *J* = 7.2 Hz, 3H), 4.12 (q, *J* = 7.2 Hz, 2H), 7.29-7.48 (c, 7H), 7.49-7.57 (m, 1H), 7.61-7.65 (c, 4H), 7.85 (dd, *J* = 8.0 Hz, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 13.6, 61.0, 126.7, 127.0, 127.2, 127.3, 128.76, 128.80, 129.8, 130.5, 131.1, 131.2, 140.0, 140.4, 140.7, 141.9, 168.8. **IR** (ATR): 3061 w, 3028 w, 2989 w, 1719 s, 1261 s. **MS**: *m/z* (EI, relative intensity, %): 303 (28), 302 (100, M^+), 274 (15), 258 (27), 257 (86), 229 (24), 228 (29), 227 (14), 226 (17), 114 (12), 113 (11). **Anal.** Calcd for $C_{21}H_{18}O_2$: C, 83.42; H, 6.00. Found: C, 83.46; H, 6.01.

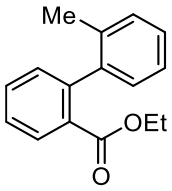
Ethyl 4'-(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylate (19d)



19d was prepared from ethyl 2-iodobenzoate (5.44 g, 19.7 mmol) following the procedure for synthesis of **19b** by using 4-(trifluoromethyl)phenylboronic acid (5.68 g, 29.9 mmol) in place of 4-(dimethylamino)phenylboronic acid. The product was isolated by flash column chromatography on silica-gel (R_f = 0.23 in hexane/EtOAc = 20/1) in 88% yield (5.12 g, 17.4 mmol) as a colorless oil. Further purification by vacuum distillation (0.10 mmHg, 74 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.01 (t, *J* = 7.2 Hz, 3H), 4.10 (q, *J* = 7.2 Hz, 2H), 7.29-7.38 (m, 1H), 7.42 (dd, *J* = 8.7 Hz, 0.7 Hz, 2H), 7.47 (td, *J* = 7.5 Hz, 1.4 Hz, 1H), 7.56 (td, *J* = 7.5 Hz, 1.4 Hz, 1H), 7.61-7.76 (m, 2H), 7.83-7.99 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 13.6, 61.0, 124.2 (q, *J* = 270.2 Hz), 124.8 (q, *J* = 3.4 Hz), 127.9, 128.8, 129.3, 130.2, 130.5, 130.8, 131.4, 141.2, 145.3, 168.0. **IR** (ATR): 2984 w, 2940 w, 1717 m, 1323 s, 1280 m. **MS**: *m/z* (EI, relative intensity, %): 294 (30, M^+), 266 (19), 265 (10), 250 (16), 249 (100), 201 (37), 152 (20). **Anal.** Calcd for $C_{16}H_{13}F_3O_2$: C, 65.31; H, 4.45. Found: C, 65.14; H, 4.50.

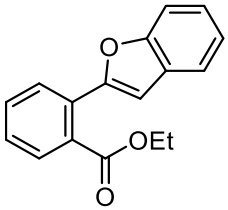
Ethyl 2'-methyl-[1,1'-biphenyl]-2-carboxylate (20)



20 was prepared from ethyl 2-iodobenzoate (5.51 g, 20.0 mmol) following the procedure for synthesis of **19b** by using 2-methylphenylboronic acid (4.13 g, 30.4 mmol) in place of 4-(dimethylamino)phenylboronic acid. The product was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 100/1 to 20/1, R_f = 0.21 in hexane/EtOAc = 20/1) in 64% yield (3.09 g, 12.8 mmol) as a colorless oil. Further purification by vacuum distillation (0.20 mmHg, 84 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 0.95 (t, *J* = 7.1 Hz, 3H), 2.08 (s, 3H), 3.92-4.15 (m, 2H), 7.08 (dd, *J* = 7.3 Hz, 1.1 Hz, 1H), 7.13-7.34 (c, 4H), 7.42 (td, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.53 (td, *J* = 7.7 Hz, 1.4 Hz, 1H), 7.96 (dd, *J* = 7.7 Hz, 1.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 13.5, 20.0, 60.6, 125.2, 127.09, 127.15, 128.5, 129.3, 129.9, 130.7, 130.8, 131.4, 135.4, 141.6, 142.6, 167.7. **IR** (ATR): 3060 w, 3019 w, 2981 w, 2929 w, 1711 s, 1285 s. **MS**: *m*/*z* (EI, relative intensity, %): 240 (32, M^+), 196 (15), 195 (100), 194 (100), 167 (51), 166 (66), 165 (91), 152 (35), 82 (12). **Anal.** Calcd for $C_{16}H_{16}O_2$: C, 79.97; H, 6.71. Found: C, 80.08; H, 6.46.

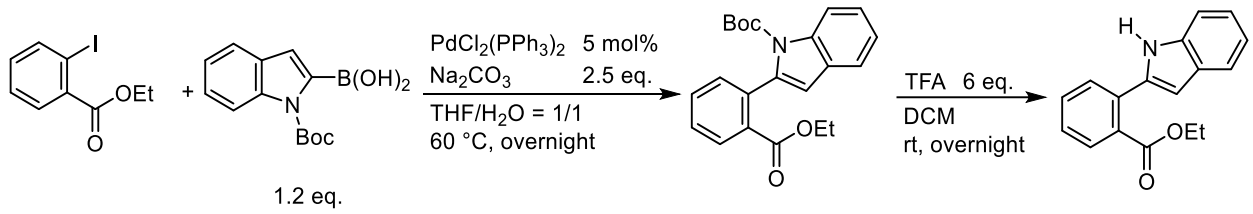
Ethyl 2-(benzofuran-2-yl)benzoate (23)



The procedure for synthesis of **19b** was modified by using ethyl 2-iodobenzoate (5.43 g, 19.7 mmol) and benzofuran-2-boronic acid (4.43 g, 27.3 mmol) in place of 4-(dimethylamino)phenylboronic acid. The product was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 100/1 to 20/1, R_f = 0.11 in hexane/EtOAc = 20/1) in 93% yield (4.86 g, 18.3 mmol) as a yellow oil. Further purification by vacuum distillation (0.12 mmHg, 127 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.12 (t, *J* = 7.2 Hz, 3H), 4.28 (q, *J* = 7.2 Hz, 2H), 6.93 (d, *J* = 0.9 Hz, 1H), 7.18-7.35 (c, 2H), 7.39-7.50 (c, 2H), 7.54 (td, *J* = 7.6 Hz, 1.4 Hz, 1H), 7.58-7.65 (m, 1H), 7.71-7.77 (c, 2H). **^{13}C NMR** ($CDCl_3$) δ: 14.0, 61.4, 104.3, 111.1, 121.1, 122.9, 124.4, 128.7, 128.8, 129.1, 129.4, 129.6, 130.9, 131.4, 154.9, 155.0, 168.8. **IR** (ATR): 3065 w, 2981 w, 1719 s, 1281 s. **MS**: *m*/*z* (EI, relative intensity, %): 267 (19), 266 (100, M^+), 238 (29), 237 (21), 222 (18), 221 (32), 220 (18), 209 (15), 194 (31), 193 (14), 181 (17), 165 (31), 164 (12), 163 (14), 83 (18). **Anal.** Calcd for $C_{17}H_{14}O_3$: C, 76.68; H, 5.30. Found: C, 76.86; H, 5.18.

Ethyl 2-(1*H*-indol-2-yl)benzoate (pre-24)

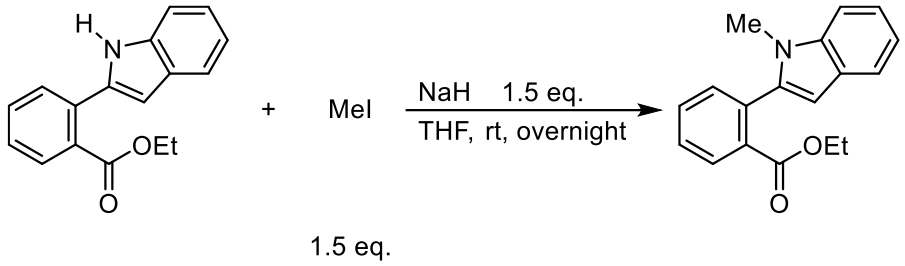


A three necked flask was purged with N_2. The flask was charged with Ethyl 2-iodobenzoate (6.96 g, 25.2 mmol), (1-(*tert*-butoxycarbonyl)-1*H*-indol-2-yl)boronic acid[21] (8.31 g, 31.8 mmol), THF (60 mL), 1N Na_2CO_3 aq (60 mL) and $PdCl_2(PPh_3)_2$ (0.883 g, 1.26 mmol). The mixture was stirred at 60 ℃ overnight. After the mixture was cooled to room temperature, H_2O (100 mL) was added and the organic layer was separated. The aqueous layer was extracted with Et_2O (100 mL×2) and the resulting mixture was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 100/1 to 20/1, R_f = 0.14 in hexane/EtOAc = 20/1) to afford the desired *tert*-Butyl 2-(2-(ethoxycarbonyl)phenyl)-1*H*-indole-1-carboxylate and unidentified by-products as an yellow oil (9.08 g, ca 25.7 mmol). The product was used in next step without further purification.

A round bottom flask was charged with *tert*-butyl 2-(2-(ethoxycarbonyl)phenyl)-1*H*-indole-1-carboxylate, TFA (13.0 mL, 169.8 mmol) and DCM (150 mL) and the mixture was stirred at rt overnight. After the reaction, sat. $NaHCO_3$ aq (100 mL) was added to the mixture, and the organic layer was separated. The aqueous layer was extracted with EtOAc (100 mL) and the combined organic layer was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 10/1, R_f = 0.19 in hexane/EtOAc = 10/1) followed by column chromatography on silica gel (eluent: hexane/EtOAc = 50/1 to 10/1, R_f = 0.19 in hexane/EtOAc = 10/1) to afford the desired **pre-24** as a yellow solid (3.62 g, 13.6 mmol, 54%).

Mp = 76.4-77.1 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.23 (t, *J* = 7.2 Hz, 3H), 4.30 (q, *J* = 7.2 Hz, 2H), 6.71 (dd, *J* = 2.0 Hz, 1.0 Hz, 1H), 7.03-7.16 (m, 1H), 7.16-7.24 (m, 1H), 7.36-7.44 (m, 2H), 7.54 (dt, *J* = 7.8, 1.7 Hz, 1H), 7.63 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.74 (dd, *J* = 7.9, 0.8 Hz, 1H), 7.79 (dd, *J* = 7.8, 1.1 Hz, 1H), 9.58 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.0, 61.8, 103.1, 111.2, 119.9, 120.5, 122.3, 127.4, 128.3, 130.1, 130.4, 130.9, 131.5, 132.6, 136.5, 136.9, 169.7. **IR** (ATR): 3350 m, 3056 w, 2983 w, 2938 w, 2906 w, 1711 s, 1255 s. **MS**: *m*/*z* (EI, relative intensity, %): 265 (50, M^+), 220 (25), 219 (100), 190 (18), 96 (10). **Anal.** Calcd for $C_{17}H_{15}NO_2$: C, 76.96; H, 5.70; N, 5.28. Found: C, 77.12; H, 5.72; N, 5.24.

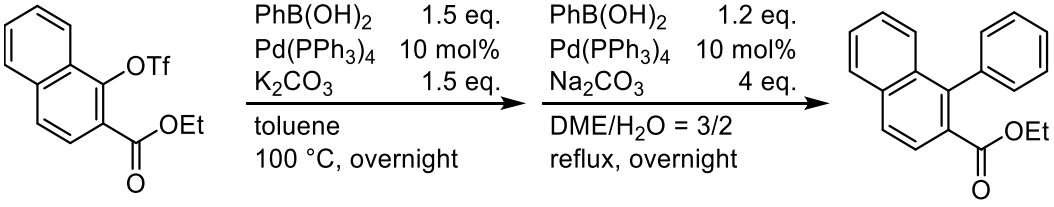
Ethyl 2-(1-methyl-1*H*-indol-2-yl)benzoate (24)



A three necked flask was flame-dried and purged with N_2. The flask was charged with NaH (60% dispersion in paraffin liquid, 0.415 g, 10.4 mmol) and THF (20 mL). A solution of **pre-24** (1.71 g, 6.45 mmol) in THF (20 mL) was added slowly to the flask at 0 °C and the mixture was stirred for 45 min at the same temperature. MeI (1.42 g, 10.0 mmol) was added to the flask at 0 °C. The mixture was stirred overnight. H_2O (50 mL) and EtOAc (30 mL) were added and the organic layer was separated. The aqueous layer was extracted with EtOAc (50 mL) and the combined organic layer was dried over Na_2SO_4. After the volatile was removed under the reduced pressure, the resulting crude mixture was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 50/1 to 10/1, R_f = 0.17 in hexane/EtOAc = 10/1) and subsequent GPC to afford the desired **24** as a pale yellow oil (0.784 g, 2.81 mmol, 44%).

^{1}H NMR ($CDCl_3$) δ: 0.85 (t, *J* = 7.1 Hz, 3H), 3.51 (s, 3H), 4.04 (q, *J* = 7.1 Hz, 2H), 6.43 (d, *J* = 0.9 Hz, 1H), 7.08-7.15 (m, 1H), 7.19-7.27 (m, 1H), 7.31-7.34 (m, 1H), 7.41-7.48 (m, 1H), 7.52 (td, *J* = 7.5, 1.6 Hz, 1H), 7.55-7.65 (m, 2H), 7.93-8.07 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 13.6, 30.4, 61.0, 101.3, 109.2, 119.5, 120.4, 121.4, 127.8, 128.6, 130.0, 131.4, 132.3, 132.4, 133.2, 137.2, 140.1, 167.4. **IR** (ATR): 3056 w, 2980 w, 2937 w, 2904 w, 1712 s, 1286 s. **MS**: *m/z* (EI, relative intensity, %): 280 (13), 279 (64, M^+), 207 (21), 206 (100), 204 (24), 102 (15). **Anal.** Calcd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.13; N, 5.01. Found: C, 77.41; H, 6.02; N, 4.93.

Ethyl 1-phenyl-2-naphthoate (25)

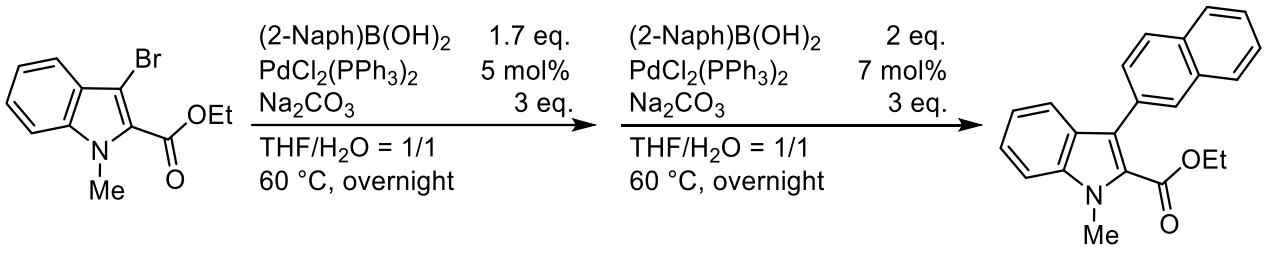


A three necked flask was purged with N_2. The flask was charged with Ethyl 1-(((trifluoromethyl)sulfonyl)oxy)-2-naphthoate (7.02 g, 20.2 mmol), Phenylboronic acid (3.48 g, 28.5 mmol), K_2CO_3 (4.32 g, 31.2 mmol), $Pd(PPh_3)_4$ (2.15 g, 1.86 mmol) and toluene (50 mL). The mixture was stirred at 100 °C overnight. After the mixture was cooled to room temperature, the volatile was removed under reduced pressure. However, a large amount of starting material was unreacted. A solution of the resulting crude mixture, $PhB(OH)_2$ (2.75 g, 22.6 mmol) and $Pd(PPh_3)_4$ (2.15 g, 1.86 mmol) in DME (120 mL) was degassed three times and the flask was charged with N_2. 1N Na_2CO_3 aq (80 mL) was

added to the flask and the mixture was stirred reflux overnight. After the mixture was cooled to room temperature, H_2O (100 mL) and Et_2O (50 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (100 mL) and the resulting mixture was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was purified by column chromatography on silica gel (eluent: hexane/EtOAc = 100/1 to 20/1, R_f = 0.17 in hexane/EtOAc = 20/1) and subsequent MPLC (rate: 100 mL/min., eluent: hexane/EtOAc = 50/1 to 20/1) to afford the desired **25** as a white solid (1.83 g, 6.69 mmol, 33%). Further purification by recrystallization from hexane/Et_2O afforded the title compound as a white solid.

Mp = 51.7-52.2 ºC. **^{1}H NMR** ($CDCl_3$) δ: 0.95 (t, *J* = 7.2 Hz, 3H), 4.05 (q, *J* = 7.2 Hz, 2H), 7.28-7.34 (c, 2H), 7.38-7.49 (c, 4H), 7.51-7.56 (m, 1H), 7.57-7.61 (m, 1H), 7.88-7.94 (c, 3H). **^{13}C NMR** ($CDCl_3$) δ: 13.6, 60.8, 125.5, 126.5, 127.2, 127.3, 127.67, 127.70, 127.8, 127.9, 128.5, 129.7, 132.5, 134.7, 139.1, 141.1, 168.6. **IR** (ATR): 3061 w, 2979 w, 1703 s. **MS**: *m/z* (EI, relative intensity, %): 277 (14), 276 (69, M^+), 232 (21), 231 (100), 203 (36), 202 (60), 201 (13), 200 (10), 101 (16). **Anal.** Calcd for $C_{19}H_{16}O_2$: C, 82.58; H, 5.84. Found: C, 82.84; H, 5.84.

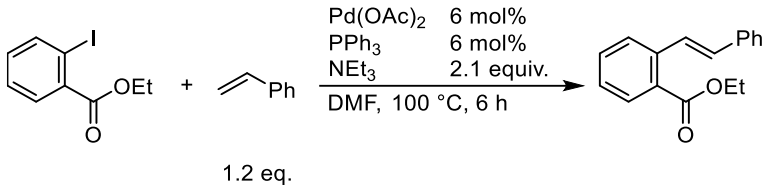
Ethyl 1-methyl-3-(naphthalen-2-yl)-1*H*-indole-2-carboxylate (26)



A three necked flask was purged with N_2. The flask was charged with ethyl 3-bromo-1-methyl-1*H*-indole-2-carboxylate[22] (3.96 g, 14.0 mmol), 2-naphthaleneboronic acid (3.97 g, 23.1 mmol), THF (40 mL), 1N Na_2CO_3 aq (40 mL, 40 mmol) and $PdCl_2(PPh_3)_2$ (0.531 g, 0.76 mmol). The mixture was stirred at 60 ℃ overnight. After the mixture was cooled to room temperature, H_2O (100 mL) and Et_2O (100 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (100 mL) and the resulting mixture was dried over Na_2SO_4. the volatile was removed under reduced pressure. However, a large amount of starting material was unreacted. A solution of the resulting crude mixture, 2-naphthaleneboronic acid (5.13 g, 29.8 mmol) and $PdCl_2(PPh_3)_2$ (0.705 g, 1.00 mmol) in THF (40 mL) and 1N Na_2CO_3 aq (40 mL) was stirred under N_2 at 60 ℃ overnight. After the mixture was cooled to room temperature, H_2O (100 mL) and Et_2O (100 mL) were added and the organic layer was separated. The aqueous layer was extracted with Et_2O (100 mL) and the resulting mixture was dried over Na_2SO_4. the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 100/1 to 10/1, R_f = 0.23 in hexane/EtOAc = 20/1) and subsequent flash column chromatography on silica gel (eluent: hexane/EtOAc = 100/1 to 20/1, R_f = 0.23 in hexane/EtOAc = 20/1) to afford the desired **26** as a colorless syrup (3.15 g, 9.56 mmol, 68%). Further purification by GPC afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 0.96 (t, *J* = 7.2 Hz, 3H), 4.10 (s, 3H), 4.15 (q, *J* = 7.2 Hz, 2H), 7.06-7.19 (m, 1H), 7.37-7.46 (c, 2H), 7.48-7.52 (c, 2H), 7.56 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.58-7.62 (m, 1H), 7.84-7.92 (c, 4H). **^{13}C NMR** ($CDCl_3$) δ: 13.7, 32.0, 60.5, 110.1, 120.7, 121.6, 124.3, 125.1, 125.3, 125.7, 125.9, 126.7, 127.0, 127.6, 127.9, 128.9, 129.3, 132.3, 132.4, 133.2, 138.5, 162.7. **IR** (ATR): 3054 w, 2980 w, 2904 w, 1699 s, 1240 s. **MS**: *m*/*z* (EI, relative intensity, %): 330 (25), 329 (100, M^+), 302 (11), 301 (50), 257 (15), 256 (11), 255 (11), 254 (16), 241 (11), 240 (12), 215 (19), 127 (12). **HRMS (DART)** Calcd for $C_{22}H_{20}NO_2$ ($[M+H]^+$): 330.14886. Found: 330.14738.

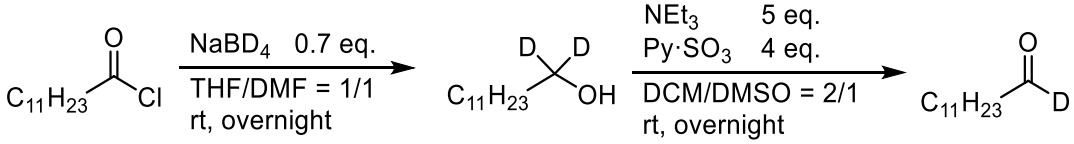
Ethyl *(E)*-2-styrylbenzoate (27)



The title compound was synthesized according to Zhang and Yang's procedure.[23] A two necked flask was flame-dried and purged with N_2. The flask was charged with ethyl 2-iodobenzoate (8.03 g, 29.1 mmol), styrene (4.2 mL, 36.7 mmol), NEt_3 (8.8 mL, 63.5 mmol), DMF (10 mL), $Pd(OAc)_2$ (0.41 g, 1.82 mmol) and NEt_3 (8.8 mL, 63.5 mmol). The mixture was stirred at 100 ℃ for 6 h. After the mixture was cooled to room temperature, 1N HCl aq (100 mL) and EtOAc (100 mL) were added. The organic layer was separated and washed with 1N HCl aq (100 mL) and Brine (50 mL). The resulting mixture was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was isolated by column chromatography on silica gel (eluent: hexane/EtOAc = 100/1 to 40/1, R_f = 0.26 in hexane/EtOAc = 20/1) and subsequent MPLC (rate: 100 mL/min., eluent: hexane only to hexane/EtOAc = 50/1) to afford the desired **27** as a colorless oil (4.00 g, 15.8 mmol, 54%). Further purification by vacuum distillation (0.22 mmHg, 128 °C) under CaH_2 afforded the title compound as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.41 (t, *J* = 7.2 Hz, 3H), 4.39 (q, *J* = 7.2 Hz, 2H), 7.00 (d, *J* = 16.2 Hz, 1H), 7.21-7.41 (c, 4H), 7.45-7.59 (c, 3H), 7.69-7.73 (m, 1H), 7.93 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.99 (d, *J* = 16.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.3, 61.0, 126.8, 126.9, 127.1, 127.5, 127.8, 128.6, 128.9, 130.6, 131.3, 132.0, 137.4, 139.1, 167.5. **IR** (ATR): 3061 w, 3025 w, 2981 w, 1711 s, 1241 s. **MS**: *m*/*z* (EI, relative intensity, %): 253 (19), 252 (100, M^+), 208 (14), 207 (34), 206 (41), 205 (18), 195 (18), 180 (12), 179 (76), 178 (71), 177 (22), 176 (19), 165 (10), 152 (18), 133 (22), 105 (14), 89 (25), 77 (12), 76 (17). **Anal.** Calcd for $C_{17}H_{16}O_2$: C, 80.93; H, 6.39. Found: C, 81.20; H, 6.36.

Dodecanal-1-*d* [CAS: 94083-57-5]



A three necked flask was purged with N_2 and charged with $NaBD_4$ (1.18 g, 28.2 mmol), THF (30 mL) and DMF (30 mL). After stirring the mixture for 5 min at 0 °C, lauroyl chloride (8.93 g, 40.8 mmol) was slowly added dropwise to the solution at 0 °C. The mixture was stirred overnight at room temperature. After adding 1N HCl aq. (50 mL) and Et_2O (50 mL), the organic layer was separated. The aqueous layer was extracted with Et_2O (50 mL) and the combined organic layers were dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 20/1 to 10/1, R_f = 0.11 in hexane/EtOAc = 10/1) to afford dodecan-1,1-*d2*-1-ol as a colorless oil (5.29 g), which contains a little amount of unidentified byproduct. However, the compound was used in next step without futher purification.

The mixture of dodecan-1,1-*d2*-1-ol (5.29 g, mixture with impurities), NEt_3 (20.0 mL, 144 mmol) and $Py{\cdot}SO_3$ (18.8 g, 118 mmol) in DCM (100 mL) and DMSO (50 mL) were stirred overnight at rt under N_2. After adding H_2O (200 mL), the organic layer was separated. The organic layer was washed with sat. $CuSO_4$ aq. (100 mL) and Brine (100 mL). After that, the organic layer was dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane only to hexane/EtOAc = 50/1, R_f = 0.34 in hexane/EtOAc = 20/1) followed by MPLC (rate: 100 mL/min., eluent: hexane only to hexane/EtOAc = 20/1) followed by bulb-to-bulb distillation (0.2-0.3 kPa, 90 °C-110 °C) to afford the desired dodecanal-1-*d* (1.32 g, 7.12 mmol, 17%).

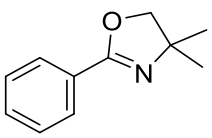
^{1}H NMR ($CDCl_3$) δ: 0.88 (t, *J* = 6.9 Hz, 3H), 1.20-1.37 (c, 16H), 1.59-1.66 (m, 2H), 2.42 (t, *J* = 7.3 Hz, 2H), 9.76 (t, *J* = 1.8 Hz, 0.05H). **^{13}C NMR** ($CDCl_3$) δ: 14.1, 22.0, 22.6, 29.1, 29.29, 29.33, 29.4, 29.5, 31.9, 43.7 (t, *J* = 3.8 Hz), 202.5 (t, *J* = 25.9 Hz). Two signals are obscured by overlap with other signals. **^{2}H NMR** ($CHCl_3$) δ: 9.79. **HRMS (DART)** Calcd for $C_{12}H_{24}OD$ ($[M+H]^+$): 186.19627. Found: 186.19658.

1.4.3 Typical Procedure

In a glovebox filled with nitrogen, $Ni(cod)_2$ (5.5 mg, 0.02 mmol, 0.1 equiv), IMes (6.1 mg, 0.02 mmol, 0.1 equiv) and toluene (0.3 mL) were added to a 10 mL-sample vial with a Teflon-sealed screwcap, and stirred for 3 min at room temperature. Aromatic ester (0.2 mmol) and toluene (0.2 mL) were then added, and the cap was applied to seal the vial. The vial was stirred at 180 °C for 14 h. After the reaction mixture was cooled to room temperature, the crude mixture was filtered through silica gel eluting with EtOAc. The filtrate was analyzed by GC using undecane as an internal standard. The crude mixture was concentrated under reduced pressure and analyzed by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. The resulting mixture was purified by flash column chromatography over silica gel.

1.4.4 Characterization of Products

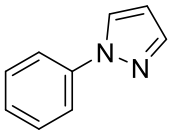
4,4-Dimethyl-2-phenyl-4,5-dihydrooxazole (2) [CAS: 19312-06-2]



2 was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 10/1, R_f = 0.54 in hexane/EtOAc = 2/1) as a colorless oil. The yield was determined by GC analysis using undecane as an internal standard due to volatility of the product.

^{1}H NMR ($CDCl_3$) δ: 1.38 (s, 6H), 4.10 (s, 2H), 7.37-7.41 (m, 2H), 7.43-7.48 (m, 1H), 7.92-7.96 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ: 28.3, 67.5, 79.0, 128.0, 128.1, 128.2, 131.1, 162.0. **HRMS (DART)** Calcd for $C_{11}H_{14}NO$ ($[M+H]^+$): 176.10699. Found: 176.10704.

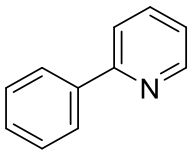
1-Phenyl-1*H*-pyrazole [CAS: 1126-00-7]



The title compound was obtained by flash column chromatography on silica-gel (R_f = 0.26 in hexane/EtOAc = 10/1) as a pale yellow oil. The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard due to volatility of the product.

^{1}H NMR ($CDCl_3$) δ: 6.47 (dd, *J* = 2.5 Hz, 1.8 Hz, 1H), 7.27-7.31 (m, 1H), 7.43-7.48 (m, 2H), 7.68-7.73 (c, 3H), 7.93 (dd, *J* = 2.5 Hz, 0.5 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 107.6, 119.2, 126.4, 126.7, 129.4, 140.2 141.0. **HRMS (DART)** Calcd for $C_9H_9N_2$ ($[M+H]^+$): 145.07602. Found: 145.07668.

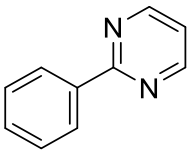
2-Phenylpyridine [CAS: 1008-89-5]



The title compound was obtained by flash column chromatography on silica-gel (R_f = 0.36 in Hexane/EtOAc = 5/1) in 90% yield (31 mg) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 7.15-7.32 (m, 1H), 7.36-7.44 (m, 1H), 7.45-7.56 (m, 2H), 7.65-7.83 (m, 2H), 7.91-8.07 (m, 2H), 8.62-8.77 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 120.6, 122.1, 126.9, 128.7, 128.9, 136.8, 139.3, 149.6, 157.4. **HRMS (DART)** Calcd for $C_{11}H_{10}N$ ($[M+H]^+$): 156.08078. Found: 156.08137.

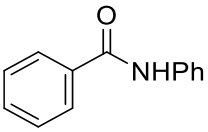
2-Phenylpyperidine [CAS: 7431-45-0]



The title compound was obtained by flash column chromatography on silica-gel (R_f = 0.32 in Hexane/EtOAc = 5/1) in 87% yield (27 mg) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 7.17 (t, *J* = 4.9 Hz, 2H), 7.46-7.52 (c, 3H), 8.41-8.47 (m, 2H), 8.80 (d, *J* = 4.9 Hz, 2H). **^{13}C NMR ($CDCl_3$)** δ: 119.0, 128.1, 128.6, 130.7, 137.6, 157.2, 164.8. **HRMS (DART)** Calcd for $C_{10}H_9N_2$ ($[M+H]^+$): 157.07602. Found: 157.07649.

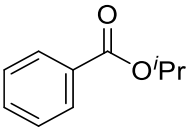
***N*-Phenylbenzamide** [CAS: 93-98-1]



The title compound was isolated by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 5/1, R_f = 0.20 in Hexane/EtOAc = 5/1) and subsequent GPC in 74% yield (27 mg) as a white solid.

^{1}H NMR ($CDCl_3$) δ 7.15 (t, *J* = 7.7 Hz, 1H), 7.37 (t, *J* = 7.7 Hz, 2H), 7.47 (t, *J* = 7.7 Hz, 2H), 7.51-7.58 (m, 1H), 7.64 (d, *J* = 7.7 Hz, 2H), 7.77-7.98 (m, 3H). **^{13}C NMR** ($CDCl_3$) δ: 120.2, 124.5, 127.0, 128.8, 129.1, 131.8, 135.0, 137.9, 165.7. **HRMS (DART)** Calcd for $C_{13}H_{12}NO$ ($[M+H]^+$): 198.09134. Found: 198.09083.

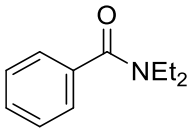
Isopropyl benzoate [CAS: 939-48-0]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 50/1, R_f = 0.26 in Hexane/EtOAc = 20/1) as a colorless oil. The yield was determined by GC analysis using undecane as an internal standard due to volatility of the product.

^{1}H NMR ($CDCl_3$) δ: 1.37 (d, *J* = 6.2 Hz, 6H), 5.26 (tt, *J* = 6.2 Hz, 1H), 7.40-7.45 (m, 2H), 7.51-7.56 (m, 1H), 8.02-8.06 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ: 21.9, 68.3, 128.2, 129.5, 131.0, 132.7, 166.1. **HRMS (DART)** Calcd for $C_{10}H_{13}O_2$ ($[M+H]^+$): 165.09101. Found: 165.09199.

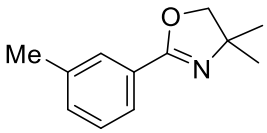
***N,N*-Diethylbenzamide** [CAS: 1696-17-9]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 10/1 to 2/1, R_f = 0.20 in Hexane/EtOAc = 2/1) in 57% yield as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.10 (br, 3H), 1.25 (br, 3H), 3.26 (br, 2H), 3.55 (br, 2H), 7.35-7.40 (c, 5H). **^{13}C NMR** ($CDCl_3$) δ: 12.9, 14.2, 39.1, 43.2, 126.2, 128.3, 129.0, 137.2, 171.2. **HRMS (DART)** Calcd for $C_{11}H_{16}NO$ ($[M+H]^+$): 178.12264. Found: 178.12174.

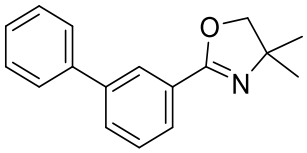
4,4-Dimethyl-2-(*m*-tolyl)-4,5-dihydrooxazole [CAS: 82946-72-3]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 10/1, R_f = 0.31 in Hexane/EtOAc = 5/1) as a pale yellow oil. The yield was determined by GC analysis using undecane as an internal standard due to volatility of the product.

^{1}H NMR ($CDCl_3$) δ: 1.38 (s, 6H), 2.38 (s, 3H), 4.10 (s, 3H), 7.27-7.31 (m, 2H), 7.71-7.73 (m, 1H), 7.79 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 21.2, 28.4, 67.5, 79.1, 125.3, 127.9, 128.2, 128.8, 132.0, 138.1, 162.3. **HRMS (DART)** Calcd for $C_{12}H_{16}NO$ ($[M+H]^+$): 190.12264. Found: 190.12292.

2-([1,1'-Biphenyl]-3-yl)-4,4-dimethyl-4,5-dihydrooxazole [CAS: 82946-71-2]

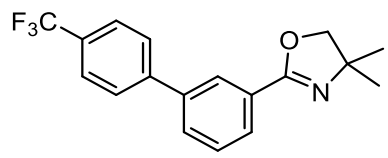


The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 20/1 to 10/1, R_f = 0.40 in Hexane/EtOAc = 5/1) in 91% yield (47 mg) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 1.41 (s, 6H), 4.14 (s, 2H), 7.32-7.40 (m, 1H), 7.40-7.52 (m, 3H), 7.59-7.67 (m, 2H), 7.71 (d, J = 7.8 Hz, 1H), 7.93 (dd, J = 7.8, 0.9 Hz, 1H), 8.20 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 28.4, 67.6, 79.2, 126.9, 127.1, 127.2, 127.6, 128.4, 128.7, 128.8, 129.9, 140.2, 141.3, 162.1. **IR** (ATR): 2972 w, 2930 w, 2896 w, 1735 s, 1650 m, 1241 s.

MS: *m/z* (EI, relative intensity, %): 251 (20, M^+), 237 (18), 236 (100), 208 (23), 180 (33), 179 (16), 152 (20). **HRMS (DART)** Calcd for $C_{17}H_{18}NO$ ($[M+H]^+$): 252.13829. Found: 252.14033.

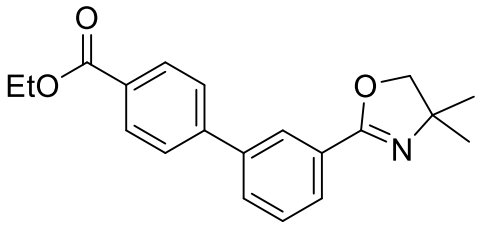
4,4-Dimethyl-2-(4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)-4,5-dihydrooxazole



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 10/1 to 5/1, R_f = 0.14 in hexane/EtOAc = 5/1) in 75% yield (48 mg) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 1.42 (s, 6H), 4.15 (s, 2H), 7.51 (t, *J* = 7.8 Hz, 1H), 7.68-7.72 (c, 3H), 7.74 (d, *J* = 8.4 Hz, 2H), 7.98 (dt, *J* = 7.8, 1.5 Hz, 1H), 8.21 (t, *J* = 1.5 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 28.4, 67.7, 79.2, 124.2 (q, *J* = 271 Hz), 125.7 (q, *J* = 3.9 Hz), 127.1, 127.5, 127.9, 128.7, 129.0, 129.3 (q, *J* = 32.6 Hz), 130.0, 139.9, 143.8, 161.8. **IR** (ATR): 2971 w, 2931 w, 2896 w, 1650 m, 1324 s, 1121 s. **MS**: *m/z* (EI, relative intensity, %): 319 (8, M^+), 305 (20), 304 (100), 289 (12), 276 (24), 249 (11), 248 (40), 247 (17), 152 (13). **HRMS (DART)** Calcd for $C_{18}H_{17}NOF_3$ ($[M+H]^+$): 320.12568. Found: 320.12496.

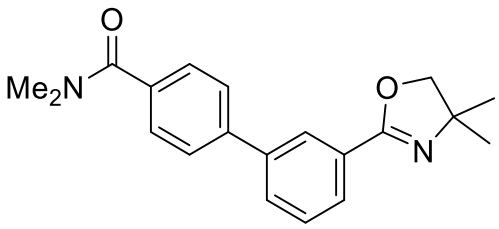
Ethyl 3'-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-[1,1'-biphenyl]-4-carboxylate [CAS: 1810071-89-6]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 10/1 to 5/1, R_f = 0.17 in hexane/EtOAc = 5/1) in 93% yield (60 mg) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 1.41 (s, 6H), 1.42 (t, *J* = 7.1 Hz, 3H), 4.15 (s, 2H), 4.41 (q, *J* = 7.1 Hz, 2H), 7.51 (t, *J* = 7.9 Hz, 1H), 7.67-7.76 (c, 3H), 7.96 (d, *J* = 7.9 Hz, 1H), 8.11 (dd, *J* = 7.9, 1.6 Hz, 2H), 8.22 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.3, 28.4, 61.0, 67.7, 79.2, 127.0, 127.1, 127.8, 128.7, 128.9, 129.5, 129.9, 130.0, 140.2, 144.6, 161.8, 166.4. **IR** (ATR): 2973 w, 2932 w, 2898 w, 2872 w, 1716 s, 1650 m, 1275 s. **MS**: *m/z* (EI, relative intensity, %): 323 (14, M^+), 309 (22), 308 (100), 293 (12), 280 (22), 252 (17), 224 (12). **HRMS (DART)** Calcd for $C_{20}H_{22}NO_3$ ($[M+H]^+$): 324.15942. Found: 324.15906.

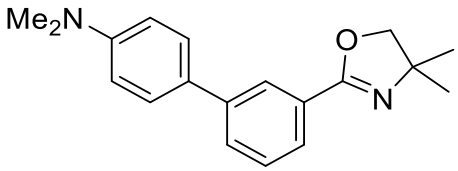
3'-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-N,N-dimethyl-[1,1'-biphenyl]-4-carboxamide



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 5/1 to 1/5, R_f = 0.03 in hexane/EtOAc = 1/1) and subsequent flash column chromatography on silica-gel (eluent: hexane/EtOAc = 1/2, R_f = 0.03 in hexane/EtOAc = 1/1) in 98% yield (65 mg) as a red oil.

^{1}H NMR ($CDCl_3$) δ: 1.41 (s, 6H), 3.03 (br, 3H), 3.14 (br, 3H), 4.14 (s, 2H), 7.48-7.51 (c, 3H), 7.67 (dt, *J* = 8.1, 1.6 Hz, 2H), 7.70 (dt, *J* = 7.9 Hz, 1.3 Hz, 1H), 7.95 (dt, *J* = 7.9, 1.3 Hz, 1H), 8.20 (t, *J* = 1.3 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 28.4, 35.4, 39.6, 67.6, 79.1, 126.9, 127.1, 127.4, 127.6, 128.6, 128.8, 129.8, 135.3, 140.4, 141.4, 161.8, 171.3. **IR** (ATR): 2966 w, 2928 w, 2895 w, 1632 s. **MS**: *m/z* (EI, relative intensity, %): 322 (38, M^+), 321 (22), 308 (13), 307 (59), 279 (29), 278 (100), 235 (15), 206 (12), 180 (12), 179 (11), 153 (15), 152 (11), 151(16). **HRMS (DART)** Calcd for $C_{20}H_{23}N_2O_2$ ($[M+H]^+$): 323.17540. Found: 323.17694.

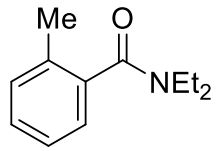
3'-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-*N,N*-dimethyl-[1,1'-biphenyl]-4-amine



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 10/1 to 5/1, R_f = 0.34 in Hexane/EtOAc = 5/1) in 87% yield (57 mg) as a pale yellow solid.

Mp = 148.3-149.2 °C. **^{1}H NMR** ($CDCl_3$) δ: 1.41 (s, 6H), 3.00 (s, 6H), 4.14 (s, 2H), 6.78-6.81 (m, 2H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.54-7.57 (m, 2H), 7.65-7.68 (m, 1H), 7.82-7.84 (m, 1H), 8.15 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 28.4, 40.5, 67.6, 79.1, 112.6, 125.8, 125.9, 127.8, 128.1, 128.3, 128.6, 128.9, 141.3, 150.1, 162.3. **IR** (ATR): 2972 w, 2929 w, 2892 w, 1648 m, 1239 s. **MS**: *m/z* (EI, relative intensity, %): 295 (22), 294 (100, M^+), 279 (27), 251 (12), 223 (14), 222 (26), 221 (13). **HRMS (DART)** Calcd for $C_{19}H_{23}N_2O$ ($[M+H]^+$): 295.18049. Found: 295.18243.

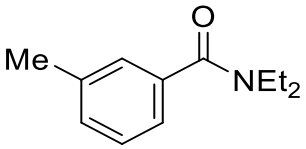
***N,N*-Diethyl-2-methylbenzamide** [CAS: 2728-04-3]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 5/1, R_f = 0.18 in Hexane/EtOAc = 2/1) in 57% yield (23 mg) as a colorless oil. Analytically pure sample was obtained by GPC.

^{1}H NMR ($CDCl_3$) δ: 1.03 (t, *J* = 7.1 Hz, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 2.29 (s, 3H), 3.12 (q, *J* = 7.1 Hz, 2H), 3.41 (br, 1H), 3.77 (br, 1H), 7.12-7.22 (m, 3H), 7.22-7.29 (m, 1H), **^{13}C NMR** ($CDCl_3$) δ: 12.8, 14.0, 18.8, 38.6, 42.5, 125.4, 125.7, 128.5, 130.2, 133.8, 137.1, 170.8. **HRMS (DART)** Calcd for $C_{12}H_{18}NO$ ($[M+H]^+$): 192.13829. Found: 192.13815.

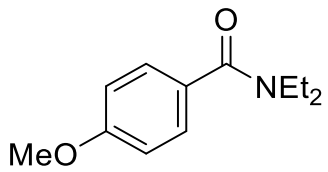
***N,N*-Diethyl-3-methylbenzamide** [CAS: 134-62-3]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 5/1, R_f = 0.14 in hexane/EtOAc = 2/1) in 64% yield (25 mg) as a pale yellow oil. Analytically pure sample was obtained by GPC.

^{1}H NMR ($CDCl_3$) δ: 1.10 (br, 3H), 1.24 (br, 3H), 2.37 (s, 3H), 3.25 (br, 2H), 3.54 (br, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 7.16-7.21 (c, 2H), 7.27 (t, *J* = 7.5 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.9, 14.2, 21.3, 39.1, 43.2, 123.1, 126.9, 128.2, 129.7, 137.2, 138.2, 171.5. **HRMS (DART)** Calcd for $C_{12}H_{18}NO$ ($[M+H]^+$): 192.13829. Found: 192.13723.

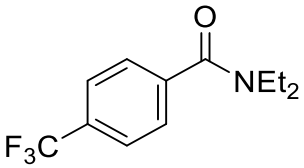
***N,N*-Diethyl-4-(methoxy)benzamide** [CAS: 7465-86-3]



The title compound was obtained by flash column chromatography on silica-gel (R_f = 0.21 in hexane/EtOAc = 2/1) in 50% yield (20 mg) as a pale yellow oil.

^{1}H NMR ($CDCl_3$) δ: 1.17 (br, 6H), 3.41 (br, 4H), 3.83 (s, 3H), 6.87-6.92 (m, 2H), 7.32-7.36 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ: 13.6, 39.6, 43.3, 55.3, 113.6, 128.2, 129.5, 160.2, 171.2. **HRMS (DART)** Calcd for $C_{12}H_{18}NO_2$ ($[M+H]^+$): 208.13321. Found: 208.13286.

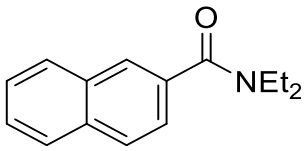
***N,N*-Diethyl-4-(trifluoromethyl)benzamide** [CAS: 95725-04-5]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 5/1 to 2/1, R_f = 0.24 in Hexane/EtOAc = 2/1) in 76% yield (38 mg) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.12 (s, 3H), 1.26 (s, 3H), 3.15-3.33 (m, 2H), 3.48-3.67 (m, 2H), 7.49 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H). **^{13}C NMR** ($CDCl_3$) δ: 12.8, 14.1, 39.3, 43.2, 123.8 (q, J = 271 Hz), 125.5 (q, J = 3.8 Hz), 126.6, 131.1 (q, J = 32 Hz), 140.8, 169.8. **HRMS (DART)** Calcd for $C_{12}H_{15}NOF_3$ ($[M+H]^+$): 246.11003. Found: 246.11043.

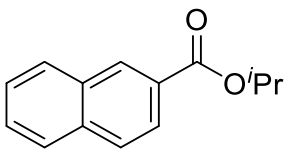
***N,N*-Diethyl-2-naphthamide** [CAS: 13577-84-9]



The title compound was obtained by flash column chromatography on silica-gel (R_f = 0.18 in Hexane/EtOAc = 2/1) in 85% yield (38 mg) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 1.12 (br, 3H), 1.29 (br, 3H), 3.30 (br, 2H), 3.60 (br, 2H), 7.46-7.48 (m, 1H), 7.50-7.54 (c, 2H), 7.84-7.88 (c, 4H). **^{13}C NMR** ($CDCl_3$) δ: 12.9, 14.2, 39.3, 43.3, 123.9, 125.7, 126.5, 126.7, 127.7, 128.20, 128.23, 132.7, 133.3, 134.5, 171.2. **HRMS (DART)** Calcd for $C_{15}H_{18}NO$ ($[M+H]^+$): 228.13829. Found: 228.13781.

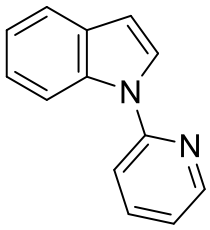
Isopropyl 2-naphthoate [CAS: 25308-57-0]



The title compound was obtained by flash column chromatography on silica-gel (R_f = 0.52 in Hexane/EtOAc = 5/1) in 45% yield (18 mg) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 1.42 (d, *J* = 6.0 Hz, 6H), 5.32 (tt, *J* = 6.0 Hz, 6.0 Hz, 1H), 7.51-7.60 (c, 2H), 7.86-7.88 (c, 2H), 7.95 (d, *J* = 7.8 Hz, 1H), 8.06 (dd, *J* = 8.5 Hz, 1.6 Hz, 1H), 8.60 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 22.0, 68.5, 125.3, 126.5, 127.7, 128.0, 128.06, 128.12, 129.3, 130.8, 132.5, 135.4, 166.3. **HRMS (DART)** Calcd for $C_{14}H_{15}O_2$ ($[M+H]^+$): 215.10666. Found: 215.10536.

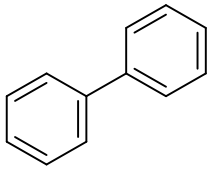
1-(Pyridin-2-yl)-1*H*-indole [CAS: 3419-91-8]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 10/1 to 5/1, R_f = 0.33 in hexane/EtOAc = 5/1) in 64% yield (24 mg) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 6.70-6.72 (m, 1H), 7.13-7.17 (m, 1H), 7.20 (td, *J* = 7.3 Hz, 0.9 Hz, 1H), 7.26-7.32 (m, 1H), 7.46-7.50 (m, 1H), 7.66 (d, *J* = 7.8 Hz, 1H), 7.72 (d, *J* = 3.2 Hz, 1H), 7.80 (ddd, *J* = 8.7 Hz, 6.9 Hz, 1.4 Hz, 1H), 8.20 (dd, *J* = 8.3 Hz, 0.9 Hz, 1H), 8.56 (ddd, *J* = 5.0 Hz, 1.8 Hz, 0.9 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 105.5, 112.9, 114.6, 120.0, 121.1, 121.2, 123.1, 125.9, 130.4, 135.0, 138.3, 149.0, 152.5. **HRMS (DART)** Calcd for $C_{13}H_{11}N_2$ ($[M+H]^+$): 195.09167. Found: 195.09188.

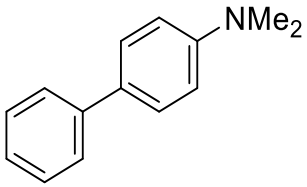
1,1'-Biphenyl [CAS: 92-52-4]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 200/1, R_f = 0.60 in hexane/EtOAc = 20/1) as a white solid. The yield was determined by GC analysis using undecane as an internal standard due to volatility of the product.

^{1}H NMR ($CDCl_3$) δ: 7.33-7.37 (m, 2H), 7.42-7.46 (m, 4H), 7.58-7.61 (m, 4H). **^{13}C NMR** ($CDCl_3$) δ: 127.16, 127.23, 128.7, 141.2. **HRMS (DART)** Calcd for $C_{12}H_{11}$ ($[M+H]^+$): 155.08553. Found: 155.08461.

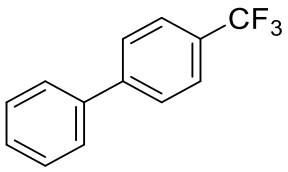
***N,N*-Dimethyl-[1,1'-biphenyl]-4-amine** [CAS: 1137-79-7]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 50/1, R_f = 0.17 in Hexane/EtOAc = 20/1) in 27% yield (11 mg) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 2.99 (s, 6H), 6.79-6.83 (m, 2H), 7.23-7.27 (m, 1H), 7.37-7.41 (m, 2H), 7.49-7.54 (m, 2H), 7.54-7.57 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ: 40.6, 112.8, 126.0, 126.3, 127.7, 128.6, 129.2, 141.2, 149.9. **HRMS (DART)** Calcd for $C_{14}H_{16}N$ ($[M+H]^+$): 198.12773. Found: 198.12783.

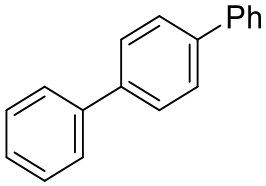
4-(Trifluoromethyl)-1,1'-biphenyl [CAS: 398-36-7]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 200/1, R_f = 0.49 in Hexane/EtOAc = 20/1) as a colorless oil. The yield was determined by GC analysis using undecane as an internal standard due to volatility of the product.

^{1}H NMR ($CDCl_3$) δ: 7.39-7.43 (m, 1H), 7.46-7.50 (m, 2H), 7.59-7.62 (m, 2H), 7.70 (s, 4H). **^{13}C NMR** ($CDCl_3$) δ: 124.3 (q, J = 270.5 Hz), 125.7 (q, J = 3.8 Hz), 127.3, 127.4, 128.2, 129.0, 129.3 (q, J = 31.9 Hz), 139.7, 144.7. **HRMS (DART)** Calcd for $C_{13}H_{10}F_3$ ($[M+H]^+$): 223.07291. Found: 223.07215.

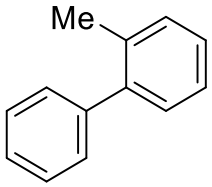
1,1':4',1''-Terphenyl [CAS: 92-94-4]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 200/1, R_f = 0.49 in Hexane/EtOAc = 20/1) in 21% yield (10 mg) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 7.33-7.39 (m, 2H), 7.43-7.50 (m, 4H), 7.59-7.72 (m, 8H). **^{13}C NMR** ($CDCl_3$) δ: 127.0, 127.3, 127.5, 128.8, 140.1, 140.7. **HRMS (DART)** Calcd for $C_{18}H_{15}$ ($[M+H]^+$): 231.11683. Found: 231.11667.

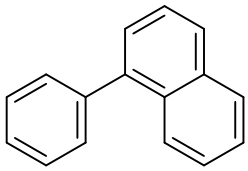
2-Methyl-1,1'-biphenyl [CAS: 643-58-3]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 200/1, R_f = 0.71 in Hexane/EtOAc = 20/1) as a colorless oil. The yield was determined by GC analysis using undecane as an internal standard due to volatility of the product.

^{1}H NMR ($CDCl_3$) δ: 2.28 (s, 3H), 7.23-7.28 (c, 4H), 7.31-7.36 (c, 3H), 7.39-7.43 (c, 2H). **^{13}C NMR** ($CDCl_3$) δ: 20.5, 125.7, 126.7, 127.2, 128.0, 129.2, 129.8, 130.3, 135.3, 141.9. One signal is obscured by overlap with other signals. **HRMS (DART)** Calcd for $C_{13}H_{13}$ ($[M+H]^+$): 169.10118. Found: 169.10192.

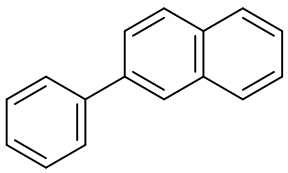
1-Phenylnaphthalene [CAS: 605-02-7]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 200/1, R_f = 0.46 in hexane/EtOAc = 20/1) in 36% yield (15 mg from **22**) or 50% yield (21 mg, from **25**) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 7.38-7.45 (m, 3H), 7.45-7.56 (m, 6H), 7.85 (d, J = 7.8 Hz, 1H), 7.88-7.96 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ: 125.4, 125.7, 126.0, 126.9, 127.2, 127.6, 128.2, 130.1, 131.6, 133.8, 140.2, 140.7. two signal is obscured by overlap with other signals. **HRMS (DART)** Calcd for $C_{16}H_{13}$ ($[M+H]^+$): 205.10118. Found: 205.10133.

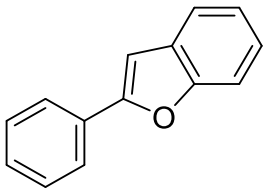
2-Phenylnaphthalene [CAS: 612-94-2]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 200/1, R_f = 0.46 in hexane/EtOAc = 20/1) in 71% yield (29 mg) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 7.31-7.42 (m, 1H), 7.42-7.59 (m, 4H), 7.63-7.80 (m, 3H), 7.80-7.98 (m, 3H), 8.04 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 125.6, 125.8, 125.9, 126.3, 127.3, 127.4, 127.6, 128.2, 128.4, 128.8, 132.6, 133.6, 138.5, 141.1. **HRMS (DART)** Calcd for $C_{16}H_{13}$ ($[M+H]^+$): 205.10118. Found: 205.10130.

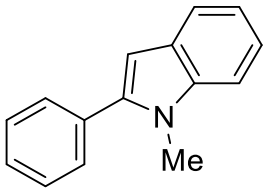
2-Phenylbenzofuran [CAS: 1839-72-1]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 100/1, R_f = 0.51 in hexane/EtOAc = 20/1) in 34% yield (13 mg) as a pale yellow solid.

^{1}H NMR ($CDCl_3$) δ: 7.03 (d, *J* = 1.0 Hz, 1H), 7.18-7.25 (m, 1H), 7.28 (td, *J* = 7.6, 1.5 Hz, 1H), 7.32-7.40 (m, 1H), 7.40-7.49 (m, 2H), 7.49-7.56 (m, 1H), 7.56-7.63 (m, 1H), 7.79-7.95 (m, 2H). **^{13}C NMR** ($CDCl_3$) δ: 101.3, 111.2, 120.9, 122.9, 124.2, 124.9, 128.5, 128.8, 129.2, 130.4, 154.8, 155.9. **HRMS (DART)** Calcd for $C_{14}H_{11}O$ ($[M+H]^+$): 195.08044. Found: 195.08144.

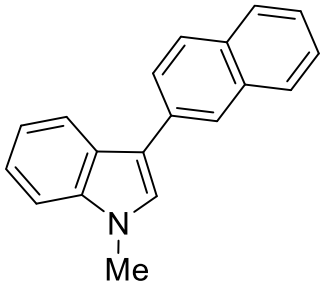
1-Methyl-2-phenylindole [CAS: 3558-24-5]



The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 100/1, R_f = 0.70 in hexane/EtOAc = 20/1) in 49% yield (19 mg) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 3.75 (s, 3H), 6.57 (d, *J* = 0.9 Hz, 1H), 7.06-7.20 (m, 1H), 7.20-7.29 (m, 1H), 7.33-7.44 (m, 2H), 7.44-7.57 (m, 4H), 7.64 (dt, *J* = 7.8, 0.9 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 31.2, 101.6, 109.6, 119.8, 120.4, 121.6, 127.8, 127.9, 128.5, 129.4, 132.8, 138.3, 141.5. **HRMS (DART)** Calcd for $C_{15}H_{14}N$ ($[M+H]^+$): 208.11208. Found: 208.11252.

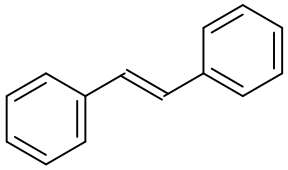
1-Methyl-3-(naphthalen-2-yl)-*1H*-indole [CAS: 1386875-78-0]



The title compound was obtained by flash column chromatography on silica-gel (R_f = 0.34 in hexane/EtOAc = 10/1) in 77% yield (40 mg) as a colorless oil.

^{1}H NMR ($CDCl_3$) δ: 3.88 (s, 3H), 7.22-7.26 (m, 1H), 7.30-7.51 (m, 5H), 7.79-7.91 (m, 4H), 8.06-8.08 (m, 1H), 8.11 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 32.9, 109.6, 116.5, 119.99, 120.02, 122.1, 124.9, 125.1, 126.1, 126.2, 126.4, 127.0, 127.65, 127.69, 128.2, 131.9, 133.1, 134.0, 137.5. **HRMS (DART)** Calcd for $C_{19}H_{16}N$ ($[M+H]^+$): 258.12773. Found: 258.12613.

***(E)*-1,2-Diphenylethene** [CAS: 103-30-0]

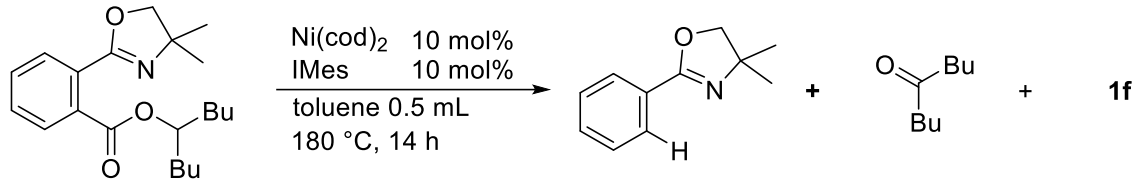


The title compound was obtained by flash column chromatography on silica-gel (eluent: hexane/EtOAc = 100/1, R_f = 0.70 in hexane/EtOAc = 20/1) and subsequent flash column chromatography on silica-gel (eluent: hexane/EtOAc = 100/1, R_f = 0.70 in Hexane/EtOAc = 20/1) in 59% yield (21 mg) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 7.11 (s, 2H), 7.22-7.30 (m, 2H), 7.30-7.41 (m, 4H), 7.49-7.54 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 126.5, 127.6, 128.7, 137.3. one signal is obscured by overlap with other signals. **HRMS (DART)** Calcd for $C_{14}H_{13}$ ($[M+H]^+$): 181.10118. Found: 181.10098.

1.4.5 Mechanistic Studies

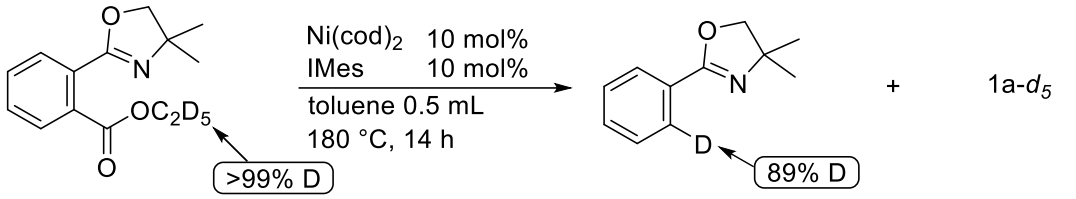
1.4.5.1 The reaction of the aromatic ester bearing large substituents on oxygen atom (Scheme 5a)



1f (0.2 mmol) **2** 92% (GC) >99% (GC) 5% (GC)

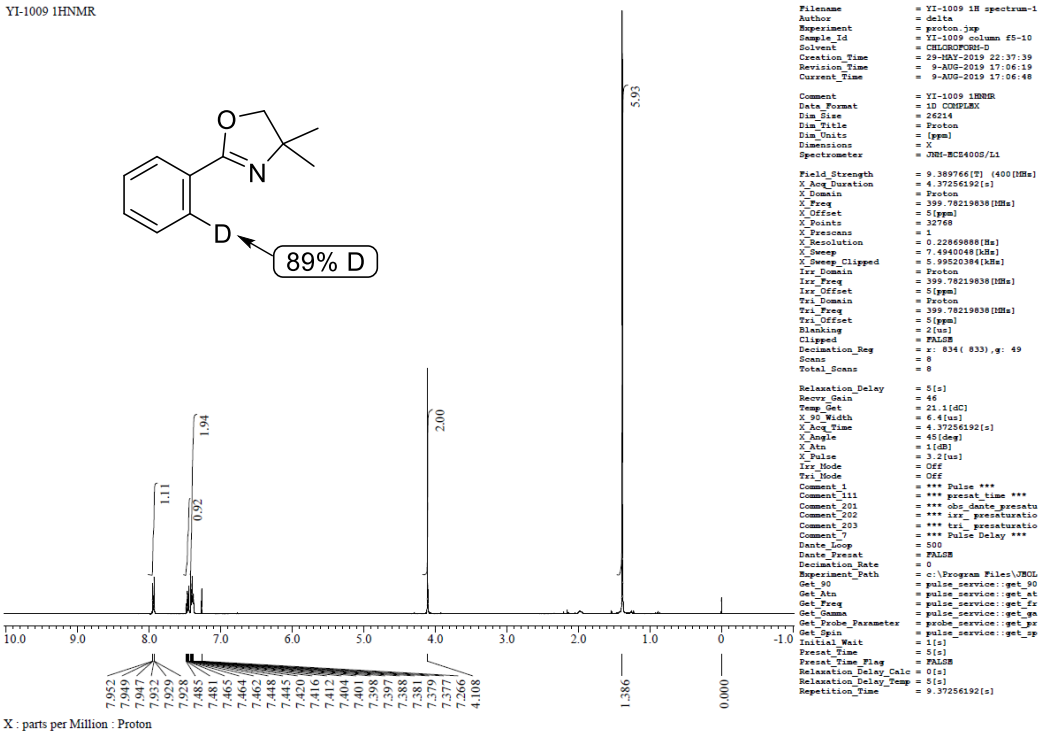
Compound **1f** was subjected to the typical procedure. The yield of products and the starting material was determined by GC analysis using undecane as an internal standard due to volatility of the product.

1.4.5.2 Labeling experiment (Scheme 5b)

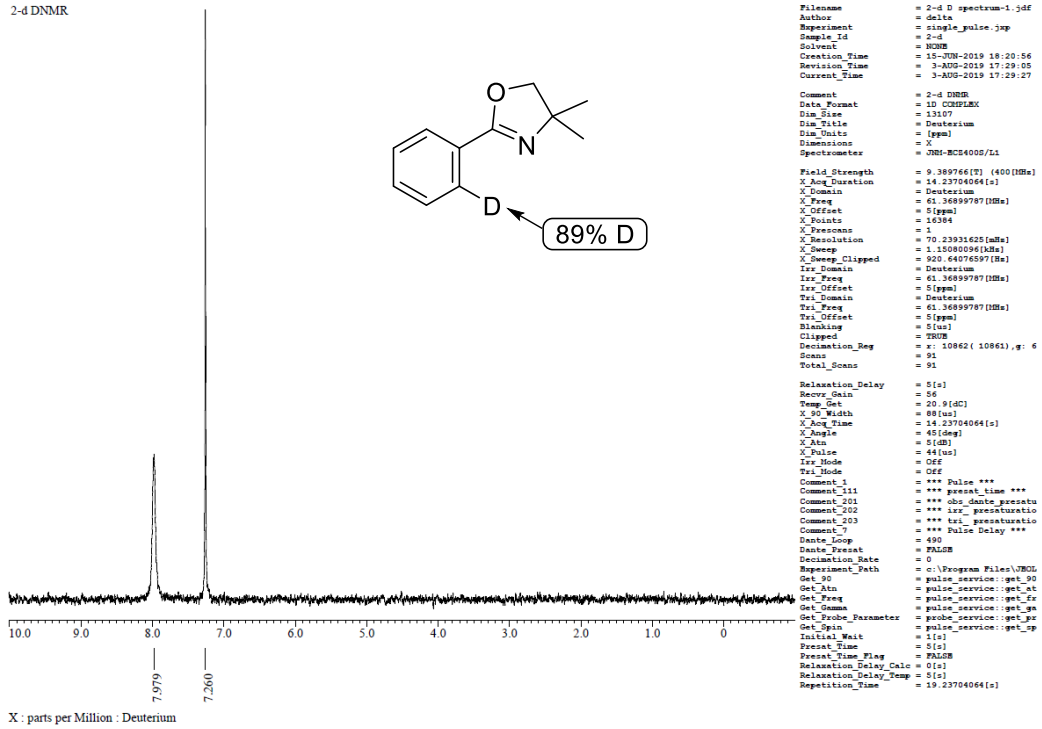


1a-d_5 0.2 mmol 2-*d* 72% (GC) 7% (GC)

Compound **1a-*d*$_5$** was subjected to the typical procedure. **2-*d*** was isolated by flash column chromatography on silica gel. The yield of the product and the starting material was determined by GC analysis using undecane as an internal standard due to volatility of the product.

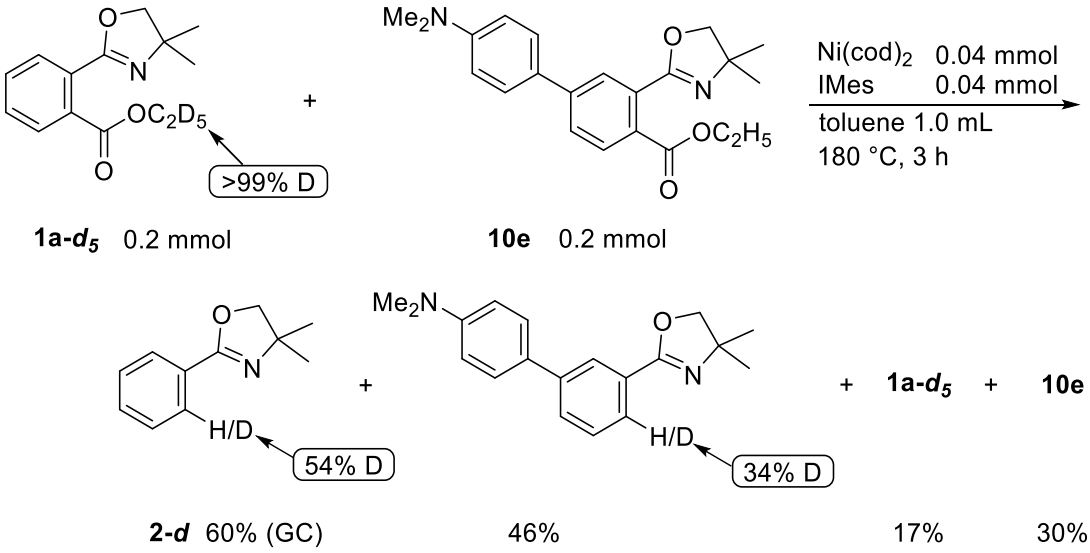


^{1}H NMR spectrum of **2-*d***

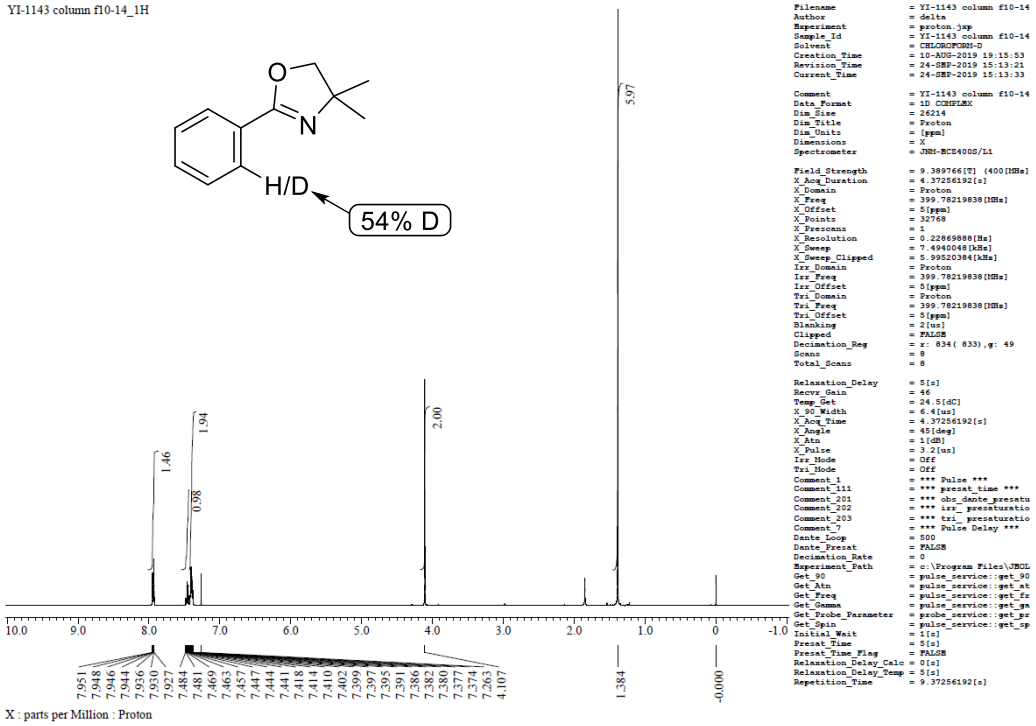


^{2}H NMR spectrum of **2-*d***

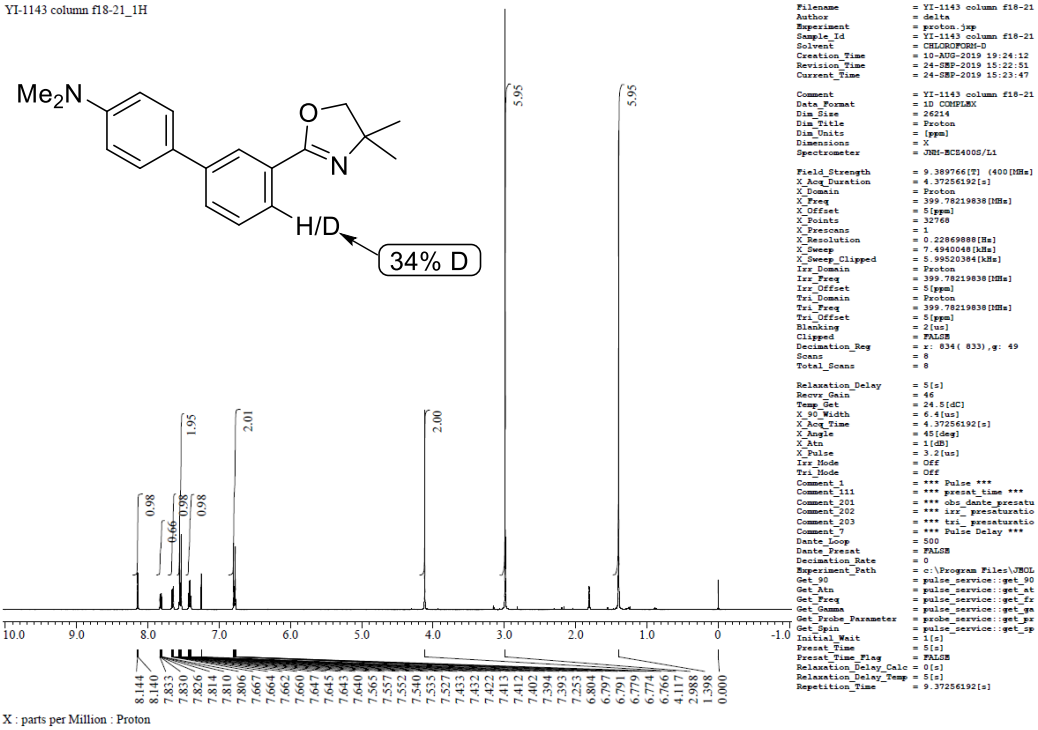
1.4.5.3 Crossover experiment (Scheme 6a).



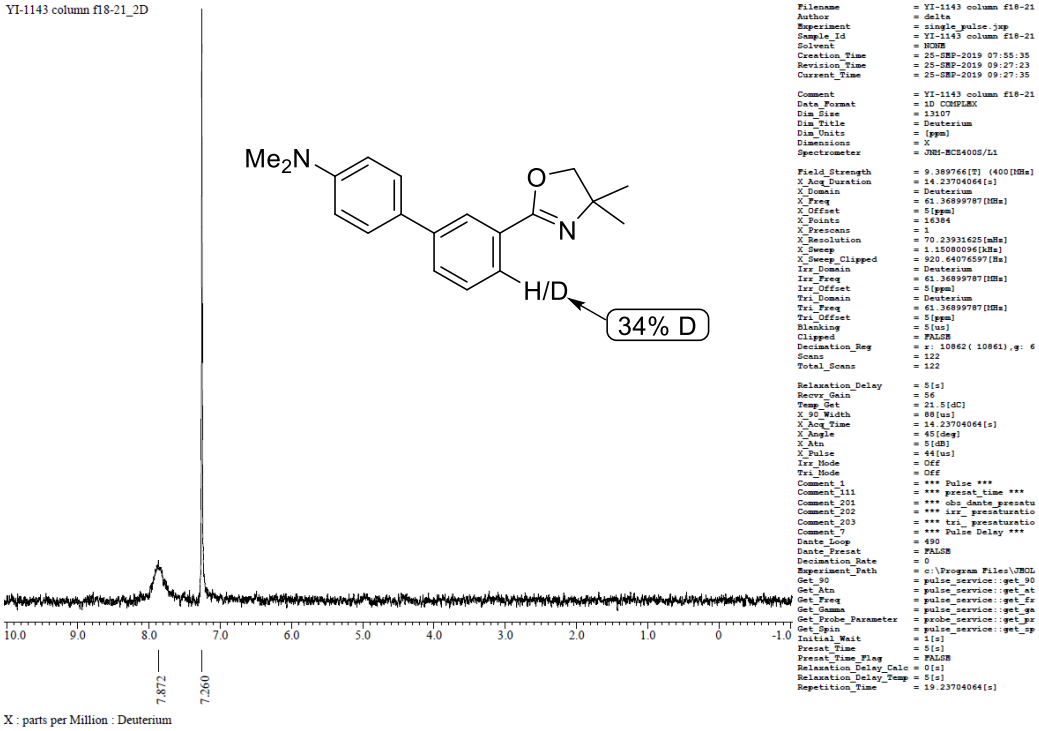
$Ni(cod)_2$ (10.6 mg, 0.039 mmol), IMes (12.0 mg, 0.039 mmol) and toluene (0.5 mL) were added to a 10 mL-vial with a Teflon-sealed screwcap in a glovebox filled with nitrogen, and the mixture was stirred for 3 min at room temperature. **1a-*d*$_5$** (52.6 mg, 0.21 mmol), **10e** (73.0 mg, 0.20 mmol) and toluene (0.5 mL) were then added to the vial, which was then sealed with a cap. The vial was stirred at 180 °C for 3 h. After the reaction mixture cooled to room temperature, the crude mixture was filtered through silica gel eluting with EtOAc. The filtrate was analyzed by GC using undecane as an internal standard. The crude mixture was concentrated under reduced pressure and analyzed by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. The resulting mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 10/1 to 5/1) to afford **2-*d*** (R_f = 0.40 in hexane/EtOAc = 2/1) as a colorless oil and 3'-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-*N,N*-dimethyl-[1,1'-biphenyl]-4-amine (R_f = 0.34 in hexane/EtOAc = 2/1) as a white solid (27 mg, 0.092 mmol, 46%). However, **1a-*d*$_5$** and **10e** could not be separated. The mixture of **1a-*d*$_5$** and **10e** were purified by GPC followed by flash column chromatography on NH_2 modified silica gel to afford **1a-*d*$_5$** (eluent: hexane/EtOAc = 5/1, R_f = 0.03 in hexane/EtOAc = 5/1) as a colorless oil (9 mg, 0.036 mmol, 17%) and **10e** (eluent: hexane/EtOAc = 5/1, R_f = 0.03 in hexane/EtOAc = 5/1) as a white solid (22 mg, 0.060 mmol, 30%).



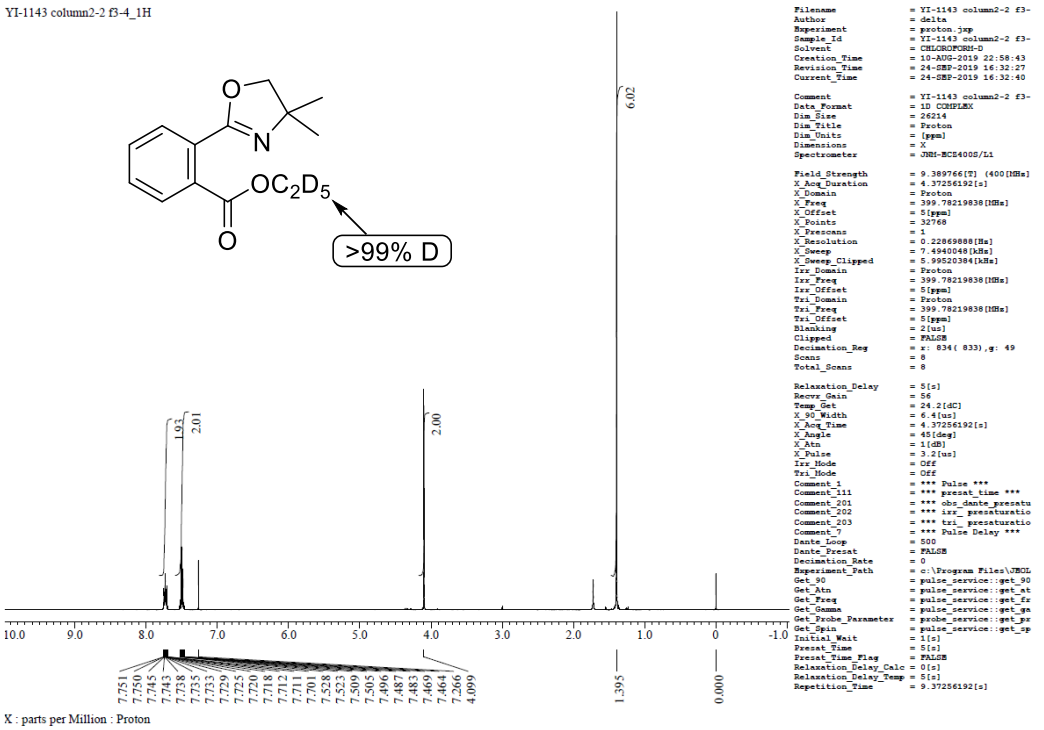
^{1}H NMR spectrum of **2-*d***



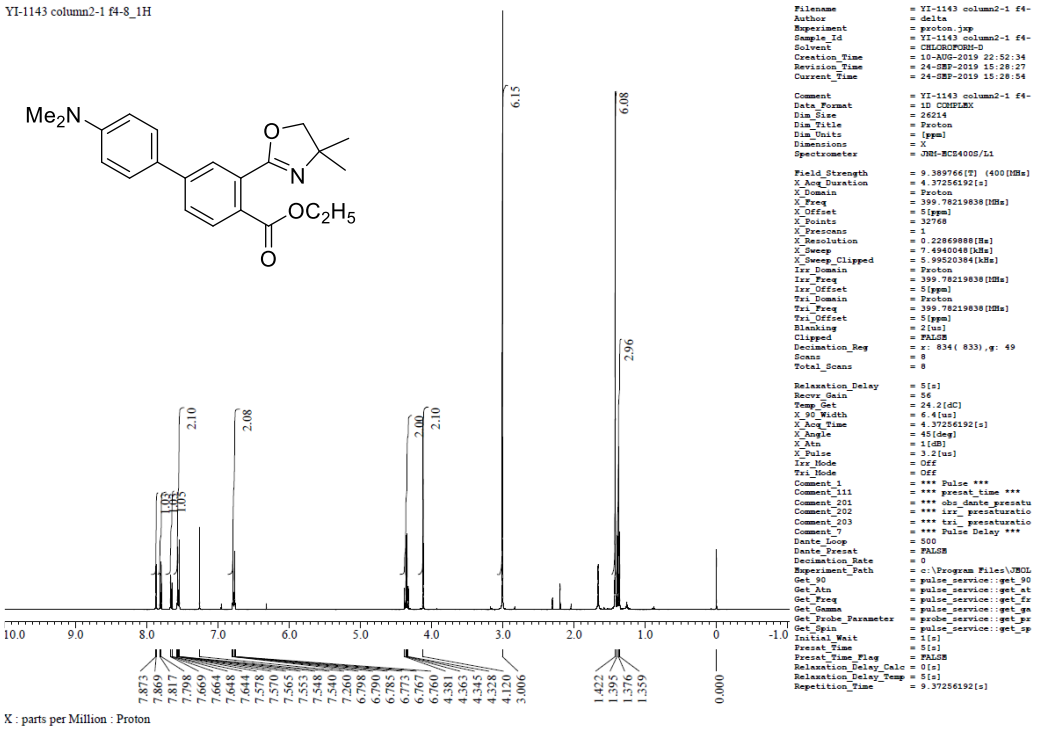
^{1}H NMR spectrum of 3'-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-*N,N*-dimethyl-[1,1'-biphenyl]-4-amine



^{2}H NMR spectrum of 3'-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-*N,N*-dimethyl-[1,1'-biphenyl]-4-amine

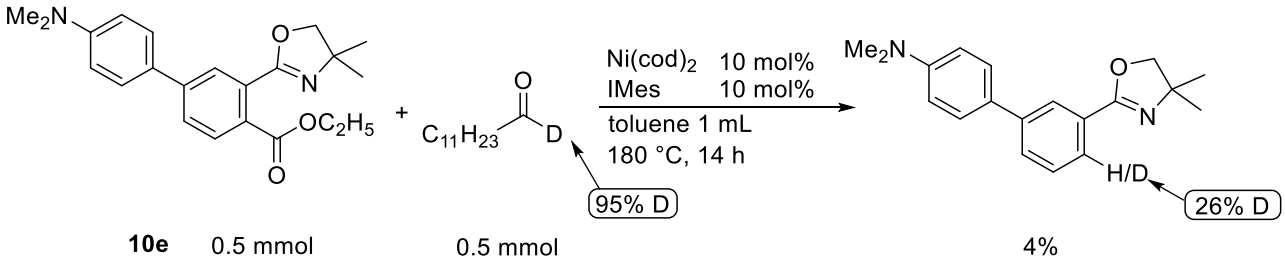


^{1}H NMR spectrum of **1a-*d*$_5$** after the reaction

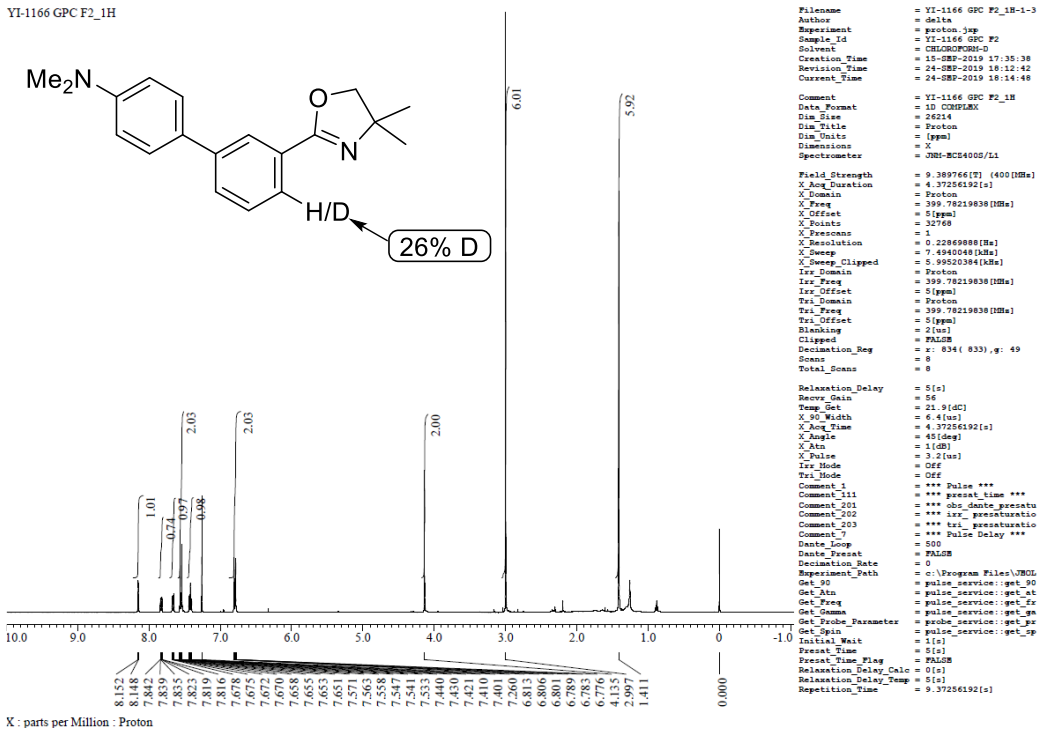


^{1}H NMR spectrum of **10e** after the reaction

1.4.5.4 Reaction with deuterium labeled aldehyde (Scheme 6b)

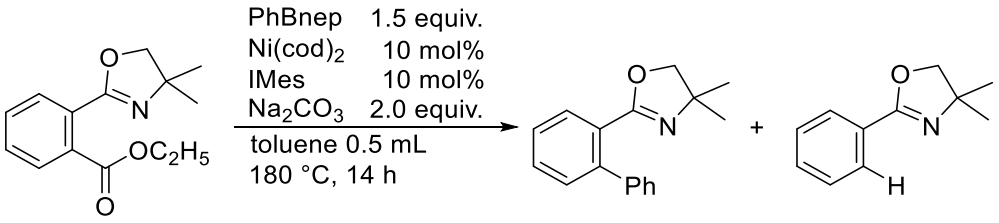


$Ni(cod)_2$ (13.3 mg, 0.048 mmol), IMes (15.3 mg, 0.050 mmol) and toluene (0.5 mL) were added to a 10 mL-vial with a Teflon-sealed screwcap in a glovebox filled with nitrogen, and the mixture was stirred for 3 min at room temperature. **10e** (181.6 mg, 0.50 mmol), dodecanal-1-*d* (91.1 mg, 0.49 mmol) and toluene (0.5 mL) were then added to the vial, which was then sealed with a cap. The vial was stirred at 180 °C for 14 h. After the reaction mixture cooled to room temperature, the crude mixture was filtered through silica-gel eluting with EtOAc. The filtrate was analyzed by GC using undecane as an internal standard. The crude mixture was concentrated under reduced pressure. The resulting mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 10/1 to 5/1, R_f = 0.29 in hexane/EtOAc = 2/1) folloed by isolation by GPC to afford the desired 3'-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)-*N,N*-dimethyl-[1,1'-biphenyl]-4-amine as a colorless oil (6 mg, 0.020 mmol, 4%).



^{1}H NMR spectrum of 3'-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-*N,N*-dimethyl-[1,1'-biphenyl]-4-amine

1.4.5.5 Reaction with boronic acid ester (eq 1)



1a 0.2 mmol 29% 29% (GC)

$Ni(cod)_2$ (6.0 mg, 0.022 mmol), IMes (7.3 mg, 0.024 mmol), Na_2CO_3 (43.4 mg, 0.40 mmol) and toluene (0.3 mL) were added to a 10 mL-vial with a Teflon-sealed screwcap in a glovebox filled with nitrogen, and the mixture was stirred for 3 min at room temperature. **1a** (47.8 mg, 0.19 mmol), PhBnep (56.8 mg, 0.30 mmol) and toluene (0.2 mL) were then added to the vial, which was then sealed with a cap. The vial was stirred at 180 °C for 14 h. After the reaction mixture cooled to room temperature, the crude mixture was filtered through silica gel eluting with EtOAc. The filtrate was analyzed by GC using undecane as an internal standard. The crude mixture was concentrated under reduced pressure and analyzed by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. The resulting mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 5/1, R_f = 0.31 in hexane/EtOAc = 2/1) to afford the desired 2-([1,1'-biphenyl]-2-yl)-4,4-dimethyl-4,5-dihydrooxazole as a colorless oil (14 mg, 0.056 mmol, 29%).

2-([1,1'-Biphenyl]-2-yl)-4,4-dimethyl-4,5-dihydrooxazole [CAS: 57598-40-0] **^{1}H NMR** ($CDCl_3$) δ: 1.29 (s, 6H), 3.79 (s, 2H), 7.32-7.41 (c, 7H), 7.46-7.50 (m, 1H), 7.71-7.74 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 28.0, 67.5, 79.5, 127.0, 127.2, 127.96, 128.02, 128.4, 130.08, 130.11, 130.4, 141.2, 141.7, 163.7. **HRMS (DART)** Calcd for $C_{17}H_{28}NO$ ($[M+H]^+$): 252.13829. Found: 252.13824.

1.5 References and notes

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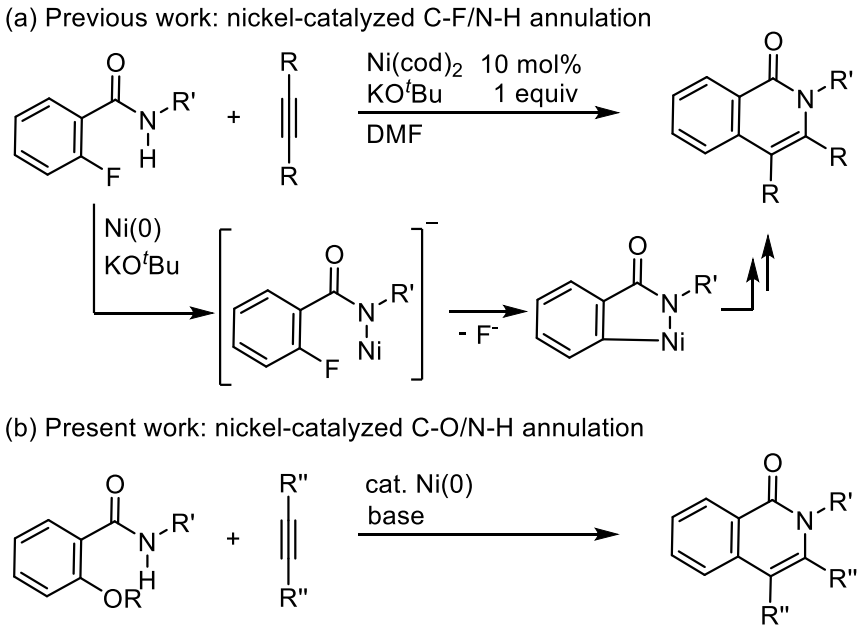
Chapter 2

Nickel-catalyzed C–O/N–H annulation of aromatic amides with alkynes

2.1 Introduction

The oxidative C-H/N-H annulation of aromatic amides with alkynes has been widely explored for the synthetic methods of isoquinolin-1(2*H*)-ones which serves as the important component of the bioactive compounds.[1] In addition, the C-X/N-H annulation (X = carbon, nitrogen or halogen) of aromatic amides with alkynes was also reported.[2] Recently, nickel-catalyzed C–F/N–H annulation of aromatic amides with alkynes was reported by our group (Scheme 1a).[3] The reaction proceeds even in the absence of a ligand at low reaction temperature. A key to the success of this reaction is the use of a base. The base abstracts a proton from amide group of the substrate, resulting in the formation of an amidate species, which reacts with nickel to give highly active nickel species. The author was interested in whether this methodology would be applicable to the cleavage of other unreactive bonds. Herein, the author investigated the C–O/N–H annulation of aromatic amides with alkynes (Scheme 1b).



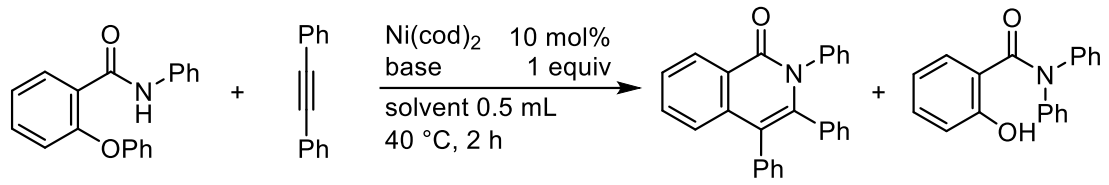
Scheme 1. Nickel-catalyzed annulation of amides with alkynes directed by amide anions.

2.2 Results and Discussion

The author began this study by optimizing the conditions for the reaction of 2-phenoxy-*N*-phenylbenzamide (**1a**) as a model substrate with diphenylacetylene (**2a**) as a coupling partner in the presence of $Ni(cod)_2$ as a catalyst (Table 1). **1a** reacted with **2a** (1.5 equiv.) in the presence of 10 mol% of $Ni(cod)_2$ and KO^{t}Bu (1 equiv.) in DMF (0.5 mL) at 40 °C for 2 h to give the desired product **3aa** in 69% yield, along with 30% of the starting amide **1a** being recovered and a trace amount of amide **4a**, which appears to be produced via the transfer of a phenyl group from an oxygen atom in **1a** to a nitrogen atom (Table 1, entry 1). After screening a series of solvents, it was found that the product

yield could be improved to 85% when DMSO was used as a solvent (entries 2–4). Next, the author examined the effect of ligands, however, the presence of ligands, such as PPh_3, dppe, and dtbbpy in the reaction mixture caused the decrease of the product yield (entries 5–7). When NaO^{t}Bu or LiO^{t}Bu were used as a base instead of KO^{t}Bu, the product yield was improved and the byproduct **4a** was not formed (entries 8 and 9). When the reaction was carried out using LiO^{t}Bu for 5 h, the starting amide **1a** was completely consumed and the desired product was obtained in 88% isolated yield (entry 10). The reaction did not proceed in the absence of the nickel catalyst (entry 11). Finally, the author determined the conditions for the reaction as shown in entry 10 as the standard conditions

Table 1. Optimization of reaction conditions.[a]



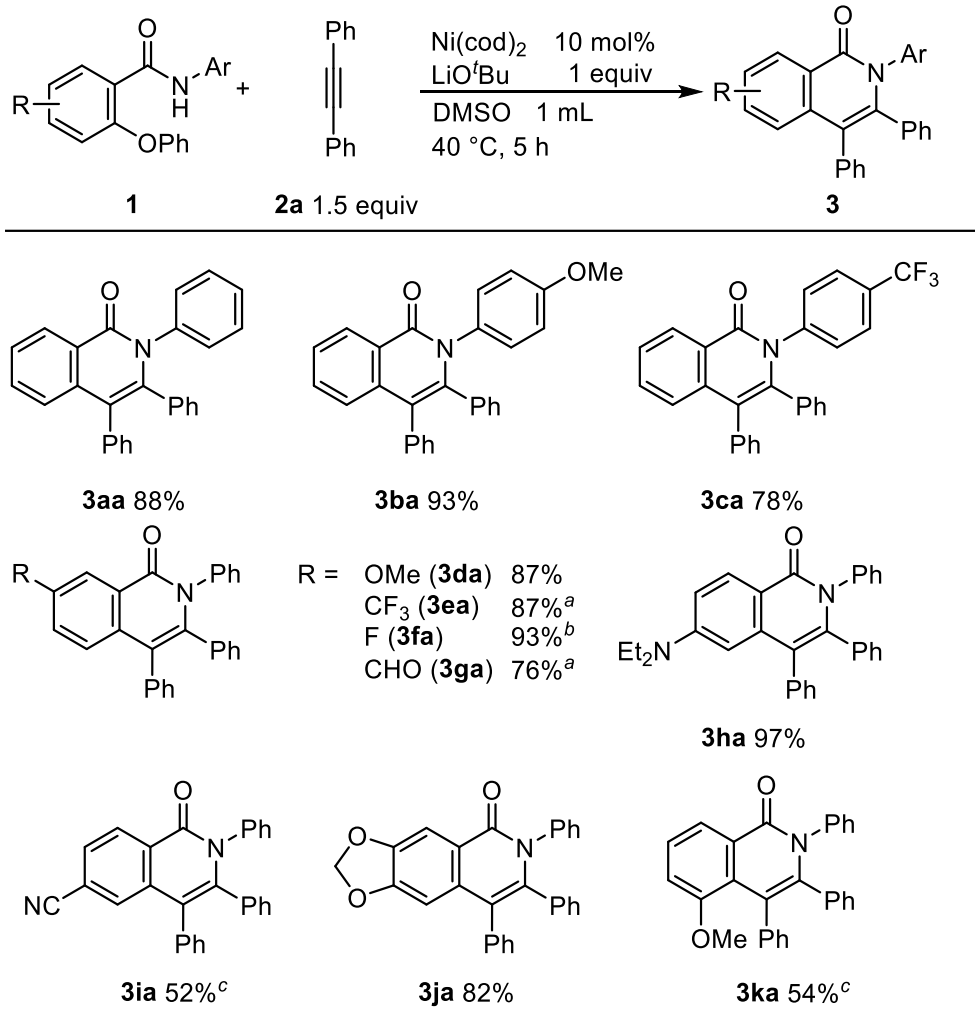
1a **2a** 1.5 eq. **3aa** **4a**

entry	solvent	ligand	base	NMR yields[b]		
				3aa	**4a**	**1a**
1	DMF	none	KO^{t}Bu	69%	trace	30%
2	toluene	none	KO^{t}Bu	10%	none	>99%
3	1,4-dioxane	none	KO^{t}Bu	48%	none	56%
4	DMSO	none	KO^{t}Bu	85%	2%	7%
5	DMSO	PPh_3	KO^{t}Bu	57%	3%	47%
6	DMSO	dppe	KO^{t}Bu	33%	3%	70%
7	DMSO	dtbpy	KO^{t}Bu	12%	5%	89%
8	DMSO	none	NaO^{t}Bu	93%	none	trace
9	DMSO	none	LiO^{t}Bu	93%	none	4%
10[c]	**DMSO**	**none**	**LiO^{t}Bu**	**>99% (88%)**[e]	**none**	**none**
11[d]	DMSO	none	LiO^{t}Bu	none	3%	>99%

[a] Reaction conditions: **1a** (0.2 mmol), **2a** (0.3 mmol), $Ni(cod)_2$ (0.02 mmol), and base (0.2 mmol) in solvent (0.5 mL) at 40 °C for 2 h. [b] NMR yields were determined from ^{1}H NMR with 1,1,1,2- tetrachloroethane as the internal standard. [c] 0.4 mmol scale, for 5 h. [d] Without $Ni(cod)_2$. [e] Isolated yield.

The results of a survey of scope of amides are shown in Scheme 2. First, the author examined the effect of the substituent group on the nitrogen atom of the amide group (**3ba** and **3ca**). An electron-withdrawing group on the nitrogen atom caused a slight decrease in the yield of the product. Various functional groups on the aromatic ring, such as methoxy, trifluoromethyl, fluoro, cyano, diethylamino, and even aldehyde groups were tolerated in the reaction. It was also found that when an amide bearing an electron-withdrawing group was used, a longer reaction time or a higher reaction temperature were required, as in **3ea**, **3fa**, **3ga**, and **3ia** suggesting that the cleavage of the C-O bond is not the rate-determining step.[4,5] While it is well known that nickel complexes have been used for the cleavage C-OMe,[6] C-F,[7] and CN bonds,[8] these bonds remained intact, as in **3ba**, **3da**, **3fa**, **3ka**, and **3ma**. The author

found that substrates bearing a substituent at the *ortho* position of the phenoxy group were also applicable to this reaction to give **3ka** in spite of the steric hinderance imposed by the phenoxy group.

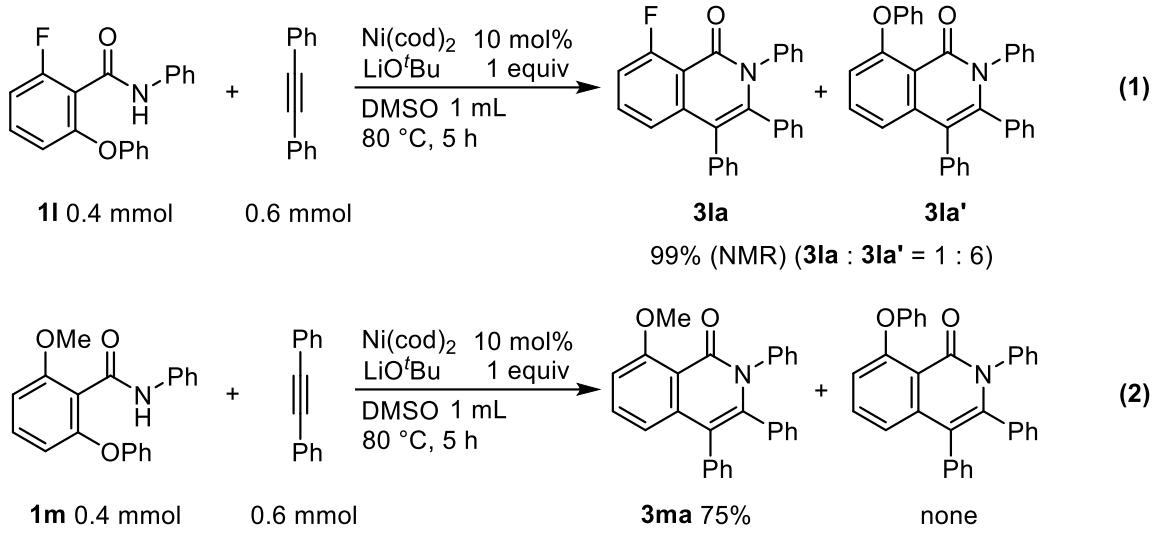


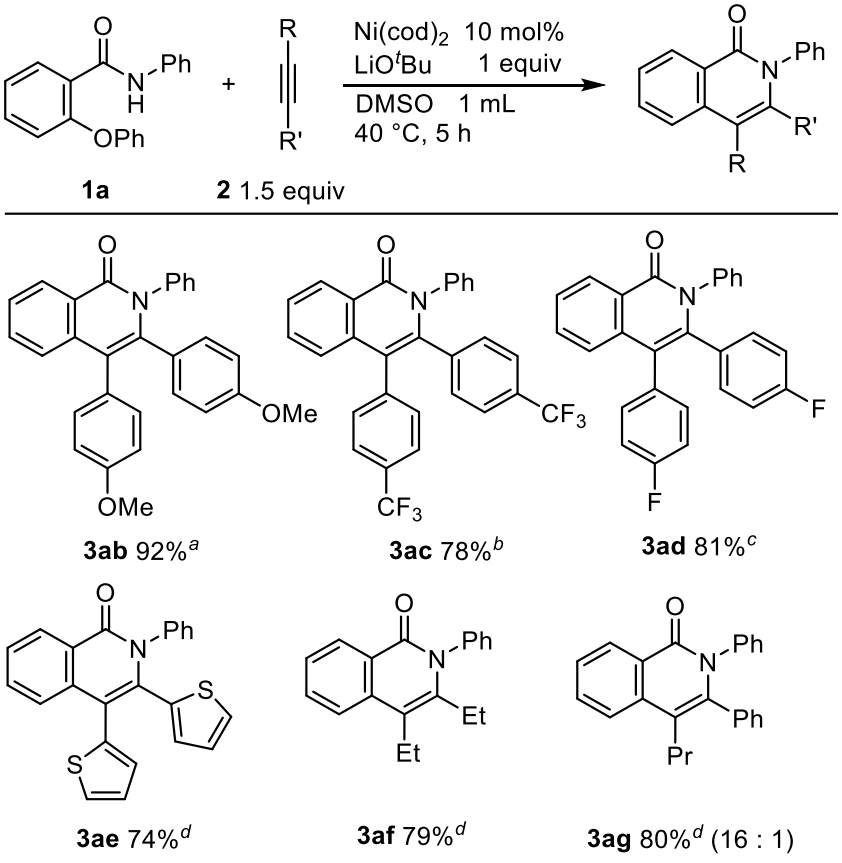
Scheme 2. Scope of amides for the reaction. Reaction conditions: amide (0.4 mmol), **2a** (0.6 mmol), $Ni(cod)_2$ (0.04 mmol), LiO^tBu (0.4 mmol) in DMSO (1 mL) at 40 °C for 5 h. Yields shown are isolated yields. [a] 60 °C. [b] 24 h. [c] 80 °C.

An amide bearing both C-OPh and C-F bonds at the *ortho* position **1l** reacted with **2** to give a mixture of two products, **3la** and **3la'** in favor of **3la'**, indicating that C-F bond activation predominated over C-O bond activation under the reaction conditions used (eq 1). In the reaction of amide **1m**, which contains both two C-O bonds at the *ortho*-position, only the C-OPh bond was selectively cleaved to give **3ma** in 75% yield (eq 2).

The author next examined the scope of the reaction with respect to alkynes (Scheme 3). An alkyne bearing an electron-donating group **2b** reacted efficiently to give **3ab** in 92% isolated yield. This reaction was carried out in DMF as a solvent due to the insolubility of **2b** to DMSO. The reaction of electron-deficient alkynes needed higher temperatures or longer reaction times (**3ac** and **3ad**). Alkynes with a thiophene ring and an aliphatic alkyne were also

applicable for this reaction (**3ae** and **3af**). When an unsymmetrical alkyne **2g** was used, the product **3ag** was obtained in a regioselective manner.

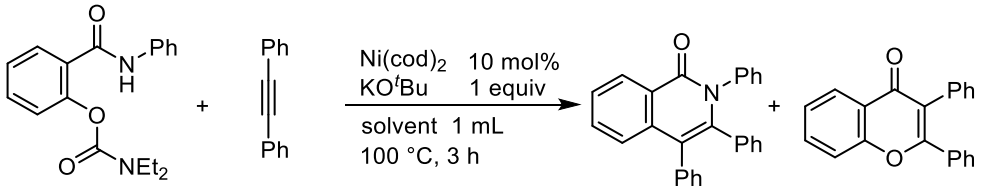




Scheme 3. Scope of alkynes. Reaction conditions: **1a** (0.4 mmol), alkyne (0.6 mmol), $Ni(cod)_2$ (0.04 mmol), LiO^tBu (0.4 mmol) in DMSO (1 mL) at 40 °C for 5 h. Yields shown are the isolated yields. [a] DMF was used instead of DMSO as a solvent. [b] 80 °C. [c] 24 h. [d] 60 °C.

In the course of our examination of other oxygen-based leaving groups, carbamates **5** were also found to participate in the reaction. The reaction of **5c** with **2a** (1.5 equiv.) in the presence of 10 mol% of $Ni(cod)_2$ and KO^{t}Bu (1 equiv.) in DMSO (1 mL) at 80 ℃ for 3 h to give the desired product **3aa** in 40% yield, along with 12% of the **6aa** being generated (Table 2, entry 1). The mechanism of the generation of **6aa** is shown in Chapter 3. After the screening of solvents, toluene was determined to be the solvent of choice at 100 °C (Table 2, entry 1-4).

Table 2. Optimization of reaction conditions for the reaction of carbamates.[a]

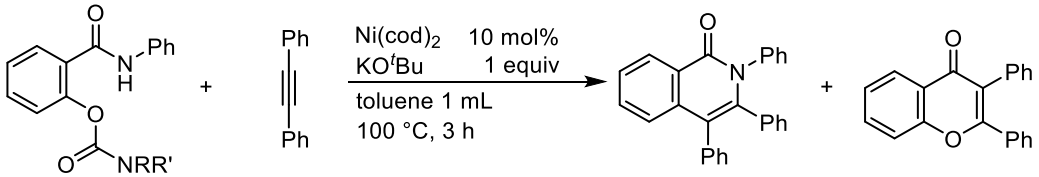


5c **2a** 2 eq. **3aa** **6aa**

entry	solvent	temp. (°C)	NMR yields[b] (isolated yields)		
			3aa	**6aa**	**5c**
1	DMSO	80	40%	12%	0%
2	DMF	80	77%	16%	0%
3	toluene	80	73%	trace	0%
4	**toluene**	**100**	**86%(86%)**	**trace**	**0%**

[a] Reaction conditions: **5c** (0.15 mmol), **2a** (0.3 mmol), $Ni(cod)_2$ (0.015 mmol), and KO^{t}Bu (0.15 mmol) in solvent (1 mL) for 3 h. [b] NMR yields were determined from ^{1}H NMR with 1,1,2,2-tetrachloroethane as the internal standard.

Table 3. Optimization of reaction conditions for the reaction of carbamates.

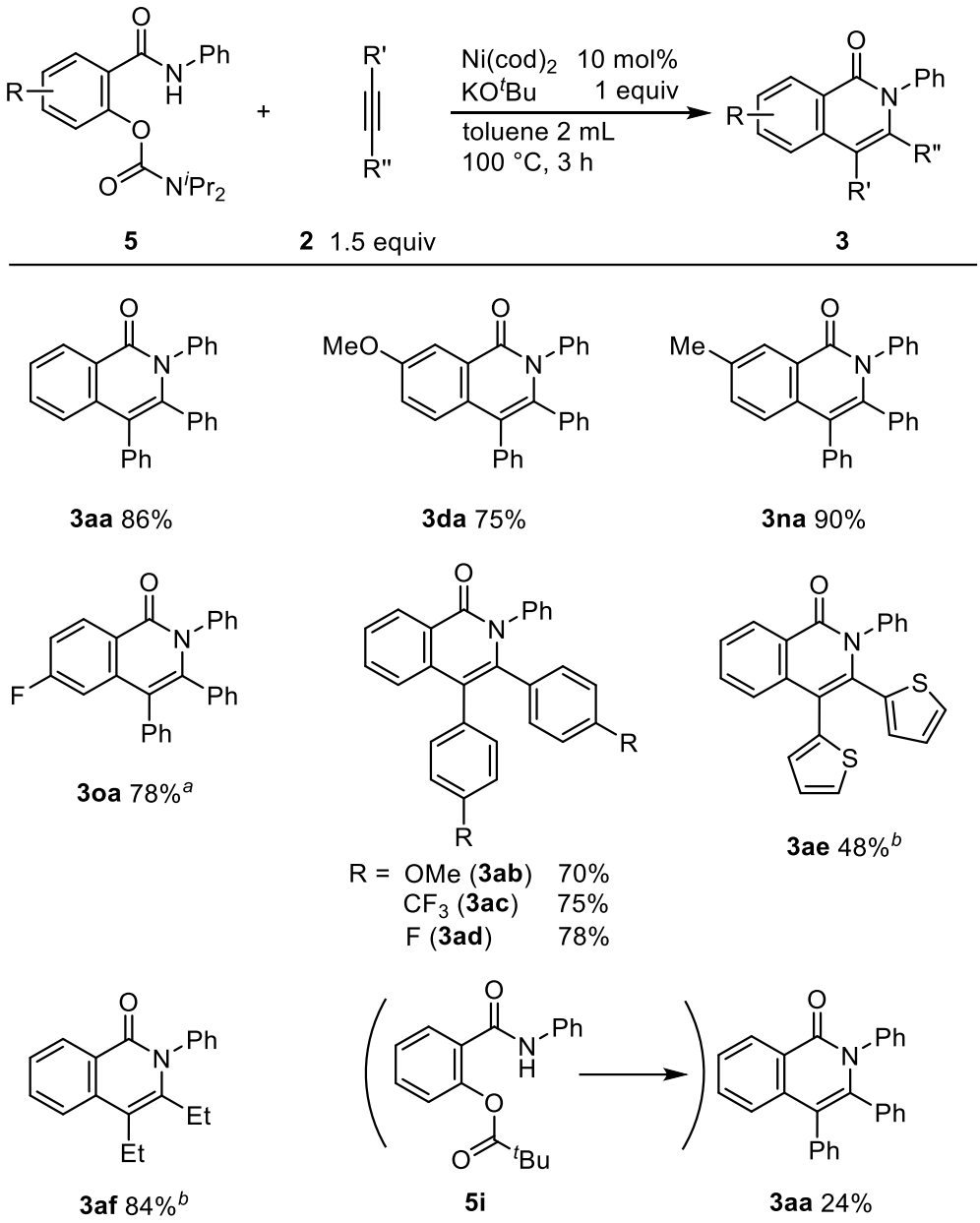


5 **2a** 1.5 equiv **3aa** **6aa**

entry	R, R'	NMR yields	
		3aa	**6aa**
1	Me, Me (**5a**)	52%	2%
2	Me, Et (**5b**)	74%	6%
3	Et, Et (**5c**)	90%	4%
4	^{i}Pr, ^{i}Pr (**5d**)	98%	none
5	Ph, Ph (**5e**)	3%	none

[a] Reaction conditions: **5** (0.2 mmol), **2a** (0.3 mmol), $Ni(cod)_2$ (0.02 mmol), and KO^{t}Bu (0.2 mmol) in toluene (1 mL) at 100 °C for 3 h. [b] NMR yields were determined from ^{1}H NMR with 1,1,2,2-tetrachloroethane as the internal standard.

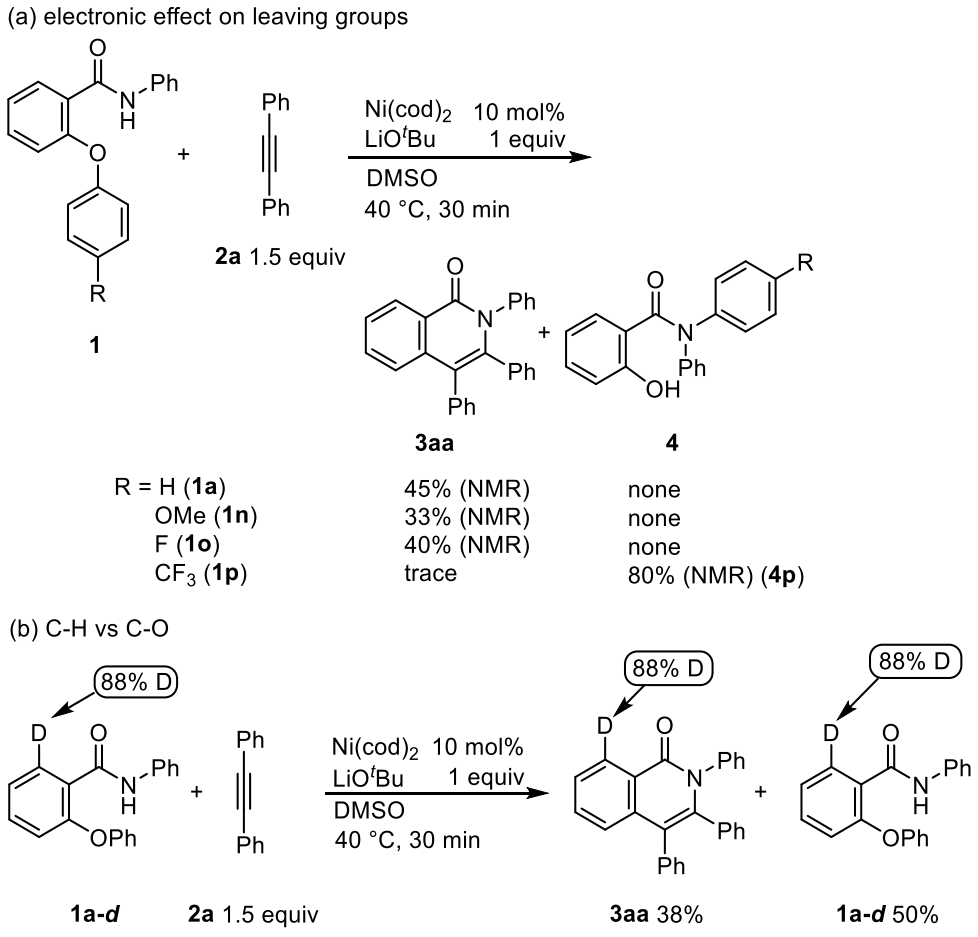
The author next examined the effect of substituents on the nitrogen-atom (Table 3). A carbamate having two methyl groups on the nitrogen atom **5a** gave the desired product **3aa** in 52% yield, but the chromone derivative **6aa** was also obtained in 2% yield as a byproduct (entry 1). When a carbamate with two isopropyl groups **5d** was used in the reaction, the desired product **3aa** was obtained in high yield and the formation of **6aa** was suppressed (entry 4). The use of **5e** gave **3aa** in only 3% yield, although the starting material was completely consumed (entry 5).



Scheme 4. Substrate scope for the reaction of carbamates. Reaction conditions: amide (0.4 mmol), alkyne (0.6 mmol), $Ni(cod)_2$ (0.04 mmol), KO^{t}Bu (0.4 mmol) in toluene (2 mL) for 3 h at 100 °C. Yields shown are isolated yields. [a] 120 °C. [b] 22 h.

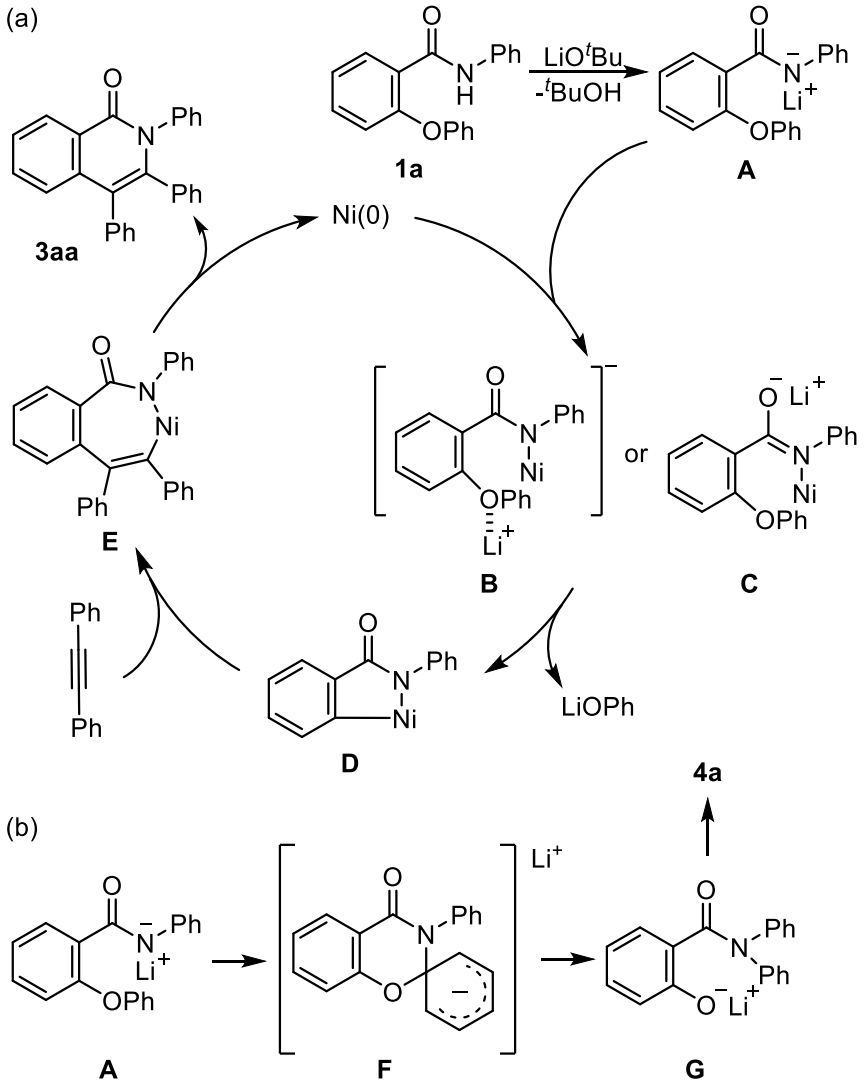
The results of the substrate scope for the reaction of carbamates are shown in Scheme 4. The reaction of substrates bearing an electron-donating group proceeded efficiently to give good yields of the desired products **3da** and **3na**. The reaction of carbamates with an electron-withdrawing fluoro group required a higher reaction temperature (120 °C) for good yields of **3oa** to be obtained. The electronic effects of substituents on the alkyne had no effect on product yields (**3ab** and **3ac**). In the reaction of heteroaromatic acetylene and aliphatic acetylene derivatives, a longer reaction time was necessary (**3ae** and **3af**). When pivalate was used as a leaving group instead of a carbamate, in **5i**, the desired product **3aa** was obtained in lower yield and *N*-phenyl salicylamide was also produced in 38% NMR yield, which shows that the pivalate is unstable under basic conditions and C(O)-O bond is cleaved.

Some mechanistic studies were conducted to gain insights into the reaction mechanism (Scheme 5). Only a negligible effect was observed in the case of **1a**, **1n**, and **1o** (Scheme 5a). In sharp contrast, the product **3aa** was not formed, but, rather, an aryl group transfer product **4p** was produced as a sole product in the reaction of aromatic amide **1p** containing a subsdtituted trifluoromethyl group, suggesting that a trifluoromethyl group promotes an aryl group transfer from an oxygen atom to a nitrogen atom. The reaction of the deuterium labeled substrate **1a-*d*** was also examined (Scheme 5b). In this case, no H/D exchange was observed in both the starting material and the product. This result indicates that C-H bond activation did not proceed under the reaction conditions employed[9] and that only C-O bond activation took place in the reaction.



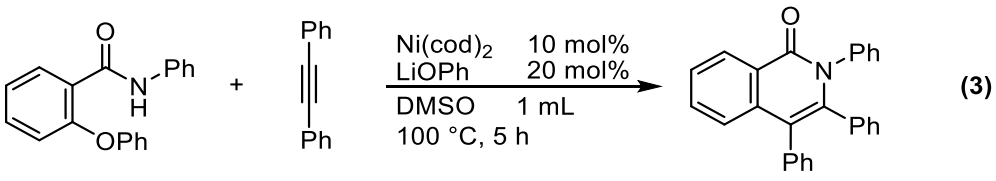
Scheme 5. Mechanistic studies.

A plausible reaction mechanism is shown in Scheme 6. The amide **1a** reacts with a base to produce the lithium amidate **A**. The amidate **A** reacts with a Ni catalyst to give the anionic Ni amide complex **B** or **C**. The oxidative addition of a C-O bond produces a five-membered nickellacycle **D** with the generation of LiOPh. The insertion of an alkyne followed by reductive elimination gives the product **3aa** with the regeneration of the Ni(0) species. A possible pathway for the formation of **4a** involves an intramolecular S_NAr type reaction via **F**, which is consistent with the experimental results showing that a trifluoromethyl group facilitates the formation of **4a**, as shown in Scheme 5a.



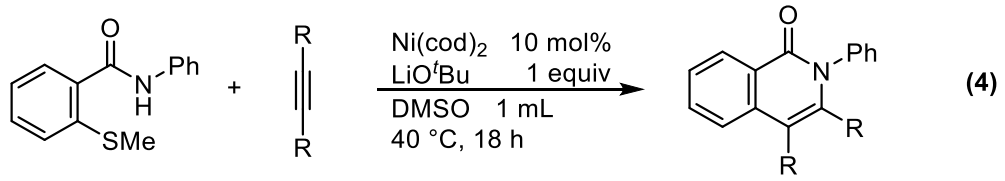
Scheme 6. A Plausible Mechanism.

In the above mechanism, LiOPh is generated in the reaction. We hypothesized that a catalytic amount of LiOPh could be used instead of a stoichiometric amount of LiO^{t}Bu. As expected, the reaction proceeded even in the presence of a catalytic amount of LiOPh (eq 3). However, a higher reaction temperature was necessary for the reaction to proceed efficiently, so we concluded that LiO^{t}Bu was the optimal base.

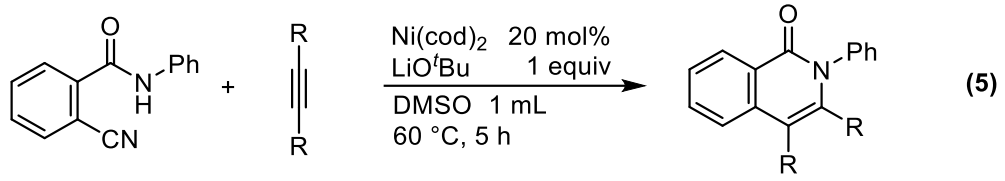


1a 0.4 mmol **2a** 1.5 equiv **3aa** 71%

The author also examined the issue of whether this methodology might also be applicable to other strong bonds (eq 4, 5). Gratifyingly, it was found that C-S bond activation also occurs to give the desired products.[10] The author also examined the possibility of C-CN bond activation, which afforded the desired products.[11]



1q 0.4 mmol **2** 1.5 equiv **3aa** 58% (R = Ph)
3af 80% (R = Et)



1r 0.4 mmol **2** 1.5 equiv **3aa** 37% (R = Ph)
3af 27% (R = Et)

2.3 Conclusion

In conclusion, the author demonstrated the nickel-catalyzed C−O/N−H, C-S/N-H and C-CN/N-H annulation of amides with alkynes, leading to the production of 1(2*H*)-isoquinolinones. This reaction proceeds in the absence of ligands under low temparature and a wide vareity of important functional groups was tolerated. This methodology is applicable to the activation of other unreactive bonds, such as C-S and C-CN bonds.

2.4 Experimental Section

2.4.1 General Information

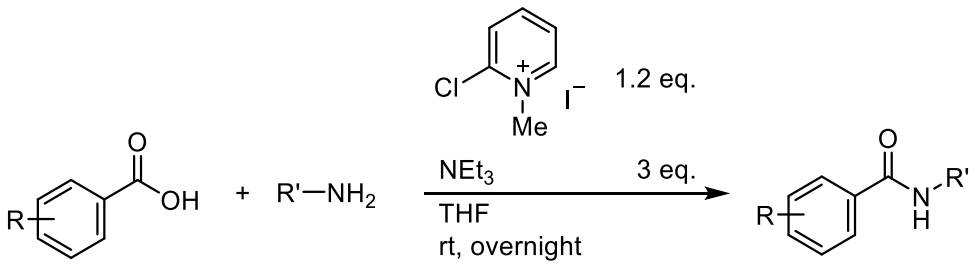
^{1}H, ^{2}H, ^{13}C and ^{19}F NMR spectra were recorded on a JEOL ECZ-400S spectrometer (except for ^{13}C NMR spectrum of **1a-*d***) or a JEOL ECS-400 spectrometer (^{13}C NMR spectrum of **1a-*d***). The chemical shifts in ^{1}H NMR spectra were recorded relative to tetramethylsilane (δ: 0.0) or DMSO *d6* (δ: 2.50). The chemical shifts in ^{2}H NMR spectra were recorded relative to $CDCl_3$ (δ: 7.26). The chemical shifts in ^{13}C NMR spectra were recorded relative to $CDCl_3$ (δ: 77.0) or DMSO *d6* (δ: 39.52). The chemical shifts in ^{19}F NMR spectra were recorded relative to $CFCl_3$ (δ: 0.0). Data are recorded as follows: chemical shifts in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad singlet, m = multiplet, c = complex), coupling constant (Hz), and integration. Infrared spectra (IR) were recorded on a JASCO FT/IR-4000 spectrometer using ATR method. Absorption data are reported in reciprocal

centimeters from 800 to 3500 cm^{-1} with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained using a SHIMADZU QP-2010 spectrometer with a quadrupole mass analyzer at 70 eV. Data are recorded as follows: mass/charge ratio and relative intensity to base peak at 100 %. High-resolution mass spectra (HRMS) were obtained using a JEOL JMS-T100LP spectrometer with a time-of-flight mass analyzer. Elemental analyses were performed by the Elemental Analysis Section of Osaka University. Melting points were determined on a Stanford Research Systems MPA100 apparatus equipped with a digital thermometer and are uncorrected. Preparative gel permeation chromatography (GPC) were carried out on a JAI LC-5060 equipped with two JAIGEL-2HR columns connected in series. Column chromatography was performed with SiO_2 (Silicycle Siliaflash F60 (230-400 mesh)) or NH_2-modified SiO_2 (Kanto Chemical, Silica gel 60 (spherical) NH_2 (40-50μm)).

2.4.2 Materials

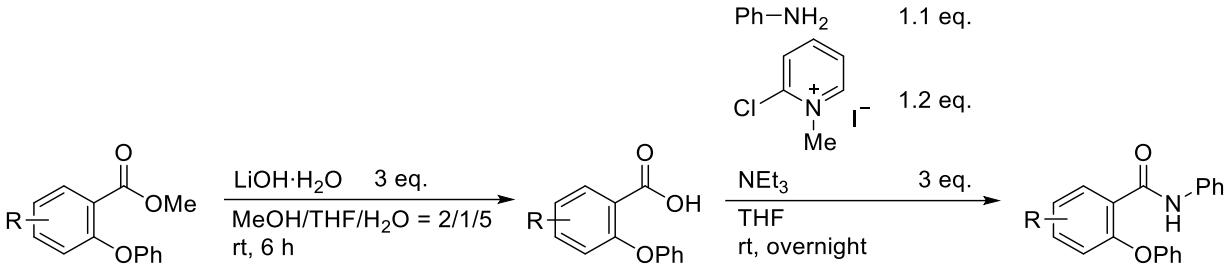
Toluene (super dehydrated), 1,4-dioxane (super dehydrated), DMF (super dehydrated), DMSO (super dehydrated), $Ni(cod)_2$, PPh_3, dppe, dttbpy, LiO^tBu, NaO^tBu and KO^tBu were purchased and used as received. Diphenyl acetylene (**2a**) was purchased and recrystalyzed from hexane before use. 3-Hexyne (**2f**) and 1-phenyl-1-pentyne (**2g**) were purchased and distilled over CaH_2 before use. 1,2-bis(4-methoxyphenyl)ethyne (**2b**)[12], 1,2-bis(4-(trifluoromethyl)phenyl)ethyne (**2c**)[13], 1,2-bis(4-fluorophenyl)ethyne (**2d**)[13], 1,2-di(thiophen-2-yl)ethyne (**2e**)[14] and 2-cyano-*N*-phenylbenzamide (**1r**)[15] were prepared according to the reported procedure. Other starting materials were prepared as described below.

General Procedure A: Synthesis of Amides from Carboxylic Acids.



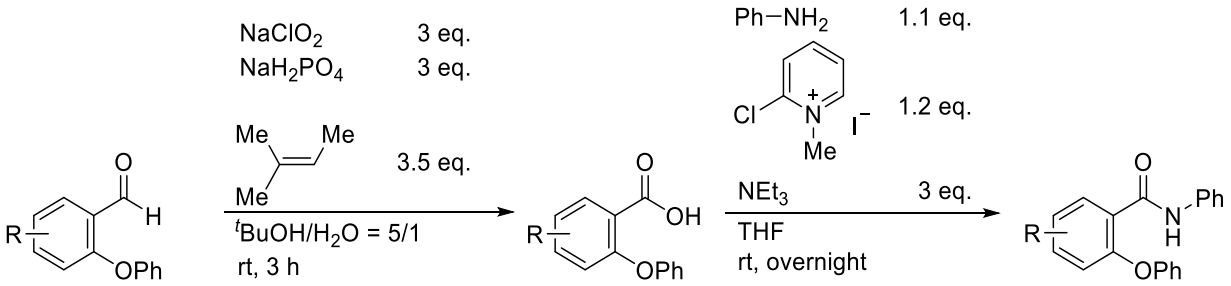
To a solution of carboxylic acid (1 eq.), aniline (1.1 eq.) and NEt_3 (3 eq.) in THF (0.5 M), 2-chloro-1-methylpyridinium iodide (1.2 eq.) was added. After stirring overnight at room temperature, the volatiles were removed under reduced pressure. EtOAc and sat. $NaHCO_3$ aq. were then added and the organic layer was separated. The organic layer was washed with 1N HCl aq. and dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by silica-gel flash column chromatography or by recrystallization.

General Procedure B: Synthesis of Amides from Esters.



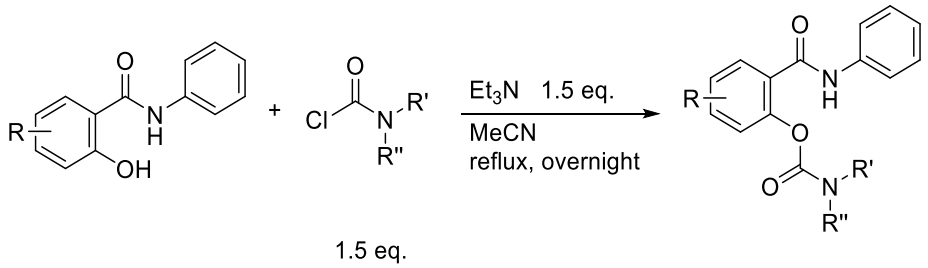
The mixture of the ester and $LiOH \cdot H_2O$ (3 eq.) in $MeOH/THF/H_2O = 2/1/5$ (0.15 M) was stirred at room temparature for 6 h. After removing the volatiles under reduced pressure, 1N HCl aq. and Et_2O were added and the organic layer was separated. The aqueous layer was extracted with Et_2O and the combined organic layer was dried over Na_2SO_4. After removing the volatiles by evaporation, the resulting crude material was used for subsquent amidation by following general procedure A without further purification.

General Procedure C: Synthesis of Amides from Aldehydes.



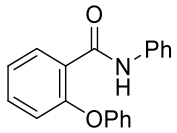
To a solution of the aldehyde in $^tBuOH/H_2O$ = 5/1 (0.33 M), NaH_2PO_4 (3 eq.), 2-methyl-2-butene (3.5 eq.) and $NaClO_2$ (3 eq.) were added) and the resulting mixture was stirred at room temparature for 3 h. After removing the volatiles under reduced pressure, 1N HCl aq. and Et_2O were added and the organic layer was dried over Na_2SO_4. After removing the volatiles in vacuo, the resulting crude material was used for subsquent amidation reactions with aniline following general procedure A without further purification.

General Procedure D: Synthesis of Carbamates.



A solution conta of the salicylanilide, dimethylcarbamoyl chloride (1.5 eq.), Et_3N (1.5 eq.) and MeCN (0.25 M) were stirred reflux overnight. After the reaction, EtOAc and 1N HCl aq were added and the organic layer was dried over Na_2SO_4. After the volatile was removed under reduced pressure, the resulting crude mixture was purified by silica-gel flash column chromatography or recrystallization.

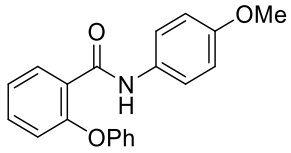
2-Phenoxy-*N*-phenylbenzamide (1a) [CAS: 140437-02-1]



1a was prepared from 2-phenoxy benzoic acid (10.5 g, 49.0 mmol) and aniline (5.04 g, 54.1 mmol) following general procedure A. The product was obtained in 64% yield (9.10 g, 31.5 mmol) as a white solid by recrystallization from EtOH.

Mp = 97.4-97.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.88 (dd, *J* = 8.2 Hz, 0.9 Hz, 1H), 7.06-7.13 (c, 3H), 7.19-7.26 (c, 2H), 7.29-7.34 (m, 2H), 7.38-7.44 (c, 3H), 7.59-7.63 (m, 2H), 8.33 (dd, *J* = 7.9 Hz, 1.7 Hz, 1H), 9.63 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 118.4, 119.4, 120.3, 123.9, 124.1, 124.3, 124.9, 128.9, 130.3, 132.4, 133.0, 138.1, 155.2, 155.3, 162.6. **IR** (ATR): 3348 w, 1657 m. **MS**: *m*/*z* (EI, relative intensity, %): 289 (18, M^+), 198 (14), 197 (100), 196 (14), 115 (13). **Anal.** Calcd for $C_{19}H_{15}NO_2$: C, 78.87; H, 5.23; N, 4.84. Found: C, 78.95; H, 5.14; N, 4.81.

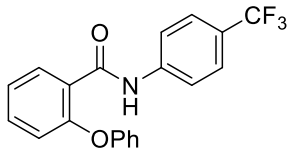
***N*-(4-methoxyphenyl)-2-phenoxybenzamide (1b)** [CAS: 349399-98-0]



1b was prepared from 2-phenoxy benzoic acid (3.24 g, 15.1 mmol) and *p*-anisidine (2.09 g, 17.0 mmol) following general procedure A. The product was obtained in 79% yield (3.79 g, 11.9 mmol) as a yellow solid by recrystallization from EtOH.

Mp = 119.9-120.6 ºC. **^{1}H NMR** ($CDCl_3$) δ: 3.76 (s, 3H), 6.82-6.89 (c, 3H), 7.09-7.11 (m, 2H), 7.19-7.25 (c, 2H), 7.37-7.42 (c, 3H), 7.50-7.54 (m, 2H), 8.32 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 9.50 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 55.4, 114.0, 118.4, 119.4, 122.0, 123.9, 124.2, 124.8, 130.2, 131.2, 132.3, 132.8, 155.1, 155.3, 156.3, 162.4. **IR** (ATR): 3382 w, 1660 m, 1235 s, 1216 s. **MS**: *m*/*z* (EI, relative intensity, %): 320 (12), 319 (52, M^+), 198 (14), 197 (100), 115 (11). **Anal.** Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.20; H, 5.30; N, 4.38.

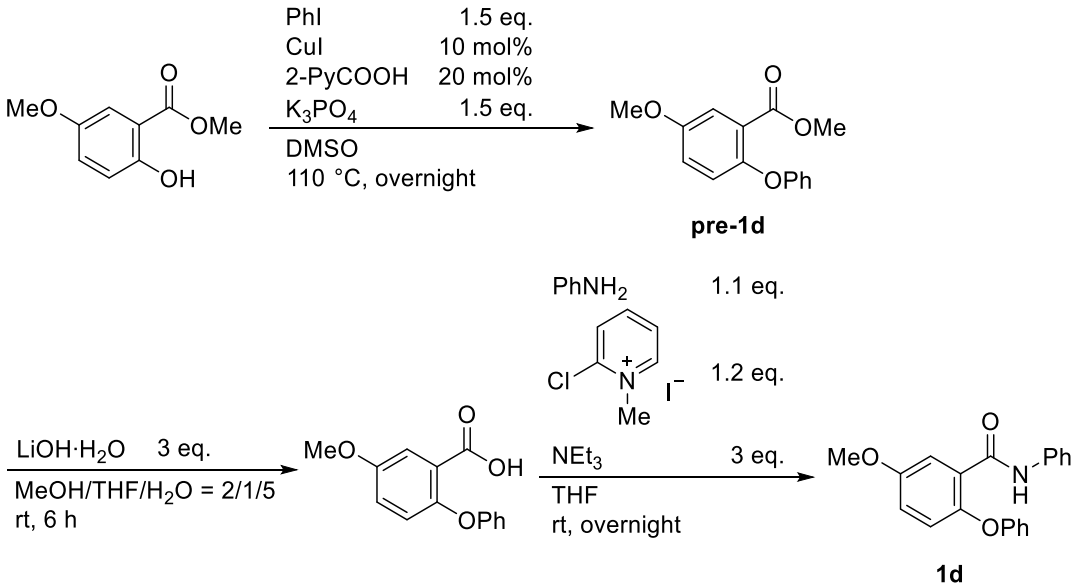
2-Phenoxy-*N*-(4-(trifluoromethyl)phenyl)benzamide (1c) [CAS: 1004245-21-9]



1c was prepared from 2-phenoxy benzoic acid (3.19 g, 14.9 mmol) and 4-aminobenzotrifluoride (2.64 g, 16.4 mmol) following general procedure A. The product was obtained in 38% yield (2.04 g, 5.71 mmol) as a white solid by recrystallization from EtOH.

Mp = 118.8-119.1 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.90 (dd, *J* = 8.2 Hz, 0.9 Hz, 1H), 7.11-7.14 (m, 2H), 7.22-7.29 (c, 2H), 7.40-7.48 (c, 3H), 7.56 (d, *J* = 8.5 Hz, 2H), 7.74 (d, *J* = 8.5 Hz, 2H), 8.33 (dd, *J* = 7.9 Hz, 1.7 Hz, 1H), 9.82 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 118.3, 119.5, 119.9, 123.5, 124.0, 124.1 (q, *J* = 270 Hz), 125.2, 125.9 (q, *J* = 32.6 Hz), 126.2 (q, *J* = 3.8 Hz) 130.4, 132.5, 133.5, 141.2, 155.0, 155.4, 162.9. **^{19}F NMR** -62.6 (s). **IR** (ATR): 3371 w, 1678 w, 1319 s. **MS**: *m*/*z* (EI, relative intensity, %): 357 (12, M^+), 198 (15), 197 (100), 115 (12). **Anal.** Calcd for $C_{20}H_{14}F_3NO_2$: C, 67.23; H, 3.95; N, 3.92. Found: C, 67.27; H, 3.88; N, 3.92.

5-Methoxy-2-phenoxy-*N*-phenylbenzamide (1d)



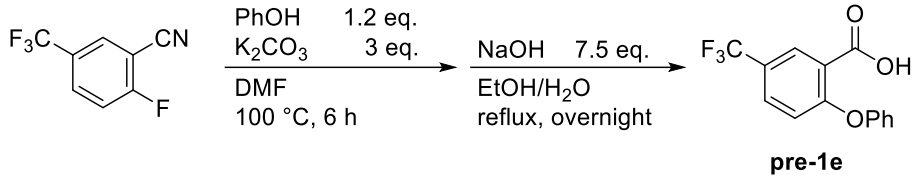
CuI (512 mg, 2.7 mmol), 2-pyridinecarboxylic acid (662 mg, 5.4 mmol) and K_3PO_4 (8.74 g, 41.1 mmol) were added to a 200 mL three-necked round-bottom flask and the flask was purged with N_2. DMSO (60 mL), methyl 5-methoxysalicylate (4.93 g, 27.1 mmol) and PhI (8.08 g, 39.6 mmol) were added to the flask and the resulting mixture was stirred overnight at 110 °C under a N_2 atmosphere. After cooling the flask to room temperature, the resulting crude mixture was suspended in EtOAc (120 mL) and the resulting suspension was filtered through a celite pad. The mixture was washed with sat. $NaHCO_3$ aq. (50 mL) and H_2O (50 mL). The organic layer was dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 40/1 to 10/1, R_f = 0.23 in hexane/EtOAc = 10/1) to afford methyl 5-methoxy-2-phenoxybenzoate (**pre-1d**) in 23% yield (1.59 g, 6.16 mmol) as a pale yellow oil.

1d was prepared from **pre-1d** (1.59 g, 6.16 mmol) following general procedure B. The product was obtained in 47% yield (932 mg, 2.91 mmol) as a white solid after recrystallization from Et_2O.

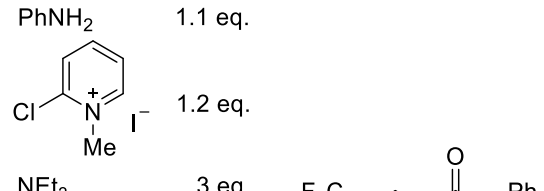
Mp = 76.1-76.9 ºC. **^{1}H NMR** ($CDCl_3$) δ: 3.89 (s, 3H), 6.91 (d, *J* = 8.9 Hz, 1H), 7.02 (dd, *J* = 8.9 Hz, 3.3 Hz, 1H), 7.04-7.08 (m, 2H), 7.08-7.13 (m, 1H), 7.14-7.19 (m, 1H), 7.30-7.34 (m, 2H), 7.36-7.41 (m, 2H), 7.56-7.62 (m, 2H), 7.85 (d, *J* = 3.3 Hz, 1H), 9.68 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 55.8, 114.8, 118.1, 120.2, 120.3, 121.3, 124.2, 124.3, 125.5, 128.9, 130.2, 138.0, 148.0, 156.1, 156.4, 162.3. **IR** (ATR): 3366 w, 1660 m, 1209 s. **MS**: *m*/*z* (EI, relative

intensity, %): 319 (33, M^+), 228 (15), 227 (100), 184 (23). **Anal.** Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.10; H, 5.36; N, 4.44.

2-Phenoxy-*N*-phenyl-5-(trifluoromethyl)benzamide (1e)



pre-1e

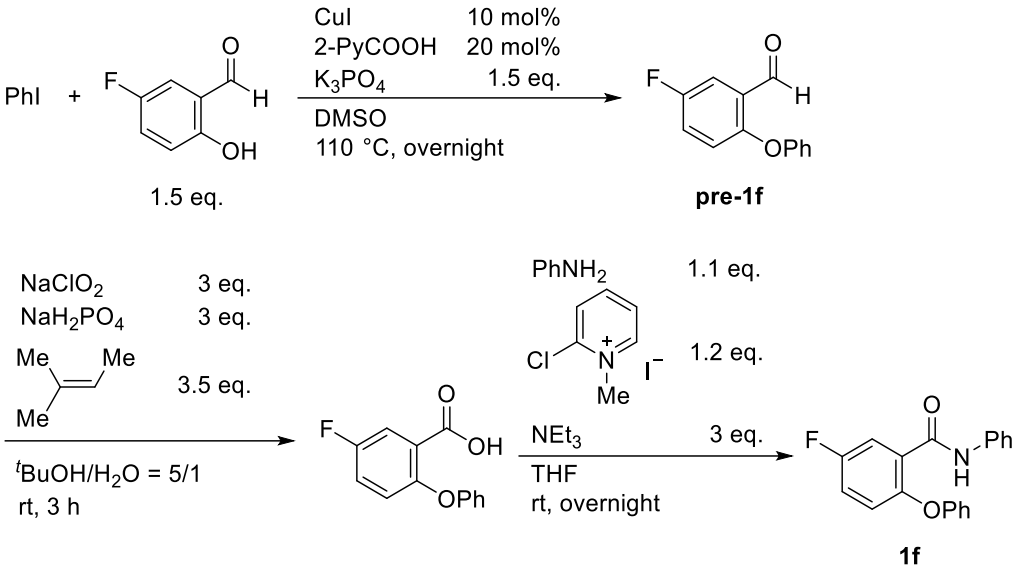


1e

2-Phenoxy-5-(trifluoromethyl)benzoic acid (**pre-1e**) was prepared from 2-fluoro-5-(trifluoromethyl)benzonitrile (5.45 g, 28.8 mmol) according to the reported procedure[16] and was then used in a subsquent amidation following general procedure A without further purification. **1e** was obtained in 34% yield (3.53 g, 9.88 mmol) as a white solid by recrystallization from Et_2O.

Mp = 100.9-101.4 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.93 (d, *J* = 8.7 Hz, 1H), 7.12-7.20 (c, 3H), 7.31-7.38 (c, 3H), 7.47-7.52 (m, 2H), 7.61-7.66 (c, 3H), 8.66 (d, *J* = 2.3 Hz, 1H), 9.64 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 117.6, 120.4, 120.5, 123.6 (q, *J* = 271 Hz), 123.8, 124.7, 125.9 (q, *J* = 33.5 Hz), 126.1, 129.1, 129.8 (q, *J* = 2.9 Hz), 130.3 (q, *J* = 3.8 Hz), 130.7, 137.7, 153.9, 158.1, 161.3. **^{19}F NMR** -62.6 (s). **IR** (ATR): 3310 w, 1648 m, 1115 s. **MS**: *m*/*z* (EI, relative intensity, %): 357 (19, M^+), 266 (15), 265 (100), 264 (23), 77 (11). **Anal.** Calcd for $C_{20}H_{14}F_3NO_2$: C, 67.23; H, 3.95; N, 3.92. Found: C, 67.09; H, 3.97; N, 3.97.

5-Fluoro-2-phenoxy-*N*-phenylbenzamide (1f) [CAS: 140437-19-0]

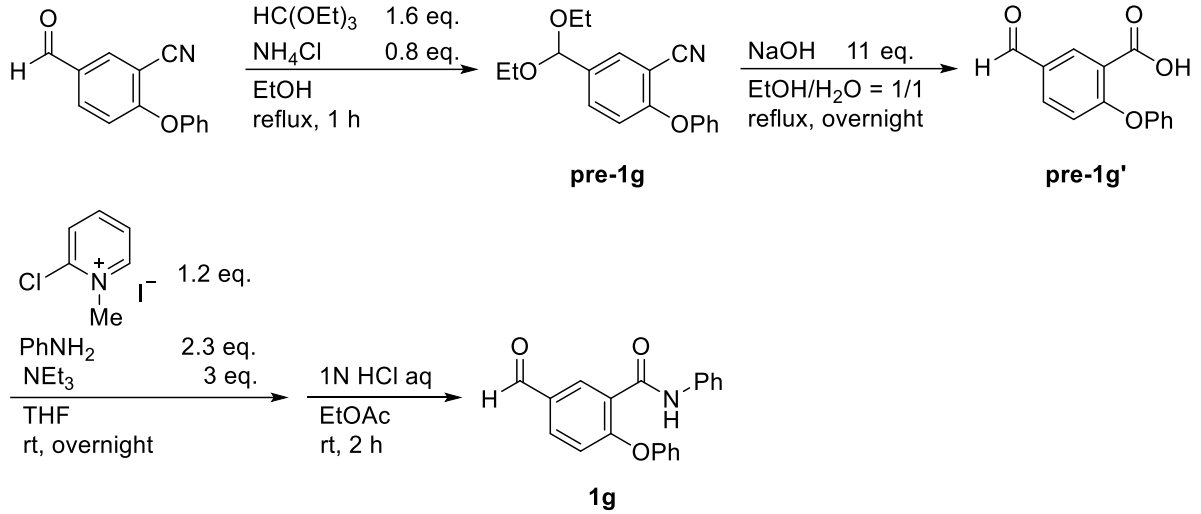


CuI (477 mg, 2.5 mmol), 2-pyridinecarboxylic acid (615 mg, 5.0 mmol) and K_3PO_4 (7.77 g, 36.6 mmol) were added to a round-bottom flask and the flask was purged with N_2. DMSO (60 mL) was added and the solution was heated at 50 °C for 10 min. PhI (5.04 g, 24.7 mmol) and 5-fluorosalicylaldehyde (5.27 g, 37.6 mmol) were added and the mixture were then stirred overnight at 110 °C under a N_2 atmosphere. After cooling the flask to room temperature, the resulting crude mixture was suspended in Et_2O (150 mL) and filtered through a Celite pad. The mixture was washed with 4N NaOH aq. (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 50/1 to 20/1, R_f = 0.20 in hexane/EtOAc = 20/1) to afford 5-fluoro-2-phenoxybenzaldehyde (**pre-1f**) in 26% yield (1.41 g, 6.52 mmol) as a pale yellow oil.

1f was prepared from **pre-1f** (1.34 g, 6.20 mmol) following general procedure C. The product was obtained in 47% yield (889 mg, 2.89 mmol) as a white solid by recrystallization from EtOAc.

Mp = 119.1-119.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.90 (dd, *J* = 9.0, 4.5 Hz, 1H), 7.08-7.16 (c, 4H), 7.20-7.24 (m, 1H), 7.30-7.34 (m, 2H), 7.40-7.44 (m, 2H), 7.58-7.60 (m, 2H), 8.04 (dd, *J* = 9.3, 3.3 Hz, 1H), 9.64 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 118.5 (d, *J* = 24.9 Hz), 118.9, 119.9 (d, *J* = 23.0 Hz), 120.4, 120.6 (d, *J* = 7.7 Hz), 124.6, 124.9, 126.0 (d, *J* = 6.7 Hz), 129.0, 130.4, 137.8, 150.9 (d, *J* = 2.9 Hz), 155.6, 158.7 (d, *J* = 242 Hz), 161.3. **^{19}F NMR** -118.2 (m). **IR** (ATR): 3375 w, 1670 m, 1197 s. **MS**: *m*/*z* (EI, relative intensity, %): 307 (27, M^+), 216 (16), 215 (100), 214 (22), 159 (11), 133 (14), 93 (11), 77 (12). **Anal.** Calcd for $C_{19}H_{14}FNO_2$: C, 74.26; H, 4.59; N, 4.56. Found: C, 74.37; H, 4.51; N, 4.56.

5-Formyl-2-phenoxy-*N*-phenylbenzamide (1g)



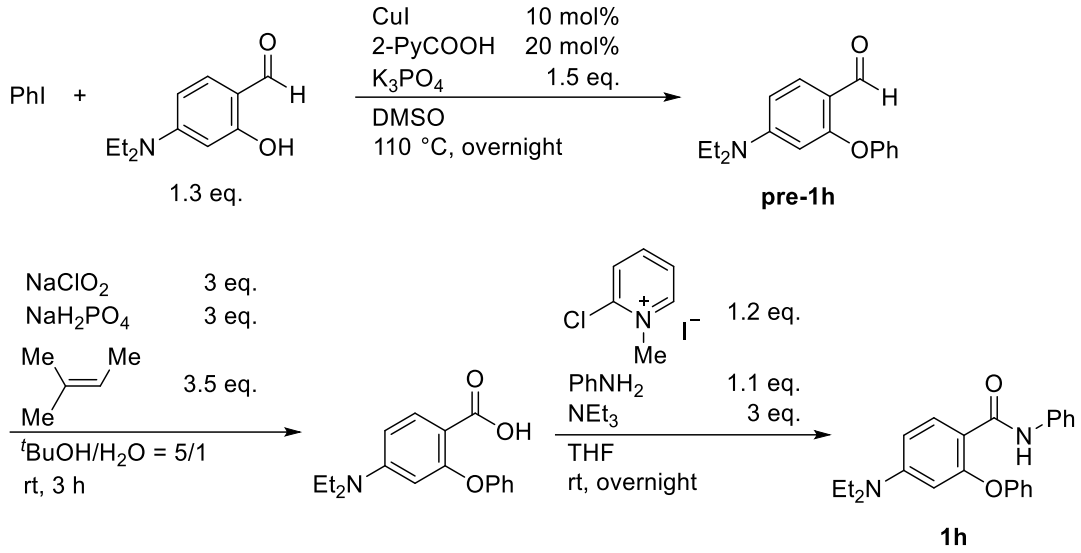
A solution of 5-formyl-2-phenoxybenzonitrile (3.15 g, 14.1 mmol)[16], triethyl orhoformate (3.41 g, 23.0 mmol) and NH_4Cl (641 mg, 12.0 mmol) in EtOH (60 mL) was stirred under reflux for 1 h. After cooling the flask to room temperature, the volatiles were removed under reduced pressure. After adding EtOAc (100 mL) and sat. $NaHCO_3$ aq (100 mL) to the mixture, the organic layer was isolated and dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 5/1, R_f = 0.37 in hexane/EtOAc = 5/1) to afford 5-(diethoxymethyl)-2-phenoxybenzonitrile (**pre-1g**) in 53% yield (2.21 g, 7.43 mmol) as a pale yellow oil..

A solution of **pre-1g** (3.94 g, 13.2 mmol) in EtOH (50 mL) and 3N NaOH aq (50 mL) was heated overnight under reflux. Et_2O (100 mL) and H_2O (100 mL) were added to the mixture and the aqueous layer was separated. The aqueous layer was acidified with 6N HCl aq and extracted with EtOAc (150 mL). The organic layer was dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The crude mixture that contained 5-formyl-2-phenoxybenzoic acid (**pre-1g'**) (1.93 g) was used in the subsequent step without further purification.

To a solution of **pre-1g'** (1.93 g, crude mixture), aniline (1.63 g, 17.5 mmol) and NEt_3 (2.26 g, 22.3 mmol) in THF (15 mL), 2-chloro-1-methylpyridinium iodide (2.31 g, 9.04 mmol) was added. After stirring the solution overnight at room temperature, the volatiles were removed under reduced pressure. 1N HCl aq (50 mL) and EtOAc (50 mL) were added and the resulting mixture was stirred at room temperature for 2 h. The organic layer was then separated and washed with 1N HCl aq. (50 mL) and sat. $NaHCO_3$ aq. (50 mL). The organic layer was dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by recrystallization from EtOAc to give **1g** in 35% yield (1.46 g, 4.60 mmol) from **pre-1g** as a pale yellow solid.

Mp = 130.8-131.2 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.93 (d, *J* = 8.6 Hz, 1H), 7.10-7.15 (m, 1H), 7.18-7.25 (m, 2H), 7.30-7.38 (c, 3H), 7.47-7.53 (m, 2H), 7.63-7.65 (m, 2H), 7.91 (dd, *J* = 8.6, 2.2 Hz, 1H), 8.80 (d, *J* = 2.2 Hz, 1H), 9.58 (br, 1H), 9.98 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 117.4, 120.4, 120.6, 123.7, 124.6, 126.2, 129.0, 130.6, 131.6, 132.2, 136.3, 137.7, 153.6, 160.2, 161.4, 190.2. **IR** (ATR): 3372 w, 1693 s, 1673 m. **MS**: *m/z* (EI, relative intensity, %): 317 (33, M^+), 226 (16), 225 (100), 224 (43), 197 (61), 141 (14), 115 (20), 93 (10), 77 (20). **Anal.** Calcd for $C_{20}H_{15}NO_3$: C, 75.70; H, 4.76; N, 4.41. Found: C, 75.63; H, 4.73; N, 4.47.

4-(Diethylamino)-2-phenoxy-*N*-phenylbenzamide (1h)

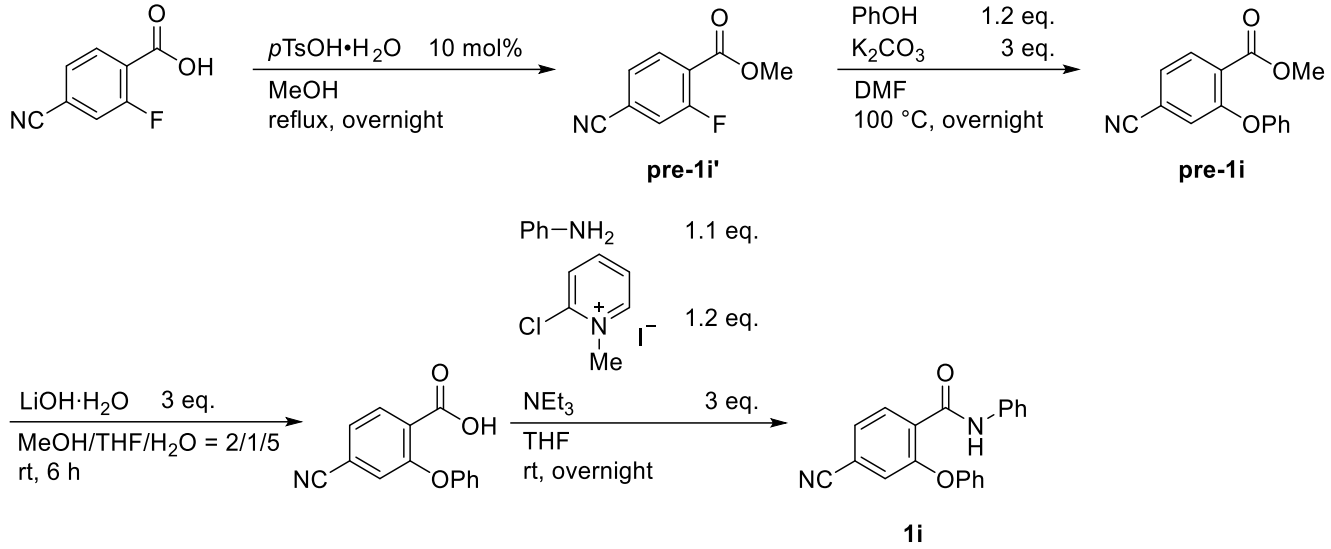


CuI (381 mg, 2.0 mmol), 2-pyridinecarboxylic acid (499 mg, 4.1 mmol) and K_3PO_4 (6.34 g, 29.9 mmol) were added to a round-bottom flask and the flask was then purged with N_2. DMSO (50 mL) was added and the resulting solution was heated at 50 °C for 10 min. PhI (4.01 g, 19.7 mmol) and 4-(diethylamino)salicylaldehyde (5.09 g, 26.3 mmol) were added and the mixture was stirred overnight at 110 °C under a N_2 atmosphere. After cooling the flask to room temperature, the resulting crude mixture was suspended in EtOAc (150 mL) and filtered through a Celite pad. The mixture was washed with sat. $NaHCO_3$ aq. (100 mL) and brine (100 mL). The organic layer was dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 20/1 to 5/1, R_f = 0.14 in hexane/EtOAc = 5/1). Et_2O (50 mL) and 4N NaOH aq. (50 mL) were then added to remove the remaining 4-(diethylamino)salicylaldehyde. The organic layer was dried over Na_2SO_4. After removing the volatiles under reduced pressure, 4-(diethylamino)-2-phenoxybenzaldehyde (**pre-1h**) was obtained in 76% yield (3.96 g, 14.3 mmol) as a yellow oil.

1h was prepared from **pre-1h** (3.79 g, 14.1 mmol) following general procedure C (H_2O was used for washing instead of 1N HCl aq). The product was obtained in 13% yield (667 mg, 1.85 mmol) as a white solid by flash column chromatography on silica gel (eluent: hexane/EtOAc = 10/1 to 5/1, R_f = 0.26 in hexane/EtOAc = 5/1) followed by recrystallization from EtOAc.

Mp = 93.6-94.1 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.09 (t, *J* = 7.1 Hz, 6H), 3.27 (q, *J* = 7.1 Hz, 4H), 6.01 (d, *J* = 2.5 Hz, 1H), 6.52 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.01-7.06 (m, 1H), 7.11-7.21 (c, 3H), 7.25-7.31 (m, 2H), 7.35-7.42 (m, 2H), 7.57-7.61 (m, 2H), 8.17 (d, *J* = 9.1 Hz, 1H), 9.51 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.4, 44.5, 100.7, 107.4, 110.7, 118.9, 120.0, 123.4, 124.3, 128.8, 130.1, 133.7, 138.8, 151.4, 155.7, 156.6, 163.2. **IR** (ATR): 3383 w, 1659 m. **MS**: *m*/*z* (EI, relative intensity, %): 360 (13, M^+), 269 (19), 268 (100), 224 (19). **Anal.** Calcd for $C_{23}H_{24}N_2O_2$: C, 76.64; H, 6.71; N, 7.77. Found: C, 76.58; H, 6.83; N, 7.73.

4-Cyano-2-phenoxy-*N*-phenylbenzamide (1i)

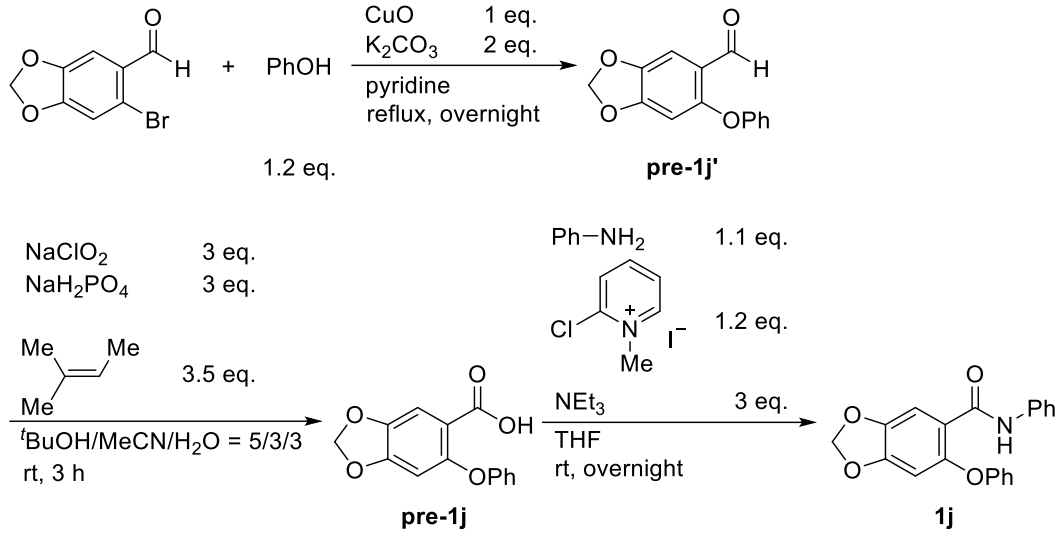


A solution of 4-cyano-2-fluorobenzoic acid (5.39 g, 32.6 mmol) and *p*-toluenesulfonic acid (619 mg, 3.3 mmol) in MeOH (65 mL) was stirred overnight under reflux. After cooling the flask to room temperature, the volatiles were removed under reduced pressure. After adding EtOAc (100 mL) and sat. $NaHCO_3$ aq (100 mL) to the mixture, the organic layer was isolated and dried over Na_2SO_4. After removing the volatiles under reduced pressure, methyl 4-cyano-2-fluorobenzoate (**pre-1i'**) was obtained in 88% yield (5.15 g, 28.7 mmol) as a white solid and used in the subsequent step without further purification.

Pre-1i' (5.15 g, 28.7 mmol) and K_2CO_3 (12.1 g, 87.5 mmol) were added to a 200 mL three-necked round-bottom flask and the flask was purged with N_2. DMF (90 mL) and phenol (3.39 g, 36.0 mmol) were added and the resulting mixture were then stirred overnight at 100 °C under a N_2 atmosphere. After cooling the flask to room temperature, EtOAc (150 mL) and H_2O (100 mL) were added and the organic layer was separated. The organic layer was washed with 1N NaOH aq. (50 mL) and brine (50 mL). The organic layer was dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The crude mixture that contained methyl 4-cyano-2-phenoxybenzoate (**pre-1i**) (6.75 g) was used in the subsequent step following general procedure B without further purification.The product **1i** was obtained by recrystallization from acetone in 15% yield (1.40 g, 4.45 mmol) from **pre-1i'** as a white solid.

Mp = 156.7-158.3 ºC. **^{1}H NMR** (DMSO-*d6*) δ: 7.07-7.13 (c, 3H), 7.18-7.22 (m, 1H), 7.30-7.35 (m, 2H), 7.38-7.45 (c, 3H), 7.64-7.69 (m, 2H), 7.74 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.82 (d, *J* = 7.8 Hz, 1H), 10.53 (br, 1H). **^{13}C NMR** (DMSO-*d6*) δ: 113.6, 117.7, 119.1, 119.6, 121.9, 123.9, 124.5, 127.4, 128.8, 130.2, 130.6, 133.6, 138.7, 153.9, 155.7, 163.1. **IR** (ATR): 3381 w, 2234 w, 1668 m. **MS**: *m/z* (EI, relative intensity, %): 314 (23, M^+), 223 (15), 222 (100), 221 (20), 77 (13). **Anal.** Calcd for $C_{20}H_{14}N_2O_2$: C, 76.42; H, 4.49; N, 8.91. Found: C, 76.18; H, 4.43; N, 8.73.

6-Phenoxy-*N*-phenylbenzo[*d*][1,3]dioxole-5-carboxamide (1j)



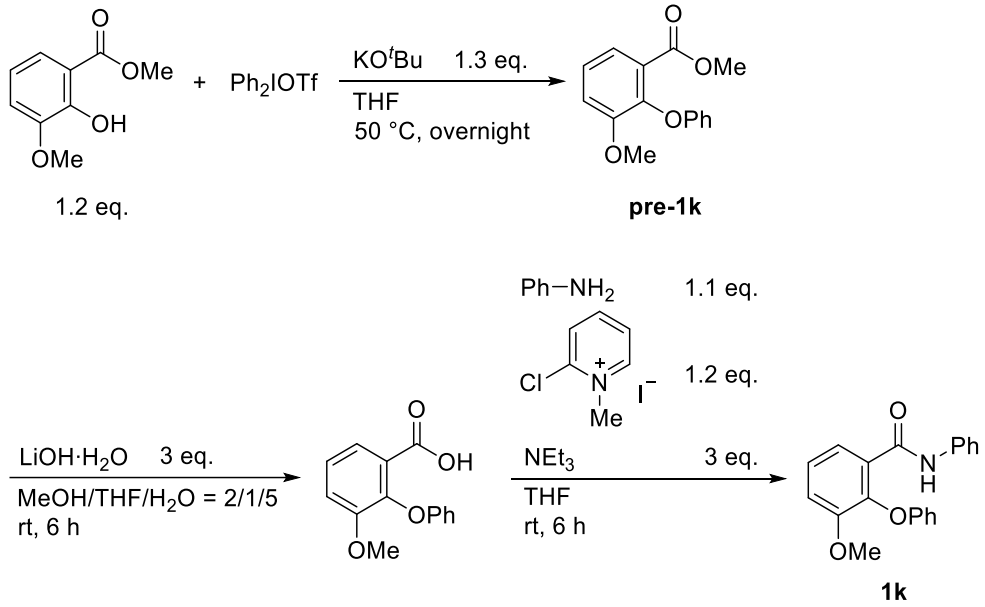
CuO (1.60 g, 20.1 mmol), K_2CO_3 (5.50 g, 39.8 mmol), 6-bromopiperonal (4.57 g, 20.0 mmol) and phenol (2.23 g, 23.7 mmol) were added to a 100 mL three-necked round-bottom flask and the flask was then purged with N_2. Pyridine (20 mL) was added and the mixture was then stirred under reflux overnight under a N_2 atmosphere. After cooling the flask to room temperature, the resulting crude mixture was suspended in toluene and filtered through a celite pad. After removing the volatiles under reduced pressure, EtOAc (100 mL) and 1N HCl aq. (100 mL) were added and the organic layer was separated. The organic layer was dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 5/1, R_f = 0.51 in hexane/EtOAc = 5/1). EtOAc (100 mL) and 1N NaOH aq. (100 mL) were then added to remove the remaining phenol. The organic layer was dried over Na_2SO_4. After removing the volatiles under reduced pressure, 6-phenoxybenzo[*d*][1,3]dioxole-5-carbaldehyde (**pre-1j'**) was obtained in 82% yield (3.97 g, 16.4 mmol) as a yellow solid.

To a solution of **pre-1j'** (3.97 g, 16.4 mmol) in ^{t}BuOH (50 mL), CH_3CN (30 mL) and H_2O (30 mL), NaH_2PO_4 (5.79 g, 48.2 mmol), 2-methyl-2-butene (3.97 g, 56.6 mmol) and $NaClO_2$ (4.36 g, 48.2 mmol) were added and the resulting mixture was stirred at room temparature for 3 h. After removing the volatiles under reduced pressure, 1N HCl aq. (50 mL) and EtOAc (100 mL) were added and the organic layer was dried over Na_2SO_4. After removing the volatiles in vacuo, the resulting crude material that contained 6-phenoxybenzo[*d*][1,3]dioxole-5-carboxylic acid (**pre-1j**) (4.59 g) was used for subsquent amidation reactions with aniline following general procedure A without further purification. .The product **1j** was obtained by recrystallization from EtOAc in 52% yield (2.84 g, 8.52 mmol) from **pre-1j'** as a white solid.

Mp = 174.0-174.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.01 (s, 2H), 6.42 (s, 1H), 7.04-7.10 (c, 3H), 7.16-7.21 (m, 1H), 7.27-7.32 (m, 2H), 7.36-7.42 (m, 2H), 7.53-7.57 (m, 2H), 7.75 (s, 1H), 9.55 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 100.8, 102.3, 110.1, 118.1, 118.6, 120.2, 124.1, 124.6, 128.9, 130.3, 138.2, 144.5, 150.7, 151.3, 155.9, 162.1. **IR** (ATR): 3346 w, 1658 m, 1205 s. **MS**: *m/z* (EI, relative intensity, %): 334 (23), 333 (36, M^+), 242 (15), 241 (100), 211 (10), 183 (19),

155 (20), 127 (14), 77 (16). **Anal.** Calcd for $C_{20}H_{15}NO_4$: C, 72.06; H, 4.54; N, 4.20. Found: C, 71.83; H, 4.52; N, 4.23.

3-Methoxy-2-phenoxy-*N*-phenylbenzamide (1k)

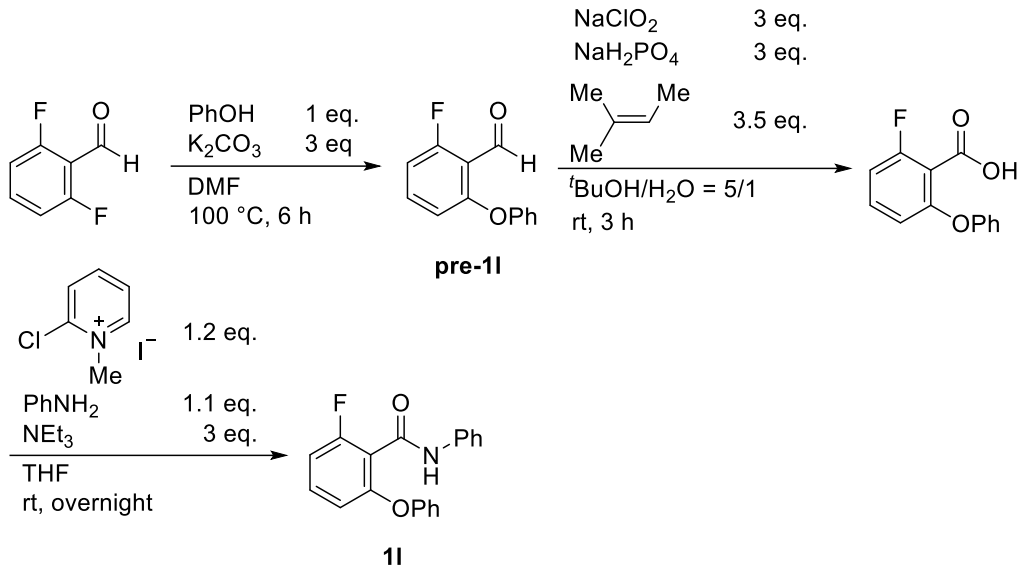


A 200 mL round-botom flask was charged with methyl 3-methoxysalicylate (4.92 g, 27.0 mmol) and THF (45 mL). KO^{t}Bu (3.35 g, 29.6 mmol) was added to the stirred solution at 0 °C. After stirring for 10 min at the same temperature, diphenyliodonium trifluoromethanesulfonate (9.98 g, 23.2 mmol) was added at the same temperature. The resulting mixture was stirred overnight at room temperature. After removing the volatiles under reduced pressure, Et_2O (100 mL) and H_2O (100 mL) were added and the organic layer was separated. The organic layer was dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 20/1 to 5/1, R_f = 0.29 in hexane/EtOAc = 5/1) to afford methyl 3-methoxy-2-phenoxybenzoate (**pre-1k**) in 41% yield (2.42 g, 9.60 mmol) as a pale yellow solid.

1k was prepared from **pre-1k** (2.42 g, 9.60 mmol) following general procedure B. The product was obtained in 26% yield (811 mg, 2.54 mmol) as a white solid after recrystallization from acetone.

Mp = 176.8-178.0 ºC. **^{1}H NMR** ($CDCl_3$) δ: 3.76 (s, 3H), 6.90-6.94 (m, 2H), 7.03-7.11 (c, 2H), 7.17 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.27-7.32 (c, 4H), 7.36 (t, *J* = 8.2 Hz, 1H), 7.49-7.52 (m, 2H), 7.87 (dd, *J* = 8.2, 1.5 Hz, 1H), 9.30 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 56.3, 114.9, 116.0, 120.1, 123.0, 123.3, 124.3, 126.2, 128.6, 128.9, 129.8, 138.0, 140.9, 152.4, 157.2, 162.4. **IR** (ATR): 3372 w, 1662 m, 1213 s. **MS**: *m*/*z* (EI, relative intensity, %): 319 (26, M^+), 228 (16), 227 (100), 212 (35), 184 (16). **HRMS (DART)** Calcd for $C_{20}H_{18}NO_3$ ($[M+H]^+$): 320.12812. Found: 320.12802.

2-Fluoro-6-phenoxy-*N*-phenylbenzamide (1l)

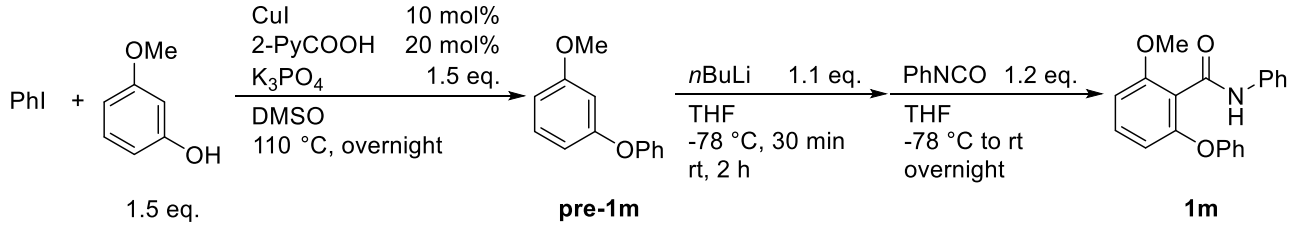


A three-necked flask was purged with N_2 and then charged with 2,6-difluorobenzaldehyde (5.09 g, 35.8 mmol), PhOH (3.49 g, 37.1 mmol), K_2CO_3 (14.7 g, 106 mmol) and DMF (70 mL). The resulting mixture were then stirred at 100 °C for 6 h under a N_2 atmosphere. After the flask was cooled to room temperature, EtOAc (100 mL) and H_2O (150 mL) were added and the organic layer was separated. The organic layer was washed with sat. $NaHCO_3$ aq. (100 mL) and was dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by bulb-to-bulb distillation (1.2 mmHg, 140-160 °C) to afford 2-fluoro-6-phenoxybenzaldehyde (**pre-1l**) in 59% yield (4.59 g, 21.2 mmol) as a yellow oil.

1l was prepared from **pre-1l** (4.59 g, 21.2 mmol) following general procedure C. The product was obtained by flash column chromatography on silica gel (eluent: hexane/EtOAc = 20/1 to 1/2, R_f = 0.14 in hexane/EtOAc = 5/1) followed by recrystallization from $CHCl_3$ in 49% yield (3.22 g, 10.5 mmol) as a white solid.

Mp = 166.5-167.9 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.70 (d, *J* = 8.5 Hz, 1H), 6.90 (t, *J* = 8.7 Hz, 1H), 7.05 (d, *J* = 7.8 Hz, 2H), 7.10-7.17 (c, 2H), 7.25-7.39 (c, 5H), 7.55 (d, *J* = 7.8 Hz, 2H), 7.84 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 111.0 (d, *J* = 22.0 Hz), 114.0 (d, *J* = 2.9 Hz), 117.3 (d, *J* = 18.2 Hz), 119.3, 120.1, 124.4, 124.7, 129.0, 130.0, 131.6 (d, *J* = 9.6 Hz), 137.6, 155.5 (d, *J* = 6.7 Hz), 156.0, 160.1, 160.7 (d, *J* = 251 Hz). **^{19}F NMR** -113.1 (dd, *J* = 9.0 Hz, 6.5 Hz). **IR** (ATR): 3289 w, 1658 m, 1234 s, 1207 m. **MS**: *m*/*z* (EI, relative intensity, %): 307 (10, M^+), 216 (14), 215 (100), 214 (48), 139 (41). **HRMS (DART)** Calcd for $C_{19}H_{15}NO_2F$ ($[M+H]^+$): 308.10813. Found: 308.10779.

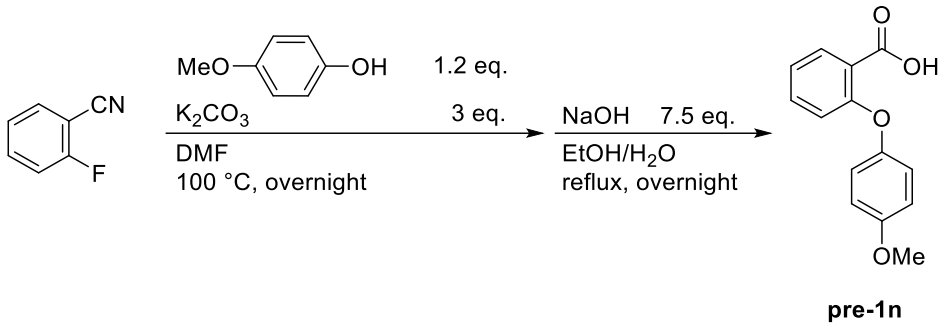
2-Methoxy-6-phenoxy-*N*-phenylbenzamide (1m)



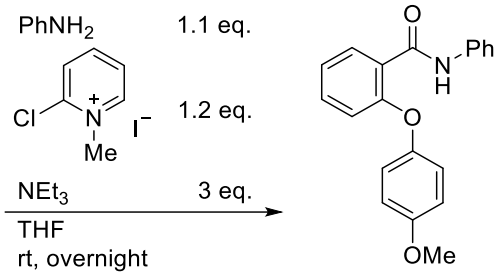
CuI (562 mg, 3.0 mmol), 2-pyridinecarboxylic acid (739 mg, 6.0 mmol) and K_3PO_4 (9.42 g, 44.3 mmol) were added to a 200 mL three-necked flask and the flask was purged with N_2. DMSO (75 mL) was added and the solution was heated at 50 °C for 10 min. PhI (6.02 g, 29.5 mmol) and 3-methoxyphenol (5.65 g, 45.5 mmol) were added and the mixture was then stirred overnight at 110 °C under a N_2 atmosphere. After cooling the flask to room temperature, the resulting crude mixture was suspended with Et_2O (150 mL) and filtered through a celite pad. The mixture was washed with 1N NaOH aq. (100 mL × 2). The organic layer was dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was dissolved in Et_2O and filtered through NH_2-modified silica gel pad to afford 1-methoxy-3-phenoxybenzene (**pre-1m**) in 90% yield (5.33 g, 26.6 mmol) as a colorless oil.
A 200 mL three-necked flask was flame-dried and purged with N_2 and charged with **pre-1m** (5.33 g, 26.6 mmol) and THF (45 mL). A 1.6 M solution of *n*BuLi (18 mL, 28.8 mmol) in hexane was slowly added to the stirred solution at -78 °C. After stirring for 30 min at the same temperature, the solution was warmed to room temperature and then stirred for 2 h. Phenyl isocyanate (3.87 g, 32.5 mmol) was added dropwise to the solution at -78 °C. After warming the solution to room temperature, the resulting mixture was stirred overnight. EtOAc (100 mL) and sat. NH_4Cl aq. (50 mL) were added and the aqueous layer was separated. The aqueous layer was extracted with EtOAc (100 mL) and the combined organic layers were dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by recrystallization from acetone to obtain **1m** in 45% yield (3.84 g, 12.0 mmol) as a white solid.

Mp = 158.4-158.6 ºC. **^{1}H NMR** ($CDCl_3$) δ: 3.87 (s, 3H), 6.53 (d, *J* = 8.2 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 2H), 7.06-7.11 (m, 2H), 7.25-7.31 (c, 5H), 7.51-7.60 (c, 3H). **^{13}C NMR** ($CDCl_3$) δ: 56.1, 106.2, 111.3, 118.8, 119.0, 119.8, 123.6, 124.2, 128.9, 129.7, 131.0, 138.0, 155.2, 156.8, 157.9, 162.7. **IR** (ATR): 1652 m, 1241 s. **MS**: *m*/*z* (EI, relative intensity, %): 319 (6, M^+), 228 (15), 227 (100), 226 (22), 213 (11), 212 (74). **Anal.** Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.14; H, 5.34; N, 4.38.

2-(4-Methoxyphenoxy)-*N*-phenylbenzamide (1n)



pre-1n

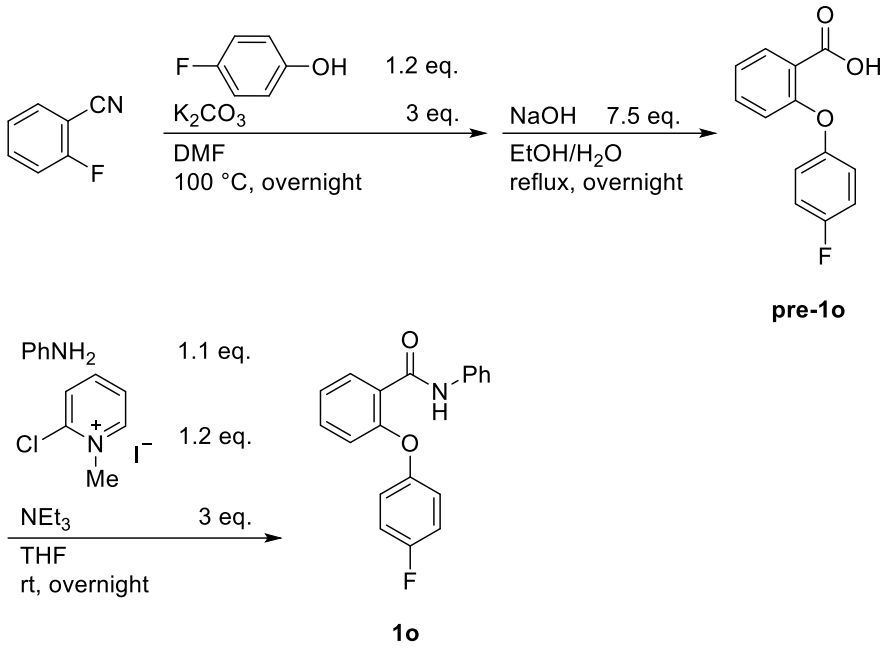


1n

2-(4-Methoxyphenoxy)benzoic acid (**pre-1n**) was prepared from 2-fluoro-benzonitrile (4.83 g, 39.9 mmol) according to the reported procedure[16] and was then used in a subsquent amidation following general procedure A without further purification. **1n** was obtained in 56% yield (7.12 g, 22.3 mmol) as a white solid by recrystallization from EtOAc.

Mp = 100.3-100.9 ºC. **^{1}H NMR** ($CDCl_3$) δ: 3.82 (s, 3H), 6.81 (dd, *J* = 8.3 Hz, 0.8 Hz, 1H), 6.92-6.98 (m, 2H), 7.06-7.13 (c, 3H), 7.18-7.22 (m, 1H), 7.30-7.35 (m, 2H), 7.36-7.40 (m, 1H), 7.64 (d, *J* = 8.0 Hz, 2H), 8.33 (dd, *J* = 7.8 Hz, 1.8 Hz, 1H), 9.77 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 55.5, 115.2, 117.0, 120.3, 121.1, 123.1 (two overlapping peaks), 124.1, 128.8, 132.2, 132.9, 138.1, 148.0, 156.3, 156.8, 162.7. **IR** (ATR): 3373 w, 1667 m, 1208 s. **MS**: *m*/*z* (EI, relative intensity, %): 319 (22, M^+), 228 (15), 227 (100), 196 (50), 184 (29). **Anal.** Calcd for $C_{20}H_{17}NO_3$: C, 75.22; H, 5.37; N, 4.39. Found: C, 75.39; H, 5.26; N, 4.39.

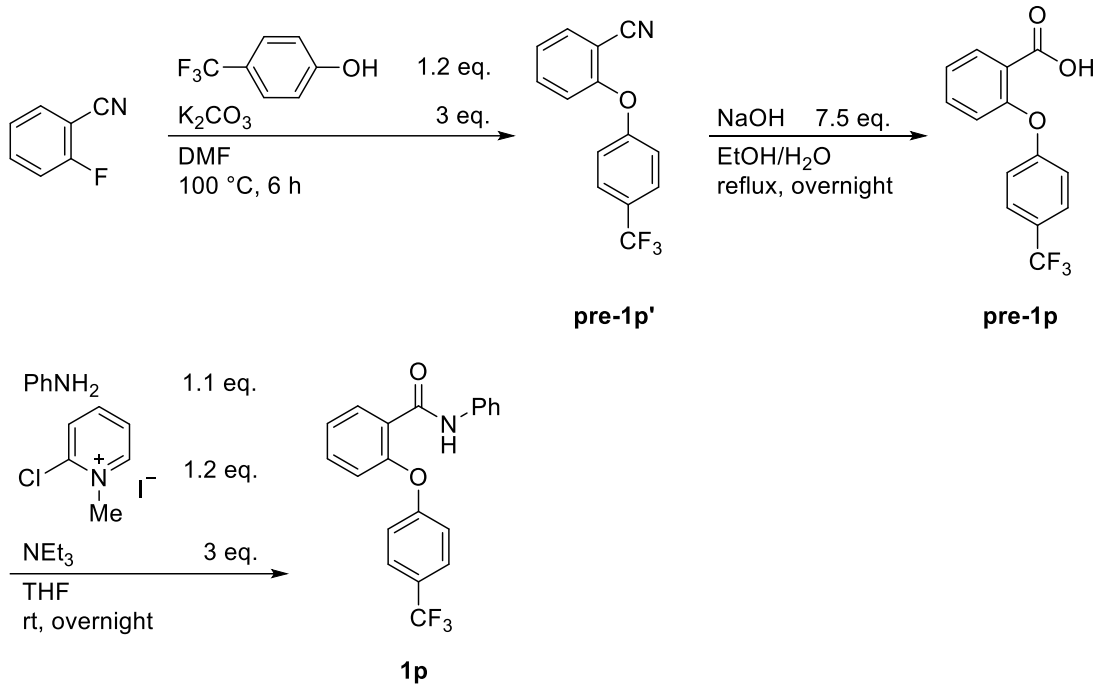
2-(4-Fluorophenoxy)-*N*-phenylbenzamide (1o)



2-(4-Fluorophenoxy)benzoic acid (**pre-1o**) was prepared from 2-fluoro-benzonitrile (4.86 g, 40.1 mmol) according to the reported procedure[16] and was then used in a subsquent amidation following general procedure A without further purification. **1o** was obtained in 49% yield (6.02 g, 19.6 mmol) as a white solid by recrystallization from EtOH.

Mp = 80.3-80.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.82 (dd, *J* = 8.2 Hz, 0.9 Hz, 1H), 7.06-7.13 (c, 5H), 7.22 (t, *J* = 7.6 Hz, 1H), 7.29-7.33 (m, 2H), 7.38-7.42 (m, 1H), 7.60-7.63 (m, 2H), 8.30 (dd, *J* = 7.6 Hz, 1.8 Hz, 1H), 9.54 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 116.9 (d, *J* = 23.9 Hz), 117.7, 120.3, 121.1 (d, *J* = 8.6 Hz), 123.85, 123.91, 124.3, 128.9, 132.4, 133.0, 138.0, 150.9 (d, *J* = 2.9 Hz), 155.4, 159.6 (d, *J* = 243 Hz), 162.5. **^{19}F NMR** -117.9 (m). **IR** (ATR): 3382 w, 1667 m, 1201 s. **MS**: *m*/*z* (EI, relative intensity, %): 307 (21, M^+), 216 (15), 215 (100), 196 (19), 133 (12). **Anal.** Calcd for $C_{19}H_{14}FNO_2$: C, 74.26; H, 4.59; N, 4.56. Found: C, 74.44; H, 4.57; N, 4.60.

***N*-Phenyl-2-(4-(trifluoromethyl)phenoxy)benzamide (1p)**



2-Fluoro-benzonitrile (6.06 g, 50.0 mmol) and K_2CO_3 (20.5 g, 149 mmol) were added to a 300 mL three-necked round-bottom flask and the flask was purged with N_2. DMF (125 mL) and 4-hydroxybenzotrifluoride (9.71 g, 59.9 mmol) were added and the resulting mixture were then stirred overnight at 100 °C under a N_2 atmosphere. After cooling the flask to room temperature, EtOAc (200 mL) and H_2O (150 mL) were added and the organic layer was separated. The organic layer was washed with 1N NaOH aq. (50 mL) and brine (100 mL). 1N HCl aq. (150 mL) was added to the combined aqueous layer and the aqueous layer was extracted with Et_2O (200 mL). The combined organic layer was dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 10/1, R_f = 0.34 in hexane/EtOAc = 10/1) followed by bulb-to-bulb distillation (2.8-3.0 mmHg, 150-170 °C) to afford 2-(4-(trifluoromethyl)phenoxy)benzonitrile (**pre-1p'**) in 35% yield (4.61 g, 17.6 mmol) as a colorless oil.

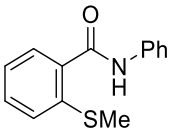
A solution of **pre-1p'** (4.61 g, 17.6 mmol) in EtOH (45 mL) and 3N NaOH aq (45 mL) was heated overnight under reflux. Et_2O (100 mL) and H_2O (100 mL) were added to the mixture and the aqueous layer was separated. The aqueous layer was acidified with 1N HCl aq and extracted with Et_2O (100 mL × 2). The organic layer was dried over Na_2SO_4 and the volatiles were removed under reduced pressure. The crude mixture was purified by flash column chromatography (eluent: hexane/EtOAc = 5/1 to 2/1, R_f = 0.43 in hexane/EtOAc = 2/1) to afford the mixture that contained 2-(4-(trifluoromethyl)phenoxy)benzoic acid (**pre-1p**) and some impurities (3.81 g).

1p was prepared from **pre-1p** (3.81 g, mixture with some impurites) with aniline (2.08 g, 22.3 mmol) following general procedure A. The product was obtained in 30% yield (1.87 g, 5.23 mmol) from **pre-1p'** as a white solid after recrystallization from Et_2O.

Mp = 102.6-103.6 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.97 (d, *J* = 8.0 Hz, 1H), 7.09-7.13 (m, 1H), 7.17 (d, *J* = 8.6 Hz, 2H), 7.30-7.36 (c, *3*H), 7.47-7.51 (m, 1H), 7.57 (d, *J* = 7.8 Hz, 2H), 7.65 (d, *J* = 8.6 Hz, 2H), 8.30 (dd, *J* = 7.9 Hz, 1.8 Hz,

1H), 9.21 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 118.6, 119.7, 120.3, 123.8 (q, J = 271 Hz), 124.5, 125.2, 125.4, 126.7 (q, J = 32.6 Hz), 127.7 (q, J = 3.6 Hz), 129.0, 132.6, 133.3, 137.8, 153.5, 158.6, 162.3. **^{19}F NMR** -62.5 (s). **IR** (ATR): 3392 w, 1664 m, 1321 s. **MS**: *m*/*z* (EI, relative intensity, %): 357 (24, M^+), 266 (20), 265 (100), 245 (11). **Anal.** Calcd for $C_{20}H_{14}F_3NO_2$: C, 67.23; H, 3.95; N, 3.92. Found: C, 67.24; H, 3.88; N, 3.87.

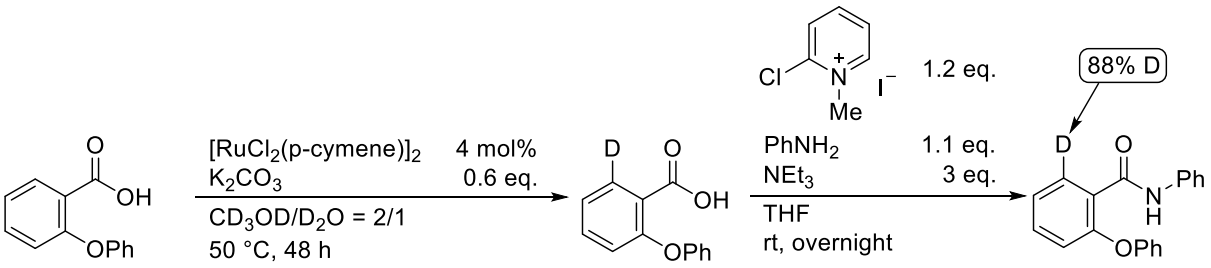
2-(Methylthio)-*N*-phenylbenzamide (1q) [CAS: 23343-16-0]



1q was prepared from 2-(methylthio)benzoic acid (2.53 g, 15.0 mmol) and aniline (1.49 g, 16.0 mmol) following general procedure A. The product was obtained in 48% yield (1.74 g, 7.15 mmol) as a white solid by recrystallization from EtOAc.

Mp = 149.1-150.3 ºC. **^{1}H NMR** ($CDCl_3$) δ: 2.48 (s, 3H), 7.12-7.17 (m, 1H), 7.23-7.28 (m, 1H), 7.33-7.39 (c, 3H), 7.40-7.44 (m, 1H), 7.65 (d, J = 7.8 Hz, 2H), 7.71 (d, J = 6.9 Hz, 1H), 8.34 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 17.0, 120.0, 124.5, 125.7, 128.0, 129.0, 129.1, 131.0, 135.1, 136.6, 137.9, 165.9. **IR** (ATR): 3289 w, 1650 s. **MS**: *m*/*z* (EI, relative intensity, %): 243 (4, M^+), 151 (100), 93 (76). **Anal.** Calcd for $C_{14}H_{13}NOS$: C, 69.11; H, 5.39; N, 5.76. Found: C, 68.98; H, 5.45; N, 5.75.

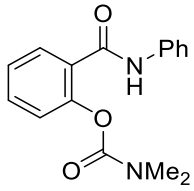
2-Phenoxy-*N*-phenylbenzamide-6-*d* (1a-*d*)



2-Phenoxybenzoic-6-*d* acid (**pre-1a-*d***) was synthesized according to Ma's procedure.[17] $[RuCl_2(p\text{-cymene})]_2$ (241 mg, 0.39 mmol), K_2CO_3 (662 mg, 6.0 mmol) and 2-phenoxybenzoic acid (2.14 g, 10.0 mmol) were added to a 25 mL schlenk tube and the tube was then purged with N_2. After adding CD_3OD (4 mL) and D_2O (2 mL) to the flask, the resulting mixture was stirred for 48 h at 50 °C under a N_2 atmosphere. After cooling the flask to room temperature, the volatiles were removed under reduced pressure. EtOAc (50 mL) and 1N HCl aq. (50 mL) were added and the aqueous layer was separated. The aqueous layer was extracted with EtOAc (50 mL) and the combined organic layer was dried over Na_2SO_4 and the solvent removed under a vaccum. These operations were repeated twice to give the crude mixture that contained **pre-1a-*d*** was obtained, which was used in a subsequent amidation with aniline following general procedure A without further purification. **1a-*d*** was obtained by flash column chromatography on silica gel (eluent: hexane/EtOAc = 5/1, R_f = 0.34 in hexane/EtOAc = 5/1) followed by recrystallization from EtOH in 59% yield (1.68 g, 5.9 mmol) as a white solid.

^{1}H NMR ($CDCl_3$) δ: 6.88 (dd, *J* = 8.2 Hz, 1.1 Hz, 1H), 7.07-7.16 (c, 3H), 7.19-7.26 (c, 2H), 7.28-7.34 (m, 2H), 7.38-7.44 (m, 3H), 7.59-7.64 (m, 2H), 8.33 (dd, *J* = 7.9 Hz, 1.7 Hz, 0.1H), 9.63 (br, 1H). **^{2}H NMR** ($CHCl_3$) δ: 8.40. **^{13}C NMR** ($CDCl_3$) δ: 118.3 (1C), 119.4 (2C), 120.3 (2C), 123.8 (0.83C), 123.9 (0.15C), 123.97 (0.88C), 124.04 (0.13C), 124.2 (1C), 124.9 (1C), 128.9 (2C), 130.2 (2C), ((132.1 (t, *J* = 25.4 Hz) and 132.37), 1C), 133.0 (1C), 138.1 (1C), 155.1 (1C), 155.2 (1C), 162.6 (1C). **HRMS (DART)** Calcd for $C_{19}H_{15}NO_2D$ ($[M+H]^+$): 291.12383. Found: 291.12411.

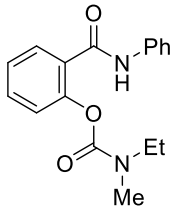
2-(Phenylcarbamoyl)phenyl dimethylcarbamate (5a) [CAS: 35410-18-5][18]



5a was prepared from salicylanilide (2.13 g, 10.0 mmol) and dimethylcarbamoyl chloride (1.62 g, 15.0 mmol) following general procedure D. The product was obtained in 97% yield (2.76 g, 9.71 mmol) as a white solid by recrystallization from hexane/EtOAc.

^{1}H NMR ($CDCl_3$) δ: 3.02 (s, 3H), 3.10 (s, 3H), 7.11-7.17 (c, 2H), 7.31-7.39 (c, 3H), 7.46-7.51 (m, 1H), 7.62 (d, *J* = 7.7 Hz, 2H), 7.78 (dd, *J* = 7.7, 1.6 Hz, 1H), 8.59 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 36.7, 36.9, 119.5, 123.3, 124.3, 126.3, 129.0, 130.0, 130.5, 131.8, 138.1, 148.0, 155.3, 164.2. **MS**: *m/z* (EI, relative intensity, %): 284 (2, M^+), 195 (11), 192 (77), 72 (100). **Anal.** Calcd for $C_{16}H_{16}N_2O_3$: C, 67.59; H, 5.67; N, 9.85. Found: C, 67.56; H, 5.71; N, 9.75.

2-(Phenylcarbamoyl)phenyl ethyl(methyl)carbamate (5b)

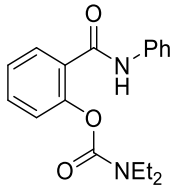


5b was prepared from salicylanilide (2.13 g, 10.0 mmol) and *N*-ethyl-*N*-methylcarbamoyl chloride (1.82 g, 15.0 mmol) following general procedure D. The product was obtained in 93% yield (2.76 g, 9.25 mmol) as a white solid by flash column chromatography on silica gel (eluent: hexane/EtOAc = 50/1 to 5/1, R_f = 0.63 in hexane/EtOAc = 1/1) followed by recrystallization from hexane/EtOAc.

Mp = 96.8-97.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.07-1.16 (t × 2, *J* = 7.2 Hz, 3H), 2.97-3.06 (s × 2, 3H), 3.36-3.47 (q × 2, *J* = 7.2 Hz, 2H), 7.10-7.14 (c, 2H), 7.29-7.36 (c, 3H), 7.44-7.49 (m, 1H), 7.59-7.63 (c, 2H), 7.71-7.78 (m, 1H), 8.58-8.63 (br × 2, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.3, 13.0, 34.0, 34.3, 44.3, 119.4, 119.5, 123.17, 123.23, 124.2, 126.2, 126.3, 129.0, 129.86, 129.94, 130.5, 130.8, 131.66, 131.70, 138.1, 147.9, 148.0, 154.8, 155.1, 164.26, 164.33. **IR** (ATR):

3309 w, 1710 s, 1676 s, 1208 s, 1158 s. **MS**: *m/z* (EI, relative intensity, %): 298 (2, M^+), 207 (11), 206 (88), 195 (13), 86 (100), 58 (56). **Anal.** Calcd for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.38; H, 6.08; N, 9.32.

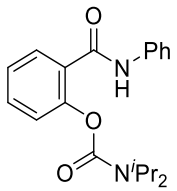
2-(Phenylcarbamoyl)phenyl diethylcarbamate (5c) [CAS: 1924681-17-3]



5c was prepared from salicylanilide (4.29 g, 20.1 mmol) and diethylcarbamoyl chloride (4.05 g, 29.9 mmol) following general procedure D. The product was obtained in 61% yield (3.85 g, 12.3 mmol) as a white solid by flash column chromatography on silica gel (eluent: hexane/EtOAc = 5/1 to 2/1, R_f = 0.11 in hexane/EtOAc = 5/1) followed by recrystallization from Et_2O.

Mp = 83.1-84.2 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.13 (t, *J* = 7.2 Hz, 3H), 1.17 (t, *J* = 7.2 Hz, 3H), 3.37 (q, *J* = 7.2 Hz, 2H), 3.42 (q, *J* = 7.2 Hz, 2H), 7.09-7.14 (c, 2H), 7.31-7.37 (c, 3H), 7.48 (td, *J* = 7.8 Hz, 1.6 Hz, 1H), 7.59-7.63 (m, 2H), 7.74 (td, *J* = 7.8 Hz, 1.6 Hz, 1H), 8.58 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 13.2, 14.0, 42.1, 42.4, 119.5, 123.2, 124.2, 126.3, 129.0, 129.9, 131.0, 131.7, 138.1, 147.9, 154.9, 164.4. **IR** (ATR): 3277 w, 3246 w, 1716 s, 1649 s, 1203 s, 1149 s. **MS**: *m/z* (EI, relative intensity, %): 312 (1, M^+), 220 (57), 100 (100), 72 (47). **HRMS (DART)** Calcd for $C_{18}H_{21}N_2O_3$ ($[M+H]^+$): 313.15467. Found: 313.15532.

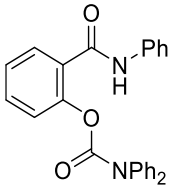
2-(Phenylcarbamoyl)phenyl diisopropylcarbamate (5d)



5d was prepared from salicylanilide (2.30 g, 10.8 mmol) and diisopropylcarbamoyl chloride (2.52 g, 15.4mmol) following general procedure D. The product was obtained in 67% yield (2.47 g, 7.26 mmol) as a white solid by recrystallization from hexane/EtOAc.

Mp = 121.8-122.0 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.19 (d, *J* = 6.8 Hz, 6H), 1.27 (d, *J* = 6.8 Hz, 6H), 3.89-3.95 (m, 1H), 4.06-4.15 (m, 1H), 7.08-7.13 (c, 2H), 7.30-7.36 (c, 3H), 7.46-7.50 (m, 1H), 7.58-7.63 (m, 2H), 7.74 (dd, *J* = 7.7 Hz, 1.6 Hz, 1H), 8.59 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 20.3, 21.3, 46.5, 47.3, 119.5, 123.2, 124.2, 126.3, 128.9, 129.9, 131.3, 131.7, 138.1, 147.8, 154.6, 164.6. **IR** (ATR): 3315 w, 1714 s, 1682 s, 1200 s, 1152 m. **MS**: *m/z* (EI, relative intensity, %): 340 (2, M^+), 248 (22), 128 (99), 121 (30), 93 (61), 86 (100). **Anal.** Calcd for $C_{20}H_{24}N_2O_3$: C, 70.57; H, 7.11; N, 8.23. Found: C, 70.25; H, 7.16; N, 8.23.

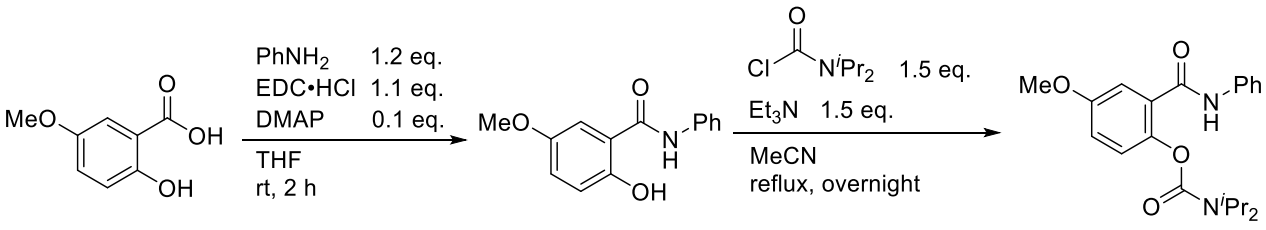
2-(phenylcarbamoyl)phenyl diphenylcarbamate (5e) [CAS: 1621339-73-8][19]



5e was prepared from salicylanilide (2.13 g, 10.0 mmol) and diphenylcarbamoyl chloride (2.30 g, 9.9 mmol) following general procedure D. The product was obtained in 84% yield (3.42 g, 8.37 mmol) as a white solid by flash column chromatography on silica gel (eluent: hexane/EtOAc = 50/1 to 3/1, R_f = 0.64 in hexane/EtOAc = 1/1).

^{1}H NMR ($CDCl_3$) δ: 7.14 (t, *J* = 7.3 Hz, 1H), 7.21-7.37 (c, 14H), 7.42-7.52 (c, 3H), 7.82 (d, *J* = 7.7 Hz, 1H), 8.08 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 120.2, 123.0, 124.5, 126.2, 126.9, 128.8, 129.1, 130.0, 130.1, 131.8, 137.7, 141.6, 147.8, 152.8, 163.8. **MS**: *m/z* (EI, relative intensity, %): 408 (2, M^+), 317 (10), 316 (45), 197 (15), 196 (100), 169 (48), 168 (45), 167 (23), 93 (11), 77 (24). **HRMS (DART)** Calcd for $C_{26}H_{21}N_2O_3$ ($[M+H]^+$): 409.15467. Found: 409.15563.

4-Methoxy-2-(phenylcarbamoyl)phenyl diisopropylcarbamate (5f)



pre-5f **5f**

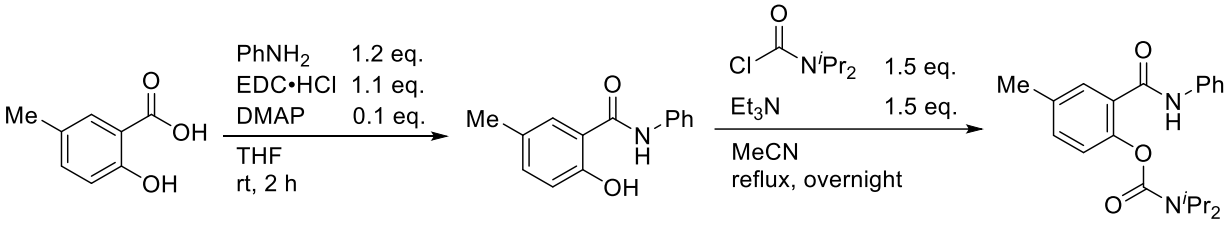
A mixture of 5-methoxysalicylic acid (2.52 g, 15.0 mmol), aniline (1.68 g, 18.0 mmol), EDC•HCl (3.16 g, 16.5 mmol), DMAP (0.18 g, 1.5 mmol) and THF (50 mL) were stirred at room temperature for 2 h. After the reaction, sat. $NaHCO_3$ aq. and EtOAc were added and the organic layer was separated. The organic layer was washed with 1N HCl aq. and dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 50/1 to 10/1, R_f = 0.60 in hexane/EtOAc = 1/1) to afford the mixture that contained 2-hydroxy-5-methoxy-*N*-phenylbenzamide (**pre-5f**) and some impurities (2.15 g).

5f was prepared fr om **pre-5f** (2.15 g, mixture with some impurities) and diisopropylcarbamoyl chloride (2.16 g, 13.2 mmol) following general procedure D. The product was obtained in 15% yield (829 mg, 2.24 mmol) from 5-methoxysalicylic acid as a white solid after flash column chromatography on silica gel (eluent: hexane/EtOAc = 20/1 to 10/1, R_f = 0.54 in hexane/EtOAc = 1/1) followed by recrystallization from hexane/EtOAc.

Mp = 119.3-120.1 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.19 (d, *J* = 6.8 Hz, 6H), 1.25 (d, *J* = 6.8 Hz, 6H), 3.83 (s, 3H), 3.86-3.94 (m, 1H), 4.06-4.17 (m, 1H), 7.00 (d, *J* = 1.6 Hz, 2H), 7.08-7.13 (m, 1H), 7.23 (t, *J* = 1.6 Hz, 1H), 7.30-7.34 (m, 2H), 7.58-7.62 (m, 2H), 8.70 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 20.3, 21.3, 46.4, 47.3, 55.8, 113.5, 118.2, 119.5, 124.17,

124.22, 128.9, 131.8, 138.0, 141.1, 155.1, 157.4, 164.4. **IR** (ATR): 3317 w, 1717 s, 1680 s, 1198 s. **MS**: *m/z* (EI, relative intensity, %): 370 (2, M^+), 243 (11), 225 (11), 151 (16), 150 (28), 128 (100), 93 (50), 86 (98). **HRMS (DART)** Calcd for $C_{21}H_{27}N_2O_4$ ([M+H]$^+$): 371.19653. Found: 371.19733.

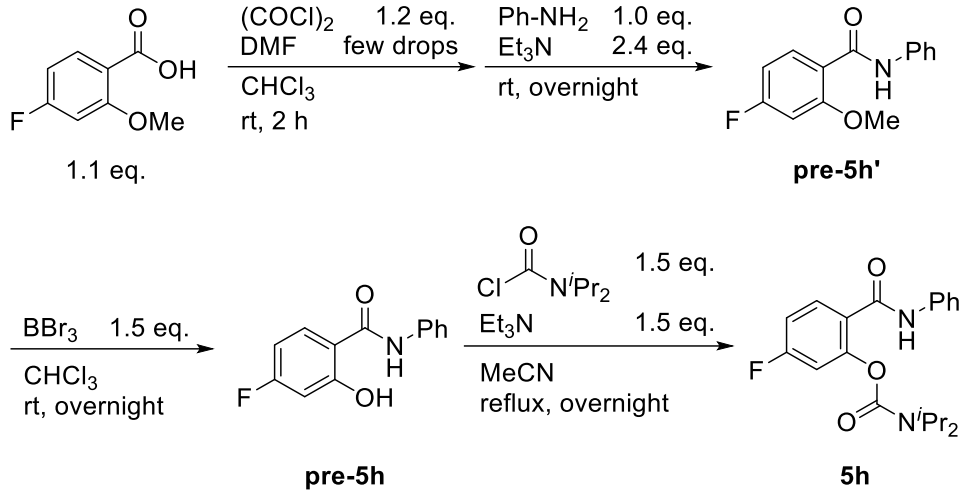
4-Methyl-2-(phenylcarbamoyl)phenyl diisopropylcarbamate (5g)



A mixture of 5-methylsalicylic acid (2.28 g, 15.0 mmol), aniline (1.68 g, 18.0 mmol), EDC•HCl (3.16 g, 16.5 mmol), DMAP (0.18 g, 1.5 mmol) and THF (50 mL) were stirred at room temperature for 2 h. After the reaction, sat. $NaHCO_3$ aq. and EtOAc were added and the organic layer was separated. The organic layer was washed with 1N HCl aq. and dried over Na_2SO_4. After the volatiles were removed under reduced pressure, the crude mixture that contained 2-hydroxy-5-methyl-*N*-phenylbenzamide (**pre-5g**) was obtained, which was used in the subsequent step without further purification according to general procedure D. **5g** was obtained by flash column chromatography on silica gel (eluent: hexane/EtOAc = 15/1 to 10/1, R_f = 0.69 in hexane/EtOAc = 1/1) in 11% yield (562 mg, 1.59 mmol). Further purification by recrystallization from hexane/EtOAc afforded the title compound as a white solid.

Mp = 137.5-140.5 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.18 (d, *J* = 6.8 Hz, 6H), 1.25 (d, *J* = 6.8 Hz, 6H), 2.38 (s, 3H), 3.82-3.95 (m, 1H), 4.05-4.15 (m, 1H), 6.97 (d, *J* = 8.2 Hz, 1H), 7.07-7.12 (m, 1H), 7.25-7.27 (m, 1H), 7.30-7.34 (m, 2H), 7.53 (d, *J* = 1.8 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 2H), 8.63 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 20.3, 20.7, 21.3, 46.4, 47.3, 119.5, 122.9, 124.1, 128.9, 130.2, 130.9, 132.3, 136.1, 138.1, 145.5, 154.9, 164.8. **IR** (ATR): 3315 w, 1713 m, 1679 s, 1200 s. **MS**: *m/z* (EI, relative intensity, %): 262 (2, M^+-92(NHPh)), 135 (34), 128 (100), 93 (67), 86 (88), 81 (15), 69 (12). **HRMS (DART)** Calcd for $C_{21}H_{27}N_2O_3$ ([M+H]$^+$): 355.20162. Found: 355.20236.

5-Fluoro-2-(phenylcarbamoyl)phenyl diisopropylcarbamate (5h)

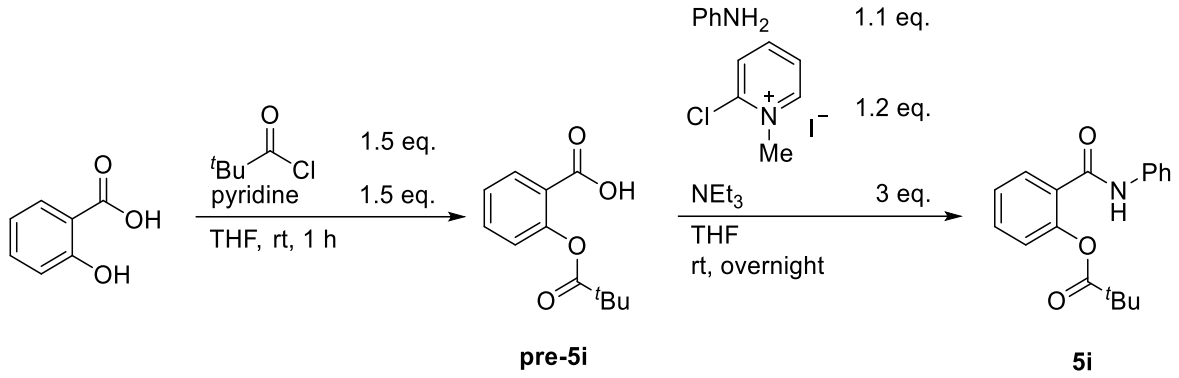


To a stirred solution of 4-fluoro-2-methoxybenzoic acid (2.73 g, 16.0 mmol) and DMF (5 drops) in $CHCl_3$ (20 mL), $(COCl)_2$ (1.5 mL, 17.5 mmol) was added dropwise. The solution was stirred at room temperature for 2 h. The solvent was then removed under reduced pressure, and the resulting residue was dissolved in $CHCl_3$. After cooling the reaction mixture to 0 °C, a solution of aniline (1.38 g, 14.8 mmol) and triethylamine (5.0 mL, 35.9 mmol) in $CHCl_3$ was added dropwise. The resulting mixture was allowed to warm to room temperature and stirred overnight. The solution containing the crude product was washed with saturated aqueous $NaHCO_3$ and $CHCl_3$. The combined organic layer was washed with 1N HCl aq. The organic phase was dried over Na_2SO_4 and the solvent was removed under vaccum. The resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 50/1 to 10/1, R_f = 0.34 in hexane/EtOAc = 5/1) to afford the mixture that contained 4-fluoro-2-methoxy-*N*-phenylbenzamide (**pre-5h'**) and some impurities (3.75 g).

A mixture of **pre-5h'** (3.75 g, mixture with some impurities), 1.0 M solution of BBr_3 (23 mL, 23 mmol) in DCM and $CHCl_3$ (30 mL) were stirred at rt overnight. After the reaction, MeOH were added. After the volatile was removed under reduced pressure, the crude mixture that cotained 4-fluoro-2-hydroxy-*N*-phenylbenzamide (**pre-5h**) was obtained, which was used in the subsequent step according to general procedure D without further purification. **5h** was obtained by flash column chromatography on silica gel (eluent: hexane/EtOAc = 10/1 to 7/1, R_f = 0.40 in hexane/EtOAc = 3/1) in 50% yield (2.65 g, 7.39 mmol) from aniline. Further purification by recrystallization from hexane/EtOAc afforded the title compound as a white solid.

Mp = 135.3-136.0 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.20 (d, *J* = 6.8 Hz, 6H), 1.26 (d, *J* = 6.8 Hz, 6H), 3.91-3.97 (m, 1H), 4.03-4.09 (m, 1H), 6.85 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.02-7.07 (m, 1H), 7.09-7.13 (m, 1H), 7.30-7.34 (m, 2H), 7.57-7.59 (m, 2H), 7.75 (dd, *J* = 8.6 Hz, 6.3 Hz, 1H), 8.50 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 20.2, 21.3, 46.7, 47.4, 110.9 (d, *J* = 24.1 Hz), 113.6 (d, *J* = 21.2 Hz), 119.6, 124.4, 127.5 (d, *J* = 2.9 Hz), 129.0, 131.5 (d, *J* = 9.6 Hz), 137.9, 149.1 (d, *J* = 11.6 Hz), 153.9, 163.7, 163.9 (d, *J* = 252 Hz). **^{19}F NMR** ($CDCl_3$) δ: -107.7 (dd, *J* = 15.0, 7.5 Hz). **IR** (ATR): 3312 w, 1739 m, 1692 s, 1321 s. **MS**: *m/z* (EI, relative intensity, %): 358 (1, M^+), 266 (13), 139 (20), 128 (91), 93 (37), 86 (100). **HRMS (DART)** Calcd for $C_{20}H_{24}N_2O_3F$ ($[M+H]^+$): 359.17655. Found: 359.17658.

2-(Phenylcarbamoyl)phenyl pivalate (5i)



To a solution of salicylic acid (3.48 g, 25.2 mmol) and pyridine (2.38 g, 30.1 mmol) in THF (25 mL), pivaloyl chloride (3.6 mL, 29.6 mmol) was added dropwise. The solution was stirred at room temperature for 1 h. After removing the volatiles under reduced pressure, EtOAc (100 mL) and 1N HCl aq. were added and the organic layer was separated. The organic layer was dried over Na_2SO_4 and the solvent was removed under vaccum. The crude mixture that contained 2-(pivaloyloxy)benzoic acid (**pre-5i**) (5.69 g) was used in the subsequent step according to general procedure A without further purification. **5i** was obtained in 34% yield (2.58 g, 8.68 mmol) as a white solid by recrystallization from EtOAc.

Mp = 163.6-164.2 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.31 (s, 9H), 7.07 (dd, *J* = 8.1 Hz, 0.8 Hz, 1H), 7.12-7.16 (m, 1H), 7.33-7.37 (c, 3H), 7.48-7.52 (m, 1H), 7.59 (d, *J* = 7.8 Hz, 2H), 7.79 (d, *J* = 7.7 Hz, 1.3 Hz, 1H), 7.89 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 27.0, 39.2, 119.7, 123.0, 124.5, 126.4, 129.1, 129.7, 129.8, 131.8, 137.7, 147.8, 163.8, 177.5. **IR** (ATR): 3307 w, 1750 m, 1659 m, 1109 s. **MS**: *m/z* (EI, relative intensity, %): 297 (9, M^+), 213 (11), 205 (37), 121 (36), 93 (100), 57 (50). **Anal.** Calcd for $C_{18}H_{19}NO_3$: C, 72.71; H, 6.44; N, 4.71. Found: C, 72.71; H, 6.44; N, 4.68.

2.4.3 Typical Procedure

Typical Procedure A: The reaction from biaryl ether, thioether and nitrile.

To an oven-dried 10 mL screw-capped vial in a glove box, $Ni(cod)_2$ (11 mg, 0.04 mmol), LiO^tBu (32 mg, 0.4 mmol), the amide (0.4 mmol), the alkyne (if solid) (0.6 mmol), DMSO (1 mL) or the alkyne (0.6 mmol), if a liquid, was added last in sequential order. The mixture was stirred at 40 °C for 5 h followed by cooling. The resulting mixture was filtered through a silica gel pad eluting with EtOAc and the filtrate was washed with 1N HCl aq, which was dried over Na_2SO_4. The crude mixture was concentrated under reduced pressure and analyzed by ^{1}H NMR using 1,1,1,2-tetrachloroethane as an internal standard. The resulting mixture was purified by flash column chromatography on silica gel.

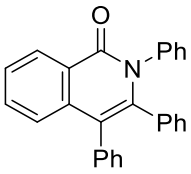
Typical Procedure B: The reaction from the carbamates and the pivalate.

To an oven-dried 10 mL screw-capped vial in a glove box, $Ni(cod)_2$ (11 mg, 0.04 mmol), KO^tBu (44 mg, 0.4 mmol), the amide (0.4 mmol), the alkyne (if solid) (0.6 mmol), toluene (1 mL) or the alkyne (0.6 mmol), if a liquid, was added last in sequential order. The mixture was stirred at 0 °C for 5 h followed by cooling. The resulting mixture was filtered through a silica gel pad eluting with EtOAc and the filtrate was washed with 1N HCl aq, which was dried

over Na_2SO_4. The crude mixture was concentrated under reduced pressure and analyzed by ^1H NMR using 1,1,2,2-tetrachloroethane as an internal standard. The resulting mixture was purified by flash column chromatography on silica gel.

2.4.4 Characterization of Products

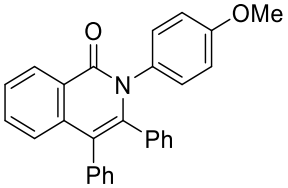
2,3,4-triphenylisoquinolin-1(2*H*)-one (3aa) [CAS: 14959-72-9]



3aa was prepared from the reaction of **1a**, **5d**, **5i**, **1q** or **1r** with **2a** following typical procedure A (**1a**, **1q**, **1r** (60 ºC)) or typical procedure B (**5d**, **5i**). The product was obtained as a white solid by flash column chromatography on silica gel (R_f = 0.14 in hexane/EtOAc = 5/1) in 88% yield (130 mg, 0.35 mmol) from **1a**, 86% yield (129 mg, 0.35 mmol) from **5d**, 24% yield (35 mg, 0.094 mmol) from **5i** or 58% yield (84 mg, 0.23 mmol) from **1q.** The product was obtained in 37% yield (54 mg, 0.15 mmol) from **1r** as a white solid by flash column chromatography on silica gel followed by GPC.

Mp = 221.2-221.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.87-6.92 (c, 5H), 7.09-7.28 (c, 11H), 7.51-7.56 (m, 1H), 7.58-7.62 (m, 1H), 8.58 (ddd, *J* = 7.9 Hz, 1.6 Hz, 0.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 118.7, 125.5, 125.6, 126.8, 126.9, 127.1, 127.2, 127.5, 127.9, 128.2, 128.6, 129.5, 131.0, 131.6, 132.5, 134.7, 136.3, 137.6, 139.4, 141.0, 162.6. **IR** (ATR): 3059 w, 3027 w, 1656 s. **MS**: *m/z* (EI, relative intensity, %): 374 (32), 373 (100, M^+), 372 (73), 180 (11), 77 (33). **Anal.** Calcd for $C_{27}H_{19}NO$: C, 86.84; H, 5.13; N, 3.75. Found: C, 86.58; H, 5.08; N, 3.76.

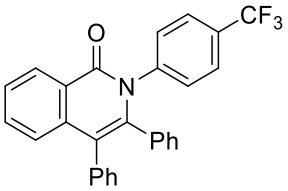
2-(4-Methoxyphenyl)-3,4-diphenylisoquinolin-1(2*H*)-one (3ba) [CAS: 1253388-47-4]



3ba was prepared from the reaction of **1b** with **2a** following typical procedure A. The product was obtained in 93% yield (152 mg, 0.38 mmol) as a pale yellow solid by flash column chromatography on silica gel (R_f = 0.29 in hexane/EtOAc = 2/1).

Mp = 214.2-216.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 3.67 (s, 3H), 6.69-6.73 (m, 2H), 6.86-6.93 (c, 5H), 6.99-7.03 (m, 2H), 7.10-7.21 (c, 5H), 7.24 (dd, *J* = 8.1 Hz, 0.6 Hz, 1H), 7.47-7.51 (m, 1H), 7.53-7.57 (m, 1H), 8.56 (dd, *J* = 7.9 Hz, 1.3 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 55.2, 113.8, 118.6, 125.4, 125.5, 126.7, 127.05, 127.10, 127.9, 128.2, 130.3, 130.9, 131.5, 132.1, 132.4, 134.8, 136.3, 137.5, 141.3, 158.4, 162.8, one signal is obscured by overlap with other signals. **IR** (ATR): 3058 w, 3024 w, 1656 s, 1247 s. **MS**: *m/z* (EI, relative intensity, %): 404 (32), 403 (100, M^+), 402 (64), 280 (10). **HRMS (DART)** Calcd for $C_{28}H_{22}NO_2$ ($[M+H]^+$): 404.16451. Found: 404.16333.

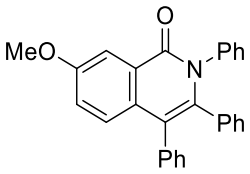
3,4-Diphenyl-2-(4-(trifluoromethyl)phenyl)isoquinolin-1(*2H*)-one (3ca) [CAS: 2151819-41-7]



3ca was prepared from the reaction of **1c** with **2a** following typical procedure A. The product was obtained in 78% yield (142 mg, 0.32 mmol) as a white solid by flash column chromatography on silica gel (R_f = 0.29 in hexane/EtOAc = 2/1) followed by flash column chromatography on NH_2-modified silica gel.

Mp = 228.0-229.6 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.86-6.93 (c, 5H), 7.12-7.31 (c, 8H), 7.48 (d, *J* = 8.2 Hz, 2H), 7.52-7.56 (m, 1H), 7.59-7.63 (m, 1H), 8.56 (dd, *J* = 7.8 Hz, 0.9 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 119.3, 123.6 (q, *J* = 272 Hz), 125.3, 125.67 (q, *J* = 3.9 Hz), 125.75, 127.0, 127.1, 127.4, 127.6, 128.0, 128.2, 129.6 (q, *J* = 32.6 Hz) 130.1, 130.9, 131.5, 132.8, 134.2, 136.0, 137.6, 140.3, 142.7, 162.4. **^{19}F NMR** ($CDCl_3$) δ: -63.1 (s) **IR** (ATR): 3061 w, 3026 w, 1658 s, 1323 s. **MS**: *m*/*z* (EI, relative intensity, %): 442 (29), 441 (100, M^+), 440 (60), 248 (10), 145 (11). **HRMS (DART)** Calcd for $C_{28}H_{19}NOF_3$ ($[M+H]^+$): 442.14133. Found: 442.13913.

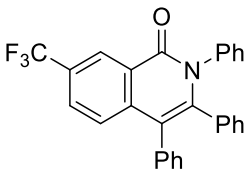
7-Methoxy-2,3,4-triphenylisoquinolin-1(*2H*)-one (3da)



3da was prepared from the reaction of **1d** or **5f** with **2a** following typical procedure A (**1d**) or typical procedure B (**5f**). The product was obtained as a white solid by flash column chromatography on silica gel (R_f = 0.06 in hexane/EtOAc = 5/1) in 87% yield (141 mg, 0.35 mmol) from **1d** or 75% yield (121 mg, 0.31 mmol) from **5d**.

Mp = 232.8-234.1 ºC. **^{1}H NMR** ($CDCl_3$) δ: 3.94 (s, 3H), 6.85-6.92 (c, 5H), 7.09-7.24 (c, 12H), 7.99 (t, *J* = 1.5 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 56.6, 108.0, 118.7, 122.8, 126.6, 126.8, 127.0, 127.1, 127.3, 127.5, 127.9, 128.5, 129.4, 131.2, 131.5, 131.6, 134.8, 136.5, 138.7, 139.6, 158.8, 162.2. **IR** (ATR): 3058 w, 1651 s. **MS**: *m*/*z* (EI, relative intensity, %): 404 (32), 403 (100, M^+), 402 (35), 388 (18), 77 (20). **Anal.** Calcd for $C_{28}H_{21}NO_2$: C, 83.35; H, 5.25; N, 3.47. Found: C, 83.04; H, 5.24; N, 3.50.

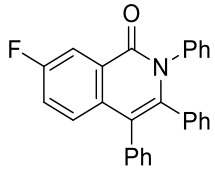
2,3,4-triphenyl-7-(trifluoromethyl)isoquinolin-1(*2H*)-one (3ea)



3ea was prepared from the reaction of **1e** with **2a** following typical procedure A (60 °C). The product was obtained in 87% yield (152 mg, 0.34 mmol) as a white solid by flash column chromatography on silica gel (R_f = 0.23 in hexane/EtOAc = 5/1).

Mp = 219.8-223.4 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.84-6.93 (c, 5H), 7.08-7.26 (c, 10H), 7.38 (d, *J* = 8.6 Hz, 1H), 7.76 (dd, *J* = 8.6 Hz, 1.6 Hz 1H), 8.83-8.85 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 118.3, 123.9 (q, *J* = 272 Hz), 125.3, 125.9 (q, *J* = 4.2 Hz), 126.5, 127.2, 127.5, 127.9, 128.2, 128.5 (q, *J* = 3.5 Hz), 128.69 (q, *J* = 33.6 Hz), 128.73, 129.3, 130.7, 131.4, 134.2, 135.6, 138.9, 140.1, 143.4, 162.0, one signal is obscured by overlap with other signals. **^{19}F NMR** ($CDCl_3$) δ: -62.8 (s). **IR** (ATR): 3060 w, 1658 s, 1314 s. **MS**: *m*/*z* (EI, relative intensity, %): 442 (29), 441 (100, M^+), 440 (75), 180 (10), 77 (33). **HRMS (DART)** Calcd for $C_{28}H_{19}NOF_3$ ($[M+H]^+$): 442.14133. Found: 442.14097.

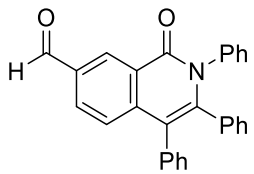
7-Fluoro-2,3,4-triphenylisoquinolin-1(*2H*)-one (3fa)



3fa was prepared from the reaction of **1f** with **2a** following typical procedure A (24 h). The product was obtained in 93% yield (141 mg, 0.36 mmol) as a pale yellow solid by flash column chromatography on silica gel (R_f = 0.49 in toluene/EtOAc = 10/1).

Mp = 227.4-229.4 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.88 (s, 5H), 7.09-7.31 (c, 12H), 8.20 (dd, *J* = 9.3 Hz, 2.2 Hz 1H). **^{13}C NMR** ($CDCl_3$) δ: 113.2 (d, *J* = 23.1 Hz), 118.3, 121.0 (d, *J* = 23.1 Hz), 127.0, 127.07, 127.12, 127.3, 127.6, 128.0, 128.2 (d, *J* = 7.7 Hz), 128.6, 129.3, 131.0, 131.4, 134.2 (d, *J* = 1.9 Hz), 134.4, 136.1, 139.2, 140.3 (d, *J* = 2.9 Hz), 161.5 (d, *J* = 249 Hz), 161.7 (d, *J* = 3.8 Hz). **^{19}F NMR** ($CDCl_3$) δ: -116.1 (m). **IR** (ATR): 3072 w, 3045 w, 1655 s. **MS**: *m*/*z* (EI, relative intensity, %): 392 (28), 391 (100, M^+), 390 (68), 180 (11), 77 (27). **HRMS (DART)** Calcd for $C_{27}H_{19}NOF$ ($[M+H]^+$): 392.14452. Found: 392.14342.

1-Oxo-2,3,4-triphenyl-1,2-dihydroisoquinoline-7-carbaldehyde (3ga)

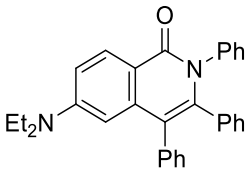


3ga was prepared from the reaction of **1g** with **2a** following typical procedure A (60 °C). The product was obtained in 76% yield (121 mg, 0.30 mmol) as a yellow solid by flash column chromatography on silica gel (R_f = 0.31 in hexane/EtOAc = 2/1).

Mp could not be measured because the title compound was decomposed at 265 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.88-6.93 (c, 5H), 7.09-7.28 (c, 10H), 7.37 (d, *J* = 8.5 Hz, 1H), 8.07 (dd, *J* = 8.5 Hz, 1.7 Hz 1H), 8.99 (d, *J* = 1.7 Hz, 1H), 10.15

(s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 118.7, 125.5, 126.6, 127.2, 127.6, 127.9, 128.2, 128.8, 129.3, 130.0, 130.6, 131.4, 133.5, 134.2, 134.5, 135.6, 138.9, 142.2, 144.6, 162.1, 191.3, one signal is obscured by overlap with other signals. **IR** (ATR): 3056 w, 1689 m, 1657 s. **MS**: *m/z* (EI, relative intensity, %): 402 (27), 401 (100, M^+), 400 (67), 77 (25). **HRMS (DART)** Calcd for $C_{28}H_{20}NO_2$ ($[M+H]^+$): 402.14886. Found: 402.14791.

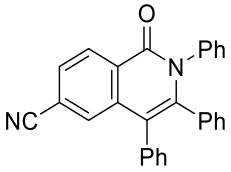
6-(Diethylamino)-2,3,4-triphenylisoquinolin-1(*2H*)-one (3ha)



3ha was prepared from the reaction of **1h** with **2a** following typical procedure A. The product was obtained in 97% yield (173 mg, 0.39 mmol) as a white solid by flash column chromatography on silica gel (R_f = 0.60 in hexane/EtOAc = 1/1).

Mp = 212.0-212.7 ºC. **^{1}H NMR** ($CDCl_3$) δ: 1.07 (t, *J* = 7.1 Hz, 6H), 3.28 (q, *J* = 7.1 Hz, 4H), 6.21 (d, *J* = 2.5 Hz, 1H), 6.83-6.92 (c, 6H), 7.05-7.22 (c, 10H), 8.36 (d, *J* = 8.9 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.3, 44.6, 104.7, 112.3, 114.4, 118.5, 126.5, 126.9, 127.1, 127.7, 128.3, 129.8, 130.0, 131.0, 131.6, 135.3, 137.1, 139.5, 139.8, 141.0, 150.5, 162.4, one signal is obscured by overlap with other signals. **IR** (ATR): 3059 w, 3026 w, 1636 s. **MS**: *m/z* (EI, relative intensity, %): 445 (22), 444 (63, M^+), 443 (10), 430 (34), 429 (100), 399 (21), 222 (11), 77 (12). **HRMS (DART)** Calcd for $C_{31}H_{29}N_2O$ ($[M+H]^+$): 445.22774. Found: 445.22615.

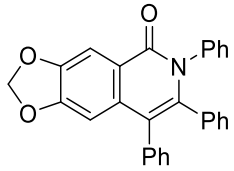
1-Oxo-2,3,4-triphenyl-1,2-dihydroisoquinoline-6-carbonitrile (3ia)



3ia was prepared from the reaction of **1i** with **2a** following typical procedure A (80 °C). The product was obtained in 52% yield (87 mg, 0.22 mmol) as a white solid by flash column chromatography on silica gel (R_f = 0.34 in hexane/EtOAc = 2/1).

Mp = 267.2-269.3 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.83-6.98 (c, 5H), 7.06-7.32 (c, 10H), 7.59 (d, *J* = 1.2 Hz, 1H), 7.68 (dd, *J* = 8.3 Hz, 1.2 Hz, 1H), 8.63 (d, *J* = 8.3 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 116.0, 117.8, 118.2, 127.2, 127.5, 127.6, 127.8, 127.9, 128.36, 128.42, 128.7, 129.1, 129.4, 130.4, 130.6, 131.3, 133.9, 134.9, 137.8, 138.8, 143.2, 161.5. **IR** (ATR): 3062 w, 3032 w, 2226 w, 1662 s. **MS**: *m/z* (EI, relative intensity, %): 399 (29), 398 (100, M^+), 397 (75), 77 (31). **HRMS (DART)** Calcd for $C_{28}H_{19}N_2O$ ($[M+H]^+$): 399.14919. Found: 399.14847.

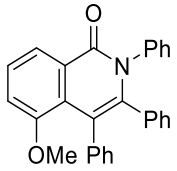
6,7,8-triphenyl-[1,3]dioxolo[4,5-*g*]isoquinolin-5(*6H*)-one (3ja)



3ja was prepared from the reaction of **1j** with **2a** following typical procedure A. The product was obtained in 82% yield (138 mg, 0.33 mmol) as a pale yellow solid by flash column chromatography on silica gel (R_f = 0.20 in hexane/EtOAc = 2/1).

Mp = 271.8-275.2 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.04 (s, 2H), 6.60 (s, 1H), 6.86-6.88 (c, 5H), 7.08-7.23 (c, 10H), 7.92 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 101.7, 103.8, 106.0, 118.6, 121.0, 126.8, 127.0, 127.1, 127.4, 128.0, 128.5, 129.4, 131.0, 131.4, 134.7, 135.0, 136.5, 139.5, 139.8, 147.7, 152.0, 161.7. **IR** (ATR): 3058 w, 3023 w, 1647 s. **MS**: *m*/*z* (EI, relative intensity, %): 418 (19), 417 (100, M^+), 416 (65), 180 (12), 77 (25). **HRMS (DART)** Calcd for $C_{28}H_{20}NO_3$ ($[M+H]^+$): 418.14377. Found: 418.14353.

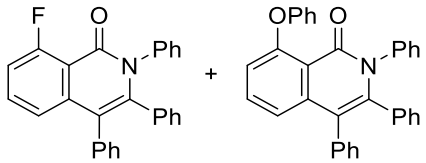
5-Methoxy-2,3,4-triphenylisoquinolin-1(*2H*)-one (3ka)



3ka was prepared from the reaction of **1k** with **2a** following typical procedure A (80 °C). The product was obtained in 54% yield (86 mg, 0.21 mmol) as a pale yellow solid by flash column chromatography on silica gel (R_f = 0.20 in hexane/EtOAc = 2/1).

Mp = 232.2-234.3 ºC. **^{1}H NMR** ($CDCl_3$) δ: 3.34 (s, 3H), 6.81-6.88 (c, 5H), 6.97-7.14 (c, 9H), 7.17-7.21 (m, 2H), 7.49 (t, *J* = 8.0 Hz, 1H), 8.24 (dd, *J* = 8.0 Hz, 1.3 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 55.9, 115.0, 116.6, 120.7, 125.3, 126.4, 126.7, 126.8, 127.38, 127.44, 127.5, 127.6, 128.5, 129.4, 130.6, 131.2, 134.8, 139.5, 140.3, 141.1, 156.2, 162.2. **IR** (ATR): 3058 w, 3026 w, 1650 s, 1268 m. **MS**: *m*/*z* (EI, relative intensity, %): 404 (19), 403 (100, M^+), 402 (21), 180 (15), 77 (25). **HRMS (DART)** Calcd for $C_{28}H_{22}NO_2$ ($[M+H]^+$): 404.16451. Found: 404.16296.

8-Fluoro-2,3,4-triphenylisoquinolin-1(2*H*)-one (3la), 8-phenoxy-2,3,4-triphenylisoquinolin-1(2*H*)-one (3la')



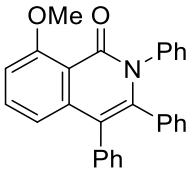
3la **3la'**

99% NMR yield (**3la**/**3la'** = 1/6)

3la and **3la'** were prepared from the reaction of **1l** with **2a** following typical procedure A (80 °C). The products were obtained as a pale yellow solid (180 mg) by flash column chromatography on silica gel (R_f = 0.06 in hexane/EtOAc = 5/1). The product yield and the ratio of products were determined by ^{1}H NMR using 1,1,2,2- tetrachloroethane as an internal standard after flash column chromatography on silica gel.

^{1}H NMR ($CDCl_3$) δ: 6.85-6.92 (c), 6.94-6.99 (m), 7.03-7.25 (c), 7.28-7.34 (m), 7.44 (t, *J* = 8.1 Hz, 1H, **3la'**), 7.49 (td, *J* = 8.2 Hz, 5.0 Hz, 1H, **3la**). **^{13}C NMR** ($CDCl_3$) for **3la'** δ: 117.6, 117.7, 117.9, 118.7, 121.1, 122.8, 126.8, 127.0, 127.14, 127.3, 127.99, 128.4, 129.5, 129.8, 130.8, 131.7, 132.8, 134.7, 136.7, 139.4, 140.7, 142.0, 157.6, 158.1, 160.3. Some peaks of **3la** are overlapped with **3la'**. Selected ^{13}C NMR peaks of **3la** are shown. δ: 127.09, 127.6, 128.03, 128.5, 129.6, 131.5. **^{19}F NMR** ($CDCl_3$) for **3la** δ: -110.2 (dd, *J* = 11.3 Hz, 4.7 Hz). **HRMS (DART)** Calcd for $C_{33}H_{24}NO_2$ (**3la'**, $[M+H]^+$): 466.18016. Found: 466.18129. Calcd for $C_{27}H_{19}NOF$ (**3la**, $[M+H]^+$): 392.14452. Found: 392.14526.

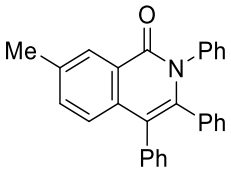
8-Methoxy-2,3,4-triphenylisoquinolin-1(2*H*)-one (3ma)



3ma was prepared from the reaction of **1m** with **2a** following typical procedure A (80 °C). The product was obtained in 75% yield (120 mg, 0.30 mmol) as a white solid by flash column chromatography on silica gel (R_f = 0.26 in hexane/EtOAc = 1/2).

Mp = 243.8-245.8 ºC. **^{1}H NMR** ($CDCl_3$) δ: 3.99 (s, 3H), 6.78 (d, *J* = 7.9 Hz, 1H), 6.87 (s, 5H), 6.94 (d, *J* = 7.9 Hz, 1H), 7.06-7.23 (c, 10H), 7.46 (t, *J* = 7.9 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 56.1, 108.4, 115.0, 117.8, 117.9, 126.6, 126.9, 127.0, 127.1, 127.8, 128.2, 129.7, 130.7, 131.6, 132.9, 134.8, 136.9, 139.6, 140.7, 141.8, 161.0, 161.3. **IR** (ATR): 3061 w, 1659 s, 1264 m. **MS**: *m/z* (EI, relative intensity, %): 404 (29), 403 (100, M^+), 402 (43), 387 (10), 386 (32), 375 (15), 374 (57), 372 (11), 357 (14), 180 (14), 77 (38). **HRMS (DART)** Calcd for $C_{28}H_{22}NO_2$ ($[M+H]^+$): 404.16451. Found: 404.16383.

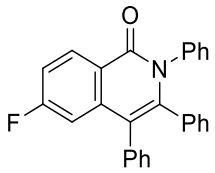
7-Methyl-2,3,4-triphenylisoquinolin-1(2*H*)-one (3na) [CAS: 1253388-60-1]



3na was prepared from the reaction of **5g** with **2a** following typical procedure B. The product was obtained in 90% yield (138 mg, 0.36 mmol) as a white solid by flash column chromatography on silica gel (R_f = 0.14 in hexane/EtOAc = 5/1).

Mp = 213.3-214.5 ºC. **^{1}H NMR** ($CDCl_3$) δ: 2.49 (s, 3H), 6.83-6.91 (c, 5H), 7.09-7.23 (c, 11H), 7.39 (dd, *J* = 8.5 Hz, 1.8 Hz, 1H), 8.37 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 21.3, 118.7, 125.3, 125.5, 126.7, 126.96, 127.04, 127.4, 127.7, 127.8, 128.5, 129.4, 131.0, 131.5, 133.9, 134.8, 135.2, 136.5, 136.9, 139.5, 140.0, 162.5. **IR** (ATR): 3059 w, 3025 w, 1657 s. **MS**: *m*/*z* (EI, relative intensity, %): 388 (31), 387 (100, M^+), 386 (59), 180 (11), 77 (30). **HRMS (DART)** Calcd for $C_{28}H_{22}NO$ ($[M+H]^+$): 388.16959. Found: 388.16859.

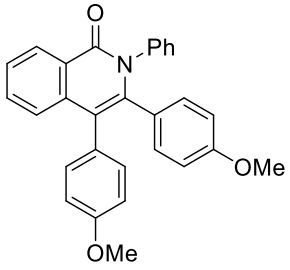
6-Fluoro-2,3,4-triphenylisoquinolin-1(2*H*)-one (3oa)



3oa was prepared from the reaction of **5h** with **2a** following typical procedure B (120 °C). The product was obtained in 75% yield (123 mg, 0.31 mmol) as a pale yellow solid by flash column chromatography on silica gel (R_f = 0.14 in hexane/EtOAc = 5/1).

Mp = 225.2-227.1 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.85-6.92 (c, 6H), 7.06-7.25 (c, 11H), 8.57 (dd, *J* = 8.9 Hz, 5.9 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 110.8 (d, *J* = 23.3 Hz), 115.5 (d, *J* = 23.3 Hz), 118.3 (d, *J* = 3.1 Hz), 122.1 (d, *J* = 1.2 Hz), 127.1, 127.2, 127.4, 127.7, 128.2, 128.6, 129.4, 130.8, 131.5 (d, *J* = 9.9 Hz), 134.5, 135.8, 139.2, 140.2 (d, *J* = 10.1 Hz), 142.4, 162.0, 165.5 (d, *J* = 252 Hz). **^{19}F NMR** ($CDCl_3$) δ: -105.8 (m). **IR** (ATR): 3060 w, 1657 s, 1327 s. **MS**: *m*/*z* (EI, relative intensity, %): 392 (27), 391 (100, M^+), 390 (83), 77 (28). **HRMS (DART)** Calcd for $C_{27}H_{19}NOF$ ($[M+H]^+$): 392.14452. Found: 392.14514.

3,4-Bis(4-methoxyphenyl)-2-phenylisoquinolin-1(2*H*)-one (3ab) [CAS: 1266570-07-3]

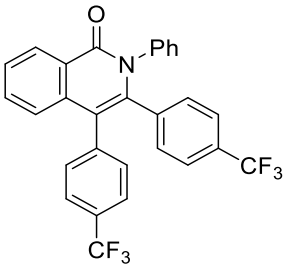


3aa was prepared from the reaction of **1a** or **5d** with **2b** following typical procedure A (**1a**, DMF was used instead of DMSO.) or typical procedure B (**5d**). The product was obtained as a yellow solid by flash column chromatography on silica gel (R_f = 0.23 in hexane/EtOAc = 2/1) in 92% yield (159 mg, 0.37 mmol) from **1a** or 70% yield (120 mg, 0.28 mmol) from **5d**.

Mp = 246.5-247.6 ºC. **^{1}H NMR** ($CDCl_3$) δ: 3.61 (s, 3H), 3.77 (s, 3H), 6.42-6.45 (m, 2H), 6.76-6.80 (c, 4H), 7.02-7.06 (m, 2H), 7.08-7.10 (c, 2H), 7.13-7.17 (m, 1H), 7.21-7.25 (c, 2H), 7.27-7.29 (m, 1H), 7.49-7.53 (m, 1H), 7.56-7.60 (m, 1H), 8.54-8.56 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 54.9, 55.1, 112.5, 113.4, 118.6, 125.4, 125.5, 126.7, 127.3, 127.4, 128.2, 128.6, 128.7, 129.4, 132.2, 132.4, 132.6, 138.0, 139.6, 141.0, 158.11, 158.15, 162.7. **IR** (ATR): 3064

w, 3036 w, 1652 s, 1243 s. **MS**: *m/z* (EI, relative intensity, %): 434 (32), 433 (100, M^+), 432 (38), 418 (10), 165 (13), 77 (13). **HRMS (DART)** Calcd for $C_{29}H_{24}NO_3$ ([M+H]$^+$): 434.17507. Found: 434.17370.

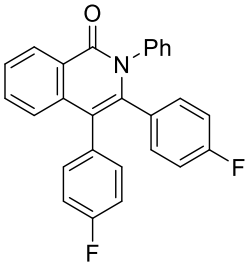
2-phenyl-3,4-bis(4-(trifluoromethyl)phenyl)isoquinolin-1(2*H*)-one (3ac)



3aa was prepared from the reaction of **1a** or **5d** with **2c** following typical procedure A (**1a**, 80 °C) or typical procedure B (**5d**). The product was obtained as a white solid by flash column chromatography on silica gel (R_f = 0.14 in hexane/EtOAc = 5/1) in 78% yield (157 mg, 0.31 mmol) from **1a** or 75% yield (154 mg, 0.30 mmol) from **5d**.

Mp = 228.2-229.9 ºC. **^{1}H NMR** ($CDCl_3$) δ: 7.03 (d, *J* = 8.0 Hz, 2H), 7.08-7.10 (m, 2H), 7.14-7.30 (c, 8H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.56-7.60 (m, 1H), 7.61-7.65 (m, 1H), 8.57-8.60 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 117.9, 123.4 (q, *J* = 272 Hz), 123.9 (q, *J* = 272 Hz), 124.3 (q, *J* = 3.5 Hz), 125.2 (q, *J* = 3.5 Hz), 125.3, 125.7, 127.6, 128.1, 128.5, 128.9, 129.3, 129.5 (q, *J* = 32.6 Hz), 129.6 (q, *J* = 32.6 Hz), 131.3, 131.9, 133.0, 136.7, 137.9, 138.8, 139.77, 139.80, 162.3. **^{19}F NMR** ($CDCl_3$) δ: -63.5 (s), -63.1 (s). **IR** (ATR): 3067 w, 1658 s, 1323 s. **MS**: *m/z* (EI, relative intensity, %): 510 (33), 509 (100, M^+), 508 (83), 244 (15), 77 (47). **HRMS (DART)** Calcd for $C_{29}H_{18}NOF_6$ ([M+H]$^+$): 510.12871. Found: 510.12885.

3,4-Bis(4-fluorophenyl)-2-phenylisoquinolin-1(2*H*)-one (3ad)

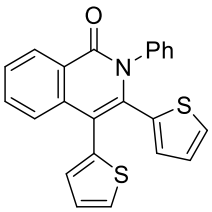


3ad was prepared from the reaction of **1a** or **5d** with **2d** following typical procedure A (**1a**, 24 h) or typical procedure B (**5d**). The product was obtained as a white solid by flash column chromatography on silica gel (R_f = 0.06 in hexane/EtOAc = 5/1) in 81% yield (135 mg, 0.33 mmol) from **1a** or 78% yield (129 mg, 0.32 mmol) from **5d**

Mp = 250.1-251.0 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.59-6.66 (m, 2H), 6.83-6.88 (m, 2H), 6.90-6.96 (m, 2H), 7.06-7.12 (c, 4H), 7.14-7.20 (m, 1H), 7.20-7.27 (c, 3H), 7.51-7.57 (m, 1H), 7.59-7.64 (m, 1H), 8.54-8.59 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 114.5 (d, *J* = 21.7 Hz), 115.2 (d, *J* = 21.4 Hz), 118.1, 125.4, 125.6, 127.2, 127.8, 128.4, 128.8, 129.4, 130.7 (d, *J* = 3.7 Hz), 132.1 (d, *J* = 3.6 Hz), 132.67 (d, *J* = 8.3 Hz), 132.70, 133.1 (d, *J* = 8.1 Hz), 137.4, 139.3, 140.3, 161.4 (d, *J* = 249 Hz), 161.7 (d, *J* = 247 Hz), 162.5. **^{19}F NMR** ($CDCl_3$) δ: -115.2 (tt, *J* = 8.9 Hz, 4.6 Hz), -113.5 (tt, *J*

= 9.2 Hz, 4.6 Hz). **IR** (ATR): 3069 w, 3043 w, 1653 s, 1221 s. **MS**: *m*/*z* (EI, relative intensity, %): 410 (28), 409 (100, M^+), 408 (81), 77 (26). **HRMS (DART)** Calcd for $C_{27}H_{18}NOF_2$ ($[M+H]^+$): 410.13510. Found: 410.13484.

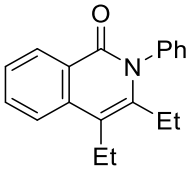
2-Phenyl-3,4-di(thiophen-2-yl)isoquinolin-1(2*H*)-one (3ae)



3ae was prepared from the reaction of **1a** or **5d** with **2e** following typical procedure A (**1a**, 60 °C) or typical procedure B (**5d**, 22 h). The product was obtained as a black solid by flash column chromatography on silica gel (R_f = 0.14 in hexane/EtOAc = 5/1) in 74% yield (113 mg, 0.29 mmol) from **1a.** The product was obtained in 48% yield (74 mg, 0.19 mmol) from **5d** by flash column chromatography on silica gel followed by GPC.

Mp = 243.7-245.1 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.58-6.62 (c, 2H), 6.93 (dd, *J* = 3.4 Hz, 1.1 Hz, 1H), 6.97 (dd, *J* = 5.1 Hz, 3.4 Hz, 1H), 7.06 (dd, *J* = 4.6 Hz, 1.6 Hz, 1H), 7.17-7.19 (c, 2H), 7.21-7.32 (c, 4H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.54-7.58 (m, 1H), 7.63-7.67 (m, 1H), 8.53 (dd, *J* = 7.9 Hz, 0.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 113.9, 125.6, 125.7, 126.56, 126.63, 127.6, 127.8, 127.9, 128.2, 128.7, 129.2, 129.8, 131.2, 132.8, 134.9, 136.2, 137.0, 137.5, 139.3, 162.5, one signal is obscured by overlap with other signals. **IR** (ATR): 3069 w, 1658 s. **MS**: *m*/*z* (EI, relative intensity, %): 387 (13), 386 (29), 385 (100, M^+), 384 (27), 352 (16), 326 (11), 282 (17), 253 (11), 77 (28). **HRMS (DART)** Calcd for $C_{23}H_{16}NOS_2$ ($[M+H]^+$): 386.06678. Found: 386.06574.

3,4-Diethyl-2-phenylisoquinolin-1(2*H*)-one (3af)



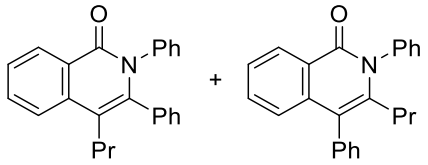
3af was prepared from the reaction of **1a, 1q, 1r** or **5d** with **2e** following typical procedure A (**1a** (60 °C), **1q**, **1r** (60 °C)) or typical procedure B (**5d**, 22 h). The product was obtained as a white solid by flash column chromatography on silica gel (R_f = 0.11 in hexane/EtOAc = 5/1) in 79% yield (89 mg, 0.32 mmol) from **1a**, 80% yield (92 mg, 0.33 mmol) from **1q** or 84% yield (93 mg, 0.34 mmol) from **5d.** The product was obtained in 27% yield (30 mg, 0.11 mmol) from **1r** as a pale yellow solid by flash column chromatography on silica gel followed by GPC.

Mp = 84.5-87.2 ºC. **^{1}H NMR** ($CDCl_3$) δ: 0.99 (t, *J* = 7.5 Hz, 3H), 1.29 (t, *J* = 7.5 Hz, 3H), 2.45 (q, *J* = 7.5 Hz, 2H), 2.82 (q, *J* = 7.5 Hz, 2H), 7.26-7.28 (m, 2H), 7.43-7.48 (m, 2H), 7.49-7.57 (c, 2H), 7.68-7.75 (c, 2H), 8.46 (dd, *J* = 7.9 Hz, 0.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 13.8, 14.7, 20.4, 23.1, 114.6, 122.6, 125.3, 125.7, 128.3, 128.5, 128.9, 129.3, 132.4, 136.8, 139.5, 140.9, 163.0. **IR** (ATR): 3064 w, 1651 s. **MS**: *m*/*z* (EI, relative intensity, %): 278 (16),

277 (69, M^+), 263 (21), 262 (100), 233 (13), 86 (14), 84 (21), 77 (22). **HRMS (DART)** Calcd for $C_{19}H_{20}NO$ ($[M+H]^+$): 278.15394. Found: 278.15341.

2,3-Diphenyl-4-propylisoquinolin-1(2*H*)-one (3ag) [CAS: 1253388-64-5]

2,4-Diphenyl-3-propylisoquinolin-1(2*H*)-one (3ag') [CAS: 1253388-65-6][20]



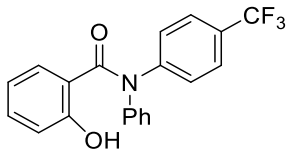
3ag **3ag'**

3ag : **3ag'** = 16 : 1

3ag and **3ag'** were prepared from the reaction of **1a** with **2g** following typical procedure A (60 °C). The products were obtained in 80% yield (109 mg, 0.32 mmol) as a white solid by flash column chromatography on silica gel (R_f = 0.11 in hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$) for **3ag** δ: 0.83 (t, *J* = 7.3 Hz, 3H), 1.51-1.61 (m, 2H), 2.42-2.46 (m, 2H), 6.98-7.21 (c, 10H), 7.51-7.58 (m, 1H), 7.73-7.78 (c, 2H), 8.56 (d, *J* = 7.8 Hz, 1H). Some peaks of **3ag'** are overlapped with **3ag**. Selected ^{1}H NMR peaks of **3ag'** are shown. δ: 0.40 (t, *J* = 7.3 Hz, 3H), 1.21-1.28 (m, 2H), 2.11-2.15 (m, 2H), 8.45 (d, *J* = 8.0 Hz, 1H). **^{13}C NMR** ($CDCl_3$) for **3ag** δ: 14.3, 23.7, 30.6, 115.3, 123.5, 126.1, 126.6, 127.4, 127.7, 127.8, 128.5, 128.7, 129.5, 130.4, 132.5, 135.1, 136.8, 139.7, 140.3, 162.4. **Anal.** Calcd for $C_{24}H_{21}NO$: C, 84.92; H, 6.24; N, 4.13. Found: C, 84.57; H, 6.14; N, 4.14.

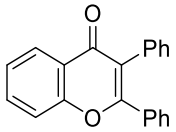
2-Hydroxy-*N*-phenyl-*N*-(4-(trifluoromethyl)phenyl)benzamide (4p)



4p was prepared from the reaction of **4p** with **2a** following typical procedure A (30 min). The product was obtained in 64% yield (91 mg, 0.25 mmol) as a yellow oil by flash column chromatography on silica gel (R_f = 0.29 in hexane/EtOAc = 5/1) followed by flash column chromatography on NH_2-modified silica gel (R_f = 0.43 in EtOAc only).

^{1}H NMR ($CDCl_3$) δ: 6.47-6.51 (m, 1H), 6.94 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 6.97 (dd, *J* = 8.5 Hz, 0.9 Hz, 1H), 7.12-7.15 (m, 2H), 7.22-7.31 (c, 4H), 7.34-7.38 (m, 2H), 7.60 (d, *J* = 8.5 Hz, 2H), 10.51 (br, 1H). **^{13}C NMR** ($CDCl_3$) δ: 115.7, 118.21, 118.22, 123.7 (q, *J* = 272 Hz), 126.4 (q, *J* = 3.6 Hz), 127.1, 127.4, 127.5, 128.5 (q, *J* = 32.9 Hz), 129.8, 130.6, 133.9, 143.4, 146.9, 161.4, 172.7. **^{19}F NMR** ($CDCl_3$) δ: -62.9. **HRMS (DART)** Calcd for $C_{20}H_{15}NO_2F_3$ ($[M+H]^+$): 358.10494. Found: 358.10490.

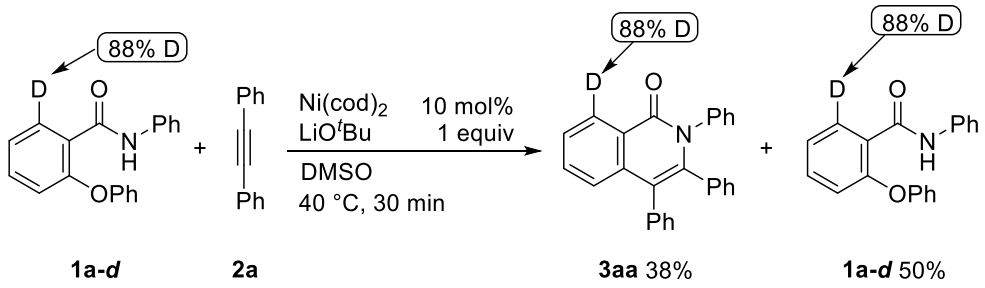
2,3-Diphenyl-4*H*-chromen-4-one (6aa) [CAS: 6005-12-5][21]



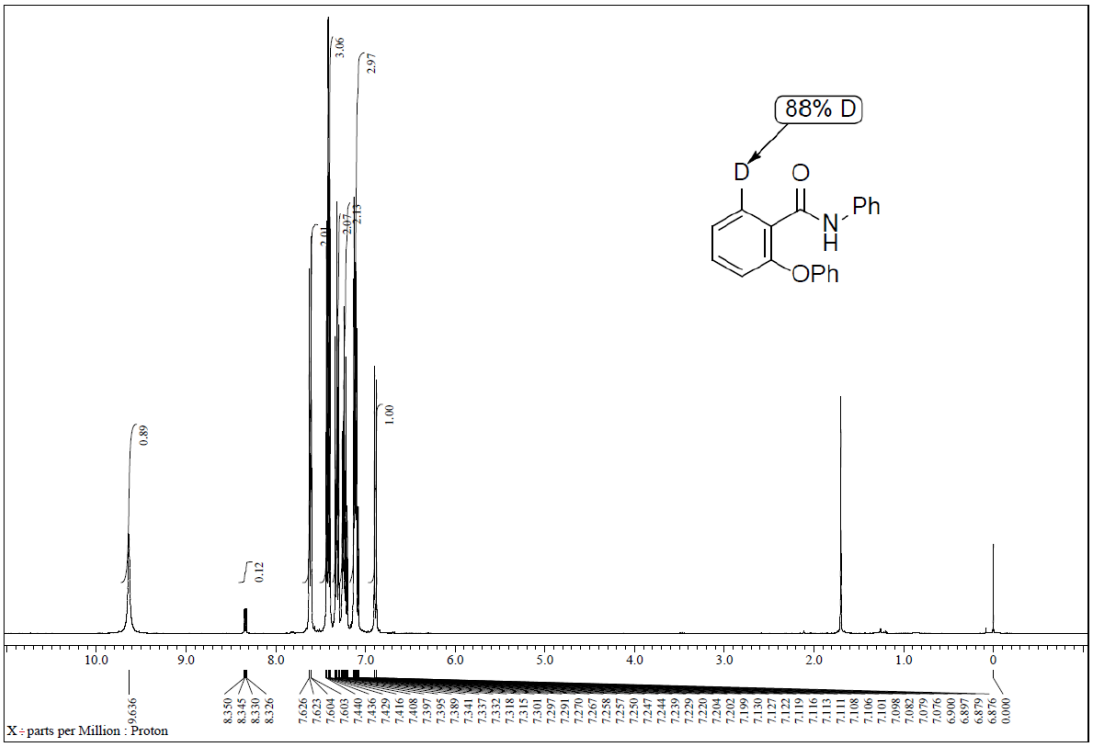
6aa was prepared from the reaction of **5c** with **2a** following typical procedure A (0.2 mmol, 80 °C, 3 h, KO^{t}Bu was used instead of LiO^{t}Bu.). The product was obtained in 11% yield (7 mg, 0.023 mmol) as a white solid by flash column chromatography on silica gel (R_f = 0.26 in hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$) δ: 7.21-7.24 (c, 2H), 7.27-7.37 (c, 6H), 7.40-7.46 (c, 3H), 7.54-7.56 (m, 1H), 7.69-7.74 (m, 1H), 8.29-8.32 (m, 1H)

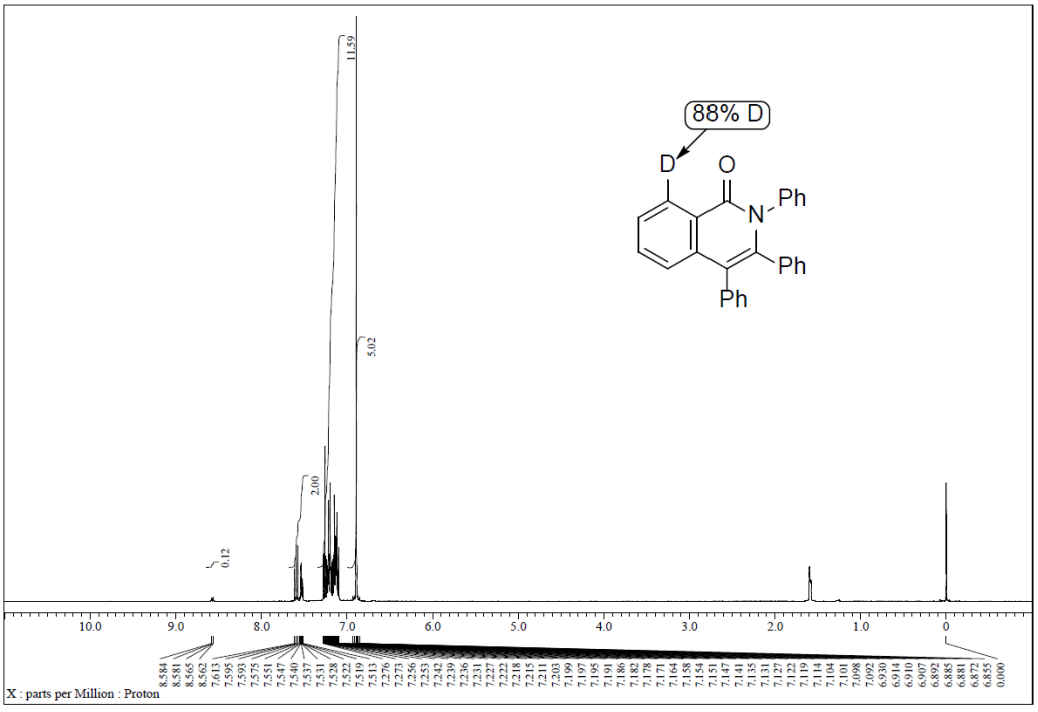
2.4.5 Labeling Experiment (Scheme 5b)



Compound **1a-*d*** was subjected to the typical procedure (30 min.). The resulting mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 10/1 to 5/1) to afford **3aa** (R_f = 0.31 in hexane/EtOAc = 5/1) as a white solid (56 mg, 0.15 mmol, 38%) and **1a-*d*** (R_f = 0.17 in hexane/EtOAc = 2/1) as a white solid (57 mg, 0.20 mmol, 50%).



^{1}H NMR spectrum of **1a-*d***



^{1}H NMR spectrum of **3aa**

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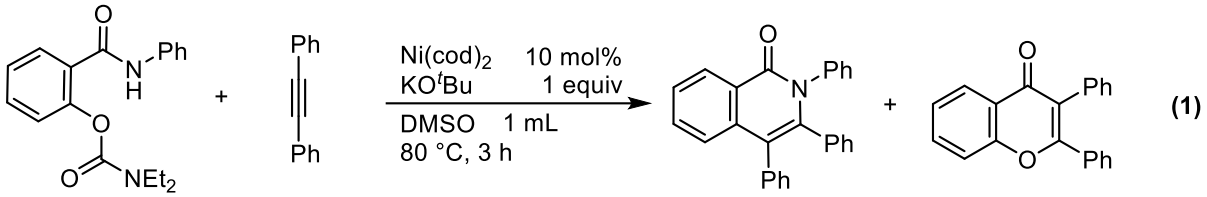
Chapter 3

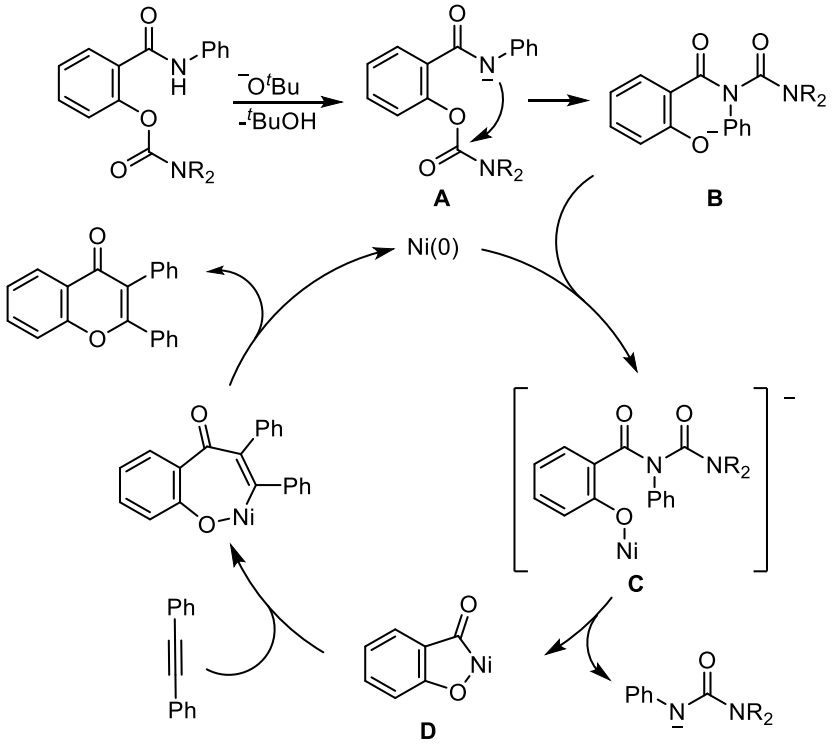
Nickel-catalyzed C–O/O–H annulation of salicylate esters with alkynes

3.1 Introduction

As described in Chapter 2, The reaction of *ortho*-carbamamoyl-substituted aromatic amides with alkynes gave a 2,3-diphenylchromone derivative as a byproduct as well as the desired isoquinolone derivatives (eq 1).

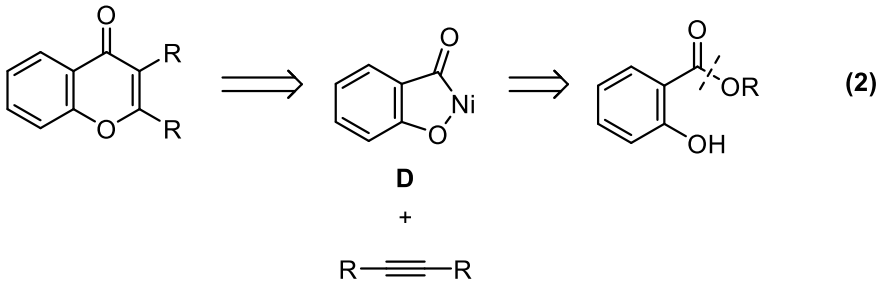


A plausible mechanism for the formation of a chromone is proposed as shown in Scheme 1. The base abstracts a proton from an amide to generate an amidate anion **A**, followed by an intramolecular rearrangement in which the carbamoyl group is transferred from an *O*-atom to an *N*-atom to produce anionic species **B**. A subsequent reaction with a nickel complex then produces the nickel-ate complex **C**. Oxidative addition generates the oxanickellacycle **D** via the cleavage of the acyl C-N bond.[1] Finally, insertion of an alkyne into oxanickellacycle **D** followed by reductive elimination gives a chromone.



Scheme 1. A plausibe mechanism of the generation of cheomones from carbamates.

Based on this unexpected discovery, the author hypothesized that the oxanickellacycle **D** could be generated from a salicylate ester via the cleavage of the acyl C-O bond directed by the hydroxy anion in the ester (eq 2).[2]

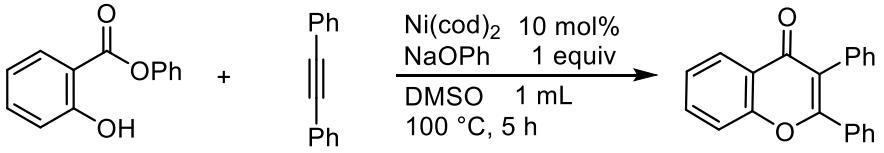


Chromones are an important structural motif in organic materials as well as bioactive molecules.[3] Synthetic methodologies for producing chromone derivatives via such an annulation from various types of substrates with alkynes have been reported, using salicylaldehyde,[4] salicylic acid ketals,[5] carbonylsalicylamides,[6] and phenols,[7] however the use of salicylate esters in such reactions has not been reported to date, to the best of my knowledge. Herein, the author investigated the nickel-catalyzed C-O/O-H annulation of phenyl salicylate esters with alkynes.

3.2 Results and Discussion

The author began this study by examining the reaction of phenyl salicylate (**1a**) as a model substrate and diphenylacetylene (**2a**) as a coupling partner in the presence of $Ni(cod)_2$ as a catalyst and NaOPh as a base to evaluate the optimal reaction conditions for such a reaction (Table 1).

Table 1. Screening of reaction conditions[a]



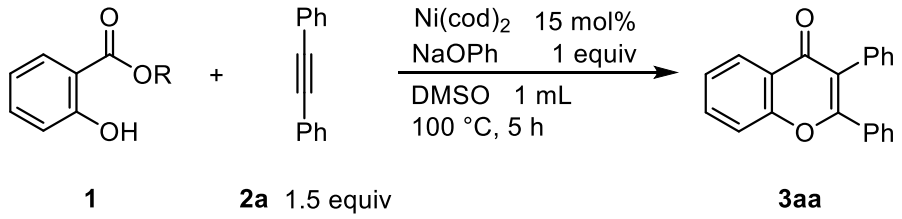
1a **2a** 1.5 equiv **3aa**

entry	deviations from the reaction conditions	NMR yield of **3aa**[b]
1	none	78%
2	KO^{t}Bu, at 80 °C, 2 h	51%
3	Cs_2CO_3	22%
4	NaOAc	none
5	NMP	33%
6	DMA	39%
7	MeCN	none
8	$Ni(cod)_2$ 15 mol%	80% (75%)[c]

[a] Reaction conditions: **1a** (0.4 mmol), **2a** (0.6 mmol), $Ni(cod)_2$ (0.04 mmol), NaOPh (0.4 mmol) in DMSO (1 mL) at 100 °C for 5 h. [b] The yields were determined from ^{1}H NMR with 1,1,1,2-tetrachloroethane as the internal standard. [c] Isolated yield.

The reaction of **1a** with **2a** in the presence of 10 mol% $Ni(cod)_2$ and 1 equiv of NaOPh at 100 °C for 5 h gave the product **3aa** in 78% NMR yield (Table 1, entry 1). Surprisingly, C-O bond activation occurred, even in the absence of a ligand. When KO^{t}Bu was used as a base, the reaction proceeded to give **3aa** in 51% NMR yield (entry 2). However, no starting material **1a** was recovered and nucleophilic acyl substitution occurred between **1a** with KO^{t}Bu, which gave *tert*-butyl salicylate as a byproduct. After screening a series of other bases and solvents, the product yield was not improved (entries 3-7). When the catalyst loading was increased to 15 mol%, **3aa** was obtained in 75% isolated yield (entry 8). Finally, the author determined that the conditions shown in entry 8 represented the standard reaction conditions.

Table 2. Screening of leaving groups[a]



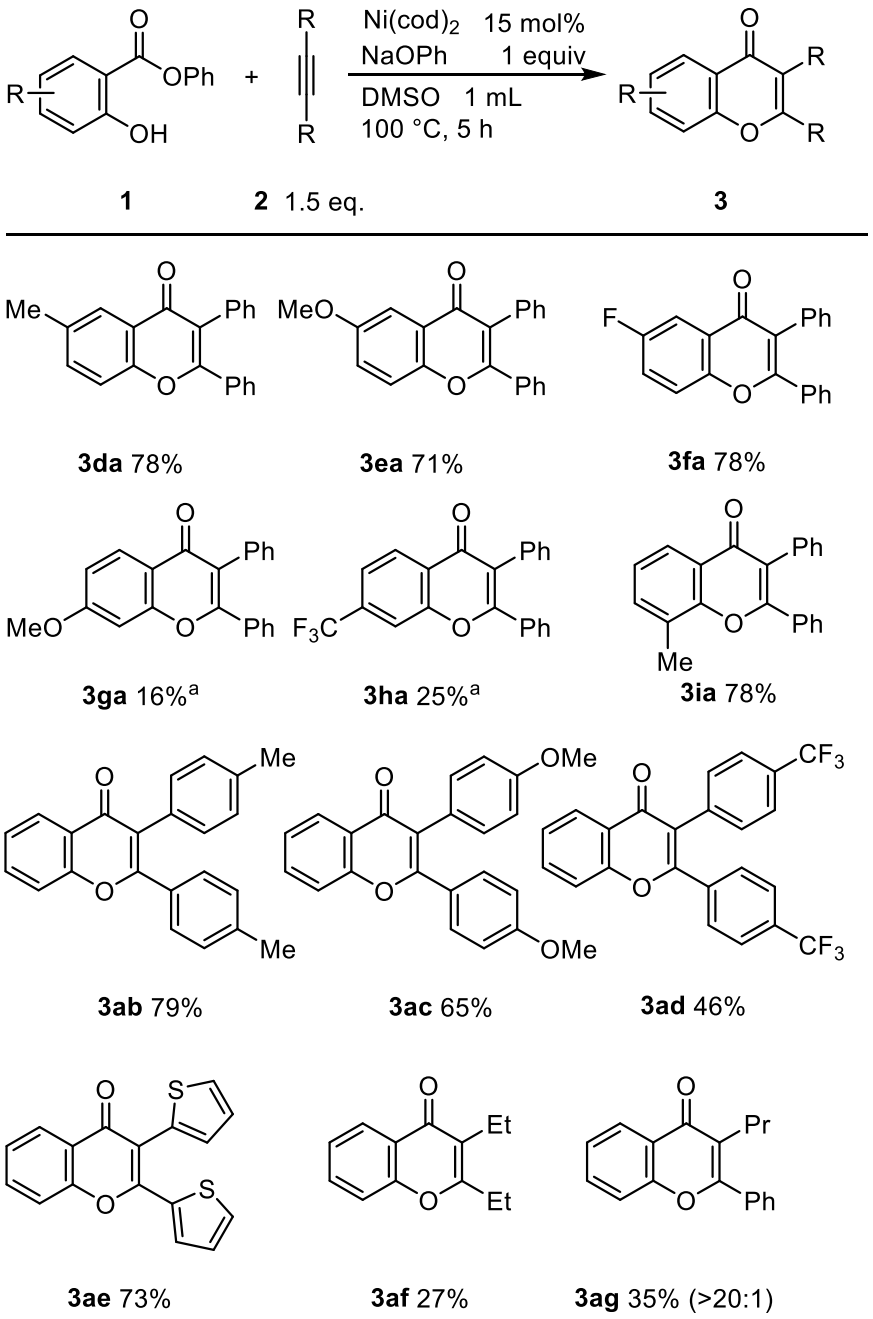
entry	R	NMR yield of **3aa**[b]
1	Ph (**1a**)	80% (75%)[c]
2	4-$MeOC_6H_4$ (**1b**)	85%
3	4-$F_3CC_6H_4$ (**1c**)	44%

[a] Reaction conditions: **1** (0.4 mmol), **2a** (0.6 mmol), $Ni(cod)_2$ (0.06 mmol), NaOPh (0.4 mmol) in DMSO (1 mL) at 100 °C for 5 h. [b] NMR yields were determined from ^1H NMR spectra with 1,1,1,2-tetrachloroethane as the internal standard. [c] Isolated yield.

The author next examined the effect of the substituents on leaving groups (Table 2). The reaction of the substrate bearing an electron donating group **1b** proceeded efficiency to give **3aa** in 85% NMR yield (entry 2). On the other hand, when an electron withdrawing group was located on the leaving group, the yield of **3aa** was decreased dramatically and some unidentified by-products were obtained (entry 3). This result suggests that ester **1c** was unstable under basic conditions due to high electrophilicity of the carbonyl group.

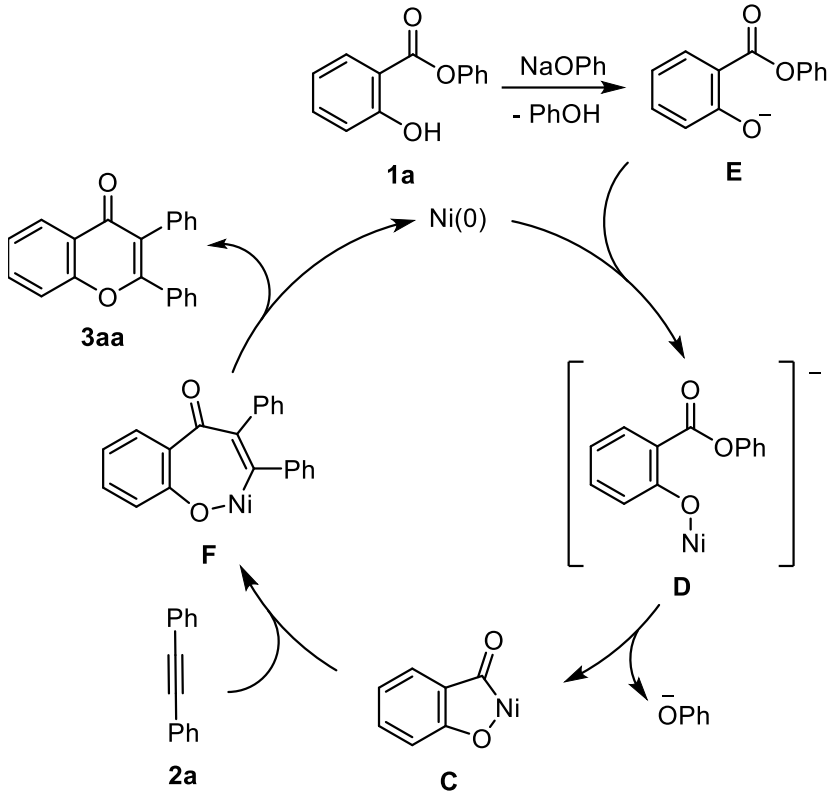
The results for substrate scope are shown in Scheme 2. A substituent at the *meta* position of the ester group had no effect on the reactivity (**3da**, **3ea**, and **3fa**). However, both electron-donating and electron-withdrawing groups at the para position of the ester resulted in a decreased product yield (**3ga** and **3ha**), although the author have no clear explanation for these results. The reaction of **1i** gave **3ia** as the product in 78% yield in spite of the steric hinderance around the hydroxy group as a directing group. Alkynes bearing electron-donating groups and electron-withdrawing groups reacted to give the corresponding products (**3ab**, **3ac**, and **3ad**). The electron deficient alkyne **2d** showed a slightly lower reactivity in this reaction. The alkynes bearing a heteroaromatic ring, such as thiophene and aliphatic

acetylene derivatives were also applicable to this reaction to give **3ae** and **3af**, respectively. When the unsymmetrical alkyne **2g** was used, the desired product **3ag** was obtained in a high regioselective manner.



Scheme 2. substrate and alkyne scope. Reaction conditions: ester (0.4 mmol), alkyne (0.6 mmol), $Ni(cod)_2$ (0.06 mmol), NaOPh (0.4 mmol) in DMSO (1 mL) at 100 °C for 5 h. Yields shown are isolated yields. [a] 120 °C, 18 h.

A plausible mechanism for the reaction is shown in Scheme 3. The ester **1a** reacts with NaOPh to generate the anion **E**. The reaction of **E** with a Ni catalyst gives the anionic Ni salicylate complex **D**. The oxidative addition of an acyl C-O bond gives an oxanickelacycle **C**. The insertion of an alkyne followed by reductive elimination gives the product **3aa** with the regeneration of the Ni(0) species.



Scheme 3. A plausible mechanism.

3.3 Conclusion

In conclusion, the author demonstrated the nickel-catalyzed C−O/O−H annulation of salicylate esters with alkynes, leading to the production of chromones. The reaction proceeded even in the absence of ligands. The presence of a base is essential for the reaction to proceed.

3.4 Experimental Section

3.4.1 General Information

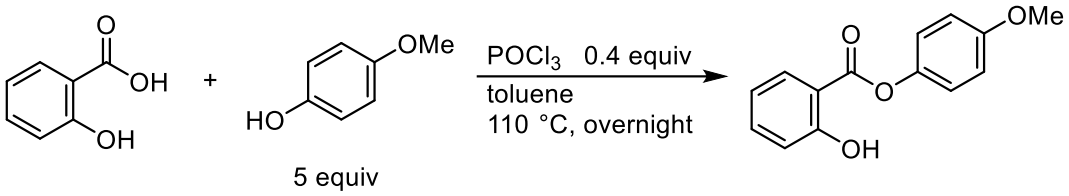
^{1}H and ^{13}C NMR spectra were recorded on a JEOL ECZ-400S spectrometer. The chemical shifts in ^{1}H NMR spectra were recorded relative to tetramethylsilane (δ: 0.0) The chemical shifts in ^{13}C NMR spectra were recorded relative to $CDCl_3$ (δ: 77.0). Data are recorded as follows: chemical shifts in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad singlet, m = multiplet, c = complex), coupling constant (Hz), and integration. Infrared spectra (IR) were recorded on a JASCO FT/IR-4000 spectrometer using ATR method. Absorption data are reported in reciprocal centimeters from 800 to 3500 cm^{-1} with the following relative intensities: s (strong), m (medium), or w (weak). Mass spectra were obtained using a SHIMDZU QP-2010 spectrometer with a quadrupole mass analyzer at 70 eV. Data are recorded as follows: mass/charge ratio and relative intensity to base peak at 100 %. High-resolution mass spectra (HRMS) were obtained using a JEOL JMS-T100LP spectrometer with a time-of-flight mass analyzer. Melting points were determined on a Stanford Research Systems MPA100 apparatus equipped with a digital thermometer and are uncorrected. Column chromatography was performed with SiO_2 (Silicycle Siliaflash F60 (230-

400 mesh)) or NH_2-modified SiO_2 (Kanto Chemical, Silica gel 60 (spherical) NH_2 (40-50μm)).

3.4.2 Materials

NMP (super dehydrated), DMA (super dehydrated), MeCN (super dehydrated), DMSO (super dehydrated), $Ni(cod)_2$, NaOAc, Cs_2CO_3 and KO^{t}Bu were purchased and used as received. Phenyl salicylate (**1a**) and diphenyl acetylene (**2a**) were purchased and recrystalyzed from hexane before use. 3-Hexyne (**2f**) and 1-phenyl-1-propyne (**2g**) were purchased and distilled over CaH_2 before use. phenyl 2-hydroxy-5-methylbenzoate (**1d**),[2a] phenyl 2-hydroxy-5-methoxybenzoate (**1e**),[2a] phenyl 2-hydroxy-4-methoxybenzoate (**1g**),[2a] phenyl 2-hydroxy-4-(trifluoromethyl)benzoate (**1h**),[2a] phenyl 2-hydroxy-3-methylbenzoate (**1i**),[2a] 1,2-bis(4-methylphenyl)ethyne (**2b**),[8] 1,2-bis(4-methoxyphenyl)ethyne (**2c**),[9] 1,2-bis(4-(trifluoromethyl)phenyl)ethyne (**2d**),[8] 1,2-di(thiophen-2-yl)ethyne (**2e**)[10] and NaOPh[11] were prepared according to the reported procedure. Other starting materials were prepared as described below.

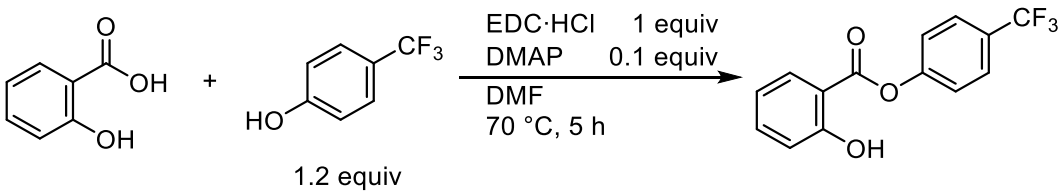
4-Methoxyphenyl 2-hydroxybenzoate (1b) [CAS: 10268-61-8][12]



A 50 mL round-bottom flask was charged with salicylic acid (2.13 g, 15.4 mmol), 4-methoxyphenol (9.20 g, 74.1 mmol) and toluene (10 mL). $POCl_3$ (914 mg, 5.96 mmol) was added and the resulting mixture was stirred overnight at 110 °C under air. After cooling the flask to room temperature, toluene (50 mL) and 1N NaOH aq (50 mL) were added and the organic layer was separated. The organic layer was washed with brine (50 mL) and dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 20/1, R_f = 0.20 in hexane/EtOAc = 20/1) followed by recrystalization from hexane/EtOAc to afford **1b** in 60% yield (2.25 g, 9.21 mmol) as a white solid.

Mp = 92.3-93.2 ºC. **^{1}H NMR** ($CDCl_3$) δ: 3.83 (s, 3H), 6.94-6.98 (c, 3H), 7.03 (dd, J = 8.3 Hz, 0.8 Hz, 1H), 7.10-7.15 (m, 2H), 7.51-7.55 (m, 1H), 8.07 (dd, J = 8.0 Hz, 1.8 Hz, 1H), 10.54 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 55.5, 111.8, 114.5, 117.7, 119.3, 122.3, 130.2, 136.3, 143.4, 157.6, 162.1, 169.2. **HRMS (DART)** Calcd for $C_{14}H_{13}O_4$ ($[M+H]^+$): 245.08084. Found: 245.08088.

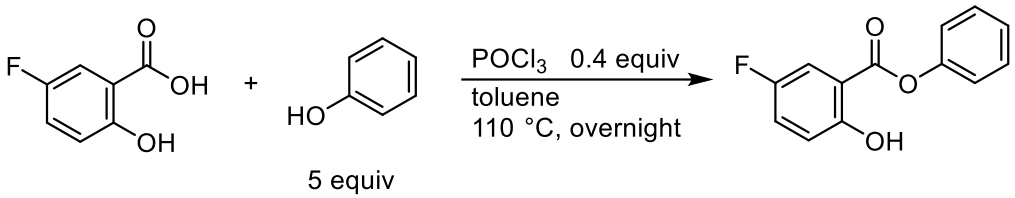
4-(Trifluoromethyl)phenyl 2-hydroxybenzoate (1c) [CAS: 862201-18-1]



A 300 mL round-bottom flask was charged with 4-hydroxybenzotrifluoride (2.89 g, 17.8 mmol), salicylic acid (2.09 g, 15.1 mmol), DMAP (192 mg, 1.57 mmol), EDC·HCl (2.91 g, 15.2 mmol) and DMF (150 mL). The resulting mixture was stirred at 70 °C for 5 h under air. After cooling the flask to room temperature, Et_2O (100 mL) and 1N HCl aq (200 mL) were added and the organic layer was separated. The organic layer was washed with sat. $NaHCO_3$ aq (100 mL) and dried over Na_2SO_4. After removing the volatiles under reduced pressure, the resulting crude mixture was purified by flash column chromatography on silica gel (eluent: hexane/EtOAc = 100/1, R_f = 0.31 in hexane/EtOAc = 20/1) followed by recrystalization from hexane to afford **1c** in 18% yield (753 mg, 2.67 mmol) as a white solid.

Mp = 91.3-91.7 ºC. **^{1}H NMR** ($CDCl_3$) δ: 6.97-7.01 (m, 1H), 7.06 (dd, *J* = 8.5 Hz, 0.9 Hz, 1H), 7.34-7.37(m, 2H), 7.54-7.59 (m, 1H), 7.71-7.74 (m, 2H), 8.07 (dd, *J* = 8.1 Hz, 1.5 Hz, 1H), 10.33 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 111.3, 118.0, 119.6, 122.2, 123.8 (q, *J* = 271 Hz), 127.0 (q, *J* = 3.8 Hz), 128.7 (q, *J* = 32.8 Hz), 130.3, 136.9, 152.5, 162.3, 168.4. **IR** (ATR): 3222 w, 1679 s, 1200 s, 1153 s, 1116 s. **MS**: *m/z* (EI, relative intensity, %): 282 (9, M^+), 122 (12), 121 (100), 93 (22), 92 (11), 65 (41) 63 (12). **HRMS (DART)** Calcd for $C_{14}H_{10}O_3F_3$ ($[M+H]^+$): 283.05766. Found: 283.05828.

Phenyl 5-fluoro-2-hydroxybenzoate (1f) [CAS: 84376-25-0]



1f was prepared from 5-fluorosalicylic acid (2.34 g, 15.0 mmol) and phenol (6.73 g, 71.5 mmol) following the procedure for the synthesis of **1b**. The product was obtained in 50% yield (1.75 g, 7.54 mmol) as a yellow solid by flash column chromatography on silica gel (eluent: hexane/EtOAc = 50/1, R_f = 0.28 in hexane/EtOAc = 20/1) followed by recrystalization from hexane

Mp = 87.6-88.0 ºC. **^{1}H NMR** ($CDCl_3$) δ: 7.01 (dd, *J* = 9.2 Hz, 4.6 Hz, 1H), 7.20-7.22 (m, 2H), 7.25-7.35 (c, 2H), 7.44-7.48 (m, 2H), 7.75 (dd, *J* = 8.7 Hz, 3.2 Hz, 1H), 10.29 (s, 1H). **^{13}C NMR** ($CDCl_3$) δ: 111.7 (d, *J* = 7.5 Hz), 115.4 (d, *J* = 24.3 Hz), 119.1 (d, *J* = 7.5 Hz), 121.5, 124.1 (d, *J* = 23.6 Hz), 126.5, 129.7, 149.8, 155.2 (d, *J* = 239 Hz), 158.4 (d, *J* = 1.0 Hz), 168.1 (d, *J* = 2.7 Hz). **IR** (ATR): 3209 w, 1682 m, 1184 s. **MS**: *m/z* (EI, relative intensity, %): 232 (13, M^+), 139 (100), 111 (14), 83 (12). **HRMS (DART)** Calcd for $C_{13}H_{10}O_3F$ ($[M+H]^+$): 233.06085. Found: 233.06089.

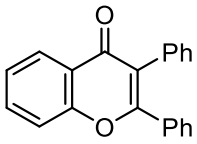
3.4.3 Typical Procedure

To an oven-dried 10 mL screw-capped vial in a glove box, $Ni(cod)_2$ (17 mg, 0.06 mmol), NaOPh (46 mg, 0.4 mmol), the ester (if solid) (0.4 mmol), the alkyne (if solid) (0.6 mmol), DMSO (1 mL) or the ester (0.4 mmol), the alkyne (0.6 mmol), if a liquid, was added last in sequential order. The mixture was stirred at 100 °C for 5 h followed by

cooling. To the resulting mixture, 1N HCl aq (5 mL) and EtOAc (5 mL) were added and the organic layer was separated. The organc layer was filtered through a silica gel pad eluting with EtOAc. Afer removing the volatiles under reduced pressure, the crude mixrture was analyzed by ^{1}H NMR using 1,1,1,2-tetrachloroethane as an internal standard. After the $CDCl_3$ was removed under a vacuum, the obtained mixture was dissolved in Et_2O and washed with 1N NaOH aq to remove the phenol. After removing the volatiles under reduced pressure, the resulting mixture was purified by flash column chromatography on silica gel.

3.4.4 Characterization of Products

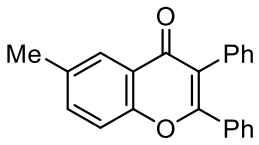
2,3-Diphenyl-4*H*-chromen-4-one (3aa) [CAS: 6005-12-5][4c]



3aa was prepared from the reaction of **1a** with **2a** following typical procedure. The product was obtained in 75% yield (92 mg, 0.31 mmol) as a white solid by flash column chromatography on silica gel (R_f = 0.26 in hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$) δ: 7.20-7.35 (c, 8H), 7.37-7.43 (c, 3H), 7.52 (dd, *J* = 8.5 Hz, 0.5 Hz, 1H), 7.66-7.71 (m, 1H), 8.29 (dd, *J* = 8.0 Hz, 1.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 117.9, 122.9, 123.4, 125.0, 126.3, 127.5, 128.0, 128.2, 129.5, 130.0, 131.1, 132.8, 133.2, 133.6, 156.0, 161.4, 177.3. **MS**: *m*/*z* (EI, relative intensity, %): 298 (40, M^+), 297 (100), 178 (21). **HRMS (DART)** Calcd for $C_{21}H_{15}O_2$ ($[M+H]^+$): 299.10666. Found: 299.10604.

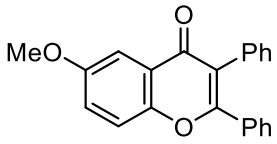
6-Methyl-2,3-diphenyl-4*H*-chromen-4-one (3da) [CAS: 861621-21-8]



3da was prepared from the reaction of **1d** with **2a** following typical procedure (the phenol was not removed in this case). The product was obtained in 78% yield (97 mg, 0.31 mmol) as a white solid by flash column chromatography on NH_2-modified silica gel followed by flash column chromatography on silica gel (R_f = 0.31 in hexane/EtOAc = 5/1).

Mp = 167.0-167.3 ºC. **^{1}H NMR** ($CDCl_3$) δ: 2.47 (s, 3H), 7.20-7.34 (c, 8H), 7.37-7.39 (m, 2H), 7.42 (d, *J* = 8.5 Hz, 1H), 7.48-7.51 (m, 1H), 8.05-8.07 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 21.0, 117.7, 122.7, 123.1, 125.5, 127.5, 128.0, 128.2, 129.5, 129.9, 131.2, 132.9, 133.3, 134.87, 134.91, 154.2, 161.2, 177.3. **IR** (ATR): 3053 w, 1637 s, 1618 s. **MS**: *m*/*z* (EI, relative intensity, %): 312 (41, M^+), 311 (100), 178 (24). **HRMS (DART)** Calcd for $C_{22}H_{17}O_2$ ($[M+H]^+$): 313.12231. Found: 313.12229.

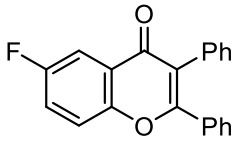
6-Methoxy-2,3-diphenyl-4*H*-chromen-4-one (3ea) [CAS: 2086696-85-5][13]



3ea was prepared from the reaction of **1e** with **2a** following typical procedure (the phenol was not removed in this case). The product was obtained in 71% yield (93 mg, 0.28 mmol) as a white solid by flash column chromatography on silica gel followed by flash column chromatography on NH_2-modified silica gel (R_f = 0.14 in hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$) δ: 3.90 (s, 3H), 7.21-7.34 (c, 9H), 7.36-7.39 (m, 2H), 7.46 (d, J = 9.1 Hz, 1H), 7.65 (d, J = 3.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 55.8, 105.3, 119.3, 122.1, 123.7, 124.0, 127.5, 128.0, 128.1, 129.5, 129.9, 131.2, 133.0, 133.3., 150.8, 156.8, 161.2, 177.0. **MS**: *m/z* (EI, relative intensity, %): 328 (44, M^+), 327 (100), 178 (16), 150 (13). **HRMS (DART)** Calcd for $C_{22}H_{17}O_3$ ($[M+H]^+$): 329.11722. Found: 329.11697.

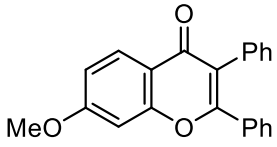
6-Fluoro-2,3-diphenyl-4*H*-chromen-4-one (3fa) [CAS: 1868139-91-6][13]



3fa was prepared from the reaction of **1f** with **2a** following typical procedure (the phenol was not removed in this case). The product was obtained in 78% yield (98 mg, 0.31 mmol) as a yellow solid by flash column chromatography on NH_2-modified silica gel (R_f = 0.34 in hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$) δ: 7.19-7.23 (c, 2H), 7.25-7.44 (c, 9H), 7.54 (dd, J = 9.1 Hz, 4.1 Hz, 1H), 7.92 (dd, J = 8.2 Hz, 3.2 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 111.0 (d, J = 23.6 Hz), 120.1 (d, J = 8.0 Hz), 121.9 (d, J = 25.5 Hz), 122.2, 124.6 (d, J = 7.5 Hz), 127.7, 128.1, 128.3, 129.5, 130.2, 131.1, 132.5, 132.9, 152.2 (d, J = 1.0 Hz), 159.5 (d, J = 246 Hz), 161.7, 176.6 (d, J = 1.9 Hz). **MS**: *m/z* (EI, relative intensity, %): 316 (42, M^+), 315 (100), 178 (25). **HRMS (DART)** Calcd for $C_{21}H_{14}O_2F$ ($[M+H]^+$): 317.09723. Found: 317.09758.

7-Methoxy-2,3-diphenyl-4*H*-chromen-4-one (3ga) [CAS: 18720-69-9][14]

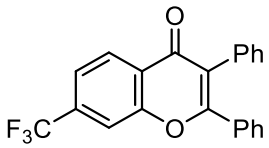


3ga was prepared from the reaction of **1g** with **2a** following typical procedure (120 °C, 18 h, the phenol was not removed in this case). The product was obtained in 16% yield (21 mg, 0.064 mmol) as a white solid by flash column chromatography on silica gel followed by flash column chromatography on NH_2-modified silica gel (R_f = 0.11 in

hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$) δ: 3.92 (s, 3H), 6.93 (d, *J* = 2.3 Hz, 1H), 7.00 (dd, *J* = 8.8 Hz, 2.3 Hz, 1H), 7.20-7.33 (c, 8H), 7.37-7.40 (m, 2H), 8.20 (d, *J* = 8.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 55.8, 100.0, 114.5, 117.3, 122.7, 127.5, 127.7, 128.0, 128.2, 129.5, 129.9, 131.2, 132.9, 133.3, 157.7, 161.0, 164.1, 176.7. **HRMS (DART)** Calcd for $C_{22}H_{17}O_3$ ($[M+H]^+$): 329.11722. Found: 329.11725.

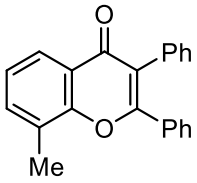
2,3-Diphenyl-7-(trifluoromethyl)-4*H*-chromen-4-one (3ha) [CAS: 2229661-96-3][13]



3ha was prepared from the reaction of **1h** with **2a** following typical procedure (120 °C, 18 h, the phenol was not removed in this case). The product was obtained in 25% yield (36 mg, 0.098 mmol) as a white solid by flash column chromatography on NH_2-modified silica gel (R_f = 0.34 in hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$) δ: 7.21-7.42 (c, 10H), 7.66 (dd, *J* = 8.3 Hz, 1.1 Hz, 1H), 7.86 (s, 1H), 8.42 (d, *J* = 8.3 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 115.9 (q, *J* = 3.9 Hz), 121.3 (q, *J* = 3.3 Hz), 123.1 (q, *J* = 273 Hz), 123.5, 125.6, 127.7, 127.9, 128.2, 128.4, 129.5, 130.4, 131.0, 132.2, 132.6, 135.2 (q, *J* = 33.3 Hz), 155.4, 162.2, 176.5. **MS**: *m*/*z* (EI, relative intensity, %): 366 (46, M^+), 365 (100), 178 (18). **HRMS (DART)** Calcd for $C_{22}H_{14}O_2F_3$ ($[M+H]^+$): 367.09404. Found: 367.09441.

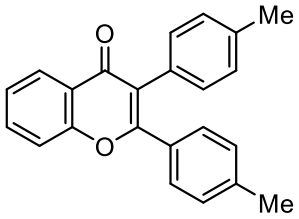
8-Methyl-2,3-diphenyl-4*H*-chromen-4-one (3ia) [CAS: 87165-75-1]



3ia was prepared from the reaction of **1i** with **2a** following typical procedure. The product was obtained in 78% yield (101 mg, 0.32 mmol) as a white solid by flash column chromatography on NH_2-modified silica gel (R_f = 0.26 in hexane/EtOAc = 5/1).

Mp = 209.7-210.5 ºC. **^{1}H NMR** ($CDCl_3$) δ: 2.56 (s, 3H), 7.22-7.34 (c, 9H), 7.41-7.43 (m, 2H), 7.54 (d, *J* = 7.1 Hz, 1H), 8.13 (dd, *J* = 7.9, 0.8 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 15.6, 122.6, 123.3, 123.9, 124.6, 127.3, 127.5, 128.1, 128.2, 129.5, 130.0, 131.2, 132.9, 133.4, 134.4, 154.5, 160.9, 177.6. **IR** (ATR): 3058 w, 1629 s. **MS**: *m*/*z* (EI, relative intensity, %): 312 (39, M^+), 311 (100), 178 (20). **HRMS (DART)** Calcd for $C_{22}H_{17}O_2$ ($[M+H]^+$): 313.12231. Found: 313.12322.

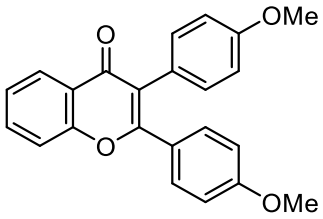
2,3-Di-*p*-tolyl-4*H*-chromen-4-one (3ab) [CAS: 1119624-80-4][4c]



3ab was prepared from the reaction of **1a** with **2b** following typical procedure. The product was obtained in 79% yield (101 mg, 0.31 mmol) as a white solid by flash column chromatography on silica gel (R_f = 0.32 in hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$) δ: 2.33 (s, 3H), 2.34 (s, 3H), 7.04-7.08 (m, 2H), 7.12 (s, 4H), 7.29-7.33 (m, 2H), 7.38-7.42 (m, 1H), 7.50-7.52 (m, 1H), 7.65-7.69 (m, 1H), 8.28 (dd, *J* = 8.0, 1.4 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 21.3, 21.4, 117.9, 122.4, 123.4, 124.9, 126.3, 128.8, 129.0, 129.4, 129.9, 130.5, 130.9, 133.5, 137.1, 140.3, 156.0, 161.3, 177.5. **MS**: *m*/*z* (EI, relative intensity, %): 327 (14), 326 (60, M^+), 325 (82), 312 (25), 311 (100), 206 (22), 205 (13), 162 (15). **HRMS (DART)** Calcd for $C_{23}H_{19}O_2$ ($[M+H]^+$): 327.13796. Found: 327.13807.

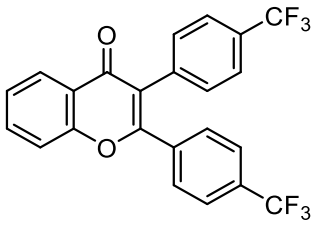
2,3-Bis(4-methoxyphenyl)-4H-chromen-4-one (3ac) [CAS: 1119624-83-7][13]



3ac was prepared from the reaction of **1a** with **2c** following typical procedure (the phenol was not removed in this case). The product was obtained in 65% yield (94 mg, 0.26 mmol) as a white solid by flash column chromatography on NH_2-modified silica gel (R_f = 0.09 in hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$) δ: 3.79 (s, 3H), 3.81 (s, 3H), 6.77-6.82 (m, 2H), 6.85-6.89 (m, 2H), 7.14-7.19 (m, 2H), 7.36-7.42 (c, 3H), 7.50-7.52 (m, 1H), 7.65-7.69 (m, 1H), 8.27 (dd, *J* = 7.8, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 55.15, 55.23, 113.5, 113.9, 117.8, 121.5, 123.4, 124.8, 125.3, 125.5, 126.2, 131.1, 132.2, 133.4, 155.9, 158.8, 160.7, 161.0, 177.5. **MS**: *m*/*z* (EI, relative intensity, %): 359 (23), 358 (100, M^+), 357 (94), 343 (23), 327 (29), 238 (21), 223 (25), 69 (13). **HRMS (DART)** Calcd for $C_{23}H_{19}O_4$ ($[M+H]^+$): 359.12779. Found: 359.12718.

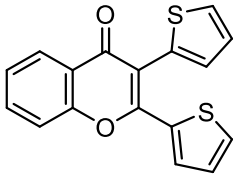
2,3-Bis(4-(trifluoromethyl)phenyl)-4*H*-chromen-4-one (3ad) [CAS: 2086696-81-1][7b]



3ad was prepared from the reaction of **1a** with **2d** following typical procedure (the phenol was not removed in this case). The product was obtained in 47% yield (85 mg, 0.196 mmol) as a white solid by flash column chromatography on NH_2-modified silica gel (R_f = 0.14 in hexane/EtOAc = 5/1).

Mp = 172.1-172.6 ºC. **^{1}H NMR** ($CDCl_3$) δ: 7.35 (d, *J* = 7.8 Hz, 2H), 7.45-7.60 (c, 8H), 7.73-7.78 (m, 1H), 8.29 (dd, *J* = 8.0, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 118.0, 122.4, 123.2, 123.5 (q, *J* = 273 Hz), 124.0 (q, *J* = 272 Hz), 125.2-125.5 (c, Two peaks are overlapped.), 125.6, 126.4, 129.9, 130.0 (q, *J* = 32.7 Hz), 131.6, 132.1 (q, *J* = 32.5 Hz), 134.3, 136.1, 136.2, 155.9, 160.2, 176.7. **IR** (ATR): 3069 w, 1642 m, 1320 s. **HRMS (DART)** Calcd for $C_{23}H_{13}O_2F_6$ ($[M+H]^+$): 435.08143. Found: 435.08033.

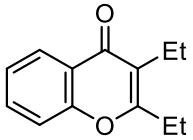
2,3-Di(thiophen-2-yl)-4*H*-chromen-4-one (3ae) [CAS: 1119624-87-1][4a]



3ae was prepared from the reaction of **1a** with **2e** following typical procedure (the phenol was not removed in this case). The product was obtained in 73% yield (94 mg, 0.303 mmol) as a pale yellow solid by flash column chromatography on NH_2-modified silica gel followed by flash column chromatography on silica gel (R_f = 0.17 in hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$) δ: 7.02 (dd, *J* = 5.1, 3.9 Hz, 1H), 7.06 (dd, *J* = 3.5, 1.3 Hz, 1H), 7.18 (dd, *J* = 5.1, 3.5 Hz, 1H), 7.39-7.43 (c, 2H), 7.47 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.53 (d, *J* = 7.8 Hz, 1H), 7.56 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.67-7.73 (m, 1H), 8.24 (dd, *J* = 7.8, 1.6 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 114.1, 117.7, 122.8, 125.2, 126.2, 127.3, 127.7, 128.4, 129.9, 131.5, 131.8, 132.8, 133.9, 134.6, 155.4, 157.0, 177.0. **IR** (ATR): 3075 w, 1633 s, 1614 s. **MS**: *m*/*z* (EI, relative intensity, %): 312 (12), 311 (28), 310 (100, M^+), 309 (91), 190 (73), 146 (11), 145 (15), 133 (15), 114 (12). **HRMS (DART)** Calcd for $C_{17}H_{11}O_2S_2$ ($[M+H]^+$): 311.01950. Found: 311.01882.

2,3-Diethyl-4*H*-chromen-4-one (3af) [CAS: 100797-34-0][4c]

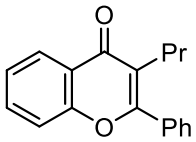


3af was prepared from the reaction of **1a** with **2f** following typical procedure (the phenol was not removed in this case). The product was obtained in 73% yield (22 mg, 0.109 mmol) as a colorless oil by flash column chromatography on NH_2-modified silica gel followed by flash column chromatography on silica gel (R_f = 0.36 in hexane/EtOAc = 20/1).

^{1}H NMR ($CDCl_3$) δ: 1.13 (t, *J* = 7.5 Hz, 3H), 1.34 (t, *J* = 7.5 Hz, 3H), 2.58 (q, *J* = 7.5 Hz, 2H), 2.74 (q, *J* = 7.5 Hz,

2H), 7.32-7.36 (m, 1H), 7.38-7.40 (m, 1H), 7.58-7.63 (m, 1H), 8.20 (dd, *J* = 7.9, 1.7 Hz, 1H). **^{13}C NMR** ($CDCl_3$) δ: 12.0, 13.9, 17.9, 25.1, 117.6, 122.0, 122.9, 124.3, 125.8, 132.9, 155.9, 166.2, 177.8. **MS**: *m/z* (EI, relative intensity, %): 203 (15), 202 (100, M^+), 201 (95), 187 (45), 174 (11), 173 (30), 121 (48), 93 (17), 92 (10), 65 (13). **HRMS (DART)** Calcd for $C_{13}H_{15}O_2$ ($[M+H]^+$): 203.10666. Found: 203.10684.

2-Phenyl-3-propyl-4*H*-chromen-4-one (3ag)



3ag was prepared from the reaction of **1a** with **2g** following typical procedure. The product was obtained in 35% yield (37 mg, 0.140 mmol) as a pale yellow oil by flash column chromatography on silica gel (R_f = 0.34 in hexane/EtOAc = 5/1).

^{1}H NMR ($CDCl_3$) δ: 0.90 (t, *J* = 7.3 Hz, 3H), 1.55-1.64 (m, 2H), 2.51-2.55 (m, 2H), 7.37-7.41 (m, 1H), 7.43 (dd, *J* = 8.5, 0.5 Hz, 1H), 7.51-7.54 (c, 3H), 7.58-7.67 (c, 3H), 8.24-8.27 (m, 1H). **^{13}C NMR** ($CDCl_3$) δ: 14.2, 22.4, 27.8, 117.9, 122.2, 122.9, 124.6, 125.9, 128.5, 128.6, 130.1, 133.3, 133.6, 156.1, 161.7, 178.5. **IR** (ATR): 3061 w, 1635 s. **MS**: *m/z* (EI, relative intensity, %): 264 (38, M^+), 263 (100), 247 (10), 235 (15), 115 (26). **HRMS (DART)** Calcd for $C_{18}H_{17}O_2$ ($[M+H]^+$): 265.12231. Found: 265.12273.

3.5 Reference and Notes

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(3) For selected reviews on the bioactivity of chromones, see: (a) Gaspar, A.; Matos, M. J.; Garrido, J.; Uriarte, E.; Borges, F. *Chem. Rev.* **2014**, *114*, 4960. (b) Keri, R. S.; Budagumpi, S.; Pai, R. K.; Balakrishna, R. G. *Eur. J. Med. Chem.* **2014**, *78*, 340. (c) Reis, J.; Gaspar, A.; Milhazes, N.; Borges, F. *J. Med. Chem.* **2017**, *60*, 7941.

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Conclusion

The research discussed in this dissertation was directed at the nickel-catalyzed C-O bond activation reactions assisted by a directing group.

The nickel-catalyzed reductive removal of ester groups without an external reductant was reported in Chapter 1. Although *O*-aryl esters are generally used for the transformation of aromatic esters, in which an inert acyl C-O bond of an *O*-alkyl ester is activated. An ester group, an amide group and a heteroaromatic ring can be used as directing groups. Surprisingly, a simple arene ring also functioned as a directing group. The source of hydrogen in this reaction was derived from the hydrogen atom of the alkoxy group, as confirmed by deuterium labeling experiments.

The C-O/N-H annulation of amides with a phenoxy group at the *ortho* position with alkynes was discussed in Chapter 2. In this reaction, the base abstracts the N-H proton of the amide to give an amide anion. The nickel ate complex which is generated by the coordination of the amide anion to the nickel catalyst is sufficient to activate an inert a C-O bond. This reaction proceeded, even at low temperature, and in the absence of a ligand. This methodology was applicable to C-S bond and C-CN bond activation.

The C-O/O-H annulation of salicylate esters with alkynes is discussed in Chapter 3. This reaction is the first example of the synthesis of chromone derivatives from salicylate esters with alkynes.

In Chapter 2 and 3, the synthesis of cyclic structures that include a directing group was developed. In these reactions, a directing group was essential. The findings in this study will contribute to the development of the activation of unreactive bonds.

List of Publications

(1) Nickel-Catalyzed Reductive Defunctionalization of Esters in the absence of an External Reductant: Activation C-O Bonds
Yasuaki Iyori, Kenjiro Takahashi, Ken Yamazaki, Yusuke Ano and Naoto Chatani
Chem. Commun. **2019**, *55*, 13610.

(2) Nickel-Catalyzed C-O/N-H, C-S/N-H, and C-CN/N-H Annulation of Aromatic Amides with Alkynes: C-O, C-S, and C-CN Activation
Yasuaki Iyori, Rina Ueno, Aoi Morishige and Naoto Chatani
Chem. Sci. in Press, DOI: 10.1039/d0sc06056a.

(3) Nickel-Catalyzed C-O/O-H Annulation of Salicylic Acid Esters with Alkynes
Yasuaki Iyori and Naoto Chatani
Chem. Lett. in Press, DOI: 10.1246/cl.200885.

Supplementary List of Publications

(1) Conversion of 3,3,3-Trisubstituted Prop-1-ynes with *tert*-Butylhydrazine into 3,3,3-Trisubstituted Propionitriles Catalyzed by $TpRh(C_2H_4)_2/P(2\text{-furyl})_3$
Yoshiya Fukumoto, Yuto Tamura, Yasuaki Iyori and Naoto Chatani
J. Org. Chem. **2016**, *81*, 3161.

(2) Direct and Regioselective Introduction of Acetals into Imidazoles at the 2-Position by the Iridium-Catalyzed Reaction with Formates in the Presence of Hydrosilanes
Yoshiya Fukumoto, Yasuaki Iyori and Naoto Chatani
Eur. J. Org. Chem. **2017**, 1662.