Development of C–H Oxygenation and Carbonylation Reactions of Arenes

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THESIS

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TABLE OF CONTENTS

Chapter 1  Introduction ................................................................................................................ 1

1.1 Background of Synthesis of Phenols via Arene C–H Oxygenation ................................. 1

1.2 Background of C–H Carbonylation Reactions of Arenes using CO as C1 Source ........ 27

References ................................................................................................................................... 55

Chapter 2  Carboxyl Group-Directed Remote C–H Oxygenation Reactions of Arenes ........ 60

2.1 Introduction .......................................................................................................................... 60

2.2 Reaction Design .................................................................................................................. 61

2.2.1 Optimization .................................................................................................................... 62

2.2.2 Scope and Limitation of the Cu-Catalyzed Remote C–H Oxygenation Reaction...... 65

2.2.3 Mechanism Study of the Cu-Catalyzed Remote C–H Oxygenation Reaction ............. 69

2.3 Development of a Novel K₂S₂O₈-Mediated C–H Oxygenation Reaction ...................... 72

2.3.1 Reaction Design Based on Understanding of the Reaction Mechanism of the Cu-  
Catalyzed C–H Oxygenation ...................................................................................................... 72

2.3.2 Development of the K₂S₂O₈ Mediated Remote C–H Oxygenation Reaction of Arenes 
............................................................................................................................................... 72

2.3.3 Proposed Reaction Mechanism of the K₂S₂O₈-Mediated Remote C–H Oxygenation  
Reaction ..................................................................................................................................... 74

2.4 Synthesis of Aryl Ethers from Benzocoumarins................................................................. 75

2.5 Conclusion .......................................................................................................................... 75

2.6 Related Methodologies and Applications Developed by Other Groups ......................... 76

References ................................................................................................................................... 78
Chapter 3  Removable Group-Directed Pd(II)-Catalyzed C–H Carbonylation Reaction of Arenes

3.1 Introduction .................................................................................................................................. 81

3.2 Silanol-Directed Pd-Catalyzed C–H Carboxylation of Phenols for Synthesis of Salicylic Acids ..................................................................................................................................... 85

3.2.1 Introduction and Reaction Design ............................................................................... 85

3.2.2 Optimization of Pd-Catalyzed C–H Carbonylation ..................................................... 87

3.2.3 Scope and Limitation of Pd-Catalyzed C–H Carboxylation ........................................ 88

3.2.4 Mechanistic Studies and Modification of Complex Phenols ....................................... 93

3.2.5 Conclusion ................................................................................................................... 94

3.3 Pd-Catalyzed PyrDipSi-Directed C–H Alkoxylcarbonylation of Arenes for Synthesis of Active Hexafluoroisopropyl Benzoates ................................................................................ 95

3.3.1 Introduction and Reaction Design ............................................................................... 95

3.3.2 Optimization of Reaction Conditions .......................................................................... 96

3.3.3 Reaction Scope ............................................................................................................. 97

3.3.4 Mechanistic Studies ................................................................................................... 103

3.3.5 Conclusion ................................................................................................................. 107

References .................................................................................................................................... 107

Chapter 4  Experimental Section ............................................................................................. 114

General Information ............................................................................................................ 114

4.1 Synthesis of Biaryl-2-Carboxylic Acids 2–4 .......................................................................... 115

4.2 C–H Oxygenation Reaction of Biaryl-2-Carboxylic Acids 2–4 ........................................ 128

4.3 Ring-Opening of the Obtained Benzocoumarins 2-1 into 2-17 ........................................ 143
4.4 Synthesis of Silanols 3-18................................. 145
4.5 Optimization of Reaction Conditions ...................... 156
4.6 Mechanistic Studies ............................................. 159
4.7 Synthesis of Salicylic Acids .................................... 163
4.8 Synthesis of Aryl Silanes (PyrDipSi-Ar) .............. 173
4.9 Optimization of Reaction Conditions .................. 187
4.10 NMR Spectroscopic Studies .............................. 190
4.11 Synthesis of Active Aryl Esters ......................... 204
4.12 Mechanistic Experiments ................................. 219
4.13 Further Transformations .................................... 222

APPENDIX I .............................................................. 228

APPENDIX II ............................................................ 399

VITA ........................................................................... 404
<table>
<thead>
<tr>
<th>SCHEME</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scheme 1.1</td>
<td>1</td>
</tr>
<tr>
<td>Scheme 1.2</td>
<td>2</td>
</tr>
<tr>
<td>Scheme 1.3</td>
<td>3</td>
</tr>
<tr>
<td>Scheme 1.4</td>
<td>4</td>
</tr>
<tr>
<td>Scheme 1.5</td>
<td>5</td>
</tr>
<tr>
<td>Scheme 1.6</td>
<td>6</td>
</tr>
<tr>
<td>Scheme 1.7</td>
<td>7</td>
</tr>
<tr>
<td>Scheme 1.8</td>
<td>8</td>
</tr>
<tr>
<td>Scheme 1.9</td>
<td>8</td>
</tr>
<tr>
<td>Scheme 1.10</td>
<td>9</td>
</tr>
<tr>
<td>Scheme 1.11</td>
<td>10</td>
</tr>
<tr>
<td>Scheme 1.12</td>
<td>10</td>
</tr>
<tr>
<td>Scheme 1.13</td>
<td>11</td>
</tr>
<tr>
<td>Scheme 1.14</td>
<td>13</td>
</tr>
<tr>
<td>Scheme 1.15</td>
<td>13</td>
</tr>
<tr>
<td>Scheme 1.16</td>
<td>15</td>
</tr>
<tr>
<td>Scheme 1.17</td>
<td>16</td>
</tr>
<tr>
<td>Scheme 1.18</td>
<td>17</td>
</tr>
<tr>
<td>Scheme 1.19</td>
<td>18</td>
</tr>
<tr>
<td>Scheme 1.20</td>
<td>19</td>
</tr>
<tr>
<td>Scheme 1.21</td>
<td>20</td>
</tr>
<tr>
<td>Scheme 1.22</td>
<td>20</td>
</tr>
</tbody>
</table>
Scheme 3.5 ................................................................. 84
Scheme 3.6 ................................................................. 85
Scheme 3.7 ................................................................. 86
Scheme 3.8 ................................................................. 87
Scheme 3.9 ................................................................. 93
Scheme 3.10 ............................................................... 94
Scheme 3.11 ............................................................... 96
Scheme 3.12 ............................................................... 102
LIST OF FIGURES

FIGURE                                                                            PAGE
Figure 1.1 Mechanistic Studies Substrates for the Pd-Catalyzed C–H Acetoxylation     ................................................................. 11
Figure 1.2 Reaction Mechanism of the Pd-Catalyzed C–H Acetoxylation Reaction ........ 12
Figure 1.3 Proposed Reaction Mechanism of the Dehydrogenative Cross-Coupling Reaction .................................................................................................................. 24
Figure 1.4 Reaction Mechanism of the Pd-Catalyzed Double C–H Carbonylation Reaction .......................................................................................................................... 46
Figure 1.5 Reaction Mechanism of the Ru-Catalyzed C–H Carbonylation Reaction .......... 53
Figure 2.1 Selected Examples of Benzocoumarin Containing Compounds ....................... 60
Figure 2.2 Reaction Design............................................................................................... 62
Figure 2.3 Proposed Reaction Mechanism of the Cu-Catalyzed C–H Oxygenation Reaction ...................................................................................................................... 71
Figure 3.1 Proposed Structure of the Hydrogen-Bonding Complex................................. 104
Figure 3.2 NMR Studies of the Hydrogen-Bonding Complexation .................................. 105
Figure 3.3 Proposed Reaction Mechanism of the Pd-Catalyzed C–H Alkoxy carbonylation Reaction .................................................................................................................. 106
## LIST OF EQUATIONS

<table>
<thead>
<tr>
<th>EQUATION</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Equation 1.1</td>
<td>28</td>
</tr>
<tr>
<td>Equation 1.2</td>
<td>28</td>
</tr>
<tr>
<td>Equation 1.3</td>
<td>36</td>
</tr>
<tr>
<td>Equation 1.4</td>
<td>37</td>
</tr>
<tr>
<td>Equation 1.5</td>
<td>37</td>
</tr>
<tr>
<td>Equation 1.6</td>
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</tr>
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<td>61</td>
</tr>
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<td>69</td>
</tr>
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<td>75</td>
</tr>
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</tr>
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</tr>
<tr>
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<td>106</td>
</tr>
</tbody>
</table>
# LIST OF TABLES

<table>
<thead>
<tr>
<th>TABLE</th>
<th>PAGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Table 2.1 Initial Optimization of the Remote C–H Oxygenation Reaction</td>
<td>63</td>
</tr>
<tr>
<td>Table 2.2 Optimization of Oxidant of the Cu-Catalyzed Remote C–H Oxygenation Reaction</td>
<td>64</td>
</tr>
<tr>
<td>Table 2.3 Further Optimization of the Cu-Catalyzed Remote C–H Oxygenation Reaction</td>
<td>65</td>
</tr>
<tr>
<td>Table 2.4 Cu-Catalyzed Remote C–H Oxygenation Reaction</td>
<td>66</td>
</tr>
<tr>
<td>Table 2.5 K₂S₂O₈-Mediated C–H Oxygenation Reaction</td>
<td>73</td>
</tr>
<tr>
<td>Table 3.1 Optimization of Pd-Catalyzed C–H Carboxylation of Phenols</td>
<td>88</td>
</tr>
<tr>
<td>Table 3.2 Synthesis of Salicylic Acids</td>
<td>90</td>
</tr>
<tr>
<td>Table 3.3 Optimization of Reaction Parameters</td>
<td>97</td>
</tr>
<tr>
<td>Table 3.4 Scope of Active HFIP Benzoates</td>
<td>98</td>
</tr>
</tbody>
</table>
### LIST OF ABBREVIATIONS

<table>
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<th>Abbreviation</th>
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</thead>
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<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>Ad</td>
<td>adamantyl</td>
</tr>
<tr>
<td>Ala</td>
<td>alanine</td>
</tr>
<tr>
<td>Alk</td>
<td>alkyl</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>AQ</td>
<td>8-aminoquinoline</td>
</tr>
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<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
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<tr>
<td>BINOL</td>
<td>1,1'-bi-2-naphthol</td>
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<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Boc</td>
<td>tert-butoxycarbonyl</td>
</tr>
<tr>
<td>BPin</td>
<td>(pinacolato)boron</td>
</tr>
<tr>
<td>BPO</td>
<td>benzoyl peroxide</td>
</tr>
<tr>
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<td>benzoquinone</td>
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<tr>
<td>Bz</td>
<td>benzoyle</td>
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<td>iBu</td>
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<td>butyl</td>
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<td>tBu</td>
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<td>Calcd</td>
<td>calculated</td>
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<tr>
<td>cat.</td>
<td>catalytic amount</td>
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<tr>
<td>CMD</td>
<td>concerted metalation deprotonation</td>
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<tr>
<td>COD</td>
<td>1,5-cyclooctadiene</td>
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Cp^+ 1,2,3,4,5-pentamethylcyclopentadienyl

*m*-CPBA *meta*-chloroperoxybenzoic acid

Cy cyclohexyl

δ chemical shifts in parts per million downfield from tetramethylsilane (NMR)

2D two-dimensional (NMR)

d doublet

dba dibenzylidene acetone

DCM dichloromethane

DCE 1,2-dichloroethane

DEPT distortionless enhancement by polarization transfer

DFT density functional theory

DG directing group

DMA dimethylacetamide

DMB 2,4-dimethoxybenzyl

DMF dimethylformamide

DMSO dimethylsulfoxide

DoM directed *ortho* metalation

dppp 1,3-bis(diphenylphosphino)propane

EDG electron-donating group

e.g. for example

EI electron impact ionization (in mass spectrometry)

Et ethyl

equiv molar equivalent
EWG  electron-withdrawing group
G    group
g    gram
GC   gas chromatography
Gly  glycine
h, hrs hour(s)
Hal  halogen
HFIP hexafluoroisopropyl
HMBC heteronuclear multiple-bond correlation spectroscopy (NMR)
HMQC heteronuclear multiple-quantum coherence spectroscopy (NMR)
HR   high resolution (mass spectrometry)
Hz   Hertz
Ile  isoleucine
IPr  1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene
J    spin-spin coupling constant (NMR)
KIE  kinetic isotope effect
L    ligand
LDA lithium diisopropylamide
Leu  leucine
m    multiplet (NMR)
MOM  methoxymethyl acetal
m.p. melting point
NBS  N-bromosuccinimide
<table>
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<th>Abbreviation</th>
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<tr>
<td>NOE</td>
<td>nuclear Overhauser effect</td>
</tr>
<tr>
<td>Ph</td>
<td>phenyl</td>
</tr>
<tr>
<td>Phe</td>
<td>phenylalanine</td>
</tr>
<tr>
<td>Phen</td>
<td>1,10-phenanthroline</td>
</tr>
<tr>
<td>PIP</td>
<td>2-(pyridin-2-yl)isopropyl amine</td>
</tr>
<tr>
<td>Piv</td>
<td>pivaloyl, trimethylacetyl</td>
</tr>
<tr>
<td>PMB</td>
<td>para-methoxybenzyl</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>Pr</td>
<td>propyl</td>
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<tr>
<td>iPr</td>
<td>isopropyl</td>
</tr>
<tr>
<td>nPr</td>
<td>propyl</td>
</tr>
<tr>
<td>PSI</td>
<td>per square inch</td>
</tr>
<tr>
<td>PyDipSi</td>
<td>pyridine diisopropylsilyl</td>
</tr>
<tr>
<td>PyrDipSi</td>
<td>pyrimidine diisopropylsilyl</td>
</tr>
<tr>
<td>q</td>
<td>quartet (NMR)</td>
</tr>
<tr>
<td>quint</td>
<td>quintet (NMR)</td>
</tr>
<tr>
<td>r.t.</td>
<td>room temperature</td>
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<tr>
<td>THQ</td>
<td>tetrahydroquinoline</td>
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<tr>
<td>s</td>
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<tr>
<td>SA</td>
<td>salicylic acid</td>
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<td>sept</td>
<td>septet (NMR)</td>
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<tr>
<td>t</td>
<td>triplet (NMR)</td>
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<tr>
<td>TBAI</td>
<td>tetrabutylammonium iodide</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Full Name</td>
</tr>
<tr>
<td>--------------</td>
<td>-----------</td>
</tr>
<tr>
<td>TBDPS</td>
<td>tert-butyl diphenylsilyl</td>
</tr>
<tr>
<td>TBHP</td>
<td>tert-butyl hydroperoxide</td>
</tr>
<tr>
<td>TBPB</td>
<td>tert-butyl peroxybenzoate</td>
</tr>
<tr>
<td>TBS</td>
<td>tert-butyl dimethylsilyl</td>
</tr>
<tr>
<td>Tf</td>
<td>trifluoromethanesulfonyl</td>
</tr>
<tr>
<td>TFA</td>
<td>trifluoroacetic acid</td>
</tr>
<tr>
<td>TFAA</td>
<td>trifluoroacetic anhydride</td>
</tr>
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<td>TF Etol</td>
<td>trifluoroethanol</td>
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<td>2,2,6,6-tetramethyl-1-piperidinyloxy</td>
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<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
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<td>tetrahydroquinoline</td>
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<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
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<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
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<tr>
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<td>transition-metal</td>
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<td>TMP</td>
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<td>para-toluenesulfonyl</td>
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SUMMARY

This thesis contains two parts. In the first part, it describes the development of the Cu-catalyzed and \( \text{K}_2\text{S}_2\text{O}_8 \)-mediated remote C–H oxygenation reaction of arenes for synthesis of benzocoumarines. In the second part, it demonstrates the Pd-catalyzed \textit{ortho} C–H carbonylation reactions of arenes using easily installable/modifiable silicon-tethered directing groups for synthesis of salicylic acids and active HFIP esters.

The first part of Chapter 1 summarizes a general approach for synthesis of phenols via aromatic C–H bond oxygenation, including transition metal-catalyzed and metal free C–H oxygenation reactions. Substrate scope, limitation, and reaction mechanism of selected reactions are discussed. The second part of Chapter 1 introduces the Pd-catalyzed C–H bond carbonylation reactions using CO as C1 source for synthesis of aryl carbonyl compounds. Substrate scope and limitation of both direct and directed carbonylation reactions are discussed. In addition, reaction mechanisms of selected examples are also presented.

Chapter 2 presents the Cu-catalyzed remote C–H oxygenation reaction of 2-aryl benzoic acids for synthesis of electron-rich and -neutral benzocoumarines. Based on the mechanistic understanding of the Cu-catalyzed reaction, a more general \( \text{K}_2\text{S}_2\text{O}_8 \)-mediated C–H oxygenation reaction was developed, which features general scope and excellent functional group tolerance. Preliminary mechanistic studies suggest a key oxygen radical intermediate is likely to be involved in this transformation.

Chapter 3 summaries the recent advances of C–H bond functionalization of arenes involving removable/modifiable silicon directing groups. It also presents the development of the Pd-catalyzed silanol \textit{ortho} C–H carboxylation of phenols for synthesis of salicylic acids. The reaction scope and limitation are presented. In addition, the reaction mechanism is discussed.
Last, an efficient Pd-catalyzed PyrDipSi-directed C–H alkoxylicarbonylation reaction of arenes is demonstrated for synthesis of active benzoates. The reaction allows for synthesis of arenes with two independent functionalizable sites, which was further elaborated on the C-7 C–H carbonylation of biologically important tetrahydrogenquinolines and the synthesis of bioactive active benzocoumarin derivative.

Experimental details for the C–H oxygenation and carbonylation reactions of arenes are described in Chapter 4, and spectral data for selected starting materials and products are presented in Appendix.
CONTRIBUTION OF AUTHORS

Several parts of this thesis are reproduced from previously published research articles co-authored with collaborators, who contributed significantly to the presented work.

Chapter 2 of this thesis is written based on the previously published article ("General and Practical Carboxyl-Group-Directed Remote C–H Oxygenation Reactions of Arenes." Wang, Y.; Gulevich, A. V.; Gevorgyan, V. Chem. Eur. J. 2013, 19, 15836-15840.). This work was accomplished by myself and Dr. Gulevich under supervision of Professor Gevorgyan. I designed the reaction, performed optimization, and finished most of the scope of this transformation (chapters 2.2 and 2.3). Dr. Gulevich partially contributed to the synthetic part of the project (chapters 2.2.2, 2.3.2, and 2.4).

Chapter 1  Introduction

1.1 Background of Synthesis of Phenols via Arene C–H Oxygenation

Phenols are widely used in pharmaceuticals, agrochemicals, and materials. Also, they are present in natural products and are produced in a variety of metabolic processes. Though phenols could be synthesized by either Sandmeyer reaction or transition metal-catalyzed cross coupling reactions, those methods require use of pre-functionalized arenes. Thus, development of efficient methods for synthesis of phenols by oxygenation of aromatic C–H bonds are highly demanded.

In 1996, the Crabtree group reported the first Pd-catalyzed direct C–H oxygenation reaction of arenes employing Phl(OAc)₂ oxidant (Scheme 1.1). Though the reaction suffered from certain limitations including a narrow scope and poor regioselectivity, it showed for the first time that arene C–H could efficiently and catalytically be converted into valuable C–O bond. Importantly, the proposed mechanism involved an intermediary of Pd(IV) species, which set a stage for development of many other C–H transformations, such as carbon–carbon and carbon–

![Scheme 1.1](image-url)

Scheme 1.1
hetero atom bond formation. Based on the analysis of the reaction kinetics, Crabtree suggested that the aromatic C–H palladation is the rate-determining step.

To overcome disadvantages of the direct C–H oxygenation, Sanford introduced a directing group strategy for C–H oxygenation reaction (Scheme 1.2). It was shown that in the presence of Pd(OAc)$_2$ catalyst and PhI(OAc)$_2$ oxidant, benzo[h]quinoline 1-2 underwent smooth mono-acetoxylation reaction to produce the corresponding oxygenated product 1-3 in 86% yield. In addition, substrates bearing other directing groups, such as pyridines, pyrazoles, diazenes, imines, and pyrrolidinones, worked well in this C–H oxygenation reaction to produce phenol derivatives 1-5 in good yields. In contrast to the Crabtree method, which demonstrated poor regioselectivity and only worked for electron-neutral and -rich substrates, this transformation showed high regioselectivity for both electron-rich and electron-deficient arenes. Likewise, a key Pd(IV) intermediate was also proposed for this transformation.

![Scheme 1.2](image)

**Scheme 1.2**

Inspired by Sanford’s work on directed C–H oxygenation reaction, a variety of other directing groups for Pd-catalyzed C–H oxygenation reactions were explored (Scheme 1.3). The Wang group illustrated a general anilide-directed (1-6a) C–H oxygenation reaction by employing
inexpensive K$_2$S$_2$O$_8$ oxidant. Later, the same group reported $N$-methoxyamide (1-6b) directed C–H alkoxylation reaction of benzamides. The bidentate directing group 8-aminoquinoline (AQ) (1-6c) was used by the Liang group for the Pd-catalyzed ortho C–H oxygenation of arenes, which exhibited excellent functional group tolerance. The Chen group disclosed pyrimidine (1-6d) as a powerful directing group for regioselective ortho C–H acetoxylation reaction of phenols. Remarkably, the Sun group reported a nitrile-directed (1-6e) Pd-catalyzed ortho alkoxylation reaction. Both electron-rich and -deficient arylnitriles participated in the reaction well to produce the corresponding oxygenated products.

![Scheme 1.3](image)

Oxygen gas is potentially an ideal oxidant due to its wide availability, low toxicity, and cheap price. Thus, it is desirable to develop C–H oxidation reaction of arenes use O$_2$ as an oxidant. To this end, the Yu group reported the first Pd-catalyzed C–H hydroxylation reaction employ O$_2$ as an oxidant. In the presence of Pd(OAc)$_2$ catalyst and molecular oxygen oxidant, benzoic acids 1-7 were efficiently mono-hydroxylated to produce salicylic acids 1-8. The reaction has a general scope, as both electron-rich and -electron deficient substrates underwent C–H oxygenation reaction to afford salicylic acids 1-8 in good yields with excellent
regioselectivity (Scheme 1.4). Mechanistic study employing $^{18}$O$_2$ revealed that O$_2$ serves as an oxygen atom source for this hydroxylation reaction.

![Scheme 1.4](image)

In 2012, the Dong group reported the first ketone-directed, Pd-catalyzed ortho C–H hydroxylation of arenes, which offered an appealing method to synthesize $o$-acylphenol compounds out of arylketones (Scheme 1.5). Both alkyl- and aryl-substituted ketones with different steric properties gave the corresponding $o$-acylphenols in good yields and with excellent regioselectivity. The trifluoro acetate ester $1\text{-}9'$ was proposed as the intermediate of this transformation, which produces the final hydroxylated arene upon hydrolysis.
Importantly, intramolecular C–H oxygenation reaction of arenes provides opportunity to construct oxygen containing heterocycles. Thus, in 2010, the Yu group reported an efficient palladium catalyzed, hydroxyl-directed C–H activation/C–O cyclization reaction for synthesis of dihydrobenzofurans 1-12 from 2-phenyl alcohols 1-11. A plausible reaction mechanism was proposed. First, the C–H bond palladation generates the Pd(II) species 1-13a, followed by oxidation to yield a reactive Pd(IV) species 1-14a, which upon reductive elimination gives dihydrobenzofurans 1-13a and releases the Pd(II) catalyst (Scheme 1.6).
Later, the Liu group reported a practical palladium catalyzed method for the synthesis of dibenzofurans 1-16 from 2-aryl phenols 1-15. The use of NHC ligand and air oxidant is crucial to the success of this transformation. Interestingly, based on the kinetic and stoichiometric studies, it is suggested that the reaction proceeded via a Pd(0)/Pd(II) catalytic cycle, and the rate-limiting step was found to be the C–O reductive elimination rather than the C–H activation, which is mechanistically distinct from analogues work by Yu discussed above (Scheme 1.7).
Scheme 1.7

In 2009, the Gevorgyan group developed silanol directed C–H oxygenation of phenol derivatives 1-17 to produce catechols 1-18 under Pd-catalyzed conditions. The directing silanol group was easily removed after the reaction, highlighting the utility of this transformation. This method is general, efficient and site-selective. Both electron-rich and -deficient silanols underwent reaction to produce catechols in good yields. In addition, halogenated phenols and naphthols survived this C–H oxygenation to afford catechols in good yields with excellent regioselectivity. Importantly, estrone also participated in the reaction to yield 2-hydroxyestrone...
1-18\textsubscript{g} in 76\% yield (Scheme 1.8). Isotope labelling studies suggested the oxygen atom in the product came from oxidant, rather than the silanol hydroxyl group, which was also confirmed by the observed oxygenated intermediate 1-19\textsubscript{h-18O} (Scheme 1.9).

Later, the Gevorgyan group disclosed the Pd-catalyzed benzylsilanol-directed C–H oxygenation of aromatic rings to produce oxasilacycles 1-21\textsuperscript{14}. Notably, the produced oxasilacycles 1-21 serve as synthon to produce synthetically useful compounds, such as phenol 1-22, aryl ether 1-23, or benzyl alcohol 1-24 (Scheme 1.10).
In comparison with the well-developed transition metal-catalyzed ortho C–H oxygenation of arenes, analogous meta functionalizations were much less explored. In 2014, the Yu group reported the first templated-directed, Pd(II)-catalyzed meta C–H oxygenation of arenes. The success of this reaction relied on the carefully designed U-shape directing group, which brought Pd catalysis to the distal meta-position to enable the transformations. The reaction worked well with various anilines 1-25 to produce products 1-26 in synthetically useful to good yields with excellent levels of meta-selectivity (90%–98%). In addition to anilines, benzyl amines also underwent the meta C–H acetoxylation under identical reaction conditions to produce the corresponding oxygenated products 1-27, thus demonstrating the versatility of this methodology. It needs to be mentioned that structurally important 2-phenylpyrrolidine and 2-phenylpiperidine also participated in this efficient meta-selective acetoxylation, which suggested potential power of this methodology for synthesis of diverse medicinally important heterocycles (Scheme 1.11). In the same year, the Movassaghi and the Yu groups disclosed a sulfonamide linked, U-shaped nitrile directing group, which promotes the Pd-catalyzed C-6 oxygenation reaction of indolines 1-28. Due to the competing electrophilic palladation at the electron-rich C-5 position, formation of substantial amounts of C-5 oxygenated products were also observed (Scheme 1.12).
Scheme 1.11

Scheme 1.12
Aiming at the better understanding of the Pd-catalyzed C–H oxygenation reaction, Sanford performed extensive mechanistic studies. First, a substantial value of KIE (\(k_H/k_D = 3.58\)) has been obtained from parallel reactions of substrate 1-30 and its deuterated analogue 1-30-\(d_7\). This result suggested that the C–H palladation is the turnover-limiting step in this Pd-catalyzed C–H acetoxylation reaction (Figure 1.1).

**Figure 1.1 Mechanistic Studies Substrates for the Pd-Catalyzed C–H Acetoxylation Reaction**

Next, a mono-nuclear Pd(IV) intermediate 1-32 was isolated in excellent yield by oxidation of known Pd(II) complex 1-31 with Phl(OAc)\(_2\). The structure of 1-32 was characterized by \(^1\)H NMR studies and further confirmed by X-ray crystallography. Thermal decomposition of 1-32 gave the acetoxylated product 1-33 in almost quantitative yield (Scheme 1.13).

**Scheme 1.13**

Based on the kinetic and stoichiometric studies, the Pd(II)/Pd(IV) catalytic cycle was proposed for this C–H oxygenation reaction. First, pyridine-directed C–H palladation of substrate 1-34 produces aryl-palladium(II) species 1-35, which upon two-electron oxidation
generates a Pd(IV) intermediate 1-32. Reductive elimination from the latter gives the oxygenated product 1-33 and regenerates the Pd(II) catalyst (Figure 1.2).

**Figure 1.2 Reaction Mechanism of the Pd-Catalyzed C–H Acetoxylation Reaction**

In 2010, Ritter proposed a Pd(III) mechanism for the Pd-catalyzed C–H acetoxylation reaction of arenes based on the following studies.\(^\text{18}\) Reaction of 2-phenyl pyridine 1-34 with Pd(OAc)\(_2\) afforded a dimeric, acetate-bridged Pd(II) complex 1-36 in nearly quantitative yield. Treatment of the latter with PhI(OAc)\(_2\) efficiently produced a structurally interesting bimetallic Pd(III)-Pd(III) complex 1-37, which upon reductive elimination gave acetoxyalted product 1-33 (Scheme 1.14). Unfortunately, it is not distinguishable whether the dinuclear Pd(III) intermediate 1-37 or the mononuclear Pd(IV) complex 1-32 is the true intermediate for the Pd-catalyzed C–H acetoxylation reaction.
Scheme 1.14

In addition to the Pd-catalyzed C–H oxygenation of arenes, Ru-based catalysts have also been proven efficient. Thus, in 2012, the Rao group reported the first ester-directed, Ru(II) catalyzed C–H hydroxylation reaction of arenes,\(^\text{10}\), which featured broad substrates scope, high regioselectivity, and good functional group tolerance. It needs to be mentioned that Pd-sensitive substrates bearing iodide and nitro groups worked well producing the corresponding oxygenated products in good yields. Moreover, the thiophene derivative also underwent smooth reaction to yield the hydroxylated product in reasonable yield (Scheme 1.15).

Scheme 1.15
Later, the Ackermann group disclosed a set of studies on Ru(II)-catalyzed C–H oxygenation reaction of arenes, utilizing different directing groups (Scheme 1.16).\textsuperscript{20} Thus, in the presence of [Ru(O\textsubscript{2}CMes\textsubscript{2}][(p-cymene)] catalyst and PhI(OAc)\textsubscript{2} oxidant, aryl amides 1-40 were smoothly converted into the corresponding hydroxylated products 1-41 in good to excellent yields and regioselectivity (Eq. 1). In addition, aryl ketones 1-42 were efficiently hydroxylated under almost identical reaction conditions, producing 2-hydroxylated aryl ketones 1-43 in good yields, however, it was limited to aryl \textit{tert}-butyl ketone substrates to secure high yields (Eq. 2). Moreover, under mild reaction conditions, synthetically important aryl Weinreb amides 1-44 produced \textit{ortho}-hydroxylated products 1-45 in good to excellent yields with a broad scope. The obtained product readily underwent reduction to produce \textit{ortho}-hydroxybenzaldehyde, thus demonstrating the utility of this reaction (Eq. 3). Next, direct oxygenation reaction of aryl carbamates 1-46 produced mono protected catechols 1-47, which represented the first ruthenium catalyzed C–H oxygenation reaction of phenols (Eq. 4). The reaction proceeded under moderate conditions with high catalytic efficiency, as well as excellent chemo- and \textit{ortho}-selectivities. Notably, in 2014, Ackermann discovered that aldehydes can also serve as a directing group for the ruthenium catalyzed C–H hydroxylation reaction of arenes, producing the corresponding salicylic aldehydes 1-49 in good yields with broad scope and excellent regioselectivity.\textsuperscript{21} This reaction demonstrated that [RuCl\textsubscript{2}-(p-cymene)]\textsubscript{2} can transform a stronger arene C–H bond in the presence of a weaker aldehyde C–H bond, which was realized by a chelation-controlled aromatic C–H activation (Eq. 5).
Though significant advances were made in the development of Pd- and Ru-catalyzed C–H oxygenation reactions of arenes, it is desirable to discover base metal mediated/catalyzed reactions, as this would provide an economical alternative to expensive noble metal catalytic protocols. In 2006, the Yu group discovered the first pyridine-directed Cu(OAc)$_2$-mediated C–H oxygenation reactions of arenes (Scheme 1.17). Though stoichiometric amount of copper was required, it set a stage for future development of Cu(II)-mediated/catalyzed C–H oxygenation...
reactions of arenes. Labelling experiment employing $\text{H}_2^{18}\text{O}$ revealed that the incorporated oxygen in the product came from Cu(OAc)$_2$. Yu proposed a radical cation mechanism for this transformation, partially based on the observed negligible KIE ($k_H/k_D = 1$) of the reaction.

![Scheme 1.17](image)

Scheme 1.17

In 2013, the Gooßen group discovered a directed copper-catalyzed regioselective dehydrogenative cross-coupling of arenes with alcohols, which allowed expedient synthesis of aryl ethers. The reaction worked with pyridine and pyrazole directing groups, whereas various alcohols 1-56 including reactive homoallylic alcohol and sterically bulky menthol underwent reaction smoothly to produce the corresponding ethers 1-57 (Scheme 1.18). Preliminary mechanistic studies revealed a radical process likely to be involved. In addition, an oxygen atmosphere was proved essential for the success of this reaction. One limitation of this transformation is employment of huge excess of alcohol.
In 2014, the Shi group developed the Cu(II)-mediated C–H hydroxylation of arenes and heteroarenes using a bidentate PIP directing group.24 Thus, in the presence of stoichiometric amounts of Cu(OAc)$_2$ and Ag$_2$CO$_3$ oxidant, arenes and heteroarenes 1-58 were efficiently transformed into the corresponding ortho C–H hydroxylated products 1-59 in good yields with excellent regioselectivity. Both electron-rich and -deficient arenes participated in this reaction. Notably, various heteroarenes, including substituted pyridines (1-59k–r), pyridazines (1-59t) and thiophenes (1-59u, v) also survived under the reaction conditions. No desired product was observed when picolinamide (1-59s) was subjected to the standard conditions, presumably due to
deactivation of the copper catalyst via formation of the $N,N,N$-pincer-type complex (Scheme 1.19).

Scheme 1.19

In 2015, the Dai and Yu group disclosed a similar Cu(II)-mediated ortho-C–H hydroxylation using a bidentate directing group. The reaction featured good functional group tolerance, as synthetically important iodo (1-61e), vinyl (1-61f), and trifluoromethyl (1-61h, m) groups survived under reaction conditions (Scheme 1.20). O$_2$ was crucial to the reaction, and water was also found to improve the yields significantly. The following observations have been made: (1) large kinetic isotope effects were observed in both inter- and intramolecular competition experiments; and (2) the addition of the commonly used radical quencher TEMPO
has negligible effect on the yield. Based on these results, the authors proposed that a Cu(II)-mediated C–H cleavage step is likely to be involved in this hydroxylation reaction, rather than an electrophilic aromatic substitution (S\text{E}\text{Ar}) or a radical process. In 2017, the Yu group reported an oxazoline ligand-promoted, weakly coordinating monodentate group directed Cu(II)-mediated ortho-hydroxylation of arenes (Scheme 1.21). This report demonstrated that ligand could play a vital role in the Cu(II)-mediated C–H oxygenation reaction.
Besides Cu(II)-catalyzed/mediated intermolecular C–H oxygenation reactions, intramolecular C–H oxygenation of arenes was also developed. In 2008, Nagasawa developed the first Cu(II)-catalyzed intramolecular dehydrogenative C–O coupling reaction for expedient conversion of imine to oxazine.
synthesis of 2-arylbenzoxazoles 1-65 from easily available N-phenylbenzamides 1-64.\textsuperscript{27} The reaction features simplified operation, excellent functional group tolerance, high regioselectivity, and use of readily available and inexpensive starting materials (Scheme 1.22).

The mechanism of this interesting C–O coupling reaction was studied by the Fu group.\textsuperscript{28} Cu(II)-assisted concerted metalation deprotonation (CMD) of 1-66 forms a copper(II)-aryl intermediate 1-67, which upon oxidation generates a reactive Cu(III) species 1-68. The latter undergoes reductive elimination to produce the desired product 1-69 and release a Cu(I) species. Fu also suggested that reductive elimination is the rate determining step of this reaction (Scheme 1.23).

Scheme 1.23

In 2016, Hirano and Uchiyama reported a one-pot, two-step process toward C–H bond hydroxylation of arenes/heteroarenes: directed deprotonative ortho C–H cupration followed by oxidation with tBuOOH.\textsuperscript{29} Compared with other Cu-mediated C–H bond hydroxylation reactions, this reaction highlights high yields with excellent regio- and chemoselectivity, as well as general scope in terms of the directing groups (Scheme 1.24). DFT calculations suggested a copper (I → III → I) redox mechanism for this hydroxylation reaction.
In 2012, the Zhu group reported a Cu(II)-catalyzed intramolecular C–H etherification of arenes with air as a sole oxidant. This reaction allows preparation of multisubstituted dibenzofurans 1-73 from easily available o-arylphenols 1-72 with good functional group tolerance. Notably, a strong electron-withdrawing group (e.g., NO$_2$) at the para position on the phenol is crucial to the success of this reaction (Scheme 1.25).

**Scheme 1.24**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Reaction Conditions</th>
<th>Yield</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-71a</td>
<td>THF, 0 °C, 2 h</td>
<td>94%</td>
<td>91% (1.41 g)</td>
</tr>
<tr>
<td>1-71b</td>
<td>THF, 0 °C, 2 h</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>1-71c</td>
<td>THF, 0 °C, 2 h</td>
<td>92%</td>
<td></td>
</tr>
<tr>
<td>1-71d</td>
<td>THF, 0 °C, 2 h</td>
<td>71%</td>
<td></td>
</tr>
<tr>
<td>1-71e</td>
<td>THF, 0 °C, 2 h</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>1-71f</td>
<td>THF, 0 °C, 2 h</td>
<td>90%</td>
<td></td>
</tr>
<tr>
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<td></td>
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<td>82%</td>
<td></td>
</tr>
<tr>
<td>1-71i</td>
<td>THF, 0 °C, 2 h</td>
<td>86%</td>
<td></td>
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<td></td>
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<td>THF, 0 °C, 2 h</td>
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<td></td>
</tr>
<tr>
<td>1-71l</td>
<td>THF, 0 °C, 2 h</td>
<td>64%</td>
<td></td>
</tr>
</tbody>
</table>
Besides copper catalysis, cobalt-based catalyst was also developed. Thus, in 2016, Wu and Tung disclosed the dehydrogenative C–H/O–H cross-coupling reaction, which allows coupling of arenes with water to form phenols. The reaction was enabled by a combination of two cooperative photoredox PC$^+$ 1-76 and cobalt(II) 1-79 catalysts. The organic photoredox catalyst PC$^+$ 1-76, upon photoexcitation, oxidizes benzene into a phenyl radical cation and a photocatalyst radical 1-78, the latter reduces Co(III) 1-81 to give Co(II) 1-79 and ground state photocatalyst 1-76 to close the photocatalytic cycle. The former reacts with hydroxide anion to give a neutral radical species, which reacts with Co(II) 1-79 to generate a radical cation species and a Co(I) 1-80 species. The radical cation species loses its proton to produce phenol as the final product. On the other hand, Co(I) 1-80 generates a Co(III) 1-81 species upon treatment with proton source and closes the cobalt catalysis cycle (Figure 1.3). The reaction works well with benzene and 1,3-dichlorobenzene to produce the corresponding phenols 1-75a and 1-75f in good
yields and with excellent regioselectivity. In terms of mono-substituted arenes, high products selectivities were observed, albeit with low conversion and poor regioselectivity (Scheme 1.26).

Figure 1.3 Proposed Reaction Mechanism of the Dehydrogenative Cross-Coupling Reaction

![Proposed Reaction Mechanism of the Dehydrogenative Cross-Coupling Reaction](image)

Scheme 1.26

In 2017, the Zhao group reported an iridium-catalyzed mild and redox-neutral ortho C–H oxygenation of acetamide-protected phenols toward synthesis of catechols 1-83. The mild reaction conditions guaranteed synthesis of catechols bearing sensitive groups. Thus, different fluorescent heteroarylated catechols 1-83a-c and bioactive catechols 1-83d-f were efficiently
produced in good yields with excellent regioselectivity. The suggested reaction mechanism is depicted below: first, Ir(III) reacts with acetamide-protected phenol 1-82 to produce a labile seven-membered Ir(III) intermediate 1-84, which undergoes reductive elimination to give the oxygenated intermediate 1-85 and releases the Ir(I) species. Next, the Ir(I) re-inserts into the reactive N–O bond of the oxygenated intermediate to generate the new Ir(III) complex 1-86, which gives catechol upon hydrolysis (Scheme 1.27). $^{18}$O-labelling experiment further confirms that the acetamide protecting group serves as the oxygen atom source.

Scheme 1.27

In 2013, the Siegel group reported a metal-free C–H oxygenation of arenes by employing phthaloyl peroxide oxidant.\textsuperscript{33} The use of phthaloyl peroxide 1-88 is of great importance to the success of this reaction. The reaction mechanism of this transformation was proposed to proceed
through three steps. First, phthaloyl peroxide 1-88 undergoes O–O bond homolytic cleavage to generate diradical 1-89. Next, the addition of one benzoyloxy radical to an arene 1-90 produces a cyclohexadienyl radical intermediate 1-91 via the C–O bond formation. Lastly, the phthaloyl ester 1-92 is produced via a 1,7-hydrogen abstraction from the cyclohexadienyl radical by another benzoyloxy radical. This reaction has a lower energy reaction profile, compared to the direct C–H abstraction/radical recombination process, which was proven by the DFT computations. The reaction is compatible with different functional groups, including alkyl silanes, allene, epoxide, terminal alkyne, terminal alkene, alkyl nitrile, alkyl chloride, alkyl azide, protected alcohol, and BPin group (Scheme 1.28).

![Chemical structure](image)

Scheme 1.28

Though significant advances were made in noble metal-catalyzed C–H oxygenation of arenes, base metal catalyzed and transition metal-free C–H oxygenation reactions of arenes are underdeveloped. In addition, C–H oxygenation of electron-deficient arenes is also a challenge task. Thus, those problems awaiting solutions.
1.2 Background of C–H Carbonylation Reactions of Arenes using CO as C1 Source

Transition metal-catalyzed carbonylation reactions of arene halides by employing CO as a C1 source serves an important role for synthesis of aryl carbonyl compounds, which are widely present in drugs, materials, and agricultural compounds. On the other hand, in recent years, transition metal-catalyzed C–H bond carbonylation reactions of arenes emerged as an appealing alternative route toward aryl carbonyl compounds, due to wider availability of arene C–H bonds compared with the C–Hal bonds.

In 1980, the pioneering Pd(OAc)$_2$-mediated C–H carbonylation of arenes was reported by the Fujiwara group, which demonstrated that it is possible to synthesize benzoic acids from simple arenes (Scheme 1.29). Unfortunately, there are several problems for this transformation: huge excess of substrates, low yields, poor selectivity, and high CO pressure.

Scheme 1.29
It was suggested that after C–H palladation of 1-94, CO migrates into the reactive Pd–C bond of 1-96 affording a benzoyl–PdOAc species 1-97, which undergoes reductive elimination to give anhydride 1-98, and subsequently benzoic acid 1-95 upon hydrolysis (Scheme 1.30).

Scheme 1.30

In 1983, the Fujiwara group reported the first Pd(OAc)$_2$-catalyzed C–H carbonylation of arenes.$^{35}$ The catalytic cycle was turned on by employing tBuOOH and allyl chloride oxidants. The reaction gained ~12 TON for benzene, while it gave low yield and poor selectivity for naphthalene (Equation 1.1). Later, the regioselectivity problem was partially solved by employment of Pd(OAc)$_2$ catalyst with a Phen ligand, reduced CO gas atmosphere and O$_2$. Under these conditions, the preferred β-carboxylation product 1-102 was obtained with 92% selectivity (Equation 1.2).$^{36}$

Equation 1.1

Equation 1.2
In 1999, the same group disclosed a mild Pd(OAc)$_2$-catalyzed C–H carboxylation of arenes, which operated at room temperature under atmospheric pressure of CO. Different aromatic compounds such as benzene, toluene, chlorobenzene, anisole, and naphthalene underwent the carboxylation reaction to produce the aromatic carboxylic acids in good yields. The use of K$_2$S$_2$O$_8$ oxidant and TFA solvent were found important for the success of this transformation (Scheme 1.31).

![Scheme 1.31](image)

In 2001, Grushin et al. reported a highly selective, Rh(III)-catalyzed C–H carboxylation of simple arenes for synthesis of carboxylic acids. Thus, toluene was carboxylated under the reaction conditions to give product 1-106d with an impressive 95% para-selectivity with 66 TON. Moreover, in contrast to the Pd-catalyzed C–H carboxylation of naphthalene, which always gave a mixture of products, this Rh-catalyzed reaction allows selective β-carboxylation to produce 2-naphthoic acid 1-106e with moderate TON (Scheme 1.32).
Scheme 1.32

In 2005, the Ishii group demonstrated the first C–H carbonylation of arenes catalyzed by Pd/V bimetallic system with O$_2$.\textsuperscript{39} It needs to mention that arenes were employed as the limiting reagents, which added synthetic value to this transformation. The reaction worked well with electron-rich substrates, producing the corresponding benzoic acids 1-108. Notably, simple phenol also underwent the carbonylation reaction to generate a 9:1 $p$-hydroxybenzoic acid and $o$-hydroxybenzoic acid mixture 1-108f in 53% overall yield (Scheme 1.33). Unfortunately, reaction of benzene was sluggish under the optimized conditions, producing only trace of the product. During the reaction, Pd catalyst served for C–H activation and carbonylation, while V catalyst activated O$_2$ and reoxidized Pd catalysis.
In 2012, the Lei group discovered the first Pd-catalyzed double C–H carbonylation of diaryl ethers to form xanthones. Various symmetrical and asymmetrical xanthones 1-110 were produced in moderate to good yields out of simple diaryl ethers 1-109 under the optimized reaction conditions. Notably, different functional groups, such as CF₃ and halides, were tolerated (Scheme 1.34). Preliminary mechanistic studies suggested that the second C–H functionalization was the rate-limiting step.
In 2004, the Orito group developed the first directed, Pd-catalyzed C–H carbonylation of \(N\)-alkyl-\(\omega\)-arylalkylamines for synthesis of benzolactams.\(^{41}\) The reaction worked well with secondary alkyl amines, in addition, various functional groups were tolerated under the reaction conditions. Both five- and six-membered lactams were obtained via this method. When the substrate has two available C–H sites, cyclization happens at the less sterically hindered site. Interestingly, when a directing group is present at the \textit{meta}-position to the alkyl amine, it directs the cyclization to the sterically more encumbered position (112s, t) (Scheme 1.35).
Scheme 1.35

In 2011, the Garcia and Granell group reported the free amine directed, Pd-catalyzed C–H carbonylation of quaternary aromatic α-amino esters to produce six-membered benzolactams. It is necessary to point out that, subjecting free amine substrate to the reaction conditions developed by the Orito group resulted in no C–H carbonylation product. Another notable feature of this reaction is that it prefers to form six-membered ring products, thus, subjecting 1-113a to the reaction conditions produced six-membered benzolactam 1-114a in 87% yield, and no five-membered benzolactam 1-116a was observed. On the other hand, the stoichiometric cyclometallation of 1-113a gave the five-membered palladacycle 1-115a as a major product. Treatment of 1-115a with CO in refluxing AcOH produced the five-membered lactam 1-116a in 86% yield as well as a minor amount (6%) of its six-membered analogue 1-
114a. These results suggest that six-membered benzolactams 1-114 are the kinetic products of the reaction (Scheme 1.36).

![Chemical structure and reaction conditions]

Scheme 1.36

In 2013, the Zhu group reported the Pd-catalyzed intramolecular C–H activation/carbonylation/cyclization of 2-arylanilines toward synthesis of phenanthridinones.  

![Chemical structure and reaction conditions]

Scheme 1.37
The reaction has general scope, as various functional groups, such as free phenol, halides and alcohol survived under these reaction conditions. In addition to free amines, alkyl and aryl amines efficiently participated in this reaction to produce the corresponding $N$-substituted phenanthridinones (Scheme 1.37, Eq. 1). Shortly after, the Zhang group reported the same transformation with a slightly different catalytic system (Eq. 2).\textsuperscript{44}

In 2016, the Inamoto and Kondo group reported the Pd(II)-catalyzed intramolecular C–H aminocarbonylation of bromo-functionalized phenethylamines to produce six-membered benzolactams.\textsuperscript{45} Importantly, under the optimized reaction conditions, the C–H/N–H coupling was favored over the undesired side C–Br/N–H coupling, thus, benzolactams 1-120 bearing a useful halogen functionality were obtained in good yields (Scheme 1.38). In the same year, the

![Reaction Scheme](image)

Scheme 1.38

Zhao group disclosed a similar Pd(II)-catalyzed intramolecular C–H aminocarbonylation of $\beta$-arylethylamines to produce 3,4-dihydroisoquinolinones.\textsuperscript{46} The key to the success of this reaction was employment of oxalyl amide as a powerful directing group. The reaction has a general scope, as amines without $\alpha$ substituents underwent efficient reaction to produce the corresponding products, in contrast to previous reports, which required $\alpha$-tertiary amines substrates. In addition,
various functional groups, such as nitro, ester, acetyl groups as well as halides survived the reaction conditions. Moreover, thiophenes were successfully carbonylated to yield the corresponding products (Scheme 1.39).

Scheme 1.39

In 2009, the Yu group discovered the first directed, Pd(II)-catalyzed oxidative C–H carbonylation of sulfonamide. The utility of this method was demonstrated by performing the late stage carbonylation on Celecoxib analogue, which successfully led to the desired product in good yield with excellent regioselectivity (Equation 1.3).

Equation 1.3
In 2011, the Rovis group developed an efficient intramolecular Rh(III)-catalyzed C–H carbonylation of aromatic amides into phthalimides. This method provides an economical approach to make phthalimides 1-126 from aromatic amides 1-125. The reaction works with electron-neutral and -rich substrates and exhibits good functional group tolerance (Equation 1.4). Similarly, the Daugulis group disclosed the first Co-catalyzed C–H carbonylation of aromatic amides toward phthalimides synthesis, which was enabled by assistance of a strongly coordinating bidentate directing group (Equation 1.5).

**Equation 1.4**

\[
\text{R}^+\text{C}^+\text{N}^-\text{R} \xrightarrow{\text{RhCp}^+(\text{MeCN})_3\text{(ClO}_4^-)\text{ (5 mol\%)}} \text{PhH} \xrightarrow{\text{Ag}_2\text{CO}_3 (2 \text{ equiv})} \text{KH}_2\text{P} \text{C}_4 (2 \text{ equiv}) \xrightarrow{\text{CO (1 atm)}} \text{fAmOH, 100 °C}} 1-126
\]

15 examples 33-95%

**Equation 1.5**

\[
\text{I}^+\text{C}^+\text{N}^-\text{R} \xrightarrow{\text{Co(acac)}_2 (20 \text{ mol\%})} \text{NaOPiv (2 equiv)} \xrightarrow{\text{Mn(OAc)}_3 (1 \text{ equiv})} \text{CC (1 atm), air} \xrightarrow{\text{CF}_3\text{CH}_2\text{OH, r.t.}} 1-128
\]

84% 1-128

In 2011, the Zhu group reported the Pd(II) catalyzed C–H carboxamidation of \(N\)-arylamidines for synthesis of quinazolin-4(3\(H\))-ones. The reaction efficiently produced different substituted quinazolin-4(3\(H\))-ones 1-130 in good yields with excellent regioselectivity from easily obtained \(N\)-arylamidines 1-129. A six-membered palladacycle 1-131 was proposed as a key intermediate in this reaction (Scheme 1.40).
In 2014, the same group discovered the palladium-catalyzed C−H pyridocarbonylation of \( N \)-aryl-2-aminopyridines, which provides a powerful tool toward 11\( H \)-pyrido[2,1-b]-quinazolin-11-one.\(^{51}\) The reaction works with both electron rich and poor substrates to produce the corresponding products in good yields. It is worth mentioning that this C−H pyridocarbonylation has a similar six-membered palladacycle 1-135 key intermediate (Scheme 1.41).

**Scheme 1.41**

\[
\text{Scheme 1.40}
\]
In 2013, the Inamoto and Kondo group reported the first Ru-catalyzed carbonylative C−H cyclization of 2-arylphenols to produce 6H-dibenzo[b,d]pyran-6-one compounds. The reaction featured good yields, excellent regioselectivity, as well as general functional group compatibility. Ester, nitrile, acetyl groups and halides, such as F, Cl, and Br atoms, were well tolerated during the reaction (Scheme 1.42). Later in the same year, the Shi group and the Cheng/Chuang group independently disclosed Pd-catalyzed intramolecular C−H activation/carbonylation/cyclization of 2-arylphenols to produce 6H-dibenzo[b,d]pyran-6-one compounds.

Scheme 1.42

In 2015, the Jiang group reported the Pd-catalyzed C−H carbonylation of aromatic oximes toward synthesis of benzo[d][1,2]oxazin-1-ones and 3-methyleneisoindolin-1-ones. It turned out that in the presence of AgOAc, the N−OH group serves as a directing group for C−H carbonylation followed by cyclization to produce benzo[d][1,2]oxazin-1-ones. On the
other hand, replacing AgOAc with K\textsubscript{2}CO\textsubscript{3} resulted exclusively in (Z)-3-methyleneisoindolin-1-ones 1-141 formation, which suggested that N–OH plays double duty in this transformation, first as a directing group and later as an internal oxidant (Scheme 1.43). Later, the Huang group disclosed the Rh-catalyzed oxidative C–H cyclocarbonylation of ketimines to produce substituted 3-methyleneisoindolin-1-ones. This method offers expedient synthesis of 3-methyleneisoindolin-1-ones 1-150 from easily available ketimines 1-149 (Equation 1.6).\textsuperscript{56}

Scheme 1.43
Equation 1.6

In 2009, the Zhang group discovered the first directed, Rh-catalyzed C–H alkoxylation of arenes.\(^5^7\) Electron-rich, electron-deficient and heterocyclic arenes \(1-151\) underwent reaction to produce the corresponding aryl alkyl esters \(1-152\) in up to 96% yield. The reaction also exhibited good functional group tolerance and excellent regioselectivities (Scheme 1.44).

Scheme 1.44

In 2010, the Shi group reported the Pd-catalyzed C–H carbonylation of substituted \(N,N\)-dimethylbenzylamines to produce the corresponding aryl esters.\(^5^8\) The carbonylation is highly regioselective, and compatible with various alcohol nucleophiles including sterically demanding
ones. Notably, a significant additive effect was observed. For instance, LiCl was found to be the best one to promote the reaction (Scheme 1.45).

In 2008, the Yu group reported the first Pd(II)-catalyzed C–H carboxylation of benzoic and phenylacetic acids to produce dicarboxylic acids. Under reaction conditions, benzoic acids were smoothly transformed into the corresponding phthalic acids in synthetically useful yields with excellent regioselectivity. Phenylacetic acids reacted at almost identical reaction conditions albeit at higher temperature to produce the 1,3-dicarboxylic acids in good yields (Scheme 1.46). The first cyclometalation complex formed from benzoic acids was isolated and confirmed by X-ray crystallography, which upon react with CO produced anhydride in quantitative yield. This suggested that the reaction undergoes C–H palladation, followed by the CO insertion and reductive elimination to yield the product.
Scheme 1.46

In 2009, Lloyd-Jones and Booker-Milburn disclosed the first Pd(II)-catalyzed, ortho-selective carbonylation of aniline derivatives. The reaction featured high efficiency, broad scope, excellent regioselectivity and exceptionally mild reaction conditions (Scheme 1.47). It was also demonstrated that the product 1-158 could readily be converted into either methyl anthranilate or anthranilic acid in good yields, which highlighted the diisopropyl urea moiety as an efficient “transformable” directing group for anilines.
Scheme 1.47

In 2010, the Yu group reported a similar Pd(II)-catalyzed ortho-C–H carboxylation of anilides to yield N-acyl anthranilic acids.\(^6\) This reaction has a general scope with good
selectivity (Scheme 1.48). Importantly, the obtained product 1-160 readily underwent various cyclization reactions to produce biologically and pharmaceutically significant heterocycles, such as benzoxazinones and quinazolinones.

In 2012, the Guan group developed a Pd-catalyzed regioselective C–H bond double carbonylation of N-alkyl anilines for synthesis of isatoic anhydrides. The reaction tolerates various functional groups and operates under mild conditions, thus allowing for expedient synthesis of substituted isatoic anhydrides 1-162 from readily available N-alkyl anilines 1-161. The synthesized isatoic anhydride 1-162 underwent efficient decarboxylation reactions to produce N-methylanthranilic acid, ethyl 2-(methylamino)benzoate, or 2-(methylamino)benzamide in high yields, which demonstrated synthetic utility of this transformation. The authors proposed the following reaction mechanism. First, Pd(OAc)$_2$ reacts with N-methyl aniline 1-161a to form complex 1-163, which upon CO insertion into the reactive Pd–C bond generates 1-164, which releases Pd(0) and produces N-methylanthranilic acid 1-165a upon reductive elimination. The former regenerates Pd(OAc)$_2$ with Cu(OAc)$_2$, whereas the latter reacts with Pd(OAc)$_2$ to form six-membered complex 1-166. Next, after CO insertion into the Pd–O bond of 1-166 and reductive elimination, isatoic anhydride 1-162a is produced. Finally, Cu(OAc)$_2$ oxides Pd(0) into Pd(OAc)$_2$ to close the catalytic cycle (Figure 1.4).
Figure 1.4 Reaction Mechanism of the Pd-Catalyzed Double C–H Carbonylation Reaction

In addition to the oxidative C–H carbonylation of arenes, redox neutral reactions were also developed. In 1992, the Moore group reported the first Ru(0)-catalyzed C–H acylation reaction of pyridines to produce C-2 acylated pyridines. The reaction is highly ortho-selective, presumably due to the coordinative nature of the pyridine nitrogen. A plausible reaction mechanism was proposed. A trinuclear ruthenium complex 1-171 undergoes C–H activation to form pyridine-ruthenium complex 1-172. After 1-hexene 1-169 insertion into the bridged hydride
of 1-172, two isomeric alkyl intermediates 1-173 and 1-173′ are produced. Next alkyl to acyl migratory insertion yields the new Ru-acyl complexes 1-174 and 1-174′, which upon reductive elimination produce 1-170 and 1-170′ (Scheme 1.49). Notably, other transition metal carbonyl compounds, such as Fe₃(CO)₁₂, Os₃(CO)₁₂, Rh₄(CO)₁₂ and Re₂(CO)₁₀, showed no catalytic activity toward this transformation.

Scheme 1.49

In 1997, Chatani and Murai reported a directed, Ru(0)-catalyzed C−H acylation reaction of arenes. In contrast to Moore’s finding, this work employed pyridine as the directing group, which enabled acylation of non-activated C−H bond of arenes. The suggested reaction mechanism is depicted below. First, Ru(0) undergoes insertion into the C−H bond to form a cyclometalated ruthenium hydride complex 1-177. Next, ethylene reacts with the hydride complex to form the ethyl complex 1-178. A subsequent CO insertion, followed by reductive
elimination, produces the final product 1-175. However, it is not determined whether CO inserts into the Ru-aryl bond or the Ru-alkyl bond of complex 1-178 (Scheme 1.50).

Scheme 1.50

In 2009, the Chatani group reported the first redox neutral, Ru(0)-catalyzed C–H carbonylation of benzoic acid derivatives to produce phthalimides. The employment of bidentate directing group is crucial to the success of this transformation. The reaction has a general scope, as substrates bearing both electron-donating and electron-withdrawing groups underwent reaction to yield desired products 1-181. In addition, various functional groups, such as ester, acyl, nitrile groups and different halides survived the reaction conditions. When substrate has two possible reactive sites, CO inserted at the less sterically demanding site (1-181j-l). Notably, the reaction did not proceed without ethylene, suggesting that ethylene played a role of H$_2$ acceptor, which is produced during the reaction. In addition, the presence of H$_2$O contributed significantly for improvement of the yields (Scheme 1.51).
In 2010, Wu and Beller reported the first three-component, Pd/Cu bimetallic-catalyzed C–H carbonylation of heteroarenes to form diaryl ketones.\(^\text{66}\) Reaction of heteroarenes 1-182 with aryl iodides 1-183 and CO under Pd/Cu catalysis produced diaryl ketones 1-184 in good to excellent yields. Different heteroarenes, such as oxazoles, thiazoles, and imidazole participated well in this reaction to produce the corresponding ketones. The authors summarized the reaction mechanism as shown below. Pd(0) 1-185 species undergoes oxidative addition with phenyl iodide to generate the aryl-Pd(II) complex 1-186, which reacts with CO to produce the key acyl-Pd(II) complex 1-187. Transmetalation between the latter and the preformed Cu-heteroaryl species 1-188, followed by reductive elimination, produces the reaction product ketone and regenerates the active Pd(0) catalyst (Scheme 1.52).
In 2015, the Skrydstrup group reported the Pd(0)-catalyzed C–H carbonylation of polyfluoroarenes for synthesis of benzopolyfluorophenones. Under Pd(0) catalysis, reaction of aryl bromides 1-190, polyfluoroarenes 1-191 and CO gave the corresponding benzopolyfluorophenones 1-192 in good yields. Notably, Pd(0) is the only catalyst for the reaction, and no additional metal is needed to facilitate the transmetallation step. The reaction has a general scope, as both electron-rich and -deficient aryl bromides participated well in the reaction. Importantly, $^{13}$C-acyl labeled benzopolyfluorophenone $^{13}$C-1-192d was successfully accessed by using $^{13}$C–COgen in moderate yield. A plausible reaction mechanism was proposed by the authors, which includes oxidative addition of phenyl bromide 1-190 to Pd(0),
followed by CO insertion to produce Pd-acyl complex 1-194, which reacts with pentafluorobenzene via a CMD mechanism to generate the new Pd(II) complex 1-195. Reductive elimination from the latter yields the ketone product 1-192 and regenerates the Pd(0) catalyst (Scheme 1.53).

Scheme 1.53

In 2015, the Tjurtrins and Arndtsen group discovered the Pd(0)-catalyzed C−H carbonylation of electron-rich arenes to form diaryl ketones. The reaction was rationalized as following. First, Pd(0) reacts with aryl iodide 1-196 followed by CO insertion to form Pd(II)-acyl complex 1-199, which undergoes reductive elimination to produce highly electrophilic aryl acyl iodide 1-200. Next, electrophilic acylation of electron-rich arene yields the desired ketone product 1-198. This reaction has a broad scope, thus, electron-rich, electron-poor, or sterically-encumbered aryl iodides were tolerated. In addition, various heterocycles, such as pyrrole, indole, benzoxazole, imidazole, and furan efficiently underwent this carbonylative functionalization to produce corresponding ketones in good yields. Normally, this novel acylation reacts at the most
electron-rich C–H site in the heterocycle, however, when t-butyl pyrrole was subjected to the reaction, only C-3 acylated product was obtained (1-198c). Replacing bulky t-butyl group with a smaller 2,6-dimethylphenyl group, expectedly led to a 1:1 mixture of C-2/C-3 acylated products 1-198d (Scheme 1.54).

Scheme 1.54

In 2013, the Beller group disclosed the first directed, three-component Ru(II)-catalyzed C–H carbonylation of arenes to form diaryl ketones. The reaction works well with both arenes and heteroarenes, such as furan and thiophenes, to produce ortho acylated products 1-203. In addition, pyridines, pyrimidine and pyrazole all worked well as directing groups to produce ketone products. When substrate has two reactive sites, reaction occurred exclusively at the more electron-rich site, suggesting this is an electrophilic C–H acylation (Scheme 1.55). The reaction
Scheme 1.55

Figure 1.5 Reaction Mechanism of the Ru-Catalyzed C–H Carbonylation Reaction

starts from the Ru(II)-mediated C–H metalation to produce the ruthenium complex 1-205, which further reacts with CO to form the six-membered ruthenium complex 1-206. Oxidative addition
of phenyl iodide to the later generates sterically encumbered ruthenium(IV) complex 1-207, which undergoes a facile reductive elimination to produce the ketone product and regenerates the Ru(II) catalyst 1-204 (Figure 1.5).

In 2017, the Driver group reported the Pd(II)-catalyzed C–H aminocarbonylation of arenes into aryl amides. The following reaction mechanism was proposed. First, Pd(OAc)$_2$ reacts with 2-phenyl pyridine to form five-membered palladacycle 1-212. Then, CO gas, which is generated in situ from decomposition of M(CO)$_6$, inserts into the Pd–aryl bond of 1-212 to yield the six-membered palladium complex 1-213. On the other hand, nitrosoarene 1-211 is produced by a Pd-catalyzed reducing reaction of nitroarene with CO reductant. Next, migratory insertion of nitrosoarene into the Pd–C bond of the 1-213 produces the new alkoxy–Pd complex 1-214, which upon reductive elimination generates the amide product 1-210 (Scheme 1.56).

Scheme 1.56

In summary, directed C–H carbonylation reaction of arenes produce important aryl carbonyl compounds. Although these directing groups are important functionalities, they are not easily removable or transformable if not needed in the final product. To address this issue, it is
necessary to introduce easily installable/removable/transformable directing groups for the C−H carbonylation reaction of arenes.

References


26. Shang, M.; Shao, Q.; Sun, S.-Z.; Chen, Y.-Q.; Xu, H.; Dai, H.-X.; Yu, J.-Q. *Chem. Sci.* 2017,


Chapter 2  Carboxyl Group-Directed Remote C–H Oxygenation Reactions of Arenes

2.1 Introduction

In line of the continuous effort on development of novel C–H functionalization methods, our group get interested in the synthesis of 3,4-benzocoumarin fragment 2-1, which exists as the core motif in medicinally important molecules, and functional materials (Figure 2.1). Existing methods toward its synthesis rely on either intramolecular C–C bond forming reaction or C–X/O–H coupling reaction, which suffer from harsh reaction conditions and limited scope (Scheme 2.1).

![Figure 2.1 Selected Examples of Benzocoumarin Containing Compounds](image-url)
Scheme 2.1

Intramolecular C–H/O–H dehydrogenative coupling of oxygen nucleophile with unactivated C(sp²)–H bond to construct C–O bond is an appealing transformation, as it allows for expedient synthesis of various valuable oxygen-containing heterocycles. Thus, the development of novel oxidative methods toward 3,4-benzocoumarins 2-1 from 2-aryl benzoic acids 2-4 is highly warranted (Equation 2.1). Unfortunately, reported methods either use stoichiometric amounts of toxic Cr(VI) or Pb(IV) oxidants, or need UV irradiation, which substantially limit practicality of these methods. We thought that it is worthwhile developing a general, user-friendly and environmentally benign oxidative C–H/O–H coupling reaction of 2-arylbenzoic acids into 3,4-benzocoumarins. It needs to mention that Dr. Anton V. Gulevich provided help to build the scope of the reaction and perform further transformations. I finished optimization and built the scope of the reaction.

Equation 2.1

2.2 Reaction Design

We envisioned that transition metal catalyst 2-5 would undergo ligand exchange with 2-phenyl benzoic acid 2-4 to produce the new metal carboxylate complex 2-6, which upon
oxidation would generate the higher oxidation state metal complex 2-7. The latter could induce the desired C–O bond forming reaction to produce the target product 2-1 and release the catalyst (Figure 2.2). We believe that the key to the success of this reaction would be the right combination of transition metal catalyst and an oxidant.

![Figure 2.2 Reaction Design](image)

**Figure 2.2 Reaction Design**

### 2.2.1 Optimization

To this end, we examined formation of 3,4-benzocoumarins from 2-aryl benzoic acid. First, we screened common transition metal catalysts using BPO oxidant in DCE (Table 2.1, entries 1-4). Employment of Pd(OAc)$_2$, which was an efficient catalyst for C–O bond forming reactions, did not produce any product (entry 1). Use of FeCl$_2$, NiCl$_2$ and AgNO$_3$ salts also gave disappointing results (entries 2-4). To our delight, employment of 20 mol% of Cu(OAc)$_2$ led to the desired product 2-1a in 80% yield (entry 5)! The control experiment without Cu(OAc)$_2$ did not produce any product, confirming the importance of the copper catalyst. Next, solvent
optimization revealed that DCE is the best solvent. Interestingly, 60% of the product was produced in water. Other tested solvents, including MeCN, toluene, DMF and DMSO, gave no product (entries 7-10). Next, various oxidants were tested for the reaction, where BPO was proven to be the best (Table 2.2).

**Table 2.1 Initial Optimization of the Remote C–H Oxygenation Reaction^[a]^**

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>yield / %^[b]^</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>DCE</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>FeCl$_2$</td>
<td>DCE</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>NiCl$_2$</td>
<td>DCE</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>AgNO$_3$</td>
<td>DCE</td>
<td>trace</td>
</tr>
<tr>
<td>5</td>
<td>Cu(OAc)$_2$</td>
<td>DCE</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>/</td>
<td>DCE</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)$_2$</td>
<td>MeCN</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OAc)$_2$</td>
<td>toluene</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Cu(OAc)$_2$</td>
<td>DMF</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OAc)$_2$</td>
<td>DMSO</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>Cu(OAc)$_2$</td>
<td>H$_2$O</td>
<td>60</td>
</tr>
</tbody>
</table>

^[a] 2-4a (0.5 mmol), catalyst (20 mol%), oxidant (3 equiv), solvent, 100 °C, 12 h.

^[b] Yield was determined using GC-MS with $nC_{15}H_{32}$ as an internal standard.

Further optimization was focused on catalyst and oxidant loadings, reaction temperature, and copper source (Table 2.3). First, the reaction temperature was lowered from 100 °C to 85 °C, which did not affect the product yield (entries 1 and 2). Next, different catalyst loadings were tested, among which 5 mol% catalyst loading was found optimal. Interestingly, employment of
stoichiometric amounts of Cu(OAc)$_2$ gave lower yield (entry 7). The product yield remained the same upon increasing the oxidant to 6 equiv (entry 8). Further lowering the reaction temperature decreased the product yield (entry 9). Employment of slow addition technique, which avoids fast decomposition of an oxidant under the reactions conditions, was not fruitful (entry 10). Notably, replace BPO with TBPB gave slightly increased yield. Finally, it was found that copper oxide also efficiently catalyzes this reaction (entry 12).

**Table 2.2 Optimization of Oxidant of the Cu-Catalyzed Remote C–H Oxygenation Reaction**

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidant</th>
<th>yield / %</th>
<th>entry</th>
<th>oxidant</th>
<th>yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H$_2$O$_2$</td>
<td>0</td>
<td>6</td>
<td>CH$_3$COOOH</td>
<td>~10</td>
</tr>
<tr>
<td>2</td>
<td>O$_2$</td>
<td>0</td>
<td>7</td>
<td>m-CPBA</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>(tBuO)$_2$</td>
<td>trace</td>
<td>8</td>
<td>CH$_3$COOOtBu</td>
<td>~15</td>
</tr>
<tr>
<td>4</td>
<td>tBuOOH</td>
<td>~5</td>
<td>9</td>
<td>K$_2$S$_2$O$_8$</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>(nC$<em>{11}$H$</em>{23}$COO)$_2$</td>
<td>trace</td>
<td>10</td>
<td>BPO</td>
<td>80</td>
</tr>
</tbody>
</table>

[a] 2-4 (0.5 mmol), catalyst (20 mol%), oxidant (3 equiv), DCE, 100 °C, ovn. [b] Yield was determined using GC-MS with $n$C$_{15}$H$_{32}$ as an internal standard.
Table 2.3 Further Optimization of the Cu-Catalyzed Remote C–H Oxygenation Reaction

<table>
<thead>
<tr>
<th>entry</th>
<th>[Cu] / mol%</th>
<th>temp / °C</th>
<th>oxidant ratio / equiv</th>
<th>yield / %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OAc)$_2$/ 20</td>
<td>100</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>2</td>
<td>Cu(OAc)$_2$/ 20</td>
<td>85</td>
<td>3</td>
<td>80</td>
</tr>
<tr>
<td>3</td>
<td>Cu(OAc)$_2$/ 10</td>
<td>85</td>
<td>3</td>
<td>80</td>
</tr>
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<td>4</td>
<td>Cu(OAc)$_2$/ 5</td>
<td>85</td>
<td>3</td>
<td>78</td>
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<td>5</td>
<td>Cu(OAc)$_2$/ 3</td>
<td>85</td>
<td>3</td>
<td>58</td>
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<td>46</td>
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<td>7</td>
<td>Cu(OAc)$_2$/ 100</td>
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<td>37</td>
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<td>80</td>
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<td>70</td>
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<td>85</td>
<td>3[a]</td>
<td>50</td>
</tr>
<tr>
<td>11</td>
<td>Cu(OAc)$_2$/ 5</td>
<td>85</td>
<td>3 TBPB</td>
<td>88</td>
</tr>
<tr>
<td>12</td>
<td>CuO / 5</td>
<td>85</td>
<td>3 TBPB</td>
<td>87</td>
</tr>
<tr>
<td>13</td>
<td>Cu$_2$O / 5</td>
<td>85</td>
<td>3 TBPB</td>
<td>50</td>
</tr>
</tbody>
</table>

[a] slow addition of oxidant via syringe pump over 2 h.

2.2.2 Scope and Limitation of the Cu-Catalyzed Remote C–H Oxygenation Reaction

With the optimized reaction conditions in hand, the scope of the Cu-catalyzed C–H oxygenation reaction of arenes was examined (Table 2.4). First, we tested substrates bearing different substitutes at the guest ring. It was found that substrates with para substituents underwent reaction to produce the desired lactone products 2-1b to 2-1j in satisfying yields. When meta-substituted-substituents were subjected to the reaction, most compounds cyclized at the sterically less hindered site (2-1k to 2-1n). Unexpectedly, the methyl-substituted compound
Table 2.4 Cu-Catalyzed Remote C−H Oxygenation Reaction\[^{[a]}\]

<table>
<thead>
<tr>
<th>Compound</th>
<th>R = H, 88% 2-1a</th>
<th>R = Me, 71% 2-1b</th>
<th>R = tBu, 68% 2-1c</th>
<th>R = OMe, 69% 2-1d</th>
<th>R = OBn, 70% 2-1e</th>
<th>R = OCF(_3), 76% 2-1f</th>
<th>X = F, 65% 2-1g</th>
<th>X = Cl, 80% 2-1h</th>
<th>X = Br, 73% 2-1i</th>
<th>X = CN, 70% 2-1j</th>
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<tbody>
<tr>
<td></td>
<td>2-1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2-1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[^{[a]}\] Isolated yield. 2-5 (0.5 mmol), Cu(OAc)\(_2\)•H\(_2\)O (5 mol%), PhCO\(_2\)tBu (3 equiv), DCE, 85 °C, 12 h.
reacted at the sterically encumbered site to produce two isomers in 4:1 ratio (2-1o). Interestingly, 2-naphthyl substituted benzoic acid underwent selective cyclization at the more electron-rich 1-position to produce the corresponding lactone 2-1p. Gratifyingly, substrates bearing 3,5-disubstituted ring also underwent efficient cyclization to give the benzocoumarin products 2-1q and 2-1r. Next, 2-phenylbenzoic acids with substituents at the C-1, C-2, and C-3 positions also reacted smoothly under the optimal reaction conditions to deliver the corresponding products 2-1s to 2-1v. Notably, various functional groups, such as different halides (2-1g to 2-1i, 2-1k, 2-1l, 2-1t and 2-1v), nitrile (2-1j) and trifluoromethoxy groups (2-1f), were tolerated under these reaction conditions. The reaction proceeded with high efficiency toward electron-neutral and -rich substrates, however, the oxygenation reaction of electron-deficient substrates was problematic. Thus, 2-arylbenzoic acids containing electron-withdrawing functional groups such as, CF$_3$ (2-5w), COMe (2-5x), and CONMe$_2$ (2-5y) produced the expected products in lower yields, whereas substrates bearing CHO (2-5z), CF$_3$ (2-5aa, 2-5ab) and NO$_2$ groups (2-5ac to 2-5ae), gave trace to no product at all (Table 2.4).

In addition, we tested substrates bearing ortho substitutes at the guest ring. When 2-4af was subject to the optimized reaction conditions, to our surprise, the desired product 2-1af was not observed, but instead complicated reaction mixtures were produced (Scheme 2.2, Eq. 1). Similarly, ortho-halogen-substituted substrates did not produce any product retaining the halogen substituent, but generated unsubstituted benzocoumarin in good yields, which represent a rare Cu-catalyzed S$_{\text{N}}$Ar substitution reaction (Eq. 2).
Moreover, 2-phenanthrene-substituted benzoic acid 2-4af underwent reaction to produce the desired product 2-1af in a low yield (Scheme 2.3, Eq. 1). Reaction of biphenyl substituted substrate 2-4ak gave almost equal amounts of the desired product 2-1ak and a structurally interesting eight-membered ring lactone 2-1ak'. The latter was formed via a very remote C–H oxygenation (Scheme 2.3, Eq. 2).
Furthermore, we attempted to employ this novel Cu-catalyzed C–H reaction toward oxygenation of C(sp³)–H bond. To this end, substrate 2-8, containing active bisbenzylic C–H bond, was prepared and tested. To our delight, the desired C(sp³)–H oxygenated product 2-9 was isolated in 53% yield, which demonstrated the generality of this method (Equation 2.2).

**Equation 2.2**

![Equation 2.2 Diagram]

**2.2.3 Mechanism Study of the Cu-Catalyzed Remote C–H Oxygenation Reaction**

Based on the results presented above, we hypothesized that the Cu-catalyzed remote C–H oxygenation reaction proceeds via radical pathway. Indeed, the reaction conducted in the presence of stoichiometric amounts of radical quencher TEMPO gave no product, suggesting the above hypothesis (Scheme 2.4, Eq. 1). In addition, reaction of 2-4a with 1 equiv Cu(OAc)₂ in the absence of an external oxidant failed to produce any lactone product, which indicated that the

![Scheme 2.4 Diagram]
reaction is likely to proceed via an active Cu(III) intermediate (Eq. 2).\textsuperscript{7}

The plausible reaction mechanism of the Cu-catalyzed remote C–H oxygenation is summarized in Figure 2.3. Ligand exchange between 2-aryl benzoic acid \textbf{2-4a} and Cu(OAc)\textsubscript{2} generates the new Cu(II) complex \textbf{2-10}, which upon oxidation produces the Cu(III) complex \textbf{2-11}, subsequently homolytic Cu–O bond cleavage of the latter forms the Cu(II)-bounded carboxylic radical species \textbf{2-12}, which promotes the C–O bond forming reaction to produce the aryl radical intermediate \textbf{2-13} and releases the Cu(II) catalyst \textbf{2-14}. The former produces the final product \textbf{2-1a} upon single electron oxidation followed by a proton loss. On the other hand, \textbf{2-14} undergoes ligand exchange with \textbf{2-4a} to close the catalytic cycle (Figure 2.3).
Figure 2.3 Proposed Reaction Mechanism of the Cu-Catalyzed C–H Oxygenation Reaction
2.3 Development of a Novel K$_2$S$_2$O$_8$-Mediated C–H Oxygenation Reaction

2.3.1 Reaction Design Based on Understanding of the Reaction Mechanism of the Cu-Catalyzed C–H Oxygenation

We aimed at the development of an efficient oxidative cyclization reaction of electron deficient 2-arylbenzoic acids, which would overcome the limitation of the Cu-catalyzed oxygenation reaction (Table 2.4). We hypothesized that the key to address this problem was to generate a ‘pure’ carboxylic radical species 2-15, which might add to the guest ring more efficiently compared to the Cu-bounded radical 2-12 (Scheme 2.5).

Scheme 2.5

2.3.2 Development of the K$_2$S$_2$O$_8$ Mediated Remote C–H Oxygenation Reaction of Arenes

We found that inexpensive K$_2$S$_2$O$_8$ oxidant smoothly converts 2-aryl benzoic acids 2-4 into the corresponding benzocoumarins 2-1 in good yields.$^8$ Notably, this operation replaces toxic DCE solvent and dangerous organic peroxides used in the Cu-catalyzed protocol with environmentally benign aqueous acetonitrile solvent and inorganic oxidant. Naturally, the scope of this promising transformation was examined (Table 2.5). Under standard reaction conditions, the benchmark product 2-1a was produced in 93% yield at a gram-scale. We are pleased to find that this new method works efficiently for both electron-neutral and -deficient substrates (entries 2-1a, i, p, r, t, u). Importantly, in the presence of K$_2$S$_2$O$_8$, substrates with meta-substituted guest...
Table 2.5 K₂S₂Os-Mediated C–H Oxygenation Reaction

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield (%)</th>
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[a] AgNO₃ (10 mol%) was added.

ring gave the corresponding products in higher selectivity than the Cu-catalyzed method (entries 2-1k-o'). Most significantly, various electron-deficient substrates, such as 2-arylbenzoic acids
bearing CF₃ (2-1w, 2-1aa), COMe (2-1x), CONMe₂ (2-1y), and CHO (2-1z) groups underwent cyclization to produce the corresponding products in good to excellent yields. In addition, for the first time, substrates with highly electron-withdrawing NO₂ group (2-1ac, 2-1ad, 2-1ae), and even two CF₃ groups (2-1ab) were readily converted into the corresponding benzocoumarin products. It should be mentioned, that in some cases, addition of a catalytic amount of AgNO₃ (10 mol%) led to substantial increases of reaction rates.

2.3.3 Proposed Reaction Mechanism of the K₂S₂O₈-Mediated Remote C–H Oxygenation Reaction

We proposed that the K₂S₂O₈-mediated oxygenation reaction proceeds as following. First
2-aryl benzoic acid 2-4a reacts with K₂S₂O₈ to produce oxygen-centered carboxylic radical 2-15, which adds to the guest aromatic ring to form an aryl radical intermediate 2-13 (Scheme 2.6, a, Path A). The latter upon oxidation loses a proton to produce the benzocoumarin product 2-1a. Notably, reactions of substrates bearing 2-halo aryl substituents (2-4ag, 2-4ah and 2-4ai) underwent standard reaction conditions to produce 2-1a as the sole product, which also supported this homolytic aromatic substitution mechanism (Scheme 2.6, b). Alternatively, mechanism involving a hydrogen atom abstraction process from intermediate 2-15 to form the aromatic radical 2-16, though unlikely, cannot be completely ruled out (Scheme 2.6, a, Path B).

2.4 Synthesis of Aryl Ethers from Benzocoumarins

With structurally diverse 3,4-benzocoumarins at hand, we attempted to convert them into structurally important biaryl ethers. Accordingly, both electron-rich and -deficient 3,4-

[Chemical structure image]

Equation 2.3

benzocoumarins 2-1 could be converted into the corresponding biaryl ethers 2-17 in nearly quantitative yields (Equation 2.3). Accordingly, this method can serve as formal remote C(sp²) – H oxygenation reaction.

2.5 Conclusion

In summary, we developed two carboxyl group-directed remote C–H oxygenation reactions of 2-aryl benzoic acids into benzocoumarins. The first Cu-catalyzed reaction allows
synthesis of various 3,4-benzocoumarins containing electron-neutral and -donating substituents. In addition, the second $\text{K}_2\text{S}_2\text{O}_8$-mediated transformation was developed, which converts various electron-rich and -deficient 2-arylbenzoic acids into the corresponding products in good yields. This protocol is highlighted by its broad scope, excellent functional group tolerance and good selectivity. It is also features environmentally friendly conditions, and is operationally simple, as well as scalable for multi-gram synthesis.

2.6 Related Methodologies and Applications Developed by Other Groups

During the preparation of our manuscript, the Martin group reported the copper-catalyzed remote C–H oxygenation reactions of 2-aryl benzoic acids (Scheme 2.7),\textsuperscript{10} which has similar substrates scope and limitation compared to our copper-catalyzed C–H oxygenation. Martin proposed two possible intermediates which might engage in the key C–O bond forming step, including the aryl radical 2-18, which forms via the C–H abstraction at the aryl ring, and a seven-membered copper complex 2-19.

\begin{center}
\begin{equation}
\begin{array}{c}
\text{COOH} \\
\text{R}^1 \\
\text{H} \\
\text{R}^2 \\
\text{2-4}
\end{array}
\begin{array}{c}
\text{Cu(OAc)}_2 (5 \text{ mol\%}) \\
\text{BPC} (1.25 \text{ equiv}) \\
\text{HFIP (0.12 M), 75} \text{ } ^\circ \text{C, 12 h}
\end{array}
\begin{array}{c}
\text{H} \\
\text{O} \\
\text{R}^1 \\
\text{R}^2 \\
\text{2-1}
\end{array}
\end{equation}
\end{center}

\begin{center}
\begin{equation}
\begin{array}{c}
\text{CO}_2\text{Cu}^{\text{II}}\text{X}_2 \\
\text{2-18}
\end{array}
\begin{array}{c}
\text{Cu}^{\text{III}}\text{X} \\
\text{2-19}
\end{array}
\end{equation}
\end{center}

Scheme 2.7

Two years after our reported $\text{K}_2\text{S}_2\text{O}_8$-mediated C–H oxygenation of arenes, the Xu group disclosed the silver catalyzed C–O cyclization of arenes.\textsuperscript{11} Notably, the reaction exhibits
excellent functional group tolerance, as various substrates, bearing useful substituents, such as halides, terminal alkene, free alcohol and acetyl protected amine groups, underwent smooth cyclization to produce the corresponding lactones (Scheme 2.8, Eq. 1). A small intermolecular KIE value ($k_{\text{H}}/k_{\text{D}} = 1.27$) of this reaction was observed, suggesting that the C–H bond cleavage is not involved in the rate-determine step. In the same year, Gonzalez-Gomez group discovered the visible-light photoredox catalyst catalyzed dehydrogenative lactonization of 2-arylbenzoic acids 2-4 (Eq. 2). An oxygen-centered radical species is proposed to be the key intermediate in this transformation.

Scheme 2.8

Based on our K$_2$S$_2$O$_8$-mediated oxygenation reaction, in 2016, the Basak group developed a modified method to synthesize DNA-intercalating 6$H$-benzo[c]chromen-6-one derivatives. Accordingly, a series of benzochromenone derivatives 2-21 were synthesized in
good yields (Equation 2.4). Subsequently, their DNA binding abilities were tested, and substantial DNA intercalative activity of these molecules was observed.

In 2017, the Kakiuchi group employed the \( \text{K}_2\text{S}_2\text{O}_8 \)-mediated oxygenation reaction toward formal synthesis of altertenuol,\(^{14} \) a toxin natural product isolated from \textit{Alternaria tenuis}. Thus, 2-aryl benzoic acid \( 2-22 \) underwent the \( \text{K}_2\text{S}_2\text{O}_8 \)-mediated oxygenation to produce lactone \( 2-23 \) in good yield with excellent regioselectivity, completing the formal synthesis of altertenuol (Equation 2.5).

![Reaction Scheme](image)

Equation 2.5

References


Chapter 3  Removable Group-Directed Pd(II)-Catalyzed C–H Carbonylation

Reaction of Arenes

3.1 Introduction

In the past two decades, transition metal catalyzed directed ortho C–H functionalization of arenes was emerging as a powerful synthetic method, which allows replacement of readily available C–H bond with various valuable functionalities. Accordingly, significant advances were made in the development of structurally diverse directing groups, which enabled conversion of C–H bond into C–C bond or C–hetero-atom bonds (Scheme 3.1). Even though these directing groups are important functionalities, if needed, they are not easily removable or transformable.

\[ \text{Scheme 3.1} \]

FG  alkyl, alkenyl, alkynyl, carbonyl, (Het)Ar, Hals, BR₂, CN, CF₃, OR, NR₂, SiR₃, SR, PR₂, etc

DG:  \( \text{H\text{\textregistered}OH} \),  \( \text{H\text{\textregistered}CO₂H} \),  \( \text{R\text{\textregistered}N\text{\textregistered}Me} \),  \( \text{H\text{\textregistered}NR₂} \),  \( \text{CN} \),  

\( \text{R\text{\textregistered}N\text{\textregistered}Ph} \),  \( \text{H\text{\textregistered}NMe₂} \),  \( \text{N\text{\textregistered}C\text{\textregistered}O} \),  \( \text{N\text{\textregistered}C\text{\textregistered}N} \),  

\( \text{N\text{\textregistered}C\text{\textregistered}C} \),  \( \text{N\text{\textregistered}C\text{\textregistered}C} \),  \( \text{O\text{\textregistered}N\text{\textregistered}Me} \),  \( \text{O\text{\textregistered}C\text{\textregistered}N} \),  

FG = functional group  DG = directing group

\( \text{Scheme 3.1} \)
To address this problem, our group introduced easily installable/removable/transformable silicon containing directing groups. In 2009, our group reported the first intramolecular C–H arylation of phenols.\(^1\) Initially, our group designed the modified tert-butyldiphenyl silane (TBDPS) protecting group, which serves as both directing group and aryl donor for the arylation of phenols. In addition, aniline also underwent this arylation to produce the corresponding product 3-5′ in good yield. Notably, upon routine desilylation of the obtained products, 2-aryl phenol 3-6 and 2-aryl aniline 3-6′ were produced in excellent yields (Scheme 3-2, Eq. 1). Moreover, oxidation of 3-5 produced valuable o-biphenols 3-7. Later, our group developed another efficient intramolecular C–H arylation reaction of phenols to produce o-biphenols (Eq. 2).\(^2\)

\[
\begin{align*}
\text{Scheme 3.2} \\
\text{In 2010, our group invented an efficient PyDipSi directing group for the Pd-catalyzed mono-selective ortho-acetoxylation of both arenes and heteroarenes 3-10.} \quad & 3
\end{align*}
\]
exhibited broad scope and high functional group tolerance (Scheme 3.3, Eq. 1). Later, our group demonstrated this PyDipSi directing group also participated in the mono-selective C–H halogenation reaction of arenes to produce the corresponding halogenated produces in good yields (Eq. 2).  

![Scheme 3.3](image)

The PyDipSi group has excellent mono-selectivity for C–H functionalization, however, it failed to produce any bisfunctionalized products. To this end, we introduced a more efficient PyrDipSi directing group, which enables double oxygenation, double halogenation, and sequential halogenation/oxygenation reactions of arenes. Recently, PyrDipSi-arenes also underwent a smooth C–H alkylation reaction to produce alkyl arenes 3-17 (Scheme 3.4).
Scheme 3.4

In 2011, our group developed the Pd-catalyzed silanol directed *ortho* C–H functionalization of phenols. Thus, *ortho* alkenylated phenols\(^9\) 3-19 and catechols\(^{10}\) 3-20 were produced in high yields and excellent regioselectivity. Obviously, the silanol group is routinely removable after the C–H functionalization (Scheme 3.5).

Scheme 3.5

Importantly, removable/modifiable group directed transition metal catalyzed C–H carbonylation reaction for synthesis of important aryl carbonyl compounds was underdeveloped.
To the best of our knowledge, the Chatani group reported the only example of such transformation.\textsuperscript{11} Thus, compound 3-21 underwent pyridine directed C−H carbonylation to produce ester 3-22 in moderate yield, which after the Rh-catalyzed deoxygenative borylation of 3-22 was converted into product 3-23 (Scheme 3.6). We hypothesized that it’s would be worthwhile to develop a general method of C−H carbonylation reaction of arenes with removable/modifiable directing group, to produce structurally diverse aryl carbonyl compounds.

![Scheme 3.6](image)

\textbf{Scheme 3.6}

**3.2 Silanol-Directed Pd-Catalyzed C−H Carboxylation of Phenols for Synthesis of Salicylic Acids**

**3.2.1 Introduction and Reaction Design**

Salicylic acids (SAs) are key motifs in medicinally and biologically active compounds,\textsuperscript{12} important synthetic intermediates,\textsuperscript{13} and useful building blocks in material science.\textsuperscript{14} Thanks to broad availability of phenols, a variety of synthetic routes employing phenols as starting material to SAs have been developed. The most commonly used method to SAs is the Kolbe-Schmitt reaction (Scheme 3.7, path A).\textsuperscript{15} Other methods include ortho-formylation of phenols, followed by oxidation (path B),\textsuperscript{16} and directed ortho metalation (DoM) of phenol, with subsequent reaction of the reactive aryllithium species with CO\textsubscript{2} (path C).\textsuperscript{17} Though widely used, the above-mentioned methods suffer from major limitations, such as limited scope, poor selectivity, as well as harsh conditions.
Pd-catalyzed intramolecular C−H alkoxycarbonylation reactions employing cheap CO is appealing since it allows synthesis of valuable lactones from the corresponding alcohols. Independently, the Yu\textsuperscript{18}, the Shi\textsuperscript{19} and the Cheng\textsuperscript{20} groups, developed the hydroxyl-directed Pd-catalyzed intramolecular C−H alkoxycarbonylation reactions of arenes into lactones and coumarins (Scheme 3.8, Eq. 1 and 2). Since there is no general, efficient and selective method for synthesis of SAs from phenols (\textit{vide supra}), we thought that the development of such methodology is highly desired.

**Existing Methods:**

\[
\begin{align*}
\text{OH} & \quad \text{CO} \text{H} \\
\text{3-26} & \quad \text{COOH}
\end{align*}
\]

- low selectivity
- harsh conditions

\[
\begin{align*}
\text{OH} & \quad \text{COOH} \\
\text{3-26} & \quad \text{OCOOH}
\end{align*}
\]

- low selectivity
- harsh conditions
- limited scope

**Scheme 3.7**

Previously, our group developed Pd-catalyzed \textit{ortho}-alkenylation\textsuperscript{9} and oxygenation\textsuperscript{10} of phenols employing silanol as a powerful traceless directing group. Hence, we hypothesized that if the phenoxy silanol \textit{3-18} could undergo a Pd-catalyzed regioselective alkoxycarbonylation reaction to generate the six-membered intermediate \textit{3-34}, upon its facile desilylation, SAs \textit{3-29} would be produced. Thus, it would constitute a highly regioselective approach to SAs \textit{3-29} from accessible phenols \textit{3-24} (Eq. 3).
3.2.2 Optimization of Pd-Catalyzed C–H Carbonylation

We initially tested the carbonylation reaction of 3-18b using a modified procedure from Yu’s report.\textsuperscript{18} Accordingly, 3-34b was observed as the only product in 17% yield (Table 3.1, entry 1). Though the yield was low, the robustness of 3-34b under the reaction conditions and the cleanness of the reaction prompted us to perform further optimizations. Notably, only negligible amounts of 3-34b was formed in a control experiment without ligand (entry 2), suggesting that ligand plays a crucial role in this transformation. Accordingly, we tested different MPAA ligands in this reaction. Pleasingly, yield of 3-34b increased to 37% with Ac-Val-OH (entry 3), among other ligands screened (entries 4-6), Boc-Leu-OH performed the best, delivering 3-34b in 90% yield (entry 6). We further screened the catalyst loading, which indicated that reducing the amount of Pd(OAc)\textsubscript{2} to 5 mol\% had a deleterious effect on the product yield (entry 7). Expectedly, no carboxylation occurred in the absence of palladium (entry 8). Moreover, other oxidants and solvents were examined. Thus, Cu(OAc)\textsubscript{2}, BQ, and O\textsubscript{2}, which are well known
oxidants for C–H functionalization, gave poor results (entries 9-11). Other solvents, such as dioxane, EtCN, and xylene, did not improve the yield either (entries 12-14).

**Table 3.1 Optimization of Pd-Catalyzed C–H Carboxylation of Phenols**

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand[a]</th>
<th>oxidant</th>
<th>solvent</th>
<th>yield, %[b]</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>L3</td>
<td>AgOAc</td>
<td>DCE</td>
<td>17</td>
</tr>
<tr>
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<td></td>
<td>AgOAc</td>
<td>DCE</td>
<td>&lt;1</td>
</tr>
<tr>
<td>3</td>
<td>L1</td>
<td>AgOAc</td>
<td>DCE</td>
<td>37</td>
</tr>
<tr>
<td>4</td>
<td>L2</td>
<td>AgOAc</td>
<td>DCE</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>L4</td>
<td>AgOAc</td>
<td>DCE</td>
<td>42</td>
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<tr>
<td>6</td>
<td>L5</td>
<td>AgOAc</td>
<td>DCE</td>
<td>90</td>
</tr>
<tr>
<td>7[c]</td>
<td>L5</td>
<td>AgOAc</td>
<td>DCE</td>
<td>59</td>
</tr>
<tr>
<td>8[d]</td>
<td>L5</td>
<td>AgOAc</td>
<td>DCE</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>L5</td>
<td>Cu(OAc)₂</td>
<td>DCE</td>
<td>5</td>
</tr>
<tr>
<td>10</td>
<td>L5</td>
<td>BQ</td>
<td>DCE</td>
<td>3</td>
</tr>
<tr>
<td>11[e]</td>
<td>L5</td>
<td>O₂</td>
<td>DCE</td>
<td>7</td>
</tr>
<tr>
<td>12</td>
<td>L5</td>
<td>AgOAc</td>
<td>Dioxane</td>
<td>&lt;1</td>
</tr>
<tr>
<td>13</td>
<td>L5</td>
<td>AgOAc</td>
<td>EtCN</td>
<td>4</td>
</tr>
<tr>
<td>14</td>
<td>L5</td>
<td>AgOAc</td>
<td>Xylene</td>
<td>20</td>
</tr>
</tbody>
</table>

[a] L1 = Ac-Val-OH; L2 = Boc-Val-OH; L3 = (+) Menthyl(O₂C)-Leu-OH; L4 = Ac-Leu-OH; L5 = Boc-Leu-OH. [b] GC yield, with nC₁₅H₃₂ as internal standard. [c] 5 mol% Pd(OAc)₂ and 10 mol% ligand was used. [d] No Pd(OAc)₂. [e] O₂ balloon.

**3.2.3 Scope and Limitation of Pd-Catalyzed C–H Carboxylation**

Under the optimized reaction conditions, followed by a facile desilylation step, silanol 3-18a was converted into salicylic acid 3-29a in 76% isolated yield (Table 3.2, entry 1). In general, all substrates underwent the reaction to give products with excellent ortho selectivity. Electron-rich substrates produced the corresponding SAs (3-29b, c, e, h) in good to excellent yields;
whereas, those electron-neutral and -deficient substrates yielded products (3-29d, 2j, 2i) in slightly diminished yields. Notably, a variety of useful functionalities, such as ester (3-29s), nitrile (3-29t), aryl chlorides (3-29g), alkyl chloride (3-29u), cyclopropyl (3-29r), and ketone (Scheme 3.10, 3-29w) survived under these reaction conditions. Importantly, only desired products were obtained when alternative competent directing groups, such as methoxy- and acetoxy- groups, were present (3-29e, f, p, q). If the silanol precursor has two potential reactive C−H sites, the carboxylation occurred preferentially at the sterically less hindered position (3-29l-p). Bis-silanol derivative 3-18v underwent this reaction to produce mono-acid 3-29v in excellent yield. Apparently, the aromatic ring was deactivated after the first carbonylation reaction, thus hampering the second C−H carboxylation event. Thanks to the mild reaction conditions, substrates containing a sensitive cinnamyl substitute at para- and meta-positions (3-18w, x) were transformed into the corresponding salicylic acids 3-29w, x in reasonable yields. Moreover, carbazole derivative 3-18y reacted smoothly to give 3-29y in 64% yield. Unfortunately, the carboxylation reaction did not proceed well with highly electron-deficient substrates. Thus, ester-bearing phenol 3-18z was much less reactive under these conditions (entry 26), whereas phenols with strongly electron-withdrawing 3-NO₂- and 4-CN-substitutes did not participate in the reaction at all. It’s worth mentioning that this method tolerates substrates with ortho-substituents, as demonstrated by the successful synthesis of 3-29h (Me), 3-29i (Ph), 3-29j (naphthalene) and 3-29k (chlo). This phenomenon is in a sharp contrast to our previous reported silanol-directed ortho C−H olefination reaction, where substrates, possessing ortho-substituents were not reactive.
Table 3.2 Synthesis of Salicylic Acids$^{[a]}$  

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield / %$^{[b]}$</th>
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<tr>
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<td>76</td>
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<td>2</td>
<td>3-18b</td>
<td>3-29b</td>
<td>91</td>
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<tr>
<td>3</td>
<td>3-18c</td>
<td>3-29c</td>
<td>92</td>
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<td>4</td>
<td>3-18d</td>
<td>3-29d</td>
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</tr>
<tr>
<td>6</td>
<td>3-18f</td>
<td>3-29f</td>
<td>71</td>
</tr>
<tr>
<td>7</td>
<td>3-18g</td>
<td>3-29g</td>
<td>49</td>
</tr>
<tr>
<td>8</td>
<td>3-18h</td>
<td>3-29h</td>
<td>89</td>
</tr>
<tr>
<td>9</td>
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<td>3-18i</td>
<td>3-29i</td>
</tr>
<tr>
<td>---</td>
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<td>10</td>
<td><img src="image2" alt="Structure" /></td>
<td>3-18j</td>
<td>3-29j</td>
</tr>
<tr>
<td>11</td>
<td><img src="image3" alt="Structure" /></td>
<td>3-18k</td>
<td>3-29k</td>
</tr>
<tr>
<td>12</td>
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<td>3-29n</td>
</tr>
<tr>
<td>15</td>
<td><img src="image7" alt="Structure" /></td>
<td>3-18o</td>
<td>3-29o</td>
</tr>
<tr>
<td>16</td>
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<td>17</td>
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<td>3-18q</td>
<td>3-29q</td>
</tr>
<tr>
<td>18</td>
<td><img src="image10" alt="Structure" /></td>
<td>3-18r</td>
<td>3-29r</td>
</tr>
<tr>
<td></td>
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<td>3-29</td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>3-18s</td>
<td>3-29s</td>
<td>76</td>
</tr>
<tr>
<td>20</td>
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<td>3-18u</td>
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<tr>
<td>25</td>
<td>3-18y</td>
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<td>64</td>
</tr>
<tr>
<td>26</td>
<td>3-18z</td>
<td>3-34z</td>
<td>(14)</td>
</tr>
</tbody>
</table>

[a] Reacton conditions: silanol 3-18 (0.2 mmol), Pd(OAc)$_2$ (0.02 mmol, 10 mol%), Boc-Leu-OH (L, 0.04 mmol, 20 mol%), AgOAc (0.6 mmol, 3 equiv), CF$_3$CH$_2$OH (0.6 mmol, 3 equiv), CO/Ar (1:8, balloon), DCE (0.8 mL, 0.25 M), 95 °C, 18 h. [b] isolated yield. [c] major:minor = 2:1. [d] major:minor = 4:1. [e] NMR yield of silacycle 3-34z after the first step.
3.2.4 Mechanistic Studies and Modification of Complex Phenols

Next, we aimed at clarifying the reaction mechanistic pathway. As previously reported in our Pd-catalyzed silanol-directed C−H oxygenation of phenols,10 18O-labelled substrate 3-18o-18O underwent the reaction to produce the 18O retention intermediate 3-35, which cyclized to give the five-membered silacycle 3-36 with no 18O atom incorporation (Scheme 3.9, a). Accordingly, we prepared 3-18b-18O and tested it under the new developed C−H carboxylation reaction conditions. In contrast to the oxygenation reaction, this carboxylation produced the six-membered silacycle 3-34b*-18O with complete retention of 18O atom (Scheme 3.8, b). This result shed light on the reaction mechanism of this C−H carboxylation. After the C−H palladation of 3-18b-18O followed by CO migratory insertion, the key intermediate 3-37 is produced, which undergoes reductive elimination to generate the 18O incorporated product 3-34b*-18O.22

![Scheme 3.9](image)

Finally, we tested this novel carboxylation method on more complex phenols. The silanol derivative of estrone 3-18aa was prepared in almost quantitative yield, which subsequently underwent the carboxylation followed by desilylation to produce 3-29aa as a single isomer in excellent yield (Scheme 3.10, a). Moreover, since many bioactive compounds contain multisubstituted phenol motif,23 we employed our method for synthesis of o,o'-bis-
unsymmetrically substituted phenolic compound. Thus, after two different C–H functionalization operations, first olefination\(^9\) followed by carboxylation, simple silanol \(3-18b\) was converted into the multisubstituted phenol \(3-39\) in 56\% overall yield (Scheme 3.10, b). As far as we are aware, this represents the first example of an iterative \(o,o'\) unsymmetrical C–H functionalization of phenols.\(^{24}\)

![Scheme 3.10](image)

3.2.5 Conclusion

In summary, we have developed a silanol-directed general and efficient method for synthesis of salicylic acids from phenols under Pd-catalyzed conditions. This method features broad substrate scope, excellent functional group tolerance, and high regioselectivity. Mechanistic study suggested that one oxygen atom of the carboxylic group comes from the
silanol group. It was also demonstrated that this method is applicable for a late-stage functionalization of complex molecules, which was illustrated by carboxylation of estrone. In addition, for the first time, synthesis of \( o,o' \)-bis-unsymmetrically substituted phenolic compound was accomplished via a stepwise C–H olefination\(^9\) and carboxylation reaction. We envision that this approach may become a useful method for synthesis of salicylic acids from phenols.

3.3 Pd-Catalyzed PyrDipSi-Directed C–H Alkoxycarbonylation of Arenes for Synthesis of Active Hexafluoroisopropyl Benzoates

3.3.1 Introduction and Reaction Design

During the past twenty years, the C–H carbonylation reaction of arenes becomes an important synthetic tool for synthesis of aryl carbonyl compounds.\(^{25}\) The direct C–H carbonylation reactions\(^ {26}\) suffer from low-selectivity and moderate efficiency, which limit broad applications in synthesis. To this end, directing group (DG)-assisted C–H carbonylation reactions were developed, which feature both high efficiency and selectivity.\(^ {27}\) Though the latter approach allows for synthesis of various benzoate esters, to the best of our knowledge, it only gives access to stable esters, which thus require extra manipulations for their derivatizations\(^ {28}\) (Scheme 3.11, Eq. 1). We hypothesized that it is justified to develop a directed C–H carbonylation method for synthesis of active ester,\(^ {29}\) which is an equivalent of acyl halide or acid anhydride toward synthesis of esters and amides.\(^ {30}\) Besides, we decided to employ the traceless/transformable PyrDipSi directing group, which proven efficient for various ortho C–H functionalization reactions of arenes.\(^ {31}\) If successful, it would give access to active benzoate esters \( 3-43 \) bearing dual functionalizable sites, an active ester group and the PyrDipSi group (Eq. 2).
3.3.2 Optimization of Reaction Conditions

Aiming at the development of PyrDipSi-directed C–H alkoxy carbonylation reactions for synthesis of active benzoate esters, the benchmark compound 3-44a was tested against commonly used weak OH nucleophiles 3-45 for synthesis of active benzoates under standard C–H alkoxy carbonylation conditions (Table 3.3).\(^\text{32}\) It was revealed that using N-hydroxyphthalimide 3-45a, N-hydroxysuccinimide 3-45b, and pentafluorophenol 3-45c hydroxide nucleophiles gave virtually no product (entries 1-3). Some promising result was obtained with 4-nitrophenol 3-45d (entry 4). Excitingly, good yield of the corresponding active ester 3-46a was obtained employing HFIP alcohol 3-45e (entry 5)! However, its sterically more hindered analog (3-45f) did not participate in this transformation (entry 6). Replacement of 3-44a with its PyDipSi analog 3-47, which possesses pyridyl directing group (\textit{vide supra}), resulted in much lower efficiency of C–H alkoxy carbonylation (entry 7). Lastly, employment of ethanol as nucleophile in the presence of carboxylic acids (entries 8, 9) also produced no product.
### Table 3.3 Optimization of Reaction Parameters\(^{[a]}\)

<table>
<thead>
<tr>
<th>entry</th>
<th>ROH</th>
<th>deviation from conditions</th>
<th>yield / %(^{[b]})</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-45a</td>
<td>-</td>
<td>trace</td>
</tr>
<tr>
<td>2</td>
<td>3-45b</td>
<td>-</td>
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<tr>
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<td>3-45c</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>3-45d</td>
<td>-</td>
<td>18</td>
</tr>
<tr>
<td>5</td>
<td>3-45e</td>
<td>-</td>
<td>85(^{[c]})</td>
</tr>
<tr>
<td>6</td>
<td>3-45f</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>3-45e</td>
<td>pyridyl- instead of pyrimidyl- group in 3-44a</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>EtOH</td>
<td>AcOH instead of 3-45e</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>EtOH</td>
<td>CF(_3)COOH instead of 3-45e</td>
<td>0</td>
</tr>
</tbody>
</table>

\(^{[a]}\) Standard conditions: 3-44a (0.05 mmol), Pd(OAc)\(_2\) (0.0050 mmol, 10 mol%), Ac-Leu-OH (0.010 mmol, 20 mol%), AgOAc (0.2 mmol, 4 equiv), ROH (0.25 mmol, 5 equiv), CO (balloon), DCE (1.0 mL, 0.05 M), 50 °C, 18 h. \(^{[b]}\) NMR yield. \(^{[c]}\) 0.20 mmol, isolated yield.

#### 3.3.3 Reaction Scope

Next, the scope of this alkoxy carbonylation reaction for synthesis of active HFIP benzoates was examined (Table 3.4). Both electron-rich and -deficient substrates gave the
Table 3.4 Scope of Active HFIP Benzoates\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>yield / %\textsuperscript{[b]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3-44a</td>
<td>3-46a</td>
<td>85</td>
</tr>
<tr>
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<tr>
<td>4</td>
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<td>3-44e</td>
<td>3-46e</td>
<td>64</td>
</tr>
<tr>
<td>6</td>
<td>3-44f</td>
<td>3-46f</td>
<td>61</td>
</tr>
</tbody>
</table>
7  3-44g  3-46g  76

8  3-44h  3-46h  70

9  3-44i  3-46i  66

10  3-44j  3-46j  76

11  3-44k  3-46k  75

12  3-44l  3-46l  65

13  3-44m  3-46m  84

14  3-44n  3-46n  77
corresponding products in good to excellent yields with excellent regioselectivity. Notably, various useful functionalities, such as aryl halides (3-46d, e, o-q), alkyl and aryl esters (3-46g, h), ketone (3-46i), amides (3-46j, x, y), protected aldehyde (3-46k), alkyl chloride (3-46r), nitrile (3-46s), and BPin (3-46l) survived under these reaction conditions. Importantly, substrates bearing competing directing groups, such as methoxy-, ketone-, ester-, and amide-, underwent this alkoxycarbonylation to give the PyrDipSi-directed products (3-46c, h, i, j, n, x, y, z). For substrates with two possible reactive C–H bonds, this alkoxycarbonylation occurred preferentially at the sterically less demanding site (3-46m-z). To our delight, this method can be extended beyond benzoates. Thus, active HFIP esters of different heterocycles, such as thiophene (3-46u), dibenzofuran (3-46v), carbazole (3-46w), indoline (3-46x), and tetrahydroquinoline (3-46y, *vide infra*), were efficiently being synthesized using this method.

The synthetic utility of the developed method was demonstrated on the preparation and further functionalization of HFIP ester of tetrahydroquinoline (THQ), which is a medicinally important heterocyclic motif.\(^{34}\) Thus, the C-6 PyrDipSi substituted THQ 3-44y was efficiently synthesized in 75% overall yield via a two-step procedure: the Au-catalyzed C–H iodination\(^{35}\) of N-pivalate THQ 3-47 followed by the Rh-catalyzed silylation reaction of the formed aryl iodide 3-48 with PyrDipSiH. Next, 3-44y underwent a smooth alkoxycarbonylation reaction to produce the active HFIP ester 3-46y in 75% yield as a single regioisomer. Expectedly, either the silyl or the active ester part of 3-46y could independently be converted into other synthetically important
Scheme 3.12

[a] AuCl$_3$ (1 mol%), NIS (1.1 equiv), DCE, 12 h. [b] Rh$_2$(OAc)$_4$ (2 mol%), PyrDipSi (1.5 equiv), K$_3$PO$_4$ (2 equiv), dioxane, 90 °C, 16 h. [c] Pd(OAc)$_2$ (10 mol%), Ac-Leu-OH (20 mol%), AgOAc (4 equiv), HFIP (2 equiv), CO (balloon), DCE, 50 °C, 16 h, then HF (5 equiv), THF, 2 h. [d] AgF (4 equiv), MeOH, 50 °C, 24 h. [e] NaOMe (2 equiv), MeOH, 2 h, then AuCl$_3$ (5 mol%), NIS (2.0 equiv), DCE, 50 °C, 24 h. [f] nHexNH$_2$ (2 equiv), MeCN, 12 h, then CsF (10 equiv), H$_2$O (10 equiv), DMF, 90 °C, 12 h. [g] nHexNH$_2$ (2 equiv), MeCN, 12 h, then AuCl$_3$ (5 mol%), NIS (2.0 equiv), DCE, 50 °C, 24 h. [h] AgN(Tf)$_2$ (10 mol%), NIS (1.3 equiv), DCM, 24 h. [i] Pd(OAc)$_2$ (20 mol%), Ac-Leu-OH (40 mol%), AgOAc (4 equiv), HFIP (6 equiv), CO (balloon), DCE, 90 °C, 8 h, then HF (5 equiv), THF, 2 h. [j] MeNH$_2$•HCl (4 equiv), Et$_3$N (8 equiv), MeCN, 4 h, then CsF (10 equiv), H$_2$O (10 equiv), DMF, 90 °C, 12 h.
groups. For instance, with two separate operations, simple nucleophilic substitution reactions followed by protodesilylations or iododesilylations, converted 3-46y into the corresponding aryl ester 3-49, iodo aryl ester 3-50, aryl amide 3-51, or iodo aryl amide 3-52 in good to excellent yields (Scheme 3.12, a). Notably, synthesis of the C-7 substituted THQs is challenging. Accordingly, this C–H alkoxy carbonylation offers an unprecedented approach for synthesis of C-7 carbonylated THQs. In addition, a 3,4-benzocoumarin core 3-53, which is present in various natural and bioactive molecules, was also functionalized employing this methodology (Scheme 3.11, b). Thus, the PyrDipSi directing group was efficiently installed onto 3-53 via iodination followed by silylation reactions to produce the PyrDipSi substituted 3,4-benzocoumarin 3-44z in good yield. Next, 3-44z underwent an efficient and selective C−H alkoxy carbonylation reaction to give the corresponding ester 3-46z, which participated into subsequent amidation and desilylation to yield the benzocoumarin amide 3-55, a potential monoamine oxidase inhibitor.

3.3.4 Mechanistic Studies

We were eager to gain insight into the role of HFIP alcohol participating in this C–H alkoxy carbonylation reaction besides acting as a nucleophile. There is no previous report on employment of HFIP alcohol coupling partner in C–H functionalization reactions. Interestingly, several challenging Pd(II)-catalyzed C–H functionalization reactions, including C–H carbonylation, used HFIP alcohol as solvent or co-solvent to improve the reaction efficiency, with no HFIP moiety to be incorporated into the product. It is well known that HFIP alcohol is a potent hydrogen bond donor, thus we hypothesized that it could form hydrogen bonding with the “spectator” nitrogen atom of the pyrimidine DG to form complex 3-56 (Figure 3.1). This hydrogen bonding effect could bring double-fold beneficial effect to this transformation: (A) by
decreasing the basicity of the DG and thus accelerating the C–H activation event, (B) as well as enhancing the nucleophilicity of the hydrogen-bonded HFIP alcohol.

![Figure 3.1 Proposed Structure of the Hydrogen-Bonding Complex](image)

To test this hypothesis, the following experiments were performed. First, NMR was employed to shed some light on this question. Thus, the $^1$H NMR spectra of **3-44a (A)**, HFIP alcohol (**B**), and the 1:1 mixture of HFIP alcohol and **3-44a (C)** were recorded (Figure 3.2). As expected, the $^1$H NMR spectrum of **C** (Figure 3.2, c) was not simply the sum of spectra of **A** (Figure 3.2, a) and **B** (Figure 3.2, b). A significant downfield shift of the OH signal was observed in HFIP alcohol from 2.9 ppm to 5.4 ppm in the **C**, this indicating a hydrogen-bonding adduct between HFIP alcohol and **3-44a**. More evidence of the adduct formation was provided by the NOE experiment between **3-44a** and HFIP alcohol. Thus, upon irradiation of the HFIP alcohol CH signal of the 1:1 mixture of **3-44a** and HFIP alcohol (**C**) at 3.8 ppm (Figure 3.2, d), a significant NOE was observed with the PyrDiPSi iPr at 1.10 ppm. Besides, a notable upfield shift of CH signal in HFIP alcohol from 4.2 ppm to 3.8 ppm in **C** suggests that the nucleophilic increases of HFIP alcohol due to the hydrogen-bonding. Similar studies between isopropanol and **3-44a** suggested no complex formation (see Experimental Section for details). Next, reaction of **3-44a** and more nucleophilic, but much less potent hydrogen bond donor than HFIP alcohol isopropanol **3-45g** under the optimized reaction conditions, did not produce the corresponding
ester product (Equation 3.1). These experiments support that the hydrogen-bonding between HFIP alcohol and the DG is crucial for the success of this transformation.

\[
\text{Figure 3.2 NMR Studies of the Hydrogen-Bonding Complexation}
\]

\(^1\text{H NMR of (a) 3-44a (A), (b) HFIP alcohol (B), (c) 1:1 mixture of 3-44a and HFIP alcohol (C), (d) 1-D gradient NOE for the 1:1 mixture of 3-44a and HFIP alcohol (C). Irradiated 1′-H \(_1\) (CH) of HFIP alcohol (B), shows NOE at isopropyl group of 3-44a (A).}\]
In addition, the performed kinetic studies \( (k_D/k_H = 1) \) suggest that the C–H bond cleavage step is not the rate-determining step.

Based on these studies, we propose the following alkoxy carbonylation reaction mechanism. First, \( \mathbf{3-44} \), upon treatment with the Pd(II) complex \( \mathbf{3-58} \) and HFIP alcohol, produces complex \( \mathbf{3-56} \), which undergoes a facile C–H palladation to generate complex \( \mathbf{3-59} \). Next, CO inserts into the Pd–C bond of \( \mathbf{3-59} \) with ligand exchange of \( \mathbf{3-59} \) to yield a seven-membered palladacycle \( \mathbf{3-60} \), which produces product \( \mathbf{3-46} \) and releases a Pd(0) \( \mathbf{3-61} \) species upon reductive elimination. The latter requires an oxidation to enter the next catalytic cycle (Figure 3.3).

**Figure 3.3** Proposed Reaction Mechanism of the Pd-Catalyzed C–H Alkoxy carbonylation Reaction
3.3.5 Conclusion

In summary, we developed an efficient Pd-catalyzed C–H alkoxy carbonylation reaction for synthesis of active HFIP esters. This method features good functional group tolerance and high selectivity. Moreover, this approach allows for synthesis of products bearing two independently modifiable sites, which was utilized for preparation of several tetrahydroquinoline derivatives and benzocumarin containing bioactive compound. In addition, this method serves as a formal ortho carboxylation reaction of aryl iodides, which is unprecedented. Our mechanistic studies suggested that the hydrogen-bonding interaction between HFIP alcohol and a directing group, is crucial to the success of this transformation.

References


31. See references 5-8.

32. We initially tested reported methods (references 27c, e) proven efficient for intermolecular alkoxylicarbonylation, however no desired product was observed. Later, we employed a slightly modified procedure from reference 27k.


39. See references 5-8.


43. For a recent report on *ortho* carboxylation reaction of aryl iodides via the Catellani reaction, see: (a) Wang, J.; Zhang, L.; Dong, Z.; Dong, G. *Chem* **2016**, *1*, 581. For a review on Catellani reaction, see: (b) Ye, J.; Lautens, M. *Nature Chem.* **2015**, *7*, 863.
Chapter 4  Experimental Section

General Information

GC/MS analysis was performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m x 0.25 mm capillary column, HP-5MS). NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz), or DPX-400 (400 MHz) instrument, and referenced to residual solvent peaks. All spectra were acquired in a 5 mm inverse probehead at 298 K in 5 mm tubes. Chemical shifts are quoted in parts per million (ppm) to the nearest 0.01 ppm with signal splitting recorded as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quin), sextet (sex), septet (sept), multiplet (m), broad singlet (br. s) and apparent doublet (app. d). Coupling constants, $J$, are measured in Hz to the nearest 0.1 Hz. LRMS and HRMS analyses were performed on Micromass 70 VSE mass spectrometer. Column chromatography was carried out employing Silicycle Silica-P flash silica gel (40-63 μm). Precoated silica gel plates F-254 were used for thin-layer analytical chromatography. Balloons (Z154997) were purchased from Sigma-Aldrich. Needles (22G x 3”) were purchased from Air-Tite. Test tubes (16 x 125 mm) were purchased from VWR. All manipulations were conducted under argon or nitrogen unless otherwise stated. DCE was dried with CaH$_2$, $i$PrOH was dried with K$_2$CO$_3$. All commercially available compounds were used without further purification.
4.1 Synthesis of Biaryl-2-Carboxylic Acids 2-4

General Procedure for the Preparation of Biaryl-2-Carboxylic Acids 2-4 via Suzuki Cross-coupling Reaction

To a 100 mL schlenk tube (or 100 mL flask equipped with argon inlet) 28 mg Pd(PPh₃)₂Cl₂ (28 mg, 0.040 mmol, 1 mol%) and arylboronic acid 4-2 (4.2 mmol, 1.05 equiv) were added, followed by a solution of Na₂CO₃ (848 mg, 8.0 mmol, 2 equiv in 10 mL H₂O) and THF (10 mL). The mixture was stirred for 2 min at room temperature, and methyl 2-iodobenzoate 4-1 (600 μL, 4.0 mmol, 1 equiv) was added. The reaction mixture was heated at 80 °C for 2-12 h (GC monitored). The resulting reaction mixture was extracted with DCM (3×15 mL). The combined organic extract was dried (Na₂SO₄), evaporated, and purified by column chromatography. To the purified product, 1.0 g NaOH (40 mmol, 10 equiv) and H₂O/THF (20 mL, 1:1) solution were added and heated at 80 °C for 2-12 h (TLC monitored). The reaction mixture was cooled to room temperature, 10 mL H₂O was added and it was extracted with DCM (3×5 mL) to remove organic impurities. To the aqueous solution HCl (10 mL, 4 M) was added to and the resulting white precipitates were extracted with EtOAc (3×15 mL). Combined organic extract was dried

(Na$_2$SO$_4$) and evaporated in vacuo, to produce the desired biaryl-2-carboxylic acid 2-4 (recrystallized from CHCl$_3$ if necessary).

![2-4b](image)

4'-Methyl-[1,1'-biphenyl]-2-carboxylic acid 2-4b: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.95 (dd, $J = 7.70, 1.10$ Hz, 1H), 7.56 (ddd, $J = 7.5, 7.5, 1.5$ Hz, 1H), 7.41 (ddd, $J = 7.5, 7.5, 1.10$ Hz, 1H), 7.38 (dd, $J = 7.70, 0.73$ Hz, 1H), 7.25 (d, $J = 8.45$ Hz, 2H), 7.21 (d, $J = 8.45$ Hz, 2H), 2.41 (s, 3H); 13C NMR (126 MHz, CDCl$_3$): ppm 173.63, 143.26, 137.10, 132.04, 131.20, 130.66, 129.33, 128.86, 128.36, 126.96, 21.20; The NMR spectra correspond to the literature data.²

![2-4c](image)

4'-(tert-Butyl)-[1,1'-biphenyl]-2-carboxylic acid 2-4c: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.96 (d, $J = 7.7$ Hz, 1H), 7.56 (dd, $J = 7.7$ Hz 1H), 7.43-7.41 (m, 3H), 7.39 (d, $J = 7.7$ Hz, 1H), 7.30 (d, $J = 8.05$ Hz, 2H), 1.37 (s, 9H); 13C NMR (126 MHz, CDCl$_3$): ppm 173.76, 150.26, 143.23, 137.91, 132.02, 131.38, 130.69, 129.33, 128.18, 126.95, 125.08, 34.56, 31.40; HRMS (ESI+) calcd. for [C$_{17}$H$_{18}$O$_2$+H]$^+$: 255.1385, found: 255.1391.

![2-4d](image)

4'-Methoxy-[1,1'-biphenyl]-2-carboxylic acid 2-4d: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.93 (d, $J = 8.8$ Hz, 1H), 7.55 (d, $J = 7.7$ Hz, 1H), 7.39 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.36 (d, $J = 7.70$ Hz, 1H), 7.28 (d, $J = 8.80$ Hz, 2H), 6.93 (d, $J = 8.44$ Hz, 2H), 3.85 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 173.31, 159.10, 142.92, 133.30, 132.04, 131.20, 130.69, 129.64, 129.24, 126.83, 113.63, 55.24; The NMR spectra correspond to the literature data.\(^3\)

![Image of 4'-Methoxy-[1,1'-biphenyl]-2-carboxylic acid 2-4d](image)

4'-(Benzyloxy)-[1,1'-biphenyl]-2-carboxylic acid 2-4e: $^1$H NMR (500 MHz, Acetone-$d_6$): ppm 7.81 (dd, $J = 7.70$, 1.10 Hz, 1H), 7.56 (ddd, $J = 7.7$, 7.7, 1.5 Hz, 1H), 7.51 (d, $J = 7.30$ Hz, 2H), 7.45-7.28 (m, 7H), 7.05 (d, $J = 8.80$ Hz, 2H), 5.15 (s, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 172.64, 158.43, 142.83, 136.94, 133.56, 132.03, 131.19, 130.68, 129.69, 128.60, 128.00, 127.59, 126.90, 114.54, 70.07; HRMS (ESI+) calcd. for [C$_{20}$H$_{16}$O$_3$+H]$^+$: 305.1178, found: 305.1178.

![Image of 4'-(Benzyloxy)-[1,1'-biphenyl]-2-carboxylic acid 2-4e](image)

4'-(Trifluoromethoxy)-[1,1'-biphenyl]-2-carboxylic acid 2-4f: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.01 (dd, $J = 7.89$, 1.28 Hz, 1H), 7.59 (dd, $J = 7.5$, 7.5, 1.5 Hz, 1H), 7.46 (ddd, $J = 7.6$, 7.6, 1.3 Hz, 1H), 7.36-7.31 (m, 3H), 7.23 (d, $J = 8.07$ Hz, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 172.58, 148.65, 142.27, 139.77, 132.38, 131.24, 131.00, 129.88, 128.90, 127.68, 120.52 (q, $J = 258$ Hz, OCF$_3$), 120.35; HRMS (ESI+) calcd. for [C$_{14}$H$_9$F$_3$O$_3$+H]$^+$: 283.0582, found: 283.0579.

4'-Fluoro-[1,1'-biphenyl]-2-carboxylic acid 2-4g: ¹H NMR (500 MHz, CDCl₃): ppm 7.97 (dd, $J = 7.70$, 1.10 Hz, 1H), 7.57 (ddd, $J = 7.5$, 7.5, 1.47 Hz, 1H), 7.44 (ddd, $J = 7.5$, 7.5, 1.10 Hz, 1H), 7.31-7.27 (m, 2H), 7.11-7.04 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): ppm 173.13, 162.37 (d, $J = 246$ Hz), 142.51, 137.04, 132.24, 130.85, 130.07 (d, $J = 9.3$ Hz), 129.10, 127.38, 114.99 (d, $J = 20.4$ Hz); The NMR spectra correspond to the literature data.²

4'-Chloro-[1,1'-biphenyl]-2-carboxylic acid 2-4h: ¹H NMR (500 MHz, CDCl₃): ppm 7.98 (dd, $J = 7.70$, 1.10 Hz, 1H), 7.58 (ddd, $J = 7.6$, 7.6, 1.28 Hz, 1H), 7.45 (ddd, $J = 7.7$, 7.7, 1.10 Hz, 1H), 7.37-7.35 (m, 2H), 7.32 (dd, $J = 7.7$, 0.72 Hz, 1H), 7.28-7.24 (m, 2H); ¹³C NMR (126 MHz, CDCl₃): ppm 172.73, 142.35, 139.55, 133.51, 132.33, 131.16, 130.95, 129.82, 128.94, 128.23, 127.58; The NMR spectra correspond to the literature data.²

4'-Bromo-[1,1'-biphenyl]-2-carboxylic acid 2-4i: ¹H NMR (500 MHz, CDCl₃): ppm 7.99 (dd, $J = 7.70$, 1.10 Hz, 1H), 7.58 (ddd, $J = 7.6$, 7.6, 1.28 Hz, 1H), 7.55-7.49 (m, 2H), 7.45 (td, $J = 7.7$, 7.7, 1.10 Hz, 1H), 7.33 (dd, $J = 7.52$, 0.92 Hz, 1H), 7.23-7.17 (m, 2H); ¹³C NMR (126 MHz,
CDCl$_3$): ppm 173.19, 142.36, 140.02, 132.39, 131.17, 131.11, 131.01, 130.14, 128.86, 127.60, 121.69; The NMR spectra correspond to the literature data.$^2$

![Image](2-4j)

**4'-Cyano-[1,1'-biphenyl]-2-carboxylic acid 2-4j:** $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.05 (d, $J = 7.0$ Hz, 1H), 7.68 (d, $J = 8.07$ Hz, 2H), 7.62 (ddd, $J = 7.7, 7.7, 1.45$ Hz, 1H), 7.51 (ddd, $J = 7.7, 7.7, 1.1$ Hz, 1H), 7.42 (d, $J = 8.44$ Hz, 2H), 7.32 (d, $J = 7.34$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 171.28, 146.12, 141.96, 132.65, 131.78, 131.28, 130.91, 129.30, 128.45, 128.35, 118.88, 111.19; HRMS (ESI+) calcd. for [C$_{14}$H$_9$NO$_2$+H]$^+$: 224.0712, found: 224.0716. The NMR spectra correspond to the literature data.$^3$

![Image](2-4k)

**3'-Fluoro-[1,1'-biphenyl]-2-carboxylic acid 2-4k:** $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.98 (dd, $J = 7.70, 0.73$ Hz, 1H), 7.58 (ddd, $J = 7.5, 7.5, 1.47$ Hz, 1H), 7.45 (ddd, $J = 7.6, 7.6, 1.28$ Hz, 1H), 7.38-7.30 (m, 2H), 7.13-7.02 (m, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 173.15, 162.43 (d, $J = 246$ Hz), 143.24 (d, $J = 7.4$ Hz), 132.30, 131.06, 130.87, 129.48 (d, $J = 9.3$ Hz), 129.09, 124.29 (d, $J = 3.7$ Hz), 115.53 (d, $J = 22$ Hz), 114.21 (d, $J = 22$ Hz); The NMR spectra correspond to the literature data.$^2$
3'-Chloro-[1,1'-biphenyl]-2-carboxylic acid 2-4l: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.00 (dd, $J = 7.8$, 0.95 Hz, 1H), 7.58 (ddd, $J = 7.6$, 7.5, 1.25 Hz, 1H), 7.46 (ddd, $J = 7.4$, 7.4, 1.05 Hz, 1H), 7.35-7.29 (m, 4H), 7.21-7.19 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 173.11, 142.86, 142.12, 133.82, 132.35, 131.11, 130.96, 129.18, 128.93, 128.46, 127.73, 127.42, 126.82; The NMR spectra correspond to the literature data.$^2$

3'-(tert-Butyl)-[1,1'-biphenyl]-2-carboxylic acid 2-4m: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.91 (d, $J = 8.25$ Hz, 1H), 7.56 (ddd, $J = 7.5$, 7.5, 0.6 Hz, 1H), 7.43-7.31 (m, 4H), 7.18 (d, $J = 7.3$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 173.81, 150.71, 143.60, 140.34, 131.92, 131.10, 129.61, 127.86, 127.00, 126.08, 125.42, 124.25, 34.70, 31.29; HRMS (ESI+) calcd. for [C$_{17}$H$_{19}$O$_2$+H]$^+$: 255.1385, found: 270.1384.

3'-Methoxy-[1,1'-biphenyl]-2-carboxylic acid 2-4n: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.93 (dd, $J = 7.70$, 1.47 Hz, 1H), 7.56 (ddd, $J = 7.5$, 7.5, 1.47 Hz, 1H), 7.43 (ddd, $J = 7.6$, 7.6, 1.28 Hz, 1H), 7.38 (dd, $J = 7.70$, 1.10 Hz, 1H), 7.30 (t, $J = 7.89$ Hz, 1H), 6.94-6.87 (m, 3H), 3.28 (s,
1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 172.34, 159.28, 143.03, 142.37, 132.00, 131.05, 130.56, 129.32, 129.10, 127.30, 121.06, 114.15, 113.00, 55.24; The NMR spectra correspond to the literature data.²

![Structure 2-4o](image)

**3’-Methyl-[1,1’-biphenyl]-2-carboxylic acid 2-4o:** $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.95 (d, $J$ = 7.70 Hz, 1H), 7.56 (dd, $J$ = 7.3, 7.3 Hz, 1H), 7.42 (d, $J$ = 7.5, 7.5 Hz, 1H), 7.38 (d, $J$ = 7.7 Hz, 1H), 7.28 (dd, $J$ = 7.7, 7.7 Hz, 1H), 7.18-7.14 (m, 3H), 2.40 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 173.65, 143.40, 140.90, 137.66, 132.00, 131.16, 130.59, 129.34, 129.10, 128.15, 127.94, 127.06, 125.63, 21.43; The NMR spectra correspond to the literature data.⁴

![Structure 2-4p](image)

**2-(Naphthalen-2-yl)benzoic acid 2-4p:** $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.98 (d, $J$ = 7.70 Hz, 1H), 7.88-7.76 (m, 4H), 7.59 (ddd, $J$ = 7.5, 7.5, 1.1 Hz, 1H), 7.55-7.41 (m, 5H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 172.37, 143.38, 138.67, 133.21, 132.55, 132.20, 131.54, 130.83, 128.13, 127.70, 127.42, 127.32, 127.13, 126.95, 126.61, 126.17, 126.02; The NMR spectra correspond to the literature data.¹

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3',5'-Dimethyl-[1,1'-biphenyl]-2-carboxylic acid 2-4q: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.93 (dd, $J = 7.70$, 1.10 Hz, 1H), 7.55 (ddd, $J = 7.6$, 7.6, 1.28 Hz, 1H), 7.41 (ddd, $J = 7.5$, 7.5, 1.10 Hz, 1H), 7.37 (dd, $J = 7.70$, 0.75 Hz, 1H), 7.00 (s, 1H), 6.98 (s, 2H), 2.35 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 173.60, 143.44, 140.82, 137.55, 131.94, 131.16, 130.52, 129.36, 129.13, 126.98, 126.32, 21.31.

3',5'-Dimethoxy-[1,1'-biphenyl]-2-carboxylic acid 2-4r: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.92 (dd, $J = 7.70$, 1.10 Hz, 1H), 7.55 (ddd, $J = 7.6$, 7.6, 1.28 Hz, 1H), 7.43 (ddd, $J = 7.6$, 7.6, 1.28 Hz, 1H), 7.39 (dd, $J = 7.70$, 0.75 Hz, 1H), 6.50 (d, $J = 2.20$ Hz, 2H), 6.48-6.45 (m, 1H), 3.80 (s, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 172.82, 160.39, 142.97, 131.95, 130.88, 130.45, 129.44, 127.36, 106.79, 99.62, 55.37; HRMS (ESI+) calcd. for [C$_{15}$H$_{13}$O$_4$+H]$^+$: 259.0970, found: 259.0974.

4-Methyl-[1,1'-biphenyl]-2-carboxylic acid 2-4s: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.77 (s, 1H), 7.42-7.30 (m, 6H), 7.27 (d, $J = 8.07$ Hz, 1H), 2.44 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$):
ppm 173.73, 140.98, 140.55, 137.07, 132.83, 131.14, 129.05, 128.51, 128.02, 127.14, 20.88. The NMR spectra correspond to the literature data.5

4-Bromo-[1,1'-biphenyl]-2-carboxylic acid 2-4t: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.09 (d, $J$ = 2.05 Hz, 1H), 7.69 (dd, $J$ = 8.2, 2.05 Hz, 1H), 7.41-7.37 (m, 3H), 7.31-7.29 (m, 2H), 7.25 (d, $J$ = 8.2 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 172.31, 142.28, 139.76, 135.07, 133.44, 132.75, 130.74, 128.28, 128.18, 127.70, 121.09; HRMS (ESI+) calcd. for [C$_{13}$H$_9$O$_2$Br+Na]$^+$: 298.9684, found: 298.9686.

5-Methoxy-[1,1'-biphenyl]-2-carboxylic acid 2-4u: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.98 (d, $J$ = 8.8 Hz, 1H), 7.38-7.35 (m, 2H), 7.34-7.28 (m, 2H), 6.90 (dd, $J$ = 8.6 Hz, 2.6 Hz, 1H), 6.8 (d, $J$ = 2.6 Hz, 1H), 3.86 (s, 3H). The NMR spectra correspond to the literature data.6

3-Fluoro-[1,1'-biphenyl]-2-carboxylic acid 2-4v: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.50-7.42 (m, 1H), 7.4 (br. s, 5H), 7.19 (d, $J = 7.6$ Hz, 1H), 7.13 (t, $J = 7.6$ Hz, 1H).

4'-Acetyl-[1,1'-biphenyl]-2-carboxylic acid 2-4x: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.01 (d, $J = 6.60$ Hz, 1H), 7.98 (d, $J = 8.07$ Hz, 2H), 7.60 (ddd, $J = 7.5$, 7.5, 1.10 Hz, 1H), 7.47 (ddd, $J = 7.7$, 7.7, 0.75 Hz, 1H), 7.42 (d, $J = 8.07$ Hz, 2H), 7.35 (d, $J = 7.70$ Hz, 1H), 2.64 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 197.96, 172.25, 146.16, 142.50, 135.92, 132.41, 131.05, 131.00, 128.85, 128.77, 128.14, 127.92, 26.65. The NMR spectra correspond to the literature data.\(^7\)

4'-(Dimethylcarbamoyl)-[1,1'-biphenyl]-2-carboxylic acid 2-4y: $^1$H NMR (500 MHz, MeOD-$d_4$): ppm 7.85 (dd, $J = 7.7$, 0.95 Hz, 1H), 7.58 (ddd, $J = 7.6$, 7.6, 1.25 Hz, 1H), 7.48-7.38 (m, 6 H). 4.87 (HDO), 3.31 (H$_2$O); $^{13}$C NMR (126 MHz, MeOD-$d_4$): ppm 173.70, 171.76, 144.64, 142.80, 135.98, 132.93, 132.40, 131.77, 130.91, 129.75, 128.71, 127.84, 40.09, 35.69; HRMS (ESI+) calcd. for [C$_{16}$H$_{15}$NO$_3$+H]$^+$: 270.1130, found: 270.1134.

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4’-Formyl-[1,1'-biphenyl]-2-carboxylic acid 2-4z: \(^{1}H\) NMR (500 MHz, CDCl\(_3\)): ppm 10.05 (s, 1H), 8.02 (dd, \(J = 7.8, 1\) Hz, 1H), 7.89 (d, \(J = 9.5\) Hz, 2H), 7.61 (ddd, \(J = 7.6, 7.5, 1.25\) Hz, 1H), 7.50-7.47 (m, 3H), 7.35 (d, \(J = 7.65\) Hz, 1H); \(^{13}C\) NMR (126 MHz, CDCl\(_3\)): ppm 192.16, 172.53, 147.62, 142.40, 135.19, 132.50, 131.14, 130.94, 129.46, 129.21, 128.77, 128.09; HRMS (ESI+) calcd. for [C\(_{14}\)H\(_{10}\)O\(_3\)+H]\(^{+}\): 227.0708, found: 270.0706.

3’-(Trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid 2-4aa: \(^{1}H\) NMR (500 MHz, CDCl\(_3\)): ppm 8.02 (dd, \(J = 7.85, 1\) Hz, 1H), 7.62-7.59 (m, 3H), 7.50-7.46 (m, 3H), 7.35 (dd, \(J = 7.65, 0.75\) Hz, 1H); \(^{13}C\) NMR (126 MHz, CDCl\(_3\)): ppm 172.69, 142.21, 141.85, 132.52, 131.88, 131.22, 131.12, 130.61 (q, \(J = 48\) Hz, CF\(_3\)), 128.81, 128.34, 127.93, 125.31 (d, \(J = 3.4\) Hz), 125.20, 124.06 (d, \(J = 3.3\) Hz); HRMS (ESI+) calcd. for [C\(_{13}\)H\(_{9}\)O\(_2\)F\(_3\)+Na]\(^{+}\): 289.0452, found: 289.0449.

3’,5’-Bis(trifluoromethyl)-[1,1'-biphenyl]-2-carboxylic acid 2-4ab: \(^{1}H\) NMR (500 MHz, CDCl\(_3\)): ppm 8.1 (d, \(J = 7.5\) Hz, 1H), 7.9 (s, 1H), 7.74 (br. s, 2H), 7.60-7.67 (m, 1H), 7.57-7.50 (m, 1H), 7.33 (m, \(J = 7.3\) Hz, 1H); \(^{13}C\) NMR (126 MHz, CDCl\(_3\)): ppm 171.6, 143.2, 140.1, 133.0, 131.6, 131.2, 130.8 (d, \(J = 33.3\) Hz), 128.9 (br.), 128.7, 128.3, 123.3 (q, \(J = 272.8\) Hz), 121.1 (br. s); HRMS (ESI+) calcd. for [C\(_{15}\)H\(_{8}\)O\(_2\)F\(_6\)+Na]\(^{+}\): 357.0326, found: 357.0326.
5-Nitro-[1,1'-biphenyl]-2-carboxylic acid 2-4ac: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.30-8.20 (m, 2H), 8.10-8.00 (m, 1H), 7.47-7.40 (m, 3H), 7.38-7.30 (m, 2H). The NMR spectra correspond to the literature data.$^8$

4'-Nitro-[1,1'-biphenyl]-2-carboxylic acid 2-4ad: $^1$H NMR (500 MHz, DMSO-$d_6$): ppm 8.25 (d, $J = 8.8$ Hz, 2H), 7.86 (d, $J = 7.7$ Hz, 1H), 7.70-7.60 (m, 1H), 7.57 (d, $J = 8.8$ Hz, 2H), 7.60-7.50 (m, 1H), 7.40 (d, $J = 7.7$ Hz, 1H). The NMR spectra correspond to the literature data.$^3$

3'-Nitro-[1,1'-biphenyl]-2-carboxylic acid 2-4ae: $^1$H NMR (500 MHz, acetone-$d_6$): ppm 8.24 (d, $J = 8.2$ Hz, 1H), 8.20 (s, 1H), 8.02 (d, $J = 7.7$ Hz, 1H), 7.80 (d, $J = 7.65$ Hz, 1H), 7.72-7.67

(m, 2H), 7.59 (dd, $J = 7.6, 7.6, 0.85$ Hz, 1H), 7.48 (d, $J = 7.6$ Hz, 1H); $^{13}$C NMR (126 MHz, acetonitrile-$d_6$): ppm 167.40, 147.66, 143.08, 140.14, 134.68, 131.49, 130.60, 130.44, 130.13, 128.92, 128.00, 122.89, 121.53; HRMS (ESI+) calcd. for $[C_{13}H_9NO_4+Na]^+$: 266.0453, found: 266.0433.

**2'-Fluoro-[1,1'-biphenyl]-2-carboxylic acid 2-4ag:** $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.06 (dd, $J = 10.1, 1.55$ Hz, 1H), 7.61 (ddd, $J = 9.4, 9.3, 1.5$ Hz, 1H), 7.47 (ddd, $J = 9.5, 9.4, 1.2$ Hz, 1H), 7.37-7.28 (m, 3H), 7.20 (ddd, $J = 9.2, 9.1, 1.2$ Hz, 1H), 7.07 (ddd, $J = 11.3, 11.3, 1$ Hz, 1H). The NMR spectra correspond to the literature data.$^2$

**2'-Chloro-[1,1'-biphenyl]-2-carboxylic acid 2-4ah:** $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.08 (dd, $J = 9.75, 1.5$ Hz, 1H), 7.61 (ddd, $J = 9.5, 9.5, 1.8$ Hz, 1H), 7.48 (ddd, $J = 9.5, 9.5, 1.8$ Hz, 1H), 7.43-7.39 (m, 1H), 7.32-7.22 (m, 4H); HRMS (ESI+) calcd. for $[C_{13}H_8O_2Cl+Na]^+$: 277.0008, found: 277.0002.

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2-4ag

2-4ah

2-4ai

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2'-Bromo-[1,1'-biphenyl]-2-carboxylic acid 2-4ai: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.09 (dd, $J = 7.85$, 0.95 Hz, 1H), 7.62-7.59 (m, 2H), 7.48 (ddd, $J = 7.7$, 7.6, 1.15 Hz, 1H), 7.34 (ddd, $J = 7.7$, 7.6, 1 Hz, 1H), 7.26-7.19 (m, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 171.78, 142.84, 142.31, 132.58, 132.17, 131.30, 130.90, 129.96, 128.89, 128.69, 127.93, 126.96, 122.88; HRMS (ESI+) calcd. for [C$_{13}$H$_9$O$_2$Br+Na]$^+$: 298.9684, found: 298.9683.

4.2 C–H Oxygenation Reaction of Biaryl-2-Carboxylic Acids 2-4

Method 1: General Procedure 1 (GP-1) for the Copper-Catalyzed Oxygenation Reaction

To a 10 mL Wheaton V-vial biaryl-2-carboxylic acid 2-4 (0.50 mmol) and Cu(OAc)$_2$•H$_2$O (5.0 mg, 5 mol%), followed by dry DCE (5 mL) were added under ambient atmosphere. The reaction mixture was stirred at 85 °C for 5 min and TBPB (1.5 mmol, 3 equiv) was added. The reaction mixture was stirred at 85 °C for 12 h, cooled to room temperature, washed with an aqueous solution of NaOH (15 mL, 1 M aq.) and extracted with DCM (3×5 mL). The combined organic layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexanes 5/95 or dichloromethane) to produce the desired product as a solid compound.

Method 2: General Procedure 2 (GP-2) for the K$_2$S$_2$O$_8$-Mediated Oxygenation Reaction

To a 10 mL Wheaton V-vial biaryl-2-carboxylic acid 2-4 (0.50 mmol) and K$_2$S$_2$O$_8$ (405 mg, 1.50 mmol, 3 equiv), followed by H$_2$O/MeCN (2 mL, 1:1) were added under air. The reaction mixture was heated for 12-18 h at 50 °C (GC or TLC monitored). Solution of NaHCO$_3$ (aq. saturated) was added to the reaction mixture, and the product was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexanes 5/95 or dichloromethane) to produce the desired product as a solid compound.
**Method 2: General Procedure 3 (GP-3) for the K$_2$S$_2$O$_8$-Mediated Oxygenation Reaction in the Presence of AgNO$_3$ Additive**

To a 10 mL Wheaton V-vial biaryl-2-carboxylic acid 2-4 (0.50 mmol), K$_2$S$_2$O$_8$ (405 mg, 1.50 mmol, 3 equiv), and AgNO$_3$ (8.5 mg, 0.05 mmol, 10 mol%), followed by H$_2$O/MeCN (2 mL, 1:1) were added under air. The reaction mixture was heated for 12-18 h at 50 °C (GC or TLC monitored). Solution of NaHCO$_3$ (aq. saturated) was added to the reaction mixture, and the product was extracted with ethyl acetate (3×10 mL). The combined organic layers were dried (Na$_2$SO$_4$) and evaporated in vacuo. The residue was purified by column chromatography (ethyl acetate/hexanes 5/95 or dichloromethane) to produce the desired product as a solid compound.

**Oxygenation Reaction of Biaryl-2-Carboxylic Acids 2-4ag-i into 2-1a**

![Oxygenation Reaction Diagram]

<table>
<thead>
<tr>
<th>X</th>
<th>Cu(II)</th>
<th>K$_2$S$_2$O$_8$</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>67%</td>
<td>95%</td>
</tr>
<tr>
<td>Cl</td>
<td>57%</td>
<td>58%</td>
</tr>
<tr>
<td>Br</td>
<td>75%</td>
<td>42%</td>
</tr>
</tbody>
</table>

*NMR yields*

The Cu-catalyzed reaction was performed on a 0.2 mmol scale according to **GP 1**. The K$_2$S$_2$O$_8$-mediated reaction was performed on a 0.2 mmol scale according to **GP 2**. The NMR yield of 2-1a was determined using CH$_2$Br$_2$ as internal standard.
6H-Benzoc[chromen-6-one 2-1a: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.40 (d, $J = 7.95$ Hz, 1H), 8.12 (d, $J = 8.05$ Hz, 1H), 8.06 (d, $J = 7.95$ Hz, 1H), 7.82 (dd, $J = 7.25$, 7.25 Hz, 1H), 7.58 (dd, $J = 7.60$, 7.60 Hz, 1H), 7.51-7.44 (m, 1H), 7.37-7.32 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 161.14, 151.26, 134.80, 134.73, 130.55, 130.41, 128.85, 124.52, 122.73, 121.65, 121.24, 118.01, 117.75; The NMR spectra correspond to the literature data.\(^2\)

![2-1b](image)

3-Methyl-6H-benzoc[chromen-6-one 2-1b: $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.39 (dd, $J = 8.07$, 0.73 Hz, 1H), 8.08 (d, $J = 8.07$ Hz, 1H), 7.93 (d, $J = 8.07$ Hz, 1H), 7.80 (ddd, $J = 7.7$, 7.7, 1.5 Hz, 1H), 7.55 (ddd, $J = 7.7$, 7.7, 1.1 Hz, 1H), 7.17 (s, 1H), 7.15 (d, $J = 8.07$ Hz, 1H), 2.45 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 161.43, 151.28, 141.28, 134.99, 134.76, 130.54, 128.35, 125.66, 122.50, 121.42, 117.89, 115.43, 21.43; The NMR spectra correspond to the literature data.\(^2\)

![2-1c](image)

3-(tert-Butyl)-6H-benzoc[chromen-6-one 2-1c: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.39 (d, $J = 7.7$ Hz, 1H), 8.09 (d, $J = 8.1$ Hz, 1H), 7.98 (d, $J = 8.80$ Hz, 1H), 7.81 (dd, $J = 7.5$, 7.5 Hz, 1H), 7.55 (dd, $J = 7.7$, 7.7 Hz, 1H), 7.41-7.36 (m, 2H), 1.37 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 161.49, 154.67, 151.19, 134.89, 134.75, 130.52, 128.85, 128.38, 122.35, 121.96, 121.47, 120.98, 115.35, 114.51, 35.00, 31.07; HRMS (ESI+) calcd. for [C$_{17}$H$_{16}$O$_2$+H]$^+$: 253.1229, found: 253.1226.
3-Methoxy-6\textit{H}-benzo[c]chromen-6-one 2-1d: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.36 (dd, $J = 7.89, 0.92$ Hz, 1H), 8.00 (d, $J = 8.07$ Hz, 1H), 7.95 (d, $J = 8.80$ Hz, 1H), 7.78 (ddd, $J = 7.7, 7.7, 1.1$ Hz, 1H), 7.50 (ddd, $J = 7.7, 7.7, 1.1$ Hz, 1H), 6.92 (dd, $J = 8.80, 2.57$ Hz, 1H), 6.87 (d, $J = 2.57$ Hz, 1H), 3.89 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 161.51, 161.48, 152.63, 135.19, 134.85, 130.57, 127.72, 123.77, 121.07, 119.99, 112.45, 111.15, 101.64, 55.69; The NMR spectra correspond to the literature data.$^2$

3-(Benzyloxy)-6\textit{H}-benzo[c]chromen-6-one 2-1e: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.01 (d, $J = 8.07$ Hz, 1H), 7.96 (d, $J = 8.80$ Hz, 1H), 7.79 (dd, $J = 7.7, 7.7$ Hz, 1H), 7.51 (dd, $J = 7.5, 7.5$ Hz, 1H), 7.48-7.33 (m, 5H), 7.00 (dd, $J = 8.80, 2.57$ Hz, 1H), 6.95 (d, $J = 2.57$ Hz, 1H), 5.15 (s, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 161.44, 160.55, 152.52, 136.03, 135.10, 134.84, 130.54, 128.72, 128.29, 127.76, 127.51, 123.79, 121.07, 120.00, 113.12, 111.37, 102.72, 70.42; HRMS (ESI+) calcd. for [C$_{20}$H$_{14}$O$_3$+H]$^+$: 303.1021, found: 303.1023.

3-(Fluorobenzyloxy)-6\textit{H}-benzo[c]chromen-6-one 2-1f:
3-(Trifluoromethoxy)-6H-benzo[c]chromen-6-one 2-1f: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.39 (dd, $J = 7.7, 0.7$ Hz, 1H), 8.08 (dd, $J = 8.62, 2.38$ Hz, 2H), 7.85 (ddd, $J = 7.7, 7.7, 1.5$ Hz, 1H), 7.61 (ddd, $J = 7.7, 7.7, 1.1$ Hz, 1H), 7.24 (s, 1H), 7.21 (dd, $J = 8.99, 1.28$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 160.47, 151.78, 150.14, 135.14, 133.77, 130.76, 129.30, 124.16, 121.74, 120.88, 120.33 (q, $J = 259$ Hz), 116.93, 116.71, 110.14; HRMS (ESI+) calcd. for [C$_{14}$H$_7$O$_3$F$_3$+H]$^+$: 281.0426, found: 281.0422.

![2-1f](image)

3-Fluoro-6H-benzo[c]chromen-6-one 2-1g: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.37 (d, $J = 8.07$ Hz, 1H), 8.07-7.99 (m, 2H), 7.82 (ddd, $J = 7.7, 7.7, 1.5$ Hz, 1H), 7.57 (dd, $J = 7.5, 7.5$ Hz, 1H), 7.11-7.02 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 163.45 (d, $J = 252$ Hz), 160.78, 152.17 ($J = 13$ Hz), 135.07, 134.25, 130.69, 128.76, 124.34 ($J = 9.3$ Hz), 121.49, 120.45, 114.63, 112.42 ($J = 22$ Hz), 105.11 ($J = 26$ Hz); The NMR spectra correspond to the literature data.

![2-1g](image)

3-Chloro-6H-benzo[c]chromen-6-one 2-1h: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.40 (d, $J = 7.7$ Hz, 1H), 8.08 (d, $J = 8.07$ Hz, 1H), 7.99 (d, $J = 8.44$ Hz, 1H), 7.85 (dd, $J = 7.5, 7.5$ Hz, 1H), 7.61 (dd, $J = 7.7, 7.7$ Hz, 1H), 7.39 (s, 1H), 7.33 (dd, $J = 8.62, 1.65$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 160.57, 151.56, 135.95, 135.07, 134.03, 130.76, 129.20, 125.02, 123.80, 121.67, 120.96, 117.99, 116.75. The NMR spectra correspond to the literature data.
3-Bromo-6\textit{H}-benzo[c]chromen-6-one 2-1i: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.39 (d, $J = 7.70$ Hz, 1H), 8.07 (d, $J = 8.07$ Hz, 1H), 7.91 (dd, $J = 8.44, 2.20$ Hz, 1H), 7.84 (ddd, $J = 7.7, 7.7, 1.45$ Hz, 1H), 7.61 (ddd, $J = 7.7, 7.7, 1.1$ Hz, 1H), 7.53 (dd, $J = 2.75, 2.02$ Hz, 1H), 7.46 (dd, $J = 8.44, 2.02$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 160.46, 151.51, 135.06, 134.02, 130.75, 129.26, 127.84, 123.94, 123.70, 121.64, 121.02, 120.90, 117.12. The NMR spectra correspond to the literature data.$^2$ 

3-Cyano-6\textit{H}-benzo[c]chromen-6-one 2-1j: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.45 (dd, $J = 7.89, 0.92$ Hz, 1H), 8.17 (dd, $J = 7.9, 7.9$ Hz, 2H), 7.92 (ddd, $J = 7.7, 7.7, 1.5$ Hz, 1H), 7.72 (ddd, $J = 7.7, 7.7, 1.1$ Hz, 1H), 7.66 (d, $J = 1.47$ Hz, 1H), 7.61 (dd, $J = 8.2, 1.5$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 159.76, 150.92, 135.34, 132.93, 130.99, 130.70, 127.69, 123.87, 122.41, 122.29, 121.80, 121.65, 117.55, 113.53; HRMS (ESI+) calcd. for [C$_{14}$H$_7$NO$_2$+H]$^+$: 222.0555, found: 222.0558.
**2-Fluoro-6H-benzo[c]chromen-6-one 2-1k**: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.39 (d, $J = 7.55$ Hz, 1H), 8.00 (d, $J = 8.05$ Hz, 1H), 7.84 (dd, $J = 7.7$, 7.7, 1.15 Hz, 1H), 7.69 (dd, $J = 9.0$, 2.85 Hz, 1H), 7.62 (dd, $J = 7.6$, 7.6, 0.55 Hz, 1H), 7.33 (dd, $J = 9.0$, 4.7 Hz, 1H), 7.20-7.16 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 160.73, 159.25 ($J = 244$ Hz), 147.33, 134.95, 133.84, 130.66, 129.54, 121.85, 121.19, 119.25 ($J = 8.7$ Hz), 119.14, 117.64 ($J = 24$ Hz), 108.75 ($J = 25$ Hz). The NMR spectra correspond to the literature data.$^9$

![2-1k](image)

**2-Chloro-6H-benzo[c]chromen-6-one 2-1l**: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.42 (d, $J = 7.90$ Hz, 1H), 8.08 (d, $J = 8.05$ Hz, 1H), 8.03 (d, $J = 2.20$ Hz, 1H), 7.86 (ddd, d, $J = 7.50$, 7.5, 1.15 Hz, 1H), 7.64 (ddd, $J = 7.30$, 7.3, 0.70 Hz, 1H), 7.44 (dd, d, $J = 8.75$, 2.35 Hz, 1H), 7.33 (d, $J = 8.75$ Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 160.61, 149.71, 135.07, 133.62, 130.77, 130.37, 130.07, 129.62, 122.64, 121.81, 121.29, 119.41, 119.23. The NMR spectra correspond to the literature data.$^2$

![2-1l](image)

**4-Chloro-6H-benzo[c]chromen-6-one 2-1l’**: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.43 (d, $J = 7.95$ Hz, 1H), 8.12 (d, $J = 8.05$ Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 7.86 (dd, $J = 7.35$, 7.35 Hz, 1H), 7.63 (d, $J = 7.45$ Hz, 1H), 7.55 (d, $J = 7.85$ Hz, 1H), 7.28 (dd, $J = 7.9$, 7.8 Hz, 1H); $^{13}$C

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NMR (126 MHz, CDCl₃): ppm 159.99, 147.11, 135.01, 134.21, 130.90, 130.75, 129.48, 124.52, 122.67, 122.02, 121.19, 121.10, 119.60; HRMS (ESI+) calcd. for [C₁₃H₁₇O₂Cl+H]⁺: 231.0213, found: 231.0212.

2-(tert-Butyl)-6H-benzo[c]chromen-6-one 2-1m: ¹H NMR (500 MHz, CDCl₃): ppm 8.39 (dd, J = 7.95, 0.85 Hz, 1H), 8.16 (d, J = 8.1 Hz, 1H), 8.05 (d, J = 2.2 Hz, 1H), 7.82 (ddd, J = 7.7, 7.7, 1.4 Hz, 1H), 7.56 (ddd, J = 7.6, 7.6, 0.95 Hz, 1H), 7.52 (dd, J = 8.4, 2.3 Hz, 1H), 7.30 (d, J = 8.65 Hz, 1H); ¹³C NMR (126 MHz, CDCl₃): ppm 161.39, 149.22, 147.43, 135.09, 134.68, 130.57, 128.58, 127.99, 121.51, 121.23, 118.88, 117.27, 117.12, 34.70, 31.42; HRMS (ESI+) calcd. for [C₁₇H₁₆O₂+H]⁺: 253.1229, found: 253.1220.

2-Methoxy-6H-benzo[c]chromen-6-one 2-1n: ¹H NMR (500 MHz, CDCl₃): ppm 8.39 (dd, J = 7.8, 0.7 Hz, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.81 (ddd, J = 7.7, 7.7, 1.25 Hz, 1H), 7.57 (ddd, J = 7.6, 7.6, 0.6 Hz, 1H), 7.46 (d, J = 2.8 Hz, 1H), 7.28 (d, J = 9 Hz, 1H), 7.03 (dd, J = 9, 2.8 Hz, 1H), 3.90 (s, 3H); ¹³C NMR (126 MHz, CDCl₃): ppm 161.25, 156.29, 145.56, 134.68, 134.58, 130.60, 128.91, 121.66, 121.30, 118.63, 118.48, 117.07, 106.30, 55.81. The NMR spectra correspond to the literature data.²
4-Methyl-6H-benzo[c]chromen-6-one 2-1o: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.42 (dd, $J$ = 7.95, 0.9 Hz, 1H), 8.13 (d, $J$ = 8.05 Hz, 1H), 7.92 (d, $J$ = 7.75 Hz, 1H), 7.82 (ddd, $J$ = 7.7, 7.6, 1.3 Hz, 1H), 7.58 (dd, $J$ = 7.7, 7.6, 0.9 Hz, 1H), 7.34 (dd, $J$ = 7.35 Hz, 1H), 7.24 (dd, $J$ = 7.8, 7.7 Hz, 2H), 2.51 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 161.25, 149.68, 135.14, 134.74, 131.78, 130.50, 128.67, 127.09, 123.98, 121.87, 121.12, 120.37, 117.72, 15.98. The NMR spectra correspond to the literature data.\(^9\)

2-Methyl-6H-benzo[c]chromen-6-one 2-1o': $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.41 (dd, $J$ = 7.9, 0.75 Hz, 1H), 8.13 (d, $J$ = 8.05 Hz, 1H), 7.86 (s, 1H), 7.82 (ddd, $J$ = 7.7, 7.6, 1.25 Hz, 1H), 7.58 (dd, $J$ = 7.9, 7.3 Hz, 1H), 7.30-7.28 (m, 2H), 2.47 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 161.38, 149.40, 134.84, 134.72, 134.09, 131.35, 130.60, 128.70, 122.74, 121.60, 121.32, 117.51, 21.12. The NMR spectra correspond to the literature data.\(^3\)

6H-Dibenzo[c,h]chromen-6-one 2-1p: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.59 (d, $J$ = 8.1 Hz, 1H), 8.47 (d, $J$ = 7.9 Hz, 1H), 8.20 (d, $J$ = 13 Hz, 1H), 8.07 (d, $J$ = 8.8 Hz, 1H), 7.89-7.86 (m,
2H), 7.77 (d, \( J = 8.7 \) Hz, 1H), 7.66-7.59 (m, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): ppm 161.22, 147.26, 135.40, 134.95, 134.25, 130.64, 128.61, 127.88, 127.64, 127.11, 124.49, 123.88, 122.32, 122.02, 121.19, 119.15, 113.02. The NMR spectra correspond to the literature data.\(^{10}\)

![](image)

2,4-Dimethyl-6\(H\)-benzo[c]chromen-6-one 2-1q: \(^1\)H NMR (500 MHz, CDCl\(_3\)): ppm 8.36 (d, \( J = 7.8 \) Hz, 1H), 8.04 (d, \( J = 8.1 \) Hz, 1H), 7.76 (ddd, \( J = 7.7, 7.6, 1.15 \) Hz, 1H), 7.62 (s, 1H), 7.53 (ddd, \( J = 7.3, 7.3, 0.5 \) Hz, 1H), 7.10 (s, 1H), 2.42 (s, 3H), 2.39 (s, 3H); \(^{13}\)C NMR (126 MHz, DCl\(_3\)): ppm 161.32, 147.64, 135.06, 134.52, 133.33, 132.74, 130.36, 128.38, 126.54, 121.69, 121.02, 120.25, 117.21, 20.98, 15.80. The NMR spectra correspond to the literature data.\(^{11}\)

![](image)

2,4-Dimethoxy-6\(H\)-benzo[c]chromen-6-one 2-1r: \(^1\)H NMR (500 MHz, CDCl\(_3\)): ppm 8.40 (dd, \( J = 7.9, 0.9 \) Hz, 1H), 8.04 (d, \( J = 8.05 \) Hz, 1H), 7.81 (ddd, \( J = 7.7, 7.7, 1.3 \) Hz, 1H), 7.58 (ddd, \( J = 7.3, 7.3, 0.8 \) Hz, 1H), 7.02 (d, \( J = 2.6 \) Hz, 1H), 6.63 (d, \( J = 2.6 \) Hz, 1H), 3.95 (s, 3H), 3.90 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): ppm 160.64, 156.42, 148.91, 135.95, 134.83, 134.61, 130.65, 128.95, 122.04, 121.51, 118.60, 101.39, 96.02, 56.22, 55.75; HRMS (ESI+) calcd. for \([C_{15}H_{13}O_4+H]^+\): 257.0814, found: 257.0812.

8-Methyl-6H-benzo[c]chromen-6-one 2-1s: \(^1\)H NMR (400 MHz, CDCl\(_3\)): ppm 8.17 (s, 1H), 8.01-7.97 (m, 2H), 7.61 (d, \(J = 8.04\) Hz, 1H), 7.46-7.43 (dd, \(J = 7.0, 7.0\) Hz, 1H), 7.36-7.29 (m, 2H), 2.48 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): ppm 161.31, 150.96, 139.18, 135.99, 132.16, 130.30, 129.85, 124.42, 122.48, 121.62, 121.03, 118.14, 117.61, 21.24; The NMR spectra correspond to the literature data.\(^9\)

9-Methoxy-6H-benzo[c]chromen-6-one 2-1u: \(^1\)H NMR (500 MHz, CDCl\(_3\)): ppm 8.26 (d, \(J = 8.8\) Hz, 1H), 7.93 (d, \(J = 7.9\) Hz, 1H), 7.46-7.40 (m, 2H), 7.32-7.26 (m, 2H), 7.05 (dd, \(J = 8.8, 2.2\) Hz, 1H), 3.96 (s, 3H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): ppm 164.8, 160.9, 151.6, 136.8, 132.8,

8-Bromo-6H-benzo[c]chromen-6-one 2-1t: \(^1\)H NMR (500 MHz, CDCl\(_3\)): ppm 8.55-8.54 (m, 1H), 8.04-7.99 (m, 2H), 7.92-7.91 (m, 1H), 7.52 (ddd, \(J = 7.8, 7.7, 1.3\) Hz, 1H), 7.39-7.34 (m, 2H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): ppm 159.90, 151.17, 137.94, 133.62, 133.17, 130.91, 124.83, 123.50, 122.78, 122.72, 117.94, 117.34; HRMS (ESI+) calcd. for [C\(_{13}\)H\(_7\)O\(_2\)Br+Na]\(^+\): 296.9527, found: 296.9538.
130.5, 124.3, 122.7, 117.9, 117.7, 116.1, 114.2, 105.0, 55.7; HRMS (ESI+) calcd. for [C_{14}H_{10}O_{3}H]^+: 227.0708, found: 227.0706.

7-Fluoro-6H-benzo[c]chromen-6-one 2-1v: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.02 (d, $J = 7.7$ Hz, 1H), 7.92 (d, $J = 7.7$ Hz, 1H), 7.82-7.75 (m, 1H), 7.49 (t, $J = 7.3$ Hz, 1H), 7.40-7.30 (m, 2H), 7.27-7.23 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 163.5 (d, $J = 268.2$ Hz), 156.7 (d, $J = 15.5$ Hz), 151.4, 137.3, 136.2 (d, $J = 10.2$ Hz), 131.2, 124.7, 123.2, 117.6, 117.6 (d, $J = 3.7$ Hz), 117.0 (br. s), 21.3 (d, $J = 21.3$ Hz), 110.1 (d, $J = 6.5$ Hz); HRMS (ESI+) calcd. for [C$_{13}$H$_7$O$_2$F+H]$^+: 215.0430, found: 215.0439.

3-(Trifluoromethyl)-6H-benzo[c]chromen-6-one 2-1w: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.41 (d, $J = 7.70$ Hz, 1H), 8.18-8.14 (m, 2H), 7.88 (ddd, $J = 7.7$, 7.7, 1.1 Hz, 1H), 7.66 (dd, $J = 7.5$, 7.5 Hz, 1H) 7.62-7.52 (m, 2H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 160.20, 150.94, 135.18, 133.33, 132.22 (q, $J = 33.4$ Hz), 130.81, 130.10, 125.43 (q, $J = 272$ Hz), 123.60, 122.16, 121.63, 121.06 (q, $J = 3.7$ Hz), 115.18 (q, $J = 3.7$ Hz). The NMR spectra correspond to the literature data.²
3-Acetyl-6H-benzo[c]chromen-6-one 2-1x: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.43 (d, $J = 8.07$ Hz, 1H), 8.16 (dd, $J = 11.37, 8.07$ Hz, 2H), 7.95-7.84 (m, 3H), 7.67 (dd, $J = 7.3, 7.4$ Hz, 1H), 2.67 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 196.46, 160.59, 151.14, 138.39, 135.10, 133.64, 130.82, 130.10, 123.86, 123.16, 122.41, 121.98, 121.79, 117.93, 26.72.

$N,N$-Dimethyl-6-oxo-6H-benzo[c]chromene-3-carboxamide 2-1y: $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.43 (d, $J = 7.70$ Hz, 1H), 8.15-8.11 (m, 2H), 7.86 (dd, $J = 7.7, 7.7$ Hz, 1H), 7.64 (dd, $J = 7.7, 7.7$ Hz, 1H), 7.42 (dd, $J = 4.03, 2.93$ Hz, 2H), 3.15 (s, 3H), 3.03 (s, 3H); $^1$H NMR (500 MHz, MeOH-$_d_4$): ppm 8.37-8.34 (m, 3H), 7.94 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.70 (dd, $J = 8.0, 8.0$ Hz, 1H), 7.45-7.44 (m, 2H), 3.14 (s, 3H), 3.06 (s, 3H); $^{13}$C NMR (126 MHz, MeOH-$_d_4$): ppm 170.25, 160.84, 150.84, 137.97, 135.14, 134.01, 129.85, 129.39, 123.51, 122.99, 122.27, 121.08, 119.21, 115.80, 38.51, 34.27; HRMS (ESI+) calcd. for [C$_{16}$H$_{13}$NO$_3$+H]$^+$: 268.0974, found: 268.0970.
6-Oxo-6\textit{H}-benzo[\textit{c}]chromene-3-carbaldehyde 2-1z: \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): ppm 10.09 (s, 1H), 8.47 (d, \textit{J} = 7.9 Hz, 1H), 8.25 (d, \textit{J} = 8.1 Hz, 1H), 8.22 (d, \textit{J} = 8.1 Hz, 1H), 7.93-7.86 (m, 3H), 7.71 (dd, \textit{J} = 7.6, 7.5 Hz, 1H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): ppm 190.59, 160.40, 151.53, 137.55, 135.18, 133.52, 130.93, 130.43, 124.58, 123.70, 123.24, 122.60, 121.93, 119.36; HRMS (ESI\textsuperscript{+}) calcd. for [C\textsubscript{14}H\textsubscript{8}O\textsubscript{3}Cl+Na]\textsuperscript{+}: 247.0371, found: 247.0374.

\begin{center}
\includegraphics[width=0.5\textwidth]{2-1aa.png}
\end{center}

2-(Trifluoromethyl)-6\textit{H}-benzo[\textit{c}]chromen-6-one 2-1aa: \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): ppm 8.43 (dd, \textit{J} = 7.9, 0.65 Hz, 1H), 8.33 (s, 1H), 8.17 (d, \textit{J} = 8.05 Hz, 1H), 7.89 (ddd, \textit{J} = 7.7, 7.7, 1.2 Hz, 1H), 7.73 (d, \textit{J} = 8.55, 1.35 Hz, 1H), 7.67 (dd, \textit{J} = 7.6, 7.6 Hz, 1H), 7.48 (d, \textit{J} = 8.6 Hz, 1H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): ppm 160.25, 153.14, 135.25, 133.54, 130.82, 129.89, 127.09 (d, \textit{J} = 3.1 Hz), 126.90, 123.75 (q, \textit{J} = 273 Hz, CF\textsubscript{3}), 121.88, 121.30, 120.47 (d, \textit{J} = 3.7 Hz), 118.56, 118.42; HRMS (ESI\textsuperscript{+}) calcd. for [C\textsubscript{13}H\textsubscript{7}O\textsubscript{2}F\textsubscript{3}+H]\textsuperscript{+}: 287.0296, found: 287.0296.

\begin{center}
\includegraphics[width=0.5\textwidth]{2-1ab.png}
\end{center}

2,4-Bis(trifluoromethyl)-6\textit{H}-benzo[\textit{c}]chromen-6-one 2-1ab: Was prepared according to the GP-3, the reaction time was 48 h at 60 °C. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): ppm 8.51 (s, 1H), 8.45 (d, \textit{J} = 8.1 Hz, 1H), 8.19 (d, \textit{J} = 8.1 Hz, 1H), 8.01 (s, 1H), 7.97-7.90 (m, 1H), 7.75-7.70 (m, 1H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): ppm 158.2, 150.6, 135.6, 132.5, 131.1, 130.8, 126.5 (d, \textit{J} = 34.2
Hz), 124.6 (br.), 124.0 (br.), 123.1 (q, $J = 272.8$ Hz), 122.1, 121.9 (q, $J = 274.7$ Hz), 121.1, 120.3 (d, $J = 33.3$ Hz), 120.0; HRMS (ESI+) calcd. for $[\text{C}_{15}\text{H}_{6}\text{O}_{2}\text{F}_{6}+\text{H}]^{+}$: 333.0350, found: 333.0242.

![2-1ac](image)

**9-Nitro-6H-benzo[c]chromen-6-one 2-1ac:** $^1$H NMR (500 MHz, CD$_2$Cl$_2$): ppm 8.98 (d, $J = 1.8$ Hz, 1H), 8.56 (d, $J = 8.6$ Hz, 1H), 8.35 (dd, $J = 8.6$, 1.8 Hz, 1H), 8.19 (d, $J = 7.7$ Hz, 1H), 7.62 (dt, $J = 8.4$ Hz, 1.3 Hz, 1H), 7.50-7.40 (m, 2H); $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$): ppm 159.7, 152.2, 152.0, 136.7, 132.8, 132.4, 125.9, 125.5, 123.7, 123.1, 118.3, 117.8, 117.2; HRMS (ESI+) calcd. for $[\text{C}_{13}\text{H}_{7}\text{NO}_{4}+\text{H}]^{+}$: 242.0453, found: 242.0456.

![2-1ad](image)

**3-Nitro-6H-benzo[c]chromen-6-one 2-1ad:** Was prepared according to the GP-3, the reaction time was 24 h at 60 °C. $^1$H NMR (500 MHz, CDCl$_3$): ppm 8.96 (s, 1H), 8.61 (d, $J = 8.6$ Hz, 1H), 8.36 (d, $J = 8.6$ Hz, 1H), 8.17 (d, $J = 7.7$ Hz, 1H), 7.60 (t, $J = 7.7$ Hz, 1H), 7.47-7.40 (m, 2H); $^{13}$C NMR (126 MHz, CD$_2$Cl$_2$): ppm 160.1, 151.4, 148.7, 135.8, 133.1, 131.3, 124.4, 124.2, 123.3, 122.2, 119.5, 113.7; HRMS (ESI+) calcd. for $[\text{C}_{13}\text{H}_{7}\text{NO}_{4}+\text{H}]^{+}$: 242.0453, found: 242.0455.

![2-1ae](image)
2-Nitro-6H-benzo[c]chromen-6-one 2-1ae: $^1$H NMR (500 MHz, CDCl$_3$): ppm 9.01 (d, $J = 2.55$ Hz, 1H), 8.46 (d, $J = 7.9$ Hz, 1H), 8.36 (dd, $J = 9.05$, 2.6 Hz, 1H), 8.24 (d, $J = 4.1$ Hz, 1H), 7.95 (ddd, $J = 7.7$, 7.7, 1.3 Hz, 1H), 7.73 (t, $J = 7.95$ Hz, 1H), 7.52 (d, $J = 9.05$ Hz, 1H), 1.58 (H$_2$O);

$^{13}$C NMR (126 MHz, CDCl$_3$): ppm 159.67, 154.97, 144.44, 135.61, 133.05, 130.98, 130.50, 125.30, 122.23, 121.18, 119.19, 118.95, 118.85; HRMS (EI+) calcd. for [C$_{13}$H$_7$NO$_4$]$^+$: 241.0375, found: 241.0378.

4.3 Ring-Opening of the Obtained Benzocoumarins 2-1 into 2-17

Ring-opening was performed according to the literature procedure.$^{12}$ To a suspension of powdered KOH (140 mg, 2.5 mmol) in MeCN (5 mL) benzocumarin 2-1 (0.5 mmol) was added, followed by methyl iodide (5 mmol). The reaction mixture was stirred for 12 h at room temperature, the solvent was evaporated and the residue was quenched with water. The product was extracted with EtOAc (3×10 mL), the extract was dried (Na$_2$SO$_4$), filtered (silica gel) and evaporated to produce 2-17 as a viscous oil.

2-17a: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.90 (dd, $J = 7.75$, 0.9 Hz, 1H), 7.56 (ddd, $J = 7.6$, 7.6, 1.3 Hz, 1H), 7.41 (ddd, $J = 7.6$, 7.6, 1.1 Hz, 1H), 7.37-7.34 (m, 2H), 7.28 (dd, $J = 7.5$, 1.6 Hz, 1H), 7.07 (ddd, $J = 7.4$, 0.8 Hz, 1H), 6.92 (d, $J = 8.2$ Hz, 1H), 3.73 (s, 3H), 3.67 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 168.52, 155.96, 138.69, 131.52, 131.47, 131.23, 130.45, 129.83, 129.26, 128.76, 127.02, 120.66, 110.04, 55.12, 51.57. The NMR spectra correspond to the literature data.

2-17b: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.93 (dd, $J = 7.9$, 1.1 Hz, 1H), 7.57 (dt, $J = 7.7$, 1.3 Hz, 1H), 7.44 (dt, $J = 7.7$, 1.3 Hz, 1H), 7.37-7.27 (m, 3H), 7.11 (s, 1H), 3.76 (s, 3H), 3.67 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 167.0, 156.3, 137.7, 134.4, 131.8, 131.2, 131.1, 130.8 (d, $J = 33.3$Hz), 130.1, 129.6, 127.8, 124.1 (q, $J = 271.9$ Hz), 117.6, 106.8, 55.5, 51.7; GC/MS: m/z 310.1 ([M]$^+$, 20.0%), 279.1 ([M-OMe]$^+$, 100.0%).
2-17c: $^1$H NMR (500 MHz, CDCl$_3$): ppm 7.97-7.90 (m, 2H), 7.75 (d, $J$ = 2.2 Hz, 1H), 7.59 (dt, $J$ = 7.5, 1.3 Hz, 1H), 7.47 (dt, $J$ = 7.5, 1.3 Hz, 1H), 7.36 (d, $J$ = 8.3 Hz, 1H), 7.27 (dd, $J$ = 7.7, 0.9 Hz, 1H), 3.80 (s, 3H), 3.7 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): ppm 167.6, 156.6, 148.3, 137.9, 137.1, 132.0, 130.9, 130.0, 128.3, 116.1, 105.1, 55.8, 51.9; HRMS (EI+) calcd. for [C$_{15}$H$_3$NO$_5$]$^+$: 288.0872, found: 288.0872.

4.4 Synthesis of Silanols 3-18

Synthesis of 3-18a to 3-18w

Silanols 3-18 were prepared according to the following procedure: to a solution of $t$Bu$_2$SiBr$_2$ (665 mg, 2.2 mmol) in dry DMF (3 mL), a solution of imidazole (300 mg, 4.4 mmol) in dry DMF (2 mL) was added at 0 °C under argon atmosphere and stirred at room temperature for 30 min. The reaction mixture was then cooled down to 0 °C and a solution of phenol 4-5 (2.0 mmol) in dry DMF (2 mL) was added slowly. The reaction mixture was warmed up to room temperature and stirred overnight, then diluted with ether (20 mL) and treated with a saturated aqueous solution of sodium bicarbonate (3 mL). The reaction mixture was stirred for an additional 30 min at room temperature, then it was extracted with EtOAc and the organic phase was washed with brine and water. The organic extract was dried with Na$_2$SO$_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: Hexanes/EtOAc) to give silanols 3-18.
Synthesis of Phenols Which are not Commercially Available

[Chemical structure image]

Synthesis of phenol for 3-18r: to a solution of hydroquinone 4-6 (1.1 g, 10 mmol) in acetone (20 mL), (bromomethyl)cyclopropane 4-7r (485 µL, 5 mmol) and K₂CO₃ (760 mg, 5.5 mmol) were added. The reaction was heated to reflux for two days and then cooled down to room temperature. The reaction mixture was filtrated through a short pad of silica gel and washed by EtOAc, the filtrate was collected and dried under vacuum. The residue was purified by silica gel column chromatography to give the desired phenol 4-5r. Other phenols for synthesis of 3-18s to 3-18u were prepared using the same procedure.

Synthesis of 3-38

[Chemical structure image]

An oven dried 2.5 mL Wheaton V-vial, containing a stirring bar, was charged with silanol 3-18b (0.2 mmol), Pd(OAc)₂ (4.5 mg, 0.02 mmol), AgOAc (133.8 mg, 0.8 mmol), and (+)-Menthyl(O₂C)-Leu-OH (L1, 12.6 mg, 0.04 mmol) under N₂ atmosphere. Dry DCE (2 mL) and butyl acrylate (0.24 mmol, 1.2 equiv) were added via syringes and the reaction vessel was capped with pressure screw cap. The reaction mixture was heated at 100 °C for 48 h. The resulting mixture was cooled down to room temperature and filtered through a celite plug with the aid of EtOAc. The filtrate was concentrated under a reduced pressure. ^1H NMR analysis of
The crude mixture showed 88% yield of 3-38 using CH₂Br₂ as an internal standard. Analytic pure 3-38 was obtained by silica gel column chromatography (eluent: Hexanes/EtOAc = 20/1).

![3-18a](image)

1H NMR (500 MHz, CDCl₃): δ ppm 7.24 (dd, J = 8.6, 7.4 Hz, 2H), 7.02-7.00 (m, 2H), 6.95 (t, J = 7.3 Hz, 1H), 2.26 (s, 1H), 1.09 (s, 18H); 13C NMR (126 MHz, CDCl₃): δ ppm 155.7, 129.4, 121.2, 119.8, 27.4, 20.6; HRMS (EI) calcd. for C₁₄H₂₄O₂Si [M]⁺: 252.15456. Found: 252.15375. This is a known compound.¹³

![3-18b](image)

1H NMR (500 MHz, CDCl₃): δ ppm 7.24 (d, J = 8.80 Hz, 2H), 6.92 (d, J = 8.80 Hz, 2H), 2.23 (s, 1H), 1.30 (s, 9H), 1.09 (s, 18H); 13C NMR (126 MHz, CDCl₃): δ ppm 153.2, 143.8, 126.1, 119.1, 34.1, 31.6, 27.4, 20.6; HRMS (EI) calcd. for C₁₈H₃₂O₂Si [M]⁺: 308.21716. Found: 308.21783. This is a known compound.¹³

![3-18c](image)

1H NMR (500 MHz, CDCl₃): δ ppm 7.03 (d, J = 8.0 Hz, 2H), 6.89 (d, J = 8.0 Hz, 2H), 2.28 (s, 3H), 1.08 (s, 18H); 13C NMR (126 MHz, CDCl₃): δ ppm 153.32, 130.40, 129.82, 119.47, 27.35, 20.57; HRMS (ESI) calcd. for C₁₅H₂₇O₂Si [M+H]⁺: 267.1780. Found: 267.1781.

---

\[ \text{3-18d} \]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 7.03 (d, $J = 8.0$ Hz, 2H), 6.89 (d, $J = 8.0$ Hz, 2H), 2.28 (s, 3H), 1.08 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 153.32, 130.40, 129.82, 119.47, 27.35, 20.57; HRMS (EI) calcd. for C$_{20}$H$_{29}$O$_2$Si [M+H]$^+$: 329.1941. Found: 329.1937.

\[ \text{3-18e} \]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 6.92 (d, $J = 9.17$ Hz, 2H), 6.77 (d, $J = 9.17$ Hz, 2H), 3.76 (s, 3H), 2.27 (s, 1H), 1.07 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 154.0, 149.5, 120.2, 114.5, 55.7, 27.4, 20.6; HRMS (EI) calcd. for C$_{15}$H$_{26}$O$_3$Si [M]$^+$: 282.16513. Found: 282.16617. This is a known compound.$^{14}$

\[ \text{3-18f} \]

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 6.98 (d, $J = 9.1$ Hz, 2H), 6.93 (d, $J = 9.1$ Hz, 2H), 2.27 (s, 3H), 1.07 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 169.82, 153.30, 144.50, 122.16, 120.19, 27.30, 21.09, 20.56; HRMS (ESI) calcd. for C$_{16}$H$_{27}$O$_4$Si [M+H]$^+$: 311.1679. Found: 311.1683.

\[ \text{3-18g} \]

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 7.18 (d, $J = 8.96$ Hz, 2H), 6.94 (d, $J = 8.96$ Hz, 2H), 2.33 (s, 1H), 1.07 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 154.4, 129.3, 126.1, 121.0, 27.3, 20.6; HRMS (EI) calcd. for C$_{14}$H$_{23}$O$_2$SiCl [$M^+$]: 286.11559. Found: 286.11510. This is a known compound.$^{14}$

![3-18h](image)

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 7.16-7.14 (m, 2H), 7.09-7.05 (m, 1H), 6.87 (td, $J = 7.37$, 1.24 Hz, 1H), 2.41 (s, 1H), 2.29 (s, 3H), 1.11 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 154.2, 130.9, 127.8, 126.6, 120.9, 118.4, 27.5, 20.7, 16.9; HRMS (EI) calcd. for C$_{15}$H$_{26}$O$_2$Si [$M^+$]: 266.17021. Found: 266.16983. This is a known compound.$^{14}$

![3-18i](image)

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 7.51-7.49 (m, 2H), 7.41-7.39 (m, 2H), 7.33-7.29 (m, 2H), 7.24-7.21 (m, 2H), 7.04-7.01 (m, 1H), 1.12 (s, 1H, OH), 0.88 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 152.79, 139.20, 132.60, 130.81, 129.80, 128.36, 127.87, 126.85, 121.45, 120.01, 27.10, 20.45; HRMS (ESI) calcd. for C$_{20}$H$_{29}$O$_2$Si [M+H]$^+$: 329.1941. Found: 329.1945.

![3-18j](image)

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.29 (m, 1H), 7.83 (m, 1H), 7.52-7.47 (m, 3H), 7.34 (t, $J = 7.9$ Hz, 1H), 7.27 (dd, $J = 7.5$, 0.6 Hz, 1H), 2.58 (s, 1H), 1.17 (s, 18H); $^{13}$C NMR (126 MHz,
CDCl$_3$: $\delta$ ppm 151.9, 135.0, 127.7, 127.1, 126.0, 125.1, 122.5, 120.8, 112.6, 27.5, 20.9.

This is a known compound.$^{14}$

![3-18k](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 7.33 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.20 (dd, $J = 8.0$, 1.5 Hz, 1H), 7.11 (ddd, $J = 8.0$, 8.0, 1.6 Hz, 1H), 6.87 (ddd, $J = 8.0$, 8.0, 1.5 Hz, 1H), 2.13 (s, 1H, OH), 1.09 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 151.72, 130.22, 127.48, 124.40, 121.79, 120.43, 27.25, 20.66; HRMS (ESI) calcd. for C$_{14}$H$_{23}$O$_2$Si [M+Na]$^+$: 309.1054. Found: 309.1055.

![3-18l](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 7.78 (d, $J = 8.15$ Hz, 1H), 7.74 (d, $J = 8.85$ Hz, 1H), 7.72 (d, $J = 8.23$ Hz, 1H), 7.43 (td, $J = 7.53$, 1.26 Hz, 1H), 7.40 (d, $J = 2.25$ Hz, 1H), 7.34 (ddd, $J = 8.12$, 6.87, 1.23 Hz, 1H), 7.25 (dd, $J = 8.81$, 2.40 Hz, 1H), 2.38 (s, 1H), 1.13 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 153.5, 134.7, 129.3, 129.2, 127.6, 126.7, 126.1, 123.7, 121.7, 114.5, 27.4, 20.7; HRMS (EI) calcd. for C$_{18}$H$_{26}$O$_2$Si [M]$^+$: 302.17021. Found: 302.17005. This is a known compound.$^{14}$

![3-18m](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 7.07 (d, $J = 8.07$ Hz, 1H), 6.88 (d, $J = 1.83$ Hz, 1H), 6.78 (dd, $J = 8.07$, 2.57 Hz, 1H), 2.94-2.74 (m, 4H), 2.25 (s, 1H), 2.13-1.94 (m, 2H), 1.10 (s, 18H);
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 154.2, 145.6, 136.6, 124.6, 117.4, 115.7, 32.1, 27.4, 26.0, 25.8, 20.6; HRMS (EI) calcd. for C$_{17}$H$_{28}$O$_2$Si [M]$^+$: 292.18586. Found: 292.18685. This is a known compound.$^{13}$

![Chemical structure](3-18n)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 6.93 (d, $J = 8.44$ Hz, 1H), 6.76 (dd, $J = 8.07$, 2.57 Hz, 1H), 6.72 (d, $J = 2.20$ Hz, 1H), 2.81-2.63 (m, 4H), 2.28 (s, 1H), 1.87-1.70 (m, 4H), 1.10 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 153.2, 138.1, 129.8, 119.7, 117.1, 29.6, 28.7, 27.4, 23.5, 23.2, 20.6; HRMS (EI) calcd. for C$_{18}$H$_{30}$O$_2$Si [M]$^+$: 306.20151. Found: 306.20234. This is a known compound.$^{13}$

![Chemical structure](3-18o)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 7.12 (t, $J = 7.52$ Hz, 1H), 6.80- 6.86 (m, 2H), 6.77 (d, $J = 6.97$ Hz, 1H), 2.31 (s, 3H), 2.24 (s, 1H), 1.09 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 155.6, 139.4, 129.1, 122.1, 120.5, 116.7, 27.4, 26.0, 20.6; HRMS (EI) calcd. for C$_{15}$H$_{26}$O$_2$Si [M]$^+$: 266.17021. Found: 266.17120. This is a known compound.$^{13}$

![Chemical structure](3-18p)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 7.12 (t, $J = 8.25$ Hz, 1H), 6.62 (dd, $J = 8.07$, 2.20 Hz, 1H), 6.58 (t, $J = 2.38$ Hz, 1H), 6.52 (dd, $J = 7.89$, 2.02 Hz, 1H), 3.78 (s, 3H), 2.40 (s, 1H), 1.08 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 160.7, 156.9, 129.7, 112.4, 106.8, 106.1, 55.2, 27.4,
20.6; HRMS (ESI) calcd. for C_{15}H_{27}O_3Si [M+H]^+: 283.1729. Found: 283.1732. This is a known compound.\textsuperscript{13}

\[
\begin{align*}
\text{AcO} & \quad \text{C} & \quad \text{Si} \quad \text{Bu} \\
\text{OH} & & \text{Bu} \\
3-18q
\end{align*}
\]

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ ppm 7.20 (dd, \(J = 8.15, 8.15\) Hz, 1H), 6.87 (dd, \(J = 8.15, 1.75\) Hz, 1H), 6.77 (s, 1H), 6.68 (dd, \(J = 8.15, 1.75\) Hz, 1H), 2.27 (s, 3H), 1.07 (s, 18H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): δ ppm 169.41, 156.51, 129.56, 117.39, 114.31, 113.43, 27.27, 21.12, 20.55; HRMS (ESI) calcd. for C\textsubscript{16}H\textsubscript{27}O_4Si [M+H]^+: 311.1679. Found: 311.1682.

\[
\begin{align*}
\text{3-18r}
\end{align*}
\]

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ ppm 6.90 (d, \(J = 9.0\) Hz, 2H), 6.77 (d, \(J = 9.0\) Hz, 2H), 5.30 (s, CH\textsubscript{2}Cl\textsubscript{2}), 3.73 (d, \(J = 6.9\) Hz, 2H), 1.27-1.23 (m, 1H), 1.06 (s, 18H), 0.63-0.61 (m, 2H), 0.33-0.32 (m, 2H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): δ ppm 153.39, 149.44, 120.20, 115.34, 73.34, 27.37, 20.55, 10.38, 3.12; HRMS (ESI) calcd. for C\textsubscript{18}H\textsubscript{31}O_3Si [M+H]^+: 323.2042. Found: 323.2049.

\[
\begin{align*}
\text{3-18s}
\end{align*}
\]

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): δ ppm 6.90 (d, \(J = 9.0\) Hz, 2H), 6.74 (d, \(J = 9.0\) Hz, 2H), 4.13 (m, 2H), 3.93 (t, \(J = 6.1\) Hz, 2H), 2.49 (t, \(J = 7.3\) Hz, 2H), 2.07 (m, 2H), 1.25 (t, \(J = 7.3\) Hz, 3H), 1.06 (s, 18H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): δ ppm 173.38, 153.16, 149.55, 120.21, 115.15, 67.20, 60.42, 30.85, 27.36, 24.72, 20.54, 14.18; HRMS (EI) calcd. for C\textsubscript{18}H\textsubscript{30}NO_3Si [M]^+: 336.1995. Found: 336.1992.
\[
\begin{align*}
&1^H NMR (500 MHz, CDCl_3): \delta ppm 6.92 (d, J = 9.0 Hz, 2H), 6.76 (d, J = 9.0 Hz, 2H), 4.01 (t, J = 5.7 Hz, 2H), 2.57 (t, J = 7.1 Hz, 2H), 2.10 (tt, J = 7.1, 5.7 Hz, 2H), 1.06 (s, 18H);\quad 1^3C NMR (126 MHz, CDCl_3): \delta ppm 152.69, 149.94, 120.34, 119.26, 115.25, 65.81, 27.35, 25.56, 20.54, 14.17; HRMS (ESI) calcd. for C_{20}H_{35}O_5Si [M+H]^+: 383.2254. Found: 383.2256. \\
&1^H NMR (500 MHz, CDCl_3): \delta ppm 6.92 (dd, J = 6.7, 2.2 Hz, 2H), 6.79 (dd, J = 6.7, 2.2 Hz, 2H), 4.17 (t, J = 6.0 Hz, 2H), 3.78 (t, J = 6.0 Hz, 2H), 1.06 (s, 18H);\quad 1^3C NMR (126 MHz, CDCl_3): \delta ppm 152.51, 150.09, 120.35, 115.69, 68.72, 42.02, 27.35, 20.55; HRMS (ESI) calcd. for C_{16}H_{28}O_3SiCl [M+H]^+: 331.1496. Found: 331.1493. \\
&1^H NMR (500 MHz, CDCl_3): \delta ppm 6.84 (s, 4H), 2.17 (s, 2H, OH), 1.06 (s, 36H);\quad 1^3C NMR (126 MHz, CDCl_3): \delta ppm 149.74, 120.15, 27.38, 20.56; HRMS (ESI) calcd. for C_{22}H_{43}O_4Si_2 [M+H]^+: 427.2700. Found: 427.2702.
\end{align*}
\]
$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.00 (d, $J = 7.8$ Hz, 2H), 7.77 (d, $J = 15.65$ Hz, 1H), 7.59-7.48 (m, 5H), 7.39 (d, $J = 15.65$ Hz, 1H), 7.06 (d, $J = 8.6$ Hz, 2H), 2.69 (s, 1H, OH), 1.09 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 190.79, 158.33, 144.96, 138.47, 132.57, 130.16, 128.55, 128.44, 128.05, 120.35, 119.90, 27.28, 20.63.

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 7.99 (d, $J = 7.7$ Hz, 1H), 7.91 (d, $J = 8.35$ Hz, 1H), 7.40 (dd, $J = 7.6$, 7.6 Hz, 1H), 7.34 (d, $J = 8.0$ Hz, 1H), 7.20 (dd, $J = 7.4$, 7.4 Hz, 1H), 6.99 (s, 1H), 6.93 (d, $J = 8.35$ Hz, 1H), 3.79 (s, 3H), 1.13 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 154.83, 142.31, 141.20, 124.43, 122.95, 120.74, 119.45, 118.87, 117.12, 112.17, 108.13, 99.24, 29.08, 27.44, 20.70. 
$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 7.93-7.91 (m, 2H), 7.05-7.03 (m, 2H), 4.33 (q, $J = 7.15$ Hz, 2H), 3.12 (s, 1H), 1.36 (t, $J = 7.15$ Hz, 3H), 1.07 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 166.72, 160.21, 131.47, 123.16, 119.55, 60.72, 27.25, 20.62, 14.32; HRMS (EI) calcd. for C$_{17}$H$_{28}$O$_4$Si [M$^+$]: 324.17569. Found: 324.17490. This is a known compound.$^{13}$

![3-18aa](image)

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 7.13 (d, $J = 8.80$ Hz, 1H), 6.80 (dd, $J = 8.44$, 2.20 Hz, 1H), 6.73 (d, $J = 2.20$ Hz, 1H), 2.94-2.78 (m, 2H), 2.50 (dd, $J = 18.89$, 8.62 Hz, 1H), 2.42-2.32 (m, 1H), 2.30-2.20 (m, 1H), 2.19-1.84 (m, 4H), 1.71-1.32 (m, 6H), 1.08 (s, 18H), 0.91 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 221.0, 153.6, 137.6, 132.5, 126.2, 119.7, 117.2, 50.5, 48.0, 44.1, 38.4, 35.9, 31.6, 29.5, 27.4, 26.6, 25.9, 21.6, 20.6, 13.9; HRMS (EI) calcd. for C$_{26}$H$_{40}$O$_3$Si [M$^+$]: 428.27468. Found: 428.27393. This is a known compound.$^{13}$

![3-38](image)

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.15 (d, $J = 16.2$ Hz, 1H), 7.53 (d, $J = 2.45$ Hz, 1H), 7.26 (dd, $J = 8.6$, 2.45 Hz, 1H), 7.13 (d, $J = 8.6$ Hz, 1H), 6.42 (d, $J = 16.2$ Hz, 1H), 4.20 (t, $J = 6.65$ Hz, 2H), 1.70-1.64 (m, 2H), 1.46-1.41 (m, 2H), 1.30 (s, 9H), 1.09 (s, 18H), 0.95 (t, $J = 7.4$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 167.54, 152.67, 143.91, 140.35, 128.66, 123.84,

### 4.5 Optimization of Reaction Conditions

General method for screening reaction conditions: Silanol 3-18b (0.2 mmol), catalyst, oxidant (0.6 mmol), and ligand (0.04 mmol) were added to a test tube (16 x 125 mm) under N$_2$ atmosphere. Dry solvent (0.8 mL), CF$_3$CH$_2$OH (44 µL, 0.6 mmol) and nC$_{15}$H$_{32}$ (20 µL, internal standard) were added via syringes and the test tube was capped with a rubber septum (14 mm). The reaction mixture was heated at 95 °C for 5 min, and then a balloon with 1:8 CO/Ar mixture gas was installed with a needle. The reaction mixture was heated at 95 °C for a certain time. The resulting mixture was cooled down to room temperature and the yield was determined by GC-MS.
Table 4.1 Optimization of Concentration

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</tr>
<tr>
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<td>0.25</td>
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<tr>
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<td>1:0.13:4.29</td>
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<tr>
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<td>1:0.14:4.46</td>
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Table 4.2 Optimization of Catalyst Loading and Reaction Time

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<th>18h</th>
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<td>59</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>54</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>66</td>
<td>89</td>
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Table 4.3 Optimization of Ligand

<table>
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<tr>
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<th>yield / %</th>
<th>entry</th>
<th>ligand</th>
<th>yield / %</th>
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<td>Ac-Gly-OH</td>
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</tr>
</tbody>
</table>

[a] pure CO was used

Ac-Gly-OH  Boc-Gly-OH  Ac-Ala-OH  Boc-Ala-OH
Ac-Phe-OH  Boc-Phe-OH  Ac-Val-OH  Boc-Val-OH
Ac-Leu-OH  Boc-Leu-OH  (+) menthyl(O2C)-Leu-OH  Bis-silanols
4.6 Mechanistic Studies

Synthesis of $^{18}$O-Labeled Silanol 3-18b-$^{18}$O

![Chemical reaction diagram]

To a solution of $t$Bu$_2$SiBr$_2$ (333 mg, 1.1 mmol) in dry DMF (3 mL), a solution of imidazole (150 mg, 2.2 mmol) in dry DMF (1 mL) was added at 0 °C under argon atmosphere and stirred for 30 min at room temperature. The reaction mixture was then cooled down to 0 °C and a solution of 4-tert-butylphenol 4-5b (1.0 mmol) in dry DMF (1 mL) was added slowly. The reaction mixture was warmed up to room temperature and stirred overnight, then it was treated with H$_2$$^{18}$O (36 µL). The reaction mixture was stirred for an additional 1 h at room temperature. The reaction mixture was extracted with EtOAc and the organic phase was washed with brine and water. The organic extract was dried with Na$_2$SO$_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography (eluent: hexanes/EtOAc) to give silanol 3-18b-$^{18}$O.

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 7.24 (d, $J$ = 8.7 Hz, 2H), 6.91 (d, $J$ = 8.7 Hz, 2H), 2.17 (s, 1H, OH), 1.29 (s, 9H), 1.08 (s, 18H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 153.15, 143.79, 126.12, 119.03, 34.06, 31.52, 27.36, 20.56; HRMS (EI) calcd. for C$_{18}$H$_{32}$O$^{18}$Si [M]$^+$: 310.2214. Found: 310.2218.
Silanol 3-18b-\textsuperscript{18}O (0.2 mmol), Pd(OAc)\textsubscript{2} (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol), and Boc-Leu-OH (9.2 mg, 0.04 mmol) were added to a test tube (16 x 125 mm) under N\textsubscript{2} atmosphere. Dry DCE (0.8 mL) and CF\textsubscript{3}CH\textsubscript{2}OH (44 \textmu L, 0.6 mmol) were added via syringes and the test tube was capped with a rubber septum (14 mm). The reaction mixture was heated at 95 °C for 5 min, and then a balloon with 1:8 CO/Ar mixture gas was installed with a needle. The reaction mixture was heated at 95 °C for 18 h. The resulting mixture was cooled down to room temperature and Pd(OAc)\textsubscript{2} (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol) were added in the glove box, then the reaction mixture was heated for another 18 h at 95 °C (this extra step is not necessary, it just drives all the starting material to product, which makes it easier for separation). The resulting mixture was cooled down to room and filtered through a celite plug with the aid of a mixture of EtOAc/hexanes (5:95). The filtrate was concentrated under a reduced pressure and purified by column chromatography on a silica gel (eluent EtOAc/hexanes = 5/95). 3-34b-\textsuperscript{18}O was obtained as a white waxy solid in 90% yield.

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \delta ppm 8.01 (d, \textit{J} = 1.85 Hz, 1H), 7.51 (dd, \textit{J} = 8.6, 1.85 Hz, 1H), 6.91 (d, \textit{J} = 8.6 Hz, 1H), 1.31 (s, 9H), 1.11 (s, 18H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): \delta ppm 144.54, 133.29, 128.39, 119.05, 116.89, 115.45, 115.33, 34.28, 31.27, 26.03, 21.04; HRMS (ESI) calcd. for C\textsubscript{19}H\textsubscript{31}O\textsuperscript{18}OSi [M+H]\textsuperscript{+}: 337.2085. Found: 337.2084.
Synthesis of 3-29b-\textsuperscript{18}O

\[
\begin{align*}
\text{3-34b-18}^\text{O} & \xrightarrow{\text{TBAF, THF}} \text{3-29b-18}^\text{O}
\end{align*}
\]

TBAF (1M, 0.4 mL) was added to a solution of 3-34b-\textsuperscript{18}O (0.1 mmol) in THF (2 mL). The solution was stirred for 30 min and then dried with silica gel under vacuum. 3-29b-\textsuperscript{18}O was isolated by column chromatography on a silica gel in quantitative yield.

HRMS (EI) calcd. for C\textsubscript{11}H\textsubscript{14}O\textsubscript{2}\textsuperscript{18}O [M]\textsuperscript{+}: 196.0985. Found: 196.0984.

Isotope Mass Spectrum of 3-18b-\textsuperscript{18}O:

![Isotope Mass Spectrum Image]
Isotope Mass Spectrum of $3\cdot3^{4b}\cdot^{18}\text{O}$:
Isotope Mass Spectrum $3\text{-}19b^{18}O$:

4.7 Synthesis of Salicylic Acids

Method 1 (for $3\text{-}29a\text{-}j$, $1\text{-}s$, $u\text{-}aa$ and $3\text{-}39$): Silanol (0.2 mmol), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol), and Boc-Leu-OH (9.2 mg, 0.04 mmol) were added to a test tube (16 x 125 mm) under N$_2$ atmosphere. Dry DCE (0.8 mL) and CF$_3$CH$_2$OH (44 µL, 0.6 mmol) were added via syringes and the test tube was capped with a rubber septum (14 mm). The reaction mixture was heated at 95 °C for 5 min, and then a balloon with 1:8 CO/Ar mixture gas was installed with a needle. The reaction mixture was heated at 95 °C for 18 h. The resulting mixture was cooled down to room temperature and filtered through a celite plug with the aid of a mixture of EtOAc/hexanes (5:95). The filtrate was concentrated under a reduced pressure. THF
(2 mL) and TBAF (0.4 mL, 0.4 mmol) were added to the residue, and the reaction was monitored
d by TLC until complete (the desilylation usually finish in 30 min). The reaction mixture was dried
under a reduced pressure and purified by silica gel column chromatography (eluent:
hexanes/EtOAc = 50/50, DCM/EtOAc = 50/50, then DCM/EtOAc/AcOH = 50/50/3).
Method 2 (for **3-29k** and **3-29t**): Silanol (0.2 mmol), Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), AgOAc
(100 mg, 0.6 mmol), and Boc-Leu-OH (9.2 mg, 0.04 mmol) were added to a test tube (16 x 125
mm) under N$_2$ atmosphere. Dry DCE (0.8 mL) and CF$_3$CH$_2$OH (44 µL, 0.6 mmol) were added
via syringes and the test tube was capped with a rubber septum (14 mm). The reaction mixture
was heated at 95 °C for 5 min, and then a balloon with 1:8 CO/Ar mixture gas was installed with
a needle. The reaction mixture was heated at 95 °C for 18 h. The resulting mixture was cooled
down to room temperature and Pd(OAc)$_2$ (4.5 mg, 0.02 mmol), AgOAc (100 mg, 0.6 mmol)
were added in the glove box, then the reaction mixture was heated for another 18 h at 95 °C. The
resulting mixture was cooled down to room temperature and filtered through a celite plug with
the aid of a mixture of EtOAc/Hexane (1/20). The filtrate was concentrated under a reduced
pressure. THF (2 mL) and TBAF (0.4 mL, 0.4 mmol) were added to the filtrate, and the reaction
was monitored by TLC until complete (the desilylation usually finish in 30 min). The mixture
was dried under a reduced pressure and purified by silica gel column chromatography (eluent:
hexanes/EtOAc =50/50, DCM/EtOAc = 50/50, then DCM/EtOAc/AcOH = 50/50/3).

![3-29a](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 10.37 (s, 1H, COOH), 7.94 (dd, $J = 8.0, 1.65$ Hz, 1H), 7.53
(m, 1H), 7.02 (dd, $J = 8.0, 0.45$ Hz, 1H), 6.94 (m, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm

1H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 10.22 (s, 1H, COOH), 7.91 (d, $J$ = 2.25 Hz, 1H), 7.59 (dd, $J$ = 8.75, 2.25 Hz, 1H), 6.96 (d, $J$ = 8.75 Hz, 1H), 1.32 (s, 9H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 175.14, 160.06, 142.39, 134.70, 126.84, 117.43, 110.47, 34.12, 31.26; HRMS (EI) calcd. for C$_{11}$H$_{15}$O$_3$ [M]$^+$: 195.1021. Found: 195.1027.

1H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 10.40 (s, 1H, COOH), 7.70 (d, $J$ = 1.5 Hz, 1H), 7.31 (dd, $J$ = 8.5, 1.5 Hz, 1H), 6.90 (d, $J$ = 8.5 Hz, 1H), 2.30 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 175.13, 160.12, 138.08, 130.51, 128.85, 117.61, 110.84, 20.32; HRMS (ESI) calcd. for C$_8$H$_8$O$_3$ [M+Na]$^+$: 175.0371. Found: 175.0378.

1H NMR (500 MHz, Acetone-$d_6$): $\delta$ ppm 8.16 (d, $J$ = 2.4 Hz, 1H), 7.86 (dd, $J$ = 8.65, 2.45 Hz, 1H), 7.64 (d, $J$ = 8.45 Hz, 2H), 7.48-7.45 (m, 2H), 7.36-7.33 (m, 1H), 7.08-7.06 (d, $J$ = 8.6 Hz, 1H); $^{13}$C NMR (126 MHz, Acetone-$d_6$): $\delta$ ppm 171.42, 161.27, 139.39, 134.12, 131.87, 128.62,
127.99, 126.76, 126.08, 117.56, 112.22; HRMS (EI) calcd. for C_{13}H_{10}O_{3} [M]^+: 214.0630. Found: 214.0628.

![Structure 3-29e](image)

$^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 10.02 (s, 1H, COOH), 7.36 (d, $J = 2.65$ Hz, 1H), 7.16 (dd, $J = 8.95$, 2.65 Hz, 1H), 6.95 (d, $J = 8.95$ Hz, 1H), 3.80 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 174.55, 156.78, 152.21, 125.68, 118.90, 112.19, 110.73, 55.86; HRMS (EI) calcd. for C$_8$H$_8$O$_4$ [M]^+: 168.0423. Found: 168.0424.

![Structure 3-29f](image)

$^{1}$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 10.33 (s, 1H, COOH), 7.63 (d, $J = 2.80$ Hz, 1H), 7.26 (dd, $J = 9.0$, 2.80 Hz, 1H), 7.01 (d, $J = 9.0$ Hz, 1H), 2.31 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 173.46, 169.84, 159.91, 142.50, 130.62, 122.91, 118.73, 111.32, 20.95; HRMS (ESI) calcd. for C$_9$H$_9$O$_5$ [M+H]^+: 197.0450. Found: 197.0457.

![Structure 3-29g](image)

$^{1}$H NMR (500 MHz, Acetone-$d_6$): $\delta$ ppm 7.84 (d, $J = 2.65$ Hz, 1H), 7.54 (dd, $J = 8.85$, 2.65 Hz, 1H), 7.00 (d, $J = 8.85$ Hz, 1H); $^{13}$C NMR (126 MHz, Acetone-$d_6$): $\delta$ ppm 170.30, 160.41, 135.30, 129.01, 122.86, 118.86, 113.13; HRMS (EI) calcd. for C$_7$H$_5$O$_3$Cl [M]^+: 171.9927. Found: 171.9929.
$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 10.62 (s, 1H, COOH), 7.79 (d, $J = 7.95$ Hz, 1H), 7.39 (d, $J = 6.75$ Hz, 1H), 6.84 (dd, $J = 7.95$, 6.75 Hz, 1H), 2.29 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 175.32, 160.63, 137.70, 128.42, 126.88, 118.89, 110.52, 15.64; HRMS (EI) calcd. for C$_8$H$_8$O$_3$ [M]+: 152.0473. Found: 152.0474.

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 10.89 (s, 1H, COOH), 7.96 (dd, $J = 8.0$, 1.75 Hz, 1H), 7.61-7.58 (m, 3H), 7.47-7.44 (m, 2H), 7.39-7.36 (m, 1H), 7.02 (dd, $J = 7.6$, 7.8 Hz, 1H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 174.72, 159.51, 137.88, 136.88, 130.72, 130.26, 129.33, 128.20, 127.53, 119.46, 111.38; HRMS (ESI) calcd. for C$_{13}$H$_{11}$O$_3$ [M+H]+: 215.0708. Found: 215.0704.

$^1$H NMR (500 MHz, Acetone-$d_6$): δ ppm 8.37 (d, $J = 8.35$ Hz, 1H), 7.90 (d, $J = 8.2$ Hz, 1H), 7.84 (d, $J = 8.75$ Hz, 1H), 7.70 (dd, $J = 8.15$, 6.9, 1.15 Hz, 1H), 7.59 (m, 1H), 7.41 (d, $J = 8.8$ Hz, 1H); $^{13}$C NMR (126 MHz, Acetone-$d_6$): δ ppm 172.54, 161.03, 137.40, 129.48, 127.63, 125.84, 124.75, 124.51, 123.31, 118.50, 105.44; HRMS (EI) calcd. for C$_{11}$H$_8$O$_3$ [M]+: 188.0473. Found: 188.0472.
$^1$H NMR (500 MHz, Acetone-$d_6$): $\delta$ ppm 7.88 (br.s, 1H), 7.64 (d, $J = 7.45$ Hz, 1H), 6.97 (br.s, 1H); $^{13}$C NMR (126 MHz, Acetone-$d_6$): $\delta$ ppm 171.17, 157.42, 135.36, 128.97, 121.15, 119.05, 114.04; HRMS (EI) calcd. for C$_7$H$_5$O$_3$Cl [M$^+$]: 171.9927. Found: 171.9929.

(a mixture, major:minor = 2:1)

$^1$H NMR (500 MHz, Acetone-$d_6$): minor: $\delta$ ppm 8.95 (d, $J = 8.85$ Hz, 1H), 8.07 (d, $J = 9$ Hz, 1H), 7.87 (d, $J = 8$ Hz, 1H), 7.41-7.36 (m, 3H), 7.18 (d, $J = 9$ Hz, 1H); major: $\delta$ ppm 8.63 (s, 2H), 7.96 (d, $J = 8.25$ Hz, 2H), 7.78 (d, $J = 8.35$ Hz, 2H), 7.32 (s, 2H); $^{13}$C NMR (126 MHz, Acetone-$d_6$): $\delta$ ppm 173.47, 171.20, 164.62, 156.57, 137.78, 136.74, 132.57, 131.94, 128.99, 128.89, 128.77, 128.40, 128.10, 126.79, 125.80, 123.58, 123.26, 118.74, 113.94, 110.77, 103.85; HRMS (EI) calcd. for C$_{11}$H$_8$O$_3$ [M$^+$]: 188.0473. Found: 188.0473.

(a mixture, major:minor = 4:1)

$^1$H NMR (500 MHz, CDCl$_3$): minor: $\delta$ ppm 10.65 (s, 1H, COO$H$), 7.34 (d, $J = 8.25$ Hz, 1H), 6.82 (d, $J = 8.25$ Hz, 1H), 3.29-3.26 (m, 2H), 2.87-2.84 (m, 2H), 2.12-2.06 (m, 2H); major: $\delta$ ppm 10.37 (s, 1H, COO$H$), 7.73 (s, 1H), 6.87 (s, 1H), 2.92-2.89 (m, 2H), 2.87-2.84 (m, 2H),
$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 176.09, 175.38, 161.76, 161.50, 155.36, 147.98, 136.08, 135.51, 132.17, 125.53, 115.69, 113.24, 108.93, 108.72, 35.52, 33.57, 31.93, 31.56, 25.60, 25.04; HRMS (ESI) calcd. for C$_{10}$H$_{11}$O$_3$ [M+H]$^+$: 179.0708. Found: 179.0710.

![3-29n](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 10.06 (s, 1H, COOH), 7.61 (s, 1H), 6.71 (s, 1H), 2.77-2.72 (m, 4H), 1.79-1.78 (m, 4H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 174.98, 159.52, 147.96, 130.83, 128.73, 117.15, 108.98, 29.98, 28.37, 23.08, 22.61; HRMS (ESI) calcd. for C$_{11}$H$_{13}$O$_3$ [M]$^+$: 193.0865. Found: 193.0870.

![3-29o](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 10.34 (s, 1H, COOH), 7.80 (d, $J$ = 8.15 Hz, 1H), 6.71 (s, 1H), 6.75 (d, $J$ = 8.15 Hz, 1H), 2.37 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 174.62, 162.17, 148.61, 130.69, 120.92, 117.90, 108.64, 21.98; HRMS (EI) calcd. for C$_8$H$_8$O$_3$ [M]$^+$: 152.0473. Found: 152.0475.

![3-29p](image)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 10.61 (s, 1H, COOH), 7.83 (d, $J$ = 8.75 Hz, 1H), 6.50-6.47 (m, 2H), 3.85 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 174.58, 166.63, 164.50, 132.33,
1H NMR (500 MHz, CDCl₃): δ ppm 10.53 (s, 1H, COOH), 7.94 (d, J = 8.75 Hz, 1H), 6.78 (d, J = 2.15 Hz, 1H), 6.71 (dd, J = 8.75, 2.15 Hz, 1H), 2.32 (s, 3H); 13C NMR (126 MHz, CDCl₃): δ ppm 172.41, 168.48, 163.49, 157.08, 132.03, 113.52, 110.72, 108.93, 21.17; HRMS (ESI) calcd. for C₈H₈O₄ [M+Na]⁺: 191.0320. Found: 191.0325.

1H NMR (500 MHz, CDCl₃): δ ppm 10.00 (s, 1H, COOH), 7.35 (d, J = 3.1 Hz, 1H), 7.18 (dd, J = 9.1, 3.1 Hz, 1H), 6.94 (d, J = 9.1 Hz, 1H), 3.78 (d, J = 6.95 Hz, 2H), 1.29-1.23 (m, 1H), 0.67-0.63 (m, 2H), 0.37-0.34 (m, 2H); 13C NMR (126 MHz, CDCl₃): δ ppm 174.70, 156.72, 151.56, 126.39, 118.82, 113.32, 110.68, 73.65, 10.20, 3.17; HRMS (EI) calcd. for C₁₁H₁₂O₄ [M]⁺: 208.0736. Found: 208.0736.

1H NMR (500 MHz, CDCl₃): δ ppm 10.06 (s, 1H, COOH), 7.34 (d, J = 2.75 Hz, 1H), 7.12 (dd, J = 9.05, 2.75 Hz, 1H), 6.93 (d, J = 9.05 Hz, 1H), 4.18-4.14 (m, 2H), 3.99-3.97 (m, 2H), 2.54-2.51 (m, 2H), 2.12-2.10 (m, 2H), 1.26 (t, J = 7.1 Hz, 3H); 13C NMR (126 MHz, CDCl₃): δ ppm
174.18, 173.49, 156.76, 151.38, 125.92, 118.80, 113.25, 110.84, 67.53, 60.61, 30.81, 24.60, 14.19; HRMS (ESI) calcd. for C_{13}H_{17}O_{6} [M+H]^+: 269.1025. Found: 269.1032.

![3-29t](image)

$^1$H NMR (500 MHz, Acetone-$d_6$): δ ppm 7.41 (d, $J = 2.8$ Hz, 1H), 7.21 (dd, $J = 9.05$, 2.8 Hz, 1H), 6.91 (d, $J = 9.05$ Hz, 1H), 4.11 (t, $J = 5.9$ Hz, 2H), 2.69 (t, $J = 7.2$ Hz, 2H), 2.14 (tt, $J = 7.2$, 5.9 Hz, 2H); $^{13}$C NMR (126 MHz, Acetone-$d_6$): δ ppm 171.40, 156.61, 151.06, 124.33, 119.34, 118.17, 113.66, 111.96, 66.53, 25.30, 13.32; HRMS (ESI) calcd. for C_{11}H_{12}NO_{4} [M+H]^+: 222.0766. Found: 222.0774.

![3-29u](image)

$^1$H NMR (500 MHz, Acetone-$d_6$): δ ppm 7.41 (d, $J = 3.1$ Hz, 1H), 7.22 (dd, $J = 9.05$, 3.1 Hz, 1H), 6.92 (d, $J = 9.05$ Hz, 1H), 4.29 (t, $J = 5.2$ Hz, 2H), 3.91 (t, $J = 5.2$ Hz, 2H); $^{13}$C NMR (126 MHz, Acetone-$d_6$): δ ppm 170.98, 156.43, 150.51, 124.31, 117.94, 113.82, 111.66, 68.60, 42.26; HRMS (EI) calcd. for C_{9}H_{9}O_{4}Cl [M]^+: 216.0189. Found: 216.0194.

![3-29v](image)

$^1$H NMR (500 MHz, Acetone-$d_6$): δ ppm 7.34 (d, $J = 2.8$ Hz, 1H), 7.06 (dd, $J = 8.85$, 2.8 Hz, 1H), 6.81 (d, $J = 8.85$ Hz, 1H); $^{13}$C NMR (126 MHz, Acetone-$d_6$): δ ppm 171.21, 155.14, 149.04, 123.67, 117.51, 114.34, 111.71; HRMS (EI) calcd. for C_{7}H_{6}O_{4} [M]^+: 154.0266. Found: 154.0265.
$^1$H NMR (500 MHz, Acetone-$d_6$): $\delta$ ppm 8.30 (s, 1H), 8.15 (d, $J = 7.05$ Hz, 2H), 8.10 (d, $J = 7.75$ Hz, 1H), 7.85-7.77 (m, 2H), 7.66-7.63 (m, 1H), 7.57-7.54 (m, 2H), 7.06 (d, $J = 8.55$ Hz, 1H); $^{13}$C NMR (126 MHz, Acetone-$d_6$): $\delta$ ppm 188.61, 171.21, 163.52, 142.62, 138.09, 135.06, 132.41, 131.44, 128.36, 128.13, 126.38, 120.28, 117.83, 112.60.

$^1$H NMR (500 MHz, Acetone-$d_6$): $\delta$ ppm 7.34 (d, $J = 7.8$ Hz, 2H), 8.00-7.95 (m, 2H), 7.74 (d, $J = 15.7$ Hz, 1H), 7.67 (dd, $J = 7.35$, 7.35 Hz, 1H), 7.57 (dd, $J = 7.6$, 7.6 Hz, 2H), 7.42 (s, 1H), 7.41 (d, $J = 15.7$ Hz, 1H). 5.61 (d, CH$_2$Cl$_2$);$^{13}$C NMR (126 MHz, Acetone-$d_6$): $\delta$ ppm 188.68, 171.00, 161.87, 142.05, 141.86, 137.69, 132.79, 130.65, 128.48, 128.32, 124.55, 118.90, 116.49, 53.81 (CH$_2$Cl$_2$).

$^1$H NMR (500 MHz, Acetone-$d_6$): $\delta$ ppm 8.67 (s, 1H), 8.12 (d, $J = 7.75$ Hz, 1H), 7.50 (d, $J = 8.0$ Hz, 1H), 7.44 (dd, $J = 7.6$, 7.6 Hz, 1H), 7.23 (dd, $J = 7.4$, 7.4 Hz, 1H), 6.95 (s, 1H), 3.86 (s, 3H); $^{13}$C NMR (126 MHz, Acetone-$d_6$): $\delta$ ppm 172.20, 161.06, 146.27, 141.89, 125.23, 122.87, 122.69, 119.71, 119.31, 115.87, 108.62, 104.47, 94.63.
$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 10.21 (s, 1H, COOH), 7.81 (s, 1H), 6.73 (s, 1H), 2.95-2.89 (m, 2H), 2.55-2.54 (m, 1H), 2.45-2.42 (m, 1H), 2.24-2.13 (m, 2H), 2.09-1.97 (m, 3H), 1.65-1.42 (m, 6H), 0.92 (s, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 221.30, 174.48, 159.81, 147.15, 131.62, 127.40, 117.15, 109.11, 50.36, 47.97, 43.52, 37.98, 35.83, 31.33, 29.73, 26.09, 25.73, 21.54, 13.78; HRMS (ESI) calcd. for C$_{19}$H$_{23}$O$_4$ [M+H]$^+$: 315.1596. Found: 315.1591.

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 11.04 (s, 1H, COOH), 7.99 (s, 1H), 7.97 (d, J = 16.2 Hz, 1H), 7.78 (s, 1H), 6.68 (d, J = 16.2 Hz, 1H), 4.24 (t, J = 6.6 Hz, 2H), 1.74-1.68 (m, 2H), 1.49-1.43 (m, 2H), 1.33 (s, 9H), 0.97 (t, J = 7.4 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 174.25, 167.76, 159.12, 142.07, 139.34, 133.68, 129.23, 122.99, 119.81, 111.38, 64.59, 34.18, 31.20, 30.77, 19.19, 13.74; HRMS (ESI) calcd. for C$_{18}$H$_{25}$O$_5$ [M+H]$^+$: 321.1702. Found: 321.1696.

4.8 Synthesis of Aryl Silanes (PyrDipSi-Ar)

General procedure for the preparation of PyrDipSi-arenes 3-44:
An oven dried 2.5 mL Wheaton V-vial, containing a stirring bar, was charged with aryl iodide 4-8 (1.0 mmol), PyrDipSiH 4-9 (1.2-1.5 equiv), Rh₂(OAc)₄ (11.5 mg, 0.025 mmol), freshly grounded K₃PO₄ (423 mg, 2.0 mmol), and dry 1,4-dioxane (1.0 mL) under N₂ atmosphere (glovebox). Reaction mixture was stirred at 80-100 °C for a certain time until judged complete by GC/MS analysis. The resulting mixture was filtered (Celite®, EtOAc) and concentrated under a reduced pressure. The residue was purified by column chromatography on silica gel (hexanes/EtOAc) to afford the corresponding PyrDipSi-arene 3-44.

**Synthesis of Aryl Iodides Which are not Commercially Available: Method 1**

Synthesis of aryl iodide for 3-44r: to a solution of 3-iodophenol 4-10 (4 mmol) in acetone (20 mL), (bromomethyl)cyclopropane 4-7 (0.48 mL, 5 mmol) and K₂CO₃ (760 mg, 5.5 mmol) were added. The reaction was heated to reflux for two days and then cooled down to room temperature. The reaction mixture was filtered through a short pad of silica gel, eluted with EtOAc, the filtrate was collected and dried under vacuum. The residue was purified by silica gel column chromatography to give the desired aryl iodide. Aryl iodide for 3-44s was prepared using the same procedure.

---

Synthesis of Aryl Iodides Which are not Commercially Available: Method 2

\[
\begin{align*}
\text{R} & \quad \text{AuCl}_3 \text{(cat.)} \\
\text{4-11} & \quad \text{NIS} \\
& \quad \to \quad \text{R} \\
& \quad \text{4-8}
\end{align*}
\]

Synthesis of aryl iodide for 3-44x: to a DCE solution of pivalate protected indoline 4-11 (203 mg, 1 mmol), AuCl$_3$ (3 mg, 0.01 mmol) and NIS (248 mg, 1.1 mmol) were added. The resulting reaction mixture was stirred for 4 h at room temperature (monitored by GC/MS). The solution was then filtered through a short silica gel and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography to give the desired aryl iodide. Other aryl iodides toward 3-44v, 3-44w, and 3-44y synthesis were prepared using a similar procedure.$^{16}$

Synthesis of Aryl Iodides Which are not Commercially Available: Method 3

\[
\begin{align*}
\text{C} & \quad \text{AgNTf}_2 \text{(cat.)} \\
\text{2-1a} & \quad \text{NIS} \\
& \quad \to \quad \text{C} \\
& \quad \text{4-8z}
\end{align*}
\]

Synthesis of aryl iodide for 3-44z: to a DCM solution of benzocoumarin 2-1a (196 mg, 1 mmol), AgNTf$_2$ (38.8 mg, 0.10 mmol) and NIS (292 mg, 1.3 mmol) were added. The resulting reaction mixture was stirred for 24 h at room temperature (monitored by GC/MS). The solution was then filtered through a short silica gel and the filtrate was concentrated under reduced pressure. The residue was purified by flash column chromatography to give the desired aryl iodide.$^{17}$

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Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.83 (d, $J = 5.0$ Hz, 2H), 7.52 (app. d, $J = 7.9$ Hz, 2H), 7.24 (t, $J = 5.0$ Hz, 1H), 7.19 (app. d, $J = 7.6$ Hz, 2H), 2.35 (s, 3H), 1.71 (sept, $J = 7.4$ Hz, 2H), 1.07 (d, $J = 7.4$ Hz, 6H), 1.06 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.90, 154.81, 139.08, 135.77, 128.58, 128.51, 119.74, 21.52, 17.75, 17.67, 10.77; HRMS (EI) calcd. for C$_{17}$H$_{25}$N$_2$Si [M]$^+$: 285.1787, found: 285.1789.

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.81 (d, $J = 5.1$ Hz, 2H), 7.62 (app. d, $J = 7.4$ Hz, 2H), 7.39-7.35 (m, 3H), 7.22 (t, $J = 5.1$ Hz, 1H), 1.70 (sept, $J = 7.3$ Hz, 2H), 1.07 (d, $J = 7.3$ Hz, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.86, 154.80, 135.72, 132.60, 129.20, 127.60, 119.80, 21.50, 17.80, 17.70, 10.80; HRMS (EI) calcd. for C$_{16}$H$_{22}$N$_2$Si [M]$^+$: 270.1547, found: 270.1547.

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.81 (d, $J = 5.1$ Hz, 2H), 7.63 (app. d, $J = 7.4$ Hz, 1H), 7.40-7.35 (m, 3H), 7.21 (t, $J = 5.1$ Hz, 1H), 1.70 (sept, $J = 7.3$ Hz, 2H), 1.07 (d, $J = 7.3$ Hz, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.86, 154.80, 135.72, 132.50, 129.15, 127.58,
119.73, 17.71, 17.65, 10.78; HRMS (ESI) calcd. for C_{16}H_{22}DN_{2}Si [M+H]^+: 272.1693, found: 272.1686.

Colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ ppm 8.81 (d, \(J = 5.1\) Hz, 2H), 7.21 (t, \(J = 5.1\) Hz, 1H), 1.70 (sept, \(J = 7.3\) Hz, 2H), 1.07 (d, \(J = 7.3\) Hz, 12H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ ppm 177.86, 154.80, 135.29 (t, \(J = 23.9\) Hz), 132.32, 128.64 (t, \(J = 23.8\) Hz), 127.05 (t, \(J = 24.2\) Hz), 119.73, 17.71, 17.64, 10.78; HRMS (ESI) calcd. for C_{16}H_{18}D_{5}N_{2}Si [M]^+: 276.1944, found: 276.1939.

Colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ ppm 8.80 (d, \(J = 5.1\) Hz, 2H), 7.57 (app. d, \(J = 8.8\) Hz, 2H), 7.21 (t, \(J = 4.9\) Hz, 1H), 6.93 (app. d, \(J = 8.2\) Hz, 2H), 3.82 (s, 3H), 1.67 (sept, \(J = 7.3\) Hz, 2H), 1.06 (d, \(J = 7.3\) Hz, 6H), 1.05 (d, \(J = 7.3\) Hz, 6H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ ppm 178.2, 160.5, 154.8, 137.2, 123.3, 119.7, 113.5, 55.0, 17.8, 17.7, 10.9; HRMS (EI) calcd. for C_{17}H_{25}N_{2}O_{5}Si [M]^+: 301.1736, found: 301.1733.
Colorless oil. $^1$H NMR (400 MHz, CDCl$_3$): δ ppm 8.81 (d, $J = 5.3$ Hz, 2H), 7.58 (app. d, $J = 8.2$ Hz, 2H), 7.36 (app. d, $J = 8.2$ Hz, 2H), 7.23 (t, $J = 5.3$ Hz, 1H), 1.67 (sept, $J = 7.6$ Hz, 2H), 1.05 (d, $J = 7.6$ Hz, 6H), 1.04 (d, $J = 7.6$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.4, 154.9, 137.1, 135.6, 131.0, 127.9, 119.9, 17.6, 17.6, 10.7; HRMS (ESI) calcd. for C$_{16}$H$_{21}$ClN$_2$Si $[M+H]^+$: 305.1241, found: 305.1244.

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.80 (d, $J = 5.1$ Hz, 2H), 7.53-7.49 (m, 4H), 7.21 (t, $J = 5.1$ Hz, 2H), 1.66 (sept, $J = 7.4$ Hz, 2H), 1.05 (d, $J = 7.4$ Hz, 6H), 1.04 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.4, 154.9, 137.1, 135.6, 131.0, 127.9, 119.9, 17.6, 17.6, 10.7; HRMS (ESI) calcd. for C$_{16}$H$_{21}$N$_2$SiBr $[M+H]^+$: 349.0736, found: 349.0738.

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.80 (d, $J = 4.7$ Hz, 2H), 7.76 (app. d, $J = 8.1$ Hz, 2H), 7.60 (app. d, $J = 8.1$ Hz, 2H), 7.23 (t, $J = 4.7$ Hz, 1H), 1.70 (sept, $J = 7.3$ Hz, 2H), 1.06 (d, $J = 7.3$ Hz, 6H), 1.04 (d, $J = 7.3$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.0, 154.9, 138.02, 136.04, 131.0 (q, $J = 32.4$ Hz), 124.3 (q, $J = 271.9$ Hz), 124.1, 120.0, 17.6, 17.5, 10.7; HRMS (EI) calcd. for C$_{17}$H$_{22}$N$_2$SiF$_3$ [M$^+$]: 339.1504, found: 339.1505.
White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.80 (d, $J = 5.1$ Hz, 2H), 7.59 (app. d, $J = 8.1$ Hz, 2H), 7.30 (app. d, $J = 8.1$ Hz, 2H), 7.22 (t, $J = 5.1$ Hz, 1H), 4.15 (q, $J = 7.3$ Hz, 2H), 3.61 (s, 2H), 1.68 (sept, $J = 7.3$ Hz, 2H), 1.26 (t, $J = 7.3$ Hz, 3H), 1.07-1.05 (m, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 177.9, 171.5, 154.8, 136.0, 135.0, 131.2, 128.5, 119.8, 60.8, 41.6, 17.8, 17.7, 14.2, 10.9; HRMS (ESI) calcd. for C$_{20}$H$_{28}$N$_2$O$_2$Si [M+H]$^+$: 357.1998 Found: 357.1192.

White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.80 (d, $J = 5.1$ Hz, 2H), 8.01 (app. d, $J = 8.1$ Hz, 2H), 7.74-7.72 (app. d, $J = 8.4$ Hz, 2H), 7.24-7.22 (t, $J = 5.1$ Hz, 1H), 3.91 (s, 3H), 1.70 (sept, $J = 7.3$ Hz, 2H), 1.06 (d, $J = 7.3$ Hz, 6H), 1.05 (d, $J = 7.3$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 177.2, 167.3, 154.9, 139.5, 135.8, 130.6, 128.3, 119.9, 52.0, 17.7, 17.6, 10.8; HRMS (EI) calcd. for C$_{18}$H$_{25}$N$_2$O$_2$Si [M]$^+$: 329.1685, found: 329.1682.
White solid. $^1$H NMR (400 MHz, CDCl$_3$): δ ppm 8.80 (d, $J = 4.8$ Hz, 2H), 7.92 (app. d, $J = 8.4$ Hz, 2H), 7.74 (app. d, $J = 8.4$ Hz, 2H), 7.23 (t, $J = 4.8$ Hz, 1H), 2.58 (s, 3H), 1.68 (sept, $J = 7.3$ Hz, 2H), 1.05 (d, $J = 7.3$ Hz, 6H), 1.03 (d, $J = 7.3$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 198.5, 177.1, 154.9, 139.8, 137.4, 136.0, 127.0, 120.0, 26.6, 17.6, 17.5, 10.7; HRMS (EI) calcd. for C$_{18}$H$_{24}$N$_2$OSi [M]$^+$: 312.1658, found: 312.1654.

White solid. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.81 (d, $J = 5.1$ Hz, 2H), 7.64 (app. d, $J = 8.1$ Hz, 2H), 7.31 (app. d, $J = 8.1$ Hz, 2H), 7.24 (t, $J = 5.1$ Hz, 1H), 3.9 (br. s, 1H), 3.5 (br. s, 1H), 1.67 (sept, $J = 7.3$ Hz, 2H), 1.5 (br. s, 6H), 1.1 (br. s, 6H), 1.06-1.03 (m, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.6, 171.1, 154.9, 139.5, 135.8, 133.8, 133.5, 124.9, 119.9, 50.8, 46.0, 20.8, 17.6, 17.5, 18.0, 10.7; HRMS (EI) calcd. for C$_{23}$H$_{35}$N$_3$Si [M]$^+$: 397.2549. Found: 397.2552.

White solid. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.80 (d, $J = 4.7$ Hz, 2H), 7.64 (app. d, $J = 7.5$ Hz, 2H), 7.48 (app. d, $J = 7.5$ Hz, 2H), 7.21 (t, $J = 4.8$ Hz, 1H), 5.97 (s, 1H), 1.68 (sept, $J = 7.4$ Hz, 2H), 1.32 (s, 6H), 1.27 (s, 6H), 1.06 (d, $J = 7.4$ Hz, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ
ppm 177.90, 154.78, 154.30, 140.42, 135.71, 133.22, 125.47, 119.72, 99.99, 82.59, 24.35, 22.19, 17.70, 17.65, 10.82; HRMS (EI) calcd. for C_{23}H_{35}N_{2}O_{2}Si [M]^+: 399.2468. Found: 399.2463.

White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.80 (d, $J = 5.0$ Hz, 2H), 7.79 (app. d, $J = 6.2$ Hz, 2H), 7.63 (app. d, $J = 6.2$ Hz, 2H), 7.21 (t, $J = 5.0$ Hz, 1H), 5.97 (s, 1H), 1.70 (sept, $J = 7.4$ Hz, 2H), 1.34 (s, 12H), 1.07-1.05 (m, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 177.71, 154.80, 136.49, 135.03, 133.59, 119.76, 83.67, 24.82, 17.69, 17.64, 10.73; HRMS (ESI) calcd. for C$_{22}$H$_{33}$BN$_2$O$_2$Si [M+H]$^+$: 397.2483. Found: 397.2481.

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.81 (d, $J = 5.0$ Hz, 2H), 7.42-7.40 (m, 2H), 7.28-7.24 (m, 1H), 7.22-7.19 (m, 2H), 2.34 (s, 3H), 1.69 (sept, $J = 7.4$ Hz, 2H), 1.08-1.06 (m, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ ppm 177.97, 154.79, 136.76, 136.31, 132.80, 132.35, 130.04, 127.47, 119.70, 21.65, 17.73, 17.67, 10.75; HRMS (ESI) calcd. for C$_{17}$H$_{25}$N$_2$Si [M+H]$^+$: 285.1787. Found: 285.1787.
Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.81 (d, $J = 5.0$ Hz, 2H), 7.30 (dd, $J = 7.8$, 7.8 Hz, 1H), 7.23-7.19 (m, 3H), 6.93 (dd, $J = 8.2$, 2.0 Hz, 1H), 3.79 (s, 3H), 1.69 (sept, $J = 7.4$ Hz, 2H), 1.073 (d, $J = 7.4$ Hz, 6H), 1.070 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.70, 158.70, 154.82, 134.15, 128.74, 128.05, 121.60, 114.26, 55.01, 17.72, 17.67, 10.81; HRMS (ESI) calcd. for C$_{17}$H$_{25}$N$_2$OSi [M+H]$^+$: 301.1736. Found: 301.1730.

![3-44c](image)

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.81 (d, $J = 5.1$ Hz, 2H), 7.41-7.33 (m, 2H), 7.23 (t, $J = 5.1$ Hz, 1H), 7.07 (dd, $J = 8.1$, 8.1 Hz, 1H), 1.68 (sept, $J = 7.3$ Hz, 2H), 1.07 (d, $J = 7.3$ Hz, 6H), 1.06 (d, $J = 7.3$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.3, 162.4 (d, $J = 247.9$ Hz), 154.9, 136.0, 131.3 (d, $J = 3.7$ Hz), 129.3 (d, $J = 5.6$ Hz), 122.1 (d, $J = 18.5$ Hz), 119.9, 116.1 (d, $J = 20.4$ Hz), 17.7, 17.6, 10.9; HRMS (ESI) calcd. for C$_{16}$H$_{21}$FN$_2$Si [M+H]$^+$: 289.1536, found: 289.1534.

![3-44p](image)

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.81 (d, $J = 5.0$ Hz, 2H), 7.60 (d, $J = 1.2$ Hz, 1H), 7.50 (d, $J = 7.2$ Hz, 1H), 7.37-7.35 (m, 1H), 7.30 (dd, $J = 7.4$, 7.4 Hz, 1H), 7.24 (t, $J = 5.0$ Hz, 1H), 1.68 (sept, $J = 7.4$ Hz, 2H), 1.062 (d, $J = 7.4$ Hz, 6H), 1.060 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.10, 154.93, 135.57, 135.34, 134.04, 133.68, 129.34, 129.03, 119.95, 17.62, 17.57, 10.73; HRMS (ESI) calcd. for C$_{16}$H$_{22}$ClN$_2$Si [M+H]$^+$: 305.1241. Found: 305.1236.
Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.81 (d, $J = 5.0$ Hz, 2H), 7.75 (s, 1H), 7.55 (d, $J = 7.3$ Hz, 1H), 7.52 (dd, $J = 8.0$, 0.9 Hz, 1H), 7.24-7.23 (m, 2H), 1.68 (sept, $J = 7.4$ Hz, 2H), 1.06 (d, $J = 7.4$ Hz, 6H), 1.058 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.06, 154.92, 138.15, 136.11, 134.10, 132.22, 129.35, 122.73, 119.95, 17.61, 17.56, 10.73; HRMS (ESI) calcd. for C$_{16}$H$_{22}$BrN$_2$Si [M+H]$^+$: 349.0736. Found: 349.0732.

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.81 (d, $J = 5.0$ Hz, 2H), 7.31 (dd, $J = 7.8$, 7.8 Hz, 1H), 7.24-7.21 (m, 3H), 6.94-6.92 (m, 1H), 4.22 (t, $J = 6.0$ Hz, 2H), 3.80 (t, $J = 6.0$ Hz, 2H), 1.68 (sept, $J = 7.4$ Hz, 2H), 1.06 (d, $J = 7.4$ Hz, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.62, 157.38, 154.84, 134.57, 128.84, 128.77, 122.17, 119.81, 119.25, 115.29, 67.81, 41.86, 17.70, 17.64, 14.18, 10.79; HRMS (ESI) calcd. for C$_{18}$H$_{26}$ClN$_2$OSi [M+H]$^+$: 349.1503. Found: 349.1501.

Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.81 (d, $J = 5.0$ Hz, 2H), 7.30 (dd, $J = 7.6$, 7.6 Hz, 1H), 7.23-7.19 (m, 3H), 6.91 (dd, $J = 8.2$, 2.0 Hz, 1H), 4.05 (t, $J = 5.7$ Hz, 2H), 2.58 (t, $J =$
7.2 Hz, 2H), 2.12 (tt, J = 7.2, 5.7 Hz, 1H), 1.68 (sept, J = 7.4 Hz, 2H), 1.07 (d, J = 7.4 Hz, 12H); 
\(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ ppm 177.61, 157.53, 154.83, 134.52, 128.82, 128.55, 121.87, 119.81, 119.25, 115.01, 65.00, 25.56, 17.70, 17.64, 14.18, 10.78; HRMS (ESI) calcd. for C\(_{20}\)H\(_{28}\)N\(_3\)OSi [M+H]\(^+\): 354.2002. Found: 354.2003.

Colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ ppm 8.84 (d, J = 4.8 Hz, 2H), 8.17 (s, 1H), 7.85-7.82 (m, 3H), 7.70 (d, J = 8.2 Hz, 2H), 7.50-7.46 (m, 2H), 7.25-7.23 (m, 1H), 1.80 (sept, J = 7.4 Hz, 2H), 1.12 (d, J = 7.4 Hz, 12H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ ppm 177.90, 154.88, 136.72, 133.88, 132.92, 131.84, 130.40, 128.24, 127.64, 126.65, 126.33, 125.62, 119.82, 17.81, 17.76, 10.96; HRMS (ESI) calcd. for C\(_{20}\)H\(_{25}\)N\(_2\)Si [M+H]\(^+\): 321.1787. Found: 321.1780.

Colorless oil. \(^1\)H NMR (500 MHz, CDCl\(_3\)): δ ppm 8.80 (d, J = 5.0 Hz, 2H), 7.80 (dd, J = 2.4, 0.8 Hz, 1H), 7.43 (dd, J = 4.8, 2.6 Hz, 1H), 7.36 (dd, J = 4.8, 0.9 Hz, 1H), 7.22 (t, J = 5.0 Hz, 1H), 1.62 (sept, J = 7.4 Hz, 2H), 1.073 (d, J = 7.4 Hz, 6H), 1.071 (d, J = 7.4 Hz, 6H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): δ ppm 178.06, 154.82, 134.49, 134.00, 132.59, 124.96, 119.79, 17.78, 17.71, 11.58; HRMS (ESI) calcd. for C\(_{14}\)H\(_{21}\)N\(_2\)SSi [M+H]\(^+\): 277.1190. Found: 277.1195.
Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.85 (d, $J = 5.0$ Hz, 2H), 8.25 (s, 1H), 7.96 (d, $J = 7.5$ Hz, 1H), 7.74 (dd, $J = 8.2, 1.1$ Hz, 1H), 7.61-7.56 (m, 2H), 7.46-7.42 (m, 1H), 7.35-7.32 (m, 1H), 7.27-7.25 (m, 1H), 1.79 (sept, $J = 7.4$ Hz, 2H), 1.11 (d, $J = 7.4$ Hz, 12H); HRMS (ESI) calcd. for C$_{22}$H$_{25}$N$_2$OSi [M+H]$^+$: 361.1736. Found: 361.1736.

Pale yellow solid. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.87 (d, $J = 5.0$ Hz, 2H), 8.38 (s, 1H), 8.11 (d, $J = 7.7$ Hz, 1H), 7.73 (d, $J = 8.2$ Hz, 1H), 7.48-7.39 (m, 3H), 7.28-7.26 (m, 1H), 7.23 (t, $J = 5.0$ Hz, 1H), 3.85 (s, 3H), 1.83 (sept, $J = 7.4$ Hz, 2H), 1.13 (d, $J = 7.4$ Hz, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 178.37, 154.86, 141.88, 140.88, 132.95, 128.06, 125.56, 122.69, 120.31, 119.73, 118.91, 108.33, 108.09, 29.00, 17.89, 17.82, 11.06; HRMS (ESI) calcd. for C$_{23}$H$_{28}$N$_3$Si [M+H]$^+$: 374.2052. Found: 374.2049.

White solid. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.78 (d, $J = 5.0$ Hz, 2H), 8.22 (d, $J = 8.2$ Hz, 1H), 7.44-7.43 (m, 2H), 7.19 (t, $J = 5.0$ Hz, 1H), 4.20 (t, $J = 8.2$ Hz, 2H), 3.12 (t, $J = 8.2$ Hz, 2H), 1.66 (sept, $J = 7.4$ Hz, 2H), 1.35 (s, 9H), 1.04 (d, $J = 7.4$ Hz, 12H); $^{13}$C NMR (126 MHz, CDCl$_3$):
δ ppm 177.98, 176.51, 154.71, 145.73, 135.11, 131.56, 130.02, 127.08, 119.63, 117.61, 49.38, 40.13, 29.28, 27.62, 17.66, 17.59, 10.76; HRMS (ESI) calcd. for C_{23}H_{34}N_{3}O_{5}Si [M+H]^+: 396.2471. Found: 396.2474.

White solid. \(^1H\) NMR (500 MHz, CDCl\(_3\)): δ ppm 8.79 (d, \(J = 5.0\) Hz, 2H), 7.371-7.366 (m, 3H), 7.121 (t, \(J = 5.0\) Hz, 1H), 3.77 (t, \(J = 6.2\) Hz, 2H), 2.76 (t, \(J = 7.0\) Hz, 2H), 1.98 (tt, \(J = 7.0, 6.2\) Hz, 2H), 1.66 (sept, \(J = 7.4\) Hz, 2H), 1.29 (s, 9H), 1.05 (d, \(J = 7.4\) Hz, 12H); \(^{13}C\) NMR (126 MHz, CDCl\(_3\)): δ ppm 178.31, 177.88, 154.78, 141.77, 136.20, 132.82, 130.56, 128.80, 124.79, 119.71, 45.15, 40.36, 28.88, 26.13, 24.08, 17.68, 17.63, 10.75; HRMS (ESI) calcd. for C_{24}H_{36}N_{3}O_{5}Si [M+H]^+: 410.2628. Found: 410.2626.

White solid. \(^1H\) NMR (500 MHz, CDCl\(_3\)): δ ppm 8.85 (d, \(J = 5.0\) Hz, 2H), 8.47 (s, 1H), 8.41 (d, \(J = 7.8\) Hz, 1H), 8.12 (d, \(J = 8.1\) Hz, 1H), 7.83-7.77 (m, 2H), 7.59-7.56 (m, 1H), 7.40 (d, \(J = 8.2\) Hz, 1H), 7.28 (t, \(J = 5.0\) Hz, 1H), 1.75 (sept, \(J = 7.4\) Hz, 2H), 1.10 (d, \(J = 7.4\) Hz, 12H); \(^{13}C\) NMR (126 MHz, CDCl\(_3\)): δ ppm 177.35, 161.22, 154.99, 152.23, 137.72, 134.98, 134.76, 130.57, 130.50, 129.05, 128.70, 121.65, 121.31, 120.03, 117.45, 117.04, 17.70, 17.66, 10.94; HRMS (ESI) calcd. for C_{25}H_{25}N_{2}O_{2}Si [M+H]^+: 389.1685. Found: 389.1678.
4.9 Optimization of Reaction Conditions

General method for screening reaction conditions: 3-44a (0.050 mmol), Pd(OAc)$_2$ (1.1 mg, 0.0050 mmol), oxidant (0.15–0.20 mmol), and ligand (0.010 mmol) were added to a test tube (16 x 125 mm) under N$_2$ atmosphere. Dry DCE (1.0 mL), HFIP alcohol (26 µL, 0.25 mmol) and $n$C$_{15}$H$_{32}$ (10 µL, internal standard) were added via syringes and the test tube was capped with a rubber septum (14 mm). The reaction mixture was heated at 50 °C for 5 min, and then a balloon with 1:8 CO/Ar mixture gas was installed with a needle. The reaction mixture was heated at given temperature for a given time. The resulting mixture was cooled down to room temperature and the yield was determined by GC-MS. See the attached picture for experimental setup.
Table 4.4 Optimization Table\textsuperscript{[a]}

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<th>entry</th>
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<td>Ac-Leu-OH</td>
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\textsuperscript{[a]} 0.05 mmol scale, GC yield using $\eta$C\textsubscript{15}H\textsubscript{32} as internal standard. \textsuperscript{[b]} 0.20 mmol scale, 50 °C, 36 h, CO, isolated yield in parenthesis. \textsuperscript{[c]} 0.20 mmol scale, 0.80 mmol AgOAc as oxidant. CO, 50 °C, isolated yield. \textsuperscript{[d]} C\textsubscript{6}F\textsubscript{5}OH instead of HFIP alcohol. \textsuperscript{[e]} (CF\textsubscript{3})\textsubscript{2}C(p-tolyl)OH instead of HFIP alcohol. \textsuperscript{[f]} HFIP alcohol as solvent. \textsuperscript{[g]} GC yield. 5 equiv of AcOH replaces of HFIP alcohol, and 5 equiv of EtOH was added as nucleophile, 0.20 mmol AgOAc as oxidant. CO, 50 °C. \textsuperscript{[h]} 5 equiv of CF\textsubscript{3}COOH replaces of HFIP alcohol, and 5 equiv of EtOH was added as nucleophile, 0.20 mmol AgOAc as oxidant. CO, 50 °C.
Picture of experimental setup
4.10 NMR Spectroscopic Studies

NMR samples were prepared as following: Sample for 3-44a (A): 3-44a (14.2 mg) was weighted and transferred to a NMR tube, followed by addition of CDCl₃ (0.50 mL). Sample for HFIP alcohol (B): HFIP alcohol (5.2 μL) was transferred to a NMR tube via a syringe, followed by addition of CDCl₃ (0.50 mL). Sample for a 1:1 mixture of 3-44a and HFIP alcohol (C): 3-44a (14.2 mg) was weighted and transferred to a NMR tube, followed by addition of HFIP alcohol (5.2 μL) and CDCl₃ (0.50 mL). Sample for iPrOH (D): iPrOH (3.8 μL) was transferred to a NMR tube via a syringe, followed by addition of CDCl₃ (0.50 mL). Sample for a 1:1 mixture of 1a and iPrOH (E): 3-44a (14.2 mg) was weighted and transferred to a NMR tube, followed by addition of iPrOH (3.8 μL) and CDCl₃ (0.50 mL).
$^1$H and $^{13}$C NMR of 3-44a (A)

$^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.83 (d, $J = 5.0$ Hz, 2H), 7.52 (app. d, $J = 7.9$ Hz, 2H), 7.24 (t, $J = 5.0$ Hz, 1H), 7.19 (app. d, $J = 7.6$ Hz, 2H), 2.35 (s, 3H), 1.71 (sept, $J = 7.4$ Hz, 2H), 1.07 (d, $J = 7.4$ Hz, 6H), 1.06 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.90, 154.81, 139.08, 135.77, 128.58, 128.51, 119.74, 21.52, 17.75, 17.67, 10.77.
$^1$H and $^{13}$C NMR of HFIP alcohol (B)

$^1$H NMR (500 MHz, CDCl₃): δ ppm 4.41 (sept, $J = 5.9$ Hz, 1H), 3.01 (d, $J = 8.2$ Hz, 1H, O-H);

$^{13}$C NMR (126 MHz, CDCl₃): δ ppm 121.35 (q, $J = 282$ Hz, CF₃), 69.62 (sept, $J = 34$ Hz, CH(CF₃)₂).
$^1$H, $^{13}$C NMR and NOE of a 1:1 mixture of 3-44a and HFIP alcohol (C)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.81 (d, $J = 5.0$ Hz, 2H), 7.46 (app. d, $J = 7.7$ Hz, 2H), 7.29 (t, $J = 5.0$ Hz, 1H), 7.21 (app. d, $J = 7.6$ Hz, 2H), 5.64 (br. s, 1H, O$H$), 3.71 (sept, $J = 6.0$ Hz, 1H), 2.35 (s, 3H), 1.71 (sept, $J = 7.4$ Hz, 2H), 1.06 (d, $J = 7.4$ Hz, 6H), 1.04 (d, $J = 7.4$ Hz, 6H);

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 177.68, 154.91, 139.51, 135.85, 128.69, 128.15, 121.63 (q, $J = 285$ Hz, CF$_3$), 119.97, 68.71 (sept, $J = 33$ Hz, CH(CF$_3$_2)), 21.39, 17.66, 17.52, 10.51.
1′-H\textsubscript{1} nuclei was irradiated and an NOE effect with 1′-H\textsubscript{1} and 10-a-H\textsubscript{6} and 10-b-H\textsubscript{6} were observed.
NMR studies of hydrogen bonding between 3-44a (A) and HFIP alcohol (B)

1H NMR of (a) 3-44a (A), (b) HFIP alcohol (B), (c) 1:1 mixture of 3-44a and HFIP alcohol (C), (d) 1-D gradient NOE for the 1:1 mixture of 3-44a and HFIP alcohol (C). Irradiated 1′-H₁ (CH) of HFIP alcohol (B), shows NOE at isopropyl group of 3-44a (A).
Comparison Table of $^1$H and $^{13}$C NMR, for 3-44a (A), HFIP alcohol (B) and a 1:1 mixture of 3-44a and HFIP alcohol (C)

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<th>HFIP alcohol (B) $\delta$ ppm</th>
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Diagram A, B, C
$^1$H and $^{13}$C NMR of $i$PrOH (D)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 4.02 (sept, $J = 6.1$ Hz, 1H), 1.40 (s, 1H, OH), 1.21 (d, $J = 6.1$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 64.42 (CH(CH$_3$)$_2$), 25.34 (CH$_3$).
$^1$H, $^{13}$C NMR of a 1:1 mixture of 3-44a and iPrOH (E)

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.81 (d, $J = 5.0$ Hz, 2H), 7.52 (app. d, $J = 7.9$ Hz, 2H), 7.22 (t, $J = 5.0$ Hz, 1H), 7.19 (app. d, $J = 7.9$ Hz, 2H), 4.02 (sept, $J = 6.1$ Hz, 1H), 2.35 (s, 3H), 1.69 (sept, $J = 7.4$ Hz, 2H), 1.20 (d, $J = 6.1$ Hz, 6H), 1.07 (d, $J = 7.4$ Hz, 6H), 1.06 (d, $J = 7.4$ Hz, 6H);

$^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 177.97, 154.78, 139.01, 135.76, 128.67, 128.48, 119.70, 64.36 25.32, 21.50, 17.73, 17.65, 10.76.
NMR studies of hydrogen bonding between 3-44a (A) and iPrOH (E)

1H NMR of (a) 3-44a (A), (b) iPrOH (D), and (c) 1:1 mixture of 3-44a and iPrOH (E). No significant change of proton chemical shift was observed, suggesting not efficient hydrogen bonding between A and D.
Comparison Table of $^1$H and $^{13}$C NMR, for **3-44a (A)**, $^i$PrOH (D) and a 1:1 mixture of **3-44a** and $^i$PrOH (E)

![Chemical structures](image)

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4.11 Synthesis of Active Aryl Esters

Synthesis of 3-36a-y

Method 1: Aryl silane 3-44 (0.20 mmol), Pd(OAc)$_2$ (4.5 mg, 0.020 mmol), AgOAc (133 mg, 0.80 mmol), and Ac-Leu-OH (6.9 mg, 0.040 mmol) were added to a test tube (16 x 125 mm) under N$_2$ atmosphere. Dry DCE (3.0 mL) and HFIP alcohol (100 µL, 1 mmol) were added via syringes and the test tube was capped with a rubber septum (14 mm). The reaction mixture was heated at 50 °C for 5 min, and then a balloon with CO gas was installed with a needle. The reaction mixture was heated at 50 °C and the reaction was monitored by GC-MS until completion (18 h). The resulting mixture was cooled down to room temperature and filtered through a silica gel plug with the aid of EtOAc. The filtrate was concentrated under a reduced pressure. In some cases, THF (2 mL) and HF (48%, 36 µL, 1.0 mmol) were added to the residue [caution: HF is dangerous to use and it should be carefully handled with proper protection], and the reaction was monitored by TLC until complete (the fluorination usually finish in 4 h). The reaction mixture was dried under a reduced pressure and purified by silica gel column chromatography.

Method 2: Aryl silane 3-44 (0.2 mmol), Pd(OAc)$_2$ (4.5 mg, 0.020 mmol), AgOAc (133 mg, 0.80 mmol), and Ac-Leu-OH (6.9 mg, 0.040 mmol) were added to a test tube (16 x 125 mm) under N$_2$ atmosphere. Dry DCE (3.0 mL) and HFIP alcohol (100 µL, 1 mmol) were added via syringes and the test tube was capped with a rubber septum (14 mm). The reaction mixture was heated at 50 °C for 5 min, and then a balloon with CO gas was installed with a needle. The reaction
mixture was heated at 50 °C for and the reaction was monitored by GC-MS, if the starting material was not consumed in 24 h, the resulting mixture was cooled down to room temperature and Pd(OAc)$_2$ (4.5 mg, 0.020 mmol), AgOAc (100. mg, 0.60 mmol) were added in the glove box to the reaction mixture, then it was heated for another 24 h. The resulting mixture was cooled down to room temperature and filtered through a silica gel plug with the aid of EtOAc. The filtrate was concentrated under a reduced pressure. In some cases, THF (2.0 mL) and HF (36 μL, 1.0 mmol) were added to the residue [caution: HF is dangerous to use and it should be carefully handled with proper protection], and the reaction was monitored by TLC until complete (the fluorination usually finish in 4 h). The reaction mixture was dried under a reduced pressure and purified by silica gel column chromatography.

[Method 1, 5 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (19/1 to 9/1). $R_f$ (hexanes/EtOAc = 9:1): 0.44. Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.70 (d, $J = 5.0$ Hz, 2H), 7.93 (s, 1H), 7.59 (d, $J = 7.6$ Hz, 1H), 7.43 (d, $J = 7.6$ Hz, 1H), 7.14 (t, $J = 5.0$ Hz, 1H), 5.70 (sept, $J = 6.2$ Hz, 1H), 2.43 (s, 3H), 1.84 (sept, $J = 7.4$ Hz, 2H), 1.10 (d, $J = 7.4$ Hz, 6H), 1.05 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 178.84, 164.35, 154.53, 139.55, 138.04, 135.08, 133.70, 133.29, 131.75, 120.54 (q, $J = 283$ Hz, CF$_3$), 119.20, 66.74 (sept, $J = 35$ Hz, CH(CF$_3$)$_2$), 21.20, 18.51, 18.38, 11.76; HRMS (ESI) calcd. for C$_{21}$H$_{25}$F$_6$N$_2$O$_2$Si [M+H]$^+$: 479.1589. Found: 479.1592.
[Method 1, 4 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (19/1 to 9/1). Rf (hexanes/EtOAc = 9/1): 0.37. Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ ppm 8.71 (d, J = 5.0 Hz, 2H), 8.14 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.5 Hz, 1H), 7.63-7.60 (m, 1H), 7.55-7.52 (m, 1H), 7.15 (t, J = 5.0 Hz, 1H), 5.69 (sept, J = 6.1 Hz, 1H), 1.86 (sept, J = 7.4 Hz, 2H), 1.11 (d, J = 7.4 Hz, 6H), 1.05 (d, J = 7.4 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃): δ ppm 178.61, 164.30, 154.55, 138.79, 137.97, 133.29, 132.81, 131.09, 129.35, 120.50 (q, J = 284 Hz, CF₃), 119.26, 66.81 (sept, J = 35 Hz, CH(CF₃)₂), 18.48, 18.36, 11.76; HRMS (ESI) calcd. for C₂₀H₂₅F₆N₂O₂Si [M+H]⁺: 465.1433. Found: 465.1438.

[Method 1, 2 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (9/1 to 4/1). Rf (hexanes/EtOAc = 9/1): 0.23. Colorless oil. ¹H NMR (500 MHz, CDCl₃): δ ppm 8.70 (d, J = 4.8 Hz, 2H), 7.67 (s, 1H), 7.66-7.61 (m, 1H), 7.16-7.12 (m, 1H), 5.69 (sept, J = 6.0 Hz, 1H), 3.87 (s, 3H), 1.83 (sept, J = 7.4 Hz, 2H), 1.11 (d, J = 7.4 Hz, 6H), 1.05 (d, J = 7.4 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃): δ ppm 178.88, 163.98, 160.25, 154.52, 139.35, 134.74, 129.08, 120.47 (q, J = 283 Hz, CF₃), 119.18, 118.06, 117.33, 66.84 (sept, J = 35 Hz, CH(CF₃)₂), 55.27, 18.49, 18.34, 11.79; HRMS (ESI) calcd. for C₂₁H₂₅F₆N₂O₃Si [M+H]⁺: 495.1539. Found: 495.1546.
[Method 1, 5 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (1/0 to 19/1). Rf (hexanes/EtOAc = 19/1): 0.46. Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.08 (d, $J = 1.3$ Hz, 1H), 7.92 (d, $J = 8.0$ Hz, 1H), 7.66 (d, $J = 2.0$ Hz, 1H), 5.97 (sept, $J = 6.0$ Hz, 1H), 1.44-1.35 (m, 2H), 1.13 (d, $J = 7.5$ Hz, 6H), 0.80 (d, $J = 7.6$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 164.70, 139.34 (d, $J = 16$ Hz), 137.84 (d, $J = 10$ Hz), 136.59, 134.32, 130.00, 120.30 (q, $J = 284$ Hz, CF$_3$), 67.64 (sept, $J = 35$ Hz, CH(CF$_3$)$_2$), 17.98, 17.50, 12.97 (d, $J = 15$ Hz); HRMS (Cl$^+$) calcd. for C$_{16}$H$_{19}$ClF$_7$O$_2$Si [M+H]$^+$: 439.0731. Found: 439.0732.

[Method 1, 5 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (1/0 to 19/1). Rf (hexanes/EtOAc = 19/1): 0.46. Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.23 (s, 1H), 7.85 (s, 2H), 5.97 (sept, $J = 6.0$ Hz, 1H), 1.42-1.36 (m, 2H), 1.13 (d, $J = 7.4$ Hz, 6H), 0.80 (d, $J = 7.6$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 164.60, 139.85 (d, $J = 16$ Hz), 137.96 (d, $J = 10$ Hz), 137.27, 132.84, 132.52, 124.65, 120.28 (q, $J = 284$ Hz, CF$_3$), 67.64 (sept, $J = 35$ Hz, CH(CF$_3$)$_2$), 17.98, 17.50, 12.94 (d, $J = 15$ Hz); HRMS (Cl$^+$) calcd. for C$_{16}$H$_{19}$BrF$_7$O$_2$Si [M+H]$^+$: 483.0226. Found: 483.0209.
[Method 2, 5 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (1/0 to 19/1). Rf (hexanes/EtOAc = 19/1): 0.44. Colorless oil. 1H NMR (500 MHz, CDCl₃): δ ppm 8.31 (s, 1H), 8.15 (d, J = 7.8 Hz, 1H), 7.96 (d, J = 7.8 Hz, 1H), 5.99 (sept, J = 5.9 Hz, 1H), 1.45-1.40 (m, 2H), 1.15 (d, J = 7.4 Hz, 6H), 0.80 (d, J = 7.6 Hz, 6H); 13C NMR (126 MHz, CDCl₃): δ ppm 164.79, 146.02 (d, J = 16 Hz), 137.28 (d, J = 10 Hz), 132.48 (d, J = 34 Hz), 131.60, 130.49, 126.34, 123.28 (q, J = 273 Hz, CF₃), 120.26 (q, J = 282 Hz, CF₃), 67.78 (sept, J = 35 Hz, CH(CF₃)₂), 17.96, 17.48, 12.96 (d, J = 15 Hz); HRMS (EI+) calcd. for C₁₄H₁₁F₁₀O₂Si [M-iPr]⁺: 429.0368. Found: 429.0387.

[Method 1, 4 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (9/1 to 4/1). Rf (hexanes/EtOAc = 3/1): 0.48. White solid. 1H NMR (500 MHz, CDCl₃): δ ppm 8.70 (d, J = 5.0 Hz, 2H), 8.03 (s, 1H), 7.67 (d, J = 7.6 Hz, 1H), 7.57-7.56 (m, 1H), 7.14 (t, J = 5.0 Hz, 1H), 5.69 (sept, J = 6.2 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 3.69 (s, 2H), 1.84 (sept, J = 7.4 Hz, 2H), 1.28 (t, J = 7.2 Hz, 3H), 1.10 (d, J = 7.4 Hz, 6H), 1.05 (d, J = 7.4 Hz, 6H); 13C NMR (126 MHz, CDCl₃): δ ppm 178.51, 170.59, 164.09, 154.54, 138.22, 137.33, 135.62, 133.71, 133.60, 131.77, 120.46 (q, J = 283 Hz, CF₃), 119.26, 66.81 (sept, J = 35 Hz, CH(CF₃)₂), 61.16, 40.93, 18.46,

[Method 1, 5 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (9/1 to 4/1). Rf (hexanes/EtOAc = 3/1): 0.52. White solid. 1H NMR (500 MHz, CDCl3): δ ppm 8.70 (d, J = 4.9 Hz, 2H), 8.25-8.23 (m, 1H), 7.80 (d, J = 7.8 Hz, 1H), 7.16 (t, J = 5.0 Hz, 1H), 5.70 (sept, J = 6.1 Hz, 1H), 3.97 (s, 3H), 1.86 (sept, J = 7.4 Hz, 2H), 1.10 (d, J = 7.4 Hz, 6H), 1.06 (d, J = 7.4 Hz, 6H); 13C NMR (126 MHz, CDCl3): δ ppm 178.08, 165.87, 163.90, 154.65, 145.04, 138.22, 133.88, 133.06, 131.40, 131.21, 120.42 (q, J = 286 Hz, CF3), 119.45, 67.05 (sept, J = 35 Hz, CH(CF3)2), 52.55, 18.44, 18.34, 11.80; HRMS (EI) calcd. for C14H24O2Si [M]+: 252.15456. Found: 252.15375. HRMS (ESI) calcd. for C22H25F6N2O4Si [M+H]+: 523.1488. Found: 523.1490.

[Method 1, 5 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (9/1 to 4/1). Rf (hexanes/EtOAc = 3/1): 0.74. White solid. 1H NMR (500 MHz, CDCl3): δ ppm 8.64 (s, 1H), 8.25-8.23 (m, 1H), 8.12 (d, J = 7.8 Hz, 1H), 6.00 (sept, J = 6.0 Hz, 1H), 2.68 (s, 3H), 1.43-1.41 (m, 2H), 1.14 (d, J = 7.4 Hz, 6H), 0.80 (d, J = 7.6 Hz, 6H); 13C NMR (126 MHz, CDCl3): δ ppm 197.68, 165.28, 146.85 (d, J = 16 Hz), 138.36, 137.11 (d, J = 10 Hz), 133.21, 131.49, 129.10,
120.32 (q, J = 283 Hz, CF$_3$), 67.68 (sept, J = 35 Hz, CH(CF$_3$)$_2$), 26.67, 17.97, 17.51, 13.00 (d, J = 15 Hz); HRMS (ESI) calcd. for C$_{18}$H$_{22}$F$_7$O$_3$Si [M+H]$^+$: 447.1226. Found: 447.1217.

[Method 1, 5 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (9/1 to 4/1).

R$_f$ (hexanes/EtOAc = 3/1): 0.67. White solid. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.07 (s, 1H), 8.00 (d, J = 7.6 Hz, 1H), 7.67 (dd, J = 7.6, 1.5 Hz, 1H), 5.98 (sept, J = 6.0 Hz, 1H), 3.83 (br. s, 1H), 3.57 (br. s, 1H), 1.56 (br. s, 6H), 1.43-1.38 (m, 2H), 1.21 (br. s, 6H), 1.14 (d, J = 7.4 Hz, 6H), 0.81 (d, J = 7.6 Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 169.07, 165.18, 141.91 (d, J = 16 Hz), 140.26, 136.82 (d, J = 10 Hz), 131.49, 131.06, 127.37, 120.33 (q, J = 285 Hz, CF$_3$), 67.52 (sept, J = 35 Hz, CH(CF$_3$)$_2$), 51.16, 46.26, 20.70, 18.04, 17.57, 13.03 (d, J = 15 Hz); HRMS (ESI) calcd. for C$_{23}$H$_{33}$F$_7$NO$_3$Si [M+H]$^+$: 532.2118. Found: 532.2121.

[Method 1, 4 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (9/1 to 4/1).

R$_f$ (hexanes/EtOAc = 3/1): 0.48. White solid. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.70 (d, J = 5.0 Hz, 2H), 8.25 (d, J = 1.2 Hz, 1H), 7.73-7.68 (m, 2H), 7.14 (t, J = 5.0 Hz, 1H), 6.00 (s, 1H), 5.69 (sept, J = 6.2 Hz, 1H), 1.84 (sept, J = 7.4 Hz, 2H), 1.34 (s, 6H), 1.28 (s, 6H), 1.09 (d, J = 7.4 Hz, 6H).
Hz, 6H), 1.04 (d, J = 7.4 Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 178.54, 164.21, 154.53, 141.19, 139.23, 138.05, 133.47, 130.78, 129.22, 120.50 (q, J = 283 Hz, CF$_3$), 119.26, 99.16, 83.09, 66.84 (sept, J = 35 Hz, CH(CF$_3$)$_2$), 24.18, 22.16, 18.47, 18.34, 11.76; HRMS (ESI) calcd. for C$_{27}$H$_{35}$F$_6$N$_2$O$_4$Si [M+H]$^+$: 593.2270. Found: 593.2274.

![3-46l](image)

[Method 2, 5 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (9/1 to 4/1). R$_f$ (hexanes/EtOAc = 3/1): 0.83. White solid. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.69 (d, J = 5.0 Hz, 2H), 8.47 (s, 1H), 8.01 (d, J = 7.4 Hz, 1H), 7.69 (d, J = 7.4 Hz, 1H), 7.14 (t, J = 5.0 Hz, 1H), 5.72 (sept, J = 6.2 Hz, 1H), 1.85 (sept, J = 7.4 Hz, 2H), 1.35 (s, 12H), 1.09 (d, J = 7.4 Hz, 6H), 1.04 (d, J = 7.4 Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 178.67, 164.66, 154.53, 142.16, 138.80, 137.33, 136.60, 132.71, 120.54 (q, J = 277 Hz, CF$_3$), 119.24, 84.24, 66.83 (sept, J = 35 Hz, CH(CF$_3$)$_2$), 24.81, 18.51, 18.39, 11.79; HRMS (ESI) calcd. for C$_{26}$H$_{34}$BF$_6$N$_2$O$_4$Si [M+H]$^+$: 591.2285. Found: 591.2288.

![3-46m](image)

[Method 1, 4 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (19/1 to 9/1). R$_f$ (hexanes/EtOAc = 9/1): 0.38. Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 8.70 (d, J = 5.0 Hz, 2H), 8.04 (d, J = 8.0 Hz, 1H), 7.48 (s, 1H), 7.32 (d, J = 7.8 Hz, 1H), 7.14 (t, J = 5.0 Hz, 2H), 7.04 (d, J = 7.4 Hz, 1H), 7.00 (d, J = 7.4 Hz, 1H), 6.98 (d, J = 7.4 Hz, 1H), 6.94 (d, J = 7.4 Hz, 1H), 6.90 (d, J = 7.4 Hz, 1H), 6.86 (d, J = 7.4 Hz, 1H), 6.82 (d, J = 7.4 Hz, 1H), 6.78 (d, J = 7.4 Hz, 1H), 6.74 (d, J = 7.4 Hz, 1H), 6.70 (d, J = 7.4 Hz, 1H), 6.66 (d, J = 7.4 Hz, 1H), 6.62 (d, J = 7.4 Hz, 1H), 6.58 (d, J = 7.4 Hz, 1H), 6.54 (d, J = 7.4 Hz, 1H), 6.50 (d, J = 7.4 Hz, 1H), 6.46 (d, J = 7.4 Hz, 1H), 6.42 (d, J = 7.4 Hz, 1H), 6.38 (d, J = 7.4 Hz, 1H), 6.34 (d, J = 7.4 Hz, 1H), 6.30 (d, J = 7.4 Hz, 1H), 6.26 (d, J = 7.4 Hz, 1H), 6.22 (d, J = 7.4 Hz, 1H), 6.18 (d, J = 7.4 Hz, 1H), 6.14 (d, J = 7.4 Hz, 1H), 6.10 (d, J = 7.4 Hz, 1H), 5.72 (sept, J = 6.2 Hz, 1H), 1.85 (sept, J = 7.4 Hz, 2H), 1.35 (s, 12H), 1.09 (d, J = 7.4 Hz, 6H), 1.04 (d, J = 7.4 Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 178.67, 164.66, 154.53, 142.16, 138.80, 137.33, 136.60, 132.71, 120.54 (q, J = 277 Hz, CF$_3$), 119.24, 84.24, 66.83 (sept, J = 35 Hz, CH(CF$_3$)$_2$), 24.81, 18.51, 18.39, 11.79; HRMS (ESI) calcd. for C$_{26}$H$_{34}$BF$_6$N$_2$O$_4$Si [M+H]$^+$: 591.2285. Found: 591.2288.
Hz, 1H), 5.68 (sept, $J = 6.1$ Hz, 1H), 2.41 (s, 3H), 1.85 (sept, $J = 7.4$ Hz, 2H), 1.12 (d, $J = 7.4$ Hz, 6H), 1.05 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 178.83, 164.16, 154.53, 143.53, 138.85, 138.77, 131.28, 130.36, 130.04, 120.54 (q, $J = 283$ Hz, CF$_3$), 119.21, 66.65 (sept, $J = 34$ Hz, CH(CF$_3$)$_2$), 21.94, 18.54, 18.43, 11.79; HRMS (ESI) calcd. for C$_{21}$H$_{25}$F$_6$N$_2$O$_2$Si $[\text{M+H}]^+$: 479.1589. Found: 479.1590.

[Method 1, 2 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (19/1 to 9/1). R$_f$ (hexanes/EtOAc = 9/1): 0.23. Colorless oil. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.71 (d, $J = 5.0$ Hz, 2H), 8.15 (d, $J = 8.8$ Hz, 1H), 7.20 (d, $J = 2.6$ Hz, 1H), 7.15 (t, $J = 5.0$ Hz, 1H), 6.97 (dd, $J = 8.8$ Hz, 2.6 Hz, 1H), 5.70 (sept, $J = 6.2$ Hz, 1H), 3.84 (s, 3H), 1.85 (sept, $J = 7.4$ Hz, 2H), 1.13 (d, $J = 7.4$ Hz, 6H), 1.06 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 178.78, 163.63, 162.94, 154.54, 141.57, 133.67, 124.91, 120.59 (q, $J = 283$ Hz, CF$_3$), 119.27, 113.12, 66.54 (sept, $J = 34$ Hz, CH(CF$_3$)$_2$), 55.35, 18.55, 18.46, 11.83; HRMS (ESI) calcd. for C$_{21}$H$_{25}$F$_6$N$_2$O$_3$Si $[\text{M+H}]^+$: 495.1539. Found: 495.1548.

[Method 1, 5 equiv HFIP alcohol] NMR yield. A mixture of two products, major is shown, and major:minor = 1.5:1. Solvent used for chromatography: hexanes/EtOAc (19/1 to 9/1). R$_f$ (hexanes/EtOAc = 9/1): 0.42. White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.71 (d, $J = 5.0$
Hz, 2H), 8.18 (dd, \( J = 5.4 \) Hz, 8.8 Hz, 1H), 7.37 (dd, \( J = 2.6, 9.4 \) Hz, 1H), 7.21-7.16 (m, 2H), 5.69 (sept, \( J = 6.1 \) Hz, 1H), 1.85 (sept, \( J = 7.4 \) Hz, 2H), 1.11 (d, \( J = 7.4 \) Hz, 6H), 1.06 (d, \( J = 7.4 \) Hz, 6H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) ppm 178.08, 165.36 (d, \( J = 259 \) Hz), 154.65, 143.75 (d, \( J = 5.8 \) Hz), 133.83 (d, \( J = 8.9 \) Hz), 129.17, 125.09 (d, \( J = 21 \) Hz), 120.46 (q, \( J = 281 \) Hz, CF\(_3\)), 119.46, 116.28 (d, \( J = 22 \) Hz), 66.87 (sept, \( J = 35 \) Hz, CH(CF\(_3\))\(_2\)), 18.44, 18.35, 11.76; HRMS (ESI) calcd. for C\(_{20}\)H\(_{22}\)F\(_7\)N\(_2\)O\(_2\)Si [M+H\(^+\)]: 483.1339. Found: 483.1342.

![3-46p](image)

[Method 1, 5 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (19/1 to 9/1). \( R_f \) (hexanes/EtOAc = 9/1): 0.42. White solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) ppm 8.71 (d, \( J = 5.0 \) Hz, 2H), 8.07 (d, \( J = 8.4 \) Hz, 1H), 7.65 (d, \( J = 2.1 \) Hz, 1H), 7.50 (dd, \( J = 8.4, 2.1 \) Hz, 1H), 7.16 (t, \( J = 5.0 \) Hz, 1H), 5.67 (sept, \( J = 6.1 \) Hz, 1H), 1.85 (sept, \( J = 7.4 \) Hz, 2H), 1.12 (d, \( J = 7.4 \) Hz, 6H), 1.07 (d, \( J = 7.4 \) Hz, 6H); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) ppm 177.98, 163.64, 154.64, 141.89, 140.19, 137.86, 132.38, 131.46, 129.49, 120.42 (q, \( J = 282 \) Hz, CF\(_3\)), 119.45, 66.91 (sept, \( J = 35 \) Hz, CH(CF\(_3\))\(_2\)), 18.43, 18.35, 11.79; HRMS (ESI) calcd. for C\(_{20}\)H\(_{22}\)ClF\(_6\)N\(_2\)O\(_2\)Si [M+H\(^+\)]: 499.1043. Found: 499.1040.

![3-46q](image)

[Method 1, 5 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (19/1 to 9/1). \( R_f \) (hexanes/EtOAc = 9/1): 0.42. White solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) ppm 8.71 (d, \( J
= 5.0 Hz, 2H), 7.98 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 1.8 Hz, 1H), 7.67 (dd, J = 8.4, 1.8 Hz, 1H), 7.17 (t, J = 5.0 Hz, 1H), 5.66 (sept, J = 6.0 Hz, 1H), 1.85 (sept, J = 7.4 Hz, 2H), 1.11 (d, J = 7.4 Hz, 6H), 1.07 (d, J = 7.4 Hz, 6H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): \textdelta ppm 177.89, 163.81, 154.64, 142.00, 140.72, 132.52, 132.43, 131.91, 129.35, 120.39 (q, J = 284 Hz, CF\textsubscript{3}), 119.45, 66.91 (sept, J = 35 Hz, CH(CF\textsubscript{3})\textsubscript{2}), 18.43, 18.34, 11.79; HRMS (ESI) calcd. for C\textsubscript{20}H\textsubscript{22}BrF\textsubscript{6}N\textsubscript{2}O\textsubscript{2}Si [M+H]\textsuperscript{+}: 543.0538. Found: 543.0537.

[Method 1, 2 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (19/1 to 9/1). R\textsubscript{f} (hexanes/EtOAc = 9/1): 0.21. White solid. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \textdelta ppm 8.71 (d, J = 5.0 Hz, 2H), 8.14 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 2.4 Hz, 1H), 7.15 (t, J = 5.0 Hz, 1H), 6.97 (dd, J = 8.8, 2.4 Hz, 1H), 5.70 (sept, J = 6.1 Hz, 1H), 4.25 (t, J = 5.8 Hz, 2H), 3.82 (t, J = 5.8 Hz, 2H), 1.85 (sept, J = 7.4 Hz, 2H), 1.12 (d, J = 7.4 Hz, 6H), 1.05 (d, J = 7.4 Hz, 6H); \textsuperscript{13}C NMR (126 MHz, CDCl\textsubscript{3}): \textdelta ppm 178.69, 163.55, 161.51, 154.57, 142.04, 133.61, 125.60, 124.99, 120.56 (q, J = 285 Hz, CF\textsubscript{3}), 119.32, 113.98, 67.92, 66.60 (sept, J = 35 Hz, CH(CF\textsubscript{3})\textsubscript{2}), 41.37, 18.55, 18.46, 11.83; HRMS (ESI) calcd. for C\textsubscript{22}H\textsubscript{26}ClF\textsubscript{6}N\textsubscript{2}O\textsubscript{3}Si [M+H]\textsuperscript{+}: 543.1305. Found: 543.1310.
[Method 1, 2 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (9/1 to 4/1).

R_f (hexanes/EtOAc = 3/1): 0.22. White solid. ¹H NMR (500 MHz, CDCl₃): δ ppm 8.71 (d, J = 5.0 Hz, 2H), 8.14 (d, J = 8.8 Hz, 1H), 7.20-7.15 (m, 3H), 6.96 (dd, J = 8.8, 2.6 Hz, 1H), 5.70 (sept, J = 6.1 Hz, 1H), 4.11 (t, J = 5.6 Hz, 2H), 2.59 (t, J = 7.1 Hz, 2H), 2.17 (tt, J = 7.1, 5.6 Hz, 2H), 1.85 (sept, J = 7.4 Hz, 2H), 1.13 (d, J = 7.4 Hz, 6H), 1.06 (d, J = 7.4 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃): δ ppm 178.70, 163.55, 161.64, 154.56, 142.00, 133.63, 125.47, 124.89, 120.50 (q, J = 282 Hz, CF₃), 119.31, 118.83, 113.74, 66.58 (sept, J = 35 Hz, CH(CF₃)₂), 65.38, 25.26, 18.54, 18.47, 14.17, 11.83; HRMS (ESI) calcd. for C₂₄H₂₈F₆N₃O₃Si [M+H]⁺: 548.1804. Found: 548.1802.

[Method 1, 4 equiv HFIP alcohol]. A mixture of two products, major is shown, and major:minor = 50:1. Solvent used for chromatography: hexanes/EtOAc (19/1 to 9/1). R_f (hexanes/EtOAc = 9/1): 0.33. White solid. ¹H NMR (500 MHz, CDCl₃): δ ppm 8.73-8.72 (m, 3H), 8.18 (s, 1H), 7.99 (d, J = 7.9 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.67-7.60 (m, 2H), 7.16 (t, J = 5.0 Hz, 1H), 5.77 (sept, J = 6.1 Hz, 1H), 1.95 (sept, J = 7.4 Hz, 2H), 1.17 (d, J = 7.4 Hz, 6H), 1.12 (d, J = 7.4 Hz, 6H); ¹³C NMR (126 MHz, CDCl₃): δ ppm 179.04, 164.43, 154.56, 139.40, 134.90, 132.97, 132.40, 132.31, 129.32, 129.26, 129.21, 128.12, 127.74, 120.59 (q, J = 282 Hz, CF₃), 119.22, 66.82 (sept, J = 35 Hz, CH(CF₃)₂), 18.60, 18.53, 12.09; HRMS (ESI) calcd. for C₂₄H₂₈F₆N₃O₃Si [M+H]⁺: 515.1589. Found: 515.1597.
[Method 1, 2 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (19/1 to 9/1). Rf (hexanes/EtOAc = 9/1): 0.25. White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.74 (d, $J$ = 5.0 Hz, 2H), 7.73 (d, $J$ = 4.8 Hz, 1H), 7.31 (d, $J$ = 4.8 Hz, 1H), 7.20 (t, $J$ = 5.0 Hz, 1H), 5.71 (sept, $J$ = 6.1 Hz, 1H), 1.85 (sept, $J$ = 7.4 Hz, 2H), 1.09 (d, $J$ = 7.4 Hz, 6H), 1.04 (d, $J$ = 7.4 Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 177.50, 158.82, 154.64, 147.17, 136.98, 134.92, 133.44, 120.42 (q, $J$ = 285 Hz, CF$_3$), 119.70, 66.72 (sept, $J$ = 35 Hz, CH(CF$_3$)$_2$), 18.08, 17.99, 11.57; HRMS (ESI) calcd. for C$_{18}$H$_{21}$F$_6$N$_2$O$_2$Si $[M+H]^+$: 471.0997. Found: 471.1001.

[Method 1, 2 equiv HFIP alcohol] NMR yield. A mixture of two products, major is shown, and major:minor = 5:1. White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.74 (d, $J$ = 5.0 Hz, 2H), 8.39 (s, 1H), 8.28 (s, 1H), 7.99 (d, $J$ = 7.7 Hz, 1H), 7.64 (d, $J$ = 8.2 Hz, 1H), 7.58-7.54 (m, 1H), 7.40 (dd, $J$ = 7.4, 7.4 Hz, 1H), 7.18 (t, $J$ = 5.0 Hz, 1H), 5.74 (sept, $J$ = 6.1 Hz, 1H), 1.96 (sept, $J$ = 7.4 Hz, 2H), 1.17 (d, $J$ = 7.4 Hz, 6H), 1.11 (d, $J$ = 7.4 Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 178.93, 164.03, 157.64, 156.04, 154.61, 152.39, 151.38, 150.09, 129.01, 128.67, 123.42, 122.86, 121.52, 119.29, 115.23, 112.14, 66.97 (sept, $J$ = 35 Hz, CH(CF$_3$)$_2$), 18.64, 18.56, 12.08; HRMS (ESI) calcd. for C$_{26}$H$_{25}$F$_6$N$_2$O$_3$Si $[M+H]^+$: 555.1539. Found: 555.1550.
[Method 1, 4 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (9/1 to 4/1). 

$R_f$ (hexanes/EtOAc = 3/1): 0.61. Pale yellow solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.73 (d, $J = 5.0$ Hz, 2H), 8.41 (s, 1H), 8.24 (s, 1H), 8.11 (d, $J = 7.7$ Hz, 1H), 7.57 (dd, $J = 7.2$, 7.2 Hz, 1H), 7.47 (d, $J = 8.2$ Hz, 1H), 7.29 (dd, $J = 7.2$, 7.2 Hz, 1H), 7.16 (t, $J = 5.0$ Hz, 1H), 5.80 (sept, $J = 6.1$ Hz, 1H), 3.94 (s, 3H), 1.97 (sept, $J = 7.4$ Hz, 2H), 1.18 (d, $J = 7.4$ Hz, 6H), 1.12 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 179.64, 164.55, 154.50, 142.51, 140.45, 129.96, 129.36, 127.54, 126.48, 126.39, 121.72, 120.67 (q, $J = 283$ Hz, CF$_3$), 121.13, 119.82, 119.09, 112.38, 108.98, 66.77 (sept, $J = 35$ Hz, CH(CF$_3$)$_2$), 29.16, 18.74, 18.64, 12.20; HRMS (ESI) calcd. for C$_{27}$H$_{28}$F$_6$N$_3$O$_2$Si [M+H]$^+$: 568.1855. Found: 568.1865.

[Method 1, 2 equiv HFIP alcohol] A mixture of two products, and major:minor = 2:1. Solvent used for chromatography: hexanes/EtOAc (9/1 to 4/1). $R_f$ (major) (hexanes/EtOAc = 3/1): 0.22. $R_f$ (minor) (hexanes/EtOAc = 3/1): 0.52. White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.94 (s, 1H), 8.71 (d, $J = 5.0$ Hz, 2H), 7.42 (s, 1H), 7.14 (t, $J = 5.0$ Hz, 1H), 5.74 (sept, $J = 6.2$ Hz, 1H), 4.28 (t, $J = 8.2$ Hz, 2H), 3.16 (t, $J = 8.2$ Hz, 2H), 1.84 (sept, $J = 7.4$ Hz, 2H), 1.38 (s, 9H), 1.10 (d, $J = 7.4$ Hz, 6H), 1.02 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 179.29, 176.82,
164.78, 154.54, 146.17, 136.15, 134.15, 133.61, 132.82, 120.51 (q, \( J = 281 \text{ Hz}, \text{CF}_3 \)), 120.42, 119.20, 66.92 (sept, \( J = 35 \text{ Hz}, \text{CH(CF}_3)\_2 \)), 49.68, 40.27, 29.69, 29.52, 27.63, 18.64, 18.50, 11.86; HRMS (ESI) calcd. for \( \text{C}_{27}\text{H}_{34}\text{F}_6\text{N}_3\text{O}_3\text{Si} [\text{M+H}]^+ \): 590.2274. Found: 590.2277.

White solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) ppm 8.68 (d, \( J = 5.0 \text{ Hz}, 2\text{H} \)), 8.49 (d, \( J = 8.2 \text{ Hz}, 1\text{H} \)), 7.55 (d, \( J = 8.2 \text{ Hz}, 1\text{H} \)), 7.13 (t, \( J = 5.0 \text{ Hz}, 1\text{H} \)), 5.69 (sept, \( J = 6.2 \text{ Hz}, 1\text{H} \)), 4.28 (t, \( J = 8.2 \text{ Hz}, 2\text{H} \)), 3.46 (t, \( J = 8.2 \text{ Hz}, 2\text{H} \)), 1.80 (sept, \( J = 7.4 \text{ Hz}, 2\text{H} \)), 1.38 (s, 9H), 1.10 (d, \( J = 7.4 \text{ Hz}, 6\text{H} \)), 1.04 (d, \( J = 7.4 \text{ Hz}, 6\text{H} \)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) ppm 179.03, 176.94, 164.56, 154.52, 147.09, 137.97, 134.18, 132.78, 129.84, 121.90, 120.47 (q, \( J = 282 \text{ Hz}, \text{CF}_3 \)), 119.12, 66.60 (sept, \( J = 35 \text{ Hz}, \text{CH(CF}_3)\_2 \)), 49.18, 40.42, 31.17, 29.69, 27.61, 18.56, 18.43, 12.03.

[Method 1, 2 equiv HFIP alcohol] Solvent used for chromatography: hexanes/EtOAc (9/1 to 4/1). \( R_f \) (hexanes/EtOAc = 3/1): 0.70. Pale yellow solid. \(^1\)H NMR (500 MHz, CDCl\(_3\)): \( \delta \) ppm 8.15 (s, 1H), 7.70 (s, 1H), 5.95 (sept, \( J = 6.0 \text{ Hz}, 1\text{H} \)), 3.82 (t, \( J = 6.1 \text{ Hz}, 2\text{H} \)), 2.89 (t, \( J = 6.9 \text{ Hz}, 2\text{H} \)), 2.04 (tt, \( J = 6.9, 6.1 \text{ Hz}, 2\text{H} \)), 1.41-1.32 (m, 2H), 1.31 (s, 9H), 1.12 (d, \( J = 7.4 \text{ Hz}, 6\text{H} \)), 0.80 (d, \( J = 7.4 \text{ Hz}, 6\text{H} \)); \(^{13}\)C NMR (126 MHz, CDCl\(_3\)): \( \delta \) ppm 178.76, 165.55, 142.24, 137.96, 137.18 (d, \( J = 9.2 \text{ Hz} \)), 135.76 (d, \( J = 15 \text{ Hz} \)), 128.16, 127.40, 120.40 (q, \( J = 282 \text{ Hz}, \text{CF}_3 \)), 67.39 (sept, \( J =
35 Hz, CH(CF$_3$)$_2$), 45.23, 40.58, 28.87, 26.78, 23.69, 18.69, 17.64, 13.07 (d, $J = 15$ Hz); HRMS (ESI) calcd. for C$_{24}$H$_{34}$F$_7$NO$_3$Si [M+H]$^+$: 544.2118. Found: 544.2119.

\[ \text{[20% Pd(OAc)$_2$, 40% Ac-Leu-OH, 90 °C, 8 h, 6 equiv HFIP alcohol]} \] Solvent used for chromatography: hexanes/EtOAc (10/1). R$_f$ (hexanes/EtOAc = 7/1): 0.50. White solid. $^1$H NMR (500 MHz, CDCl$_3$): $\delta$ ppm 8.67 (s, 1H), 8.47 (d, $J = 7.9$ Hz, 1H), 8.36 (d, $J = 8.1$ Hz, 1H), 8.15 (s, 1H), 7.95-7.92 (m, 1H), 7.74-7.71 (m, 1H), 5.98 (sept, $J = 6.0$ Hz, 1H), 1.48-1.43 (m, 2H), 1.18 (d, $J = 7.4$ Hz, 6H), 0.84 (d, $J = 7.4$ Hz, 6H); $^{13}$C NMR (126 MHz, CDCl$_3$): $\delta$ ppm 164.70, 160.07, 151.98, 135.78 (d, $J = 15.2$ Hz), 135.30, 133.27, 131.90, 131.25 (d, $J = 10.4$ Hz), 130.79 (d, $J = 24.9$ Hz), 123.11, 123.02, 122.13, 120.28 (q, $J = 284$ Hz, CF$_3$), 119.81, 67.76 (sept, $J = 35$ Hz, CH(CF$_3$)$_2$), 18.08, 17.57, 13.07 (d, $J = 15.3$ Hz); HRMS (ESI) calcd. for C$_{23}$H$_{22}$F$_7$O$_4$Si [M+H]$^+$: 523.1176. Found: 523.1171.

### 4.12 Mechanistic Experiments

**Determination of Intramolecular Kinetic Isotope Effect:**

\[ \begin{array}{c}
\text{Si} \\
\text{H-C} \\
\text{3-44b-d$_1$} \\
\end{array} + \begin{array}{c}
\text{HO-CF$_3$} \\
\text{4 equiv} \\
\end{array} \xrightarrow{\text{Pd(OAc)$_2$ (10 mol%), Ac-Leu-OH (20 mol%)}} \begin{array}{c}
\text{Si} \\
\text{C} \\
\text{3-46b-d$_1$} \\
\end{array} + \begin{array}{c}
\text{Si} \\
\text{C} \\
\text{3-46b} \\
\end{array} \]

$^3$-44b-d$_1$ (13.5 mg, 0.050 mmol), Pd(OAc)$_2$ (1.1 mg, 0.0050 mol), AgOAc (33.4 mg, 0.20 mmol), and Ac-Leu-OH (1.7 mg, 0.010 mmol) were added to a test tube (16 x 125 mm) under N$_2$ atmosphere. Dry DCE (1.0 mL), HFIP alcohol (21 µL, 0.20 mmol) were added via syringes and
the test tube was capped with a rubber septum (14 mm). The reaction mixture was heated at 50 °C for 5 min, and then a balloon with CO gas was installed with a needle. The reaction mixture was heated at 50 °C for 3 h and cooled down to room temperature, filtered through a short pad of silica gel and perform $^1$H NMR analysis (d1 = 30 s, ns = 4). $^1$H NMR analyses of the crude mixtures of 3-46b and 3-46b-$d_1$ showed 22% hydrogen content at 7.72-7.69 ppm (78% D- incorporation). Based on these results, the kinetic isotope effect ($k_H/k_D$) is 3.5.
Determination of Intermolecular Kinetic Isotope Effect:

3-44b (6.8 mg, 0.025 mmol), 3-44b-d5 (6.9 mg, 0.025 mmol), Pd(OAc)$_2$ (1.1 mg, 0.0050 mol), AgOAc (33.4 mg, 0.20 mmol), and Ac-Leu-OH (1.7 mg, 0.010 mmol) were added to a test tube (16 x 125 mm) under N$_2$ atmosphere. Dry DCE (1.0 mL), HFIP alcohol (21 \(\mu\)L, 0.20 mmol) were added via syringes and the test tube was capped with a rubber septum (14 mm). The reaction mixture was heated at 50 °C for 5 min, and then a balloon with CO gas was installed with a needle. The reaction mixture was heated at 50 °C for 3 h and cooled down to room temperature, filtered through a short pad of silica gel and perform $^1$H NMR analysis (d1 = 30 s, ns = 4). $^1$H NMR analyses of the crude mixtures of 3-46b and 3-46b-d4 showed 51% hydrogen content at 7.72-7.69 ppm (49% D-incorporation). Based on these results, the kinetic isotope effect ($k_H/k_D$) is 1.0.
4.13 Further Transformations

3-46y (11 mg, 0.020 mmol) and AgF (13 mg, 0.040 mmol) were added to an oven dried 1 mL Wheaton V-vial containing a stirring bar under N₂ atmosphere (glovebox), then MeOH (0.5 mL) was added and the reaction vessel was capped with a pressure screw cap. The resulting suspension was stirred for at 50 °C for 24 h. Then it was cooled down to room temperature,
filtered through a short pad of silica gel, concentrated, and purified by chromatography (silica gel, hexanes/EtOAc 70/30) to afford 3-49 as a white solid. R_f (hexanes/EtOAc = 3/1): 0.40. ¹H NMR (500 MHz, CDCl₃): δ ppm 8.06 (s, 1H), 7.74 (dd, J = 8.0, 1.4 Hz, 1H), 7.19 (d, J = 8.0 Hz, 1H), 3.89 (s, 3H), 3.80 (t, J = 6.2 Hz, 2H), 2.83 (t, J = 7.0 Hz, 2H), 2.01 (tt, J = 7.0, 6.2 Hz, 2H), 1.32 (s, 9H); ¹³C NMR (126 MHz, CDCl₃): δ ppm 178.30, 166.88, 140.78, 136.76, 128.72, 127.74, 127.15, 125.84, 52.06, 45.11, 40.32, 28.86, 26.35, 23.83; HRMS (ESI) calcd. for C₁₆H₂₂NO₃ [M+H]⁺: 276.1600. Found: 276.1597.

3-46y (11 mg, 0.020 mmol) and NaOMe (2.2 mg, 0.040 mmol) were added to an oven dried 1 mL Wheaton V-vial containing a stirring bar under N₂ atmosphere (glovebox), then MeOH (0.5 mL) was added and the reaction vessel was capped with a pressure screw cap. The resulting solution was stirred at room temperature for 2 h. The resulting mixture was filtered through a short pad of silica gel. The filtrate was concentrated and dried, and transferred to another 1 mL Wheaton V-vial, to which AuCl₃ (0.30 mg), NIS (9.0 mg, 0.040 mmol) and DCE (0.5 mL) were added. The resulting suspension was stirred at 50 °C for 24 h. Then it was cooled down to room temperature, filtered through a short pad of silica gel, concentrated, and purified by chromatography (silica gel, hexanes/EtOAc = 70/30) to afford 3-50 as a pale yellow solid. R_f (hexanes/EtOAc = 3/1): 0.40. ¹H NMR (500 MHz, CDCl₃): δ ppm 7.98 (s, 1H), 7.75 (s, 1H),

![Reactions](image-url)
3.89 (s, 3H), 3.80 (t, J = 5.9 Hz, 2H), 2.80 (t, J = 7.0 Hz, 2H), 1.99 (tt, J = 7.0, 5.9 Hz, 2H), 1.34 (s, 9H); 13C NMR (126 MHz, CDCl3): δ ppm 177.99, 166.36, 141.49, 140.57, 136.12, 131.45, 128.78, 88.20, 52.43, 45.19, 40.19, 28.67, 25.74, 23.48; HRMS (ESI) calcd. for C16H21NO3 [M+H]+: 402.0566. Found: 402.0558.

3-46y (11 mg, 0.020 mmol) was added to an oven dried 1 mL Wheaton V-vial containing a stirring bar, then MeCN (0.5 mL) was added and the reaction vessel was capped with a pressure screw cap. The resulting solution was stirred for 5 min and nHexNH2 (5.3 μL, 0.040 mmol) was added to the solution. The mixture was stirred overnight then it was filtered through silica gel. The filtrate was concentrated, dried, and transferred to a 1 mL Wheaton V-vial, to which CsF (30.4 mg, 0.20 mmol), H2O (3.6 μL, 0.20 mmol) and DMF (0.5 mL) were added. The resulting suspension was stirred at 90 °C for 12 h. Then it was cooled down to room temperature, filtered through a short pad of silica gel, concentrated, and purified by chromatography (silica gel, hexanes/EtOAc = 50/50) to afford 3-51 as a pale yellow solid. Rf (hexanes/EtOAc = 1/1): 0.44. 1H NMR (500 MHz, CDCl3): δ ppm 7.78 (s, 1H), 7.52 (d, J = 7.8 Hz, 1H), 7.18 (d, J = 7.8 Hz, 1H), 6.21 (br. s, 1H, NH), 3.81 (t, J = 6.0 Hz, 2H), 3.43-3.39 (m, 2H), 2.84 (t, J = 7.0 Hz, 2H), 2.02 (tt, J = 7.0, 6.0 Hz, 2H), 1.61-1.58 (m, 2H), 1.35 (s, 9H), 1.32-1.31 (m, 6H), 0.89 (t, J = 6.6 Hz, 3H); 13C NMR (126 MHz, CDCl3): δ ppm 178.08, 167.31, 140.50, 134.33, 132.43, 129.13,
123.96, 123.66, 45.29, 40.12, 31.49, 29.64, 28.75, 26.65, 26.09, 23.88, 22.54, 14.00; HRMS (ESI) calcd. for C$_{21}$H$_{33}$N$_2$O$_2$ [M+H]$^+$: 345.2542. Found: 345.2534.

3-46y (11 mg, 0.020 mmol) was added to an oven dried 1 mL Wheaton V-vial containing a stirring bar, then MeCN (0.5 mL) was added and the reaction vessel was capped with a pressure screw cap. The resulting solution was stirred for 5 min and nHexNH$_2$ (5.3 µL, 0.040 mmol) was added to the solution. The solution was stirred overnight then it was filtered through silica gel. The filtrate was concentrated, dried, and transferred to a 1 mL Wheaton V-vial, to which AuCl$_3$ (0.30 mg), NIS (9.0 mg, 0.040 mmol) and DCE (0.5 mL) were added. The resulting suspension was stirred at 50 °C for 24 h. Then it was cooled down to room temperature, filtered through a short pad of silica gel, concentrated, and purified by chromatography (silica gel, hexanes/EtOAc = 50/50) to afford 3-52 as a pale yellow solid. R$_f$ (hexanes/EtOAc = 1/1): 0.52. $^1$H NMR (500 MHz, CDCl$_3$): δ ppm 7.16 (s, 1H), 7.52 (s, 1H), 5.96 (br. s, 1H, NH), 3.78 (t, $J$ = 5.8 Hz, 2H), 3.43-3.38 (m, 2H), 2.79 (t, $J$ = 7.1 Hz, 2H), 1.99 (tt, $J$ = 7.1, 5.8 Hz, 2H), 1.64-1.59 (m, 2H), 1.35 (s, 9H), 1.33-1.31 (m, 6H), 0.89 (t, $J$ = 6.9 Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 177.96, 168.98, 140.55, 140.05, 139.21, 133.86, 125.79, 86.55, 45.25, 40.16, 40.01, 31.44, 29.32, 28.56, 26.65, 25.55, 23.58, 22.55, 14.02; HRMS (ESI) calcd. for C$_{21}$H$_{32}$IN$_2$O$_2$ [M+H]$^+$: 471.1508. Found: 471.1504.
3-44z (38.9 mg, 0.10 mmol), Pd(OAc)$_2$ (4.5 mg, 0.020 mol), AgOAc (66.8 mg, 0.40 mmol), and Ac-Leu-OH (6.9 mg, 0.040 mmol) were added to a test tube (16 x 125 mm) under N$_2$ atmosphere. Dry DCE (2.0 mL), HFIP alcohol (63 μL, 0.60 mmol) were added via syringes and the test tube was capped with a rubber septum (14 mm). The reaction mixture was heated at 90 °C for 5 min, and then a balloon with CO gas was installed with a needle. The reaction mixture was heated at 90 °C for 8 h and cooled down to room temperature, filtered through a short pad of silica gel with aid of EtOAc and concentrated under reduced pressure to obtain a grey solid. The solid was transferred to a 25 mL round flask, to which THF (4 mL) and HF (18.2 μL) was added. The mixture was stirred at room temperature for 2 h and was filtered through a short pad of silica gel with aid of EtOAc. The filtrate was dried under reduced pressure and transfer to a 25 mL round flask charged with a stirring bar, to which MeNH$_2$•HCl (27 mg, 0.40 mmol), MeCN (4 mL) and Et$_3$N (113 μL, 0.80 mmol) were added. The mixture was stirred at room temperature for 4 h and
was filtered through a short pad of silica gel with aid of EtOAc. The filtrate was dried and transferred to a 3 mL Wheaton V-vial containing a stirring bar, then CsF (152 mg, 1.0 mmol), DMF (2 mL) and H$_2$O (18 mL, 1.0 mmol) were added. The reaction mixture was stirred at 90 °C for 12 h, and the reaction mixture was washed with HCl (1 M, 10 mL) and extracted by DCM (3×10 mL). The filtrate was concentrated and purified by chromatography (silica gel, hexanes/EtOAc = 50/50 to EtOAc 100%) to afford 3-55 as a white solid. R$_f$ (EtOAc): 0.38. $^1$H NMR (500 MHz, DMSO-$d_6$): δ ppm 8.65 (br. s, 1H, NH), 8.50-8.45 (m, 2H), 8.27 (d, $J=7.6$ Hz, 1H), 7.99-7.96 (m, 1H), 7.85-7.82 (m, 2H), 7.74-7.71 (m, 1H), 2.81 (d, $J=3.3$ Hz, 3H); $^{13}$C NMR (126 MHz, CDCl$_3$): δ ppm 165.51, 160.57, 150.95, 136.63, 135.91, 134.09, 130.45, 130.29, 124.31, 123.62, 121.44, 120.46, 116.26, 26.81; HRMS (ESI) calcd. for C$_{15}$H$_{12}$NO$_3$ [M+H]$^+$: 254.0817. Found: 254.0818.
APPENDIX I

Selected NMR Spectra
$^1$H NMR Spectrum of 2-4b

$^{13}$C NMR Spectrum of 2-4b
$^1$H NMR Spectrum of 2-4c

![H NMR spectrum of 2-4c](image)

$^{13}$C NMR Spectrum of 2-4c

![C NMR spectrum of 2-4c](image)
$^1$H NMR Spectrum of 2-4d

$^{13}$C NMR Spectrum of 2-4d
$^1$H NMR Spectrum of 2-4e

\[
\begin{align*}
\text{Chemical Shift (ppm):} & \\
7.80 & 7.75 & 7.42 & 7.38 & 7.36 & 7.34 & 7.32 & 7.31 & 7.30 & 7.06 & 7.05 & 6.15 & 1.51
\end{align*}
\]

\[
\begin{align*}
\end{align*}
\]

$^{13}$C NMR Spectrum of 2-4e

\[
\begin{align*}
172.63 & 158.43 & 142.83 & 136.94 & 133.56 & 132.03 & 131.19 & 130.68 & 129.69 & 128.61 & 127.69 & 114.81
\end{align*}
\]

\[
\begin{align*}
\end{align*}
\]
$^1$H NMR Spectrum of 2-4f

$^{13}$C NMR Spectrum of 2-4f
$^1$H NMR Spectrum of 2-4g

$^{13}$C NMR Spectrum of 2-4g
$^1$H NMR Spectrum of $2-4h$

$^{13}$C NMR Spectrum of $2-4h$
$^1$H NMR Spectrum of 2-4i

$^{13}$C NMR Spectrum of 2-4i
$^1$H NMR Spectrum of 2-4j

$^{13}$C NMR Spectrum of 2-4j
$^1$H NMR Spectrum of 2-4k

$^{13}$C NMR Spectrum of 2-4k
$^1$H NMR Spectrum of 2-4l

$^{13}$C NMR Spectrum of 2-4l
$^1$H NMR Spectrum of 2-4m

$^{13}$C NMR Spectrum of 2-4m
$^1$H NMR Spectrum of 2-4n

$^{13}$C NMR Spectrum of 2-4n
\(^1H\) NMR Spectrum of 2-4o

\(\text{C NMR Spectrum of 2-4o}\)
$^1$H NMR Spectrum of 2-4p

$^{13}$C NMR Spectrum of 2-4p
$^1$H NMR Spectrum of 2-4q

$^{13}$C NMR Spectrum of 2-4q
$^1$H NMR Spectrum of 2-4r

$^{13}$C NMR Spectrum of 2-4r
$^1$H NMR Spectrum of 2-4s

$^{13}$C NMR Spectrum of 2-4s
$^1$H NMR Spectrum of 2-4t

$^{13}$C NMR Spectrum of 2-4t
$^1$H NMR Spectrum of 2-4x

$^{13}$C NMR Spectrum of 2-4x
$^1$H NMR Spectrum of 2-4y

$^{13}$C NMR Spectrum of 2-4y
\( ^1H \) NMR Spectrum of 2-4z

\( ^{13}C \) NMR Spectrum of 2-4z
$^1$H NMR Spectrum of 2-4aa

$^{13}$C NMR Spectrum of 2-4aa
$^1$H NMR Spectrum of 2-4ab

$^{13}$C NMR Spectrum of 2-4ab
$^1$H NMR Spectrum of 2-4ae

$^{13}$C NMR Spectrum of 2-4ae
$^1$H NMR Spectrum of 2-4ag

$^1$H NMR Spectrum of 2-4ah
$^1$H NMR Spectrum of 2-4ai

$^{13}$C NMR Spectrum of 2-4ai
$^1$H NMR Spectrum of 2-1b

\[
\begin{align*}
\text{Chemical Shift (ppm)} & \\
3.62 & \\
1.14 & \\
0.98 & \\
1.11 & \\
1.11 & \\
1.20 & \\
1.20 & \\
1.00 & \\
\end{align*}
\]

$^{13}$C NMR Spectrum of 2-1b

\[
\begin{align*}
\text{Chemical Shift (ppm)} & \\
21.428 & \\
76.746 & \\
77.000 & \\
77.254 & \\
115.430 & \\
117.890 & \\
120.889 & \\
121.416 & \\
122.497 & \\
125.655 & \\
128.351 & \\
130.538 & \\
134.756 & \\
134.994 & \\
141.284 & \\
151.279 & \\
161.430 & \\
\end{align*}
\]
$^1$H NMR Spectrum of 2-1c

$^{13}$C NMR Spectrum of 2-1c
**$^1$H NMR Spectrum of 2-1d**

![1H NMR Spectrum of 2-1d]

**$^{13}$C NMR Spectrum of 2-1d**

![13C NMR Spectrum of 2-1d]
$^1$H NMR Spectrum of 2-1e

$^1$C NMR Spectrum of 2-1e
$^1$H NMR Spectrum of 2-1f

$^1$C NMR Spectrum of 2-1f
$^1$H NMR Spectrum of 2-1g

$^{13}$C NMR Spectrum of 2-1g
$^1$H NMR Spectrum of 2-1h

$^{13}$C NMR Spectrum of 2-1h
$^1$H NMR Spectrum of 2-1i

$^{13}$C NMR Spectrum of 2-1i
\(^1\)H NMR Spectrum of 2-1j

\[^{13}\text{C}\] NMR Spectrum of 2-1j
$^1$H NMR Spectrum of 2-II (major)

$^{13}$C NMR Spectrum of 2-II (major)
\(^1\)H NMR Spectrum of 2-II' (minor)

\(^{13}\)C NMR Spectrum of 2-II' (minor)
$^1$H NMR Spectrum of 2-1m

13C NMR Spectrum of 2-1m
$^1$H NMR Spectrum of 2-1n

$^{13}$C NMR Spectrum of 2-1n

![Chemical Structure](image)
$^1$H NMR Spectrum of 2-1o (major)

$^{13}$C NMR Spectrum of 2-1o (major)
$^1$H NMR Spectrum of 2-10' (minor)

$^{13}$C NMR Spectrum of 2-10' (minor)
\[ ^1H \text{NMR Spectrum of 2-1q} \]

\[ ^{13}\text{C NMR Spectrum of 2-1q} \]
$^1$H NMR Spectrum of 2-1r

13C NMR Spectrum of 2-1r
**1H NMR Spectrum of 2-1s**

![H NMR Spectrum of 2-1s](image)

**13C NMR Spectrum of 2-1s**

![C NMR Spectrum of 2-1s](image)
$^1$H NMR Spectrum of 2-1u

$^{13}$C NMR Spectrum of 2-1u
$^1$H NMR Spectrum of 2-1v

$^{13}$C NMR Spectrum of 2-1v
$^1$H NMR Spectrum of 2-1w

$^{13}$C NMR Spectrum of 2-1w
$^1$H NMR Spectrum of 2-1x

![NMR Spectrogram](image)

$^{13}$C NMR Spectrum of 2-1x

![NMR Spectrogram](image)
$^1$H NMR Spectrum of 2-1y (500 MHz, CDCl$_3$)

$^1$H NMR Spectrum of 2-1y (500 MHz, MeOH-$d_4$)
$^{13}$C NMR Spectrum of 2-1y (126 MHz, MeOH-$d_4$)

\[
\begin{align*}
C_{22}H_{19}N_2O_5 & : \\
& \text{ppm} \\
C & 34.273, 38.510, 47.056, 47.226, 47.396, 47.567, 47.737, 47.908, 48.078 \\
& 115.799, 119.214, 121.076, 122.272, 122.989, 123.508, 129.392, 129.847, 134.014, 135.137, 137.966 \\
& 150.835, 160.842, 170.522
\end{align*}
\]
$^1$H NMR Spectrum of 2-1z

$^{13}$C NMR Spectrum of 2-1z
$^1$H NMR Spectrum of 2-1aa

$^{13}$C NMR Spectrum of 2-1aa
$^1$H NMR Spectrum of 2-1ab

$^{13}$C NMR Spectrum of 2-1ab
$^1$H NMR Spectrum of 2-1ac

$^{13}$C NMR Spectrum of 2-1ac
$^1$H NMR Spectrum of 2-1ad

$^{13}$C NMR Spectrum of 2-1ad
$^{1}H$ NMR Spectrum of 2-1ae

$^{13}C$ NMR Spectrum of 2-1ae
$^1$H NMR Spectrum of 3-18c

$^{13}$C NMR Spectrum of 3-18c
$^1$H NMR Spectrum of 3-18d

\[
\begin{array}{c}
\text{Ph} \quad \text{C} \quad \text{fBu} \\
\text{O} \quad \text{S} \quad \text{fBu} \\
\end{array}
\]

13C NMR Spectrum of 3-18d

\[
\begin{array}{c}
\text{Ph} \quad \text{O} \quad \text{S} \quad \text{fBu} \\
\text{Ph} \quad \text{C} \quad \text{S} \quad \text{fBu} \\
\end{array}
\]
$^1$H NMR Spectrum of 3-18f

$^{13}$C NMR Spectrum of 3-18f
$^1\text{H NMR Spectrum of 3-18i}$

$^{13}\text{C NMR Spectrum of 3-18i}$
\( ^1H \) NMR Spectrum of 3-18k

\( ^{13}C \) NMR Spectrum of 3-18k
$^1$H NMR Spectrum of 3-18q

$^{13}$C NMR Spectrum of 3-18q
$^1$H NMR Spectrum of 3-18r

$^{13}$C NMR Spectrum of 3-18r
$^1$H NMR Spectrum of 3-18s

\[ \begin{align*}
\text{EtC}_2\text{C} & \quad \text{C-Si} & \quad \text{rBu} \\
\text{OH} & \\
\end{align*} \]

$^{13}$C NMR Spectrum of 3-18s

\[ \begin{align*}
\text{EtC}_2\text{C} & \quad \text{C-Si} & \quad \text{rBu} \\
\text{OH} & \\
\end{align*} \]
$^1$H NMR Spectrum of 3-18t

$^{13}$C NMR Spectrum of 3-18t
$^1$H NMR Spectrum of 3-18u

$^{13}$C NMR Spectrum of 3-18u
$^1$H NMR Spectrum of 3-18w

$^{13}$C NMR Spectrum of 3-18w
$^1$H NMR Spectrum of 3-18x

$^{13}$C NMR Spectrum of 3-18x
$^1$H NMR Spectrum of 3-18y

$^{13}$C NMR Spectrum of 3-18y
$^1$H NMR Spectrum of 3-18z

$^{13}$C NMR Spectrum of 3-18z
$^1$H NMR Spectrum of 3-38

$^{13}$C NMR Spectrum of 3-38
$^1$H NMR Spectrum of 3-29a

$^{13}$C NMR Spectrum of 3-29a
\textbf{\(^{1}\text{H NMR Spectrum of 3-29b}\)}

\begin{center}
\includegraphics[width=0.8\textwidth]{hnmr.png}
\end{center}

\textbf{\(^{13}\text{C NMR Spectrum of 3-29b}\)}

\begin{center}
\includegraphics[width=0.8\textwidth]{cnmr.png}
\end{center}
$^1$H NMR Spectrum of 3-29c

\[
\begin{array}{c}
\text{Me} \\
\text{OH} \\
\end{array}
\]

$^{13}$C NMR Spectrum of 3-29c

\[
\begin{array}{c}
\text{Me} \\
\text{OH} \\
\end{array}
\]
$^1$H NMR Spectrum of 3-29d

$^{13}$C NMR Spectrum of 3-29d
$^1$H NMR Spectrum of 3-29e

$^{13}$C NMR Spectrum of 3-29e
$^1$H NMR Spectrum of 3-29f

$^{13}$C NMR Spectrum of 3-29f
$^1$H NMR Spectrum of 3-29g

$^{13}$C NMR Spectrum of 3-29g
$^1$H NMR Spectrum of 3-29h

$^{13}$C NMR Spectrum of 3-29h
$^1$H NMR Spectrum of 3-29i

$^{13}$C NMR Spectrum of 3-29i
1H NMR Spectrum of 3-29j

\[ \text{H NMR Spectrum of 3-29j} \]

\[ \begin{align*}
    &2.046 &2.050 &2.054 &2.059 &
\end{align*} \]

\[ \text{13C NMR Spectrum of 3-29j} \]

\[ \begin{align*}
\end{align*} \]
$^1$H NMR Spectrum of 3-29k

$^{13}$C NMR Spectrum of 3-29k
$^1$H NMR Spectrum of 3-29l

$^{13}$C NMR Spectrum of 3-29l
$^1$H NMR Spectrum of 3-29m

$^{13}$C NMR Spectrum of 3-29m
$^1$H NMR Spectrum of 3-29n

$^{13}$C NMR Spectrum of 3-29n
$^{1}$H NMR Spectrum of 3-29o

$^{13}$C NMR Spectrum of 3-29o
$^1$H NMR Spectrum of 3-29p

OH
MeO

$^{13}$C NMR Spectrum of 3-29p

MeO

OH

OH
MeO
$^1$H NMR Spectrum of 3-29q

AcO

\[ \text{H}_2\text{O} \]

$^{13}$C NMR Spectrum of 3-29q

AcO

\[ \text{H}_2\text{O} \]

ppm
$^1$H NMR Spectrum of $3-29r$

$^{13}$C NMR Spectrum of $3-29r$
$^1$H NMR Spectrum of 3-29s

$^{13}$C NMR Spectrum of 3-29s
$^1$H NMR Spectrum of 3-29t

$^{13}$C NMR Spectrum of 3-29t
$^1$H NMR Spectrum of 3-29u

$^{13}$C NMR Spectrum of 3-29u
$^{1}$H NMR Spectrum of 3-29v

$^{13}$C NMR Spectrum of 3-29v
$^1$H NMR Spectrum of 3-29w

$^{13}$C NMR Spectrum of 3-29w
$^1$H NMR Spectrum of 3-29x

$^{13}$C NMR Spectrum of 3-29x
$^1$H NMR Spectrum of 3-29y

$^{13}$C NMR Spectrum of 3-29y
$^1$H NMR Spectrum of 3-18z and 3-34z

[Diagram of NMR spectra with chemical structures and peak assignments]
$^1$H NMR Spectrum of 3-29aa

$^{13}$C NMR Spectrum of 3-29aa
$^1$H NMR Spectrum of 3-39

$^{13}$C NMR Spectrum of 3-39
$^1$H NMR Spectrum of 3-18b-$^{18}$O

$^{13}$C NMR Spectrum of 3-18b-$^{18}$O
$^1$H NMR Spectrum of 3-34b-$^{18}$O

$^{13}$C NMR Spectrum of 3-34b-$^{18}$O
$^1$H NMR Spectrum of 3-44a

$^{13}$C NMR Spectrum of 3-44a
\textbf{\textsuperscript{1}H NMR Spectrum of 3-44b}

\textbf{\textsuperscript{13}C NMR Spectrum of 3-44b}
$^1\text{H NMR Spectrum of 3-44b-}d_1$

$^{13}\text{C NMR Spectrum of 3-44b-}d_1$
$^1$H NMR Spectrum of 3-44b-$d_5$

$^{13}$C NMR Spectrum of 3-44b-$d_5$
$^1$H NMR Spectrum of 3-44c

$^{13}$C NMR Spectrum of 3-44c
$^1$H NMR Spectrum of **3-44e**

![H NMR Spectrum](image)

$^{13}$C NMR Spectrum of **3-44e**

![C NMR Spectrum](image)
$^1$H NMR Spectrum of 3-44f

$^{13}$C NMR Spectrum of 3-44f
$^1$H NMR Spectrum of 3-44g

$^{13}$C NMR Spectrum of 3-44g
$^1$H NMR Spectrum of 3-44h

$^{13}$C NMR Spectrum of 3-44h
$^1$H NMR Spectrum of 3-44i

$^{13}$C NMR Spectrum of 3-44i
$^1$H NMR Spectrum of 3-44j

$^{13}$C NMR Spectrum of 3-44j
$^1$H NMR Spectrum of 3-44k

$^{13}$C NMR Spectrum of 3-44k
$^1$H NMR Spectrum of 3-44l

$^{13}$C NMR Spectrum of 3-44l
$^1$H NMR Spectrum of 3-44m

$^{13}$C NMR Spectrum of 3-44m
\(^1\)H NMR Spectrum of 3-44o

\(^1\)C NMR Spectrum of 3-44o
$^1$H NMR Spectrum of 3-44q

$^{13}$C NMR Spectrum of 3-44q
$^1$H NMR Spectrum of 3-44r

$^{13}$C NMR Spectrum of 3-44r
$^1$H NMR Spectrum of 3-44s

$^{13}$C NMR Spectrum of 3-44s
$^1$H NMR Spectrum of 3-44t

$^{13}$C NMR Spectrum of 3-44t
$^1$H NMR Spectrum of 3-44u

$^{13}$C NMR Spectrum of 3-44u
$^1$H NMR Spectrum of 3-44v
$^1$H NMR Spectrum of 3-44w

$^{13}$C NMR Spectrum of 3-44w
$^1$H NMR Spectrum of 3-44x

$^{13}$C NMR Spectrum of 3-44x
$^1$H NMR Spectrum of 3-44y

$^{13}$C NMR Spectrum of 3-44y
$^1$H NMR Spectrum of 3-46a

13C NMR Spectrum of 3-46a
$^{1}H$ NMR Spectrum of 3-46b

$^{13}C$ NMR Spectrum of 3-46b
$^1$H NMR Spectrum of 3-46d

$^{13}$C NMR Spectrum of 3-46d
$^1$H NMR Spectrum of 3-46e

$^{13}$C NMR Spectrum of 3-46e
$^{1}H$ NMR Spectrum of 3-46f

$^{13}C$ NMR Spectrum of 3-46f
1H NMR Spectrum of 3-46g

13C NMR Spectrum of 3-46g
$^1$H NMR Spectrum of 3-46h

$^{13}$C NMR Spectrum of 3-46h
$^1$H NMR Spectrum of 3-46i

$^{13}$C NMR Spectrum of 3-46i
$^1$H NMR Spectrum of 3-46j

$^{13}$C NMR Spectrum of 3-46j
$^1$H NMR Spectrum of 3-46k

$^{13}$C NMR Spectrum of 3-46k
$^1$H NMR Spectrum of 3-461

$^{13}$C NMR Spectrum of 3-461
$^1$H NMR Spectrum of **3-46m**

![H NMR Spectrum of 3-46m](image)

$^{13}$C NMR Spectrum of **3-46m**

![C NMR Spectrum of 3-46m](image)
$^1$H NMR Spectrum of 3-46n

$^{13}$C NMR Spectrum of 3-46n
1H NMR Spectrum of 3-46o

13C NMR Spectrum of 3-46o
$^1$H NMR Spectrum of 3-46q

$^{13}$C NMR Spectrum of 3-46q
$^1$H NMR Spectrum of 3-46r

$^{13}$C NMR Spectrum of 3-46r
$^1$H NMR Spectrum of 3-46s

$^{13}$C NMR Spectrum of 3-46s
$^1$H NMR Spectrum of 3-46t

$^{13}$C NMR Spectrum of 3-46t
\textsuperscript{1}H NMR Spectrum of 3-46u

\textsuperscript{13}C NMR Spectrum of 3-46u
$^{1}H$ NMR Spectrum of 3-46w

$^{13}C$ NMR Spectrum of 3-46w
$^1$H NMR Spectrum of 3-46x (major)

$^{13}$C NMR Spectrum of 3-46x (major)
$^1$H NMR Spectrum of 3-46x' (minor)

$^{13}$C NMR Spectrum of 3-46x' (minor)
$^1$H NMR Spectrum of 3-46y

$^{13}$C NMR Spectrum of 3-46y
$^1$H NMR Spectrum of 3-46z

$^{13}$C NMR Spectrum of 3-46z
$^1$H NMR Spectrum of 3-49

$^{13}$C NMR Spectrum of 3-49
$^{1}$H NMR Spectrum of 3-50

$^{13}$C NMR Spectrum of 3-50
$^1$H NMR Spectrum of 3-51

$^{13}$C NMR Spectrum of 3-51
$^1$H NMR Spectrum of 3-55

$^{13}$C NMR Spectrum of 3-55
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PUBLICATIONS:


1. Xie, B.; Shi, H.; Liu, G.; Zhou, Y.; Wang Y.; Zhao, Y.; Wang, D.*
   “Preparation of Surface Porous Microcapsules Templated by Self-
   assembly of Nonionic Surfactant Micelles.” Chem. Mater. 2008, 20, 3099-
   3104.

PRESENTATIONS: 6. Wang, Y.; Gevorgyan, V.* “Palladium Catalyzed ortho
   Alkoxycarbonylation of Aryl Silanes” Gordon Research Conference-
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5. Wang, Y.; Gevorgyan, V.* “Palladium Catalyzed ortho
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4. Wang, Y.; Gevorgyan, V.* “Cu-Catalyzed and Metal-Free
   Dehydrogenative C–H/O–H Coupling Reactions – A Green Approach”
   International Symposium on Green Chemistry at UIC, IL, 2014 (oral talk)
3. Wang, Y.; Gevorgyan, V.* “Pd(II) Catalyzed Synthesis of Salicylic
   Acids from Phenols via a Silanol Intermediate” 7th Negishi-Brown
   Lectures, IN, 2014 (poster)
2. Wang, Y.; Gevorgyan, V.* “Copper Catalyzed Remote $sp^2$ C–H or
   benzylic C–H Oxygenation Reactions Directed by a Carboxylic Group”
   OMCOS 17, CO, 2013 (poster)
1. Wang, Y.; Gevorgyan, V.* “Copper Catalyzed Remote $sp^2$ C–H or
   benzylic C–H Oxygenation Reactions Directed by a Carboxylic Group”
   The 3rd International Symposium on Molecular Activation, CO, 2013
   (oral talk)