TRANSITION METAL CATALYZED C\((sp^2)\)-C AND C\((sp^2)\)-N BOND FORMING REACTIONS

MANIKANTHA MARASWAMI

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MANIKANTHA MARASWAMI

School of Physical and Mathematical Sciences

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<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>δ</td>
<td>chemical shift</td>
</tr>
<tr>
<td>°C</td>
<td>degree centigrade</td>
</tr>
<tr>
<td>Ac</td>
<td>acetyl</td>
</tr>
<tr>
<td>acac</td>
<td>acetylacetone</td>
</tr>
<tr>
<td>Ac$_2$O</td>
<td>acetic anhydride</td>
</tr>
<tr>
<td>AcOH</td>
<td>acetic acid</td>
</tr>
<tr>
<td>aq</td>
<td>aqueous</td>
</tr>
<tr>
<td>Ar</td>
<td>aryl</td>
</tr>
<tr>
<td>atm</td>
<td>atmosphere</td>
</tr>
<tr>
<td>BINOL</td>
<td>1,1'-bi-2-naphthol</td>
</tr>
<tr>
<td>Bn</td>
<td>benzyl</td>
</tr>
<tr>
<td>Box</td>
<td>bisoxazoline</td>
</tr>
<tr>
<td>brs</td>
<td>broad singlet</td>
</tr>
<tr>
<td>Cp</td>
<td>cyclopentadienyl</td>
</tr>
<tr>
<td>Cod</td>
<td>1,5-cyclooctadiene</td>
</tr>
<tr>
<td>Cy</td>
<td>cyclohexane</td>
</tr>
<tr>
<td>d</td>
<td>doublet</td>
</tr>
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<td>DBE</td>
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</tr>
<tr>
<td>DCE</td>
<td>1,2-dichloroethane</td>
</tr>
<tr>
<td>DMAD</td>
<td>diethyl acetylenedicarboxylate</td>
</tr>
<tr>
<td>DMF</td>
<td>N,N-dimethylformamide</td>
</tr>
<tr>
<td>2D NMR</td>
<td>two-dimensional nuclear magnetic resonance spectroscopy</td>
</tr>
<tr>
<td>dppe</td>
<td>1,2-bis(diphenylphosphino)ethane</td>
</tr>
<tr>
<td>dppp</td>
<td>1,3-bis(diphenylphosphanyl)propane</td>
</tr>
<tr>
<td>dr</td>
<td>diastereomeric ratio</td>
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<tr>
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<tr>
<td>ee</td>
<td>enantiomeric excess</td>
</tr>
<tr>
<td>ESI</td>
<td>electrospray ionization</td>
</tr>
<tr>
<td>Et</td>
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Et$_3$SiH triethyldisilane
$EWG$ electron-withdrawing group
$h$ hour
$HRMS$ high resolution mass spectrometry
$hv$ photoirradiation
$Hz$ Hertz
$i^Bu$ isobutyl
$i^Pr$ isopropyl
$J$ coupling constant
$m$-CPBA 3-chloroperbenzoic acid
$MS$ molecular sieve
$n^Pr$ n-propyl
$n^Bu$ n-butyl
$n^Hex$ n-hexane
$NMM$ $N$-methylmaleimide
$NOESY$ Nuclear Overhauser Enhancement spectroscopy
$p$ para
$m$ multiplet
$NMR$ nuclear magnetic resonance
$NHC$ $N$-heterocyclic carbene
$OTf$ triflate
$PCy_3$ tricyclohexylphosphine
$Ph$ phenyl
$Ph_2$SiHCl chlorodiphenylsilane
$PIDA$ (diacetoxyiodo)benzene
$PivOH$ pivalic acid
$p$-TsOH $p$-toluenesulfonic acid
$q$ quartet
$rt$ room temperature
$rr$ regioisomeric ratio
$s$ singlet
<table>
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<tr>
<td>( t )</td>
<td>triplet</td>
</tr>
<tr>
<td>( 'Bu )</td>
<td>tert-butyl</td>
</tr>
<tr>
<td>tfacac</td>
<td>trifluoroacetylacetone</td>
</tr>
<tr>
<td>( \text{Tf}_2\text{NH} )</td>
<td>trifluoromethanesulfonimide</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>THP</td>
<td>tetrahydropyran</td>
</tr>
<tr>
<td>TIPS</td>
<td>triisopropylsilyl</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMS</td>
<td>trimethylsilyl</td>
</tr>
<tr>
<td>TMSX</td>
<td>trimethylsilyl halide</td>
</tr>
<tr>
<td>( \alpha )</td>
<td>alpha</td>
</tr>
<tr>
<td>( \beta )</td>
<td>beta</td>
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<td>( \gamma )</td>
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ABSTRACT

The thesis describes the development of transition metal catalysed C-H functionalization of C(sp²)-H bonds of arenes and their application in organic synthesis.

In the first chapter, recent advancements in the transition metal catalysed sp² C-H functionalization of aromatic compounds by the installation of directing groups like amide, carbamate and ketimines are described concisely.

In the second chapter, a general protocol for iridium catalyzed direct C-H amidation of cyclic N-sulfonyl ketimines using sulfonyl, acyl and aryl azides as nitrogen source is discussed. Benefiting from the robustness and high efficiency of this transformation, a variety of functional groups were well tolerated during this mild process. With the use of sultams as directing group, monoamidation products can be produced efficiently in excellent ortho-selective manner, providing a simple method for the synthesis of biologically relevant aminosultam compounds.

In the third chapter, we reported a synthetic protocol for the trifluoroethylation of N-alkyl benzamides with mesityl(2,2,2-trifluoroethyl)iodonium salt. The very mild reaction condition employed allows a compatibility of a vast variety of...
synthetic useful functional groups. Further, we isolated the dimeric palladacycle complex with arene amide and carried out some mechanistic studies.

In chapter four, we described a new synthetic route to *meta*-arylated phenol and its derivatives. We achieved this transformation by employing cheap copper catalyst under mild conditions using phenol carbamates and diaryliodonium salts as coupling partners. The reported method is compatible with a broad range of phenols as well as diaryliodonium salts. The *meta*-arylated carbamate products obtained from this reaction can be further functionalized to get multisubstituted biaryl systems.
CHAPTER 1

INTRODUCTION
In modern chemistry organic synthesis direct functionalization of C-H bond has evolved as a powerful tool to synthesis complex molecules starting from simple synthons and thus increasing the efficiency of this transformation. In recent years, an enormous progress has been achieved in transition metal catalyzed C-H functionalization to discover many pioneering works.\(^1\) However, controlling the site selectivity and strong C-H bond cleavage are the two challenges in these transformations. The use of directing group can solve these challenges. The functionalizable C-H bond can be activated by the initial coordination of directing groups with transition metal (Scheme 1-1).

![Scheme 1-1. Directing group assisted C-H activation](image)

In the past three decades, many directing groups, such as amides, ketones, ester, carboxylic acids, sulfonamides, aldehydes, esters, imines, carbamtes etc. have been employed to achieve site selective C-H functionalization. As the directing group chemistry is too vast, here we are going to discuss about only some particular groups, which have been utilized for C-H activation projects of current thesis.

1.1 Amide directed C-H functionalization

Among the directing groups reported to date, amide provides vital platform for the optimization and discovery of new transformations though C-H activation because of their ability to coordinate with the transition metals. An enormous efforts have
been put forward to explore the utility of amide directing group which coordinates to the metal through oxygen and nitrogen atoms.

### 1.1.1 C-H functionalization catalyzed by Palladium

In 2002, Leeuwen et al. developed palladium catalyzed oxidative coupling reaction to form ortho-olefinated anilides at room temperature with acrylates (Scheme 1-2). This one was the first report to employ amide as a directing group. Followed by this discovery, many studies of anilide olefination have been reported.

![Scheme 1-2. ortho-olefination of anilides with acrylates](image)

Although achieved much success in olefination, employing aliphatic olefins for these transformations was a challenge because of β hydrogen elimination possibility. Recently Jiang and co-workers reported a transformation to get functionalized indolines via a reaction between anilides and norbornene in presence of palladium catalyst (Scheme 1-3).

![Scheme 1-3. Coupling of anilides with norbornenes](image)
In 2005, Daugulis reported the arylation of anilides in presence of palladium catalyst (Scheme 1-4).\textsuperscript{5} They achieved this transformation by employing AgOAc and aryl iodides to provide a range of diarylated anilides.

![Scheme 1-4. Arylation of anilides catalyzed by palladium](image)

Arylation by using organometallic reagents via C-H bond oxidative coupling is a challenging task.\textsuperscript{6a} This pioneer work of applying boronic acids as the coupling partner to achieve arylation of the arenes directed by acetamino group was reported by Shi et al. in 2007 (Scheme 1-5a).\textsuperscript{6b} Later the same group extended their oxidative arylation strategy using arylsilanes as the coupling partners for the first time (Scheme 1-5b).\textsuperscript{6c} Later Shi and co-workers developed double C-H activation strategy to arylate anilide derivatives in presence of palladium catalyst and copper additive (Scheme 1-5c).\textsuperscript{6d} Employing simple arenes as the coupling partner in place of metallic aromatics or aryl halides was the striking feature of this transformation.

![Scheme 1-5. Arylation of anilides with various arylating agents](image)
But this reaction did not find vast application because of the requirement of using arenes as solvents. Later Buchwald et al. developed a coupling reaction with 4-11 equivalents of simple arenes to obtain biaryls in presence of palladium catalyst in TFA (Scheme 1-6).  

\[ \text{Scheme 1-6. ortho-arylation of anilides} \]

In 2010, Dong et al. developed an advanced method for the arylation of benzamides and phenylacetamides by using sodium persulfate as the oxidant (Scheme 1-7). They were able to study the mechanistic pathways of this transformation by isolating the bridged bimetallic Pd-complex.

\[ \text{Scheme 1-7. Pd-catalyzed ortho-arylation of arenes} \]

Recently, You and co-workers reported an arylation reaction of anilides by employing [Pd(TFA)]\(^+\) catalyst at room temperature (Scheme 1-8). The same group extended their strategy to achieve ortho-acetoxylation of anilides.

\[ \text{Scheme 1-8. Arylation at room temperature} \]
In 2014, aryl acylperoxides have been utilized as arylating agents for the decarboxylative arylation of anilide derivatives under Pd-catalysis by Wang et al. (Scheme 1-9). They also reported the synthesis of phenanthridinones by the cyclisation reaction followed by decarboxylation using N-methoxyarylamides as starting materials.

![Scheme 1-9](image)

**Scheme 1-9. Decarboxylative ortho-arylation of anilides**

Yu and co-workers demonstrated carbon monoxide mediated ortho-carboxylation of anilide derivatives under palladium catalysis to provide an efficient route for the synthesis of biologically important synthons. They adapted relatively acidic conditions using HOAc as co-solvent and p-TsOH as an additive (Scheme 1-10).

![Scheme 1-10](image)

**Scheme 1-10. ortho-C-H carboxylation**

In 2010, Ge et al. described ortho-acylation of anilides in presence of palladium catalyst with decarboxylation. Both aliphatic and aryl α-oxocarboxylic acids gave products in good to excellent yields at room temperature by releasing CO$_2$. C7-acylated indolines can be prepared by applying this method. Later, Wang, Kwong and Yu employed readily available aliphatic and aromatic aldehydes to acylate...
anilide derivatives by using TBHP as oxidant. Even toluene and benzyl alcohols can be used as the acylating reagents in presence of excess TBHP (Scheme 1-11).

Tan et al. described ortho-esterification of anilides in presence of palladium catalyst with glyoxylates (Scheme 1-12a). Later You’s group reported the esterification of anilides employing commercially available DEAD as source of ester group at room temperature and proposed a mechanism involving Pd(II)/Pd(IV) catalytic cycle (Scheme 1-12b).

Tan et al. described ortho-esterification of anilides in presence of palladium catalyst with glyoxylates (Scheme 1-12a). Later You’s group reported the esterification of anilides employing commercially available DEAD as source of ester group at room temperature and proposed a mechanism involving Pd(II)/Pd(IV) catalytic cycle (Scheme 1-12b).
N-nosyloxocarbamates have been used as nitrogen source in palladium catalyzed amidation reaction of anilide derivatives (Scheme 1-13)\textsuperscript{18}. The reaction was compatible with ample functional groups. They proposed the involvement of dimeric Pd(III) or Pd(IV) complex.

\[ \text{Scheme 1-13. Anilide amidation by palladium catalyst} \]

The use of N-flurobenzenesulfonamide (NFSI), an oxidant and fluorine source as an aminating source has been disclosed by Zhang et al. in 2011. Anilides were either ortho- or para-aminated using NFSI in presence of palladium catalyst (Scheme 1-14)\textsuperscript{19}.

\[ \text{Scheme 1-14. NFSI mediated amination of anilides} \]

Formation of C-X bond by activating C-H bond was undisclosed until Shi et al. report in 2006. They achieved the regioselective formation of C-X bond by the
chelating effect of amide group using palladium catalyst and CuBr$_2$ or CuCl$_2$ as halide sources (Scheme 1-15)$^{20}$.

![Scheme 1-15](image)  
**Scheme 1-15.** Halogenation of anilides with copper halides

Further advancement in constructing C-X bond was achieved by Bedford’s group. They used p-toluenesulfonic acid as an additive for this transformation in presence of palladium catalyst employing N-halosuccinimides as halide sources at ambient temperature (Scheme 1-16)$^{21}$.

![Scheme 1-16](image)  
**Scheme 1-16.** N-halosuccinimide mediated halogenation of anilides

Aryl alkyl ether formation was disclosed by Wang’s group using amide as a directing group under Pd-catalysis at room temperature (Scheme 1-17)$^{22}$. An array of aryl alkyl ethers can produced by this method by the ortho-alkoxylation of anilide derivatives.

![Scheme 1-17](image)  
**Scheme 1-17.** ortho-alkoxylation of anilides

The study of ortho-trifluoromethylation of anilides and its mechanism was described by Shi et al. in 2013 using palladium catalysis (Scheme 1-18)$^{23}$. They employed
Umemoto’s salt as a source of trifluoromethyl group and achieved regioselective synthesis of variety of trifluoromethylated anilides and converted these products into many active molecules by known methods.

Scheme 1-18. ortho-Trifluoromethylation of anilides

In 2011, Yu et al. reported Pd-catalyzed the ortho-arylation of aromatic amide derivatives using simple arenes as arylating source (Scheme 1-19)\textsuperscript{24}. The preferred para-selectivity in this reaction was suppressed by using NFSI as an additive to control regioselectivity. The mechanism studies of this transformation revealed the involvement of two C-H activation process.

Scheme 1-19. Pd-catalyzed the ortho-arylation of aromatic amide

The ability of simple amide as directing group was explored by Wang’s group by developing Pd-catalysed ortho-arylation of simple benzamide with aryl iodides (Scheme 1-20)\textsuperscript{25}. These methods provide an alternative platform to form novel biaryl derivatives.
In 2011, Zhu et al. reported a method to form isoindolinones by the olefination/annulation reaction of benzamide derivatives with variety of alkenes using tosyl amide as directing group in presence of palladium catalyst (Scheme 1-21). The reaction was environmentally benign process as it employed molecular oxygen as oxidant and produced water as the only byproduct.

In 2013, Kim et al. achieved the acylation of phenylacetamides catalyzed by palladium with α-oxocarboxylic acids under mild conditions (Scheme 1-22). They successfully synthesized monoacylated and bisacylated products with unsymmetrical and symmetric phenylacetamides respectively.

Zhao et al. reported the synthesis of hydroxy isoindolines from benzaldehyde and N-OMe benzamides using palladium catalyst (Scheme 1-23). This method had advantages over the previous reported method such as atom economy and shorter time.
Scheme 1-23. Synthesis of hydroxy isoindolines

Yu et al. explored a new directing group in 2011 to achieve $sp^2$ C-H functionalization. They used sulfonamide as an effective directing group to carry out reactions like arylation, olefination, alkylation, carbonylation, carboxylation and iodination (Scheme 1-24).

Scheme 1-24. C-H activation directed by sulfonamide group

1.1.2 Rh catalyzed C-H functionalization

In recent years, Rh catalysts have been widely used in C-H functionalization reactions. In olefination reaction of benzamides and acetanilides Rh catalysts exhibit significance advances over palladium catalysts such as high reactivity, functional group tolerance and lower catalyst loading. In 2010, Glorius et al. reported Rh catalyzed ortho-vinylation and olefination of acetanilide derivatives (Scheme 1-25).
Lu and co-workers developed a method in 2013, to synthesis ortho-olefinated phenols in presence of Rh catalyst with alkenes and N-phenoxyacetamides under mild conditions (Scheme 1-26). The N-O bond served as an internal oxidant for this alkenylation reaction.

In 2014, Wang et al. achieved the ortho-alkenylation of N-phenoxyacetamides under Rh catalysis using diazoesters or N-tosylhydrazones as coupling partners (Scheme 1-27). The method was applicable to a range of substances to produce ortho-alkenyl phenol derivatives in good to excellent yields.
In contrast to alkynes and alkenes, allenes are less explored as coupling partners in C-H functionalization reactions. Recently, Glorius et al. reported Rh-catalyzed the synthesis of 3,4-dihydroisoquinolin-(2H)-ones by the annulation of allenes and N-pivoloyloxy benzamides (Scheme 1.28)\(^{36}\).

\[
\begin{align*}
\text{Scheme 1-28. Annulation with allenes}
\end{align*}
\]

In 2013, Ma and group reported the synthesis of polysubstituted allenylsilanes by Rh catalyzed allenylation of N-methoxybenzamides under mild conditions (Scheme 1-29)\(^{37}\). The method is applicable to broad range of amide derivatives with high efficiency. The products were obtained at room temperature and the moisture or air did not influence the reaction yields.

\[
\begin{align*}
\text{Scheme 1-29. Synthesis of polysubstituted allenylsilanes}
\end{align*}
\]

Cheng et al. in 2012 developed Rh(III) catalyzed dual C-H activation of N-methoxybenzamides with aryl boronic acids to produce substituted phenanthridinones\(^{38}\) via C-C/C-N bond formation in good yields (Scheme 1-30)\(^{39}\). Equivalents of AgOAc was proved crucial for the reaction to get the highest yields. Later same group developed one more method to synthesis phenanthridinones by
replacing aryl boronic acid with aryltriethoxysilanes as coupling partner (Scheme 1-31)\textsuperscript{40}.

![Scheme 1-30. Arylation of arylboronic acids](image)

Scheme 1-30. Arylation of arylboronic acids

![Scheme 1-31. Arylation with arylsilanes](image)

Scheme 1-31. Arylation with arylsilanes

In 2012, Glorius and co-workers disclosed Rh(III)-catalyzed double C-H activation to provide biaryl compounds through a cross-coupling reaction between aryl halides and benzamides (Scheme 1-32)\textsuperscript{41}. To note, the halogens survived without taking part in the reaction. A range of benzamides were explored to get ortho-arylated products in good to excellent yields.

![Scheme 1-32. Rh(III)-catalyzed double C-H activation](image)

Scheme 1-32. Rh(III)-catalyzed double C-H activation

Following this, Glorius et al. extended their Rh(III)-catalysed dehydrogenative coupling reaction with simple arenes to react with benzamide derivatives to get biaryl products in moderate to good yields (Scheme 1-33)\textsuperscript{42}. The reaction was promoted by polybrominated benzene, which served as a cooxidant/additive.
Allylarenes are important motif in biologically active medicinal compounds and natural products. C-H allylation by C-H functionalization is rarely explored. Glorius et al. reported the Rh-catalyzed direct C-H allylation of benzamide employing readily available allyl carbonate as coupling partner (Scheme 1-34). Mechanistic studies revealed that concerted metallation-deprotonation is the vital step in this transformation.

In 2014, You et al. used Wilkinson catalyst [Rh(PPh₃)₃Cl] instead of classical [RhCp*Cl₂]/AgSbF₆ for regioselective coupling of heteroarenes with aromatic amine derivatives to form aryl-heteroaryl compounds (Scheme 1-35). The new catalytic system was more potential and less expensive than the classical one.

Alkynes are important structural features in many natural products. Transition metal catalyzed C-H alkylation is a vital tool to introduce alkyne functionality group. In
2014, Loh et al. reported the ortho-C-H alkylation of using hypervalent iodine reagent as alkyne source directed by amide group in presence of rhodium(III) catalysis (Scheme 1-36)\(^{45}\). The reaction occurs at room temperature yielding products with excellent regioselectivity.

![Scheme 1-36. Alkynylation of benzamide derivatives](image)

Rhodium-catalyzed acylation of benzamides was reported by Kim and group in 2011 using aldehydes as acyl source (Scheme 1-37)\(^{46}\). An array of biologically important functional aryl ketones were prepared from various aldehydes and benzamides employing silver carbonate as an oxidant.

![Scheme 1-37. ortho-acylation of benzamides](image)

In 2010, Fagnou and co-workers described the synthesis of pyrroles and indoles by Rh(III)-catalyzed C-H functionalization/annulation of enamines and acetanilides with internal alkynes (Scheme 1-38)\(^{47a}\). The catalyst \([\text{Cp}^*\text{Rh(MeCN)}]_3[\text{SbF}_6]_2\) used in this method in contrast to catalyst \([\text{RhCp}^*\text{Cl}_2]_2\) used in their previous report\(^{47b}\) had advantages like milder conditions and higher efficiency. Molecular oxygen was used as terminal oxidant.
Isoquinolones are common motifs in drugs, bioactive molecules and natural products. In 2010, Guimond et al. developed Rh(III)-catalysed annulation reaction of alkynes with benzhydroxamic acid derivatives (Scheme 1-39a)48a. The method was applicable to wide variety of alkyne and arene derivatives employing very mild conditions to produce isoquinolones in moderate to good yields. Later, the same group reported a new method for the synthesis of isoquinolones by modifying their previous procedure using terminal alkene and alkynes as coupling partners with arenes (Scheme 1-39b)48b. A detailed mechanistic studies have been conducted and proved the involvement of N-O bond as an internal oxidant48c.

α-(psuedo)halo ketones were used in cross-coupling reaction developed by Glorius et al. in 2014 to form N-heterocycles in presence of Rh(III)-catalysis under mild conditions (Scheme 1-40)49.
Azepine and its analogues are present in various synthetic compounds and natural products. Glorius and group reported intermolecular annulation reaction catalyzed by rhodium(III)-catalyst between unsaturated ketone or aldehyde with readily available benzamides (Scheme 1-41). They employed PivOH as additive and reaction was very efficient producing water as the only byproduct. A wide range of azepines were synthesized in excellent yields.

![Scheme 1-41. Cyclization of amides](image)

Rovis et al. described the synthesis of dihydroisoquinolines by alkene migratory insertion reaction with benzhydroxamic acid derivatives and alkene. Di-tert-butylcyclopentadienyl ligand was used to achieve high regioselectivity over classical Cp* ligand (Scheme 1-42).

![Scheme 1-42. Synthesis of dihydroisoquinolines](image)

Fused heterocycles with nitrogen atom are prepared from the Rh(III)-catalyzed [4+2] annulations between alkynes and carboxamides. Application of this strategy for pyridine derivatives is difficult as they are electron deficient and suffer low reaction
rate and poor selectivity. In 2013, Huckins’s group reported the C-H activation/annulation reaction of pyridine N-oxides with alkene or alkynes to provide N-oxide heterocycles (Scheme 1-43)\(^52\).

![Scheme 1-43. Synthesis of naphthyridinones](image)

Shi et al. employed carboxylic acid derivatives in C-H activation/annulation reaction with alkynes to form an array of indenone derivatives (Scheme 1-44)\(^53\). N-Acyloxazolidinone was selected as effective directive group for this transformation. Decaline was suitable solvent for the reaction.

![Scheme 1-44. C–H activation/annulation of benzimides](image)

Addition of internal alkynes with sulfonamide derivatives in presence of rhodium(III)-catalyst to form synthetically valuable sultams was reported by Cramer’s group 2012 (Scheme 1-45)\(^54\). Molecular oxygen and copper acetate were used as terminal oxidants to obtain sulfonamides in high yields.

![Scheme 1-45. Synthesis of Sultams](image)
Rh(III)-catalyzed C-H activation/cyclisation of methylenecyclopropanes and benzamides to synthesis spiro dihydroisoquinolinones and furan fused azepinones was reported by Cui and group (Scheme 1-46). Mechanistic studies revealed the involvement of concerted metalation/deprotonation pathway.

**Scheme 1-46.** Rh(III)-catalyzed C-H activation/cyclisation

In 2012, Park et al. demonstrated the synthesis of 2-pyridine derivatives by Rh(III)-catalyzed intramolecular annulation of alkyne tethered hydroxamic esters (Scheme 1-47a). The obtained products in good yields under mild conditions without employing any external oxidants. This method can be successfully applied for the synthesis of biologically active phenanthroindolizidine alkaloids. Following this, Zhou and Li reported the intramolecular C-H activation/annulation reaction catalyzed by rhodium(III)-catalyst (Scheme 1-47b).

**Scheme 1-47.** Rh(III)-catalyzed intramolecular annulation
Zhao and co-workers demonstrated synthesis of 1,2-oxazepines by Rh(III)-catalyzed intermolecular [4+3] annulation with α, β-unsaturated aldehydes and N-phenoxyacetamides (Scheme 1-48). The azepine products obtained were transformed into synthetically useful chroman derivatives. Earlier, Liu et al. described Rh(III)-catalyzed redox neutral coupling of alkynes and N-phenoxyacetamides (Scheme 1-49). They obtained benzofurans or ortho-hydroxyphenyl substituted enamides in good yields with high regioselectivity.

Scheme 1-48. Annulation of N-phenoxyacetamides

Scheme 1-49. Redox-neutral coupling of alkynes and N-phenoxyacetamides

Glorius et al. reported a convenient method to provide arylamine products. They developed C-H amination reaction in presence of rhodium(III)-catalyst using N-chloramines as nitrogen source and N-pivaloyloxy benzamides as coupling partner (Scheme 1-50).

Scheme 1-50. Amination using N-chloramines
In 2014, Zhag and co-workers demonstrated C-H amination of aromatic amide derivatives employing readily available N-boc hydroxyamine as nitrogen source by the combined synergetic catalysis of rhodium and copper (Scheme 1-51)\(^{60}\). This efficient protocol was applied to obtain various bioactive benzo[c]isoxazole derivatives.

![Scheme 1-51. Hydroxyamination of aryl C–H bonds](image)

The first example of rhodium(III) catalyzed halogenation of arenes was reported by glorius’s group in 2012. They developed convenient synthesis method for the regioselective ortho-halogenation by employing N-halosuccinimides as halide sources and amides as effective directive group (Scheme 1-52)\(^ {61a}\). Later the same group extended their method for the halogenation of vinylic C-H bonds for the synthesis of substutured haloacrylic derivatives\(^ {61b}\).

![Scheme 1-52. Rh(III)-catalyzed halogenation of amides](image)

1.1.3 Ru-catalyzed C-H functionalization

Compared to the development of rhodium and palladium catalysis, ruthenium catalysts are less explored in C-h activation and annulation reactions. Being less expensive than rhodium, ruthenium provides room for the development of new
transformation reactions. The \([\text{RuCl}_2(\text{p-cymene})_2]\) complex has been used as catalyst in C-H activation reactions due to its selectivity and reactivity. Ackermann’s group reported the first oxidative annihilation reaction catalyzed by ruthenium using benzamides and alkynes as reacting partners, to form isoquinolone derivatives (Scheme 1-53a)\(^{62a}\). Later, they extended this method to form 2-pyridones with the annihilation reaction of acrylamides with alkynes (Scheme 1-53b)\(^{62b}\).

\[
\begin{align*}
\text{Scheme 1-53. Annihilation reaction catalyzed by ruthenium} \\
\end{align*}
\]

In 2012, Ackermann and co-workers developed cross-dehydrogenative alkenylation of benzamides and anilides catalyzed by cationic ruthenium(II) complex (Scheme 1-54)\(^{63}\). Water was used as a solvent.

\[
\begin{align*}
\text{Scheme 1-54. Alkenylation of benzamides and anilides} \\
\end{align*}
\]

Wang et al. disclosed the first report of C-H olefination of N-methoxybenzamides with various olefinic coupling partners using ruthenium catalyst (Scheme 1-55)\(^{64}\). Different products were obtained by choosing variety of olefins such as acrylates,
styrenes and norbornenes in good yields. Detailed mechanistic investigations suggested C-H bond activation by carboruthenation, followed by reductive elimination to provide desired products.

Scheme 1-55. Ru-catalysed C-H bond olefination

Ruthenium catalyzed ortho-arylation of benzamide derivatives was achieved by Jeganmohan et al. in 2012 using arylboronic acids as arylating agent (Scheme 1-56a)\textsuperscript{65a}. They even showed the alkenylation of N-alkyl benzamides employing alkenylboronic acids. The obtained products were further transformed into useful fluorenone derivatives. The same group extended their ruthenium catalyzed arylation strategy to acetalinide derivatives by some modifications (Scheme 1-56b)\textsuperscript{65b}. This methodology provided routes to synthesis carbazole and phenanthridine derivatives.

Scheme 1-56. Arylation of benzamides and anilides

Ackermann and co-workers reported ortho-selective hydroxylation reaction catalyzed by ruthenium with benzamides (Scheme 1-57)\textsuperscript{66}. The method has some
striking factors such as low catalyst loading, weakly coordinating amide directing group, high regioselectivity and efficiency. Later, they reported similar method to oxygenate aryl Weinreb amide derivatives to get hydroxylated products, which are further converted to corresponding aldehydes and ketones. The first report of Ru(II)-catalyzed mono- and dihydroxylation of anilide derivatives was disclosed by Rao et al. in 2013 using 2,6-difluorobenzoyl group as the directing group (Scheme 1-58).

![Scheme 1-57. ortho-selective hydroxylation](image)

![Scheme 1-58. Mono and dihydroxylaton of benzamides](image)

Yu et al. reported Ru(II)-catalyzed ortho-C-H amination reaction of aryl amides using weak cooradinating amide group as effective directing group employing O-benzoylhydroxylamines a nitrogen source (Scheme 1-59).

![Scheme 1-59. o-Amination of benzamide](image)
1.1.4 Ir, Cu, Co catalyzed C-H functionalization

Chang and group reported the first report of site selective C-H amidation of alkenes and aryls catalyzed by iridium using acyl azides as aminating source (Scheme 1-60a)\(^7\). They did not use any external oxidants for this transformations. Acyl azide, itself acted as internal oxidant producing nitrogen gas as the only byproduct of the reaction. This method was applicable to an array of substrates having different functional groups and amidated products were obtained in excellent yields. Later the same group, developed amination method of benzamides using commercially available anilines as amination source at ambient temperature (Scheme 1-60b)\(^7\). This is the first report, which made use of simple anilines for nitrogen source.

Carretero et al. described the halogenation of aryl sulfonamides catalyzed by copper catalyst using N-halosuccinimides as halide source (Scheme 1-61)\(^7\). Sulfonamides, being easily removable group, provides a route to synthesis various ortho-halogenated aniline derivatives of biological interest. Following year, the same group reported the copper catalyzed nitration of amide derivatives using nitric acid as nitrating source (Scheme 1-62)\(^7\).
Nakamura et al. developed alkylation of benzamides using cyclohexyl magnesium chloride and alkyl chloride in presence of cobalt catalyst at room temperature (Scheme 1-63). An ample range of alkyl chlorides were tolerated in this reaction giving products in good yields. Later, the same group reported the alkylation of 2-phenylpyridine and benzamides using alkyl Grignard reagents as alkyl source in presence of cobalt catalyst and air (Scheme 1-64).

1.2 Aryl carbamates directed C-H functionalization

Phenols and its derivatives are important motifs of many natural products and medicinal compounds. Hence substituted phenols and protected phenols have drawn
intensive attention from the synthetic community working on transition metal catalyzed C-H functionalization\textsuperscript{76}. A common strategy to access these phenol derivatives was reported by Snieckus and group directed \textit{ortho}-metallation of \textit{O}-phenylcarbamates\textsuperscript{77}. The restricted use of carbamates as a protecting was has been exploited by developing carbamate directed cross coupling reactions and Snieckus-Fries rearrangement\textsuperscript{78}.

Bedford and group, in 2009, described the \textit{ortho}-arylation of phenol carbamates catalyzed by palladium using either diaryliodonium salt or aryl iodide as arylating agent (Scheme 1-65)\textsuperscript{79}. Diaryliodonium salts gave exclusively mono-arylated phenols while aryl iodides yielded both mono- and diarylated products. Diaryliodonium salts insitu cleaved the carbamate group to form parental phenols, which can further transformed into useful dibenzopyranone derivatives through lactonization.

![Scheme 1-65](image)

\textbf{Scheme 1-65.} Arylation of carbamates with aryl iodide

Cross-coupling reactions to synthesis biaryl linkages from simple arenes are considered as atom economical and ecofriendly. Such transformation involves the cleavage of two C-H bonds to form new C-C bond. In 2010, Dong et al. described the arylation of \textit{O}-phenylcarbamates in presence of palladium catalyst using simple arene as coupling partner (Scheme 1-66)\textsuperscript{80}. TFA and Na\textsubscript{2}S\textsubscript{2}O\textsubscript{8} promoted the reaction
rate by playing their role as additive and oxidant respectively. Mechanistic studies revealed the involvement of Pd(0)/Pd(II) catalytic cycle.

![Scheme 1-66. Arylation of carbamates with simple arenes](image)

Fu and Liu reported Pd(II)-catalyzed acyloxy directed C-H arylation of phenol esters to synthesis various ortho-arylated phenol derivatives (Scheme 1-67)\(^81\). Triflic acid (TfOH) was used as an additive to adjust the electrophilicity of palladium and thus to stabilize the Pd(II) intermediates. The formation mono- and diarylated products can be controlled by stoichiometric addition of the reactants and tuning the temperature.

![Scheme 1-67. Arylation with diaryliodonium salt](image)

Liu et al. developed ortho-olefenation reaction catalyzed by Rh(III) species using phenyl carbamates as the starting material (Scheme 1-68)\(^82a\). Both styrenes and substituted acrylates gave corresponding olefinated carbamate products good to excellent yield. Mechanistic studies have been conducted to study the mode of reaction, which disclosed the pathway involving three major steps: ortho-C-H activation by acetate assistance, alkene insertion and β-H elimination. Loh and group reported similar transformation in the same year using rhodium catalyst\(^82b\).
Ackermann and group extended their interest in ruthenium catalyzed C-H functionalization reaction by developing ortho-alkenylation of phenol carbamates in 2012 (Scheme 1-69)\textsuperscript{83}. Ruthenium complex, being less expensive, moisture and air stable provides a platform for environment friendly transformation. Similar reaction of ortho-olefination was reported at the same time by two other research groups. All the reported methods\textsuperscript{84} employed Cu(OAc)\textsubscript{2}·H\textsubscript{2}O in stoichiometric amount to promote the reaction under atmospheric conditions.

Jeganmohan and group reported ruthenium catalyzed phenyl carbamate C-H bond alkenylation using alkynes as coupling partner (Scheme 1-70)\textsuperscript{85}. Various highly substituted and stereospecific alkene derivatives are obtained by this reaction. A wide range of alkyne and phenol carbamates have been explored for this transformation.
Acyl group of the carbamates have been used extensively as directing group in many transformations such as oxygenation, chlorination, bromination, borylation and decarboxylative acylation (Scheme 1-71). Nicholas et al. reported ortho-C-H bromination of aryl carbamates using NBs as the bromide source. Extensive mechanistic studies conducted by isolating series of cyclometalated species revealed the possibility of Pd(II)/Pd(IV) catalytic cycle. Following this, Rao et al. demonstrated the chlorination and bromination of carbamates at room temperature using NCS and NBS as halide source.

Kim et al. developed the ortho-acylation of phenol carbamates in presence of palladium catalyst using α-oxocarboxylic acid as acyl source employing ammonium persulfate as an oxidant. Though electron-releasing groups and halogens on aryl carbamates promoted the reaction, electron withdrawing groups did not favor the product formation.

Ackermann and group reported the ortho-oxygenation of aryl carbamates in presence of [RuCl₂(p-cymene)₂] catalyst using PhI(OAc)₂ as an oxidant. A variety of ortho-hydroxylated phenol derivatives have been synthesized using less expensive
ruthenium catalyst. In 2010, Sawamura et al. reported regioselective ortho-borylation of aryl carbamtes with immobilized monophosphine-Ir catalysis system.

### 1.3 Ketimine directed C-H functionalization

Ketimines and aldimines are prepared from readily available ketones and aldehydes respectively. Imines possess strong co-ordinating ability towards transition metals and thus directs the incoming groups. Hence they provide an easy access to modify and functionalize ketones and aldehydes. Here we are discussing the transformations reported using ketimines as effective directing groups. In 2000, Jun and group reported the first example of ortho-alkylation of arenes using imine as an effective directing group in presence of rhodium catalyst (Scheme 1-72)\(^87\). Imine as a directing group was way advantageous than ketones, as it tolerated broad range of functionalized alkenes for the coupling giving highly regioselective ortho-alkylated aryl ketones obtained after acid hydrolysis.

![Scheme 1-72. Alkylation of aromatic imines](image)

Ellmann and Bergmann developed rhodium catalyzed intramolecular alkylation of arenes assisted by imine. Dihydrobenzofuran, indane, dihydroindole and tetralone derivatives are prepared from intramolecular annulation of ortho-positin tethered allylamines and allyl ethers as coupling partner (Scheme 1-73a)\(^88\). But the developed method had disadvantages of high reaction temperature and low substance scope.
Later, the same group reported a method to enhance reactivity and expand the substance scope of the reaction at lower temperature employing $[\text{RhCl(coc)}_2]_2$ as catalyst with chiral phosphoramidate ligands (Scheme 1-73b).  

![Scheme 1-73. Annulation of aromatic amines](image)

In 2013, Yoshikai et al. described cobalt-$N$-heterocyclic carbene (NHC) catalyzed ortho-alkylation of imines with alkyl halides (Scheme 1-74). A wide variety of primary and secondary alkyl bromide and chlorides were tolerated in this transformation. The yield and selectivity were dependent on the selection of NHC ligands. Mechanistic investigation showed the formation of alkyl radical via SET mechanism.  

![Scheme 1-74. Alkylation catalyzed by cobalt](image)

The first example of ortho-olefination catalyzed by rhodium for aromatic ketimines with alkynes was reported by Jun and co-workers. In 2011, Yoshikai and group reported cobalt catalyzed ortho-alkenylation of imine derivatives with alkyne at ambient temperature (Scheme 1-75).
In 2002, Oi et al. reported the arylation of aromatic imines catalyzed by ruthenium with aryl bromide as arylating partner (Scheme 1-76)\(^3\). They studied the mechanism to explain the formation of ruthenacycle intermediate, followed by reductive elimination to form desired arylated products.

Ackermann reported the ortho-arylation of imines catalyzed by ruthenium using aryl chloride as coupling partner (Scheme 1-77)\(^4\). Reaction was well tolerated with both electron-poor and electron rich aryl chlorides.

Nakamura and group used diarylzinc reagents for the ortho-arylation of aromatic imines in presence of iron catalyst at room temperature to achieve broad substrate scope of the reaction (Scheme 1-78)\(^5\).
Reports of C-H activation by using N-sulfonyl ketimines have been discussed in chapter 2.

Though tremendous advances are achieved in transition metal catalyzed C($sp^2$)-H functionalization, discovery of new methods are always encouraged. In following chapters, we are going to discuss some new methods catalyzed by transition metals.

1.4 References


(b) Guimond, N.; Gorelsky, S. I.; Fagnou, K. J. Am. Chem. Soc. 2011, 133, 6449


CHAPTER 2

IR(III)-CATALYZED SELECTIVE AND MILD C-H AMIDATION OF N-SULFONYL KETIMINES WITH ORGANIC AZIDES
2.1 Introduction

2.1.1 Metal catalyzed C-N bond formation

In recent years, transition metal catalyzed C-H activation has gained a lot of attraction from the synthetic community to form new chemical bonds and thus forming new compounds.\(^1\) Though a number of methods are reported for carbon and nitrogen bond formation, among them, in modern synthetic chemistry transition metal catalyzed amination represents one of the significant and elemental C-N bond formation reactions.\(^2\) By facilitating introduction of versatile synthetic amine fragments onto a great diversity of arenes and heteroarens, these reactions find immense applications in medicinal chemistry, agrochemistry, natural product synthesis and material chemistry.\(^3\) Thus, it is not surprising that, in the past decades tremendous efforts have been made by synthetic chemists to develop reliable and advanced synthetic route to construct C-N bond.\(^4\) The inclusion of transition metal catalysts bring unique approaches to derivatize lesser functionality raw chemicals into versatile molecules of synthetic importance over the traditional organic transformations, which are mainly relying on the innate reactivity of functional groups.\(^5\) In principle, there are two approaches to form C-N bond via transition metal catalysis. The first approach involves the reaction of amines with alkene or aryl halides or psuedohalides partner to form new covalent C-N bond. The examples for this conventional method includes copper mediated amination developed by Ullmann-Goldberg and palladium mediated reaction developed by Buchwald-Hartwig.\(^6\) Despite the efficiency and versatility, these reactions require prefunctionalized species. The other approach to form C-N bond is to directly
functionalize hydrocarbon substrates by applying C-H amination strategy without prior installation of reactive groups. But this approach is only feasible under highly effective catalytic systems, which target the desired C-H bonds selectively.

An array of aminating reagents have been used in the transition metal catalyzed C-H amination reactions. The prefunctionalized amides and amines, being the most desirable amination sources, require use of external oxidants to catalyse the C-H amination. In other case, the aminating reagents, possessing polarized bonds derived from the functionalization of parental amine source readily react without any aid of external oxidants and cleaved oxidatively by the action of transition metals, thus helps to avoid the use of stoichiometric external oxidants for the catalytic process.

Among the different source of aminating reagents, here we discuss about the use of organic azides as aminating reagents. Organic azides are very easy to synthesize and convenient to handle. Organic azides have been considered as ecofriendly green reagents, as they release non-toxic nitrogen gas as the byproduct. Under the thermal and photo-irradiated conditions corresponding nitrenes are produced due to the decomposition of parental azides. Based on the nature of the substrates and reaction conditions, transition metal complexes react with azides to produce corresponding metal-nitrenoid species or metal-azide addition compounds. Further studies have disclosed the synthetic usefulness of both species in nitrogen-atom transfer reactions such as imination of sulfoxides, sulformidation, C-H amination and aziridination.
The use of organic azides as aminating source was seminally disclosed by Bach and coworkers in late 1990s.\(^9\) They found that in presence of acetylacetone, 10-20 mol\% of FeCl\(_2\) can catalyze the sulfide imidation with Boc\(_3\). Other metal salts such as RuCl\(_3\), Co(OAc)\(_2\), CuCl, Rh\(_2\)(OAc)\(_4\), FeCl\(_3\) and Fe(SO\(_4\))\(_2\) were less effective in this sulfimidation reaction (Scheme 2-1).

![Scheme 2-1. Sulfimidation reaction by Bach Group](image)

Later, Katsuki and co-workers reported highly enantioselective imidation of alkyl aryl sulifides catalyzed by Ru(salen) complex with arylsulfonyl azides at room temperature (Scheme 2-2).\(^10\) Furthermore, they even enriched the enantioselectivity by increasing steric bulkiness and electron-withdrawing effect of alkyl group.

![Scheme 2-2. Ru- catalyzed sulfimidation reaction by Katsuki group](image)
Following this, Bach and co-workers reported the synthesis of allylic sulfonamides by the reaction between allylic sulfides and BocN₃ \((\text{Scheme 2-3a})\).\textsuperscript{11a} Later Murakami and Katsuki demonstrated enantioselective imidation of allylic sulfides in presence of complex A, with tosyl azide \((\text{Scheme 2-3a, 3b})\).\textsuperscript{11b,c}

\[ \text{Scheme 2-3. Synthesis of allylic sulfonamides by Bach’s group} \]

Important arene moieties, Indole derivatives can be prepared by the intramolecular reaction from the decomposition of rhodium(II) species of acyl and vinyl azides \((\text{Scheme 2-4})\).\textsuperscript{12} To surprise, rhodium complexes generate nitrene intermediates from azides thus involving insertion of nitrenes into \(sp^2\) C-H bond via stepwise electrophilic additions.
In recent years, Chang and Musaev demonstrated the reaction of alkyl azide with benzamide derivatives in presence of cyclometallated species of metals (Rh, Ir and Co) to introduce amine moiety in the arenes (Scheme 2-5). They also studied catalytic activity of different metals by DFT calculations.

\[
\text{Scheme 2-5. Cobalt catalyzed amination by Chang’s group}
\]

Kanai and co-workers extended the use of azides for selective $sp^2$ C-H amination. They pioneered the use of cobalt catalysts for this transformation. They synthesized air stable cobalt catalyst species from the commercially available cobalt precursor cobalt octacarbonyl. They revealed selective and efficient amidation of N-pyrimidylindole with sulfonyl azides. Later the same group, extended their applicability of cobalt catalyst to aminate N-pyrimidylindoles with phosphoryl azides without any aid of external acetate base source (Scheme 2-6).
Later Zhu and co-workers employed acyl and sulfonyl azides to achieve C-H amidation by chelation assistance catalyzed by copper catalyst. They performed the reaction at high temperature, without employing any external oxidants to get satisfactory aminated products. The same reaction conditions were applied to imine and amidine substrates to isolate indazole derivatives through a tandem process (Scheme 2-7)\textsuperscript{15}.

\begin{scheme}
\includegraphics{scheme2-6.png}
\end{scheme}

\textbf{Scheme 2-6.} Amidation works by Kanai’s group

Later many research groups explored the reactivity of organic azides with different arenes to aminate C-H bond of aromatic ring by the directing group effect employing Ru(II) catalyst (Scheme 2-8).\textsuperscript{16} In fact, the explored substances are rather analogous in nature. All the research groups explored the ruthenium catalyst almost in similar
conditions employing silver salts and at a reaction temperature of 80-120 °C. A number of directing groups possessing \(N\)- and \(O\)-chelators were utilized well to get \(sp^2\) C-H amination.

\[
\text{Scheme 2-8. Ruthenium catalyzed amination reports}
\]

In 2012, Chang et al. reported a new protocol for amination using organic azides. They disclosed the reactivities of various azides including alkyl\(^{17a}\), sulfonyl\(^{17b}\) and aryl\(^{17c}\) with alkene and arene substrates bearing ketone, amide or pyridine directing groups (Scheme 2-9). The developed method was environmental friendly producing \(N_2\) as the only byproduct.
Further this protocol was extended to the introduction of amine group through an array of substrates including 2,4-diarylquinolines, 2-pyrimidylindoles, 2-arylpurines and quinolone-8-carbaldehyde. Lu et al. reported amination method using aryl azides with 2-phenylpyridines in water.\textsuperscript{17d} The synthetic utility of this reaction was explored by different groups. Glorious reported Rh catalyzed synthesis of 1\textit{H}-indazoles by amidation followed by Cu mediated N-N coupling reaction (\textbf{Scheme 2-10a}).\textsuperscript{18a} Ellman demonstrated the synthesis of nitrogen heterocycles using azides as aminating source (\textbf{Scheme 2-10b}).\textsuperscript{18b} Lee et al. developed a method to synthesize 2-aryl-2\textit{H}-benzotriazoles by the amidation of azobenzenes (\textbf{Scheme 2-10c}).\textsuperscript{18c}
Scheme 2-10. Amination under Rh catalysts

Iridium complexes are known to display remarkable reactivity toward stoichiometric C−H activation of hydrocarbons,\(^\text{19}\) it is tempting to investigate the corresponding catalytic functionalizations to introduce functional groups directly into inert molecules. Such a perspective, however, has been less explored, mainly due to the inherent stability of iridacyclic complexes. Inspired by significant advances in the Cp*Rh(III)-catalyzed C−H amination, the Chang group envisioned the use of a Cp*Ir(III) complex, group 9 congener, for analogous transformations.\(^\text{20}\) Indeed, acyl azides displayed remarkable reactivity toward C−H amidation under Ir-catalyzed mild conditions. Acyl azides were found to be a challenging amino group source in the Cp*Rh(III) catalysis because of their thermal instability, thus leading to poor amination efficiency. In contrast, the Cp*Ir(III) catalyst system allowed a highly efficient C−H amidation with acyl azides that were not decomposed to isocyanates via Curtius rearrangement under mild optimized conditions (Scheme 2-11).
A broad range of combinations in regard to substrates and organic azides has been extensively investigated for the synthesis of valuable C–H aminated product motifs, as summarized in Table 2-1. Remarkably diverse substrates including aryl carbamates,\textsuperscript{21a} triarylphosphine oxides,\textsuperscript{21b,c} quinoline N-oxides,\textsuperscript{21d} benzoic acids,\textsuperscript{21e,f} alkyl benzoates,\textsuperscript{21g} indolines,\textsuperscript{21h} indoles,\textsuperscript{21i,j} acylsilanes,\textsuperscript{21k} aryl nitrones,\textsuperscript{21l} benzylic amines,\textsuperscript{21m} and 2-aryl-1,2,3-triazole N-oxides\textsuperscript{21n} were successfully coupled with sulfonyl azides as the amidating sources. In addition, azido formates,\textsuperscript{21o} phosphoryl azides,\textsuperscript{21p,q} aryl azides,\textsuperscript{21a} and alkyl azides\textsuperscript{21r} were also found to work as efficient amino precursors under the same catalytic system. Recently, Lu utilized this C–H amidation strategy for the synthesis of functionalized quinazoline-2,4(1H,3H)-diones, where a subsequent intramolecular cyclization was conducted.\textsuperscript{21s} Recently, Bolm disclosed a mechanochemical process for the Ir-catalyzed C–H amidation in solvent-free conditions.\textsuperscript{21t}
More recently, Chang and co-workers reported an Ir-catalyzed intermolecular amidation of sp³ C–H bonds by using organic azides as a powerful amino group source. This amidation occurs selectively at the methyl sp³ C–H bonds in a wide range of substrates (Scheme 2-12).²² Importantly, the reaction works highly efficiently under mild conditions and in the absence of external oxidants to release nitrogen gas as a single byproduct, thus making this protocol applicable to the late stage C–H functionalization of complex compounds bearing labile functional groups.

Table 2-1. Iridium catalyzed C-H amination reports

<table>
<thead>
<tr>
<th>Scheme 2-12</th>
<th>Ref 20</th>
<th>Ref 21a, 21t</th>
<th>Ref 21o</th>
<th>Ref 21p</th>
<th>Ref 21a</th>
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<td>Ref 2C</td>
<td>Ref 21a-21c</td>
<td>Ref 21e-21g</td>
<td>Ref 21h</td>
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<td>Ref 21a</td>
<td>Ref 21c</td>
<td>Ref 21h</td>
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<tr>
<td>Scheme 2-15</td>
<td>Ref 21h</td>
<td>Ref 21a, 21h-21j</td>
<td>Ref 21o</td>
<td>Ref 21p</td>
<td>Ref 21h</td>
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</tr>
<tr>
<td>Scheme 2-16</td>
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<td>Ref 21c</td>
<td>Miscellaneous</td>
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<td></td>
</tr>
</tbody>
</table>

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52
The Ir-catalyzed amidation of sp³ C–H bonds was also applied to the preparation of 1,2-amino alcohols starting from ketoxime derivatives. Taking advantage of the strong coordinating ability of the ketoxime directing group, the amination was designed to occur at the β-methyl group selectively. Importantly, removal of the directing group was facile, leading to the corresponding β-hydroxyl sulfonamides in high yields (Scheme 2-13).

A number of nonheme Fe-based catalysts have been extensively investigated on the basis of the C–H amination approach, especially in recent years. Among those, the Betley group’s report on the utility of iron–dipyrromethane complexes is particularly noteworthy. A high-spin Fe(II) complex B was shown to catalyze an amination of
toluene solvent with alkyl azides at the benzylic C(sp³)−H bonds. Stoichiometric reactions enabled the isolation of an iron complex C, and the spin state of this species was determined to be S = 2 with the aid of 57Fe Mössbauer spectroscopy and also by theoretical calculations. The combined results indicated that the high-spin Fe(III) center is antiferromagnetically coupled to the imido-based ligand. Subsequent addition of toluene to C readily provided the C−H aminated product (Scheme 2-14).

Scheme 2-14. Iron catalyzed amination with organic azides

The same research group further characterized analogous iron complexes that are capable of catalyzing C−H amination processes. For instance, by having a sterically less-hindered tertbutyl substituent in the dipyrrinato ligand, a dimeric Fe(III) complex D bearing a bridging imido moiety was successfully isolated. The authors presented a catalytic C−H amination of cyclohexene and toluene in more details (Scheme 2-15).
scheme 2-15. Betley’s report on sp³ C-H amination catalyzed by iron

2.1.2 Cyclic N-Sulfonyl Ketimines (cyclic-NSK)

Being a ubiquitous motif in many pharmaceuticals and biologically active molecules, cyclic N-sulfonyl ketimines, are considered as an important class of sulfur and nitrogen containing heterocyclic molecules.²⁶ N-sulfonyl ketimines are valuable synthons to access a myriad of prevalent nitrogen containing molecules.²⁷ Although cyclic N-sulfonyl ketimines are commonly used building blocks²⁸ and chiral auxiliaries²⁹ in many organic transformations, their use as a directing group for C-H functionalization is still in a primitive stage. In contrast, acyclic N-sulfonyl ketimines are well explored as directing groups.³⁰ The limited exploration of these sultams as directing groups may be attributed to the lower coordination ability of nitrogen atom, due to the electron withdrawing effect of conjugated sulfonyl moiety.

Though Li et al. reported the synthesis of indenamines from N-tosyl aldimines and internal alkynes by C-H activation using Ru catalyst (Scheme 2-16),³¹ the first C-H
functionalization of cyclic N-sulfonyl ketimines to form spirocyclic sultams with 1,3 dienes and alkynes was reported by Nishimura et al. and Dong et al. using Ir (Scheme 2-17)\textsuperscript{32} and Rh (Scheme 2-18)\textsuperscript{33} catalyst respectively. Later Wei group demonstrated olefination, arylation, allylation and vinylation of sultam derivatives utilizing Rh catalysts and cyclic N-sulfonyl ketimines (Schemes 19-22)\textsuperscript{34} as effective directing groups. In early 2016, Cramer reported the synthesis of chiral spirocyclic sultams using Rh complexes (Scheme 2-23).\textsuperscript{35} These approaches are generally limited to C-C bond formation and only one example features C-N bond construction.\textsuperscript{36} Our continuous research interest in C-N bond forming reactions,\textsuperscript{37} prompted us to investigate cyclic N-sulfonyl ketimine assisted amidation of C-H bonds. Described herein is a Cp*Ir(III)-catalyzed mild and effective diect C-H amidation of sultam derivatives using organic azides, which furnishes monoamidation products in a highly chemo and regioselective manner.

**Scheme 2-16.** Synthesis of Indanamines by Li’s group

**Scheme 2-17.** Reaction of cyclic-NSK with 1,3-dienes reported by Nishimura et al.
Scheme 2-18. Reaction of cyclic-NSK with alkynes reported by Dong et al.

Scheme 2-19. Alkenylation of cyclic-NSK

Scheme 2-20. Allylation of cyclic-NSK

Scheme 2-21. Vinylation of cyclic-NSK

Scheme 2-22. Arylation of cyclic-NSK
2.2 Result and Discussions

In preliminary experiments, readily accessible sultam derivative 1a, was selected as the model substrate. Initial reaction of 1a with p-toluenesulfonyl azide 2a, in the presence of [Cp*IrCl$_2$]$_2$ and AgNTf$_2$ in DCE at room temperature resulted in no conversion. To our surprise, when the reaction was heated at 60 °C, complete conversion was observed within 4 hours and product 3aa was isolated in 80% yield, without the aid of any external oxidants. Other comparative catalysts Rh$^{III}$, Co$^{III}$ were ineffective for this conversion, while Ru$^{II}$ showed some activity, but in inferior effectiveness. Test reactions justified vital roles of the Iridium catalyst and the additive. The effects of reaction temperature and additives were also examined. It was found that decreasing the temperature resulted in lower conversion, while elevated temperatures furnished monoamidated sultam 3aa as sole product in quantitative yield in shorter time. AgNTf$_2$ provided optimal results among a representative set of silver additives. With this exciting results in hand, a systematic screening of solvents was performed. The reaction displayed a prominent solvent dependence characteristic. While THF, 1,4-dioxane, DCM, t-AmOH, MeOH and acetone afforded secondary results compared to DCE. The solvents possessing coordinating ability, such as DMF and MeCN, completely retarded the reaction. To
our delight, when reaction was performed in CF₃CH₂OH, product 3aa was isolated in excellent yield.

### 2.2.1 Screening of catalyst

![Chemical structure]

<table>
<thead>
<tr>
<th>Entry</th>
<th>catalyst (mol %)</th>
<th>additive (mol %)</th>
<th>temp (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[IrCp*Cl₂]₂ (4)</td>
<td>AgNTf₂ (16)</td>
<td>rt</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>2c</td>
<td>[IrCp*Cl₂]₂ (4)</td>
<td>AgNTf₂ (16)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>[RhCp*Cl₂]₂ (4)</td>
<td>AgSbF₆ (16)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>[Ru(p-cymene)₂Cl₂]₂ (4)</td>
<td>AgNTf₂ (16)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>[CoCp*I₂]₂ (4)</td>
<td>AgSbF₆ (16)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>[IrCp*Cl₂]₂ (4)</td>
<td>--------------</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR</td>
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<tr>
<td>7</td>
<td>--------------</td>
<td>AgNTf₂ (16)</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

*Reaction conditions: To a mixture of catalyst (4% mmol), additive (16 mol%) were added 1a (0.3 mmol), 2a (0.36 mmol), solvent (0.5mL) and allowed to stir for particular time at indicated temperature under air atmosphere. *isolated yield.

### 2.2.2 Screening of temperature
Entry | temp (°C) | time (h) | yield |
--- | --- | --- | --- |
1 | rt | 24 | NR |
2 | 30 | 24 | 22 |
3 | 40 | 24 | 30 |
4 | 50 | 24 | 60 |
5 | 60 | 4 | 80 |
6 | 70 | 3 | 82 |
7 | 80 | 2 | 91 |

*aReaction conditions: To a mixture of catalyst (4% mmol), additive (16 mol%) were added 1a (0.3 mmol), 2a (0.36 mmol), solvent (0.5mL) and allowed to stir for particular time at indicated temperature under air atmosphere. *bisolated yield.

### 2.2.3 Screening of additives

Entry | additive (mol%) | yield |
--- | --- | --- |
1 | AgNTf$_2$ (16) | 91 |
2 | AgPF$_6$ (16) | 75 |
3 | AgSbF$_6$ (16) | 69 |
4 | AgBF$_4$ (16) | 60 |
aReaction conditions: To a mixture of catalyst (4% mmol), additive (16 mol%) were added 1a (0.3 mmol), 2a (0.36 mmol), solvent (0.5mL) and allowed to stir for particular time at indicated temperature under air atmosphere. bisolated yield.

2.2.4 Screening of solvents

![Chemical reaction diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>solvent</th>
<th>yield (%) b</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DCE</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>THF</td>
<td>62</td>
</tr>
<tr>
<td>3</td>
<td>Acetone</td>
<td>23</td>
</tr>
<tr>
<td>4</td>
<td>DCM</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>CF\textsubscript{3}CH\textsubscript{2}OH</td>
<td>98</td>
</tr>
<tr>
<td>6</td>
<td>DMF</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>Dioxane</td>
<td>58</td>
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<tr>
<td>8</td>
<td>MeCN</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>MeOH</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>t-AmOH</td>
<td>38</td>
</tr>
</tbody>
</table>

aReaction conditions: To a mixture of catalyst (4% mmol), additive (16 mol%) were added 1a (0.3 mmol), 2a (0.36 mmol), solvent (0.5mL) and allowed to stir for particular time at indicated temperature under air atmosphere. bisolated yield.

With the established conditions in hand, we next tested the scope of the reaction with respect to various sulfonyl azides using 1a as the model substrate. Sulfonyl azides bearing both electron donating and electron withdrawing groups at para- position gave mono sulfamidated products in excellent yields except 2f with p-cyano group.
Table 2-2. Substrate Scope for Sulfonyl Azides with 1a under Optimized Condition

Under the optimized condition, 3-methylbenzenesulfonyl azide furnished product 3ah in 97% yield. Arylsulfonyl azide having bromo group at ortho position could readily participate in this sulfamidation reaction, providing 3ai in moderate yield. To our surprise, reaction with sulfonyl azide bearing trifluoromethyl groups at ortho- and para- position, yielded 3aj in 94% yield, while the substrate with the same substituent at 3- and 5- position provided 3ak in only 77% yield. In addition, amidation reaction of 1a with 2-naphthalenesulfonyl azide occurred efficiently to furnish corresponding aminosultam 3al in high yield. Moreover, alkanesulfonyl azides were also compatible under the standard amidation condition.

We then set out to expand the scope of this transformation to substituted cyclic N-sulfonyl ketimines with respect to sulfonyl azide 2a. We were pleased to observe
that the amidation occurred smoothly irrespective of the position and electronic nature of substituents, thus giving rise to the corresponding C-6 sulfamidated sultams in high efficiency and regioselectivity. Indeed, substrates bearing methyl (1b and 1j), alkoxy (1d, 1e, 1i and 1k), trifluoromethyl (1c), phenyl (1g), chloro (1f) and fluoro (1h) groups at the C2-, 3-, 4- and 5-position of cyclic N-sulfonyl ketimines were all well suited for the present sulfamidation. Sultam bearing naphthyl group 1l, also reacted effectively to produce 4al in excellent yield. Furthermore ketimine derived from substituted saccharin 1m was also suitable substrate for C-H amidation reaction, furnishing 4am in 93% yield.

**Table 2-3. Substrate Scope of Ir-Catalyzed C-H Amidation of Cyclic N-sulfonyl Ketimines**

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>4ab</td>
<td>84%</td>
</tr>
<tr>
<td>CF3</td>
<td>4ac</td>
<td>90%</td>
</tr>
<tr>
<td>OMe</td>
<td>4ad</td>
<td>90%</td>
</tr>
<tr>
<td>OPh</td>
<td>4ae</td>
<td>85%</td>
</tr>
<tr>
<td>Cl</td>
<td>4af</td>
<td>92%</td>
</tr>
<tr>
<td>Ph</td>
<td>4ag</td>
<td>82%</td>
</tr>
<tr>
<td>F</td>
<td>4ah</td>
<td>96%</td>
</tr>
<tr>
<td>Me</td>
<td>4aj</td>
<td>86%</td>
</tr>
<tr>
<td>OMe</td>
<td>4ak</td>
<td>79%</td>
</tr>
</tbody>
</table>

The reaction was performed under the following reaction conditions: 1 (0.3 mmol), 2a (0.36 mmol), [Cp*IrCl₂]₂ (4 mol%), AgNTf₂ (16 mol%), in 0.6 mL CF₃CH₂OH at 80 °C under air atmosphere for 2 hours.

Next we turned our attention to exploring the compatibility of acyl azides for our reaction. Under the optimized amidation conditions for sulfonyl azides, acyl azide
5a was unreactive. Pleasingly, the reactivity of acyl azide was dramatically enhanced when an oxidant AgOAc was added to the reaction performed in DCE at room temperature to give amidated compound 6aa in 89% yield after 24 h. Only DCE and AgOAc furnished optimal results among a representative set of solvents and oxidants screened. With this optimized iridium catalytic system, we tested scope of acyl azides with cyclic N-sulfonil ketimines.

An array of para-, meta- and ortho-substituted azides 5 bearing electron-withdrawing or electron-donating groups were successfully converted into desired amide products 6. In addition, reaction of 1a with acyl azide derived from naphthalene occurred efficiently to furnish 6al in high yield. Moreover, the acyl azides of cyclobutane and 3-thiazole displayed only moderate efficiencies in present catalytic system. Even aryl azide, derived from 3,5-bis(trifluoromethyl)benzene furnished the corresponding aminated product 6ao albeit in moderate yield.

**Table 2-4. Scope of acyl azides**

![Reaction Scheme]

<table>
<thead>
<tr>
<th>Acyl Azide</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>5a</td>
<td>6aa, 89%</td>
</tr>
<tr>
<td>5b</td>
<td>6aj, 55%</td>
</tr>
<tr>
<td>5c</td>
<td>6ak, 14%</td>
</tr>
<tr>
<td>5d</td>
<td>6al, 90%</td>
</tr>
<tr>
<td>5e</td>
<td>6am, 36%</td>
</tr>
<tr>
<td>5f</td>
<td>6an, 93%</td>
</tr>
<tr>
<td>5g</td>
<td>6ao, 37%</td>
</tr>
</tbody>
</table>

![Chemical Structures]
The reaction was performed under the following reaction conditions: 1a (0.3 mmol), 5 (0.36 mmol), [Cp*IrCl₂]₂ (4 mol%), AgNTf₂ (16 mol%), AgOAc (30 mol%) in 0.6 mL DCE at room temperature under air atmosphere for 24 hours.

To probe the generality of cyclic N-sulfonyl ketimines towards amidation, a set of derivatized sultams 1 were tested. The para- and ortho-substituted sultams were selectively transformed into corresponding amide products 7ai-hi. The catalytic system exhibited phenomenal chemo selectivity and hence tolerated a plethora of valuable functional groups such as Cl, F, OMe, OPh, Ph and CF₃. Even under steric control, meta- substituted sultams furnished 7ii-ki in moderate yield with an excellent site selectivity. Under the optimized conditions, sultam with naphthyl group, saccharin derived ketimine and cyclic ketimine reacted exceptionally well to yield respective aminosultams 7li, 7mi and 7ni.

Table 2-5. Scope of sultams with acyl azide 5i

<table>
<thead>
<tr>
<th>R</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Me</td>
<td>7ai</td>
<td>85%</td>
</tr>
<tr>
<td>CF₃</td>
<td>7bi</td>
<td>80%</td>
</tr>
<tr>
<td>OMe</td>
<td>7ci</td>
<td>99%</td>
</tr>
<tr>
<td>OPh</td>
<td>7di</td>
<td>84%</td>
</tr>
<tr>
<td>Ph</td>
<td>7ei</td>
<td>95%</td>
</tr>
<tr>
<td>F</td>
<td>7fi</td>
<td>79%</td>
</tr>
</tbody>
</table>

The reaction was performed under the following reaction conditions: 1a (0.3 mmol), 5 (0.36 mmol), [Cp*IrCl₂]₂ (4 mol%), AgNTf₂ (16 mol%), AgOAc (30 mol%) in 0.6 mL DCE at room temperature under air atmosphere for 24 hours.
Finally, to acquire some insights into mechanistic pathway of our current amidation reaction, intermolecular competition and parallel experiments between 1a and its penta-deuterated analog 1a-ds with tosyl azide 2a (eq. 1 and 2) as well as acyl azide 5i (eq. 3 and 4) were carried out separately. The kinetic isotope effect values (KIE) of 2.7 and 3.2 were observed, after the reactions were stirred for 3 min and 60 min, respectively. Notable KIE values for C(sp²)-H amidation suggest that C-H bond cleavage is plausibly involved in the rate determining step.
molecular competition experiments with various substituted sultams 1 (eq. 5) and acyl azides 5 (eq. 6), unveiled electron rich sultams and acyl azides to be intrinsically reactive substrates. The relatively faster rate of acyl azide 5e may be due to more electron richness of 5e compared to 5f. Based on these studies and previous results16, a plausible pathway for amidation reaction is proposed as shown in Scheme 2-24. Initially, the dimeric iridium species forms a cationic species I with AgNTf₂, which in turn initiates the directed C6-H bond activation of cyclic N-sulfonyl ketimines via the formation of five membered cyclometallated iridium complex by chelation assistance of iminyl nitrogen atom on sultams. Then the interaction of azide with iridium metal centre of II generates III, which forms IV upon migratory insertion of an imido group into Iridium-Carbon bond with simultaneous expulsion of N₂. The complex IV, after protodemetallation furnishes amidated product with the regeneration of active catalyst.

**Scheme 2-24. Proposed Plausible Mechanism for the Iridium-Catalyzed Amidation of Sultams.**
2.3 Experimental Section

2.3.1 Preparation of N-Sulfonylimines

Cyclic N-sulfonyl ketimines (1) were prepared from saccharin according to the known procedures reported in the literature.

To a degassed THF (15 mL) solution of saccharin (1.0 g, 10.0 mmol) at 25 °C was added fresh corresponding Grignard reagent (20.0 mmol in THF 10 mL) dropwise. The resulting mixture was further stirred at the same temperature overnight before being quenched with a saturated aqueous NH₄Cl solution. The aqueous layer was
extracted further with CH₂Cl₂ (50 mL×3); then the combined organic layer was washed with brine and dried over Na₂SO₄. Evaporation of the solvent gave the intermediate. TsOH (0.751 g, 8.0 mmol) was added to a solution of cyclic N-sulfonyl amine in toluene (25 mL). The resulting solution was heated to reflux for overnight. The solvent was removed in vacuo after being cooled to room temperature and then a saturated aqueous NH₄Cl solution (30 mL) was added. The aqueous layer was extracted with CH₂Cl₂ (50 mL×3), and the organic extracts were dried over anhydrous Na₂SO₄. After concentration in vacuo, the residue was finally purified by flash chromatography to afford the cyclic imines 1.

2.3.2 Preparation of Sulfonyl azides

\[
\text{RSCO₂Cl} \quad \text{NaN₃} \quad \text{Acetone} \quad \text{H₂O} \quad \text{RSO₂N₃}
\]

Aqueous sodium azide, approx. 20 mmol in 5 mL of water, was added dropwise over 5 min. to a solution of sulfonyl chloride (10 mmol) in acetone (20 mL) at 0°C. The reaction was allowed to warm up to ambient temperature and stirred for 16 h. The acetone was removed under reduced pressure at 25 °C and the reaction mixture was extracted with ether (2 x 75 mL) The combined organic layers were washed with water (2 x 10 mL), 5% Na₂CO₃ (10 mL) and water (10 mL), dried over Na₂SO₄ and the solvent was removed under reduced pressure to afford sulfonyl azide as a colorless oil.

2.3.3 Preparation of Acyl azides

\[
\text{RCOC} \quad \text{NaN₃} \quad \text{Acetone, H₂O} \quad \text{RCON₃}
\]
To a solution of sodium azide (1.00 g, 20 mmol) in water (5 mL) was added dropwise (over 1 h) a solution of acyl chloride (15 mmol) in acetone (10 mL) at 0 °C. The reaction mixture was warmed up to room temperature and stirred for 11 h. Acetone was removed under reduced pressure and the reaction mixture was extracted with EtOAc (30 mL x 3). The combined organic layers were dried over MgSO4 and solvent was removed under reduced pressure. The residue was purified using silica gel column chromatography (n-Hexane/EtOAc).

2.3.4 Experimental Procedure for Ir-Catalyzed C-H Amidation of Cyclic N-sulfonyl Ketimines & Spectroscopic Data of Compounds Obtained in this Study

2.3.4.1 General procedure for amidation of 1a with sulfonyl azides

To a screw capped vial with stir bar were added cyclic N-sulfonyl ketimine (1a, 0.12 mmol), sulfonyl azide (2, 0.14 mmol), [IrCp*Cl2]2 (3.9 mg, 0.004 mmol, 4 mol %), AgNTf2 (7.6 mg, 0.019 mmol, 16 mol %) and 2, 2, 2-trifluoroethanol (0.5 ml) under atmospheric conditions. The reaction mixture was stirred at 80 °C for 2 h, filtered through a pad of celite and then washed with dichloromethane (10 mL x 3). Organic solvents were removed under reduced pressure and the residue was purified by chromatography on silica gel (n-hexane/EtOAc) to give the desired product 3.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)-4-methylbenzenesulfonamide

Following the general procedure 1, 3aa was obtained as a white solid (50 mg, 0.121mmol, 98%). M. p. = 208-210 °C. 1H NMR (400 MHz, CDCl3) δ 8.82 (s, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.92 (d, J = 7.7 Hz, 1H), 7.82 (t, J = 7.3 Hz, 1H), 7.73 – 7.63 (m, 2H), 7.58 (dd, J = 7.8, 1.4 Hz, 1H), 7.44 (td, J = 7.7, 1.0 Hz, 1H), 7.35 (d, J = 8.3 Hz, 2H), 7.31 – 7.27 (m, 1H), 6.75 (d, J = 8.1 Hz, 2H), 1.95 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 168.4, 143.3, 139.8, 136.6, 134.7, 133.8, 133.5, 133.2, 133.0.
N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)benzenesulfonamide

Following the general procedure 1, 3ab was obtained as an off white solid (50 mg, 0.125 mmol, 99%). M. p. = 171-173 °C. 1H NMR (400 MHz, CDCl3) δ 8.89 (s, 1H), 7.96 (d, J = 7.5 Hz, 1H), 7.91 (d, J = 7.9 Hz, 1H), 7.78 (t, J = 7.3 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.65 – 7.60 (m, 1H), 7.57 (dd, J = 7.8, 1.4 Hz, 1H), 7.49 (dd, J = 8.0, 1.5 Hz, 2H), 7.41 (td, J = 7.8, 0.9 Hz, 1H), 7.28 – 7.23 (m, 1H), 7.00 – 6.91 (m, 3H). 13C NMR (101 MHz, CDCl3) δ 168.3, 139.8, 137.8, 136.5, 133.9, 133.7, 133.3, 132.4, 130.1, 129.7, 128.6, 128.0, 127.1, 126.7, 125.9, 122.9, 122.6. HRMS (ESI): m/z calculated for C20H16N2O4S2 [M+H]+: 413.0630, found: 413.0630.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)-4-bromobenzenesulfonamide

Following the general procedure 1, 3ac was obtained as an off white solid (194 mg, 0.414 mmol, 97%). M. p. = 206-208 °C. 1H NMR (400 MHz, CDCl3) δ 8.81 (s, 1H), 8.01 (d, J = 7.5 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.76 – 7.70 (m, 2H), 7.61 (dd, J = 7.8, 1.4 Hz, 1H), 7.49 (dd, J = 11.0, 4.2 Hz, 1H), 7.35 – 7.27 (m, 3H), 7.10 – 7.04 (m, 2H). 13C NMR (101 MHz, CDCl3) δ 168.3, 139.8, 136.5, 135.9, 134.1, 133.9, 133.3, 132.4, 130.1, 129.7, 128.6, 128.0, 127.7, 126.6, 126.1, 123.3, 123.0. HRMS (ESI): m/z calculated for C19H14BrN2O4S2 [M+H]+: 478.5324, found: 478.5321.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)-4-nitrobenzenesulfonamide

Following the general procedure 1, 3ad was obtained as a pale yellow solid (57.1 mg, 0.128 mmol, 96%). M. p. = 219-221 °C. 1H NMR (400 MHz, CDCl3) δ 8.81 (s, 1H), 8.02 – 7.94 (m, 2H), 7.83 – 7.73 (m, 4H), 7.63 (dd, J = 12.5, 8.4 Hz, 3H), 7.59 – 7.51 (m, 2H), 7.21
(d, J = 7.8 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 167.8, 149.5, 143.1, 139.6, 135.2, 134.2, 134.1, 133.3, 130.1, 129.5, 129.1, 128.5, 127.1, 126.0, 123.8, 123.4, 123.2. HRMS (ESI): m/z calculated for C₁₉H₁₃N₃O₆S₂ [M+H]⁺: 444.0324, found: 444.0320.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)-4-methoxybenzenesulfonamide

Following the general procedure 1, 3ae was obtained as an off white solid (30 mg, 0.070mmol, 94%). M. p. = 233-235 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.76 (s, 1H), 8.00 (d, J = 7.5 Hz, 1H), 7.94 (d, J = 8.2 Hz, 1H), 7.80 (t, J = 7.5 Hz, 1H), 7.71 (t, J = 7.8 Hz, 1H), 7.65 (t, J = 7.6 Hz, 1H), 7.59 (d, J = 7.0 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.41 (t, J = 6.6 Hz, 2H), 7.31 (s, 1H), 6.42 (d, J = 8.8 Hz, 2H), 3.51 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.4, 162.6, 139.9, 136.7, 133.8, 133.5, 133.2, 130.0, 129.7, 129.3, 129.2, 128.6, 126.5, 126.08, 123.1, 122.7, 113.6, 55.1. HRMS (ESI): m/z calculated for C₂₀H₁₆N₂O₅S₂ [M+H]⁺: 429.0579, found: 429.0580.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)-4-(trifluoromethyl)benzenesulfonamide

Following the general procedure 1, 3ag was obtained as a yellow solid (55.3 mg, 0.118mmol, 95%). M. p. = 207-209 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 7.97 (t, J = 8.1 Hz, 2H), 7.78 (dt, J = 11.8, 7.7 Hz, 2H), 7.64 (dd, J = 7.7, 3.0 Hz, 4H), 7.50 (t, J = 7.6 Hz, 1H), 7.26 (dd, J = 14.1, 7.9 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ -62.95. ¹³C NMR (101 MHz, CDCl₃) δ 168.1, 141.3, 139.5, 135.8, 134.1, 134.1, 133.7, 130.3, 129.4, 128.8, 127.8, 126.7, 126.0, 125.8, 125.7 (q, JCF = 267 Hz), 124.0, 123.0, 122.9. HRMS (ESI): m/z calculated for C₂₀H₁₃¹⁹F₃N₂O₅S₂ [M+H]⁺: 467.0347, found: 467.0349.
N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)-3-methylbenzenesulfonamide

Following the general procedure 1, 3ah was obtained as a white solid (49.7 mg, 0.120mmol, 97%). M. p. = 212-214 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.84 (s, 1H), 7.93 (dd, J = 14.0, 7.8 Hz, 2H), 7.78 (t, J = 7.5 Hz, 1H), 7.67 (dt, J = 14.5, 4.4 Hz, 2H), 7.57 (dd, J = 7.8, 1.4 Hz, 1H), 7.42 (td, J = 7.8, 0.9 Hz, 1H), 7.34 (s, 1H), 7.29 – 7.23 (m, 1H), 7.16 (d, J = 7.8 Hz, 1H), 6.84 (t, J = 7.7 Hz, 1H), 6.71 (d, J = 7.6 Hz, 1H), 1.96 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.3, 139.7, 139.3, 137.5, 136.6, 133.9, 133.6, 133.2, 133.2, 130.0, 129.7, 128.3, 128.2, 127.2, 126.6, 126.1, 124.2, 122.9, 122.8, 20.7. HRMS (ESI): m/z calculated for C₂₀H₁₆N₂O₄S₂ [M+H]⁺: 413.0630, found: 413.0638.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)-2-bromobenzenesulfonamide

Following the general procedure 1, 3ai was obtained as a white solid (41 mg, 0.085mmol, 70%). M. p. = 217-219 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.84 (s, 1H), 8.21 (dd, J = 7.9, 1.3 Hz, 1H), 8.21 (dd, J = 7.5 Hz, 1H), 7.85 (d, J = 8.2 Hz, 2H), 7.80 – 7.72 (m, 3H), 7.56 (t, J = 7.4 Hz, 1H), 7.50 (d, J = 7.9 Hz, 1H), 7.41 (t, J = 7.5 Hz, 1H), 7.33 – 7.29 (m, 1H), 7.27 (d, J = 2.6 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ 168.8, 140.1, 138.0, 137.2, 135.3, 134.2, 134.0, 133.8, 133.6, 132.2, 131.1, 130.4, 127.6, 127.0, 123.9, 123.2, 121.2, 120.3, 119.1. HRMS (ESI): m/z calculated for C₁₉H₁₃BrN₂O₄S₂ [M+H]⁺: 476.9574, found: 476.9574.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)-2,5-bis(trifluoromethyl)benzenesulfonamide

Following the general procedure 1, 3aj was obtained as a white solid (60.5 mg, 0.113mmol, 94%). M. p. = 164-166 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.24 (s, 1H), 8.22 (s, 1H), 7.99 (d, J = 7.5 Hz, 1H), 7.90 (d, J = 8.2 Hz, 1H), 7.85 – 7.79 (m, 2H), 7.78 – 7.74 (m, 2H), 7.73 – 7.70 (m, 1H), 7.69 (s, 1H), 7.66 (dd, J = 7.9, 4.6 Hz, 1H), 7.47 – 7.40 (m,
1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.4, 139.9, 139.4, 136.1, 134.2, 133.9, 133.7, 130.9, 129.8, 129.7, 129.6 (q, $^{1}J_{CF} = 273$ Hz), 128.0 (q, $^{1}J_{CF} = 272$ Hz), 126.7, 125.5, 124.9, 123.1, 120.9. HRMS (ESI): m/z calculated for C$_{21}$H$_{12}$F$_{6}$N$_{2}$O$_{4}$S$_{2}$ [M+H]$^+$: 535.0221, found: 535.0223.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)-3,5-bis(trifluoromethyl)benzenesulfonamide

Following the general procedure 1, 3ak was obtained as a white solid (47.5 mg, 0.088 mmol, 77%). M. p. = 208-210 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 9.10 (s, 1H), 8.00 (d, $^{1}J = 8.2$ Hz, 1H), 7.95 (d, $^{1}J = 7.5$ Hz, 1H), 7.88 (s, 2H), 7.81 (ddd, $^{1}J = 11.5$, 5.3, 2.4 Hz, 2H), 7.74 – 7.63 (m, 2H), 7.56 (td, $^{1}J = 7.7$, 0.9 Hz, 1H), 7.51 (s, 1H), 7.36 (d, $^{1}J = 7.7$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 167.5, 140.4, 139.5, 135.5, 134.4, 134.0, 133.4, 132.7, 132.4, 130.4, 128.9, 128.3, 127.2 (q, $^{1}J_{CF} = 269$ Hz), 126.9, 126.1 (q, $^{1}J_{CF} = 271$ Hz), 123.5, 123.2, 122.8, 120.5. HRMS (ESI): m/z calculated for C$_{21}$H$_{12}$F$_{6}$N$_{2}$O$_{4}$S$_{2}$ [M+H]$^+$: 535.0221, found: 535.0222.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)naphthalene-2-sulfonamide

Following the general procedure 1, 3al was obtained as an off white solid (54.3 mg, 0.121 mmol, 91%). M. p. = 195-197 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 8.83 (s, 1H), 8.00 (d, $^{1}J = 11.9$ Hz, 2H), 7.78 – 7.69 (m, 2H), 7.66 (d, $^{1}J = 7.7$ Hz, 1H), 7.48 – 7.34 (m, 9H), 7.05 (t, $^{1}J = 7.6$ Hz, 1H), 6.73 (d, $^{1}J = 7.7$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 168.2, 139.1, 136.2, 134.4, 134.2, 133.7, 133.2, 132.8, 131.6, 129.8, 129.2, 129.1, 128.9, 128.9, 128.5, 128.5, 127.5, 127.1, 126.4, 125.4, 123.6, 122.4, 122.3. HRMS (ESI): m/z calculated for C$_{23}$H$_{16}$N$_{2}$O$_{4}$S$_{2}$ [M+H]$^+$: 449.0630, found: 449.0634.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)cyclohexanesulfonamide

Following the general procedure 1, 3am was obtained as a yellow solid (49.3 mg, 0.121 mmol, 99%). M. p. =
N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)butane-1-sulfonamide

Following the general procedure 1, \(3an\) was obtained as a yellow solid (54.9 mg, 0.145 mmol, 96%). M. p. = 156-158 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.08 (s, 1H), 8.06 (d, \(J = 6.9\) Hz, 1H), 7.93 – 7.80 (m, 5H), 7.74 – 7.68 (m, 1H), 7.41 (td, \(J = 7.8, 1.1\) Hz, 1H), 3.07 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 169.0, 139.9, 138.1, 134.6, 134.0, 134.0, 131.3, 130.4, 127.3, 124.0, 123.2, 121.8, 118.7, 52.7, 25.2, 21.3, 13.2. HRMS (ESI): m/z calculated for C\(_{17}\)H\(_{22}\)N\(_2\)O\(_4\)S\(_2\) [M+H]\(^+\): 379.0786, found: 379.0786.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)methane-1-sulfonamide

Following the general procedure 1, \(3ao\) was obtained as a yellow off white solid (46.5 mg, 0.138 mmol, 97%). M. p. = 142-144 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.05 (s, 1H), 8.06 (dd, \(J = 6.8, 0.8\) Hz, 1H), 7.93 – 7.88 (m, 3H), 7.87 – 7.79 (m, 2H), 7.74 – 7.68 (m, 1H), 7.41 (td, \(J = 7.8, 1.1\) Hz, 1H), 3.07 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 169.0, 139.9, 138.1, 134.6, 134.0, 134.0, 131.3, 130.4, 127.3, 124.0, 123.2, 121.8, 118.7, 52.7, 25.2, 21.3, 13.2. HRMS (ESI): m/z calculated for C\(_{14}\)H\(_{12}\)N\(_2\)O\(_4\)S\(_2\) [M+H]\(^+\): 337.0316, found: 337.0316.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)-1-phenylmethanesulfonamide

Following the general procedure 1, \(3ap\) was obtained as a pale yellow solid (37.9 mg, 0.091 mmol, 67%). M. p. = 150-152 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 9.17 (s, 1H), 8.01...
(d, J = 7.2 Hz, 1H), 7.88 – 7.70 (m, 5H), 7.56 (t, J = 7.8 Hz, 1H), 7.28 (dd, J = 14.4, 6.7 Hz, 1H), 7.17 (d, J = 7.1 Hz, 2H), 7.05 (dq, J = 14.5, 7.1 Hz, 3H), 4.40 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.4, 140.0, 138.8, 134.4, 133.8, 133.7, 131.1, 130.4, 130.3, 128.8, 127.8, 127.3, 123.6, 123.2, 121.1, 118.0, 59.1. HRMS (ESI): m/z calculated for C$_{20}$H$_{16}$N$_2$O$_4$S$_2$ [M+H]$^+$: 413.0630, found: 413.0630.

2.3.4.2 General procedure for amidation of cyclic N-sulfonyl ketimine with tosyl azide

To a screw capped vial with stir bar were added cyclic N-sulfonyl ketimine (1, 0.12 mmol), sulfonyl azide (2a, 0.14 mmol), [IrCp*Cl$_2$]$_2$ (3.9 mg, 0.004 mmol, 4 mol %), AgNTf$_2$ (7.6 mg, 0.019 mmol, 16 mol %) and 2, 2, 2-trifluoroethanol (0.5 ml) under atmospheric conditions. The reaction mixture was stirred at 80 °C for 2 h, filtered through a pad of celite and then washed with dichloromethane (10 mL x 3). Organic solvents were removed under reduced pressure and the residue was purified by chromatography on silica gel (n-hexane/EtOAc) to give the desired product 4.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-5-methylphenyl)-4-methylbenzenesulfonamide

Following the general procedure 2, 4ab was obtained as a white solid (41.5 mg, 0.097mmol, 84%). M. p. = 200-202 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.85 (s, 1H), 7.95 (d, J = 7.5 Hz, 1H), 7.78 (t, J = 7.4 Hz, 1H), 7.71 (s, 1H), 7.63 (dd, J = 9.8, 5.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.34 (d, J = 8.2 Hz, 2H), 7.30 – 7.26 (m, 1H), 7.21 (d, J = 7.5 Hz, 1H), 6.73 (d, J = 8.1 Hz, 2H), 2.51 (s, 3H), 1.92 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.3, 145.4, 143.2, 139.8, 136.7, 134.7, 133.3, 133.1, 130.1, 129.9, 129.2, 128.7, 127.27, 127.0, 126.6, 122.8, 120.1, 21.9, 21.2. HRMS (ESI):
m/z calculated for C$_{21}$H$_{18}$N$_2$O$_4$S$_2$ [M+H]$^+$: 427.0786, found: 427.0780.

**N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-5-(trifluoromethyl)phenyl)-4-methylbenzenesulfonamide**

Following the general procedure 2, 4ac was obtained as an off white solid (48 mg, 0.099mmol, 90%). M. p. = 203-205 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.84 (s, 1H), 8.19 (s, 1H), 8.02 (d, $J$ = 7.5 Hz, 1H), 7.86 (td, $J$ = 7.5, 0.6 Hz, 1H), 7.69 (ddd, $J$ = 12.3, 8.9, 5.1 Hz, 4H), 7.40 (d, $J$ = 8.3 Hz, 2H), 7.29 (d, $J$ = 3.5 Hz, 1H), 6.83 (d, $J$ = 8.0 Hz, 2H), 2.00 (s, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ -63.36. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.6, 143.8, 139.7, 137.4, 134.6, 133.9, 133.5, 130.6, 129.8, 129.5, 129.2, 127.2, 126.9, 126.2, 125.4, 124.6 (q, $^1$J$_{CF}$ = 273 Hz), 123.2, 122.4 (d, $^3$J$_{CF}$ = 3 Hz), 21.3. HRMS (ESI): m/z calculated for C$_{21}$H$_{15}$F$_3$N$_2$O$_4$S$_2$ [M+H]$^+$: 481.0504, found: 481.0505.

**N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-5-methoxyphenyl)-4-methylbenzenesulfonamide**

Following the general procedure 2, 4ad was obtained as an off white solid (52 mg, 0.117mmol, 90%). M. p. = 243-245 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.34 (s, 1H), 8.00 (d, $J$ = 7.3 Hz, 1H), 7.79 (t, $J$ = 7.2 Hz, 1H), 7.66 (t, $J$ = 7.4 Hz, 1H), 7.60 (d, $J$ = 8.6 Hz, 1H), 7.51 - 7.38 (m, 5H), 7.29 (s, 1H), 6.90 (d, $J$ = 8.5 Hz, 1H), 6.85 (d, $J$ = 7.4 Hz, 2H), 3.98 (s, 3H), 2.01 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 167.7, 143.4, 139.7, 134.6, 133.4, 133.2, 132.0, 130.3, 129.2, 127.3, 126.6, 122.8, 114.3, 112.6, 111.3, 55.9, 21.2. HRMS (ESI): m/z calculated for C$_{21}$H$_{18}$N$_2$O$_5$S$_2$ [M+H]$^+$: 443.0735, found: 443.0735.

**N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-5-phenoxyphenyl)-4-methylbenzenesulfonamide**

Following the general procedure 2, 4ae was obtained as an off white solid (43 mg, 0.085mmol, 85%). M. p. = 214-216 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.34 (s, 1H), 8.00 (d, $J$ = 7.5 Hz, 1H), 7.81 (td, $J$ = 7.5, 0.7 Hz, 1H), 7.69 (td, $J$ = 7.7, 0.9 Hz, 1H), 7.64 (d, $J$ = 8.8 Hz, 1H), 7.53 – 7.43 (m, 6H), 7.40 (d, $J$ = 2.5 Hz, 1H), 7.32 (t, $J$ = 7.4 Hz, 1H), 7.18 – 7.13 (m, 2H), 6.96 – 6.86 (m, 3H), 2.07 (s, 3H). $^{13}$C NMR (101 MHz,
N-(5-chloro-2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)-4-methylbenzenesulfonamide

Following the general procedure 2, 4af was obtained as a pale yellow solid (49.5 mg, 0.110 mmol, 92%). M. p. = 234-236 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.95 (s, 1H), 8.01 (d, J = 7.5 Hz, 1H), 7.95 (d, J = 2.0 Hz, 1H), 7.83 (t, J = 7.3 Hz, 1H), 7.68 (td, J = 7.7, 0.8 Hz, 1H), 7.55 (d, J = 8.4 Hz, 1H), 7.44 (d, J = 8.3 Hz, 2H), 7.42 – 7.38 (m, 1H), 7.29 (s, 1H), 6.84 (d, J = 8.1 Hz, 2H), 2.00 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 167.7, 143.6, 140.3, 139.8, 138.2, 134.7, 133.7, 133.3, 131.0, 129.5, 129.4, 127.5, 127.2, 126.2, 126.1, 123.1, 120.6, 21.3. HRMS (ESI): m/z calculated for C₂₀H₁₅N₃ClO₄S₂ [M+H]⁺: 447.0240, found: 447.0247.

N-(4-(1,1-dioxidobenzo[d]isothiazol-3-yl)-[1,1ʹ-biphenyl]-3-yl)-4-methylbenzenesulfonamide

Following the general procedure 2, 4ag was obtained as an off white solid (39.5 mg, 0.080 mmol, 82%). M. p. = 239-241 °C. ¹H NMR (400 MHz, CDCl₃) δ 8.98 (s, 1H), 8.19 (s, 1H), 8.01 (d, J = 7.5 Hz, 1H), 7.82 (dd, J = 7.5, 6.9 Hz, 1H), 7.78 – 7.72 (m, 2H), 7.71 – 7.64 (m, 3H), 7.59 – 7.47 (m, 4H), 7.42 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 7.8 Hz, 1H), 6.79 (d, J = 8.0 Hz, 2H), 1.96 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 168.1, 146.7, 143.3, 139.9, 138.3, 137.4, 134.8, 133.4, 133.2, 130.6, 129.8, 129.3, 129.2, 129.1, 127.3, 127.3, 126.5, 126.3, 124.3, 122.9, 121.2, 21.2. HRMS (ESI): m/z calculated for C₂₆H₂₀N₂O₄S₂ [M+H]⁺: 489.0943, found: 489.0948.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-5-fluorophenyl)-4-methylbenzenesulfonamide

Following the general procedure 2, 4ah was obtained as a white solid (49.5 mg, 0.114 mmol, 96%). M. p. = 241-243 °C. ¹H NMR (400 MHz, CDCl₃) δ 9.16 (s, 1H), 8.02 (d, J = 7.5 Hz, 1H), 7.84 (t, J = 7.2 Hz, 1H), 7.72 – 7.63 (m, 3H), 7.48 (d, J = 8.3 Hz, 2H), 7.36 (d,
Following the general procedure 2, 4ai was obtained as a pale yellow solid (47.7 mg, 0.107 mmol, 90%). M. p. = 205-207 °C. 1H NMR (400 MHz, CDCl3) δ 8.25 (s, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.71 (t, J = 7.5 Hz, 1H), 7.60 (t, J = 8.3 Hz, 1H), 7.56 – 7.45 (m, 2H), 7.33 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 8.2 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 8.1 Hz, 2H), 3.70 (s, 3H), 1.99 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 168.9, 158.1, 143.2, 138.8, 136.5, 135.1, 133.9, 132.7, 132.7, 130.6, 129.1, 126.9, 126.5, 121.9, 120.1, 113.2, 109.1, 55.7, 21.3. HRMS (ESI): m/z calculated for C21H18N2O5S2 [M+H]+: 443.0735, found: 443.0729.

Following the general procedure 2, 4aj was obtained as an off white solid (46.8 mg, 0.109 mmol, 85%). M. p. = 214-216 °C. 1H NMR (400 MHz, CDCl3) δ 8.61 (s, 1H), 7.97 (d, J = 7.5 Hz, 1H), 7.81 (ddd, J = 8.3, 5.6, 1.9 Hz, 2H), 7.66 (td, J = 7.7, 0.9 Hz, 1H), 7.50 (dd, J = 8.3, 1.7 Hz, 1H), 7.37 (dd, J = 9.9, 4.8 Hz, 3H), 7.25 (d, J = 7.7 Hz, 1H), 6.72 (d, J = 8.0 Hz, 2H), 2.45 (s, 3H), 1.92 (s, 3H). 13C NMR (101 MHz, CDCl3) δ 168.5, 143.1, 139.8, 136.5, 134.6, 134.6, 133.8, 133.4, 133.2, 130.2, 129.6, 129.2, 128.8, 127.2, 126.6, 123.2, 122.8, 21.2, 21.0. HRMS (ESI): m/z calculated for C21H18N2O5S2 [M+H]+: 427.0786, found: 427.0785.
N-(2-(1,1-dioxidobenzo[\text{d}]isothiazol-3-yl)-4-methoxyphenyl)-4-methylbenzenesulfonamide

Following the general procedure 2, 4ak was obtained as a yellow solid (44.2 mg, 0.099 mmol, 79%). M. p. = 208-210 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.35 (s, 1H), 7.97 (d, $J = 7.5$ Hz, 1H), 7.84 (d, $J = 9.0$ Hz, 1H), 7.80 (t, $J = 7.5$ Hz, 1H), 7.63 (t, $J = 7.6$ Hz, 1H), 7.32 – 7.27 (m, 3H), 7.26 – 7.20 (m, 2H), 7.01 (d, $J = 2.9$ Hz, 1H), 6.69 (d, $J = 8.1$ Hz, 2H), 3.88 (s, 3H), 1.88 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.1, 157.6, 143.0, 139.8, 134.4, 133.4, 133.1, 131.3, 129.4, 129.1, 128.6, 127.3, 126.3, 124.9, 119.4, 118.2, 115.7, 55.8, 21.2. HRMS (ESI): m/z calculated for C$_{20}$H$_{16}$N$_2$O$_4$S$_2$ [M+H]$^+$: 443.0735, found: 443.0729.

N-(2-(1,1-dioxidobenzo[\text{d}]isothiazol-3-yl)naphthalen-2-yl)-4-methylbenzenesulfonamide

Following the general procedure 2, 4al was obtained as a brownish yellow solid (47.8 mg, 0.103 mmol, 97%). M. p. = 202-204 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.67 (s, 1H), 8.36 (s, 1H), 8.10 (s, 1H), 8.03 (d, $J = 7.5$ Hz, 2H), 7.91 (d, $J = 8.1$ Hz, 1H), 7.84 (t, $J = 7.4$ Hz, 1H), 7.74 (t, $J = 7.4$ Hz, 1H), 7.71 – 7.61 (m, 2H), 7.34 (d, $J = 8.0$ Hz, 3H), 6.69 (d, $J = 8.0$ Hz, 2H), 1.91 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.4, 145.1, 143.0, 140.0, 135.2, 135.1, 133.4, 133.1, 132.2, 131.4, 130.3, 129.8, 129.8, 129.2, 128.5, 128.4, 128.0, 127.7, 127.3, 126.5, 122.9, 122.3, 21.2. HRMS (ESI): m/z calculated for C$_{24}$H$_{18}$N$_2$O$_4$S$_2$ [M+H]$^+$: 463.0786, found: 463.0782.

4-methyl-N-(2-(5-methyl-1,1-dioxidobenzo[\text{d}]isothiazol-3-yl)phenyl)benzenesulfonamide

Following the general procedure 2, 4am was obtained as a white solid (47.4 mg, 0.111 mmol, 93%). M. p. = 195-197 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 8.78 (s, 1H), 7.91 (dd, $J = 8.2$, 0.9 Hz, 1H), 7.85 (d, $J = 7.7$ Hz, 1H), 7.72 – 7.66 (m, 1H), 7.57 (dd, $J = 9.3$, 7.8, 1.0 Hz, 2H), 7.44 (td, $J = 7.7$, 1.1 Hz, 1H), 7.35 (d, $J = 8.3$ Hz, 2H), 7.00 (s, 1H), 6.76 (d, $J = 7.9$ Hz, 2H), 2.50 (s, 3H), 1.95 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.5, 144.5, 143.1, 137.1, 136.4, 134.7, 134.0, 133.7, 130.2, 130.0, 129.1, 128.4, 127.3, 127.0,
2.3.4.3 General procedure for amidation of 1a with acyl azides

To a screw capped vial with stir bar were added cyclic N-sulfonyl ketimine (1a, 0.012 mmol), acyl azide (5, 0.014 mmol), [IrCp*Cl₂]₂ (3.9 mg, 0.004 mmol, 4 mol %), AgNTf₂ (7.6 mg, 0.016 mmol, 16 mol %), AgOAc (6.2 mg, 0.037 mmol, 30 mol %) and 1,2-dichloroethane (0.5 ml) under atmospheric conditions. The reaction mixture was stirred at 25 °C for 24 h, filtered through a pad of celite and then washed with dichloromethane (10 mL x 3). Organic solvents were removed under reduced pressure and the residue was purified by chromatography on silica gel (n-hexane/EtOAc) to give the desired product 6.

N-(2-(1,1-dioxidobenz[d]isothiazol-3-yl)-phenyl)-3-methoxybenzamide

Following the general procedure 3, 6aa was obtained as a pale yellow solid (41.6 mg, 0.106mmol, 89%). M. p. = 193-195 °C. ¹H NMR (400 MHz, CDCl₃) δ 10.79 (s, 1H), 8.82 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 7.2 Hz, 1H), 7.93 (d, J = 7.4 Hz, 1H), 7.89 (d, J = 7.7 Hz, 1H), 7.85 – 7.76 (m, 2H), 7.72 (t, J = 7.8 Hz, 1H), 7.59 (d, J = 7.7 Hz, 1H), 7.54 (s, 1H), 7.44 (t, J = 7.9 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 7.12 (dd, J = 8.2, 2.3 Hz, 1H), 3.92 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.6, 165.5, 160.0, 139.9, 139.0, 135.3, 134.5, 133.9, 133.8, 130.8, 130.7, 130.0, 127.6, 123.5, 123.2, 123.1, 119.4, 119.3, 118.3, 111.8, 55.6. HRMS (ESI): m/z calculated for C₂₁H₁₈N₂O₄S [M+H]⁺: 393.0909, found: 393.0908.

N-(2-(1,1-dioxidobenz[d]isothiazol-3-yl)-phenyl)benzamide

Following the general procedure 3, 6ab was obtained as a yellow solid (46.2 mg, 0.127mmol, 96%). M. p. = 176-178 °C. ¹H
NMR (400 MHz, CDCl$_3$) δ 10.84 (s, 1H), 8.83 (d, $J = 8.4$ Hz, 1H), 8.05 (dd, $J = 12.8$, 7.2 Hz, 3H), 7.94 (d, $J = 7.4$ Hz, 1H), 7.90 (d, $J = 7.7$ Hz, 1H), 7.82 (dt, $J = 18.7$, 7.4 Hz, 2H), 7.74 (t, $J = 7.8$ Hz, 1H), 7.63 – 7.51 (m, 3H), 7.37 (t, $J = 7.6$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.6, 165.6, 140.0, 139.0, 134.4, 133.9, 133.8, 133.8, 132.3, 130.8, 128.9, 127.5, 127.4, 123.4, 123.2, 123.1, 118.4. HRMS (ESI): m/z calculated for C$_{20}$H$_{14}$N$_2$O$_3$S [M+H]$^+$: 363.0803, found: 363.0805.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-phenyl)-4-methylbenzamide

Following the general procedure 3, 6ac was obtained as a pale yellow solid (51.1 mg, 0.135mmol, 98%). M. p. = 180-182 ºC. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.81 (s, 1H), 8.83 (d, $J = 8.2$ Hz, 1H), 8.06 (d, $J = 6.7$ Hz, 1H), 7.90 (dd, $J = 17.9$, 6.9 Hz, 4H), 7.82 (dd, $J = 17.2$, 8.1 Hz, 2H), 7.72 (t, $J = 7.3$ Hz, 1H), 7.34 (d, $J = 6.9$ Hz, 3H), 2.44 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.6, 165.6, 143.0, 140.0, 139.1, 134.5, 133.8, 133.8, 131.1, 130.8, 129.6, 127.5, 127.4, 123.3, 123.1, 123.1, 118.2, 21.5. HRMS (ESI): m/z calculated for C$_{21}$H$_{16}$N$_2$O$_3$S [M+H]$^+$: 377.0960, found: 377.0962.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-phenyl)-4-nitrobenzamide

Following the general procedure 3, 6ad was obtained as a yellow solid (49 mg, 0.120mmol, 92%). M. p. = 217-219 ºC. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.99 (s, 1H), 8.80 (d, $J = 8.4$ Hz, 1H), 8.39 (d, $J = 8.7$ Hz, 2H), 8.19 (d, $J = 8.7$ Hz, 2H), 8.11 (d, $J = 7.4$ Hz, 1H), 7.97 (t, $J = 8.2$ Hz, 2H), 7.92 – 7.83 (m, 2H), 7.79 (dd, $J = 14.8$, 6.6 Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.6, 163.4, 150.0, 139.9, 139.4, 138.3, 134.6, 134.0, 134.0, 130.7, 130.6, 128.6, 127.5, 124.2, 124.1, 123.3, 123.3, 118.6. HRMS (ESI): m/z calculated for C$_{20}$H$_{13}$N$_3$O$_3$S [M+H]$^+$: 408.0654, found: 408.0651.
N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-phenyl)-4-methoxybenzamide

Following the general procedure 3, 6ae was obtained as a yellow solid (50 mg, 0.127mmol, 91%). M. p. = 147-149 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.99 (s, 1H), 8.80 (d, $J = 8.4$ Hz, 1H), 8.39 (d, $J = 8.7$ Hz, 2H), 8.19 (d, $J = 8.7$ Hz, 2H), 8.11 (d, $J = 7.4$ Hz, 1H), 7.97 (t, $J = 8.2$ Hz, 2H), 7.92 – 7.83 (m, 2H), 7.79 (dd, $J = 14.8$, 6.6 Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.6, 163.4, 150.0, 139.9, 139.4, 138.3, 134.6, 134.0, 130.7, 130.6, 128.6, 127.5, 124.2, 124.1, 123.3, 123.3, 118.6. HRMS (ESI): m/z calculated for C$_{21}$H$_{16}$N$_2$O$_4$S $[M+H]^+$: 393.0909, found: 393.0917.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-phenyl)-4-fluorobenzamide

Following the general procedure 3, 6af was obtained as a yellow solid (41.4 mg, 0.108mmol, 90%). M. p. = 187-189 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.82 (s, 1H), 8.81 (dd, $J = 8.4$, 0.7 Hz, 1H), 8.11 – 8.02 (m, 3H), 7.96 (d, $J = 7.2$ Hz, 1H), 7.91 (dd, $J = 7.9$, 1.5 Hz, 1H), 7.84 (dd, $J = 10.2$, 7.5, 1.1 Hz, 2H), 7.78 – 7.72 (m, 1H), 7.39 (td, $J = 7.8$, 1.1 Hz, 1H), 7.26 – 7.19 (m, 2H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ -106.70. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.6, 166.3 (d, $^1J_{CF} = 254$ Hz), 164.5, 140.0, 138.9, 134.5, 133.9, 133.9, 130.7 (d, $^2J_{CF} = 19$ Hz), 130.1 (d, $^3J_{CF} = 3$ Hz), 129.9 (d, $^3J_{CF} = 9$ Hz), 127.5, 123.5, 123.2 (d, $^4J_{CF} = 2$ Hz), 118.3, 116.0 (d, $^2J_{CF} = 22$ Hz). HRMS (ESI): m/z calculated for C$_{20}$H$_{16}$FN$_2$O$_3$S $[M+H]^+$: 381.0709, found: 381.0714.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-phenyl)-4-(trifluoromethyl)benzamide

Following the general procedure 3, 6ah was obtained as a white solid (40.6 mg, 0.094mmol, 81%). M. p. = 167-169 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.93 (s, 1H), 8.82 (d, $J = 8.4$ Hz, 1H), 8.15 (d, $J = 8.1$ Hz, 2H), 8.12 – 8.07 (m, 1H), 7.98 – 7.91 (m, 2H), 7.91 – 7.73 (m, 5H), 7.42 (td, $J = 7.8$, 1.0 Hz, 1H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ -62.98. $^{13}$C
NMR (101 MHz, CDCl$_3$) $\delta$ 169.6, 164.2, 140.0, 138.5, 137.1, 134.6, 133.9 (d, $^3$J$_{CF} =$ 2 Hz), 130.7 (d, $^2$J$_{CF} =$ 6 Hz), 127.9, 127.5, 126.0 (q, $^1$J$_{CF} =$ 272 Hz), 123.9, 123.3 (d, $^3$J$_{CF} =$ 5 Hz), 118.5. HRMS (ESI): m/z calculated for C$_{21}$H$_{13}$F$_3$N$_2$O$_3$S [M+H]$^+$: 431.0677, found: 431.0675.

4-chloro-N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)benzamide

Following the general procedure 3, 6ai was obtained as a yellow solid (37.2 mg, 0.093 mmol, 93%). M. p. = 189-191 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.85 (s, 1H), 8.85 – 8.77 (m, 1H), 8.13 – 8.06 (m, 1H), 8.00 – 7.94 (m, 3H), 7.92 (dd, $J = 7.9$, 1.4 Hz, 1H), 7.84 (dd, $J = 10.2$, 7.5, 1.1 Hz, 2H), 7.78 – 7.72 (m, 1H), 7.56 – 7.51 (m, 2H), 7.40 (td, $J = 7.9$, 1.1 Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.6, 164.5, 140.0, 138.8, 138.7, 134.5, 133.9, 132.3, 130.8, 130.6, 129.2, 128.8, 127.5, 123.6, 123.2, 118.4. HRMS (ESI): m/z calculated for C$_{20}$H$_{13}$ClN$_2$O$_3$S [M+H]$^+$: 397.0414, found: 397.0415.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-phenyl)-3-fluorobenzamide

Following the general procedure 3, 6aj was obtained as a brownish solid (27.3 mg, 0.071 mmol, 55%). M. p. = 176-178 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 10.84 (s, 1H), 8.80 (d, $J = 8.4$ Hz, 1H), 8.08 (d, $J = 7.2$ Hz, 1H), 7.93 (dd, $J = 15.6$, 7.6 Hz, 2H), 7.82 (ddd, $J = 31.9$, 15.9, 8.1 Hz, 6H), 7.54 (dd, $J = 13.6$, 7.8 Hz, 1H), 7.40 (t, $J = 7.6$ Hz, 1H), 7.29 (t, $J = 7.2$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 169.6, 164.3 (d, $^1$J$_{CF} =$ 253 Hz), 140.0, 138.6, 136.2 (d, $^3$J$_{CF} =$ 7 Hz), 134.5, 133.9, 130.7 (d, $^3$J$_{CF} =$ 7 Hz), 130.6, 127.5, 123.7, 123.2, 122.5 (d, $^4$J$_{CF} =$ 3 Hz), 119.4 (d, $^3$J$_{CF} =$ 21 Hz), 118.5, 115.1 (d, $^3$J$_{CF} =$ 24 Hz). HRMS (ESI): m/z calculated for C$_{20}$H$_{13}$F$_3$N$_2$O$_3$S [M+H]$^+$: 381.0709, found: 381.0714.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-phenyl)-2-fluorobenzamide

Following the general procedure 3, 6ak was obtained as a brownish solid (7 mg,
0.018 mmol, 14%). M. p. = 207-209 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.61 (d, \(J = 10.3\) Hz, 1H), 8.65 (d, \(J = 8.3\) Hz, 1H), 8.17 – 8.02 (m, 2H), 7.94 – 7.69 (m, 6H), 7.55 (d, \(J = 5.6\) Hz, 1H), 7.40 (t, \(J = 7.5\) Hz, 1H), 7.36 – 7.19 (m, 3H). \(^{19}\)F NMR (377 MHz, CDCl\(_3\)) \(\delta\) -111.53.

\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 169.3, 162.2, 160.5 (d, \(^1\)J\(_{CF}\) = 253 Hz) 140.2, 137.9, 134.1 (d, \(^3\)J\(_{CF}\) = 9 Hz) 133.8, 133.7 (d, \(^3\)J\(_{CF}\) = 8 Hz) 131.8, 130.8, 130.3, 127.1, 124.8 (d, \(^4\)J\(_{CF}\) = 3 Hz), 124.6, 124.1, 123.0, 121.2 (d, \(^2\)J\(_{CF}\) = 11 Hz), 119.7, 116.6 (d, \(^2\)J\(_{CF}\) = 24 Hz).

HRMS (ESI): m/z calculated for C\(_{20}\)H\(_{13}\)FN\(_2\)O\(_3\)S [M+H]\(^+\): 381.0709, found: 381.0713.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-phenyl)-2-naphthamide

Following the general procedure 3, 6al was obtained as a yellow solid (52.2 mg, 0.126 mmol, 90%). M. p. = 169-171 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 11.07 (s, 1H), 8.96 – 8.90 (m, 1H), 8.57 (d, \(J = 1.4\) Hz, 1H), 8.17 – 8.06 (m, 3H), 8.01 – 7.93 (m, 2H), 7.93 – 7.88 (m, 2H), 7.86 – 7.73 (m, 3H), 7.64 – 7.56 (m, 2H), 7.37 (td, \(J = 7.8, 1.1\) Hz, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 169.7, 165.7, 140.0, 139.1, 135.1, 134.6, 133.9, 133.8, 132.8, 131.0, 130.9, 130.6, 129.6, 128.8, 128.1, 128.1, 127.6, 126.9, 123.9, 123.4, 123.1, 118.3. HRMS (ESI): m/z calculated for C\(_{24}\)H\(_{16}\)N\(_2\)O\(_3\)S [M+H]\(^+\): 413.0960, found: 413.0959.

N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)cyclobutanecarboxamide

Following the general procedure 3, 6am was obtained as a brown solid (52.2 mg, 0.126 mmol, 90%). M. p. = 177-179 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.58 (d, \(J = 8.4\) Hz, 1H), 8.07 (d, \(J = 7.2\) Hz, 1H), 7.90 (d, \(J = 7.5\) Hz, 1H), 7.88 – 7.76 (m, 3H), 7.67 (t, \(J = 7.8\) Hz, 1H), 7.31 (dd, \(J = 14.2, 6.5\) Hz, 2H), 3.32 – 3.21 (m, 1H), 2.36 (dt, \(J = 12.2, 9.5\) Hz, 4H), 2.04 (dd, \(J = 19.0, 9.5\) Hz, 1H), 1.97 – 1.85 (m, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 174.0, 169.4, 140.0, 138.8, 134.3, 133.8, 133.7, 130.9, 130.4, 127.4, 123.2, 123.2, 123.1, 118.1, 41.2, 25.3, 17.9. HRMS (ESI): m/z calculated for C\(_{18}\)H\(_{16}\)N\(_2\)O\(_3\)S [M+H]\(^+\): 341.0960, found: 341.0962.
N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)thiophene-3-carboxamide

Following the general procedure 3, 6an was obtained as a yellow solid (52.2mg, 0.126mmol, 90%). M. p. = 174-176 ºC. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.73 (s, 1H), 8.84 (d, $J = 8.5$ Hz, 1H), 8.17 – 8.14 (m, 1H), 8.10 (d, $J = 7.3$ Hz, 1H), 7.96 (d, $J = 7.5$ Hz, 1H), 7.93 – 7.81 (m, 3H), 7.74 (t, $J = 7.9$ Hz, 1H), 7.65 (d, $J = 5.2$ Hz, 1H), 7.45 (dd, $J = 4.9$, 3.0 Hz, 1H), 7.37 (t, $J = 7.6$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.6, 161.0, 140.0, 139.1, 137.3, 134.6, 133.9, 133.8, 130.9, 130.6, 129.8, 127.6, 127.0, 126.3, 123.3, 123.2, 123.0, 117.9. HRMS (ESI): m/z calculated for C$_{18}$H$_{12}$N$_2$O$_3$S$_2$ [M+H]$^+$: 369.0368, found: 369.0366.

3-(2-((3,5-bis(trifluoromethyl)phenyl)amino)phenyl)benzo[d]isothiazole 1, 1 – dioxide

Following the general procedure, 6ao was obtained as an orange solid (18.2mg, 0.126mmol, 37%). M. p. = 183-185 ºC. $^1$H NMR (400 MHz, CDCl$_3$) δ 9.25 (s, 1H), 8.07 (d, $J = 6.6$ Hz, 1H), 8.03 (d, $J = 6.9$ Hz, 1H), 7.94 (d, $J = 8.8$ Hz, 1H), 7.82 (dd, $J = 9.9$, 4.3 Hz, 2H), 7.64 (s, 2H), 7.59 (t, $J = 7.8$ Hz, 1H), 7.52 (d, $J = 8.3$ Hz, 2H), 7.20 (t, $J = 7.5$ Hz, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.7, 143.9, 142.4, 139.9, 134.6, 133.6 (q, $^1$J$_{CF} = 273$ Hz), 131.9, 131.1, 130.5 (q, $^1$J$_{CF} = 269$ Hz), 127.3, 123.1, 120.9, 119.7, 119.6, 117.5, 116.8, 116.0, 116.0. HRMS (ESI): m/z calculated for C$_{21}$H$_{12}$F$_6$N$_2$O$_2$S $^{[M+H]}$: 471.0602, found: 471.0601.

2.3.4.4 General procedure for amidation of cyclic N-sulfonyl ketimine with 4-chlorobenzoyl azide

To a screw capped vial with stir bar were added cyclic N-sulfonyl ketimine (1, 0.012 mmol), acyl azide (5i, 0.014 mmol), [IrCp*Cl$_2$]$_2$ (3.9 mg, 0.004 mmol, 4 mol %), AgNTf$_2$ (7.6 mg, 0.016 mmol, 16 mol %), AgOAc (6.2 mg, 0.037 mmol, 30 mol%)
and 1,2-dichloroethane (0.5 ml) under atmospheric conditions. The reaction mixture was stirred at 25 °C for 24 h, filtered through a pad of celite and then washed with dichloromethane (10 mL x 3). Organic solvents were removed under reduced pressure and the residue was purified by chromatography on silica gel (n-hexane/EtOAc) to give the desired product 7.

4-chloro-N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-5-methylphenyl)benzamide,

Following the general procedure 4, 7ai was obtained as a yellow solid (42 mg, 0.102 mmol, 85%). M. p. = 214-216 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.96 (s, 1H), 8.68 (s, 1H), 8.07 (d, $J$ = 7.0 Hz, 1H), 7.97 (dd, $J$ = 7.7, 6.0 Hz, 3H), 7.87 – 7.77 (m, 3H), 7.52 (d, $J$ = 8.5 Hz, 2H), 7.19 (d, $J$ = 8.1 Hz, 1H), 2.55 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.4, 164.6, 146.3, 140.0, 139.0, 138.7, 133.8, 133.7, 132.4, 131.0, 130.7, 129.2, 128.9, 127.5, 124.6, 123.5, 123.1, 115.7, 22.3. HRMS (ESI): m/z calculated for C$_{21}$H$_{15}$ClN$_2$O$_3$S [M+H]$^+$: 411.0570, found: 411.0569.

4-chloro-N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-5-(trifluoromethylphenyl)benzamide

Following the general procedure 4, 7bi was obtained as a white solid (38 mg, 0.081 mmol, 80%). M. p. = 245-247 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.83 (s, 1H), 9.19 (s, 1H), 8.15 – 8.10 (m, 1H), 8.03 (d, $J$ = 8.2 Hz, 1H), 7.96 (d, $J$ = 8.6 Hz, 2H), 7.91 (dd, $J$ = 6.8, 4.9 Hz, 2H), 7.88 – 7.84 (m, 1H), 7.64 (d, $J$ = 8.2 Hz, 1H), 7.54 (d, $J$ = 8.6 Hz, 2H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ -63.48. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.9, 164.5, 139.9, 139.3, 139.2, 135.9, 135.6, 134.3, 134.1, 131.7, 130.9, 130.2, 129.4, 128.8, 127.1, 124.4, 123.5, 120.4 (q, $^1$J$_{CF}$ = 272 Hz). HRMS (ESI): m/z calculated for C$_{21}$H$_{15}$ClF$_3$N$_2$O$_3$S [M+H]$^+$: 465.0288, found: 465.0286.
4-chloro-N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-5-methoxyphenyl)benzamide

Following the general procedure 4, 7ci was obtained as a yellow solid (41.6 mg, 0.097 mmol, 89%). M. p. = 205-207 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 11.42 (s, 1H), 8.59 (d, \(J = 2.5\) Hz, 1H), 8.09 – 8.05 (m, 1H), 8.00 (d, \(J = 8.6\) Hz, 3H), 7.93 (d, \(J = 8.9\) Hz, 1H), 7.86 – 7.76 (m, 2H), 7.57 – 7.50 (m, 2H), 6.89 (dd, \(J = 8.9, 2.6\) Hz, 1H), 4.01 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.6, 165.0, 164.9, 142.2, 140.0, 138.8, 133.6, 133.5, 132.7, 132.4, 131.3, 129.3, 128.9, 127.4, 123.0, 111.1, 110.5, 106.4, 55.9. HRMS (ESI): m/z calculated for C\(_{21}\)H\(_{15}\)ClN\(_2\)O\(_4\)S \([\text{M+H}]^+\): 427.0519, found: 427.0520.

4-chloro-N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-5-phenoxyphenyl)benzamide

Following the general procedure 4, 7di was obtained as a yellow solid (38.4 mg, 0.078 mmol, 84%). M. p. = 169-171 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 11.25 (s, 1H), 8.56 (d, \(J = 2.5\) Hz, 1H), 8.08 (d, \(J = 7.0\) Hz, 1H), 8.02 – 7.90 (m, 4H), 7.88 – 7.76 (m, 2H), 7.56 – 7.45 (m, 4H), 7.30 (dd, \(J = 9.7, 5.2\) Hz, 1H), 7.21 (d, \(J = 7.7\) Hz, 2H), 6.92 (dd, \(J = 8.8, 2.5\) Hz, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.7, 164.6, 163.6, 154.6, 141.7, 140.0, 138.8, 133.7, 132.9, 132.3, 131.1, 130.2, 129.2, 128.9, 127.4, 125.3, 123.2, 120.6, 112.3, 112.2, 111.0. HRMS (ESI): m/z calculated for C\(_{26}\)H\(_{17}\)ClN\(_2\)O\(_4\)S \([\text{M+H}]^+\): 489.0676, found: 489.0674.

4-chloro-N-(5-chloro-2-(1,1-dioxidobenzo[d]isothiazol-3-yl)phenyl)benzamide

Following the general procedure 4, 7ei was obtained as a yellow solid (46 mg, 0.106 mmol, 95%). M. p. = 210-212 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 10.96 (s, 1H), 8.94 (d, \(J = 1.6\) Hz, 1H), 8.09 (d, \(J = 7.2\) Hz, 1H), 7.94 (d, \(J = 8.6\) Hz, 3H), 7.91 – 7.79 (m, 3H), 7.52 (d, \(J = 8.5\) Hz, 2H), 7.36 (dd, \(J = 8.5, 1.8\) Hz, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 168.9, 164.5, 141.3, 140.0, 139.9, 139.0, 134.1, 134.0,
131.9, 131.6, 130.5, 129.3, 128.9, 127.2, 123.9, 123.3, 122.9, 116.3. HRMS (ESI): m/z calculated for C$_{21}$H$_{13}$Cl$_2$N$_2$O$_3$S [M+H]$^+$: 431.0024, found: 431.0027.

4-chloro-N-(4-(1,1-dioxidobenzo[d]isothiazol-3-yl)-[1,1′-biphenyl]-3-yl)benzamide

Following the general procedure 4, 7fi was obtained as a yellow solid (37.3 mg, 0.078mmol, 79%). M. p. = 202-204 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 11.05 (s, 1H), 9.16 (d, $J = 1.6$ Hz, 1H), 8.10 (d, $J = 6.8$ Hz, 1H), 8.04 – 7.97 (m, 4H), 7.90 – 7.82 (m, 2H), 7.81 – 7.76 (m, 2H), 7.62 (dd, $J = 8.3$, 1.7 Hz, 1H), 7.57 – 7.51 (m, 4H), 7.41 – 7.38 (m, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.3, 164.7, 147.4, 144.0, 139.5, 139.0, 138.8, 133.9, 133.8, 132.3, 131.3, 130.9, 129.3, 129.1, 129.0, 128.9, 127.5, 127.4, 123.2, 122.1, 121.4, 116.9. HRMS (ESI): m/z calculated for C$_{26}$H$_{17}$ClN$_2$O$_3$S [M+H]$^+$: 473.0727, found: 473.0723.

4-chloro-N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-5-fluorophenyl)benzamide

Following the general procedure 4, 7gi was obtained as a pale yellow solid (45.8 mg, 0.110mmol, 91%). M. p. = 199-201 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 11.13 (s, 1H), 8.71 (dd, $J = 1.1$, 2.5 Hz, 1H), 8.09 (d, $J = 7.2$ Hz, 1H), 7.97 (t, $J = 8.2$ Hz, 4H), 7.91 – 7.79 (m, 2H), 7.53 (d, $J = 8.5$ Hz, 2H), 7.13 – 7.03 (m, 1H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ -99.22, -99.24, -99.25. $^{13}$C NMR (101 MHz, CDCl$_3$) δ 168.8, 166.2 (d, $^1$J$_{CF}$ = 256 Hz), 164.6, 144.1 (d, $^3$J$_{CF}$ = 13 Hz), 139.9, 139.0, 134.0 (d, $^4$J$_{CF}$ = 6 Hz), 132.9 (d, $^3$J$_{CF}$ = 11 Hz), 131.9, 130.7, 129.3, 128.9, 127.3, 123.3, 114.1, 114.1, 111.1 (d, $^2$J$_{CF}$ = 23 Hz) 110.2 (d, $^2$J$_{CF}$ = 28 Hz).

HRMS (ESI): m/z calculated for C$_{20}$H$_{12}$ClFN$_2$O$_3$S [M+H]$^+$: 415.0319, found: 415.0321.
4-chloro-N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-3-methoxyphenyl)benzamide

Following the general procedure 4, 7hi was obtained as a yellow solid (41.2 mg, 0.096mmol, 84%). M. p. = 225-227 °C. 

$^1$H NMR (400 MHz, CDCl$_3$) δ 9.88 (s, 1H), 8.26 (d, $J = 8.4$ Hz, 1H), 8.00 (d, $J = 7.5$ Hz, 1H), 7.92 (d, $J = 8.6$ Hz, 2H), 7.77 (t, $J = 7.4$ Hz, 1H), 7.67 (dt, $J = 16.9$, 8.0 Hz, 2H), 7.51 (dd, $J = 11.1$, 8.3 Hz, 3H), 6.92 (d, $J = 8.4$ Hz, 1H), 3.84 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 170.4, 164.2, 158.4, 139.2, 138.7, 138.0, 134.3, 133.5, 133.4, 132.1, 131.7, 129.1, 128.8, 127.4, 122.2, 115.6, 107.0, 55.6. 

HRMS (ESI): m/z calculated for C$_{21}$H$_{15}$ClN$_2$O$_4$S [M+H]$^+$: 427.0519, found: 427.0519.

4-chloro-N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-4-methylphenyl)benzamide

Following the general procedure 4, 7ii was obtained as a yellow solid (35.8 mg, 0.087mmol, 73%). M. p. = 169-171 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ 10.69 (s, 1H), 8.65 (d, $J = 8.6$ Hz, 1H), 8.11 – 8.05 (m, 1H), 7.98 – 7.91 (m, 3H), 7.89 – 7.79 (m, 2H), 7.68 (d, $J = 1.2$ Hz, 1H), 7.55 (dd, $J = 8.6$, 1.6 Hz, 1H), 7.53 – 7.48 (m, 2H), 2.50 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.6, 164.4, 140.0, 138.6, 136.2, 135.3, 133.8, 133.8, 133.5, 132.4, 130.8, 130.6, 129.2, 128.8, 127.5, 123.3, 123.1, 118.5, 21.0. 

HRMS (ESI): m/z calculated for C$_{21}$H$_{15}$ClN$_2$O$_3$S [M+H]$^+$: 411.0570, found: 411.0572.

4-chloro-N-(2-(1-dioxidobenzo[d]isothiazol-3-yl)-4-methoxyphenyl)benzamide,

Following the general procedure 4, 7ji was obtained as a pale orange solid (39.2 mg, 0.087mmol, 77%). M. p. = 200-202 °C.

$^1$H NMR (400 MHz, CDCl$_3$) δ 10.44 (s, 1H), 8.64 (d, $J = 9.2$ Hz, 1H), 8.09 (d, $J = 6.9$ Hz, 1H), 8.00 – 7.91 (m, 3H), 7.84 (dtd, $J = 20.5$, 7.5, 1.1 Hz, 2H), 7.54 – 7.49 (m, 2H), 7.38 (d, $J = 2.9$ Hz, 1H), 7.33 – 7.30 (m, 1H), 3.94 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.3, 164.4, 155.5, 140.0, 138.5, 133.9, 133.9, 132.4,
131.5, 130.7, 129.2, 128.7, 127.3, 125.4, 123.2, 120.0, 119.1, 116.0, 55.8. HRMS (ESI): m/z calculated for C_{21}H_{15}^{35}Cl_{2}N_{2}O_{3}S [M+H]^+: 427.0519, found: 427.0523.

4-chloro-N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)-(trifluoromethylphenyl)benzamide

Following the general procedure 4, 7ki was obtained as a white solid (33 mg, 0.071mmol, 71%). M. p. = 220-222 °C. ¹H NMR (400 MHz, CDCl₃) δ 11.00 (s, 1H), 9.04 (d, J = 8.9 Hz, 1H), 8.18 (s, 1H), 8.13 (d, J = 6.9 Hz, 1H), 7.98 (dd, J = 11.8, 5.1 Hz, 3H), 7.92 (ddd, J = 9.8, 6.0, 3.2 Hz, 3H), 7.55 (d, J = 8.6 Hz, 2H). ¹⁹F NMR (377 MHz, CDCl₃) δ -62.36. ¹³C NMR (101 MHz, CDCl₃) δ 168.6, 164.6, 141.8, 139.9, 139.3, 134.3 (d, J_{CF} = 3 Hz), 131.7, 131.1 (q, J_{CF} = 267 Hz), 130.1, 127.6, 127.1, 125.7, 125.4, 124.7, 123.5, 123.0, 122.0, 117.9. HRMS (ESI): m/z calculated for C_{21}H_{12}^{35}Cl_{3}F_{3}N_{2}O_{3}S [M+H]^+: 465.0288, found: 465.0292.

1-dioxidobenzo[d]isothiazol-3-yl)-4-

Following the general procedure 4, 7li was obtained as a brownish solid (51.3 mg, 0.114mmol, 98%). M. p. = 242-244 °C. ¹H NMR (400 MHz, CDCl₃) δ 10.69 (s, 1H), 9.20 (s, 1H), 8.43 (s, 1H), 8.13 (dd, J = 6.6, 1.0 Hz, 1H), 8.06 – 7.93 (m, 5H), 7.92 – 7.83 (m, 2H), 7.72 – 7.67 (m, 1H), 7.60 – 7.51 (m, 3H). ¹³C NMR (101 MHz, CDCl₃) δ 169.8, 164.4, 140.1, 138.6, 135.9, 134.0, 133.3, 132.9, 132.5, 130.0, 129.2, 128.8, 128.8, 128.7, 128.2, 127.5, 126.6, 123.3, 120.8, 119.0. HRMS (ESI): m/z calculated for C_{24}H_{15}^{35}Cl_{3}F_{3}N_{2}O_{3}S [M+H]^+: 447.0570, found: 447.0571.

4-chloro-N-(2-(1,1-dioxidobenzo[d]isothiazol-3-yl)naphthalen-2-yl)benzamide

Following the general procedure 4, 7mi was obtained as a white solid (47.5 mg, 91
0.115mmol, 98%). M. p. = 211-213 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 10.82 (s, 1H), 8.79 (d, $J = 8.4$ Hz, 1H), 7.95 (t, $J = 8.5$ Hz, 3H), 7.89 (d, $J = 7.0$ Hz, 1H), 7.74 (t, $J = 7.9$ Hz, 1H), 7.70 (s, 1H), 7.64 (d, $J = 7.7$ Hz, 1H), 7.51 (d, $J = 8.5$ Hz, 2H), 7.40 (t, $J = 7.5$ Hz, 1H), 2.56 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 169.7, 164.5, 145.3, 138.7, 137.3, 134.4, 134.4, 132.3, 131.3, 130.6, 129.2, 128.9, 128.0, 123.6, 123.2, 123.0, 118.5, 21.9. HRMS (ESI): m/z calculated for C$_{21}$H$_{15}$ClN$_2$O$_3$S [M+H]$^+$: 411.0570, found: 411.0573.

4-chloro-N-(2-(1-dioxido-4,5-dihydroisothiazol-3-yl)phenyl)benzamide

Following the general procedure 4, 7ni was obtained as a white solid (47.5 mg, 0.115mmol, 98%). M. p. = 204-206 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ 12.16 (s, 1H), 9.07 (d, $J = 8.6$ Hz, 1H), 8.02 (d, $J = 8.5$ Hz, 2H), 7.78 (d, $J = 7.9$ Hz, 1H), 7.74 (t, $J = 7.9$ Hz, 1H), 7.56 (d, $J = 8.5$ Hz, 2H), 3.90 – 3.82 (m, 2H), 3.51 – 3.44 (m, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 175.4, 165.2, 141.6, 138.8, 136.4, 132.8, 130.2, 129.3, 129.0, 123.3, 121.4, 116.9, 43.0, 35.2. HRMS (ESI): m/z calculated for C$_{16}$H$_{13}$ClN$_2$O$_3$S [M+H]$^+$: 347.0257, found: 411.0572

2.4 Summary

In conclusion, we have described an iridium-catalyzed mild and regioselective amidation protocol for cyclic N-sulfonyl ketimines with a range of organic azides to furnish the amidated products in moderate to excellent yields, which offers an efficient route to the synthesis of biologically relevant aminosultam compounds.

2.5 References


CHAPTER 3

PALLADIUM CATALYZED DIRECT C-H
TRIFLUROETHYLATION OF
AROMATIC AMIDES
3.1 Introduction

In recent years, naturally existing organohalogen compounds have been considered as a vital role in natural products field. Thousands of various compounds have been found processing an array of diverse structures. Bacteria, plants, marine animals and fungi have an amazing capacity of biosynthesizing such compounds.\(^1\) To date, approximately more than 3000 natural products have been reported to contain halogens, mainly bromine, iodine and chlorine.\(^2\)

To surprise, fluorine, being the most ample halogen in the earth’s crust, is an integral part of only 13 metabolites. In reality, only 6 natural products are identified as 8 out of 13 are derived from the seeds of the same plant (Scheme 3-1).\(^3\) It was in 1943, the first organo-fluorine compound, fluoroacetate, was discovered from Dichapetalum cymosum, Southern African plant.\(^4\)

![Scheme 3-1. Fluorine containing natural products](image)

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The nature of biological fluorination process is one fascinating feature of fluorinated metabolites. Despite a range of hypothetical approaches and considerable concern, to the mechanism, till date there exist no particular informations about the fluorination biochemistry in any organism. Experimentally, the first enzymatic synthesis of carbon-fluorine bonds was reported by Withers et al. in 2001.\(^5\) In **Scheme 3-2** Abg E358S catalyses nucleophilic fluorination of 2,4-dinitrophenyl yS-glucoside and subsequently transfers α-glucosyl fluoride to a second equivalent of substrate.

![Scheme 3-2](image)

**Scheme 3-2.** Abg E358S catalyzing nucleophilic fluorination

In **Scheme 3-3** Man2A E429A catalyses nucleophilic fluorination of the mannosylenzyme covalent intermediate and forms β-D-mannosyl fluoride (DNP = 2,5-dinitro phenyl).
The feasibility of occurrence of nucleophilic fluorination mechanism in nature can be demonstrated by the evidence of carbon-fluorine bond formation catalyzed by two unrelated glycosidases mutants. Desolvation of the anion and hydrogen bonding may be involved in this catalyzed nucleophilic fluorination mechanism.

Even in medicinal chemistry fluorine plays important roles. Till 1970, there were no reports of using fluorinated compounds in medicine, evidently no flourinated molecules had been utilized in the traditional Chinese medicine as most of the medicines were derived from naturally occurring compounds and their derivatives.⁶

The introduction of fluorine in organic molecules largely affects its biological properties. Fluorine being the smallest in size and having the highest electronegativity among the halogens⁷ in the periodic table has profound effects in medicinal chemistry. Insertion of a fluorine atom, or a trifluoromethyl (-CF₃) group or trifluoroethyl (-CH₂CF₃) group or perfluoroalkyl groups changes both pharmacokinetics and pharmacodynamics of an organic molecule. The presence of fluorine in the molecule increases lipid solubility, modifies the absorption ability,
eases drug transport in the plasma and also increases binding affinity to a targeted protein.\textsuperscript{3,8} By replacing the oxidizable C-H bond with C-F bond, the metabolism of the medicinal drugs by the enzymes can be reduced thus increasing the half-life and bioavailability of the drugs.\textsuperscript{3,9} Hence, just introduction of a fluorine atom increases metabolic stability. Because of its electronegativity fluorine atom increases acidity of molecules and at the same time it decreases basicity by decreasing the pKa of molecules.\textsuperscript{3,10}

\textbf{Scheme 3-4. Fluorine containing steroids and uracil analogues}

Fluorous functionalization of organic molecules is of vital importance in synthetic manipulations in drug discovery, agrochemicals and material science, thanks to the profound changes in the physiochemical and pharmacokinetic properties of the substrates invoked by the installation of bioisosteric fluorine/perfluoro groups.\textsuperscript{11} While substantial progress has already been achieved in C-C bond forming trifluoromethylations,\textsuperscript{12} the corresponding homologues trifluoroethylations\textsuperscript{13} are understandably more challenging owing to a number of factors such as the poor propensity of alkyl electrophiles to engage in the classical transition-metal catalyzed
pathways\textsuperscript{13a} (possibly because of the decay of the organometallic species to decay via beta-fluoride elimination),\textsuperscript{13f} drastic reaction conditions\textsuperscript{13d, 13h} and the need to pre-functionalize the substrates in many cases.\textsuperscript{13a-g} The advent of C-H functionalization methods has improved efficiency, selectivity and environmental appeal of cross-coupling reactions as this chemistry obviates the need for oxidized substrates by effecting intramolecular ligand-directed carbo-metalations on C-H bonds.\textsuperscript{14} Hypervalent iodonium reagents, on the other hand, are proving to be extremely useful reagents in organic synthesis owing to their enhanced electrophilicity, longer shelf-life and non-toxicity.\textsuperscript{15} Though directed C-H functionalization exploiting the reactivity of a variety of iodonium salts have advanced the efficient construction of many different types of $sp^2$c-$sp^2$c scaffolds,\textsuperscript{16} mild, direct-trifluoroethylation is still highly underdeveloped. Recently, Novák’s group has reported the palladium-catalysed trifluoroethylations of anilides and ureas employing hypervalent iodonium reagents as the perfluoroalkyl source, and it features the only report pertaining to this chemistry so far.\textsuperscript{13m-n} As a continuum of our own interest in directing group-assisted C-H bond functionalizations and perfluoroalkylations\textsuperscript{17}, we herein disclose an efficient palladium-catalyzed method for the trifluoroethylation of benzoamides using mesityl(2,2,2-trifluoroethyl)iodonium salt as the coupling partner.

In 2012, Hu et al. reported the trifluorethelation of arylboronic acids with the commercially available reagent employing palladium catalyst and xantphos ligand (\textbf{Scheme 3-5}). The reported method was applicable for the trifluoroethylolation of both
ary and alkenyl boronic esters. They even applied this method for the late stage modification of target molecules by installing trifluoroethyl group.

\[
\begin{align*}
BR_2 & \xrightarrow{[\text{Pd}_{2}\text{dba}_3]\cdot\text{CHCl}_3 \text{ (cat)} \cdot \text{Xanthos}} \xrightarrow{\text{Cs}_2\text{CO}_3, \text{CF}_3\text{CH}_2\text{I}} \xrightarrow{\text{dioxane/H}_2\text{O}, 80^\circ\text{C}} \text{CH}_2\text{CF}_3 \\
R &= \text{OH or OR}^1 \\
\text{Scheme 3-5. Trifluoroethylation of arylboronic esters by Hu et al.}
\end{align*}
\]

In the same year, Wu et al. achieved the cross-coupling reaction of aryl and heteroaryl boronic esters with 1,1,1-trifluoro-2-iodoethane. This reported, palladium catalyzed protocol helps to introduce trifluoroethyl group into various aryl and heteroaryl moieties (Scheme 3-6).

\[
\begin{align*}
\text{BnO} & \xrightarrow{\text{Pc cat. Ligand. base}} \xrightarrow{\text{solvent. additive, heat}} \text{BnO} \\
\text{Scheme 3-6. Trifluoroethylation of arylboronic esters by Wu et al.}
\end{align*}
\]

In the following year, Wu et al. extended their research to introduce trifluoroethyl group into aryl moieties by developing a Suzuki cross-coupling reaction of aryl boronic acids with CF\textsubscript{3}CH\textsubscript{2}OTs (OTs = 4-methylbenzene sulfonate) (Scheme 3-7).

\[
\begin{align*}
\text{Ar-OH} + \text{CF}_3\text{CH}_2\text{OTs} & \xrightarrow{5\text{ mol}\% \text{ Pd(OAc)}_2, 4\text{ mol}\% \text{ palladacycle}} \xrightarrow{1\text{ mol}\% \text{ PPh}_3, 3.0\text{ equiv Na}} \xrightarrow{3.0\text{ equiv K}_3\text{PO}_4} \xrightarrow{\text{DMSO, } 150^\circ\text{C, } 4\text{ h, Ar}} \text{Ar-CF}_3 \\
\text{Scheme 3-7. Trifluoroethylation of arylboronic acids by Wu et al.}
\end{align*}
\]
In 2014, Ackermann et al. reported nickel catalyzed alkylation and trifluoroethylation of unactivated arenes with high catalytic efficacy and substantial substrate scope (Scheme 3-8).

Scheme 3-8. Nickel catalyzed alkylation by Ackermann et al.

In 2014, Liu et al. explored the palladium catalyst for the synthesis of trifluoroethylstyrenes with a cascade C-H bond trifluoroethylation and heck reaction between aryl iodides, 1,1,1-trifluoro-2-iodoethane and styrenes (Scheme 3-9). They even carried out some preliminary mechanistic studies to show the involvement of Pd$^{IV}$ intermediate in this reaction.

Scheme 3-9. Synthesis of trifluoroethylstyrenes by Liu’s group
In 2015, Novak et al. developed selective C3-trifluoroethylation of indoles without employing any metal catalysts using 2,2,2-trifluoroethyl(mesityl)-iodonium triflate as the coupling partner (Scheme 3-10). This method is compatible with range of functional groups and is very mild. They employed triflate salt for the first time to introduce trifluoroethyl group.

![Scheme 3-10. C3-trifluoroethylation of indoles by Novak’s group](image)

Later in 2015, Yang et al. reported the first example of trifluoroethylation of aryl and heteroaryl boronic acids catalyzed by nickel (Scheme 3-11). They developed mild and efficient $C(sp^3)$-$C(sp^2)$ coupling reaction between boronic acids and alkyl halides.

![Scheme 3-11. Trifluoroethylation of aryl boronic acids catalyzed by Nickel](image)

Yamakawa et al. developed fluoroalkylation reactions using cobalt/diamine as catalysts. They used aryl Grignard reagents and fluoroalkyl halides as two components of reaction (Scheme 3-12).
In mid of 2016, Xu et al. developed a method for trifluoroethylation of imidazopyridines using 1,1,1-trifluoro-2-iodoethane as radical source by utilizing visible light photoredox catalyst (Scheme 3-13). The method reports ample functional group tolerance and high regioselectivity.

Scheme 3-13. Trifluoroethylation of imidazopyridines by Xu et al.

In late 2016, Novak et al. extended their work with 2,2,2-trifluoroethyl substituted iodonium salt to report trifluoroethylation of anilide derivatives under mild conditions in presence of palladium acetate catalyst (Scheme 3-14).

Scheme 3-14. Trifluoroethylation of anilide derivatives
Later in early 2017, the same group explored their trifluoroethylation method to ureas with modifying their previous procedure (Scheme 3-15). They reported high yield product formation in 3 hours with a range of aromatic ureas. They also carried out DFT studies to understand the reaction mechanism and explained the formation of palladacycle in the reaction.

![Scheme 3-15. Trifluoroethylation of urea derivatives](image)

### 3.2 Results and Discussions

At the outset, optimization of the reaction began with N-methyl benzamide (1a) as the model substrate. Palladium (II) acetate was employed as the catalyst and dichloroethane (DCE) was the solvent of choice (Table 3-1, entries 1-10, Supporting Information for more details). It was pleasing to observe that the reaction conditions enabled directed $o$-trifluoroethylation of the amide substrate at room temperature, although the conversion was marginal (Table 3-1, entry 1). Acid additives are known to enhance the catalytic efficiency of palladium salts and as such the reaction was repeated in the presence of stoichiometric trifluoroacetic acid (TFA). Gratifyingly, complete conversion was obtained (24 h) and the trifluoroethylated product (3) was isolated in a near-perfect yield of 96% (Table 3-1, entry 2). Other additives were also tested, but none of them were found to be as effective as TFA (Table 3-1, entries 3-5 and SI). Other palladium salts including Pd(TFA)$_2$ were found to be less ideal.
and metals other than palladium were totally ineffective towards effecting this reaction (SI and Table 3-1, entries 6-7). That the control experiment in the absence of the metal catalyst did not produce any product established the absolute requirement of the palladium catalyst and also has ruled out the possible involvement of a protic/Lewis acid mediated pathway (Table 3-1, entry 8). A wide range of solvents were also screened: while dichloromethane (DCM) was almost on par with DCE (Table 3-1, entry 9), co-coordinating solvents like MeOH (Table 1, entry 10), DMF, DMSO, MeCN totally inhibited the reaction (SI). Catalyst loading could be reduced to 7.5 mol % at the expense of the isolated yield (Table 3-1, entry 11).

**Table 3-1. Key optimization results for the trifluoroethylation of benzamide 1**[^a]

\[
\text{[Pd] (10 mol %)} \quad \text{additive (1 equiv)} \quad \text{solvent, 25 °C, 24 h} \quad \text{yield (\%)[b]}
\]

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>solvent</th>
<th>additive</th>
<th>yield (%)[b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$</td>
<td>DCE</td>
<td>-</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>Pd(OAc)$_2$</td>
<td>DCE</td>
<td>TFA</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>Pd(OAc)$_2$</td>
<td>DCE</td>
<td>HBF$_4$</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
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<td>DCE</td>
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<td>Pd(OAc)$_2$</td>
<td>DCE</td>
<td>TFA</td>
<td>67</td>
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</table>

[^a]: Unless otherwise specified, the reaction conditions are as follows: 1a (0.1 mmol), solvent (0.5 mL), Pd(OAc)$_2$ (10 mol %), additive (1 equiv) stirred for 24 h at rt. [b]: See SI for detailed optimization.
Having established the right set of conditions, we proceeded to explore the robustness of the protocol with respect to the ring substituents of the substrate. It was found that a range of substituents could be accommodated without any serious compromise in the reaction efficiency (Scheme 3-16, entries 3a-3t). *ortho*-Substituents like methyl and chloro were tolerated though *t*-butyl group understandably induced steric inhibition (Scheme 3-16, entries 3a-c). Substituents *meta* to the directing group imposed no significant electronic bias and substrates bearing methyl, functionally manipulable groups like methoxy, chloro and trifluoromethyl groups all reacted efficiently to provide the corresponding products in good yields (Scheme 3-16, entries 3d-g). *para*-Substituted amides were also tested and both electron-donating as well as electron-depleting groups were well tolerated (Scheme 3-16, entries 3h-n). Highly substituted benzene rings are generally averse to further cross-coupling, but the current protocol allowed for the easy synthesis of tetra-substituted trifluoroethyl benzamides in high yields (Scheme 3-16, entries 3o-q). Both 1 and 2-napthamides reacted with the same ease and a heterocyclic substrate like 1t could also be trifluoroethylated albeit with a low yield (Scheme 3-16, entry 3t).

In order to further the substrate scope and to identify if the substituents on the amide nitrogen atom pose any crucial bearing to the reaction profile, a variety of differently N-substituted handles were tested under the standard conditions (Scheme 3-17, entries 5a-m). The screening showed that the electronic nature of the N-substituents did not exert any crucial influence and a variety of substrates
Scheme 3-16. Exploration of the substrate scope of aromatic amides featuring alkyl/cycloalkyl, benzyl (no competing trifluoroethylation was observed on the phenyl ring on the handle) and amino acid residues were all tolerated with no striking disparity. That being the case, it was interesting to observe that increasing the steric bulk on the heteroatom substituent had a positive influence on the reaction efficiency (Scheme 3-17, entries 5f & 5j). Importantly, the preservation and no loss of enantiopurity was detected during the coupling reaction (Scheme 3-17, entries 5j-1). Another vital observation was the total lack of reactivity of N-disubstituted
substrate hinting at the indispensability of an N-H bond for the reaction to occur (Scheme 3-17, entry 5e) (vide infra).

Having established the substrate generality of the process, a set of experiments to understand the mechanistic course of the palladium-catalysed transformation were set forth. Cyclopalladated species are viable intermediates in directed C-H functionalizations and the first attempt was to experimentally validate the operation of such a species under our reaction conditions. In this

Scheme 3-17. Scope of N-substituents on the amide
direction, isolation of a potential palladacycle that could be generated upon the treatment of the amide substrate with stoichiometric amounts of palladium acetate in TFA was envisaged.\textsuperscript{18} To our delight, dimeric palladacycle 6 could be isolated from the N-adamantyl substituted amide 4j (Scheme 3-18, eq 1). X-ray quality crystals were generated thereby establishing the structural integrity of 6 beyond dispute (Scheme 3-18).\textsuperscript{19} As expected, the organopalladium species (6) has collapsed upon exposure to the alkyl electrophile (2), forming the trifluoroethylated product (5j) in 80\% isolated yield (Scheme 3-18, eq 2). That this step worked in the absence of added TFA specifies the latter’s role in the reaction mechanism. These experiments have amply supported a direct C-H alkylation pathway and the intermediacy of a cyclopalladated species (Figure 1).

\textbf{Scheme 3-18. Isolation of the palladacycle and its trifluoroethylation}
Figure 3-1. Crystal structure of the dimeric palladacycle

Intramolecular isotopic studies were then conducted with an equimolar mixture of 1a and [D5]-1a (Scheme 4). Trifluoroethylation favoured the cleavage of the C-H bond over C-D and a kinetic isotopic effect (KIE) of 1.98 was calculated from the 1H-NMR spectra. The presence of KIE indicates that the breakage of the C-H bond could well be a kinetically relevant step in the mechanistic profile. The recovered starting material 1a did not show any significant H/D exchange which is an indicator of a largely irreversible cyclometallation.

Scheme 3-19. Isotopic studies in trifluoroethylation of 1a

Based on the mechanistic data gathered, a plausible mechanism is proposed (Scheme 3-20). The protic acid TFA supposedly activate the palladium catalyst through ligand exchange3n,20 which then undergoes C-H insertion assisted by the directing group forming the cyclometallated intermediate A (the feasibility of A to exist in
equilibrium with the N-palladated species A is a realistic possibility considering the indispensability of an N-H bond in the substrate.\textsuperscript{[10c]} The strongly oxidizing conditions served by the presence of the hypervalent iodonium reagent could enable the conversion of the putative intermediate A to an oxidatively added Pd(IV) species B.\textsuperscript{18b, 20c, 21} Reductive elimination from B furnishes the product, closing the catalytic cycle through the regeneration of the active Pd(II) oxidation state.

Scheme 3-20. Plausible mechanism

3.3 Experimental Section

3.3.1  Mesityl(2,2,2-trifluoroethyl)iodonium trifluoromethanesulfonate (2)

2 was prepared following the procedure of previous literature.\textsuperscript{22}

3.3.2. Preparation of arene substrates

3.3.2.1. Procedure for the synthesis of N-methyl benzamides\textsuperscript{23}
MeNH₂ methanol solution (33.3%) (1.5 equiv.), acid chloride (1.0 equiv.), Et₃N (2.0 equiv.) and Et₂O (0.5 M) were added into a round bottom flask capped with a septum. The mixture was stirred at room temperature. After 1 h, the crude reaction mixture was extracted with Et₂O, purified by flash chromatography to get the corresponding N-methyl benzamides.

3.3.2.2 Preparation of additional arene substrates

Methyl benzoyl-L-phenylalaninate,²⁴ methyl benzoyl-L-leucinate,²⁵ and other benzamides were prepared according to the previously reported synthetic methods.

3.3.3 Optimization of reaction conditions

3.3.3.1 Solvent Effect

A 4 mL screw-cap vial equipped with a stirring bar was charged with palladium(II) acetate (0.007 mmol, 10 mol%, 1.6 mg), N-methylbenzamide (0.07 mmol, 10.0 mg) and mesityl(2,2,2-trifluoroethyl)iodonium trifluoromethanesulfonate (0.08 mmol, 42.4 mg). 0.5 mL solvent was added and the dark brown mixture was stirred at room temperature. Trifluoroacetic acid (0.05 mmol, 3.8 μl) was added instantly and the vessel was capped for 24 hours. After that reaction conversion was initially checked by TLC. The solvent was then removed under vacuum and the crude was dissolved in CDCl₃ solvent and NMR was run for the sample to calculate the percentage of conversion.
<table>
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<th>Solvent</th>
<th>Yield</th>
</tr>
</thead>
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</tr>
<tr>
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<td>CH₃CN</td>
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</tr>
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<td>3</td>
<td>Acetone</td>
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</tr>
<tr>
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### 3.3.3.2 Screening of catalysts

A 4 mL screw-cap vial equipped with a stirring bar was charged with metal catalyst (0.007 mmol, 10 mol%), N-methylbenamide (0.07 mmol, 10.0 mg) and mesityl(2,2,2-trifluoroethyl)iodonium trifluoromethanesulfonate (0.08 mmol, 42.4 mg). 0.5 mL 1, 2-dichloroethane was added and the dark brown mixture was stirred at room temperature. Trifluoroacetic acid (0.05 mmol, 3.8 μl) was added instantly and the vessel was capped for 24 hours. After that reaction conversion was initially checked by TLC. Then the solvent was removed under vacuum and the crude was dissolved in CDCl₃ solvent and NMR was run for the sample to calculate the percentage of conversion.
### Entry Catalyst Yield

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<th>Entry</th>
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<th>Yield</th>
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</tr>
<tr>
<td>2</td>
<td>Cu(OAc)$_2$</td>
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<td>3</td>
<td>Zn(OAc)$_2$</td>
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<td>4</td>
<td>Cu(OTf)$_2$</td>
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<td>Fe(OAc)$_2$</td>
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<td>Pd(TFA)$_2$</td>
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<tr>
<td>8</td>
<td>Pd(dba)$_3$</td>
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</tr>
<tr>
<td>9</td>
<td>Pd(OAc)$_2$</td>
<td>96</td>
</tr>
</tbody>
</table>

#### 3.3.3.3. Effect of Acid additives

A 4 mL screw-cap vial equipped with a stirring bar was charged with palladium(II) acetate (0.007 mmol, 10 mol%, 1.6 mg), N-methylbenamide (0.07 mmol, 10.0 mg) and mesityl(2,2,2-trifluoroethyl)iodonium trifluoromethanesulfonate (0.08 mmol, 42.4 mg). 0.5 mL 1, 2-dichloroethane was added and the dark brown mixture was stirred at room temperature. Acid additive (0.05 mmol, 3.8 μl) was added instantly and the vessel was capped for 24 hours. After that reaction conversion was initially checked by TLC. Then the solvent was removed under vaccum and the crude was dissolved in CDCl$_3$ solvent and NMR was run for the sample to calculate the percentage of conversion.
<table>
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<th>Entry</th>
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<tr>
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<td>H$_2$SO$_4$</td>
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</tr>
<tr>
<td>3</td>
<td>HBF$_4$</td>
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<tr>
<td>5</td>
<td>TfOH</td>
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</tr>
<tr>
<td>6</td>
<td>TsOH. H$_2$O</td>
<td>88</td>
</tr>
<tr>
<td>7</td>
<td>BF$_3$.OEt</td>
<td>91</td>
</tr>
</tbody>
</table>

3.3.3.4. Catalyst Loading

A 4 mL screw-cap vial equipped with a stirring bar was charged with palladium(II) acetate (x mol%), N-methylbenamide (0.07 mmol, 10.0 mg) and mesityl(2,2,2-trifluoroethyl)iodonium trifluoromethanesulfonate (0.08 mmol, 42.4 mg). 0.5 mL 1,2-dichloroethane was added and the dark brown mixture was stirred at room temperature. Trifluoroacetic acid (0.05 mmol, 3.8 μl) was added instantly and the vessel was capped for 24 hours. After that reaction conversion was initially checked by TLC. Then the solvent was removed under vaccum and the crude was dissolved in CDCl$_3$ solvent and NMR was run for the sample to calculate the percentage of conversion.
### 3.3.4 Experimental Procedure for Pd-Catalyzed C-H Trifluoroethylation of Arenes and Spectroscopic Data of Compounds Obtained in this Study

#### 3.3.4.1 Palladium catalyzed direct C-C bond formation of N-methyl aromatic amides with 1

A 4 mL screw-cap vial equipped with a stirring bar was charged with *palladium(II) acetate* (0.1 mmol, 10 mol%), *N*-methylbenzamide (1, 1 mmol) and *mesityl*(2,2,2-trifluoroethyl)iodonium trifluoromethanesulfonate (2,1.2 mmol). 0.5 mL *DCE* was added and the dark brown mixture was stirred at room temperature. *Trifluoroacetic*
acid (1 mmol) was added instantly and the vessel was capped for 24 hours. After the completion, the reaction mixture was washed with NaHCO$_3$ solution and extracted with EtOAc (3 x 20mL). The combined organics were dried over MgSO$_4$, filtered and dried under vacuum to get the crude product, which was further purified by flash column chromatography using EtOAc and Hexane solvent system to furnish the desired product 3.

**N-methyl-2-(2,2,2-trifluoroethyl)benzamide (3a)**

Following the general procedure, 3a was obtained as a white solid (42 mg, 0.193 mmol, 96%). MP = 168-169 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.47 – 7.33 (m, 4H), 6.00 (s, 1H), 3.80 (q, $J$=11.0 Hz, 2H), 2.98 (d, $J$=4.9 Hz, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -65.33. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) $\delta$ = 170.1, 137.5, 132.2, 130.1, 128.7 (dd, $J$ = 5.8, 2.8 Hz), 128.2, 127.2, 127.1, 124.5, 36.2 (q, $J$ = 29.7 Hz), 26.6. HRMS (ESI): m/z calculated for C$_{10}$H$_{10}$F$_3$NO $[M+H]^+$: 218.0793, found: 218.0804.

**N,2-dimethyl-6-(2,2,2-trifluoroethyl)benzamide (3b)**

Following the general procedure, 3b was obtained as a white solid (34 mg, 0.147 mmol, 70%). MP = 126-127 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.26 (t, $J$=7.6 Hz, 1H), 7.18 (t, $J$=6.8 Hz, 2H), 5.80 (s, 1H), 3.44 (q, $J$=10.9 Hz, 2H), 3.01 (d, $J$=4.9 Hz, 3H), 2.34 (s, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -64.99. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) $\delta$ = 169.9, 138.9, 134.93, 130.1, 128.9, 128.4, 127.1, 126.8 (q, $J$ = 2.8 Hz), 124.4, 37.1 (q, $J$ = 29.8 Hz), 26.3, 19.4. HRMS (ESI): m/z calculated for C$_{11}$H$_{12}$F$_3$NO $[M+H]^+$: 232.0949, found: 232.0960.

**2-chloro-N-methyl-6-(2,2,2-trifluoroethyl)benzamide (3c)**

Following the general procedure 3c was obtained as a white yellow solid (25 mg, 0.099 mmol, 52%). MP = 108-109 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.41 – 7.24 (m, 3H), 5.85 (s, 1H), 3.51 (q, $J$=10.6 Hz, 2H), 3.03 (d, $J$=4.9 Hz, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -64.99. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) $\delta$ = 166.9, 137.9, 131.3, 130.1, 129.6 (q, $J$ = 2.5 Hz), 129.6, 129.5, 129.2, 126.8, 124.0, 37.0 (q, $J$ =
30.3 Hz), 26.5. HRMS (ESI): m/z calculated for C_{10}H_{9}ClF_{3}NO [M+H]^+: 252.0403, found: 252.0411.

\[ \text{N,5-dimethyl-2-(2,2,2-trifluoroethyl)benzamide (3d) and N,3-dimethyl-2-(2,2,2-trifluoroethyl)benzamide (3d')} \]

Following the general procedure, 3d and 3d' were obtained as inseparable mixture as white solid (40 mg, 0.173 mmol, 82%, 3d: 3d' = 5:1). MP = 196-197 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.30 – 7.18 (m, 4H), 5.87 (s, 1H), 3.73 (q, J = 11.0 Hz, 2H), 2.98 (d, J = 4.9 Hz, 3H), 2.35 (s, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -64.37. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) $\delta$ = 170.2, 138.1, 137.4, 137.4, 132.1, 130.8, 127.7, 125.6 (q, J = 2.6 Hz), 120.0, 35.8 (q, J = 29.7 Hz), 26.6, 20.9. HRMS (ESI): m/z calculated for C_{11}H_{12}F_{3}NO [M+H]^+: 232.0949, found: 232.0941.

\[ \text{5-methoxy-N-methyl-2-(2,2,2-trifluoroethyl)benzamide (3e) and 3-methoxy-N-methyl-2-(2,2,2-trifluoroethyl)benzamide (3e')} \]

Following the general procedure, 3e and 3e' were obtained as inseparable mixture as white solid (34.3 mg, 0.138 mmol, 77%, 3e: 3e' = 5:1). MP = 165-166 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.27 (dd, J = 7.9, 4.2 Hz, 1H), 6.96 – 6.90 (m, 2H), 5.96 (s, 1H), 3.81 (s, 3H), 3.67 (q, J = 11.0 Hz, 2H), 2.96 (d, J = 4.9 Hz, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -64.92. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) $\delta$ = 169.9, 159.2, 133.4, 129.2, 127.3, 124.6,
5-chloro-N-methyl-2-(2,2,2-trifluoroethyl)benzamide (3f) and 3-chloro-N-methyl-2-(2,2,2-trifluoroethyl)benzamide (3f')

Following the general procedure, 3f and 3f' were obtained as white solid (25 mg, 0.099 mmol, 56%). **Major 3f**

MP = 175-176 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.54 (dd, $J$=6.9, 2.5 Hz, 1H), 7.37 – 7.30 (m, 2H), 5.91 (s, 1H), 4.15 (q, $J$=10.7 Hz, 2H), 3.02 (d, $J$=4.9 Hz, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -64.45. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) $\delta$ = 169.5, 139.7, 137.4, 131.5, 129.3, 127.2, 127.1, 125.5, 124.4, 33.5 (q, $J$ = 29.6 Hz), 26.7. HRMS (ESI): m/z calculated for C$_{11}$H$_{12}$F$_3$NO$_2$ [M+H]$^+$: 248.0898, found: 248.0894.

**Minor 3f'** (7.4 mg, 0.029 mmol, 16.5%) MP = 170-171 °C.

$^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.45 – 7.39 (m, 2H), 7.33 (d, $J$=8.1 Hz, 1H), 5.94 (s, 1H), 3.77 (q, $J$=10.9 Hz, 2H), 3.01 (d, $J$=4.9, 3H). $^{19}$F NMR (376 MHz, CDCl$_3$) $\delta$ = -65.42. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) $\delta$ = 168.6, 138.9, 134.3, 133.5, 130.2, 127.3, 127.3, 127.3, 127.2, 124.2, 35.8 (q, $J$ = 29.7 Hz), 26.7. HRMS (ESI): m/z calculated for C$_{10}$H$_9$ClF$_3$NO [M+H]$^+$: 252.0403, found: 252.0414.

N-methyl-2-(2,2,2-trifluoroethyl)-5-( trifluoromethyl)benzamide (3g)

Following the general procedure, 3g was obtained as a white solid (28.6 mg, 0.100 mmol, 67%). MP = 177-178 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.69 (d, $J$=5.9 Hz, 2H), 7.52 (d, $J$=8.4 Hz, 1H), 5.99 (s, 1H), 3.85 (q, $J$=10.8 Hz, 2H), 3.01 (d, $J$=4.9 Hz, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -62.89, -65.08. $^{13}$C NMR (101
\[ N,4\text{-dimethyl-2-(2,2,2-trifluoroethyl)benzamide (3h)} \]

Following the general procedure, 3h was obtained as a white solid (51.7 mg, 0.223 mmol, 78%). MP = 199-200 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.31 \text{ (d, } J=7.7 \text{ Hz, 1H), 7.15 \text{ (d, } J=10.6 \text{ Hz, 2H), 5.86 \text{ (s, 1H), 3.78 (q, } J=11.0 \text{ Hz, 2H), 2.97 (d, } J=9.7 \text{ Hz, 3H), 2.37 (s, 3H).} \)

\(^{19}\)F NMR (377 MHz, CDCl\(_3\)) \(\delta = -65.28\). \(^{13}\)C NMR (101 MHz, \(^{19}\)F coupled, CDCl\(_3\)) \(\delta = 170.2, 140.4, 134.6, 133.0, 128.8, 127.3, 127.1, 124.6, 36.1 \text{ (q, } J=29.7 \text{ Hz), 26.7, 21.2. HRMS (ESI): m/z calculated for C}_{11}H_{12}F_3NO [M+H]^+: 232.0949, \text{ found: 232.0955.} \)

\[ 4\text{-fluoro-N-methyl-2-(2,2,2-trifluoroethyl)benzamide (3i)} \]

Following the general procedure, 3i was obtained as a white solid (55 mg, 0.0234 mmol, 68%). MP = 160-161 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.12 \text{ - 7.00 (m, \text{ 2H), 5.94 (s, 1H), 3.80 (q, } J=10.8 \text{ Hz, 2H), 2.97 (d, } J=4.9 \text{ Hz, 3H).} \)

\(^{19}\)F NMR (377 MHz, CDCl\(_3\)) \(\delta = -65.22, -109.54 - -109.60\). \(^{13}\)C NMR (101 MHz, \(^{19}\)F coupled, CDCl\(_3\)) \(\delta = 169.2, 164.3, 161.8, 133.7 (d, } J=3.5 \text{ Hz), 131.7, 131.6, 129.1 (d, } J=8.7 \text{ Hz), 126.9, 124.2, 119.2 (d, } J=22.3 \text{ Hz), 115.1 (d, } J=21.3 \text{ Hz), 36.2 (qd, } J=H, 26.7. HRMS (ESI): m/z calculated for C}_{10}H_{9}F_4NO [M+H]^+: 236.0699, \text{ found: 236.0706.} \)

\[ 4\text{-chloro-N-methyl-2-(2,2,2-trifluoroethyl)benzamide (3j)} \]

Following the general procedure, 3j was obtained as a white solid (55 mg, 0.219 mmol, 75%). MP = 168-169 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.40 \text{ - 7.30 (m, \text{ 4H), 5.93 (s, 1H), 3.77 (q, } J=10.8 \text{ Hz, 2H), 2.97 (d, } J=4.9 \text{ Hz, 3H).} \)

\(^{19}\)F NMR (377 MHz, CDCl\(_3\)) \(\delta = -65.20\). \(^{13}\)C NMR (101 MHz, \(^{19}\)F coupled, CDCl\(_3\)) \(\delta = 169.1, 136.1, 135.8, 132.2, 130.8 (q, } J=3.0 \text{ Hz), 128.4, 128.4, 126.9, 124.1, 36.0 (q, } J=30.1 \text{ Hz), 26.7. HRMS (ESI): m/z calculated for C}_{10}H_{9}ClF_3NO [M+H]^+: 252.0403, \text{ found: 252.0403.} \)

\[ 4\text{-methoxy-N-methyl-2-(2,2,2-trifluoroethyl)benzamide (3k)} \]

Following the general procedure, 3k was obtained as a white solid (37.3 mg, 0.151 mmol, 84%). MP = 196-197 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.40 \text{ (d, } J=8.4 \text{ Hz, 1H), 6.94 \text{ - 6.84} \)

123
N-methyl-2-(2,2,2-trifluoroethyl)-4-(trifluoromethyl)benzamide (3l)

Following the general procedure, 3l was obtained as a white solid (37.6 mg, 0.131 mmol, 74%). Mp = 171-172 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ = 7.64 (d, \(J=6.3\) Hz, 2H), 7.55 (d, \(J=8.4\) Hz, 1H), 5.95 (s, 1H), 3.83 (q, \(J=10.8\) Hz, 2H), 3.01 (d, \(J=4.9\) Hz, 3H). \(^{19}\)F NMR (377 MHz, CDCl\(_3\)) δ = -63.06, -65.28. \(^{13}\)C NMR (101 MHz, \(^{19}\)F coupled, CDCl\(_3\)) δ = 168.7, 140.8, 132.8, 132.4, 132.1, 131.8, 129.9 (d, \(J=2.9\) Hz), 129.1 (dd, \(J=6.8, 3.0\) Hz), 127.6, 126.8, 125.3 (q, \(J=3.7\) Hz), 124.6, 124.0, 121.9, 36.2 (q, \(J=30.2\) Hz), 26.8. HRMS (ESI): m/z calculated for C\(_{11}\)H\(_9\)F\(_6\)NO\(_2\) [M+H\(^+\)]: 286.0667, found: 286.0667.

N-methyl-4-nitro-2-(2,2,2-trifluoroethyl)benzamide (3m)

Following the general procedure, 3m was obtained as a white solid (28.0 mg, 0.106 mmol, 65%). MP = 225-226 °C. \(^1\)H NMR (400 MHz, DMSO) δ = 8.70 (d, \(J=4.2\) Hz, 1H), 8.37 (d, \(J=1.9\) Hz, 1H), 8.30 (dd, \(J=8.4\) Hz, 2.4, 1H), 7.74 (d, \(J=8.4\) Hz, 1H), 4.12 (q, \(J=11.4\) Hz, 2H), 2.79 (d, \(J=4.5\) Hz, 3H). \(^{19}\)F NMR (376 MHz, DMSO) δ = -63.84. \(^{13}\)C NMR (101 MHz, \(^{19}\)F coupled, DMSO) δ = 167.7, 148.1, 143.8, 143.8, 130.9, 130.8, 129.9, 127.3 (q, \(J=2.7\) Hz), 124.9, 123.7, 35.1 (q, \(J=29.7\) Hz), 26.5. HRMS (ESI): m/z calculated for C\(_{10}\)H\(_9\)F\(_3\)N\(_2\)O\(_3\) [M+H\(^+\)]: 263.0644, found: 263.0641.

N-methyl-3-(2,2,2-trifluoroethyl)-[1, 1'-biphenyl]-4-carboxamide (3n)

Following the general procedure, 3n was obtained as a white solid (48 mg, 0.163 mmol, 82%). MP = 230-231 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ = 7.57 (dt, \(J=4.8, 1.6\) Hz, 4H), 7.47 (t, \(J=11.5\) Hz, 3H), 7.42 – 7.36 (m, 1H), 5.95 (s, 1H), 3.88 (q, \(J=11.0\) Hz, 2H), 3.01 (d, \(J=4.9\) Hz, 3H). \(^{19}\)F NMR (377 MHz, CDCl\(_3\)) δ = -65.19. \(^{13}\)C NMR (101 MHz, \(^{19}\)F coupled, CDCl\(_3\)) δ = 169.9, 143.2, 139.6, 136.1, 131.0, 129.4 (q, \(J=3.0\) Hz), 128.9, 128.1, 127.6, 127.3, 127.1, 126.8, 124.5, 53.4, 36.3 (q, \(J=29.8\) Hz), 26.7. HRMS (ESI): m/z calculated for C\(_{16}\)H\(_{14}\)F\(_3\)NO [M+H\(^+\)]: 294.1106, found: 294.1115.
3, 5-difluoro-N-methyl-2-(2,2,2-trifluoroethyl)benzamide (3o)

Following the general procedure, 3o was obtained as a white solid (46.3 mg, 0.183 mmol, 65%). MP = 159-160 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.01 – 6.90 (m, 2H), 6.17 (s, 1H), 3.84 (q, $J$=10.6 Hz, 2H), 2.97 (d, $J$=4.8 Hz, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ = -65.70, -65.73, -65.75, -65.78, -108.09 - -108.65. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) δ = 167.7 (t, $J$= 2.7 Hz), 163.5 (d, $J$= 11.9 Hz), 161.0 (d, $J$= 11.9 Hz), 140.3 (dd, $J$= 7.7, 4.3 Hz), 126.7, 124.0, 112.8 (dt, $J$= 17.2, 3.5 Hz), 110.5 (dd, $J$= 22.7, 3.7 Hz), 105.6 (dd, $J$= 27.0, 24.9 Hz), 28.6 (qd, $J$= 31.5, 3.4 Hz), 26.7. HRMS (ESI): m/z calculated for C$_{10}$H$_8$F$_5$NO $[M+H]^+$: 254.0604, found: 254.0608.

4, 5-dichloro-N-methyl-2-(2,2,2-trifluoroethyl)benzamide (3p)

Following the general procedure, 3p was obtained as a white solid (31 mg, 0.108 mmol, 67%). MP = 216-217 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.53 (s, 1H), 7.47 (s, 1H), 5.89 (s, 1H), 3.75 (q, $J$=10.7 Hz, 2H), 2.99 (d, $J$=4.9 Hz, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ = -65.28. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) δ = 167.7, 136.9, 134.4, 134.0, 132.6, 129.0, 128.9 (q, $J$= 3.0 Hz), 35.6 (q, $J$= 30.4 Hz), 26.8. HRMS (ESI): m/z calculated for C$_{10}$H$_8$Cl$_2$F$_3$NO $[M+H]^+$: 286.0013, found: 286.0011.

4, 5-dimethoxy-N-methyl-2-(2,2,2-trifluoroethyl)benzamide (3q)

Following the general procedure, 3q was obtained as a white solid (38.1 mg, 0.137 mmol, 79%). MP = 208-209 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ = 6.91 (s, 1H), 6.81 (s, 1H), 5.92 (s, 1H), 3.89 (d, $J$=10.0 Hz, 6H), 3.72 (q, $J$=10.9 Hz, 2H), 2.97 (d, $J$=4.7 Hz, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ = -65.40. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) δ = 169.8, 150.0, 148.4, 130.0, 127.3, 124.5, 121.5, 114.6, 110.4, 56.0, 56.0, 35.9 (q, $J$= 29.8 Hz), 26.7. HRMS (ESI): m/z calculated for C$_{12}$H$_{14}$F$_3$NO$_3$ $[M+H]^+$: 278.1004, found: 278.1003.

N-methyl-2-(2,2,2-trifluoroethyl)-1-naphthamide (3r)

Following the general procedure, 3r was obtained as a white solid (31.8 mg, 0.119 mmol, 67%). MP = 160-161 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.89 (ddd, $J$=15.8, 7.9, 1.5 Hz, 2H), 7.54 – 7.45 (m, 3H), 7.42 (d, $J$=8.0 Hz, 1H), 6.21 (s, 1H), 4.01 (dd, $J$=21.2, 10.5 Hz, 2H), 3.05 (d, $J$=4.9 Hz, 3H). $^{19}$F
NMR (377 MHz, CDCl\textsubscript{3}) \(\delta = -64.58\). \(^{13}\)C NMR (101 MHz, \(^{19}\)F coupled, CDCl\textsubscript{3}) \(\delta = 173.1, 135.1, 134.3, 132.1, 131.5, 130.0, 128.7, 127.2 (q, \(J = 2.5\) Hz), 126.2, 126.2, 125.8, 124.8, 124.4, 37.9 (q, \(J = 29.8\) Hz), 27.0. HRMS (ESI): m/z calculated for C\(_{14}\)H\(_{12}\)F\(_{3}\)NO [M+H]+: 268.0949, found: 268.0949

\(\text{N}-\text{methyl-3-(2,2,2-trifluoroethyl)-2-naphthamide (3s)}\)

Following the general procedure, 3s was obtained as a white solid (34.8 mg, 0.130 mmol, 75%). MP = 217-218 °C. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta = 7.96 (s, 1\text{H}), 7.87 (d, \(J=7.6\) Hz, 3H), 7.63 – 7.54 (m, 2H), 6.08 (s, 1H), 4.00 (q, \(J=11.0\) Hz, 2H), 3.08 (d, \(J=4.9\) Hz, 3H). \(^{19}\)F NMR (377 MHz, CDCl\textsubscript{3}) \(\delta = -65.36\). \(^{13}\)C NMR (101 MHz, \(^{19}\)F coupled, CDCl\textsubscript{3}) \(\delta = 173.1, 135.1, 134.3, 132.1, 131.5, 130.0, 128.7, 127.2 (q, \(J = 2.5\) Hz), 126.2, 126.2, 125.8, 124.8, 124.4, 37.9 (q, \(J = 29.8\) Hz), 27.0. HRMS (ESI): m/z calculated for C\(_{14}\)H\(_{12}\)F\(_{3}\)NO [M+H]+: 268.0949, found: 268.0952

\(\text{N}-\text{methyl-3-(2,2,2-trifluoroethyl)thiophene-2-carboxamide (3t)}\)

Following the general procedure, 3t was obtained as a white solid (18 mg, 0.080 mmol, 20%). MP = 147-148 °C. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta = 7.32 (d, \(J=5.1\) Hz, 1H), 7.09 (d, \(J=5.0\) Hz, 1H), 5.91 (s, 1H), 3.97 (q, \(J=10.9\) Hz, 2H), 2.97 (d, \(J=4.9\) Hz, 3H). \(^{19}\)F NMR (377 MHz, CDCl\textsubscript{3}) \(\delta = -65.00\). \(^{13}\)C NMR (101 MHz, \(^{19}\)F coupled, CDCl\textsubscript{3}) \(\delta = 162.9, 133.9 (q, \(J = 3.1\) Hz), 133.5, 130.9, 126.9, 126.0, 124.2, 32.9 (q, \(J = 30.7\) Hz), 26.7. HRMS (ESI): m/z calculated for C\(_{8}\)H\(_{8}\)F\(_{3}\)NOS [M+H]+: 224.0357, found: 224.0366.

3.3.4.1 Palladium catalyzed direct C-C bond formation of aromatic amides with

\(\text{1}\)

\(\text{N-ethyl-2-(2,2,2-trifluoroethyl)benzamide (5a)}\)

Following the general procedure, 5a was obtained as a white solid (42.8 mg, 0.185 mmol, 76%). MP = 142-143 °C. \(^1\)H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta = 7.45 – 7.30 (m, 4\text{H}), 5.98 (s, 1\text{H}), 3.78 (q, \(J=11.0\) Hz, 2H), 3.44 (qd, \(J=7.3, 5.9\) Hz, 2H), 1.21 (t, \(J=7.3\) Hz, 3H). \(^{19}\)F NMR (377 MHz, CDCl\textsubscript{3}) \(\delta = -65.25\). \(^{13}\)C NMR (101 MHz, \(^{19}\)F coupled, CDCl\textsubscript{3}) \(\delta = 169.4, 137.7, 132.2, 130.0, 128.6 (q, \(J = 2.9\) Hz), 128.1, 127.3, 127.0, 124.5, 36.2 (q, \(J = 29.8\) Hz), 34.8, 14.6. HRMS (ESI): m/z
calculated for C_{11}H_{12}F_{3}NO [M+H]^+: 232.0949, found: 232.0952.

**N-benzyl-2-(2,2,2-trifluoroethyl)benzamide (5b)**

Following the general procedure, 5b was obtained as a white solid (21.5 mg, 0.073 mmol, 52%). MP = 146-147 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.47 – 7.27 (m, 9H), 6.20 (s, 1H), 4.60 (d, J = 5.7 Hz, 2H), 3.82 (q, J = 11.0 Hz, 2H). ¹⁹F NMR (377 MHz, CDCl₃) δ = -65.17. ¹³C NMR (101 MHz, ¹⁹F coupled, CDCl₃) δ = 169.2, 137.7, 137.2, 132.3, 130.3, 128.9, 128.9, 128.8, 128.2, 127.9, 127.7, 127.2, 127.1, 44.1, 36.2 (q, J = 29.7 Hz). HRMS (ESI): m/z calculated for C_{16}H_{14}F_{3}NO [M+H]^+: 294.1106, found: 294.1112

**N-propyl-2-(2,2,2-trifluoroethyl)benzamide (5c)**

Following the general procedure, 5c was obtained as a white solid (41.5 mg, 0.169 mmol, 80%). MP = 130-131 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.45 – 7.30 (m, 4H), 5.99 (s, 1H), 3.78 (q, J = 11.0 Hz, 2H), 3.41 – 3.34 (m, 2H), 1.68 – 1.55 (m, 2H), 0.97 (t, J = 7.4 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ = -65.24. ¹³C NMR (101 MHz, ¹⁹F coupled, CDCl₃) δ = 169.4, 137.8, 132.2, 130.0, 128.6 (q, J = 2.9 Hz), 128.1, 127.3, 127.0, 124.5, 41.6, 36.2 (q, J = 29.7 Hz), 22.7, 11.3. HRMS (ESI): m/z calculated for C_{12}H_{14}F_{3}NO [M+H]^+: 246.1106, found: 246.1112

**N-butyl-2-(2,2,2-trifluoroethyl)benzamide (5d)**

Following the general procedure, 5d was obtained as a white solid (32.6 mg, 0.125 mmol, 72%). MP = 127-129 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.45 – 7.31 (m, 4H), 5.95 (s, 1H), 3.78 (q, J = 11.0 Hz, 2H), 3.41 (dd, J = 13.1, 7.0 Hz, 2H), 1.62 – 1.53 (m, 2H), 1.40 (dq, J = 14.4, 7.3 Hz, 2H), 0.95 (t, J = 7.3 Hz, 3H). ¹⁹F NMR (377 MHz, CDCl₃) δ = -65.24. ¹³C NMR (101 MHz, ¹⁹F coupled, CDCl₃) δ = 169.4, 137.8, 132.2, 130.0, 128.6, 128.3 (q, J = 2.9 Hz), 127.3, 127.0, 124.5, 39.7, 36.2 (q, J = 29.8 Hz), 31.5, 20.0, 13.6. HRMS (ESI): m/z calculated for C_{13}H_{16}F_{3}NO [M+H]^+: 260.1262, found: 260.1273

**N-(tert-butyl)-2-(2,2,2-trifluoroethyl)benzamide (5f)**

Following the general procedure, 5f was obtained as a white solid (41.5 mg, 0.160 mmol, 85%). MP = 117-118 °C. ¹H NMR (400 MHz, CDCl₃) δ = 7.43 – 7.29 (m, 4H), 5.71 (s,
**N-cyclopentyl-2-(2,2,2-trifluoroethyl)benzamide (5g)**

Following the general procedure, 5g was obtained as a white solid (33.1 mg, 0.122 mmol, 73%). MP = 154-155 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.44 – 7.32 (m, 4H), 5.86 (s, 1H), 4.44 – 4.30 (m, 1H), 3.77 (q, $J=11.0$ Hz, 2H), 2.12 – 2.01 (m, 2H), 1.75 – 1.60 (m, 4H), 1.48 (tt, $J=13.1$, 4.0 Hz, 2H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ = -65.20. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) δ = 169.1, 137.9, 132.2, 130.0, 128.5 (dd, $J=6.4$, 3.4 Hz), 127.3, 127.1, 124.5, 51.6, 36.2 (q, $J=29.6$ Hz), 33.0, 23.0. HRMS (ESI): m/z calculated for C$_{14}$H$_{16}$F$_3$NO $[M+H]^+$: 272.1275, found: 272.1275

**N-cyclohexyl-2-(2,2,2-trifluoroethyl)benzamide (5h)**

Following the general procedure, 5h was obtained as a white solid (35.4 mg, 0.124 mmol, 78%). MP = 189-190 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.47 – 7.34 (m, 4H), 5.79 (d, $J=6.6$ Hz, 1H), 4.03 – 3.92 (m, 1H), 3.80 (q, $J=11.0$ Hz, 2H), 2.10 – 2.00 (m, 2H), 1.82 – 1.73 (m, 2H), 1.66 (dd, $J=9.2$, 5.3 Hz, 1H), 1.53 – 1.39 (m, 2H), 1.23 (tdd, $J=16.8$, 7.6, 4.1 Hz, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ = -65.14. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) δ = 168.6, 138.0, 132.2, 130.0, 128.5 (dd, $J=5.3$, 2.3 Hz), 128.2, 127.3, 127.0, 126.8, 124.5, 48.6, 36.2 (q, $J=29.7$ Hz), 32.9, 25.5, 24.8. HRMS (ESI): m/z calculated for C$_{15}$H$_{18}$F$_3$NO $[M+H]^+$: 286.1419, found: 286.1416.

**N-(4-methoxybenzyl)-2-(2,2,2-trifluoroethyl)benzamide (5i)**

Following the general procedure, 5i was obtained as a white solid (33.0 mg, 0.102 mmol, 64%). MP = 141-142 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.44 – 7.31 (m, 4H), 7.29 – 7.24 (m, 2H), 6.88 (d, $J=8.6$ Hz, 2H), 6.13 (s, 1H), 4.54 (d, $J=5.6$ Hz, 2H), 3.90 – 3.72 (m, 5H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ = -65.17. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) δ = 169.1, 159.2, 137.3, 132.3, 130.2, 129.8, 129.2, 128.8 (q, $J=2.8$ Hz), 128.2, 127.3, 127.1, 124.5, 114.2, 55.3, 43.6, 36.1 (q, $J=29.8$ Hz). HRMS (ESI): m/z calculated for C$_{17}$H$_{18}$F$_3$NO $[M+H]^+$: 324.1211, found: 324.1213.
**N-((3s, 5s, 7s)-adamantan-1-yl)-2-(2,2,2-trifluoroethyl)benzamide (5j)**

Following the general procedure, 5j was obtained as a white solid (36.0 mg, 0.106 mmol, 88%). MP = 184-185 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.42 – 7.31 (m, 4H), 6.89 – 6.85 (m, 1H), 5.54 (s, 1H), 3.76 (q, $J$=11.0 Hz, 2H), 2.43 (s, 2H), 2.12 (d, $J$=7.5 Hz, 9H), 1.72 (s, 6H). $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -64.96. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) $\delta$ = 168.7, 141.7, 138.9, 137.3, 132.1, 129.7, 129.2, 128.2 (dd, $J$ = 5.9, 2.9 Hz), 128.1, 127.9, 127.4, 127.0, 124.6, 52.7, 41.5, 36.3, 36.1 (q, $J$ = 29.7 Hz), 29.4. HRMS (ESI): m/z calculated for C$_{19}$H$_{22}$F$_3$NO $[M+H]^+$: 338.1732, found: 338.1716.

**(S)-N-(phenylethyl)-2-(2,2,2-trifluoroethyl)benzamide (5k)**

Following the general procedure, 5k was obtained as a white solid (26.0 mg, 0.084 mmol, 46%). MP = 160-161 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ = 7.45 – 7.26 (m, 9H), 6.14 (d, $J$=6.9 Hz, 1H), 5.35 – 5.24 (m, 1H), 3.87 (dq, $J$=14.8, 11.0 Hz, 1H), 1.58 (d, $J$=6.9 Hz, 3H). $^{19}$F NMR (377 MHz, CDCl$_3$) $\delta$ = -65.13. $^{13}$C NMR (101 MHz, $^{19}$F coupled, CDCl$_3$) $\delta$ = 168.4, 142.7, 137.5, 132.3, 130.2, 128.7, 128.2, 127.5, 127.3, 127.1, 126.2, 124.5, 49.2, 36.1 (q, $J$ = 29.7 Hz), 21.4. HRMS (ESI): m/z calculated for C$_{17}$H$_{16}$F$_3$NO $[M+H]^+$: 308.1262, found: 308.1273. ee = 96%. HPLC with an AS-H column at 254 nm (2-propanol: hexane = 10:90), 1.0 mL/min; major enantiomer $t_{\text{major}}$= 11.49 min, minor enantiomer $t_{\text{minor}}$= 14.38 min.
Methyl (2-(2,2,2-trifluoroethyl)benzoyl)-D-leucinate (5l)

Following the general procedure, 5l was obtained as a white solid (36.0 mg, 0.108 mmol, 74%). MP = 125-126 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.44 (ddd, J = 18.0, 14.4, 4.8 Hz, 4H), 6.26 (d, J = 7.7 Hz, 1H), 4.81 (dd, J = 10.2, 7.2 Hz, 1H), 3.96 – 3.65 (m, 5H), 1.81 – 1.57 (m, 3H), 0.98 (dd, J = 8.9, 5.6 Hz, 6H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ = -65.19. $^{13}$C NMR (101 MHz, CDCl$_3$) δ = 173.2, 169.0, 136.9, 132.2, 130.4, 128.9 (q, J = 2.9 Hz), 128.2, 127.4, 127.2, 124.4, 52.3, 51.0, 41.4, 36.1 (q, J = 29.7 Hz), 24.9, 22.8, 21.8. HRMS (ESI): m/z calculated for C$_{17}$H$_{16}$F$_3$NO [M+H]$^+$: 332.1474, found: 332.1466. ee = 95%. HPLC with an AS-H column at 254 nm (2-propanol: hexane = 10:90), 1.0 mL/min; major enantiomer $t_{\text{major}}$ = 6.32 min, minoe enantiomer $t_{\text{minor}}$ = 9.18 min.

Methyl (2-(2,2,2-trifluoroethyl)benzoyl)-D-phenylalaninate (5m)

Following the general procedure, 5m was obtained as a white solid (28.4 mg, 0.077 mmol, 65%). MP = 155-156 °C. $^1$H NMR (400 MHz, CDCl$_3$) δ = 7.49 – 7.25 (m, 7H), 7.19 (d, J = 5.2 Hz, 2H), 6.35 (s, 1H), 5.16 – 5.05 (m, 1H), 3.82 (t, J = 9.0 Hz, 5H), 3.27 (ddd, J = 19.2, 13.8, 8.3 Hz, 2H). $^{19}$F NMR (377 MHz, CDCl$_3$) δ = -65.28. $^{13}$C NMR (101 MHz, CDCl$_3$) δ = 171.7, 168.6, 136.5, 135.7, 132.2, 130.5, 129.2, 129.0, 128.7, 128.2, 127.2 (q, J = 2.8 Hz), 124.4, 53.4, 52.4, 37.9, 36.0 (q, J = 29.8 Hz). HRMS (ESI): m/z calculated for C$_{17}$H$_{16}$F$_3$NO [M+H]$^+$: 366.1317, found: 366.1312. ee = 99%.
HPLC with an AS-H column at 254 nm (2-propanol: hexane = 10:90), 1.0 mL/min; major enantiomer \( t_{\text{major}} = 11.81 \) min.

3.3.5 Mechanistic Studies

3.3.5.1 Deuterium labeling test

To a screw cap vial equipped with a stirbar were added \( N \)-methylbenzamide (1a, 15 mg, 0.1 mmol), \( N \)-methylbenzamide (1a-D\(_5\), 15 mg, 0.1 mmol), mesityl(2,2,2-trifluoroethyl)iodonium trifluoromethanesulfonate (2, 127 mg, 0.24 mmol), Pd(OAc)\(_2\) (5.0 mg, 0.01 mmol, 10 mol %) and 1,2-dichloroethane (1.0 mL) under atmospheric conditions. Trifluoroacetic acid (0.1 mmol) was added instantly and the
vessel was capped for 4 hours. After reaction mixture was washed with NaHCO₃ solution and extracted with EtOAc (3 x 20mL). Organic solvents were removed under reduced pressure and the residue was purified by chromatography on silica gel (n-hexane/EtOAc) to obtain the desired products with recovery of starting materials.

### 3.3.5.2. Procedure for the synthesis of Palladacycle compound

To a 15ml sealed-tube were added N-((3s,5s,7s)adamantan-1-yl)benzamide, 4j (50 mg, 0.20 mmol), Pd(OAc)₂ (44mg, 0.20 mmol) and 1ml TFA. The tube was sealed and stirred at rt for 24h. Then the reaction mixture was filtered and washed with hexane to give the desired TFA bridged palladacycle product 6 as a yellowish green solid (78 mg, 82%). The yellowish green solid was then recrystallized from hexane/DCE to give crystal that can be characterized by X-ray crystallography.

\[ ^{1}H \text{NMR (400 MHz, CD}_{2}\text{Cl}_{2}) \delta = 7.15 \text{ (s, 2H), 6.97 (s, 1H), 6.71 (d, J=34.4 Hz, 1H), 6.34 (s, 1H), 5.09 (s, 2H), 2.13 (s, 9H), 1.70 (s, 6H).}^{19}F \text{NMR (377 MHz, CD}_{2}\text{Cl}_{2}) \delta = -73.88, -74.26, -74.35, -74.83, -76.08. }^{13}C \text{NMR (101 MHz, }^{19}F \text{ coupled, CD}_{2}\text{Cl}_{2}) \delta = 179.1, 143.9, 140.6, 131.9, 131.05 130.9, 130.8, 130.8, 125.0, 124.3, 54.8, 41.0, 35.9, 29.5. \]

![Diagram of reaction](image)

To a 15ml sealed-tube were also added 2 (1.2 eq) and DCE (0.5 mL), 25 °C, 4 h.

To a 15ml sealed-tube were also added 2 (1.2 eq) and DCE (0.5 mL), 25 °C, 4 h.

\[ \text{eq 2} \]
A 4 mL screw-cap vial equipped with a stirring bar was charged with palladacycle compound (6, 20.0 mg, 0.2 mmol) and mesityl(2,2,2-trifluoroethyl)iodonium trifluoromethanesulfonate (2, 0.22 mmol). Then 0.5 mL DCE was added and started to stir the dark brown mixture at room temperature. After the completion of the reaction, reaction mixture was washed with NaHCO₃ solution and extracted with EtOAc (3 x 20mL). The combined organics were dried over MgSO₄, filtered and dried under vacuum to get the crude product, which was further purified by flash column chromatography using EtOAc and Hexane solvent system to furnish desired product 5j in 80% yield.

3.4 Summary

In summary, a palladium-catalysed method for the direct trifluoroethylation of aromatic amides has been developed. Substrate scope is elaborated and sound mechanistic data have been collected. The report adds to a nascent field of direct-fluoroalkylations and future efforts are channelled towards expanding the strategy to other structural platforms.

3.5 References


19. Crystallographic data for the crystal structure of 6 has been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number 1542567.


CHAPTER 4

COPPER CATALYZED SITE SELECTIVE META-ARYLATION OF PHENOL DERIVATIVES
4.1 Introduction

In material science and synthetic chemistry, transition metal catalyzed site selective C-H functionalization has been considered as a high impactful strategy. Arenes are the most common units of composite molecular entities and functionalization of those units has gained a lot of attraction from the synthetic community. Organic molecules with aromatic nuclei have important applications in numerous fields of science such as polymer chemistry, pharmaceutical, drug development and material science. In the past few decades, a lot of attempts have been made to functionalize these arenes at specific sites. But most of the reports focus on selective ortho-functionalization of aromatic rings with directing group strategy (Figure 4-1).

As shown in scheme ortho and para-substitution reactions of arenes have been well explored by many organic reactions. On the other hand, site selective functionalization of meta-position requires much more scientific investigations as this position is least activated (Figure 4-2) and meta-functionalization of arenes is still at its infancy.
Figure 4-2. *meta*-activation possibility

Hence activation of the *meta*-position is very essential as it leads to novel products functionalized at *meta*-positions thus providing a new paths to synthesis several agrochemicals, medicinal drugs, natural products etc. with *meta*-functional groups.

**Approaches for *meta*-C-H activation**

Approach 1: Donor atom assistance (Figure 4-3)$^6a$

Appoach 2: Using an end-on template (Figure 4-4)$^5a$

Approach 3: Through remote C-H activation (Figure 4-5)$^{4c}$
In recent years, through these approaches many functional group transformation reactions have been reported such as olefination, arylation, acetoxylation, hydroxylation, alkylation and halogenation.

In this introduction section we are going to discuss only the meta-arylation reactions developed by all those approaches mentioned above. The pioneer work of transition metal catalyzed meta-arylation was reported by Gaunt et al. in 2009. They described copper catalyzed aromatic C-H bond functionalization approach that gives exclusively meta-isomer (Scheme 4-1). They employed cheap copper catalyst and the method was very simple and mild to get meta-arylated products with anilides and diaryliodonium salts as coupling partners.

![Scheme 4-1. meta-arylation of anilides by Gaunt’s group](image)

In 2011, Larrosa described traceless directing group relay strategy to achieve meta-selective arylation of benzoic acids. The carboxylic acid group was used as directing group to direct incoming group. This reported protocol involves initial arylation followed by protodecarboxylation to obtain meta-arylated arenes (Scheme 4-2). They employed cheap starting material, benzoic acids and iodoarenes as coupling partners for this transformation. This method proceeded in presence of palladium catalyst and silver salt.
The template based strategy was further exploited by Yu in 2013 by extending their research of palladium catalysts. They developed a cross-coupling reaction of arenes with aryl boronic esters (Scheme 4-3). They achieved this transformation by choosing suitable palladium catalyst, mono-protected amino acid (MPAA) and silver additive.

Moreover, they even reported an example of meta-methylation with MeBF₃K (Scheme 4-4).
In 2014 Larrosa et al. achieved the meta-C-H activation of phenols by extending their traceless directing group strategy. This method had the advantage over Yu’s method which required insertion of template, synthesized over 5 independent synthetic reactions. They installed a carboxylic group by Kolbe-Schmidt reaction, achieved arylation ortho to the carboxylic acid group and later decarboxylation provided one pot synthesis of meta-arylated phenols (Scheme 4-5). This reported procedure can be applied over a variety of iodoarenes and phenolic compounds. Although, this method has harsh conditions for installing and removing carboxylic acid group, they proved its efficiency by synthesizing a γ-secretase inhibitor.
Indolines constitute an important motif in many natural products.\textsuperscript{9} Though, active positions of indolines are functionalized with different methods, the activation of C-H bond at \textit{meta}-position of the indolines was a challenge. This ground breaking work was achieved by Yu et al. in 2014. By using sulfonyl based template with nitrile as donor group, they obtained the \textit{meta}-arylated indoline derivatives using aryl boronic esters as arylationing agent (Scheme 4-6).\textsuperscript{5b}

\begin{center}
\textbf{Scheme 4-6.} \textit{meta}-arylation of indoles
\end{center}

Salicyclic acids have been used as an effective precursors for the synthesis of \textit{meta}-arylated phenols (Scheme 4-7).\textsuperscript{6e} In 2015, Larrosa group developed a new method to overcome the difficulties of their previously reported method. As salicylic acid derivatives are readily available and are prepared from simple reactions, the modified new report was advantageous over the earlier one.

\begin{center}
\textbf{Scheme 4-7.} \textit{meta}-arylation of salicyclic acid derivatives
\end{center}

In addition to this, Larrosa even reported \textit{meta}-arylation of phenols employing aldehydes as the directing group. They formylated the phenol derivatives at \textit{ortho}-position and used silver salt for in situ oxidation the formyl group into carboxylic
group and thus achieved meta-C-H activation. Finally, the decarboxylation resulted to produce meta-arylated phenols (Scheme 4-8).

![Scheme 4-8. meta-arylation of salicylaldehyde derivatives](image)

Though the reactivity of norbornene was disclosed in late 1990s, it was in March 2015, Yu et al. demonstrated norbornene as a mediator to achieve selective meta-C-H functionalization with the help of ortho-directing groups. Phenylacetic derivatives were selectively underwent alkylation and arylation reaction in presence of palladium catalyst and pyridine based ligand with an array of alkyl and aryl iodides (Scheme 4-9).

![Scheme 4-9. Norbornene mediated meta-arylation](image)

After Yu’s publication, within a period of month, Dong et al. individually reported similar type of transformation reaction by using palladium/norbornene system with simple amines as directing group. They employed AsPh₃ as ligand, chlorobenzene as solvent and acetate cocktail to enhance reaction speed and to improve the yields (Scheme 4-10). They even showed the efficiency of this transformation by derivatizing the obtained products into useful synthons.
In late 2014, Wang et al. reported the \textit{meta}-C-H arylation of naphthol carbamates using AgOAc with K$_2$S$_2$O$_8$ as oxidant and Pd(OAc)$_2$ as pre catalyst with an array of aryl boronic acids (\textbf{Scheme 4-11})$^{13}$. Preliminary mechanistic investigations revealed that this process involves initial \textit{ortho}-carbometallation followed by \textit{meta}-C-H arylation.

\textbf{Scheme 4-10.} Dong group’s \textit{meta}-arylation protocol

In mid of 2016, Yu et al. extended their norbornene chemistry to arylate heterocyclic aromatic amines, 2-benzyl heterocycles, phenols and anilines selectively at \textit{meta}-C-H position (\textbf{Scheme 4-12})$^{14}$. They demonstrated a protocol without using any silver salts for the first time.

\textbf{Scheme 4-11.} \textit{meta}-arylation of naphthol carbamates

\textbf{Scheme 4-12.} Ligand mediated \textit{meta}-arylation
In late 2016, Yu et al. disclosed meta-C-H arylation of 2-aryl anilines using a combination of pyridine based ligands and norbornene. The developed protocol was applied to a diverse range of aryl iodides as well as benzylamines and phenethylamines (Scheme 4-13).

![Scheme 4-13. meta-arylations of amine derivatives](image)

**4.2 Results and Discussions**

Although great breakthroughs have been made, these approaches require the incorporation and removal of bulky directing groups, high temperature and suffer from narrow substrate scope. Hence development of more general and efficient approaches to direct meta-arylation of phenol derivatives remains a significant task.

Given our continued interest in the direct C-H functionalization and copper catalysis, our lab has focused on inventing reactivities of widely available and broadly useful substrates. Copper being an earth abundant metal, makes its use more viable and more cost efficient than precious transition metal catalysts. Such an economical method is always desirable.

To test this speculation, we treated phenyl carbamate 1a with Ph₂I⁻OTf in the presence of 10 mol% Cu(OTf)₂ in DCE solvent at 70 °C. Arylation took place at the meta-position to furnish 2a and 2a' in a combined yield of 80% (Table 4-1, entry 1);
and in agreement with our hypothesis, products arylated at either para or ortho-position were not observed (resolved by $^1$H nuclear magnetic resonance analysis).

Inspired by this result, we initiated optimization of reaction retaining 1a as our model substrate. We found that changing the acyl group has a large effect on the selectivity and yield of the reaction (Table 4-1, entries 1-5). The reaction works with acetate and pivalate groups although the selectivity and conversions are moderate (Table 4-1, entries 2 and 3). However, carbonates and esters were screened only to retain the starting materials without affording the desired arylated products (Table 4-1, entries 4 and 5). Having identified the suitable phenol derivative for the arylation, we focused on identifying a suitable condition for the hydrolysis of carbamates in order to afford meta-arylated phenols in one pot. After optimization, we found that treating the reaction crude after Cu(OTf)$_2$ reaction with 10 equivalents of NaOH in EtOH at 80 °C for 12 h, provides selective meta-arylated phenol 2a in 74% isolated.

![Chemical reaction image](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>product</th>
<th>yield (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^c$</td>
<td>NMe$_2$</td>
<td>2a' + 2a</td>
<td>55 + 25</td>
</tr>
<tr>
<td>2$^c$</td>
<td>Me</td>
<td>2b' + 2b</td>
<td>40 + 13</td>
</tr>
<tr>
<td>3$^c$</td>
<td>CMe$_3$</td>
<td>2c' + 2c</td>
<td>52 + 12</td>
</tr>
<tr>
<td>4</td>
<td>OMe</td>
<td>2d' + 2d</td>
<td>NIL</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>2e' + 2e</td>
<td>NIL</td>
</tr>
</tbody>
</table>

$^a$The yields were determined by GC. $^b$isolated yield. $^c$observed ortho-arylated product

Table 4-1. Screening of acyl group.
yield after column chromatography (Table 4-2, entry 1). Next, we screened other substituents on the nitrogen atom and found that the optimized condition is applicable for even morpholine (Table 4-2, entry 4) and pyrrolidine (Table 4-2, entry 5) derived carbamates. Further reaction conditions with respect to temperature and catalyst loading have been screened (Table 4-3). Among the diaryliodonium salts screened, tetrafluoroborate salt furnished the product 2a in good yield. The source of the Cu catalyst proved crucial for this transformation. Both Cu(I) and Cu(II) species provided phenol product in moderate to good yield with Cu(OTf)₂ leading to the best yields among the catalysts examined. Even simple copper powder can provide meta-arylated product in moderate yield (Table 4-3, entry 9). To our surprise, meta-arylated product was isolated in 20% yield without any catalyst but at a time span of 5 days.¹⁷

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₃</td>
<td>74</td>
</tr>
<tr>
<td>2</td>
<td>CH₃</td>
<td>65</td>
</tr>
<tr>
<td>3</td>
<td>CH₃CH₃</td>
<td>68</td>
</tr>
<tr>
<td>4</td>
<td>(CH₂CH₃)₂C</td>
<td>70</td>
</tr>
<tr>
<td>5</td>
<td>(CH₃)₄</td>
<td>71</td>
</tr>
</tbody>
</table>

Reactions conditions: 1. 1a (1 equiv), salt (1.2 equiv), catalyst (10 mol%) in DCE (2.0 mL) for 24 h. 2. NaOH (10 equiv.) in EtOH (5 mL) at 80 °C for 12 h. †Isolated yields after column chromatography. ²2.(C₅H₅)₂ZrHCl (3 equiv.) in THF (5 mL) at room temperature for 15 h.

Table 4-2. Effect of Substituents on the Nitrogen atom.
Reactions were carried out with 1a (1 equiv), salt (1.2 equiv), catalyst (10 mol%) in DCE (1.0 mL) for 24 h. \(^b\)Isolated yields after column chromatography. \(^c\)reaction was run for 5 days

Table 4-3. Optimization of Arylation of Phenol carbamate

With the optimized conditions in hand, the scope of this copper mediated meta-arylation of phenol derivatives was investigated. A wide variety of phenol substituents were tolerated in this transformation, furnishing products in moderate to excellent yields. A series of ortho-substituted phenol carbamates including electron-releasing (Me and OMe) and electron-withdrawing (F, Cl and Br) substituents provided arylated products in moderate to good yields. Arylation of 2-aryl substituted (1k and 1m) and 2-cyclohexyl (1l) substituted phenol carbamates exclusively occurred at 3-position yielding products (2k, 2l and 2m) in good yields. Substrates bearing electron-withdrawing and electron-releasing meta-substituents were also reactive in this protocol (2n-2q). Carbamate with 3-OMe group furnished the meta-arylated phenol (2p) in 72% yield, with ortho-arylated product (para to
OMe group) only in negligible amount (less than 5% by GCMS) which is in contrast to the previously reported results. This may be due to a stronger influence of carbamates over -OMe group to direct the incoming aryl group. The simple phenol carbamate system forms the \textit{meta}-monoarylated and diarylated products (\textbf{2r} and \textbf{2s}), which can be accessed by controlling the stoichiometry. Gratifyingly, substituent at C-4 position is also tolerated, furnishing the diarylated phenol (\textbf{2t}) in good yield. It is noteworthy that 3,4-dimethyl substituted phenol carbamate underwent arylation at both 5 and 6 positions to give pentasubstituted phenol (\textbf{2u}). Further investigations revealed that carbamate derived from 2,4-disubstituted phenol can deliver \textit{meta}-arylated product (\textbf{2v}) in good yield and high selectivity.
Next we extended scope of our copper mediated meta-arylation of carbamates with an array of diaryliodonium salts and the results were summarized (Scheme 4-15). The arylating coupling partners possessing both electron-releasing and electron-withdrawing groups produced selective meta-arylated products in good to moderate yields (2w and 2aa were obtained in 80% and 57% isolated yield). Further, salts bearing halides (F, Cl and Br) were compatible under the optimized reaction
condition furnishing monoarylated products (2x, 2y and 2z) in good yield. These results provide a platform for further utilization of meta-arylated products via transition metal catalyzed cross-coupling reactions. Diaryliodonium salts bearing electron-releasing or electron withdrawing meta-substituents were also effective in this protocol furnishing corresponding products (2ab-2ad).

Scheme 4-15. Scope of diaryliodonium salts
Even o-methoxy iodonium salt reacted smoothly to furnish meta-arylated carbamate (2ae) in 48% yield. To explore the applicability of this process on a preparative scale, we performed reaction in gram scale with substrate 1a and diphenyliodonium tetrafluoroborate salt. Gratifyingly, our copper catalyzed meta-arylation of carbamates worked well in gram scale, products 2a and 2a' were isolated in 18% and 65% yield respectively (Scheme 4-16).

\[
\begin{align*}
\text{Me} \quad \text{O} \quad \text{CONMe}_2 \\
\text{Ph} \quad \text{NMe}_2 \\
\text{Ph} \\
\end{align*}
\]

Scheme 4-16. Gram scale synthesis

To demonstrate the synthetic utility of this meta-arylation reaction, we attempted diversification of 2r' using carbamate as a synthetic handle. Carbamate 2r' was converted into desirable synthons in good yields by reported methods such as reductive cleavage\textsuperscript{18a} and cross-coupling\textsuperscript{18b} reactions.

\[
\begin{align*}
\text{OCONMe}_2 \\
\text{Ph} \\
\text{Ph} \\
\end{align*}
\]

Scheme 4-17. Diversification of m-Aryl carbamate 2r'
4.3 Experimental Section

4.3.1 General Procedure for the synthesis of m-arylated phenols derivatives

To a solution of the appropriate phenol carbamate (0.30 mmol) in 1,2-dichloroethane (2.0 mL) was added the appropriate iodonium salt (0.36 – 0.90 mmol) and Cu(OTf)$_2$ (11 mg, 0.030 mmol). The reaction was stirred for the 24 h at 70 °C before dilution with CH$_2$Cl$_2$ (25 mL) and washing with saturated sodium bicarbonate solution (15 mL). The aqueous phase was extracted with further CH$_2$Cl$_2$ (25 mL) and the combined organics were dried over magnesium sulphate and evaporated in vacuo. The crude residue was dissolved in EtOH (5 mL) and 10 equivalents of NaOH were added. The reaction mixture was heated at 80 °C for 12 h. After cooling, solvent was evaporated and the crude was acidified with 2 N HCl solution. Aqueous layer was further extracted with diethyl ether (3 x 25 mL). The combined organic layers were dried, evaporated and purified by flash column chromatography to yield the pure m-arylphenol.

4.3.2 Characterization data

4-methyl-[1, 1’-biphenyl]-3-ol (2a)

Following the general procedure, phenol carbamate 1a (54.0 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate (134.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 4-methyl-[1, 1’-biphenyl]-3-ol (2a) as white solid (41.0 mg, 74%). MP. 76-78 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57 – 7.52 (m, 2H), 7.41 (dd, $J$ = 10.3, 4.8 Hz, 2H), 7.35 – 7.29 (m, 1H), 7.18 (d, $J$ = 7.8 Hz, 1H), 7.09 (dd, $J$ = 7.7, 1.7 Hz, 1H), 7.01 (d, $J$ = 1.6 Hz, 1H), 4.85 (s, 1H), 2.29 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 154.0, 140.7, 140.5, 131.3, 128.7, 127.2, 126.9, 122.8, 119.5, 113.6, 15.4. HRMS: calcd for C$_{13}$H$_{13}$O, 185.0966 (M+H$^+$); found, 185.0966.
4-(tert-butyl)-[1, 1'-biphenyl]-3-ol (2f)

Following the general procedure, phenol carbamate 1f (67.0 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate (134.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 4-(tert-butyl)-[1,1'-biphenyl]-3-ol (2f) as off white solid (56.8 mg, 83%). MP. 83-85 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.62 – 7.58 (m, 2H), 7.50 – 7.44 (m, 2H), 7.41 – 7.35 (m, 2H), 7.17 (dd, \(J = 8.1, 1.9\) Hz, 1H), 6.93 (d, \(J = 1.9\) Hz, 1H), 4.94 (s, 1H), 1.51 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 154.4, 140.4, 140.2, 135.2, 128.7, 127.5, 127.2, 126.9, 119.3, 115.2, 34.4, 29.6. HRMS: calcd for C\(_{16}\)H\(_{19}\)O, 227.1436 (M+H\(^+\)); found, 227.1438.

4-isopropyl-[1, 1'-biphenyl]-3-ol (2g)

Following the general procedure, phenol carbamate 1g (62.8 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate (134.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 4-isopropyl-[1, 1'-biphenyl]-3-ol (2g) as pale yellow solid (50.0 mg, 78%), MP. 66-68 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.55 (d, \(J = 7.5\) Hz, 2H), 7.41 – 7.35 (m, 2H), 7.25 (s, 1H), 7.20 – 7.09 (m, 2H), 6.97 (s, 1H), 4.83 (s, 1H), 3.29 – 3.16 (m, 1H), 1.51 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 154.4, 140.4, 140.2, 135.2, 128.7, 127.5, 127.2, 126.9, 119.3, 115.2, 34.4, 29.6. HRMS: calcd for C\(_{15}\)H\(_{17}\)O, 213.1279 (M+H\(^+\)); found, 213.1279.

4-methoxy-[1, 1'-biphenyl]-3-ol (2h)

Following the general procedure, phenol carbamate 1h (59.20 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate (134.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 4-methoxy-[1, 1'-biphenyl]-3-ol (2h) as brown solid (53.4 mg, 88%). MP. 106-108 °C. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.58 – 7.52 (m, 2H), 7.50 – 7.44 (m, 2H), 7.17 (dd, \(J = 8.1, 1.9\) Hz, 1H), 6.93 (d, \(J = 1.9\) Hz, 1H), 4.94 (s, 1H), 1.51 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 146.1, 145.8, 140.7, 134.8, 128.7,
4-chloro-[1, 1'-biphenyl]-3-ol (2i)

Following the general procedure, phenol carbamate 1i (60.5 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate (134.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 4-chloro-[1,1'-biphenyl]-3-ol (2i) as brown oil (40.32 mg, 65%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.55 (dd, $J = 5.3, 3.4$ Hz, 2H), 7.46 – 7.40 (m, 2H), 7.38 – 7.32 (m, 2H), 7.25 (d, $J = 2.1$ Hz, 1H), 7.10 (dd, $J = 8.3, 2.1$ Hz, 1H), 5.61 (s, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 151.5, 141.9, 139.8, 129.1, 128.8, 127.7, 127.0, 120.1, 119.0, 114.8. HRMS: calcd for C$_{12}$H$_{10}$ClO, 205.0420 (M+H$^+$); found, 205.0422.

4-bromo-[1, 1'-biphenyl]-3-ol (2j)

Following the general procedure, phenol carbamate 1j (74.0 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate (134.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 4-bromo-[1,1'-biphenyl]-3-ol (2j) as brown oil (45.3 mg, 60%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.60 (dd, $J = 5.2, 3.4$ Hz, 2H), 7.55 (d, $J = 8.3$ Hz, 1H), 7.50 – 7.44 (m, 2H), 7.41 (ddd, $J = 7.3, 3.7, 1.2$ Hz, 1H), 7.30 (d, $J = 2.1$ Hz, 1H), 7.09 (dd, $J = 8.3, 2.1$ Hz, 1H), 5.62 (s, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 152.4, 142.7, 139.8, 132.1, 128.8, 127.8, 126.9, 120.6, 114.7, 109.2. HRMS: calcd for C$_{12}$H$_{10}$BrO, 248.9915 (M+H$^+$); found, 248.9905.

[1, 1':4, 1''-terphenyl]-2'-ol (2k)

Following the general procedure, phenol carbamate 1k (73.0 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate (134.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford [1, 1':4, 1''-terphenyl]-2'-ol (2k) as off white solid (57.4 mg, 77%) MP. 174-176 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.63 (d, $J = 7.1$ Hz, 2H), 7.51 (s, 4H),
7.47 – 7.38 (m, 3H), 7.34 (dd, \( J = 18.0, 8.1 \) Hz, 2H),
7.23 (s, 2H), 5.30 (s, 1H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 152.7, 142.3, 140.4, 136.8, 130.6, 129.3,
129.0, 128.8, 127.9, 127.5, 127.1, 127.0, 119.7, 114.4.
HRMS: calcd for C\(_{18}\)H\(_{15}\)O, 247.1123 (M+H\(^+\)); found,
247.1120.

4-cyclohexyl-[1, 1'-biphenyl]-3-ol (2l)

Following the general procedure, phenol carbamate 1l
(75.0 mg, 0.3 mmol) was reacted with
diphenylidonium tetrafluoroborate (134.0 mg 0.36
mmol). The crude product was purified by flash
column chromatography (Hexane: Ether 95:5) to
afford 4-cyclohexyl-[1, 1'-biphenyl]-3-ol (2l) as off
white solid (55.0 mg, 72%) MP. 85-87 oC;
\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.55 (dd, \( J = 8.3, 1.2 \) Hz, 2H),
7.44 – 7.37 (m, 2H), 7.34 – 7.28 (m, 1H), 7.25 (s, 1H),
7.16 – 7.12 (m, 1H), 6.98 (d, \( J = 1.8 \) Hz, 1H), 4.80 (s, 1H),
2.91 – 2.72 (m, 1H), 1.97 – 1.82 (m, 4H), 1.82 –
1.73 (m, 1H), 1.54 – 1.36 (m, 4H), 1.35 – 1.22 (m, 1H).
\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) \( \delta \) 152.9, 140.7,
139.9, 132.6, 128.7, 127.3, 127.1, 126.9, 119.7, 37.2,
33.1, 27.0, 26.3. HRMS: calcd for C\(_{18}\)H\(_{21}\)O, 253.1592
(M+H\(^+\)); found, 253.1589.

4-methoxy-[1, 1':4, 1''-terphenyl]-2'-ol (2m)

Following the general procedure, phenol carbamate 1m
(73.0 mg, 0.3 mmol) was reacted with
diphenylidonium tetrafluoroborate (134.0 mg 0.36
mmol). The crude product was purified by flash column
chromatography (Hexane: Ether 95:5) to
afford 4-methoxy-[1, 1':4, 1''-terphenyl]-2'-ol (2m) as brown solid (57.4 mg, 77%) MP. 100-
102 oC; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.66
(d, \( J = 7.3 \) Hz, 2H), 7.51 – 7.45 (m, 4H), 7.40
(d, \( J = 7.3 \) Hz, 1H), 7.33 (d, \( J = 8.3 \) Hz, 1H),
7.28 – 7.24 (m, 2H), 7.08 (d, \( J = 8.7 \) Hz, 2H),
5.34 (s, 1H), 3.90 (s, 3H).\(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 159.4, 152.8, 141.9, 140.5, 130.5,
130.2, 128.9, 128.7, 127.4, 127.1, 126.0,
126.8, 119.6, 114.8, 114.3, 55.4. HRMS: calcd
for C\(_{19}\)H\(_{17}\)O\(_2\), 277.1229 (M+H\(^+\)); found,
277.1231.
**5-(tert-butyl)-[1, 1’-biphenyl]-3-ol (2n)**

Following the general procedure, phenol carbamate 1n (67.0 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate 5a (156.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 5-(tert-butyl)-[1, 1’-biphenyl]-3-ol (2n) as off white solid (50.7 mg, 74%) MP. 82-84 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta = 7.62 - 7.58\) (m, 2H), 7.49 – 7.44 (m, 2H), 7.40 – 7.35 (m, 1H), 7.22 (t, \(J=1.6\), 1H), 6.91 (p, \(J=2.4\), 1H), 4.85 (s, 1H), 1.39 (s, 9H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 155.5, 153.7, 142.6, 141.4, 128.7, 127.3, 127.2, 117.2, 111.6, 111.3, 34.8, 31.3\). HRMS: calcd for C\(_{16}\)H\(_{19}\)O, 227.1436 (M+H\(^+\)); found, 227.1444.

**5-methyl-[1, 1’-biphenyl]-3-ol (2o)**

Following the general procedure, phenol carbamate 1o (54.0 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate 5a (156.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 5-methyl-[1, 1’-biphenyl]-3-ol (2o) as pale yellow oil (36.7 mg, 66%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.59 - 7.53\) (m, 2H), 7.42 (dd, \(J = 10.3, 4.8\) Hz, 2H), 7.36 – 7.30 (m, 1H), 6.99 (s, 1H), 6.87 (s, 1H), 6.65 (s, 1H), 4.83 (s, 0H), 2.37 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 154.0, 140.7, 140.5, 131.3, 128.7, 127.1, 126.9, 122.8, 119.5, 113.6, 15.4\). HRMS: calcd for C\(_{13}\)H\(_{13}\)O, 185.0966 (M+H\(^+\)); found, 185.0969.

**5-methoxy-[1, 1’-biphenyl]-3-ol (2p)**

Following the general procedure, phenol carbamate 1p (59.2 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate 5a (156.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 5-methoxy-[1, 1’-biphenyl]-3-ol (2p) as pale brown oil (36.7 mg, 66%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.59\) (dd, \(J = 5.2, 3.4\) Hz, 2H), 7.48 – 7.42 (m, 2H), 7.41 – 7.35 (m, 1H), 6.78 – 6.75 (m, 1H), 6.72 – 6.68 (m, 1H), 6.46 (t, \(J = 2.2\) Hz, 1H), 5.64 (s, 1H), 3.86 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 161.1, 157.0, 143.7, 140.8, 128.7, 127.6, 127.1, 107.0, 105.6, 100.4, 55.4\). HRMS: calcd for C\(_{13}\)H\(_{13}\)O\(_2\), 201.0916 (M+H\(^+\)); found, 201.0918.

**5-fluoro-[1, 1’-biphenyl]-3-ol (2q)**

Following the general procedure, phenol carbamate 1q (55.5 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate 5a (156.0 mg 0.36 mmol). The crude
product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 5-fluoro-[1, 1’-biphenyl]-3-ol (2q) as brown oil (33.6 mg, 56%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.57 (dt, $J = 3.2, 1.9$ Hz, 2H), 7.51 – 7.44 (m, 2H), 7.42 (ddd, $J = 7.2, 3.6, 1.3$ Hz, 1H), 6.96 – 6.91 (m, 1H), 6.90 – 6.87 (m, 1H), 6.61 (dt, $J = 9.8, 2.3$ Hz, 1H), 5.53 (s, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 163.8 (d, $J = 245.0$ Hz), 156.9 (d, $J = 12.2$ Hz), 144.3 (d, $J = 9.8$ Hz), 139.7 (d, $J = 2.6$ Hz), 130.2, 128.9, 128.0, 127.0, 110.0 (d, $J = 2.6$ Hz), 106.7 (d, $J = 22.4$ Hz), 102.0 (d, $J = 24.8$ Hz). HRMS: calcd for C$_{12}$H$_{10}$FO, 189.0716 (M+H$^+$); found, 189.0716.

[1, 1’-biphenyl]-3-ol (2r)

Following the general procedure, phenol carbamate 1r (120.0 mg, 0.72 mmol) was reacted with diphenyliodonium tetrafluoroborate (134.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford [1, 1’-biphenyl]-3-ol (2r) as light brown solid (39.7 mg, 64%) MP. 64-66 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.56 (d, $J = 7.9$ Hz, 2H), 7.42 (t, $J = 7.5$ Hz, 2H), 7.37 – 7.27 (m, 2H), 7.17 (d, $J = 7.7$ Hz, 1H), 7.06 (s, 1H), 6.82 (dd, $J = 8.0, 2.3$ Hz, 1H), 5.07 (s, 1H).

$^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 155.8, 143.0, 140.7, 130.0, 128.7, 127.5, 127.1, 119.8, 114.2, 114.1. HRMS: calcd for C$_{12}$H$_{11}$O, 171.0810 (M+H$^+$); found, 171.0808.

[1, 1’:3, 1’’-terphenyl]-5’-ol (2s)

Following the general procedure, phenol carbamate 1s (50.0 mg, 0.30 mmol) was reacted with diphenyliodonium tetrafluoroborate (334.0 mg 0.90 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford [1, 1’:3, 1’’-terphenyl]-5’-ol (2s) as light brown oil (45.5 mg, 61%) MP. 69-71 °C; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.61 (d, $J = 7.3$ Hz, 4H), 7.44 (t, $J = 7.5$ Hz, 4H), 7.37 (dd, $J = 12.3, 4.4$ Hz, 3H), 7.04 (d, $J = 1.3$ Hz, 2H), 5.19 (s, 1H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 156.2, 143.4, 140.8, 128.8, 127.6, 127.2, 118.9, 113.1. HRMS: calcd for C$_{18}$H$_{15}$O, 247.1123 (M+H$^+$); found, 247.1126.

2’-ethyl-[1, 1’:3, 1’’-terphenyl]-5’-ol (2t)

Following the general procedure, phenol carbamate 1t (58.5 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate 5a (334.0 mg 0.90 mmol). The crude product was purified by flash
column chromatography (Hexane: Ether 95:5) to afford 2'-ethyl-[1, 1':3, 1''-terphenyl]-5'-ol (2t) as light orange gummy solid (49.8 mg, 60%). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.37 (m, 4H), 7.35 (dt, $J$ = 6.5, 2.9 Hz, 6H), 6.69 (s, 2H), 4.69 (s, 1H), 2.47 (q, $J$ = 7.4 Hz, 2H), 0.65 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 152.3, 143.8, 142.2, 132.0, 129.1, 127.9, 126.8, 116.3, 22.2, 15.4. HRMS: calcd for C$_{20}$H$_{19}$O, 275.1436 (M+H$^+$); found, 275.1437.

2', 4'-dimethyl-[1, 1':3, 1''-terphenyl]-5'-ol (2u)

Following the general procedure, phenol carbamate 1u (58.5 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate 5a (334.0 mg 0.90 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 2', 4'-dimethyl-[1, 1':3, 1''-terphenyl]-5'-ol (2u) as white solid (58.0 mg, 70%) MP. 110-112 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.51 (t, $J$ = 7.4 Hz, 2H), 7.41 (dd, $J$ = 12.1, 7.2 Hz, 4H), 7.37 – 7.29 (m, 6H), 6.79 (s, 1H), 4.64 (s, 1H), 2.13 (s, 3H), 2.04 (s, 3H).

$^{13}$C NMR (101 MHz, CDCl$_3$) δ 150.2, 142.7, 142.4, 136.1, 136.0, 130.5, 129.4, 129.3, 128.1, 128.0, 127.5, 126.7, 126.0, 114.0, 18.0, 17.0. HRMS: calcd for C$_{20}$H$_{19}$O, 275.1436 (M+H$^+$); found, 275.1437.

4-((3s)-adamantan-1-yl)-6-methyl-[1, 1'-biphenyl]-3-yl- dimethylcarbamate (2v)

Following the general procedure, phenol carbamate 1v (58.5 mg, 0.3 mmol) was reacted with diphenyliodonium tetrafluoroborate 5a (334.0 mg 0.90 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 4-((3s)-adamantan-1-yl)-6-methyl-[1, 1'-biphenyl]-3-yl- dimethylcarbamate (2v) as white solid (58.0 mg, 70%) MP. 185-187 °C; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.43 – 7.31 (m, 5H), 7.22 (s, 1H), 6.94 (s, 1H), 3.22 (s, 3H), 3.08 (s, 3H), 2.31 (s, 3H), 2.13 (d, $J$ = 12.1 Hz, 10H), 1.82 (s, 6H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 155.1, 147.8, 141.0, 139.9, 139.7, 131.7, 129.3, 128.8, 127.9, 126.7, 125.7, 41.3, 37.0, 36.4, 29.0, 20.2. HRMS: calcd for C$_{26}$H$_{32}$NO$_2$, 390.2433 (M+H$^+$); found, 390.2437.
4, 4′-dimethyl-[1, 1′-biphenyl]-3-ol (2w)

Following the general procedure, phenol carbamate 1a (54.0 mg, 0.3 mmol) was reacted with \( p\)-tolyl(mesityl)iodonium trifluoromethanesulfonate (176.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 4, 4′-dimethyl-[1,1′-biphenyl]-3-ol (2w) as pale yellow solid (47.8 mg, 80%) MP. 84-86 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.45 (d, \( J = 8.1 \) Hz, 2H), 7.22 (d, \( J = 8.0 \) Hz, 2H), 7.16 (d, \( J = 7.8 \) Hz, 1H), 7.07 (dd, \( J = 7.7, \) 1.7 Hz, 1H), 6.99 (d, \( J = 1.6 \) Hz, 1H), 4.76 (s, 1H), 2.38 (s, 3H), 2.28 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 154.0, 140.4, 137.8, 136.9, 131.3, 129.4, 126.7, 122.4, 119.3, 113.4, 21.0, 15.4. HRMS: calcd for C\(_{14}\)H\(_{15}\)O, 199.1123 (M+H\(^+\)); found, 199.1120.

4′-fluoro-4-methyl-[1,1′-biphenyl]-3-ol (2x)

Following the general procedure, phenol carbamate 1a (54.0 mg, 0.3 mmol) was reacted with 4-fluorophenyl(mesityl)iodonium trifluoromethanesulfonate (177.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 4′-fluoro-4-methyl-[1,1′-biphenyl]-3-ol (2x) as brown solid (41.5 mg, 68%) MP. 60-62 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.56 – 7.50 (m, 2H), 7.21 (d, \( J = 7.7 \) Hz, 1H), 7.16 – 7.10 (m, 2H), 7.07 (dd, \( J = 7.7, \) 1.7 Hz, 1H), 6.99 (d, \( J = 1.6 \) Hz, 1H), 4.93 (s, 1H), 2.32 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \( \delta \) 162.4 (d, \( J = 246.1 \) Hz), 154.0, 139.5, 136.8 (d, \( J = 3.3 \) Hz), 131.4, 128.4 (d, \( J = 8.0 \) Hz), 122.8, 119.3, 115.5 (d, \( J = 21.4 \) Hz), 113.5, 15.4. HRMS: calcd for C\(_{13}\)H\(_{12}\)FO, 203.0872 (M+H\(^+\)); found, 203.0872.

4′-chloro-4-methyl-[1,1′-biphenyl]-3-ol (2y)

Following the general procedure, phenol carbamate 1a (54.0 mg, 0.3 mmol) was reacted with 4-chloro phenyl(mesityl)iodonium trifluoromethanesulfonate (183.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether
95:5) to afford 4'-chloro-4-methyl-[1,1'-biphenyl]-3-ol (2y) as brown solid (42.8 mg, 65%) MP. 66-68 °C; 1H NMR (400 MHz, CDCl₃) δ 7.47 (d, J = 8.4 Hz, 2H), 7.38 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 7.7 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.97 (s, 1H), 4.84 (s, 1H), 2.29 (s, 3H). 13C NMR (101 MHz, CDCl₃) δ 154.1, 139.2, 133.2, 131.4, 128.8, 128.1, 123.1, 119.3, 113.4, 15.4. HRMS: calcd for C₁₃H₁₂ClO, 219.0577 (M+H⁺); found, 219.0575.

**4'-bromo-4-methyl-[1,1'-biphenyl]-3-ol (2z)**

Following the general procedure, phenol carbamate 1a (54.0 mg, 0.3 mmol) was reacted with 4-bromophenyl(mesityl)iodonium trifluoromethanesulfonate (199.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane:Ether 95:5) to afford 4'-bromo-4-methyl-[1,1'-biphenyl]-3-ol (2z) as brown solid (48.3 mg, 61%) MP. 93-95 °C; 1H NMR (400 MHz, CDCl₃) δ 7.53 (d, J = 8.4 Hz, 2H), 7.41 (d, J = 8.4 Hz, 2H), 7.18 (d, J = 7.7 Hz, 1H), 7.04 (d, J = 7.8 Hz, 1H), 6.97 (s, 1H), 4.90 (s, 1H), 2.28 (s, 3H). 13C NMR (101 MHz, CDCl₃) δ 154.1, 139.6, 139.2, 131.8, 131.4, 128.5, 123.2, 121.3, 119.2, 113.3, 15.4. HRMS: calcd for C₁₃H₁₂BrO, 263.0072 (M+H⁺); found, 263.0075.

**4-methyl-4'-(trifluoromethyl)-[1,1'-biphenyl]-3-ol (2aa)**

Following the general procedure, phenol carbamate 1a (54.0 mg, 0.3 mmol) was reacted with 4-(trifluoromethyl)phenyl(mesityl)iodonium trifluoromethanesulfonate (195.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane:Ether 95:5) to afford 4-methyl-4'(trifluoromethyl)-[1,1'-biphenyl]-3-ol (2aa) as off white solid (43.3 mg, 57%) MP. 75-76 °C; 1H NMR (400 MHz, CDCl₃) δ 7.67 – 7.62 (m, 4H), 7.21 (d, J = 7.7 Hz, 1H), 7.09 (dd, J = 7.7, 1.7 Hz, 1H), 7.02 (d, J = 1.6 Hz, 1H), 4.92 (s, 1H), 2.30 (s, 3H). 19F NMR (377 MHz, CDCl₃) δ -62.37. 13C
NMR (101 MHz, CDCl\(_3\))  \(\delta\) 154.2, 144.2, 138.9, 131.5, 127.1, 125.6 (q, \(J = 267.0\) Hz), 123.9, 119.6, 113.7, 15.4. HRMS: calcd for C\(_{14}\)H\(_{12}\)F\(_3\)O, 253.0840 (M+H\(^+\)); found, 253.0842.

3', 4-dimethyl-[1,1'-biphenyl]-3-ol (2ab)

Following the general procedure, phenol carbamate 1a (54.0 mg, 0.3 mmol) was reacted with m-tolyl(mesityl)iodonium trifluoromethanesulfonate (176.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 3', 4-dimethyl-[1,1'-biphenyl]-3-ol (2ab) as pale yellow oil (42.4 mg, 71%). \(^1\)H NMR (400 MHz, CDCl\(_3\))  \(\delta\) 7.40 (d, \(J = 10.6\) Hz, 2H), 7.35 (t, \(J = 7.5\) Hz, 1H), 7.20 (dd, \(J = 11.4, 7.6\) Hz, 2H), 7.13 (dd, \(J = 7.7, 1.5\) Hz, 1H), 7.04 (d, \(J = 1.3\) Hz, 1H), 4.96 (s, 1H), 2.45 (s, 3H), 2.33 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\))  \(\delta\) 154.0, 140.7, 140.6, 138.3, 131.3, 128.6, 127.9, 127.7, 124.0, 122.7, 119.5, 113.6, 21.5, 15.4. HRMS: calcd for C\(_{14}\)H\(_{15}\)O, 199.1123 (M+H\(^+\)); found, 199.1123.

3'-bromo-4-methyl-[1,1'-biphenyl]-3-ol (2ac)

Following the general procedure, phenol carbamate 1a (54.0 mg, 0.3 mmol) was reacted with 3-bromophenyl (mesityl)iodonium trifluoromethanesulfonate 5a (199.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 3'-bromo-4-methyl-[1,1'-biphenyl]-3-ol (2ac) as yellow oil (42.8 mg, 54%). \(^1\)H NMR (400 MHz, CDCl\(_3\))  \(\delta\) 7.69 (s, 1H), 7.46 (t, \(J = 8.2\) Hz, 2H), 7.28 (d, \(J = 7.8\) Hz, 1H), 7.18 (d, \(J = 7.7\) Hz, 1H), 7.05 (d, \(J = 7.8\) Hz, 1H), 6.97 (s, 1H), 4.88 (s, 1H), 2.29 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\))  \(\delta\) 154.1, 142.8, 138.9, 131.4, 130.2, 130.1, 129.9, 125.5, 123.5, 122.8, 119.4, 113.5, 15.4. HRMS: calcd for C\(_{13}\)H\(_{12}\)BrO, 263.0072 (M+H\(^+\)); found, 263.0073.

3'-methoxy-4-methyl-[1,1'-biphenyl]-3-yl dimethylcarbamte (2ad)

Following the general procedure, phenol carbamate 1a (54.0 mg, 0.3 mmol) was reacted with 3-methoxyphenyl (mesityl)iodonium trifluoromethanesulfonate (182.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether
95:5) to afford 3′-methoxy-4-methyl-[1,1′-biphenyl]-3-yl dimethylcarbamate (2ad) as yellow solid (56.7 mg, 66%) MP. 82-84 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.40 – 7.32 (m, 3H), 7.30 (dd, \(J = 8.2, 2.8\) Hz, 1H), 7.19 (d, \(J = 7.7\) Hz, 1H), 7.15 – 7.12 (m, 1H), 6.93 – 6.88 (m, 1H), 3.88 (s, 3H), 3.19 (s, 3H), 3.07 (s, 3H), 2.28 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 159.9, 154.6, 150.2, 141.9, 140.0, 131.2, 129.6, 129.5, 124.1, 121.0, 119.5, 112.8, 112.6, 55.3, 36.8, 36.4, 15.9. HRMS: calcd for C\(_{17}\)H\(_{20}\)NO\(_3\), 286.1443 (M+H\(^+\)); found, 286.1440.

2′-methoxy-4-methyl-[1,1′-biphenyl]-3-yl dimethylcarbamate (2ae)

Following the general procedure, phenol carbamate 1a (54.0 mg, 0.3 mmol) was reacted with 2-methoxy phenyl(mesityl)iodonium trifluoromethanesulfonate (182.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford 2′-methoxy-4-methyl-[1,1′-biphenyl]-3-yl dimethylcarbamate (2ae) as pale yellow oil (41.3 mg, 48%). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.39 – 7.27 (m, 5H), 7.02 (ddd, \(J = 13.0, 9.8, 4.6\) Hz, 2H), 3.84 (s, 3H), 3.18 (s, 3H), 3.06 (s, 3H), 2.29 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 156.5, 154.7, 149.6, 137.3, 130.8, 130.3, 129.9, 128.9, 128.5, 126.6, 123.3, 120.8, 111.2, 55.6, 36.7, 36.4, 15.9. HRMS: calcd for C\(_{17}\)H\(_{20}\)NO\(_3\), 286.1443 (M+H\(^+\)); found, 286.1434.

Methyl 3′-((dimethylcarbamoyl)oxy)-4′-methyl-[1,1′-biphenyl]-4-carboxylate (2af)

Following the general procedure, phenol carbamate 1a (54.0 mg, 0.3 mmol) was reacted with (4-(methoxycarbonyl)phenyl)(mesityl)iodoniumtrifluoromethanesulfonate (192.0 mg 0.36 mmol). The crude product was purified by flash column chromatography (Hexane: Ether 95:5) to afford Methyl 3′-((dimethylcarbamoyl)oxy)-4′-methyl-[1,1′-biphenyl]-4-carboxylate (2af) as
brown solid (75.5 mg, 80%) MP. 67-69 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.07 (d, \(J = 8.3\) Hz, 2H), 7.63 (d, \(J = 8.3\) Hz, 2H), 7.40 – 7.33 (m, 2H), 7.29 (d, \(J = 7.8\) Hz, 1H), 3.93 (s, 3H), 3.15 (s, 3H), 3.04 (s, 3H), 2.26 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 167.0, 154.5, 150.4, 144.7, 138.8, 131.4, 130.4, 130.0, 128.8, 126.8, 124.1, 121.1, 52.0, 36.8, 36.4, 15.9. HRMS: calcd for C\(_{18}\)H\(_{20}\)NO\(_4\), 314.1392 (M+H\(^+\)); found, 314.1393.

### 4.3.3. Scale up reaction of \textit{m}-arylated phenol carbamate 1a

![Reaction Scheme](image)

To a solution of the appropriate phenol carbamate 1a (1.032 g, 5.76 mmol) in 1,2-dichloroethane (20.0 mL) was added the diphenyliodonium tetrafluoroborate (2.54 g, 6.90 mmol, 1.2 equiv) and Cu(OTf)\(_2\) (0.208 g, 0.57 mmol). The reaction was stirred for 24 h at 70 °C before dilution with CH\(_2\)Cl\(_2\) (25 mL) and washing with saturated sodium bicarbonate solution (25 mL). The aqueous phase was extracted with further CH\(_2\)Cl\(_2\) (25 mL) and the combined organics were dried over magnesium sulphate and evaporated in vacuo. The crude was purified by flash column chromatography using Hexane: Ether (90:10) to get products 2a′ and 2a.
Spectral data for 2a': $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.59 – 7.54 (m, 1H), 7.40 (dd, $J$ = 10.3, 4.8 Hz, 2H), 7.36 – 7.31 (m, 2H), 7.29 (d, $J$ = 12.6 Hz, 2H), 7.25 (s, 1H), 3.15 (s, 3H), 3.04 (s, 3H), 2.25 (s, 3H). $^{13}$C NMR (101 MHz, CDCl$_3$) $\delta$ 154.6, 150.3, 140.3, 140.1, 131.2, 129.3, 128.6, 127.2, 127.0, 124.0, 120.9, 36.7, 36.4, 15.9. HRMS: calcd for C$_{18}$H$_{20}$NO$_4$, 314.1392 (M+H$^+$); found, 314.1393.

4.3.4 Diversification of 2r’

1. Reductive cleavage of carbamates

A 8-mL vial was charged with anhydrous powdered K$_3$PO$_4$ (0.289 g, 1.36 mmol, 4.5 equiv) and a magnetic stir bar. The vial and contents were flame-dried under reduced pressure, then allowed to cool under N$_2$. [1, 1’-biphenyl]-3-yl dimethylcarbamate 2r’ (73.0, 0.3 mmol, 1 equiv) and NiCl$_2$(PCy$_3$)$_2$ (10.5 mg, 0.015 mmol, 5 mol%) were added. Subsequently, tetramethyldisiloxane (TMDSO) (0.14 mL, 0.75 mmol, 2.5 equiv) and toluene (1.5 mL) were added. The septum cap was replaced with a Teflon-lined screw cap. The heterogeneous mixture was stirred at 115 °C for 24 h. The reaction vessel was cooled to 23 °C. The reaction mixture was diluted with EtOAc (5 mL), filtered over a pad of celite (eluted with an additional 5 mL of EtOAc), and evaporated to dryness. The crude residue was purified by flash chromatography to yield deoxygenated product 3a (41.0 mg, 88% yield) as a white solid. MP. 70-72 °C;
Spectral data for 3a: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.59 (d, J = 7.3 Hz, 4H), 7.44 (t, J = 7.3 Hz, 4H), 7.34 (t, J = 7.3 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.2, 128.7, 127.2, 127.2. HRMS: calcd for C$_{12}$H$_{11}$, 155.0861 (M+H$^+$); found, 155.0861.

2. Suzuki-Miyaura coupling of carboxamides

A 8-mL vial was charged with anhydrous powdered K$_3$PO$_4$ (0.462 g, 2.18 mmol, 7.2 equiv) and a magnetic stir bar. The vial and contents were flame-dried under reduced pressure, then allowed to cool under N$_2$. [1, 1'-biphenyl]-3-yl dimethylcarbamate 2r' (73.0 mg, 0.3 mmol, 1 equiv), phenylboronic acid (0.147 g, 1.2 mmol, 4 equiv) and NiCl$_2$(PCy$_3$)$_2$ (21.0 mg, 0.03 mmol, 10 mol%) were added. The vial was then evacuated and back filled with N$_2$ and toluene (1.5 mL) was added. The septum cap was replaced with a Teflon-lined screw cap. The heterogeneous mixture was allowed to stir at room temperature for 1 h, then heated to 130 °C for 24 h. The reaction vessel was cooled to 23 °C. The reaction mixture was diluted with DCM, silica gel was added and evaporated to dryness. The crude residue was purified by flash chromatography to yield product 3b (41.0 mg, 71% yield) as a white solid. MP. 88-90 °C;

Spectral data for 3b: $^1$H NMR (400 MHz, CDCl$_3$) δ 7.87 (s, 1H), 7.71 (d, J = 7.4 Hz, 4H), 7.64 (d, J = 7.8 Hz, 2H), 7.50 (d, J = 7.0 Hz, 1H), 7.52 (t, J = 7.3 Hz, 4H), 7.43 (t, J = 7.3 Hz, 2H). $^{13}$C NMR (101 MHz, CDCl$_3$) δ 141.8, 141.2, 129.2, 128.8, 127.4, 127.3, 126.2, 126.1. HRMS: calcd for C$_{18}$H$_{15}$, 231.1174 (M+H$^+$); found, 231.1177.
4.4 Summary

In summary, we demonstrated the first example of meta-arylation of phenol derivatives catalyzed by copper. The developed protocol displays outstanding functional group tolerance. The current method provides room for further functionalization of the obtained products and thus would find vast applications in pharmaceuticals and complex molecule synthesis.

4.5 References


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LIST OF PUBLICATIONS


3. Copper Catalyzed Site Selective *meta*-Arylation of Phenyl Derivatives. Manikantha Maraswami, Gang Chen and Teck-Peng Loh. (*In communication*).


5. Selective Binding to mRNA Duplex Regions by Chemically Modified PNAs Stimulates Ribosomal Frameshifting. Ru Ying Puah, Huan Jia, Manikantha Maraswami, Desiree-Faye Kaixin Toh, Kiran M. Patil, Ruimin Sun, Cailing Tong, Mei Huang, Xin Chen, Teck-Peng Loh, Ding Xiang Liu and Gang Chen. (*Equal first author*) *ACS Biochemistry*, 2017 DOI:10.1021/acs.biochem.7b00744.

CONFERENCE

Manikantha Maraswami, Gang Chen, Teck-Peng Loh (Poster Presentation)