Reactivity and Selectivity in Aryl C–H Functionalization by Electrophilic Radicals

REACTIVITY AND SELECTIVITY IN ARYL C–H FUNCTIONALIZATION BY ELECTROPHILIC RADICALS

A dissertation presented

by

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Abstract

Two main challenges hinder the development of new, broadly useful C–H functionalization reactions: (1) most C–H bonds constitute part of the relatively inert backbone of an organic molecule, so it is difficult to elicit sufficient *reactivity* from these bonds, and (2) C–H bonds are ubiquitous in organic molecules, so it is difficult to control the *selectivity* of which C–H bond is functionalized. The subject of this thesis is the functionalization of C–H bonds in aromatic molecules. In addition to the relevant background, herein are described two new reactions which address the challenges of reactivity and selectivity in C–H functionalization described above.

In Chapter 1 is described a new reaction in which an amine-*N*-oxide-ligated palladium complex, in conjunction with a silver cocatalyst, catalyzes imidation of arenes by the reagent *N*-fluorobenzenesulfonimide. The reaction enables imidation of a variety of arenes at or below room temperature, requires no coordinating directing group on the substrate, and gives synthetically useful yields with the arene as the limiting reagent. Mechanistic data is presented which implicates an unusual mechanism devoid of commonly invoked organometallic intermediates: oxidation of the palladium catalyst occurs as the turnover-limiting step, while C–H bond functionalization occurs subsequently at a higher oxidation state of the catalyst. The unusual imidation reactivity is ascribed to unique features of the amine-*N*-oxide ligand, which are also discussed.

Described in Chapter 2 is a new radical aromatic substitution reaction with nearly complete *para* selectivity for a variety of monosubstituted arenes. We present a rationale for the unprecedented degree of

positional selectivity exhibited by the reaction: we propose that arene-to-radical charge transfer in the transition state of radical addition, elicited by the unusually high electron affinity of the radical, is the factor primarily responsible for the positional selectivity. The utility of the reaction is illustrated by a direct synthesis of aryl piperazines, a common motif in medicinal chemistry.

Dedicated to my parents, Claire and John Boursalian

TABLE OF CONTENTS

List of abbreviations:

bipy: 2,2'-bipyridine
DFT: Density Functional Theory
DG: Directing Group
DMF: dimethylformamide
dtbipy: 4,4'-di-*tert*-butyl-2,2'-bipyridine
EA: Electron Affinity
EPR: Electron Paramagnetic Resonance
KIE: Kinetic Isotope Effect
m-CPBA: *meta*-chloroperoxybenzoic acid
MS: Mass Spectrometry
    ESI-TOF: Electrospray Ionization – Time of Flight
    HRMS: High Resolution Mass Spectrometry
NBO: Natural Bond Orbital
NFBS: N-fluorobenzenesulfonimide
NMR: Nuclear Magnetic Resonance spectroscopy
    COSY: ^{1}H-^{1}H Correlation Spectroscopy
    NOE(SY): Nuclear Overhauser Effect (Spectroscopy)
    TOCSY: Total Correlation Spectroscopy
PVDF: polyvinylidine difluoride
TEDA: *N*-(chloromethyl)-triethylenediamine^{+}

Publications

Portions of Chapter 1 of this dissertation have been reproduced, with permission, from the following publication:

> **Boursalian, G. B.**,† Ngai, M.-Y.,† Hojczyk, K. N. & Ritter, T. Pd-Catalyzed Aryl C–H Imidation with Arene as the Limiting Reagent. *Journal of the American Chemical Society* **135**, 13278-13281, doi:10.1021/ja4064926 (2013).

The work described in Chapter 2 of this dissertation has been accepted for publication in *Nature Chemistry*, but has not yet appeared in print at the time of this writing:

> **Boursalian, G. B.**, Ham, W. S., Mazzotti, A. R. & Ritter, T. Charge Transfer Directed Radical Addition Enables *para*-Selective C–H Functionalization. *Nature Chemistry*, *accepted*

In addition to the work presented in this thesis, additional investigations conducted during my Ph.D. studies have been published as contributions to the following publications:

> Lee, E.,† Kamlet, A. S.,† Powers, D. C., Neumann, C. N., **Boursalian, G. B.**, Furuya T., Choi, D. C., Hooker, J. M. & Ritter, T. A Fluoride-Derived Electrophilic Late-Stage Fluorination Reagent for PET Imaging. *Science* **334**, 639-642, doi:10.1126/science.1212625 (2011).

> Brandt, J. R., Lee, E., **Boursalian, G. B.** & Ritter, T. Mechanism of Electrophilic Fluorination with Pd(IV): Fluoride Capture and Subsequent Oxidative Fluoride Transfer. *Chemical Science*, **5**, 169-179, doi: 10.1039/c3sc52367e (2013)

† denotes equal contribution

Acknowledgements

In 2009, after I had graduated from Cal, I agonized over what my next steps would be. I must admit that I only reluctantly decided to go to grad school in chemistry. A major factor that tipped the scales was the influence of terrific professors, including Phil Geisler, Matt Francis, Dirk Trauner, and of course, my undergraduate research advisor Peter Vollhardt. Peter especially infected me with his attitude towards science, and I've often found myself reading through his old papers for inspiration during my time in the Ritter lab. Especially influential on me was his advice "Don't do anything you don't want to do. It's bad for your soul."‡ During my time at Harvard, I can't say I was always successful in avoiding things I didn't want to do, but I've done my best and I think my soul is better for it.

Arriving at Harvard, I was blessed to find myself with a friendly, supportive, and remarkably drama-free cohort. Without them my life during the last five years would certainly have been a lot harder and a lot less fun. Thanks in particular to Raúl Hernández Sánchez and Alejandra Bueno Martinez for being terrific friends and roommates, and for welcoming me into their homes in Chihuahua City, Mexico. Thanks also to Juan Pablo Maianti and Nicole Darricarrère for their close friendship and support over the years. Joshua Klobas is one of the most interesting people I've ever met, and I've tremendously enjoyed our time hanging around in bars, playing backgammon and talking about all sorts of things. Thanks Jarrod McClean and Anh Nguyen (Go Bears!) for lots of fun times together. Further thanks to Jarrod for scientific conversations over coffee in Lise café; the insights Jarrod gave me into computational chemistry during these coffee breaks led to new directions in my work on aromatic substitution by extremely electrophilic radicals (Chapter 2), which brought the whole project to a higher level. Thanks to Yongho Park for our regular lunches, as well as our many concert trips. I must also acknowledge the Kebab Factory crew – Jarrod McClean, Janine May, Reem Hannun, Stéphanie Valleau, Garrett Drayna, Anders

‡ Vollhardt, K. P. C. Author Profile. *Angewandte Chemie International Edition* **50**, 34-36, doi:10.1002/anie.201007503 (2011).

Hansen – for our regular kebab runs.

Ahmed Badran, though strictly speaking in a different program, has become one of my best friends during my time at Harvard. I'll never forget the many times we made each other laugh so hard that I thought one of us would die (*hiccup!*).

Thanks to those members of the Ritter lab over the years who have helped make the lab a fun place to work. First among them is Eunsung Lee, who is certainly the most impressive experimental chemist I know, and who managed to pass to me only a tiny fraction of his skill (my fault, not his), a gift which has nevertheless helped me again and again throughout my PhD. Thanks also to Anthony Mazzotti, Ming Yu Ngai, Kasia Hojczyk, and Won Seok Ham, whose collaboration was instrumental in the work presented in this thesis. Thanks to Heejun Lee, Mike Campbell, Teppei Fujimoto, Andrew Hoover, Pavel Ivashkin, and Filippo Sladojevich for being good friends and helping me waste time when that was what was needed.

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I've had the opportunity to be a Teaching Fellow for three classes during my time at Harvard: Experimental Organic Chemistry (Chem 135), graduate-level Organotransition Metal Chemistry (Chem 153), and second semester Organic Chemistry (Chem 30). The work I've done as TF and head TF for these courses has been the most personally rewarding work I've done at Harvard. I am incredibly grateful

to all my students in these courses; my interactions with them have been a tremendous source of joy and inspiration, and have made me a better teacher and human being. Thanks as well to the leaders of these courses, Ryan Spoering (Chem 135) and Tobias Ritter (Chem 153 and 30) for entrusting me with the responsibilities in these courses which have been so personally enriching.

Thanks to my friends Sydney Sims, Janice Daurio, and Paul Ford for their continuing love and support ever since I was their student at Moorpark College.

Lastly and most importantly, I am very fortunate to have been born to extremely loving and dedicated parents; I feel like I've won the lottery in this regard. Without their love and support, I would not have made it as far as I have. Thanks mom and dad for everything. I love you very much.

I've done a lot of work that I'm very proud of during my time at Harvard, and most of the space in this thesis is dedicated to that work, so I wanted to take these few pages to thank those people behind the scenes that made it all possible, whether through scientific, professional, or emotional support. I'm glad I came to Harvard, partly because over the last five years I've become a better scientist than I imagined I could be as an undergraduate, but mostly because of the people I've gotten to know while I've been here. I've never been part of such a group of uniformly interesting people before, and I doubt I ever will be again. I'm grateful to have had the opportunity, and I'm certain I'll remember it for the rest of my life.

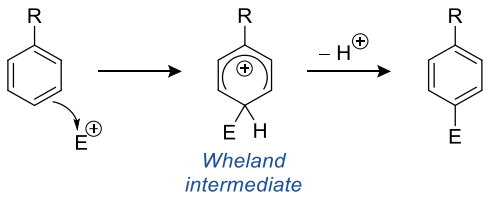
Introduction

I.1 On the Functionalization of Aromatic C–H Bonds

The topic of this thesis is the development of new reactions for the functionalization of aromatic C–H bonds. The term *C–H functionalization* is used throughout, and to avoid ambiguity, we define this term here. A C–H functionalization reaction is one which converts a hydrogen atom bound to carbon into a different atom. In the following sections, we discuss three approaches to the functionalization of aromatic C–H bonds which are relevant as background to the original research described in the Results and Discussion section.

I.2 Electrophilic Aromatic Substitution

The oldest and most extensively studied class of reactions for the conversion of an aromatic hydrogen substituent into a functional group is electrophilic aromatic substitution.[1] The general mechanistic scheme for electrophilic aromatic substitution is depicted in Scheme I.1. An electrophilic species E^+, often generated *in situ* from appropriate precursors, undergoes nucleophilic attack by an arene ring, resulting in the formation of a delocalized carbocation intermediate, called the σ-complex or Wheland intermediate. Common examples of electrophiles include the nitronium ion (for aromatic nitration), bromonium ions (bromination), and carbocations (alkylation).[2]



Scheme I.1. Mechanism of electrophilic aromatic substitution

Substituted arenes may present multiple nonequivalent C–H bonds as potential sites for substitution,

raising the issue of positional selectivity. The positional selectivity of electrophilic aromatic substitution is highly dependent on the nature of the electrophile, the substitution pattern of the arene substrate, and the reaction conditions employed. However, general trends emerge: resonance and inductive electron-donating groups direct substitution *ortho* and *para* to themselves, while resonance electron-withdrawing groups direct *meta* to themselves (Figure I.1a and b).

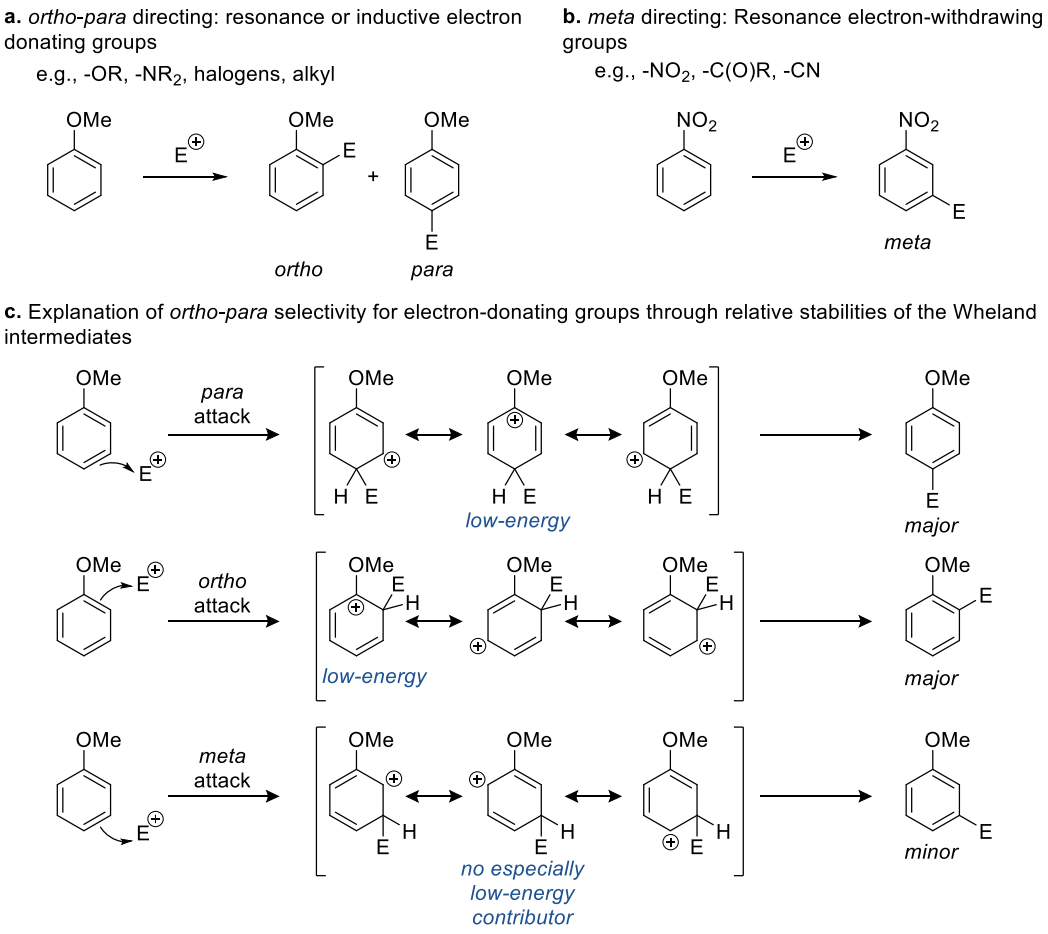


Figure I.1. Electrophilic aromatic substitution selectivity and rationalization through relative energetics of Wheland intermediates.

The formation of the Wheland intermediate is typically an endothermic process. Therefore, Hammond's postulate indicates that the transition state of addition will be similar in structure to the Wheland intermediate, and so factors which stabilize the Wheland intermediate can be expected to stabilize the

transition state as well. Thus, relative rates of electrophile addition to different positions can be predicted by inspection of the Wheland intermediate arising from electrophilic attack at each position (Figure I.1c).

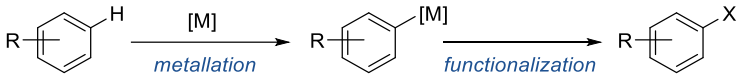
Electron donating groups direct electrophilic aromatic substitution to occur predominantly in the *ortho* and *para* positions. This selectivity is readily explained through inspection of the major resonance contributors in the Wheland intermediate: the intermediates resulting from *ortho* and *para* attack have especially stable contributors in which the positive charge is stabilized by electron-donation from the substituent, whereas the intermediate arising from *meta* attack lacks any such stabilization. A similar argument explains the *ortho*/*para* directing nature of inductive electron-donating groups such as alkyl groups. Resonance electron-withdrawing groups direct electrophilic substitution *meta* to themselves; attack at the *ortho* and *para* positions results in intermediates with destabilizing resonance contributors.[2]

The application of electrophilic aromatic substitution in synthesis faces certain limitations. The palette of functional groups that can be installed by electrophilic substitution is limited by the accessibility of suitable electrophiles. For example, although nitro groups can often be readily installed through electrophilic substitution by NO_2^+, aniline derivatives cannot be directly synthesized as there exist no suitable electrophiles for this purpose. Likewise, C–O and C–F bond formations are challenging; aromatic hydroxylations by peroxides and fluorinations by elemental fluorine are thought to proceed through radical mechanisms (see Section I.4).[1] Furthermore, although we have seen above that substituents can have significant directing effects on the positional selectivity of aromatic substitution, mixtures still often result, engendering lower yield of the desired isomer and waste in the form of undesired isomers. Another problem is encountered if the desired positional isomer of the functionalized product is not that which is favored by the substitution pattern of the starting material. To address these limitations in scope and selectivity, alternative approaches for aromatic C–H functionalization have been sought.

I.3 Transition Metal Catalyzed Approaches: Metalation-Functionalization

In order to promote otherwise unfavorable aromatic substitutions, a strategy has emerged involving

transition metal catalysis which may be termed the metalation-functionalization approach. A transition metal catalyst reacts with the aromatic substrate to form an aryl-metal σ-bond. Subsequent functionalization of the carbon-metal bond yields the product, resulting in a net C–H functionalization (Scheme I.2). The metalation-functionalization approach can be subdivided into two broad categories: the chelation-assisted approach and the non-chelation-assisted approach.



Scheme I.2. The metallation-functionalization approach

Chelation-assisted C–H metallation

Many transition metal catalyzed C–H functionalization reactions rely on the presence of a coordinating functional group on the arene substrate. Binding of a catalyst to the coordinating functional group serves to promote C–H metalation by rendering the metalation step intramolecular, as well as to influence selectivity by directing the catalyst to proximal C–H bonds.

In 1993, Murai and coworkers reported a ruthenium catalyzed alkylation of aryl ketones, in which the new carbon-carbon bond is formed adjacent to the ketone substituent due to chelation-assistance from the carbonyl group.[3] Since then, very many such examples of *ortho* C–H functionalization have been reported. The field has been extensively reviewed,[4-7] and a few select examples are shown in Figure I.2.

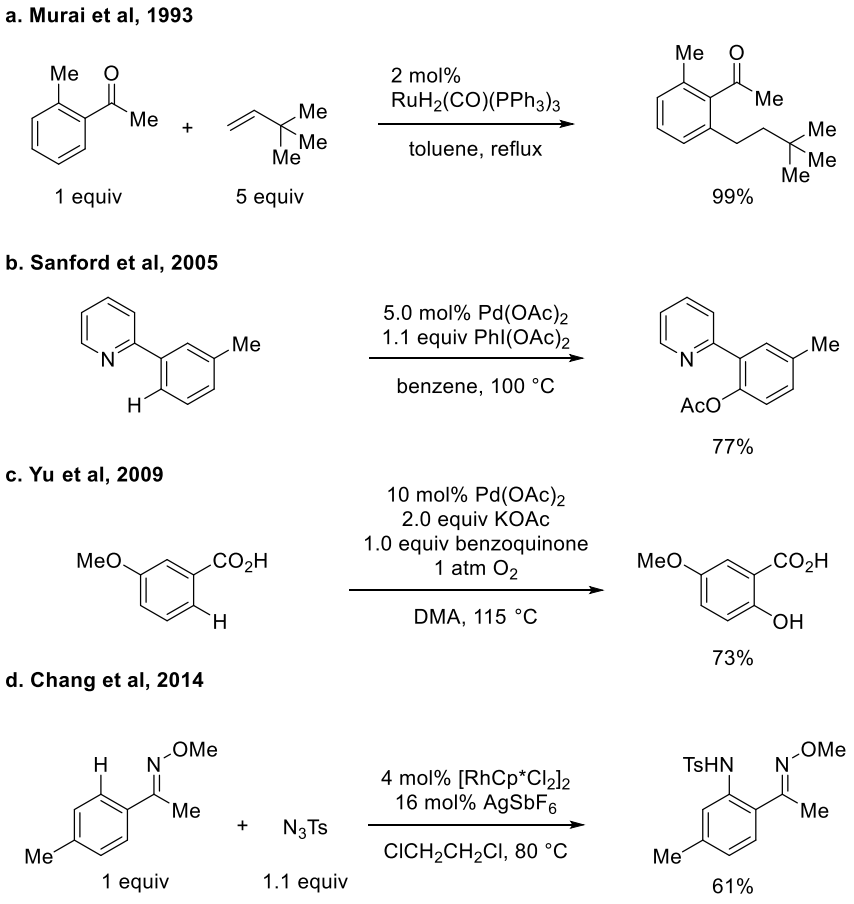


Figure I.2. Selected examples of chelation-assisted aromatic C–H functionalization[8-10]

Recently, Yu has identified molecular fragments which, when attached to an arene, direct C–H functionalization reactions *meta* to themselves.[11] These fragments are meant to be installed on the arene substrate prior to the functionalization reaction, and subsequently removed to yield an overall *meta*-functionalized product.

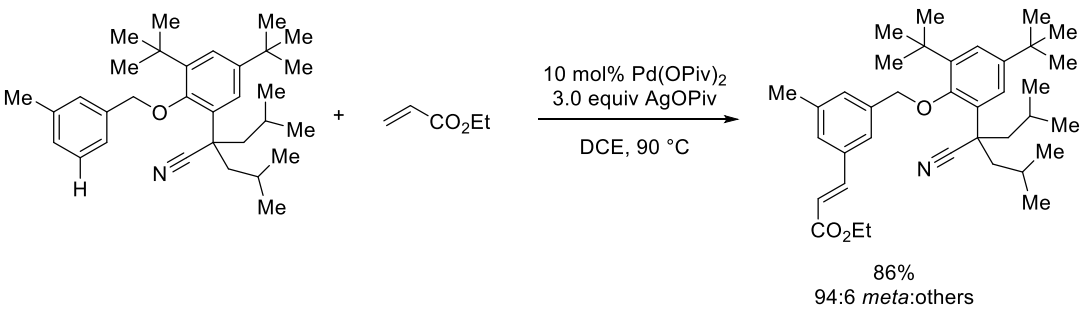


Figure I.3. Chelation-assisted *meta*-selective C–H functionalization

The chelation-assisted approach to C–H functionalization has enabled a broad variety of highly selective transformations of aromatic C–H bonds, including C–O bond formations, C–N bond formations, halogenations, olefinations, alkylations, and others. [4-7] Clearly, the applicability of the chelation-assisted approach depends on whether an appropriate coordinating directing group is available in the correct position to promote the desired C–H functionalization reaction on a given substrate. As the field has developed, the variety of Lewis basic functional groups which can be made to provide chelation-assistance to transition metal catalysts has accordingly expanded. Despite the considerable success of the chelation-assisted approach, a fundamental limitation remains: a specific functional group is required in a specific position to promote a specific reaction. Furthermore, although there is a great variety of *ortho* C–H functionalization reactions, and since recently a few examples of *meta*, there is currently no chelation-assisted *para* selective C–H functionalization reaction. These facts taken together indicate a need for C–H functionalization reactions with selectivity complementary to that enabled by the chelation-assisted approach. Such reactions would be especially powerful if no special functional group is required to control positional selectivity.

Non-chelation-assisted C–H metallation

If a coordinating directing group is not present on the arene substrate, the advantage of intramolecularity is lost and metalation reactivity is substantially diminished. In this case, multiple equivalents, and in some cases even solvent quantities, of arene are required to drive the metalation step.[12] Such a requirement is

prohibitive if functionalization of a valuable, synthetically advanced arene is desired.

There are few, highly significant examples of non-chelation-assisted C–H functionalization reactions in which the arene functions as the limiting reagent. A major breakthrough came in 2002, when Ishiyama, Takagi, Hartwig, and Miyaura reported an iridium-catalyzed C–H borylation reaction, which affords high yields of aryl boronate esters (based on arene) from a 2:1 ratio of arene to bis(pinacolato)diboron (Figure I.4). Previous aromatic C–H borylation reactions had utilized the arene substrate as the reaction solvent. Mechanistic investigations have pointed to an Ir(III) *tris*-boryl complex as the species responsible for C–H bond cleavage.[13] It is proposed that the C–H bond cleavage step may occur by σ-bond metathesis with participation of the empty *p*-orbital on the boryl ligand.

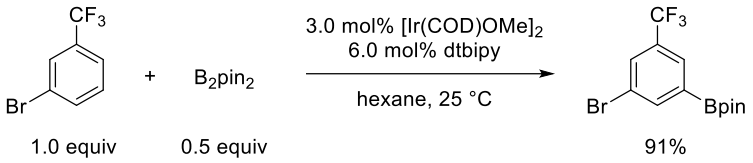


Figure I.4. Stoichiometric iridium-catalyzed borylation

Another example of a non-chelation-assisted C–H functionalization reaction in which the arene substrate can act as limiting reagent is the rhodium-catalyzed silylation reaction reported by Cheng and Hartwig in 2014. The authors rationalize the observed positional selectivity of the silylation reaction as being determined mainly by steric effects: silylation adjacent to substituents on the aromatic ring, when observed, occurs only in small amounts. Monosubstituted arenes generally yield a mixture of *para* and *meta* substituted products (Figure I.5).[14]

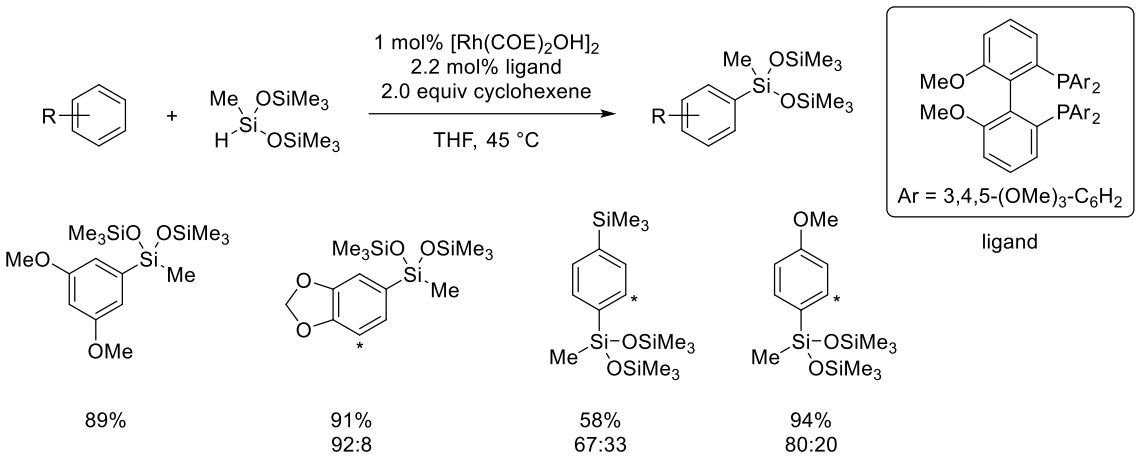


Figure I.5. Rhodium-catalyzed silylation with arene as limiting reagent

The borylation and silylation reactions described above illustrate an additional challenge in non-chelation-assisted C–H functionalization: even when sufficient reactivity is mustered to enable the arene to act as limiting reagent, product mixtures reemerge as the regiocontrol afforded by a coordinating directing group is lost. The positional selectivity of the Hartwig borylation and silylation reactions is rationalized as determined by the steric influence of the ring substituents. Steric hindrance has fundamental limitations as a strategy for the control of positional selectivity in C–H functionalization. In a monosubstituted arene, the substituent can have a strong steric influence on the *ortho* position, and in many cases substitution at this position can be effectively suppressed through the use of a bulky catalyst. However, the substituent can exert at best a marginal steric influence on the *meta* position; thus, steric differentiation between the *meta* and *para* positions is extremely difficult to achieve.

The difficulty of realizing complete control of positional selectivity through steric hindrance is illustrated in a 2015 report by Saito, Segawa, and Itami on iridium-catalyzed C–H borylation. By employing a bulky bidentate phosphine ligand, the authors were able to achieve unprecedented selectivity for the *para* position of monosubstituted arenes (Figure I.6). The best *para*:*meta* selectivities, in the neighborhood of 9:1, were achieved for very large substituents such as triethylsilyl and *tert*-butyl, or larger. However, the *para*:*meta* selectivity falls precipitously for smaller substituents, such as *iso*-propyl (58:42), nearly

reaching the statistical ratio in ethyl benzene (31:68). To the best of our knowledge, there is no transition metal catalyzed C–H functionalization reaction which can afford significant levels of *para* selectivity for a broad range of monosubstituted arenes.

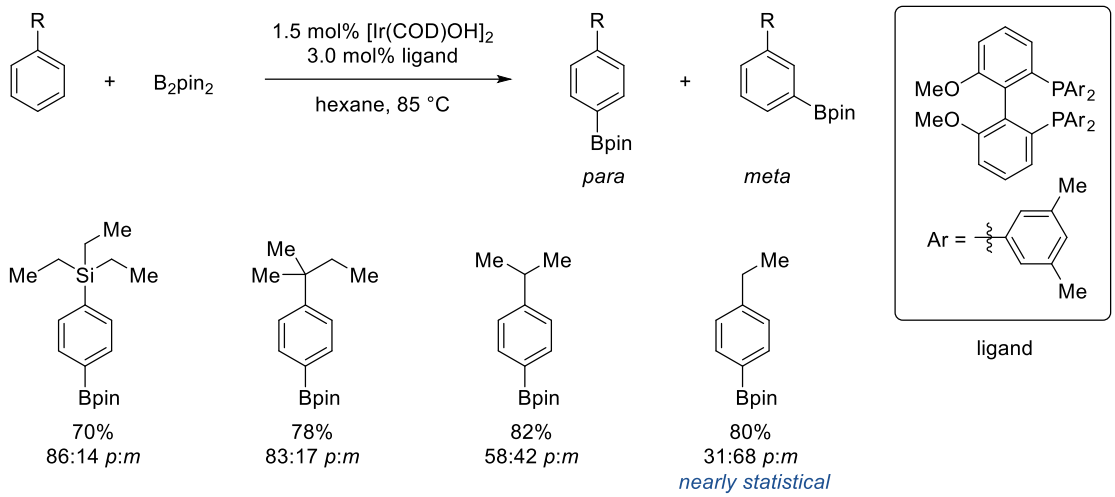
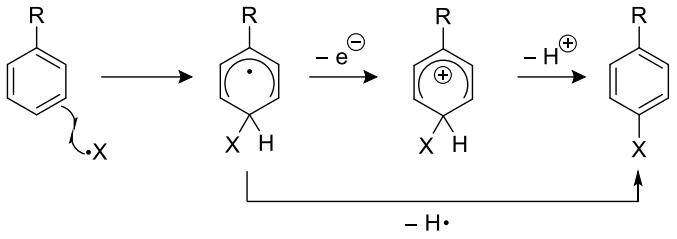


Figure I.6. Steric control of site selectivity in C–H borylation

I.4 Radical Aromatic Substitution

The final class of reaction for the functionalization of aromatic C–H bonds that will be discussed is radical aromatic substitution, which is also often called homolytic aromatic substitution. Radical aromatic substitution is related to electrophilic aromatic substitution; the difference is that a radical adds to the aromatic ring instead of an electrophile. The delocalized radical intermediate thus formed, which is analogous to the Wheland intermediate in electrophilic substitution, can be rearomatized through either hydrogen abstraction, or single electron oxidation followed by deprotonation (Scheme I.3).



Scheme I.3. Mechanism of radical aromatic substitution

Radical aromatic substitution by aryl radicals, generated from diazo compounds, to form biaryls has been known since at least 1895.[15] For much of the time since then, radical aromatic substitution never found widespread use in synthesis, in part due to the notion, widely held by organic chemists, that the highly reactive nature of radicals precluded any useful degree of selectivity. The following passage from the 2007 edition of the standard textbook *Advanced Organic Chemistry* by Carey and Sundberg nicely sums up these concerns in the context of positional selectivity:[16]

> "*There are some inherent limits to the usefulness of such reactions. Radical substitutions are only moderately sensitive to substituent directing effects, so that substituted reactants usually give a mixture of products. This means that the practical utility is limited to symmetrical reactants, such as benzene, where the position of attack is immaterial.*"

Indications that radical aromatic substitution could engender useful positional selectivity under certain conditions emerged in the 1960's and 70's in seminal work by Minisci.[17-20] Minisci showed that cationic aminium radicals, derived from reduction of *N*-chloroamines under acidic conditions, could undergo radical aromatic substitution with positional selectivity that mirrored electrophilic aromatic substitution, with electron-donating substituents directing substitution to the *ortho* and *para* positions (Figure I.1).

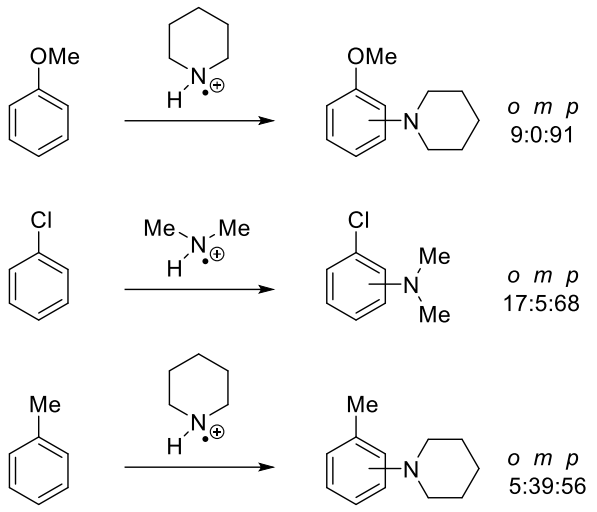


Figure I.7. Aromatic radical amination by cationic aminium radicals

Minisci explained the observed selectivity as arising from radical polar effects, invoking what he called "polar forms" in the transition state: contributions from full or partial electron transfer from the arene to the cationic radical.[18,19] The contribution from charge transfer is especially pronounced in reactions of cationic aminium radicals due to their high electrophilicity. Despite this key insight (see Chapter 2), Minisci did not elaborate on the nature of this charge transfer contribution, and did not explain specifically how the proposed charge transfer effect led to the observed selectivities.

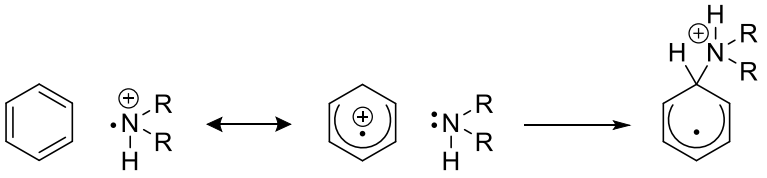


Figure I.8. Minisci's depiction of charge transfer contributions to radical addition.[19]

Minisci's contribution, though remarkable, did little to change the notion that radical aromatic substitution is inherently unselective, as evidenced by the passage from the 2007 edition of Carey and Sundberg quoted above. Quite recently, radical aromatic substitution has received increased attention from the methodology development community, especially in regard to aromatic substitution by fluoroalkyl

radicals. For example, in 2011, Nagib and MacMillan disclosed an aromatic C–H trifluoromethylation reaction which operates by radical aromatic substitution, in which the trifluoromethyl radical is generated from trifluoromethylsulfonyl chloride by single electron reduction by a photoexcited transition metal catalyst.[21] The trifluoromethyl radical adds rather indiscriminately to different positions in most arenes, giving rise to the product mixtures which are typical of radical aromatic substitution. Remarkably, the tendency of the radical trifluoromethylation to afford product mixtures can be a strength: in some applications, such as the synthesis of drug analogues, obtaining several products from a single reaction can be advantageous, even if each product is isolated in low yield. Nagib and MacMillan demonstrated this concept through trifluoromethylation of the drug Lipitor, which yielded three trifluoromethylated products in roughly 25% yield each, separable by Supercritical Fluid Chromatography (Figure I.9). Thus, in one step, three derivatives are obtained for potential biological testing.

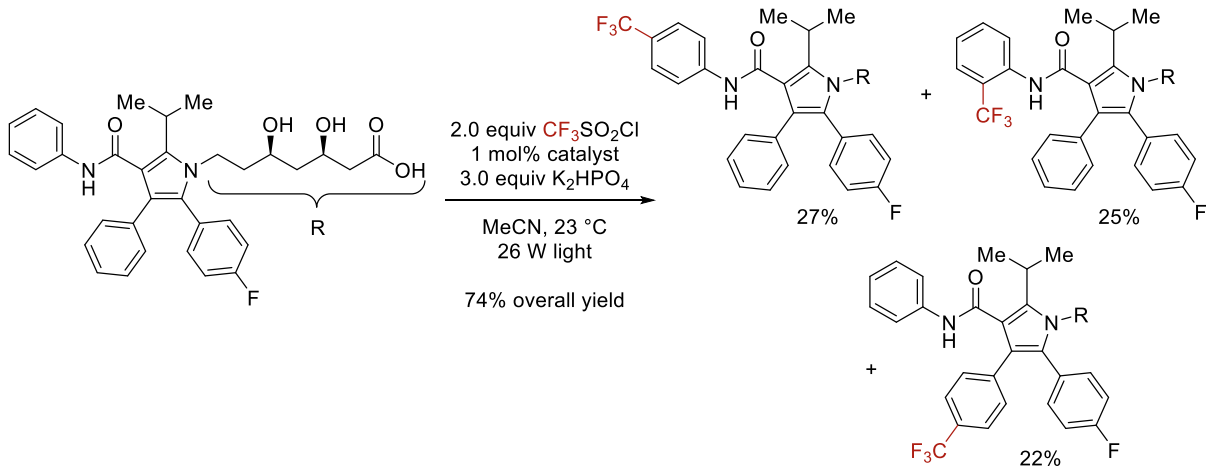


Figure I.9. Radical trifluoromethylation of Lipitor

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Chapter 1. Intermolecular Aromatic C–H Imidation with Arene as Limiting Reagent

1.1 Specific Background

In this chapter, we describe a catalytic, intermolecular C–H imidation of arenes which was published in the Journal of the American Chemical Society in September 2013.[1] The reaction is enabled by a new palladium catalyst **1.1**, which effects group transfer without the formation of conventionally targeted organometallic intermediates. Unlike previous aromatic imidation reactions of unactivated arenes, this transformation affords synthetically useful yields *with the arene substrate as limiting reagent*.

Historically, perhaps the most important method of introducing an amino group into arenes has been electrophilic aromatic nitration followed by reduction of the nitro group.[2] However, nitration of arenes typically requires strongly acidic or oxidizing reaction conditions, which limits its use on substrates with sensitive functional groups. Alternatively, several aniline derivatives can be reliably prepared by transition-metal catalyzed directed C–H amidation,[3-8] but the requirement for a coordinating directing group limits the potential substrate scope. Non-chelation-assisted transition metal catalyzed C–H amination reactions,[9-14] as well as metal-free approaches involving the use of an oxidant and amine to introduce the C–N bond, have also been reported.[13,15-17] However, unless the arene has particularly acidic C–H bonds, such as in perfluoroarenes or benzoxazole derivatives,[11-13] these methods require a minimum of 1.5 equivalents, and not uncommonly solvent quantities of arene substrate, and yields are often based on the amidating reagent, not the arene.

1.2 Reaction Parameters and Substrate Scope

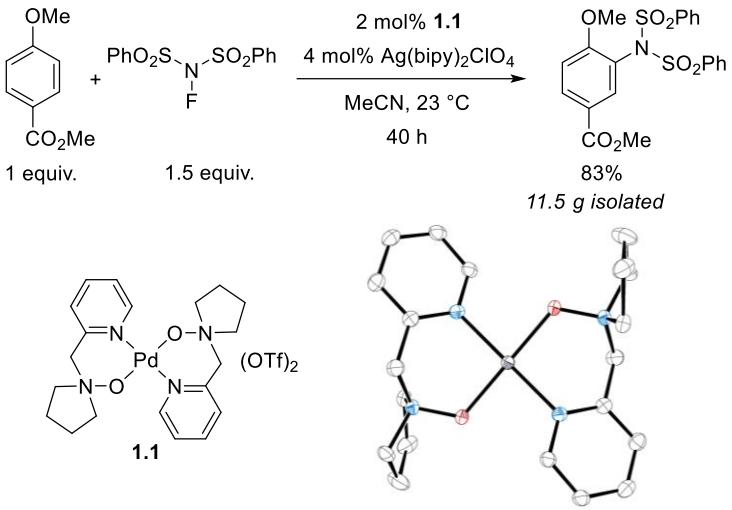
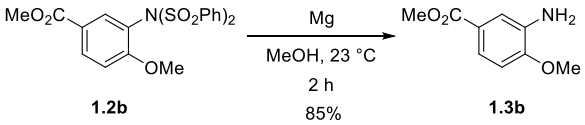


Figure 1.1. C–H imidation catalyzed by **1.1** and $Ag(bipy)_2ClO_4$, and x-ray structure of the cation of **1.1** (elipsoids drawn at 50% probability)

Imidation of arenes by the reagent N-fluorobenzenesulfonimide (NFBS) is catalyzed by **1.1** and $Ag(bipy)_2ClO_4$ as shown in Figure 1.1. Both catalyst **1** and the silver co-catalyst are required in the reaction; control experiments in which either is omitted gave less than 10% of imidated product, although the silver co-catalyst can be replaced with $Ru(bipy)_3(PF_6)_2$ with similar results (Table 1.1, compounds **1.2a** and **1.2b**). The reaction proceeds equally well in the presence or absence of light. Catalyst **1.1** was readily prepared from tetrakis(acetonitrile)palladium(II) triflate and the N-(2-pyridylmethyl)pyrrolidine-*N*-oxide ligand, which itself is available in two steps from commercial starting materials. The catalyst can also be generated in situ by mixing $Pd(NCMe)_4(OTf)_2$ and the ligand with nearly identical results as obtained with isolated and purified **1.1**. Because catalyst **1.1** is easily prepared and stored, we have used it directly in our investigations. The unusual pyridine-*N*-oxide ligand motif is exceptionally effective for the catalytic imidation, and several other palladium-based catalysts supported by ligands such as bipyridine afforded product in at most 3% yield (see Chapter E1, page 78)

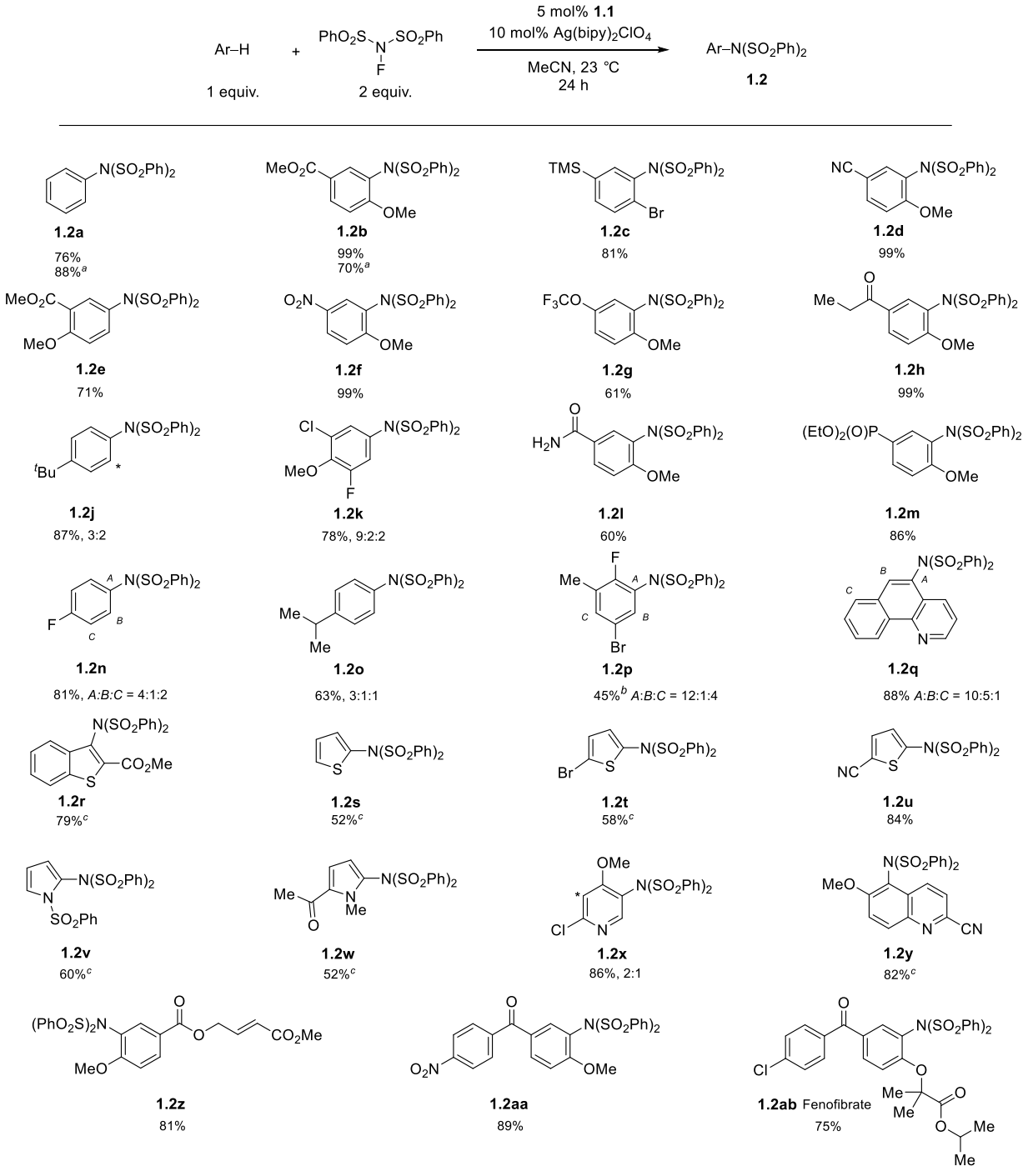
A variety of arenes, including N- and S-heteroarenes, could be efficiently imidated (Table 1.1). Selectivity

is substrate-intrinsic; resonance donors, such as alkoxy and halogen groups, direct imidation *ortho*/*para*, similar to electrophilic aromatic substitution. Inductive donors do not direct as effectively (e.g., **1.2c**, **1.2j**), and substrates that lack a strong directing bias (e.g. **1.2n**, **1.2o**, **1.2p**) afford mixtures of constitutional isomers. Functional groups that can cause problems for nitration such as esters and silanes are tolerated. Arenes more electron-poor than those shown in Table 1 show diminished reactivity and give lower yields. Competitive C–H fluorination and double imidation are significant side-reactions for more electron-rich arenes, though performing the reaction at lower temperature (4 °C) can substantially reduce both side reactions for some substrates (**1.2r-t**, **1.2v**, **1.2w**, **1.2y**). Potential coordinating directing groups do not influence regioselectivity as they do in directed catalytic C–H functionalization reactions[5] (**1.2b**, **1.2e**, **1.2l**, **1.2q**). The reactions for which the data is shown in Table 1 were performed rigorously dry and air-free, but similar results were obtained for reactions performed in air with reagent quality solvents. Product **1.2b**, synthesized on 11 g scale with this methodology, was chosen to demonstrate the removal of the sulfonyl protecting groups. Treatment of **1.2b** with magnesium in methanol under sonication produced aniline **1.3b** in 85% yield (Scheme 1.1).



Scheme 1.1. Reduction of aryl sulfonamide products to anilines

Table 1.1 Substrate scope of aromatic imidation.



[a]$Ru(bipy)_3(PF_6)_2$ (2.5 mol%) used in place of $Ag(bipy)_2ClO_4$, 50 °C reaction temperature, 0.2 M. [b]Along with arene imidation, 4% benzylic imidation was observed. [c]Reaction performed at 4 °C. * denotes site of amidation of other constitutional isomer.

1.3 Mechanistic Investigations

Mechanistic data, detailed below, unambiguously implicate a mechanism with the following noteworthy features: 1) oxidation of the bis-cationic Pd(II) complex **1.1** enabled by the amine-*N*-oxide ligands, 2) involvement of the co-catalyst in single-electron redox chemistry, 3) irreversible substrate binding prior to C–H bond functionalization, and 4) C–N bond formation occurring without C–H palladation. A plausible mechanistic proposal including these features is depicted in Figure 1.2.

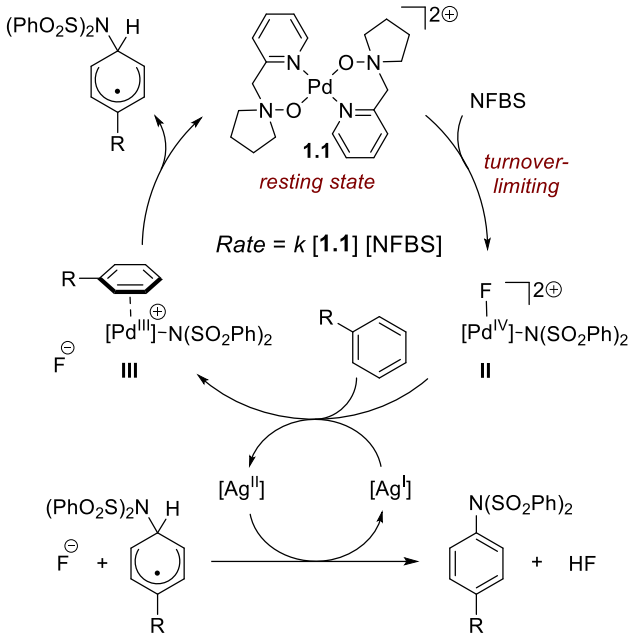


Figure 1.2. Proposed catalytic cycle

Turnover-limiting oxidation of catalyst **1.1** yields Pd(IV) complex **II**. Single-electron reduction of **II** by $Ag(bipy)_2^+$ and substrate association follow to form Pd(III) intermediate **III**. Intermediate **III** formally transfers sulfonimidyl radical to the bound substrate, which expels a delocalized radical and regenerates **1.1**. Oxidation of the radical intermediate by $Ag(bipy)_2^{2+}$, followed by deprotonation, yields the sulfonimidated product.

Turnover-limiting oxidation of **1.1** by NFBS is supported by the measured rate law of the reaction, which

is first order with respect to both **1.1** and NFBS, and zero-order with respect to arene and $Ag(bipy)_2ClO_4$. When only NFBS and **1.1** are combined in acetonitrile, catalytic reduction of NFBS to $HN(SO_2Ph)_2$ and HF is observed, with the reducing equivalents evidently derived from the solvent. The rate of catalytic reduction of NFBS in the absence of substrate or cocatalyst is identical to the rate of NFBS consumption in the imidation reaction (Figure 1.3). The rate law and the identical rate for both reactions shown in Figure 1.3 establish turnover-limiting oxidation of **1.1** by NFBS to yield a common, short-lived high-valent palladium intermediate such as **II**.

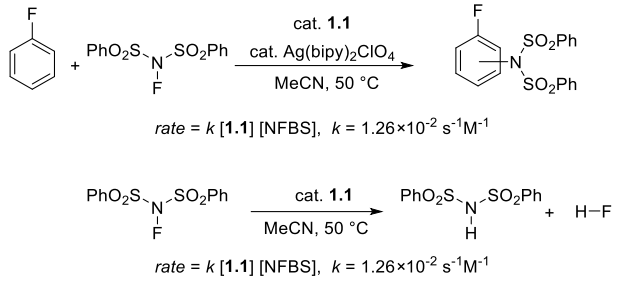


Figure 1.3. Kinetic studies of imidation and NFBS reduction catalyzed by **1.1**

Oxidation of Pd(II) complexes typically requires strongly σ-donating anionic ligands such as hydrocarbyl ligands, which are absent from **1.1**.[18-20] DFT calculations suggest that the HOMO of **1.1** is an extended M–L π-antibonding orbital of d_{xz} parentage from palladium, instead of the d_{z^2}-based orbital more typical of square-planar d^8 complexes. The oxygen lone pairs of the amine-*N*-oxide ligand interact strongly with the Pd-based d_{xz} orbital, driving it higher in energy than the d_{z^2}-based orbital (Figure 1.4). This interaction may explain how complex **1.1** can be oxidized by NFBS, despite its two formal positive charges.

We propose that the silver co-catalyst serves to provide access to intermediate **III**, which is the putative intermediate responsible for C–N bond formation. $Ag(bipy)_2^{2+}$ was observed by EPR spectroscopy during catalysis, which implicates the co-catalyst in redox reactivity. Inner-sphere reactivity of the co-catalyst can be ruled out because coordinatively saturated $Ru(bipy)_3(PF_6)_2$ is also an effective co-catalyst. Furthermore, the oxidation of $Ru(bipy)_3^{2+}$ to $Ru(bipy)_3^{3+}$ by NFBS is substantially accelerated in the presence of **1.1**,

consistent with oxidation of **1.1** to **II** by NFBS followed by single electron oxidation of $Ru(bipy)_3^{2+}$ by **II** (see Chapter E1, pg 92–98). Reduction of **II** by the co-catalyst to yield the C–N bond forming species **III** explains why for most arenes, substrate consumption is not observed in the absence of the co-catalyst.

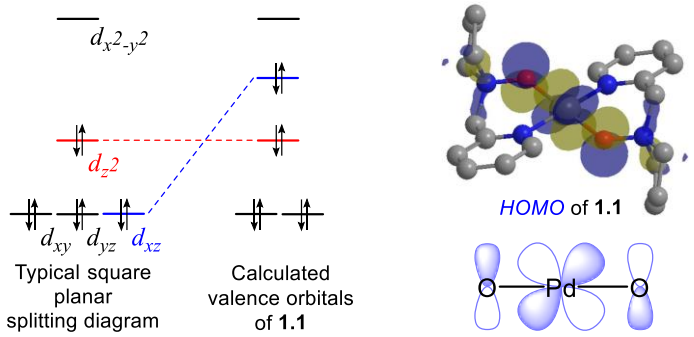


Figure 1.4. Valence orbital diagram of **1.1**

Because oxidation of **1.1** by NFBS is turnover-limiting, the C–N bond forming step cannot be studied kinetically. We have therefore employed competition kinetic isotope effect (KIE) experiments to probe this step (Figure 1.5). An inverse secondary intramolecular k_H/k_D of 0.80 ± 0.01 for imidation of 1,3,5-trideuterobenzene was measured. The measured KIE implicates rehybridization of the C–H bond from sp^2 to sp^3 in the product-determining transition state, consistent with C–N bond formation via inner-sphere addition of dibenzenesulfonimidyl radical to the bound arene in intermediate **III**. Inverse secondary KIEs are unusual for palladium-catalyzed C–H functionalization reactions; C–H palladations at Pd(II)[21] and Pd(IV)[22-24] typically display primary KIE values. Electrophilic addition would also be consistent with the observed intramolecular isotope effect. However, inverse secondary KIE values for electrophilic substitution are rare;[25-27] most commonly, KIEs close to unity are observed for electrophilic processes due to the opposing effects of rehybridization and hyperconjugation on the zero-point vibrational energy of the affected C–H bond.[28-30] Addition of nitrogen-based radicals to arenes is well-precedented, including catalytic imidations with NFBS which are proposed to proceed through high-valent transition metal imidyl radical species.[14] Inner-sphere attack from an intermediate such as **III** to form the putative aryl radical is supported by an intermolecular competition k_H/k_D of 1.03 ± 0.02. The absence of a KIE in this case is

consistent with irreversible substrate binding prior to C–N bond formation.[21,23]

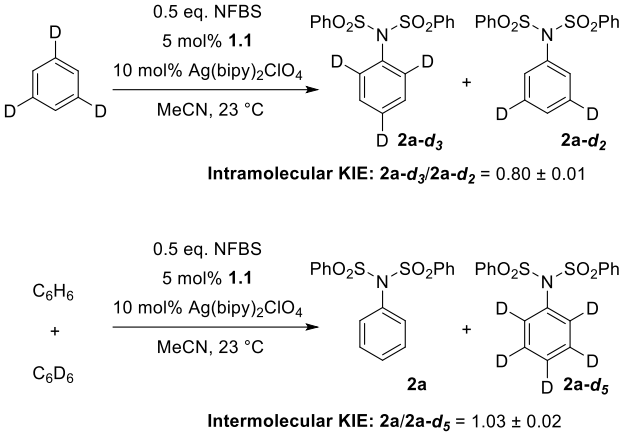


Figure 1.5. Intramolecular and Intermolecular Kinetic Isotope Effect

We have described in this chapter the first aryl C–H imidation reaction which gives synthetically useful yields with only one equivalent of arene and does not require coordinating directing groups. The transformation is made possible by a departure from the most common strategies: we have developed a catalyst supported by amine-*N*-oxide ligands, which enable oxidation of the doubly cationic Pd(II) complex prior to substrate activation. C–H functionalization proceeds from a high oxidation state complex without the formation of conventional organometallic intermediates. We anticipate that this distinct approach may find utility in other C–H functionalization reactions.

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Chapter 2. Charge Transfer Directed Radical Addition Enables *para*-Selective C–H Functionalization

2.1 Specific Background

As discussed in the introduction, the attainment of high *para* selectivity in aromatic C–H functionalization has been a persistent, largely unmet challenge. Electrophilic aromatic substitution typically affords mixtures of products (Figure 2.1a),[1,2] and transition-metal catalyzed reactions have generally struggled with the same limitations in positional selectivity, except through the use of chelation assistance, in which a coordinating directing group on the arene substrate is utilized to position the catalyst within close proximity to a specific C–H bond.[3,4] However, although chelation-assistance can enable C–H functionalization *ortho*,[5,6] and in some cases *meta*,[7] to the coordinating directing group (Figure 2.1b), chelation assistance for *para* selective C–H functionalization has not been observed. Steric hindrance has been explored as a strategy to control positional selectivity in non-chelation-assisted C–H functionalization, but product mixtures still result, particularly for monosubstituted arenes.[8-10] There have been isolated reports of non-chelation-assisted aromatic C–H functionalization reactions with anomalously high *para* selectivity for monosubstituted arenes; however, these reactions either require solvent quantities of arene or work only on activated arenes, and the origin of their *para* selectivity is unknown, precluding generalization to the design of other *para* selective functionalization reactions.[11-13] Thus, a successful approach for highly *para*-selective C–H functionalization would satisfy an unmet need in aromatic substitution, especially if no particular directing group is required.

In this chapter, we describe how aromatic substitution by highly electrophilic radicals, which are capable of eliciting significant charge transfer from the arene in the transition state of addition, exhibits high selectivity for positions *para* to substituents on the arene (Figure 2.1c). Radical aromatic substitution reactions normally do not proceed with synthetically useful positional selectivity on substituted arenes. For example, in the 2007 edition of *Advanced Organic Chemistry* by Carey and Sundberg, it is claimed

that "*there are some inherent limits to the usefulness of such reactions. Radical Substitutions are only moderately sensitive to substituent directing effects, so that substituted reactants usually give a mixture of products. This means that the practical utility is limited to symmetrical reactants, such as benzene, where the position of attack is immaterial.*"[14] The results reported herein demonstrate that, contrary to prior assumptions, radical aromatic substitution can furnish novel, useful products with high chemo- and positional selectivity when an appropriately electrophilic radical is used. We show that for most substrates, including monosubstituted arenes, only one of the possible positional isomers is observed in significant amounts. The charge transfer directed concept does not require a coordinating directing group as do chelation-assisted C–H functionalization reactions because selectivity is determined by the electronic structure in the transition state as opposed to enforced proximity of the catalyst.

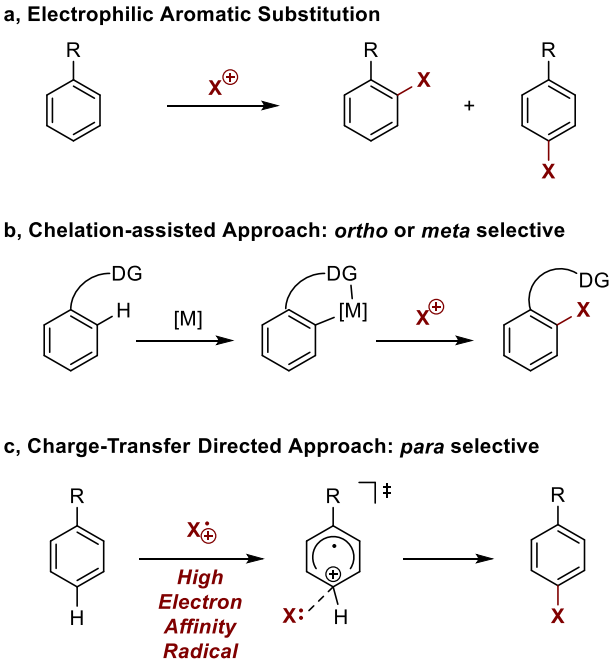


Figure 2.1. Selective C–H functionalization. a, Electrophilic Aromatic Substitution generally yields mixtures of isomers. b, Lewis basic directing groups direct functionalization to proximal bonds by chelation assistance. DG = Directing Group. c, Charge-transfer directed approach: arene-to-radical charge transfer, elicited by highly electrophilic radicals, leads to high *para* selectivity.

2.2 Charge Transfer Directed Radical Substitution

The doubly cationic radical $TEDA^{2+\bullet}$, derived from single electron reduction of Selectfluor, is capable of engaging in radical aromatic substitution to yield *N*-aryl-*N'*-chloromethyl-diazoniabicyclo[2.2.2]octane salts, which we have termed Ar–TEDA compounds (Figure 2.3). The reaction is enabled by a dual catalyst combination: Pd catalyst **2.1**, which is identical to **1.1** but with a different counteranion, and $Ru(bipy)_3(PF_6)_2$ (Figure 2.3a). As is the case for the imidation reaction described in Chapter 1, photoirradiation is not required for reaction, which works equally well when shielded from light. For most arenes only one of the possible positional isomers of the Ar–TEDA product is observed as judged by nuclear magnetic resonance spectroscopy; fluorobenzene, for example, yields the *para* substituted product in >99:1 positional selectivity (Figure 2.2). All monosubstituted arenes tested give the *para* substituted product as the only significant isomer. Disubstituted arenes and some heteroarenes likewise undergo clean substitution at the position *para* to the group with the strongest directing effect. Thus, the synthesis of Ar–TEDA compounds described here constitutes a general non-chelation-assisted C–H functionalization reaction, with the arene as the limiting reagent, with nearly exclusive positional selectivity across a broad range of substitution patterns.

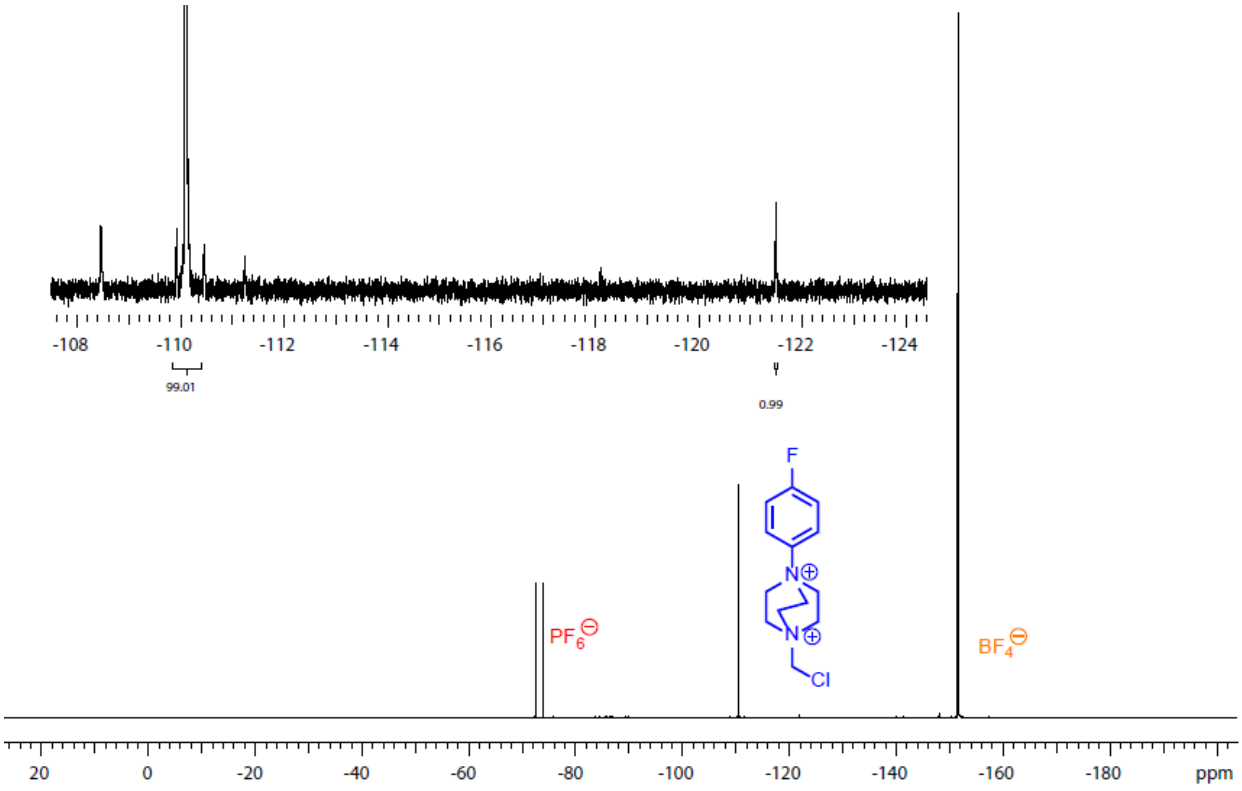


Figure 2.2. Determination of positional selectivity of TEDA addition to fluorobenzene by ^{19}F NMR. The next largest aryl fluoride peak after that of **2.2a** has <1% intensity. See experimental section for full experimental details.

The $TEDA^{2+\bullet}$ radical is an electrophilic radical, with an electron affinity of 12.4 eV, calculated by DFT. The high electron affinity of $TEDA^{2+\bullet}$ should favor a large contribution of charge-transfer in the transition state of addition (Figure 2.3b), which in turn leads to high selectivity for aromatic substitution at the position from which charge transfer is the greatest.[15-17] Therefore, a predictive tool for the positional selectivity of the reaction would be a metric which indicates the greatest extent of charge transfer that can be expected upon attack at a given position. We found Fukui nucleophilicity indices to be well-suited to this purpose. The Fukui nucleophilicity index of an atom, determined by simple quantum chemical calculations, is a measure of how readily electron density is transferred to an incoming electrophilic species attacking at the relevant atom.[18-20] Fukui indices are especially convenient as a predictive tool because the Fukui index for all atoms in a given molecule are determined by a pair of simple calculations

on the arene itself; there is no need to map the potential energy surface of the reaction by computing the transition states of various pathways.

Figure 2.3c shows several Ar–TEDA products and the corresponding starting material, with each aromatic carbon atom of the starting material labeled with its Fukui nucleophilicity index. The Fukui nucleophilicity index is successful in predicting the site of substitution by $TEDA^{2+\bullet}$ in almost all cases. Certain 1,4-disubstituted arenes, including 1,4-dichlorobenzene and 4-chloroanisole, yield *ipso* substitution of the halogen as the primary product.[21] Gratifyingly, Fukui nucleophilicity indices correctly predict even the observed *ipso* substitution in these cases. If a non-substitutable functional group is present at the site with the highest Fukui index, substitution at the site with the next highest Fukui index is observed, as in methyl 4-methoxybenzoate (**2.2g**). Although steric hindrance to *ortho* attack may serve to further augment the *para* selectivity of the reaction, the fact that even fluorobenzene, with a single small substituent, gives >99:1 selectivity renders unlikely steric hindrance as the primary factor governing selectivity.

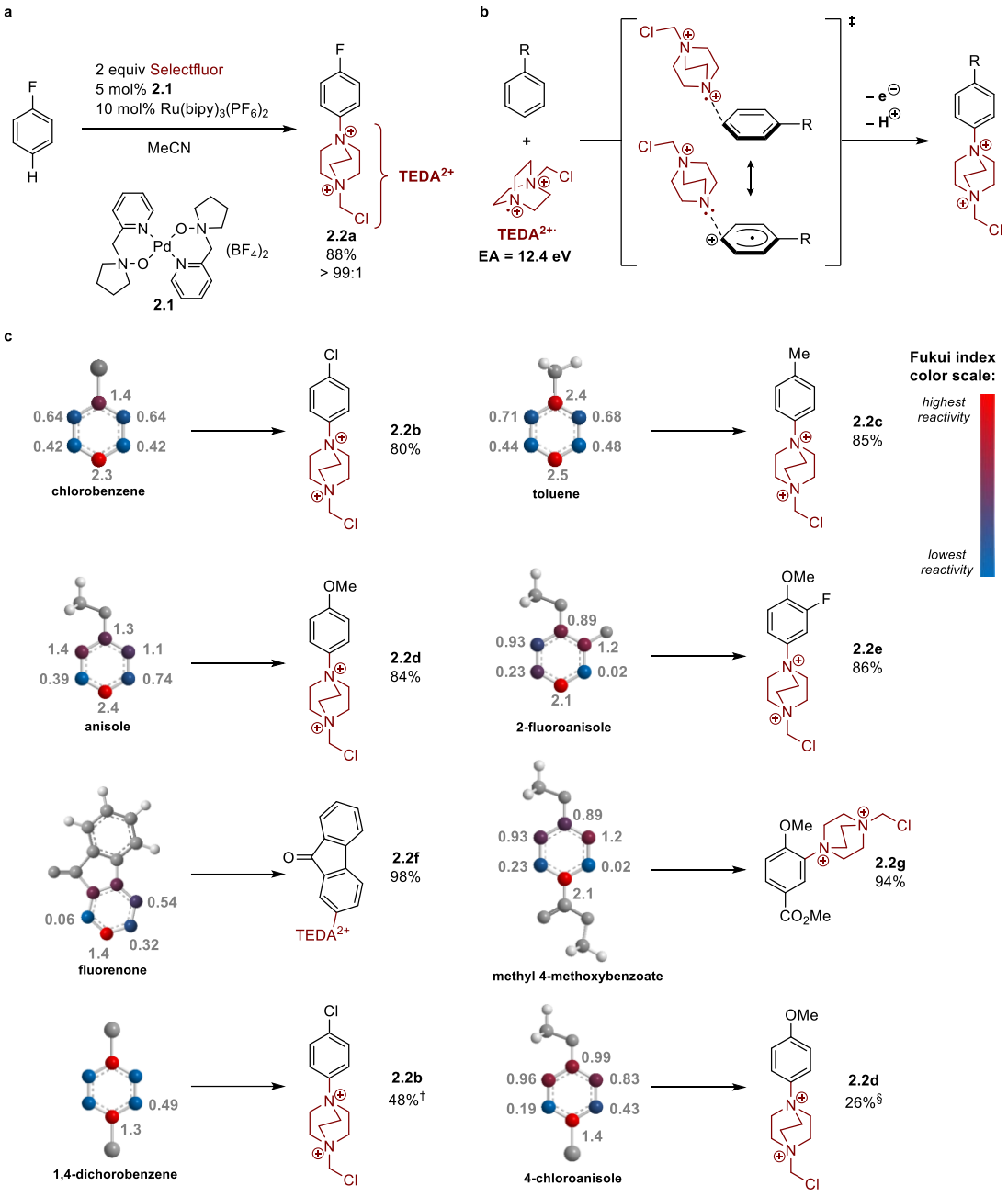


Figure 2.3. Charge transfer directed aromatic substitution. a, Conversion of fluorobenzene to the corresponding Ar–TEDA compound **2.2a**. **b,** Positional selectivity of $TEDA^{2+\cdot}$ substitution is due to the stabilizing effect of arene-to-radical charge transfer in the transition state of addition. EA = Electron Affinity, refers to gas phase adiabatic electron affinity calculated by DFT. **c,** The position of substitution by $TEDA^{2+\cdot}$ is predictable by Fukui indices. Fukui indices depicted are multiplied by ten for simplicity of presentation. Note that Fukui indices are computed for one conformation of the molecule, so indices of positions that are symmetrically disposed about a substituent need not be equal. † Substitution in the 2-position was observed in 11% yield in addition to *ipso* substitution. § Substitution in the 2-position was observed in 10% yield in addition to *ipso* substitution.

The high degree of positional selectivity we report here is unusual, especially in the context of radical aromatic substitution. A reason may be a lack of studies of substitution reactions by radicals of high electron affinity. While the $TEDA^{2+\bullet}$ radical dication has been proposed as an intermediate in recently reported aliphatic C–H oxidation methodologies utilizing Selectfluor,[22-24] to our knowledge addition of this radical to unsaturated systems has not been investigated. The most commonly employed radicals in a synthetic context are uncharged carbon-, oxygen-, nitrogen-, and halogen-based radicals, which have electron affinities in the range of 0.8–3.6 eV, far below the value for $TEDA^{2+\bullet}$ (12.44 eV, Figure 2.1). Aromatic substitution reactions of most neutral radicals are known to proceed with low selectivity.[13] For example, the phenyl radical has an electron affinity of 1.1 eV, and under conditions reported by Li, undergoes aromatic substitution with fluorobenzene to give an *ortho*:*meta*:*para* ratio of 47:16:37.[25] The neutral phthalimide radical has a higher electron affinity (EA = 3.66 eV). We have found that the phthalimide radical, when generated under conditions reported by Sanford,[26] undergoes aromatic substitution with fluorobenzene in a 37:11:52 ratio of *ortho*, *meta*, and *para* isomers; the selectivity for the *para* position is higher, though the other isomers still abound.

Positive charge increases electron affinity, and based on our findings and proposal, positively charged radicals should result in more selective arene substitution reactions. Monocationic aminium radicals have electron-affinities in the range of 7–8 eV, and their aromatic substitution reactivity was thoroughly investigated in seminal work by Minisci, who noted the higher selectivity of aminium radical addition compared to less electrophilic radicals. Under Minisci's conditions, the monocationic aminium radical derived from piperidine (EA = 7.74 eV) adds to fluorobenzene more selectively than the neutral phthalimide radical to afford an *o*:*m*:*p* ratio of 11:10:79. Minisci described the selectivity of monocationic aminium radicals as similar to the selectivity of electrophilic aromatic substitution, affording products of *ortho* and *para* substitution of monosubstituted arenes bearing electron donating groups.[27-29] We have discovered that, for sufficiently electrophilic radicals, charge transfer in the transition state of addition can lead to high selectivity for the *para* position over *ortho*; we have rationalized the phenomenon in terms of

charge transfer in the transition state, and have introduced Fukui indices as a tool for predicting the site of substitution. The second positive charge of the $TEDA^{2+\bullet}$ aminium radical increases the electron affinity to 12.44 eV, and at this level, nearly absolute selectivity for the *para* position is observed for monosubstituted arenes.

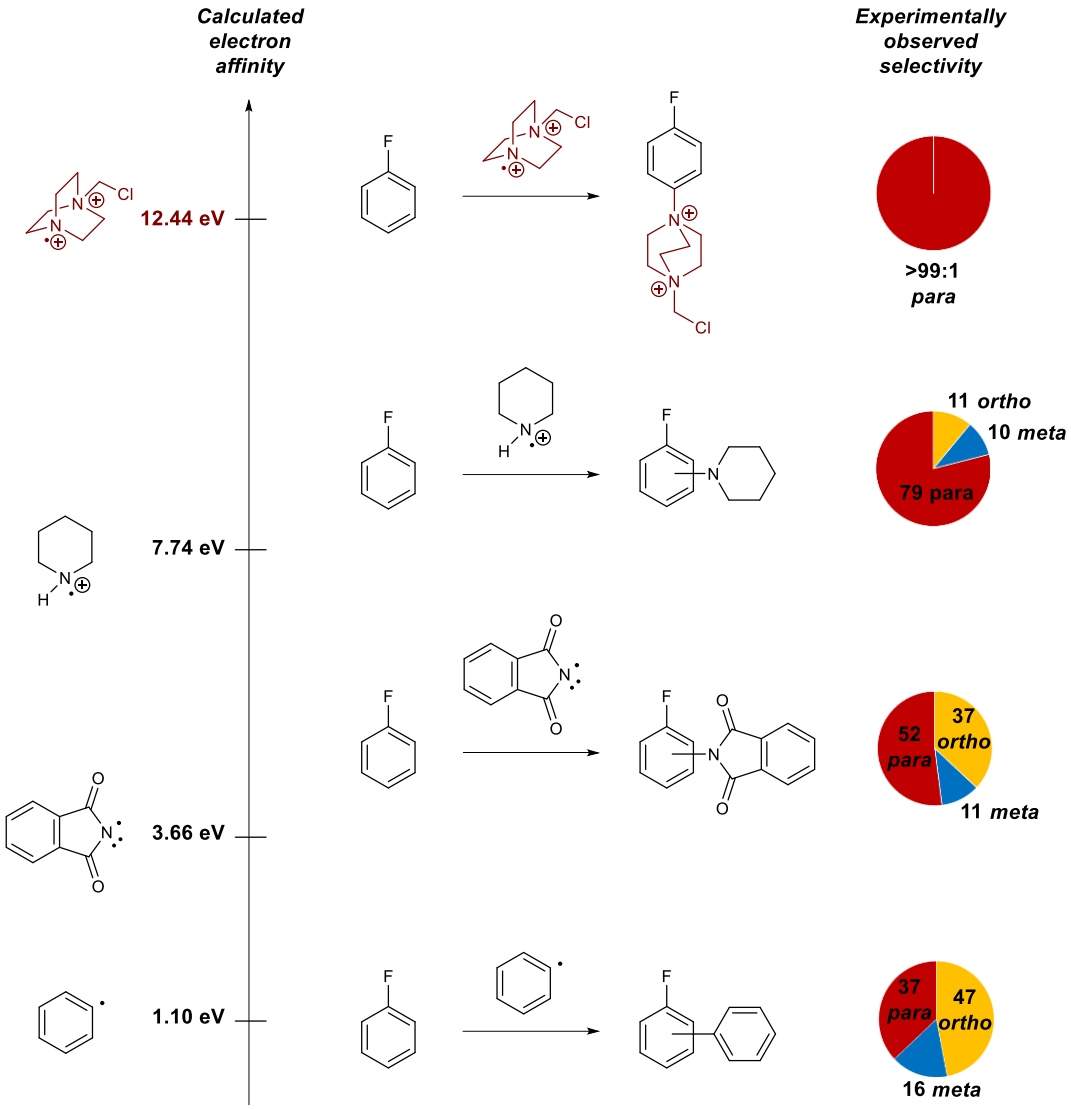


Figure 2.4. Selectivity for *para* substitution increases with increasing electron affinity of the radical. Electron affinities refer to gas phase adiabatic electron affinity calculated at the (U)B3LYP/6-311G(d) level of theory.

The general applicability of the charge-transfer directed concept will depend on whether other radicals of comparable electron affinity to $TEDA^{2+\bullet}$ can be designed. The uncommonly high electron affinity of $TEDA^{2+\bullet}$ is due to its two positive charges; doubly cationic organic radicals are rare, presumably because there has been a lack of generally appreciated applications and because strategies for accessing them are unexplored. We anticipate that the correlation between electron affinity and positional selectivity described herein will stimulate research in high electron affinity radicals due to their potential to address the longstanding challenge of positional selectivity in C–H functionalization.

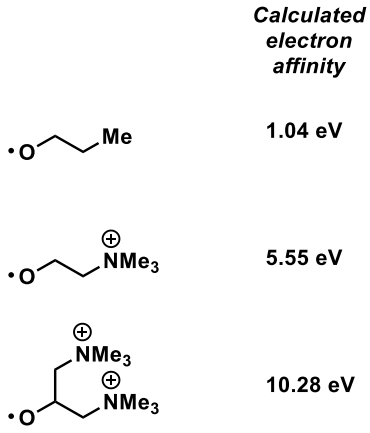


Figure 2.5. Electron affinity of alkoxyl radicals increases with increasing positive charge. Electron affinities refer to gas phase adiabatic electron affinity calculated at the (U)B3LYP/6-311G(d) level of theory.

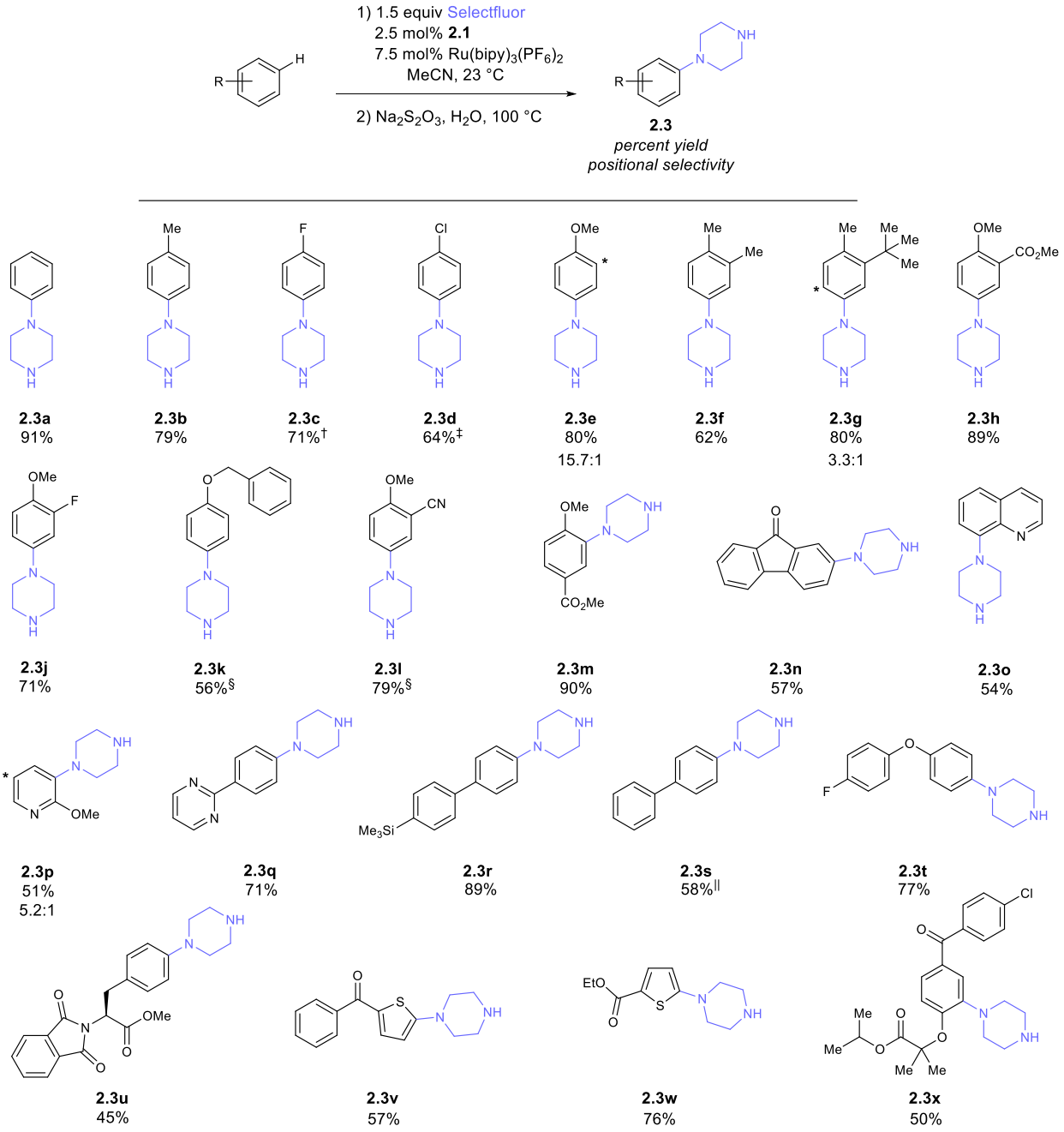
We furthermore note that radicals of electron affinity comparable to $TEDA^{2+\bullet}$ need not in principle be based on cationic aminium radicals. For example, DFT calculations indicate that alkoxyl radicals exhibit a similar trend with increasing positive charge, though the septet oxygen atom itself lacks a formal charge (Figure 2.5). We rationalize these results in terms of electrostatic effects. When an electron is absorbed by $TEDA^{2+\bullet}$, the Coulombic repulsion between the two proximal positive charges is alleviated, which leads to a large energetic benefit. For the oxyl radicals, Coulombic attraction is created instead, which is worth the same amount of energy, but with opposite sign. Thus, highly electrophilic radicals could be designed for

the installation of a variety of functional groups (not just C–N bonds), since radicals centered on any atom could be made to have electron affinity comparable to $TEDA^{2+\bullet}$ through incorporation of proximal positive charges.

2.3 Application to the synthesis of aryl piperazines

As one synthetic application of the charge transfer directed radical substitution concept, we have developed a two-step, one-pot synthesis of aryl piperazines from the corresponding aryl C–H compounds (**Table 2.1.** Two-step, one-pot synthesis of aryl piperazines by charge transfer directed C–H functionalization). The procedure involves reduction of the Aryl–TEDA compounds by sodium thiosulfate, which converts the TEDA moiety into a piperazine heterocycle. Piperazines are a common motif in pharmaceuticals and materials; they constitute the third most common heterocycle present in the small molecule pharmaceuticals listed in the FDA Orange Book.[30] Aryl piperazines are commonly synthesized by Buchwald-Hartwig cross coupling reactions of aryl electrophiles with piperazine derivatives.[31] The direct synthesis of aryl piperazines reported here is advantageous because it does not require a pre-functionalized substrate, such as an aryl halide. Importantly, this advantage relies on the high and predictable positional selectivity of the reaction, which enables the high-yield synthesis of a single desired positional isomer. The reaction is operationally simple, and can be performed under air with commercial-quality solvent. Furthermore, the piperazine moiety is obtained with an unprotected secondary amine, ready for subsequent manipulation.

Table 2.1. Two-step, one-pot synthesis of aryl piperazines by charge transfer directed C–H functionalization.



† 40 °C reaction temperature in the first step. ‡ 45 °C reaction temperature in the first step. § 2.5 equiv Selectfluor, 5.0 mol% **2.1**, and 10 mol% $Ru(bipy)_2(PF_6)_2$ in first step. ‖ 1.0 equiv Selectfluor used in first step. * denotes the site of piperazination of the other constitutional isomer.

A variety of arenes, including 5- and 6-membered heteroarenes, undergo piperazination. Generally, attack of $TEDA^{2+\bullet}$ *ortho* to substituents is unfavorable, and occurs only for arenes in which the preferred *para* position for substitution is blocked by a group which cannot undergo *ipso* substitution; this observation can be applied to block piperazination of certain positions, or even entire arene rings, as in substrates **2.3r** and **2.3t**. Product **2.3g** demonstrates the limits of the positional selectivity of the reaction: the two substituents in 2-methyl-tert-butylbenzene differ only slightly in their electron-donating ability, and the product was isolated as a 3.3:1 mixture of isomeric products. Although $TEDA^{2+\bullet}$ is known to engage in sp^3 C–H bond cleavage, we have observed no evidence of such side-reactions in our investigations, despite the fact that several substrates contain weak C–H bonds adjacent to aromatic rings (e.g., **2.3f**) or ether oxygen atoms (e.g., **2.3e**, **2.3k**); addition of $TEDA^{2+\bullet}$ to the unsaturated aromatic system outcompetes C–H bond cleavage.

For most substrates, nearly full conversion to the Ar–TEDA compound is observed, and in several cases the yield of the piperazine following the thiosulfate-mediated stage is lower. For example, the anti-cholesterol drug Fenofibrate undergoes Ar–TEDA formation in 88% yield, but upon treatment with sodium thiosulfate at 100 °C the yield of piperazine **2.3x** is 51%. The Ar–TEDA formation reaction exhibits significant functional group tolerance, despite the highly reactive and electrophilic nature of the $TEDA^{2+\bullet}$ radical intermediate; for most substrates in **Table 2.1**, the majority of mass balance is lost in the piperazine formation step, not the Ar–TEDA formation step.

We have shown that the doubly cationic nitrogen-based radical $TEDA^{2+\bullet}$ undergoes radical substitution with arenes with higher positional selectivity than any conventional methodology for arene substitution. We put forth a previously underappreciated rationale to explain and predict positional selectivities in charge transfer directed radical aromatic substitution: high selectivity is achieved through a high degree of charge-transfer in the transition state of addition. This charge transfer effect is maximized for radicals with high electron affinity. Our results can rationalize why known electrophilic radical substitution reactions of neutral radicals are typically not selective, and more importantly, they provide a framework to guide the

design of new, selective arene substitution chemistry.

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Chapter E1: Experimental Methods and Data for Chapter 1

E1.1 Materials and Methods

All air- and moisture-insensitive reactions were carried out under an ambient atmosphere, magnetically stirred, and monitored by thin layer chromatography (TLC) using EMD TLC plates pre-coated with 250 μm thickness silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. Flash chromatography was performed on Dynamic Adsorbents Silica Gel 40–63 μm particle size using a forced flow of eluent at 0.3–0.5 bar pressure.[1] All air- and moisture-sensitive manipulations were performed using oven-dried glassware, including standard Schlenk and glovebox techniques under an atmosphere of nitrogen. Acetonitrile and acetonitrile-d_3 were dried over P_2O_5 and vacuum-distilled. MeOH was degassed at –30 ºC under dynamic vacuum (10^{-4} Torr) for one hour and stored over 3Å sieves. All chemicals were used as received. All deuterated solvents were purchased from Cambridge Isotope Laboratories. NMR spectra were recorded on either a Varian Unity/Inova 600 spectrometer operating at 600 MHz for ^{1}H acquisitions, a Varian Unity/Inova 500 spectrometer operating at 500 MHz and 125 MHz for ^{1}H and ^{13}C acquisitions, respectively, or Varian Mercury 400 spectrometer operating at 375 MHz and 101 MHz for ^{19}F and ^{13}C acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (^{1}H: $CDCl_3$, δ 7.26; $(CD_3)_2SO$, δ 2.50; $(CD_3)_2CO$, δ 2.05; CD_3CN, δ 1.94), (^{13}C: $CDCl_3$, δ 77.16; $(CD_3)_2SO$, δ 39.52; $(CD_3)_2CO$, δ 29.84; CD_3CN, δ 1.32),[2] or added 3-nitrofluorobenzene (–112.0 ppm) for ^{19}F spectra. Signals are listed in ppm, and multiplicity identified as s = singlet, br = broad, d = doublet, t = triplet, q = quartet, quin = quintet, sep = septet, m = multiplet; coupling constants in Hz; integration. High-resolution mass spectra were obtained using an Agilent ESI-TOF (6210) mass spectrometer or a Bruker q-TOF Maxis Impact mass spectrometer. Concentration under reduced pressure was performed by rotary evaporation at 25–30 ºC at appropriate pressure. Purified compounds were further dried under high vacuum (0.01–0.05 Torr). Yields refer to purified and spectroscopically pure

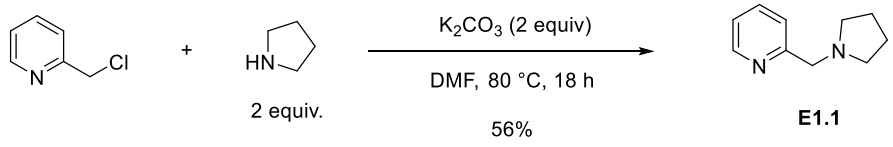
compounds.

E1.2 Standard procedure for C–H imidation reactions

Under N_2 atmosphere, an oven-dried 4 mL vial was charged with (hetero)arene (0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added to react with the remaining NFBS and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel. It was observed that addition of triethylamine to the appropriate solvent system (1% of the final volume) aided the removal of dibenzenesulfonimide, which otherwise co-eluted with the desired product.

E1.3 Procedures for the preparation of complex 1.1 and $Ag(bipy)_2ClO_4$

2-(Pyrrolidin-1-ylmethyl)pyridine (E1.1)

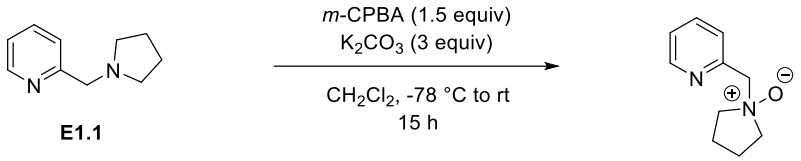


To a solution of 2-(chloromethyl)pyridine (66.2 g, 0.519 mol, 1.00 equiv) in DMF (650 ml, c = 0.800 M) was added potassium carbonate (144 g, 1.04 mol, 2.00 equiv) and the mixture was stirred at 80 °C for 5 min. Pyrrolidine (73.8 g, 1.04 mol, 2.00 equiv) was then added, and the reaction mixture was stirred at 80 °C for 18 h. H_2O (3.50 L) was added and the mixture was extracted with Et_2O (4 × 250 ml). The combined organic layers were washed with H_2O (2 × 200 mL), brine (200 mL), dried ($MgSO_4$), and concentrated *in vacuo* to afford 47.3 g of the title compound as a brown oil (56% yield), which was analytically pure and was used in the next step without further purification.

NMR Spectroscopy: ^1H NMR (600 MHz, CD_3CN, 23 °C, δ): 8.51–8.56 (m, 1H), 7.63 (td, J = 7.7, 1.8 Hz, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.14 (ddd, J = 7.5, 4.9, 1.1 Hz, 1H), 3.76 (s, 2H), 2.53–2.60 (m, 4H), 1.76–

1.82 (m, 4H). These spectroscopic data correspond to previously reported data.[3]

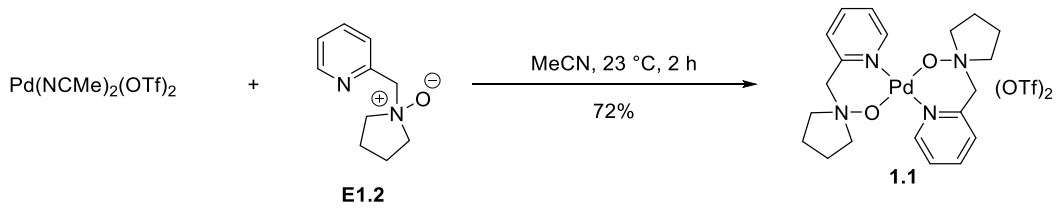
1-(Pyridin-2-ylmethyl)pyrrolidine 1-oxide (E1.2)



To a suspension of K_2CO_3 (91.0 g, 0.656 mol, 3.00 equiv) and 2-(pyrrolidin-1-ylmethyl)pyridine (**E1.1**) (35.5 g, 0.219 mol, 1.00 equiv) in dichloromethane (1.20 L, c = 0.183 M) at –78 °C was added *m*-CPBA (56.6 g, 0.328 mol, 1.50 equiv). The resulting mixture was slowly warmed from –78 °C to 23 °C over 5 h and was stirred at 23 °C for 15 h. The solids were removed by filtration and washed with dichloromethane (3 × 20 mL). The combined filtrates were concentrated *in vacuo* to afford 39.0 g of the title compound (92% yield) as a brown solid, which was used directly for the preparation of **1.1**. The characterization data was recorded on pure product, which was obtained by triturating the title compound (500 mg) with THF (3 x 2 mL, 15 min each time) at 23 °C.

R_f = 0.39 (CH_2Cl_2/MeOH 4:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 8.56–8.60 (m, 1H), 7.92 (d, *J* = 7.6 Hz, 1H), 7.77 (td, *J* = 7.6, 1.8 Hz, 1H), 7.31–7.36 (m, 1H), 4.96 (s, 2H), 3.73–3.81 (m, 2H), 3.66–3.73 (m, 2H), 2.29–2.40 (m, 2H), 2.03–2.12 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 150.6, 149.4, 137.2, 128.3, 124.5, 70.8, 67.1, 21.5. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{10}H_{15}N_2O$ ($[M+ H]^+$), 179.1179, found, 179.1181.

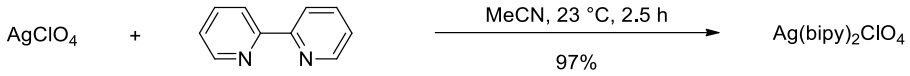
Palladium complex 1.1



1-(Pyridin-2-ylmethyl)pyrrolidine 1-oxide (**E1.2**) (3.13 g, 17.6 mmol, 2.00 equiv) and $Pd(MeCN)_4(OTf)_2$ (5.00 g, 8.80 mmol, 1.00 equiv) were dissolved in acetonitrile (70.0 mL, c = 0.125 M). After stirring at 23 °C for 2 h, the reaction mixture was filtered through a pad of celite and the filtrate was concentrated *in vacuo*. The product was triturated with THF (3 x 10 mL, 15 min each time) at 23 °C and dried under vacuum for 8 h to afford 4.79 g of the title compound as a light brown solid (72% yield).

Melting point: 188 °C (decomp). NMR Spectroscopy: ^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 8.45 (dd, J = 5.9, 1.2 Hz, 2H), 8.20 (td, J = 7.6, 1.8 Hz, 2H), 7.71–7.78 (m, 4H), 5.15 (s, 4H), 3.39–3.50 (m, 8H), 2.23–2.32 (m, 4H), 2.05–2.14 (m, 4H). ^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 150.5, 149.0, 143.0, 129.3, 127.5, 71.7, 68.9, 22.5. Anal: calcd for $C_{22}H_{28}F_6N_4O_8S_2Pd$: C, 34.72; H, 3.71; N, 7.36; found: C, 34.66; H, 3.42; N, 7.24. UV-VIS Spectroscopy (MeCN, 23 ˚C): 265 nm ($\varepsilon = 1.53 \times 10^3$ M^{-1} cm^{-1}); 226 nm ($\varepsilon = 4.77 \times 10^3$ M^{-1} cm^{-1}). X-ray data included in X-Ray Crystallographic Analysis Section.

$Ag(bipy)_2ClO_4$

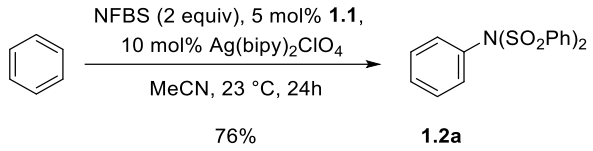


A solution of silver perchlorate (3.27 g, 15.8 mmol, 1.00 equiv) and 2,2'-bipyridine (5.05 g, 32.4 mmol, 2.05 equiv) in acetonitrile (100 mL, c = 0.158 M) was stirred at 23 °C for 2.5 h. The reaction mixture was then concentrated *in vacuo*. The resulting solid was triturated with Et_2O and dried under vacuum to afford 7.93 g of the title compound as a yellow powder (97% yield).

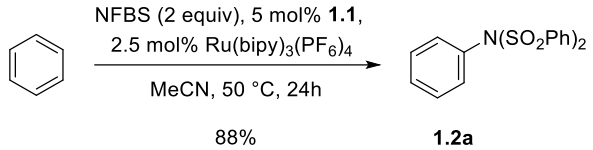
NMR Spectroscopy: ^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 8.66 (dd, J = 4.1, 1.8 Hz, 2H), 8.34 (dt, J = 8.2, 1.2 Hz, 2H), 8.04 (td, J = 7.6, 1.8 Hz, 2H), 7.53–7.56 (m, 2H). ^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 153.5, 151.7, 139.9, 126.4, 123.5. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{20}H_{16}AgN_4^+$ ($Ag(bipy)_2^+$), 419.0420, found, 419.0427.

E1.4 Procedures for C–H imidation reactions

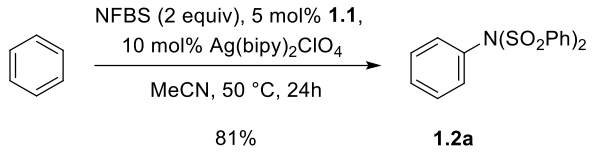
_N_-Phenyl-_N_-(phenylsulfonyl)benzenesulfonamide (1.2a)



*$Ag(bipy)_2ClO_4$-catalyzed synthesis of **1.2a**, 23 °C:* Under N_2 atmosphere, an oven-dried 4 mL vial was charged with benzene (23.4 mg, 26.8 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 84.7 mg of the title compound as a colorless solid (76% yield).



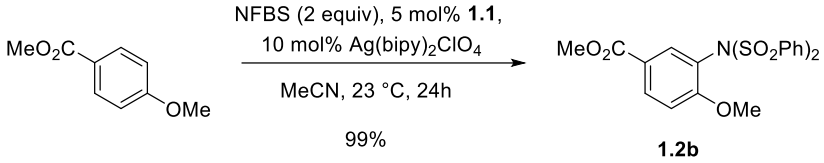
*$Ru(bipy)_3(PF_6)_2$-catalyzed synthesis of **1.2a**, 50 °C:* Under N_2 atmosphere, an oven-dried 4 mL vial was charged with benzene (39.1 mg, 44.7 µL, 0.500 mmol, 1.00 equiv), palladium complex **1.1** (19.0 mg, 25.0 µmol, 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (10.7 mg, 13.0 µmol, 2.50 mol%), and NFBS (0.315 g, 1.00 mmol, 2.00 equiv). Acetonitrile (2.5 mL, c = 0.20 M) was added and the reaction mixture was stirred in a sealed vial at 50 °C for 24 h. Subsequently, triethylamine (50.8 mg, 70.0 µL, 0.500 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 165 mg of the title compound as a colorless solid (88% yield).



*Ag(bipy)$_2$ClO$_4$-catalyzed synthesis of **1.2a**, 50 °C:* Under N_2 atmosphere, an oven-dried 4 mL vial was charged with benzene (23.4 mg, 26.8 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), Ag(bipy)$_2$ClO$_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 50 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 90.7 mg of the title compound as a colorless solid (81% yield).

R_f = 0.51 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.95 (dd, *J* = 8.8, 1.2 Hz, 4H), 7.66–7.69 (m, 2H), 7.53–7.57 (m, 4H), 7.44–7.47 (m, 1H), 7.34–7.38 (m, 2H), 7.02–7.05 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 139.6, 134.3, 134.1, 131.7, 130.4, 129.4, 129.1, 128.7. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{16}NO_4S_2$ ($[M + H]^+$), 374.0515, found, 374.0524.

Methyl 4-methoxy-3-(*N*-(phenylsulfonyl)phenylsulfonamido)benzoate (1.2b)



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with methyl 4-methoxybenzoate (49.9 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), Ag(bipy)$_2$ClO$_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently,

triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 7:3 (v/v) with 1% triethylamine), to afford 137 mg of the title compound as a colorless solid (99% yield).

*Alternative procedure for the preparation of **1.2b**:* Under N_2 atmosphere, an oven-dried 4 mL vial was charged with methyl 4-methoxybenzoate (49.9 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (1.5 mL, c = 0.20 M) was added and the reaction mixture was stirred in a sealed vial at 50 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 97 mg of the title compound as a colorless solid (70% yield).

Preparation of 1.2b under ambient atmosphere:

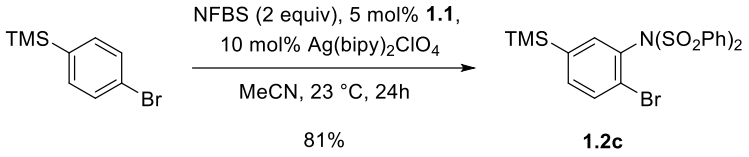
A 4 mL vial was charged with methyl 4-methoxybenzoate (166.2 mg, 1.000 mmol, 1.000 equiv), palladium complex **1.1** (38.1 mg, 50.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (51.7 mg, 10.0 µmol, 10.0 mol%), and NFBS (636.0 mg, 2.017 mmol, 2.017 equiv). Acetonitrile (2.5 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 333.7 mg of the title compound as a colorless solid (72% yield).

Preparation of 1.2b under nitrogen, with components weighed out under air:

R_f = 0.56 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 8.11 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 4H), 7.81 (d, *J* = 2.3 Hz, 1H), 7.62–7.71 (m, 2H), 7.54 (t, *J*

= 7.6 Hz, 4H), 6.87 (d, *J* = 8.8 Hz, 1H), 3.88 (s, 3H), 3.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 165.8, 161.3, 140.0, 134.8, 134.0, 133.9, 129.0, 128.9, 123.2, 123.0, 111.7, 55.7, 52.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{20}NO_7S_2$ ([M+ H]$^+$), 462.0676, found, 462.0690.

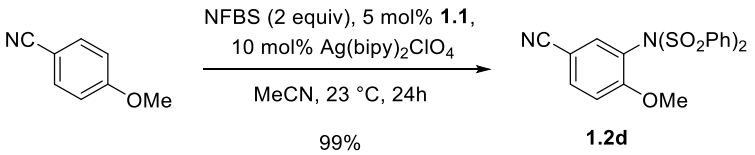
***N*-(2-Bromo-5-(trimethylsilyl)phenyl)-*N*-(phenylsulfonyl)benzenesulfonamide (1.2c)**



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with (4-bromophenyl)trimethylsilane (68.8 mg, 58.6 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 128 mg of the title compound as a colorless solid (81% yield).

R_f = 0.57 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 8.00–8.04 (m, 4H), 7.67–7.71 (m, 2H), 7.62 (d, *J* = 8.2 Hz, 1H), 7.53–7.58 (m, 4H), 7.39 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.02 (d, *J* = 1.8 Hz, 1H), 0.18 (s, 9 H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 141.3, 139.5, 138.6, 136.4, 134.3, 134.0, 133.5, 129.5, 129.0, 127.7, –1.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{22}BrNNaO_4S_2Si$ [M + Na]$^+$, 547.9815, found, 547.9821.

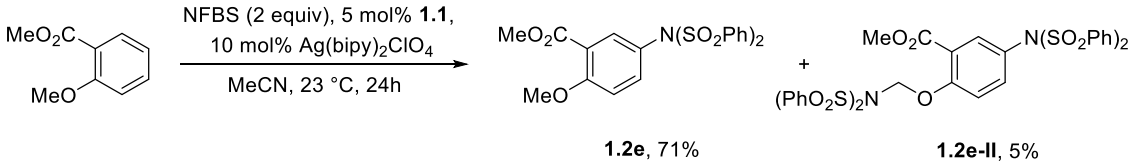
_N_-(5-Cyano-2-methoxyphenyl)-_N_-(phenylsulfonyl)benzenesulfonamidebenzenesulfonamide (1.2d)



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with 4-methoxybenzonitrile (39.9 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 3:2 (v/v) with 1% triethylamine), to afford 128 mg of the title compound as an off-white solid (99% yield).

R_f = 0.42 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.94 (d, *J* = 8.2 Hz, 4H), 7.66–7.72 (m, 3H), 7.56 (t, *J* = 7.6 Hz, 4H), 7.40 (d, *J* = 2.3 Hz, 1H), 6.91 (d, *J* = 8.2 Hz, 1H), 3.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 161.3, 139.7, 137.0, 136.4, 134.2, 129.0, 128.9, 124.1, 117.9, 112.9, 104.7, 55.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{20}H_{17}N_2O_5S_2$ ($[M + H]^+$), 429.0573, found, 429.0566.

Methyl 2-methoxy-5-(_N_-(phenylsulfonyl)phenylsulfonamido)benzoate (1.2e)



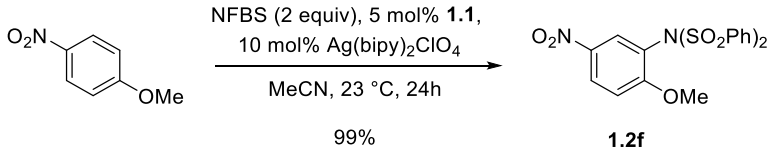
Under N_2 atmosphere, an oven-dried 4 mL vial was charged with methyl 2-methoxybenzoate (49.9 mg, 43.1 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%),

$Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 7:3 (v/v) with 1% triethylamine), to afford 110 mg of the mixture of the title compound and methyl 5-(*N*-(henylsulfonyl)phenylsulfonamido)-2-((*N*-(phenylsulfonyl)phenylsulfonamido)methoxy)benzoate (**1.2e-II**) (76% yield). Purification for characterization was accomplished by preparative TLC.

Data for **1.2e**: colorless solid; R_f = 0.31 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.90–7.94 (m, 4H), 7.66–7.70 (m, 2H), 7.53–7.58 (m, 4H), 7.44 (d, *J* = 2.3 Hz, 1H), 7.11 (dd, *J* = 9.1, 2.6 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 3.92 (s, 3H), 3.82 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 165.1, 160.5, 139.3, 136.5, 135.0, 134.2, 129.2, 128.6, 126.1, 120.7, 112.6, 56.4, 52.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{20}NO_7S_2$ $[M + H]^+$, 462.0676, found, 462.0686.

Data for **1.2e-II**: colorless solid; NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 8.04–8.07 (m, 4H), 7.91–7.93 (m, 4H), 7.64–7.73 (m, 4H), 7.51– 7.59 (m, 9H), 7.01–7.06 (m, 1H), 6.79–6.83 (m, 1H), 5.83 (s, 2H), 3.72 (s, 3H).

***N*-(2-Methoxy-5-nitrophenyl)-*N*-(phenylsulfonyl)benzenesulfonamide (1.2f)**

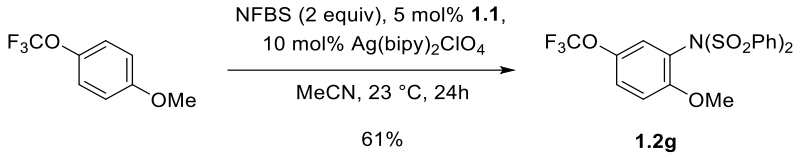


Under N_2 atmosphere, an oven-dried 4 mL vial was charged with 1-methoxy-4-nitrobenzene (45.9 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c

= 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 1:1 (v/v) with 1% triethylamine), to afford 134 mg of the title compound as an off-white solid (99% yield).

R_f = 0.27 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 8.34 (dd, *J* = 9.1, 2.6 Hz, 1H), 7.99 (d, *J* = 2.9 Hz, 1H), 7.96 (dt, *J* = 7.0, 1.8 Hz, 3H), 7.70 (tt, *J* = 7.6, 1.2 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 4H), 6.94 (d, *J* = 9.4 Hz, 1H), 3.52 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 162.9, 141.2, 139.7, 134.3, 129.3, 129.1, 128.9, 128.0, 123.6, 111.7, 56.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{19}H_{17}N_2O_7S_2$ ([M+ H]$^+$), 449.0472, found, 449.0484.

_N_-(2-Methoxy-5-(trifluoromethoxy)phenyl)-_N_-(phenylsulfonyl)benzenesulfonamide (1.2g)

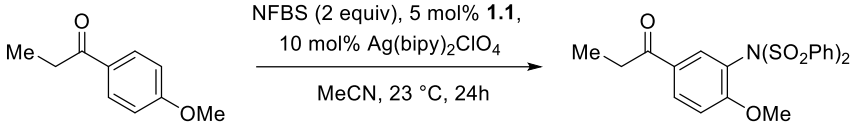


Under N_2 atmosphere, an oven-dried 4 mL vial was charged with 1-methoxy-4-(trifluoromethoxy)benzene (57.6 mg, 45.5 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 89.2 mg of the title compound as a colorless solid (61% yield).

R_f = 0.30 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.97 (d, *J* = 7.6 Hz, 4H), 7.65–7.69 (m, 2H), 7.54 (t, *J* = 7.6 Hz, 4H), 7.29 (dd, *J* = 9.5, 2.9 Hz, 1H), 6.95 (d, *J* =

2.9 Hz, 1H), 6.85 (d, J = 8.6 Hz, 1H), 3.43 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 156.8, 141.8, 139.8, 134.0, 128.9, 128.9, 126.5, 125.1, 123.4, 120.6 (q, J = 255 Hz), 112.4, 55.8. ^{19}F NMR (375 MHz, $CDCl_3$, 23 ºC, δ): –59.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{20}H_{20}F_3N_2O_6S_2$ [M + NH_4]$^+$, 505.0709, found, 505.0721.

_N_-(2-Methoxy-5-propionylphenyl)-_N_-(phenylsulfonyl)benzenesulfonamide (1.2h)



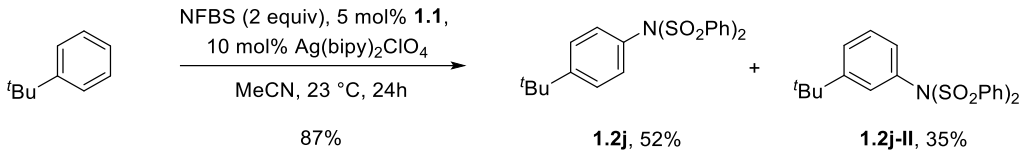
1.2h

Under N_2 atmosphere, an oven-dried 4 mL vial was charged with 1-(4-methoxyphenyl)propan-1-one (49.2 mg, 45.7 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 7:3 (v/v) with 1% triethylamine), to afford 136 mg of the title compound as a colorless solid (99% yield).

R_f = 0.33 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 8.05 (dd, J = 6.5, 2.3 Hz, 1H), 7.93–7.97 (m, 4H), 7.64–7.68 (m, 3H), 7.54 (t, J = 8.2 Hz, 4H), 6.89 (d, J = 8.8 Hz, 1H), 3.45 (s, 3H), 2.84 (q, J = 7.0 Hz, 2H), 1.18 (t, J = 7.0 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 198.2, 161.2, 139.9, 134.0, 133.4, 132.4, 130.2, 128.9, 128.8, 122.9, 111.8, 55.7, 31.6, 8.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{22}H_{21}NNaO_6S_2$ ([M + Na]$^+$), 482.0702, found, 482.0716.

_N_-(4-(*tert*-Butyl)phenyl)-_N_-(phenylsulfonyl)benzenesulfonamide (1.2j) and _N_-(3-(*tert*-Butyl)phenyl)-

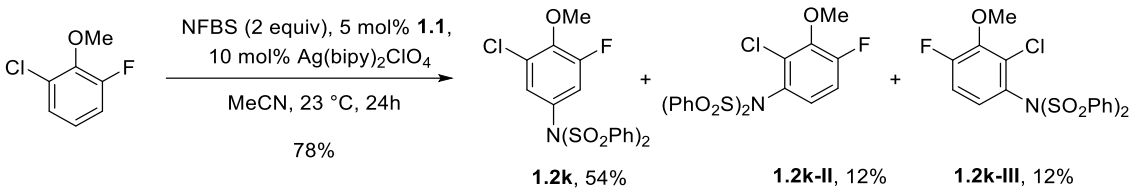
***N*-(phenylsulfonyl)benzenesulfonamide (1.2j-II)**



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with *tert*-butylbenzene (40.3 mg, 46.4 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (9:1 (v/v) with 1% triethylamine), to afford 112.0 mg of the mixture of the title compounds as a colorless solid (87% yield).

The products could not readily be separated by silica gel chromatography or preparative TLC, so they were characterized as a mixture. Data for **1.2j** and **1.2j-II**: R_f = 0.63 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.94–7.97 (m, 10H), 7.65–7.69 (m, 5H), 7.52–7.58 (m, 10H), 7.44–7.48 (m, 1H), 7.34–7.38 (m, 3H), 7.29–7.33 (m, 1H), 6.92–6.97 (m, 4H), 6.84 (t, *J* = 2.1 Hz, 1H), 1.33 (s, 13.5H), 1.20 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 153.7, 152.5, 139.7, 139.7, 134.1, 134.0, 134.0, 131.5, 131.0, 129.1, 129.0, 128.7, 128.7, 128.5, 127.3, 126.4, 35.0, 34.7, 31.4, 31.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{22}H_{27}N_2O_4S_2$ ($[M + NH_4]^+$), 447.1407, found, 447.1399.

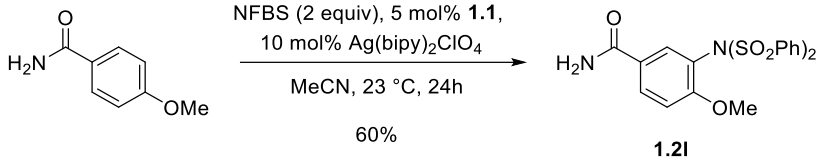
***N*-(3-Chloro-5-fluoro-4-methoxyphenyl)-*N*-(phenylsulfonyl)benzenesulfonamide (1.2k)**



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with 1-chloro-3-fluoro-2-methoxybenzene (48.2 mg, 38.9 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 106.7 mg of a mixture of the title compound and its two constitutional isomers (78% yield). Purification for characterization was accomplished by preparative TLC.

Data for **1.2k**: colorless solid; R_f = 0.59 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.93–7.97 (m, 4H), 7.70–7.74 (m, 2H), 7.57–7.61 (m, 4H), 6.83 (t, *J* = 2.1 Hz, 1H), 6.72 (dd, *J* = 10.9, 2.6 Hz, 1H), 4.04 (d, *J* = 2.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 155.1 (d, *J* = 251.3 Hz), 146.4 (d, *J* = 12.5 Hz), 139.1, 134.5, 129.4, 129.1 (d, *J* = 3.8 Hz), 128.8 (d, *J* = 1.1 Hz), 128.7, 128.4 (d, *J* = 5.5 Hz), 119.4 (d, *J* =20 Hz), 61.7 (d, *J* = 6.3 Hz). ^{19}F NMR (375 MHz, $CDCl_3$, 23 ºC, δ): –129.0 (d, *J* = 9.8 Hz). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{19}H_{19}ClFN_2O_5S_2$ $[M + NH_4]^+$, 473.0402, found, 473.0415.

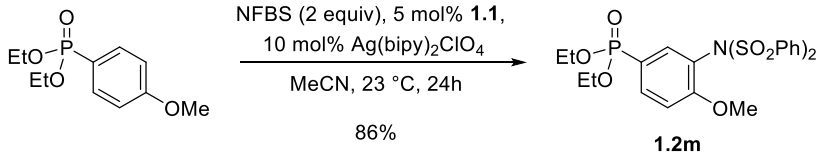
4-Methoxy-3-(*N*-(phenylsulfonyl)phenylsulfonamido)benzamide (1.2l)



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with 4-methoxybenzamide (45.3 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 μmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 μmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 μL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (1:4 (v/v) with 1% triethylamine), to afford 80.0 mg of the title compound as an off-white solid (60% yield).

R_f = 0.39 (EtOAc). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.94–7.98 (m, 5H), 7.65–7.69 (m, 2H), 7.52–7.56 (m, 4H), 7.50 (d, *J* = 2.3 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 3.45 (s, 3H). ^{13}C NMR (125 MHz, $(CD_3)_2CO$, 23 ºC, δ): 167.2, 160.9, 140.9, 134.9, 133.7, 132.6, 129.7, 129.6, 127.8, 123.4, 112.6, 55.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{20}H_{19}N_2O_6S_2$ ($[M + H]^+$), 447.0679, found, 447.0684.

Diethyl (4-methoxy-3-(*N*-(phenylsulfonyl)phenylsulfonamido)phenyl)phosphonate (1.2m)

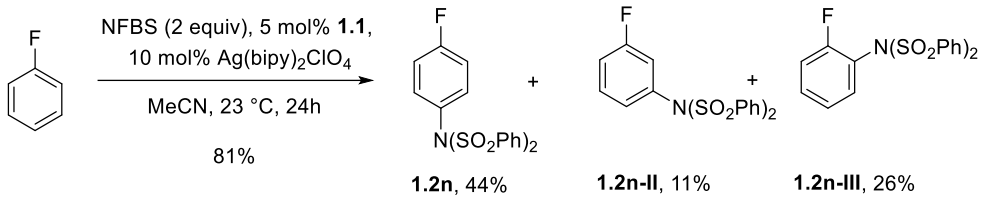


Under N_2 atmosphere, an oven-dried 4 mL vial was charged with diethyl (4-methoxyphenyl)phosphonate (73.3 mg, 65.4 μL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 μmol, 5.00 mol%),

$Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (3:2 to 1:9 (v/v) with 1% triethylamine), to afford 138.4 mg of the title compound as a colorless solid (86% yield).

R_f = 0.52 (EtOAc). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.92–7.94 (m, 4H), 7.88 (ddd, *J* = 12.8, 8.4, 1.8 Hz, 1H), 7.63–7.67 (m, 2H), 7.52 (t, *J* = 7.9 Hz, 4H), 7.46 (dd, *J* = 13.2, 2.1 Hz, 1H), 6.91 (dd, *J* = 8.5, 3.8 Hz, 1H), 4.00–4.14 (m, 4H), 3.44 (s, 3H), 1.30 (t, *J* = 7.3 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 160.8 (d, *J* = 3.4 Hz), 139.9, 136.8 (d, *J* = 10.0 Hz), 136.3 (d, *J* = 10.0 Hz), 133.9, 128.9, 128.8, 123.2 (d, *J* = 20.0 Hz), 120.6 (d, *J* = 193.4 Hz), 112.1 (d, *J* = 17.5 Hz), 62.3 (d, *J* = 5.0 Hz), 55.6, 16.4 (d, *J* = 6.3 Hz). Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{23}H_{27}NO_8PS_2$ $[M + H]^+$, 540.0910, found, 540.0922.

_N_-(4-Fluorophenyl)-_N_-(phenylsulfonyl)benzenesulfonamide (1.2n)



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with fluorobenzene (28.8 mg, 28.2 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with

hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford two fractions: fraction A (36.9 mg) contained a 7.1:1 ratio of **1.2n**:**1.2n-II**, and fraction B (58.6 mg) contained a 1.35:1:2.35 ratio of **1.2n**:**1.2n-II**:**1.2n-III**. The total yield is therefore 95.5 mg (81% yield) with a product ratio of **1.2n**:**1.2n-II**:**1.2n-III** = 4:1:2.3.

The major component (**1.2n**) was able to be further separated for characterization from fraction A by column chromatography eluting with hexanes/EtOAc (19:1 to 4:1 (v/v). Compound **1.2n-II** was assigned by COSY of the mixture in fraction A (Figure E1.1). Compound **1.2n-III** was assigned by process of elimination.

Data for **1.2n**: R_f = 0.47 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.95–7.92 (m, 4H), 7.71–7.67 (m, 2H), 7.58–7.54 (m, 4H), 7.07–7.02 (m, 2H), 7.02–6.98 (m, 2H),. ^{13}C NMR (100 MHz, $CDCl_3$, 23 ºC, δ): 166.1 (d, *J* = 252.6 Hz), 139.2 (s), 134.3 (s), 134.1 (s), 133.5 (d, *J* = 9.3 Hz), 130.1 (s), 128.8 (d, *J* = 54.4 Hz), 116.4 (d, J = 23.2). ^{19}F NMR (125 MHz, $CDCl_3$, 23 ºC, δ): -108.7. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{15}FNO_4S_2$ ($[M + H]^+$), 392.0421, found, 392.0416.

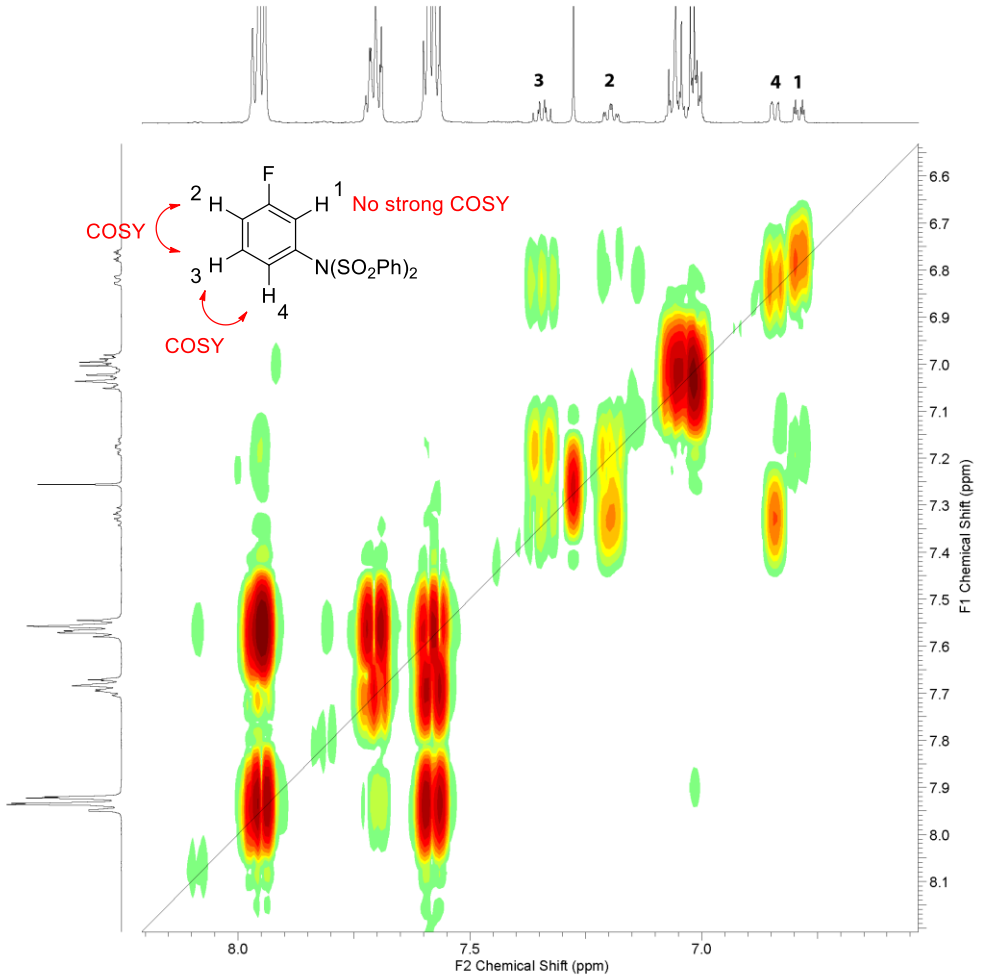
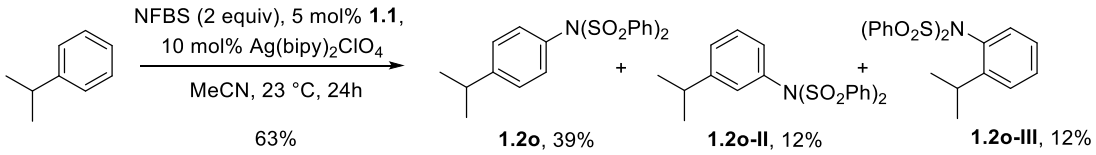


Figure E1.1. COSY for structural assignment of **1.2n-II** ($CDCl_3$, 23 °C)

***N*-(4-*iso*Propylphenyl)-*N*-(phenylsulfonyl)benzenesulfonamide (1.2o)**



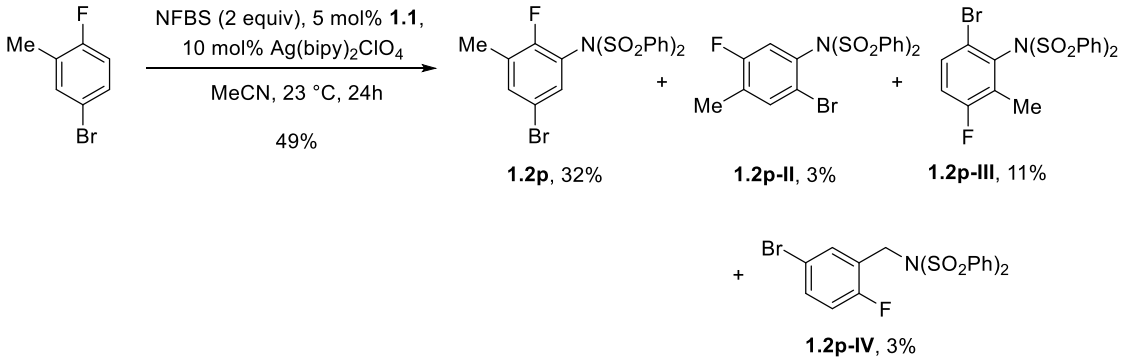
Under N_2 atmosphere, an oven-dried 4 mL vial was charged with cumene (36.1 mg, 40.3 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently,

triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 with 1% triethylamine), to afford 78.4 mg of the mixture of the title compounds as a yellow solid (63% yield).

The products could not readily be separated by silica gel chromatography or preparative TLC, so they were characterized as a mixture. Data for **1.2o** and **1.2o-II** and **1.2o-III**:

R_f = 0.54 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 23 ºC, δ): 8.00–7.90 (m, 6.7H), 7.71–7.64 (m, 3.5H), 7.59–7.50 (m, 6.8H), 7.44–7.36 (m, 0.9H), 7.32–7.28 (m, 0.6H), 7.24–7.17 (m, 2H), 7.12–7.16 (m, 0.4H), 6.97–6.88 (m, 2.3H), 6.81–6.72 (m, 0.6H), 3.02 (sept, 0.3H), 2.94 (sept, 1H), 2.83 (sept, 0.3H), 1.26 (d, 6H), 1.14 (d, 1.9H), 1.04 (d, 1.9H). ^{13}C NMR (100 MHz, $CDCl_3$, 23 ºC, δ): 151.3, 151.2, 150.0, 139.6, 139.5, 139.2, 134.1, 134.0, 133.8, 131.6, 131.4, 131.2, 130.7, 129.6, 129.0, 128.9, 128.8, 128.6, 128.5, 127.7, 127.3, 125.9, 33.8, 33.6, 28.4, 24.0, 23.7, 23.6. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{21}H_{21}NO_4S_2$ ($[M + H]^+$), 416.0985, found, 416.0986.

_N_-(4-_iso_Propylphenyl)-_N_-(phenylsulfonyl)benzenesulfonamide (1.2p)



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with 2-fluoro-5-bromotoluene (56.7 mg, 38.3 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c

= 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 μL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 with 1% triethylamine), to afford 71.0 mg of the mixture of the title compounds as a yellow solid (63% yield).

The products could not readily be separated by silica gel chromatography or preparative TLC, so they were characterized as a mixture. Compounds **1.2p–1.2p-IV** were assigned through a combination of 1-D TOCSY and NOESY experiments (see Figure E1.2–Figure E1.5 for assignment details). Data for **1.2p** and **1.2p-II** and **1.2p-III**:

R_f = 0.57 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 8.07 (d, *J* = 8.2 Hz, 1.3H), 8.00 (d, *J* = 8.2 Hz, 4H), 7.96 (d, *J* = 8.2 Hz, 0.4H), 7.91 (d, *J* = 8.2 Hz, 0.6H), 7.72–7.68 (m, 2.9H), 7.66–7.62 (m, 0.3H), 7.59–7.54 (m, 5.7H), 7.53–7.49 (m, 0.7H), 7.46–7.42 (m, 1.5H), 7.31–7.27 (m, 0.2H), 7.25–7.22 (m, 0.2H), 7.01 (dd, *J* = 8.7, 8.7 Hz, 0.45H), 6.87 (dd, *J* = 9.6, 9.6 Hz, 0.2H), 6.81 (d, *J* = 9.6 Hz, 1H), 5.01 (s, 0.3H), 2.30 (s, 3H), 2.21 (s, 0.2H), 1.84 (s, 1.0H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): Peaks are not listed because the mixture of four compounds, as well as splitting of aryl carbons by ^{19}F, precluded assignment. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{19}H_{15}BrNNaO_4S_2$ ($[M + Na]^+$), 505.9504, found, 505.9502.

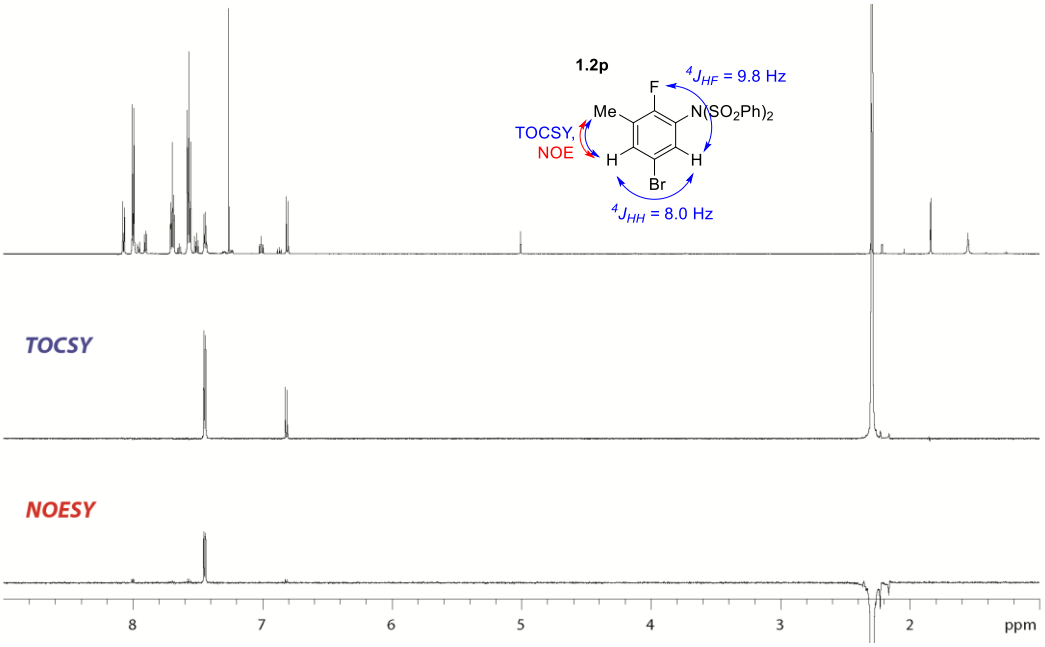


Figure E1.2. Structural assignment of **1.2p** by 1-D TOCSY and NOESY NMR ($CDCl_3$, 23 °C)

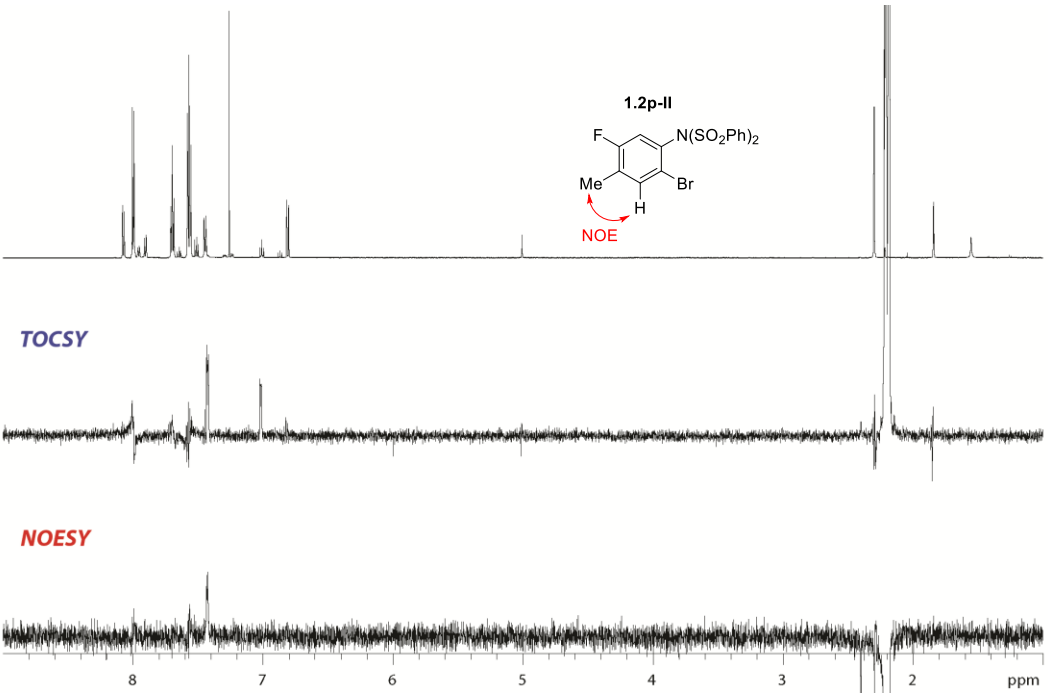


Figure E1.3. Structural assignment of **1.2p-II** by 1-D TOCSY and NOESY NMR ($CDCl_3$, 23 °C)

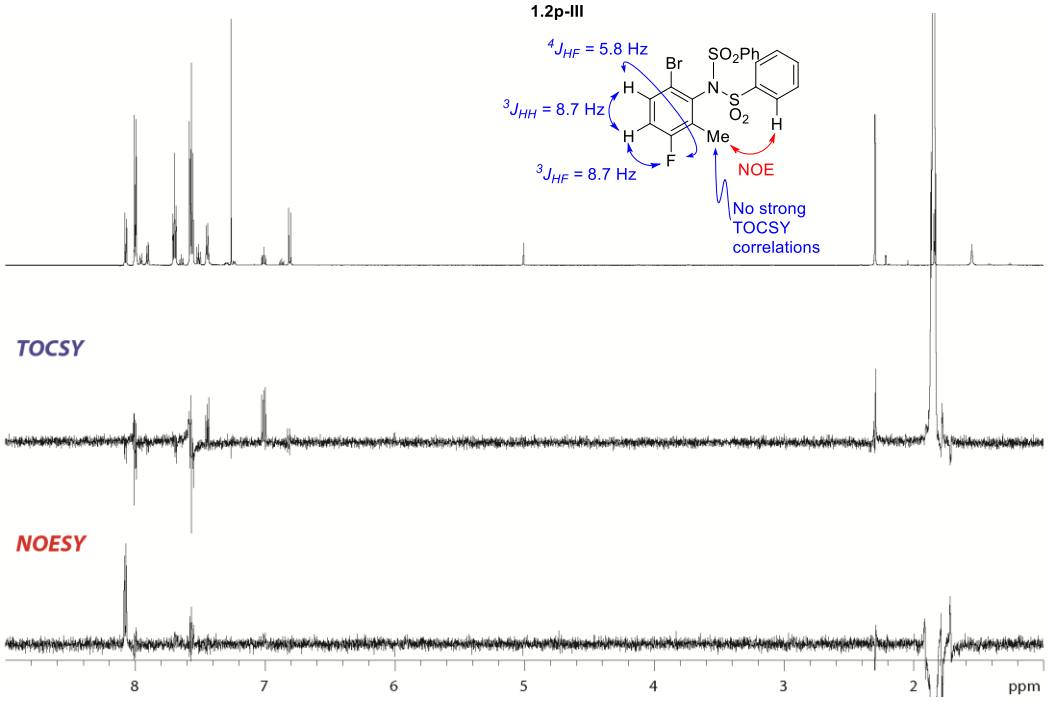


Figure E1.4. Structural assignment of **1.2p-III** by 1-D TOCSY and NOESY NMR ($CDCl_3$, 23 °C)

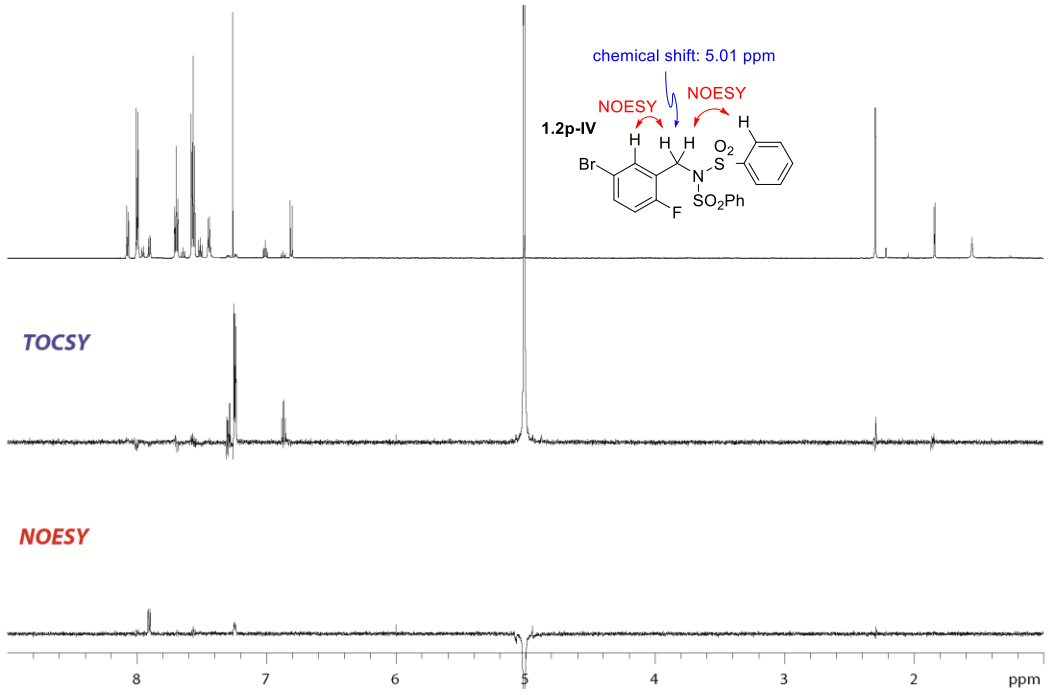
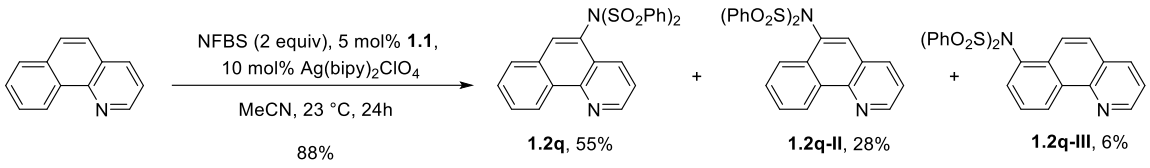


Figure E1.5. Structural assignment of **1.2p-IV** by 1-D TOCSY and NOESY NMR ($CDCl_3$, 23 °C)

N-(Benzo[h]quinolin-5-yl)-N-(phenylsulfonyl)benzenesulfonamide (1.2q)



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with benzo[*h*]quinoline (56.7 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 μmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 μmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 μL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 27.5 mg of the title compound as a colorless solid, along with 97.6 mg of a 6.7:4.3:1 mixture of **1.2q**, **1.2q-II**, and **1.2q-III** (88% yield overall). Compounds **1.2q-II** and **1.2q-III** were separated from **1.2q** by preparative thin layer chromatography (eluting twice with 1:4 EtOAc:hexanes), and were assigned as a mixture through a combination of one-dimensional TOCSY and NOESY NMR experiments (see Figure E1.6–Figure E1.7 for assignment details). Data for **1.2q**:

R_f = 0.47 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 9.32 (d, J = 8.7 Hz, 1H), 8.96 (dd, *J* = 4.3 Hz, 1.7 Hz, 1H), 7.96 (dd, J = 7.96, 1.0 Hz, 4H), 7.88 (dd, J = 8.5, 1.8 Hz, 1H), 7.83 (ddd, J = 8.1, 6.7, 1.4 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.72 (m, 3H), 7.54 (m, 4 H), 7.46 (s, 1H), 7.31 (dd, *J* = 8.1, 4.4 Hz. 1H); ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 149.3, 147.0, 138.8, 134.3, 132.8, 132.6, 132.3, 131.9, 129.1, 129.0, 128.8, 128.6, 128.5, 125.8, 124.7, 121.8. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{25}H_{18}N_2NaO_4S_2$ ($[M + Na]^+$), 497.0600, found, 497.0595.

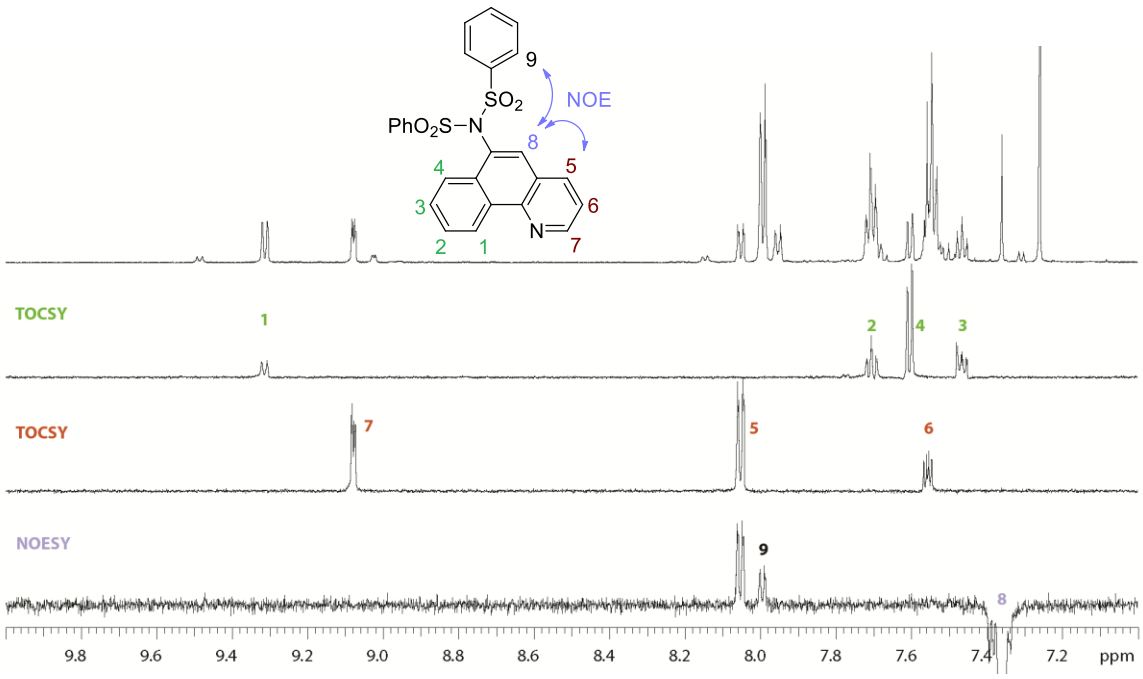


Figure E1.6. Structural assignment of **1.2q-II** by 1-D TOCSY and NOESY NMR ($CDCl_3$, 23 °C)

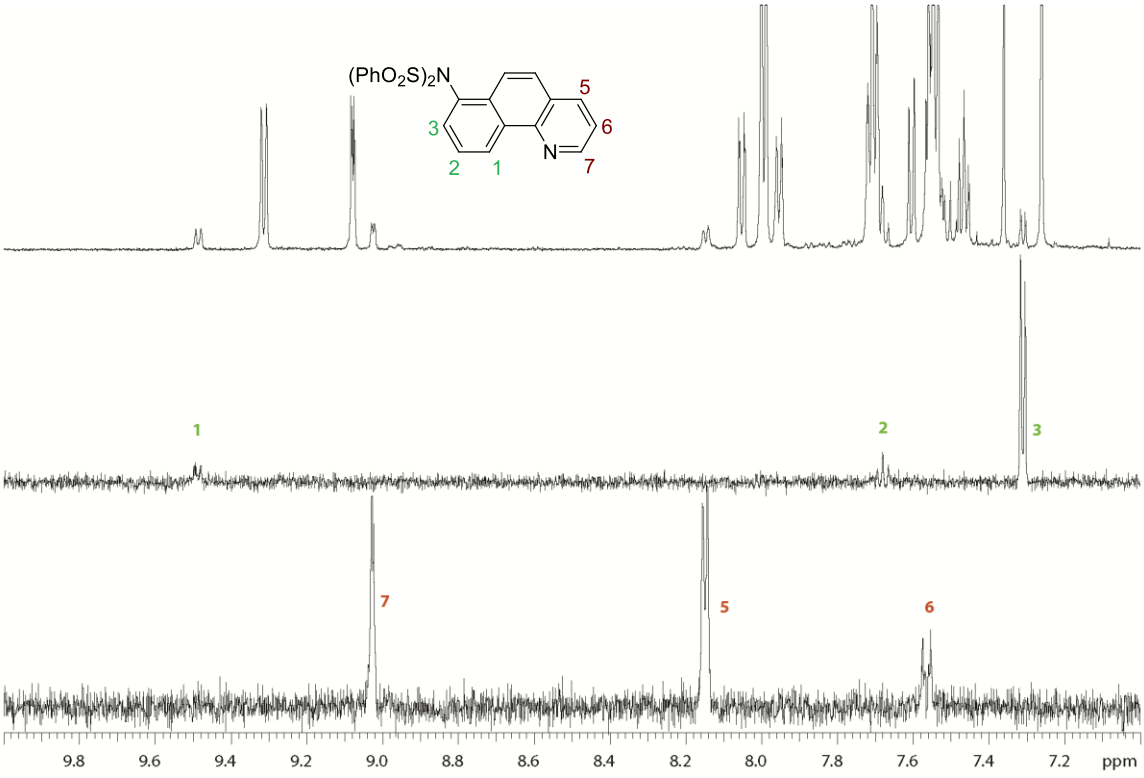
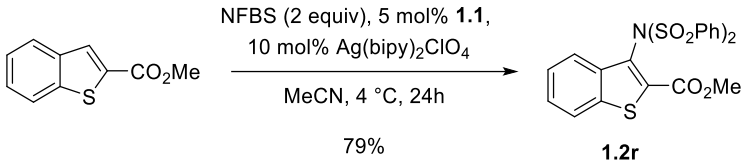


Figure E1.7. Structural assignment of **1.2q-III** by 1-D TOCSY and NOESY NMR ($CDCl_3$, 23 °C)

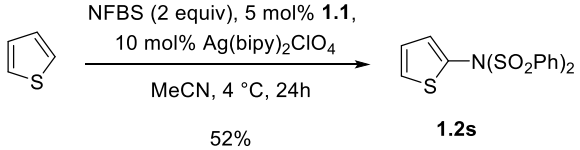
Methyl 3-(*N*-(phenylsulfonyl)phenylsulfonamido)benzo[*b*]thiophene-2-carboxylate (1.2r)



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with methyl benzo[*b*]thiophene-2-carboxylate (27.7 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 4 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 115 mg of the title compound as a colorlesssolid (79% yield).

R_f = 0.38 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.98–8.00 (m, 4H), 7.83 (d, *J* = 8.2 Hz, 1H), 7.66–7.70 (m, 2H), 7.53 (t, *J* = 7.9 Hz, 4H), 7.46 (td, *J* = 7.6, 1.2 Hz, 1H), 7.30–7.33 (m, 1H), 7.25–7.28 (m, 1H), 3.39 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 160.9, 139.8, 138.2, 137.4, 134.6, 134.2, 129.4, 128.9, 128.8, 127.8, 125.4, 124.8, 122.8, 52.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{22}H_{21}N_2O_6S_3$ $[M + NH_4]^+$, 505.0556, found, 505.0569.

***N*-(Phenylsulfonyl)-*N*-(thiophen-2-yl)benzenesulfonamide (1.2s)**

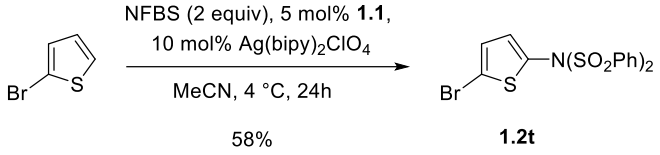


Under N_2 atmosphere, an oven-dried 4 mL vial was charged with thiophene (25.2 mg, 24.4 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$

(16.0 mg, 30.0 μmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 4 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 μL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (99:1 to 5.6:1 (v/v) with 1% triethylamine), to afford 59.7 mg of the title compound as a colorless solid (52% yield).

R_f = 0.53 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.99 (dd, *J* = 8.3, 1.1 Hz, 4H), 7.68–7.71 (m, 2H), 7.55–7.59 (m, 4H), 7.38 (dd, *J* = 5.5, 1.7 Hz, 1H), 6.94 (dd, *J* = 5.5, 3.9 Hz, 1H), 6.74 (dd, *J* = 3.9, 1.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 138.8, 134.4, 134.0, 131.4, 129.2, 128.9, 128.8, 125.8. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{16}H_{13}NNaO_4S_3$ ($[M + Na]^+$), 401.9899, found, 401.9913.

_N_-(5-Bromothiophen-2-yl)-_N_-(phenylsulfonyl)benzenesulfonamide (1.2t)

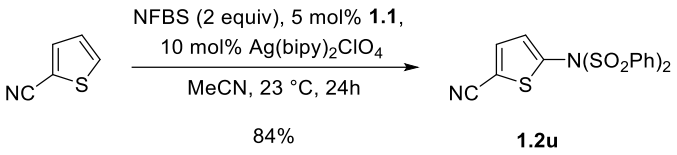


Under N_2 atmosphere, an oven-dried 4 mL vial was charged with 2-bromothiophene (48.9 mg, 29.0 μL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 μmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 μmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 4 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 μL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 80.3 mg of the title compound as a colorless solid (58% yield).

R_f = 0.52 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.97–

8.02 (m, 4H), 7.71 (t, J = 7.3 Hz, 2H), 7.58 (t, J = 7.9 Hz, 4H), 6.94 (d, J = 4.1 Hz, 1H), 6.50 (d, J = 4.1 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 138.6, 134.6, 134.3, 132.3, 129.3, 128.9, 128.8, 115.8. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{16}H_{12}BrNNaO_4S_3$ $[M + Na]^+$, 481.8983, found, 481.8987.

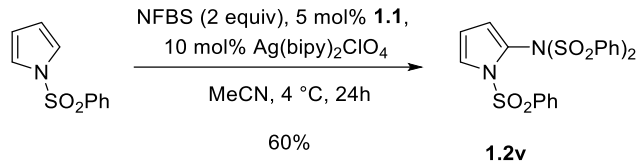
_N_-(5-Cyanothiophen-2-yl)-_N_-(phenylsulfonyl)benzenesulfonamide (1.2u)



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with thiophene-2-carbonitrile (27.9 µL, 32.7 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 102 mg of the title compound as a colorless solid (84% yield).

R_f = 0.41 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.97 (d, J = 7.6 Hz, 4H), 7.74 (t, J = 7.6 Hz, 2H), 7.60 (t, J = 7.9 Hz, 4H), 7.46 (d, J = 4.1 Hz, 1H), 6.77 (d, J = 4.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$, 23 ºC, δ): 140.3, 138.1, 135.8, 135.0, 131.6, 129.5, 128.9, 113.2, 112.6. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{17}H_{12}N_2NaO_4S_3$ ($[M + Na]^+$), 426.9851, found, 426.9861.

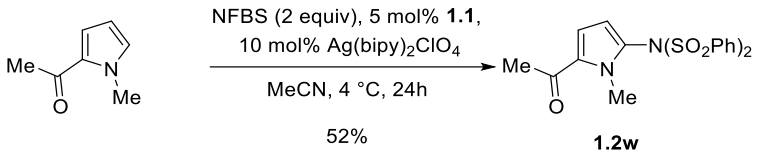
***N*-(Phenylsulfonyl)-*N*-(1-(phenylsulfonyl)-1H-pyrrol-2-yl)benzenesulfonamide (1.2v)**



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with methyl 1-(phenylsulfonyl)-1H-pyrrole (62.2 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 μmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 μmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 4 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 μL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 4:1 (v/v) with 1% triethylamine), to afford 90.5 mg of the title compound as a colorless solid (60% yield).

R_f = 0.46 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.95–7.99 (m, 6H), 7.67–7.70 (m, 2H), 7.58–7.61 (m, 1H), 7.52–7.56 (m, 4H), 7.47–7.51 (m, 2H), 7.22 (dd, *J* = 3.5, 1.8 Hz, 1H), 6.26 (t, *J* = 3.5 Hz, 1H), 6.04 (dd, *J* = 3.5, 1.8 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 139.0, 138.4, 134.4, 134.3, 129.8, 129.1, 128.9, 128.5, 124.8, 122.6, 117.7, 111.0. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{22}H_{19}N_2O_6S_3$ ($[M + H]^+$), 503.0400, found, 503.0397.

***N*-(5-Acetyl-1-methyl-1*H*-pyrrol-2-yl)-*N*-(phenylsulfonyl)benzenesulfonamide (1.2w)**

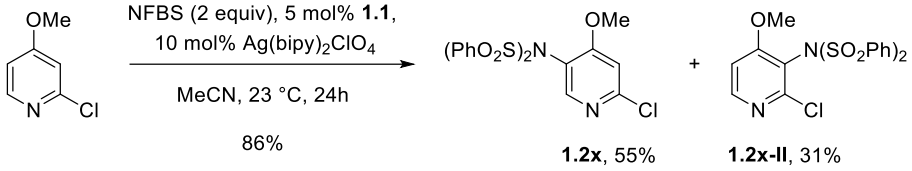


Under N_2 atmosphere, an oven-dried 4 mL vial was charged with 1-(1-methyl-1H-pyrrol-2-yl)ethanone (36.9 mg, 35.5 μL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 μmol, 5.00 mol%),

$Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 4 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 3:1 (v/v) with 1% triethylamine), to afford 65.8 mg of the title compound as a colorless solid (52% yield).

R_f = 0.46 (hexanes/EtOAc 3:2 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.90–7.94 (m, 4H), 7.68–7.72 (m, 2H), 7.56 (t, *J* = 8.2 Hz, 4H), 6.89 (d, *J* = 4.7 Hz, 1H), 5.92 (d, *J* = 4.1 Hz, 1H), 3.42 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 189.1, 138.7, 134.7, 131.4, 129.3, 128.9, 127.5, 117.5, 111.4, 33.1, 27.3. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{19}H_{19}N_2O_5S_2$ ($[M + H]^+$), 419.0730, found, 419.0734.

_N_-(6-Chloro-4-methoxypyridin-3-yl)-_N_-(phenylsulfonyl)benzenesulfonamide (1.2x) and _N_-(2-Chloro-4-methoxypyridin-3-yl)-_N_-(phenylsulfonyl)benzenesulfonamide (1.2x-II)



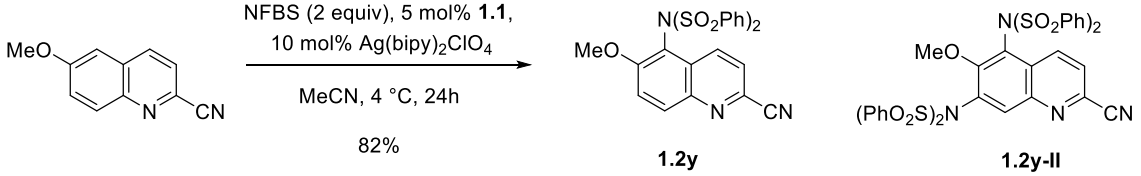
Under N_2 atmosphere, an oven-dried 4 mL vial was charged 2-chloro-4-methoxypyridine (43.1 mg, 34.2 µL, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (7:3 to 2:3 (v/v) with 1% triethylamine), to afford 72.4 mg (55% yield) of **1.2x** and 40.2

mg (31% yield) of **1.2x-II**.

Data for **1.2x**: yellow solid; R_f = 0.61 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.94–7.98 (m, 4H), 7.91 (s, 1H), 7.66–7.71 (m, 2H), 7.54–7.58 (m, 4H), 6.82 (s, 1H), 3.50 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 164.8, 154.7, 152.3, 139.6, 134.3, 129.1, 128.9, 120.6, 108.2, 56.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{16}ClN_2O_5S_2$ ([M + H]$^+$), 439.0184, found, 439.0200.

Data for **1.2x-II**: yellow oil; R_f = 0.22 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 8.29 (d, *J* = 5.9 Hz, 1H), 8.03 – 8.06 (m, 4H), 7.65–7.69 (m, 2H), 7.55 (t, *J* = 7.9 Hz, 4H), 6.77 (d, *J* = 5.9 Hz, 1H), 3.46 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 165.9, 155.0, 151.5, 139.9, 134.2, 129.5, 128.8, 119.1, 107.2, 56.2. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{18}H_{16}ClN_2O_5S_2$ ([M + H]$^+$), 439.0184, found, 439.0184.

_N_-(6-Methoxy-2-methylquinolin-7-yl)-_N_-(phenylsulfonyl)benzenesulfonamide (1.2y) and _N_,_N_'-(6-Methoxy-2-methylquinoline-5,7-diyl)bis(_N_-(phenylsulfonyl)benzenesulfonamide) (1.2y-II)



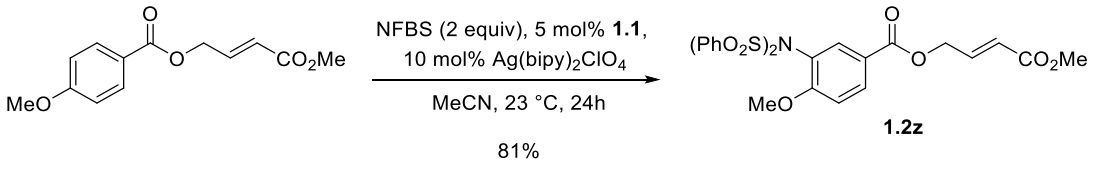
Under N_2 atmosphere, an oven-dried 4 mL vial was charged with 6-methoxyquinoline-2-carbonitrile (55.3 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 μmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 μmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 4 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 μL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 1:1 (v/v) with 1% triethylamine), to afford 115 mg of the title

compound (82% yield). When the reaction was performed at 23 °C, a 6:5 mixture of **1.2y** and **1.2y-II** was formed in 77% yield.

Data for **1.2y**: colorless solid; R_f = 0.33 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 8.28 (d, *J* = 9.4 Hz, 1H), 8.01 (d, *J* = 8.8 Hz, 1H), 7.91 (dd, *J* = 8.8, 1.2 Hz, 4H), 7.68–7.72 (m, 2H), 7.52–7.56 (m, 5H), 7.51 (d, *J* = 2.9 Hz, 1H), 3.49 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 158.4, 143.9, 139.6, 134.9, 134.3, 133.4, 131.9, 130.5, 129.3, 128.9, 124.4, 117.8, 117.5, 115.8, 56.1. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{23}H_{18}N_3O_5S_2$ ([M + H]$^+$), 480.0682, found, 480.0695.

Data for **1.2y-II**: colorless solid; R_f = 0.40 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 8.03 (d, *J* = 8.2 Hz, 1H), 7.88 (dd, *J* = 8.8, 1.2 Hz, 4H), 7.85 (dd, *J* = 8.8, 1.2 Hz, 4H), 7.70–7.74 (m, 2H), 7.64–7.68 (m, 2H), 7.53–7.57 (m, 5H), 7.48–7.52 (m, 4H), 7.40 (d, *J* = 8.8 Hz, 1H), 3.42 (s, 3 H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 157.8, 141.2, 139.2, 138.3, 135.6, 134.5, 134.0, 131.7, 130.8, 129.5, 129.3, 129.0, 128.9, 124.7, 123.6, 118.1, 116.5, 56.5. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{35}H_{27}N_4O_9S_4$ ([M + H]$^+$), 775.0655, found, 775.0668.

(*E*)-4-methoxy-4-oxobut-2-en-1-yl-4-methoxy-3-(*N*-(phenylsulfonyl)phenylsulfonamido) benzoate (1.2z)

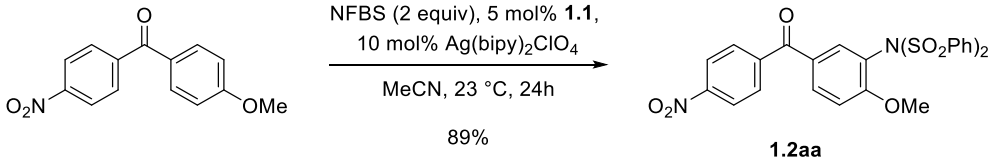


Under N_2 atmosphere, an oven-dried 4 mL vial was charged with (*E*)-4-methoxy-4-oxobut-2-en-1-yl 4-methoxybenzoate (75.1 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a

sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (9:1 to 7:3 (v/v) with 1% triethylamine), to afford 132.7 mg of the title compound as an off-white solid (81% yield).

R_f = 0.25 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 8.13 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.96 (d, *J* = 8.2 Hz, 4H), 7.76 (d, *J* = 1.8 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 2H), 7.54 (t, *J* = 7.9 Hz, 4H), 7.02 (dt, *J* = 15.4, 4.6 Hz, 1H), 6.90 (d, *J* = 8.8 Hz, 1H), 6.05 (dt, *J* = 15.8, 1.8 Hz, 1H), 4.94 (dd, *J* = 4.7, 1.8 Hz, 2H), 3.78 (s, 3H), 3.47 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 166.3, 164.4, 161.7, 141.5, 139.9, 134.8, 134.1, 134.0, 128.9, 128.9, 123.1, 122.4, 122.0, 111.8, 63.1, 55.7, 51.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{25}H_{27}N_2O_9S_2$ ($[M+ NH_4]^+$), 563.1152, found, 563.1162.

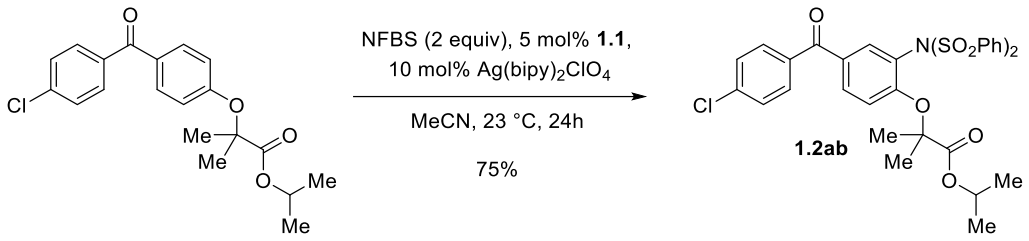
_N_-(2-Methoxy-5-(4-nitrobenzoyl)phenyl)-_N_-(phenylsulfonyl)benzenesulfonamide (1.2aa)



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with (4-methoxyphenyl)(4-nitrophenyl)methanone (45.9 mg, 0.300 mmol, 1.00 equiv), palladium complex **1.1** (11.4 mg, 15.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 µmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 µL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 3:2 (v/v) with 1% triethylamine), to afford 148 mg of the title compound as an off-white solid (89% yield).

R_f = 0.47 (hexanes/EtOAc 1:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 8.33 (dt, *J* = 8.8, 1.8 Hz, 2H), 7.98 (dd, *J* = 8.5, 2.1 Hz, 1H), 7.95 (dd, *J* = 7.6, 1.2 Hz, 4H), 7.87 (dt, *J* = 8.8, 2.3 Hz, 2H), 7.67 (t, *J* = 7.6 Hz, 2H), 7.58 (d, *J* = 1.8 Hz, 1H), 7.54 (t, *J* = 8.2 Hz, 4H), 6.97 (d, *J* = 8.2 Hz, 1H), 3.49 (s, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 192.2, 161.9, 149.9, 142.9, 139.9, 135.8, 134.6, 134.1, 130.6, 129.1, 128.9, 128.9, 123.8, 123.2, 112.2, 55.9. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{26}H_{21}N_2O_8S_2$ ($[M + H]^+$), 553.0734, found, 553.0723.

Isopropyl 2-(4-(4-chlorobenzoyl)-2-(*N*-(phenylsulfonyl)phenylsulfonamido)phenoxy)-2-methylpropanoate (1.2ab)



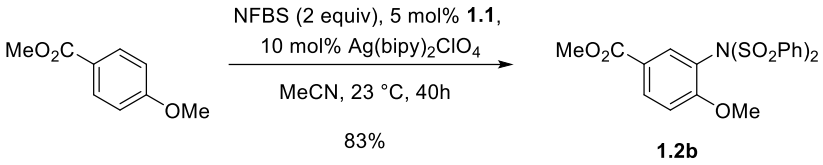
Under N_2 atmosphere, an oven-dried 4 mL vial was charged Fenofibrate (isopropyl 2-(4-(4-chlorobenzoyl)phenoxy)-2-methylpropanoate) (108.2 mg, 0.3000 mmol, 1.00 equiv), palladium complex **1** (11.4 mg, 15.0 μmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (16.0 mg, 30.0 μmol, 10.0 mol%), and NFBS (0.189 g, 0.600 mmol, 2.00 equiv). Acetonitrile (0.75 mL, c = 0.40 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, triethylamine (30.5 mg, 42.0 μL, 0.300 mmol, 1.00 equiv) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (19:1 to 5.7:1 (v/v) with 1% triethylamine), to afford 148.4 mg of the title compound as a colorless solid (75% yield).

R_f = 0.57 (hexanes/EtOAc 7:3 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 8.01–8.04 (m, 4H), 7.86 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.68–7.70 (m, 2H), 7.64–7.68 (m, 2H), 7.56 (d, *J* = 2.3 Hz, 1H), 7.53–7.56 (m, 4H), 7.43–7.46 (m, 2H), 6.70 (d, *J* = 8.8 Hz, 1H), 5.07 (sep, *J* = 6.3 Hz, 1H), 1.34 (s, 6H), 1.25 (d, *J* = 6.5 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 ºC, δ): 192.8, 172.6, 158.0, 140.4, 138.9,

136.0, 135.7, 133.8, 133.1, 131.3, 129.8, 129.0, 129.0, 128.8, 124.4, 115.9, 80.5, 69.5, 24.3, 21.7. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_{32}H_{34}ClN_2O_8S_2$ ($[M + NH_4]^+$), 673.144, found, 673.1455.

E1.5 Procedure for the multi-gram scale C–H imidation reaction

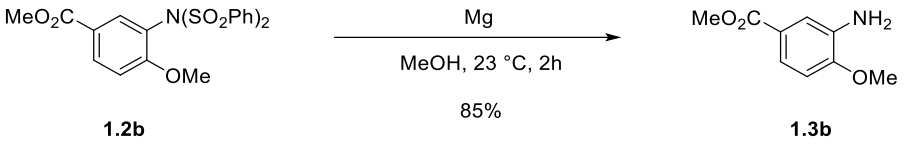
Methyl 4-methoxy-3-(*N*-(phenylsulfonyl)phenylsulfonamido)benzoate (1.2b)



To a flame dried 250 mL round bottom flask charged with stir bar, *N*-fluoro-*N*-(phenylsulfonyl)benzenesulfonamide (14.2 g, 45.0 mmol, 1.50 equiv), palladium complex **1.1** (0.457 g, 0.600 mmol, 2.00 mol%), and $Ag(bipy)_2ClO_4$ (0.624 g, 1.20 mmol, 4.00 mol%) in dry MeCN (30.0 mL, c = 1.00 M) was added methyl 4-methoxybenzoate (4.99 g, 30.0 mmol, 1.00 equiv). The reaction vessel was sealed and stirred at 23 °C for 40 h. Triethylamine (5mL) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with (hexanes/EtOAc 5:1 (v/v) with 1% triethylamine) to afford 11.5 g of the title compound (83% yield), which is spectroscopically identical to the compound prepared according to the standard procedure (*vide supra*).

E1.6 Procedure for removal of phenylsulfonyl groups

Methyl 3-amino-4-methoxybenzoate (1.3b)



0.108 mmol scale:

To a solution of methyl 4-methoxy-3-(*N*-(phenylsulfonyl)phenylsulfonamido)benzoate (**1.2b**) (49.8 mg, 0.108 mmol, 1 equiv) in dry MeOH (3.6 mL, c = 0.030 M) was added Mg powder (31.6 mg, 1.30 mmol, 12 equiv) and the suspension was sonicated under nitrogen atmosphere at 23 °C for 2 h. Saturated solution of NH_4Cl (2.0 mL) was then added and the resulting mixture was extracted with diethyl ether (3 × 15 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (5:1 (v/v) with 1% triethylamine) to afford 16.7 mg of the title compound as a yellow solid (85% yield).

R_f = 0.70 (CH_2Cl_2/MeOH 9:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $(CD_3)_2SO$, 23 ºC, δ): 7.26 (d, *J* = 2.3 Hz, 1H), 7.21 (dd, *J* = 8.2, 2.3 Hz, 1H), 6.87 (d, *J* = 8.8 Hz, 1H), 4.97 (br s, 2H), 3.82 (s, 3H), 3.76 (s, 3 H). ^{13}C NMR (125 MHz, $(CD_3)_2SO$, 23 ºC, δ): 166.5, 150.1, 137.7, 122.0, 118.3, 113.8, 109.8, 55.5, 51.6. Mass Spectrometry: HRMS (ESI-TOF) (m/z): calcd for $C_9H_{12}NO_3$ ($[M + H]^+$), 182.0812, found, 182.0815.

0.217 mmol scale:

To a solution of methyl 4-methoxy-3-(*N*-(phenylsulfonyl)phenylsulfonamido)benzoate (**1.2b**) (100 mg, 0.217 mmol, 1 equiv) in dry MeOH (7.2 mL, c = 0.030 M) was added Mg powder (63.2 mg, 2.60 mmol, 12 equiv) and the suspension was sonicated under nitrogen atmosphere at 23 °C for 2 h. Saturated solution of NH_4Cl (4.0 mL) was then added and the resulting mixture was extracted with diethyl ether (3 × 30 mL). The combined organic layers were dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was purified by flash chromatography on silica gel, eluting with hexanes/EtOAc (5:1 (v/v) with 1% triethylamine) to afford 29.0 mg of the title compound as a yellow solid (74% yield). Spectroscopic data are the same as described above.

E1.7 Control Experiments: Catalytic imidation in the absence of 1.1, $Ag(bipy)_2ClO_4$, and light

Table E1.1. Experimental details

	Catalyst (5 mol%)	**Co-Catalyst (10 mol%)**	**Light**	**NMR-Yield of 1.2b**
Standard	palladium complex **1.1**	$Ag(bipy)_2ClO_4$	Yes	Quantitative
Absence of **1.1**	none	$Ag(bipy)_2ClO_4$	Yes	< 10%
Absence of $Ag(bipy)_2ClO_4$	palladium complex **1.1**	none	Yes	No Reaction
Absence of light	palladium complex **1.1**	$Ag(bipy)_2ClO_4$	No	Quantitative

Standard:

Under N_2 atmosphere, an oven-dried 4 mL vial was charged with methyl 4-methoxybenzoate (8.3 mg, 0.05 mmol, 1.0 equiv), palladium complex **1.1** (1.9 mg, 2.5 µmol, 5.0 mol%), $Ag(bipy)_2ClO_4$ (2.6 mg, 5.0 µmol, 10 mol%), and NFBS (32 mg, 0.10 mmol, 2.0 equiv). Acetonitrile (0.250 mL, c = 0.20 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, dimethylurea (2.2 mg, 0.025 mmol, 0.50 equiv) was added as an internal standard for the NMR measurement and the reaction mixture was concentrated *in vacuo*. The NMR of the crude reaction mixture indicated full conversation of starting material to the desired product **1.2b**.

In the absence of 1.1:

Under N_2 atmosphere, an oven-dried 4 mL vial was charged with methyl 4-methoxybenzoate (8.3 mg, 0.050 mmol, 1.0 equiv), $Ag(bipy)_2ClO_4$ (2.6 mg, 5.0 µmol, 10 mol%), and NFBS (32 mg, 0.10 mmol, 2.0 equiv). Acetonitrile (0.250 mL, c = 0.20 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, dimethylurea (2.2 mg, 0.025 mmol, 0.50 equiv) was added as an internal standard for the NMR measurement and the reaction mixture was concentrated *in vacuo*. The

NMR of the crude reaction mixture indicated less than 10% conversation of starting material to the desired product **1.2b**.

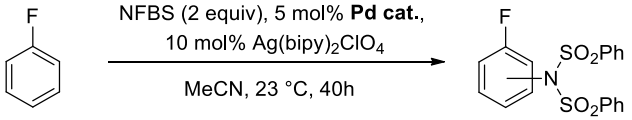
In the absence of $Ag(bipy)_2ClO_4$:

Under N_2 atmosphere, an oven-dried 4 mL vial was charged with methyl 4-methoxybenzoate (8.3 mg, 0.050 mmol, 1.0 equiv), palladium complex **1.1** (1.9 mg, 2.5 μmol, 5.0 mol%), and NFBS (32 mg, 0.10 mmol, 2.0 equiv). Acetonitrile (0.250 mL, c = 0.20 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, dimethylurea (2.2 mg, 0.025 mmol, 0.50 equiv) was added as an internal standard for the NMR measurement and the reaction mixture was concentrated *in vacuo*. The NMR of the crude reaction mixture indicated full conversation of starting material to the desired product **1.2b**.

In the absence of light:

Under N_2 atmosphere, an oven-dried amber 4 mL vial was charged with methyl 4-methoxybenzoate (8.3 mg, 0.050 mmol, 1.0 equiv), palladium complex **1.1** (1.9 mg, 2.5 μmol, 5.0 mol%), $Ag(bipy)_2ClO_4$ (2.6 mg, 5.0 μmol, 10 mol%), and NFBS (32 mg, 0.10 mmol, 2.0 equiv). The vial was wrapped with electrical tape and acetonitrile (0.250 mL, c = 0.20 M) was added. The reaction mixture was stirred in a sealed vial at 23 °C for 24 h. Subsequently, dimethylurea (2.2 mg, 0.025 mmol, 0.50 equiv) was added as an internal standard for the NMR measurement and the reaction mixture was concentrated *in vacuo*. The NMR of the crude reaction mixture indicated full conversation of starting material to the desired product **1.2b**.

E1.8 Control Experiments: Evaluation of Palladium Catalysts Other than 1.1



Under N_2 atmosphere, in a 4 mL vial was prepared a solution of NFBS (387.6 mg, 1.200 mmol, 2.0 equiv)

and $Ag(bipy)_2ClO_4$ (31.2 mg, 0.0604 mmol, 10 mol%) in acetonitrile (3.00 mL). In 5 separate vials were weighed palladium source (0.0050 mmol, 5.0 mol%), and ligand (0.010 mmol, 10.0 mol%) if applicable (see Table E1.2. Evaluation of Pd catalysts for details). To each of the five Pd/ligand-containing vials was added 0.500 mL of the NFBS/Ag solution. Finally, fluorobenzene (9.3 μL, 0.100 mmol, 1.0 equiv) was added to each vial. The five reactions were stirred magnetically at room temperature for 40 h, after which 2.0 uL 4-fluoronitrobenzene was added to each of the reaction mixtures as an internal standard and the product yields were analyzed by ^{19}F NMR (Table E1.2. Evaluation of Pd catalysts).

Table E1.2. Evaluation of Pd catalysts

Reaction	Pd Catalyst	Vial Contents	Total yield of 2xx
1	$Pd(OAc)_2$	1.1 mg $Pd(OAc)_2$	> 1%
2	$Pd(NCMe)_4(OTf)_2$	2.8 mg $Pd(NCMe)_4(OTf)_2$	3%
3	$Pd(OAc)_2$ + 2 bathocuproine	1.1 mg $Pd(OAc)_2$ 3.6 mg bathocuproine	> 1%
4	$Pd(NCMe)_4(OTf)_2$ + 2 bipyridine	2.8 mg $Pd(NCMe)_4(OTf)_2$ 1.6 mg bipyridine	> 1%
5	$Pd(NCMe)_4(OTf)_2$ + 2 phenanthroline	2.8 mg $Pd(NCMe)_4(OTf)_2$ 1.8 mg phenanthroline	3%

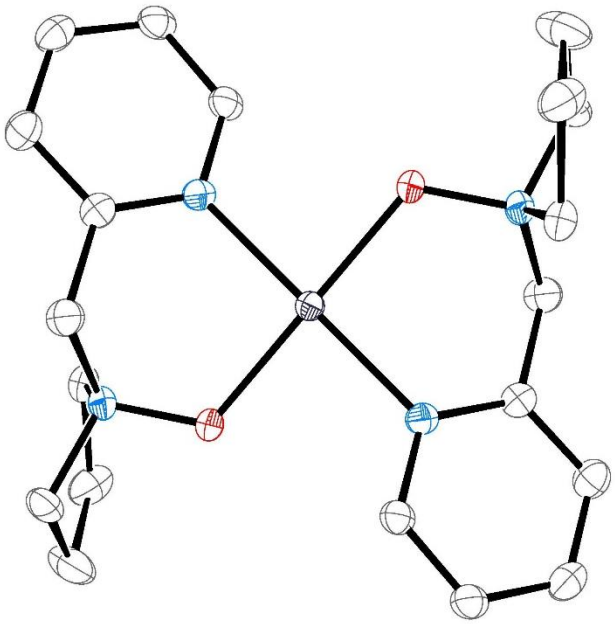
E1.9 X-ray Crystallographic Analysis

Palladium complex 1.1 (CCDC 943631)

Experimental

X-Ray quality crystals of 1.1 were grown by layering Et_2O (ca. 0.2 mL) on top of a solution of ca. 5 mg of 1.1 in 0.2 mL MeCN. A crystal was mounted on a nylon loop using Paratone-N oil, and transferred to a Bruker APEX II CCD diffractometer ($Mo K\alpha$ radiation, λ=0.71073 Å) equipped with an Oxford Cryosystems nitrogen flow apparatus. The sample was held at 100 K during the experiment. The collection method involved 0.5° scans in ω at 28° in 2θ. Data integration down to 0.82 Å resolution was carried out using SAINT V7.46 A (Bruker diffractometer, 2009) with reflection spot size optimisation. Absorption corrections were made with

the program SADABS (Bruker diffractometer, 2009). The structure was solved by the direct methods procedure and refined by least-squares methods again F_2 using SHELXS-97 and SHELXL-97 (Sheldrick, 2008). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Restraints on bond lengths and constraints of the atomic displacement parameters on each pair of disorder fragments (SADI and EADP instructions of SHELXL97), as well as the restraints of the atomic displacement parameters (SIMU/DELU instructions of SHELXL97) if necessary, have been applied for the disorder refinement. Crystal data as well as details of data collection and refinement are summarized in .



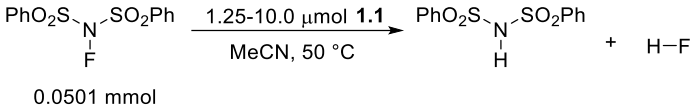
X-ray structure of **1.1**. Thermal ellipsoids are drawn at the 50% probability level; triflate anions and hydrogen atoms omitted for clarity

Table E1.3. Crystallographic details

	Compound **1.1**
Crystal data	
Chemical formula	$C_{22}H_{28}F_6N_4O_8PdS_2$
M_r	761.00
Crystal system, space group	Monoclinic, $P2_1/n$
Temperature (K)	100
a, b, c (Å)	11.9987 (11), 8.0328 (8), 14.4450 (14)
β (°)	96.490 (1)
V (Å^3)	1383.3 (2)
Z	2
Radiation type	Mo $K\alpha$
μ (mm^{-1})	0.92
Crystal size (mm)	0.40 × 0.30 × 0.20
Data collection	
Diffractometer	CCD area detector diffractometer
Absorption correction	Multi-scan *SADABS* (Sheldrick, 2009)
T_{min}, T_{max}	0.711, 0.838
No. of measured, independent and observed [$I > 2\sigma(I)$] reflections	22660, 3095, 2838
R_{int}	0.033
$(\sin \theta/\lambda)_{max}$ (Å^{-1})	0.644
Refinement	
$R[F^2 > 2\sigma(F^2)]$, $wR(F^2)$, S	0.044, 0.109, 1.04
No. of reflections	3095
No. of parameters	197
No. of restraints	13
H-atom treatment	H-atom parameters constrained
$\Delta\rho_{max}$, $\Delta\rho_{min}$ (e Å^{-3})	1.23, -1.19

Computer programs: *APEX2* v2009.3.0 (Bruker-AXS, 2009), *SAINT* 7.46A (Bruker-AXS, 2009), *SHELXS97* (Sheldrick, 2008), *SHELXL97* (Sheldrick, 2008), Bruker *SHELXTL*.

E1.10 Rate Law for NFBS Reduction Catalyzed by 1.1



This experiment was carried out under an N_2 atmosphere. A 0.167 M solution of NFBS in CD_3CN was prepared in a vial and sealed with a septum cap. In five separate septum-sealed screw cap NMR tubes, solutions of **1.1** (1.25, 2.5, 3.75, 5.0, and 10 μmol) and 3-nitro-fluorobenzene (0.019–0.038 μmol) in 0.200 mL CD_3CN were prepared in the following way:

1.25 and 2.50 μmol reactions: A stock solution of 3.8 mg **1.1** (5.0 μmol) and 8.0 μL of 3-nitro-fluorobenzene (0.076 μmol) in 0.400 mL CD_3CN was prepared. To one NMR tube (1.25 μmol **1.1**) was added 0.100 mL of the stock solution and 0.100 mL pure CD_3CN. To the other tube (2.5 μmol **1.1**) was added 0.200 mL of the stock solution.

3.75 and 5.0 μmol reactions: A stock solution of 7.6 mg **1.1** (10 μmol) in 0.400 mL CD_3CN was prepared. To one NMR tube (3.75 μmol **1.1**) was added 0.150 mL of the stock solution, 4.0 μL (0.038 μmol) 3-nitrofluorobenzene, and 0.050 mL pure CD_3CN. To the other tube (5.0 μmol **1.1**) was added 0.200 mL of the stock solution and 4.0 μL (0.038 μmol) 3-nitrofluorobenzene.

10 *μmol* reaction: A solution of 7.6 mg (10 μmol) **1.1** and and 4.0 μL (0.038 μmol) 3-nitrofluorobenzene in 0.200 mL CD_3CN was prepared in an NMR tube.

For each reaction, 0.300 mL of the NFBS solution was added to the NMR tube via syringe, the sample was immediately inserted into the NMR probe pre-heated at 50 °C, and the consumption of NFBS was followed by integration of the ^{19}F NMR spectra with 3-nitro-fluorobenzene. The reactions were followed over 15-30% conversion, except the last one (10.0 μmol **1.1**), which was followed through 90% conversion (>3 half-lives). The plot of ln[NFBS] vs. time shows excellent linearity throughout, indicating an overall reaction order of unity. Pseudo-first-order analysis was therefore applied to determine the dependence of k_{obs} on [**1.1**]. A plot of ln(k_{obs}) vs ln[**1.1**] reveals a first order dependence on [**1.1**]. The

overall rate law is therefore *rate* = *k*[**1.1**][NFBS]. A plot of k_{obs} vs. [**1.1**] revealed a slope of 1.26×10^{-2} $M^{-1}s^{-1}$, which is the value of *k*. See Figure E1.8 for kinetic plots.

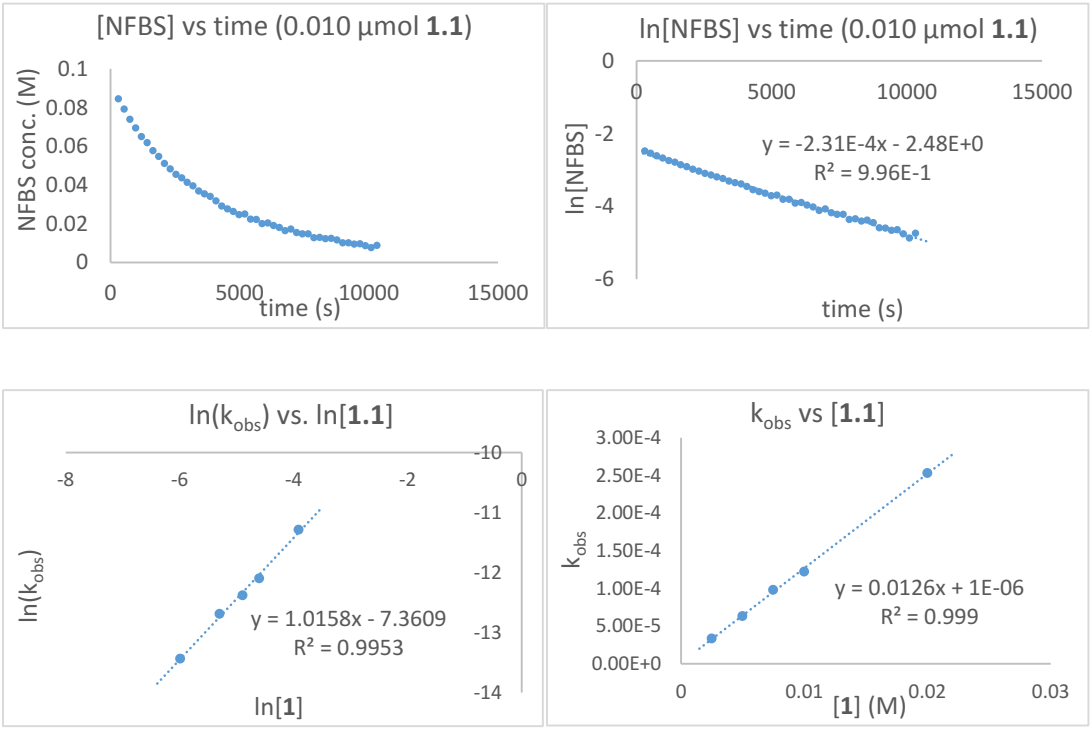
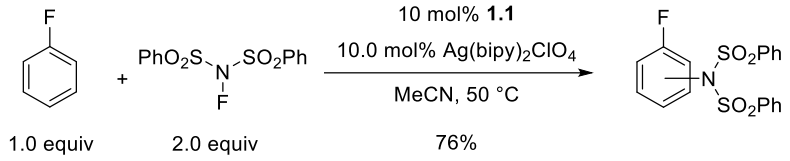


Figure E1.8. Kinetic data for determination of the rate law for NFBS reduction catalyzed by **1.1**

E1.11 Rate Law of Imidation Catalyzed by 1.1 and $Ag(bipy)_2ClO_4$

Fluorobenzene was chosen as the substrate for the determination of the rate law of the catalytic imidation reaction because fluorobenzene is a competent substrate for the imidation reaction (81% yield, Chapter 1, Table 1.1), and the consumption of fluorobenzene and appearance of the products could be followed concurrently with the consumption of NFBS by ^{19}F NMR. The data was acquired at 50 °C because this temperature was found to facilitate a more convenient rate of reaction for kinetic analysis. To justify the acquisition of kinetic data with fluorobenzene as a substrate at a reaction temperature of 50 °C, we have performed the catalytic imidation on fluorobenzene under these conditions, and found no substantial diminution in yield.

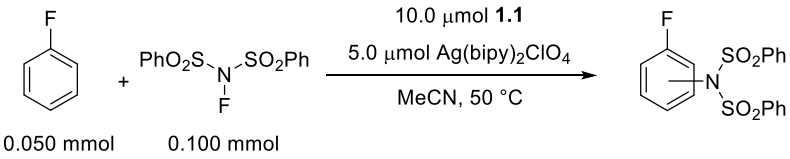
Imidation of fluorobenzene at 50 °C



Under N_2 atmosphere, an oven-dried 4 mL vial was charged with fluorobenzene (9.3 µL, 0.10 mmol, 1.0 equiv), palladium complex **1.1** (7.6 mg, 10 µmol, 10 mol%), $Ag(bipy)_2ClO_4$ (5.2 mg, 10 µmol, 10 mol%), and NFBS (63.0 mg, 0.20 mmol, 2.0 equiv). Acetonitrile (0.500 mL, c = 0.20 M) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 12 h. Subsequently, 4-nitrofluorobenzene (2.0 µL, 0.0188 mmol) was added as an internal standard and the yield of the imidated products was measured by ^{19}F NMR.

***para* (–108.7 ppm)**	***meta* (–110.0 ppm)**	***ortho* (–115.2 ppm)**	**Total**
30%	12%	34%	76%

Time course of the reaction



This experiment was carried out under an N_2 atmosphere. A 0.333 M solution of NFBS in CD_3CN was prepared in a vial and sealed with a septum cap. In a septum-sealed screw cap NMR tube was prepared a solution containing **1.1** (7.6 mg, 10 µmol), $Ag(bipy)_2ClO_4$ (2.6 mg, 5.0 µmol), fluorobenzene (4.7 µL, 0.050 mmol), and 3-nitro-fluorobenzene (2.0 µL, 0.019 µmol) in 0.200 mL CD_3CN. With a syringe, 0.300 mL of the NFBS solution was added to the NMR tube, the sample was immediately inserted into the NMR probe pre-heated to 50 °C, and the consumption of NFBS and fluorobenzene were followed over 4.5 h by measuring against 3-nitro-fluorobenzene by ^{19}F NMR. The consumption of NFBS follows clean

first-order kinetics through ca. 95% conversion (>4 half-lifes, Figure E1.9).

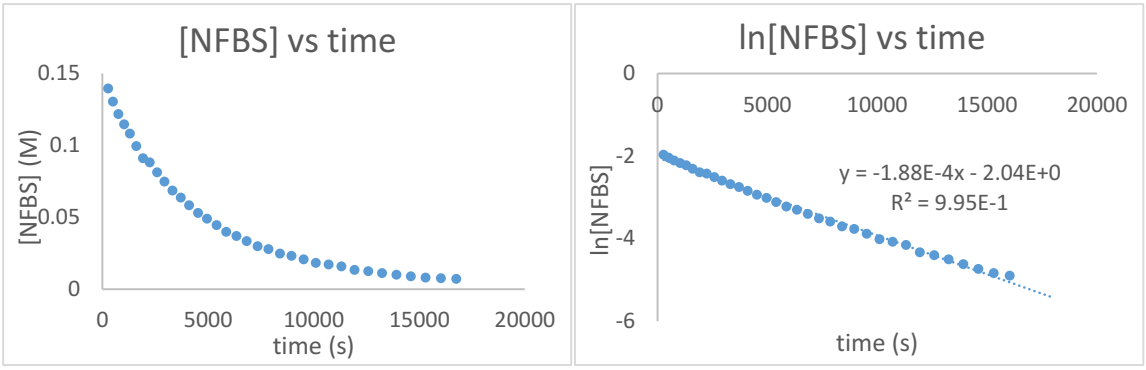


Figure E1.9. Time course of NFBS consumption in the imidation of fluorobenzene

The consumption of fluorobenzene followed first-order kinetics only through ca. 70% conversion (**Figure E1.10**).

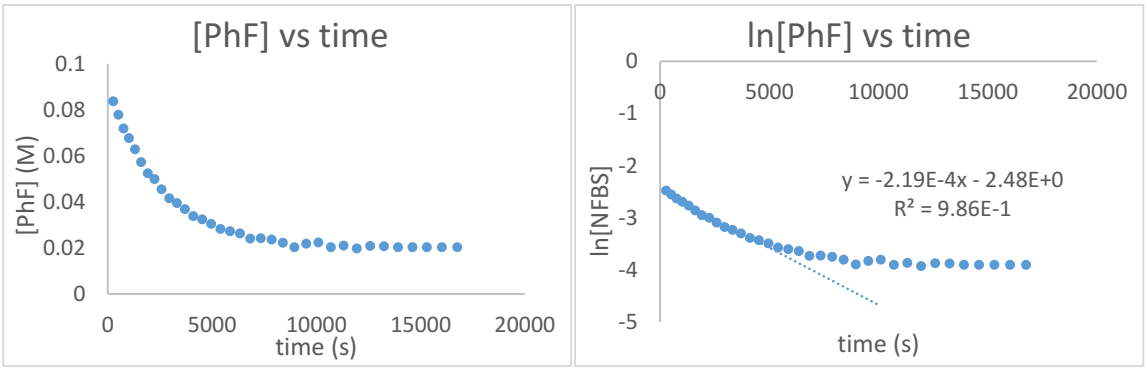
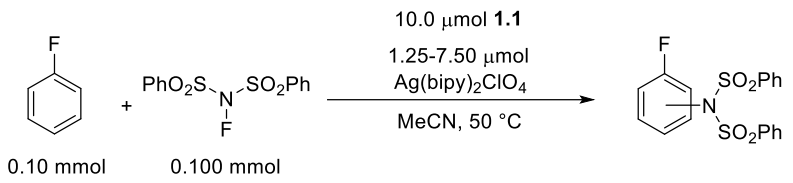


Figure E1.10. Time course of fluorobenzene consumption in the imidation of fluorobenzene.

This observation can be explained considering the presence of a competitive, nonproductive NFBS reduction pathway. This nonproductive pathway causes NFBS to be expended before the arene substrate, which prematurely slows rate of fluorobenzene consumption. Since the consumption of fluorobenzene was followed only for the first ca. 20% for the purpose of rate law determination, pseudo first-order kinetic analysis is still appropriate.

Determination of order in $Ag(bipy)_2ClO_4$



This experiment was carried out under an N_2 atmosphere. A 0.333 M solution of NFBS in CD_3CN was prepared in a vial and sealed with a septum cap. In five separate septum-sealed screw cap NMR tubes, solutions containing **1.1** (10.0 μmol), $Ag(bipy)_2ClO_4$ (1.3, 2.6, 5.0, 7.5 μmol), fluorobenzene (0.10 mmol), and 3-nitro-fluorobenzene (0.019 mmol) in 0.200 mL CD_3CN were prepared in the following way. A stock solution containing 22.8 mg **1.1** (0.030 mmol), 27.9 uL fluorobenzene (0.300 mmol), and 6.0 μL 3-nitrofluorobenzene (0.056 mmol) in CD_3CN was prepared. Into four vials were weighed 0.8 mg, 1.6 mg, 3.1 mg, and 4.7 mg $Ag(bipy)_2ClO_4$, respectively. The content of each vial was dissolved in 0.240 mL of the stock solution, and 0.200 mL of this mixture was transferred to an NMR tube. For each reaction, 0.300 mL of the NFBS solution was added to the NMR tube via syringe, the sample was immediately inserted into the NMR probe pre-heated to 50 °C, and the consumption of NFBS and fluorobenzene were followed by ^{19}F NMR, with 3-nitro-fluorobenzene as internal standard. The reactions were followed over ca. 20% conversion, and the results were subjected to pseudo first-order kinetic analysis (Figure E1.11).

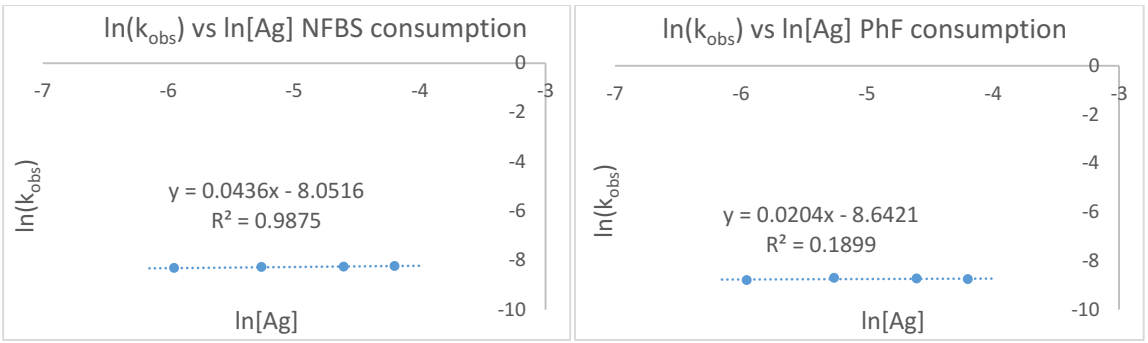


Figure E1.11. Determination of order in $Ag(bipy)_2ClO_4$

Determination of order in arene substrate

This experiment was carried out under an N_2 atmosphere. A 0.333 M solution of NFBS in CD_3CN was prepared in a vial and sealed with a septum cap. In five separate septum-sealed screw cap NMR tubes were prepared solutions containing **1.1** (7.6 mg, 10 μmol), $Ag(bipy)_2ClO_4$ (1.3 mg, 2.5 μmol), and 3-nitro-fluorobenzene (2.0 μL, 0.019 μmol) in 0.200 mL CD_3CN. To each tube was then added 4.7, 9.4, 14.1, 18.8, and 27.9 μL fluorobenzene (0.050, 0.10, 0.150, 0.200, and 0.300 mmol, respectively). For each reaction, 0.300 mL of the NFBS solution was added to the NMR tube via syringe, the sample was immediately inserted into the NMR probe pre-heated to 50 °C, and the consumption of NFBS was followed by ^{19}F NMR, with 3-nitro-fluorobenzene as internal standard. The reactions were followed over ca. 20% conversion, and the results were subjected to pseudo first-order kinetic analysis (Figure E1.12).

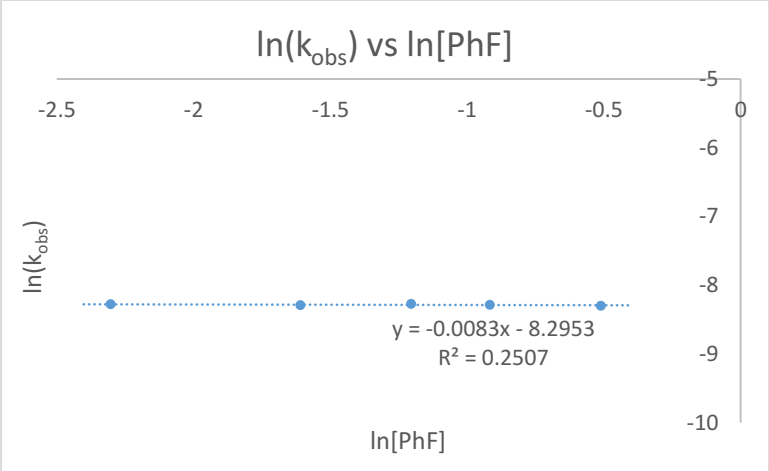
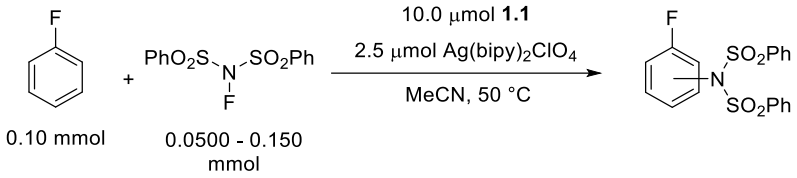


Figure E1.12. Determination of order in fluorobenzene

Determination of order in NFBS



This experiment was carried out under an N_2 atmosphere. A solution of NFBS (0.500 M) in CD_3CN was prepared in a vial and sealed with a septum cap. In five separate septum-sealed screw cap NMR tubes were prepared solutions containing **1.1** (7.6 mg, 10.0 μmol), $Ag(bipy)_2ClO_4$ (1.3 mg, 2.5 μmol), fluorobenzene (9.3 μL, 0.10 mmol), and 3-nitro-fluorobenzene (2.0 μL, 0.019 μmol) in the volume of CD_3CN which would make 0.500 mL after addition of the NFBS solution (see below). The NFBS solution was added to the NMR tube via syringe (0.10 mL, 0.15 mL, 0.20 mL, 0.25 mL, and 0.30 mL). The sample was immediately inserted into the NMR probe pre-heated to 50 °C, and the consumption of fluorobenzene was followed by ^{19}F NMR, with 3-nitro-fluorobenzene as internal standard. The reactions were followed over ca. 20% conversion, and the results were subjected to pseudo first-order kinetic analysis (Figure E1.13).

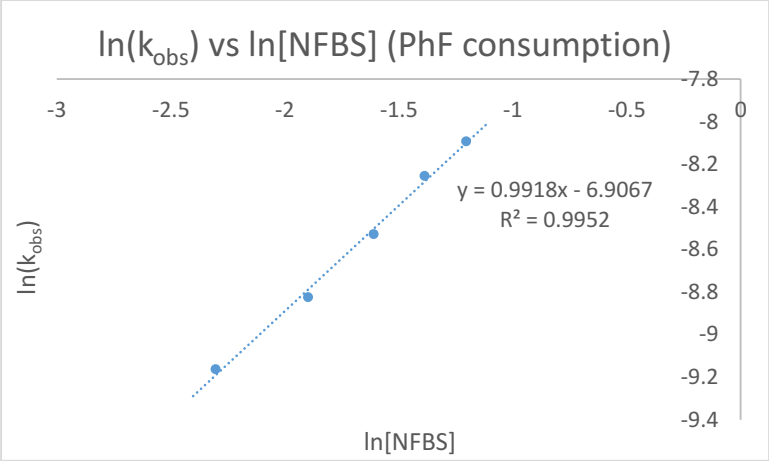
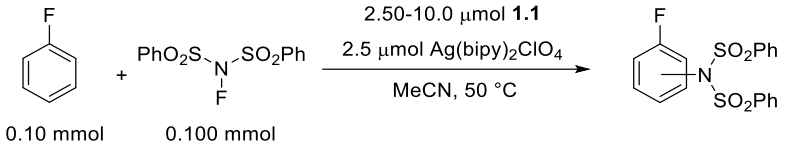


Figure E1.13. Determination of order in NFBS

Determination of order in 1.1



This experiment was carried out under an N_2 atmosphere. A 0.333 M solution of NFBS in CD_3CN was prepared in a vial and sealed with a septum cap. In five separate septum-sealed screw cap NMR tubes, solutions containing **1.1** (2.50, 3.75, 5.00, 7.50, and 10.0 μmol), $Ag(bipy)_2ClO_4$ (1.3 mg, 2.5 μmol), fluorobenzene (9.3 μL, 0.10 mmol), and 3-nitro-fluorobenzene (2.0 μL, 0.019 μmol) in 0.200 mL CD_3CN were prepared in the following way:

*3.75 and 7.5 μmol **1.1**:* Two stock solutions were prepared. Solution A contained 11.4 mg **1.1** (0.0150 mmol) in CD_3CN, and Solution B contained 5.2 mg $Ag(bipy)_2ClO_4$ (0.010 mmol), 37.2 μL fluorobenzene (0.400 mmol), and 8.0 μL 3-nitrofluorobenzene (0.075 mmol) in 0.200 mL CD_3CN. To one NMR tube (3.75 μmol **1.1**) were added 0.075 mL Solution A, 0.050 mL Solution B, and 0.075 mL pure CD_3CN. To another NMR tube (7.5 μmol **1.1**) were added 0.150 mL Solution A and 0.050 mL Solution B.

*2.5 and 5.0 μmol **1.1**:* Two stock solutions were prepared. Solution A contained 7.6 mg **1.1** (0.015 mmol)

in CD_3CN, and Solution B contained 5.2 mg $Ag(bipy)_2ClO_4$ (0.010 mmol), 37.2 μL fluorobenzene (0.400 mmol), and 8.0 μL 3-nitrofluorobenzene (0.075 mmol) in 0.200 mL CD_3CN. To one NMR tube (2.5 μmol **1.1**) were added 0.075 mL Solution A, 0.050 mL Solution B, and 0.075 mL pure CD3CN. To another NMR tube (5.0 μmol **1.1**) were added 0.150 mL Solution A and 0.050 mL Solution B.

*10 μmol **1.1**:* Two stock solutions were prepared. Solution A contained 15.2 mg **1.1** (0.020 mmol) in CD_3CN, and Solution B contained 5.2 mg $Ag(bipy)_2ClO_4$ (0.010 mmol), 37.2 μL fluorobenzene (0.400 mmol), and 8.0 μL 3-nitrofluorobenzene (0.076 mmol) in 0.200 mL CD_3CN. To an NMR tube was added 0.150 mL Solution A and 0.050 mL Solution B.

For each reaction, 0.300 mL of the NFBS solution was added to the NMR tube via syringe, the sample was immediately inserted into the NMR probe pre-heated to 50 °C, and the consumption of NFBS and fluorobenzene were followed by by ^{19}F NMR, with 3-nitro-fluorobenzene as internal standard. The reactions were followed over ca. 20% conversion, and the results were subjected to pseudo first-order kinetic analysis.

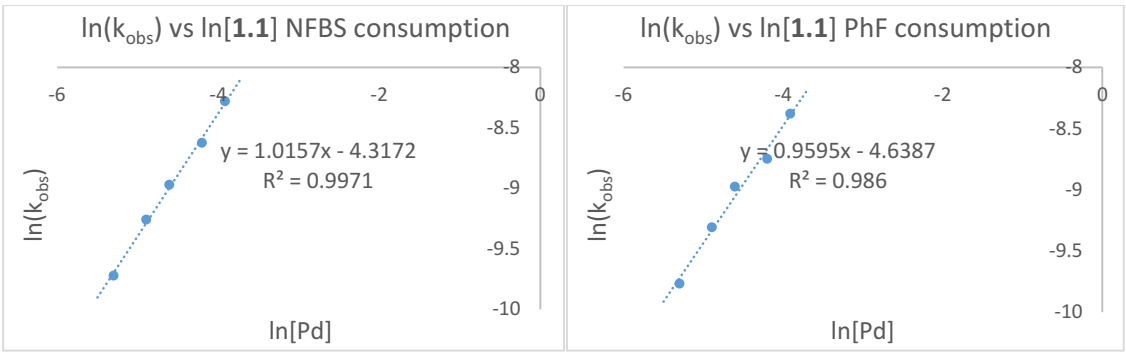


Figure E1.14. Determination of order in **1.1**

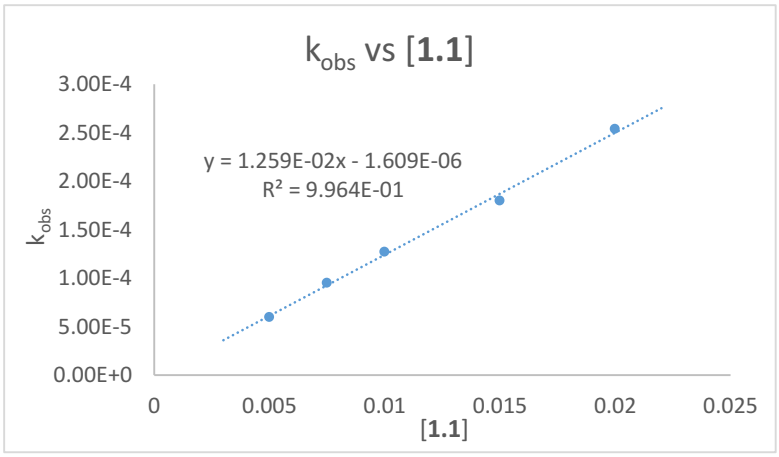
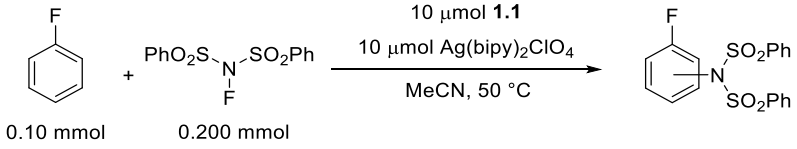


Figure E1.15. Determination of the second-order rate constant

E1.12 Determination of the Resting State



Under an N_2 atmosphere, into a vial (A) a solution of **1.1** (15.6 mg, 0.204 mmol) and 1,2-dichloroethane (8.0 μL, 0.10 mmol) in CD_3CN (1.000 mL) was prepared. In a separate vial (B) were weighed NFBS (63.0 mg, 0.200 mmol, 2.00 equiv) and $Ag(bipy)_2ClO_4$ (5.2 mg, 0.010 mmol, 10 mol%). The contents of vial B were dissolved in half of the solution in vial A (0.500 mL), and fluorobenzene (9.3 μL, 0.10 mmol) was added to vial B. The contents of each vial was transferred to an NMR tube. The solution from vial A

(containing only **1.1** and 1,2-dichloroethane) was analyzed by ^{1}H NMR, and the actual ratio of complex **1.1**:1,2-dichloroethane was measured to be 0.22:1. The solution from vial B (catalytic imidation reaction) was inserted into an NMR probe pre-heated to 50 °C. After 12 minutes, the conversion was measured to be ca. 31% by ^{19}F NMR. A ^{1}H NMR of the reaction mixture was also recorded, and the actual ratio of complex 1:1,2-dichloroethane was measured to be 0.15:1. Complex **1.1** was therefore found to account for 67% of the palladium-containing species. We attribute the diminution in the amount of **1.1** to decomposition during catalysis.

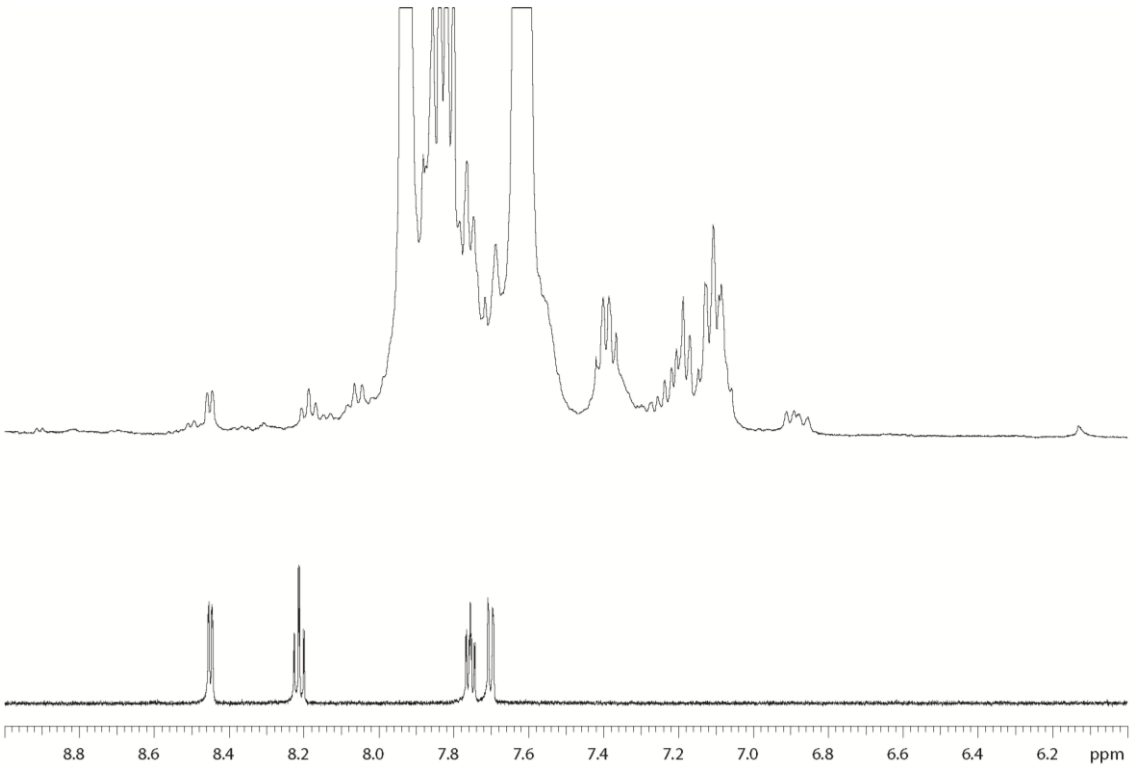


Figure E1.16. *In-situ* ^{1}H NMR of catalytic imidation (top), and pure **1.1** (bottom) (CD_3CN, 50 °C)

E1.13 Role of the Co-catalyst

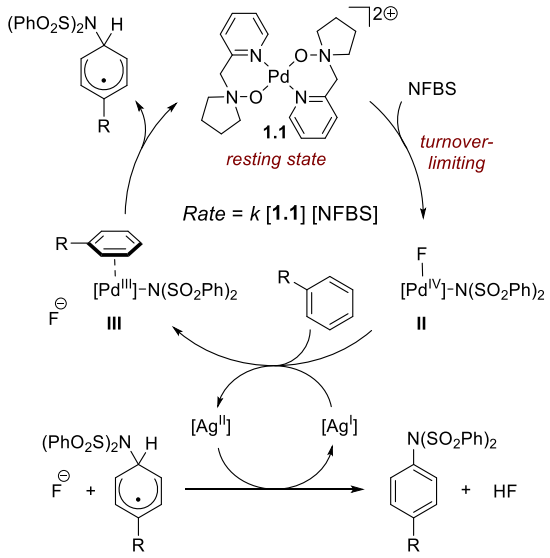
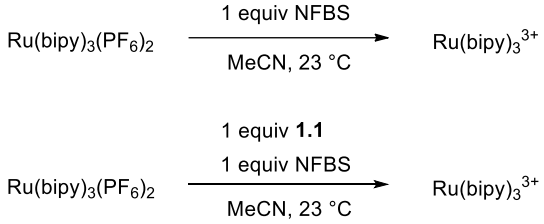


Figure 1.2. Mechanistic hypothesis

The co-catalyst is proposed to be responsible for the reduction of intermediate **II** in order to generate intermediate **III**, the actual C–N bond forming species. Evidence supporting this proposal is outlined below.

Oxidation of $Ru(bipy)_3(PF_6)_2$ mediated by 1.1



Under an N_2 atmosphere, two solutions were prepared in NMR tubes: Solution A contained $Ru(bipy)_3(PF_6)_2$ (5.0 mg, 5.8 μmol) and NFBS (1.8 mg, 5.7 μmol) in CD_3CN (0.80 mL), and Solution B contained **1.1** (4.4 mg, 5.8 μmol), $Ru(bipy)_3(PF_6)_2$ (5.0 mg, 5.8 μmol) and NFBS (1.8 mg, 5.7 μmol) in CD_3CN (0.80 mL). After 10 minutes, each solution was analyzed by ^1H NMR (Figure E1.17a). The spectrum of Solution A showed sharp signals for $Ru(bipy)_3(PF_6)_2$ and NFBS, while Solution B showed sharp signals for **1.1** and NFBS, but dramatically broadened signals for $Ru(bipy)_3(PF_6)_2$. After standing for 4 hours at room temperature, the solutions were analyzed again by ^1H and ^{19}F NMR (Figure E1.17b). The ^1H NMR spectrum of Solution A showed sharp signals for NFBS but broadened signals for $Ru(bipy)_2(PF_6)_2$, and the ^{19}F NMR of Solution A showed only 9% NFBS consumption. The ^1H NMR spectrum of Solution B showed no sign of $Ru(bipy)_3(PF_6)_2$ (Figure E1.17), and the ^{19}F NMR of solution B showed 61% NFBS conversion.

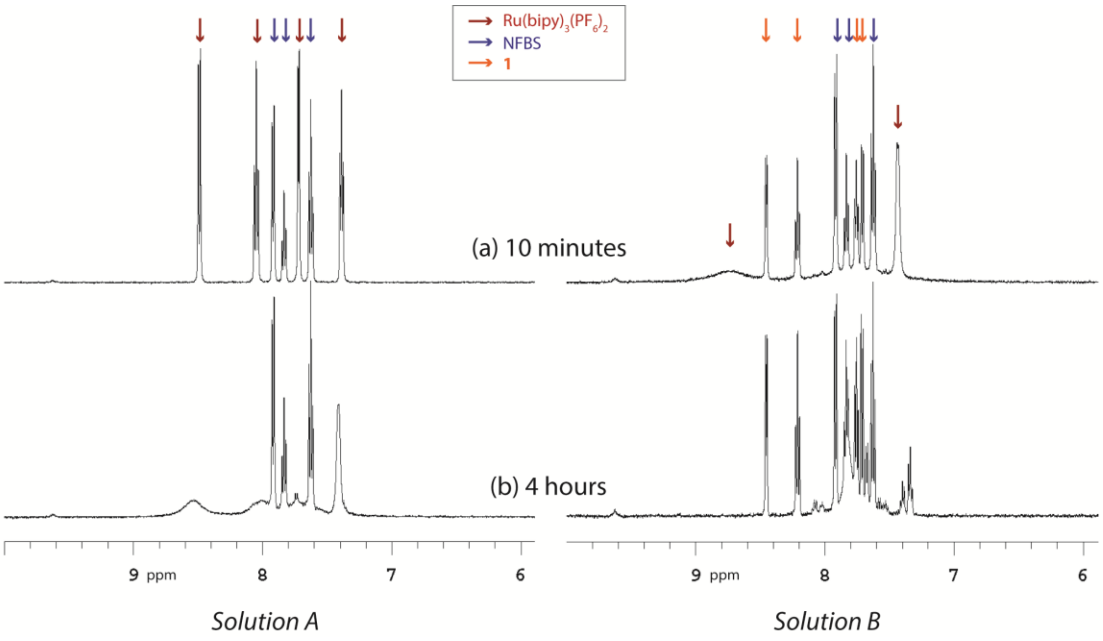


Figure E1.17. ^{1}H NMR spectra of Solution A (left) and Solution B (right) after 10 minutes (a, top) and 4 hours (b, bottom)

The broadening of the signals due to $Ru(bipy)_3^{2+}$ is attributed to partial oxidation to $Ru(bipy)_3^{3+}$, with rapid redox exchange between the Ru(II) and Ru(III) species causing the broadening. This interpretation is supported by low temperature NMR of Solution A after 4 hours of standing at room temperature, which shows the peaks due to $Ru(bipy)_3^{2+}$ sharpening as temperature decreases, consistent with slower exchange at lower temperature (Figure E1.18).

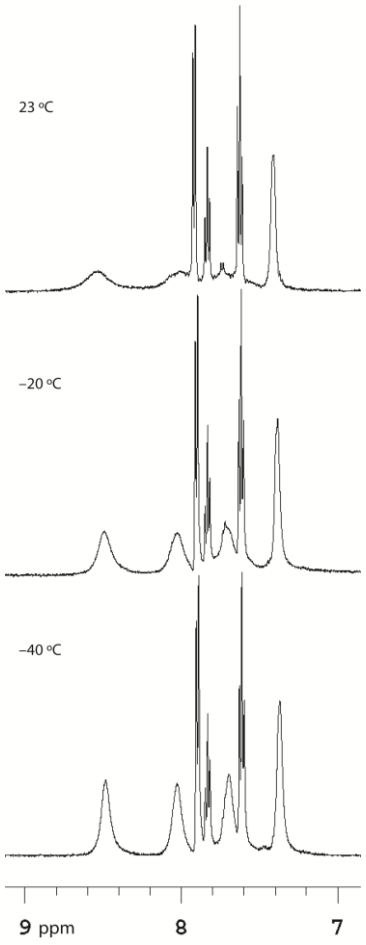


Figure E1.18. ^{1}H NMR peak broadness at 23 °C, –20 °C, and –40 °C (CD_3CN, 23 °C)

EPR spectroscopy provides evidence for the formation of $Ru(bipy)_3^{3+}$ in Solution B. After 5 hours, Solution B was transferred to an EPR tube and frozen in liquid nitrogen. The resulting glass was analyzed by EPR spectroscopy along with a sample containing pure $Ru(bipy)_3(PF_6)_3$, prepared according to a literature procedure.[4] The EPR spectrum of Solution B (Figure E1.19) shows a paramagnetic resonance assignable to $Ru(bipy)_3^{3+}$, along with a partially overlapping second resonance (possibly a Pd(III) species generated upon oxidation of $Ru(bipy)_3^{2+}$).

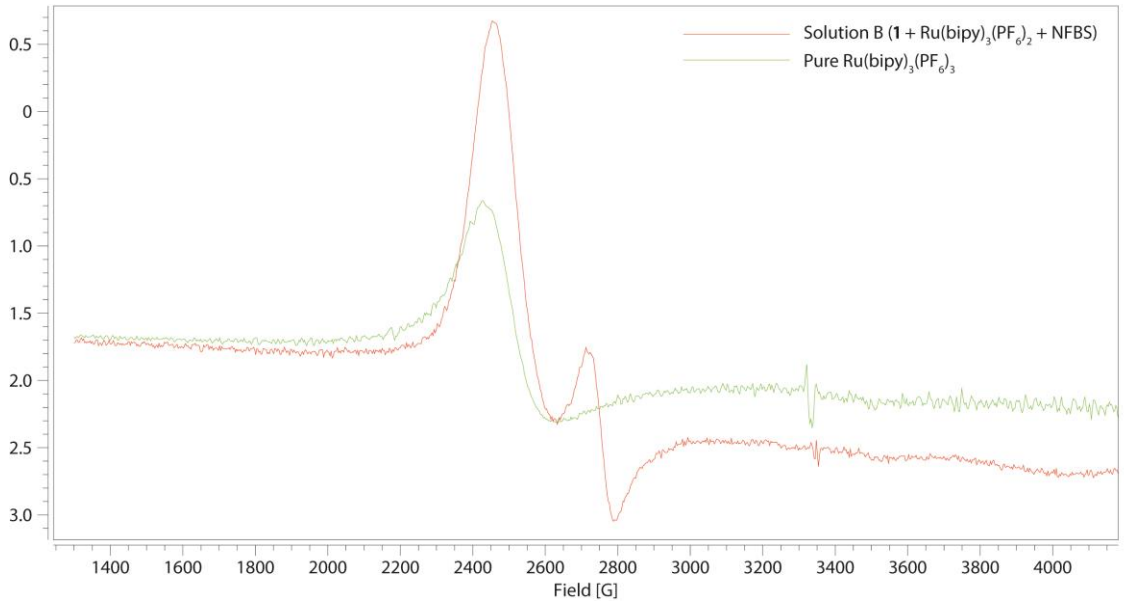


Figure E1.19. EPR spectra of Solution B and pure $Ru(bipy)_3(PF_6)_3$

The data shown in Figure E1.17–Figure E1.19 combined demonstrate an acceleration of the oxidation of $Ru(bipy)_2^{2+}$ to $Ru(bipy)_2^{3+}$ in the presence of **1.1**.

Comparison of rates of NFBS reduction by 1.1, and 1.1 + $Ru(bipy)_3(PF_6)_2$

Under an N_2 atmosphere, two solutions were prepared in NMR tubes: Solution C contained **1.1** (4.4 mg, 5.8 μmol) and NFBS (1.8 mg, 5.7 μmol) in CD_3CN (0.60 mL), and Solution D contained **1.1** (4.4 mg, 5.8 μmol), $Ru(bipy)_3(PF_6)_2$ (5.0 mg, 5.8 μmol) and NFBS (1.8 mg, 5.7 μmol) in CD_3CN (0.60 mL). The consumption of NFBS in both solutions was followed by ^{19}F NMR over 26 hours, and the rates were found to be identical (Figure E1.20).

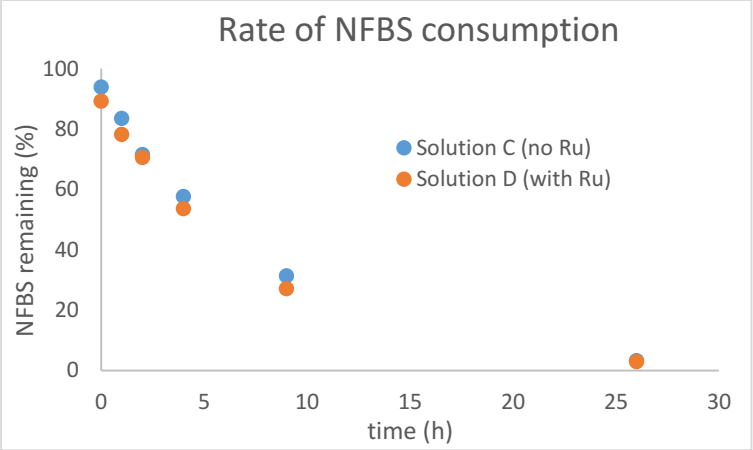


Figure E1.20. Rates of NFBS consumption by $Ru(bipy)_3(PF_6)_2$ vs. by **1.1** + $Ru(bipy)_3(PF_6)_2$

Discussion

The above data indicate the following: (1) NFBS reacts with palladium catalyst **1.1** more rapidly than with $Ru(bipy)_3^{2+}$, (2) $Ru(bipy)_3^{3+}$ forms much more rapidly in the presence of **1.1** and NFBS than with NFBS alone, (3) the rate of NFBS oxidation of $Ru(bipy)_3^{2+}$ mediated by **1.1** is limited by the rate of oxidation of **1.1** by NFBS. These observations combined are consistent with a scenario in which palladium catalyst **1.1** is oxidized by NFBS to give the putative high-valent intermediate **II**, followed by single electron oxidation of $Ru(bipy)_3^{2+}$ by **II** to yield $Ru(bipy)_3^{3+}$ and a Pd(III) intermediate (possibly a progenitor to **III** in Figure 1.2).

Observation of $Ag^{II}(bipy)_2$ in the catalytic imidation reaction

Under an N_2 atmosphere, two solutions were prepared. Solution E contained **1.1** (3.8 mg, 5.0 μmol), $Ag(bipy)_2ClO_4$ (5.2 mg, 10 μmol), NFBS (63.1 mg, 0.200 mmol), and fluorobenzene (9.4 μL, 0.10 mmol) in 0.50 mL MeCN. Solution F contained $Ag(bipy)_2ClO_4$ (5.2 mg, 10 μmol) and NFBS (63.1 mg, 0.200 mmol) in 0.50 mL MeCN. Both solutions were transferred to EPR tubes and were frozen in liquid nitrogen after 1 hour, and the resulting glasses were analyzed by EPR spectroscopy (Figure E1.21). Both spectra show the same signal, assigned to an $Ag(bipy)_2^{2+}$ species.

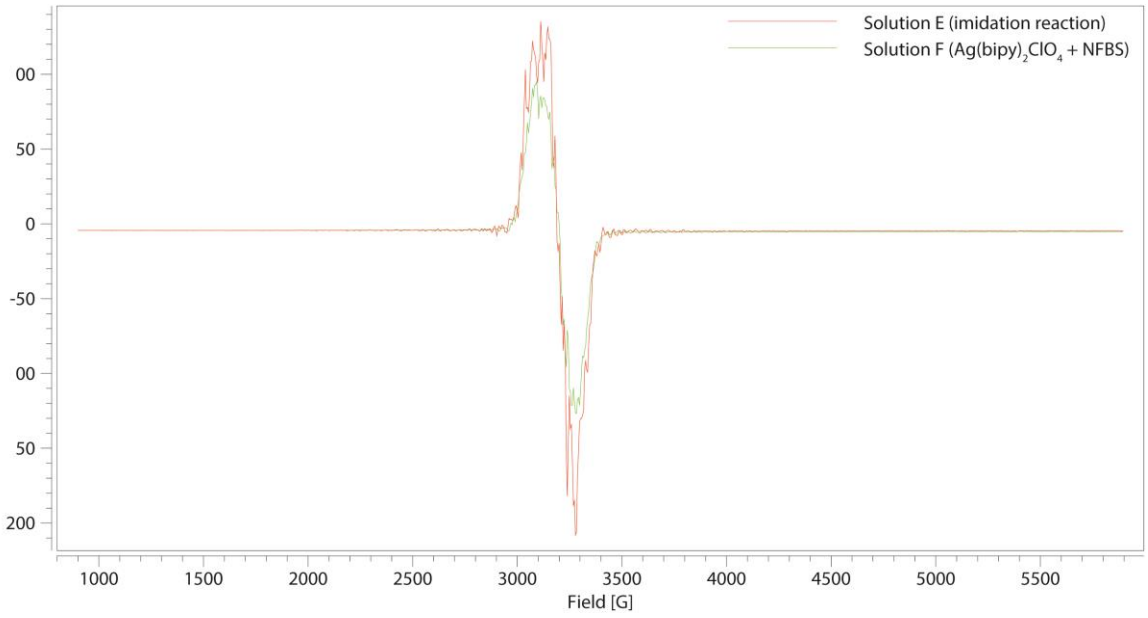
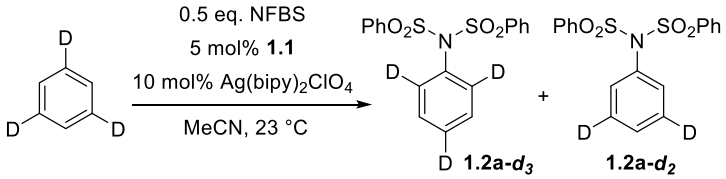


Figure E1.21. EPR spectra of Solutions E and F

The above data demonstrates that an $Ag(bipy)_2^{2+}$ species is present in the catalytic imidation reaction mixture.

E1.14 Competition Kinetic Isotope Effect Experiments

Intramolecular Competition KIE Experiment



Intramolecular KIE: 1.2a-d_3/1.2a-d_2 = 0.80 ± 0.01

Under N_2 atmosphere, an oven-dried 4 mL vial was charged with 1,3,5-trideuterobenzene (89.2 µL, 1.00 mmol, 2.00 equiv), palladium complex **1.1** (19.0 mg, 25.0 µmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (25.8 mg, 50.0 µmol, 10.0 mol%), and NFBS (0.158 g, 0.500 mmol, 1.00 equiv). Acetonitrile (1.25 mL) was added and the reaction mixture was stirred in a sealed vial at 23 °C for 29 h. Subsequently, triethylamine (200 µL) was added and the reaction mixture was concentrated *in vacuo*. The residue was

purified by chromatography on silica gel, eluting with hexanes/EtOAc (4:1 (v/v)), to afford 118.0 mg of the title compound as a colorless solid (0.314 mmol, 63% yield based on NFBS).

R_f = 0.51 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.95 (dd, *J* = 8.8, 1.2 Hz, 4H), 7.66–7.69 (m, 2H), 7.53–7.57 (m, 4H), 7.44–7.47 (m, 0.57H), 7.34–7.38 (m, 1.01H), 7.02–7.05 (m, 1.11H).

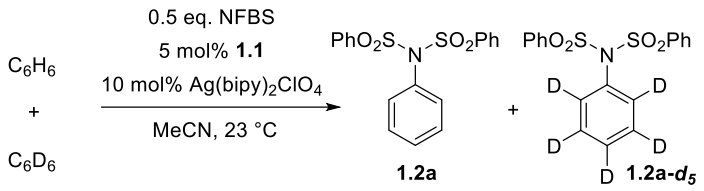
*Ratio of **1.2a-d_3**/**1.2a-d_2**, measured by ^{1}H NMR:* the ^{1}H NMR spectrum was recorded nine times with seven minutes between spectra to assure full relaxation. The peak at 7.03 ppm (the 2- and 6-positions in **2a-d_2**) were integrated against the peak at 7.95 ppm (the 2- and 6- positions in the sulphonyl phenyl groups, set to 4.0H) in each spectrum. The average of these measurements yielded **1.2a-d_3**/**1.2a-d_2** = 0.80, with a standard deviation of 0.0056 (95% confidence interval: ± 0.011).

*Ratio of **1.2a-d_3**/**1.2a-d_2**, measured by mass spectrometry:* the mixture was analyzed three times by GC/MS (EI detector) in single ion mode, counting $M^{+\bullet}$ at m/z = 375 and 376. Because the peak at m/z=376 has a contribution from both **1.2a-d_3** and (M+1) for **1.2a-d_2** (natural abundance: 19.5%), the following formula was necessary to extract the ratio of **1.2a-d_3**/**1.2a-d_2**:

$$\frac{k_H}{k_D} = \frac{[\mathbf{1.2a\text{-}d_3}]}{[\mathbf{1.2a\text{-}d_2}]} = \frac{A_{376} - 0.195 \times A_{375}}{A_{375}}$$

Where A_{376} and A_{375} are the areas for the peaks at m/z = 376 and 375, respectively. Through this treatment, the three measurements yielded **1.2a-d_3**/**1.2a-d_2** = 0.80 (average), with a standard deviation of 0.017 (95% confidence interval: ± 0.034).

Intermolecular Competition KIE Experiment



Intermolecular KIE: 1.2a/1.2a-d_5 = 1.03 ± 0.02

Under N_2 atmosphere, an oven-dried 4 mL vial (A) was charged with palladium complex **1.1** (19.0 mg, 25.0 μmol, 5.00 mol%), $Ag(bipy)_2ClO_4$ (25.8 mg, 50.0 μmol, 10.0 mol%), and NFBS (0.158 g, 0.500 mmol, 1.00 equiv). In a separate vial (B), a solution of C_6H_6 (90.2 μL, 1.00 mmol) and C_6D_6 (88.6 μL, 1.00 mmol) was prepared in 2.50 mL acetonitrile. The contents of vial A were dissolved in 1.25 mL of the solution in vial B, and the reaction mixture was stirred in the sealed vial at 23 °C for 8 h. Subsequently, triethylamine (200 μL) was added and the reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel, eluting with hexanes/EtOAc (4:1 (v/v)), to afford 73.3 mg of the title compound as a colorless solid (0.195 mmol, 39% yield based on NFBS). The remainder of the solution in vial B was subjected to GC/MS analysis, and the actual ratio of C_6H_6 to C_6D_6 was measured.

R_f = 0.51 (hexanes/EtOAc 4:1 (v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 ºC, δ): 7.95 (dd, *J* = 8.8, 1.2 Hz, 4H), 7.66–7.69 (m, 2H), 7.53–7.57 (m, 4H), 7.44–7.47 (m, 0.53H), 7.34–7.38 (m, 1.04H), 7.02–7.05 (m, 1.04H).

*Ratio of **1.2a**/**1.2a-d_5**, measured by ^{1}H NMR:* the ^{1}H NMR spectrum was recorded nine times with seven minutes between spectra to assure full relaxation. The peak at 7.03 ppm (the 2- and 6-positions in **1.2a**) were integrated against the peak at 7.95 ppm (the 2- and 6- positions in the sulphonyl phenyl groups, set to 4.0H) in each spectrum. The average of these measurements, correcting for the measured actual starting ratio of C_6H_6 to C_6D_6, yielded **1.2a**/**1.2a-d_5** = 1.03, with a standard deviation of 0.010 (95% confidence interval: ± 0.020).

*Ratio of **1.2a**/**1.2a-d_5**, measured by mass spectrometry:* the mixture was analyzed three times by GC/MS

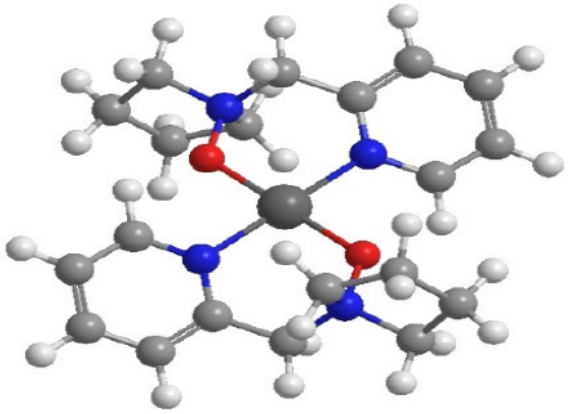
(EI detector) in single ion mode, counting $M^{+\bullet}$ at m/z = 373 and 378. Division of the areas of the resulting peaks yielded **1.2a**/**1.2a-*d*$_5$** = 1.03, with a standard deviation of 0.0038 (95% confidence interval: ± 0.076). Correcting for the measured actual starting ratio of C_6H_6 to C_6D_6, this corresponds to k_H/k_D = 0.99 ± 0.076.

E1.15 DFT Calculations

Density functional theory (DFT) calculations were performed using Gaussian09[5] on the Odyssey cluster at Harvard University. Geometry optimization was carried out using the atomic coordinates from the crystal structure of **1.1** as a starting point. BS I includes SDD quasirelativistic pseudopotentials on Pd (MWB28) with basis sets (Pd: (8s7p6d)/[6s5p3d]) extended by polarization functions (Pd: f, 1.472)[6] and 6-31G(d,p)[7] on H, C, N. All geometry optimizations were performed using the B3PW91 functional with the BS I basis set. Molecular orbitals were generated using an isosurface value of 0.03 with B3PW91/BS I. Images were generated using Chem3D.

Table E1.4. Optimized structure of **1.1** with B3PW91 and Cartesian Coordinates

Atom	X	Y	Z
Pd	5.999378	0.000108	0.000129
O	7.943265	0.526134	0.062967
N	6.342291	-1.852816	0.827158
N	8.91326	-0.358592	0.527153
C	5.344906	-2.479767	1.476335
H	4.399548	-1.951777	1.504105
C	8.659543	-1.744523	0.015094
H	9.584661	-2.314277	0.119394
H	8.436598	-1.62791	-1.049754
C	5.504448	-3.733043	2.053905
H	4.668135	-4.195557	2.566382
C	10.23979	0.190486	0.037144
H	10.984836	-0.592736	0.203955
H	10.144756	0.386886	-1.030801
C	7.552038	-2.45029	0.744641
C	6.738743	-4.363119	1.961056
H	6.899983	-5.343865	2.397368
C	9.03959	-0.244825	2.030555
H	9.637431	-1.098483	2.364786
H	8.039567	-0.310526	2.458308
C	7.774736	-3.70504	1.301551
H	8.753386	-4.165735	1.214057
C	9.750721	1.091741	2.252214
H	10.440573	1.010404	3.094488
H	9.031599	1.876081	2.491626
C	10.482564	1.40646	0.922526
H	10.075292	2.306766	0.461018
H	11.554128	1.561904	1.06216
O	4.055564	-0.526119	-0.062922
N	5.656352	1.853038	-0.826886
N	3.085538	0.35851	-0.527216
C	6.6537	2.480106	-1.47601
C	3.339029	1.744447	-0.015062
C	6.49406	3.733385	-2.05355
C	1.759016	-0.190761	-0.037405
C	4.446532	2.450378	-0.744452



Atom	X	Y	Z
C	5.259697	4.363332	-1.960754
C	2.95942	0.244798	-2.030643
C	4.223733	3.705119	-1.301341
C	2.248429	-1.091817	-2.252473
C	1.516529	-1.406731	-0.922865
H	7.599111	1.952212	-1.503755
H	2.413855	2.314095	-0.119451
H	3.561863	1.627823	1.049809
H	7.330353	4.195998	-2.56597
H	1.013898	0.592376	-0.204295
H	1.85393	-0.387187	1.030546
H	5.098374	5.344066	-2.397061
H	2.361554	1.098422	-2.364916
H	3.959494	0.310608	-2.458258
H	3.245019	4.165691	-1.213924
H	1.558621	-1.010462	-3.094782
H	2.967636	-1.876068	-2.491919
H	1.923926	-2.306985	-0.461364
H	0.445004	-1.562361	-1.0626

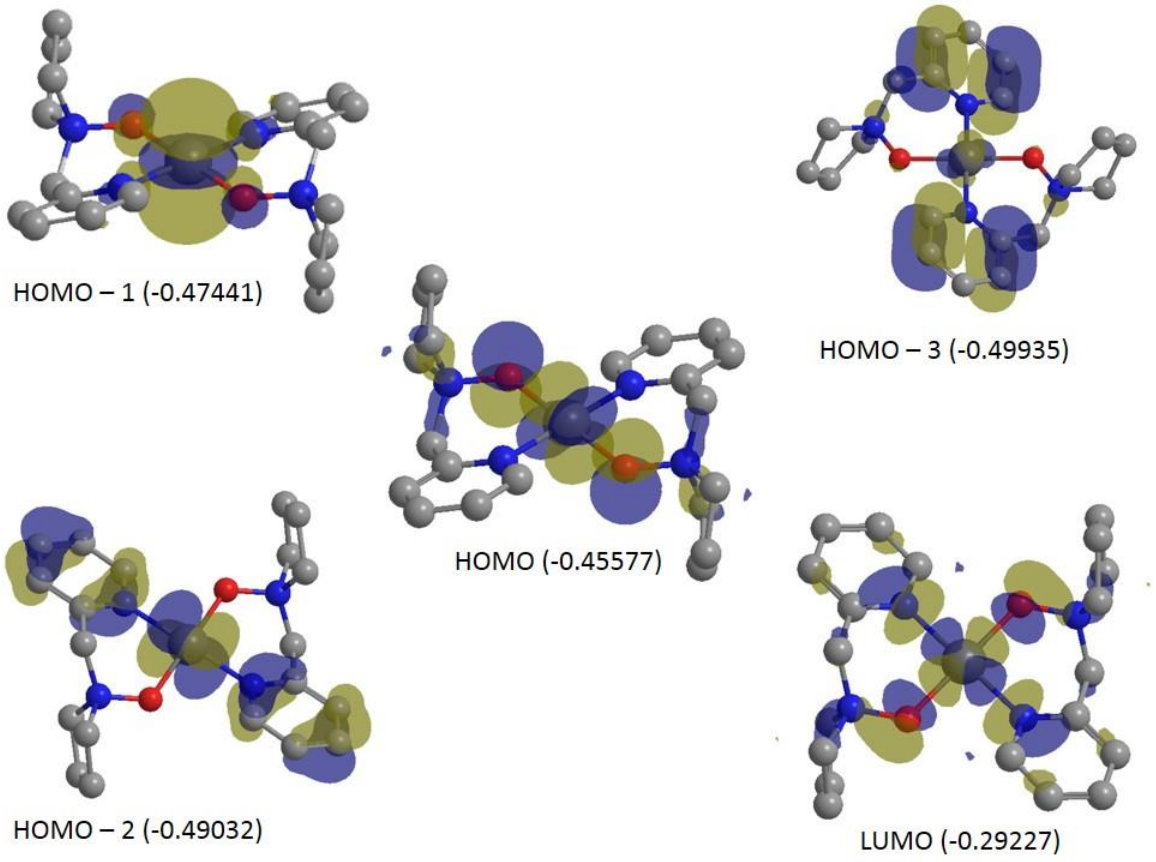


Figure E1.22. Valence orbitals and LUMO of **1.1** with energies in Hartrees

E1.16 References:

1 Still, W. C., Kahn, M. & Mitra, A. Rapid Chromatographic Technique for Preparative Separations with Moderate Resolution. *The Journal of Organic Chemistry* **43**, 2923-2925, doi:10.1021/jo00408a041 (1978).

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3 Sanders, E. B., Secor, H. V. & Seeman, J. I. Use of α-Cyano Amines for the Regiospecific Synthesis of Multisubstituted Pyridines. Preparation of Nicotine Analogs. *The Journal of Organic Chemistry* **43**, 324-330, doi:10.1021/jo00396a032 (1978).

4 Biner, M., Buergi, H. B., Ludi, A. & Roehr, C. Crystal and Molecular Structures of $[Ru(bpy)_3](PF_6)_3$ and $[Ru(bpy)_3](PF_6)_2$ at 105 K. *Journal of the American Chemical Society* **114**, 5197-5203, doi:10.1021/ja00039a034 (1992).

5 Gaussian 09 (Gaussian, Inc., Wallingford, CT, USA, 2009).

6 Andrae, D., Häußermann, U., Dolg, M., Stoll, H. & Preuß, H. Energy-adjusted ab initio Pseudopotentials for the Second and Third Row Transition Elements. *Theoret. Chim. Acta* **77**, 123-141, doi:10.1007/bf01114537.

7 Hariharan, P. C. & Pople, J. A. The Influence of Polarization Functions on Molecular Orbital Hydrogenation Energies. *Theoret. Chim. Acta* **28**, 213-222, doi:10.1007/BF00533485 (1973).

Chapter E2: Experimental Methods and Data for Chapter 2

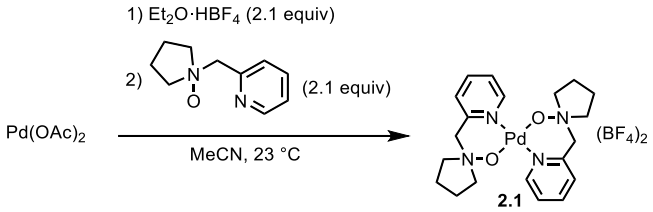
E2.1 Materials and Methods

All air- and moisture-insensitive reactions were carried out under an ambient atmosphere, magnetically stirred, and monitored by thin layer chromatography (TLC) using EMD TLC plates pre-coated with 250 μm thickness silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. Flash chromatography was performed on Dynamic Adsorbents Silica Gel 40–63 μm particle size using a forced flow of eluent at 0.3–0.5 bar pressure.[1] All air- and moisture-sensitive manipulations were performed using oven-dried glassware, including standard Schlenk and glovebox techniques under an atmosphere of nitrogen. Acetonitrile and acetonitrile-d_3 were dried over P_2O_5 and vacuum-distilled. MeOH was degassed at –30 ºC under dynamic vacuum (10^{-4} Torr) for one hour and stored over 3Å sieves. All chemicals were used as received. All deuterated solvents were purchased from Cambridge Isotope Laboratories. NMR spectra were recorded on either a Varian Unity/Inova 600 spectrometer operating at 600 MHz for ^{1}H acquisitions, a Varian Unity/Inova 500 spectrometer operating at 500 MHz and 125 MHz for ^{1}H and ^{13}C acquisitions, respectively, or Varian Mercury 400 spectrometer operating at 375 MHz and 101 MHz for ^{19}F and ^{13}C acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (^{1}H: $CDCl_3$, δ 7.26; $(CD_3)_2SO$, δ 2.50; $(CD_3)_2CO$, δ 2.05; CD_3CN, δ 1.94), (^{13}C: $CDCl_3$, δ 77.16; $(CD_3)_2SO$, δ 39.52; $(CD_3)_2CO$, δ 29.84; CD_3CN, δ 1.32),[2] or added 3-nitrofluorobenzene (–112.0 ppm) for ^{19}F spectra. Signals are listed in ppm, and multiplicity identified as s = singlet, br = broad, d = doublet, t = triplet, q = quartet, quin = quintet, sep = septet, m = multiplet; coupling constants in Hz; integration. High-resolution mass spectra were obtained using an Agilent ESI-TOF (6210) mass spectrometer or a Bruker q-TOF Maxis Impact mass spectrometer. Concentration under reduced pressure was performed by rotary evaporation at 25–30 ºC at appropriate pressure. Purified compounds were further dried under high vacuum (0.01–0.05 Torr). Yields refer to purified and spectroscopically pure

compounds, unless otherwise noted.

E2.2 Procedure for Preparation of Complex 2.1

Palladium complex 2.1



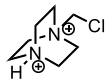
A flame-dried, 250 mL 2-neck flask under nitrogen was charged with $Pd(OAc)_2$ (5.00 g, 22.3 mmol, 1.00 equiv), and the flask was evacuated and refilled with N_2. Through a septum was added dry acetonitrile (50 mL, Aldrich Sure/Seal™), followed by $Et_2O{\cdot}HBF_4$ (6.4 mL, 47. mmol, 2.1 equiv). The resulting suspension was stirred at 23 °C for 30 min, after which 1-(pyridine-2-ylmethyl)pyrrolidine 1-oxide (8.334 g, 46.77 mmol, 2.10 equiv) was added as a solution in dry acetonitrile (40 mL, Aldrich Sure/Seal™). The resulting mixture was stirred for 1 hr, after which the reaction mixture was diluted with 100 mL acetonitrile to dissolve the precipitated product, and the solution was filtered through celite and then concentrated by rotary evaporation. The resulting brown solid was triturated with dichloromethane (40 mL) by sonication. The product was collected by filtration on a glass frit, then washed with dichloromethane (40 mL) followed by tetrahydrofuran (40 mL), then allowed to dry on the frit with applied suction to yield 10.61 g of **2.1** as a yellow powder (16.66 mmol, 75%).

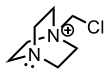
NMR Spectroscopy: ^{1}H NMR (600 MHz, DMSO, 23 °C, δ): 8.50 (dd, J = 5.8, 1.2 Hz, 2H), 8.30 (ddd, J = 7.7, 7.7, 1.5 Hz, 2H), 7.86 (ddd, J = 7.5, 5.8, 1.4 Hz, 2H), 7.79 (dd, J = 7.8, 1.2 Hz, 2H), 5.35 (s, 4H), 3.56–3.46 (m, 4H), 3.45–3.36 (m, 4H), 2.26–2.15 (m, 4H), 2.10–1.99 (m, 4H). ^{13}C NMR (125 MHz, DMSO, 23 °C, δ): 149.2, 148.2, 142.0, 128.2, 126.5, 70.1, 67.2, 21.3.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{20}H_{28}N_4O_2Pd$ $[M]^{2+}$, 231.0622; found, 231.0632.

Anal. Calcd for $C_{20}H_{28}B_2F_8N_4O_2Pd$: C, 37.74; H, 4.43; N, 8.80. Found: C, 37.83; H, 4.14; N, 9.04.

E2.3 General Considerations for Aromatic C–H TEDAylation Reactions





The Aryl–TEDA products are doubly cationic compounds, and similar cationic compounds are formed as byproducts of the reaction, including H–TEDA^{2+} and TEDA^{+}. Therefore, it is difficult to isolate the Aryl–TEDA products from the reaction mixture. We have found that performing the reaction with an excess (at least five equivalents) of the arene substrate minimizes formation of H–TEDA^{2+} and TEDA^{+} byproducts. Upon reaction completion, evaporation of the solvent, followed by trituration of the residue with CH_2Cl_2/methanol mixtures to remove the excess arene, and the palladium and ruthenium catalysts, results in material that is sufficiently clean for characterization, albeit still contaminated to varying degrees with H–TEDA^{2+} and TEDA^{+}. Therefore, we have performed the Ar–TEDA formation reactions twice for each of the Ar–TEDA products **2.2a-g**: once utilizing the arene as limiting reagent (with yield determined by NMR integration relative to an internal standard), and once with excess arene (for characterization purposes). For Ar–TEDA compounds synthesized through the use of excess arene, yields of Ar–TEDA, H–TEDA^{2+}, and TEDA^{+} are calculated relative to Selectfluor, and were determined via NMR analysis of a known amount of the mixture by integrating against an internal standard.

The Ar–TEDA products may be isolated from H–TEDA^{2+}, and TEDA^{+} by repeated recrystallization. The Ar–TEDA product derived from fluorenone (**2.2f**) was isolated in this way and characterized as a pure compound.

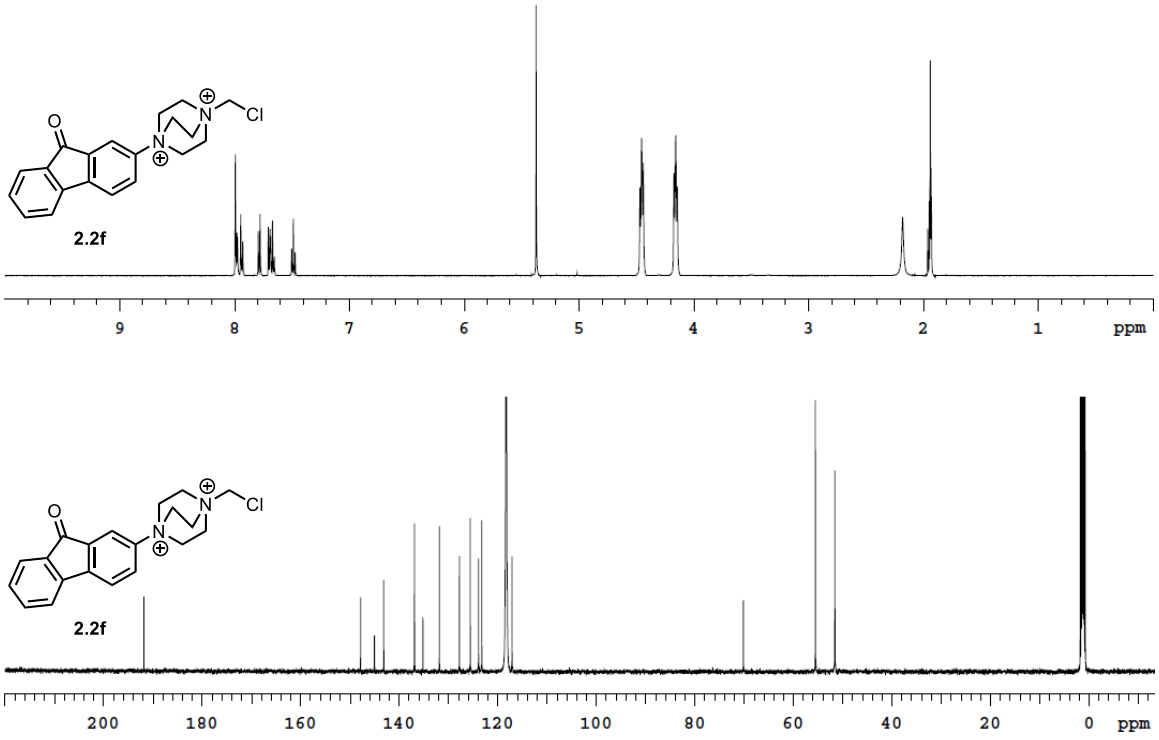
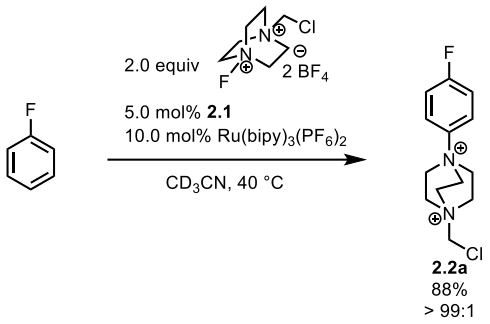


Figure E2.1. ^{1}H and ^{13}C NMR of pure Ar–TEDA **2.2f** (CD_3CN, 23 °C)

E2.4 Procedure for Aromatic C–H TEDAylation Reactions (1 Equiv Arene)

1-(Chloromethyl)-4-(4-fluorophenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2a)



A 4 mL vial was charged with Selectfluor (70.9 mg, 0.200 mmol, 2.00 equiv), **2.1** (3.2 mg, 5.0 µmol, 5.0 mol%), and $Ru(bipy)_3(PF_6)_2$ (8.6 mg, 10. µmol, 10. mol%), and 0.50 mL CD_3CN, and finally fluorobenzene (9.4 µL, 0.10 mmol, 1.0 equiv). The vial was sealed and the mixture stirred at 40 °C for 36 h. The reaction mixture was diluted with 0.25 mL CD_3CN and filtered through a 0.22 µm PVDF syringe

filter, and an additional 0.25 mL CD_3CN was washed through the filter to elute any remaining soluble material. The solution was analyzed by ^{19}F NMR:

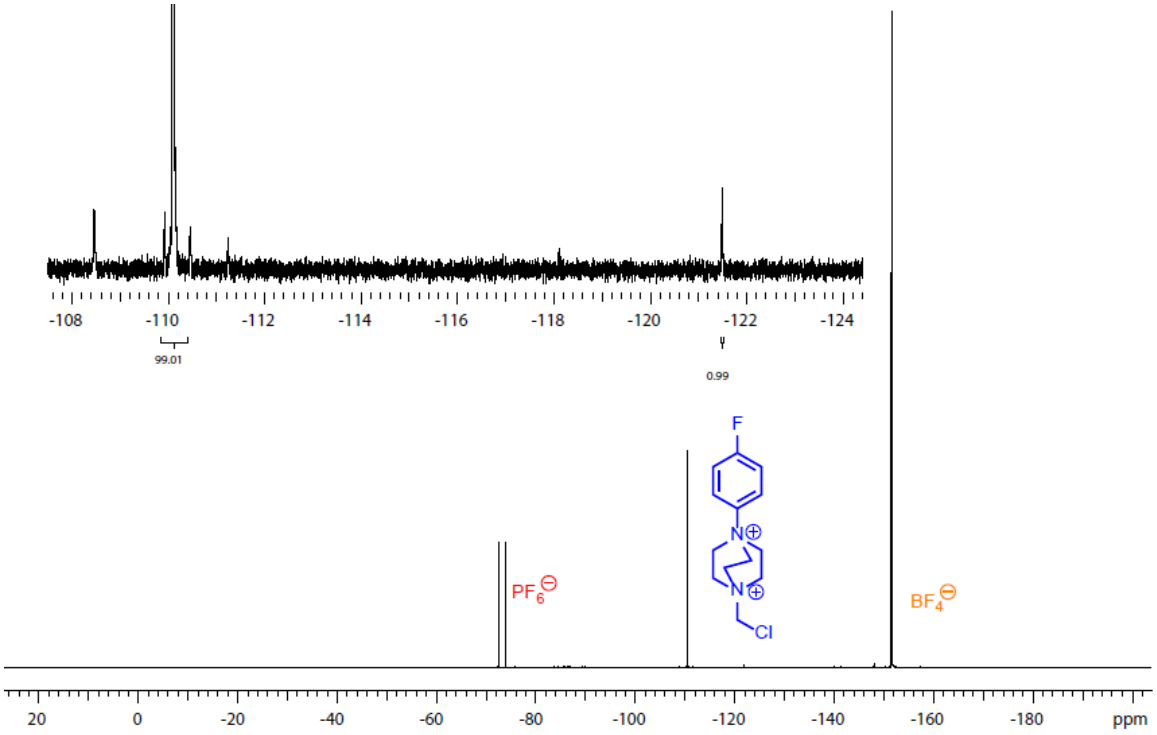


Figure E2.2. ^{19}F NMR evaluation of positional selectivity

Only one significant aryl fluoride peak was observed in ^{19}F NMR, corresponding to the title compound. After 24 scans with a relaxation delay of 20 s, another peak in the aromatic region was observed at –121.5 ppm, at a ratio of 0.99:99.01 relative to the peak corresponding to **2.2a**. The ratio between the Ar–F signal and the rms noise over a 100 Hz range was measured to be 1286 (command 'dsnmax(100)' in VNMR), implying that any other products have a maximum concentration of 0.08% of the title compound. Given that the next largest peak in the aromatic region had an intensity of below 1% of the signal of **2.2a**, and given the magnitude of the noise level, we conclude that the positional selectivity of the TEDAylation reaction of fluorobenzene is >99:1 in favor of *para* substitution.

The product mixture of the reaction to form **2.2a** was analyzed by ^{19}F NMR in several different solvents in

order to rule out coincidental overlap with any peaks corresponding to constitutional isomers of **2.2a**. The analysis was carried out by evaporating the acetonitrile solvent from the reaction mixtures and dissolving the residue in 5:1 CD_3CN:C_6D_6, d_6-DMSO, and d_5-pyridine, respectively. In each of these cases, only one aryl fluoride signal was observed by ^{19}F NMR (Figure E2.3).

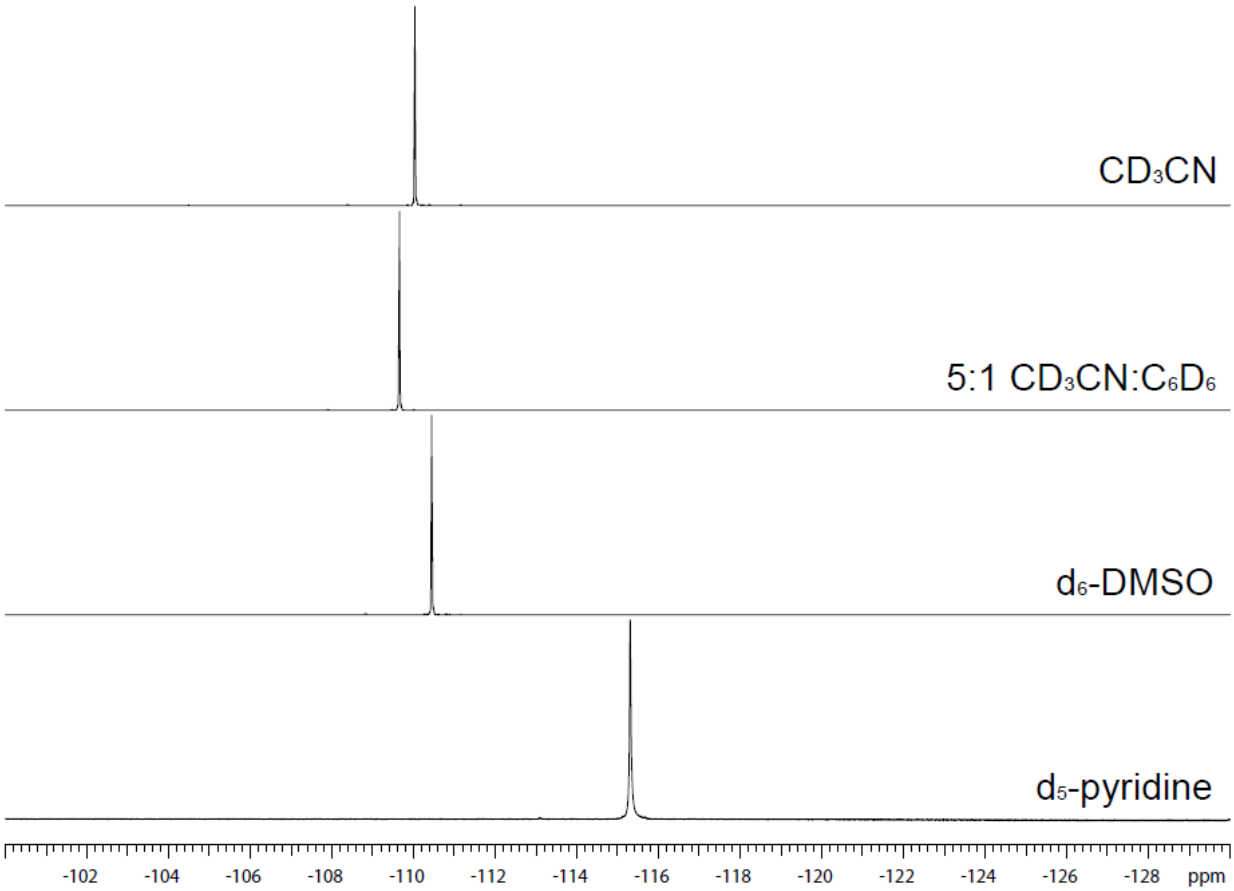
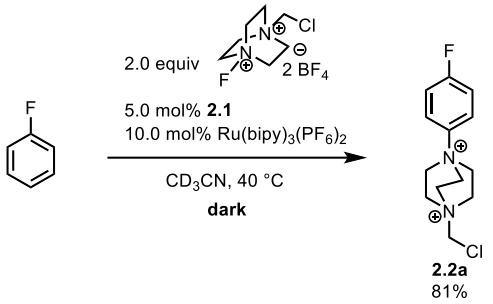


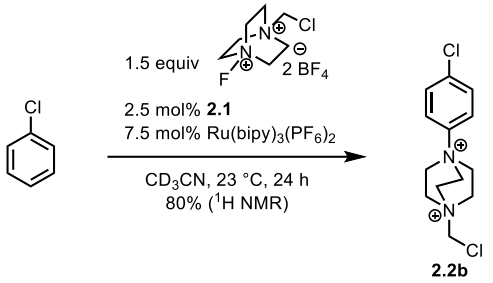
Figure E2.3. ^{19}F NMR evaluation of positional selectivity in different solvents (23 °C)

Formation of 2.2a in the absence of light



A 4 mL vial, completely covered with aluminum foil, was charged with Selectfluor (70.9 mg, 0.200 mmol, 2.00 equiv), **2.1** (3.2 mg, 5.0 µmol, 5.0 mol%), and $Ru(bipy)_3(PF_6)_2$ (8.6 mg, 10 µmol, 10. mol%), and 0.50 mL CD_3CN, and finally fluorobenzene (9.4 µL, 0.10 mmol, 1.0 equiv). The vial was sealed and the mixture stirred in the dark at 40 °C for 24 h, after which 2.0 µL of 3-fluoronitrobenzene was added as an internal standard. The reaction mixture was diluted with 0.50 mL CD_3CN, and passed through a 0.22 µm PVDF syringe filter. The resulting solution was analyzed by ^{19}F NMR, and comparison of the Ar–F peak of the product (–110 ppm) with that of the internal standard (–112 ppm) revealed a yield of 81% of **2.2a**.

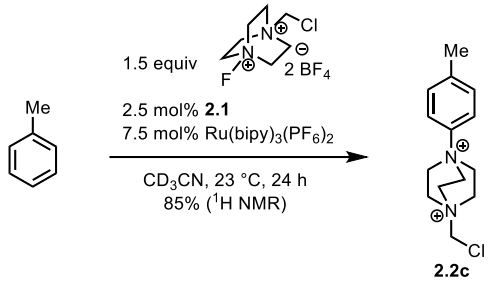
1-(Chloromethyl)-4-(4-chlorophenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2b)



Palladium complex **2.1** (10.3 mg, 16.2 µmol) and $Ru(bipy)_3(PF_6)_2$ (41.9 mg, 48.8 µmol) were dissolved in d_3-acetonitrile (3.25 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (52.2 mg, 0.147 mmol, 1.50 equiv). The stock solution (491. µL) containing **2.1** (2.45 µmol, 2.50 mol%) and $Ru(bipy)_3(PF_6)_2$ (7.37 µmol, 7.50 mol%) was added, followed by chlorobenzene (10.0 µL 98.2 µmol, 1.00 equiv, c = 0.200 M) via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-

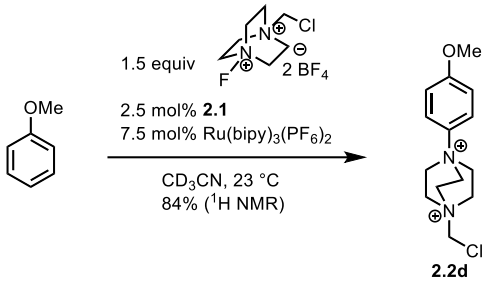
acetonitrile (3.0 mL). The yield of **2.2b** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 µL, 51. µmol) as an internal standard. Comparison of the integral of the peak of **2.2b** at 7.78–7.81 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 80% yield of **2.2b**.

1-(Chloromethyl)-4-(4-methylphenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2c)



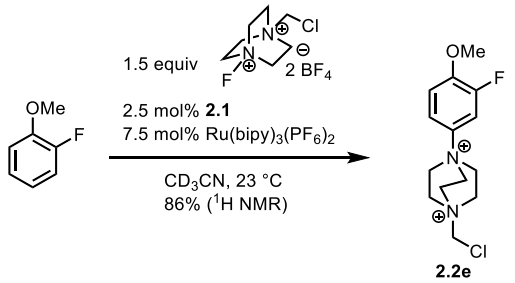
Palladium complex **2.1** (10.3 mg, 16.2 µmol) and $Ru(bipy)_3(PF_6)_2$ (41.9 mg, 48.8 µmol) were dissolved in d_3-acetonitrile (3.25 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (49.9 mg, 0.141 mmol, 1.50 equiv). The stock solution (469. µL) containing **2.1** (2.34 µmol, 2.50 mol%) and $Ru(bipy)_3(PF_6)_2$ (7.04 µmol, 7.50 mol%) was added, followed by toluene (10.0 µL, 93.9 µmol, 1.00 equiv, c = 0.20 M) via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (3.0 mL). The yield of **2.2c** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 µL, 51. µmol) as an internal standard. Comparison of the integral of the peak of **2.2c** at 7.67–7.65 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 85% yield of **2.2c**.

1-(Chloromethyl)-4-(4-methoxyphenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2d)



Palladium complex **2.1** (10.3 mg, 16.2 μmol) and $Ru(bipy)_3(PF_6)_2$ (41.9 mg, 48.8 μmol) were dissolved in d_3-acetonitrile (3.25 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (48.9 mg, 0.138 mmol, 1.50 equiv). The stock solution (460. μL, c = 0.200 M) containing **2.1** (2.34 μmol, 2.50 mol%) and $Ru(bipy)_3(PF_6)_2$ (7.04 μmol, 7.50 mol%) was added, followed by anisole (10.0 μL, 92.0 μmol, 1.00 equiv) via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (3.0 mL). The yield of **2.2d** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **2.2d** at 7.72–7.69 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 84% yield of **2.2d**.

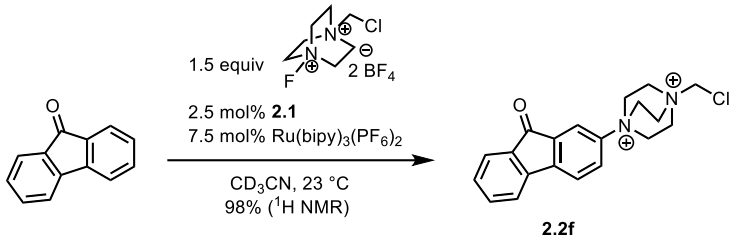
1-(Chloromethyl)-4-(3-fluoro-4-methoxyphenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2e)



Palladium complex **2.1** (11.3 mg, 17.8 μmol) and $Ru(bipy)_3(PF_6)_2$ (45.9 mg, 53.4 μmol) were dissolved in d_3-acetonitrile (3.56 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (47.3 mg, 0.134 mmol, 1.50 equiv). The stock solution (445. μL, c = 0.200 M) containing **2.1** (2.23 μmol, 2.50

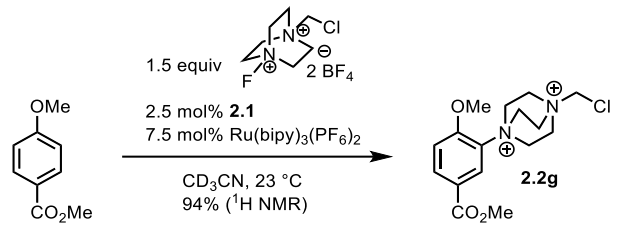
mol%) and $Ru(bipy)_3(PF_6)_2$ (6.68 μmol, 7.50 mol%) was added, followed by 2-fluoroanisole (10.0 μL, 89.0 μmol, 1.00 equiv) via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.5 mL). The yield of **2.2e** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **2.2e** at 7.34 ppm (aromatic C–H, 1H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 86% yield of **2.2e**.

1-(Chloromethyl)-4-(fluorenon-2-yl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2f)



Palladium complex **2.1** (11.3 mg, 17.8 μmol) and $Ru(bipy)_3(PF_6)_2$ (45.9 mg, 53.4 μmol) were dissolved in d_3-acetonitrile (3.56 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (47.3 mg, 0.134 mmol, 1.50 equiv) and fluorenone (16.0 mg, 89.0 μmol, 1.00 equiv). The stock solution (445. μL, c = 0.200 M) containing **2.1** (2.23 μmol, 2.50 mol%) and $Ru(bipy)_3(PF_6)_2$ (6.68 μmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.0 mL). The yield of **2.2f** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **2.2f** at 7.94–7.93 ppm (aromatic C–H, 1H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 98% yield of **2.2f**.

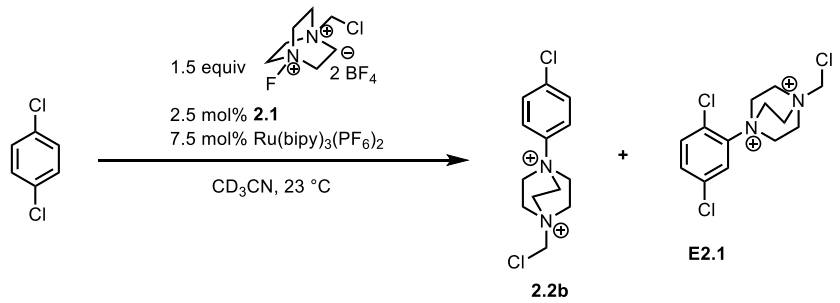
1-(Chloromethyl)-4-(2-methoxy-5-(methoxycarbonyl)phenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2g)



Palladium complex **2.1** (10.3 mg, 16.2 μmol) and $Ru(bipy)_3(PF_6)_2$ (41.9 mg, 48.8 μmol) were dissolved in d_3-acetonitrile (3.25 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (53.1 mg, 0.150 mmol, 1.50 equiv) and methyl 4-methoxybenzoate (16.6 mg, 100. μmol, 1.00 equiv). The stock solution (500. μL, c = 0.200 M) containing **2.1** (2.50 μmol, 2.50 mol%) and $Ru(bipy)_3(PF_6)_2$ (7.50 μmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (3.0 mL).

The yield of **2.2g** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **2.2g** at 7.46 ppm (aromatic C–H, 1H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed a 94% yield of **2.2g**.

1-(Chloromethyl)-4-(4-chlorophenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2b) from 1,4-dichlorobenzene



Palladium complex 2.**1** (11.3 mg, 17.8 μmol) and $Ru(bipy)_3(PF_6)_2$ (45.9 mg, 53.4 μmol) were dissolved in d_3-acetonitrile (3.56 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (47.3 mg, 0.134 mmol, 1.50 equiv) and 1,4-dichlorobenzene (13.1 mg, 89.0 μmol, 1.00 equiv). The stock solution

(445 µL, c = 0.200 M) containing **2.1** (2.23 µmol, 2.50 mol%) and $Ru(bipy)_3(PF_6)_2$ (6.68 µmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.0 mL).

The yield of **2.2b** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 µL, 51. µmol) as an internal standard. Comparison of the integral of the peak of **2.2b** at 7.74–7.72 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 48% yield of **2.2b**.

Another compound, consistent with structure **E2.1**, was observed in 11% yield:

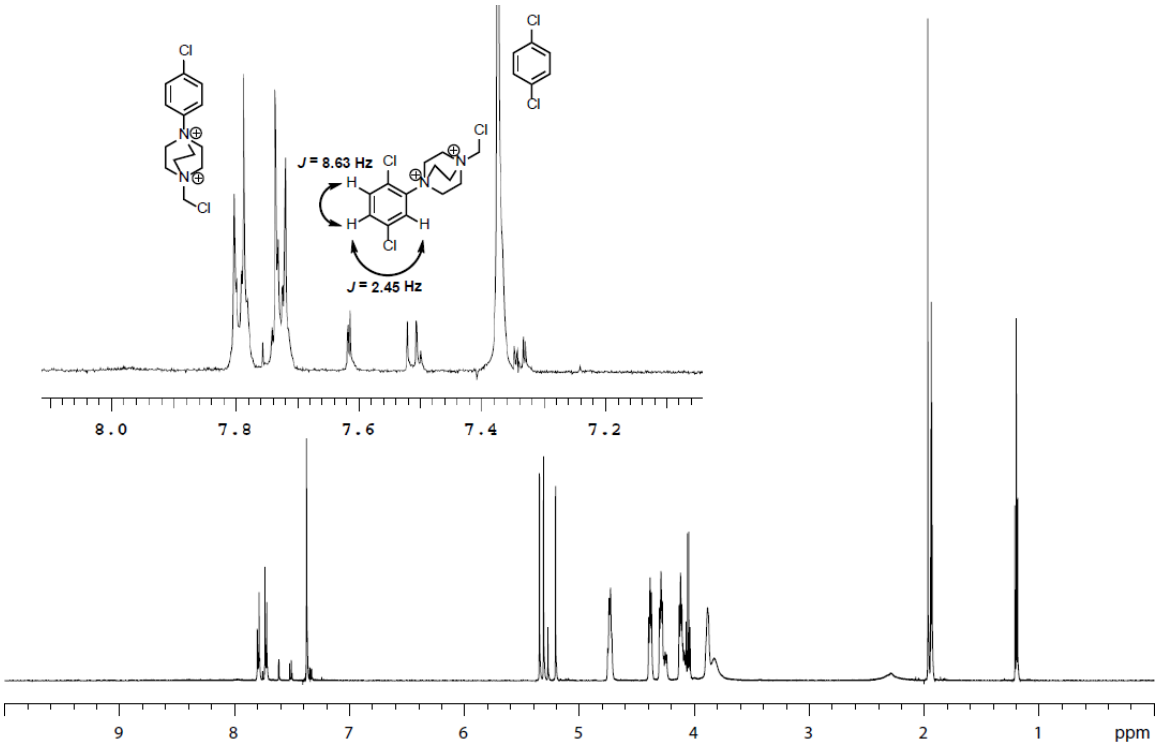
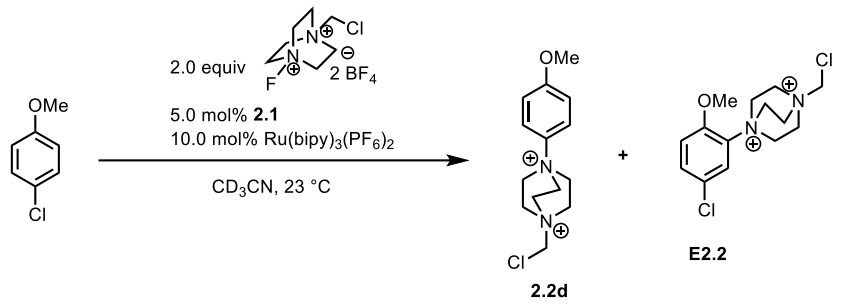


Figure E2.4. ^{1}H NMR of product mixture of TEDAylation of 1,4-dichlorobenzene (CD_3CN, 23 °C)

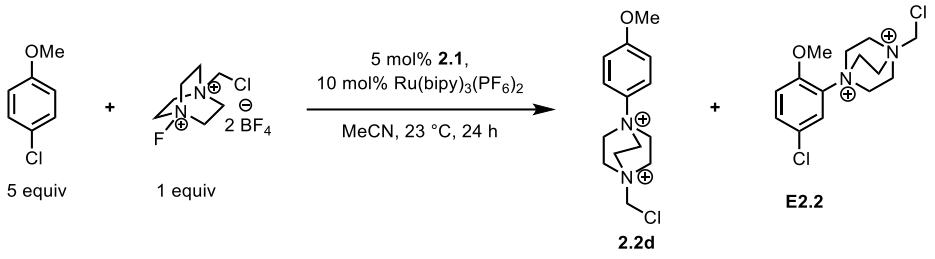
1-(Chloromethyl)-4-(4-methoxyphenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2d) from 4-chloroanisole



A stock solution was prepared, containing **2.1** (11.4 mg, 15.0 μmol) and $Ru(bipy)_3(PF_6)_2$ (25.8 mg, 30.0 μmol) were dissolved in d_3-acetonitrile (1.50 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (35.4 mg, 0.100 mmol, 2.0 equiv) and 4-chloroanisole (6.1 μL, 0.050 mmol, 1.0 equiv). The stock solution (250 μL, c = 0.20 M) containing **2.1** (2.5 μmol, 5.0 mol%) and $Ru(bipy)_3(PF_6)_2$ (5.00 μmol, 10.0 mol%) was added via syringe. After stirring at 23 °C for 48 h, the reaction mixture was diluted with d_3-acetonitrile (0.50 mL).

The yield of **2.2d** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **2.2d** at 7.21–7.17 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 26% yield of **2.2d**.

The above reaction was repeated with 5 equivalents of 4-chloroanisole in order to isolate the Ar–TEDA products from other products.



To a 20 mL vial were weighed **2.1** (31.8 mg, 50.0 μmol, 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (86.0 mg, 0.100 mmol, 10.0 mol%), and Selectfluor (354. mg, 1.00 mmol, 1.00 equiv). Acetonitrile was added (5.0 mL, c

= 0.20 M), followed by 4-chloroanisole (612. µL, 5.00 mmol, 5.00 equiv). The mixture was stirred for 24 hours at room temperature, after which the mixture was diluted with 10 mL acetonitrile, then filtered through celite. The filtrate was concentrated, and the residue was triturated with 20 mL of 9:1 dichloromethane:methanol. The solid was collected by filtration, then washed with 10 mL 9:1 dichloromethane:methanol, then dichloromethane (3 × 10 mL). The solid was dried in vacuo to yield 316. mg of a tan solid. ^{1}H NMR analysis revealed **2.2d** as the dominant Ar–TEDA product, along with ca. 29% of **E2.2**:

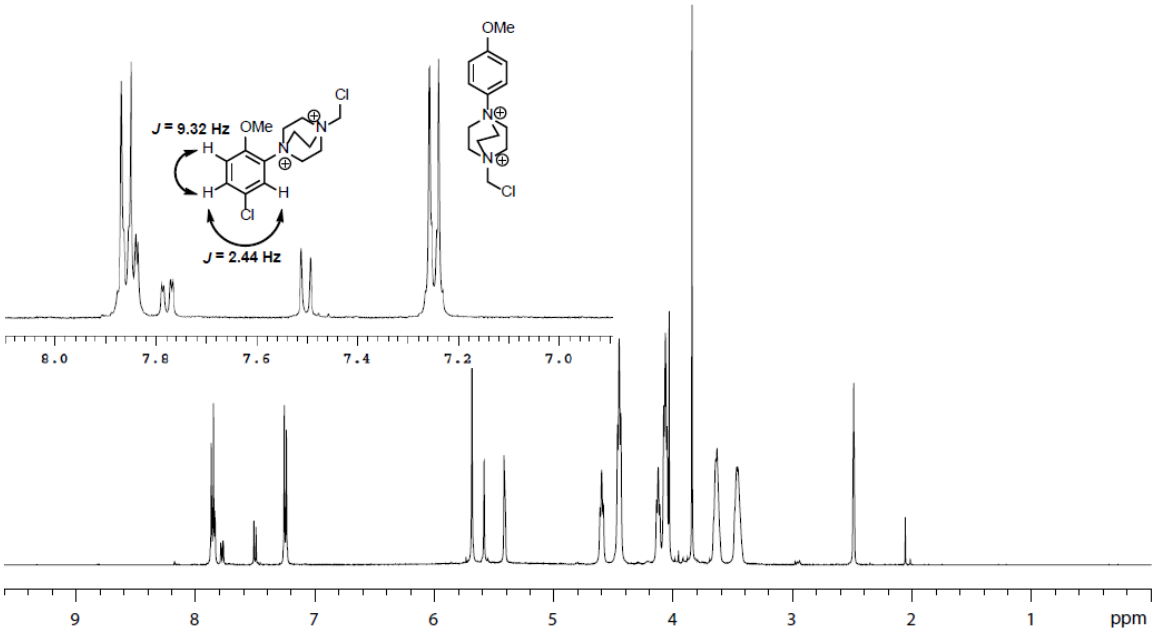
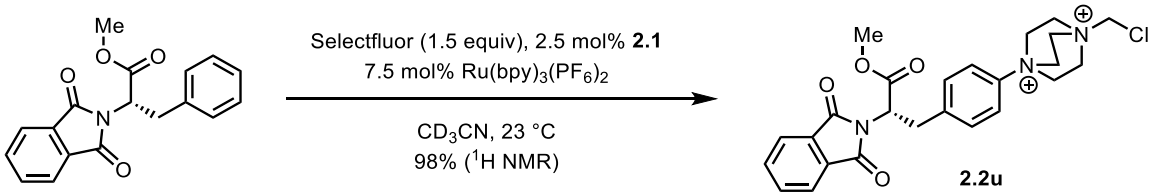


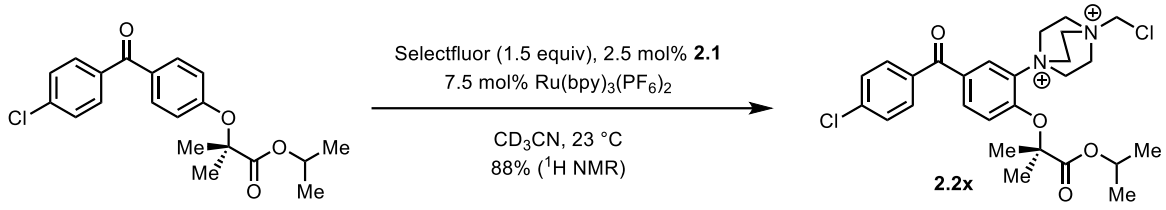
Figure E2.5. ^{1}H NMR spectrum of TEDAylation reaction mixture of 4-chloroanisole

(*S*)-1-(Chloromethyl)-4-(4-(2-(1,3-dioxoisoindolin-2-yl)-3-methoxy-3-oxopropyl)phenyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium (2.2u)



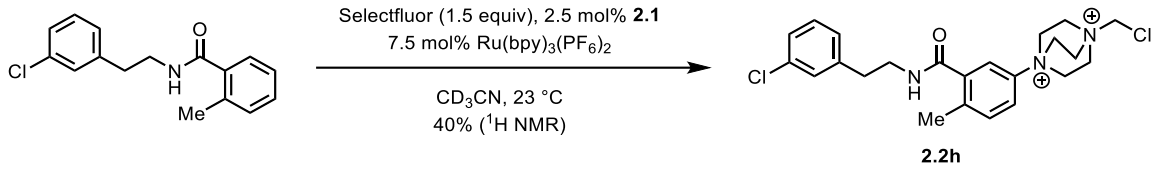
Palladium complex **2.1** (3.5 mg, 5.5 μmol) and $Ru(bipy)_3(PF_6)_2$ (14.2 mg, 16.5 μmol) were dissolved in d_3-acetonitrile (1.10 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (53.1 mg, 0.150 mmol, 1.50 equiv) and methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (30.9 mg, 0.100 mmol, 1.00 equiv). The stock solution (1.0 mL, c = 0.20 M) containing **2.1** (2.5 μmol, 2.5 mol%) and $Ru(bipy)_3(PF_6)_2$ (7.50 μmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.0 mL). The yield of **2.2u** was determined via ^{1}H NMR spectroscopy using *N,N*-dimethylformamide (5.0 μL, 64. μmol) as an internal standard. Comparison of the integral of the peak of **2.2u** at 4.28–4.30 ppm (3 × CH_2, 6H) with that of the peak of *N,N*-dimethylformamide at 2.89 ppm (CH_3, 3H) revealed an 98% yield of **2.2u**.

1-(5-(4-Chlorobenzoyl)-2-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)phenyl)-4-(chloromethyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium (2.2x)



Palladium complex 2.**1** (3.5 mg, 5.5 μmol) and $Ru(bipy)_3(PF_6)_2$ (14.2 mg, 16.5 μmol) were dissolved in d_3-acetonitrile (1.10 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (53.1 mg, 0.150 mmol, 1.50 equiv) and fenofibrate (36.1 mg, 0.100 mmol, 1.00 equiv). The stock solution (1.0 mL, c = 0.20 M) containing 2.**1** (2.5 μmol, 2.5 mol%) and $Ru(bipy)_3(PF_6)_2$ (7.50 μmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.0 mL). The yield of **2.2x** was determined via ^{1}H NMR spectroscopy using *N,N*-dimethylformamide (5.0 μL, 64. μmol) as an internal standard. Comparison of the integral of the peak of **2.2x** at 4.61–4.64 ppm (alkyl C–H, 6H) with that of the peak of *N,N*-dimethylformamide at 2.89 ppm (CH_3, 3H) revealed an 88% yield of **2.2x**.

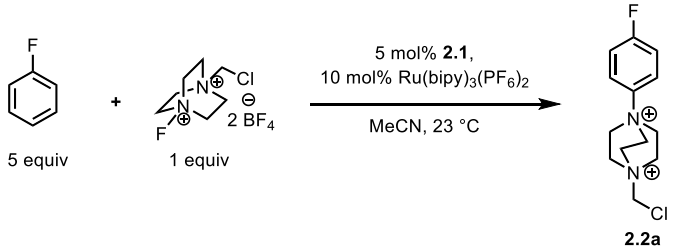
1-(Chloromethyl)-4-(3-((3-chlorophenethyl)carbamoyl)-4-methylphenyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium (2.2h)



Palladium complex **2.1** (7.2 mg, 11. μmol) and $Ru(bipy)_3(PF_6)_2$ (29.0 mg, 33.8 μmol) were dissolved in d_3-acetonitrile (2.25 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (26.6 mg, 75.0 μmol, 1.50 equiv) and *N*-(3-chlorophenethyl)-2-methylbenzamide (13.7 mg, 50.0 μmol, 1.00 equiv). The stock solution (0.25 mL, c = 0.20 M) containing **2.1** (1.2 μmol, 2.5 mol%) and $Ru(bipy)_3(PF_6)_2$ (3.75 μmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.0 mL). The yield of **2.2h** was determined via ^{1}H NMR spectroscopy using *N,N*-dimethylformamide (2.0 μL, 26. μmol) as an internal standard. Comparison of the integral of the peak of **2.2h** at 7.66 ppm (aromatic C–H, 1H) with that of the peak of *N,N*-dimethylformamide at 2.89 ppm (CH_3, 3H) revealed an 40% yield of **2.2h**.

E2.5 Procedure for Aromatic C–H TEDAylation Reactions (Excess Arene)

1-(Chloromethyl)-4-(4-fluorophenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2a)



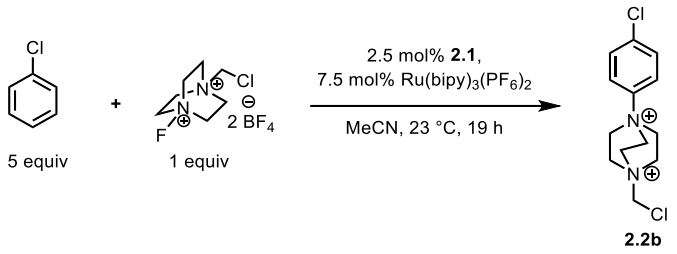
To a 20 mL vial were added palladium complex **2.1** (31.8 mg, 50.0 μmol, 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (86.0 mg, 100. μmol, 10.0 mol%), Selectfluor (354. mg, 1.00 mmol, 1.00 equiv), and fluorobenzene (0.530 mL, 5.00 mmol, 5.00 equiv), and acetonitrile (2.5 mL, c = 0.20 M). The reaction mixture was

stirred at 40 °C for 48 h. The reaction mixture was diluted with acetonitrile, filtered through celite, and the filtrate was concentrated *in vacuo*. The residue was triturated with 20 mL methanol:dichloromethane. The solid was collected by filtration on a glass frit, washed with 10 mL 1:9 methanol:dichloromethane, followed by 3 × 10 mL dichloromethane, then dried *in vacuo* to afford 341. mg of a tan powder. For yield determination, an NMR sample in d_3-acetonitrile was prepared containing 10.0 mg of the product mixture and 5.0 μL of ethyl acetate (51. μmol) as internal standard. Comparison of the integral of the peak of **2.2a** at 4.45–4.37 ppm (3 × CH_2, 6H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.60 mmol of **2.2a** (60% yield). Also present was 0.18 mmol H–TEDA^{2+} (18%), measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H).

NMR Spectroscopy: ^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.91–7.84 (m, 2H), 7.49–7.42 (m, 2H), 5.36 (s, 2H), 4.45–4.37 (m, 6H), 4.18–4.11 (m, 6H). ^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 163.4 (d, J = 252.4 Hz), 140.7 (s), 123.8 (d, J = 9.6 Hz), 118.9 (d, J = 24.0 Hz), 70.1 (s), 55.6 (s), 51.6 (s). ^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –110.0.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{13}H_{17}ClFN_2$ $[M–H]^+$, 255.1059; found, 255.1061.

1-(Chloromethyl)-4-(4-chlorophenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2b)



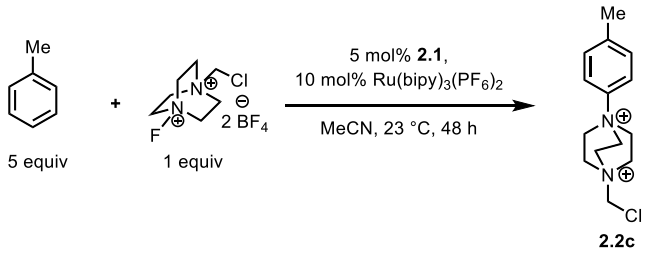
A 50 mL round-bottom flask was charged with palladium complex **2.1** (31.8 mg, 50.0 μmol. 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (86.0 mg, 0.100 mmol, 10.0 mol%), and Selectfluor (354. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added, followed by chlorobenzene (509 μL, 5.00 mmol, 5.00 equiv) via syringe. After stirring at 23 °C for 19 h, the reaction mixture was filtered through celite and

concentrated *in vacuo*. The residue was triturated with a solvent mixture of dichloromethane/methanol (9/1 (v/v), 10 mL) and dichloromethane (5 × 10 mL) at 23 °C to afford 463 mg of the title compound as a light yellow solid. For yield determination, an NMR sample in d_3-acetonitrile was prepared containing 20.0 mg of the product mixture and 3.0 μL of ethyl acetate (31. μmol) as internal standard. Comparison of the integral of the peak of **2.2b** at 7.79–7.77 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.80 mmol of **2.2b** (80% yield). Also present was 0.14 mmol H–TEDA^{2+} (14%), measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H).

NMR Spectroscopy: ^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.79–7.82 (m, 2H), 7.70–7.73 (m, 2H), 5.36 (s, 2H), 4.40–4.43 (m, 6H), 4.13–4.15 (m, 6H). ^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 142.9, 137.9, 131.6, 122.9, 69.7, 55.1, 51.2.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{13}H_{18}Cl_2N_2^{2+}$ [M]$^{2+}$, 136.0418; found, 136.0419.

1-(Chloromethyl)-4-(4-methyl-phenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2c)



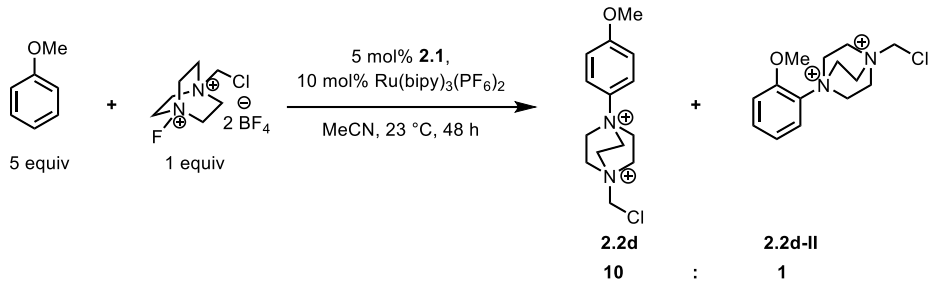
To a 20 mL vial were added palladium complex **2.1** (31.8 mg, 50.0 μmol, 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (86.0 mg, 100. μmol, 10.0 mol%), Selectfluor (354. mg, 1.00 mmol, 1.0 equiv), and toluene (0.530 mL, 5.00 mmol, 5.00 equiv), and acetonitrile (2.5 mL, c = 0.20 M). The reaction mixture was stirred at 23 °C for 48 h. The reaction mixture was concentrated *in vacuo*, then triturated with CH_2Cl_2 to afford 324 mg of a tan powder. For yield determination, an NMR sample in d_3-acetonitrile was prepared containing 10.0 mg of the product mixture and 5.0 μL of ethyl acetate (51. μmol) as internal standard. Comparison of the integral of the peak of **2.2c** at 4.37–4.32 ppm (3 × CH_2, 6H) with that of the peak of ethyl acetate at 1.20

ppm (CH_3, 3H) revealed the bulk mixture to contain 0.59 mmol of **2.2c** (59% yield). Also present was 0.18 mmol H–TEDA^{2+} (18%), measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H).

NMR Spectroscopy: ^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.67–7.63 (m, 2H), 7.54–7.00 (m, 2H), 5.33 (s, 2H), 4.37–4.32 (m, 6H), 4.11–4.07 (m, 6H), 2.44 (s, 3H). ^{13}C NMR (125 MHz, DMSO, 23 °C, δ): 142.1, 141.4, 131.0, 120.3, 68.2, 53.94, 50.4, 20.3.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{14}H_{20}ClN_2^+$ $[M–H]^+$, 251.1310; found, 251.1312.

1-(Chloromethyl)-4-(4-methyl-phenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2d)



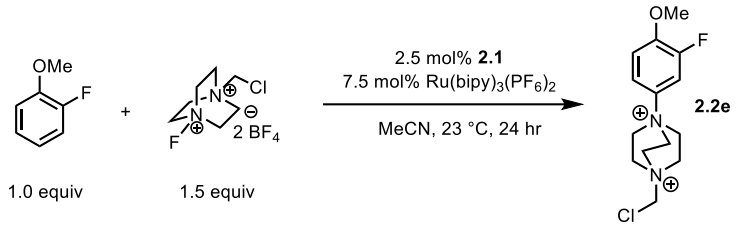
To a 20 mL vial were added palladium complex **2.1** (31.8 mg, 50.0 μmol, 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (86.0 mg, 100. μmol, 10.0 mol%), Selectfluor (354. mg, 1.00 mmol, 1.0 equiv), and anisole (0.544 mL, 5.00 mmol, 5.0 equiv), and acetonitrile (2.5 mL, c = 0.20 M). The reaction mixture was stirred at 23 °C for 48 h. The reaction mixture was concentrated *in vacuo*, then triturated with CH_2Cl_2 to afford 324. mg of a tan powder. For yield determination, an NMR sample in d_3-acetonitrile was prepared containing 10.0 mg of the product mixture and 5.0 μL of ethyl acetate (51. μmol) as internal standard. Comparison of the integral of the peak of **2.2d** at 4.36–4.31 ppm (3 × CH_2, 6H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.43 mmol of **2.2d** (43% yield). An additional compound was observed in 4.3% yield, assignable to **2.2d-II**; (upon reduction, *N*-(2-methoxyphenyl)piperazine (**2.3e-II**) is observed in small amounts, see page 148). Also present was 0.31 mmol H–TEDA^{2+} (31%), measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H).

NMR Spectroscopy: ^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.72–7.67 (m, 2H), 7.21–7.17 (m, 2H), 5.33

(s, 2H), 4.36–4.31 (m, 6H), 4.20–4.15 (m, 6H), 3.88 (s, 3H). ^{13}C NMR (125 MHz, DMSO, 23 °C, δ): 160.5, 137.0, 122.1, 115.5, 68.2, 54.1, 50.4, 43.4.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{14}H_{20}ClN_2O^+$ $[M–H]^+$, 267.1259; found, 267.1263.

1-(Chloromethyl)-4-(3-fluoro-4-methoxyphenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2e)



A 50 mL round-bottom flask was charged with palladium complex **2.1** (31.8 mg, 50.0 μmol. 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (86.0 mg, 0.100 mmol, 10.0 mol%), and Selectfluor (531. mg, 1.50 mmol, 1.50 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added, followed by 2-fluoroanisole (112 μL, 1.00 mmol, 1.00 equiv) via syringe. After stirring at 23 °C for 24 h, the reaction mixture was filtered through celite and concentrated *in vacuo*. The residue was triturated with a solvent mixture of dichloromethane/methanol (9/1 (v/v), 10 mL) and dichloromethane (5 × 10 mL) at 23 °C to afford 573 mg of an orange solid. The solid was triturated with a solvent mixture of dichloromethane/methanol (9/1 (v/v), 10 mL) and dichloromethane (5 × 10 mL) at 23 °C to afford 562 mg of the **2.2e** as a light orange solid. For yield determination, an NMR sample in d_3-acetonitrile was prepared containing 20.0 mg of the product mixture and 3.0 μL of ethyl acetate (3.1×10^{-5} mol) as internal standard. Comparison of the integral of the peak of **2.2e** at 7.34 ppm (aromatic C–H, 1H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.76 mmol of **2.2e** (76% yield). Also present was 0.42 mmol H–TEDA^{2+} (42%) measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H). The structure of **2.2e** was determined by 1-D NOESY NMR (Figure E2.6).

NMR Spectroscopy: ^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.67 (dd, J = 12.2, 3.3 Hz, 1H), 7.59 (ddd, J = 9.3, 3.3, 1.6 Hz, 1H), 7.34 (dd, J = 9.3, 9.3 Hz, 1H), 5.36 (s, 2H), 4.36–4.38 (m, 6H), 4.11–4.13 (m, 6H),

3.96 (s, 3H). ^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 152.0 (d, J = 249.4 Hz), 150.3 (d, J = 9.7 Hz), 135.9 (d, J = 7.8 Hz), 117.5 (d, J = 3.8 Hz), 114.9 (d, J = 2.8 Hz), 110.0 (d, J = 25.0 Hz), 69.5, 55.1, 51.0, 50.4. ^{19}F NMR (475 MHz, CD_3CN, 23 °C, δ): –130.2.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{14}H_{20}ClFN_2O^{2+}$ $[M]^{2+}$, 143.0619; found, 143.0626.

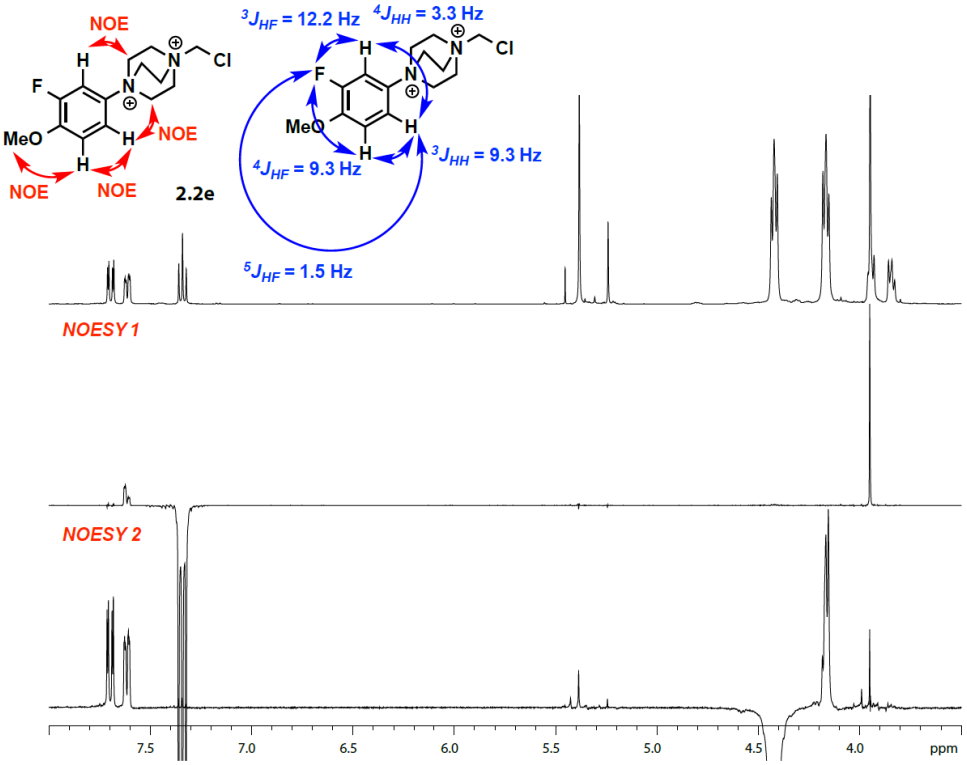
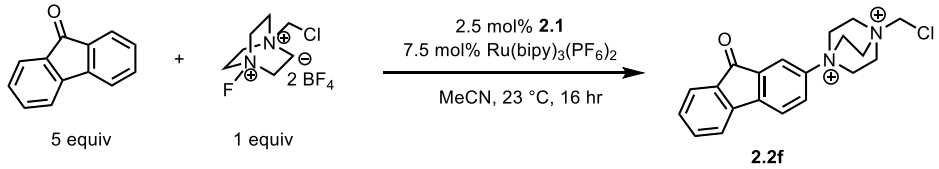


Figure E2.6. Assignment of **2.2e** by 1-D NOESY NMR

1-(Chloromethyl)-4-(fluorenon-2-yl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2f)



A 50 mL round-bottom flask was charged with palladium complex **2.1** (31.8 mg, 50.0 µmol. 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (86.0 mg, 0.100 mmol, 10.0 mol%), Selectfluor (354. mg, 1.00 mmol, 1.00 equiv), and

9*H*-fluoren-9-one (901 mg, 5.00 mmol, 5.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. After stirring at 23 °C for 16 h, the reaction mixture was filtered through celite and concentrated *in vacuo*. The residue was triturated with a solvent mixture of dichloromethane/methanol (9/1 (v/v), 10 mL) and dichloromethane (5 × 10 mL) at 23 °C to afford 559. mg of a yellow solid. The solid was triturated with a solvent mixture of dichloromethane/methanol (9/1 (v/v), 10 mL) and dichloromethane (5 × 10 mL) at 23 °C to afford 468. mg of a bright yellow solid. The solid was triturated with a solvent mixture of dichloromethane/methanol (9/1 (v/v), 10 mL) and dichloromethane (5 × 10 mL) at 23 °C to afford 453. mg of the title compound as a bright yellow solid. For yield determination, an NMR sample in d_3-acetonitrile was prepared containing 20.0 mg of the product mixture and 3.0 μL of ethyl acetate (3.1×10^{-5} mol) as internal standard. Comparison of the integral of the peak of **2.2f** at 5.36 ppm (CH_2Cl, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.77 mmol of **2.2f** (77% yield). Also present was 0.069 mmol H–TEDA^{2+} (7%), measured by integration of the peak at 3.85–3.81 ppm ($3 \times CH_2$, 6H).

The product mixture of **2.2f** obtained above (50 mg) was further purified through repeated recrystallization by vapor diffusion of diethyl ether into an acetonitrile solution. Pure product **2.2f** (15 mg) was obtained as yellow crystals and characterized.

Note: Compound **2.2f** exhibits concentration-dependent chemical shifts. The chemical shifts listed below were recorded from a sample of 12 mg **2.2f** in 7.5 mL CD_3CN.

NMR Spectroscopy: ^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 8.00–7.97 (m, 2H), 7.95–7.92 (m, 1H), 7.80–7.77 (m, 1H), 7.71–7.65 (m, 2H), 7.51–7.47 (m, 1H), 5.38 (s, 2H), 4.45–4.47 (m, 6H), 4.15–4.18 (m, 6H). ^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 191.7, 147.7, 145.0, 143.0, 136.8, 136.7, 135.0, 131.7, 127.7, 125.4, 123.8, 123.1, 116.9, 70.0, 55.4, 51.5.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{20}H_{21}ClN_2O^{2+}$ $[M]^{2+}$, 170.0666; found, 170.0672.

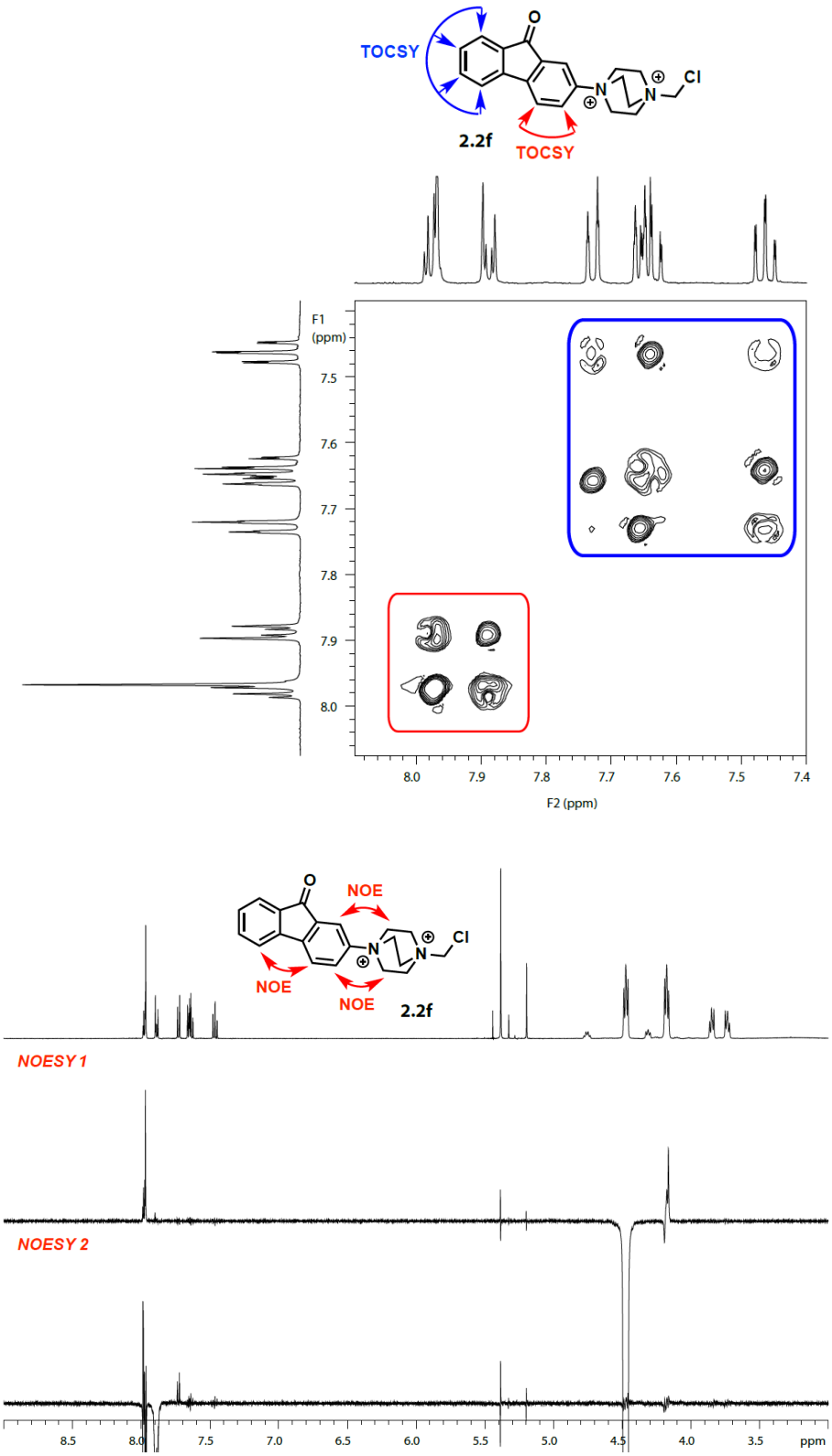
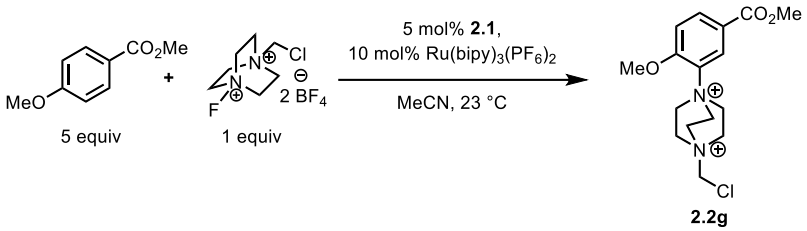


Figure E2.7. Structural assignment of **2.2f** by TOCSY and 1-D NOESY NMR

1-(Chloromethyl)-4-(5-methoxy-2-(methoxycarbonyl)phenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2g)

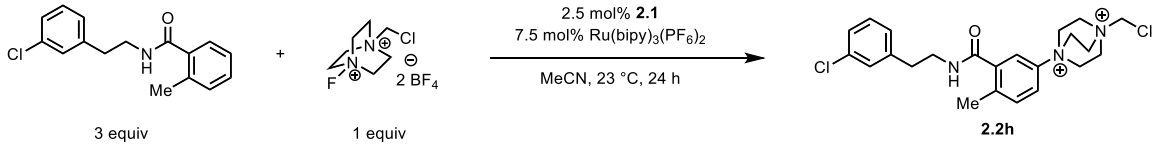


To a 20 mL vial were added palladium complex **2.1** (19.0 mg, 25.0 μmol, 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (43.0 mg, 5.00 μmol, 10.0 mol%), Selectfluor (177. mg, 0.500 mmol, 1.00 equiv), and methyl 4-methoxybenzoate (416 mg, 2.50 mmol, 5.00 equiv), and acetonitrile (2.5 mL, c = 0.20 M). The reaction mixture was stirred at 23 °C for 48 h. The reaction mixture was concentrated *in vacuo*, then triturated with CH_2Cl_2 to afford 191. mg of a tan powder. ^{1}H NMR shows ca. 35% contamination by H–TEDA^{2+}.

NMR Spectroscopy: ^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 8.27 (dd, *J* = 8.9, 1.8 Hz, 1H), 8.21 (d, *J* = 1.8 Hz, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 5.33 (s, 2H), 4.62–4.54 (m, 6H), 4.15–4.09 (m, 6H), 4.14 (s, 3H), 3.92 (s, 3H). ^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 165., 156.51, 135.4, 130.8, 124.7, 124.3, 116.6, 70.4, 58.4, 53.7, 51.6, 45.1.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{16}H_{22}ClN_2O_3^+$ $[M–H]^+$, 325.1313; found, 325.1315.

1-(Chloromethyl)-4-(3-((3-chlorophenethyl)carbamoyl)-4-methylphenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (2.2h)



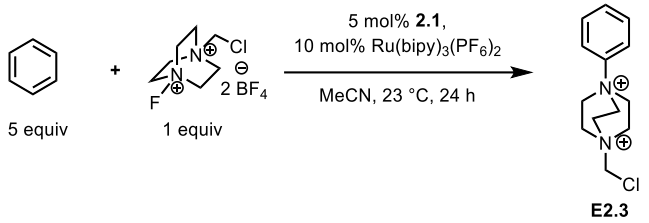
A 4 mL vial was charged with palladium complex **2.1** (3.2 mg, 5.0 μmol. 2.5 mol%), $Ru(bpy)_3(PF_6)_2$ (12.9 mg, 15.0 μmol, 7.50 mol%), Selectfluor (70.9 mg, 0.200 mmol, 1.00 equiv), and *N*-(3-chlorophenethyl)-2-methylbenzamide (164. mg, 0.600 mmol, 3.00 equiv). Acetonitrile (1.0 mL, c = 0.20 M) was added via syringe, and the reaction mixture was stirred at 23 °C for 24 h. The reaction mixture was concentrated *in*

vacuo to afford a red heterogeneous solid mixture. The solid was triturated with dichloromethane to afford 62 mg of the title compound as a light yellow solid (20% yield). Also present was ca. 49% contamination by H–TEDA^{2+}, measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H).

NMR Spectroscopy: ^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.71 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.67 (d, *J* = 2.9 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.30–7.33 (m, 2H), 7.23–7.25 (m, 2H), 6.99 (bs, 1H), 5.36 (s, 2H), 4.38–4.40 (m, 6H), 4.12–4.15 (m, 6H), 3.61–3.64 (m, 2H), 2.91 (t, *J* = 6.9 Hz, 2H), 2.34 (s, 3H). ^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 168.2, 142.9, 142.0, 141.3, 140.1, 134.6, 134.1, 131.0, 129.9, 128.6, 127.3, 121.9, 120.0, 70.1, 55.4, 51.6, 41.4, 35.8, 19.3.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{23}H_{29}Cl_2N_3O^{2+}$ [M]2+, 216.5838; found, 216.5846.

1-(Chloromethyl)-4-phenyl-1,4-diazabicyclo[2.2.2]octane^{2+} (E2.3)



To a 20 mL vial were added palladium complex **2.1** (31.8 mg, 50.0 μmol, 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (86.0 mg, 100. μmol, 10.0 mol%), Selectfluor (354. mg, 1.00 mmol, 1.00 equiv), and benzene (0.446 mL, 5.00 mmol, 5.0 equiv), and acetonitrile (2.5 mL, c = 0.20 M). The reaction mixture was stirred at 23 °C for 48 h. The reaction mixture was concentrated *in vacuo*, then triturated with CH_2Cl_2 to afford 360 mg of a tan powder. For yield determination, an NMR sample in d_3-acetonitrile was prepared containing 10.0 mg of the product mixture and 5.0 μL of ethyl acetate (51. μmol) as internal standard. Comparison of the integral of the peak of **E2.3** at 4.41–4.36 ppm (3 × CH_2, 6H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.67 mmol of **E2.3** (67% yield). Also present was 0.15 mmol H–TEDA^{2+} (15%), measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H).

NMR Spectroscopy: ^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.82–7.77 (m, 2H); 7.75–7.69 (m, 3H), 5.35

(s, 2H), 4.41–4.36 (m, 6H), 4.41–4.09 (m, 6H). ^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 144.4, 131.3, 130.8, 120.7, 68.2, 53.9, 50.4.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{13}H_{18}ClN_2^+$ $[M–H]^+$, 237.1153; found, 237.1154.

E2.6 Fluoro-*N*,*N*,*N*-trimethylanilinium Cations

We have synthesized *ortho*-, *meta*-, and *para*-fluoro-*N*,*N*,*N*-trimethylanilinium iodide to ascertain the likelihood of the ^{19}F NMR signal overlap of the different constitutional isomers of fluoroaryl trialkylammonium salts. We found the ^{19}F chemical shifts in CD_3CN of the *para*, *meta*, and *ortho* isomers to be –112.4 ppm, –110.2 ppm, and –113.3 ppm, respectively:

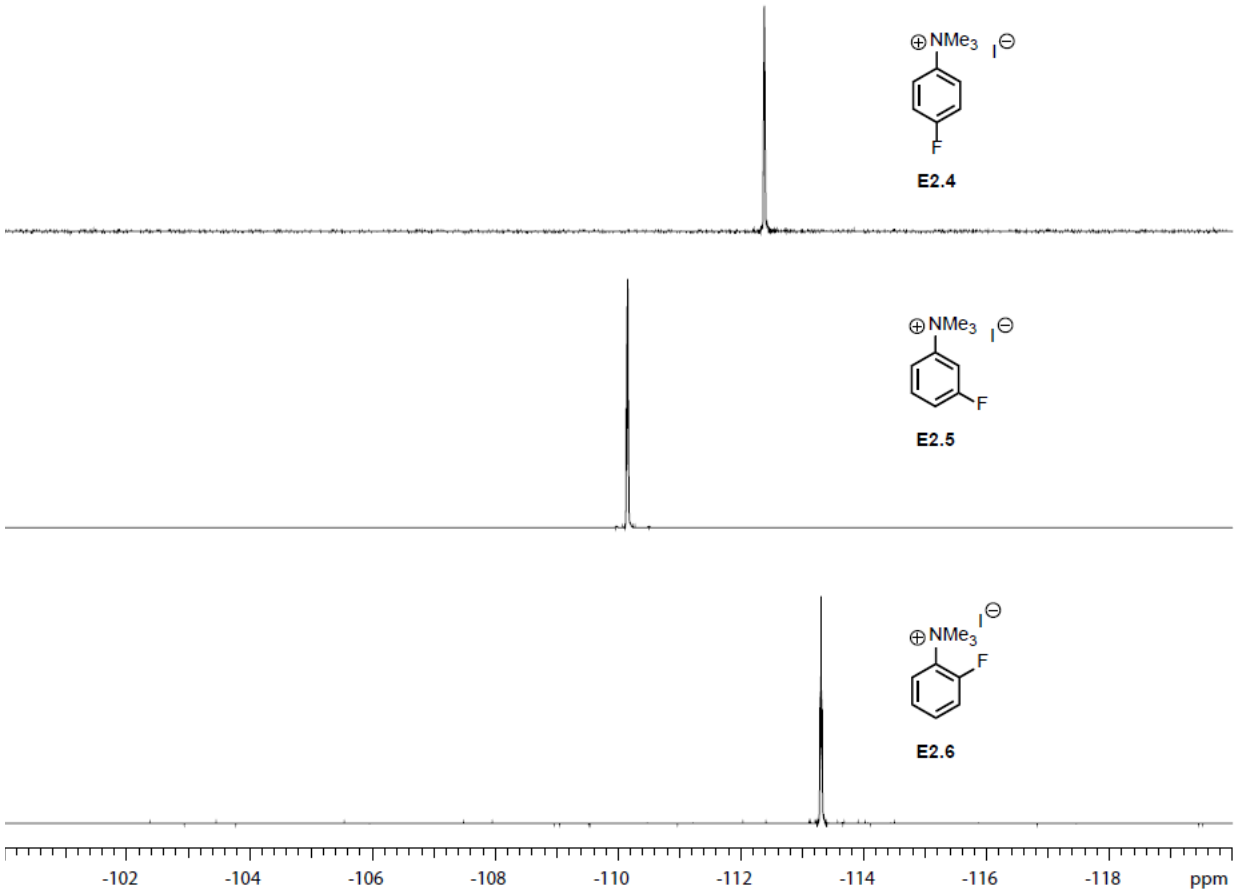
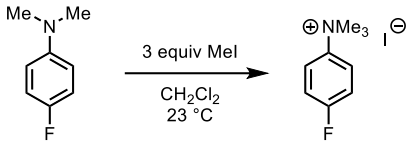


Figure E2.8. ^{19}F NMR chemical shifts of **E2.4**, **E2.5**, and **E2.6** (CD_3CN, 23 °C)

4-Fluoro-*N*,*N*,*N*-trimethylanilinium iodide (E2.4)



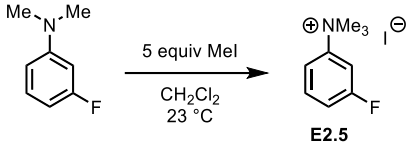
E2.4

In a 20 mL vial, *N,N*-dimethylaniline (696. mg, 5.00 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (5.0 mL), and iodomethane (0.93 mL, 15. mmol, 3.0 equiv) was added dropwise via syringe. The mixture was stirred at room temperature for 4 hours, over which time a white precipitate formed. The precipitate was collected by filtration, then washed with dichloromethane (3 × 5 mL) to afford 767. mg of 4-fluoro-*N*,*N*,*N*-trimethylanilinium iodide as a white powder (2.73 mmol, 55%).

NMR Spectroscopy: ^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.89–7.84 (m, 2H), 7.39–7.34 (m, 2H), 3.58 (s, 9H). ^{13}C NMR (125 MHz, DMSO, 23 °C, δ): 161.8 (d, J = 248.6 Hz), 143.3 (d, J = 3.1 Hz), 123.3 (d, J = 9.3 Hz), 116.6 (d, J = 23.5 Hz), 56.7 (s). ^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –112.4.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_9H_{13}NF$ $[M]^+$, 154.1027; found, 154.1023.

3-Fluoro-*N*,*N*,*N*-trimethylanilinium iodide (E2.5)



E2.5

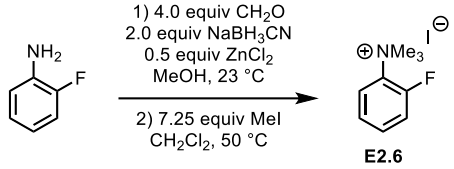
In a 20 mL vial, *N,N*-dimethylaniline (500 mg, 3.59 mmol, 1.0 equiv) was dissolved in CH_2Cl_2 (5.0 mL), and iodomethane (1.12 mL, 18.0 mmol, 5.0 equiv) was added dropwise via syringe. The mixture was stirred at room temperature for 48 hours, over which time a white precipitate formed. The precipitate was collected by filtration, then washed with dichloromethane (3 × 5 mL) to afford 754 mg of 4-fluoro-*N*,*N*,*N*-trimethylanilinium iodide as a white powder (2.68 mmol, 75%).

NMR Spectroscopy: ^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.80–7.73 (m, 2H), 7.68–7.63 (ddd, J = 6.47

Hz, 8.50 Hz, 14.7 Hz, 1H), 7.39–7.34 (ddd, J = 0.83 Hz, 2.33 Hz, 7.86 Hz, 1H), 3.67 (s, 9H). ^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 161.8 (d, J = 246.4 Hz), 148.3 (d, J = 9.1 Hz), 131.8 (d, J = 9.0 Hz), 117.1 (d, J = 21.0 Hz), 116.9 (d, J = 3.8 Hz), 109.2 (d, J = 27.4 Hz), 56.5 (s). ^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –110.2.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_9H_{13}NF$ $[M]^+$, 154.1027; found, 154.1020.

2-Fluoro-*N*,*N*,*N*-trimethylanilinium iodide (E2.6)



E2.6

In a round bottom flask were added 3-fluoroaniline (1.50 mL, 15.6 mmol, 1.00 equiv), methanol (50 mL), and 37% aqueous formaldehyde (5.0 mL, 62 mmol, 4.0 equiv). To this mixture was added a solution of sodium cyanoborohydride (2.010 g, 32.01 mmol, 2.00 equiv) and zinc chloride (1.090 g, 8.00 mmol, 0.500 equiv) in 50 mL methanol. The mixture was stirred for 12 hours at room temperature, after which time 50 mL 0.16 M NaOH was added, and the methanol was removed by rotary evaporation. The aqueous mixture was then extracted with dichloromethane (4 × 20 mL). The combined organic layers were dried over $MgSO_4$ and concentrated to give a brown oil. The residue was redissolved in 15 mL dichloromethane and added to a pressure vessel, along with 7.00 mL of iodomethane (112. mmol, 7.25 equiv). The vessel was sealed and heated to 50 °C for 12 hours, over which time a white precipitate formed. The precipitate was collected by filtration, washed with dichloromethane (5 × 20 mL), and dried in vacuo to afford 2.27 g of 2-fluoro-*N*,*N*,*N*-trimethylanilinium iodide as a white powder (8.08 mmol, 52%).

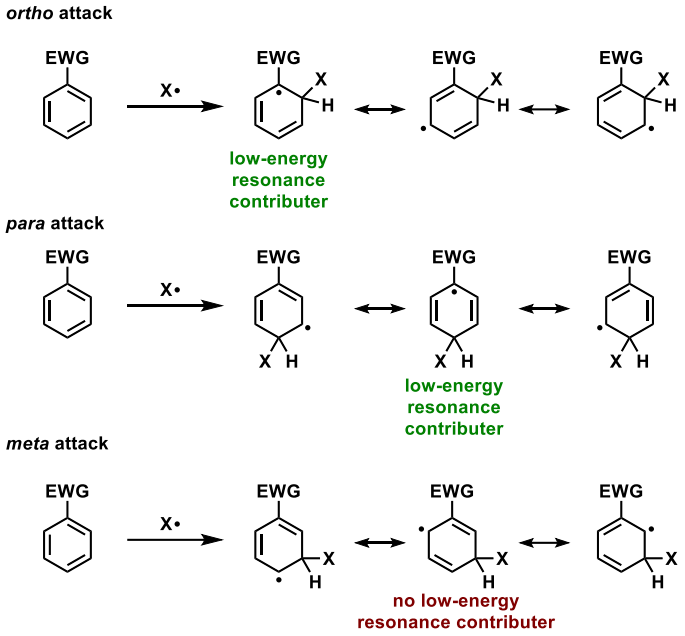
NMR Spectroscopy: ^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.85–7.79 (dd, J = 8.6, 1.4 Hz, 1H), 7.69–7.64 (dddd, J = 8.3, 7.5, 4.7, 1.5 Hz, 1H), 7.50–7.55 (ddd, J = 14.3, 8.3, 1.5 Hz, 1H), 7.45–7.41 (ddd, J = 7.5, 1.4, 0.80 Hz, 1H), 3.68 (s, 9H). ^{13}C NMR (125 MHz, DMSO, 23 °C, δ): 154.1 (d, J = 251.2 Hz), 132.9 (d, J = 6.4), 132.9 (d, J = 9.6 Hz), 125.8 (d, 3.6 Hz), 122.9 (s), 118.8 (d, J = 22.3), 56.1 (d, J = 5.5

Hz). ^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –113.3.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_9H_{13}NF$ $[M]^+$, 154.1027; found, 154.1027.

E2.7 Selectivity of TEDAylation with Resonance Electron-withdrawing Substituents

Radicals are stabilized both by electron-donating and electron-withdrawing substituents. Therefore, in radical aromatic substitution of arenes bearing electron-withdrawing groups, intermediates resulting from radical attack at the *ortho* and *para* positions are more stable than the one arising from attack at the *meta* position, because the *ortho* and *para* addition isomers provide opportunity for resonance stabilization of the radical. Therefore, by Hammond's postulate, the rate of attack in the *ortho* and *para* position is more rapid. This stands in contrast to electrophilic aromatic substitution, in which resonance electron-withdrawing substituents direct electrophilic attack to the *meta* position.



We have found that upon reaction with $TEDA^{2+\cdot}$, benzonitrile yields the *para* substituted Ar–TEDA isomer in ca. 10% conversion. No other isomer is observable. This result can be understood by considering the resonance stabilization effect described above. For arenes substituted with electron-donating groups,

attack at the *ortho* and *para* positions are favored by resonance considerations, while attack at the *para* position is further favored by charge transfer in the transition state of addition. In the case of arenes bearing resonance electron-withdrawing groups, we rationalize that attack is constrained to the *ortho* and *para* positions by resonance stabilization considerations. Thus, attack occurs at the *para* position, even though the *meta* position may be capable of greater charge-transfer stabilization.

TEDAylation of benzonitrile

In a 4 mL vial, palladium complex **2.1** (3.2 mg, 5.0 μmol, 5.0 mol%), $Ru(bipy)_3(PF_6)_2$ (8.6 mg, 10. μmol, 10.0 mol%), and Selectfluor (70.9 mg, 0.200 mmol, 2.00 equiv) were dissolved in d_3-acetonitrile (0.50 mL). Finally, 10.2 μL benzonitrile (0.100 mmol, 1.00 equiv) was added, and the solution was stirred at 40 °C for 48 h. The reaction mixture was diluted with d_3-acetonitrile (0.25 mL), passed through a 0.2 μm PVDF syringe filter, and analyzed by ^{1}H NMR:

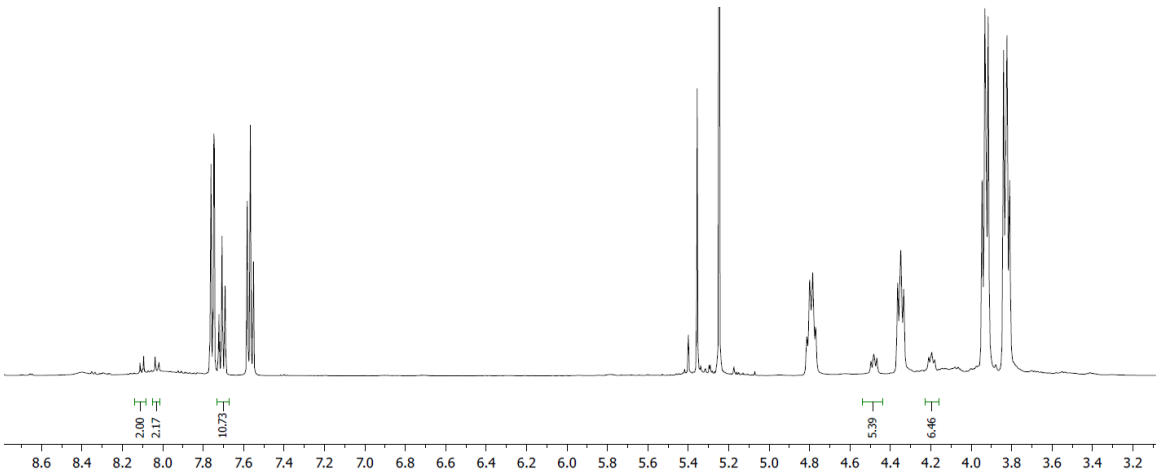


Figure E2.9. ^{1}H NMR of reaction mixture of TEDAylation of benzonitrile (CD_3CN, 23 °C)

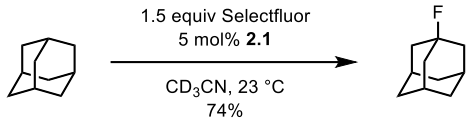
E2.8 Evidence for $TEDA^{2+\cdot}$ Radical Dication as the C–N Bond Forming Species

Lectka has reported that treatment of adamantane with Selectfluor in the presence of various radical initiators leads to C–H fluorination.[22,23] It was proposed that such reactions proceed through the

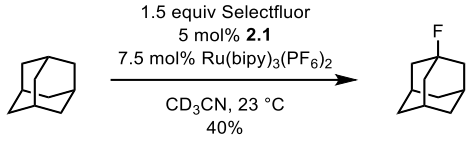
intermediacy of $TEDA^{2+\cdot}$, which abstracts a hydrogen atom from the substrate. We have observed aliphatic C–H fluorination in the presence of Selectfluor and **2.1**, which is consistent with the formation of $TEDA^{2+\cdot}$ through the action of **2.1** on Selectfluor. We propose that the yield is diminished in the presence of $Ru(bipy)_3(PF_6)_2$ due to oxidation by Ru^{III} of the alkyl radical generated upon hydrogen atom abstraction, leading to non-fluorinated products.

We have furthermore observed the formation of **2.2a** from fluorobenzene via copper catalysis, under conditions similar to those reported by Baran.[24] This finding indicates that neither **2.1** or $Ru(bipy)_3(PF_6)_2$ is uniquely effective catalyst for Ar–TEDA formation, and is consistent with the free $TEDA^{2+\cdot}$ radical as the C–N bond forming species.

Observation of aliphatic C–H fluorination under TEDAylation conditions



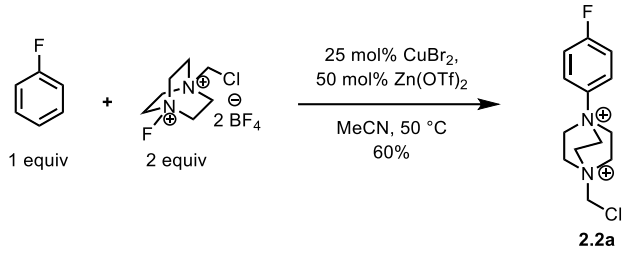
To a 4 mL vial were added adamantane (13.6 mg, 0.100 mmol, 1.00 equiv), Selectfluor (53.2 mg, 0.150 mmol, 1.50 equiv), **2.1** (3.2 mg, 5.0 μmol, 5.0 mol%), and CD_3CN (0.70 mL). The reaction was stirred for 16 hours at room temperature, after which 2.0 μL of 3-fluoronitrobenzene was added as an internal standard, and the solution was analyzed by ^{19}F NMR. 1-Fluoroadamantane was observed in 74% yield.



To a 4 mL vial were added adamantane (13.6 mg, 0.100 mmol, 1.00 equiv), Selectfluor (53.2 mg, 0.150 mmol, 1.50 equiv), **2.1** (3.2 mg, 5.0 μmol, 5.0 mol%), $Ru(bipy)_3(PF_6)_2$ (6.4 mg, 7.5 μmol, 7.5 mol%) and CD_3CN (0.70 mL). The reaction was stirred for 16 hours at room temperature, after which 2.0 μL of 3-fluoronitrobenzene was added as an internal standard, and the solution was analyzed by ^{19}F NMR. 1-

Fluoroadamantane was observed in 40% yield.

Observation of Aryl–TEDA formation under copper catalysis



To a 4 mL vial were added cupric bromide (7.3 mg, 33. μmol, 25 mol%), zinc triflate (23.6 mg, 64.9 μmol, 50.0 mol%), and Selectfluor-PF_6 (135. mg, 0.286 mmol, 2.00 equiv). Acetonitrile-d_3 (1.0 mL) was then added, followed by fluorobenzene (12.0 μL, 0.128 mmol, 1.00 equiv). The reaction mixture was stirred for 16 hours at 50 °C. The mixture was allowed to cool to room temperature, 2.0 μL of 3-fluoronitrobenzene was added as internal standard. The mixture was filtered through a PVDF syringe filter to remove insoluble materials, and the filtrate was analyzed by ^{1}H and ^{19}F NMR. Compound **2.2a** was observed in 60% yield, along with ca. 32% of 4-fluorobromobenzene.

The NMR sample was concentrated by rotary evaporation, and the residue was triturated with dichloromethane (3 × 1 mL), then tetrahydrofuran (2 × 2 mL) to yield a tan powder. Analysis by ^{1}H and ^{19}F NMR shows **2.2a** is the only Ar–TEDA product formed in significant amounts (Figure E2.10).

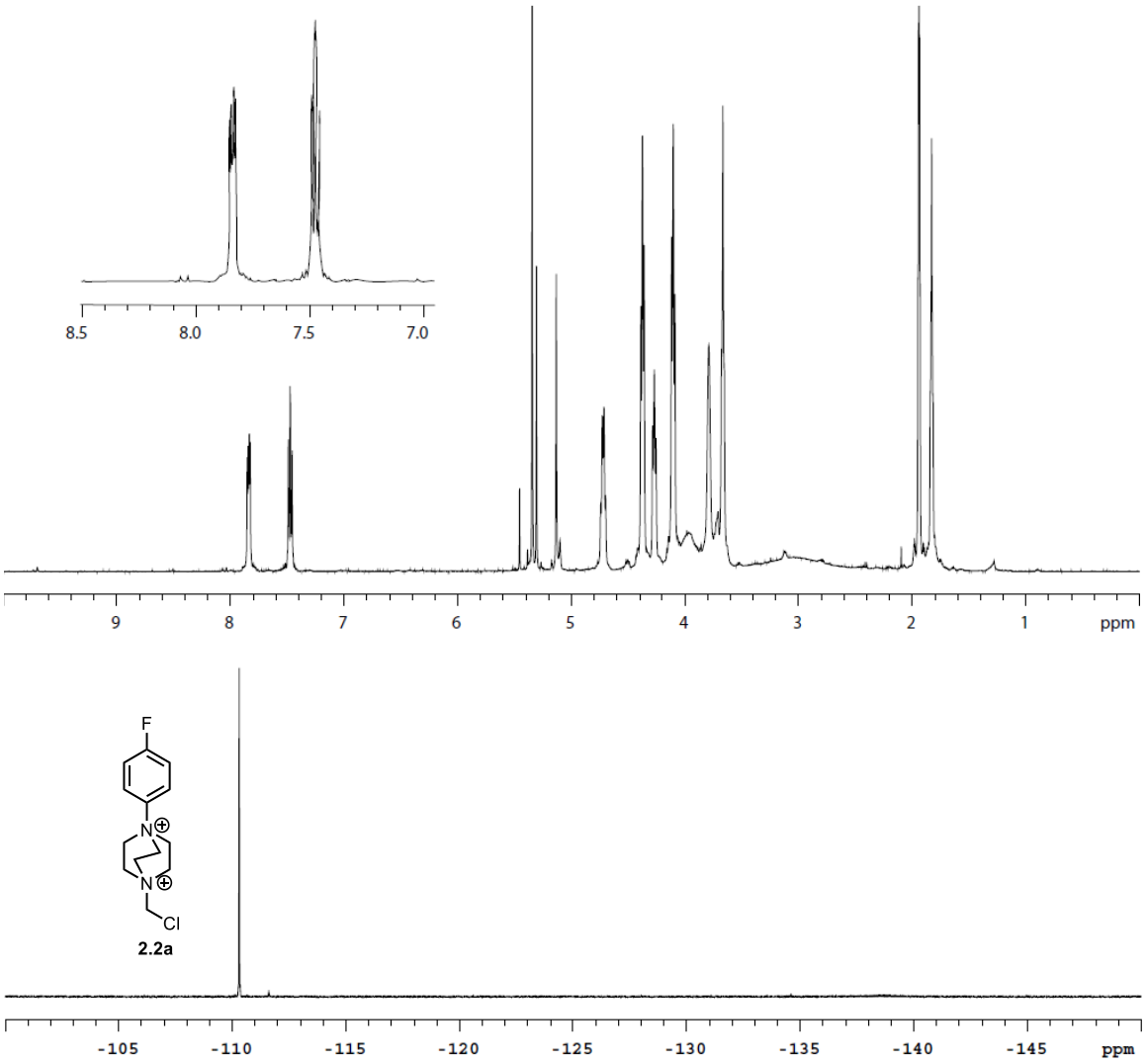
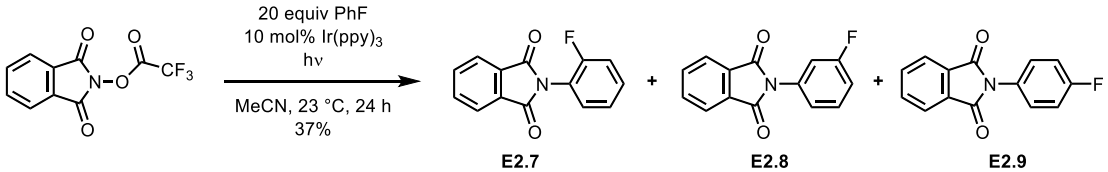


Figure E2.10. ^{1}H and ^{19}F NMR of **2.2a** synthesized via copper catalysis (CD_3CN, 23 °C)

E2.9 Aromatic substitution of fluorobenzene by phthalimidyl radical



In an N_2-filled glovebox, into a 4 mL vial were weighed *N*-trifluoroacetoxy phthalimide (13.0 mg, 50.2 μmol, 1.00 equiv) and tris(2-phenylpyridyl)iridium(III) (3.3 mg, 5.0 μmol, 10. mol%). Acetonitrile (1.0 mL) was then added, followed by fluorobenzene (94. μL, 1.0 mmol, 20 equiv). The vial was sealed,

removed from the glovebox, and stirred magnetically for 24 hours at room temperature under irradiation by a 60 W desk lamp. The volatile components were removed by rotary evaporation. The residue was taken up in CD_3CN, and 2.0 µL (18.8 µmol) of 3-fluoronitrobenzene was added as internal standard. The mixture was filtered through a PVDF syringe filter to remove all insoluble materials, and the filtrate was analyzed by ^{19}F NMR. The following amounts of **E2.7**, **E2.8**, and **E2.9** were observed:

N-(2-fluorophenyl)phthalimide (**E2.7**)	7.1 µmol
N-(3-fluorophenyl)phthalimide (**E2.8**)	1.9 µmol
N-(4-fluorophenyl)phthalimide (**E2.9**)	9.7 µmol

The total yield is thus 18.7 µmol (37%), and the *ortho*:*meta*:*para* ratio is 37:11:52.

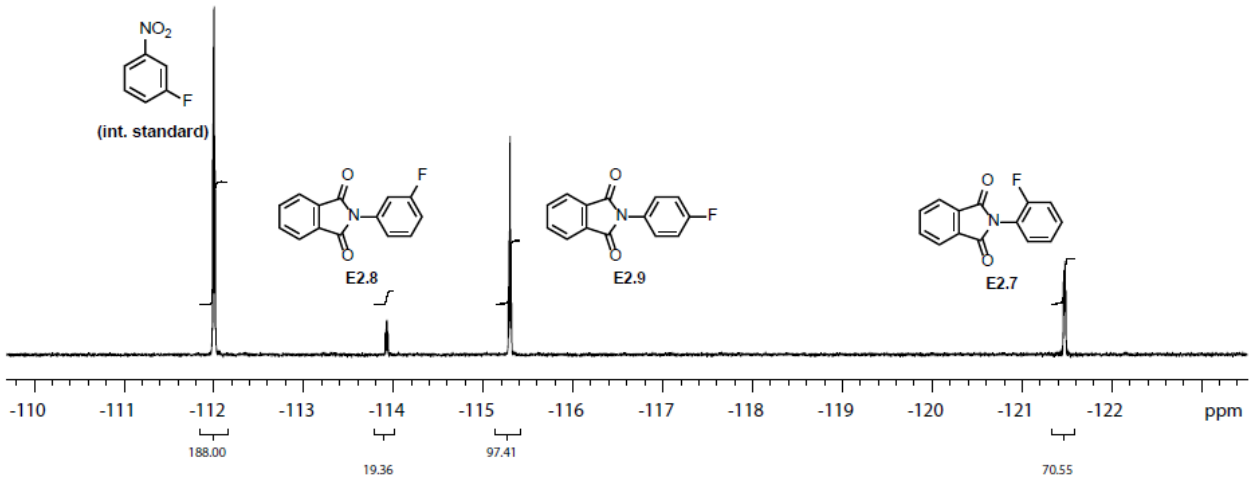
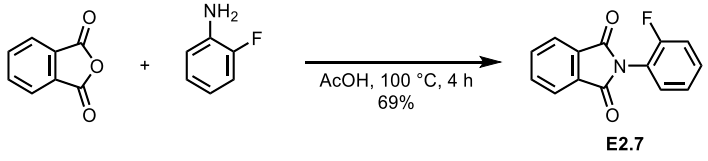


Figure E2.11. ^{19}F NMR analysis of product mixture of phthalimidyl radical substitution (CD_3CN, 23 °C)

E2.10 Synthesis of Authentic Samples of E2.7, E2.8, and E2.9

***N*-(2-Fluorophenyl)-phthalimide (E2.7)**

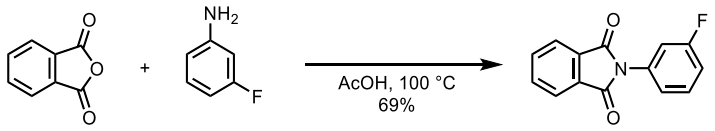


To a 20 mL vial were added phthalic anhydride (296. mg, 2.00 mmol, 1.00 equiv), acetic acid (5.0 mL), and 2-fluoroaniline (193. µL, 2.00 mmol, 1.00 equiv). The vial was sealed and magnetically stirred for 4 hr at 100 °C. The reaction mixture was allowed to come to room temperature, and 10 mL water was added to precipitate the product. The precipitate was collected by filtration, washed with water (4 × 10 mL), and dried *in vacuo* to yield 334. mg (1.38 mmol, 69%) of the title compound as a colorless powder.

NMR Spectroscopy: ^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.97–7.93 (m, 2H), 7.90–7.86 (m, 2H), 7.57–7.51 (m, 1H), 7.49–7.44 (m, 1H), 7.39–7.32 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 166.4 (s), 157.8 (d, J = 252.7 Hz), 134.4 (s), 131.8 (s), 130.7 (d, J = 8.0 Hz), 129.8 (d, J = 0.9 Hz), 124.6 (d, J = 4.0 Hz), 123.8 (s), 119.3 (d, J = 13.2 Hz), 116.7 (d, J = 19.5 Hz). ^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –113.9.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{14}H_9FNO_2$ $[M+H]^+$, 242.0612; found, 242.0613.

***N*-(3-Fluorophenyl)-phthalimide (E2.8)**



E2.8

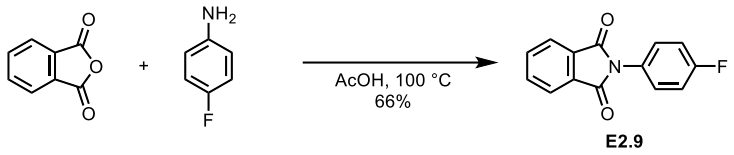
To a 20 mL vial were added phthalic anhydride (296. mg, 2.00 mmol, 1.00 equiv), acetic acid (5.0 mL), and 3-fluoroaniline (192. µL, 2.00 mmol, 1.00 equiv). The vial was sealed and magnetically stirred for 2 hr at 100 °C. The reaction mixture was allowed to come to room temperature, and 10 mL water was added to precipitate the product. The precipitate was collected by filtration, washed with water (4 × 10 mL), and dried *in vacuo* to yield 334. mg (1.38 mmol, 69%) of the title compound as a colorless powder.

NMR Spectroscopy: ^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.96–7.92 (m, 2H), 7.89–7.85 (m, 2H), 7.55 (ddd, J = 14.7, 8.3, 6.4 Hz, 1H), 7.32 (ddd, J = 8.0, 1.9, 0.9 Hz, 1H), 7.28–7.24 (m, 1H), 7.21 (ddd, J = 8.7, 2.6, 0.9 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 166.8 (s), 162.6 (d, J = 246.7 Hz), 134.6 (s), 133.0 (d, J = 10.3 Hz), 131.5 (s), 130.2 (d, J = 9.0 Hz), 123.9 (s), 122.0 (d, J = 3.5 Hz), 115.0 (d, J = 21.1

Hz), 113.9 (d, J = 24.7 Hz). ^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –121.5.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{14}H_9FNO_2$ $[M+H]^+$, 242.0612; found, 242.0611.

***N*-(4-Fluorophenyl)-phthalimide (E2.9)**



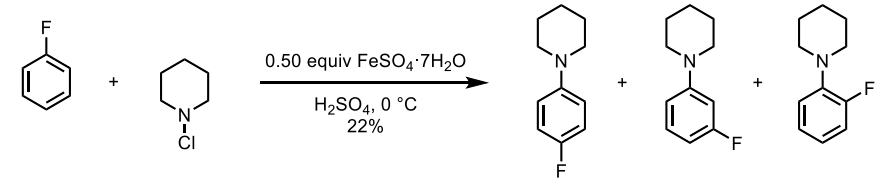
E2.9

To a 20 mL vial were added phthalic anhydride (296. mg, 2.00 mmol, 1.00 equiv), acetic acid (5.0 mL), and 4-fluoroaniline (190. µL, 2.00 mmol, 1.00 equiv). The vial was sealed and magnetically stirred for 2 hr at 100 °C. The reaction mixture was allowed to come to room temperature, and 10 mL water was added to precipitate the product. The precipitate was collected by filtration, washed with water (4 × 10 mL), and dried *in vacuo* to yield 319. mg (1.32 mmol, 66%) of the title compound **E2.9** as a tan powder.

NMR Spectroscopy: ^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.94–7.90 (m, 2H), 7.88–7.84 (m, 2H), 7.48–7.43 (m, 2H), 7.30–7.25 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 167.1 (s), 161.8 (d, J = 247.6 Hz), 134.4 (s), 131.5 (s), 128.3 (d, J = 8.7 Hz), 127.5 (d, J = 3.2 Hz), 123.7 (s), 116.1 (d, J = 22.5 Hz). ^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –115.3.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{14}H_9FNO_2$ $[M+H]^+$, 242.0612; found, 242.0615.

E2.11 Aromatic Substitution of Fluorobenzene by Piperidine Aminium Radical



2.0 equiv 1.0 equiv **E2.10** **E2.11** **E2.12**

To 2.00 g of concentrated sulfuric acid in a 20 mL vial at 0 °C were added 188. µL of fluorobenzene (2.00 mmol, 2.00 equiv), 120. mg of N-chloropiperidine (1.00 mmol, 1.00 equiv), and finally 139. mg of

pulverized ferrous sulfate heptahydrate (0.500 mmol, 0.500 equiv). The mixture rapidly turned brown upon addition of ferrous sulfate heptahydrate, and was stirred at 0 °C for 2 hours, after which significant beige precipitate was observed. The reaction mixture was poured onto ice and filtered through a glass frit. The acidic filtrate was extracted with diethyl ether (2 × 10 mL), then brought to pH 14 with 6 M NaOH. The basic mixture was extracted with dichloromethane (5 × 20 mL), until no more UV-active compound was observed in the organic extract. The combined organic layers were dried over Na_2SO_4 and concentrated to yield 39.1 mg of a brown oil (0.218 mmol, 22%). ^{19}F NMR analysis revealed an *o*:*m*:*p* ratio of 11:10:79.

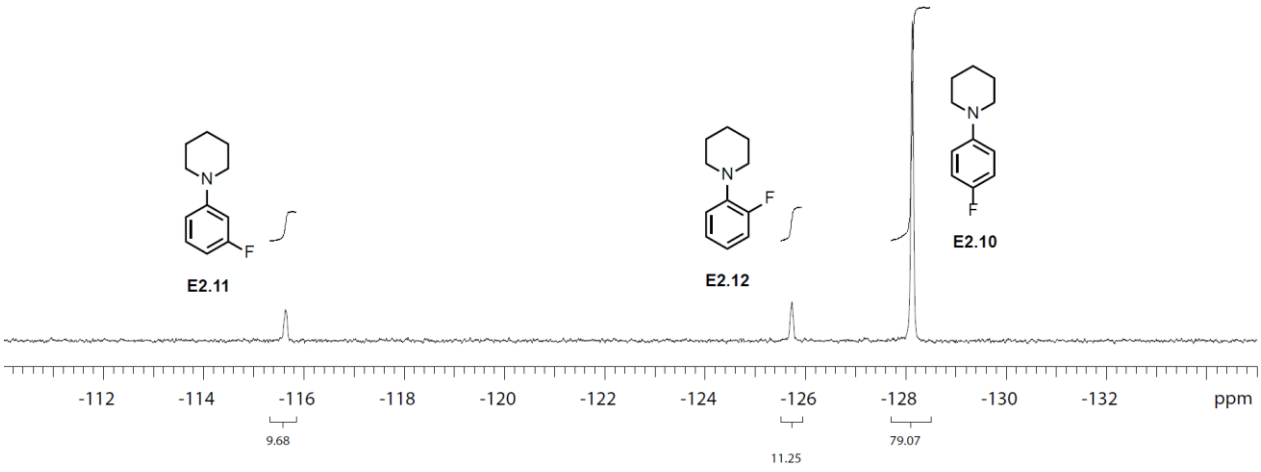
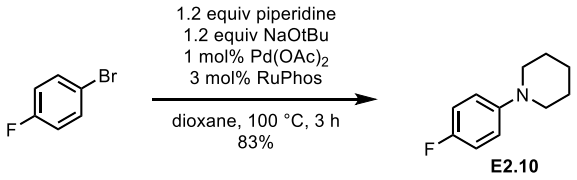


Figure E2.12. ^{19}F NMR analysis of product mixture of piperidine aminium radical substitution ($CDCl_3$, 23 °C)

E2.12 Synthesis of Authentic Samples of E2.10, E2.11, and E2.12

1-(4-Fluorophenyl)piperidine (E2.10)



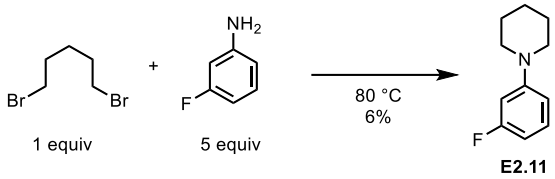
To a flame-dried 50 mL Schlenk flask were added 22.5 mg palladium acetate (22.5 mg, 0.100 mmol, 1.00

mol%), 140. mg RuPhos (0.300 mmol, 3.00 mol%), and 1.153 g of sodium *tert*-butoxide (12.00 mmol, 1.20 equiv). The flask was sealed with a septum, then evacuated and refilled with N_2 three times. Anhydrous dioxane (10.0 mL) was added via syringe through the septum, followed by 1.75 g 4-fluorobromobenzene (10.0 mmol, 1.00 equiv) and 1.19 mL piperidine (12.0 mmol, 1.20 equiv). The mixture was degassed via N_2 sparge for 10 minutes, then heated at 100 °C for 3 hours. The reaction mixture was diluted with ethyl acetate to 50 mL, and filtered through celite to remove the precipitated palladium metal. The filtrate was washed with water (3 × 50 mL) and brine (2 × 50 mL), dried over $NaSO_4$, and concentrated. The residue was purified by flash chromatography on silica gel (hexanes → 19:1 hexanes:EtOAc) to yield 1.48 g of the title compound as a brown oil (8.28 mmol, 83%).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.94–7.90 (m, 2H), 7.88–7.84 (m, 2H), 7.48–7.43 (m, 2H), 7.30–7.25 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 167.1 (s), 161.8 (d, J = 247.6 Hz), 134.4 (s), 131.5 (s), 128.3 (d, J = 8.7 Hz), 127.5 (d, J = 3.2 Hz), 123.7 (s), 116.1 (d, J = 22.5 Hz). ^{19}F NMR (470 MHz, $CDCl_3$, 23 °C, δ): –128.1.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{11}H_{15}FN$ [M+H]+, 180.1183; found, 180.1182.

1-(3-Fluorophenyl)piperidine (E2.11)



To a 20 mL vial were added 0.55 mL 1,5-dibromopentane (4.0 mmol, 1.0 equiv) and 1.92 mL 3-fluoroaniline (20.0 mmol, 5.0 equiv). The vial was sealed, and the mixture was heated with stirring at 80 °C for 4 hours, after which the mixture was allowed to come to room temperature, and 10 mL of 6 M NaOH was added. The mixture was then extracted with diethyl ether (3 × 10 mL), and the combined organic layers were concentrated. To the residue was added 10 mL Ac_2O, and the mixture was stirred for 30 minutes at room temperature. To the mixture was added 20 mL of 1 M HCl and 10 mL water. The

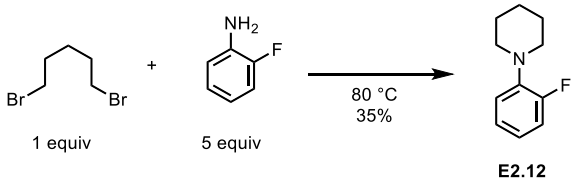
mixture was extracted with dichloromethane (2 × 20 mL), then basified to pH 14 with 6 M NaOH. The basic mixture was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, and concentrated to give a brown oil. The brown oil was distilled with a Hickmann still to give 126. mg of a colorless oil.

To remove the remaining 3-fluoroacetanilide impurity, the oil was dissolved in 20 mL diethyl ether, and extracted with (3 × 10 mL) 0.1 HCl. The combined acidic aqueous layers were basified to pH 14 with 6 M NaOH, then extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated to yield 40.0 mg of **E2.11** as a colorless liquid (0.223 mmol, 6%).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.20–7.14 (m, 1H), 6.71–6.68 (m, 1H), 6.64–6.59 (m, 1H), 6.52–6.47 (m, 1H), 3.20–3.16 (m, 4H), 1.74–1.68 (m, 4H), 1.63–1.58 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 163.9 (d, J = 242.6 Hz), 153.6 (d, 10.9 Hz), 129.9 (d, J = 10.1 Hz), 111.4 (d, J = 2.2 Hz), 105.1 (d, J = 21.6 Hz), 102.8 (d, J = 24.8 Hz), 50.0 (s), 25.5 (s), 24.2 (s). ^{19}F NMR (470 MHz, $CDCl_3$, 23 °C, δ): –115.6.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{11}H_{15}FN$ $[M+H]^+$, 180.1183; found, 180.1183.

1-(2-Fluorophenyl)piperidine (E2.12)



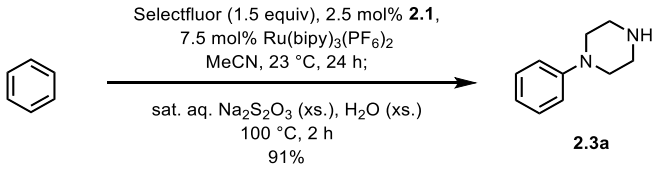
To a 20 mL vial were added 2.20 mL 1,5-dibromopentane (16.2 mmol, 1.00 equiv) and 7.80 mL 3-fluoroaniline (80.8 mmol, 5.00 equiv). The vial was sealed, and the mixture was heated with stirring at 80 °C for 24 hours, after which the mixture was allowed to come to room temperature, and 20 mL of 1 M NaOH was added. The mixture was then extracted with dichloromethane (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4, then concentrated. To the residue was added 50 mL Ac_2O, and the

mixture was stirred for 2 hours at room temperature. To the solution was added 50 mL of 1 M HCl and ice. The mixture was extracted with dichloromethane (5 × 25 mL), then basified to pH 14 with 6 M NaOH. The basic mixture was extracted with dichloromethane (5 × 25 mL). The combined organic layers were dried over Na_2SO_4, and concentrated to give 994. mg of the title compound as a yellow oil (5.55 mmol, 35%).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.09–6.97 (m, 3H), 6.95–6.90 (m, 1H), 3.07–3.04 (m, 4H), 1.81–1.76 (m, 4H), 1.64–1.58 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 155.8 (d, J = 245.6 Hz), 141.3 (d, J = 8.4 Hz), 124.2 (d, J = 3.6 Hz), 121.9 (d, J = 7.9 Hz), 119.1 (d, J = 3.2 Hz), 115.8 (d, J = 21.1 Hz), 52.0 (s), 26.1 (s), 24.2 (s). ^{19}F NMR (470 MHz, $CDCl_3$, 23 °C, δ): –125.7.

E2.13 Procedures for the Preparation of Aryl Piperazines

1-Phenylpiperazine (2.3a)



A 100 mL pressure tube was charged with palladium complex **2.1** (17.8 mg, 28.0 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (72.1 mg, 83.9 μmol, 7.50 mol%), and Selectfluor (595. mg, 1.68 mmol, 1.50 equiv). Acetonitrile (5.6 mL, c = 0.20 M) was added, followed by benzene (100. μL, 1.12 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (11 mL) and water (11 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL) and ethylenediamine (1.5 mL) were added and the organic layer was washed with 6 M aqueous sodium hydroxide (5 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were extracted with 1 M aqueous hydrochloric acid (2 × 10 mL). Ethylenediamine (6.5 mL) was added to the combined acidic aqueous layers, followed by basification

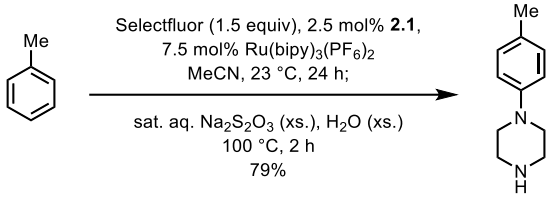
with 6 M aqueous sodium hydroxide (5 mL). The basic aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (190. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (95.5/4.0/0.5 (v/v/v)) to afford 163. mg of the title compound as a yellow oil (91% yield).

R_f = 0.32 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.27 (dd, *J* = 9.0, 7.8 Hz, 2H), 6.94 (d, *J* = 7.8 Hz, 2H), 6.86 (t, *J* = 7.8 Hz, 1H), 3.14–3.16 (m, 4H), 3.03–3.05 (m, 4H), 1.65 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 151.9, 129.2, 119.9, 116.3, 50.5, 46.3.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{10}H_{15}N_2$ $[M+H]^+$, 163.1230; found, 163.1238.

1-(*p*-Tolyl)piperazine (2.3b)



2.3b

A 100 mL pressure tube was charged with palladium complex **2.1** (13.6 mg, 21.4 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (55.2 mg, 64.2 μmol, 7.50 mol%), and Selectfluor (455. mg, 1.28 mmol, 1.50 equiv). Acetonitrile (4.3 mL, c = 0.20 M) was added, followed by toluene (91.1 μL, 0.856 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (8.6 mL) and water (8.6 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL) and ethylenediamine (1.5 mL) were added and the organic layer was washed with 6 M aqueous sodium hydroxide (5 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were extracted with 1 M aqueous hydrochloric acid (2 × 15 mL).

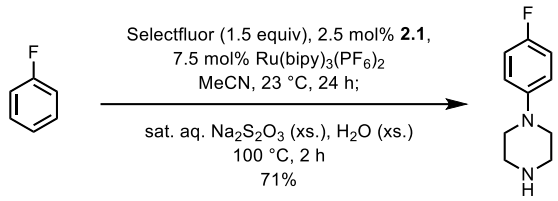
Ethylenediamine (5.0 mL) was added to the combined acidic aqueous layers, followed by basification with 6 M aqueous sodium hydroxide (8 mL). The basic aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (143. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (97.5/2.0/0.5 (v/v/v)) to afford 119. mg of the title compound **2.3b** as a yellow oil (79% yield).

R_f = 0.35 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.07–7.09 (m, 2H), 6.84–6.86 (m, 2H), 3.07–3.10 (m, 4H), 3.01–3.04 (m, 4H), 2.28 (s, 3H), 1.68 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 149.7, 129.7, 129.3, 116.5, 50.9, 46.1, 20.5.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{11}H_{17}N_2$ $[M+H]^+$, 177.1386; found, 177.1387.

1-(4-Fluorophenyl)piperazine (2.3c)



2.3c

A 100 mL pressure tube was charged with palladium complex **2.1** (17.0 mg, 26.6 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (68.7 mg, 80.0 μmol, 7.50 mol%), and Selectfluor (566. mg, 1.60 mmol, 1.50 equiv). Acetonitrile (11 mL, c = 0.10 M) was added, followed by fluorobenzene (100. μL, 1.06 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (21 mL) and water (21 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (30 mL) and ethylenediamine (1.5 mL) were added and the organic layer was washed with 6 M aqueous sodium hydroxide (5 mL). The aqueous layer was extracted with dichloromethane (2 ×

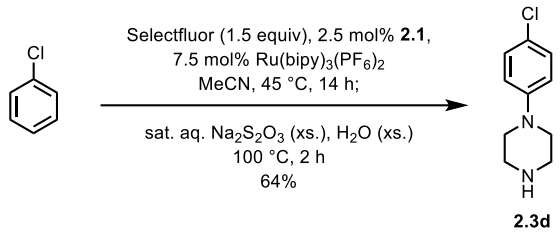
15 mL). The combined organic layers were extracted with 1 M aqueous hydrochloric acid (2 × 15 mL). Ethylenediamine (6.5 mL) was added to the combined acidic aqueous layers, followed by basification with 6 M aqueous sodium hydroxide (5 mL). The basic aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (160. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (91.5/8.0/0.5 (v/v/v)) to afford 136. mg of the title compound as a yellow oil (71% yield).

R_f = 0.14 (dichloromethane/methanol/28% aqueous ammonium hydroxide 91.5:8.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 6.94–6.96 (m, 2H), 6.85–6.87 (m, 2H), 3.03–3.07 (m, 8H), 2.45 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 157.3 (d, J = 238.8 Hz), 148.5 (d, J = 2.8 Hz), 118.0 (d, J = 7.7 Hz), 115.6 (d, J = 22.0 Hz), 51.4 (s), 46.1 (s). ^{19}F NMR (500 MHz, $CDCl_3$, 23 °C, δ): –127.4.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{10}H_{14}FN_2$ $[M+H]^+$, 181.1136; found, 181.1128.

1-(4-Chlorophenyl)piperazine (2.3d)



2.3d

A 100 mL pressure tube was charged with palladium complex **2.1** (15.6 mg, 24.6 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (63.3 mg, 73.7 μmol, 7.50 mol%), and Selectfluor (522 mg, 1.47 mmol, 1.50 equiv). Acetonitrile (4.9 mL, c = 0.20 M) was added, followed by chlorobenzene (100. μL, 0.982 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 45 °C for 14 h. Saturated aqueous sodium thiosulfate (9.8 mL) and water (9.8 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a

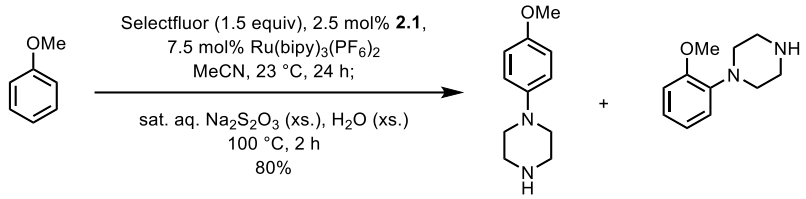
separatory funnel. Dichloromethane (20 mL), ethylenediamine (0.5 mL), and 6 M aqueous sodium hydroxide (5 mL) were added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were extracted with 1 M aqueous hydrochloric acid (3 × 10 mL). Ethylenediamine (5.0 mL) was added to the combined acidic aqueous layers, followed by basification with 6 M aqueous sodium hydroxide (5 mL). The basic aqueous layer was extracted with dichloromethane (4 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (180. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (94.5/5.0/0.5 (v/v/v)) to afford a yellow solid (171. mg). The residue was further purified by preparatory HPLC with a solvent mixture of water/acetonitrile/trifluoroacetic acid (89.9/10.0/0.1 to 49.9/50.0/0.1 (v/v/v)) to afford 125. mg of the title compound as a bright yellow solid (64% yield).

R_f = 0.26 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.18–7.21 (m, 2H), 6.81–6.84 (m, 2H), 3.08–3.10 (m, 4H), 3.00–3.02 (m, 4H), 1.62 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, 23 °C, δ): 150.6, 129.0, 124.6, 117.4, 50.5, 46.2.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{10}H_{14}ClN_2$ $[M+H]^+$, 197.0846; found, 197.0846.

1-(4-Methoxyphenyl)piperazine (2.3e)



A 100 mL pressure tube was charged with palladium complex **2.1** (14.6 mg, 23.0 μmol. 2.50 mol%),

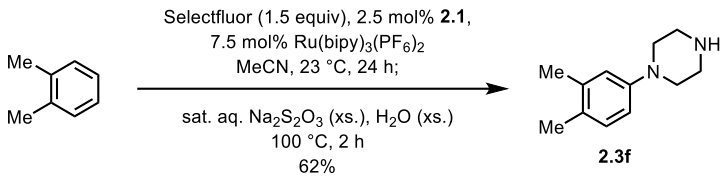
$Ru(bipy)_3(PF_6)_2$ (59.3 mg, 69.0 μmol, 7.50 mol%), and Selectfluor (489. mg, 1.38 mmol, 1.50 equiv). Acetonitrile (4.6 mL, c = 0.20 M) was added, followed by anisole (100. μL, 0.920 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (9.2 mL) and water (9.2 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (25 mL) and ethylenediamine (3.0 mL) were added and the organic layer was washed with 6 M aqueous sodium hydroxide (5 mL). The aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were extracted with 1 M aqueous hydrochloric acid (2 × 15 mL). Ethylenediamine (6.5 mL) was added to the combined acidic aqueous layers, followed by basification with 6 M aqueous sodium hydroxide (5 mL). The basic aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (170. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (93.0/6.5/0.5 (v/v/v)) to afford 152. mg of the title compound as a light yellow solid (80% yield), containing 1-(2-methoxyphenyl)piperazine (6%). For characterization, 35. mg of the mixture was further purified by preparatory HPLC with a solvent mixture of water/acetonitrile/trifluoroacetic acid (89.9/10.0/0.1 to 69.9/30.0/0.1 (v/v/v)) to afford 23. mg of the title compound as an off-white solid.

R_f = 0.46 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 6.86–6.89 (m, 2H), 6.81–6.84 (m, 2H), 3.74 (s, 3H), 3.03 (s, 8H), 2.74 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 153.9, 146.1, 118.4, 114.5, 55.6, 51.7, 46.1.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{11}H_{17}N_2O$ $[M+H]^+$, 193.1335; found, 193.1332.

1-(3,4-Dimethylphenyl)piperazine (2.3f)



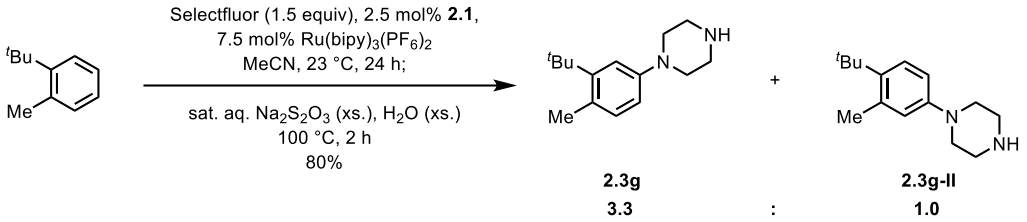
A 100 mL pressure tube was charged with palladium complex **2.1** (13.2 mg, 20.7 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (53.4 mg, 62.1 μmol, 7.50 mol%), and Selectfluor (440. mg, 1.24 mmol, 1.50 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added, followed by *o*-xylene (100. μL, 1.00 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (8.3 mL) and water (8.3 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, ethylenediamine (5.0 mL) and water (15 mL) were added, and the mixture was stirred for 1 h further. The reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were extracted with 1 M aqueous hydrochloric acid (3 × 10 mL). Ethylenediamine (2.0 mL) was added to the combined acidic aqueous layers, followed by basification with 6 M aqueous sodium hydroxide (6 mL). The basic aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (117. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (97.5/2.0/0.5 (v/v/v)) to afford 97.0 mg of the title compound as a yellow solid (62% yield).

R_f = 0.32 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.03 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 2.6 Hz, 1H), 6.69 (dd, *J* = 8.2, 2.6 Hz, 1H), 3.09 (m, 4H), 3.03 (m, 4H), 2.24 (s, 3H), 2.19 (s, 3H), 1.72 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 150.3, 137.2, 130.2, 128.2, 118.2, 114.0, 51.2, 46.4, 20.3, 18.9.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{12}H_{19}N_2$ $[M+H]^+$, 191.1543; found, 191.1538.

1-(3-(*tert*-Butyl)-4-methylphenyl)piperazine (2.3g), 1-(4-(*tert*-Butyl)-3-methylphenyl)piperazine (2.3g-II)



A 100 mL pressure tube was charged with palladium complex **2.1** (7.16 mg, 11.2 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (29.0 mg, 33.8 μmol, 7.50 mol%), and Selectfluor (239. mg, 0.675 mmol, 1.50 equiv). Acetonitrile (2.2 mL, c = 0.20 M) was added, followed by 1-(*tert*-butyl)-2-methylbenzene (75.0 μL, 0.450 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (4.5 mL) and water (4.5 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL), ethylenediamine (0.5 mL), water (5 mL) and 6 M aqueous sodium hydroxide (0.5 mL) were added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were extracted with 1 M aqueous hydrochloric acid (3 × 10 mL). Ethylenediamine (2.0 mL) was added to the combined acidic aqueous layers, followed by basification with 6 M aqueous sodium hydroxide (5 mL). The basic aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (91.4 mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (96.5/3.0/0.5 (v/v/v)) to afford 83.5 mg of the title compounds (**2.3g**: **2.3g-II** = 3.3 : 1.0, see Figure E2.13 and Figure E2.14 for structural assignment) as a yellow oil (80% yield).

R_f = 0.25 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): **2.3g** 7.01–7.03 (m, 2H), 6.68 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.09–3.13 (m, 4H), 3.01–3.06 (m, 4H), 2.46 (s, 3H), 1.88 (s, 1H), 1.40 (s, 9H). **2.3g-II** 7.26 (d, *J* = 8.7 Hz, 1H), 6.67–6.72 (m, 2H), 3.09–3.13 (m, 4H), 3.01–3.06 (m, 4H), 2.51 (s, 3H), 1.38 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 150.0, 149.6, 148.6, 139.5, 137.1, 133.4, 128.0, 126.9, 120.6, 115.6, 113.6, 113.0, 51.3, 50.4, 46.4, 46.3, 36.2, 35.2, 31.2, 30.8, 23.6, 22.5.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{15}H_{25}N_2$ $[M+H]^+$, 233.2012; found, 233.2022.

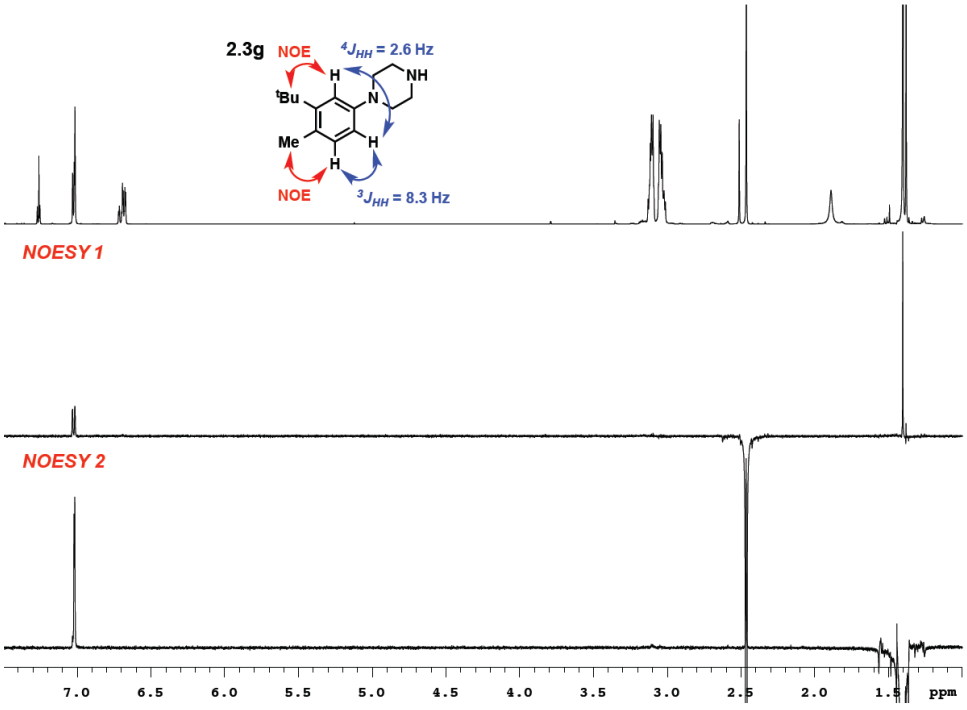


Figure E2.13. Structural assignment of **2.3g** by 1-D NOESY NMR

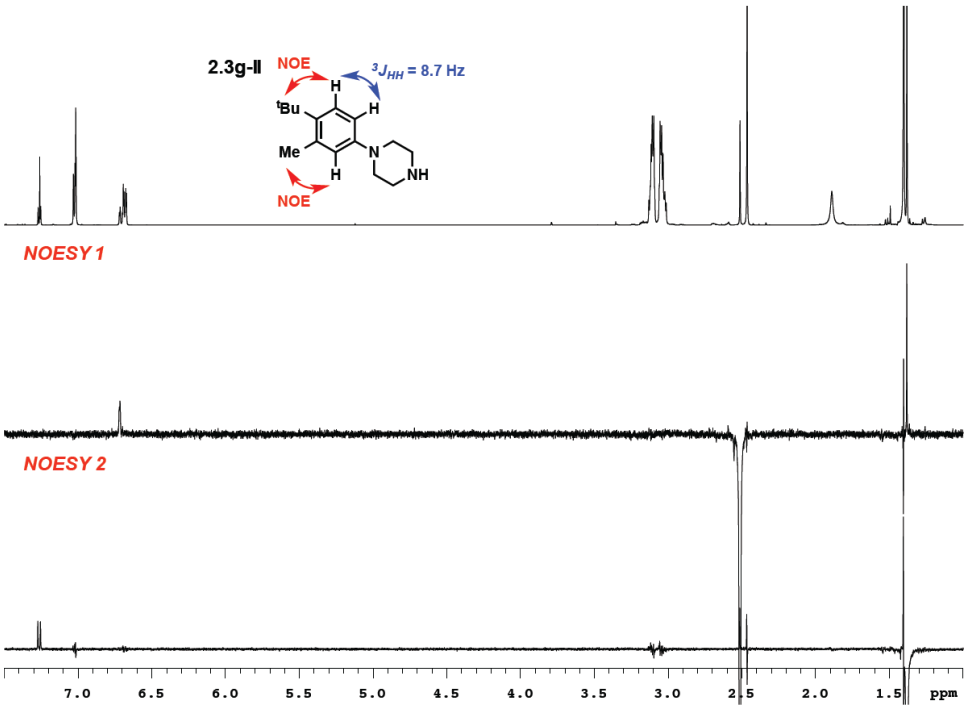
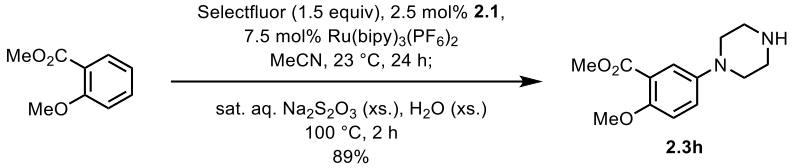


Figure E2.14. Structural assignment of **2.3g-II** by 1-D NOESY NMR

Methyl 2-methoxy-5-(piperazin-1-yl)benzoate (2.3h)



A 100 mL pressure tube was charged with palladium complex **2.1** (11.1 mg, 17.4 µmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (44.9 mg, 52.2 µmol, 7.50 mol%), and Selectfluor (370. mg, 1.04 mmol, 1.50 equiv). Acetonitrile (3.5 mL, c = 0.20 M) was added, followed by methyl 2-methoxybenzoate (100. µL, 0.700 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (7.0 mL) and water (7.0 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL) and ethylenediamine (0.3 mL) were added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined

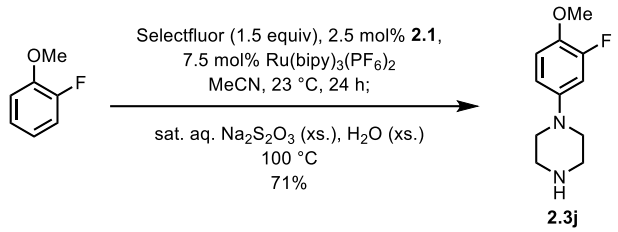
organic layers were extracted with 10% aqueous glacial acetic acid (2 × 15 mL). The combined acidic aqueous layers were basified with ethylenediamine (4.0 mL). The basic aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (175. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (96.5/3.0/0.5 (v/v/v)) to afford 155. mg of the title compound as a yellow oil (89% yield).

R_f = 0.16 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (125 MHz, $CDCl_3$, 23 °C, δ): 7.35 (d, *J* = 3.0 Hz, 1H), 7.03 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.98–3.03 (m, 8H), 1.67 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, 23 °C, δ): 166.9, 153.2, 145.6, 122.1, 120.3, 119.8, 113.5, 56.6, 52.1, 51.5, 46.2.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{13}H_{18}N_2O_3Na$ $[M+Na]^+$, 273.1210; found, 273.1207.

1-(3-Fluoro-4-methoxyphenyl)piperazine (2.3j)



2.3j

A 100 mL pressure tube was charged with palladium complex **2.1** (15.9 mg, 25.0 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor (531.5 mg, 1.500 mmol, 1.50 equiv), and 2-fluoroanisole (112 μL, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 1 h. After cooling to 23 °C, the reaction mixture was filtered through celite, and the filter cake was extracted with 5 × 15 mL acetonitrile and 2 × 15 mL water. The acetonitrile was removed from the filtrate by rotary evaporation. To the remaining aqueous mixture 0.50 mL ethylene diamine was added, and the

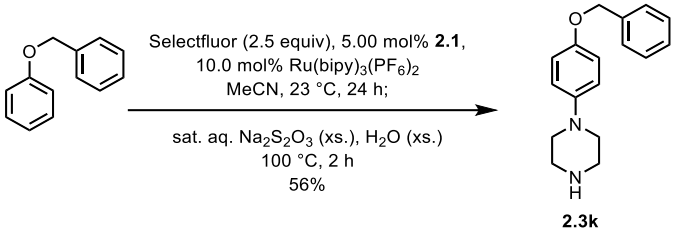
aqueous mixture was basified to pH 14 with 6 M NaOH, then transferred to a separatory funnel. The aqueous layer was extracted with dichloromethane (5 × 15 mL). The combined organic layers were extracted with 1 M HCl (5 × 15 mL). To the combined acidic aqueous layers was added ethylene diamine (0.5 mL), and the mixture was basified to pH 14 with 6 M NaOH. The basic aqueous layer was extracted with dichloromethane (5 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The residue was purified by chromatography on silica gel eluting with dichloromethane/methanol 9:1 (v/v) to afford 150. mg of the title compound as a brown oil (71% yield).

R_f = 0.28 (dichloromethane/methanol 9:1 (v/v)).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 6.86 (dd, *J* = 9.1, 9.1 Hz, 1H), 6.69 (dd, *J* = 14.0, 2.8 Hz, 1H), 6.59 (m, 1H), 3.81 (s, 4H), 3.63 (br, 1H), 3.05 (s, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 152.8 (d, *J* = 243.7 Hz), 146.3 (d, *J* = 7.8 Hz), 141.3 (d, *J* = 10.6 Hz), 114.6 (d, *J* = 2.9 Hz), 111.6 (d, *J* = 3.5 Hz), 105.7 (d, *J* = 21.1 Hz), 56.9 (s), 50.5 (s), 45.5 (s).

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{11}H_{16}FN_2O$ $[M+H]^+$, 211.1247; found, 211.1245.

1-(4-(Benzyloxy)phenyl)piperazine (2.3k)



2.3k

A 100 mL pressure tube was charged with palladium complex **2.1** (31.8 mg, 50.0 μmol. 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (86.0 mg, 100. μmol, 10.0 mol%), Selectfluor (886. mg, 2.50 mmol, 2.50 equiv), and benzyl phenyl ether (184. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at

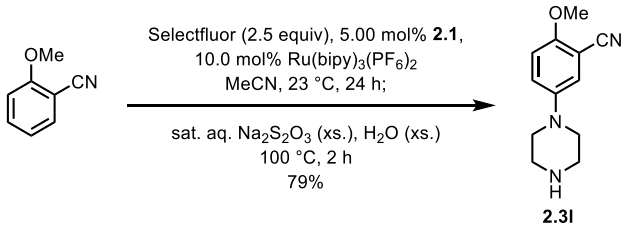
100 °C for 2 h. After cooling to 23 °C, 0.5 mL ethylene diamine was added and the reaction mixture was basified to pH 14 with 6 M NaOH, then filtered through celite. The filter cake was extracted with acetonitrile (5 × 15 mL). The acetonitrile was removed from the filtrate by rotary evaporation. The remaining aqueous mixture was transferred to a separatory funnel and extracted with dichloromethane (5 × 15 mL). The combined organic layers were extracted with 1 M HCl (5 × 15 mL). To the combined acidic aqueous layers was added ethylene diamine (0.5 mL), and the mixture was basified to pH 14 with 6 M NaOH. The basic aqueous layer was extracted with dichloromethane (5 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The residue was purified by chromatography on silica gel eluting with dichloromethane/methanol 19:1 ⟶ 9:1 (v/v) to afford 151. mg of the title compound as an off-white powder (56% yield).

R_f = 0.35 (dichloromethane/methanol 9:1 (v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.44–7.41 (m, 2H), 7.40–7.33 (m, 2H), 7.34–7.30 (m, 1H), 6.94–6.88 (m, 4H), 5.02 (s, 2H), 3.07 (s, 8H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 153.1, 146.2, 137.3, 128.5, 127.8, 127.5, 118.3, 115.6, 70.5, 51.4, 46.0.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{17}H_{21}N_2O$ $[M+H]^+$, 269.1648; found, 269.1635.

2-Methoxy-5-(piperazin-1-yl)benzonitrile (2.3l)



2.3l

A 100 mL pressure tube was charged with palladium complex **2.1** (31.8 mg, 50.0 μmol. 5.00 mol%), $Ru(bipy)_3(PF_6)_2$ (86.0 mg, 100. μmol, 10.0 mol%), Selectfluor (886. mg, 2.50 mmol, 2.50 equiv), and 2-methoxybenzonitrile (122. μL, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via

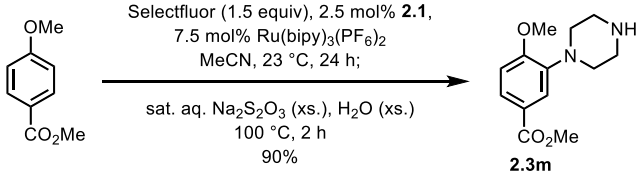
syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, 0.5 mL ethylene diamine was added and the reaction mixture was basified to pH 14 with 6 M NaOH, then filtered through celite. The filter cake was extracted with acetonitrile (5 × 15 mL). The acetonitrile was removed from the filtrate by rotary evaporation. The remaining aqueous mixture was transferred to a separatory funnel and extracted with dichloromethane (5 × 15 mL), then 9:1 dichloromethane/methanol (v/v) (3 × 15 mL). The combined organic layers were extracted with 1 M HCl (5 × 15 mL). To the combined acidic aqueous layers was added ethylene diamine (0.5 mL), and the mixture was basified to pH 14 with 6 M NaOH. The basic aqueous layer was extracted with 9:1 dichloromethane/methanol (v/v) (6 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The residue was purified by chromatography on silica gel eluting with dichloromethane/methanol 9:1 (v/v) to afford 190. mg of the title compound as a brown oil (79% yield).

R_f = 0.31 (dichloromethane/methanol 9:1 (v/v)).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.12 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.07 (d, *J* = 3.1 Hz, 1H), 6.88 (d, *J* = 9.1 Hz, 1H), 3.86 (s, 4H), 3.04 (s, 4H), 2.56 (br, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 155.2, 145.8, 123.2, 121.1, 116.7, 112.3, 101.7, 56.2, 50.9, 40.8.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{12}H_{16}N_3O$ $[M+H]^+$, 218.1293; found, 218.1300.

Methyl 4-methoxy-3-(piperazin-1-yl)benzoate (2.3m)



A 100 mL pressure tube was charged with palladium complex **2.1** (15.9 mg, 25.0 μmol. 2.50 mol%),

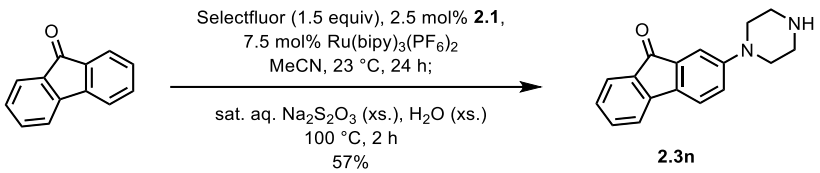
$Ru(bipy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor (531. mg, 1.50 mmol, 1.50 equiv), and methyl 4-methoxybenzoate (166. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, ethylenediamine (1.5 mL) and water (15 mL) were added, and the mixture was stirred for 1 h further. The reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were extracted with 10% aqueous glacial acetic acid (2 × 15 mL). The combined acidic aqueous layers were basified with ethylenediamine (4.5 mL). The basic aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (252. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (91.5/8.0/0.5 (v/v/v)) to afford 226. mg of the title compound as a yellow solid (90% yield).

R_f = 0.16 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.74 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.09–3.11 (m, 8H), 1.67 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 167.1, 156.2, 141.3, 125.6, 122.9, 119.7, 110.5, 55.8, 52.0, 51.6, 46.0.

Mass Spectrometry: HRMS-FIA (m/z) calcd for $C_{13}H_{18}N_2O_3Na$ $[M+Na]^+$, 273.1210; found, 273.1215.

2-(Piperazin-1-yl)-9*H*-fluoren-9-one (2.3n)



2.3n

A 100 mL pressure tube was charged with palladium complex **2.1** (8.83 mg, 13.9 μmol. 2.50 mol%),

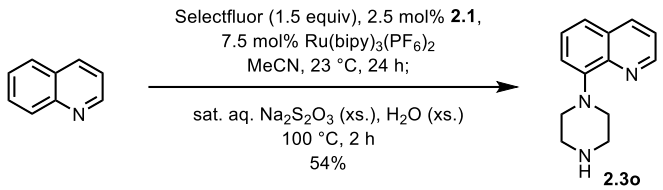
$Ru(bipy)_3(PF_6)_2$ (35.8 mg, 41.6 μmol, 7.50 mol%), Selectfluor (295. mg, 0.832 mmol, 1.50 equiv), and fluorenone (100. mg, 0.555 mmol, 1.00 equiv). Acetonitrile (2.8 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (5.5 mL) and water (5.5 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL) and ethylenediamine (0.3 mL) were added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were extracted with 10% aqueous glacial acetic acid (3 × 15 mL). Ethylenediamine (3.0 mL) was added to the combined acidic aqueous layers, followed by basification with saturated aqueous sodium carbonate (5 mL). The basic aqueous layer was extracted with dichloromethane (4 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (102. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (96.0/3.5/0.5 (v/v/v)) to afford 83.1 mg of the title compound as a yellow solid (57% yield).

R_f = 0.34 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.57 (d, *J* = 7.3 Hz, 1H), 7.40 (td, *J* = 7.4, 1.1 Hz, 1H), 7.34–7.36 (m, 2H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.15 (td, *J* = 7.4, 1.1 Hz, 1H), 6.93 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.19–3.21 (m, 4H), 3.02–3.04 (m, 4H), 1.74 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 194.6, 152.9, 145.4, 135.7, 135.1, 134.9, 134.4, 127.6, 124.3, 121.2, 120.5, 119.5, 111.9, 50.1, 46.1.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{17}H_{17}N_2O$ $[M+H]^+$, 265.1335; found, 265.1341.

8-(Piperazin-1-yl)quinoline (2.3o)



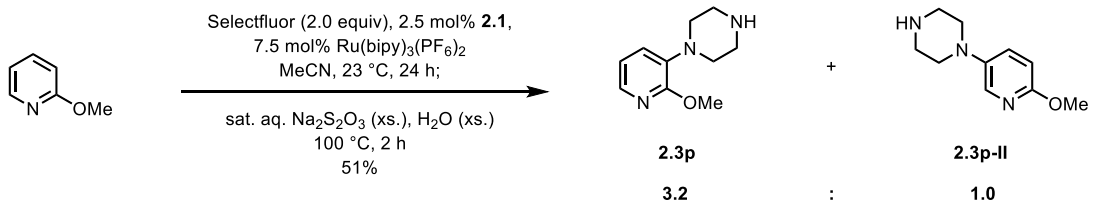
A 100 mL pressure tube was charged with palladium complex **2.1** (13.5 mg, 21.2 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (54.6 mg, 63.5 μmol, 7.50 mol%), and Selectfluor (450. mg, 1.27 mmol, 1.50 equiv). Acetonitrile (4.2 mL, c = 0.20 M) was added, followed by quinoline (100. μL, 84.6 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (8.5 mL) and water (8.5 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL) and ethylenediamine (2.5 mL) were added and the organic layer was washed with 6 M aqueous sodium hydroxide (5 mL). The aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were extracted with 1 M aqueous hydrochloric acid (2 × 15 mL). Ethylenediamine (5.0 mL) was added to the combined acidic aqueous layers, followed by basification with 6 M aqueous sodium hydroxide (5 mL). The basic aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (137. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (91.5/8.0/0.5 (v/v/v)) to afford 98.2 mg of the title compound as a yellow oil (54% yield).

R_f = 0.18 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 8.86 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.08 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.42–7.44 (m, 2H), 7.34 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.12 (dd, *J* = 6.5, 2.4 Hz, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 149.8, 148.3, 142.8, 136.6, 129.7, 126.8, 121.8, 120.9, 116.1, 53.2, 46.2.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{13}H_{16}N_3$ $[M+H]^+$, 214.1339; found, 214.1328.

1-(2-Methoxypyridin-3-yl)piperazine (2.3p), 1-(6-methoxypyridin-3-yl)piperazine (2.3p-II)



A 100 mL pressure tube was charged with palladium complex **2.1** (15.1 mg, 23.8 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (61.3 mg, 71.3 μmol, 7.50 mol%), and Selectfluor (674. mg, 1.90 mmol, 2.00 equiv). Acetonitrile (4.8 mL, c = 0.20 M) was added, followed by 2-methoxypyridine (100. μL, 0.951 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (9.5 mL) and water (9.5 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (15 mL) and ethylenediamine (2.5 mL) were added and the organic layer was washed with 6 M aqueous sodium hydroxide (5 mL). Volume of the aqueous layer was reduced by half and then the aqueous layer was extracted with dichloromethane (2 × 15 mL) and then mixture of dichloromethane/methanol (9.0/1.0 (v/v), 3 × 15 mL). The combined organic layers were extracted with 1 M aqueous hydrochloric acid (3 × 15 mL). Ethylenediamine (5.0 mL) was added to the combined acidic aqueous layers, followed by basification with 6 M aqueous sodium hydroxide (5 mL). The basic aqueous layer was extracted with dichloromethane (2 × 15 mL) and then mixture of dichloromethane/methanol (9.0/1.0 (v/v), 3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (120. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (96.0/3.5/0.5 (v/v/v)) to afford 94.5 mg of the title compounds (**2.3p**:**2.3p-II** = 3.2:1.0, see Figure E2.15 and Figure E2.16 for structural assignment) as a yellow oil (51% yield).

R_f = 0.16 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): **2.3p** 7.76 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.05 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.80 (dd, *J* = 7.7, 4.9 Hz, 1H), 3.95 (s, 3H), 2.98–3.02 (m, 8H), 2.19 (s, 1H). **2.3p-II** 7.74 (d, *J* = 3.0 Hz, 1H), 7.24 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 1H), 3.84 (s, 3H), 2.98-3.02 (m, 8H), 2.19 (s, 1H). ^{13}C NMR (500 MHz, $CDCl_3$, 23 °C, δ): **2.3p** 156.9, 139.0, 136.6, 124.7, 117.1, 53.4, 51.3, 46.1. **2.3p-II** 158.9, 142.9, 134.6, 129.8, 110.7, 53.4, 51.6, 46.1.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{10}H_{16}N_3O$ $[M+H]^+$, 194.1293; found, 194.1295.

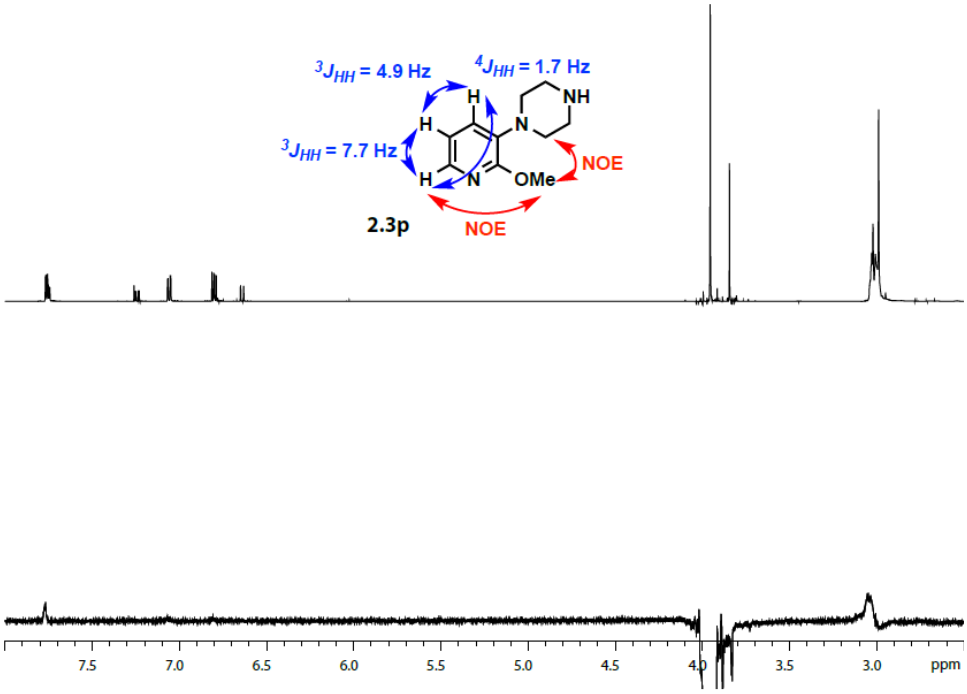


Figure E2.15. Structural assignment of **2.3p** by 1-D NOESY NMR

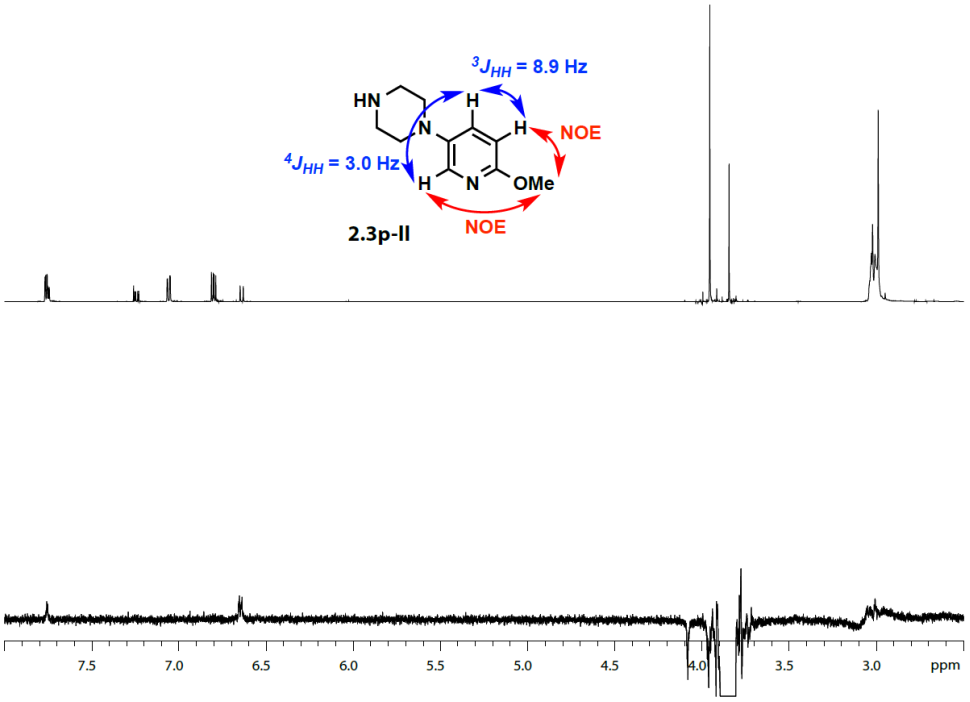
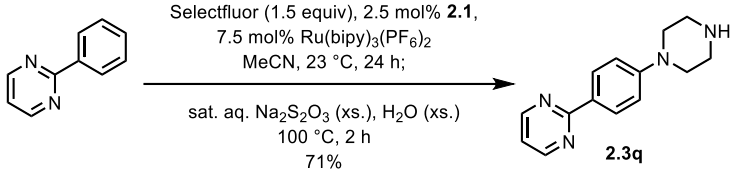


Figure E2.16. Structural assignment of **2.3p-II** by 1-D NOESY NMR

2-(4-(Piperazin-1-yl)phenyl)pyrimidine (2.3q)



A 100 mL pressure tube was charged with palladium complex **2.1** (15.9 mg, 25.0 µmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (64.5 mg, 75.0 µmol, 7.50 mol%), Selectfluor (531. mg, 1.50 mmol, 1.50 equiv), and 2-phenylpyrimidine (156. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was basified with aqueous 6 M sodium hydroxide solution (10 mL) and ethylenediamine (0.5 mL), filtered through celite rinsing with acetonitrile

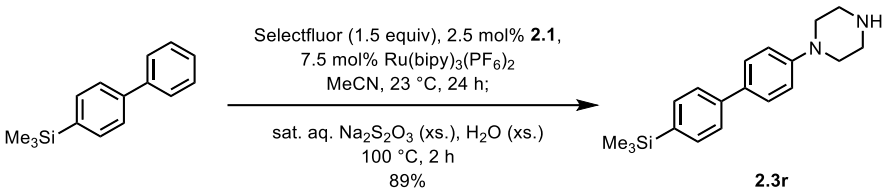
(5 × 15 mL), and acetonitrile removed *in vacuo* to afford a brown aqueous solution. The aqueous layer was transferred to a separatory funnel and extracted with a solvent mixture of methanol/dichloromethane (1/9 (v/v), 5 × 15 mL). The combined organic layers were extracted with aqueous 1M hydrochloric acid solution (3 × 15 mL). The combined acidic aqueous layers were basified to pH 14 with aqueous 6M sodium hydroxide solution and ethylenediamine (0.5 mL). The basic aqueous layer was extracted with a solvent mixture of methanol/dichloromethane (1/9 (v/v), 5 × 15 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol (9/1 (v/v)) to to afford 171. mg of the title compound as an off-white solid (71% yield).

R_f = 0.08 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (500 MHz, DMSO-d_6, 23 °C, δ): 8.77 (d, *J* = 5.0 Hz, 2H), 8.23 (d, *J* = 9.5 Hz, 2H), 7.27 (t, *J* = 4.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 3.21 (t, *J* = 5.0 Hz, 4H), 2.86 (t, *J* = 5.0 Hz, 4H). ^{13}C NMR (125 MHz, DMSO-d_6, 23 °C, δ): 163.5, 157.4, 153.0, 128.8, 126.7, 118.4, 114.1, 47.9, 45.2.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{14}H_{17}N_4$ $[M+H]^+$, 241.1448; found, 241.1457.

1-(4'-(Trimethylsilyl)-[1,1'-biphenyl]-4-yl)piperazine (2.3r)



A 100 mL pressure tube was charged with palladium complex **2.1** (7.03 mg, 11.0 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (28.5 mg, 33.1 μmol, 7.50 mol%), Selectfluor (235. mg, 0.662 mmol, 1.50 equiv), and [1,1'-biphenyl]-4-yltrimethylsilane (100. mg, 0.442 mmol, 1.00 equiv). Acetonitrile (2.2 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium

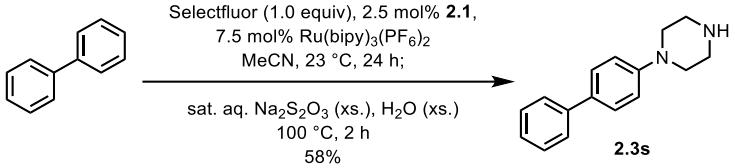
thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, ethylenediamine (2.5 mL) and water (20 mL) were added, and the mixture was stirred for 1 h further. The reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (220. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (97.5/2.0/0.5 (v/v/v)) to afford 122. mg of the title compound as a yellow solid (89% yield).

R_f = 0.31 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.56–7.60 (m, 4H), 7.53–7.55 (m, 2H), 6.99–7.02 (m, 2H), 3.21–3.23 (m, 4H), 3.06–3.08 (m, 4H), 2.16 (s, 1H), 0.31 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 151.2, 141.4, 138.2, 133.9, 132.3, 127.8, 125.9, 116.2, 50.2, 46.2, -0.9.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{19}H_{27}N_2Si$ $[M+H]^+$, 311.1938; found, 311.1950.

1-([1,1'-Biphenyl]-4-yl)piperazine (2.3s)



A 100 mL pressure tube was charged with palladium complex **2.1** (15.9 mg, 25.0 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor (531. mg, 1.00 mmol, 1.00 equiv), and 1,1'-biphenyl (154. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. An aliquot was removed, concentrated, redissolved in CD_3CN, and analyzed by ^{1}H NMR, which showed a 9:1 mixture of biphenyl–TEDA:biphenyl, with no significant double TEDAylation product:

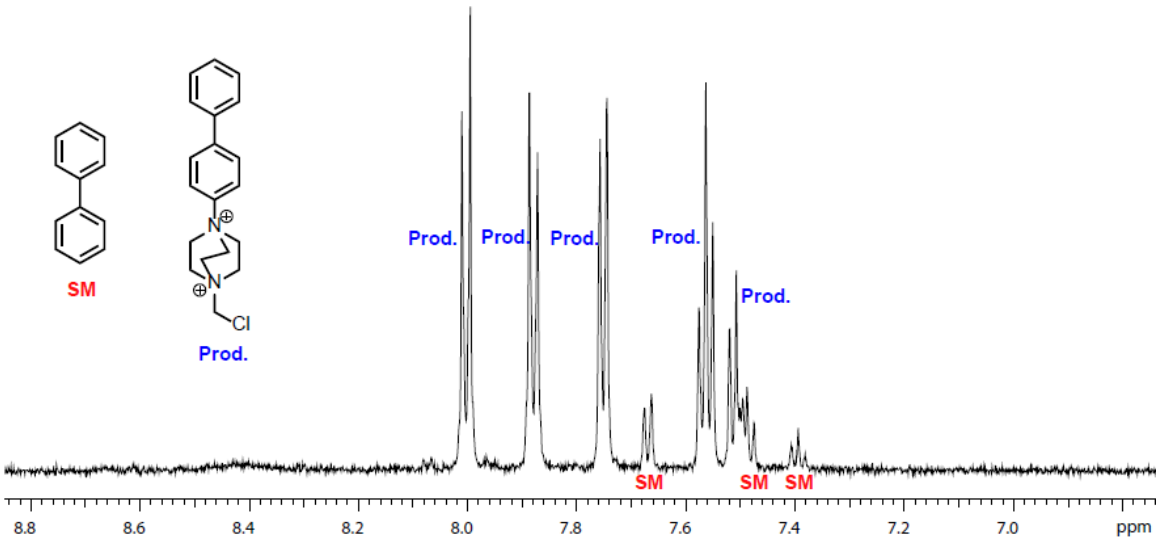


Figure E2.17. ^{1}H NMR of biphenyl TEDAylation reaction mixture (CD_3CN, 23 °C)

Saturated aqueous sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was basified with aqueous 6 M sodium hydroxide solution (10 mL) and ethylenediamine (0.5 mL), filtered through celite rinsing with acetonitrile (5 × 15 mL), and acetonitrile removed *in vacuo* to afford a brown aqueous solution. The aqueous layer was transferred to a separatory funnel and extracted with a solvent mixture of methanol/dichloromethane (1/9 (v/v), 5 × 15 mL). The combined organic layers were extracted with aqueous 1M hydrochloric acid solution (3 × 15 mL). The combined acidic aqueous layers were basified to pH 14 with aqueous 6M sodium hydroxide solution and ethylenediamine (0.5 mL). The basic aqueous layer was extracted with a solvent mixture of methanol/dichloromethane (1/9 (v/v), 5 × 15 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol (9/1 (v/v)) to afford 138. mg of the title compound as an off-white solid (58% yield).

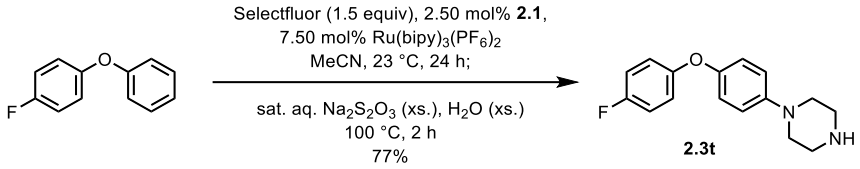
R_f = 0.10 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, F_3CO_2D, 23 °C, δ): 7.83 (m, 2H), 7.65 (m, 2H), 7.53 (m, 2H),

7.41 (m, 2H), 7.36 (m, 1H), 4.31 (s, 4H), 4.15 (s, 4H). ^{13}C NMR (125 MHz, F_3CO_2D, 23 °C, δ): 149.6, 141.4, 133.0, 132.2, 132.0, 130.1, 123.6, 55.9, 45.8.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{16}H_{19}N_2$ $[M+H]^+$, 239.1543; found, 239.1545.

1-(3-Fluoro-4-methoxyphenyl)piperazine (2.3t)



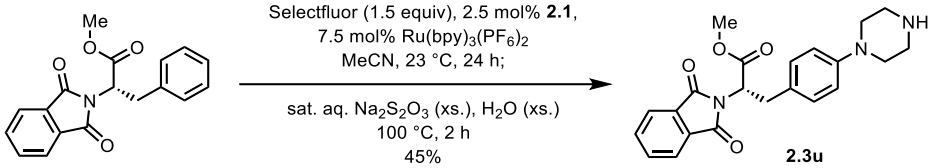
A 100 mL pressure tube was charged with palladium complex **2.1** (15.9 mg, 25.0 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor (532. mg, 1.50 mmol, 1.50 equiv), and phenyl 4-fluorophenyl ether (188. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was filtered through celite, and the filter cake was extracted with 5 × 15 mL acetonitrile and 2 × 15 mL water. The acetonitrile was removed from the filtrate by rotary evaporation. To the remaining aqueous mixture 0.50 mL ethylene diamine was added, and the aqueous mixture was basified to pH 14 with 6 M NaOH, then transferred to a separatory funnel. The aqueous layer was extracted with dichloromethane (7 × 30 mL). The combined organic layers were extracted with 1 M HCl (5 × 30 mL). To the combined acidic aqueous layers was added ethylene diamine (0.5 mL), and the mixture was basified to pH 14 with 6 M NaOH. The basic aqueous layer was extracted with dichloromethane (5 × 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (220. mg). The residue was purified by chromatography on silica gel eluting with dichloromethane/methanol 19:1 ⟶ 9:1 (v/v) to afford 190. mg of the title compound as an off-white powder (77% yield).

R_f = 0.35 (dichloromethane/methanol 9:1 (v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.00–6.95 (m, 2H), 6.94–6.88 (m, 6H), 3.74 (br, 1H), 3.19–3.12 (m, 4H), 3.12–3.06 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 158.3 (d, J = 240.4 Hz), 154.1 (d, J = 2.5 Hz), 156.6 (s), 147.9 (s), 119.8 (s), 119.2 (d, J = 8.1 Hz), 117.9 (s), 116.0 (d, J = 23.2 Hz), 50.6 (s), 45.7 (s).

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{16}H_{18}FN_2O$ $[M+H]^+$, 273.1398; found, 273.1397.

Methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(4-(piperazin-1-yl)phenyl)propanoate (2.3u)

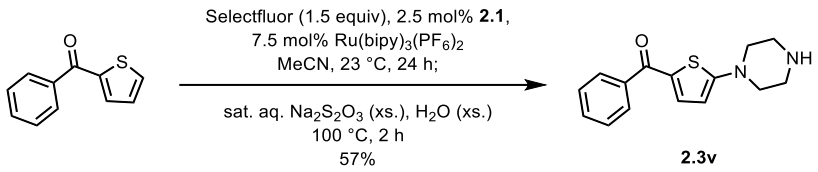


A 100 mL pressure tube was charged with palladium complex **2.1** (5.9 mg, 9.3 μmol. 2.5 mol%), $Ru(bpy)_3(PF_6)_2$ (24.0 mg, 27.9 μmol, 7.50 mol%), and Selectfluor (198 mg, 0.558 mmol, 1.50 equiv). Solution of methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (115 mg, 0.372 mmol, 1.00 equiv) in dry acetonitrile (1.9 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (3.8 mL) and water (3.8 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, water (5 mL) and saturated aqueous sodium carbonate (1 mL) were added, and the mixture was filtered over a glass frit with a filter paper. The filtrate was transferred to a separatory funnel. Dichloromethane (30 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (123 mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (93.7/6.0/0.3 (v/v/v)) to afford 66.3 mg of the title compound as a yellow solid (45% yield).

R_f = 0.76 (dichloromethane/methanol/28% aqueous ammonium hydroxide 93.7:6.0:0.3 (v/v/v)). NMR

Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.76–7.79 (m, 2H), 7.68–7.70 (m, 2H), 7.04–7.07 (m, 2H), 6.72–6.75 (m, 2H), 5.12 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.77 (s, 3H), 3.46–3.53 (m, 2H), 3.08–3.11 (m, 4H), 3.04–3.06 (m, 4H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 169.6, 167.6, 150.1, 134.2, 131.8, 129.7, 128.4, 123.6, 116.7, 53.5, 53.0, 49.4, 45.5, 33.8. Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{22}H_{23}N_3O_4$ [M+H]+, 394.1761; found, 394.1760.

Phenyl(5-(piperazin-1-yl)thiophen-2-yl)methanone (2.3v)



A 100 mL pressure tube was charged with palladium complex **2.1** (8.5 mg, 13. μmol. 2.5 mol%), $Ru(bipy)_3(PF_6)_2$ (34.2 mg, 40.0 μmol, 7.50 mol%), Selectfluor (282. mg, 0.800 mmol, 1.50 equiv), and phenyl(thiophen-2-yl)methanone (100. mg, 0.530 mmol, 1.00 equiv). Acetonitrile (2.6 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (5.3 mL) and water (5.3 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL), ethylenediamine (0.5 mL) and saturated aqueous sodium carbonate (5 mL) were added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were extracted with 1 M aqueous hydrochloric acid (3 × 10 mL). Ethylenediamine (6.0 mL) was added to the combined acidic aqueous layers, followed by basification with 3 M aqueous sodium hydroxide (6 mL). The basic aqueous layer was extracted with dichloromethane (4 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (126. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (95.5/4.0/0.5 (v/v/v)) to afford 82. mg of the title compound as a yellow solid (57%

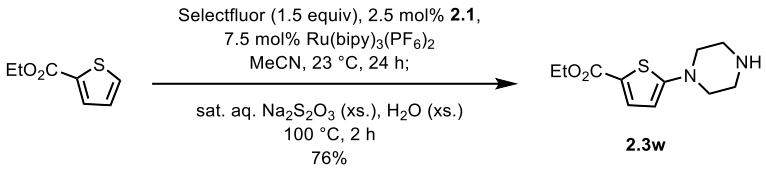
yield).

R_f = 0.38 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.73 (d, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 4.3 Hz, 1H), 6.03 (d, *J* = 4.3 Hz, 1H), 3.30 (t, J = 4.9 Hz, 4H), 2.99 (t, *J* = 4.9 Hz, 4H), 2.00 (s, 1H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 186.7, 167.8, 139.0, 138.3, 131.1, 128.7, 128.3, 127.5, 104.4, 50.6, 45.2. Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{15}H_{16}N_2OS$ $[M+H]^+$, 273.1056; found, 273.1046.

Mass spectrometry: HRMS-FIA(m/z) calcd for $C_{15}H_{17}N_2OS$ $[M+H]^+$, 273.1056; found, 273.1044.

Ethyl 5-(piperazin-1-yl)thiophene-2-carboxylate (2.3w)



A 100 mL pressure tube was charged with palladium complex **2.1** (11.8 mg, 18.6 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (47.9 mg, 55.7 μmol, 7.50 mol%), and Selectfluor (395. mg, 1.11 mmol, 1.50 equiv). Acetonitrile (3.7 mL, c = 0.20 M) was added, followed by ethyl thiophene-2-carboxylate (100. μL, 0.743 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (7.4 mL) and water (7.4 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL) and ethylenediamine (0.5 mL) were added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (2 × 15 mL). The combined organic layers were extracted with 10% aqueous glacial acetic acid (3 × 10 mL). The combined acidic aqueous layers were basified with ethylenediamine (4.5 mL). The basic aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (156. mg). The residue was purified by chromatography on

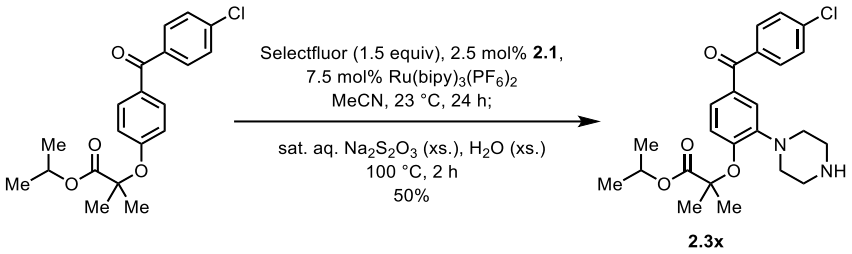
silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (95.5/4.0/0.5 (v/v/v)) to afford 135. mg of the title compound as a yellow solid (76% yield).

R_f = 0.52 (dichloromethane/methanol/28% aqueous ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

NMR Spectroscopy: ^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.52 (d, *J* = 4.3 Hz, 1H), 6.00 (d, *J* = 4.3 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.19–3.20 (m, 4H), 2.98–2.99 (m, 4H), 2.17 (s, 1H), 1.30 (t, *J* = 7.1 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 165.2, 162.9, 134.9, 116.9, 104.1, 60.5, 50.8, 45.2, 14.5.

Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{11}H_{17}N_2O_2S$ $[M+H]^+$, 241.1005; found, 241.0995.

Isopropyl 2-(4-(4-chlorobenzoyl)-2-(piperazin-1-yl)phenoxy)-2-methylpropanoate (2.3x)



A 100 mL pressure tube was charged with palladium complex **2.1** (4.4 mg, 6.9 μmol. 2.5 mol%), $Ru(bpy)_3(PF_6)_2$ (17.9 mg, 20.8 μmol, 7.50 mol%), Selectfluor (147 mg, 0.416 mmol, 1.50 equiv), and fenofibrate (100 mg, 0.277 mmol, 1.00 equiv). Acetonitrile (1.4 mL, c = 0.20 M) was added via syringe, and the reaction mixture was stirred at 23 °C for 24 h. Saturated aqueous sodium thiosulfate (2.8 mL) and water (2.8 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, water (10 mL), saturated aqueous sodium carbonate (0.25 mL), and ethylenediamine (70 μL) were added, and the mixture was filtered over a glass frit with a filter paper. The filtrate was transferred to a separatory funnel. Dichloromethane (40 mL) was added and the organic layer was separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (146 mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of

dichloromethane/methanol/28% aqueous ammonium hydroxide (96.5/3.0/0.5 to 94.5/5.0/0.5 (v/v/v)) to afford 62 mg of the title compound as a yellow solid (50% yield).

R_f = 0.11 (dichloromethane/methanol/28% aqueous ammonium hydroxide 95.5:4.0:0.5 (v/v/v)). NMR Spectroscopy: ^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.69–7.71 (m, 2H), 7.51–7.53 (m, 2H), 7.37 (d, J = 2.2 Hz, 1H), 7.31 (dd, J = 8.4, 2.2 Hz, 1H), 6.73 (d, J = 8.4 Hz, 1H), 5.02 (hept, J = 6.2 Hz, 1H), 3.01–3.06 (m, 8H), 2.68 (bs, 1H), 1.65 (s, 6H), 1.18 (d, J = 6.2 Hz, 6H). ^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 195.0, 173.7, 153.4, 144.4, 138.6, 137.8, 132.2, 131.4, 129.4, 126.4, 121.1, 116.7, 80.8, 70.2, 51.7, 46.5, 25.6, 21.7. Mass Spectrometry: HRMS-FIA(m/z) calcd for $C_{24}H_{29}ClN_2O_4$ [M+H]+, 445.1889; found, 445.1888.

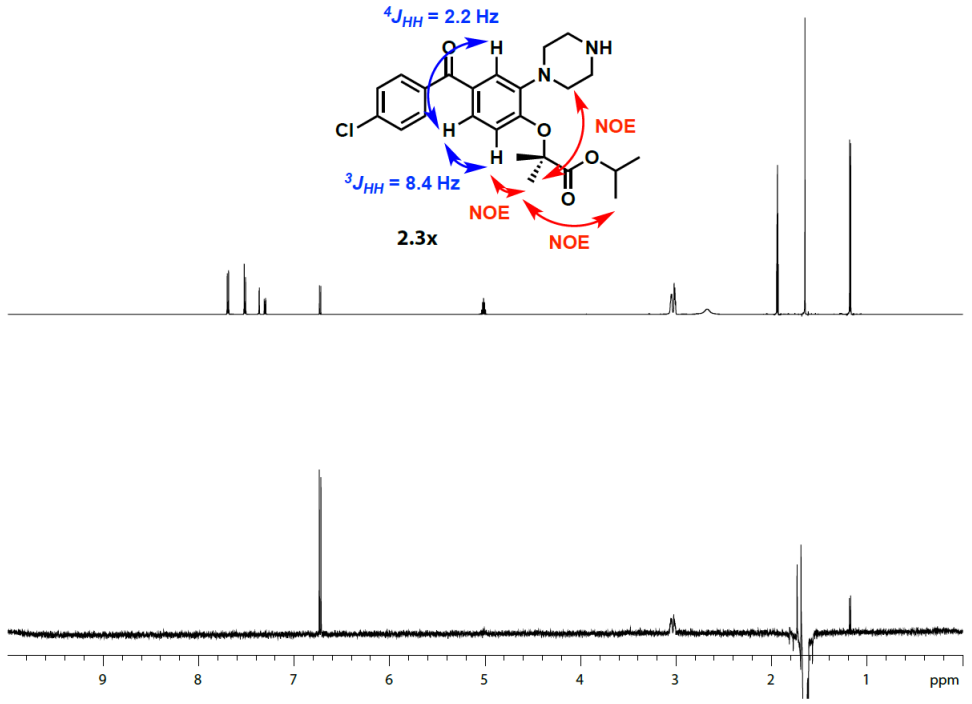


Figure E2.18. Structural assignment of **2.3x** by 1-D NOESY NMR

2.14 DFT Calculations

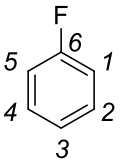
Density functional theory (DFT) calculations were performed using Gaussian09[3] on the Odyssey cluster at Harvard University. BS I includes 6-311G(d) on H and 6-31G(d,p) on all other nuclei.[4] All geometry optimizations were performed using the B3PW91 functional with the BS I basis set. Geometry optimization was carried out using the atomic coordinates from MM2 optimization in Chem3D as a starting point. Images were generated using Chem3D.

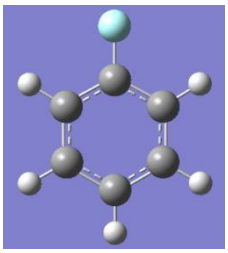
E2.15 Calculation and Visualization of Fukui Indices

Fukui indices were calculated in the following way: The neutral arene (with *N* electrons) was subjected to a geometry optimization, and total local atomic electron populations were determined by NBO analysis. NBO electron populations of the corresponding cationic arene (*N*–1 electrons) were calculated without geometry reoptimization. Fukui nucleophilicity indices were calculated for each atom by subtracting the atomic electron population in the cationic arene from the population in the neutral arene. A color gradient for the set of Fukui values was generated using the conditional formatting tool in Microsoft Excel 2013, with the maximum value assigned a shade of red (RGB code 255:00:00) and the smallest value assigned a shade of blue (RGB 0:112:192).

Fluorobenzene

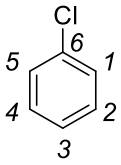
Atom	No.	X	Y	Z	neutral pop.	cation pop.	f-	RGB color
C	1	0.259886	1.216343	0.000001	6.3189	6.2378	0.0811	36:96:165
C	2	-1.134888	1.20758	0.000002	6.22836	6.17806	0.0503	0:112:192
C	3	-1.83353	0	-0.000003	6.26548	6.00175	0.26373	255:00:00
C	4	-1.134888	-1.20758	-0.000001	6.22836	6.17806	0.0503	0:112:192
C	5	0.259886	-1.216343	0.000004	6.3189	6.2378	0.0811	36:96:165
C	6	0.926134	0	0.000001	5.57659	5.38877	0.18782	164:40:69
H	7	2.284414	0	-0.000003				
H	8	0.823179	2.140225	0				
H	9	-1.672798	2.147473	0.000007				
H	10	-2.916086	0	-0.000008				
H	11	-1.672798	-2.147473	-0.000004				
H	12	0.823179	-2.140225	0.000011				

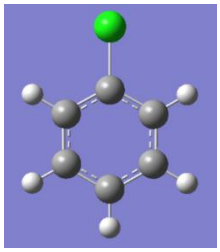




Chlorobenzene

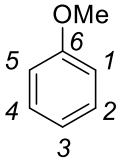
Atom	No.	X	Y	Z	neutral pop.	cation pop.	f-	RGB color
C	1	0.179285	-1.21559	0.000165	6.27732	6.2134	0.06392	30:99:170
C	2	1.573669	-1.2065	0.000139	6.22736	6.1853	0.04206	0:112:192
C	3	2.27212	0	-0.000004	6.24852	6.02219	0.22633	10.625
C	4	1.573669	1.2065	0.000105	6.22736	6.1853	0.04206	0:112:192
C	5	0.179285	1.21559	0.000197	6.27732	6.2134	0.06392	30:99:170
C	6	-0.496734	0	0.000085	6.01645	5.87299	0.14346	140:51:87
Cl	7	-2.266123	0	-0.000282				
H	8	-0.368529	-2.148194	0.000212				
H	9	2.109408	-2.147525	0.000224				
H	10	3.354575	0	-0.000209				
H	11	2.109408	2.147525	0.000097				
H	12	-0.368529	2.148194	0.000342				

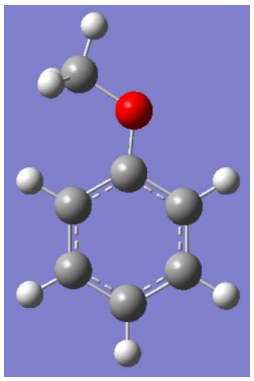




Anisole

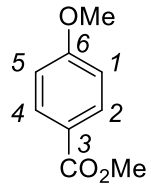
Atom	No.	X	Y	Z	neutral pop.	cation pop.	f-	RGB code
C	1	-0.033836	1.060164	0.000014	6.33899	6.24884	0.09015	100:68:117
C	2	1.332708	1.351578	0.000002	6.22761	6.18489	0.04272	41:94:161
C	3	2.282523	0.334411	-0.000005	6.28458	6.07066	0.21392	255:00:00
C	4	1.854924	-0.996328	-0.00001	6.23365	6.22391	0.00974	0:112:192
C	5	0.499813	-1.302165	-0.000013	6.29766	6.18131	0.11635	133:54:92
C	6	-0.453266	-0.274134	0.000006	5.671	5.56534	0.10566	119:60:102
O	7	-1.757597	-0.674453	0.000051				
C	8	-2.775555	0.326026	-0.000034				
H	9	-0.75023	1.869366	0.000028				
H	10	1.648206	2.388251	0.000004				
H	11	3.339052	0.570766	-0.000001				
H	12	2.580826	-1.80078	-0.000015				
H	13	0.156078	-2.329145	-0.000018				
H	14	-3.721506	-0.212468	-0.000184				
H	15	-2.717873	0.956111	0.892796				
H	16	-2.717645	0.956213	-0.892776				

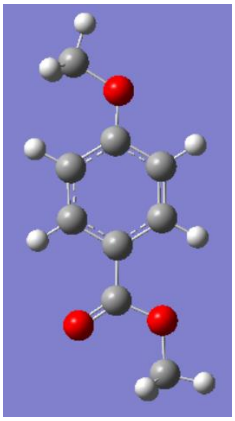




Methyl 4-methoxybenzoate

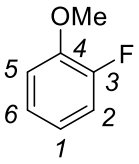
Atom	No.	X	Y	Z	neutral pop	cation pop.	f-	RGB code
C	1	-1.601873	0.989296	-0.002515	6.33589	6.24271	0.09318	116:61:105
C	2	-0.227542	1.197998	-0.003572	6.17724	6.1546	0.02264	30:99:170
C	3	0.668545	0.125151	-0.003953	6.19724	5.99103	0.20621	255:00:00
C	4	0.157707	-1.183531	-0.004934	6.19285	6.195	-0.00215	0:112:192
C	5	-1.20764	-1.404584	-0.004408	6.29373	6.17326	0.12047	150:47:80
C	6	-2.100704	-0.320323	-0.002287	5.64165	5.55312	0.08853	110:64:109
O	7	-3.416329	-0.641362	0.000343				
C	8	2.122181	0.416199	-0.00178				
O	9	2.873255	-0.703082	0.001834				
O	10	2.603652	1.531646	-0.002239				
C	11	4.301648	-0.5117	0.007744				
C	12	-4.383654	0.413925	0.008411				
H	13	-2.267946	1.839732	-0.001523				
H	14	0.162764	2.20751	-0.003306				
H	15	0.837023	-2.024738	-0.005716				
H	16	-1.611431	-2.408873	-0.004859				
H	17	4.727268	-1.512171	0.010726				
H	18	4.619059	0.034312	-0.881153				
H	19	4.61118	0.036185	0.898343				
H	20	-5.354109	-0.0776	0.011292				
H	21	-4.285845	1.033512	0.903987				
H	22	-4.294588	1.039928	-0.88353				

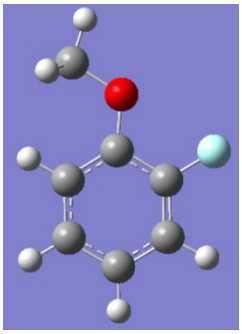




2-Fluoroanisole

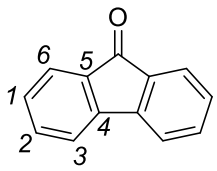
Atom	No.	X	Y	Z	neutral pop.	cation pop.	f-	RGB code
C	1	2.262553	-0.684283	0.00009	6.2645	6.07427	0.19023	255:00:00
C	2	1.860767	0.654606	0.000099	6.30621	6.30142	0.00479	0:112:192
C	3	0.51384	0.954606	-0.000018	5.61834	5.50098	0.11736	154:45:83
C	4	-0.476755	-0.039137	-0.000116	5.73459	5.62397	0.11062	145:49:83
C	5	-0.061865	-1.373036	-0.000126	6.32203	6.26755	0.05448	68:82:141
C	6	1.300232	-1.687381	-0.000036	6.24341	6.16008	0.08333	108:65:111
O	7	-1.763375	0.39429	-0.000224				
C	8	-2.800369	-0.589598	0.000232				
F	9	0.116766	2.251437	-0.000008				
H	10	3.316139	-0.930699	0.000182				
H	11	2.57862	1.464685	0.000207				
H	12	-0.792961	-2.168943	-0.000239				
H	13	1.599854	-2.727755	-0.000069				
H	14	-3.734618	-0.031988	-0.000278				
H	15	-2.750507	-1.219218	-0.892868				
H	16	-2.750829	-1.217995	0.894177				

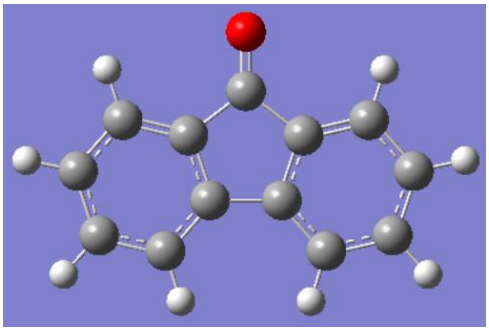




Fluorenone

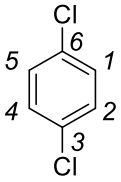
Atom	No.	X	Y	Z	neutral pop	cation pop	f-	RGB color
C	1	-3.464482	-0.066685	0.00001	6.24593	6.10276	0.14317	255:00:00
C	2	-3.02693	-1.392015	0.000004	6.20893	6.17721	0.03172	48:91:156
C	3	-1.660952	-1.708684	-0.000006	6.23588	6.18207	0.05381	89:73:125
C	4	-0.741884	-0.668882	-0.000007	6.01765	5.94323	0.07442	127:57:97
C	5	-1.188548	0.666481	-0.000003	6.12856	6.05053	0.07803	134:54:92
C	6	-2.537913	0.98222	0.000004	6.19665	6.19085	0.0058	0:112:192
C	7	0.741884	-0.668882	-0.000007				
C	8	1.188548	0.666481	-0.000003				
C	9	0	1.576164	-0.000006				
C	10	1.660952	-1.708684	-0.000007				
C	11	3.02693	-1.392015	0.000004				
C	12	3.464482	-0.066685	0.000011				
C	13	2.537913	0.982221	0.000005				
O	14	0	2.792501	-0.000007				
H	15	-4.525551	0.148606	0.000021				
H	16	-3.756128	-2.193077	0.000009				
H	17	-1.343091	-2.743965	-0.000011				
H	18	-2.863832	2.015329	0.000009				
H	19	1.343091	-2.743965	-0.000012				
H	20	3.756128	-2.193077	0.000008				
H	21	4.525551	0.148606	0.000022				
H	22	2.863832	2.015329	0.00001				

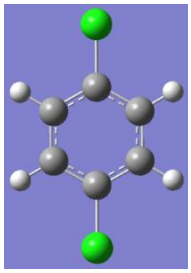




1,4-Dichlorobenzene

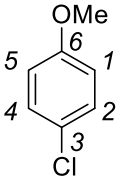
Atom	No.	X	Y	Z	neutral pop.	cation pop.	f-	RGB code
C	1	-0.696474	-1.213336	-0.000036	6.25498	6.20651	0.04847	0:112:192
C	2	0.696474	-1.213336	0	6.25498	6.20651	0.04847	0:112:192
C	3	1.37651	0	0.000038	6.02094	5.89246	0.12848	255:00:00
C	4	0.696474	1.213336	0.000047	6.25498	6.20651	0.04847	0:112:192
C	5	-0.696474	1.213336	0.000014	6.25498	6.20651	0.04847	0:112:192
C	6	-1.37651	0	-0.000031	6.02094	5.89246	0.12848	255:00:00
Cl	7	-3.13958	0	-0.000085				
Cl	8	3.13958	0	0.000071				
H	9	-1.239177	-2.148648	-0.000069				
H	10	1.239177	-2.148648	-0.000002				
H	11	1.239177	2.148648	0.000079				
H	12	-1.239177	2.148648	0.000022				

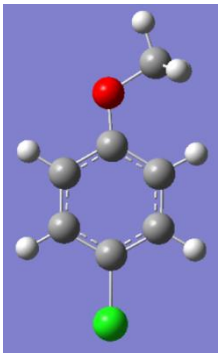




4-Chloroanisole

Atom	No	X	Y	Z	neutral pop.	cation pop.	total f-	RGB color
C	1	0.797679	-0.99734	-0.00153	6.31747	6.23401	0.08346	138:52:88
C	2	-0.59062	-1.14466	-0.00118	6.25568	6.21406	0.04162	50:91:155
C	3	-1.40103	-0.01937	-0.00024	6.04578	5.90732	0.13846	255:00:00
C	4	-0.85138	1.261271	0.000005	6.26128	6.2433	0.01798	0:112:192
C	5	0.528284	1.406969	-0.00049	6.2745	6.17893	0.09557	164:40:69
C	6	1.364223	0.281188	-0.00106	5.66925	5.56888	0.10037	174:36:61
O	7	2.700233	0.535292	-0.00096				
Cl	8	-3.16102	-0.20975	0.000878				
C	9	3.603996	-0.57207	0.002255				
H	10	1.414708	-1.88405	-0.0022				
H	11	-1.0265	-2.13458	-0.00156				
H	12	-1.49132	2.133269	0.000755				
H	13	0.977672	2.391617	-0.00017				
H	14	4.601996	-0.13856	0.002292				
H	15	3.47503	-1.18804	0.897014				
H	16	3.476992	-1.19211	-0.88994				





E2.16 Electron Affinity Calculations

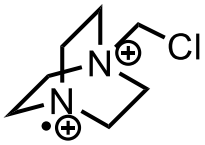
Adiabatic gas-phase electron affinities were calculated by performing independent geometry optimizations on the neutral amine (*N* electrons) and the corresponding aminium radical cation (*N*–1 electrons). The energy of the optimal geometry of the neutral species was subtracted from that of the cation to obtain the electron affinity. The computational methodology was validated by comparing computed and experimental electron affinities of amines for which experimental data is available: computed electron affinities of the dimethylamine radical cation and the piperazine radical cation were both within experimental error of the values measured by photoelectron spectroscopy.

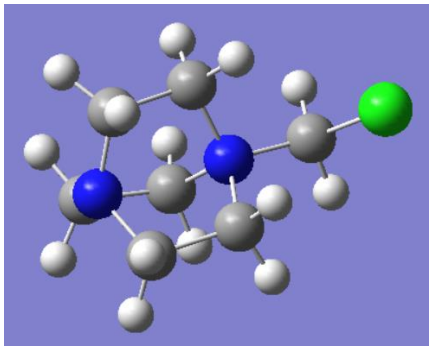
$TEDA^{2+\cdot}$ aminium radical electron affinity

	B3LYP Energy (Hartrees)	EA (Hartrees)	EA (eV)
TEDA-radical	-844.269588	0.45723623	12.44186
TEDA-amine	-844.7268242		

Aminium radical coordinates:

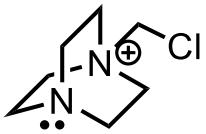
Atom	No.	X	Y	Z
C	1	-1.502796	-1.053089	1.17534
N	2	-2.081089	-0.422573	0.001872
C	3	-2.224674	1.020409	0.092382
C	4	-0.018599	-0.552881	-1.192487
C	5	-0.074436	-0.385706	1.291968
N	6	0.213142	0.373179	-0.000623
C	7	-0.749673	1.55458	-0.100918
C	8	-1.560298	-0.902954	-1.265036
C	9	1.655183	0.933436	-0.002893
Cl	10	2.870297	-0.338254	0.000836
H	11	-2.100747	-0.8362	2.061814
H	12	-1.436613	-2.129349	1.023332
H	13	-2.631327	1.293433	1.06508
H	14	-2.875104	1.3901	-0.70155
H	15	0.58468	-1.44623	-1.048307
H	16	0.3007	-0.039896	-2.09928
H	17	-0.034077	0.329972	2.11247
H	18	0.691474	-1.147074	1.429798
H	19	-0.503325	2.276454	0.677428
H	20	-0.617851	2.012672	-1.08054
H	21	-2.054477	-0.390531	-2.089246
H	22	-1.704096	-1.980554	-1.353857
H	23	1.756835	1.543483	0.89278
H	24	1.756278	1.53703	-0.903006

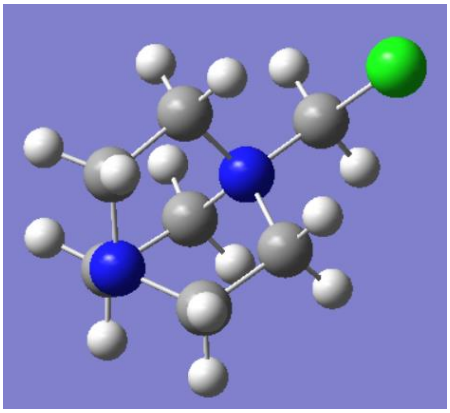




Amine coordinates:

Atom	No.	X	Y	Z
C	1	-1.52039	-0.97889	1.177463
N	2	-2.20498	-0.44473	0.001019
C	3	-2.19114	1.01465	0.039047
C	4	-0.03551	-0.51737	-1.21788
C	5	-0.06416	-0.42926	1.27014
N	6	0.22812	0.364061	-6.1E-05
C	7	-0.72967	1.554396	-0.0538
C	8	-1.54381	-0.91583	-1.21508
C	9	1.633869	0.914167	-0.00103
Cl	10	2.889936	-0.34304	0.000453
H	11	-2.07823	-0.705	2.073361
H	12	-1.51093	-2.06716	1.112894
H	13	-2.65914	1.348855	0.965326
H	14	-2.78159	1.403113	-0.79108
H	15	0.626516	-1.37658	-1.13689
H	16	0.250636	0.062813	-2.09572
H	17	0.074763	0.260884	2.103103
H	18	0.682059	-1.21783	1.339754
H	19	-0.47067	2.21366	0.774959
H	20	-0.53251	2.072774	-0.99243
H	21	-2.05201	-0.48833	-2.07993
H	22	-1.64019	-1.99987	-1.27725
H	23	1.752754	1.520072	0.893925
H	24	1.752484	1.517753	-0.8976





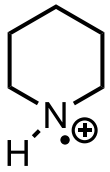
Piperadine aminium radical electron affinity

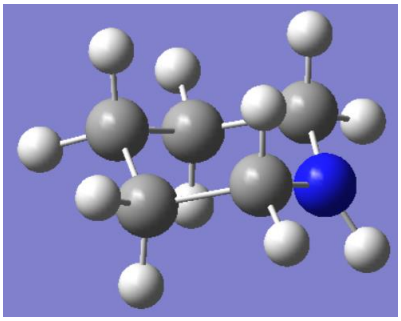
	B3LYP Energy (Hartrees)	EA (Hartrees)	EA (eV)
piperidine-radical	-251.6866948	0.28432455	7.736755
piperidine-amine	-251.9710194		

The gas-phase adiabatic electron affinity of the piperazine aminium radical was measured by photoelectron spectroscopy to be 7.78±0.1 eV.[5] Therefore, the computed electron affinity is within experimental error.

Aminium radical coordinates

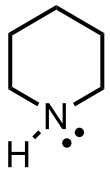
Atom	No.	X	Y	Z
C	1	-1.2674	0.722618	-0.23782
C	2	-1.23889	-0.78513	0.236564
N	3	0.00005	-1.35192	-0.20833
C	4	1.23901	-0.78503	0.236397
C	5	1.26733	0.722812	-0.23765
C	6	-0.00012	1.439559	0.224229
H	7	-2.17206	1.160151	0.188847
H	8	-1.36391	0.742646	-1.32591
H	9	-2.07727	-1.34799	-0.16937
H	10	-1.26126	-0.79989	1.330253
H	11	0.000001	-1.93408	-1.04411
H	12	2.077366	-1.34771	-0.16985
H	13	1.261626	-0.80008	1.330083
H	14	2.171829	1.16041	0.189278
H	15	1.364063	0.743055	-1.32572
H	16	-0.00022	1.543908	1.31352
H	17	-0.00016	2.454033	-0.18903

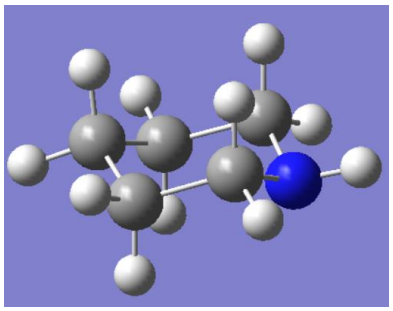




Amine coordinates:

Atom	No.	X	Y	Z
C	1	-1.30906	0.629959	-0.22682
C	2	-1.16377	-0.83228	0.206876
N	3	0.092106	-1.37689	-0.315
C	4	1.264356	-0.66972	0.20663
C	5	1.213439	0.798713	-0.22658
C	6	-0.09743	1.454954	0.232918
H	7	-2.23538	1.047365	0.178815
H	8	-1.38159	0.662432	-1.31864
H	9	-1.99119	-1.42774	-0.18922
H	10	-1.22068	-0.88329	1.310862
H	11	0.158196	-2.36509	-0.09977
H	12	2.163568	-1.14972	-0.18989
H	13	1.327906	-0.71324	1.310598
H	14	2.075799	1.335918	0.17951
H	15	1.281378	0.841131	-1.31833
H	16	-0.102	1.521478	1.327989
H	17	-0.16598	2.479185	-0.14513





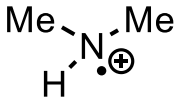
Dimethylamine radical cation

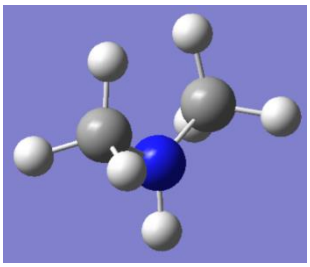
	B3LYP Energy (Hartrees)	EA (Hartrees)	EA (eV)
dimethylamine-radical	-134.9054068	0.29774864	8.102038
dimethylamine-amine	-135.2031554		

The gas-phase adiabatic electron affinity of the piperazine aminium radical was measured by photoelectron spectroscopy to be 8.08±0.1 eV.[5] Therefore, the computed electron affinity is within experimental error.

Aminium radical coordinates:

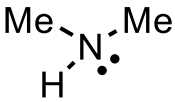
Atom	No.	X	Y	Z
C	1	1.279205	0.207143	-0.0037
N	2	0.000034	-0.444643	-0.00405
C	3	-1.278752	0.20804	0.002496
H	4	1.166922	1.278438	-0.150269
H	5	1.91543	-0.240072	-0.777665
H	6	1.776845	0.007374	0.959843
H	7	-0.000709	-1.466021	0.007209
H	8	-1.832183	-0.084906	-0.903177
H	9	-1.867394	-0.161104	0.854054
H	10	-1.161861	1.287694	0.045576

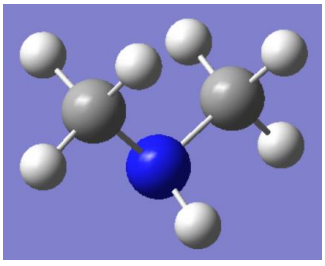




Amine coordinates:

Atom	No.	X	Y	Z
C	1	1.215605	-0.222816	0.020462
N	2	0	0.563444	-0.147187
C	3	-1.215605	-0.222816	0.020462
H	4	1.280145	-0.965613	-0.780483
H	5	1.27918	-0.76513	0.980323
H	6	2.088595	0.428644	-0.063204
H	7	0	1.333879	0.511497
H	8	-1.279179	-0.765131	0.980323
H	9	-2.088595	0.428644	-0.063203
H	10	-1.280146	-0.965612	-0.780484



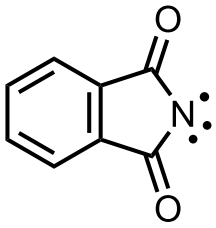


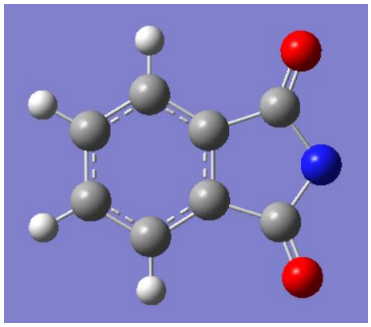
Phthalimide radical

	B3LYP Energy (Hartrees)	EA (Hartrees)	EA (eV)
phthalimide-radical	-512.5232453	0.13462626	3.663315
phthalimide-anion	-512.6578715		

Radical coordinates

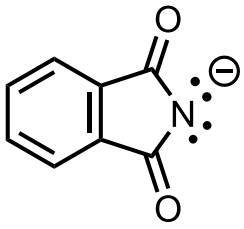
Atom	No.	X	Y	Z
C	1	2.519142	0.702378	0.000171
C	2	2.519141	-0.70238	0.000186
C	3	1.326846	-1.42438	0.009011
C	4	0.142758	-0.69785	0.012201
C	5	0.142758	0.697852	0.012195
C	6	1.326847	1.424379	0.008988
C	7	-1.27998	-1.15123	0.01175
N	8	-2.09713	0.000001	0.229165
C	9	-1.27998	1.151234	0.011756
O	10	-1.71191	2.269465	-0.12492
O	11	-1.71192	-2.26946	-0.12494
H	12	3.465318	1.2294	-0.01006
H	13	3.465317	-1.2294	-0.01003
H	14	1.317325	-2.50664	0.008664
H	15	1.317326	2.506639	0.008622

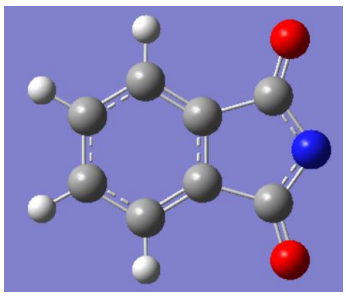




Anion coordinates

Atom	No.	X	Y	Z
C	1	-2.53043	0.698872	-0.000052
C	2	-2.53041	-0.69904	0.000581
C	3	-1.32437	-1.41527	0.000104
C	4	-0.14256	-0.69334	-0.000595
C	5	-0.14259	0.693361	-0.00063
C	6	-1.32443	1.415172	-0.000413
C	7	1.326985	-1.11371	-0.000106
N	8	2.115615	-4.7E-05	0.000547
C	9	1.32692	1.113913	-0.000157
O	10	1.675405	2.293616	0.00047
O	11	1.675676	-2.29351	-0.000191
H	12	-3.47668	1.231066	-0.000013
H	13	-3.47664	-1.23125	0.001487
H	14	-1.30962	-2.49976	0.000585
H	15	-1.30973	2.499652	-0.000515



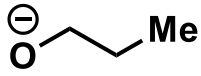


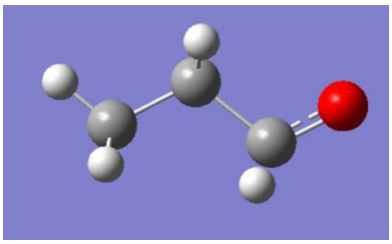
Propyloxyl radical

	B3LYP Energy (Hartrees)	EA (Hartrees)	EA (eV)
oxyl-radical	-193.7386246	0.03826599	1.041255854
oxyl-adiab	-193.7768906		

Oxide coordinates

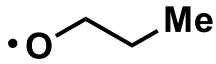
Atom	No.	X	Y	Z
C	1	0.763732	-0.43796	-0.00011
C	2	-0.47058	0.544986	-0.0001
O	3	1.937513	0.150841	0.000133
C	4	-1.83673	-0.15272	0.00009
H	5	0.534858	-1.13448	0.889117
H	6	0.535038	-1.13425	-0.88954
H	7	-0.37396	1.193723	-0.88044
H	8	-0.37382	1.193933	0.880077
H	9	-2.68559	0.543467	-0.0005
H	10	-1.93777	-0.79695	0.881912
H	11	-1.93743	-0.79803	-0.88099

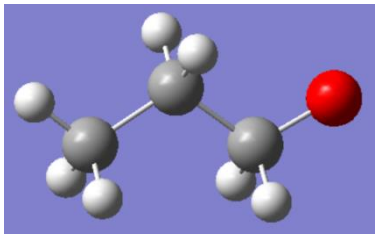




Radical coordinates

Atom	No.	X	Y	Z
C	1	0.705869	-0.42319	0.001047
C	2	-0.47505	0.550545	0.000715
O	3	1.947649	0.143382	-0.00068
C	4	-1.82722	-0.1683	-0.00062
H	5	0.653282	-1.11833	0.864516
H	6	0.654521	-1.11517	-0.86529
H	7	-0.3879	1.198174	-0.87669
H	8	-0.38937	1.197086	0.879089
H	9	-2.65307	0.545654	-0.00146
H	10	-1.94108	-0.80444	0.88226
H	11	-1.93921	-0.80437	-0.88381



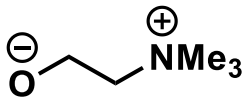


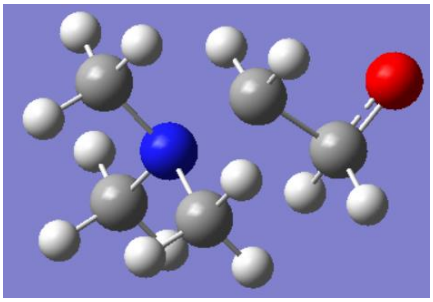
2-(trimethylammonium)ethyl-oxyl radical

	B3LYP Energy (Hartrees)	EA (Hartrees)	EA (eV)
oxyl-ium-radical	-328.0938967	0.20405086	5.552427951
oxyl-ium-adiab	-328.2979475		

Oxide coordinates

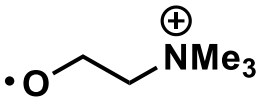
Atom	No.	X	Y	Z
C	1	-1.86801	-0.435	0.000092
C	2	-0.65391	0.552462	-0.00081
O	3	-2.88665	0.390796	-0.00031
N	4	0.878361	0.023995	-3.5E-05
C	5	1.814541	1.18381	-0.00172
C	6	1.097568	-0.80077	1.224285
C	7	1.097998	-0.80456	-1.2217
H	8	-1.7524	-1.12517	-0.89084
H	9	-1.75215	-1.12366	0.892317
H	10	-0.72042	1.171774	0.893078
H	11	-0.72017	1.170197	-0.8958
H	12	2.850333	0.834773	0.006975
H	13	1.633037	1.779764	-0.89469
H	14	1.62184	1.790948	0.881286
H	15	2.121396	-1.18021	1.235152
H	16	0.382097	-1.61954	1.227742
H	17	0.923361	-0.17734	2.099921
H	18	0.913328	-0.18672	-2.09913
H	19	2.125133	-1.17488	-1.23652
H	20	0.390134	-1.62991	-1.21771

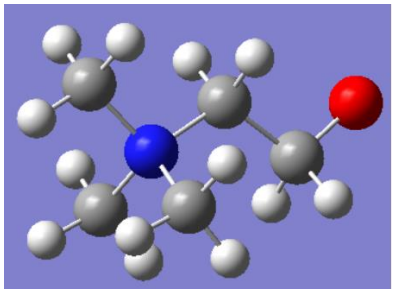




Radical coordinates

Atom	No.	X	Y	Z
C	1	-1.76307	-0.36881	-6.9E-05
C	2	-0.57413	0.615749	-0.00826
O	3	-2.93211	0.32905	0.000177
N	4	0.830879	0.019991	-2.4E-05
C	5	1.820594	1.161259	-0.02513
C	6	1.061778	-0.79366	1.248917
C	7	1.055773	-0.84322	-1.21627
H	8	-1.77203	-1.0454	-0.87245
H	9	-1.76672	-1.03902	0.87736
H	10	-0.64592	1.25885	0.869294
H	11	-0.64331	1.240845	-0.89896
H	12	2.829461	0.752275	-0.01506
H	13	1.664044	1.74477	-0.93036
H	14	1.662635	1.785398	0.852353
H	15	2.095226	-1.13588	1.257254
H	16	0.396794	-1.65407	1.25459
H	17	0.872429	-0.16701	2.118828
H	18	0.85082	-0.25572	-2.10966
H	19	2.092315	-1.17604	-1.22201
H	20	0.399284	-1.70926	-1.17759



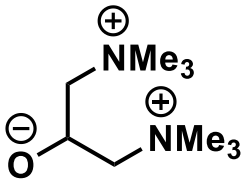


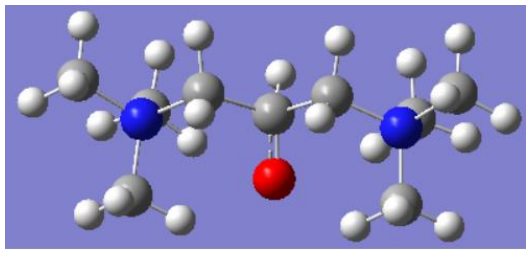
2-(trimethylammonium)-1-(trimethylammoniummethyl)ethyl-oxyl radical

	B3LYP Energy (Hartrees)	EA (Hartrees)	EA (eV)
oxyl-diium-radical	-541.0113122	0.37791639	10.28348289
oxyl-diium-adiab	-541.3892286		

Oxide coordinates

Atom	No.	X	Y	Z
C	1	0.003972	0.082421	0.33451
O	2	0.001594	-1.17519	-0.06517
C	3	1.258936	0.88764	-0.17453
N	4	2.535536	0.107476	-0.02127
C	5	3.714939	1.054572	-0.11223
C	6	2.593767	-0.6241	1.299861
C	7	2.641502	-0.90692	-1.13822
C	8	-1.25427	0.898854	-0.15155
N	9	-2.55073	0.111279	-0.0254
C	10	-3.70511	1.051243	-0.11679
C	11	-2.6426	-0.90787	-1.14078
C	12	-2.60063	-0.62004	1.302508
H	13	-0.00151	0.227491	1.424172
H	14	1.184025	1.150219	-1.22523
H	15	1.383749	1.83829	0.414384
H	16	4.635672	0.47366	-0.09962
H	17	3.643194	1.610744	-1.04393
H	18	3.688909	1.733993	0.733137
H	19	3.569584	-1.1009	1.389718
H	20	1.792942	-1.34699	1.292212
H	21	2.468739	0.106017	2.108177
H	22	2.736597	-0.37066	-2.08172
H	23	3.529742	-1.51996	-0.97034
H	24	1.718505	-1.48611	-1.10079
H	25	-1.38436	1.824445	0.406385
H	26	-1.18069	1.153561	-1.23884
H	27	-4.63524	0.469773	-0.10575
H	28	-3.69079	1.731341	0.730114
H	29	-3.64083	1.610057	-1.04619
H	30	-3.52584	-1.52244	-0.96826
H	31	-1.7115	-1.49518	-1.09734
H	32	-2.73266	-0.377	-2.07892
H	33	-2.46751	0.109132	2.105681

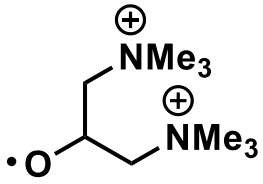


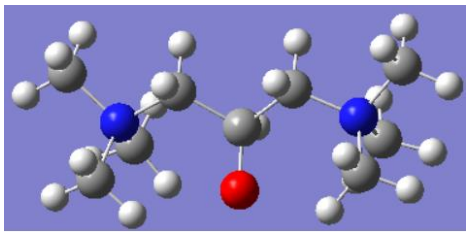


H	34	-3.56259	-1.09468	1.388782
H	35	-1.78767	-1.3494	1.295525

Radical coordinates

Atom	No.	X	Y	Z
C	1	-0.0057	-0.03555	0.177828
O	2	-0.00119	-1.36205	-0.09346
C	3	1.26408	0.748281	-0.31241
N	4	2.627074	0.12118	-0.01488
C	5	3.681719	1.185113	-0.25827
C	6	2.727635	-0.34261	1.435245
C	7	2.921764	-1.06837	-0.93445
C	8	-1.27162	0.744921	-0.31466
N	9	-2.61992	0.122391	-0.00592
C	10	-3.67365	1.179757	-0.26033
C	11	-2.91034	-1.05432	-0.92768
C	12	-2.72158	-0.34284	1.426886
H	13	-0.00362	-0.01253	1.288262
H	14	1.222717	0.86727	-1.38614
H	15	1.262237	1.729523	0.148307
H	16	4.631522	0.741642	-0.12027
H	17	3.56892	1.542206	-1.26471
H	18	3.528728	1.99126	0.448004
H	19	3.740306	-0.63678	1.620674
H	20	2.060791	-1.1876	1.597292
H	21	2.462091	0.495955	2.094908
H	22	2.882601	-0.70528	-1.94496
H	23	3.88048	-1.42501	-0.69407
H	24	2.164008	-1.82908	-0.77142
H	25	-1.27056	1.725545	0.143449
H	26	-1.22763	0.864193	-1.38953
H	27	-4.65455	0.731339	-0.12331
H	28	-3.53634	1.990987	0.444053
H	29	-3.57467	1.540283	-1.28085
H	30	-3.90544	-1.44012	-0.69204
H	31	-2.1616	-1.83909	-0.76828
H	32	-2.88715	-0.71096	-1.95797
H	33	-2.46918	0.499853	2.091176
H	34	-3.76013	-0.6421	1.622159
H	35	-2.06798	-1.18634	1.595646





E2.17 References

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