

C–H Functionalization through Nucleophilic and Radical Addition to the Aromatic π -System

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C–H Functionalization through Nucleophilic and Radical Addition to the Aromatic π -System**Abstract**

Electrophilic, nucleophilic or radical addition to the aromatic π -system is an approach to aromatic C–H functionalization that bypasses the difficult C–H metalation step typical of modern C–H activation chemistry. π -Addition strategies can provide enhanced reactivity, complementary selectivity and improved practicality for aromatic C–H functionalization. This dissertation describes two strategies for aromatic C–H functionalization that proceed through an addition to the aromatic π -system, either by a nucleophile or a radical.

First, an aromatic C–H hydroxylation protocol in which the arene is activated through η^6 -coordination to an iridium(III) complex is described. η^6 -Coordination of the arene increases its electrophilicity and allows for nucleophilic attack on the aromatic π -system, even for electron-rich arenes. The use of oxygen nucleophiles for C–H functionalization with η^6 -arene complexes is reported for the first time. High positional selectivity of hydroxylation at the site of least electron density is observed. Through investigation of intermediate η^5 -cyclohexadienyl adducts and arene exchange reactions, incorporation of arene π -activation into a catalytic cycle for C–H functionalization is evaluated.

Second, a direct radical aromatic C–H amination reaction with a dramatic improvement in substrate scope compared to prior art is reported. Addition of the ammoniumyl radical, derived from a cationic hydroxylamine derivative, to the aromatic π -system is proposed for the amination reaction, which is fast, practical, scalable, and tolerant of air and moisture. An iron(II) salt accelerates the reaction but is not necessary for full conversion when the reaction is conducted in hexafluoroisopropanol (HFIP). Factors that rationalize the expansion of the substrate scope are presented: hydrogen bonding by the solvent HFIP to anions of cationic species results in their enhanced reactivity.

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NOTE

Portions of this thesis have been taken, with permission, from the following publications:

D'Amato, E. M.; Neumann, C. N. N.; Ritter, T. Selective Aromatic C–H Hydroxylation Enabled by η^6 -Coordination to Iridium(III). *Organometallics* **2015**, *34*, 4626–4631. © 2015 American Chemical Society

D'Amato, E. M.; Börgel, J.; Ritter, T. Aromatic C–H Amination in Hexafluoroisopropanol. *Manuscript in preparation.*

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LIST OF ABBREVIATIONS

Ac	acyl
Ad	1-adamantyl
AIBN	azobisisobutyronitrile
Ar	aryl
BHAS	base-assisted homolytic aromatic substitution
Boc	<i>tert</i> -butoxycarbonyl
Bpy	2,2'-bipyridyl
ⁱ Bu	<i>iso</i> -butyl
^t Bu	<i>tert</i> -butyl
Bz	benzyl
CAN	ceric ammonium nitrate
cat.	catalytic
cod	1,5-cyclooctadiene
coe	cyclooctene
Cp	cyclopentadienyl
Cp*	1,2,3,4,5-pentamethylcyclopentadienyl
Cy	cyclohexyl
DCE	1,2-dichloroethane
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DG	directing group
DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMSO	dimethylsulfoxide
dr	diastereomeric ratio
E ⁺	electrophile
EAS	electrophilic aromatic substitution
equiv	equivalents
esp	$\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid
Et	ethyl
Fc	ferrocene
HFIP	1,1,1,3,3,3-hexafluoroisopropanol
HOSA	hydroxylamine- <i>O</i> -sulfonic acid
ICP-MS	inductively coupled plasma-mass spectrometry
L	ligand
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
<i>m</i>	<i>meta</i>
[M]	metal
<i>m</i> CPBA	<i>meta</i> -chloroperbenzoic acid
Me	methyl
3-Me-Ox	3-methyl-2-oxazolidinone
Mes	mesityl
mol%	mole percent
Ms	mesyl
NCS	<i>N</i> -chlorosuccinimide
Nf	nonafluorobutanesulfonyl
NFBS	<i>N</i> -fluorobenzenesulfonamide

NFSI	<i>N</i> -fluorobenzenesulfonamide
NMR	nuclear magnetic resonance
n.r.	no reaction
Ns	<i>ortho</i> -nitrobenzenesulfonyl
Nu	nucleophile
<i>o</i>	<i>ortho</i>
[O]	oxidant/oxidation
<i>p</i>	<i>para</i>
pin	pinacol
Piv	pivaloyl
Ph	phenyl
phen	1,10-phenanthroline
Phth	phthalimidyl
ppb	parts per billion
ppy	2-phenylpyridine
¹ Pr	<i>iso</i> -propyl
py	pyridine
pyr	pyrrole
S _N Ar	nucleophilic aromatic substitution
t _{1/2}	half life
TBAF	tetrabutylammonium fluoride
TEMPO	(2,2,6,6-tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
TFE	1,1,1-trifluoroethanol
THF	tetrahydrofuran
Tp ^{Br}	tris(3,5-dibromo-1-pyrazolyl)borate
TMP	2,2,6,6-tetramethylpiperidine
TMS	trimethylsilyl
Ts	<i>para</i> -toluenesulfonyl
TTMSS	tris(trimethylsilyl)silane
VNS	vicarious nucleophilic substitution

1. INTRODUCTION

1.1. Aromatic C–H functionalization

C–H functionalization is a highly desirable reaction in the field of organic synthesis. C–H bonds are ubiquitous in organic molecules and can easily be carried through a synthesis without functional group compatibility issues. Prefunctionalization of a specific position is therefore not necessary, which reduces step count and expands opportunities for diversification.¹ For example, functionalization of C–H bonds at the late-stage of a synthesis allows for a target scaffold in medicinal chemistry to be turned into a library of test compounds without repeating the synthesis for each individual molecule.^{1a,e,f,2} However, C–H functionalization is difficult due to the strength and low polarity of a typical C–H bond, which generally results in methods with harsh conditions and limited practical value.³

In particular, aromatic C–H functionalization is attractive due to the substantive presence of arenes in pharmaceutical, agrochemical and material science compounds, and therefore, much work has been focused on this field. While there are many approaches to aromatic C–H functionalization, any useful method for aromatic late-stage C–H functionalization will have two important characteristics: The arene starting material is used as the limiting reagent, and high functional group tolerance is realized.^{1e} The question of positional selectivity is also relevant, though the need for an entirely selective reaction varies and can depend on the goal of the project and the ease of isomer separation.^{1f,g,4}

¹ a. Godula, K.; Sames, D. *Science* **2006**, *312*, 67–72; b. McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885–1898; c. Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976–1991; d. Yamaguchi, J.; Yamaguchi, A. D.; Itami, K. *Angew. Chem. Int. Ed.* **2012**, *51*, 8960–9009; e. Wencel-Delord, J.; Glorius, F. *Nature Chem.* **2013**, *5*, 369–375; f. Hartwig, J. F.; *J. Am. Chem. Soc.* **2016**, *138*, 2–24; g. Cernak, T.; Dykstra, K. D.; Tyagarajan, S.; Vachal, P.; Krska, S. W. *Chem. Soc. Rev.* **2016**, *45*, 546–576.

² a. Dai, H.-X.; Stepan, A. F.; Plummer, M. S.; Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2011**, *133*, 7222–7228; b. Schönherr, H.; Cernak, T. *Angew. Chem. Int. Ed.* **2013**, *52*, 12256–12267; c. Wu, N.; Song, F.; Yan, L.; Li, J.; You, J. *Chem. Eur. J.* **2014**, *20*, 3408–3414; d. Sekizawa, H.; Amaike, K.; Itoh, Y.; Suzuki, T.; Itami, K.; Yamaguchi, J. *ACS Med. Chem. Lett.* **2014**, *5*, 582–586; e. He, J.; Hamann, L. G.; Davies, H. M. L.; Beckwith, R. E. J. *Nat. Commun.* **2015**, *6*, 5943–5951; f. Xu, Y.; Yan, G.; Ren, Z.; Dong, G. *Nature Chem.* **2015**, *7*, 829–834.

³ a. Shilov, A. E.; Shul'pin, G. B. *Chem. Rev.* **1997**, *97*, 2879–2932; b. Labinger, J. A.; Bercaw, J. E. *Nature* **2002**, *417*, 507–514; c. Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740–4761; c. Gensch, T.; Hopkinson, M. N.; Glorius, F.; Wencel-Delord, J. *Chem. Soc. Rev.* **2016**, *45*, 2900–2936.

⁴ Regalado, E. L.; et. al. *Org. Biomol. Chem.* **2014**, *12*, 2161–2166.

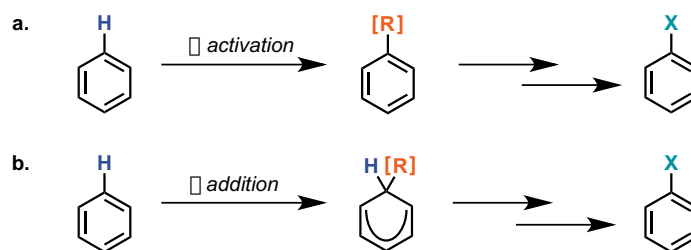


Figure 1.1. Categories of C–H functionalization mechanisms. a. C–H functionalization *via* interaction with the C–H σ -bond; b. C–H functionalization *via* interaction with the aromatic π -system.

Conceptually, aromatic C–H functionalization mechanisms can be divided into two categories – those that interact with the C–H σ -bond, such as metalation, and those that interact with the aromatic π -system, such as electrophilic aromatic substitution (Figure 1.1). Reactions that fall into the first category provide access to versatile carbon–metal intermediates but are usually limited by the difficulty of the C–H activation step.^{3a,5} Reactions in the second category are attractive, because they avoid the challenging C–H metalation step and generally form the new C–X bond readily; however, the design of reaction manifolds to achieve the desired reactivity and selectivity still need improvement. This thesis presents two approaches to aromatic C–H functionalization utilizing π -addition strategies – C–H hydroxylation enabled by η^6 -coordination to iridium(III) (Chapter 2) and radical C–H amination in hexafluoroisopropanol (Chapter 3).

The introduction first provides an overview of aromatic C–H functionalization organized by type of mechanism, with a more detailed discussion of η^6 -arene activation and radical addition. Then, a brief summary of modern methods for aromatic C–H hydroxylation and aromatic C–H amination is presented.

1.1.1. Aromatic C–H functionalization through C–H σ -bond activation

⁵ a. Kuhl, N.; Hopkinson, M. N.; Wencel-Delord, J.; Glorius, F. *Angew. Chem. Int. Ed.* **2012**, *51*, 10236–10254; b. Hartwig, J. F.; Larsen, M. A. *ACS Cent. Sci.* **2016**, *2*, 281–292.

Aromatic C–H bonds are strong (BDE ~112 kcal/mol) and non-acidic ($pK_a \sim 43$), which makes direct functionalization of the C–H σ -bond challenging.⁶ The most common approach for C–H functionalization through a direct interaction with the C–H σ -bond is metalation with either a transition metal (*e.g.* palladium) or a non-transition metal (*e.g.* lithium). Other σ -bond-activating mechanisms, such as carbene⁷ or nitrene⁸ insertion or H-atom abstraction, are quite rare in aromatic C–H functionalization chemistry, despite being prevalent in aliphatic C–H functionalization.^{1,3,9}

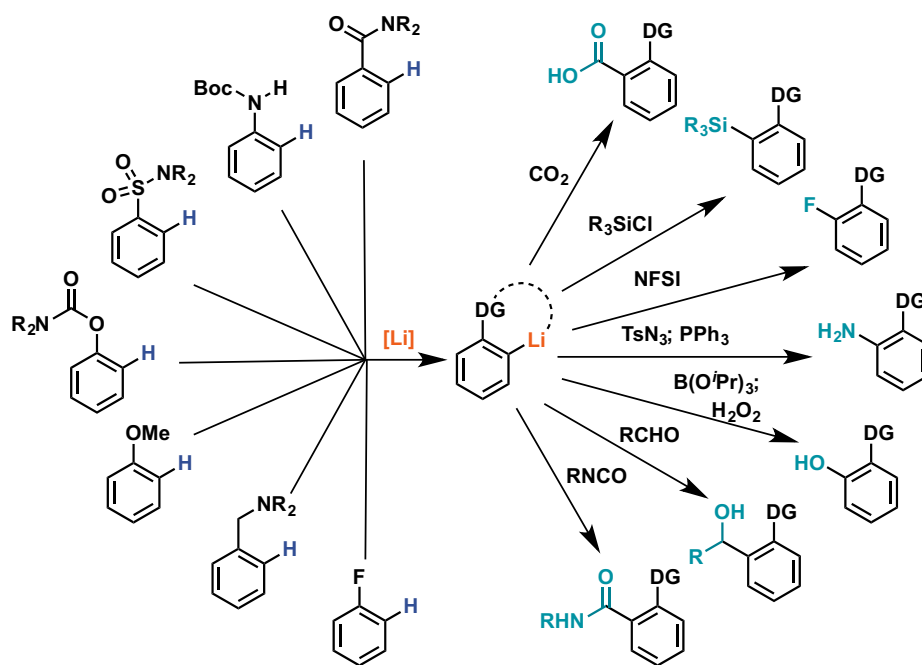


Figure 1.2. Aromatic C–H metalation with non-transition metals. A variety of directing groups (left) can be used to assist lithiation, followed by quenching with various electrophiles (right). Examples shown are not exhaustive.

⁶ a. Qin, Y.; Zhu, L.; Luo, S. *Chem. Rev.* DOI: 10.1021/acs.chemrev.6b00657; b. Xue, X.-S.; Ji, P.; Zhou, B.; Cheng, J.-P. *Chem. Rev.* DOI: 10.1021/acs.chemrev.6b00664.

⁷ a. Rosenfeld, M. J.; Ravi Shankar, B. K.; Shechter, H. *J. Org. Chem.* **1988**, *53*, 2699–2705; b. Rivilla, I.; Gómez-Emeterio, B. P.; Frutos, M. R.; Díaz-Requejo, M. M.; Pérez, P. J. *Organometallics* **2011**, *30*, 2855–2860.

⁸ a. Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058–12059; b. Paudyal, M. P.; Adebesin, A. M.; Burt, S. R.; Ess, D. H.; Ma, Z.; Kürti, L.; Falck, J. R. *Science* **2016**, *353*, 1144–1147.

⁹ Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439–2463.

Metalation with non-transition metals, first reported in 1934,¹⁰ is effectively a deprotonation of an aryl C–H bond by a strong alkali metal base – typically an organolithium or lithium amide. The base is used stoichiometrically to form an aryl-metal species that is quenched in a subsequent step with an electrophile.¹¹ In this way, a variety of functionality can be installed onto an aromatic ring without prefunctionalization of an aryl C–H bond (Figure 1.2). A directing metalation group (DG) on the arene that can coordinate to the metal to assist deprotonation is generally required for synthetically useful reactivity in lithiation reactions. The intramolecularity enforced by a DG has been termed the “complex induced proximity effect”¹² and is a strategy that is found in transition metal metalation reactions as well.

A number of factors have been shown to affect reactivity and selectivity of lithiation reactions: lithium source, solvents, additives and other metals can all influence the aggregation state and basicity of the base and can lead to different reaction outcomes.^{11,13} Furthermore, the identity of the DG and the other substituents on the arene can also affect the positional selectivity of metalation. Guidelines have been proposed to assist in the fine-tuning of reaction parameters to achieve the desired reaction outcome; in some cases, all possible isomers can be obtained through modification of the reaction conditions.¹⁴ Access to such diversity is quite valuable.

One prominent application of lithiation reactions is the synthesis of aryl electrophiles for cross-coupling reactions. Aryl boron, aryl silicon, aryl tin and aryl zinc reagents can all be synthesized utilizing

¹⁰ Gilman, H.; Young, R. V. *J. Am. Chem. Soc.* **1934**, *56*, 1415–1416.

¹¹ a. Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933; b. Leroux, F. R.; Mortier, J. Directed Metalation of Arenes with Organolithiums, Lithium Amides and Superbases. In *Arene Chemistry: Reaction Mechanisms and Methods for Aromatic Compounds*; Mortier, J., Ed.; John Wiley & Sons, Inc.: Hoboken, 2016; pp 743–776.

¹² Whisler, M. C.; MacNeil, S.; Snieckus, V.; Beak, P. *Angew. Chem. Int. Ed.* **2004**, *43*, 2206–2225.

¹³ a. Mongin, F.; Maggi, R.; Schlosser, M. *Chimia* **1996**, *50*, 650–652; b. Haag, B.; Mosrin, M.; Ila, H.; Malakhov, V.; Knochel, P. *Angew. Chem. Int. Ed.* **2011**, *50*, 9794–9824.

¹⁴ Schlosser, M. *Angew. Chem. Int. Ed.* **2005**, *44*, 376–393.

metalation reactions and then used in subsequent Suzuki, Hiyama, Stille, and Negishi cross couplings.^{11b}

C–H metalation/cross-coupling sequences have even been optimized for industrial scale (Figure 1.3).¹⁵

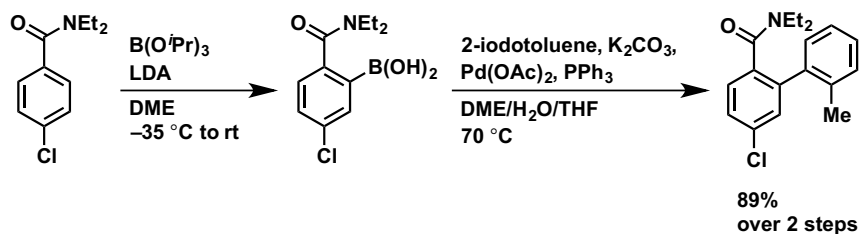


Figure 1.3. A C–H lithiation/quench/cross coupling sequence that has been performed on >300 g scale (*ref 15a*).

While non-transition metal metalation reactions provide access to diverse products, the reaction conditions require strong, nucleophilic bases that preclude broad functional group tolerance and generate stoichiometric alkali metal waste. The use of transition metals can improve functional group tolerance and reduce waste by using catalytic quantities of metal. Similar to lithiation reactions, metalation with transition metals can provide great variety of products with good positional selectivity but often requires the use of a coordinating directing group, which can increase step count if the group is not part of the desired final compound.

Transition metals are known to metalate C–H bonds through four general mechanisms: oxidative addition, σ -bond metathesis, electrophilic metalation¹⁶ and concerted metalation deprotonation (CMD). After metalation, a carbon–metal bond can undergo numerous transformations to install functionality. However, metalation steps tend to be slow, which can hinder the synthetic utility of these reactions by requiring high concentrations of arene (often used as a solvent).⁵ The use of a chelating directing group is one way to alleviate a slow metalation step and enable the use of arene as the limiting reagent (Figure 1.4a). Incorporation of a chelation-assisted metalation into a catalytic cycle was first reported in 1993,¹⁷

¹⁵ a. Limanto, J.; Dorner, B. T.; Hartner, F. W.; Tan, L. *Org. Process Res. Dev.* **2008**, *12*, 1269–1272; b. Han, Y.-H.; Zhou, T.; Sui, Y.; Hua, R. *Org. Process Res. Dev.* **2014**, *18*, 1229–1233.

¹⁶ An electrophilic metalation mechanism is not strictly a σ -bond activation; it is more reminiscent of electrophilic aromatic substitution (see Section 1.1.2).

¹⁷ Murai, S.; Kakiuchi, F.; Sekine, S.; Tanaka, Y.; Kamatani, A.; Sonoda, M.; Chatani, N. *Nature* **1993**, *366*, 529–531.

(Figure 1.4b) and since then, significant work has demonstrated the broad utility of this approach¹⁸ (Figure 1.4c).

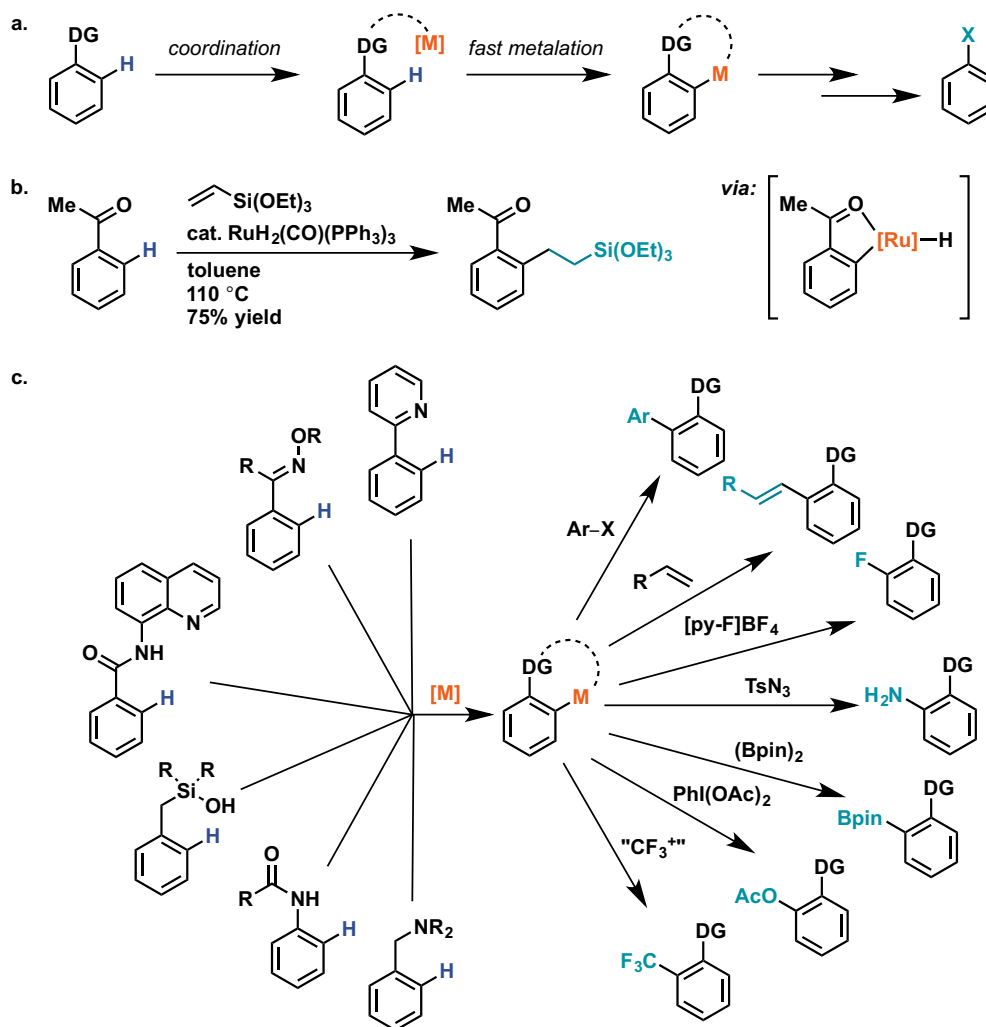


Figure 1.4. Chelation-directed C–H metalation by transition metals. a. A chelating directing group (DG) accelerates C–H metalation by introducing intramolecularity; b. First catalytic reaction that utilized a chelating DG (*ref 17*); c. A variety of directing groups (left) can be utilized to form a versatile carbon–metal intermediate that can be used to install numerous functional groups (right). Examples are not exhaustive.

¹⁸ a. Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2009**, *48*, 5094–5115; b. Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624–655; c. Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147–1169; d. Ackermann, L. *Chem. Rev.* **2011**, *111*, 1315–1345; e. Arockiam, P. B.; Bruneau, C.; Dixneuf, P. H. *Chem. Rev.* **2012**, *112*, 5879–5918; f. Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802; g. Emmert, M. H.; Legacy, C. J. Chelate-Assisted Arene C–H Bond Functionalization. In *Arene Chemistry: Reaction Mechanisms and Methods for Aromatic Compounds*; Mortier, J., Ed.; John Wiley & Sons, Inc.: Hoboken, 2016; pp 648–673.

Most chelating directing groups orient the metalation event to the *ortho* position with good selectivity, but auxiliaries have been designed to reach the *meta*¹⁹ and *para*²⁰ positions as well (Figure 1.5a). Several elegant examples of *meta* functionalization²¹ have also been achieved through transient functionalization of the *ortho* position (Figure 1.5b and Figure 1.5c).²²

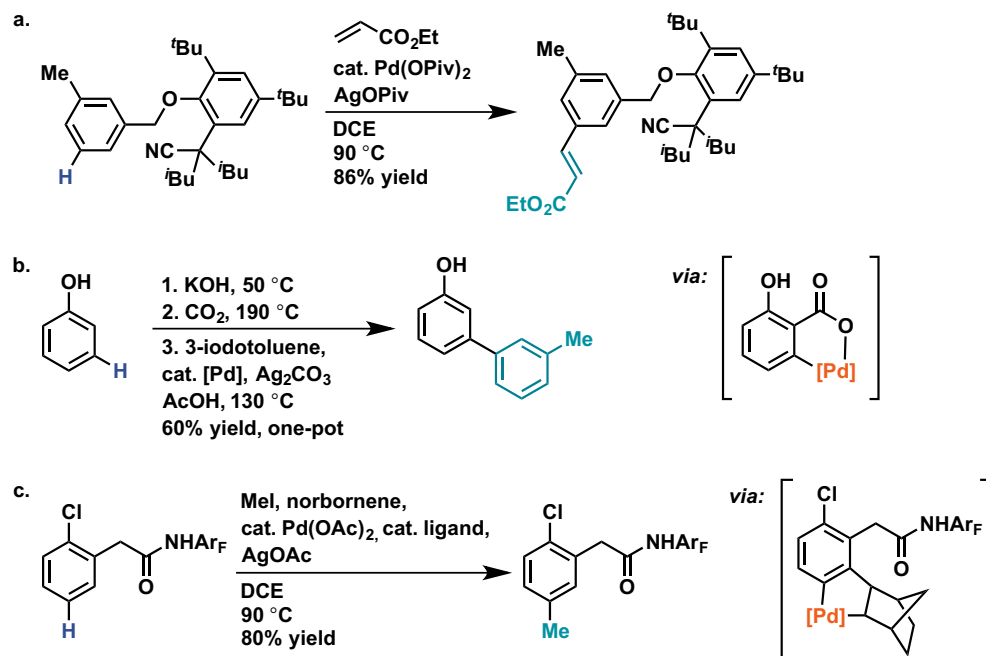


Figure 1.5. *Meta* C–H functionalization strategies. a. U-shaped template for *meta*-olefination (ref 19a); b. Transient carboxylation of the *ortho* position for *meta*-arylation (ref 22a); c. Norbornene-mediated *meta*-alkylation (ref 22b). Ar_F = 4-(CF_3)- C_6F_4 .

A major drawback of directed C–H functionalization chemistry is the existence of the directing group itself, which might need to be installed and removed, increasing the overall step count. Efforts have

¹⁹ a. Leow, D.; Li, G.; Mei, T.-S.; Yu, J.-Q. *Nature* **2012**, *486*, 518–522; b. Lee, S.; Lee, H.; Tan, K. L. *J. Am. Chem. Soc.* **2013**, *135*, 18778–18781; c. Tang, R.-Y.; Li, G.; Yu, J.-Q. *Nature* **2014**, *507*, 215–220; d. Bera, M.; Modak, A.; Patra, T.; Maji, A.; Maiti, D. *Org. Lett.* **2014**, *16*, 5760–5763.

²⁰ a. Bag, S.; et. al. *J. Am. Chem. Soc.* **2015**, *137*, 11888–11891; b. Patra, T.; Bag, S.; Kancharla, R.; Mondal, A.; Dey, A.; Pimparkar, S.; Agasti, S.; Modak, A.; Maiti, D. *Angew. Chem. Int. Ed.* **2016**, *55*, 7751–7755.

²¹ a. Yang, J. *Org. Biomol. Chem.* **2015**, *13*, 1930–1941; b. Li, J.; De Sarkar, S.; Ackermann, L. *Top Organomet. Chem.* **2016**, *55*, 217–258; c. Dey, A.; Agasti, S.; Maiti, D. *Org. Biomol. Chem.* **2016**, *14*, 5440–5453.

²² a. Luo, J.; Preciado, S.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, *136*, 4109–4112; b. Wang, X.-C.; Gong, W.; Fang, L.-Z.; Zhu, R.-Y.; Li, S.; Engle, K. M.; Yu, J.-Q. *Nature* **2015**, *519*, 334–338; c. Dong, Z.; Wang, J.; Dong, G. *J. Am. Chem. Soc.* **2015**, *137*, 5887–5890; d. Shen, P.-X.; Wang, X.-C.; Wang, P.; Zhu, R.-Y.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 11574–11577.

consequently been aimed at broadening the scope of possible directing groups so that either the inherent functionality of a target molecule can be utilized as a directing group²³ or the directing group can be installed, removed or functionalized *in situ*.²⁴ An early example of a catalytic directing group used a phosphinite that undergoes transesterification with phenol substrates (Figure 1.6a). More recently, the Yu group has demonstrated the use of an *in situ* imine formation for palladium-catalyzed C–H functionalization to install a variety of functional groups (Figure 1.6b).

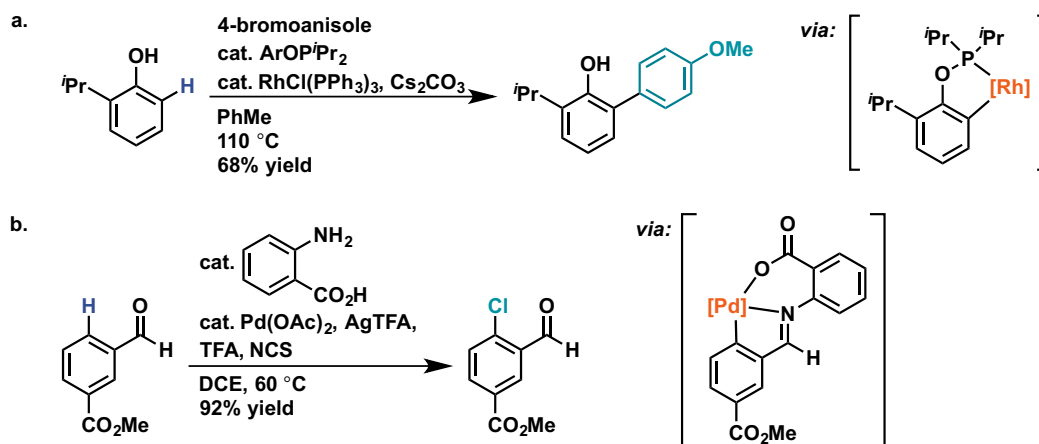


Figure 1.6. C–H metalation with directing groups formed *in situ*. a. Phosphinite transesterification for C–H arylation of phenols (ref 24a); b. *In situ* imine formation for palladium-catalyzed C–H functionalization (ref 24f).

Ideally, the same level of reactivity and selectivity of C–H metalation reactions can be accessed without the prerequisite for a coordinating directing group. In 1969, Fujiwara reported a palladium-catalyzed oxidative coupling of olefins and arenes without a directing group²⁵ that set a precedent for the large body of work that followed it. However, “undirected” C–H metalations still typically require the use

²³ a. Engle, K. M.; Mei, T.-S.; Wasa, M.; Yu, J.-Q. *Acc. Chem. Res.* **2012**, *45*, 788–802; b. De Sarkar, S.; Liu, W.; Kozhushkov, S. I.; Ackermann, L. *Adv. Synth. Catal.* **2014**, *356*, 1461–1479; c. Li, G.; Wan, L.; Zhang, G.; Leow, D.; Spangler, J.; Yu, J.-Q. *J. Am. Chem. Soc.* **2015**, *137*, 4391–4397; d. Zhu, R.-Y.; Farmer, M. E.; Chen, Y.-Q.; Yu, J.-Q. *Angew. Chem. Int. Ed.* **2016**, *55*, 10578–10599; e. Pichette Drapeau, M.; Goossen, L. J. *Chem. Eur. J.* **2016**, *22*, 18654–18677.

²⁴ a. Bedford, R. B.; Coles, S. J.; Hursthouse, M. B.; Limmert, M. E. *Angew. Chem. Int. Ed.* **2003**, *42*, 112–114; b. Boebel, T. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 7534–7535; c. Ihara, H.; Sugimoto, M. *J. Am. Chem. Soc.* **2009**, *131*, 7502–7503; d. Preshlock, S. M.; Plattner, D. L.; Maligres, P. E.; Krska, S. W.; Maleczka, R. E., Jr.; Smith, M. R., III *Angew. Chem. Int. Ed.* **2013**, *52*, 12915–12919; e. Zhang, F.; Spring, D. R. *Chem. Soc. Rev.* **2014**, *43*, 6906–6919; f. Liu, X.-H.; Park, H.; Hu, J.-H.; Hu, Y.; Zhang, Q.-L.; Wang, B.-L.; Sun, B.; Yeung, K.-S.; Zhang, F.-L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2017**, *139*, 888–896.

²⁵ Fujiwara, Y.; Moritani, I.; Danno, S.; Asano, R.; Teranishi, S. *J. Am. Chem. Soc.* **1969**, *91*, 7166–7169.

of excess arene and/or give more than one isomeric product.^{5a} Two reaction classes are notable exceptions – C–H borylation or silylation and C–H arylation where one arene contains an acidic C–H bond.^{1f}

Aromatic C–H borylation²⁶ proceeds under iridium catalysis²⁷ with the arene as the limiting reagent (Figure 1.7a).²⁸ The synthetic utility of this reaction has been demonstrated in total synthesis²⁹ and in heterocycle borylation.³⁰ Selectivity is governed by steric control, and borylation generally gives mixtures of *meta* and *para* isomers, due to poor steric differentiation between these positions. Itami disclosed a bulky bis-phosphine ligand for an iridium catalyst that gives preferential *para* selectivity for borylation in some cases.³¹ In depth mechanistic studies performed by the Hartwig group support a C–H oxidative addition, possibly assisted by a coordinated boryl ligand, at an iridium(III) center to generate an iridium(V) aryl complex.³²

Aromatic C–H silylation³³ using one equivalent of arene has also been reported by the Hartwig group (Figure 1.7b). Initial studies used a bis-phosphine-ligated rhodium catalyst,³⁴ but they later disclosed that the use of a bipyridine-ligated iridium catalyst increased functional group tolerance and decreased cost.³⁵ The silanes used for silylation are cheaper than the diboron reagents needed for

²⁶ a. Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992–2002; b. Ros, A.; Fernández, R.; Lassaletta, J. M. *Chem. Soc. Rev.* **2014**, *43*, 3229–3243.

²⁷ a. Cho, J.-Y.; Tse, M. K.; Holmes, D.; Maleczka, R. E., Jr.; Smith, M. R., III *Science* **2002**, *295*, 305–308; b. Ishiyama, T.; Takagi, J.; Ishida, K.; Miyaura, N.; Anastasi, N. R.; Hartwig, J. F. *J. Am. Chem. Soc.* **2002**, *124*, 390–391.

²⁸ Ishiyama, T.; Takagi, J.; Hartwig, J. F.; Miyaura, N. *Angew. Chem. Int. Ed.* **2002**, *41*, 3056–3058.

²⁹ Fischer, D. F.; Sarpong, R. *J. Am. Chem. Soc.* **2010**, *132*, 5926–5927.

³⁰ Larsen, M. A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 4287–4299.

³¹ Saito, Y.; Segawa, Y.; Itami, K. *J. Am. Chem. Soc.* **2015**, *137*, 5193–5198.

³² Boller, T. M.; Murphy, J. M.; Hapke, M.; Ishiyama, T.; Miyaura, N.; Hartwig, J. F. *J. Am. Chem. Soc.* **2005**, *127*, 14263–14278.

³³ Cheng, C.; Hartwig, J. F. *Chem. Rev.* **2015**, *115*, 8946–8975.

³⁴ a. Cheng, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2014**, *136*, 12064–12072; b. Cheng, C.; Hartwig, J. F. *Science* **2014**, *343*, 853–857.

³⁵ Cheng, C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2015**, *137*, 592–595.

borylation, but silylation requires the use of a H₂ acceptor (cyclohexene), which is not required in borylation reactions. Both aromatic C–H borylation and silylation provide valuable aryl electrophile products that can be easily diversified into a variety of functional groups through cross coupling or oxidation processes.³⁶

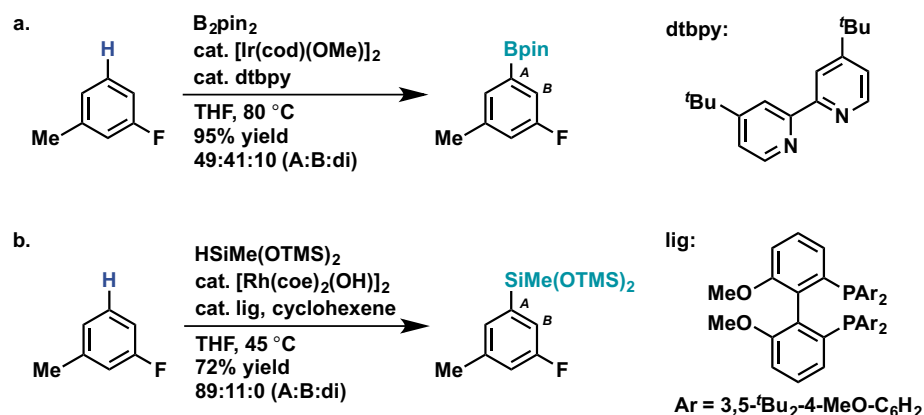


Figure 1.7. Synthesis of versatile aryl-metal species using one equivalent of arene (*ref 34b*). a. Iridium-catalyzed aromatic C–H borylation; b. Rhodium-catalyzed aromatic C–H silylation.

Aromatic C–H arylation provides valuable biaryl products without the need for prefunctionalization of at least one of the arenes, which minimizes waste and decreases step count. The difficulty of these reactions, however, is the prevention of homo-coupling products that arise from slow C–H metalation steps without using a large excess of the C–H arene. Since concerted metalation deprotonation is a prominent mechanistic pathway,^{18d,37} the most successful reactions incorporate C–H metalation of a fairly acidic arene, such as a heteroarene (Figure 1.8a)³⁸ or a highly fluorinated benzene

³⁶ Hartwig, J. F. *Acc. Chem. Res.* **2012**, *45*, 864–873.

³⁷ a. Lapointe, D.; Fagnou, K. *Chem. Lett.* **2010**, *39*, 1118–1126; b. Gorelsky, S. I.; Lapointe, D.; Fagnou, K. *J. Org. Chem.* **2012**, *77*, 658–668.

³⁸ a. Liégault, B.; Lapointe, D.; Caron, L.; Vlassova, A.; Fagnou, K. *J. Org. Chem.* **2009**, *74*, 1826–1834; b. Lapointe, D.; Markiewicz, T.; Whipp, C. J.; Toderian, A.; Fagnou, K. *J. Org. Chem.* **2011**, *76*, 749–759; c. Rossi, R.; Bellina, F.; Lessi, M.; Manzini, C. *Adv. Synth. Catal.* **2014**, *356*, 17–117; d. Kazzouli, S. E.; Koubachi, J.; Brahmi, N. E.; Guillaumet, G. *RSC Adv.* **2015**, *5*, 15292–15327; e. Théveau, L.; Schneider, C.; Fruit, C.; Hoarau, C. *ChemCatChem* **2016**, *8*, 3183–3194; f. Yamaguchi, J.; Amaike, K.; Itami, K. *Synthesis of Natural Products and Pharmaceuticals via Catalytic C–H Functionalization. In Transition Metal-Catalyzed Heterocycle Synthesis via C–H Activation*; Wu, X.-F., Ed.; Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2016; pp 505–550.

(Figure 1.8b)³⁹. In a conceptually related approach, Larossa and coworkers have shown that the C–H metalation reactivity of non-acidic arenes can be increased with η^6 -coordination to $[\text{Cr}(\text{CO})_3]$ and can be used in arylation reactions with low equivalents (1.3–1.5:1.0 ratios) (Figure 1.8c).⁴⁰

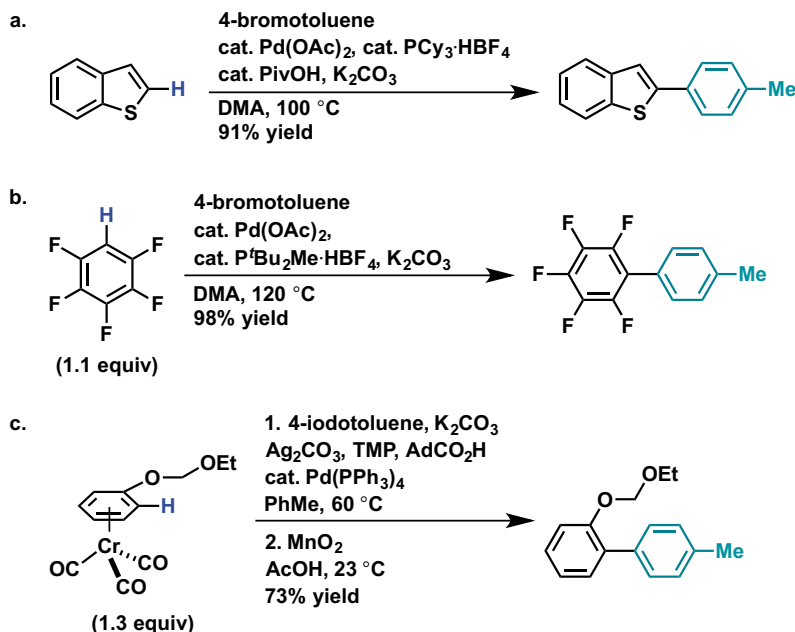


Figure 1.8. Aromatic C–H arylation with near equimolar arene to arene ratios. Palladium-catalyzed arylation of a. heterocycles (*ref 38a*); b. perfluoroarenes (*ref 39*); and c. η^6 -coordinated non-acidic arenes (*ref 40b*).

1.1.2. Aromatic C–H functionalization through π -addition

π -Addition approaches to C–H functionalization involve attack of an electrophile, a nucleophile or a radical onto the π -system of an arene to give a cyclohexadienyl cation, anion or radical, respectively. The subsequent step involves loss of a proton, a hydride or an H-atom to restore aromaticity and provide the functionalized product (Figure 1.9); regeneration of aromaticity is generally a driving force in these reactions. All three modes of π -addition can enable overall C–H functionalization of arenes, but perhaps the most traditionally utilized is electrophilic aromatic substitution (EAS).

³⁹ Lafrance, M.; Rowley, C. N.; Woo, T. K.; Fagnou, K. *J. Am. Chem. Soc.* **2006**, 128, 8754–8756.

⁴⁰ a. Ricci, P.; Krämer, K.; Cambeiro, X. C.; Larrosa, I. *J. Am. Chem. Soc.* **2013**, 135, 13258–13261; b. Ricci, P.; Krämer, K.; Larrosa, I. *J. Am. Chem. Soc.* **2014**, 136, 18082–18086.

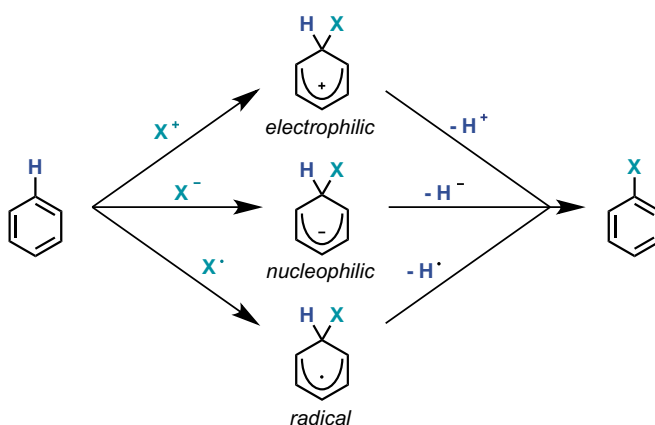


Figure 1.9. Three modes of π -addition for aromatic C–H functionalization – electrophilic, nucleophilic and radical addition.

Electrophilic aromatic substitution (EAS) is a workhorse of synthetic chemistry. Known since 1877,⁴¹ electrophilic aromatic substitution is used for the industrial synthesis of feedstock and commodity chemicals on a scale of millions of tons annually.⁴² Furthermore, a vast body of work was generated studying the mechanism and fundamental physical organic chemistry of EAS^{42,43} and still generates discussion today.⁴⁴ The classical EAS mechanism involves nucleophilic attack of an arene on an electrophile to form a cyclohexadienyl cation, called the Wheland intermediate or σ -complex, followed by deprotonation and elimination to form the product (Figure 1.9). Positional selectivity is governed by the substituents on the arene substrate, with more nucleophilic positions being substituted preferentially: electron-releasing substituents direct *ortho/para* functionalization and electron-withdrawing substituents direct *meta* functionalization.

⁴¹ a. Friedel, C.; Crafts, J. M. *Compt. Rend.* **1877**, 84, 1392–1395; b. Friedel, C.; Crafts, J. M. *Compt. Rend.* **1877**, 84, 1450–1454.

⁴² a. Carey, F. A.; Sundberg, R. J. *Advanced Organic Chemistry, Part A: Structure and Mechanisms*; Springer: New York, 2006; pp 551–604; b. Klumpp, D. A. Electrophilic Aromatic Substitution: Mechanism. In *Arene Chemistry: Reaction Mechanisms and Methods for Aromatic Compounds*; Mortier, J., Ed.; John Wiley & Sons, Inc.: Hoboken, 2016; pp 3–31.

⁴³ Olah, G. A. *Acc. Chem. Res.* **1971**, 4, 240–248.

⁴⁴ Nieves-Quinones, Y.; Singleton, D. A. *J. Am. Chem. Soc.* **2016**, 138, 15167–15176.

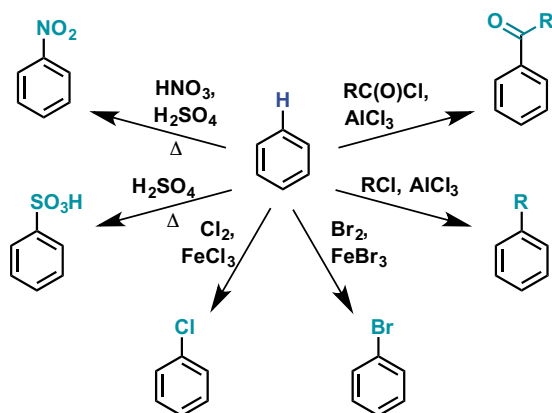


Figure 1.10. Electrophilic aromatic substitution. Examples are not exhaustive.

A variety of electrophiles can be used in EAS (Figure 1.10); they are typically cationic species generated *in situ* from less reactive precursors. For example, the active nitrating agent in aromatic nitration reactions is the nitronium ion (NO_2^+), generated by mixing sulfuric and nitric acids.⁴⁵ Other common EAS reactions include halogenation, sulfonation, and Friedel-Crafts alkylation or acylation.⁴² EAS generally has a broad substrate scope, with the strongest electrophiles reacting with quite electron-poor arenes, such as in the synthesis of 2,4,6-trinitrotoluene (TNT) (Figure 1.11a).⁴⁶ However, reactions with electron-rich arenes proceed under milder conditions and exhibit greater functional group tolerance, such as in the total synthesis of podophyllotoxin (Figure 1.11b).⁴⁷

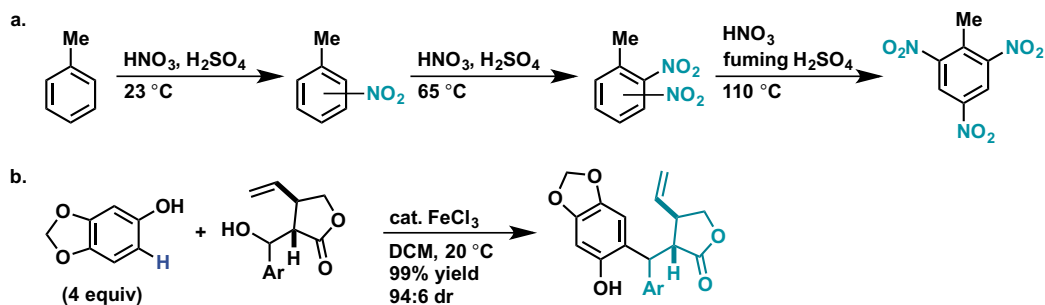


Figure 1.11. Electronic properties of the arene dictate harshness of EAS reaction conditions. a. Successive nitration of toluene with increasingly forceful conditions (*ref* 46); b. Mild Friedel-Crafts alkylation of an electron-rich arene (*ref* 47). Ar = 3,4,5-(OMe)₃-C₆H₂.

⁴⁵ Olah, G. A.; Malhotra, R.; Narang, S. C. *Nitration: Methods and Mechanism*; VCH Publishers, Inc.: New York, 1989.

⁴⁶ Russell, R. A.; Switzer, R. W.; Longmore, R. W. *J. Chem. Educ.* **1990**, 67, 68–69.

⁴⁷ Stadler, D.; Bach, T. *Angew. Chem. Int. Ed.* **2008**, 47, 7557–7559.

Nucleophilic aromatic substitution is the conceptual opposite of electrophilic aromatic substitution: the arene behaves as an electrophile and is attacked by a nucleophile. The resulting cyclohexadienyl anion, also called a Meisenheimer intermediate, must undergo oxidation, with formal loss of a hydride, to give a C–H functionalized arene (Figure 1.9). Since hydride is a poor leaving group, nucleophilic aromatic substitution for C–H functionalization⁴⁸ is quite rare, and displacement of a good leaving group (*e.g.* fluoride) is more common. However, mechanistic evidence has shown that the initial nucleophilic attack on an arene is fast and reversible at C–H bonds to form the σ_{H} -adduct; if a pathway for oxidation is accessible, C–H functionalization will occur over formation of the σ_{X} -adduct and leaving group displacement (Figure 1.12).⁴⁹ Practically, nucleophilic aromatic substitution is only observed with nitro-substituted arenes that can stabilize the buildup of negative charge in the Meisenheimer intermediate.⁵⁰

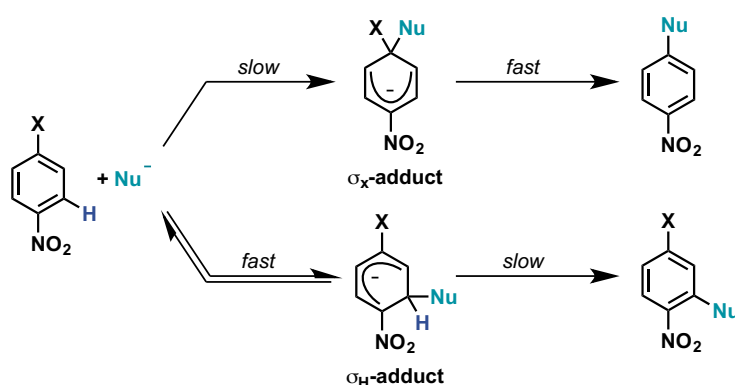


Figure 1.12. Relative rates of nucleophilic addition to electron-poor arenes at C–H vs. C–X bonds.

There are two main pathways for oxidation of σ_{H} -adducts in nucleophilic aromatic substitution: external oxidation and vicarious nucleophilic substitution (VNS).⁴⁸ External oxidation involves use of an

⁴⁸ a. Mąkosza, M. *Chem. Soc. Rev.* **2010**, 39, 2855–2868; b. Mąkosza, M. *Synthesis* **2011**, 15, 2341–2356; c. Mąkosza, M. Nucleophilic Substitution of Hydrogen in Electron-Deficient Arenes. In *Arene Chemistry: Reaction Mechanisms and Methods for Aromatic Compounds*; Mortier, J., Ed.; John Wiley & Sons, Inc.: Hoboken, 2016; pp 269–298.

⁴⁹ a. Mąkosza, M.; Glinka, T. *J. Org. Chem.* **1983**, 48, 3861–3863; b. Mąkosza, M.; Kwast, A. *J. Phys. Org. Chem.* **1998**, 11, 341–349; c. Mąkosza, M.; Lemek, T.; Kwast, A.; Terrier, F. *J. Org. Chem.* **2002**, 67, 394–400.

⁵⁰ a. Bunnett, J. F.; Zahler, R. E. *Chem. Rev.* **1951**, 49, 273–412; b. Terrier, F. *Chem. Rev.* **1982**, 82, 77–152; c. Seeliger, F.; Błażej, S.; Bernhardt, S.; Mąkosza, M.; Mayr, H. *Chem. Eur. J.* **2008**, 14, 6108–6118.

oxidant, such as KMnO_4 or O_2 , in combination with a nucleophile; naturally, the nucleophile must be resistant to oxidation. An example of an external oxidation is the C–H amination of 4-chloro-1,3-dinitrobenzene, which occurs at low temperature and with KMnO_4 as the oxidant (Figure 1.13a).⁵¹ Selectivity for C–H amination over C–Cl amination is notable. Vicarious nucleophilic substitution utilizes nucleophiles that contain internal leaving groups as a strategy to combine the nucleophile and oxidant into one reagent. For example, the carbanion of chloromethyl phenyl sulfone adds to 4-chloronitrobenzene to generate a σ_{H} -adduct, which then undergoes elimination of chloride (Figure 1.13b).⁵² Protonation of the resulting anion gives the aromatized C–H alkylated product. VNS has been used to form new C–N⁵³ and C–O⁵⁴ bonds as well.

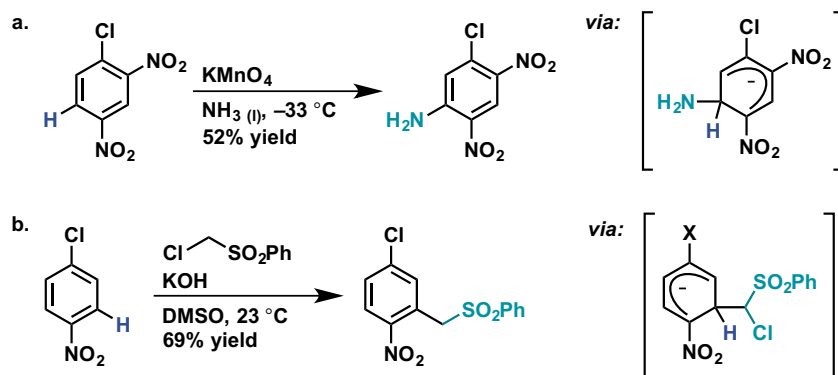


Figure 1.13. C–H functionalization through nucleophilic aromatic substitution. a. *In situ* oxidation of the Meisenheimer complex gives an aniline product (*ref* 51); b. Vicarious nucleophilic substitution with chloromethyl phenyl sulfone (*ref* 52).

Despite the interesting reactivity, as well as the complementary selectivity, nucleophilic aromatic substitution suffers from a significantly smaller substrate scope as compared to electrophilic aromatic substitution, which limits its overall synthetic utility. One strategy to overcome the electronic limits of the

⁵¹ Szpakiewicz, B.; Grzegozek, M. *Russ. J. Org. Chem.* **2004**, *40*, 829–833.

⁵² a. Goliński, J.; Mąkosza, M. *Tetrahedron Lett.* **1978**, *37*, 3495–3498; b. Mąkosza, M.; Goliński, J.; Baran, J. J. *Org. Chem.* **1984**, *49*, 1488–1494.

⁵³ a. Katritzky, A. R.; Laurenzo, K. S. *J. Org. Chem.* **1986**, *51*, 5039–5040; b. Mąkosza, M.; Białecki, M. *J. Org. Chem.* **1992**, *57*, 4784–4785; c. Pagoria, P. F.; Mitchell, A. R.; Schmidt, R. D. *J. Org. Chem.* **1996**, *61*, 2934–2935; d. Mąkosza, M.; Białecki, M. *J. Org. Chem.* **1998**, *63*, 4878–4888; e. Rozhkov, V. V.; Shevelev, S. A.; Chervin, I. I.; Mitchell, A. R.; Schmidt, R. D. *J. Org. Chem.* **2003**, *68*, 2498–2501.

⁵⁴ a. Mattersteig, G.; Pritzkow, W.; Voerckel, V. *J. Prakt. Chem.* **1990**, *332*, 569–572; b. Mąkosza, M.; Sienkiewicz, K. *J. Org. Chem.* **1998**, *63*, 4199–4208.

arene starting material is η^6 -coordination of an arene to a transition metal; complexation withdraws significant electron density from the aromatic ring and enables nucleophilic attack on otherwise electron-rich arenes. Due to its relevance to Chapter 2 of this thesis, C–H functionalization of η^6 -coordinated arenes will be discussed in detail in Section 1.2.

The final mode of π -addition for C–H functionalization is radical addition to arenes (Figure 1.9). The resulting cyclohexadienyl radicals either are oxidized to the cation and deprotonated or undergo H-atom abstraction to generate the functionalized arene. Due to its relevance to Chapter 3 of this thesis, C–H functionalization *via* radical addition will be discussed in detail in Section 1.3.

1.2. η^6 -Arene complexes for aromatic C–H functionalization

η^6 -Coordination of an arene to a transition metal appreciably affects its reactivity. The transition metal pulls electron density out of the aromatic π -system, which results in enhanced electrophilicity of the arene and increased acidity of ring and benzylic protons (Figure 1.14).⁵⁵ For example, anisole has a $pK_a \sim 39$, while $[(\eta^6\text{-anisole})\text{CrCO}_3]$ has a $pK_a \sim 33$.⁵⁶ Methods have been developed to take advantage of this activation mode for C–H functionalization based on two general pathways⁵⁵ – lithiation of an acidic proton, followed by quenching with an electrophile⁵⁷ and nucleophilic attack on the arene, followed by oxidation (Figure 1.14).⁵⁸ Similar to what is observed in non-metal-mediated nucleophilic aromatic substitution (Section 1.1.2), nucleophilic attack is kinetically favored at positions bearing a C–H bond, but if reversible, attack at a C–X bond and displacement of leaving group will occur. As might be predicted, regioselectivity of nucleophilic attack is dictated, at least in part, by the most electrophilic

⁵⁵ a. Kane-Maguire, L. A. P.; Honig, E. D.; Sweigart, D. A. *Chem. Rev.* **1984**, *84*, 525–543; b. Pike, R. D.; Sweigart, D. A. *Coord. Chem. Rev.* **1999**, *187*, 183–222; c. Pape, A. R.; Kaliappan, K. P.; Kündig, E. P. *Chem. Rev.* **2000**, *100*, 2917–2940; d. Merlic, C. A.; Miller, M. M.; Hietbrink, B. N.; Houk, K. N. *J. Am. Chem. Soc.* **2001**, *123*, 4904–4918.

⁵⁶ Fraser, R. R.; Mansour, T. S. *J. Organomet. Chem.* **1986**, *310*, C60–C62.

⁵⁷ a. Berger, A.; Djukic, J.-P.; Michon, C. *Coord. Chem. Rev.* **2002**, *225*, 215–238; b. Semmelhack, M. F.; Chlenov, A. *Top. Organomet. Chem.* **2004**, *7*, 21–42.

⁵⁸ Semmelhack, M. F.; Chlenov, A. *Top. Organomet. Chem.* **2004**, *7*, 43–69.

position of the arene.⁵⁹ In a subsequent step after C–H functionalization, arenes must be decomplexed from the transition metal, usually oxidatively or photochemically.⁶⁰

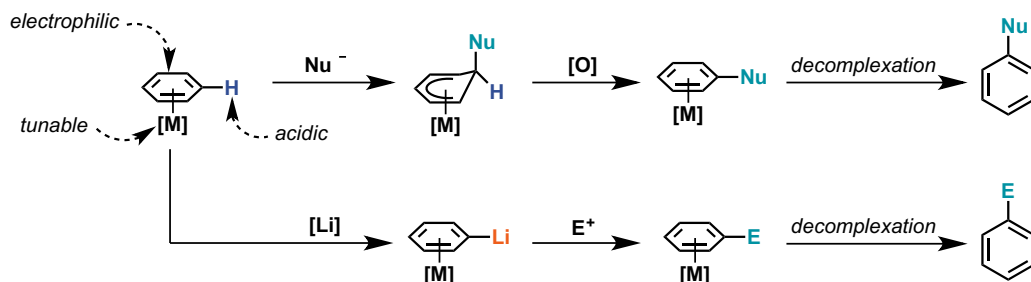


Figure 1.14. C–H functionalization with η^6 -arene complexes occurs through nucleophilic attack/oxidation (top) or lithiation/quenching (bottom).

Several transition metal fragments are used for η^6 -arene C–H functionalization chemistry (Figure 1.15a).⁵⁸ Electrophilicity of the metal complexes varies, with more highly charged complexes generally exhibiting increased acidity and reactivity with weaker nucleophiles. η^6 -Arene complexes have been described by the k_{CO}^* parameter, which provides a quantitative ranking of their electrophilicity based on the hypothetical replacement of the arene with three carbonyl ligands and correlates well with observed reactivity.⁶¹ The varying effects of the metal fragment are also evident upon inspection of η^6 -phenol complexes (Figure 1.15b). More electron-withdrawing transition metal fragments acidify coordinated phenol to a greater extent, and the mitigated basicity of the corresponding phenoxide is evident from its reactivity with electrophiles. $[\text{Cr}(\text{CO})_3]$, one of the least electron-withdrawing fragments shows minimal distortion from η^6 -coordination, has a C–O bond length reminiscent of a single bond, and reacts readily with TsCl .⁶² On the other hand, one of the most electron-withdrawing fragments, $[\text{Cp}^*\text{Ir}]^{2+}$, shows a 22°

⁵⁹ a. Semmelhack, M. F.; Clark, G. *J. Am. Chem. Soc.* **1977**, *99*, 1675–1676; b. Semmelhack, M.F.; Clark, G. R.; Farina, R.; Saeman, M. *J. Am. Chem. Soc.* **1979**, *101*, 217–218; c. Semmelhack, M. F.; Garcia, J. L.; Cortes, D.; Farina, R.; Hong, R.; Carpenter, B. K. *Organometallics* **1983**, *2*, 467–469.

⁶⁰ Kündig, E. P. *Top. Organomet. Chem.* **2004**, *7*, 3–20.

⁶¹ Bush, R. C.; Angelici, R. J. *J. Am. Chem. Soc.* **1986**, *108*, 2735–2742.

⁶² Heppert, J. A.; Boyle, T. J.; Takusagawa, F. *Organometallics* **1989**, *8*, 461–467.

bend out of the η^6 -plane, has effectively a C–O double bond, and does not react with MeOTf.⁶³ As would be expected, $[\text{Cp}^*\text{Ru}]^+$ has characteristics in between.⁶⁴

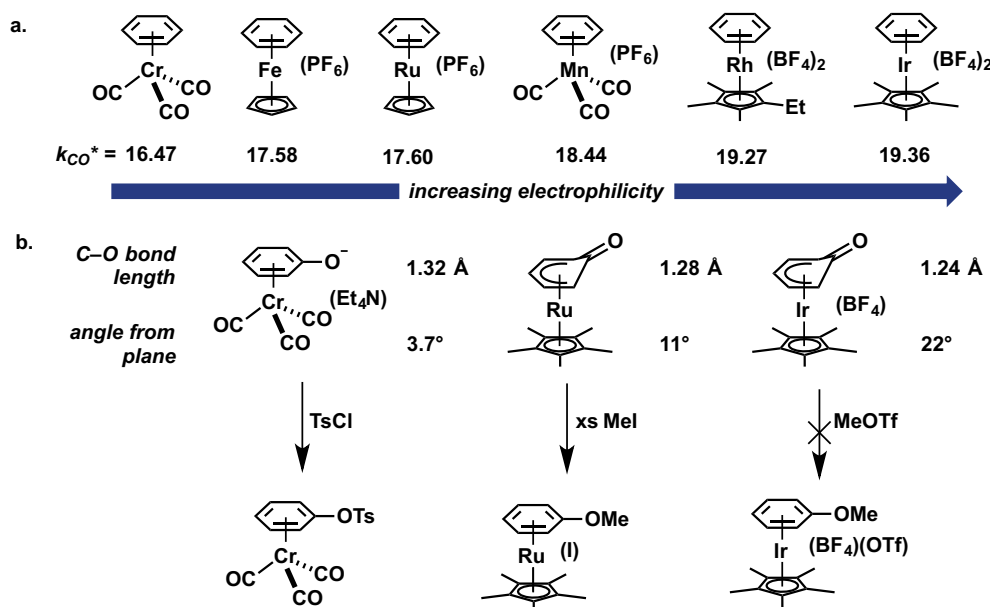


Figure 1.15. Comparison of common η^6 -arene complexes. a. Electrophilicity is compared using the k_{CO}^* parameter; b. Structural parameters and reactivity of η^6 -phenol complexes demonstrates how the charge of the complex affects electrophilicity.

1.2.1. Stoichiometric C–H functionalization with η^6 -arene complexes

As introduced above in Section 1.2, there are two main pathways for C–H functionalization with η^6 -arene complexes – lithiation/quenching and nucleophilic attack/oxidation. Both are inspired by chemistry on uncomplexed arenes, but complexation imparts benefits – namely increased reactivity and selectivity. In particular, nucleophilic aromatic substitution chemistry is restricted to nitro-substituted arenes, but through η^6 -coordination, the scope of these transformations can be expanded significantly to include electron-rich arenes as well.

Lithiation/quenching procedures most commonly employ $[(\eta^6\text{-arene})\text{Cr}(\text{CO})_3]$ complexes, due to their low propensity for nucleophilic attack. Typical electrophiles include halogens, alkyl halides,

⁶³ Bras, J. L.; Amouri, H. E.; Besace, Y.; Vaissermann, J.; Jaouen, G. *Bull. Soc. Chim. Fr.* **1995**, 132, 1073–1082.

⁶⁴ He, X. D.; Chaudret, B.; Dahan, F.; Huang, Y.-S. *Organometallics* **1991**, 10, 970–979.

aldehydes, acyl chlorides, disulfides, silyl chlorides and carbon dioxide.⁵⁷ For example, $[(\eta^6\text{-benzene})\text{Cr}(\text{CO})_3]$ is methylated with methyl iodide, followed by oxidative decomplexation with ceric ammonium nitrate (CAN) to give toluene in 71% yield (Figure 1.16a).⁶⁵ η^6 -Coordination is used as a strategy in the total synthesis of 7,8-dihydroxycalamenenes, which includes a C–H silylation step (Figure 1.16b).⁶⁶ Decomplexation is performed several steps further into the synthesis.

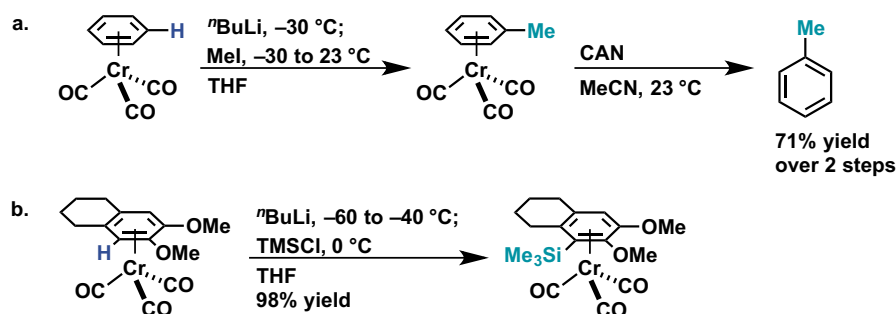


Figure 1.16. η^6 -Arene complexes for C–H lithiation and quenching with electrophiles. a. Methylation with methyl iodide (*ref 65*); b. Silylation with trimethylsilyl chloride (*ref 66*).

Nucleophilic attack on η^6 -arene complexes with strong nucleophiles is well documented with a variety of transition metal complexes.^{55,58, 67} The subsequent oxidation and decomplexation steps, however, are not trivial with all complexes, which limits the potential of η^6 -arene chemistry for C–H functionalization. A typical reaction scheme is outlined in Figure 1.17a. Nucleophilic attack on an η^6 -arene complex generates an η^5 -cyclohexadienyl intermediate. Nucleophilic attack is generally reversible, but the η^5 -cyclohexadienyl complex must be favored in the equilibrium in order for productive oxidation to take place in the next step. Conditions for oxidation are usually not compatible with nucleophilic addition, so the η^5 -cyclohexadienyl complex must persist until an oxidant is added. Practically for $\text{Cr}(\text{CO})_3$ complexes, this only occurs for carbanions where the pK_a of the nucleophile is >22 , such as

⁶⁵ Card, R. J.; Trahanovsky, W. S. *J. Org. Chem.* **1980**, *45*, 2555–2559.

⁶⁶ Schmalz, H.-G.; Arnold, M.; Hollander, J.; Bats, J. W. *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 109–111.

⁶⁷ a. Davies, S. G.; Green, M. L. H.; Mingos, D. M. P. *Tetrahedron* **1978**, *34*, 3047–3077; b. Astruc, D. *Synlett* **1991**, 369–380.

lithoacetonitrile (Figure 1.17b).⁶⁸ One exception using a nitrogen nucleophile has been reported; the η^5 -cyclohexadienyl intermediate is likely favored due to a second deprotonation (Figure 1.17c).⁶⁹ With more electrophilic arene complexes, weaker nucleophiles, such as silyl enol ethers⁷⁰ (Figure 1.17d) can be used to generate η^5 -cyclohexadienyl complexes. However, oxidation tends to be more difficult, which restricts the overall protocol.

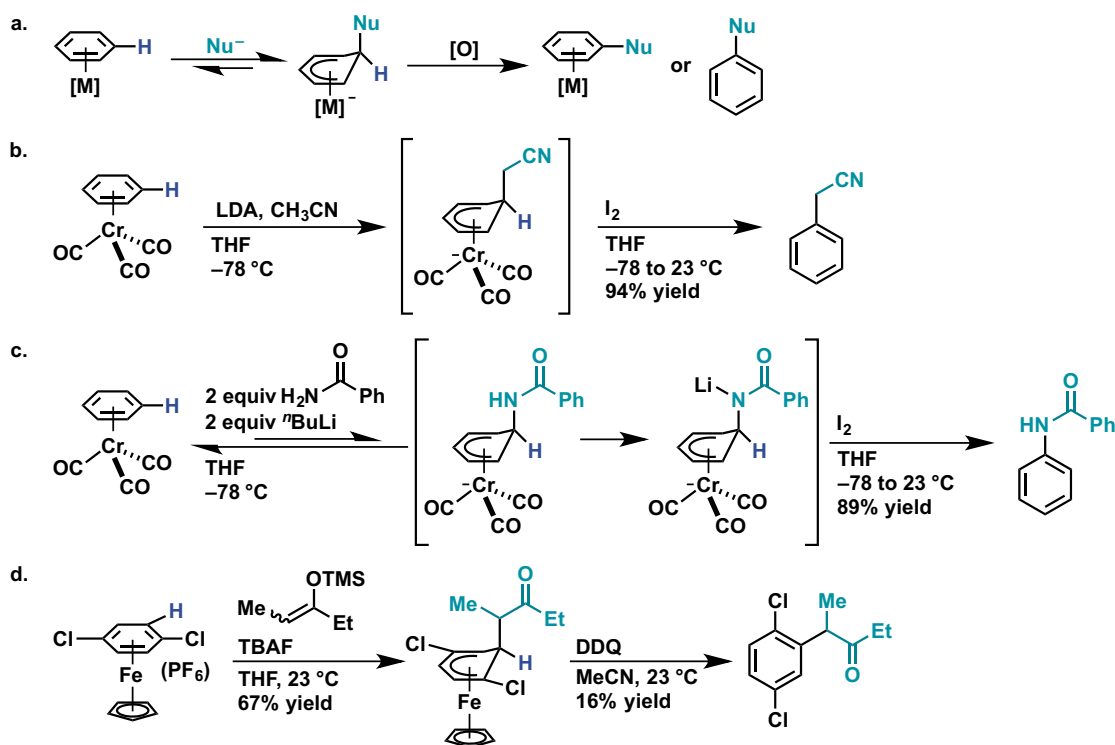


Figure 1.17. Nucleophilic attack/oxidation sequence for C–H functionalization with η^6 -arene complexes. a. General reaction pathway for nucleophilic attack/oxidation; b. Strong nucleophilic carbanions add to $\text{Cr}(\text{CO})_3$ complexes; c. Sole example of heteroatomic nucleophile for the sequence with $[\text{Cr}(\text{CO})_3]$; d. Silyl enol ether addition to $[\text{FeCp}]^+$ works well, but oxidation is difficult.

1.2.2. Toward catalytic C–H functionalization with η^6 -arene complexes

⁶⁸ Semmelhack, M. F.; Hall, H. T., Jr.; Farina, R.; Yoshifuji, M.; Clark, G.; Bargar, T.; Hirotsu, K.; Clardy, J. *J. Am. Chem. Soc.* **1979**, *101*, 3535–3544.

⁶⁹ Keller, L.; Times-Marshall, K.; Behar, S.; Richards, K. *Tetrahedron Lett.* **1989**, *30*, 3373–3376.

⁷⁰ Cambie, R. C.; Coulson, S. A.; Mackay, L. G.; Janssen, S. J.; Rutledge, P. S.; Woodgate, P. D. *J. Organomet. Chem.* **1991**, *409*, 385–409.

The vast majority of reaction chemistry using η^6 -arene complexes is stoichiometric in the metal fragment, and no catalytic C–H functionalization reactions have been reported using η^6 -arene complexes. A catalytic reaction would reduce the step count by avoiding complexation and decomplexation steps in a synthesis, as well as decrease the cost of materials. The prototypical catalytic cycle involves functionalization of the coordinated arene, either by C–H functionalization or S_NAr , followed by arene exchange to release the product and regenerate the starting complex. A major challenge in the realization of catalysis is the compatibility between the functionalization step and the exchange step. Most complexes that promote functionalization exhibit slow arene exchange kinetics, and *vice versa*.

The process of arene exchange has been studied in detail for many η^6 -arene complexes,⁷¹ and the generally accepted mechanism involves a rate-determining η^6 to η^4 slip (Figure 1.18a). Lewis basic donor molecules have been shown to accelerate arene exchange and are hypothesized to stabilize the η^4 -arene intermediate (Figure 1.18b).⁷² Addition of Lewis bases, however, must not outcompete the incoming arene, a balance that is difficult to achieve in practice. In 2005, Semmelhack reported an elegant approach to replace one carbonyl ligand of $[(\eta^6\text{-arene})Cr(CO)_3]$ complexes with a bidentate ligand designed to have one strongly coordinating group and one weakly coordinating group to act as a donor molecule to accelerate arene exchange (Figure 1.18c).⁷³ While arene exchange was accelerated, the conditions were disappointingly not amenable for a catalytic S_NAr reaction. Other reports have investigated the use of $[(\eta^6\text{-arene})IrCp^*]^{2+}$ complexes in a potential catalytic cycle for aromatic ether hydrolysis⁷⁴ and arene hydrogenation.⁷⁵

⁷¹ a. Muetterties, E. L.; Bleeke, J. R.; Sievert, A. C. *J. Organomet. Chem.* **1979**, 178, 197–216; b. Nolan, S. P.; Martin, K. L.; Stevens, E. D.; Fagan, P. J. *Organometallics* **1992**, 11, 3947–3953.

⁷² a. Semmelhack, M. F.; Seufert, W.; Keller, L. *J. Organomet. Chem.* **1982**, 226, 183–190; b. Traylor, T. G.; Stewart, K. J.; Goldberg, M. J. *J. Am. Chem. Soc.* **1984**, 106, 4445–4454; c. Kündig, E. P.; Kondratenko, M.; Romanens, P. *Angew. Chem. Int. Ed.* **1998**, 37, 3146–3148.

⁷³ Semmelhack, M. F.; Chlenov, A.; Ho, D. M. *J. Am. Chem. Soc.* **2005**, 127, 7759–7773.

⁷⁴ Miller, A. J. M.; Kaminsky, W.; Goldberg, K. I. *Organometallics* **2014**, 33, 1245–1252.

⁷⁵ Grundy, S. L.; Maitlis, P. M. *J. Chem. Soc. Chem. Commun.* **1982**, 379–380.

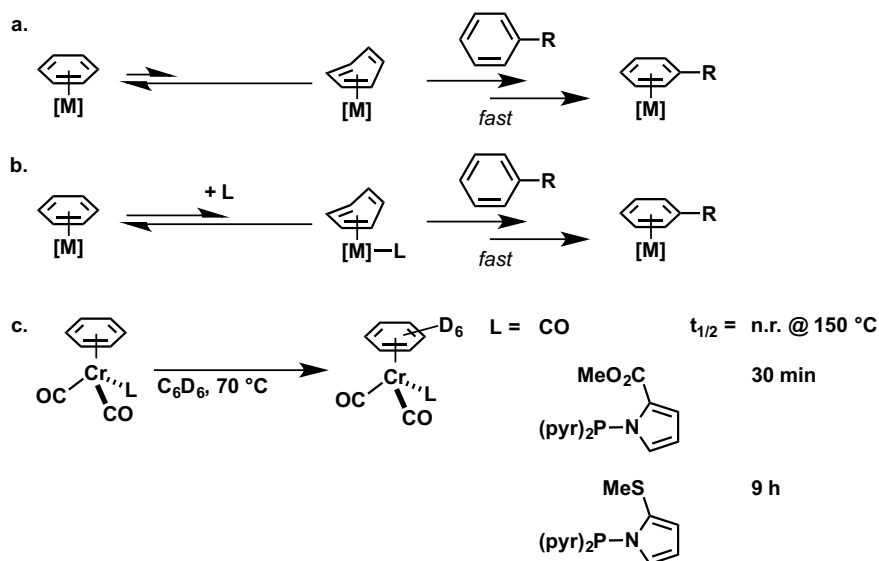


Figure 1.18. Arene exchange of η^6 -arene complexes. a. The slip from η^6 - to η^4 -coordination is disfavored; b. Addition of Lewis basic donors can alter the equilibrium between η^6 - and η^4 -coordination; c. Ligands designed to incorporate a Lewis basic donor accelerate arene exchange (*ref* 73).

A few examples of possible catalytic S_NAr using η^6 -arene complexes have been reported, though the conditions tend to be harsh and the scope limited. First reported in 1980, the intramolecular cyclization of alcohols onto aryl fluorides using $[(\eta^6\text{-arene})\text{RhCp}^*]^{2+}$ as a catalyst works with up to 3.3 turnovers (Figure 1.19a).⁷⁶ The intermolecular reaction of fluorobenzene and methanol proved more challenging, but did proceed. Displacement of an aryl chloride was more demanding still, and the chloride ion had to be periodically removed from the reaction to observe turnover.⁷⁷ Shibata reported a catalytic intermolecular S_NAr of fluoroarenes with amines using a ruthenium complex ligated with a cyclometallated bis-phosphine ligand (Figure 1.19b).⁷⁸ Unfortunately, the scope is fairly limited with only cyclic secondary amines being competent in the reaction, and the arene exchange reactivity seems to be low, given that 5 equivalents of arene are used. Walton reported a similar ruthenium-mediated S_NAr

⁷⁶ Houghton, R. P.; Voyle, M. J. *Chem. Soc. Perkin Trans. I* **1984**, 925–931.

⁷⁷ Goryunov, L. I.; Shteingarts, V. D. *Russ. J. Org. Chem.* **1997**, 33, 632–635.

⁷⁸ a. Otsuka, M.; Endo, K.; Shibata, T. *Chem. Commun.* **2010**, 46, 336–338; b. Otsuka, M.; Yokoyama, H.; Endo, K.; Shibata, T. *Synlett* **2010**, 17, 2601–2606.

reaction with amines, but with the use of aryl chlorides instead of aryl fluorides.⁷⁹ At extremely high temperatures (180 °C) and long reaction times (14 d), up to 9 turnovers could be observed. Under similarly harsh conditions, Grushin reported an S_NAr of aryl chlorides with CsF that gave up to 8.9 turnovers. (Figure 1.19c)⁸⁰ Since displacement of a chloride leaving group on the η⁶-arene complex occurs stoichiometrically at a lower temperature, arene exchange is the postulated slow step in these reactions.

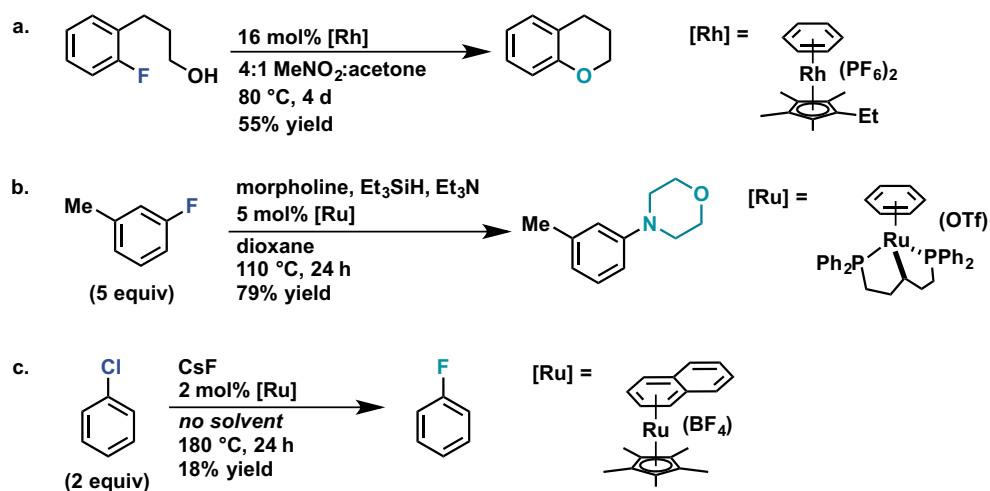


Figure 1.19. Catalytic S_NAr reactions with η⁶-arene complexes. a. Intramolecular aryl fluoride displacement to form chromans (*ref* 76); b. Intermolecular aryl fluoride displacement to form aryl amines (*ref* 78); c. Aryl fluoride formation from aryl chlorides (*ref* 80).

1.3. Radical addition for aromatic C–H functionalization

C–H functionalization *via* radical addition generally has a two-step mechanism: radical addition to the aromatic π-system, followed by formal loss of a H-atom from the cyclohexadienyl radical to form the aromatic product (Figure 1.20). Selectivity of radical addition reactions is usually poor, which has led the synthetic community to overlook the broad potential of these reactions.⁸¹ However, a diverse range of

⁷⁹ Walton, J. W.; Williams, J. M. J. *Chem. Commun.* **2015**, 51, 2786–2789.

⁸⁰ Kononov, A. I.; Gorbacheva, E. O.; Miloserdov, F. M.; Grushin, V. V. *Chem. Commun.* **2015**, 51, 13527–13530.

⁸¹ a. Ingold, K. U. *Pure Appl. Chem.* **1997**, 69, 241–243; b. Yan, M.; Lo, J. C.; Edwards, J. T.; Baran, P. S. *J. Am. Chem. Soc.* **2016**, 138, 12692–12714.

functionality can be installed when the myriad techniques to generate radicals are coupled to effective synthetic methods. Advances in radical addition methodology have even demonstrated selective radical additions and begun to rationalize the origin of the effect.⁸² Furthermore, a lack of selectivity can sometimes be advantageous, particularly for the diversification of target molecules.

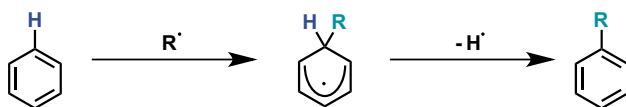


Figure 1.20. Basic addition-elimination mechanism of aromatic C–H functionalization through radical addition.

1.3.1. Mechanistic features of radical addition to arenes

While the basic two-step addition-elimination mechanism of homolytic aromatic substitution provides a mechanistic framework, the details can be varied and complex.⁸³ The rate of the first step, radical addition, depends on the nature of the radical and the electron density of the arene (Table 1.1). Addition to benzene proceeds fastest with electrophilic radicals, such as hydroxyl radical,⁸⁴ and slowest with nucleophilic radicals, such as methyl radical⁸⁵. Phenyl radical addition proceeds at an intermediary rate, reflecting its slight electrophilic character.⁸⁶ This difference in rate is attributed to polar effects,^{83,87}

⁸² a. O'Hara, F.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2013**, *135*, 12122–12134; b. Boursalian, G. B.; Ham, W. S.; Mazzotti, A. R.; Ritter, T. *Nature Chem.* **2016**, *8*, 810–815.

⁸³ a. Dermer, O. C.; Edmison, M. T. *Chem. Rev.* **1957**, *57*, 77–122; b. Perkins, J. M. Aromatic Substitution. In *Free Radicals*; Kochi, J. K., Ed.; John Wiley & Sons, Inc.: New York, 1973; pp 231–271; c. Fossey, J.; Lefort, D.; Sorba, J. *Free Radicals in Organic Chemistry*; John Wiley & Sons, Inc.: New York, 1995; pp 166–180; d. Studer, A.; Curran, D. P. *Angew. Chem. Int. Ed.* **2016**, *55*, 58–102; e. Rossi, R. A.; Budén, M. E.; Guastavino, J. F. Homolytic Aromatic Substitution. In *Arene Chemistry: Reaction Mechanisms and Methods for Aromatic Compounds*; Mortier, J., Ed.; John Wiley & Sons, Inc.: Hoboken, 2016; pp 219–242.

⁸⁴ a. Anbar, M.; Meyerstein, D.; Neta, P. *J. Phys. Chem.* **1966**, *70*, 2660–2662; b. Ashton, L.; Buxton, G. V.; Stuart, C. R. *J. Chem. Soc. Faraday Trans.* **1995**, *91*, 1631–1633.

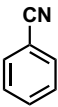
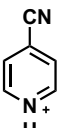
⁸⁵ Zytowski, T.; Fischer, H. *J. Am. Chem. Soc.* **1997**, *119*, 12869–12878.

⁸⁶ Scaiano, J. C.; Stewart, L. C. *J. Am. Chem. Soc.* **1983**, *105*, 3609–3614.

⁸⁷ a. Minisci, F. *Synthesis* **1973**, 1–24; b. Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *J. Am. Chem. Soc.* **1977**, *99*, 7960–7968.

where a more electrophilic radical will add to an electron-rich arene faster than a nucleophilic radical. The trend is reversed when an electron-poor protonated pyridine is used as a substrate – alkyl radicals add to an electron-poor substrate at a much greater rate.⁸⁸ The necessity of polarity matching between the radical and the arene limits the scope of radical reactions in most cases.

Table 1.1. Representative rate constants for radical addition to arenes.

	Me [•]	ⁿ Bu [•]	Ph [•]	HO [•]
	4.6 × 10 ²	3.8 × 10 ²	4.5 × 10 ⁵	3.3 × 10 ⁹
	5.0 × 10 ³	N/A	N/A	2.2 × 10 ⁹
	N/A	8.9 × 10 ⁵	6.0 × 10 ⁶	N/A

Rate constants given in M⁻¹·s⁻¹; values taken from *ref* 84, 85, 86, and 88.

The second step, elimination of a hydrogen-atom, can proceed through many different pathways (Figure 1.21).⁸³ The cyclohexadienyl radical can be oxidized to the cation, and then deprotonated to generate the aromatized product. This is most common in the presence of oxidizing transition metals, such as Fe(III) or Ti(IV). The oxidation potential of a prototypical cyclohexadienyl radical has been estimated to be ~0 V, which indicates a fairly easy reaction.⁸⁹ Direct H-atom abstraction has also been proposed, especially in the presence of oxygen or AIBN.⁹⁰ An H-atom abstraction step will be subject to polar effects as well, and the use of a polarity reversal catalyst (PhSeH) has been shown to accelerate this

⁸⁸ Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M. *J. Org. Chem.* **1986**, *51*, 4411–4416.

⁸⁹ a. Bhatia, K.; Schuler, R. H. *J. Phys. Chem.* **1974**, *78*, 2335–2338; b. Anderson, R. F. *Radiat. Phys. Chem.* **1979**, *13*, 155–157; c. Buxton, G. V.; Langan, J. R.; Smith, J. R. L. *J. Phys. Chem.* **1986**, *90*, 6309–6313.

⁹⁰ a. Hendry, D. G.; Schuetzle, D. *J. Am. Chem. Soc.* **1975**, *97*, 7123–7127; b. Estupiñán, E.; Villenave, E.; Raoult, S.; Rayez, J. C.; Rayez, M. T.; Lesclaux, R. *Phys. Chem. Chem. Phys.* **2003**, *5*, 4840–4845; c. Beckwith, A. L. J.; Bowry, V. W.; Bowman, W. R.; Mann, E.; Parr, J.; Storey, J. M. D. *Angew. Chem. Int. Ed.* **2004**, *43*, 95–98; d. Shiga, Y.; Koshi, M.; Tonokura, K. *Chem. Phys. Lett.* **2009**, *470*, 35–38.

step.⁹¹ Deprotonation of the cyclohexadienyl radical to generate an arene radical anion, followed by single electron oxidation has been implicated in a number of cases and is referred to as base-assisted homolytic aromatic substitution (BHAS).⁹² Disproportionation of two cyclohexadienyl radicals to one aromatic product and one diene has also been observed, but full conversion of the aromatic starting material cannot be achieved in this case. Side reactions of the cyclohexadienyl radical must also be avoided – most commonly, dimerization, which occurs when productive aromatization is not a fast enough process.

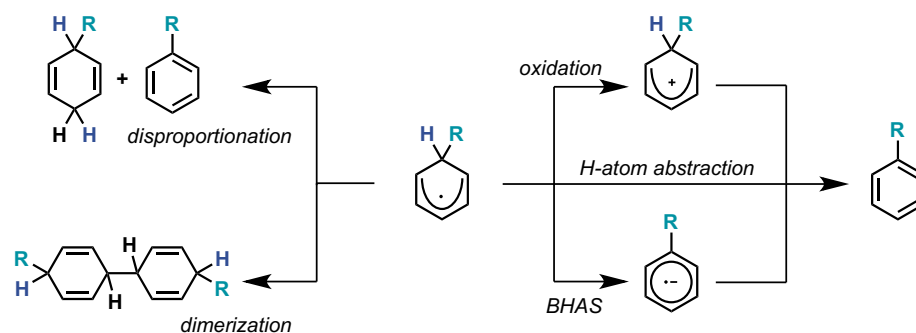


Figure 1.21. Reaction pathways of the cyclohexadienyl radical.

1.3.2. Reactions that proceed through radical addition to arenes

A variety of reactions proceed through a radical addition to an arene. While radical hydroxylation and amination chemistry will be included in Sections 1.4 and 1.5, respectively, a brief overview of arylation and alkylation chemistry that proceeds through radical addition is presented here.

Homolytic aromatic arylation, first reported as early as 1896,⁹³ is a well-studied reaction and has provided a lot of the mechanistic insight into radical reactions that we have today.⁹⁴ Classical methods for generation of an aryl radical include thermolytic decomposition of aroyl peroxides or metal-mediated

⁹¹ Crich, D.; Hwang, J.-T. *J. Org. Chem.* **1998**, 63, 2765–2770.

⁹² Studer, A.; Curran, D. P. *Angew. Chem. Int. Ed.* **2011**, 50, 5018–5022.

⁹³ a. Pschorr, R. *Ber. Dtsch. Chem. Ges.* **1896**, 29, 496–501; b. Gomberg, M.; Bachmann, W. E. *J. Am. Chem. Soc.* **1924**, 46, 2339–2343.

⁹⁴ a. Augood, D. R.; Williams, G. H. *Chem. Rev.* **1957**, 57, 123–190; b. Bolton, R.; Williams, G. H. *Chem. Soc. Rev.* **1986**, 15, 261–289; c. Galli, C. *Chem. Rev.* **1988**, 88, 765–792.

decomposition of aryl diazonium salts. Aryl halides have also been used as aryl radical precursors: Curran reported an improvement to the typical Bu_3SnH protocol that utilized $\text{HSi}(\text{SiMe}_3)_3$ under aerobic conditions to propagate the chain (Figure 1.22a).⁹⁵ Multiple concurrent reports of potassium *tert*-butoxide-mediated arylation have demonstrated metal-free arylation chemistry that likely proceeds through a BHAS mechanism (Figure 1.22b).⁹⁶ Based on Minisci's initial work, Baran reported the arylation of protonated heterocycles with aryl boronic acids under oxidative conditions (Figure 1.22c).⁹⁷ A low aryl boronic acid to heterocycle ratio could be used, which suggests that the aryl radical is somewhat nucleophilic with good polarity matching. Despite many advances in homolytic aromatic arylations, especially with respect to practicality, the drawbacks of homolytic aromatic arylation are typical of a C–H functionalization reaction: large excess of arene is required and poor positional selectivity is obtained.

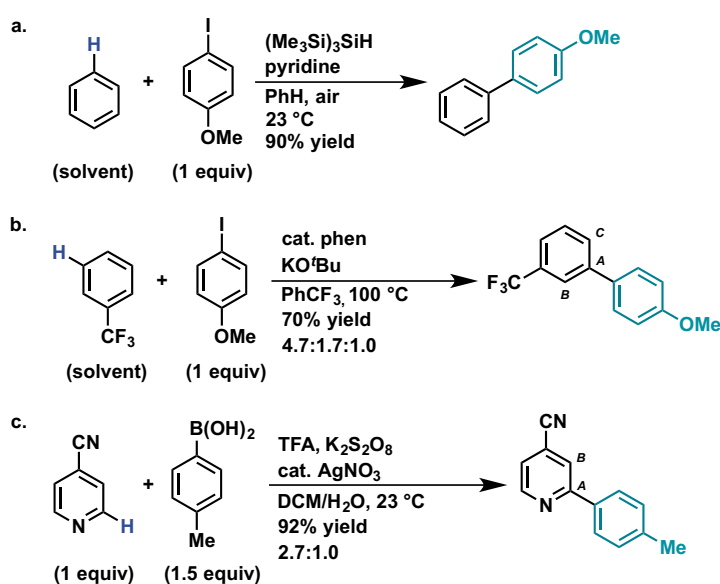


Figure 1.22. Radical arylation reactions. a. Arylation of aryl iodides using TTMSS under aerobic conditions (*ref* 95); b. Metal-free arylation via BHAS (*ref* 96a); c. Updated Minisci arylation of protonated heterocycles (*ref* 97).

⁹⁵ Curran, D. P.; Keller, A. I. *J. Am. Chem. Soc.* **2006**, *128*, 13706–13707.

⁹⁶ a. Sun, C.-L., et. al. *Nature Chem.* **2010**, *2*, 1044–1049; b. Shirakawa, E.; Itoh, K.-I.; Higashiro, T.; Hayashi, T. *J. Am. Chem. Soc.* **2010**, *132*, 15537–15539; c. Liu, W.; Cao, H.; Zhang, H.; Chung, K. H.; He, C.; Wang, H.; Kwong, F. Y.; Lei, A. *J. Am. Chem. Soc.* **2010**, *132*, 16737–16740.

⁹⁷ Seiple, I. B.; Su, S.; Rodriguez, R. A.; Gianatassio, R.; Fujiwara, Y.; Sobel, A. L.; Baran, P. S. *J. Am. Chem. Soc.* **2010**, *132*, 13194–13196.

Radical alkylation reactions tend to be more difficult than arylation reactions when the radical is adding to a carbocyclic arene, because the arene is typically too electron-rich for good polarity matching. However, radical alkylation of protonated heterocycles was originally developed by Minisci and usually can proceed with fairly low concentrations of arene (typical alkyl radical precursor to heterocycle ratios are 1:1 to 4:1) (Figure 1.23a).^{87a} Alkyl radicals can be generated in several ways, such as decarboxylation, H-atom abstraction, halogen abstraction or peroxide decomposition. Minisci did note that alkyl radicals adjacent to electron-withdrawing groups, such as esters or nitriles, were unreactive toward protonated heterocycles, which is attributed to the increased electrophilicity of these radicals.^{88,98} Acylation and aminocarbonylation can also be effected under similar conditions.⁹⁹ Baran has developed zinc sulfinate reagents for easy access to alkyl radicals for heterocycle alkylation.¹⁰⁰

The trifluoromethyl radical presents a unique case of alkylation reactions, because the trifluoromethyl radical is much more electrophilic than a typical alkyl radical.¹⁰¹ Efficient trifluoromethylation of electron-rich arenes was reported by the MacMillan group (Figure 1.23b),¹⁰² and later by the Stephenson group,¹⁰³ using a photoredox-mediated approach. Baran's zinc sulfinate reagents work well for trifluoromethylation, as well as for difluoromethylation (Figure 1.23c), reactions of heterocycles.¹⁰⁴ The prospect of being able to efficiently decorate aromatic rings without prefunctionalization makes continued development of radical reactions an important goal.

⁹⁸ Minisci, F.; Fontana, F.; Pianese, G.; Yan, Y. M. *J. Org. Chem.* **1993**, *58*, 4207–4211.

⁹⁹ Minisci, F. *Synth. Mech. Org. Chem.* **1976**, 1–48.

¹⁰⁰ Gui, J.; Zhou, Q.; Pan, C.-M.; Yabe, Y.; Burns, A. C.; Collins, M. R.; Ornelas, M. A.; Ishihara, Y.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, *136*, 4853–4856.

¹⁰¹ Studer, A. *Angew. Chem. Int. Ed.* **2012**, *51*, 8950–8958.

¹⁰² Nagib, D. A.; MacMillan, D. W. C. *Nature* **2011**, *480*, 224–228.

¹⁰³ Beatty, J. W.; Douglas, J. J.; Cole, K. P.; Stephenson, C. R. J. *Nat. Commun.* **2015**, *6*, 7919.

¹⁰⁴ a. Ji, Y.; Brueckl, T.; Baxter, R. D.; Fujiwara, Y.; Seiple, I. B.; Su, S.; Blackmond, D. G.; Baran, P. S. *Proc. Natl. Acad. Sci.* **2011**, *108*, 14411–14415; b. Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494–1497; c. Fujiwara, Y., et. al. *Nature* **2012**, *492*, 95–99.

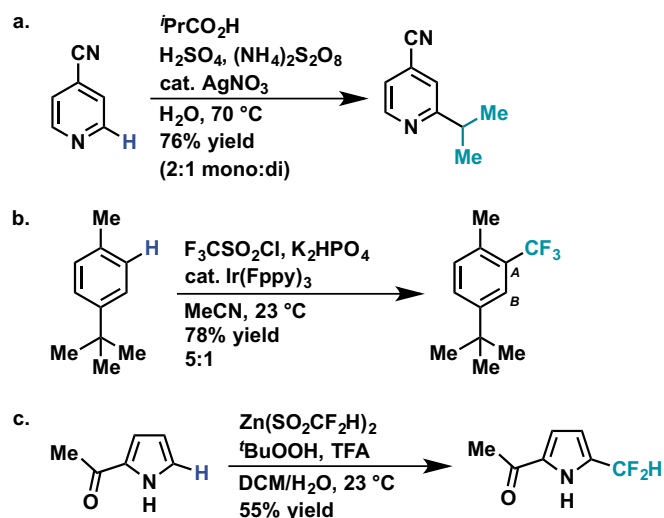


Figure 1.23. Radical alkylation of arenes and heteroarenes. a. Minisci's decarboxylative alkylation of protonated heterocycles (*ref 87a*); b. Photoredox-mediated trifluoromethylation (*ref 102*); c. Baran's zinc sulfinate reagent for difluoromethylation (*ref 104b*).

1.4. Aromatic C–H hydroxylation

Oxidation of aromatic C–H bonds is an important process that provides valuable phenol products, used profusely as commodity and fine chemicals.¹⁰⁵ Phenol is produced industrially on approximately 9 million ton scale annually through the cumene process.¹⁰⁶ However, over-oxidation and wasteful byproducts are still challenges in most aromatic oxidation reactions. In fact, large scale heterogeneous oxidations are often run to only very low conversions in order to optimize the yield of mono-oxidized product.¹⁰⁵ For small scale fine chemical applications, the field of aromatic C–H hydroxylation also emphasizes positional selectivity of oxidation and functional group tolerance. This section will focus on aromatic C–H to C–O bond forming reactions that provide synthetically useful yields of phenols and demonstrate an adequate substrate scope.

¹⁰⁵ a. Lücke, B.; Narayana, K. V.; Martin, A.; Jähnisch, K. *Adv. Synth. Catal.* **2004**, *346*, 1407–1424; b. Kholdeeva, O. A. Selective Oxidation of Aromatic Rings. In *Arene Chemistry: Reaction Mechanisms and Methods for Aromatic Compounds*; Mortier, J., Ed.; John Wiley & Sons, Inc.: Hoboken, 2016; pp 365–398.

¹⁰⁶ Weber, M.; Weber, M. Phenols. In *Phenolic Resins: A Century of Progress*; Pilato, L., Ed.; Springer-Verlag: Berlin, 2010; 9–23.

1.4.1. Aromatic C–H hydroxylation through σ -bond activation

Transition metal catalysis is the predominant strategy for aromatic C–H hydroxylation through σ -bond activation, whereby a metalation event precedes C–O bond formation.¹⁰⁷ Palladium catalysis to form phenol from benzene and oxygen was first reported by Fujiwara in 1987 at high temperatures and pressures (Figure 1.24a).¹⁰⁸ Crabtree soon after reported palladium-catalyzed acetoxylation using $\text{PhI}(\text{OAc})_2$ as the terminal oxidant.¹⁰⁹ While these first reports suffered from low turnover and poor selectivity, they highlighted the potential of using transition metals for aromatic oxidation chemistry. Sanford has since expanded the use of hypervalent iodine reagents for intermolecular chemistry and found that precise control of ligand to catalyst ratios was crucial for promoting C–H metalation (Figure 1.24b).¹¹⁰ The existence of an open coordination site allowed even electron-poor arenes to undergo C–H acetoxylation in moderate yield, albeit while using an excess of aromatic substrate. Furthermore, installation of a masked hydroxyl group in the form of an acetoxy group prevents significant over-oxidation by deactivating the ring towards electrophilic metalation. A two-step protocol for C–H hydroxylation using one equivalent of arene can also be achieved *via* C–H borylation, followed by oxidation (Figure 1.24c).³⁰

¹⁰⁷ a. Alonso, D. A.; Nájera, C.; Pastor, I. M.; Yus, M. *Chem. Eur. J.* **2010**, *16*, 5274–5284; b. Enthaler, S.; Company, A. *Chem. Soc. Rev.* **2011**, *40*, 4912–4924; c. Liu, Y.; Liu, S.; Xiao, Y. *Bielstein J. Org. Chem.* **2017**, *13*, 589–611.

¹⁰⁸ Jintoku, T.; Taniguchi, H.; Fujiwara, Y. *Chem. Lett.* **1987**, 1865–1868.

¹⁰⁹ Yoneyama, T.; Crabtree, R. H. *J. Mol. Catal. A* **1996**, *108*, 35–40.

¹¹⁰ Emmert, M. H.; Cook, A. K.; Xie, Y. J.; Sanford, M. S. *Angew. Chem. Int. Ed.* **2011**, *50*, 9409–9412.

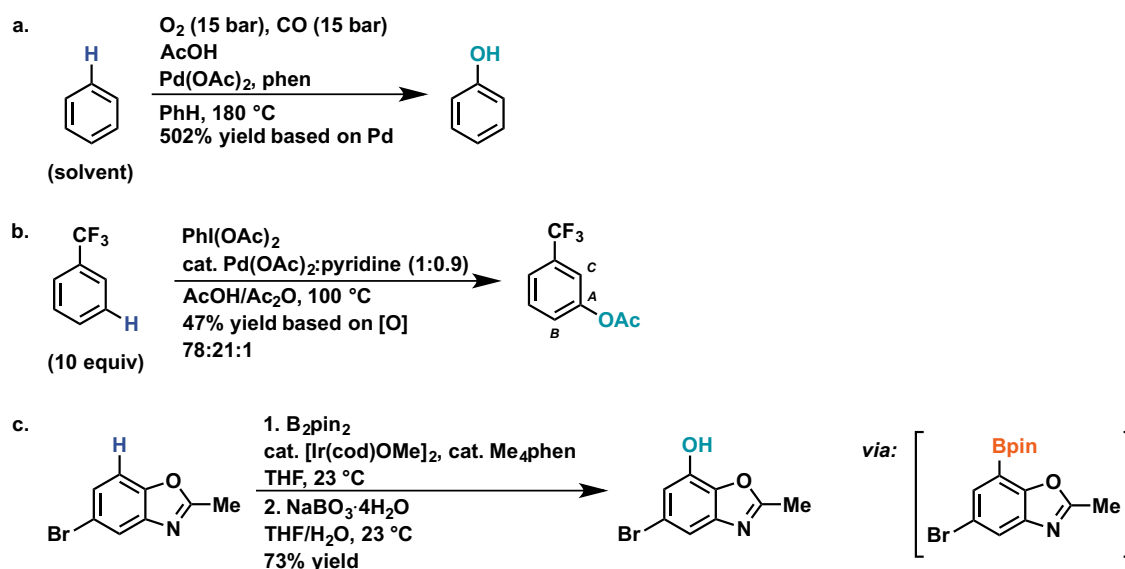


Figure 1.24. Undirected aromatic C–H hydroxylation through metalation. a. Initial report of aerobic palladium-catalyzed hydroxylation (*ref 108*); b. Hypervalent iodine reagents for aromatic C–H acetoxylation (*ref 110*); c. Two-step borylation/oxidation protocol (*ref 30*).

The challenge of positional selectivity has been solved in part by the use of coordinating directing groups to aid the C–H metalation step, generally by directing it to the *ortho* position. Early work in this area was reported by Sanford and coworkers, who demonstrated palladium-catalyzed acetoxylation of phenyl pyridine derivatives (Figure 1.25a).¹¹¹ Key to their success was the intermediacy of a Pd(IV) complex, which enabled difficult C–O reductive elimination, due to its high oxidation state. Yu and coworkers described a variant of the original Fujiwara reaction that utilized carboxylate directing groups under aerobic palladium catalysis to give *ortho*-hydroxylated products (Figure 1.25b).¹¹² Other directing groups adapted for aromatic C–H hydroxylation include ketones, esters, and benzamides for *ortho* functionalization (Figure 1.25c)¹¹³ and nitrile-based templates for *meta* functionalization.^{19c,114} Directed aromatic C–H functionalization permits the use of arene as a limiting reagent and generally provides a

¹¹¹ Dick, A. R.; Hull, K. L.; Sanford, M. S. *J. Am. Chem. Soc.* **2004**, *126*, 2300–2301.

¹¹² Zhang, Y.-H.; Yu, J.-Q. *J. Am. Chem. Soc.* **2009**, *131*, 14654–14655.

¹¹³ a. Shan, G.; Yang, X.; Ma, L.; Rao, Y. *Angew. Chem. Int. Ed.* **2012**, *51*, 13070–13074; b. Mo, F.; Trzepakowski, L. J.; Dong, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 13075–13079; c. Yang, Y.; Lin, Y.; Rao, Y. *Org. Lett.* **2012**, *14*, 2874–2877; d. Thirunavukkarasu, V. S.; Hubrich, J.; Ackermann, L. *Org. Lett.* **2012**, *14*, 4210–4213.

¹¹⁴ Maji, A.; Bhaskararao, B.; Singha, S.; Sunoj, R. B.; Maiti, D. *Chem. Sci.* **2016**, *7*, 3147–3153.

single isomeric product, but C–H hydroxylation is still plagued by undesirable reactions, such as high temperatures and/or wasteful oxidants in most cases.

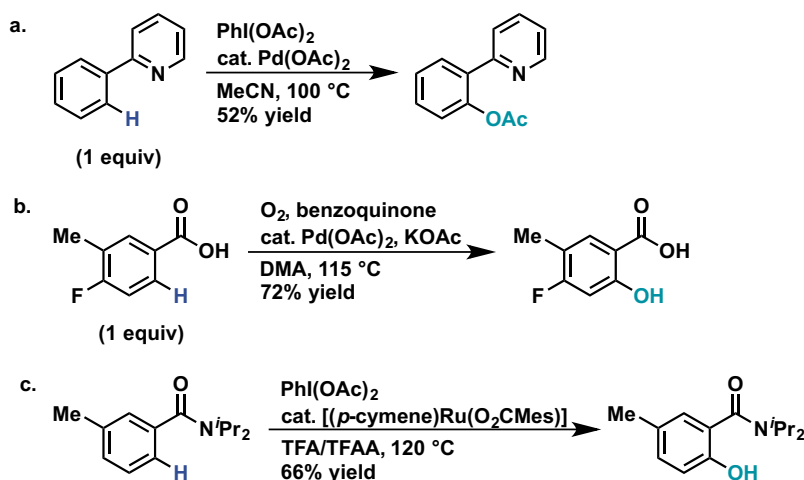


Figure 1.25. Directed aromatic C–H hydroxylation. a. Acetoxylation of phenyl pyridines (*ref 111*); b. Hydroxylation of carboxylic acids (*ref 112*); c. Ruthenium-catalyzed hydroxylation of benzamides (*ref 113d*).

1.4.2. Aromatic C–H hydroxylation through π -addition

While oxidation through σ -bond activation has become popular in recent years, aromatic C–H hydroxylation through π -addition has been investigated for much longer. In part, inspiration has come from the mechanisms of enzymatic hydroxylation, which typically proceed through high-valent metal oxo species that can add to an arene through an electrophilic or radical mechanism.¹¹⁵ A rough mimic of iron-containing enzymes, Fenton's reagent, consisting of an Fe(II) salt and hydrogen peroxide, was developed in 1894¹¹⁶ and oxidizes a number of species, including aromatic rings (Figure 1.26a). The mechanism of Fenton chemistry is proposed to proceed through hydroxyl radicals, though whether they are free hydroxyl radicals or are associated with a metal is not entirely clear, and side products of radical-radical

¹¹⁵ a. Meunier, B.; de Visser, S. P.; Shaik, S. *Chem. Rev.* **2004**, *104*, 3947–3980; b. Abu-Omar, M. M.; Loaiza, A.; Hontzas, N. *Chem. Rev.* **2005**, *105*, 2227–2252; c. Shaik, S.; Kumar, D.; de Visser, S. P.; Altun, A.; Thiel, W. *Chem. Rev.* **2005**, *105*, 2279–2328.

¹¹⁶ Fenton, H. J. H. *J. Chem. Soc. Trans.* **1894**, *65*, 899–910.

dimerization or radical fragmentation are often observed.¹¹⁷ The nature and distribution of side products changes when other metal salts are used, such as copper(II), but the electrophilic nature of the hydroxyl radical has been confirmed by the isomer distributions obtained in Fenton reactions (Figure 1.26b).

Other oxygen-centered radicals have also been used in combination with a metal salt. For example, Kovacic reported the reaction of diisopropyl peroxydicarbonate and copper(II) with arenes to form new C–O bonds (Figure 1.26c) and hypothesized that the isopropoxycarboxy radical was more electrophilic than the hydroxyl radical based on relative reaction rates.¹¹⁸ In contrast to the traditional Fenton chemistry, no dimerization byproducts were observed, which is consistent with minimal buildup of the hydroxycyclohexadienyl intermediate. A similar situation is observed using a picolinate-ligated vanadium complex, which gives hydroxylated arenes with minimal byproducts (Figure 1.26d).¹¹⁹ The peroxy radical is hypothesized to be coordinated to vanadium during addition to the arene. The major drawback to these metal-mediated oxygen-centered radical addition reactions is the use of stoichiometric or near-stoichiometric quantities of the metal. Catalytic turnover has been investigated but is generally not overly successful.

¹¹⁷ a. Walling, C.; Johnson, R. A. *J. Am. Chem. Soc.* **1975**, *97*, 363–367; b. Walling, C. *Acc. Chem. Res.* **1975**, *8*, 125–131.

¹¹⁸ Kurz, M. E.; Kovacic, P.; Bose, A. K.; Kugajevsky, I. *J. Am. Chem. Soc.* **1968**, *90*, 1818–1822.

¹¹⁹ a. Mimoun, H.; Saussine, L.; Daire, E.; Postel, M.; Fischer, J.; Weiss, R. *J. Am. Chem. Soc.* **1983**, *105*, 3101–3110; b. Bonchio, M.; Conte, V.; Di Furia, F.; Modena, G. *J. Org. Chem.* **1989**, *54*, 4368–4371.

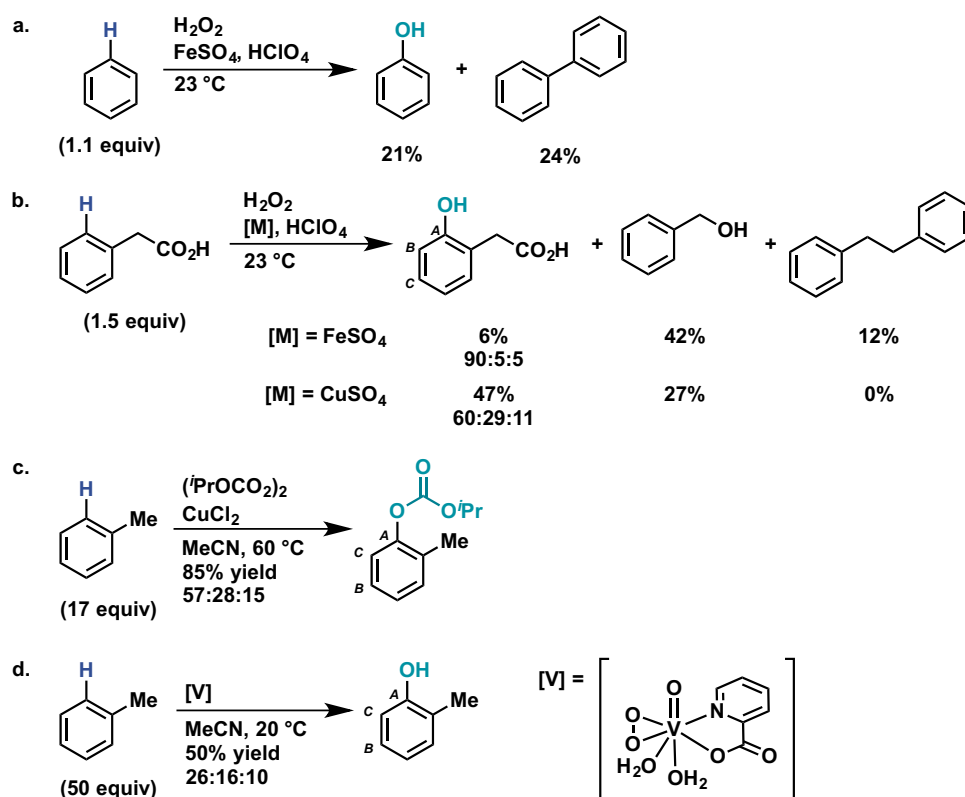


Figure 1.26. Metal-mediated oxygen-centered radical addition to arenes. a. Traditional Fenton reaction (*ref 117a*); b. Effect of metal salt on product distribution (*ref 117a*); c. Copper-mediated C–O bond formation (*ref 118*); d. Vanadium-peroxo complexes for C–H hydroxylation (*ref 119a*).

As opposed to development of catalysis, the development of a more active hydroxylating reagent can accomplish the same goals and avoid the use of a metal altogether. In 2013, Siegel reported aromatic C–H hydroxylation using phthaloyl peroxide (Figure 1.27).¹²⁰ A unique reverse rebound mechanism was proposed based on DFT calculations where after initial radical addition, intramolecular H-atom abstraction induces rearomatization. The substrate scope includes mostly electron-rich arenes, though a dichlorinated derivative of the reagent was subsequently shown to somewhat expand the scope somewhat.¹²¹ Positional selectivity follows trends typical of an electrophilic radical addition – the most electron rich positions react preferentially.

¹²⁰ Yuan, C.; Liang, Y.; Hernandez, T.; Berriochoa, A.; Houk, K. N.; Siegel, D. *Nature* **2013**, 499, 192–196.

¹²¹ Camelio, A. M.; Liang, Y.; Eliassen, A. M.; Johnson, T. C.; Yuan, C.; Schuppe, A. W.; Houk, K. N.; Siegel, D. J. *Org. Chem.* **2015**, 80, 8084–8095.

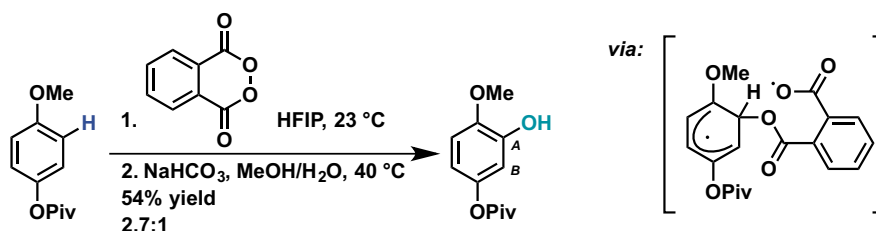


Figure 1.27. Phthaloyl peroxide for aromatic C–H hydroxylation (*ref 120*).

Other mechanisms for aromatic C–H hydroxylation through π -addition have been explored. Kochi reported a cobalt(III)-mediated trifluoroacetoxylation of arenes that proceeds through an observable arene radical cation that is then trapped by trifluoroacetate.¹²² A later report achieved up to 12 turnovers with the slow addition of trifluoroperacetic acid to a solution of cobalt(II) (Figure 1.28a).¹²³ However, the approach is inherently limited in scope to arenes that can readily be oxidized, *i.e.* those that are electron-rich. Similar limitations in scope are observed in gold-catalyzed acetoxylation reactions.¹²⁴ The authors take advantage of the established electrophilic metalation reactivity of gold(III) with electron-rich arenes (Figure 1.28b). The aryl gold intermediates then undergo reductive elimination to give acetoxylation arenes.

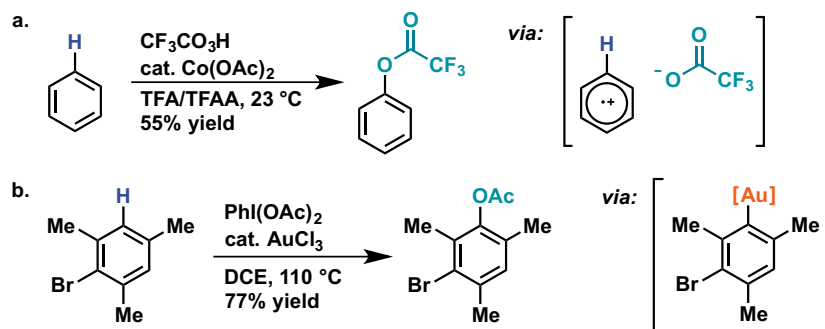


Figure 1.28. Alternate mechanisms for aromatic C–H hydroxylation through π -addition. a. Oxidation to the aromatic radical cation, followed by trapping with nucleophiles (*ref 122*); b. Electrophilic auration, followed by acetoxylation (*ref 124a*).

¹²² Kochi, J. K.; Tang, R. T.; Bernath, T. *J. Am. Chem. Soc.* **1973**, *95*, 7114–7123.

¹²³ DiCosimo, R.; Szabo, H.-C. *J. Org. Chem.* **1986**, *51*, 1365–1367.

¹²⁴ a. Qiu, D.; Zheng, Z.; Mo, F.; Xiao, Q.; Tian, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 4988–4991; b. Pradal, A.; Toullec, P. Y.; Michelet, V. *Org. Lett.* **2011**, *13*, 6086–6089.

Formation of aromatic C–O bonds from C–H bonds is still quite challenging, as is described above. Particularly, aromatic C–H hydroxylation methods that are amenable for late-stage functionalization are scarce. Most C–H oxygenation reactions use electrophilic oxygen sources, resulting in substrate scopes that are inclined toward electron-rich arenes only. Furthermore, the high electronegativity of oxygen results in very reactive electrophilic oxygen sources that limit functional group tolerance. The use of nucleophilic oxygen sources for C–H functionalization has not been explored considerably but is usually hampered by the compatibility of the oxygen nucleophile with the oxidant. Creative solutions to expand the scope and functional group tolerance of aromatic C–H hydroxylation reactions are desirable.

1.5. Aromatic C–H amination

Aryl amines are widespread in molecules found in nature, medicine, materials and agriculture. Classically, amino groups are installed through an electrophilic nitration/reduction sequence, though these acidic conditions can be harsh and give limited isomeric diversity.^{45,125} Modern aromatic amination methods have relied heavily on metal-catalyzed cross coupling (Buchwald-Hartwig amination) using prefunctionalized aryl halides.¹²⁶ Ideally, amines can be directly installed onto an aromatic ring through C–H functionalization, a formal oxidative process.¹²⁷ An abundance of nitrogen-based oxidants have been used for this transformation (Figure 1.29), whether as two-electron oxidants in metalation processes, as nitrene precursors or as nitrogen-centered radical sources. In addition, some reactions have decoupled the nitrogen source and the oxidant, which in theory allows for greater variety in the nitrogen group.¹²⁸ Yet, most commonly used nitrogen sources install a protected amino group, which may need to be deprotected

¹²⁵ Hoggett, J. G.; Moodie, R. B.; Penton, J. R.; Schofield, K. *Nitration and Aromatic Reactivity*; Cambridge University Press: New York, 1971.

¹²⁶ Ruiz-Castillo, P.; Buchwald, S. L. *Chem. Rev.* **2016**, *116*, 12564–12649.

¹²⁷ a. Louillat, M.-L.; Patureau, F. W. *Chem Soc. Rev.* **2014**, *43*, 901–910; b. Jiao, J.; Murakami, K.; Itami, K. *ACS Catal.* **2016**, *6*, 610–633; c. Park, Y.; Kim, Y.; Chang, S. *Chem. Rev.* **2017**, doi: 10.1021/acs.chemrev.6b00644.

¹²⁸ Kim, H.; Chang, S. *ACS Catal.* **2016**, *6*, 2341–2351.

in an additional step; few aromatic C–H amination reactions provide access to free amines in a single step.¹²⁹ This section gives an overview of aromatic C–H amination reactions that proceed through both σ -bond activation and π -addition.

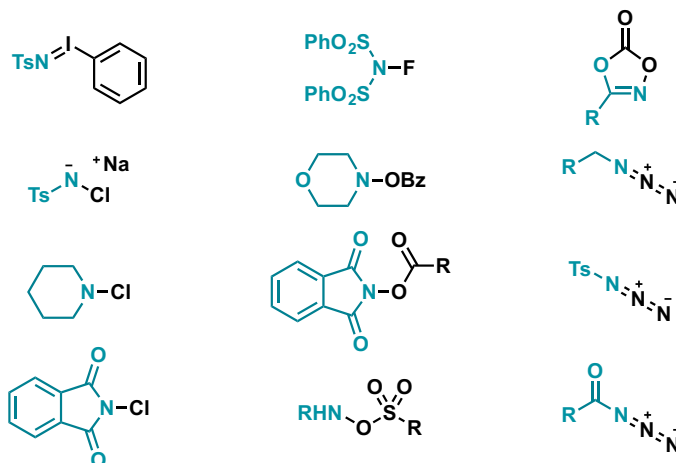


Figure 1.29. Commonly employed nitrogen-based oxidants for aromatic C–H amination.

1.5.1. Aromatic C–H amination through σ -bond activation

Aromatic C–H amination through σ -bond activation can be divided into three categories – nitrene insertion, metalation with a nitrogen-based oxidant, and metalation with a decoupled oxidant and nitrogen source. By far most reported reactions utilize a chelating directing group to assist the difficult metalation step in combination with a nitrogen-based oxidant. However, for the sake of synthetic versatility, other pathways are promising as well.

Direct nitrene insertion into an aromatic C–H bond is quite rare. In 2003, Pérez and coworkers reported the first example of a nitrene insertion into an aromatic C–H bond, utilizing a copper(I) catalyst (Figure 1.30a).¹³⁰ Benzene was used as a solvent, and when arenes containing non-aromatic C–H bonds were used, the nitrene preferentially inserted into those. A more synthetically useful transformation was

¹²⁹ Legnani, L.; Bhawal, B. N.; Morandi, B. *Synthesis* **2017**, 49, 776–789.

¹³⁰ a. Mar Díaz-Requejo, M.; Belderráin, T. R.; Nicasio, M. C.; Trofimenko, S.; Pérez, P. J. *J. Am. Chem. Soc.* **2003**, 125, 12078–12079; b. Frutos, M. R.; Trofimenko, S.; Mar Díaz-Requejo, M.; Pérez, P. J. *J. Am. Chem. Soc.* **2006**, 128, 11784–11791.

reported by Driver and coworkers, who showed that a rhodium-catalyzed intramolecular aromatic C–H nitrene insertion could be exploited for the synthesis of indoles (Figure 1.30b).¹³¹ A dimeric rhodium-catalyst was subsequently used for intermolecular aromatic C–H amination by Falck and coworkers in 2015 (Figure 1.30c).^{8b} Notably, the reaction was selective for aromatic ring protons over other activated C–H bonds in the benzylic position and used the arene as the limiting reagent. The unique reactivity is attributed to a protonated rhodium nitrenoid intermediate, which is in contrast to the more commonly encountered unprotonated rhodium nitrenoid.

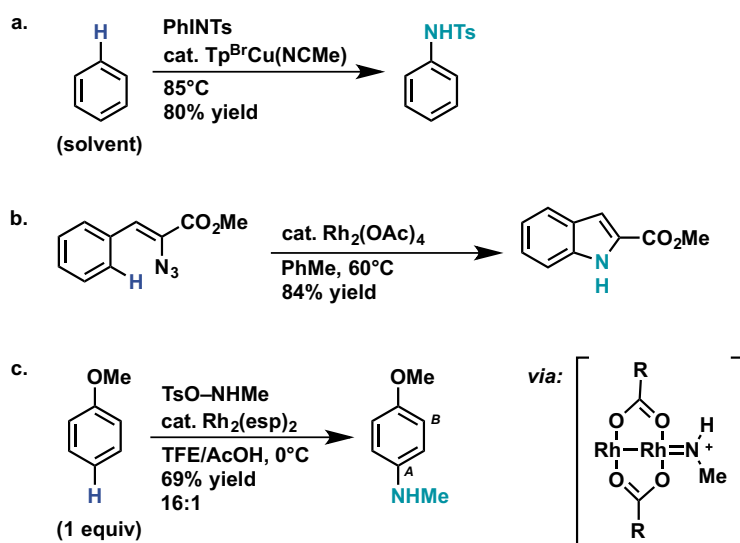


Figure 1.30. Direct nitrene insertion into aromatic C–H bonds. a. First report of nitrene insertion into aromatic C–H bonds (*ref 130b*); b. Intramolecular nitrene insertion to form indoles (*ref 131*); c. Aromatic amination *via* rhodium-nitrenoid intermediates (*ref 8b*).

While reports of nitrene insertion into free aromatic C–H bonds are sparse, there are a number of studies that purport a directed C–H metalation step prior to nitrenoid insertion. Such reactions work well due to the imposed intramolecularity of the nitrene insertion step, but have the same drawbacks as previously discussed chelation-assisted metalation processes (see Section 1.1.1). Chang and coworkers initially reported a Rh(III)-catalyzed amination of 2-phenylpyridine derivatives using sulfonyl azides as a nitrene precursor (Figure 1.31a).¹³² Subsequent mechanistic studies implicated a Rh(V) nitrenoid as an

¹³¹ Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129*, 7500–7501.

¹³² Kim, J. Y.; Park, S. H.; Ryu, J.; Cho, S. H.; Kim, S. H.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 9110–9113.

active species.¹³³ The method can be used with a variety of azide sources, including sulfonyl, acyl, aryl, and alkyl azides.¹³⁴ Weaker directing groups can be used when switching to an analogous Ir(III) catalyst.¹³⁴ Further improvement of the system was discovered with the use of 1,4,2-dioxazol-5-ones instead of azides, which present safety hazards for handling; the new aminating reagents are proposed to bind to the metal center more efficiently than azides, thereby increasing the amount of active catalyst in solution (Figure 1.31b).¹³⁵

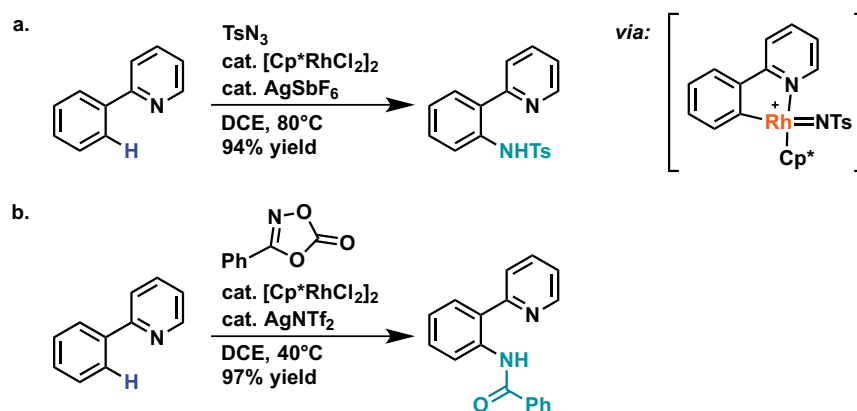


Figure 1.31. Chelation-assisted metalation and nitrene insertion. a. Sulfonyl azides as aminating reagents (*ref 132*); b. 1,4,2-dioxazol-5-ones as aminating reagents (*ref 135*).

Another directing group metalation strategy for C–H amination involves metal-centered oxidation, followed by C–N reductive elimination (Figure 1.32a). The oxidant can either be the nitrogen source itself or an external oxidizing reagent. An excess of reactions have been reported that fall into this category.¹²⁷ A range of directing groups, metal catalysts, and nitrogen-containing oxidants can be utilized for primarily *ortho* functionalization of aromatic C–H bonds (Figure 1.32b). Reactions that use a distinct nitrogen source and oxidant are less common, and the nitrogen groups need to be protected with electron-withdrawing groups, such as sulfonamides, phthalimides, or carbamates, in order to make them compatible with the oxidant. An early example was reported by Che and coworkers, who used palladium

¹³³ Park, S. H.; Kwak, J.; Shin, K.; Ryu, J.; Park, Y.; Chang, S. *J. Am. Chem. Soc.* **2014**, *136*, 2492–2502.

¹³⁴ Shin, K.; Kim, H.; Chang, S. *Acc. Chem. Res.* **2015**, *48*, 1040–1052.

¹³⁵ Park, Y.; Park, K. T.; Kim, J. G.; Chang, S. *J. Am. Chem. Soc.* **2015**, *137*, 4534–4542.

catalysis in combination with trifluoroacetamide and potassium persulfate for a directed C–H to C–N transformation (Figure 1.32c).¹³⁶ Other commonly employed oxidants include $\text{PhI}(\text{OAc})_2$, fluoropyridinium salts and oxygen, though very high temperatures are needed under aerobic conditions. C–H aminations that proceed through an undirected metalation step are essentially unreported, likely because other mechanistic approaches to C–H functionalization have proven more applicable for the formation of C–N bonds.

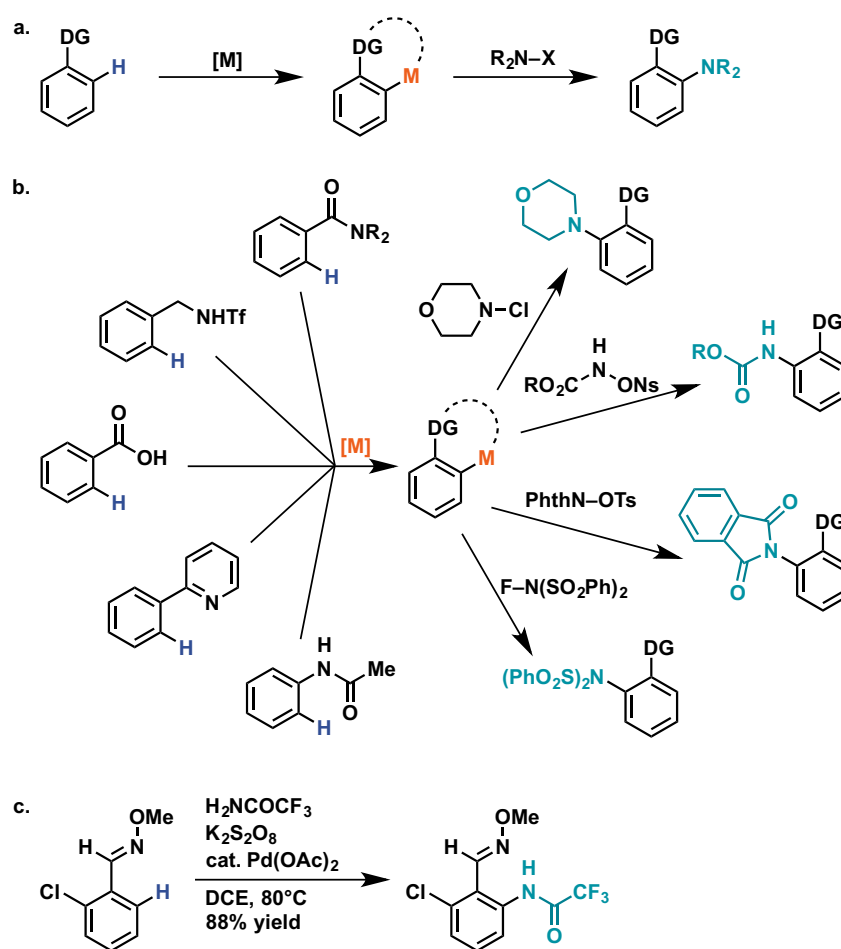


Figure 1.32. Chelation-assisted metalation, followed by amination. a. General reaction scheme; b. A variety of directing groups (left) and nitrogen-containing oxidants (right) can be used to install amino functionality. Examples are not exhaustive; c. An early example of a decoupled oxidant and nitrogen source (*ref* 136).

1.5.2. Aromatic C–H amination through π -addition

¹³⁶ Thu, H.-Y.; Yu, W.-Y.; Che, C.-M. *J. Am. Chem. Soc.* **2006**, *128*, 9048–9049.

Some of the oldest processes for synthesizing aryl amines are π -addition methods. The electrophilic nature of nitrogen lends itself toward high reactivity with arenes when activated in some way (e.g. as a nitronium ion or an aminyl radical, *etc.*). Modern chemistry has developed based on this precedent, with methods that proceed through electrophilic aromatic substitution, radical addition, and nucleophilic addition to arene radical cations.

Electrophilic nitration is a versatile reaction with a broad substrate scope and is readily amenable to industrial scale-up.^{45,125,137} Reactions are typically performed under acidic conditions in the presence of a nitrating reagent that forms a nitronium ion (NO_2^+) *in situ* as the active electrophile in the reaction (Figure 1.33a). Typical of electrophilic aromatic substitution reactions, nitration is selective for the most electron-rich position of an arene, with electron-donating groups directing *ortho/para* and electron-withdrawing groups directing *meta*. The selectivity is good,¹²⁵ as shown in Table 1.2, but accessing the complementary isomers is therefore difficult. After installation of a nitro group, a reduction step is necessary to access the free amine. Reduction generally works well and is performed with a heterogeneous catalyst under an atmosphere of hydrogen gas. Occasional selectivity issues are observed when alkenes, alkynes, carbonyls, benzyl protecting groups, or multiple aryl halides are present in a substrate.¹³⁸

¹³⁷ Nitration is a very exothermic reaction, which has generated safety concerns due to the potential for runoff reactions, especially upon scale-up; flow chemistry can be utilized to address some of these concerns and can often be readily coupled to the reduction step to maximize efficiency: Movsisyan, M; Delbeke, E. I. P.; Berton, J. K. E. T.; Battilocchio, C.; Ley, S. V.; Stevens, C. V. *Chem. Soc. Rev.* **2016**, *45*, 4892–4928.

¹³⁸ Blaser, H.-U.; Steiner, H.; Studer, M. *ChemCatChem* **2009**, *1*, 210–221.

Table 1.2. Selectivity of nitration on monosubstituted arenes (*ref 125*).

R	ortho	% yield meta	para
OMe	30-40	0-2	60-70
Me	56-60	2-4	34-40
Br	36-43	0-2	56-62
F	9-13	0-1	86-91
CN	15-17	81-83	1-2
SO ₂ Me	0-8	88-98	0-3
NO ₂	5-6	91-93	1-2

Other C–H aminations that proceed through an electrophilic aromatic substitution mechanism are not plentiful and generally lack the scope of nitration. Kovacic reported a Friedel-Crafts amination in 1961 using a combination of AlCl₃ and hydroxylamine-*O*-sulfonic acid (HOSA).¹³⁹ More recently, gold(III) has been used as a catalyst in combination with electrophilic nitrogen sources for reactions that are proposed to proceed through an initial electrophilic auration step (Figure 1.33b).¹⁴⁰ In both of these cases, a large excess of arene is used and the scope is narrow in comparison to nitration.

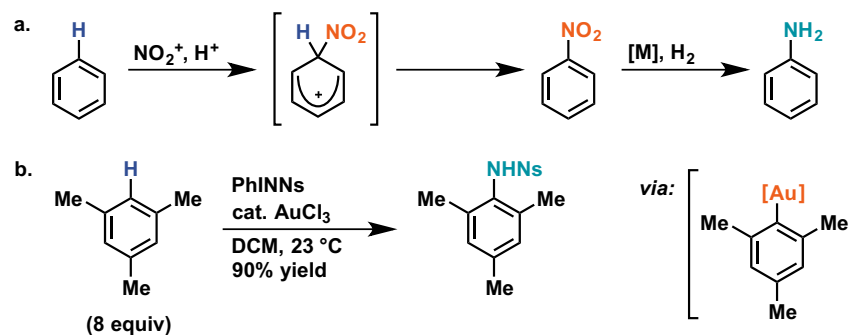


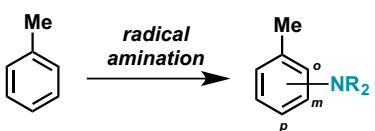
Figure 1.33. Electrophilic aromatic substitution for C–H amination. a. General reaction scheme for nitration/reduction protocol; b. Gold-catalyzed aromatic amination (*ref 140a*).

¹³⁹ Kovacic, P.; Bennett, R. P. *J. Am. Chem. Soc.* **1961**, *83*, 221–224.

¹⁴⁰ a. Li, Z.; Capretto, D. A.; Rahaman, R. O.; He, C. *J. Am. Chem. Soc.* **2007**, *129*, 12058–12059; b. Gu, L.; Neo, B. S.; Zhang, Y. *Org. Lett.* **2011**, *13*, 1872–1874; c. Marchetti, L.; Kantak, A.; Davis, R.; DeBoef, B. *Org. Lett.* **2015**, *17*, 358–361.

Radical addition to arenes for C–H amination is commensurate with electrophilic nitration chemistry in many ways: generally the arene can be used as the limiting reagent and selectivity favors the most electron-rich position. However, radical addition has the potential to complement electrophilic nitration by providing a more even distribution of all positional isomers, due to decreased selectivity. Toluene provides an exemplary case: electrophilic nitration gives low yields of the *meta* isomer (Table 1.2), while a significant fraction of the products from an assortment of radical addition aminations are the *meta* product (Table 1.3.).

Table 1.3. Selectivity of select radical addition reactions for C–H amination of toluene.

			
conditions	ortho	% yield meta	para
CINMe ₂ , H ⁺ , Fe(II) ¹⁴¹	9-10	43-59	30-46
HOSA, Fe(II) ¹⁴³	36	23	42
PhthNCl, [Ir], hν ^{145b}	52	21	27
PhthNOC(O)CF ₃ , [Ir], hν ^{145a}	44	24	29
[MsONH ₃]OTf, Fe(II) ¹⁴⁴	28	25	48

Pioneering work by Minisci demonstrated the use of chloroamines under acidic conditions for aromatic C–H amination chemistry (Figure 1.34a).¹⁴¹ Interestingly, the protonation state of the nitrogen-centered radical was shown to affect the selectivity, with charged aminiumyl radicals giving more selective reactions.¹⁴² Minisci also highlighted the use of [N–O] reagents, such as HOSA, as aminiumyl radical precursors for the installation of free amino groups, which are difficult to access with [N–Cl] reagents due to the instability of chloramine (Figure 1.34b).¹⁴³ An updated version of this reaction was reported by Morandi, who used [MsO–NH₃]OTf as an easy-to-handle aminating reagent (Figure 1.34c).¹⁴⁴

¹⁴¹ Minisci, F. *Synthesis* **1973**, 1–24.

¹⁴² Clerici, A.; Minisci, F.; Perchinunno, M.; Porta, O. *J. Chem. Soc. Perkin Trans. 2* **1974**, 416–419.

¹⁴³ Citterio, A.; Gentile, A.; Minisci, F.; Navarrini, V.; Serravalle, M.; Ventura, S. *J. Org. Chem.* **1984**, 49, 4479–4482.

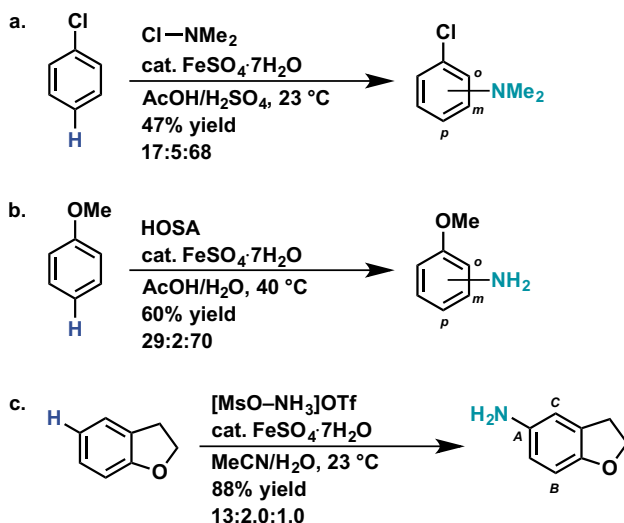


Figure 1.34. Aminiumyl radical addition to arenes. a. Minisci's amination reaction with chloroamines (*ref 141*); b. Minisci's amination reaction with HOSA (*ref 143*); c. Morandi's amination with hydroxylamine derivatives (*ref 144*).

The installation of amide or imide functionality *via* radical addition has proven efficient. The synthesis of *N*-aryl phthalimides under photoredox conditions was reported by the Sanford, Lee, and Studer groups, who used *N*-trifluoroacetoxyphthalimide, *N*-chlorophthalimide, and *N*-phthaloylpyridinium respectively, as radical precursors (Table 1.4).¹⁴⁵ Single electron reduction of the precursor by a photo-activated metal catalyst leads to formation of the nitrogen-centered radical and addition to the arene. Phthalimides can be readily deprotected with hydrazine, which gives easy access to the free aniline. Baran reported a ferrocene-catalyzed synthesis of *N*-aryl succinimides that does not require light activation and uses the arene as the limiting reagent, unlike the aryl phthalimide syntheses; a new *N*-succinimidyl perester reagent was developed for the method (Figure 1.35a).¹⁴⁶ However, deprotection of succinimides requires harsher conditions, making the products somewhat less versatile. Ritter reported the use of *N*-fluorobenzenesulfonimide for a palladium- and silver-catalyzed imidation of

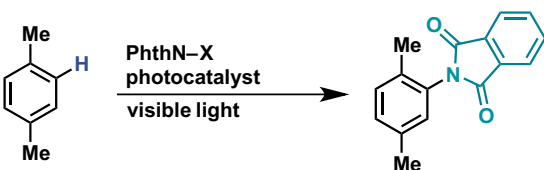
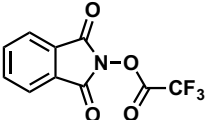
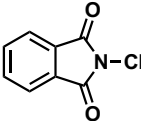
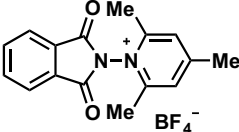
¹⁴⁴ Legnani, L.; Prina Cerai, G.; Morandi, B. *ACS Catal.* **2016**, 6, 8162–8165.

¹⁴⁵ a. Allen, L. J.; Cabrera, P. J.; Lee, M.; Sanford, M. S. *J. Am. Chem. Soc.* **2014**, 136, 5607–5610; b. Kim, H.; Kim, T.; Lee, D. G.; Roh, S. W.; Lee, C. *Chem. Commun.* **2014**, 50, 9273–9276; c. Greulich, T. W.; Daniliuc, C. G.; Studer, A. *Org. Lett.* **2015**, 17, 254–257.

¹⁴⁶ Foo, K.; Sella, E.; Thomé, I.; Eastgate, M. D.; Baran, P. S. *J. Am. Chem. Soc.* **2014**, 136, 5279–5282.

arenes (Figure 1.35b).¹⁴⁷ Similar to the subsequent Baran report, the arene is used as the limiting reagent, but the protecting groups on nitrogen are difficult to deprotect. In all cases for the C–H amination reactions described above, more than one isomeric product is generated, as is typical for radical additions. A promising exception was reported by Ritter in 2016, where the use of the extremely electrophilic TEDA²⁺ derived from SelectFluor leads to highly *para*-selective C–N bond formation (Figure 1.35c).^{82b} Synthetically interesting aryl piperazines were synthesized from the initial *N*-aryl-TEDA products.

Table 1.4. *N*-aryl phthalimide synthesis using photoredox catalysis.

			
PhthN-X	photocatalyst	conditions	yield
	Ir(ppy) ₃	10 equiv arene MeCN, 23 °C	88% ^{145a}
	Ir(dFppy) ₃	2 equiv arene AcOH, K ₂ CO ₃ MeCN, 23 °C	40% ^{145b}
	Ru(bpy) ₃ Cl ₂	10 equiv arene mol. sieves MeCN, 40 °C	89% ^{145c}

¹⁴⁷ Boursalian, G. B.; Ngai, M.-Y.; Hojczyk, K. N.; Ritter, T. *J. Am. Chem. Soc.* **2013**, *135*, 13278–13281.

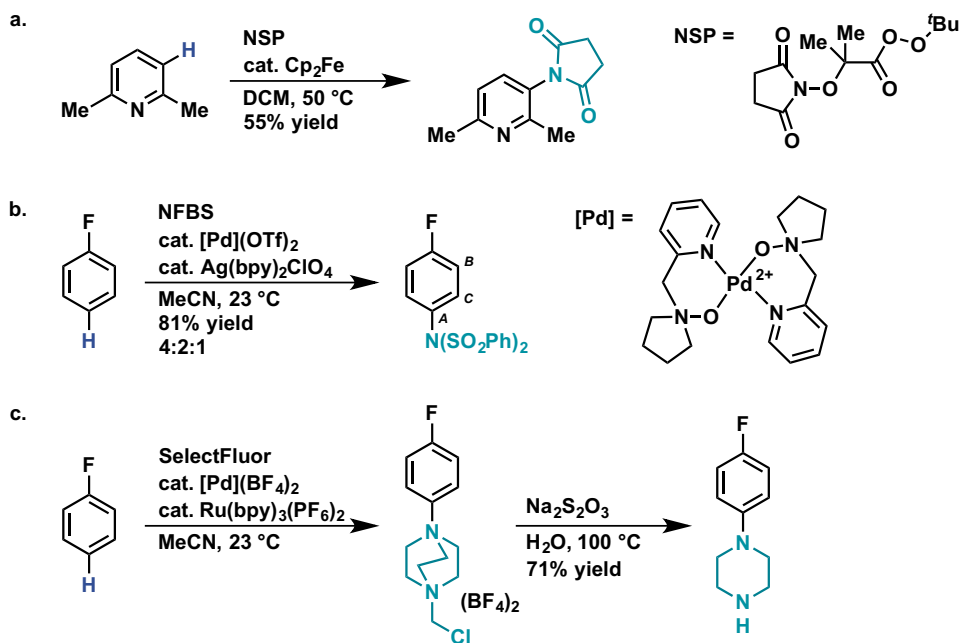


Figure 1.35. Aromatic C–H to C–N bond transformations that proceed through radical addition. a. NSP as a new reagent for radical imidation (*ref 146*); b, c. [N–F] reagents for aromatic amination (*ref 147, 82b*).

A complementary strategy for aromatic C–H amination through a radical mechanism is nucleophilic addition to an aromatic radical cation, generated through single electron oxidation of the arene. However, oxidation is generally only a facile process for electron-rich arenes, which limits the scope of reactions in this category. The radical cation is then readily trapped by nucleophiles to form cyclohexadienyl radical intermediates, which proceed through the typical reaction pathways (Figure 1.36a). A major challenge for the aromatic radical cation mechanism is ensuring compatibility between the oxidant and the nucleophile. Anodic oxidation of arenes in the presence of pyridine generates aryl pyridinium salts that undergo ring opening with piperidine in a subsequent step to reveal free anilines.¹⁴⁸ The strategic use of pyridine as a nitrogen source allows for selective oxidation of the arene in the presence of the nucleophile. Hypervalent iodine reagents have been shown to engage in charge-transfer interactions with electron-rich arenes, which effectively generates an arene radical cation. Trapping with

¹⁴⁸ Morofuji, T.; Shimizu, A.; Yoshida, J.-I. *J. Am. Chem. Soc.* **2013**, *135*, 5000–5003.

various nucleophiles, including azide and phthalimide, have been reported.¹⁴⁹ Finally, photocatalysts with strongly oxidizing excited states have also been used to generate arene radical cations. Nicewicz reported the use of an acridinium photocatalyst and catalytic TEMPO under aerobic conditions to form C–N bonds between arenes and nitrogen heterocycles.¹⁵⁰ They further demonstrated the value of their method by using ammonium carbamate as a nucleophile to synthesize free anilines under their reaction conditions (Figure 1.36b). Wu and Tang demonstrated the use of a quinolinium photocatalyst in combination with a cobalt catalyst for aromatic amination.¹⁵¹ Their mechanistic proposal involves single electron oxidation of the arene, followed by trapping with ammonia and rearomatization through cobalt-assisted oxidation and deprotonation. Notably, benzene could be used as a substrate, in contrast to other arene radical cation methods that work only with more electron-rich arenes. Despite the conceptual innovations, C–H amination through arene radical cation intermediates lacks the scope of electrophilic or radical aromatic substitution reactions.

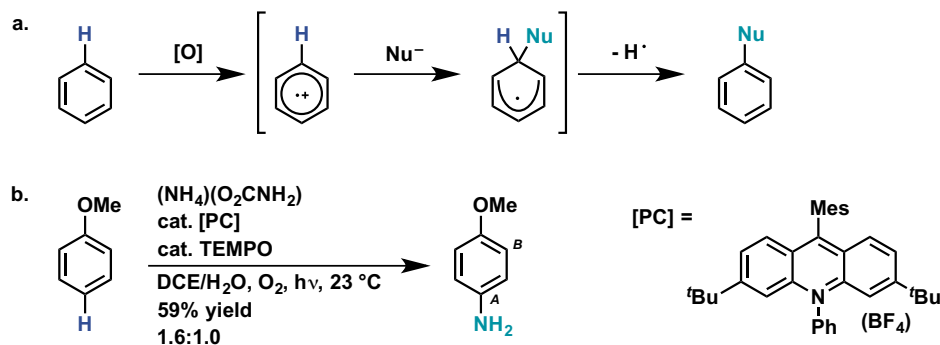


Figure 1.36. Aromatic C–H amination *via* nucleophilic trapping of an arene radical cation. a. General reaction scheme; b. Photocatalytic amination that proceeds through single electron oxidation of the arene (*ref* 150).

In comparison to aromatic C–H hydroxylation, aromatic C–H amination is more developed, with a greater variety of available and easy-to-handle nitrogen sources. However, challenges still persist:

¹⁴⁹ a. Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684–3691; b. Kantak, A. A.; Potavathri, S.; Barham, R. A.; Romano, K. M.; DeBoef, B. *J. Am. Chem. Soc.* **2011**, *133*, 19960–19965.

¹⁵⁰ Romero, N. A.; Margrey, K. A.; Tay, N. E.; Nicewicz, D. A. *Science* **2015**, *349*, 1326–1330.

¹⁵¹ Zheng, Y.-W.; Chen, B.; Ye, P.; Feng, K.; Wang, W.; Meng, Q.-Y.; Wu, L.-Z.; Tung, C.-H. *J. Am. Chem. Soc.* **2016**, *138*, 10080–10083.

synthesis of free amines in a single step remains rare, and amination of electron-poor arenes occurs with low yields, due to the electrophilic character of the most commonly used nitrogen sources. Synthetic methods that address these unmet needs would be valuable.

1.6. Summary of introduction

The field of aromatic C–H functionalization has the potential revolutionize the way synthetic chemists think about constructing molecules, developing compound libraries and addressing chemical questions. The chemistry presented above demonstrates a variety of mechanistic strategies to functionalize aromatic C–H bonds. Activation of the C–H σ -bond with alkali metal bases and with transition metals has provided access to a diverse range of products after the formation of a carbon–metal intermediate, often with the assistance of a chelating directing group. On the other hand, π -addition approaches, including electrophilic, nucleophilic, and radical aromatic substitution, overcome the challenge of direct C–H metalation to provide various products. Specifically, π -addition mechanisms that use η^6 -arene complexes enable nucleophilic attack on otherwise unreactive arenes, and radical addition provides access to complementary isomers in a single electron manifold. In particular, C–H oxygenation and C–H amination provide desirable functionalized aromatic products through both σ -bond activation and π -addition mechanisms. Despite the many advances in aromatic C–H functionalization, current goals include using the arene as the limiting reagent, avoiding the use of chelating directing groups, increasing functional group tolerance and expanding substrate scope. Two π -addition strategies that seek to target solutions to these problems are presented next in Chapters 2 and 3.

2. SELECTIVE AROMATIC C–H HYDROXYLATION ENABLED BY η^6 -COORDINATION TO IRIDIUM(III)

2.1. η^6 -Coordination for C–H functionalization

Transition metal-mediated C–H functionalization methods typically involve the formation of a metal–carbon σ -bond through oxidative addition, σ -bond metathesis, or electrophilic metalation.^{5a} Slow metalation processes, due to the strength and low polarity of the aromatic C–H bond, are difficult to overcome and hinder the improvement of current methodologies. We identified η^6 -coordination of the aromatic π -system to a transition metal as an alternative activation manifold that could facilitate aromatic C–H functionalization. The catalytic cycle we envision involves nucleophilic attack on an η^6 -coordinated arene, oxidation of the resulting η^5 -cyclohexadienyl adduct, and arene exchange (Figure 2.1). By employing nucleophilic functionalization reagents, as opposed to the conventionally used electrophilic reagents, the π -activation mode is well suited for the formation of C–X bonds, where X is an electronegative atom, such as O, N, or F. Additional benefits of the π -activation approach include the ability to target aromatic rings without introduction of a coordinating directing group and the reversal of positional selectivity observed for traditional C–H functionalization chemistry. In this chapter, we present C–H hydroxylation utilizing iridium(III) η^6 -arene complexes and demonstrate the first use of oxygen nucleophiles for C–H functionalization with transition metal η^6 -arene complexes. We anticipate that these advances in stoichiometric C–O bond formation will provide valuable insight for translation into a catalytic cycle.

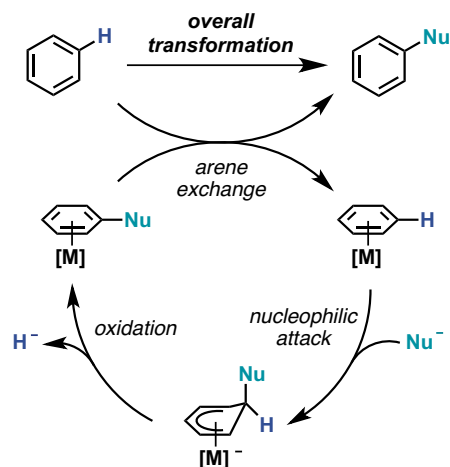


Figure 2.1. C–H functionalization utilizing η^6 -arene activation.

Several strategies have been employed to form metal–carbon σ -bonds as intermediates for subsequent functionalization, despite the slow C–H metalation of arenes (see Section 1.1.1). The use of coordinating directing groups for both *ortho*¹⁸ and more remote^{19–24} C–H functionalization has been thoroughly explored by several groups to enforce intramolecularity for the difficult metalation step. However, introduction and further modification of a directing group increases step count and is often challenging. On the other hand, C–H metalation without a coordinating directing group typically requires an excess of arene (*i.e.* as solvent) to increase the concentration of substrate. Notable exceptions include iridium-catalyzed borylation,^{26–32} rhodium-catalyzed silylation,^{33–35} and arylation with acidic arenes^{37–40}. An opposing strategy is to avoid formation of a metal–carbon σ -bond altogether, such as electrophilic aromatic substitution^{42–43} or reactions that proceed through a radical addition to an arene (see Chapter 1.3). For example, MacMillan’s iridium-catalyzed trifluoromethylation¹⁰² and Ritter’s palladium and silver co-catalyzed C–H imidation¹⁴⁷ utilize transition metal catalysts to form reactive radical species that interact with the aromatic substrate. In an effort to expand upon methods that do not rely upon formation of a metal–carbon σ -bond during catalysis, we focused on utilizing η^6 -arene complexes to provide a different mechanism for C–H functionalization.

η^6 -Coordination of an arene has long been recognized as a tool for *umpolung* aromatic substitution chemistry, which facilitates nucleophilic attack on otherwise unactivated aromatic π -

systems.^{55,58,67,152} Nucleophilic attack at C–H bonds is well-established with a variety of transition metal complexes, such as η^6 -arene complexes of the $[\text{Cr}(\text{CO})_3]$, $[\text{Mn}(\text{CO})_3]^+$, $[\text{FeCp}]^+$, $[\text{RuCp}]^+$, and $[\text{IrCp}^*]^{2+}$ fragments, and is kinetically preferred over C–X bonds⁵⁸ in most cases. Strong nucleophiles, such as some carbanions, form stable η^5 -cyclohexadienyl adducts via irreversible nucleophilic attack.^{55,58,67,68} Stable adducts can be oxidized in a subsequent step to provide overall C–H functionalized products (Figure 2.2). However, the use of heteroatomic nucleophiles (HNR_2 , OR^- , etc.) for this two-step sequence is quite limited, because η^5 -cyclohexadienyl adduct formation is usually reversible with equilibrium favoring the starting materials.^{153,154} Furthermore, an example where nucleophilic attack and oxidation have occurred in the same reaction vessel at the same time, as is necessary for a catalytic reaction and is reported here, is unprecedented. We targeted C–H hydroxylation as a reaction that would be an advancement of known stoichiometric η^6 -arene chemistry, as well as a desirable synthetic transformation.^{105,107}

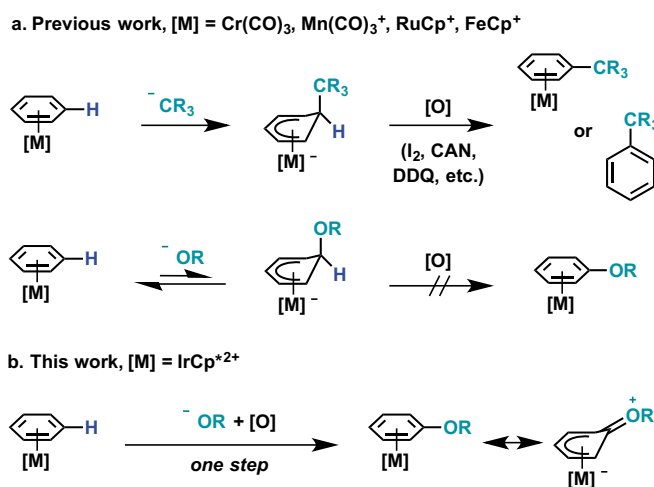


Figure 2.2. C–H functionalization *via* nucleophilic attack on η^6 -arene complexes. a. Previously reported work with strong nucleophiles; b. This work with weak nucleophiles for a one step nucleophilic attack and oxidation process.

¹⁵² η^2 -Arene complexes have also been used for *umpolung* aromatic substitution chemistry: Harman, W. D. *Chem. Rev.* **1997**, 97, 1953–1978.

¹⁵³ a. For an exception that uses a nitrogen nucleophile: see *ref* 69; b. For an exception that uses an oxygen nucleophile: Le Bras, J.; Amouri, H.; Vaissermann, J. *Organometallics* **1996**, 15, 5706–5712.

¹⁵⁴ For examples where heteroatomic nucleophiles are used to form η^5 -cyclohexadienyl adducts but are not oxidized to aromatic products: a. Moussa, J.; Chamoreau, L.-M.; Boubekeur, K.; Amouri, H.; Rager, M. N.; Grotjahn, D. B. *Organometallics* **2008**, 27, 67–71; b. Shirin, Z.; Pramanik, A.; Ghosh, P.; Mukherjee, R. *Inorg. Chem.* **1996**, 35, 3431–3433; c. Kvietok, F.; Allured, V.; Carperos, V.; DuBois, M. R. *Organometallics* **1994**, 13, 60–68; Robertson, D. R.; Robertson, I. W.; Stephenson, T. A. *J. Organomet. Chem.* **1980**, 202, 309–318; e. Bailey, N. A.; Blunt, E. H.; Fairhurst, G.; White, C. J. *Chem. Soc. Dalton Trans.* **1980**, 829–836.

2.2. Discovery of a C–H hydroxylation reaction using $[(\eta^6\text{-arene})\text{IrCp}^*](\text{BF}_4)_2$

We identified air and moisture stable arene complex **2.1**¹⁵⁵ as a good target for studying the desired oxidation reaction, due to its high electrophilicity.^{61,156} Complex **2.1** is readily synthesized from the commercially available $[\text{Cp}^*\text{IrCl}_2]_2$ by chloride abstraction with AgBF_4 (Figure 2.3). Upon addition of NaClO_2 , in conjunction with 2-methyl-2-butene as an HOCl scavenger,¹⁵⁷ **2.1** is converted directly into η^5 -phenoxo complex **2.2**¹⁵⁸ in 3 h at 23 °C in 85% yield. The conversion of **2.1** into **2.2** is an overall aromatic C–H to C–O bond transformation that represents both the nucleophilic attack and oxidation steps of the proposed catalytic cycle from Figure 2.1. Importantly, the control reaction using uncoordinated benzene instead of complex **2.1** results in no formation of phenol. By increasing the electrophilicity of the arene complex and identifying the appropriate functionalization reagent (NaClO_2), nucleophilic attack and oxidation occur concurrently, which circumvents issues of an unfavorable equilibrium for the initial attack step. To the best of our knowledge, no other transition metal η^6 -arene complex has afforded hydroxylated aromatic products through initial nucleophilic attack at a C–H bond.

After protonation of **2.2** and heating at 80 °C in acetonitrile, phenol is recovered in 75% isolated yield and tris(acetonitrile) complex **2.3** is isolated in 85% yield. The iridium can be recycled to convert complex **2.3** into **2.1** in 81% yield by heating in a 1:1 mixture of benzene and acetone. In this way, all steps of the proposed catalytic cycle have been demonstrated individually.

¹⁵⁵ White, C.; Thompson, S. J.; Maitlis, P. M. *J. Chem. Soc. Dalton Trans.* **1977**, 1654–1661.

¹⁵⁶ Grundy, S. L.; Smith, A. J.; Adams, H.; Maitlis, P. M. *J. Chem. Soc. Dalton Trans.* **1984**, 1747–1754.

¹⁵⁷ Kraus, G. A.; Roth, B. *J. Org. Chem.* **1980**, 45, 4825–4830.

¹⁵⁸ a. White, C.; Thompson, S. J.; Maitlis, P. M. *J. Organomet. Chem.* **1977**, 127, 415–421; b. Amouri, H.; Le Bras, J.; Vaissermann, J. *Organometallics* **1998**, 17, 5850–5857.

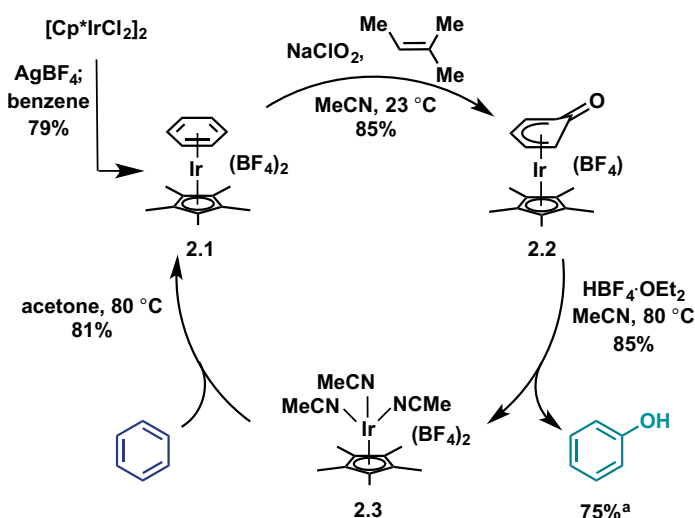
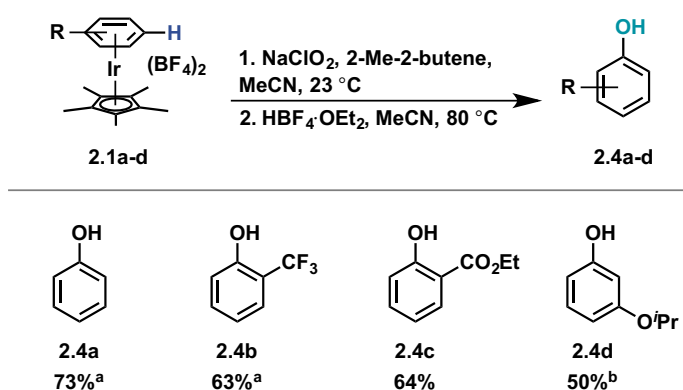


Figure 2.3. Synthetic cycle for oxidation of benzene to phenol. ^aIsolated as the *p*-toluenesulfonate due to volatility of phenol.

Upon discovery of the above C–H oxidation protocol, the effect of arene substitution on selectivity was investigated (Table 2.1). Interestingly, C–O bond formation occurs selectively *ortho* to electron-withdrawing groups, as in the case of trifluorotoluene complex **2.1b** and ethyl benzoate complex **2.1c**. Only one isomeric product was observed in the reactions of both **2.1b** and **2.1c**. C–O bond formation was observed primarily *meta* to the resonance electron-donating group in isopropoxybenzene complex **2.1d**. A small amount (5%) of the *para* hydroxylation product was also isolated from the reaction of **2.1d**.

Table 2.1. Effect of arene substitution on site selectivity of C–H hydroxylation.



^aIsolated as the aryl *p*-toluenesulfonate due to volatility of phenol; ^{bi}PrCN used instead of MeCN for step 2; isolated as a 95:5 mixture of *meta*:*para* isopropoxyphenol.

While nucleophilic addition of carbanions to η^6 -arene complexes has been shown to occur with similar selectivity,^{55a,58,59c, 159} typical C–H hydroxylation chemistry does not proceed in such high selectivity. In addition, the positional selectivity of the products in Table 2.1 is opposite that of most C–H oxidation protocols, which broadly rely on the arene to act as nucleophile. For example, Siegel reported aromatic C–H hydroxylation using phthaloyl peroxide and observed only *ortho* and *para* products (*o:p* = 1.4:1.0) for anisole, a substrate with a single resonance donor.¹²⁰ Similarly, Sanford reported a palladium-catalyzed acetoxylation that gives C–O bond formation predominantly *meta* to the electron-withdrawing trifluoromethyl group (*o:m:p* = 1:78:21).¹¹⁰ In contrast, by enhancing the electrophilicity of the arene through η^6 -coordination, our protocol has the potential to complement these selectivities, with hydroxylation occurring at the position of least electron density.

2.3. Mechanistic insight into C–O bond formation

With the goal of catalysis in mind, we examined more closely the mechanism of the promising C–H hydroxylation protocol described above. The C–H to C–O bond transformation can be divided into two general steps – nucleophilic attack to form an η^5 -cyclohexadienyl adduct, followed by oxidation to form η^5 -phenoxo complex **2.2** (Figure 2.4a). While there are reports of nucleophilic attack on complex **2.1**, albeit with stronger nucleophiles than NaClO₂,¹⁵⁶ the oxidation step is unprecedented. Only starting material (**2.1**) and the final product (**2.2**) could be observed in the NaClO₂ oxidation reaction when monitored by ¹H NMR spectroscopy. We, therefore, were prompted to investigate other nucleophile/oxidant combinations that react with **2.1** to learn about the nucleophilic attack and oxidation steps that lead to C–O bond formation.

In a reaction analogous to that with NaClO₂, complex **2.1** reacts with *m*CPBA in the presence of Na₂CO₃ to give η^5 -phenoxo complex **2.2** in 85% yield (Figure 2.4b). Furthermore, an η^5 -cyclohexadienyl adduct of *m*-chloroperbenzoate (**2.5**) was observed when the reaction was followed by ¹H NMR

¹⁵⁹ a. Kündig, E. P.; Desobry, V.; Simmons, D. P.; Wenger, E. *J. Am. Chem. Soc.* **1989**, *111*, 1804–1814; b. Sutherland, R. G.; Chowdhury, R. L.; Piórko, A.; Lee, C. C. *Can. J. Chem.* **1986**, *64*, 2031–2037.

spectroscopy. Adduct **2.5** could not be isolated due to its propensity to form complex **2.2**, but it was distinguished by the significant upfield shift of the observed ^1H NMR and ^{13}C NMR signals, compared to those of η^6 -arene complex **2.1**, a feature characteristic of all known η^5 -cyclohexadienyl adducts.¹⁶⁰ After comparing adduct **2.5** with the proposed η^5 -cyclohexadienyl adduct of chlorite, we hypothesized that a cyclic 5- or 6-membered transition state for *syn* elimination might facilitate oxidation.

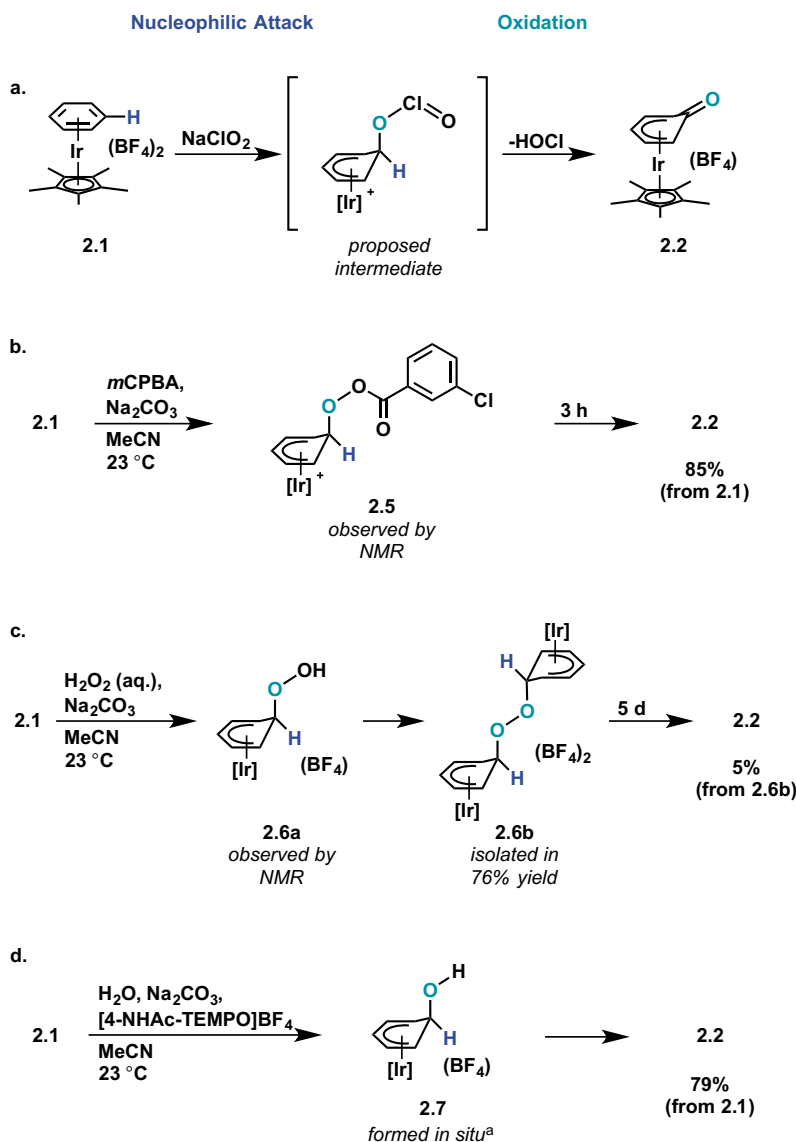


Figure 2.4. C–O bond formation via η^5 -cyclohexadienyl adducts. $[\text{Ir}] = [\text{Cp}^*\text{Ir}(\text{III})]$; ^aComplex **2.7** may be isolated in the absence of $[\text{4-NHAc-TEMPO}]\text{BF}_4$.

¹⁶⁰ Notably, adduct **2.5** features the most downfield shifts for the *ipso* and *ortho* protons and carbons of any reported adduct formed from complex **2.1**, (*ref 156*) which is likely due to the electron-withdrawing nature of the *m*-chloroperbenzoate group.

To probe the hypothesis of a cyclic transition state, we next evaluated hydrogen peroxide, a nucleophilic oxidant that would not be expected to readily undergo *syn* elimination after attack on complex **2.1**. Reaction of **2.1** with H₂O₂ and Na₂CO₃ resulted in dialkylated peroxide η^5 -cyclohexadienyl adduct **2.6b**, which, unlike **2.5**, could be isolated and characterized (Figure 2.4c). Monoalkylated peroxide adduct **2.6a** could be observed by NMR and is likely on-path in the formation of **2.6b**. Adduct **2.6b** was observed to form complex **2.2** in low conversion (5%) over the course 5 days, which suggests a different mechanism for oxidation, or at least one that is significantly slowed when using H₂O₂, and supports our hypothesis of *syn* elimination in the cases of NaClO₂ and *m*CPBA.

To further probe possible mechanisms for C–H oxidation, we attempted to decouple the nucleophile and oxidant but maintain the possibility for a cyclic transition state for *syn* elimination. Reaction of complex **2.1**, H₂O, Na₂CO₃ and [4-NHAc-TEMPO]BF₄, a reagent known for oxidation of alcohols to aldehydes or ketones,¹⁶¹ results in isolation of complex **2.2** in 79% yield (Figure 2.4d). Formation of adduct **2.7** is observed, and the adduct can be isolated if the reaction is run in the absence of oxidant. Previously reported mechanistic investigations for alcohol oxidation with [4-NHAc-TEMPO]BF₄ suggest that oxidation proceeds through a 5-membered transition state.¹⁶²

Based on the observed positional selectivity and the formation of η^5 -cyclohexadienyl adducts with oxygen nucleophiles, our mechanistic hypothesis for the C–O bond forming reaction involves nucleophilic attack of chlorite on arene complex **2.1** in analogy to nucleophilic attack of chlorite on an aldehyde in the Lindgren-Pinnick oxidation.¹⁶³ Nucleophilic attack is quickly followed by oxidation, possibly through a *syn* elimination, to generate η^5 -phenoxo complex **2.2** and hypochlorous acid.

2.4. Formation of C–N bonds using [(η^6 -arene)IrCp*](BF₄)₂

¹⁶¹ Mercadante, M. A.; Kelly, C. B.; Bobbitt, J. M.; Tilley, L. J.; Leadbeater, N. E. *Nat. Protoc.* **2013**, 8, 666–676.

¹⁶² Bailey, W. F.; Bobbitt, J. M.; Wiberg, K. B. *J. Org. Chem.* **2007**, 72, 4504–4509.

¹⁶³ a. Lindgren, B. O.; Nilsson, T. *Acta Chem. Scand.* **1973**, 27, 888–890; b. Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, 37, 2091–2096.

Based on the success of decoupling the nucleophile and the oxidant for aromatic C–H hydroxylation (Figure 2.4d), we hypothesized that other functional groups could be installed in this manner. Oxidation of primary amines to imines¹⁶⁴ or nitriles¹⁶⁵ has been reported using similar oxoammonium reagents to what was successful for our C–O bond formation; these reports led us to investigate C–N bond formation. Reaction of **2.1** with NH₃ (diox) and [4-NHAc-TEMPO](BF₄) produces [(η⁶-aniline)IrCp*](BF₄)₂¹⁶⁶ (**2.8**) in 21% yield, along with starting material as the remainder, and demonstrates a rare example of C–H amination using η⁶-arene activation (Figure 2.5). The iridium complex **2.8** is proposed to be less energetically downhill than iridium complex **2.2**, the product of C–H hydroxylation, which could be promising for a catalytic C–H amination reaction. Attempts to use other nucleophiles (RO[−], RNH₂, F[−]) in this transformation were unsuccessful.

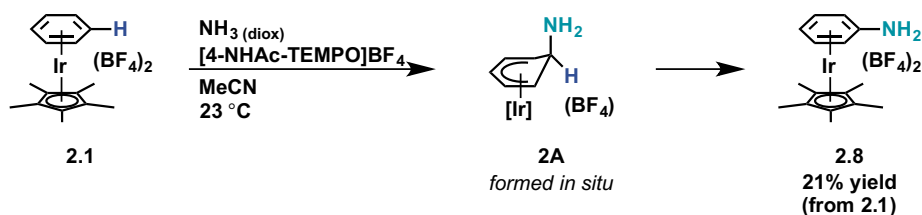


Figure 2.5. C–N bond formation using η⁶-arene complexes.

2.5. Toward a catalytic reaction

Ultimately, our goal is to develop the selective C–H oxidation described above into a catalytic reaction. Initial experiments have indicated that each step in the cycle shown in Figure 2.3 involves conditions that are not compatible with those for the other steps. For example, NaClO₂ is known to decompose under acidic conditions (pH < 2 in aqueous solutions),¹⁶⁷ while complex **2.2** requires strong acid for protonation and displacement from iridium. In addition, tris(acetonitrile) complex **2.3** forms

¹⁶⁴ Sonobe, T.; Oisaki, K.; Kanai, M. *Chem. Sci.* **2012**, 3, 3249–3255.

¹⁶⁵ Kim, J.; Stahl, S. S. *ACS Catal.* **2013**, 3, 1652–1656.

¹⁶⁶ Espinet, P.; Bailey, P. M.; Downey, R. F.; Maitlis, P. M. *J. Chem. Soc. Dalton Trans.* **1980**, 1048–1054.

¹⁶⁷ a. Krapcho, A. P. *Org. Prep. Proc. Int.* **2006**, 38, 177–216; b. Horváth, A. K.; Nagypál, I.; Peintler, G.; Epstein, I. R.; Kustin, K. *J. Phys. Chem. A* **2003**, 107, 6966–6973.

readily from **2.2** under acidic conditions, but benzene does not easily displace acetonitrile ligands to reform **2.1** unless a solvent less coordinating than acetonitrile is used (*e.g.* acetone).

Preliminary progress toward a catalytic cycle has shown that use of trifluoroacetic acid (TFA) as a solvent allows for direct conversion of complex **2.2** into starting arene complex **2.1** in 42% yield after 18 h (Figure 2.6a). The efficiency of the arene exchange reaction seems to be unique to TFA: Arene exchange under the next best conditions ($\text{HBF}_4 \cdot \text{OEt}_2$ in 3-methyl-2-oxazolidinone) is slowed by an unfavorable equilibrium, as coordination of phenol is thermodynamically favored over coordination of benzene (Figure 2.6b). The phenol product must be repeatedly removed from the reaction mixture in order for conversion to continue. The detection of phenyl trifluoroacetate suggests that some esterification occurs under the conditions with TFA, which likely changes the equilibrium position, as the incoming arene (benzene) is now more electron rich than the outgoing arene (phenyl trifluoroacetate). While the change in solvent can promote direct transformation of **2.2** into **2.1**, the issue of incompatibility between NaClO_2 and strong acid remains unsolved. Furthermore, in general, the use of an acidic solvent precludes nucleophilic attack by protonating the nucleophile.

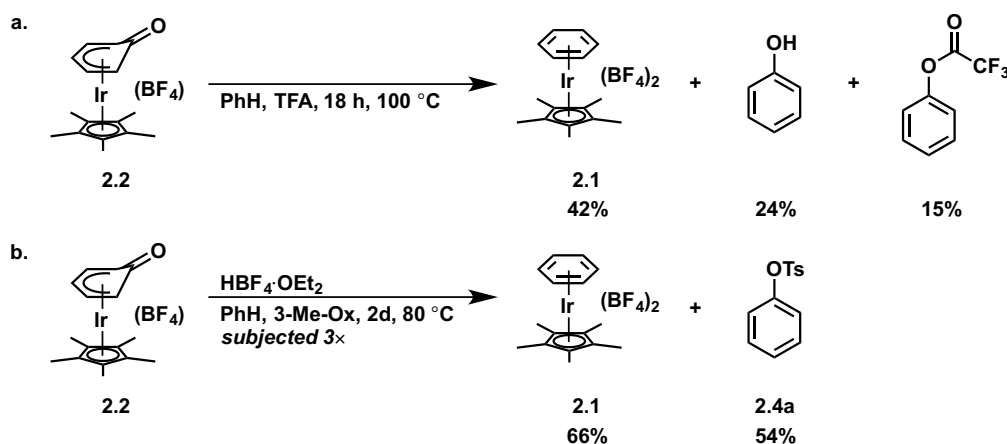


Figure 2.6. Arene exchange reactions of complex **2.2** with benzene.

2.6. Conclusions and outlook

In conclusion, we present aromatic C–H hydroxylation enabled by η^6 -coordination to an iridium(III) complex that proceeds with high positional selectivity through nucleophilic attack, followed by oxidation. By conceptually reversing the role of the arene in C–H functionalization chemistry (from nucleophile to electrophile), π -arene activation provides a new platform for the synthesis of arenes that makes use of nucleophilic functionalization reagents and gives products with complementary selectivity to traditional approaches.

While a catalytic C–H functionalization reaction using η^6 -arene coordination has yet to be realized, the $[(\eta^6\text{-arene})\text{IrCp}^*]^{2+}$ complexes may be privileged for such an application. The high electrophilicity of $[(\eta^6\text{-arene})\text{IrCp}^*]^{2+}$ allows for the use of weak nucleophiles, particularly in comparison to other commonly used η^6 -arene complexes; weak nucleophiles are more likely to be compatible with oxidants. The work presented above in this chapter is an example, demonstrating a previously unrealized pathway for C–H oxidation with η^6 -arene complexes, whereby nucleophilic oxidants attack the arene and undergo a *syn* elimination.

High electrophilicity of the η^6 -arene complex will also impart greater stability of the η^5 -cyclohexadienyl adduct, which is desirable, especially if the nucleophile and the oxidant are decoupled, to maintain a large enough concentration of the adduct for the oxidant to react with. For the same reason, relative kinetic stability of the coordinated arene toward displacement is advantageous; if the arene is too labile, nucleophiles will bind to the metal center and displace the arene instead of attacking the arene itself. Such a situation is often observed with the related $[(\eta^6\text{-arene})\text{RhCp}^*]^{2+}$ complexes, which are reported to display similar electrophilicity as their iridium counterparts but are significantly more labile. Consequently, examples of nucleophilic attack on $[(\eta^6\text{-arene})\text{RhCp}^*]^{2+}$ are rare. Understanding the interplay between arene electrophilicity and lability may be vital to developing a catalytic C–H functionalization reaction with η^6 -arene complexes.

With regards to the arene exchange step, in comparison to commonly used η^6 -arene complexes, $[(\eta^6\text{-arene})\text{IrCp}^*]^{2+}$ demonstrates one of the best compromises of electrophilicity and temperature for arene exchange (80 °C), although it is probably not the ideal. Arene exchange at a lower temperature will

facilitate a greater range of nucleophilic attack/oxidation variations. Since arene exchange would be the “slow” step in a hypothetical catalytic cycle, the nucleophile and oxidant need to survive at the arene exchange temperature for an extended period of time; this is not the case with current oxidation conditions.

Furthermore, experimental evidence has suggested that identification of a suitable solvent is of utmost importance for arene exchange and that the coordination strength of the solvent should be strong enough to assist an η^6 - to η^4 -slip but weak enough to allow an incoming arene to coordinate. The optimal solvent will be highly dependent on the identity of the metal complex. The solvent will also need to be compatible with the nucleophile, a problem that was encountered when TFA was used as a solvent in Section 2.5. However, the fact that a solvent was even identified for arene exchange with $[(\eta^6\text{-arene})\text{IrCp}^*]^{2+}$ bodes well for the development of catalytic reactions with related complexes or conditions.

Recommended future experiments involve the evaluation of rhodium(III) and iridium(III) η^6 -arene complexes, ligated with Cp/Cp* derivatives with an emphasis on solvent/nucleophile/oxidant compatibility. For example, investigation of nucleophilic reactions that occur under acidic conditions could be fruitful, given the promising arene exchange results in TFA. On the other hand, evaluation of non-acidic solvents with similar properties to TFA (*e.g.* fluorinated esters or alcohols) could allow for compatibility with nucleophiles. The experimental groundwork presented in Chapter 2 verifies that each step in the catalytic cycle can work and should be taken as inspiration for the development of catalytic reactions. We believe that catalytic activation of the aromatic π -system has great potential as an alternative approach to C–H functionalization chemistry.

3. RADICAL AROMATIC C–H AMINATION IN HEXAFLUOROISOPROPANOL

3.1. Radical addition for aromatic C–H functionalization

Radical addition to arenes is an attractive strategy for aromatic C–H functionalization, because it avoids the difficult C–H metalation step that is common to several C–H functionalization processes.^{5a} Instead, radical addition mechanisms typically proceed through a facile C–H deprotonation as the final step. Radical addition to arenes has been used to install a variety of functional groups onto aromatic rings, including aryl, alkyl, hydroxyl and amino groups, and often delivers multiple isomeric products, which can be useful for small molecule diversification.^{83e,87a,94,101} However, the radical must be matched in polarity with the arene for a productive reaction.^{83c,142,168} Therefore, the substrate scope of any particular radical addition is typically limited, with electrophilic radicals only reacting with nucleophilic arenes and *vice versa*. Herein, we demonstrate and rationalize the previously unappreciated beneficial, scope-expanding effect of the solvent hexafluoroisopropanol (HFIP) on a radical aromatic C–H amination that provides free anilines in a single step. Electron rich *and* electron poor arenes, such as nitrobenzene, can be aminated using the reaction protocol described here (Figure 3.1a). Our method showcases how ion pair disruption through specific hydrogen bonding interactions with HFIP can expand the substrate scope of a radical C–H functionalization and can obviate the need for the metal catalyst used in conventional reactions. Our hypothesis could be universally guiding in the development of other radical addition reactions and in the expansion of their scope.

Aryl amines are broadly useful in the pharmaceutical, agrochemical and material science fields and have been traditionally synthesized on scale using an electrophilic nitration/reduction sequence.^{45,125,138} While modern aromatic C–H amination methods have failed to match the scope of electrophilic nitration, reaction development has succeeded in increasing functional group tolerance, reducing the two-step sequence to a one-step process, and improving the safety of the reaction.^{127–129}

¹⁶⁸ a. Tiecco, M. *Pure Appl. Chem.* **1981**, 53, 239–258; b. Bravo, A.; Bjørsvik, H.-R.; Fontana, F.; Liguori, L.; Mele, A.; Minisci, F. *J. Org. Chem.* **1997**, 62, 7128–7136.

Advances in C–H amination to provide unprotected anilines have been reported by Nicewicz,¹⁵⁰ under whose conditions ammonium carbamate traps an arene radical cation intermediate, and by Falck,^{8b} under whose conditions a rhodium nitrene intermediate is proposed to insert into a C–H bond. A third approach to direct aromatic C–H amination was pioneered by Minisci in the 1960s, in which hydroxylamine-*O*-sulfonic acid (HOSA) is used as an ammoniumyl radical precursor in the presence of iron(II) salts.^{87a,143} In 2016, Morandi revised the Minisci protocol with the use of the reagent [MsO–NH₃]⁺OTf[–] (**3.1**).¹⁴⁴ However, all reported modern amination methods to make free anilines break down if an electron-poor arene is used as a substrate (Figure 3.1b). For example, no reaction has been reported to afford more than 5% conversion with benzonitrile as a substrate, and most reactions do not afford synthetically useful yields for arenes less electron-rich than bromobenzene.

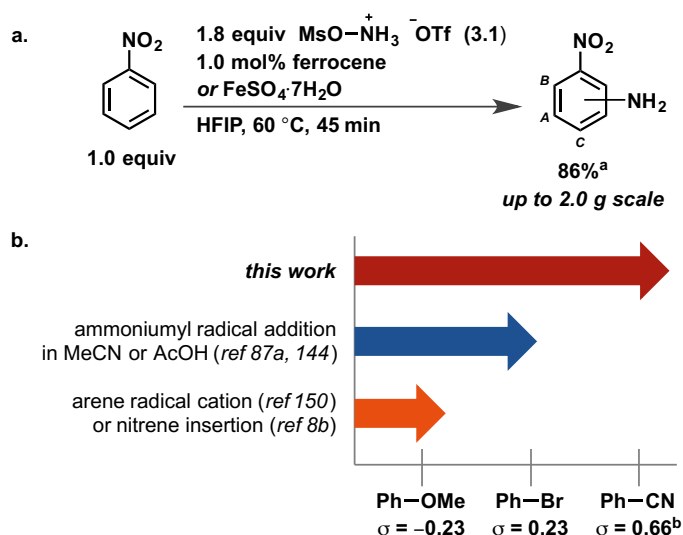


Figure 3.1. Scope of electrophilic radical addition to arenes. ^aCombined yield of analytically pure individual isomers; ratio A:B:C = 2.4:1.0:1.0; ^bWhile σ -values cannot be used to compare reactions proceeding through different mechanisms, they do provide a semi-quantitative measure of arene electron density.

3.2. HFIP as a superior solvent for radical C–H amination

Herein, we show that the combination of the easy-to-handle hydroxylamine-derived reagent **3.1**, 1.0 mol% iron(II) catalyst, and HFIP as solvent affords unprotected anilines from aromatic C–H bonds across an electronic range of arenes broader in scope than any modern aromatic C–H amination reaction.

The reaction is characterized by a simple setup that does not require any special precautions to exclude air or moisture and by reaction times shorter than 2h. In addition, multiple iron sources, including ferrocene and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$, are competent for the reaction. For example, on a 2.0 g scale, nitrobenzene is aminated in 86% yield within 45 min with 1.0 mol% iron loading (Figure 3.1a). All possible constitutional isomers are usually obtained and isolated as individual, analytically pure samples.

The remarkable expansion of the scope is attributed to the unique properties of the solvent HFIP, including high polarity, low nucleophilicity, and strong hydrogen bond-donating ability.¹⁶⁹ As a result, the use of HFIP has been shown to have a great effect on reactivity and/or selectivity in a number of reactions.^{169,170} We propose that HFIP increases the electrophilicity of several cationic species in our reaction through hydrogen-bonding with their anionic counterions, which in turn leads to effective amination of more electron-poor arenes. Based on our experiments, we propose the mechanism shown in Figure 3.2a: An ammoniumyl radical, generated either through N–O bond homolysis or iron-mediated single electron reduction, adds to an arene to generate a putative cationic cyclohexadienyl radical (**3A**). Intermediate **3A** is then rearomatized to the aniline product through one of three pathways: single electron oxidation by iron(III),⁸⁹ aerobic oxidation^{95,171,172} or chain propagation^{83d}.

¹⁶⁹ Shuklov, I. A.; Dubrovina, N. V.; Börner, A. *Synthesis* **2007**, 2925–2943.

¹⁷⁰ a. Kita, Y.; Tohma, H.; Hatanaka, K.; Takada, T.; Fujita, S.; Mitoh, S.; Sakurai, H.; Oka, S. *J. Am. Chem. Soc.* **1994**, *116*, 3684–3691; b. Imada, Y.; Iida, H.; Ono, S.; Murahashi, S.-I. *J. Am. Chem. Soc.* **2003**, *125*, 2868–2869; c. Berkessel, A.; Adrio, J. A.; Hüttenhain, D.; Neudörfl, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 8421–8426; d. Berkessel, A.; Adrio, J. A. *J. Am. Chem. Soc.* **2006**, *128*, 13412–13420; e. Libman, A.; Shalit, H.; Vainer, Y.; Narute, S.; Kozuch, S.; Pappo, D. *J. Am. Chem. Soc.* **2015**, *137*, 11453–11460; f. Colomer, I.; Batchelor-McAuley, C.; Odell, B.; Donohoe, T. J.; Compton, R. G. *J. Am. Chem. Soc.* **2016**, *138*, 8855–8861; g. Pünner, F.; Sohtome, Y.; Sodeoka, M. *Chem. Commun.* **2016**, *52*, 14093–14096.

¹⁷¹ a. Hendry, D. G.; Schuetzle, D. *J. Am. Chem. Soc.* **1975**, *97*, 7123–7127; b. Fang, X.; Pan, X.; Rahmann, A.; Schuchmann, H.-P.; von Sonntag, C. *Chem. Eur. J.* **1995**, *1*, 423–429; c. Estupiñán, E.; Villenave, E.; Raoult, S.; Rayez, J. C.; Rayez, M. T.; Lesclaux, R. *Phys. Chem. Chem. Phys.* **2003**, *5*, 4840–4845.

¹⁷² Eberhardt, M.; Eliel, E. L. *J. Org. Chem.* **1962**, *27*, 2289–2290.

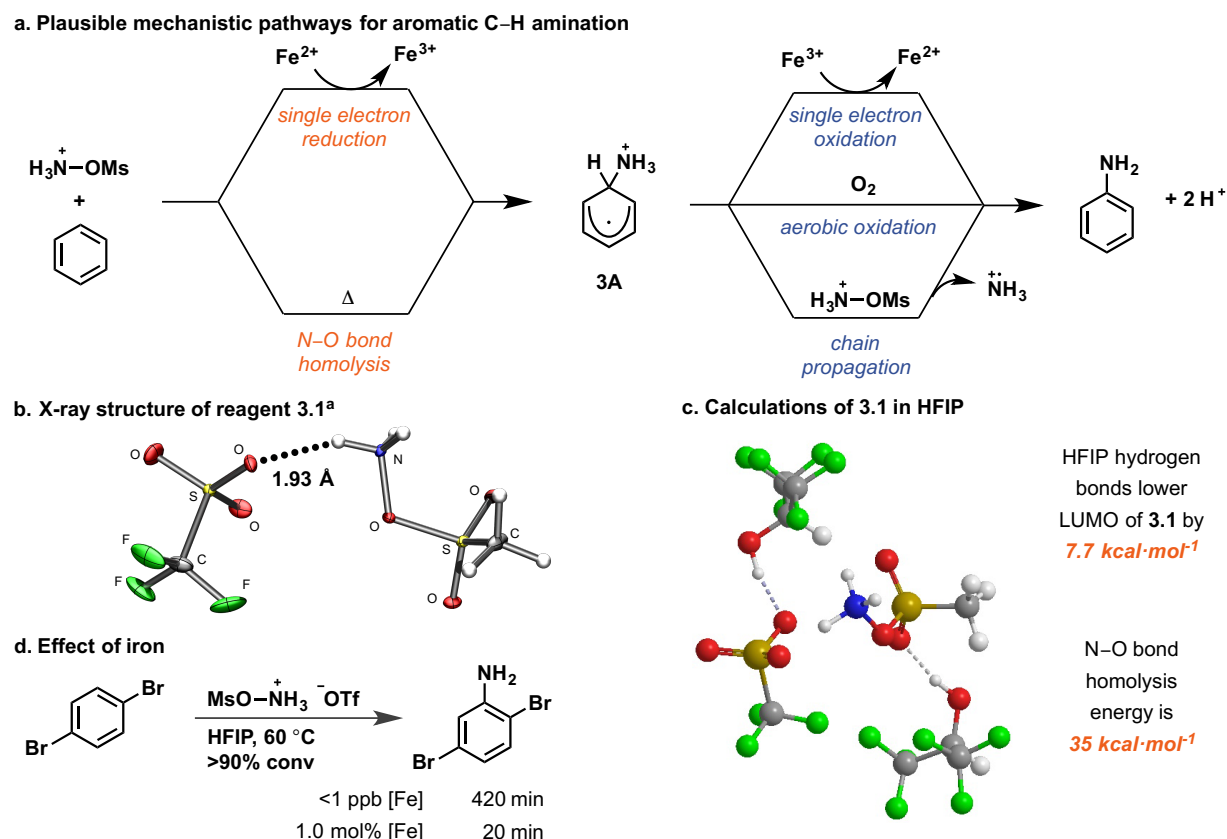


Figure 3.2. Mechanistic hypothesis for aromatic C–H amination. ^aX-ray crystal structure shown with 50% probability ellipsoids.

We identified a hydrogen bond in reagent **3.1** between one N–H and the triflate counterion in the solid state (Figure 3.2b). HFIP likely disrupts the internal hydrogen-bonding and ion pairing of **3.1**, because it functions as a hydrogen-bond donor to the triflate counterion but cannot function as a hydrogen-bond acceptor to $[\text{MsO-NH}_3]^+$.¹⁷³ The result of the HFIP-triflate hydrogen bond is a less associated ion pair with a more localized cation on nitrogen. A second hydrogen bond can occur between an oxygen of the mesyl group and HFIP. Consequently, the cation of **3.1** is more electrophilic when it is dissolved in HFIP.¹⁷⁴ DFT calculations with explicit HFIP solvent molecules support our hypothesis and show that the LUMO of reagent **3.1** is 7.7 kcal/mol lower in energy when both hydrogen-bonding

¹⁷³ a. Matesich, M. A.; Knoefel, J.; Feldman, H.; Evans, D. F. *J. Phys. Chem.* **1973**, *77*, 366–369; b. Evans, D. F.; Matesich, M. A. *J. Solution Chem.* **1973**, *2*, 193–215.

¹⁷⁴ A mixture of MeCN and H₂O, as was used in *ref 144*, would not have the same effect on **3.1**, as the solvent can both donate and accept hydrogen bonds, and the zwitterionic nature of the reagent (HOSA) used by Minisci (*ref 87a*) mitigates any such disruption of ion pairing.

interactions are present (Figure 3.2c). The increased reactivity of reagent **3.1** in HFIP is confirmed by its reduction potential, which we measured by cyclic voltammetry in both HFIP (-0.77 V vs. Fc/Fc^+) and MeCN (-1.28 V vs. Fc/Fc^+). The difference in the reduction potential of reagent **3.1** in the two solvents is ~ 0.5 V and indicates that the reagent is a notably stronger oxidant in HFIP, which supports our hydrogen-bonding hypothesis. In addition, attempts to synthesize derivatives of **3.1** that contain counterions less capable of hydrogen bonding (*e.g.* PF_6) were unsuccessful, which suggests that the hydrogen bond between the triflate counterion and the reagent is an important stabilizing factor before **3.1** is activated by dissolution in HFIP.

HFIP may not only have an effect on the reactivity of **3.1** but also may increase the reactivity of cationic reaction intermediates, specifically the ammoniumyl radical and intermediate **3A** (Figure 3.2a), through hydrogen-bonding interactions with their triflate counterions. Decreased ion pairing and the lack of a hydrogen-bond accepting solvent would lower the LUMO of the ammoniumyl radical derived from the cation of **3.1** and would enable addition to more electron-poor arenes. Similarly, increased reactivity of the cationic cyclohexadienyl radical **3A** would enable more efficient oxidation to the final product. The overall increased electrophilicity of **3.1**, the ammoniumyl radical, and **3A** would synergize to give the much improved substrate scope presented herein.

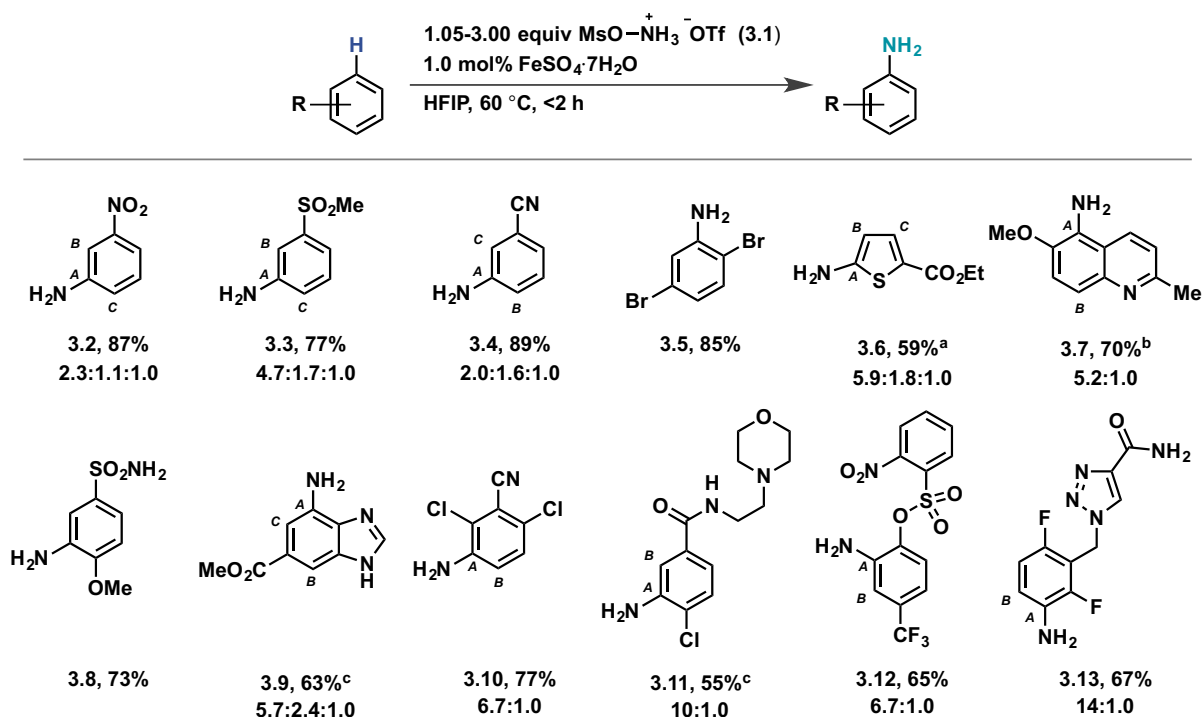
HFIP also enables a metal-free reaction (<1 ppb Fe detected) to occur (Figure 3.2d). Metal-free activation does not occur under any previously reported conditions for ammoniumyl radical addition to arenes but is viable due to the activating properties of HFIP, albeit with longer reaction times. Such a background reaction pathway is a common feature of radical chain reactions.^{83d} Under metal-free conditions, we identified N–O bond homolysis as a likely initiation step to generate the ammoniumyl radical. The N–O bond homolysis energy was calculated using DFT (ωB97XD) to be 35 kcal/mol (Figure 3.2c). N–O bond homolysis can therefore be considered feasible under the reaction conditions, regardless of the presence of an iron salt. Rearomatization of cyclohexadienyl radical **3A** could then occur either by aerobic oxidation or chain propagation.

When $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ is present in the reaction, formation of the ammoniumyl radical can occur through single electron reduction of reagent **3.1**. A third pathway for rearomatization then becomes available – single electron oxidation of **3A** by iron(III) generated in the reduction of **3.1**. Iron(III) has been shown capable of oxidizing cyclohexadienyl radicals,⁸⁹ but whether the iron(II) salt in our reaction is turning over as a catalyst or acting as a radical chain initiator cannot be discerned from our data.

3.3. Substrate scope of C–H amination in HFIP

Based on our discovery of the beneficial effects of HFIP on radical C–H amination, we synthesized a number of anilines utilizing our new protocol (Table 3.1). While previous methods demonstrate efficient amination of arenes no more electron poor than bromobenzene, our method is suitable for the amination of arenes such as nitrobenzene (**3.2**), methyl phenyl sulfone (**3.3**), and benzonitrile (**3.4**). Reactivity is maintained with electron-rich arenes as well. Most halides are tolerated (**3.5**, **3.10**, **3.11**, **3.13**), as are tertiary amines (**3.11**) and benzylic C–H bonds (**3.7**, **3.13**). Amination can occur on five-membered heterocycles (**3.6**) and on benzofused five- and six-membered heterocycles (**3.7**, **3.9**). However, no amination has been observed on six-membered heterocycles. While esters (**3.6**, **3.9**), amides (**3.11**, **3.13**), nitriles (**3.10**, **3.4**), and sulfonamides (**3.8**) are suitable substrates, aldehydes, ketones and alkenes typically undergo side reactions without appreciable ring amination. To demonstrate the amenability of our method to late-stage functionalization, drug molecules mocleboamide and rufinamide were aminated to give derivatives **3.11** and **3.13**, respectively.

Table 3.1. Aromatic C–H amination in HFIP.



^aPerformed at 40 °C; ^bPerformed under an atmosphere of oxygen; ^cTfOH (1.00 equiv) added.

3.4. Conclusions and outlook

In conclusion, we present a practical aromatic C–H amination reaction and provide a mechanistic framework for understanding the effect of the solvent HFIP on the reaction. Though aminiumyl radical additions have been known for over half a century, the mechanistic insight presented herein has resulted in a previously unrealized reaction utility. HFIP is proposed to comprise a unique solvent environment that increases the electrophilicity of multiple cationic species in the reaction to provide a drastically expanded substrate scope. Both electron rich and electron poor arenes are suitable substrates for our method, which uses a bench-stable reagent and an inexpensive iron salt under ambient conditions for fast C–H amination.

While our work presents a unique rationale for the effect of HFIP on a radical addition reaction, a testament to its value would be to use what has been learned for future reaction design. Similar reactivity

enhancement is expected for substituted cationic nitrogen sources, which would allow for the synthesis of aryl amines other than free anilines. Carbon-based radicals adjacent to ammonium functionality (*e.g.* $[\text{H}_3\text{N}-\text{CH}_2\cdot]^+$) might also exhibit greater aromatic substitution reactivity in HFIP. Use of the ammoniumyl radical as an H-atom abstraction reagent could also be explored, and perhaps the increased electrophilic character in HFIP will permit abstraction from strong, polarity mismatched C–H bonds.

Other more practical applications of our method may include development of a one-pot, two-step protocol for aryl ammonium synthesis, followed by diazotization of the amine for use as an aryl electrophile in substitution and cross coupling chemistry. Examination of the relationship between leaving group ability and hydrogen-bond accepting ability of the oxygen-based leaving group in the reagent is also warranted, as the two effects should be inversely correlated and could lead to identification of a more functional group tolerant reagent. We anticipate that our findings will inform further investigation and development of radical addition reactions for aromatic C–H functionalization.

4. CONCLUSION

C–H functionalization is an attractive synthetic strategy that transforms a typically unreactive functional group – the C–H bond – into a handle for diversification. π -Addition is a useful reaction mode for aromatic C–H functionalization, because it circumvents a difficult C–H bond cleavage (*i.e.* σ -bond activation) by forming the new C–X bond first. π -Addition reactions have been underappreciated and often deemed too harsh, unselective or narrowly applicable. This thesis aimed to highlight the advantages and disadvantages of previous π -addition methodologies and to contribute to that body of work by presenting two strategies for C–H functionalization through nucleophilic and radical addition to the aromatic π -system.

C–H hydroxylation with η^6 -arene complexes (Chapter 2) demonstrated the conceptual merging of two fundamental steps of a proposed catalytic cycle – nucleophilic attack and oxidation – and provided a complete synthetic cycle for the transformation of benzene to phenol. Of all π -addition reactions, nucleophilic aromatic substitution is by far the least used for C–H functionalization, which leaves much space for innovation. The use of η^6 -arene complexes for C–H functionalization has been prohibited by the use of expensive metals and harsh conditions. While we have not fully addressed these concerns, I hope our work provides inspiration and evidence that catalytic η^6 -arene chemistry is not a lost cause.

C–H amination with ammoniumyl radical precursors (Chapter 3) provided a practical advancement in the substrate scope of radical addition reactions and a conceptual explanation for the observed reactivity. The designation of radical reactions as uncontrollable and inherently limited has persisted in the chemical community. I hope our work joins a number of recent contributions that demonstrate how radical reactions can exceed expectations and be synthetically useful.

5. EXPERIMENTAL

5.1. Materials and methods

All manipulations were carried out under ambient atmosphere unless otherwise noted.

5.1.1. Solvents

Acetone was dried by distillation from B₂O₃. Anhydrous nitromethane was purchased from SigmaAldrich and used as received. HFIP was purchased from Oakwood Chemicals and used as received except where noted. Where it is noted that HFIP was distilled and degassed, HFIP was distilled from 3 Å molecular sieves and degassed by the freeze-pump-thaw method. Anhydrous diethyl ether, tetrahydrofuran, dichloromethane and acetonitrile were obtained by filtration through drying columns on an mBraun system.¹⁷⁵

5.1.2. Chromatography

Thin layer chromatography (TLC) was performed using EMD TLC silica gel 60 F₂₅₄ plates pre-coated with 250 µm thickness silica gel and visualized by fluorescence quenching under UV light and KMnO₄ stain. Preparative TLC was performed using Analtech Uniplates pre-coated with 1000 µm thickness silica gel GF. Flash chromatography was performed using silica gel (230-400 mesh) purchased from Silicycle Inc.

5.1.3. Spectroscopy and instruments

NMR spectra were recorded on either a Varian Unity/Inova 600 spectrometer operating at 600 MHz for ¹H acquisitions or a Varian Unity/Inova 500 spectrometer operating at 500 MHz, 470 MHz and 125 MHz for ¹H, ¹⁹F and ¹³C acquisitions, respectively or a Varian Mercury 400 spectrometer operating at 400 MHz

¹⁷⁵ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518–1520.

and 375 MHz for ^1H and ^{19}F acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance as the internal standard. For ^1H NMR: CDCl_3 , δ 7.26; CD_3CN , δ 1.94; $(\text{CD}_3)_2\text{CO}$, δ 2.05; $(\text{CD}_3)_2\text{SO}$, δ 2.50; CD_2Cl_2 , δ 5.32; CD_3OD , δ 3.31; CD_3NO_2 , δ 4.33. For ^{13}C NMR: CDCl_3 , δ 77.16; CD_3CN , δ 1.32; $(\text{CD}_3)_2\text{CO}$, δ 29.84; $(\text{CD}_3)_2\text{SO}$, δ 39.52; CD_2Cl_2 , δ 54.00; CD_3OD , δ 49.00; CD_3NO_2 , δ 62.8.¹⁷⁶ Chemical shifts for ^{19}F acquisitions were externally referenced to 3-nitro-1-fluorobenzene (δ -112.0). Data is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants in Hz; integration. High resolution mass spectra were obtained using an Agilent ESI-TOF (6220) mass spectrometer. IR spectra were recorded on a Bruker ALPHA FT-IR spectrometer. ICP-MS analysis was performed by Robertson Microlit Laboratories. Electrochemical measurements were made using a CH Instruments Model 600E Series Electrochemical Analyzer/Workstation.

5.1.4. Starting materials

All chemicals were used as received unless otherwise specified. NaClO_2 (technical grade, 80%) was purchased from Alfa Aesar. *m*CPBA was purchased from Sigma Aldrich, dissolved in DCM, washed with 0.1 M aqueous phosphate buffer pH = 7.5, dried over MgSO_4 , and used as a solution. $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ was ground into a fine powder before use.

5.1.5. Computational details

Density functional theory (DFT) calculations were performed using Gaussian09¹⁷⁷ at the computer cluster at the Max-Planck Institute für Kohlenforschung. Basis set I (BS I) includes 6-31G(d,p)¹⁷⁸ on H and 6-311G(d)⁸ on C, N, O, F, S.

¹⁷⁶ Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. *Organometallics* **2010**, 29, 2176–2179.

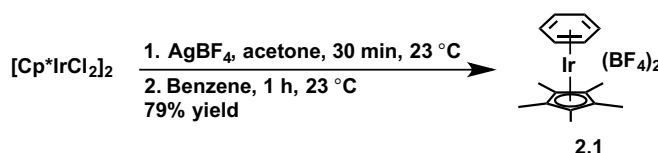
¹⁷⁷ Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.;

Geometry optimizations and frequency calculations were carried out at the ω B97XD¹⁷⁹/BS I level using the atomic coordinates of the crystal structure of **3.1**. Explicit solvent molecules have been added using GaussView5. The conductor-like polarizable continuum model (CPCM) has been used to simulate solvent effects (1,1,1,3,3,3-hexafluoro-2-propanol (HFIP), acetonitrile).¹⁸⁰ Ground state energies are given with respect to the thermal free energy correction at 298.15 K. Time-dependent DFT (TD-DFT) calculations have been carried out using the coordinates of the optimized ground state structures. Images of molecular structures and orbital plots were generated using GaussView5 and Chem3D.

5.2. Experimental details for chapter 2

5.2.1. Compound synthesis and characterization

$[(\eta^6\text{-Benzene})\text{IrCp}^*](\text{BF}_4)_2$ (**2.1**)



Preparation of complex **2.1** was adapted from the method of White et. al.¹⁵⁵ $[\text{Cp}^*\text{IrCl}_2]_2$ (300. mg, 0.377 mmol, 1.00 equiv) and AgBF_4 (293 mg, 1.51 mmol, 4.00 equiv) were added to a flame-dried round bottom flask. The flask was evacuated and backfilled with N_2 . Acetone (6 mL) was then added. The mixture was allowed to stir for 30 minutes at 23 °C, affording a yellow solution and an off-white

Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; J. A. Montgomery, J.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J. Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Normand, J. Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Cossi, J. M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adam, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D. Farkas, O.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J. Fox, D. J. *Gaussian 09, Revision D.01*; Gaussian, Inc.: Wallingford CT, **2013**.

¹⁷⁸ Harihara, P.C.; Pople, J. A. *Theor. Chim. Acta* **1973**, 28, 213–222.

¹⁷⁹ Chai, J.-D.; Head-Gordon, M. *Phys. Chem. Chem. Phys.* **2008**, 10, 6615–6620.

¹⁸⁰ a. Barone, V.; Cossi, M. *J. Phys. Chem. A* **1998**, 102, 1995–2001; Tomasi, J.; Mennucci, B.; Cammi, R. *Chem. Rev.* **2005**, 105, 2999–3094.

precipitate (AgCl). Filtration through glass wool afforded a clear yellow solution, to which benzene (3 mL) was added. The mixture was stirred for 1 h at 23 °C to give a pale yellow solution and the formation of a colorless precipitate. Et₂O (5 mL) was added to this mixture. Centrifugation, followed by decantation of the supernatant yielded a colorless solid that was washed with Et₂O (10 mL). This solid was dissolved in acetonitrile (10 mL). Et₂O (10 mL) was added to the solution affording a colorless precipitate. Centrifugation followed by decantation of the supernatant and drying under high vacuum yielded 346 mg of the title compound as a colorless solid (79% yield).

NMR spectroscopy:

¹H NMR (500 MHz, CD₃CN, 23 °C, δ): 7.27 (s, 6H), 2.32 (s, 15H).

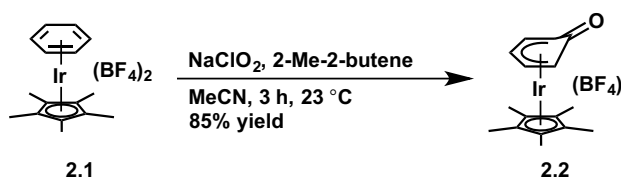
¹³C NMR (125 MHz, CD₃CN, 23 °C, δ): 107.2, 99.2, 10.6.

FT-IR spectroscopy: (neat, cm⁻¹): 3085, 1474, 1438, 1396, 1039, 1002, 522.

Elemental analysis: calc'd for C₁₆H₂₁B₂F₈Ir: C, 33.18; H, 3.65; found: C, 33.00; H, 3.79.

HRMS-FIA (m/z): calc'd for C₁₆H₂₁Ir [M]²⁺, 203.0636; found, 203.0633.

[(η⁵-Phenoxo)IrCp*](BF₄) (**2.2**)



Complex **2.1** (116 mg, 0.200 mmol, 1.00 equiv) was added to a flame-dried round bottom flask. Acetonitrile (10 mL), a solution of 2-methyl-2-butene in THF (0.800 mL, 1.60 mmol, 8.00 equiv, 2.0 M), and freshly powdered sodium chlorite (45.2 mg, 0.400 mmol, 2.00 equiv) were then added. The mixture was allowed to stir for 3 h at 23 °C. Filtration through glass wool afforded a clear, pale yellow solution. The filtrate was concentrated to 3 mL. Et₂O (10 mL) was added to the filtrate. Centrifugation followed by decantation of the supernatant yielded a tan residue. The residue was extracted with DCM (100 mL). The extracts were filtered through glass wool, concentrated to 10 mL and Et₂O (10 mL) added. Centrifugation

followed by decantation of the supernatant yielded a residue that was washed with Et₂O (10 mL) and dried under high vacuum to afford 86.7 mg of the title compound as a colorless solid (85% yield). Spectroscopic data match that reported for related compounds [(η⁵-phenoxo)IrCp*]PF₆ and [(η⁵-phenoxo)IrCp*]I.¹⁵⁸

NMR spectroscopy:

¹H NMR (500 MHz, CD₃CN, 23 °C, δ): 6.38 (t, *J* = 5.5 Hz, 1H), 6.27 (dd, *J* = 7.5, 5.5 Hz, 2H), 5.54 (d, *J* = 7.5 Hz, 2H), 2.18 (s, 15H).

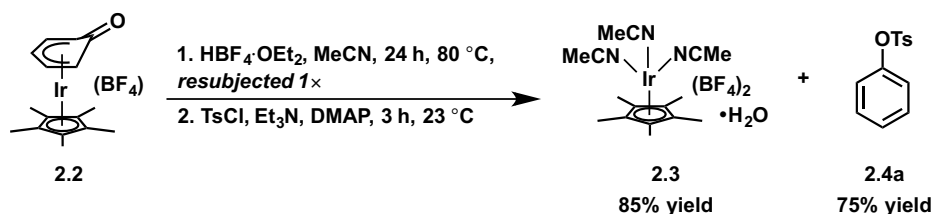
¹³C NMR (125 MHz, CD₃CN, 23 °C, δ): 163.8, 100.7, 96.0, 84.6, 81.5, 10.2.

FT-IR spectroscopy: (neat, cm⁻¹): 3091, 3033, 1633, 1597, 1470, 1392, 1050, 1036, 694, 522, 454.

Elemental analysis: calc'd for C₁₆H₂₀BF₄IrO: C, 37.88; H, 3.97; found: C, 37.68; H, 4.25.

HRMS-FIA (*m/z*): calc'd for C₁₆H₂₀OIr [M]⁺, 421.1143; found 421.1147.

[Tris(acetonitrile)IrCp*](BF₄)₂·H₂O (**2.3**)



Complex **2.2** (50.8 mg, 0.100 mmol, 1.00 equiv) was added to a flame-dried round bottom flask equipped with a reflux condenser. Acetonitrile (10 mL) and HBF₄·OEt₂ (27 μL, 0.20 mmol, 2.0 equiv) were added. The mixture was allowed to stir at 80 °C for 24 h. After cooling to ambient temperature, the reaction mixture was poured into Et₂O (100 mL). The oily precipitate was allowed to settle, and the supernatant was decanted and saved (see below). The residue was washed with Et₂O (10 mL) to afford crude material of 93% purity, as judged by ¹H NMR. The major impurity observed was the starting material, complex **2.2**. The crude material was added to a flame-dried round bottom flask equipped with a reflux condenser. Acetonitrile (10 mL) and HBF₄·OEt₂ (27 μL, 0.20 mmol, 2.0 equiv) were added. The mixture was allowed to stir at 80 °C for 24 h. After cooling to ambient temperature, the reaction mixture was poured

into Et₂O (100 mL). The oily precipitate was allowed to settle, and the supernatant was decanted. The residue was washed with Et₂O (10 mL) and dried under high vacuum to afford 54.4 mg of the title compound as a pale yellow solid (85% yield).

NMR spectroscopy:

¹H NMR (500 MHz, CD₃CN, 23 °C, δ): 1.96 (s, 9H), 1.75 (s, 15H).

¹³C NMR (125 MHz, CD₃NO₂, 23 °C, δ): 124.6, 94.7, 9.1, 3.7.

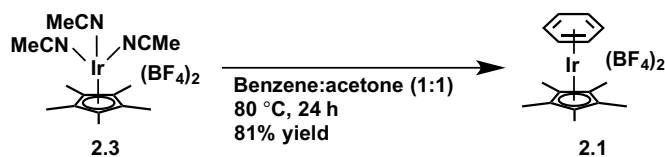
FT-IR spectroscopy: (neat, cm⁻¹): 3638, 3011, 2944, 2329, 2300, 1544, 1460, 1426, 1389, 1048, 1019, 520, 469.

Elemental analysis: calc'd for C₁₆H₂₄B₂F₈IrN₃O: C, 29.92; H, 4.08; N, 6.54; found: C, 30.22; H, 3.95; N, 6.64.

LRMS-FIA (m/z): calc'd for C₁₁H₁₅IrNaO₂ [M-(CH₃CN)₃-H⁺+Na⁺+(HCO₂)⁻]⁺, 395.0599; found 395.1087.

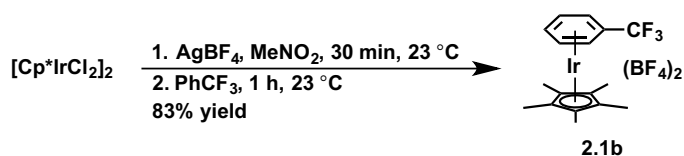
Isolation of phenyl tosylate (**2.4a**): Due to the volatility of phenol, the supernatant was concentrated to 20 mL, and *p*-toluenesulfonyl chloride (57.3 mg, 0.300 mmol, 3.00 equiv), 4-dimethylaminopyridine (12.2 mg, 0.100 mmol, 1.00 equiv), and triethylamine (123 μL, 0.900 mmol, 9.00 equiv) were added. The mixture was allowed to stir for 3 h at 23 °C. DCM (20 mL) and H₂O (20 mL) were added, and the reaction mixture was poured into a separatory funnel. The layers were separated. The aqueous layer was extracted with DCM (2 × 10 mL). The combined organic layers were washed with 1 M HCl_(aq) (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a solvent mixture of Et₂O/pentane (5:95 (v/v)) to afford 18.6 mg of the title compound as a colorless solid (75% yield). Spectroscopic data matched those described below for compound **2.4a**.

Regeneration of 2.1 from 2.3



Iridium complex **2.3** (62.4 mg, 0.100 mmol, 1.00 equiv) was added to a 20 mL scintillation vial. Acetone (2 mL) and benzene (2 mL) were added. The vial was sealed, and the reaction mixture was allowed to stir at 80 °C for 24 h. After cooling to ambient temperature, Et₂O (15 mL) was added to the reaction mixture. Centrifugation, followed by decantation of the supernatant gave a yellow-brown residue. Acetonitrile (3 mL) was added to the crude material, and the mixture was filtered through glass wool to give a yellow filtrate. Et₂O (10 mL) was added to the filtrate to afford a colorless precipitate. Centrifugation, followed by decantation of the supernatant yielded a residue that was washed with Et₂O (10 mL) and dried under high vacuum to afford 46.8 mg of **2.1** as a colorless solid (81% yield). Spectroscopic data matched those described above for compound **2.1**.

[(η^6 -Trifluoromethylbenzene)IrCp*](BF₄)₂ (2.1b**)**



[Cp*IrCl₂]₂ (300. mg, 0.377 mmol, 1.00 equiv) and AgBF₄ (293 mg, 1.51 mmol, 4.00 equiv) were added to a flame-dried round bottom flask. The flask was evacuated and backfilled with N₂. Nitromethane (6 mL) was then added. The mixture was allowed to stir for 30 minutes at 23 °C, affording an orange solution and an off-white precipitate (AgCl). Filtration through glass wool afforded a clear orange solution, to which trifluoromethylbenzene (2 mL) was added. The mixture was stirred for 1 h at 23 °C to give a pale tan solution and the formation of a colorless precipitate. Et₂O (5 mL) was added to this mixture. Centrifugation followed by decantation of the supernatant yielded a colorless solid that was washed with Et₂O (10 mL). Acetonitrile (20 mL) was added to the crude material. The mixture was filtered through glass wool, and the filtrate was concentrated to approximately 4 mL. Et₂O (15 mL) was

added to afford a colorless precipitate. Centrifugation followed by decantation of the supernatant and drying under high vacuum yielded a residue that was washed with Et₂O (10 mL) to afford 403 mg of the title compound as a colorless solid (83% yield).

NMR spectroscopy:

¹H NMR (500 MHz, CD₃CN, 23 °C, δ): 7.75 (d, *J* = 6.8 Hz, 2H), 7.56–7.49 (m, 3H), 2.34 (s, 15H).

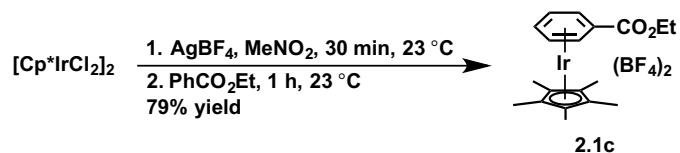
¹³C NMR (125 MHz, CD₃NO₂, 23 °C, δ): 122.8 (q, *J* = 275.4 Hz), 110.8, 103.3 (q, *J* = 39.1 Hz), 102.4, 100.1, 97.0, 10.4.

¹⁹F NMR (471 MHz, CD₃CN, 23 °C, δ): –63.4, –151.4.

Elemental analysis: calc'd for C₁₇H₂₀B₂F₁₁Ir: C, 31.55; H, 3.12; found: C, 31.61; H, 3.17.

HRMS-FIA (m/z): calc'd for C₁₇H₂₀F₃Ir [M]²⁺, 237.0573; not found; calc'd for C₁₇H₂₁F₃IrO [M+OH]⁺, 491.1174; found 491.1194.

[(η⁶-Ethyl benzoate)IrCp*](BF₄)₂ (2.1c)



[Cp*IrCl₂]₂ (300. mg, 0.377 mmol, 1.00 equiv) and AgBF₄ (293 mg, 1.51 mmol, 4.00 equiv) were added to a flame-dried round bottom flask. The flask was evacuated and backfilled with N₂. Nitromethane (6 mL) was then added. The mixture was allowed to stir for 30 minutes at 23 °C, affording an orange solution and an off-white precipitate (AgCl). Filtration through glass wool afforded a clear orange solution, to which ethyl benzoate (2 mL) was added. The mixture was stirred for 1 h at 23 °C to give a pale tan solution and the formation of a colorless precipitate. Et₂O (5 mL) was added to this mixture. Centrifugation followed by decantation of the supernatant yielded a colorless solid that was washed with Et₂O (10 mL). Acetonitrile (50 mL) was added to the crude material. The mixture was filtered through glass wool, and the filtrate was concentrated to approximately 5 mL. Et₂O (10 mL) was added to afford a

colorless precipitate. Centrifugation followed by decantation of the supernatant yielded a residue that was washed with Et₂O (5 mL) and dried under high vacuum to afford 387 mg of the title compound as a colorless solid (79% yield).

NMR spectroscopy:

¹H NMR (600 MHz, CD₃CN, 23 °C, δ): 7.72 (br, 2H), 7.45 (br, 3H), 4.58 (q, *J* = 7.1 Hz, 2H), 2.29 (s, 15H), 1.47 (t, *J* = 7.2 Hz, 3H).

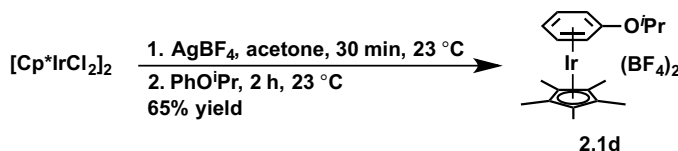
¹³C NMR (125 MHz, CD₃NO₂, 23 °C, δ): 161.8, 109.4, 101.7, 100.4, 100.2, 99.2, 67.1, 14.4, 10.4.

FT-IR spectroscopy: (neat, cm⁻¹): 3091, 2988, 2945, 1745, 1469, 1395, 1297, 1031, 1009, 777, 522, 472.

Elemental analysis: calc'd for C₁₉H₂₅B₂F₈IrO₂: C, 35.04; H, 3.87; found: C, 35.10; H, 3.91.

HRMS-FIA (*m/z*): calc'd for C₁₉H₂₅IrO₂ [M]²⁺, 239.07421; not found; calc'd for C₁₉H₂₆IrO₃ [M+OH]⁺, 495.1511; found, 495.1528.

[(η⁶-Isopropoxybenzene)IrCp*](BF₄)₂ (2.1d)



[Cp*IrCl₂]₂ (300. mg, 0.377 mmol, 1.00 equiv) and AgBF₄ (293 mg, 1.51 mmol, 4.00 equiv) were added to a flame-dried round bottom flask. The flask was evacuated and backfilled with N₂. Acetone (6 mL) was then added. The mixture was allowed to stir for 30 minutes at 23 °C, affording a yellow solution and an off-white precipitate (AgCl). Filtration through glass wool afforded a clear yellow solution, to which isopropoxybenzene (1 mL) was added. The mixture was stirred for 2 h at 23 °C to give a pale yellow solution and the formation of a colorless precipitate. Et₂O (5 mL) was added to this mixture. Centrifugation followed by decantation of the supernatant yielded a colorless solid that was washed with Et₂O (10 mL). Acetonitrile (20 mL) was added to the crude material. The mixture was filtered through glass wool, and the filtrate was concentrated to approximately 2 mL. Et₂O (10 mL) was added to afford a

colorless precipitate. Centrifugation followed by decantation of the supernatant yielded a residue that was washed with Et₂O (10 mL) to afford 315 mg of the title compound as a colorless solid (65% yield).

NMR spectroscopy:

¹H NMR (600 MHz, CD₃CN, 23 °C, δ): 7.09 (dd, *J* = 7.2, 5.4 Hz, 2H), 7.04 (d, *J* = 6.9 Hz, 2H), 6.98 (t, *J* = 5.4 Hz, 1H), 4.83 (sep, *J* = 6.0 Hz, 1 H), 2.27 (s, 15H), 1.43 (d, *J* = 6.1 Hz, 6H).

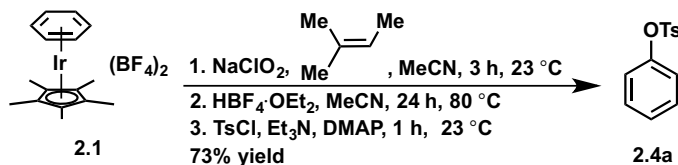
¹³C NMR (125 MHz, CD₃CN, 23 °C, δ): 145.3, 106.0, 97.9, 93.9, 84.8, 79.0, 21.6, 10.4.

FT-IR spectroscopy: (neat, cm⁻¹): 3106, 3092, 2993, 1535, 1466, 1387, 1275, 1052, 1015, 915, 669, 519, 468.

Elemental analysis: calc'd for C₁₉H₂₇B₂F₈IrO: C, 35.81; H, 4.27; found: C, 35.81; H, 4.23.

HRMS-FIA (m/z): calc'd for C₁₉H₂₇IrO [M]²⁺, 232.0846; not found; calc'd for C₁₆H₂₁IrO [M-C₃H₇+H]²⁺, 211.0611; found, 211.0598.

Phenyl *p*-toluenesulfonate (2.4a)



Iridium complex **2.1** (116 mg, 0.200 mmol, 1.00 equiv) was added to a flame-dried round bottom flask. Acetonitrile (10 mL), a solution of 2-methyl-2-butene in THF (0.800 mL, 1.60 mmol, 8.00 equiv, 2.0 M), and freshly powdered sodium chlorite (45.2 mg, 0.400 mmol, 2.00 equiv) were then added. The mixture was allowed to stir for 3 h at 23 °C. Filtration through glass wool afforded a clear, pale yellow solution. The filtrate was concentrated to 2 mL, and Et₂O (15 mL) was added. The mixture was centrifuged, and the supernatant decanted. The precipitate was dissolved in acetonitrile (10 mL) and transferred to a flame-dried round bottom flask equipped with a reflux condenser. HBF₄·OEt₂ (55 μL, 0.40 mmol, 2.0 equiv) was then added. The mixture was allowed to stir for 24 h at 80 °C. After cooling to ambient temperature, the reaction mixture was filtered over a plug of silica and washed with Et₂O (200 mL). Due to the volatility of phenol, the filtrate was concentrated to 10 mL at 23 °C, and *p*-toluenesulfonyl chloride (38.1

mg, 0.200 mmol, 1.00 equiv), 4-(dimethylamino)pyridine (2.4 mg, 0.020 mmol, 0.10 equiv), and triethylamine (84 μ L, 0.60 mmol, 3.0 equiv) were added. The mixture was allowed to stir for 1 h at 23 °C. DCM (20 mL) and H₂O (20 mL) were added, and the reaction mixture was poured into a separatory funnel. The layers were separated. The aqueous layer was extracted with DCM (2 $\times$ 10 mL). The combined organic layers were washed with 1 M HCl_(aq) (10 mL) and brine (10 mL), dried over MgSO₄, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a solvent mixture of Et₂O/pentane (5:95 (v/v)) to afford 36.2 mg of the title compound as a colorless solid (73% yield). Spectroscopic data match previously reported data.¹⁸¹

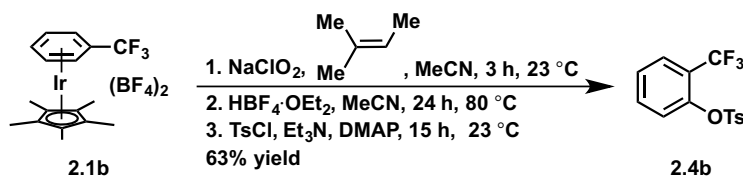
NMR spectroscopy:

¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.71 (d, J = 8.4 Hz, 2H), 7.32–7.22 (m, 5H), 6.98 (d, J = 8.4 Hz, 2H), 2.45 (s, 3H).

¹³C NMR (125 MHz, CD₃CN, 23 °C, δ): (125 MHz, CDCl₃, 23 °C, δ): 149.8, 145.4, 132.6, 129.9, 129.7, 128.7, 127.2, 122.5, 21.9.

HRMS-FIA (m/z): calc'd for C₁₃H₁₃O₃S [M+H]⁺, 249.0585; found, 249.0571.

2-Trifluoromethylphenyl *p*-toluenesulfonate (2.4b)



Iridium complex **2.1b** (129 mg, 0.200 mmol, 1.00 equiv) was added to a flame-dried round bottom flask. Acetonitrile (10 mL), a solution of 2-methyl-2-butene in THF (0.800 mL, 1.60 mmol, 8.00 equiv, 2.0 M), and freshly powdered sodium chlorite (45.2 mg, 0.400 mmol, 2.00 equiv) were then added. The mixture was allowed to stir for 3 h at 23 °C. Filtration through glass wool afforded a clear, pale yellow solution. The filtrate was concentrated to 2 mL, and Et₂O (15 mL) was added. Once the solid had settled, the supernatant was decanted. The precipitate was dissolved in acetonitrile (10 mL) and transferred to a

¹⁸¹ Laha, J. K.; Jethava, K. P.; Dayal, N. *J. Org. Chem.* **2014**, 79, 8010–8019.

flame-dried round bottom flask equipped with a reflux condenser. $\text{HBF}_4 \cdot \text{OEt}_2$ (55 μL , 0.40 mmol, 2.0 equiv) was then added. The mixture was allowed to stir for 24 h at 80 $^\circ\text{C}$. After cooling to ambient temperature, the reaction mixture was filtered over a plug of silica and washed with Et_2O (200 mL). Due to volatility of phenol, the filtrate was concentrated to 20 mL, and *p*-toluenesulfonyl chloride (38.1 mg, 0.200 mmol, 1.00 equiv), 4-dimethylaminopyridine (2.4 mg, 0.020 mmol, 0.10 equiv), and triethylamine (84 μL , 0.60 mmol, 3.0 equiv) were added. The mixture was allowed to stir for 15 h at 23 $^\circ\text{C}$. DCM (20 mL) and H_2O (20 mL) were added, and the reaction mixture was poured into a separatory funnel. The layers were separated. The aqueous layer was extracted with DCM (2×10 mL). The combined organic layers were washed with 1 M $\text{HCl}_{(\text{aq})}$ (10 mL) and brine (10 mL), dried over MgSO_4 , filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a solvent mixture of Et_2O /pentane (5:95 (v/v)) to afford 39.9 mg of the title compound as a colorless solid (63% yield).

NMR spectroscopy:

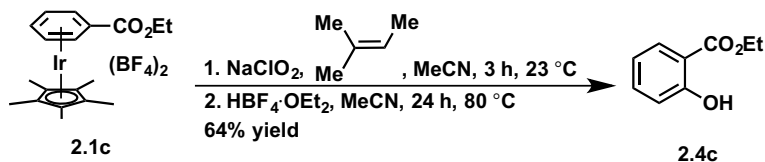
^1H NMR (500 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): 7.83 (d, $J = 8.4$ Hz, 2H), 7.65–7.54 (m, 3H), 7.38–7.32 (m, 3H), 2.46 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): 147.1, 146.0, 133.4, 132.8, 130.0, 128.6, 127.6, 126.6, 123.0 (q, $J = 31.5$ Hz), 122.8, 122.5 (q, $J = 271.6$ Hz), 21.8.

^{19}F NMR (471 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): –56.7.

HRMS-FIA (m/z): calc'd for $\text{C}_{14}\text{H}_{11}\text{F}_3\text{NaO}_3\text{S}$ $[\text{M}+\text{Na}]^+$, 339.0279; found, 339.0275.

Ethyl salicylate (2.4c)



Iridium complex **2.1c** (130. mg, 0.200 mmol, 1.00 equiv) was added to a flame-dried round bottom flask. Acetonitrile (10 mL), a solution of 2-methyl-2-butene in THF (0.800 mL, 1.60 mmol, 8.00 equiv, 2.0 M),

and freshly powdered sodium chlorite (45.2 mg, 0.400 mmol, 2.00 equiv) were then added. The mixture was allowed to stir for 3 h at 23 °C. Filtration through glass wool afforded a clear, pale yellow solution. The filtrate was concentrated to 2 mL, and Et₂O (15 mL) was added. The mixture was centrifuged and the supernatant was decanted. The precipitate was dissolved in acetonitrile (10 mL) and transferred to a flame-dried round bottom flask equipped with a reflux condenser. HBF₄·OEt₂ (55 µL, 0.40 mmol, 2.0 equiv) was then added. The mixture was allowed to stir for 24 h at 80 °C. After cooling to ambient temperature, the reaction mixture was filtered over a plug of silica and washed with Et₂O (200 mL). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel eluting with a solvent mixture of Et₂O/pentane (1:200 (v/v)) to afford 21.2 mg of the title compound as a colorless oil (64% yield). Spectroscopic data matched that of an authentic sample purchased from Alfa Aesar.

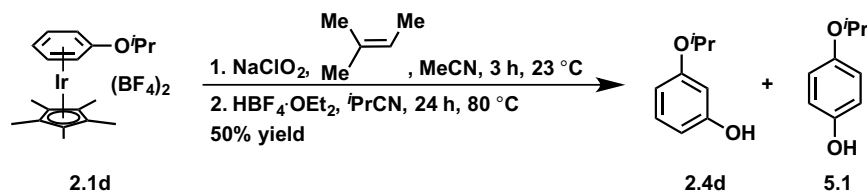
NMR spectroscopy:

¹H NMR (600 MHz, CDCl₃, 23 °C, δ): 10.84 (s, 1H), 7.85 (dd, *J* = 8.0, 1.7 Hz, 1H), 7.45 (ddd, *J* = 8.5, 7.2, 1.7 Hz, 1H), 6.98 (dd, *J* = 8.4, 0.9 Hz, 1H), 6.87 (dd, *J* = 7.6, 7.6 Hz, 1H), 4.41 (q, *J* = 7.1 Hz, 2H), 1.42 (t, *J* = 7.2 Hz, 3H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 170.3, 161.8, 135.7, 130.0, 119.2, 117.7, 112.8, 61.5, 14.3.

HRMS-FIA (*m/z*): calc'd for C₉H₁₁O₃ [M+H]⁺, 167.0703; found, 167.0699.

3-Isopropoxyphenol (2.4d) and 4-isopropoxyphenol (5.1)



Iridium complex **2.1d** (128 mg, 0.200 mmol, 1.00 equiv) was added to a flame-dried round bottom flask. Acetonitrile (10 mL), a solution of 2-methyl-2-butene in THF (0.800 mL, 1.60 mmol, 8.00 equiv, 2.0 M),

and freshly powdered sodium chlorite (45.2 mg, 0.400 mmol, 2.00 equiv) were then added. The mixture was allowed to stir for 3 h at 23 °C. Filtration through glass wool afforded a clear, pale yellow solution. The filtrate was concentrated to 2 mL, and Et₂O (15 mL) was added. Once the solid had settled, the supernatant was decanted. The precipitate was dissolved in isobutyronitrile (10 mL) and transferred to a flame-dried round bottom flask equipped with a reflux condenser. HBF₄·OEt₂ (55 µL, 0.40 mmol, 2.0 equiv) was then added. The mixture was allowed to stir for 24 h at 80 °C. After cooling to ambient temperature, the reaction mixture was filtered over a plug of silica and washed with Et₂O (200 mL). The filtrate was concentrated, and the residue was purified by column chromatography on silica gel eluting with a solvent mixture of Et₂O/pentane (1:9 (v/v)) to afford 14.9 mg of the title mixture (95:5 **2.4d**:**5.1** determined by ¹H NMR spectroscopy) as a colorless oil (50% yield). Spectroscopic data match previously reported data.¹⁸²

NMR spectroscopy:

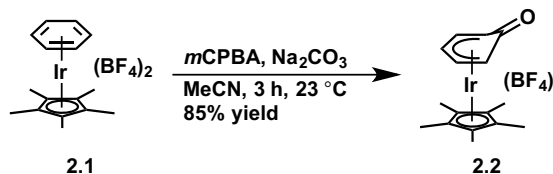
¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.11 (dd, *J* = 8.5, 8.5 Hz, 1H), 6.80* (d, *J* = 9.1 Hz, 2H), 6.75* (d, *J* = 9.1 Hz, 2H), 6.48 (ddd, *J* = 8.3, 2.2, 0.9 Hz, 1H), 6.41-6.39 (m, 2H), 4.93 (br, 1H), 4.51 (sep, *J* = 6.1 Hz, 1H), 4.41* (sep, *J* = 6.1 Hz, 1H), 1.33 (d, *J* = 6.1 Hz, 6H), 1.33* (d, *J* = 6.1 Hz, 6H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 159.4, 156.8, 130.2, 108.5, 107.7, 103.5, 70.2, 22.2.

*Indicates signals from minor isomer (**5.1**). ¹³C-NMR signals could not be detected for **5.1**.

HRMS-FIA (m/z): calc'd for C₉H₁₃O₂ [M+H]⁺, 153.0916; found, 153.0925.

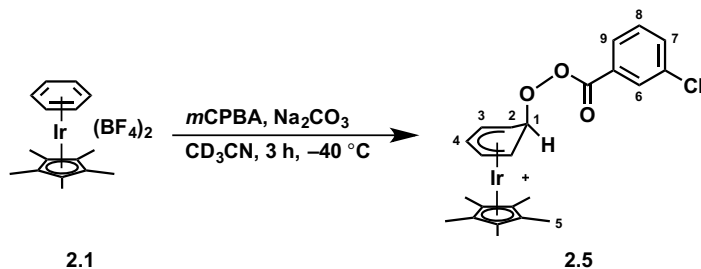
Reaction of 2.1 with *m*CPBA



¹⁸² a. Boxhall, J. Y.; Page, P. C. B.; Chan, Y.; Hayman, C. M.; Heaney, H.; McGrath, M. J. *Synlett* **2003**, 997–1001; b. Gu, Y. G. *et. al. J. Med. Chem.* **2006**, 49, 3770–3773.

Iridium complex **2.1** (57.9 mg, 0.100 mmol, 1.00 equiv) and sodium carbonate (106 mg, 1.00 mmol, 10.0 equiv) were added to a round bottom flask. Acetonitrile (5 mL) was added, followed by a solution of *m*CPBA in DCM (1.00 mL, 0.100 mmol, 1.00 equiv, 0.10 M). Reaction mixture was allowed to stir for 3 h at 23 °C, during which time the mixture became cloudy with colorless precipitate. The reaction mixture was filtered over glass wool. The filtrate was then concentrated to 2 mL and Et₂O (10 mL) was added affording a colorless precipitate. Centrifugation, followed by decantation of the supernatant yielded a colorless solid. The solid was extracted with DCM (100 mL). The extracts were filtered through glass wool, concentrated to 10 mL and Et₂O (10 mL) added. Centrifugation, followed by decantation of the supernatant yielded a colorless solid that was washed with Et₂O (10 mL) and dried under high vacuum to afford 43.0 mg of **2.2** as a colorless solid (85% yield). Spectroscopic data matched those described above for compound **2.2**. The byproduct of this reaction is sodium *m*-chlorobenzoate.

η^5 -Cyclohexadienyl adduct of *m*CPBA and **2.1** (**2.5**)



Complex **2.1** (17.3 mg, 0.0300 mmol, 1.00 equiv) and Na₂CO₃ (63.6 mg, 0.600 mmol, 20.0 equiv) were added to a NMR tube. A solution of *m*CPBA in CD₃CN (1.00 mL, 0.0300 mmol, 1.00 equiv, 0.030 M) was added, the tube was inverted once, and immediately placed into the pre-cooled (−40 °C) NMR machine.

NMR spectroscopy:

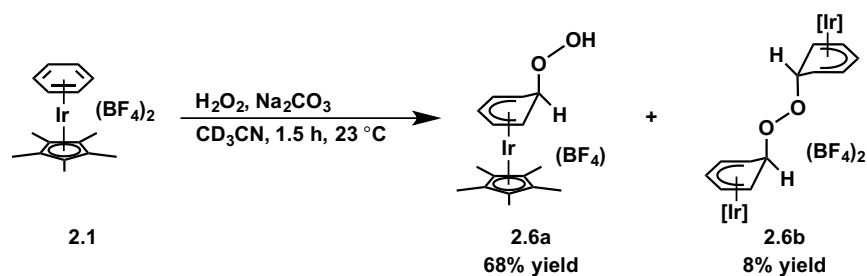
¹H NMR (500 MHz, CD₃CN, −40 °C, δ): 7.87 (s, 1H, H₆), 7.79 (d, *J* = 7.9 Hz, 1H, H₉), 7.68 (d, *J* = 8.1 Hz, 1H, H₇), 7.51 (dd, *J* = 8.0, 8.0 Hz, 1H, H₈), 6.47 (t, *J* = 5.2 Hz, 1H, H₄), 5.50 (dd, *J* =

5.8, 5.8 Hz, 2H, H3), 4.89 (t, $J = 6.0$ Hz, 1H, H1), 4.43 (dd, $J = 6.1$ Hz, 6.1 Hz, 2H, H2), 2.14 (s, 15H, H5).

^{13}C NMR (125 MHz, CD_3CN , -40°C , δ): 134.4 (C7), 131.3 (C8), 129.2 (C6), 128.1 (C9), 88.5 (C3), 87.3 (C4), 72.8 (C1), 45.9 (C2), 9.9 (C5).

NMR spectra also contain complex **2.1**, complex **2.2**, *m*CPBA, and *m*-chlorobenzoic acid.

Monoalkylated η^5 -cyclohexadienyl adduct of H_2O_2 and **2.1** (**2.6a**)



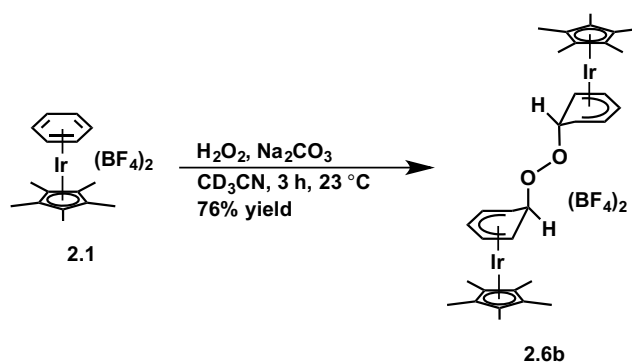
Complex **2.1** (29.0 mg, 0.0500 mmol, 1.00 equiv), Na_2CO_3 (10.6 mg, 0.100 mmol, 2.00 equiv), CD_3CN (1.0 mL) and H_2O_2 (aq.) (28 μL , 0.25 mmol, 5.0 equiv, 30 wt%) were added to a 4 mL scintillation vial. The mixture was allowed to stir for 1.5 h at 23°C . The mixture was filtered through glass wool into an NMR tube. The yield of the title compound was determined by internal standard (dioxane) to be 68%. Dimeric adduct **2.6b** (see below) was observed in 8% yield.

NMR spectroscopy:

^1H NMR (600 MHz, CD_3CN , 23°C , δ): 9.78 (br, 1H), 6.40 (t, $J = 5.2$ Hz, 1H), 5.39 (dd, $J = 5.8$ Hz, 5.8 Hz, 2H), 4.35 (t, $J = 5.9$ Hz, 1H), 4.26 (dd, $J = 5.9$ Hz, 5.9 Hz, 2H), 2.15 (s, 15H).

^{13}C NMR (125 MHz, CD_3CN , 23°C , δ): 98.9, 88.8, 87.5, 71.9, 47.2, 10.3.

Bisalkylated η^5 -cyclohexadienyl adduct of H_2O_2 and **2.1** (**2.6b**)



Complex **2.1** (116 mg, 0.200 mmol, 1.00 equiv), Na_2CO_3 (106 mg, 1.00 mmol, 5.00 equiv), acetonitrile (10 mL), and H_2O_2 (aq.) (14 μL , 0.12 mmol, 0.60 equiv, 30 wt%) were added to a 20 mL scintillation vial. The mixture was allowed to stir for 3 h at 23 $^\circ\text{C}$. The mixture was filtered through glass wool and the filtrate was concentrated to 3 mL. The solid residue was extracted with DCM (50 mL), filtered and the filtrate was concentrated. The solid residue was dissolved in acetonitrile (10 mL) and NaBF_4 (400 mg) was added. The mixture was stirred for 3 h at 23 $^\circ\text{C}$. The mixture was filtered through glass wool and the filtrate was concentrated. The solid residue was extracted with DCM (50 mL), filtered, and the filtrate was concentrated to afford 77.8 mg of the title compound as a colorless solid (76% yield).

NMR spectroscopy:

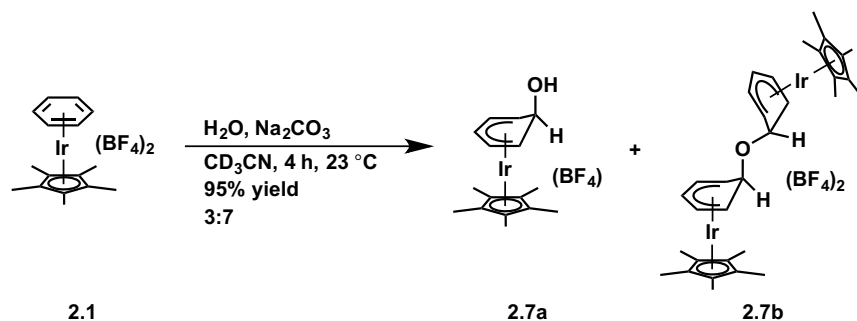
^1H NMR (600 MHz, CD_3CN , 23 $^\circ\text{C}$, δ): 6.38 (t, $J = 5.3$ Hz, 2H), 5.38 (dd, $J = 5.9$ Hz, 5.9 Hz, 4H), 4.26 (t, $J = 5.9$ Hz, 2H), 4.18 (dd, $J = 6.1$ Hz, 6.1 Hz, 4H), 2.15 (s, 30H).

^{13}C NMR (125 MHz, CD_3CN , 23 $^\circ\text{C}$, δ): 99.0, 88.8, 87.6, 70.9, 47.4, 10.3.

Elemental analysis: calc'd for $\text{C}_{32}\text{H}_{42}\text{B}_2\text{F}_8\text{Ir}_2\text{O}_2$: C, 37.80; H, 4.16; found: C, 38.03; H, 4.14.

Adduct **2.6b** decomposes to give complex **2.2** upon standing in CD_3CN solution. Complex **2.2** is generated in 5% yield after 5 d at 23 $^\circ\text{C}$.

Mono- and bisalkylated η^5 -cyclohexadienyl adduct of H_2O and **2.1** (**2.7a**, **2.7b**)



Complex **2.1** (57.9 mg, 0.100 mmol, 1.00 equiv), Na₂CO₃ (212 mg, 2.00 mmol, 20.0 equiv), acetonitrile (5 mL), and H₂O (9.0 μ L, 0.50 mmol, 5.0 equiv) were added to a 20 mL scintillation vial. The mixture was allowed to stir for 4 h at 23 °C. The mixture was filtered through glass wool and the filtrate was concentrated to 2 mL. Et₂O (15 mL) was added. Centrifugation, followed by decantation of the supernatant and drying under high vacuum afforded 50.1 mg of a 3:7 mixture of the title compounds as a colorless solid (95% yield). This solid also contained NaBF₄; the reported yield accounts for this impurity as judged from elemental analysis results.

NMR spectroscopy:

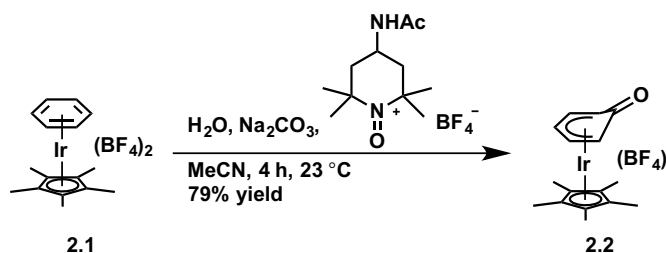
¹H NMR (600 MHz, CD₃CN, 23 °C, δ): 6.39* (t, J = 5.2 Hz, 1H), 6.35 (t, J = 5.2 Hz, 2H), 5.28* (dd, J = 6.5 Hz, 5.4 Hz, 2H), 5.22 (dd, J = 5.9, 5.9 Hz, 4H), 4.28* (dd, J = 6.4, 6.4 Hz, 2H), 4.18 (dd, J = 6.3, 6.3 Hz, 4H), 3.95* (dt, J = 7.2, 6.2 Hz, 1H), 3.88 (t, 6.1 Hz, 2H), 3.30* (d, J = 7.4 Hz, 1H), *2.15 (s, 15H), 2.14 (s, 30H).

¹³C NMR (125 MHz, CD₃CN, 23 °C, δ): 98.6, 98.4, 87.6, 87.6, 87.5, 87.4, 87.3, 87.3, 63.4, 59.0, 51.2, 48.6, 10.3, 10.3.

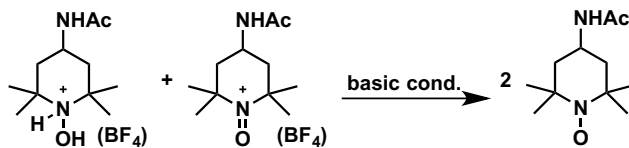
*Indicates signals from minor isomer **2.7a**; ¹³C NMR signals for minor isomer could not be fully assigned due to overlapping. ¹³C NMR data was obtained by performing the reaction above in CD₃CN (1.0 mL), filtering after completion, transferring to an NMR tube and directly measuring the reaction mixture.

Elemental analysis: found for a mixture containing 0.22 **2.7a** (C₁₆H₂₂BF₄IrO) : 0.53 **2.7b** (C₃₂H₄₂B₂F₈Ir₂O₂) : 0.25 NaBF₄: C, 28.51; H, 3.16.

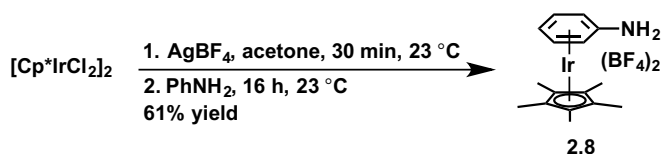
Reaction of **2.1** with H₂O, Na₂CO₃, and [4-NHAc-TEMPO]BF₄



Iridium complex **2.1** (57.9 mg, 0.100 mmol, 1.00 equiv), sodium carbonate (212 mg, 2.00 mmol, 20.0 equiv), and [4-NHAc-TEMPO]BF₄ (60.0 mg, 0.200 mmol, 2.00 equiv) were added to a 20 mL scintillation vial. Acetonitrile (5 mL) and water (9.0 μ L, 0.50 mmol, 5.0 equiv) were added. Reaction mixture was allowed to stir for 4 h at 23 °C. The reaction mixture was filtered over glass wool. The filtrate was then concentrated to 2 mL and Et₂O (15 mL) was added affording a colorless precipitate. Centrifugation, followed by decantation of the supernatant yielded a colorless solid. The solid was extracted with DCM (50 mL). The extracts were filtered through glass wool and concentrated. The solid residue was dissolved in acetonitrile (2 mL) and Et₂O was added (10 mL) to afford a colorless precipitate. Centrifugation, followed by decantation of the supernatant yielded a colorless solid that was washed with Et₂O (10 mL) to afford 40.1 mg of **2.2** as a colorless solid (79% yield). Spectroscopic data matched those described above for compound **2.2**. The byproduct of this reaction is 4-NHAc-TEMPO, which forms from comproportionation of [4-NHAc-TEMPOH₂]⁺BF₄⁻ and [4-NHAc-TEMPO][•]BF₄⁻.¹⁶¹



[(η^6 -Aniline)IrCp*](BF₄)₂ (**2.8**)



[Cp*IrCl₂]₂ (300. mg, 0.377 mmol, 1.00 equiv) and AgBF₄ (293 mg, 1.51 mmol, 4.00 equiv) were added to a 20-mL vial. Acetone (6 mL) was then added. The mixture was allowed to stir for 30 minutes at 23 °C, affording a yellow solution and an off-white precipitate (AgCl). Filtration through glass wool afforded a clear yellow solution, to which aniline (68.8 μL, 0.754 mmol, 2.00 equiv) was added. The mixture was stirred for 16 h at 23 °C to give a red solution and the formation of a colorless precipitate. Centrifugation followed by decantation of the supernatant yielded a colorless solid that was washed with Et₂O (2×10 mL) to afford 274 mg of the title compound as a colorless solid (61% yield). Spectroscopic data matched previously reported data.¹⁶⁶

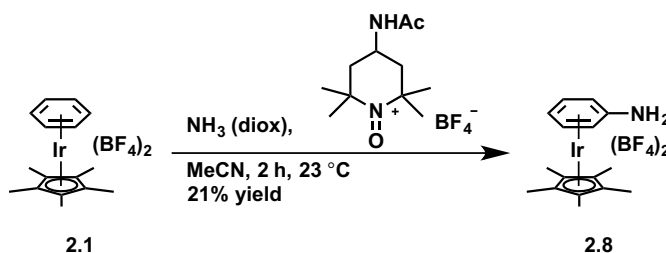
NMR spectroscopy:

¹H NMR (500 MHz, CD₃CN, 23 °C, δ): 6.76–6.71 (m, 3H), 6.47–6.43 (m, 2H), 6.34 (br s, 2H), 2.20 (s, 15H).

¹³C NMR (125 MHz, CD₃CN, 23 °C, δ): 141.2, 103.8, 96.0, 89.7, 77.1, 9.9.

HRMS-FIA (m/z): calc'd for C₁₆H₂₂IrN [M]²⁺, 210.5691; found, 210.5701.

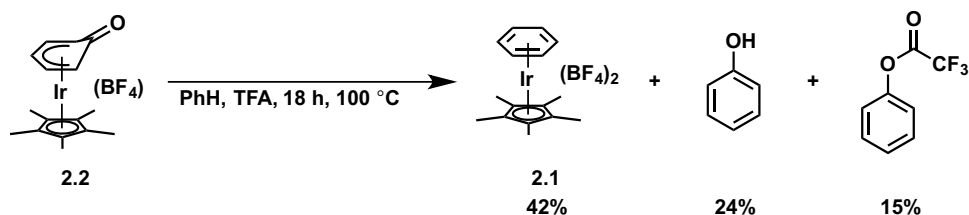
Reaction of **2.1** with NH₃ and [4-NHAc-TEMPO]BF₄



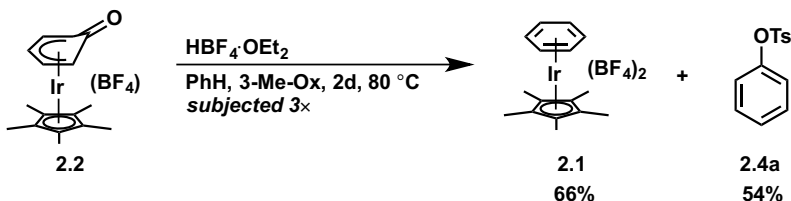
Iridium complex **2.1** (5.8 mg, 0.010 mmol, 1.0 equiv) and [4-NHAc-TEMPO]BF₄ (6.0 mg, 0.020 mmol, 2.0 equiv) were added to a 4 mL scintillation vial. Acetonitrile (700 μL) and a solution of ammonia in dioxane (100. μL, 0.050 mmol, 5.0 equiv, c = 0.5 M) were added. The reaction mixture was allowed to stir for 2 h at 23 °C. The reaction mixture was concentrated. The residue was dissolved in CD₃CN and an internal standard was added (MeNO₂, 2.0 μL). The yield of complex **2.8** (21%) was determined by integration versus the internal standard.

5.2.2. Mechanistic experiments

Arene exchange reactions



Iridium complex **2.1** (25.4 mg, 0.0500 mmol, 1.00 equiv), benzene (0.250 mL) and trifluoroacetic acid (0.250 mL) were added to a 4 mL scintillation vial. The reaction mixture was allowed to stir at 100 °C for 18 h. After cooling to room temperature, Et₂O (3 mL) was added. Centrifugation, followed by decantation of the supernatant afforded a colorless precipitate. The supernatant was set aside and saved (see below). The precipitate was dried under high vacuum and was analyzed by ¹H NMR spectroscopy to contain **2.1** and **2.2**. The yield of **2.1** was determined by integration against an internal standard (nitromethane, 2 μL) to be 42%. The supernatant was concentrated and was analyzed by ¹H NMR spectroscopy to contain phenol, phenyl trifluoroacetate and **2.2**. The yield of phenol was determined by integration against an internal standard (nitromethane, 2 μL) to be 24%, and the yield of phenyl trifluoroacetate was determined to be 15%.



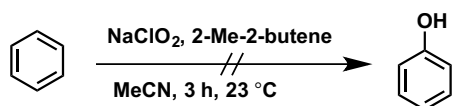
Iridium complex **2.1** (10.2 mg, 0.0200 mmol, 1.00 equiv), benzene (0.20 mL), 3-methyl-2-oxazolidinone (0.20 mL) and HBF₄·OEt₂ (5.0 μL, 0.040 mmol, 2.0 equiv) were added to a 4 mL scintillation vial. The reaction mixture was allowed to stir at 80 °C for 2 d. After cooling to room temperature, Et₂O (3 mL) was added. Centrifugation, followed by decantation of the supernatant afforded a brown oil. The supernatant was set aside and saved (see below). The brown oil was dissolved in 3-methyl-2-oxazolidinone (0.20 mL). Benzene (0.20 mL) and HBF₄·OEt₂ (5.0 μL, 0.040 mmol, 2.0 equiv) were added. The reaction

mixture was again allowed to stir at 80 °C for 2 d. The workup described above was repeated, and the supernatant was again saved. The resulting brown oil was dissolved in 3-methyl-2-oxazolidinone (0.20 mL) for a final time. Benzene (0.20 mL) and $\text{HBF}_4 \cdot \text{OEt}_2$ (5.0 μL , 0.040 mmol, 2.0 equiv) were added. The reaction mixture was allowed to stir at 80 °C for 2 d. The workup described above was repeated, and the supernatant was saved. The brown oil was dissolved in acetonitrile (0.50 mL) and Et_2O (3 mL) was added. Centrifugation, followed by decantation and drying under high vacuum afforded a colorless solid that was analyzed by ^1H NMR spectroscopy to contain **2.1**, **2.2**, 3-methyl-2-oxazolidinone and protonated *N*-methylethanolamine. The yield of **2.1** was determined by integration against an internal standard (dioxane, 2 μL) to be 66%.

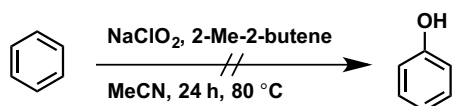
Isolation of phenyl tosylate (**2.4a**): Due to the volatility of phenol, the supernatant was concentrated to 5 mL, and *p*-toluenesulfonyl chloride (34.2 mg, 0.180 mmol, 9.00 equiv), 4-dimethylaminopyridine (7.2 mg, 0.060 mmol, 3.0 equiv), and triethylamine (75 μL , 0.54 mmol, 27 equiv) were added. The mixture was allowed to stir for 15 h at 23 °C. DCM (10 mL) and H_2O (10 mL) were added, and the reaction mixture was poured into a separatory funnel. The layers were separated. The aqueous layer was extracted with DCM (2×10 mL). The combined organic layers were washed with 1 M $\text{HCl}_{(\text{aq})}$ (10 mL) and brine (10 mL), dried over MgSO_4 , filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a solvent mixture of Et_2O /pentane (5:95 (v/v)) to afford 2.7 mg of the title compound as a colorless solid (54% yield). Spectroscopic data matched those described above for compound **2.4a**.

Control reactions

Two control reactions were performed by replacing benzene with complex **2.1**. One was performed under the exact conditions used to form complex **2.2** (see above), and the other was performed under more forcing conditions. Neither resulted in formation of phenol.

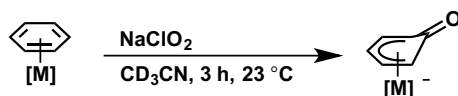


Control reaction #1. Benzene (17.8 μ L, 0.200 mmol, 1.00 equiv) was added to a flame-dried round bottom flask. Acetonitrile (10 mL), a solution of 2-methyl-2-butene in THF (0.800 mL, 1.60 mmol, 8.00 equiv, 2.0 M), and freshly powdered sodium chlorite (45.2 mg, 0.400 mmol, 2.00 equiv) were then added. The mixture was allowed to stir for 3 h at 23 $^{\circ}$ C. TLC analysis (hexanes/ethyl acetate, 4:1 (v/v)) showed no phenol formation. Filtration of reaction mixture through glass wool afforded a clear, colorless solution. The filtrate was concentrated and analyzed by ^1H NMR. No phenol was observed.



Control reaction #2. Benzene (17.8 μ L, 0.200 mmol, 1.00 equiv) was added to a flame-dried round bottom flask equipped with a reflux condenser. Acetonitrile (1.0 mL), a solution of 2-methyl-2-butene in THF (0.800 mL, 1.60 mmol, 8.00 equiv, 2.0 M), and freshly powdered sodium chlorite (45.2 mg, 0.400 mmol, 2.00 equiv) were then added. The mixture was allowed to stir for 24 h at 80 $^{\circ}$ C. TLC analysis (hexanes/ethyl acetate, 4:1 (v/v)) showed no phenol formation. Filtration of reaction mixture through glass wool afforded a clear, colorless solution. The filtrate was concentrated and analyzed by ^1H NMR. No phenol was observed.

Evaluation of other η^6 -arene complexes



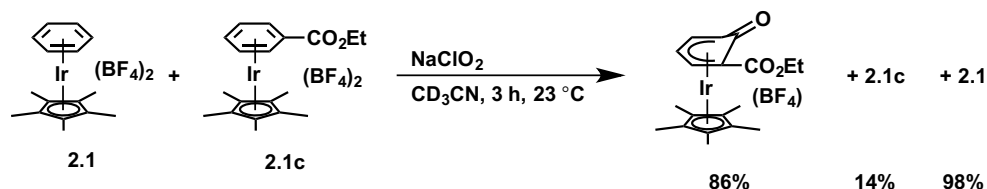
The η^6 -arene complex (0.010 mmol, 1.0 equiv), sodium chlorite (2.3 mg, 0.020 mmol, 2.0 equiv), and CD_3CN (0.75 mL) were added to a 4-mL vial. The reaction mixture was allowed to stir at 23 $^{\circ}$ C for 3 h. Dioxane (2 μ L) was added as an internal standard, and the mixture was filtered through glass wool into an NMR tube. Product yield was determined by internal standard in ^1H NMR (Table 5.1). Only complex **2.1**, the most electrophilic arene complex tested, showed significant C–H oxidation.

Table 5.1. Evaluation of other η^6 -arene complexes

<i>Complex</i>	<i>Yield of pdt</i>	<i>Yield of SM remaining</i>	<i>k_{CO}^{*a}</i>
$[(\eta^6\text{-Benzene})\text{IrCp}^*](\text{BF}_4)_2$ (2.1)	64%	9%	19.36
$[(\eta^6\text{-Benzene})\text{Ru}[(\eta^6\text{-C}_6\text{Me}_6)](\text{PF}_6)_2$	11%	19%	N/A ^b
$[(\eta^6\text{-Benzene})\text{Mn}(\text{CO})_3](\text{PF}_6)$	0%	53%	18.44
$[(\eta^6\text{-Benzene})\text{RuCp}](\text{PF}_6)$	0%	100%	17.60
$[(\eta^6\text{-Benzene})\text{FeCp}](\text{PF}_6)$	0%	63%	17.58
$(\eta^6\text{-Benzene})\text{Cr}(\text{CO})_3$	0%	0%	16.47

^ak_{CO}^{*} is a parameter to measure the electrophilicity of arene complexes (see *ref 61*). ^bk_{CO}^{*} was not reported for $[(\eta^6\text{-Benzene})\text{Ru}(\eta^6\text{-C}_6\text{Me}_6)](\text{PF}_6)_2$, but a value of k_{CO}^{*} = 18.90 was reported for $[(\eta^6\text{-Benzene})_2\text{Ru}]^{2+}$.

Competition reaction between **2.1** and **2.1c**



Iridium complex **2.1** (5.8 mg, 0.010 mmol, 1.0 equiv), iridium complex **2.1c** (6.5 mg, 0.010 mmol, 1.0 equiv), sodium chlorite (1.1 mg, 0.010 mmol, 1.0 equiv), and CD₃CN (0.75 mL) were added to a 4-mL vial. The reaction mixture was allowed to stir at 23 °C for 3 h. Dioxane (2 μ L) was added as an internal standard, and the mixture was filtered through glass wool into an NMR tube. Product yield was determined by internal standard in ¹H NMR. Complex **2.1c** was oxidized in 86% yield (14% yield of **1c** remained, 98% yield of **2.1** remained). Therefore, more electron poor arene complexes are preferentially oxidized under these conditions.

5.2.3. X-ray crystallography

$[(\eta^5\text{-Phenoxo})\text{IrCp}^*](\text{BF}_4)$ (**2.2**) (CCDC 1414178)

X-ray quality crystals of **2.2** were grown by slow diffusion of Et₂O (3 mL) into an acetonitrile solution containing **2.6b** (approx. 15 mg **2.6b** in 0.5 mL MeCN). A crystal was mounted on a nylon loop using Paratone-N oil, and transferred to a Bruker APEX II CCD diffractometer (MoK α 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 optimization. Absorption corrections were made with the programs SADABS (Bruker diffractometer, 2009). The structure was solved by the direct methods procedure and refined by least-squares methods against F² 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) have been applied for the disorder refinement. Constraints of the atomic displacement parameters on carbons of the cyclopentadienyl ring (EADP instructions of SHELXL97) have been applied. Crystal data as well as details of data collection and refinement are summarized in Table 5.2 below.

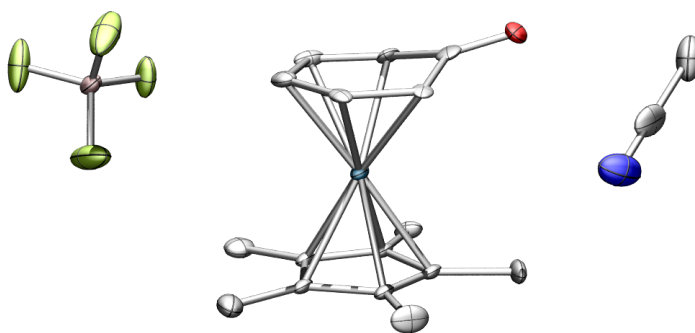


Figure 5.1. X-ray structure of **2.2**. Thermal ellipsoids are drawn at the 50% probability level. H-atoms are omitted for clarity.

Table 5.2. Experimental details for **2.2**.

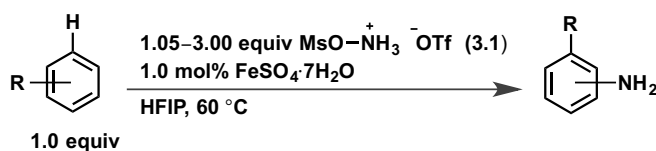
Empirical formula	C ₁₆ H ₂₀ IrO·BF ₄ ·C ₂ H ₃ N
Formula weight	548.38
Temperature	100(2) K
Wavelength	0.71073 Å

Crystal system	monoclinic	
Space group	<i>P</i> 21/ <i>c</i>	
Unit cell dimensions	<i>a</i> = 26.4511 (17) Å	$\alpha = 90^\circ$
	<i>b</i> = 9.2696 (7) Å	$\beta = 97.784 (2)^\circ$
	<i>c</i> = 39.413 (3) Å	$\gamma = 90^\circ$
Volume	9574.7 (12) Å ³	
<i>Z</i>	20	
Density (calculated)	1.902 Mg/m ³	
Absorption coefficient	7.02 mm ⁻¹	
<i>F</i> (000)	5280.0	
Crystal size	0.18 × 0.12 × 0.05 mm ³	
θ range for data collection	2.41 to 25.00°	
Index ranges	-31 ≤ <i>h</i> ≤ 31, -11 ≤ <i>k</i> ≤ 11, -47 ≤ <i>l</i> ≤ 47	
Reflections collected	135625	
Independent reflections	16909 [<i>R</i> _{int} = 0.075]	
Reflections with <i>I</i> > 2σ(<i>I</i>)	12881	
Max. and min. transmission	0.561 and 0.745	
Data / restraints / parameters	16909 / 84 / 1061	
Goodness-of-fit on <i>F</i> ²	1.165	
Final <i>R</i> indices [<i>I</i> > 2σ(<i>I</i>)]	<i>R</i> ₁ = 0.0485, <i>wR</i> ² = 0.0830	
<i>R</i> indices (all data)	<i>R</i> ₁ = 0.0713, <i>wR</i> ² = 0.0889	
Largest diff. peak and hole	2.67 and -2.87 e·Å ⁻³	

5.3. Experimental details for chapter 3

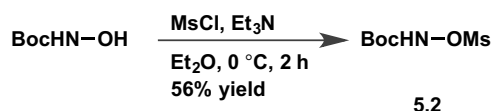
5.2.1. Compound synthesis and characterization

General procedure for amination



Reagent **3.1** (1.05–3.00 equiv), FeSO₄·7H₂O (0.8 mg, 3 μmol, 0.01 equiv), and the arene (if solid) (0.300 mmol, 1.00 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, c = 0.2 M) and the arene (if liquid). The reaction mixture was stirred at 60 °C for 15–120 min, or until judged complete by the color and/or TLC. The reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na₂CO₃. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography and/or preparative TLC.

***N*-Boc-*O*-Mesylhydroxylamine (5.2)**



N-Boc-hydroxylamine (5.00 g, 37.6 mmol, 1.00 equiv) and triethylamine (3.81 g, 5.24 mL, 37.6 mmol, 1.00 equiv) were dissolved in anhydrous diethyl ether (190 mL, c = 0.2 M) in a flame-dried round bottom flask. The reaction mixture was cooled in a water-ice bath. Methanesulfonyl chloride (4.31 g, 2.91 mL, 37.6 mmol, 1.00 equiv) was then added slowly over 1 minute. The mixture was stirred at 0 °C for 2 h, then allowed to warm to room temperature. The mixture was filtered over Celite, and the filtrate was concentrated. The residue was purified by column chromatography on silica gel eluting with a solvent mixture of ethyl acetate/hexane (15:85 (v/v)) to afford 4.43 g of the title compound as a colorless solid (56% yield). Spectroscopic data matched those previously reported.¹⁸³

R_f = 0.92 (ethyl acetate/hexanes, 40:60 (v/v)).

NMR Spectroscopy:

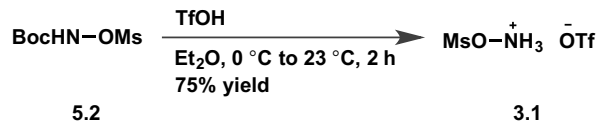
¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.83 (br s, 1H), 3.18 (s, 3H), 1.52 (s, 9H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 154.9, 84.8, 36.3, 28.1.

¹⁸³ Stafford, J. A.; Gonzales, S. S.; Barrett, D. G.; Suh, E. M.; Feldman, P. L. *J. Org. Chem.* **1998**, 63, 10040–10044.

HRMS-FIA(*m/z*): calc'd for C₆H₁₇N₂O₅S [M+NH₄]⁺, 229.0858; found, 229.0860.

[MsO–NH₃]⁺OTf[–] (3.1)



Reagent **3.1** was synthesized by the method of Morandi¹⁴⁴ and Fagnou¹⁸⁴. Compound **5.2** (1.50 g, 7.10 mmol, 1.00 equiv) was dissolved in anhydrous diethyl ether (36 mL, c = 0.2 M) in a flame-dried two-neck round bottom flask. The flask was evacuated and backfilled with nitrogen, then cooled in a water-ice bath. Triflic acid (1.07 g, 627 μL, 7.10 mmol, 1.00 equiv) was added using a plastic pipettor. The reaction mixture was stirred at 23 °C for 2 h, during which time a colorless precipitate formed. Pentane (20 mL) was added to the flask. The colorless solid was collected on a Buchner funnel, rinsed with pentane (20 mL) and dried under high vacuum to give 1.39 g of the title compound as a colorless solid (75% yield). Spectroscopic data matched those previously reported.¹⁴⁴

NMR Spectroscopy:

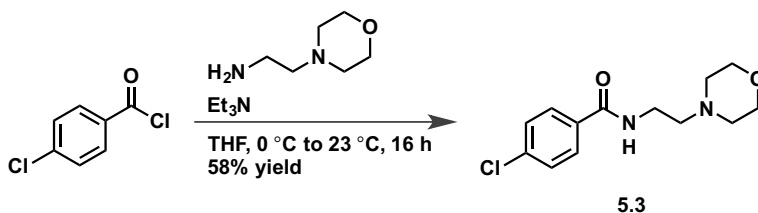
¹H NMR (500 MHz, CD₃CN, 23 °C, δ): 8.01–7.82 (br s, 3H), 3.36 (s, 3H).

¹³C NMR (125 MHz, CD₃CN, 23 °C, δ): 121.4 (q, *J* = 317 Hz), 39.9.

¹⁹F NMR (375 MHz, CD₃CN, 23 °C, δ): –79.8.

HRMS-FIA(*m/z*): calc'd for CH₆NO₃S [M]⁺, 112.0068; found, 112.0069.

Mocleboamide (5.3)



¹⁸⁴ Guimond, N.; Gorelsky, S. I.; Fagnou, K. *J. Am. Chem. Soc.* **2011**, 133, 6449–6457.

Mocleboamide (**5.3**) was synthesized by the method of Ahn.¹⁸⁵ 4-Chlorobenzoyl chloride (1.33 g, 977 μ L, 7.62 mmol, 1.00 equiv) was dissolved in anhydrous tetrahydrofuran (35 mL, c = 0.2 M) in a flame-dried round bottom flask. The solution was cooled in a water-ice bath. Triethylamine (771 mg, 1.06 mL, 7.62 mmol, 1.00 equiv) and *N*-2-(aminoethyl)morpholine (992 mg, 1.00 mL, 7.62 mmol, 1.00 equiv) were then added. The reaction mixture was allowed to warm to room temperature and stir for 16 h at 23 °C. The reaction mixture was poured into a separatory funnel containing EtOAc (100 mL) and water (200 mL). The layers were separated, and the aqueous layer was extracted with EtOAc (1 x 100 mL). The combined organic layers were dried over Na₂SO₄, filtered and concentrated. The residue was recrystallized from a mixture of EtOAc and hexanes at -5 °C. The solid was collected on a Buchner funnel and washed with pentane (100 mL) to give 1.19 g of the title compound as a tan solid (58% yield).

R_f = 0.13 (ethyl acetate/hexanes, 40:60 (v/v)).

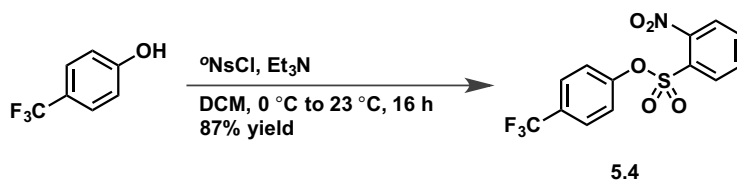
NMR Spectroscopy:

¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.72 (d, J = 7.9 Hz, 2H), 7.42 (d, J = 8.5 Hz, 2H), 6.72 (br s, 1H), 3.74 (br s, 4H), 3.56 (br s, 2H), 2.62 (br s, 2H), 2.52 (br s, 4H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 166.4, 137.7, 133.1, 128.9, 128.4, 67.1, 56.9, 53.4, 36.2.

HRMS-FIA(m/z): calc'd for C₁₃H₁₈ClN₂O₂ [M+H]⁺, 269.1051; found, 269.1047.

4-(Trifluoromethyl)phenyl-2-nitrobenzenesulfonate (**5.4**)



The title compound was synthesized by the method of Williams.¹⁸⁶ 4-(Trifluoromethyl)phenol (400. mg, 2.47 mmol, 1.00 equiv) was dissolved in anhydrous dichloromethane (12 mL, c = 0.2 M) in a flame-dried

¹⁸⁵ Kim, D.; Sambasivan, S.; Nam, H.; Kim, K. H.; Kim, J. Y.; Joo, T.; Lee, K.-H.; Kim, K.-T.; Ahn, K. H. *Chem. Commun.* **2012**, 48, 6833–6835.

¹⁸⁶ Thea, S.; Guanti, G.; Hopkins, A. R.; Williams, A. *J. Org. Chem.* **1985**, 50, 3336–3341.

round bottom two neck flask. Triethylamine (250 mg, 344 μ L, 2.47 mmol, 1.00 equiv) was added and the mixture was cooled in a water-ice bath. 2-Nitrobenzenesulfonyl chloride (547 mg, 2.47 mmol, 1.00 equiv) was then added. The reaction mixture was stirred at 23 $^{\circ}$ C for 16 h. The reaction mixture was then poured into a separatory funnel containing 1M HCl (aq) (25 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (2×15 mL). The combined organic layers were dried over Na_2SO_4 , filtered and concentrated. The residue was purified by column chromatography on a short plug of silica gel eluting with a solvent mixture of ethyl acetate/pentane (30:70 (v/v)). Purification afforded 747 mg of the title compound as a colorless solid (87% yield).

R_f = 0.54 (ethyl acetate/hexanes, 40:60 (v/v)).

NMR Spectroscopy:

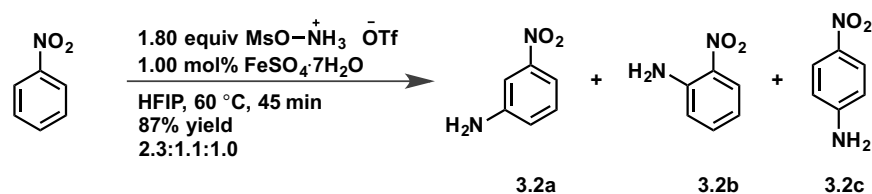
^1H NMR (500 MHz, CDCl_3 , 23 $^{\circ}$ C, δ): 8.00 (d, J = 7.6 Hz, 1H), 7.90–7.84 (m, 2H), 7.76–7.70 (m, 1H), 7.64 (d, J = 8.4 Hz, 2H), 7.36 (d, J = 8.5 Hz, 2H).

^{13}C NMR (125 MHz, CDCl_3 , 23 $^{\circ}$ C, δ): 151.4, 148.8, 135.9, 132.4, 132.2, 130.1 (q, J = 32.9 Hz), 128.2, 127.5 (q, J = 3.7 Hz), 125.2, 123.6 (q, J = 271 Hz), 122.9.

^{19}F NMR (470 MHz, CDCl_3 , 23 $^{\circ}$ C, δ): –62.5.

HRMS-FIA(m/z): calc'd for $\text{C}_6\text{H}_7\text{N}_2\text{O}_5\text{S}$ [$\text{M}+\text{NH}_4$] $^+$, 365.0414; found, 365.0410.

3-Nitroaniline (3.2a), 2-nitroaniline (3.2b), and 4-nitroaniline (3.2c)



Reagent **3.1** (141 mg, 0.540 mmol, 1.80 equiv) and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μ mol, 0.01 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, c = 0.2 M) and nitrobenzene (36.9 mg, 30.8 μ L, 0.300 mmol, 1.00 equiv). The reaction mixture was stirred at 60 $^{\circ}$ C for 45 min. The orange reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl

acetate and poured into a separatory funnel containing 10 mL sat. aq. Na₂CO₃. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ¹H NMR spectrum of the residue indicated a ratio of **3.2a**:**3.2b**:**3.2c** = 2.3:1.1:1.0 by integrating the signal of **3.2a** at 6.94 ppm, the signal of **3.2b** at 6.76 ppm, and the signal of **3.2c** at 6.62 ppm. The residue was purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (20:80 (v/v)) and finishing with diethyl ether/pentane (50:50 (v/v)). Purification afforded 2-nitroaniline (**3.2b**) in one fraction (8.1 mg) and 3-nitroaniline (**3.2a**) and 4-nitroaniline (**3.2c**) in a second fraction (27.8 mg) for a combined yield of 35.9 mg (87% yield). The second fraction was further purified by preparative TLC using a solvent system of diethyl ether/pentane (20:80 (v/v)) to give **3.2a** (14.9 mg) and **3.2c** (9.7 mg) as separate samples. Characterization data matched previously reported data for **3.2a**, **3.2b**, and **3.2c**.¹⁸⁷

3-Nitroaniline (**3.2a**):

R_f = 0.50 (ethyl acetate/hexanes, 40:60 (v/v)).

NMR Spectroscopy:

¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.57 (ddd, *J* = 8.2, 2.1, 0.9 Hz, 1H), 7.49 (dd, *J* = 2.2, 2.2 Hz, 1H), 7.27 (dd, *J* = 8.1, 8.1 Hz, 1H), 6.94 (ddd, *J* = 8.0, 2.3, 0.8 Hz, 1H), 4.00 (br s, 2H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 149.4, 147.6, 130.0, 120.7, 113.3, 109.2.

HRMS-FIA(*m/z*): calc'd for C₆H₇N₂O₂ [M+H]⁺, 139.0502; found, 139.0506.

2-Nitroaniline (**3.2b**):

R_f = 0.35 (diethyl ether/pentanes, 30:70 (v/v)).

NMR Spectroscopy:

¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 8.12 (d, *J* = 8.6 Hz, 1H), 7.36 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.80 (d, *J* = 8.4 Hz, 1H), 6.71 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.05 (br s, 2H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 144.8, 135.8, 132.3, 126.2, 118.9, 117.0.

¹⁸⁷ Gao, X.; Fu, H.; Qiao, R.; Jiang, Y.; Zhao, Y. *J. Org. Chem.* **2008**, 73, 6864–6866.

HRMS-FIA(*m/z*): calc'd for C₆H₇N₂O₂ [M+H]⁺, 139.0502; found, 139.0505.

4-Nitroaniline (**3.2c**):

R_f = 0.36 (ethyl acetate/hexanes, 40:60 (v/v)).

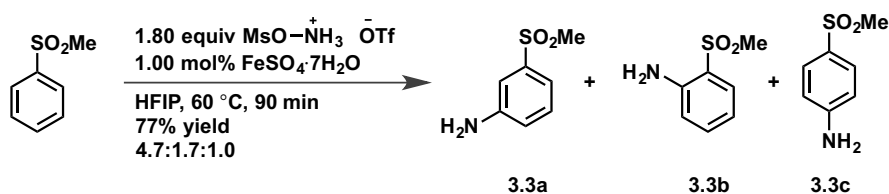
NMR Spectroscopy:

¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 8.06 (d, *J* = 9.1 Hz, 2H), 6.62 (d, *J* = 9.1 Hz, 2H), 4.38 (br s, 2H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 152.6, 139.3, 126.5, 113.5.

HRMS-FIA(*m/z*): calc'd for C₆H₇N₂O₂ [M+H]⁺, 139.0502; found, 139.0500.

3-(Methylsulfonyl)aniline (3.3a), 2-(methylsulfonyl)aniline (3.3b), and 4-(methylsulfonyl)aniline (3.3c)



Reagent **3.1** (141 mg, 0.540 mmol, 1.80 equiv), FeSO₄·7H₂O (0.8 mg, 3 μmol, 0.01 equiv), and phenyl methylsulfone (46.9 mg, 0.300 mmol, 1.00 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, *c* = 0.2 M). The reaction mixture was stirred at 60 °C for 90 min. The orange reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na₂CO₃. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ¹H NMR spectrum of the residue indicated a ratio of **3.3a**:**3.3b**:**3.3c** = 4.7:1.7:1.0 by integrating the signal of **3.3a** at 6.87 ppm, the signal of **3.3b** at 6.76 ppm, and the signal of **3.3c** at 6.68 ppm. The residue was purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (50:50 (v/v)) and finishing with diethyl ether. Purification afforded 2-(methylsulfonyl)aniline (**3.3b**) in one

fraction (10.5 mg) and 3-(methylsulfonyl)aniline (**3.3a**) and 4-(methylsulfonyl)aniline (**3.3c**) in a second fraction (29.2 mg) for a combined yield of 39.7 mg (77% yield). The second fraction was further purified by preparative TLC using a solvent system of ethyl acetate/pentane (30:70 (v/v)) to give **3.3a** (14.6 mg) and **3.3c** (3.6 mg) as separate samples. Characterization data matched previously reported data for **3.3b**^{188a} and **3.3c**^{188b}.

3-(Methylsulfonyl)aniline (**3.3a**)

R_f = 0.17 (ethyl acetate/hexanes, 40:60 (v/v)).

NMR Spectroscopy:

¹H NMR (600 MHz, CDCl₃, 23 °C, δ): 7.31 (dd, J = 7.9, 7.9 Hz, 1H), 7.26 (ddd, J = 7.8, 1.4, 1.4 Hz, 1H), 7.20 (dd, J = 2.0, 2.0 Hz, 1H), 6.89 (ddd, J = 8.0, 2.4, 1.0 Hz, 1H), 4.01 (br s, 2H), 3.02 (s, 3H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 147.6, 141.5, 130.4, 119.8, 116.8, 112.9, 44.5.

HRMS-FIA(m/z): calc'd for C₇H₁₃N₂O₂S [M+NH₄]⁺, 172.0427; found, 172.0418.

2-(Methylsulfonyl)aniline (**3.3b**):

R_f = 0.57 (diethyl ether/pentanes, 80:20 (v/v)).

NMR Spectroscopy:

¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.74 (d, J = 8.0 Hz, 1H), 7.37 (dd, J = 7.7, 7.7 Hz, 1H), 6.83 (dd, J = 7.6, 7.6 Hz, 1H), 6.76 (d, J = 8.2 Hz, 1H), 5.00 (br s, 2H), 3.06 (s, 3H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 146.3, 135.3, 129.6, 122.2, 118.2, 117.7, 42.4.

HRMS-FIA(m/z): calc'd for C₇H₁₀NO₂S [M+H]⁺, 172.0427; found, 172.0422.

4-(Methylsulfonyl)aniline (**3.3c**):

R_f = 0.13 (ethyl acetate/hexanes, 40:60 (v/v)).

NMR Spectroscopy:

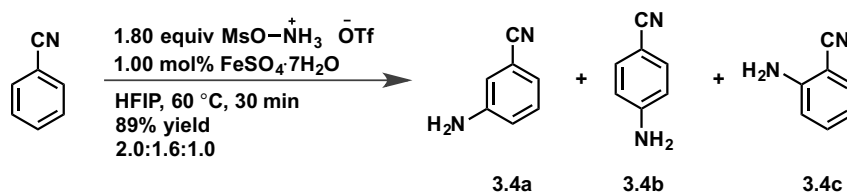
¹⁸⁸ a. Anderson, K. K.; Chumpradit, S.; McIntyre, D. J. *J. Org. Chem.* **1988**, 53, 4667–4675; b. Courtin, A. *Helv. Chim. Acta* **1983**, 66, 1046–1052.

^1H NMR (600 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): 7.69 (d, J = 8.8 Hz, 2H), 6.71 (d, J = 8.8 Hz, 2H), 4.20 (br s, 2H), 3.00 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): 151.4, 129.6, 129.1, 114.2, 45.1.

HRMS-FIA(m/z): calc'd for $\text{C}_7\text{H}_{13}\text{N}_2\text{O}_2\text{S}$ $[\text{M}+\text{NH}_4]^+$, 172.0427; found, 172.0422.

3-Aminobenzonitrile (**3.4a**), 4-aminobenzonitrile (**3.4b**), and 2-aminobenzonitrile (**3.4c**)



Reagent **3.1** (141 mg, 0.540 mmol, 1.80 equiv) and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, c = 0.2 M) and benzonitrile (31.0 mg, 31.0 μL , 0.300 mmol, 1.00 equiv). The reaction mixture was stirred at 60 $^\circ\text{C}$ for 30 min. The red reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue indicated a ratio of **3.4a**:**3.4b**:**3.4c** = 2.0:1.6:1.0 by integrating the signal of **3.4a** at 7.00 ppm, the signal of **3.4b** at 6.64 ppm, and the signal of **3.4c** at 6.76 ppm. The residue was purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (20:80 (v/v)) and finishing with diethyl ether/pentane (50:50 (v/v)). Purification afforded 2-aminobenzonitrile (**3.4c**) in one fraction (6.4 mg) and 3-aminobenzonitrile (**3.4a**) and 4-aminobenzonitrile (**3.4b**) in a second fraction (25.2 mg) for a combined yield of 31.6 mg (89% yield). The second fraction was further purified by preparative TLC using a solvent system of acetone/pentane (10:90 (v/v)) to give **3.4a** (10.0 mg) and

3.4b (9.1 mg) as separate samples. Characterization data matched previously reported data for **3.4a**, **3.4b**, and **3.4c**.¹⁸⁹

3-Aminobenzonitrile (**3.4a**):

R_f = 0.50 (ethyl acetate/hexanes, 40:60 (v/v)).

NMR Spectroscopy:

¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.22 (dd, J = 7.9, 7.9 Hz, 1H), 7.01 (ddd, J = 7.6, 1.4, 1.0 Hz, 1H), 6.90 (dd, J = 1.7, 1.7, 1H), 6.86 (ddd, J = 8.2, 2.4, 1.0 Hz, 1H), 3.87 (br s, 2H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 147.0, 130.2, 122.1, 119.3, 119.3, 117.6, 113.1.

HRMS-FIA(m/z): calc'd for C₇H₇N₂ [M+H]⁺, 119.0604; found, 119.0608.

4-Aminobenzonitrile (**3.4b**):

R_f = 0.38 (ethyl acetate/hexanes, 40:60 (v/v)).

NMR Spectroscopy:

¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.41 (d, J = 8.8 Hz, 2H), 6.64 (d, J = 8.8 Hz, 2H), 4.14 (br s, 2H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 150.5, 134.0, 120.2, 114.6, 100.5.

HRMS-FIA(m/z): calc'd for C₇H₇N₂ [M+H]⁺, 119.0604; found, 119.0601.

2-Aminobenzonitrile (**3.4c**):

R_f = 0.38 (diethyl ether/pentanes, 40:60 (v/v)).

NMR Spectroscopy:

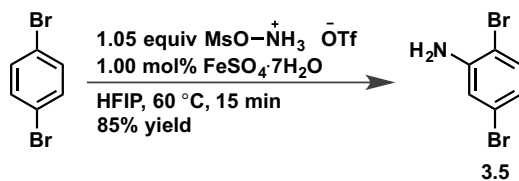
¹H NMR (600 MHz, CDCl₃, 23 °C, δ): 7.39 (dd, J = 8.0, 1.5 Hz, 1H), 7.33 (dd, J = 7.9, 7.9 Hz, 1H), 6.76–6.72 (m, 2H), 4.39 (br s, 2H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 149.7, 134.1, 132.5, 118.2, 117.7, 115.3, 96.3.

HRMS-FIA(m/z): calc'd for C₇H₇N₂ [M+H]⁺, 119.0604; found, 119.0604.

2,5-Dibromoaniline (**3.5**)

¹⁸⁹ Rahaim, R. J., Jr.; Maleczka, R. E., Jr. *Org. Lett.* **2005**, 7, 5087–5090.



Reagent **3.1** (82.3 mg, 0.315 mmol, 1.05 equiv), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv), and 1,4-dibromobenzene (70.8 mg, 0.300 mmol, 1.00 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, $c = 0.2 \text{ M}$). The reaction mixture was stirred at 60 $^\circ\text{C}$ for 15 min. The red reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate ($2 \times 10 \text{ mL}$). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a solvent system of ethyl acetate/hexane (5:95 (v/v)). Purification afforded 64.2 mg of the title compound as a light orange solid (85% yield). Characterization data matched a commercial sample.

$R_f = 0.85$ (ethyl acetate/hexanes, 40:60 (v/v)).

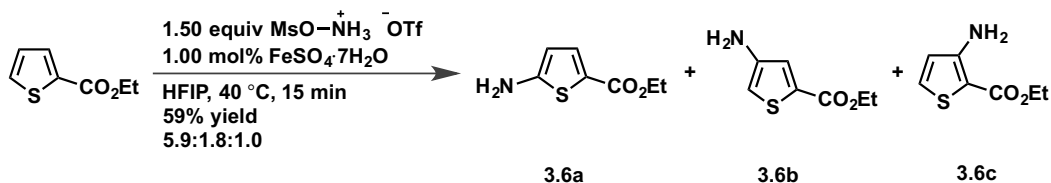
NMR Spectroscopy:

^1H NMR (600 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): 7.25 (d, $J = 8.5 \text{ Hz}$, 1H), 6.91 (d, $J = 2.0 \text{ Hz}$, 1H), 6.74 (dd, $J = 8.5, 2.2 \text{ Hz}$, 1H), 4.23 (br s, 2H).

^{13}C NMR (125 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): 145.4, 133.7, 122.3, 121.8, 118.2, 107.9.

HRMS-FIA(m/z): calc'd for $\text{C}_6\text{H}_5\text{Br}_2\text{N}$ $[\text{M}+\text{H}]^+$, 251.8841; found, 251.8839.

Ethyl 5-aminothiophene-2-carboxylate (3.6a), ethyl 4-aminothiophene-2-carboxylate (3.6b), and ethyl 3-aminothiophene-2-carboxylate (3.6c)



Reagent **3.1** (118 mg, 0.450 mmol, 1.50 equiv) and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, $c = 0.2 \text{ M}$) and ethyl 2-thiophenecarboxylate (46.9 mg, 40.3 μL , 0.300 mmol, 1.00 equiv). The reaction mixture was stirred at 40 °C for 15 min. The red reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate ($2 \times 10 \text{ mL}$). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue indicated a ratio of **3.6a**:**3.6b**:**3.6c** = 5.9:1.8:1.0 by integrating the signal of **3.6a** at 6.09 ppm, the signal of **3.6b** at 6.39 ppm, and the signal of **3.6c** at 6.55 ppm. The residue was purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (5:95 (v/v)) and finishing with diethyl ether/pentane (50:50 (v/v)). Purification afforded ethyl 3-aminothiophene-2-carboxylate (**3.6c**) in one fraction (2.9 mg), ethyl 5-aminothiophene-2-carboxylate (**3.6a**) in a second fraction (18.0 mg), and ethyl 4-aminothiophene-2-carboxylate (**3.6b**) in a third fraction (6.6 mg) for a combined yield of 30.5 mg (59% yield). Characterization data matched previously reported data for **3.6a**.¹⁹⁰

Ethyl 5-aminothiophene-2-carboxylate (**3.6a**):

$R_f = 0.40$ (diethyl ether/pentanes, 50:50 (v/v)).

NMR Spectroscopy:

^1H NMR (500 MHz, CD_2Cl_2 , 23 °C, δ): 7.41 (d, $J = 4.0 \text{ Hz}$, 1H), 6.09 (d, $J = 4.0 \text{ Hz}$, 1H), 4.45 (br s, 2H), 4.24 (q, $J = 7.1 \text{ Hz}$, 2H), 1.31 (t, $J = 7.2 \text{ Hz}$, 3H).

^{13}C NMR (125 MHz, CD_2Cl_2 , 23 °C, δ): 162.8, 159.5, 134.9, 118.2, 107.9, 60.8, 14.6.

HRMS-FIA(m/z) calc'd for $\text{C}_9\text{H}_9\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$, 172.0427; found, 172.0422.

Ethyl 4-aminothiophene-2-carboxylate (**3.6b**):

$R_f = 0.24$ (diethyl ether/pentanes, 50:50 (v/v)).

NMR Spectroscopy:

¹⁹⁰ Robin, A.; Meslin, J.-C.; Deniaud, D. *Synthesis* **2004**, 1633–1640.

^1H NMR (500 MHz, CD_2Cl_2 , 23 °C, δ): 7.28 (d, J = 1.9 Hz, 1H), 6.39 (d, J = 1.8 Hz, 1H), 4.28 (q, J = 7.1 Hz, 3H), 3.70 (br s, 2H), 1.33 (t, J = 7.1 Hz, 2H).

^{13}C NMR (125 MHz, CD_2Cl_2 , 23 °C, δ): 162.4, 146.3, 133.3, 126.1, 107.4, 61.4, 14.5.

HRMS-FIA(m/z): calc'd for $\text{C}_7\text{H}_9\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$, 172.0427; found, 172.0422.

Ethyl 3-aminothiophene-2-carboxylate (**3.6c**):

R_f = 0.56 (diethyl ether/pentanes, 50:50 (v/v)).

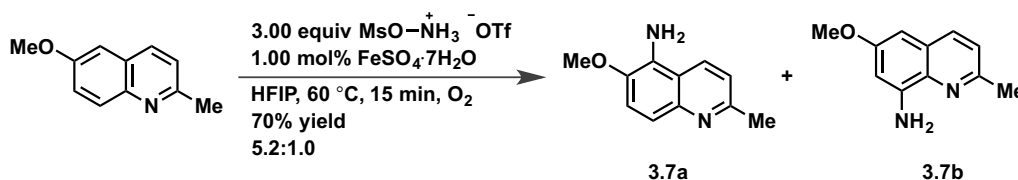
NMR Spectroscopy:

^1H NMR (500 MHz, CD_2Cl_2 , 23 °C, δ): 7.28 (d, J = 5.4 Hz, 1H), 6.55 (d, J = 5.4 Hz, 1H), 5.45 (br s, 2H), 4.26 (q, J = 7.1 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, CD_2Cl_2 , 23 °C, δ): 164.9, 154.3, 131.6, 120.3, 101.7, 60.4, 14.7.

HRMS-FIA(m/z): calc'd for $\text{C}_7\text{H}_9\text{NO}_2\text{S}$ $[\text{M}+\text{H}]^+$, 172.0427; found, 172.0421.

5-Amino-6-methoxy-2-methylquinoline (**3.7a**) and 8-amino-6-methoxy-2-methylquinoline (**3.7b**)



Reagent **3.1** (235 mg, 0.900 mmol, 3.00 equiv), $\text{FeSO}_4\cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv), and 6-methoxy-2-methylquinoline (52.0 mg, 0.300 mmol, 1.00 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, c = 0.2 M). The reaction mixture was stirred at 60 °C for 15 min under an atmosphere of oxygen. The dark green reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue indicated a ratio of **3.7a**:**3.7b** = 5.2:1.0 by integrating the signal of **3.7a** at 8.01 ppm and the signal of **3.7b** at 7.84 ppm. The residue was purified by column chromatography on silica gel

eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (10:90 (v/v)) and finishing with diethyl ether. Purification afforded 5-amino-6-methoxy-2-methylquinoline (**3.7a**) in one fraction (13.5 mg) and 8-amino-6-methoxy-2-methylquinoline (**3.7b**) in a second fraction (26.2 mg) for a combined yield of 39.7 mg (70% yield).

5-Amino-6-methoxy-2-methylquinoline (**3.7a**):

R_f = 0.14 (ethyl acetate/hexanes, 50:50 (v/v)).

NMR Spectroscopy:

^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 8.01 (d, J = 9.0 Hz, 1H), 7.50 (d, J = 9.1 Hz, 1H), 7.38 (d, J = 9.1 Hz, 1H), 7.17 (d, J = 8.7 Hz, 1H), 4.23 (br s, 2H), 3.95 (s, 3H), 2.69 (s, 3H).

^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{CO}$, 23 °C, δ): 156.7, 145.0, 142.2, 132.1, 130.7, 120.5, 118.0, 117.3, 117.3, 57.0, 25.0.

HRMS-FIA(m/z): calc'd for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$, 189.1022; found, 189.1014.

8-Amino-6-methoxy-2-methylquinoline (**3.7b**):

R_f = 0.61 (ethyl acetate/hexanes, 50:50 (v/v)).

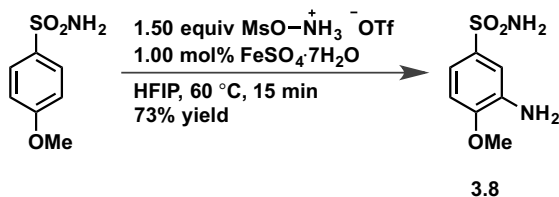
NMR Spectroscopy:

^1H NMR (600 MHz, CDCl_3 , 23 °C, δ): 7.84 (d, J = 8.3 Hz, 1H), 7.20 (d, J = 8.3 Hz, 1H), 6.55 (d, J = 2.6 Hz, 1H), 6.45 (d, J = 2.6 Hz, 1H), 5.00 (br s, 2H), 3.86 (s, 3H), 2.66 (s, 3H).

^{13}C NMR (125 MHz, CDCl_3 , 23 °C, δ): 158.2, 153.7, 144.6, 135.1, 134.9, 127.8, 122.7, 101.6, 94.8, 55.4, 25.0.

HRMS-FIA(m/z): calc'd for $\text{C}_{11}\text{H}_{13}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$, 189.1022; found, 189.1022.

3-Amino-4-methoxybenzenesulfonamide (**3.8**)



Reagent **3.1** (118 mg, 0.450 mmol, 1.50 equiv), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv), and 4-methoxybenzenesulfonamide (56.2 mg, 0.300 mmol, 1.00 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, $c = 0.2$ M). The reaction mixture was stirred at 60 °C for 15 min. The dark green reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (70:30 (v/v)) and finishing with diethyl ether. Purification afforded 44.4 mg of the title compound (73% yield).

$R_f = 0.15$ (ethyl acetate/hexanes, 50:50 (v/v)).

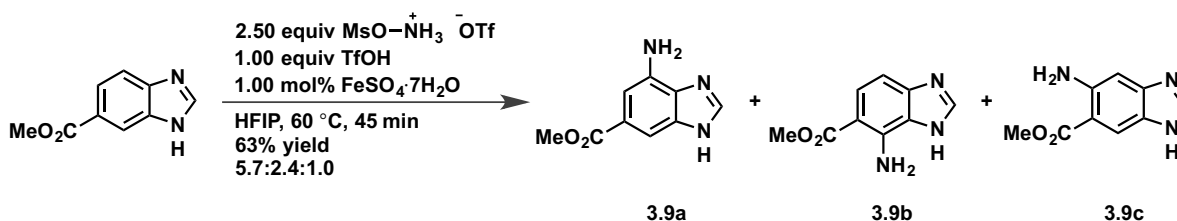
NMR Spectroscopy:

^1H NMR (500 MHz, CD_3OD , 23 °C, δ): 7.24–7.20 (m, 2H), 6.91 (d, $J = 8.1$ Hz, 1H), 3.90 (s, 3H).

^{13}C NMR (125 MHz, CD_3OD , 23 °C, δ): 151.5, 138.7, 136.7, 117.3, 112.8, 110.6, 56.3.

HRMS-FIA(m/z): calc'd for $\text{C}_7\text{H}_{11}\text{N}_2\text{O}_3\text{S}$ $[\text{M}+\text{H}]^+$, 203.0485; found, 203.0477.

Methyl 4-amino-1H-benzimidazole-6-carboxylate (3.9a), methyl 7-amino-1H-benzimidazole-6-carboxylate (3.9b) and methyl 5-amino-1H-benzimidazole-6-carboxylate (3.9c)



$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv) and methyl 1H-benzimidazole-6-carboxylate (52.9 mg, 0.300 mmol, 1.00 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, $c = 0.2$ M) and TfOH (26.5 μL , 0.300 mmol, 1.00 equiv). Reagent **3.1** (196 mg, 0.750 mmol, 2.50 equiv) was then added to the vial. The reaction mixture was stirred at 60 °C for 45 min. The brown reaction mixture was allowed to cool to room

temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na₂CO₃. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ¹H NMR spectrum of the residue indicated a ratio of **3.9a**:**3.9b**:**3.9c** = 5.7:2.4:1.0 by integrating the signal of **3.9a** at 7.22 ppm, the signal of **3.9b** at 6.76 ppm, and the signal of **3.9c** at 6.85 ppm. The residue was purified by column chromatography on basified silica gel (NH₄OH) eluting with a gradient solvent system, starting with a solvent mixture of methanol/dichloromethane (2:98 (v/v)) and finishing with methanol/dichloromethane (5:95 (v/v)). Purification afforded methyl 7-amino-1*H*-benzimidazole-6-carboxylate (**3.9b**) and a small amount of unreacted starting material in one fraction and methyl 4-amino-1*H*-benzimidazole-6-carboxylate (**3.9a**) and methyl 5-amino-1*H*-benzimidazole-6-carboxylate (**3.9c**) in a second fraction (31.7 mg). The first fraction was further purified by preparative TLC using a solvent system of methanol/dichloromethane (2:98 (v/v)) to give **3.9b** (4.3 mg). The second fraction was characterized as a mixture. A combined yield of 36.0 mg (63% yield) was obtained. Characterization data matched previously reported data for **3.9c**.¹⁹¹

Methyl 4-amino-1*H*-benzimidazole-6-carboxylate (**3.9a**) and methyl 5-amino-1*H*-benzimidazole-6-carboxylate (**3.9c**):

R_f = 0.19 (methanol/dichloromethane, 5:95 (v/v)).

NMR Spectroscopy:

¹H NMR (500 MHz, CD₃OD, 23 °C, δ): 8.16 (s, 1H), 8.15* (s, 1H), 8.03* (s, 1H), 7.61 (s, 1H), 7.22 (s, 1H), 6.85* (s, 1H), 3.87 (s, 3H), 3.87* (s, 3H).

¹³C NMR (125 MHz, CD₃OD/CD₂Cl₂, 23 °C, δ): 170.1*, 169.7, 148.8*, 144.1*, 143.0*, 143.0, 138.6, 136.4, 135.2*, 134.0, 126.8, 121.0*, 109.9*, 108.1, 106.2, 99.2*, 52.6, 52.1*.

*Denotes signals of minor isomer (**3.9c**).

HRMS-FIA(*m/z*): calc'd for C₉H₁₀N₃O₂ [M+H]⁺, 192.0768; found, 192.0762.

¹⁹¹ Meyer, E. A.; Donati, N.; Guillot, M.; Schweizer, W. B.; Diederich, F.; Stengl, B.; Brenk, R.; Reuter, K.; Klebe, G. *Helv. Chim. Acta* **2006**, 89, 573–597.

Methyl 7-amino-1*H*-benzimidazole-6-carboxylate (**3.9b**):

R_f = 0.54 (methanol/dichloromethane, 5:95 (v/v)).

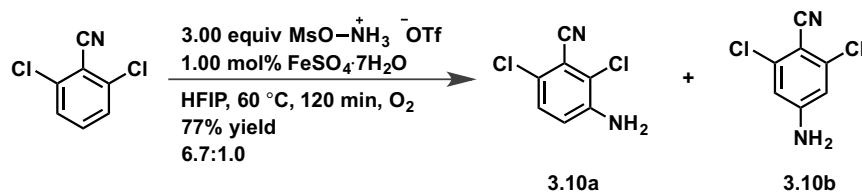
NMR Spectroscopy:

^1H NMR (500 MHz, CD_3OD , 23 °C, δ): 8.05 (s, 1H), 7.73 (d, J = 8.8 Hz, 1H), 6.76 (d, J = 8.3 Hz, 1H), 3.86 (s, 3H).

^{13}C NMR (125 MHz, CD_3OD , 23 °C, δ): 170.6, 145.1, 141.0, 138.5, 131.2, 127.3, 103.7, 101.6, 51.7.

HRMS-FIA(m/z): calc'd for $\text{C}_9\text{H}_{10}\text{N}_3\text{O}_2$ $[\text{M}+\text{H}]^+$, 192.0768; found, 192.0760.

3-Amino-2,6-dichlorobenzonitrile (**3.10a**) and 4-amino-2,6-dichlorobenzonitrile (**3.10b**)



Reagent **3.1** (235 mg, 0.900 mmol, 3.00 equiv), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv), and 2,6-dichlorobenzonitrile (51.6 mg, 0.300 mmol, 1.00 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, c = 0.2 M). The reaction mixture was stirred at 60 °C for 120 min under an atmosphere of oxygen. The orange reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue indicated a ratio of **3.10a**:**3.10b** = 6.7:1.0 by integrating the signal of **3.10a** at 6.86 ppm and the signal of **3.10b** at 6.68 ppm. The residue was purified by column chromatography on silica gel eluting with a solvent system of ethyl acetate/pentane (20:80 (v/v)). Purification afforded 3-amino-2,6-dichlorobenzonitrile (**3.10a**) and 4-amino-2,6-dichlorobenzonitrile (**3.10b**) in one fraction for a

combined yield of 43.4 mg (77% yield). The fraction was further purified by preparative TLC using a solvent system of dichloromethane/pentane (50:50 (v/v)) to give **3.10a** (32.4 mg) and **3.10b** (3.9 mg).

3-Amino-2,6-dichlorobenzonitrile (**3.10a**):

R_f = 0.50 (ethyl acetate/hexanes, 40:60 (v/v)).

NMR Spectroscopy:

^1H NMR (500 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$, 23 °C, δ): 6.86 (d, J = 8.9 Hz, 1H), 6.67 (d, J = 8.9 Hz, 1H).

^{13}C NMR (125 MHz, $\text{CDCl}_3/\text{CD}_3\text{OD}$, 23 °C, δ): 143.7, 128.1, 124.1, 119.9, 119.6, 113.6, 112.8.

HRMS-FIA(m/z): calc'd for $\text{C}_7\text{H}_5\text{Cl}_2\text{N}_2$ $[\text{M}+\text{H}]^+$, 186.9824; found, 186.9818.

4-Amino-2,6-dichlorobenzonitrile (**3.10b**):

R_f = 0.46 (ethyl acetate/hexanes, 40:60 (v/v)).

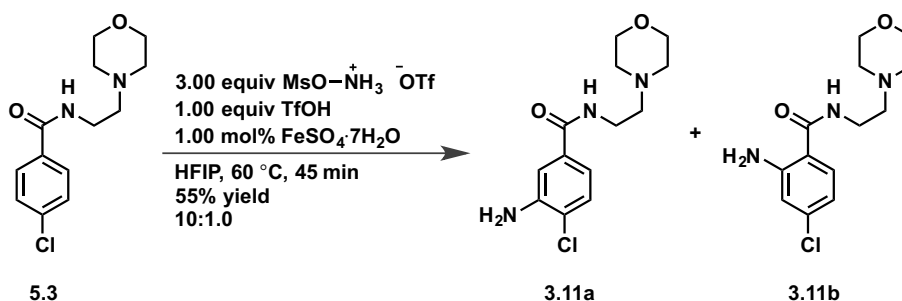
NMR Spectroscopy:

^1H NMR (500 MHz, CD_3OD , 23 °C, δ): 6.68 (s, 2H).

^{13}C NMR (125 MHz, CD_3OD , 23 °C, δ): 156.6, 139.7, 116.0, 113.5, 99.2.

HRMS-FIA(m/z): calc'd for $\text{C}_7\text{H}_5\text{Cl}_2\text{N}_2$ $[\text{M}+\text{H}]^+$, 186.9824; found, 186.9828.

3-Aminomoclebobomide (**3.11a**) and 2-Aminomoclebobomide (**3.11b**)



$\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv) and moclebobomide (**5.3**) (80.6 mg, 0.300 mmol, 1.00 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, c = 0.2 M) and TfOH (26.5 μL , 0.300 mmol, 1.00 equiv). Reagent **3.1** (235 mg, 0.900 mmol, 3.00 equiv) was then added to the vial. The reaction mixture was stirred at 60 °C for 45 min. The red brown reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory

funnel containing 10 mL sat. aq. Na₂CO₃. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ¹H NMR spectrum of the residue indicated a ratio of **3.11a**:**3.11b** = 10:1.0 by integrating the signal of **3.11a** at 7.25 ppm and the signal of **3.11b** at 6.63 ppm. The residue was purified by column chromatography on basified silica gel (NH₄OH) eluting with a gradient solvent system, starting with a solvent mixture of methanol/dichloromethane (1:99 (v/v)) and finishing with methanol/dichloromethane (5:95 (v/v)). Purification afforded 2-aminomoclebobomide (**3.11b**) in one fraction and 3-aminomoclebobomide (**3.11a**) in a second fraction (42.6 mg). The first fraction was further purified by preparative TLC using a solvent system of methanol/dichloromethane (2:98 (v/v)) to give **3.11b** (3.8 mg). A combined yield of 46.4 mg (55% yield) was obtained.

3-Aminomoclebobomide (**3.11a**):

R_f = 0.18 (methanol/dichloromethane, 5:95 (v/v)).

NMR Spectroscopy:

¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.28 (d, *J* = 8.2 Hz, 1H), 7.25 (d, *J* = 2.0 Hz, 1H), 6.97 (dd, *J* = 8.2, 2.1 Hz, 1H), 6.69 (br s, 1H), 4.21 (br s, 2H), 3.72 (t, *J* = 4.6 Hz, 4H), 3.51 (dt, *J* = 5.7, 5.7 Hz, 2H), 2.58 (t, *J* = 6.1 Hz, 2H), 2.49 (br s, 4H).

¹³C NMR (125 MHz, CDCl₃, 23 °C, δ): 166.9, 143.4, 134.4, 129.5, 122.2, 116.5, 114.8, 67.1, 57.0, 53.5, 36.2.

HRMS-FIA(m/z): calc'd for C₁₃H₁₉ClN₃O₂ [M+H]⁺, 284.1160; found, 284.1163.

2-Aminomoclebobomide (**3.11b**):

R_f = 0.25 (methanol/dichloromethane, 5:95 (v/v)).

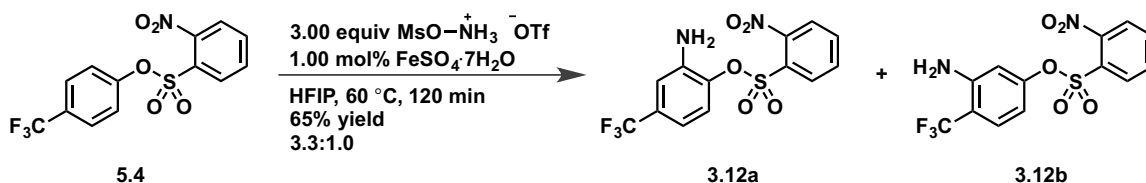
NMR Spectroscopy:

¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 7.25 (d, *J* = 7.7 Hz, 1H), 6.67 (d, *J* = 1.9 Hz, 1H), 6.63 (dd, *J* = 8.4, 2.0 Hz, 1H), 5.67 (br s, 1H), 3.74 (br s, 4H), 3.51 (dt, *J* = 5.7, 5.7 Hz, 2H), 2.61 (t, *J* = 5.7 Hz, 2H), 2.52 (br s, 4H).

^{13}C NMR (125 MHz, CDCl_3 , 23 °C, δ): 168.7, 150.0, 138.2, 128.6, 116.9, 116.7, 114.5, 67.0, 57.0, 53.5, 35.8.

HRMS-FIA(m/z): calc'd for $\text{C}_{13}\text{H}_{19}\text{ClN}_3\text{O}_2$ $[\text{M}+\text{H}]^+$, 284.1160; found, 284.1158.

2-Amino-4-(trifluoromethyl)phenyl 2-nitrobenzenesulfonate (3.12a) and 3-amino-4-(trifluoromethyl)phenyl 2-nitrobenzenesulfonate (3.12b)



Reagent **3.1** (235 mg, 0.900 mmol, 3.00 equiv), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv), and 4-(trifluoromethyl)phenyl 2-nitrobenzenesulfonate (**5.4**) (104 mg, 0.300 mmol, 1.00 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, $c = 0.2$ M). The reaction mixture was stirred at 60 °C for 120 min. The orange reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue indicated a ratio of **3.12a**:**3.12b** = 3.3:1.0 by integrating the signal of **3.12a** at 6.91 ppm and the signal of **3.12b** at 6.58 ppm. The residue was purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (20:80 (v/v)) and finishing with diethyl ether. Purification afforded 2-amino-4-(trifluoromethyl)phenyl 2-nitrobenzenesulfonate (**3.12a**) and 3-amino-4-(trifluoromethyl)phenyl 2-nitrobenzenesulfonate (**3.12b**) in one fraction for a combined yield of 71.0 mg (65% yield). The fraction was further purified by preparative TLC using a solvent system of acetone/pentane (10:90 (v/v)) to give **3.12a** (47.3 mg) and **3.12b** (11.1 mg) as separate samples.

2-Amino-4-(trifluoromethyl)phenyl 2-nitrobenzenesulfonate (**3.12a**):

$R_f = 0.14$ (ethyl acetate/hexanes, 20:80 (v/v)).

NMR Spectroscopy:

^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 7.93 (d, $J = 8.0$ Hz, 1H), 7.89–7.83 (m, 2H), 7.71 (ddd, $J = 7.9$, 6.4, 2.5 Hz, 1H), 7.34 (d, $J = 8.5$ Hz, 1H), 6.93 (dd, $J = 8.6$, 1.8 Hz, 1H), 6.91 (d, $J = 1.9$ Hz, 1H), 4.27 (br s, 2H).

^{13}C NMR (125 MHz, CDCl_3 , 23 °C, δ): 148.7, 140.2, 137.9, 136.0, 132.5, 132.3, 130.7 (q, $J = 32.6$ Hz), 128.5, 125.2, 124.1, 123.7 (q, $J = 270.9$ Hz), 114.9 (q, $J = 3.8$ Hz), 113.7 (q, $J = 3.8$ Hz).

^{19}F NMR (470 MHz, CDCl_3 , 23 °C, δ): –63.2.

HRMS-FIA(m/z): calc'd for $\text{C}_{13}\text{H}_{10}\text{F}_3\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$, 363.0257; found, 363.0246.

3-Amino-4-(trifluoromethyl)phenyl 2-nitrobenzenesulfonate (**3.12b**):

$R_f = 0.10$ (ethyl acetate/hexanes, 20:80 (v/v)).

NMR Spectroscopy:

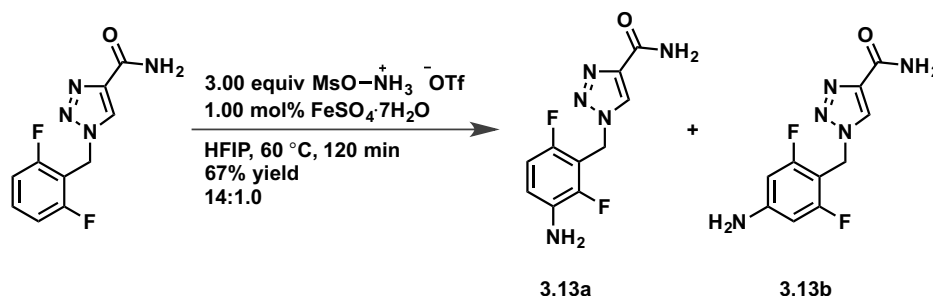
^1H NMR (500 MHz, CDCl_3 , 23 °C, δ): 8.02 (d, $J = 8.0$ Hz, 1H), 7.88–7.82 (m, 2H), 7.72 (ddd, $J = 8.0$, 6.0, 2.7 Hz, 1H), 7.37 (d, $J = 8.7$ Hz, 1H), 6.65 (d, $J = 1.9$ Hz, 1H), 6.58 (ddd, $J = 8.7$, 1.5, 0.8 Hz, 1H), 4.32 (br s, 2H).

^{13}C NMR (125 MHz, CDCl_3 , 23 °C, δ): 152.3, 148.8, 146.4, 135.7, 132.3, 132.3, 128.6 (q, $J = 5.2$), 128.5, 125.1, 124.5 (q, $J = 272$ Hz), 113.0 (q, $J = 30.7$ Hz), 110.8, 110.3.

^{19}F NMR (470 MHz, CDCl_3 , 23 °C, δ): –63.2.

HRMS-FIA(m/z): calc'd for $\text{C}_{13}\text{H}_{10}\text{F}_3\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{H}]^+$, 363.0257; found, 363.0528.

3-Aminorufinamide (3.13a) and 4-aminorufinamide (3.13b)



Reagent **3.1** (235 mg, 0.900 mmol, 3.00 equiv), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv), and rufinamide (71.5 mg, 0.300 mmol, 1.00 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, $c = 0.2 \text{ M}$). The reaction mixture was stirred at 60 °C for 120 min. The red reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate ($2 \times 10 \text{ mL}$). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue indicated a ratio of **3.13a**:**3.13b** = 14:1.0 by integrating the signal of **3.13a** at 8.47 ppm and the signal of **3.13b** at 8.37 ppm. The residue was purified by column chromatography on silica gel basified with NH_4OH eluting with a gradient solvent system, starting with a solvent mixture of methanol/dichloromethane (1:99 (v/v)) and finishing with methanol/dichloromethane (2:98 (v/v)). Purification afforded 3-aminorufinamide and 4-aminorufinamide in one fraction for a combined yield of 51.0 mg (67% yield). The two isomers were characterized as a mixture.

$R_f = 0.10$ (methanol/dichloromethane, 2:98 (v/v)).

NMR Spectroscopy:

^1H NMR (500 MHz, $(\text{CD}_3)_2\text{SO}$, 23 °C, δ): 8.47 (s, 1H), 8.37* (s, 1H), 7.85 (s, 1H), 7.46 (s, 1H), 6.90–6.84 (m, 1H), 6.83–6.76 (m, 1H), 6.23* (d, $J = 10.4$, 2H), 5.65 (s, 2H), 5.47* (s, 2H).

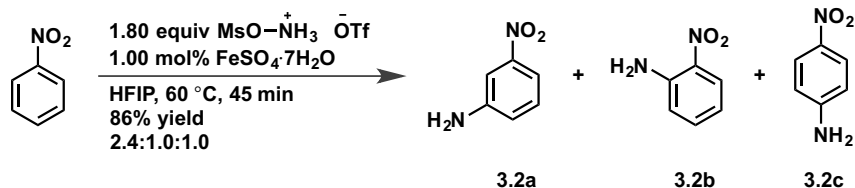
^{13}C NMR (125 MHz, $(\text{CD}_3)_2\text{SO}$, 23 °C, δ): 161.8* (dd, $J = 242.4$, 11.2 Hz), 161.3, 161.2*, 151.3 (dd, $J = 235.5$, 5.7 Hz), 148.2 (dd, $J = 242.0$, 6.9 Hz), 151.9* (d, $J = 14.5$ Hz), 142.8, 142.7*, 133.1 (d, $J = 12.8$ Hz), 116.3 (dd, $J = 6.4$, 6.4 Hz), 111.0 (dd, $J = 21.7$, 3.5 Hz), 110.5 (dd, $J = 19.8$, 16.4 Hz), 96.5* (m), 96.1–95.8* (m), 41.6 (dd, $J = 3.7$, 3.7 Hz), 41.2* (t, 3.7 Hz).

^{19}F NMR (470 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): -120.6^* , -134.5 , -141.1 .

*Denotes signals of minor isomer (**3.13b**).

HRMS-FIA(m/z): calc'd for $\text{C}_{10}\text{H}_{10}\text{F}_2\text{N}_5\text{O}$ $[\text{M}+\text{H}]^+$, 254.0848; found, 254.0842.

Gram-scale amination reaction



Reagent **3.1** (7.64 g, 29.2 mmol, 1.80 equiv) and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (450. mg, 1.62 mmol, 0.0100 equiv) were added to a round bottom flask equipped with a reflux condenser, followed by HFIP (80 mL, $c = 0.2$ M) and nitrobenzene (1.99 g, 1.67 mL, 16.2 mmol, 1.00 equiv). The reaction mixture was stirred at 60 $^\circ\text{C}$ for 45 min. The orange reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 200 mL ethyl acetate and poured into a separatory funnel containing 200 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×200 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue indicated a ratio of **3.2a**:**3.2b**:**3.2c** = 2.4:1.0:1.0 by integrating the signal of **3.2a** at 6.94 ppm, the signal of **3.2b** at 6.76 ppm, and the signal of **3.2c** at 6.62 ppm. The residue was purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (10:90 (v/v)) and finishing with diethyl ether/pentane (60:40 (v/v)). Purification afforded 2-nitroaniline (**3.2b**) in one fraction (472 mg), 3-nitroaniline (**3.2a**) in a second fraction (479 mg) and 4-nitroaniline (**3.2c**) in a third fraction (139 mg). A fourth fraction was collected that contained both **3.2a** and **3.2c**. The fourth fraction was further purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (10:90 (v/v)) and finishing with diethyl ether/pentane (60:40 (v/v)), to afford one fraction containing **3.2a**

(507 mg) and a second fraction containing **3.2c** (338 mg). A combined yield of 1.94 g (86% yield) was obtained.

Comparison to other amination methods

In comparison to other reported modern amination methods that use an ammoniumyl radical precursor, our method is applicable to a much broader electronic scope of aromatic substrates. The most relevant conditions are compared in Table 5.3.

Table 5.3. Comparison of modern amination methods.

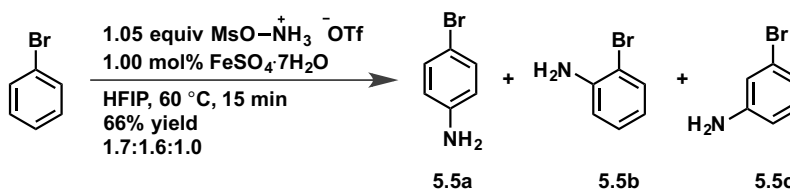
<i>conditions</i>	<i>Ph-OMe</i>	<i>Ph-Br</i>	<i>Ph-CN</i>
this work [MsO–NH ₃]OTf (1.5–1.8 equiv), FeSO ₄ ·7H ₂ O (0.01 equiv), HFIP, 60 °C	57%	66%	89%
ref 144 [MsO–NH ₃]OTf (1.5–4.0 equiv), FeSO ₄ ·7H ₂ O (0.05 equiv), MeCN/H ₂ O (degassed), 23 °C	65%	77%	n.r.
ref 87a HOSA (1.0 equiv), FeSO ₄ ·7H ₂ O (0.03 equiv), AcOH/H ₂ O, 40 °C	60%	30%	5%

Our method also works in the absence of an iron salt, albeit with longer reaction times. When other reported methods are used in the absence of an iron salt, essentially no reaction is observed. Bromobenzene was used to compare reactivity in the absence of iron (Table 5.4).

Table 5.4. Comparison of modern amination methods in the absence of iron.

<i>conditions</i>	<i>NMR yield of 5.5</i>
this work [MsO–NH ₃]OTf (1.5 equiv), HFIP, 60 °C	83%
ref 144 [MsO–NH ₃]OTf (4.0 equiv), MeCN/H ₂ O (degassed), 23 °C	0%
ref 87a HOSA (1.0 equiv), AcOH/H ₂ O, 40 °C	3%

4-Bromoaniline (**5.5a**), 2-bromoaniline (**5.5b**), and 3-bromoaniline (**5.5c**)



Standard procedure (Table 5.3). Reagent **3.1** (82.3 mg, 0.315 mmol, 1.05 equiv) and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, $c = 0.2 \text{ M}$) and bromobenzene (47.1 mg, 31.5 μL , 0.300 mmol, 1.00 equiv). The reaction mixture was stirred at 60 °C for 30 min. The purple reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 $\times$ 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue indicated a ratio of **5.5a**:**5.5b**:**5.5c** = 1.7:1.5:1.0 by integrating the signal of **5.5a** at 7.40 ppm, the signal of **5.5b** at 7.22 ppm, and the signal of **5.5c** at 7.00 ppm. The residue was purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (5:95 (v/v)) and finishing with a solvent mixture of diethyl ether/pentane (30:70 (v/v)). Purification afforded 2-bromoaniline (**5.5b**), 3-bromoaniline (**5.5c**) and 4-bromoaniline (**5.5a**) in one fraction for a combined yield of 34.3 mg (66% yield). Further purification by column chromatography eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (5:95 (v/v)) and finishing with a solvent mixture of diethyl ether/pentane (30:70 (v/v)) gave **5.5b** (10.0 mg), **5.5c** (3.7 mg), and **5.5a** (12.8 mg) in separate fractions. Characterization data matched previously reported data for **5.5a**, **5.5b**, and **5.5c**.¹⁴⁴

This work (Table 5.4). Reagent **3.1** (86.2 mg, 0.330 mmol, 1.10 equiv) was added to a flame-dried Schlenk tube, followed by HFIP (1.5 mL, $c = 0.2 \text{ M}$) and bromobenzene (47.1 mg, 31.5 μL , 0.300 mmol, 1.00 equiv). The reaction mixture was stirred at 60 °C for 16 h. The brown reaction mixture was allowed

to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na₂CO₃. An ethyl acetate solution containing 1,3,5-trimethoxybenzene (0.1 mmol) was added as an internal standard, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ¹H NMR spectrum of the residue was taken, and yield was determined based on integration against the internal standard to be 83%.

Ref 144 (Table 5.4). Reagent **3.1** (313 mg, 1.20 mmol, 4.00 equiv) was added to a flame-dried Schlenck tube, followed by degassed MeCN/H₂O (2:1, 900 μL, c = 0.33 M) and bromobenzene (47.1 mg, 31.5 μL, 0.300 mmol, 1.00 equiv). The reaction mixture was stirred at 23 °C for 16 h. The colorless reaction mixture was diluted with 1.0 M NaOH (aq) (10 ml) and was poured into a separatory funnel. An ethyl acetate solution containing 1,3,5-trimethoxybenzene (0.1 mmol) was added as an internal standard, and the aqueous layer was extracted with dichloromethane (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ¹H NMR spectrum of the residue was taken, and yield was determined based on integration against the internal standard to be 0%.

Ref 87a (Table 5.4). Hydroxylamine-*O*-sulfonic acid (33.9 mg, 0.300 mmol, 1.00 equiv) was added to a flame-dried Schlenck tube, followed by AcOH/H₂O (2:1, 500 μL, c = 0.60 M) and bromobenzene (47.1 mg, 31.5 μL, 0.300 mmol, 1.00 equiv). The reaction mixture was stirred at 40 °C for 16 h. The colorless reaction mixture was basified with 1.0 M NaOH (aq) (~10 ml) and was poured into a separatory funnel. An ethyl acetate solution containing 1,3,5-trimethoxybenzene (0.1 mmol) was added as an internal standard, and the aqueous layer was extracted with diethyl ether (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ¹H NMR spectrum of the residue was taken, and yield was determined based on integration against the internal standard to be 3%.

4-Bromoaniline (**5.5a**):

R_f = 0.28 (ethyl acetate/hexanes, 20:80 (v/v)).

NMR Spectroscopy:

^1H NMR (500 MHz, CD_2Cl_2 , 23 $^\circ\text{C}$, δ): 7.22 (d, J = 8.8 Hz, 2H), 6.57 (d, J = 8.8 Hz, 2H), 3.74 (br s, 2H).

^{13}C NMR (125 MHz, CD_2Cl_2 , 23 $^\circ\text{C}$, δ): 146.4, 132.3, 116.9, 109.9.

HRMS-FIA(m/z): calc'd for $\text{C}_6\text{H}_7\text{NBr}$ $[\text{M}+\text{H}]^+$, 171.9756; found, 171.9751.

2-Bromoaniline (**5.5b**):

R_f = 0.61 (ethyl acetate/hexanes, 20:80 (v/v)).

NMR Spectroscopy:

^1H NMR (500 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): 7.40 (dd, J = 8.0, 1.3 Hz, 1H), 7.10 (dd, J = 7.7, 7.7 Hz, 1H), 6.77 (dd, J = 8.0, 1.5 Hz, 1H), 6.62 (dd, J = 7.0, 7.0 Hz, 1H), 4.09 (br s, 2H).

^{13}C NMR (125 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): 144.2, 132.7, 128.5, 119.5, 115.9, 109.5.

HRMS-FIA(m/z): calc'd for $\text{C}_6\text{H}_7\text{NBr}$ $[\text{M}+\text{H}]^+$, 171.9756; found, 171.9758.

3-Bromoaniline (**5.5c**):

R_f = 0.38 (ethyl acetate/hexanes, 20:80 (v/v)).

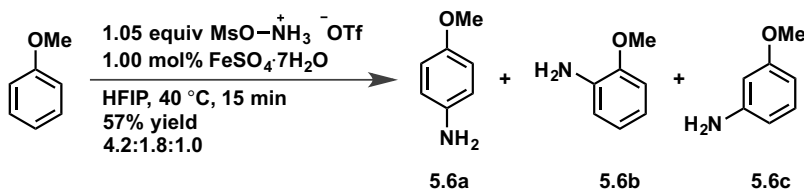
NMR Spectroscopy:

^1H NMR (500 MHz, CD_2Cl_2 , 23 $^\circ\text{C}$, δ): 7.00 (dd, J = 8.0, 8.0 Hz, 1H), 6.85–6.80 (m, 2H), 6.62–6.57 (m, 1H), 3.78 (br s, 2H).

^{13}C NMR (125 MHz, CD_2Cl_2 , 23 $^\circ\text{C}$, δ): 148.7, 131.0, 123.2, 121.3, 117.8, 113.9.

HRMS-FIA(m/z): calc'd for $\text{C}_6\text{H}_7\text{NBr}$ $[\text{M}+\text{H}]^+$, 171.9756; found, 171.9754.

4-Methoxyaniline (**5.6a**), 2-methoxyaniline (**5.6b**), and 3-methoxyaniline (**5.6c**)



Reagent **3.1** (137 mg, 0.525 mmol, 1.05 equiv) and $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (1.4 mg, 5.0 μmol , 0.010 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, c = 0.2 M) and anisole (54.1 mg, 54.3 μL , 0.500 mmol,

1.00 equiv). The reaction mixture was stirred at 40 °C for 15 min. The blue reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 15 mL ethyl acetate and poured into a separatory funnel containing 15 mL sat. aq. Na₂CO₃. The layers were separated, and the aqueous layer was extracted with ethyl acetate (2 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ¹H NMR spectrum of the residue indicated a ratio of **5.6a**:**5.6b**:**5.6c** = 4.2:1.8:1.0 by integrating the signal of **5.6a** at 6.72 ppm, the signal of **5.6b** at 6.79 ppm and the signal of **5.6c** at 7.06 ppm. The residue was purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (10:90 (v/v)) and finishing with a solvent mixture of diethyl ether/pentane (40:60 (v/v)). Purification afforded 2-methoxyaniline (**5.6b**), 3-methoxyaniline (**5.6c**) and 4-methoxyaniline (**5.6a**) in one fraction for a combined yield of 35.3 mg (57% yield). Further purification by column chromatography eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (10:90 (v/v)) and finishing with a solvent mixture of diethyl ether/pentane (40:60 (v/v)) gave **5.6b** (5.9 mg), **5.6c** (3.0 mg), and **5.6a** (14.9 mg) in separate fractions. Characterization data matched previously reported data for **5.6a**, **5.6b**, and **5.6c**.¹⁴⁴

4-Methoxyaniline (**5.6a**):

R_f = 0.14 (ethyl acetate/hexanes, 20:80 (v/v)).

NMR Spectroscopy:

¹H NMR (500 MHz, CD₂Cl₂, 23 °C, δ): 6.72 (d, J = 8.9 Hz, 2H), 6.62 (d, J = 9.0 Hz, 2H), 3.71 (s, 3H), 3.45 (br s, 2H).

¹³C NMR (125 MHz, CD₂Cl₂, 23 °C, δ): 153.0, 140.8, 116.4, 115.1, 56.0.

HRMS-FIA(m/z): calc'd for C₇H₁₀NO [M+H]⁺, 124.0757; found, 124.0758.

2-Methoxyaniline (**5.6b**):

R_f = 0.63 (ethyl acetate/pentanes, 30:70 (v/v)).

NMR Spectroscopy:

¹H NMR (500 MHz, CDCl₃, 23 °C, δ): 6.79 (m, 2H), 6.73 (m, 2H), 3.85 (s, 3H), 3.78 (br s, 2H).

^{13}C NMR (125 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): 147.5, 136.3, 121.2, 118.6, 115.2, 110.6, 55.6.

HRMS-FIA(m/z): calc'd for $\text{C}_7\text{H}_{10}\text{NO}$ $[\text{M}+\text{H}]^+$, 124.0757; found, 124.0755.

3-Methoxyaniline (**5.6c**):

R_f = 0.43 (ethyl acetate/pentanes, 30:70 (v/v)).

NMR Spectroscopy:

^1H NMR (500 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): 7.06 (dd, J = 8.1, 8.1 Hz, 1H), 6.33 (ddd, J = 8.2, 2.3, 0.8 Hz, 1H), 6.30 (ddd, J = 7.9, 2.1, 0.8 Hz, 1H), 6.25 (dd, J = 2.3, 2.3 Hz, 1H), 3.76 (s, 3H), 3.66 (br s, 2H).

^{13}C NMR (125 MHz, CDCl_3 , 23 $^\circ\text{C}$, δ): 160.9, 147.9, 130.3, 108.1, 104.1, 101.2, 55.2.

HRMS-FIA(m/z): calc'd for $\text{C}_7\text{H}_{10}\text{NO}$ $[\text{M}+\text{H}]^+$, 124.0757; found, 124.0755.

5.3.2. Mechanistic experiments

Effect of iron and oxygen on the amination reaction

The presence of both iron and oxygen has an effect on the reaction time with the shortest reaction times being observed when both are present. 1,4-Dibromobenzene was used to show the effect of iron and oxygen. See below for a description of reaction setup and trace metal analysis for metal-free experiments.

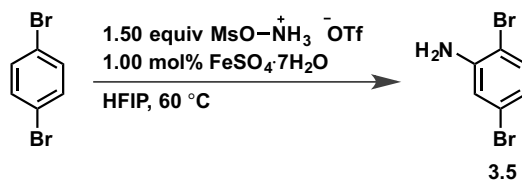


Table 5.5. Effect of iron and oxygen on reaction time

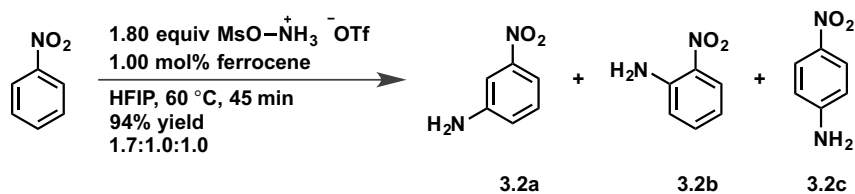
conditions	NMR yield of 2,5-dibromoaniline (3.5)	time
no [Fe], under N_2	88%	7 h
no [Fe], under air	89%	5 h
under N_2	89%	20 min
under air	90%	13 min

Under nitrogen. Reagent **3.1** (118 mg, 0.450 mmol, 1.50 equiv), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv), and 1,4-dibromobenzene (70.8 mg, 0.300 mmol, 1.00 equiv) were added to a flame-dried Schlenk tube. The vessel was evacuated and backfilled with nitrogen three times. Distilled, degassed HFIP (1.5 mL, $c = 0.2 \text{ M}$) was then added. The reaction mixture was stirred at 60 °C until judged complete. The red reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . An ethyl acetate solution containing 1,3,5-trimethoxybenzene (0.1 mmol) was added as an internal standard, and the layers were separated. The aqueous layer was extracted with ethyl acetate ($2 \times 10 \text{ mL}$). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue was taken, and yield was determined based on integration against the internal standard.

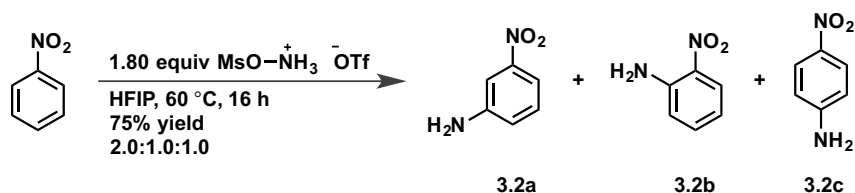
Under air. Reagent **3.1** (118 mg, 0.450 mmol, 1.50 equiv), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv), and 1,4-dibromobenzene (70.8 mg, 0.300 mmol, 1.00 equiv) were added to a flame-dried Schlenk tube. Distilled HFIP (1.5 mL, $c = 0.2 \text{ M}$) that had been vigorously stirred under air for >20 min was then added. The reaction mixture was stirred at 60 °C until judged complete. The red reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . An ethyl acetate solution containing 1,3,5-trimethoxybenzene (0.1 mmol) was added as an internal standard, and the layers were separated. The aqueous layer was extracted with ethyl acetate ($2 \times 10 \text{ mL}$). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue was taken, and yield was determined based on integration against the internal standard.

Effect of iron source

Multiple iron(II) and iron(III) sources were observed to promote the amination reaction effectively, and the reaction also works in the absence of iron for multiple substrates. Nitrobenzene was used to show the effect of the iron source.



With ferrocene. Reagent **3.1** (141 mg, 0.540 mmol, 1.80 equiv) and ferrocene (0.6 mg, 3.0 μ mol, 0.010 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, $c = 0.2$ M) and nitrobenzene (36.9 mg, 30.8 μ L, 0.300 mmol, 1.00 equiv). The reaction mixture was stirred at 60 $^\circ$ C for 45 min. The orange reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue indicated a ratio of **3.2a**:**3.2b**:**3.2c** = 1.7:1.0:1.0 by integrating the signal of **3.2a** at 6.94 ppm, the signal of **3.2b** at 6.76 ppm, and the signal of **3.2c** at 6.62 ppm. The residue was purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (20:80 (v/v)) and finishing with diethyl ether/pentane (40:60 (v/v)). Purification afforded 2-nitroaniline (**3.2b**), 3-nitroaniline (**3.2a**) and 4-nitroaniline (**3.2c**) in separate fractions for a combined yield of 39.0 mg (94% yield).

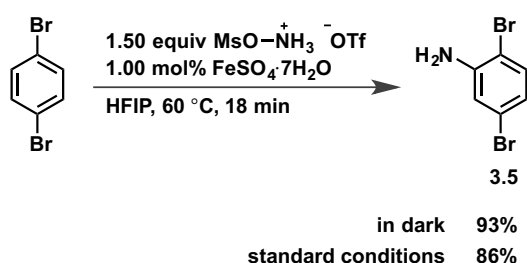


No iron source. Reagent **3.1** (141 mg, 0.540 mmol, 1.80 equiv) was added to an oven-dried Schlenk tube, followed by HFIP (1.5 mL, $c = 0.2$ M) and nitrobenzene (36.9 mg, 30.8 μ L, 0.300 mmol, 1.00 equiv). The reaction mixture was stirred at 60 $^\circ$ C for 16 h. The orange reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . The layers were separated, and the aqueous layer was extracted with ethyl acetate (2×10 mL). The combined organic layers were dried over

sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue indicated a ratio of **3.2a:3.2b:3.2c** = 2.0:1.0:1.0 by integrating the signal of **3.2a** at 6.94 ppm, the signal of **3.2b** at 6.76 ppm, and the signal of **3.2c** at 6.62 ppm. The residue was purified by column chromatography on silica gel eluting with a gradient solvent system, starting with a solvent mixture of diethyl ether/pentane (20:80 (v/v)) and finishing with diethyl ether/pentane (40:60 (v/v)). Purification afforded 2-nitroaniline (**3.2b**), 3-nitroaniline (**3.2a**) and 4-nitroaniline (**3.2c**) in separate fractions for a combined yield of 31.1 mg (75% yield).

Effect of light

Ambient light was found to have no effect on the results of the amination reaction. A reaction run in the dark (wrapped in foil) gave similar results to the standard reaction conditions.

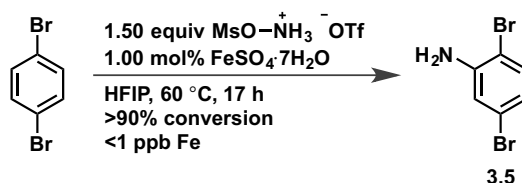


Reagent **3.1** (118 mg, 0.450 mmol, 1.50 equiv), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv), and 1,4-dibromobenzene (70.8 mg, 0.300 mmol, 1.00 equiv) were added to a 4-mL vial, followed by HFIP (1.5 mL, $c = 0.2 \text{ M}$). The reaction mixture was stirred at 60 $^\circ\text{C}$ for 18 min. The red reaction mixture was allowed to cool to room temperature and was concentrated. The residue was dissolved in 10 mL ethyl acetate and poured into a separatory funnel containing 10 mL sat. aq. Na_2CO_3 . An ethyl acetate solution containing 1,3,5-trimethoxybenzene (0.1 mmol) was added as an internal standard, and the layers were separated. The aqueous layer was extracted with ethyl acetate ($2 \times 10 \text{ mL}$). The combined organic layers were dried over sodium sulfate, filtered and concentrated. A ^1H NMR spectrum of the residue was taken, and yield was determined based on integration against the internal standard.

Trace metal analysis

Reactions performed in the absence of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ were conducted with the following precautions: All glassware and stirbars were washed with aqua regia solution, rinsed with deionized water and dried in an oven. Solids were handled with glass pipettes. Solvents were distilled before use.

ICP-MS analysis was performed by Robertson Microlit Laboratories, 1705 U.S. Highway 46, Suite 1D, Ledgewood, NJ 07852. Samples were prepared and sent out for analysis in the following way:



Reagent **3.1** (82.3 mg, 0.315 mmol, 1.05 equiv), $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ (0.8 mg, 3 μmol , 0.01 equiv), and 1,4-dibromobenzene (70.8 mg, 0.300 mmol, 1.00 equiv) were added to a flame-dried Schlenk tube. The vessel was evacuated and backfilled with nitrogen three times. Distilled, degassed HFIP (1.5 mL, $c = 0.2$ M) was then added. The reaction mixture was stirred at 60 °C for 17 h. The red reaction mixture was allowed to cool to room temperature. A small aliquot was taken to determine conversion, which was always >90% as judged by ^1H NMR. The bulk of the reaction mixture was transferred to a glass vial, sealed and sent out for ICP-MS analysis. Duplicate samples were analyzed in this manner. One contained <1 ppb Fe and 60 ppb Cu, while the other contained <1 ppb Fe and <1 ppb Cu.

Consumption studies of reagent 3.1

Reagent **3.1** is consumed to generate methanesulfonic acid (MsOH) even when an arene substrate is not added to the reaction. MsOH is formed faster in the presence of $\text{FeSO}_4 \cdot 7\text{H}_2\text{O}$ and/or residual moisture.

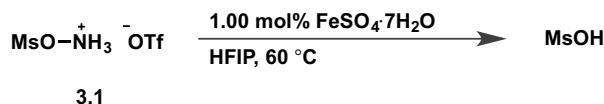


Table 5.6. Consumption of reagent **3.1** in the absence of arene.

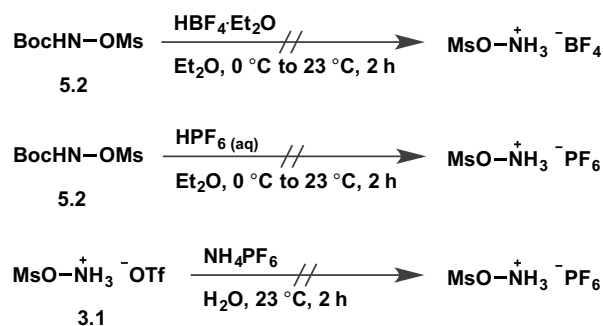
<i>change from reaction conditions</i>	<i>NMR yield of MsOH</i>
no [Fe], under N ₂ , 16h	5%
no [Fe], under air, 16h	33%
under N ₂ , 4h	33%
under air, 4h	52%
under N ₂ , 16h	100%
under air, 16h	100%

Under nitrogen. Reagent **3.1** (78.4 mg, 0.300 mmol, 1.00 equiv) and FeSO₄·7H₂O (0.8 mg, 3 μmol, 0.01 equiv) were added to a flame-dried Schlenck tube. The vessel was evacuated and backfilled with nitrogen three times. Distilled, degassed HFIP (1.5 mL, c = 0.2 M) was then added. The reaction mixture was stirred at 60 °C for the designated time. The reaction mixture was allowed to cool to room temperature and was concentrated. A solution containing nitromethane (0.1 mmol) in CD₃CN was added as an internal standard. A ¹H NMR spectrum of the residue was taken, and yield was determined based on integration against the internal standard.

Under air. Reagent **3.1** (78.4 mg, 0.300 mmol, 1.00 equiv) and FeSO₄·7H₂O (0.8 mg, 3 μmol, 0.01 equiv) were added to a flame-dried Schlenck tube. Distilled HFIP (1.5 mL, c = 0.2 M) that had been vigorously stirred under air for >20 min was then added. The reaction mixture was stirred at 60 °C for the designated time. The reaction mixture was allowed to cool to room temperature and was concentrated. A solution containing nitromethane (0.1 mmol) in CD₃CN was added as an internal standard. A ¹H NMR spectrum of the residue was taken, and yield was determined based on integration against the internal standard.

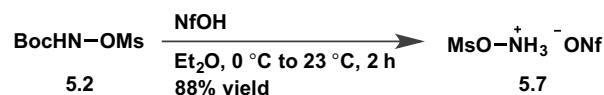
Synthesis of reagent **3.1** with other counterions

Attempts to synthesize [MsO–NH₃]⁺ with counterions less capable of hydrogen bonding were unsuccessful:



Synthesis of the reagent with a nonaflate counterion was successful, as might be expected due to its similar hydrogen bond donating ability as compared to triflate:

[MsO-NH₃]⁺ONf⁻ (5.7)



Compound **5.2** (1.00 g, 4.73 mmol, 1.00 equiv) was dissolved in anhydrous diethyl ether (24 mL) in a flame-dried round bottom flask. The flask was evacuated and backfilled with nitrogen, then cooled in a water-ice bath. Nonafluorobutanesulfonic acid (1.42 g, 784 μL , 4.73 mmol, 1.00 equiv) was added. The reaction mixture was allowed to stir at room temperature for 2 h, during which time a colorless precipitate formed. Heptane (15 mL) was added to the flask. The colorless solid was collected on a Buchner funnel, rinsed with heptane (10 mL) and dried under high vacuum to give 1.72 g of the title compound as a colorless solid (88% yield). ¹³C NMR peaks for the nonaflate counterion were not observed due to the complex C-F splitting. The presence of a nonaflate counterion was confirmed by ¹⁹F NMR spectroscopy.

NMR Spectroscopy:

¹H NMR (500 MHz, (CD₃)₂CO, 23 $^\circ\text{C}$, δ): 3.15 (s, 3H).

¹³C NMR (125 MHz, (CD₃)₂CO, 23 $^\circ\text{C}$, δ): 36.6.

¹⁹F NMR (470 MHz, CD₃CN, 23 $^\circ\text{C}$, δ): -82.1 (tt, J = 10.1, 2.8 Hz, 3F), -116.0 (m, 2F), -122.6 (m, 2F), -127.0 (m, 2F).

HRMS-FIA(m/z): calc'd for CH₆NO₃S [M]⁺, 112.0068; found, 112.0049.

5.3.3. Electrochemical data

General methods

Cyclic voltammetry (CV) was performed in a nitrogen-filled glovebox using a solution of approximately 2 mg/mL of reagent [MsO–NH₃]OTf (**3.1**) in 0.1 M Bu₄NOTf in either HFIP or MeCN. HFIP and MeCN were distilled and degassed. Bu₄NOTf was recrystallized from DCM/Et₂O at –10 °C and dried under high vacuum at 65 °C for 24 h. Cyclic voltammetry was measured using a three-electrode setup with a glassy carbon working electrode, a platinum wire counter electrode and a Ag⁰ quasi-reference electrode. Ferrocene was used as an external standard, and potentials are reported vs. Fc/Fc⁺. For each solvent, the CV of reagent **3.1** was measured at five different scan rates (25, 50, 100, 200 and 400 mV/s). The irreversible reduction events are assigned a reduction potential that corresponds to the potential at half the maximum current (E_{p/2}).¹⁹²

[MsO–NH₃]OTf (**3.1**) in HFIP

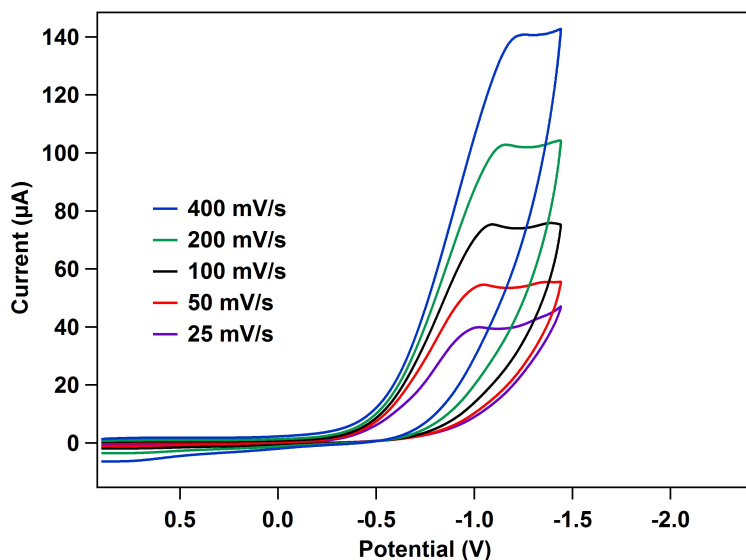


Figure 5.2. CV of [MsO–NH₃]OTf (**3.1**) in HFIP.

[MsO–NH₃]OTf (**3.1**) in MeCN

¹⁹² Roth, H. G.; Romero, N. A.; Nicewicz, D. A. *Synlett* **2016**, 27, 714–723.

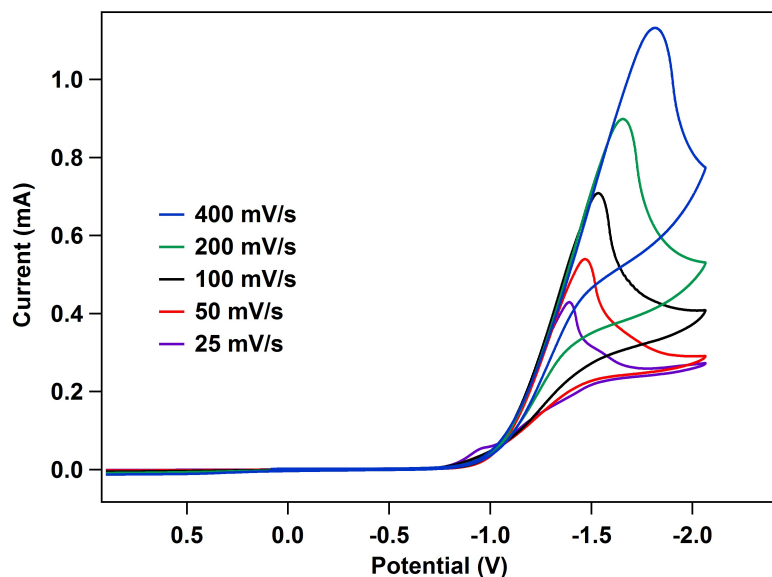


Figure 5.3. CV of $[\text{MsO-NH}_3]\text{OTf}$ (**3.1**) in MeCN.

Comparison of electrochemical data

Table 5.7. Dependence of the reduction potential of $[\text{MsO-NH}_3]\text{OTf}$ (**3.1**) on scan rate in HFIP and MeCN.

Scan rate (mV/s)	$E_{p/2}$ (HFIP)	$E_{p/2}$ (MeCN)
25	-0.74 V	-1.12 V
50	-0.74 V	-1.25 V
100	-0.77 V	-1.28 V
200	-0.81 V	-1.35 V
400	-0.86 V	-1.43 V

In both HFIP and MeCN, the reduction potential of $[\text{MsO-NH}_3]\text{OTf}$ (**3.1**) is scan rate dependent, as is summarized in Table 5.7. However, there is a clear difference in reduction potential between the two solvents despite the scan rate, with the reduction potential being ~ 0.5 V less negative in HFIP than MeCN. Therefore, $[\text{MsO-NH}_3]\text{OTf}$ (**3.1**) is a stronger oxidant in HFIP than in MeCN.

5.3.4. DFT calculations

DFT results for 3.1 in HFIP

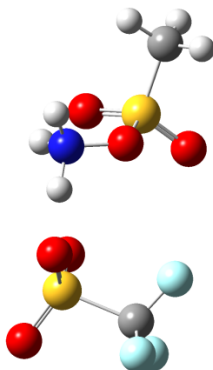


Figure 5.4. Optimized structure of **3.1**.

Table 5.8. Cartesian coordinates (Å) of optimized structure of **3.1** with ω B97XD/BS I.

Atom	X	Y	Z
S	1.796119	-0.804916	-0.286781
F	3.233472	0.913433	1.094697
O	1.334813	-1.387044	1.004446
O	0.697022	-0.643827	-1.234329
F	2.655681	1.609426	-0.867493
F	1.201110	1.548177	0.729083
O	3.028937	-1.381853	-0.790420
C	2.250219	0.926183	0.198942
S	-2.693440	0.317373	-0.287657
O	-2.713364	-0.775045	-1.229209
O	-2.222457	1.624092	-0.631403
O	-1.621029	-0.178356	0.938170
N	-1.257345	-1.527771	0.895352
C	-4.210494	0.407179	0.617176
H	-1.764932	-2.035396	1.622092
H	-0.186057	-1.544840	1.044402
H	-1.470844	-1.919339	-0.033632
H	-4.963931	0.769301	-0.081610
H	-4.075160	1.110424	1.435881
H	-4.462625	-0.588301	0.975089

DFT results for 3.1 in MeCN

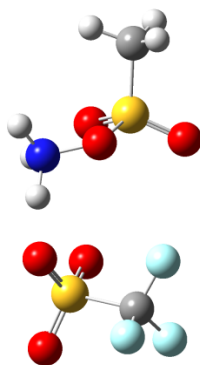


Figure 5.5. Optimized structure of **3.1**.

Table 5.9. Cartesian coordinates (Å) of optimized structure of **3.1** with ω B97XD/BS I.

Atom	X	Y	Z
S	1.800599	-0.804773	-0.288553
F	3.232280	0.904859	1.109498
O	1.329137	-1.385153	0.998805
O	0.711034	-0.637109	-1.245728
F	2.686222	1.601880	-0.861530
F	1.209946	1.554982	0.715742
O	3.034840	-1.387158	-0.783772
C	2.261007	0.923572	0.200738
S	-2.704718	0.316999	-0.288489
O	-2.722171	-0.777341	-1.227877
O	-2.237715	1.624202	-0.636971
O	-1.623723	-0.169575	0.932908
N	-1.268377	-1.521772	0.904108
C	-4.219560	0.403721	0.619703
H	-1.769899	-2.016751	1.643961
H	-0.197729	-1.542517	1.042738
H	-1.495674	-1.925443	-0.016270
H	-4.976867	0.755550	-0.079961
H	-4.086409	1.114135	1.432451
H	-4.464816	-0.590362	0.986057

The hydrogen bond length between the triflate anion and the $[\text{MsO-NH}_3]^+$ cation in the optimized structures in continuum HFIP and continuum acetonitrile is found to be 1.53 Å, which is 0.40 Å shorter than in the crystal structure. Significantly shorter ion-pair distances in calculated structures have been observed previously and were attributed to steric effects.¹⁹³

DFT results for HFIP

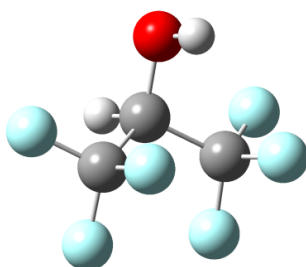


Figure 5.6. Optimized structure of HFIP.

Table 5.10. Cartesian coordinates (Å) of optimized structure of HFIP with ω B97XD/BS I.

Atom	X	Y	Z
H	-0.000233	1.962522	0.779924
C	0.000008	0.533793	-0.530643
H	0.000092	0.471179	-1.619331
C	-1.284463	-0.150012	-0.042764
C	1.284507	-0.149938	-0.042746
O	-0.000104	1.879411	-0.179037
F	-2.345488	0.456622	-0.580588
F	-1.406670	-0.064486	1.290796
F	-1.336208	-1.440603	-0.378578
F	1.336619	-1.440255	-0.379610
F	2.345565	0.457321	-0.579751
F	1.406255	-0.065493	1.290911

¹⁹³ Zhang, S.; Chen, Z.; Lu, Y.; Xu, Z.; Wu, W.; Zhu, W.; Peng, C.; Liu, H. *RSC Adv.* **2015**, 5, 74284–74294.

DFT results for 3.1·HFIP (OMs)

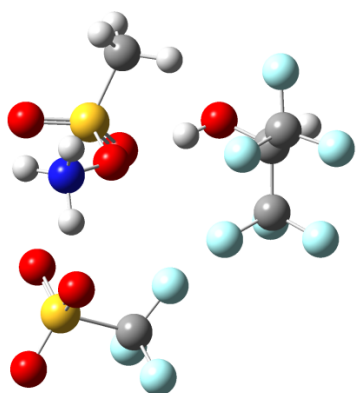


Figure 5.7. Optimized structure of 3.1·HFIP (OMs).

Table 5.11. Cartesian coordinates (Å) of optimized structure of 3.1·HFIP (OMs) with ω B97XD/BS I.

Atom	X	Y	Z
S	-3.473665	-0.641749	-0.038481
F	-2.574829	-2.856120	1.065888
O	-3.541288	0.019003	1.295876
O	-2.926154	0.251969	-1.055774
F	-1.843894	-2.498932	-0.936160
F	-1.060129	-1.356094	0.722125
O	-4.661430	-1.397788	-0.388175
C	-2.153618	-1.919969	0.220176
S	-0.276784	2.473025	-0.641640
O	-1.333915	3.166014	-1.332130
O	-0.986649	1.842275	0.761408
N	-2.292756	2.277462	1.011275
C	0.900786	3.591360	0.058247
H	-2.273532	2.963178	1.768576
H	-2.853405	1.383948	1.258724
H	-2.691716	2.696947	0.158643
H	1.490352	3.978178	-0.772333
H	1.527575	3.030140	0.747831
H	0.363456	4.391875	0.561755
O	0.386066	1.338785	-1.222309
H	2.134488	0.684036	-1.354443
C	3.457469	-0.369143	-0.389210

H	4.538516	-0.508081	-0.441072
C	2.823083	-1.746074	-0.632998
C	3.162000	0.202023	1.005038
O	3.089296	0.521854	-1.385669
F	3.289880	-2.254832	-1.777404
F	1.492084	-1.660210	-0.746800
F	3.097532	-2.616680	0.342911
F	3.641742	-0.566592	1.982893
F	3.722684	1.410987	1.120870
F	1.843264	0.359701	1.217009

3.1·HFIP (OMs) is found to be 5.9 kcal/mol higher in energy than **3.1** and a free HFIP molecule.

DFT results for **3.1·HFIP (OTf)**

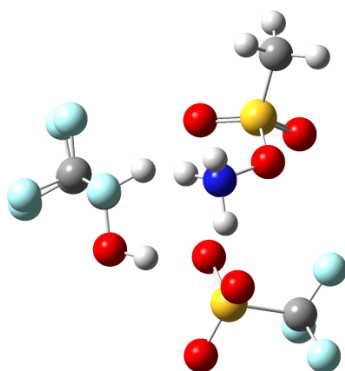


Figure 5.8. Optimized structure of **3.1·HFIP (OTf)**.

Table 5.12. Cartesian coordinates (Å) of optimized structure of **3.1·HFIP (OTf)** with ω B97XD/BS I.

Atom	X	Y	Z
S	2.086636	-1.472640	0.603406
F	4.555115	-1.821527	-0.218333
O	2.580400	-0.658431	1.737944
O	0.918230	-0.842606	-0.037118
F	3.071290	-1.915007	-1.786489
F	3.629124	-0.007237	-0.938678
O	1.985760	-2.894410	0.859339

C	3.423813	-1.290519	-0.668777
S	0.626680	2.711856	-0.566268
O	1.724792	2.175883	0.618847
N	1.151856	1.550538	1.730173
C	0.582973	4.448615	-0.236207
H	1.150055	2.199820	2.519533
H	1.760740	0.689616	1.903854
H	0.191275	1.235679	1.516733
H	-0.056960	4.886772	-1.001518
H	1.596659	4.834943	-0.313492
H	0.160892	4.606189	0.753422
O	1.305962	2.435150	-1.794070
O	-0.627927	2.090055	-0.216739
C	-2.293283	-0.651059	-0.221455
H	-1.732267	0.154097	-0.706153
H	-0.635401	-1.616283	-0.125543
O	-1.584436	-1.838152	-0.125014
C	-3.523163	-0.918606	-1.089343
C	-2.644023	-0.139804	1.181565
F	-3.135920	-1.235620	-2.329318
F	-4.262545	-1.931611	-0.627063
F	-4.316238	0.157937	-1.175353
F	-3.403903	-0.989740	1.872302
F	-3.260502	1.043952	1.160304
F	-1.499886	0.020663	1.887910

3.1·HFIP (OTf) is found to be 0.8 kcal/mol higher in energy than **3.1** and a free HFIP molecule.

DFT results for **3.1·2HFIP**

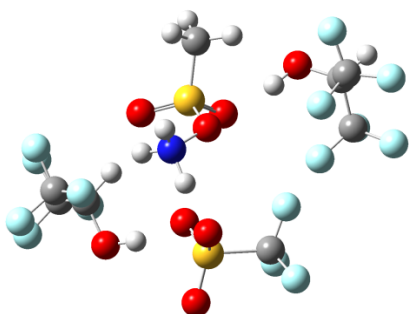


Figure 5.9. Optimized structure of **3.1·2HFIP**.

Table 5.13. Cartesian coordinates (Å) of optimized structure of **3.1·2HFIP** with ω B97XD/BS I.

Atom	X	Y	Z
S	-0.789858	2.765024	-0.382283
F	1.350688	4.225629	0.037819
O	-0.587276	2.820805	-1.849649
O	-1.154309	1.405516	0.053830
F	0.919508	2.804574	1.607809
F	1.754361	2.125630	-0.265841
O	-1.576337	3.846210	0.173573
C	0.922983	2.994238	0.293868
S	0.102062	-1.586078	-1.233650
O	0.354402	-0.181709	-2.146124
N	-0.794228	0.364108	-2.729221
C	0.843838	-2.804323	-2.276980
H	-0.784355	0.161335	-3.730895
H	-0.741221	1.414859	-2.517723
H	-1.644264	-0.027467	-2.292000
H	0.794787	-3.745324	-1.729728
H	1.877642	-2.516411	-2.455727
H	0.273082	-2.861408	-3.201632
O	0.887191	-1.371342	-0.051360
H	2.509902	-2.007067	0.605562
C	4.404047	-1.587500	0.772822
H	5.309608	-2.141903	1.024597
C	4.252244	-0.481106	1.827313
C	4.615699	-1.041186	-0.647408

O	3.332933	-2.465519	0.830827
F	4.304487	-1.017002	3.050420
F	3.073605	0.145254	1.715358
F	5.216458	0.440855	1.742608
F	5.780160	-0.398135	-0.764798
F	4.617828	-2.053340	-1.521813
F	3.642567	-0.196697	-1.020417
O	-1.329689	-1.741122	-1.166780
C	-3.658520	-0.537915	0.720610
H	-2.701307	-1.041782	0.556025
H	-2.663683	1.100543	0.861950
O	-3.526258	0.766717	1.169224
C	-4.389542	-1.325952	1.808287
C	-4.384917	-0.552353	-0.630426
F	-3.641799	-1.358899	2.916458
F	-5.565217	-0.777456	2.131911
F	-4.619441	-2.592765	1.436937
F	-5.604591	-0.017121	-0.570563
F	-4.495458	-1.780281	-1.143229
F	-3.678278	0.186739	-1.516858

3.1·2HFIP is found to be 6.6 kcal/mol higher in energy than **3.1** and two free HFIP molecules, which suggests HFIP destabilizes reagent **3.1**. The sum of the individual effects of one HFIP hydrogen bonding to $[\text{MsO-NH}_3]^+$ (5.9 kcal/mol) and one HFIP hydrogen bonding to the triflate counterion (0.8 kcal/mol) is 6.7 kcal/mol, which is consistent with the results of the calculation with two HFIP hydrogen bonding interactions.

DFT results for $[\text{NH}_3]^+(\text{OTf})$ (**5.8**)

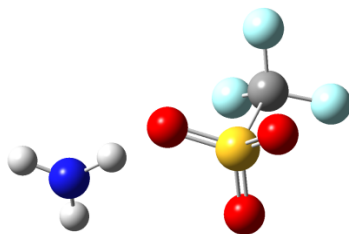


Figure 5.10. Optimized structure of $[\text{NH}_3]^+(\text{OTf})$ (**5.8**).

Table 5.14. Cartesian coordinates (Å) of optimized structure of $[\text{NH}_3]^+(\text{OTf})$ (**5.8**) with $\omega\text{B97XD/BS I}$.

Atom	X	Y	Z
S	-0.088001	0.824335	0.019420
F	1.473110	-0.886948	-1.239373
O	-1.198631	0.352257	-0.856073
O	-0.475925	0.959109	1.415595
F	2.120072	-0.394575	0.761894
F	0.434535	-1.714799	0.465358
O	0.679733	1.907240	-0.568632
C	1.057172	-0.634100	-0.001692
N	-3.324336	-0.817477	-0.011555
H	-4.037069	-1.124406	-0.669113
H	-2.414690	-0.323134	-0.342151
H	-3.503772	-0.996815	0.973541

DFT results for MsO^+ (**5.9**)

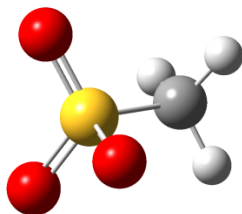
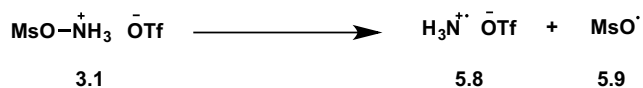


Figure 5.11. Optimized structure of MsO· (5.9).

Table 5.15. Cartesian coordinates (Å) of optimized structure of MsO· (5.9) with ω B97XD/BS I.

Atom	X	Y	Z
S	-0.100444	0.072405	0.000071
O	-0.373948	1.488671	0.000135
O	-0.700174	-0.694735	-1.136201
O	-0.700326	-0.695102	1.135911
C	1.644592	-0.200872	0.000029
H	2.055581	0.264806	-0.894046
H	1.823804	-1.273744	0.000077
H	2.055743	0.265026	0.893903

Calculation of homolysis energy



The homolysis energy $E_{\text{homolysis}}$ of **3.1** has been calculated using the following equation:

$$E_{\text{homolysis}} = E(\text{S7}) + E(\text{S8}) - E(1) = 35.6 \text{ kcal} \cdot \text{mol}^{-1} \quad (1)$$

The homolysis energy of $35.6 \text{ kcal} \cdot \text{mol}^{-1}$ implies that homolysis is a feasible mechanistic step to generate ammoniumyl and mesyloxy radicals.

Comparison of LUMO energy differences and reduction potentials

The LUMO energies of **3.1**, **3.1·HFIP(OMs)**, **3.1·HFIP(OTf)** and **3.1·2HFIP** have been calculated by addition of the corresponding HOMO energies to the transition energy ΔE^1 to the first excited state determined by TD-DFT calculations.¹⁹⁴

$$\Delta E^1 = E(\text{LUMO}) - E(\text{HOMO}) \leftrightarrow E(\text{LUMO}) = \Delta E^1 + E(\text{HOMO}) \quad (2)$$

The LUMO of **3.1·2HFIP** is 7.7 kcal·mol⁻¹ lower in energy than the LUMO of **3.1** in HFIP and 8.3 kcal·mol⁻¹ lower than the LUMO of **3.1** in acetonitrile. The LUMO of **3.1·HFIP(OMs)** is 4.8 kcal·mol⁻¹ lower in energy than the LUMO of **3.1** and the LUMO of **3.1·HFIP(OTf)** is 3.2 kcal·mol⁻¹ lower than the LUMO of **3.1**. Their sum (8.0 kcal·mol⁻¹) is consistent with the value calculated from **3.1·2HFIP**.

The energy difference of 8.3 kcal mol⁻¹ would correspond to a difference in the reduction potential of $\Delta E = 0.4$ V between **3.1** in MeCN and **3.1·2HFIP** coordination. This value is consistent with our experimentally measured CV data, which show ~0.5 V difference between the reduction potential of **3.1** in MeCN and HFIP (see Table 5.7).

$$\Delta E = \frac{34.7 \text{ J}}{96.5 \text{ C}} = 0.4 \text{ V}$$

The LUMO of **3.1·2 HFIP** shows large contributions of the $\sigma^*(\text{N-O})$ orbital.

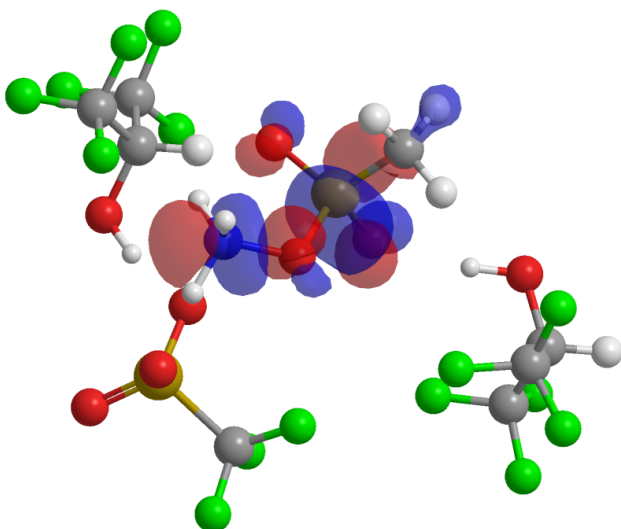


Figure 5.12. LUMO of **3.1·2HFIP** plotted with an isosurface value of 0.05.

¹⁹⁴ Zhang, G.; Musgrave, C. B. *J. Phys. Chem. A* **2007**, *111*, 1554–1561.

5.3.5. X-ray crystallography

[MsO–NH₃]⁺OTf[−] (3.1) (CCDC 1545194)

Reagent **3.1** was crystallized from HFIP (~20 mg in 2 mL) at −10 °C. A crystal was mounted on a nylon loop using Paratone-N oil, and transferred to a Bruker APEX II CCD diffractometer (MoK α 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 V8.34 C (Bruker diffractometer, 2014) with reflection spot size optimization. Absorption corrections were made with the programs SADABS (Bruker diffractometer, 2014). The structure was solved by the direct methods procedure and refined by least-squares methods against F² using SHELXT-2014 and SHELXL-2014 (Sheldrick, 2015). Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were allowed to ride on the respective atoms. Crystal data as well as details of data collection and refinement are summarized in Table 5.16 below.

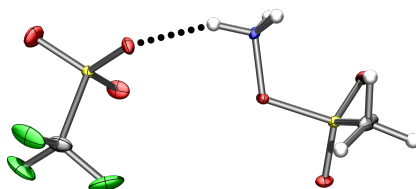


Figure 5.13. X-ray crystal structure of [MsO–NH₃]⁺OTf[−] (**3.1**). Thermal ellipsoids are drawn at 50% probability level. Red = oxygen, blue = nitrogen, yellow = sulfur, green = fluorine.

Table 5.16. Experimental details for [MsO–NH₃]⁺OTf[−] (**3.1**).

Empirical formula	C ₂ H ₆ F ₃ NO ₆ S ₂
Formula weight	261.20
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	orthorhombic

Space group	Pna2 ₁	
Unit cell dimensions	a = 8.9227(15) Å	$\alpha = 90^\circ$
	b = 18.531(3) Å	$\beta = 90^\circ$
	c = 5.5268(9) Å	$\gamma = 90^\circ$
Volume	913.8(3) Å ³	
Z	4	
Density (calculated)	1.899 Mg/m ³	
Absorption coefficient	0.639 mm ⁻¹	
F(000)	528.0	
Crystal size	0.82 × 0.13 × 0.08 mm ³	
θ range for data collection	2.198 to 25.013°	
Index ranges	-10 ≤ h ≤ 10, -22 ≤ k ≤ 22, -6 ≤ l ≤ 6	
Reflections collected	12755	
Independent reflections	1623 [R _{int} = 0.0221]	
Reflections with I>2σ(I)	1597	
Max. and min. transmission	0.7772 and 0.8620	
Data / restraints / parameters	1623 / 1 / 129	
Goodness-of-fit on F ²	1.080	
Final R indices [I>2σ(I)]	R ₁ = 0.0228, wR ² = 0.0557	
R indices (all data)	R ₁ = 0.0232, wR ² = 0.0560	
Largest diff. peak and hole	0.356 and -0.289 e·Å ⁻³	