Polar- and Enthalpic Effects on the Selectivity of Aromatic Substitution by Cationic Radicals

POLAR- AND ENTHALPIC EFFECTS ON THE SELECTIVITY OF AROMATIC SUBSTITUTION BY CATIONIC RADICALS

A dissertation presented

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Abstract

The field of radical aromatic substitution consistently receives attention from synthetic organic community, in parts due to the versatile reactivity of radicals towards formation of valuable carbon–heteroatom bonds. One of the biggest goals associated with the development of useful radical aromatic substitution reactions is to achieve sufficient degree of regiocontrol, so that the maximum yield of a specific target molecule can be obtained.

On the other hand, it may also be of synthetic value to develop an aromatic substitution reaction that is able to generate a wide spectrum of constitutional product isomers from a single starting material. It would be especially so if such a reaction also does not discriminate much between differentially activated aromatic substrates, thereby achieving a broad substrate scope.

The subject of this dissertation is on the efforts to understand fundamental chemical effects that govern radical reactivity, and to address the above-mentioned challenges based on the reactivity principles.

In Chapter 1 is described a non-chelation-assisted, highly *para*-selective aryl C–H substitution reaction with a doubly cationic nitrogen radical. High degree of charge-transfer in the transition state of radical addition is attributed to the predictable, exquisite positional selectivity. The high electron affinity of the bond-forming species engenders significant polar effects that are responsible for the sensitivity of the reaction towards substituent directing effects.

In Chapter 2, the synthetic utility of the *para*-selective C–H functionalization is extended by using the functionalized product as a branch point for installation of valuable functional groups. Efficient transition-metal-catalyzed cross-coupling reactions convert the aryl ammonium intermediate into methylarenes, constituting an overall *para*-selective aryl C–H methylation sequence.

In Chapter 3, aromatic substitution by another highly reactive nitrogen radical cation is introduced. While also possessing high electron affinity, the novel sp^2-nitrogen radical cation exhibits unexpectedly low positional selectivity, and at the same time, is able to functionalize an unprecedentedly broad range of aromatic substrates in terms of electronic activation. Dominant reactivity control by enthalpic effects is elucidated by investigation of selectivity relationships. The C–N bond forming reaction is applied towards late-stage amination of (hetero)arenes with a substrate scope that addresses the limitations of current C–H amination methodology.

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List of abbreviations

° C	degree Celsius
A	ampere
Ac	acetyl
aq.	aqueous
bpy	2,2´-bipyridine
Bu	butyl
cal	calorie
calc´d	calculated
d	*deuterio*
D	deuterium
DCM	dichloromethane
DFT	density functional theory
DG	directing group
DMSO	dimethyl sulfoxide
$E_{1/2}$	half-wave potential
EDG	electron-donating group
equiv	equivalent
ESI-TOF	electrospray ionization – time of flight
Et	ethyl
eV	electronvolt
EWG	electron-withdrawing group
FIA	flow injection analysis

g	gram
h	hour
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
i	*iso*
J	coupling constant
J	joule
k	kilo
KIE	kinetic isotope effect
LCMS	liquid chromatography-mass spectrometry
m	*meta*
m	milli
M	molar
m/z	mass-to-charge ratio
Me	methyl
min	minute
mol	mole
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance
o	*ortho*
p	*para*
Ph	phenyl

ppm	parts per million
Pr	propyl
PTFE	polytetrafluoroethylene
SCE	saturated calomel electrode
S_EAr	electrophilic aromatic substitution
t	*tert*
TEDA	*N*-(chloromethyl)-triethylenediamine$^+$
TEMPO	2,2,6,6,-tetramethylpiperidin-1-yl)oxyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFE	2,2,2-trifluoroethanol
THF	tetrahydrofuran
TLC	thin-layer chromatography
Tol	tolyl
V	volt
α	alpha
μ	micro
π	pi
ρ	rho
σ	sigma

Publications

Portions of Chapter 1 of this dissertation have been reproduced, according to the policy of Springer Nature, from the following publication:

> Boursalian, G. B.; **Ham, W.**; Mazzotti, A. R.; Ritter, T., Charge-Transfer-Directed Radical Substitution Enables *para*-Selective C–H Functionalization. *Nature Chemistry* **2016,** *8*, 810-815.

Portions of Chapter 2 of this dissertation have been reproduced, with permission, from the following publication:

> Serpier, F.; Pan, F.; **Ham, W.**; Jacq, J.; Genicot, C.; Ritter, T., Selective Methylation of Arenes: A Radical C−H Functionalization/Cross-Coupling Sequence. *Angewandte Chemie International Edition* **2018,** *57* (33), 10697-10701.

Portions of Chapter 3 of this dissertation have been reproduced, with permission, from the following publication:

> **Ham, W.**; Hillenbrand, J.; Jacq, J.; Genicot, C.; Ritter, T., Divergent Late-Stage (Hetero)Aryl C–H Amination by the Pyridinium Radical Cation. *Angewandte Chemie International Edition* **2019**, *58* (2), 532-536.

Acknowledgements

I had never imagined, at the time I graduated from high school in Busan, that I would be here finishing off the 5.5-year-PhD. I especially never knew that I would be writing these acknowledgements in Mülheim an der Ruhr, Germany. Thinking back, I probably wouldn' have expected to go to Columbia after graduating from middle school. College life at Columbia was already full of new things going on to the Korean kid that had never stayed outside the homeland. Luckily enough, I met wonderful friends and great mentors there, and gradually started to think about what I should focus on, after a while of getting used to how it was to live and study abroad.

It was again a huge luck to take the very first college orgo class taught by Professor Ron Breslow, who passed away almost exactly a year ago. Now that I think about it, it was a really stupid move to randomly call his office phone after the first semester, without having thought that I actually had access to my laptop and my email account, to ask if I could work in his lab. He let me in, and allowed me to realize that I was completely wrong in thinking that I kind of knew what real chemistry research was like.

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I actually, honestly, didn't mean to join the research group of Tobias when I decided to come to Harvard. Not that I didn't like his research or anything, but just that I was still pretty stupid and didn't really understand what kind of research each professor was working on. I met

Tobias during the visiting weekend, and decided to rotate in his lab for the summer before the school started. I was then fascinated with the projects, became friends with everyone in the group, and started to enjoy working with Tobias. I was quite surprised to find out that I would have to leave Harvard just after joining the group, but after all this time, I appreciate that I am probably having wonderful moments in Europe that maybe I could never have had, if not under this circumstance. There certainly were rough moments in the lab, the last-minute SI cleanup before the paper submission, and the long, long time waiting for my paper to be accepted somewhere, which actually was a pretty painful time. Regardless, I did learn a lot from Tobias, the knowledge, the way he approaches science, and the guidance towards what I should be doing after this lab. I am grateful to Tobias for training me to become a real chemist who can think intelligently about chemistry.

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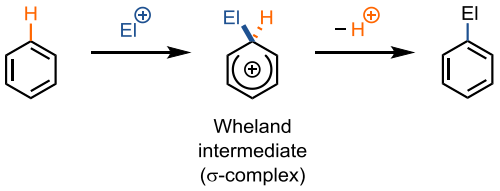
To my parents, Ae Ran Lee and Sang Seon Ham

Introduction

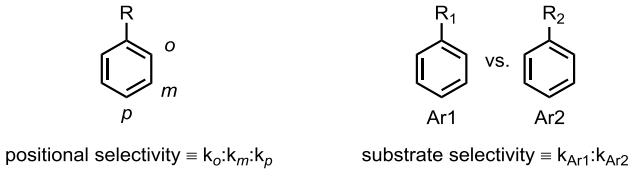
I.1 Electrophilic Aromatic Substitution

Electrophilic aromatic substitution (S_EAr) is perhaps the most extensively studied reaction class for the functionalization of aromatic C–H bonds.[1] In a simplified, generally accepted mechanistic scheme (Scheme I.1) of electrophilic aromatic substitution, an arene and an electrophile (El^+) initially react to form a cyclohexadienyl cation, called the Wheland intermediate.



Scheme I.1. A simplified mechanism of electrophilic aromatic substitution.

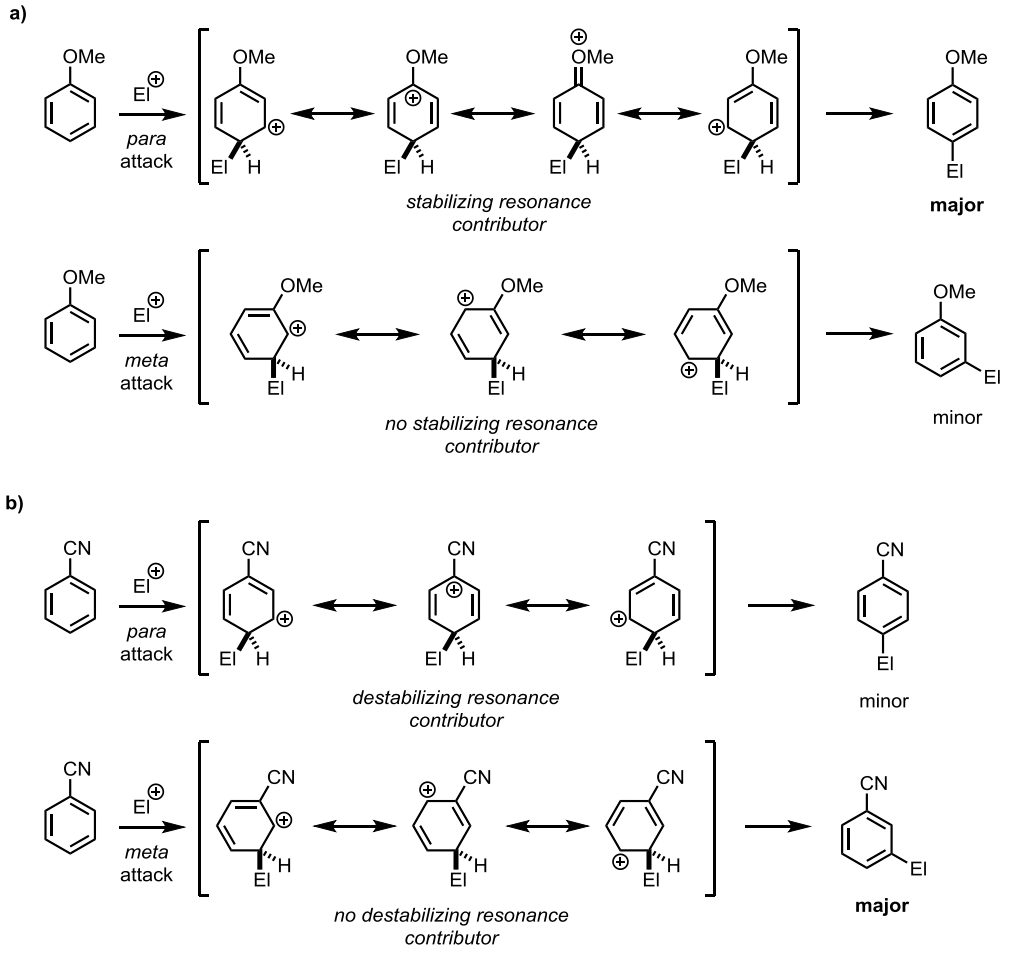
When nonequivalent C–H bonds exist in the structure of an arene substrate, electrophilic aromatic substitution may result in a mixture of constitutional isomers (Scheme I.2). For example, there are three nonequivalent aryl C–H bonds in a mono-substituted arene, located *ortho*, *meta*, or *para* to the substituent. An electrophilic aromatic substitution reaction may proceed to substitute a certain C–H bond faster than other C–H bonds located on the same aromatic ring. In other words, the S_EAr reaction exhibits a certain degree of positional selectivity. An S_EAr reaction also may occur faster on one aromatic ring than on another aromatic ring with different substituents, in which case the reaction exhibits substrate selectivity.



Scheme I.2. Positional- and substrate selectivity of aromatic substitution.

I.1.1 Substituent Directing Effects

A substituent on an arene can either be electron-donating or electron-withdrawing, induction-wise or resonance-wise. Inductive and resonance electron-donating groups (EDG´s) direct an electrophile to the C–H bonds *ortho* or *para* to themselves, while resonance electron-withdrawing groups (EWG´s) direct the electrophile to the positions *meta* to themselves.[2] The substituent directing effects also lead to substrate selectivity; an aromatic ring substituted with electron-donating groups will react faster than an arene with electron-withdrawing groups.



Scheme I.3. Substituent directing effects in electrophilic aromatic substitution. Directing effects for *ortho*- and *para* attacks are analogous. a) Methoxy group as an example of an electron-donating group. b) Cyano group as an example of a resonance electron-withdrawing group.

Such directing effects are generally understood with regards to the relative stabilities of the Wheland intermediates upon addition of an electrophile to different aromatic nuclear positions (Scheme I.3). The transition state of electrophilic addition, in part, resembles the structure of the Wheland intermediate, therefore a low-energy transition state is expected when the addition leads to a stabilized Wheland intermediate. Electrophilic addition to positions *ortho* or *para* to an EDG is favored due to the stabilization of the positive charge by the substituent in the ensuing Wheland intermediate, while the addition *ortho* or *para* to a resonance EWG is disfavored due to destabilizing resonance contributors.

I.1.2 Differential Degrees of Polarity Matching

The positional- and substrate selectivity engendered by nuclear substituents can further be generalized in terms of polarity matching. Specifically, electrophilic reagents will preferentially react with nucleophilic aromatic π-systems, and will be directed to C–H bonds with highly nucleophilic characters. The selectivity of electrophilic aromatic substitution arises because of differential polar interactions between the reactants in the transition state of addition.

The sensitivity of an electrophilic aromatic substitution reaction towards the polar effects can differ. In fact, there exist both S_EAr reactions that are highly selective and the ones that are virtually non-selective (Figure I.1).

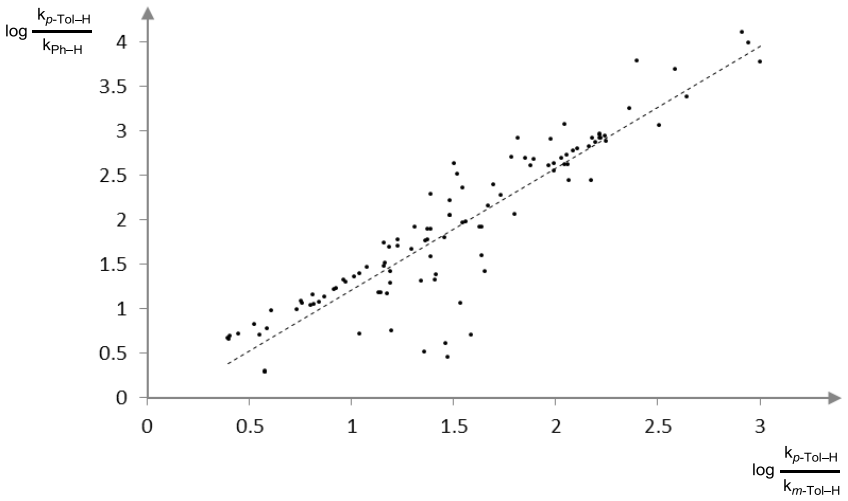


Figure I.1. Selectivity relationships between the substrate selectivity ($k_{p\text{-Tol–H}}$ vs. $k_{Ph–H}$) and the *meta-para* selectivity ($k_{p\text{-Tol–H}}$ vs. $k_{m\text{-Tol–H}}$) of electrophilic aromatic substitution reactions.

A satisfactory linear correlation between the substrate selectivity and the *meta-para* positional selectivity of S_EAr reactions is apparent from the selectivity relationships, originally introduced by Brown[3] and extended by Perrin,[4] depicted in Figure I.1. The location of an electrophilic substitution reaction on the diagram can be understood as an indicator of how advanced the transition state of electrophilic addition is towards the Wheland intermediate. An early transition state of addition, according to the Hammond postulate, would not resemble the structure of the Wheland intermediate, and therefore would not involve a large extent of polarity matching between the reactants. Consequently, the aromatic substitution is not sensitive to the substituent directing effects and exhibits both low positional- and substrate selectivity. On the contrary, an S_EAr reaction with a late transition state of addition will be highly selective.

The extent of polarity matching in the transition state is mainly controlled by enthalpic effects. Both the substrate selectivity, between toluene and benzene, and the positional selectivity, between the *meta* and *para* C–H bonds of toluene, decrease as the incoming electrophile becomes more electron-deficient in Friedel-Crafts acylation, aroylation, sulfonylation, and

benzylation.[5] The higher enthalpic gain in the addition of a more reactive electrophile would result in an early transition state of addition.

On the other hands, the selectivity between the *ortho* and *para* C–H bonds cannot easily be rationalized. There is no clear correlation between the ortho/para selectivity and the substrate selectivity (Figure I.2).[4]

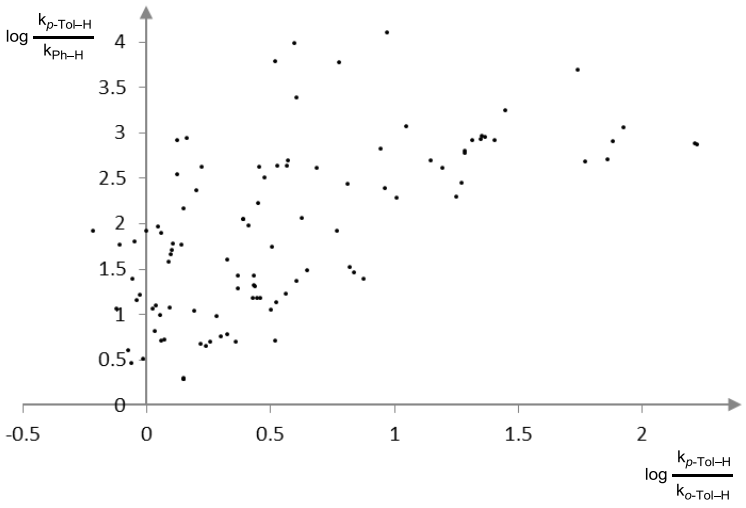


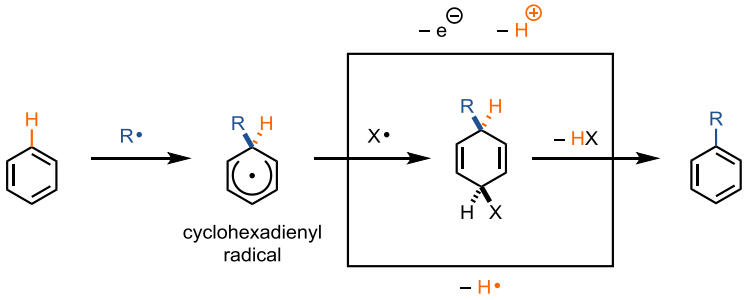
Figure I.2. Selectivity relationships between the substrate selectivity ($k_{p\text{-Tol–H}}$ vs. $k_{Ph–H}$) and the *ortho-para* selectivity ($k_{p\text{-Tol–H}}$ vs. $k_{o\text{-Tol–H}}$) of electrophilic aromatic substitution reactions.

It is difficult to extract the electronic substituent directing effects away from steric effects with respect to the reactivity of *ortho* C–H bonds. As of yet, there is no generally accepted rationale for *ortho* selectivity, while it has been suggested that there is a slight difference in the capacities of *para*- and *ortho* positions for accommodating the positive charge buildup in the aromatic ring during the electrophilic addition.[5]

I.2 Polarity Matching in Radical Aromatic Substitution

Radical aromatic substitution (RAS), or homolytic aromatic substitution, proceeds through a mechanism analogous to electrophilic substitution, except that the bond-forming species is an organic radical with an odd electron. Radical addition to an arene results in a cyclohexadienyl

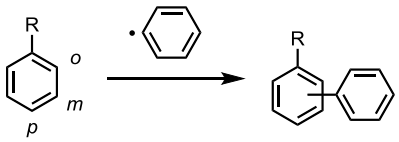
radical intermediate, which subsequently re-aromatize via formal loss of a hydrogen atom (Scheme I.4).



Scheme I.4. A general mechanistic scheme of radical aromatic substitution.

I.2.2 On the Selectivity of Radical Aromatic Substitution

Radical aromatic substitution is historically associated with a notion that the highly reactive radicals undergo aromatic substitution with low selectivity. The neutral, delocalized cyclohexadienyl radical intermediate may be considered intrinsically insensitive to the polar effects exerted by aromatic substituents. For example, homolytic arylation of mono-substituted arenes by aryl radicals typically yields a nearly statistical mixture of the three possible constitutional isomers (Scheme I.5).[6]

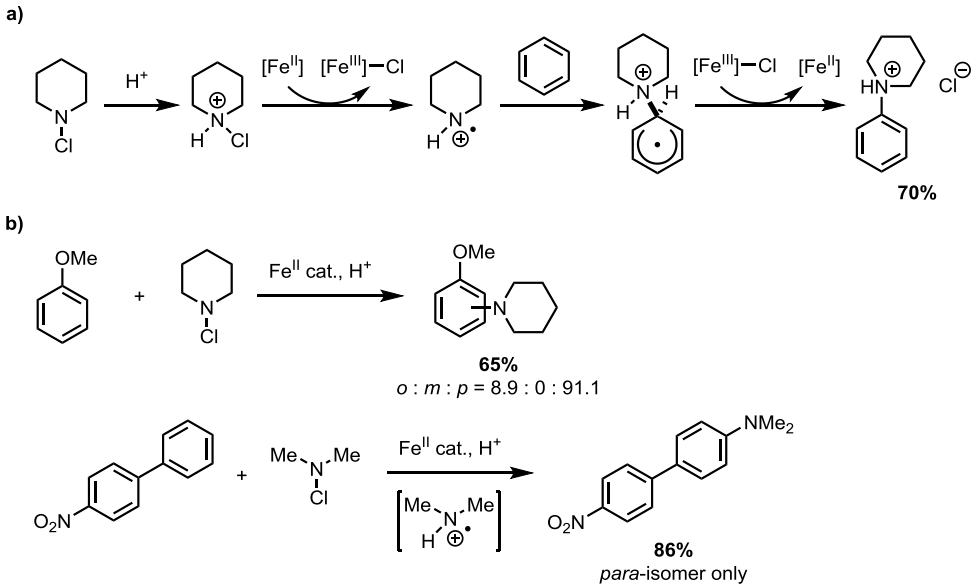


R	k_o : k_m : k_p
Me	2.4 : 0.74 : 1.1
Et	1.4 : 0.76 : 1.0
Cl	1.8 : 0.81 : 1.1

Scheme I.5. Aromatic positional reactivity towards phenyl radical.

Another significant feature of radical aromatic substitution that has prohibited practical applications is the often very low chemo-selectivity of the radical species. For example, aryl,[7] aryloxy,[8] alkyl,[9] and aminyl[10] radicals can undergo highly competitive hydrogen abstraction reactions, while acyloxy[11] and aryloxy[8] radicals are susceptible to decarboxylation. The rate constants for the reactions of the phenyl radical with a variety of organic molecules, including

alcohols, alkenes, arenes, and acetonitrile are similar.[12] A majority of radical aromatic substitution procedures require a large excess amount of an arene substrate to ensure a selective aromatic substitution reaction.

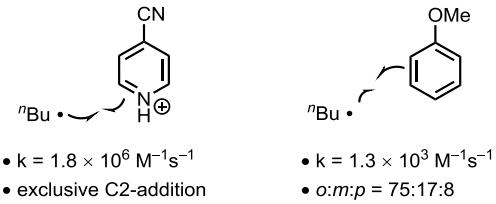


Scheme I.6. Selective aromatic amination by aminium radical cations. a) Amination of benzene and mechanistic pathways. b) *Para*-selective amination of mono-substituted arenes.

Remarkably, however, Minisci developed a series of aromatic amination reactions using protonated aminium radical cations, which exhibit high reactivity and high selectivity towards simple arenes (Scheme I.6).[6] Unlike neutral aminyl radicals, aminium radical cations undergo a selective addition to arenes without significant hydrogen abstraction.[13] The homolytic amination is highly sensitive to the polar effects of the aromatic substituents; very high yields of *para*-aminated products are obtained from arenes with electron-donating substituents. Moreover, the *para* C–H bonds in toluene and biphenyl are 51 and 598 times more reactive than the C–H bonds of benzene,[6] thus high substrate selectivity.

I.2.2 Charge-Transfer in the Transition State of Polar Radical Addition

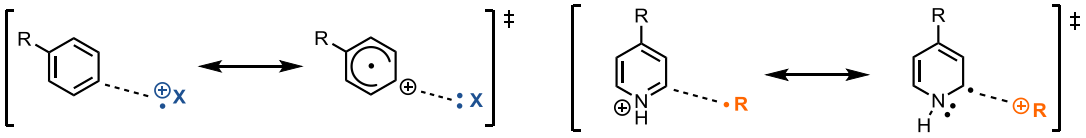
An important aspect of Minisci's results is that the enhanced reactivity of the aminium radical cations by protonation results in the very high positional- and substrate selectivity; the partial rate factor for the *para* position of anisole is close to 10^3, while the aminium radical cations are nearly unreactive towards arenes with electron-withdrawing substituents, such as benzonitrile and nitrobenzene.[6] Moreover, the more reactive arenes (anisole, acetanilide, biphenyl, etc.) undergo amination with higher positional selectivity than less activated arenes such as toluene and chlorobenzene (isomeric ratios of aminated toluene and chlorobenzene are *o*:*m*:*p* = 5:23:72 and 18:6:76, respectively).[6]



Scheme I.7. Higher reactivity and selectivity of *n*-butyl radical towards a protonated pyridine than towards anisole.

Nucleophilic carbon-based radicals also exhibit a high degree of polar effects towards electron-poor, protonated heteroaromatic bases (Scheme I.7). For example, the primary alkyl radicals add to protonated 4-cyanopyridine 10^3 times faster than to anisole, yet alkylation of 4-cyanopyridine is completely selective towards the 2-position, while the rates of substitution of *meta*- and *para* positions of anisole are virtually equal.[14]

The selectivity of those polar radicals may be understood in light of a transition state of radical addition to which a large contribution of a charge-transfer form occurs (Scheme I.8).

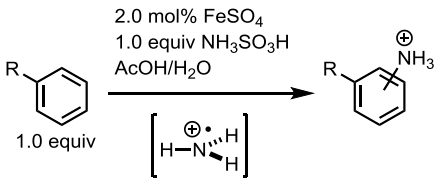


Scheme I.8. Stabilizing charge-transfer forms in the transition states of polar radical additions.

When there is sufficiently large polar interactions between the nucleophilic and the electrophilic reaction partners, a significant charge buildup (or release) in the aromatic ring during the course of the reaction can be expected. Certain positions or certain substrates that can accommodate such charge-transfer better than others would undergo faster radical addition due to the transition state stabilization. In such a manner, the polar radical aromatic substitution reactions can exhibit high selectivity that resembles that of ionic reactions, e.g. electrophilic aromatic substitution.

I.2.3 Enthalpic Effects on the Selectivity of Polar Radical Substitution

While the electrophilic and nucleophilic radicals can, as discussed in I.2.2, display high sensitivity to the polar effects, there are also circumstances in which enthalpic effects still dominate as the governing factor of polar radical reactivity. Minisci reported that ammonia radical cation, generated through redox catalysis analogous to other aminium radical cations, show markedly lower selectivity with regards to aromatic substitution (Scheme I.9).[15]



R	yield (%)	isomeric ratio (%)			k_{Ph-R} / k_{Ph-H}
		o	*m*	*p*	
OMe	60	28.5	1.7	69.8	4.80
Me	53	35.7	22.7	41.5	1.70
Cl	24	20.7	20.6	58.7	0.15
CO_2Et	21	23.0	45.6	31.4	0.012
CN	5	9.8	51.6	38.6	0.011

Scheme I.9. Reaction characteristics of aromatic amination by ammonia radical cation.

Unlike other aminium radicals, the ammonia radical cation is able to functionalize ethyl benzoate and benzonitrile in 21% and 5% yields, respectively, when the arenes are the limiting agents. Furthermore, the positional selectivity for each substrate is significantly lower than what is observed with other aminium radicals, while a moderately electrophilic character is still observed. The low selectivity is explained in terms of the energy of the C–N bond that forms upon radical addition; ammonia radical cation would form a stronger bond than aliphatic aminium radicals

would. The N–H BDE of ammonium cation (127 kcal/mol) is higher than that of dimethylaminium cation (101.3 kcal/mol) by 26 kcal/mol.[16] The larger enthalpic gain in the radical addition is suggested to lead to an earlier transition state that is less sensitive to the polar effects.

I.2.4 Selectivity Relationships of Radical Aromatic Substitution Reactions

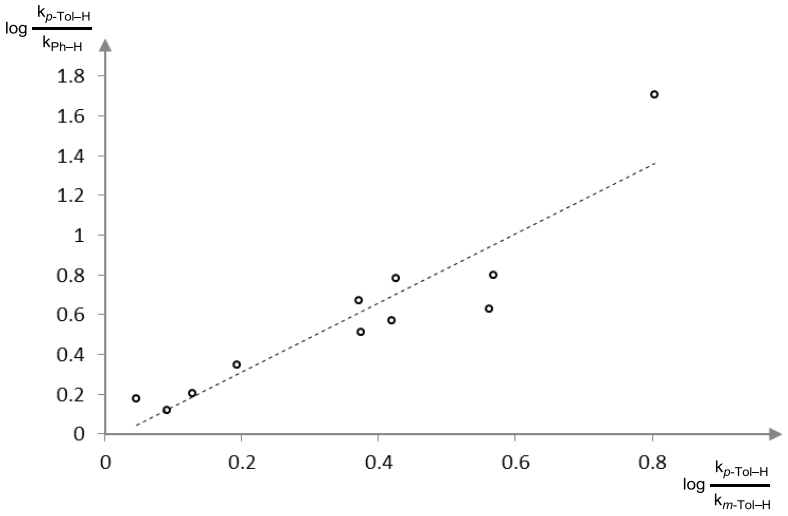


Figure I.3. RAS selectivity data plotted into the format of Brown-Stock diagram. See Section 3.6.9 for further details.

Although there are not as many selectivity data for polar radical substitution of carboarenes as those for electrophilic aromatic substitution, the literature values for important reaction classes of radical aromatic substitution with electrophilic characters (amination,[6,15] arylation,[17] acyloxylation,[18,19] perfluoroalkylation,[20] cyanation,[21] alkynylation,[22] and dinitromethylation[23]) can be plotted as in Figure I.3. A linear free-energy relationship between the substrate- and the positional selectivity is also observed, at least for the RAS reactions whose selectivity data are available.

I.3 Utility of Selectivity in Aromatic Substitution: A Discussion

High positional selectivity of a C–H functionalization reaction has always been considered a virtue in the field of organic methodology development. Due to the intrinsically ubiquitous nature of C–H bonds in most organic molecules, the ability to discriminate between different C–H bonds towards functionalization directly leads to the maximum theoretical yield of a single constitutional product isomer. Therefore, high degree of regio-control is desirable for syntheses of specific target molecules through C–H functionalization, and it remains a goal of organic synthesis to develop highly regio-selective reactions.

However, in aromatic substitution, whether electrophilic or homolytic, high positional selectivity is associated with high substrate selectivity, according to the Brown-Stock selectivity relationships. In other words, an aromatic substitution reaction with high positional selectivity based on polar effects may not be able to functionalize substrates without sufficient electronic activation. The high substrate selectivity can be beneficial in terms of avoiding over-functionalization of substrates with multiple aromatic rings,[24] but it is expected that there is a range of aromatic substrates that the polar-effect-controlled, regio-selective aromatic functionalization reactions cannot cover.

Moreover, the high positional selectivity elicited by the electrophilic character of the bond-forming species would, at the same time, be synonymous to the lack of ability to functionalize the rest of the aromatic C–H bonds (especially, positions *meta* to electron-donating groups) available in a substrate. When the selectivity originates from the discrimination of different C–H bonds based on their abilities to accommodate a partial positive charge buildup, the same approach would no longer be effective towards activation of the positions without such capacities.

The potential synthetic utility of aromatic substitution reactions with low selectivity is especially relevant with regard to small molecule discovery, when the eventual target molecule is not yet known, as in drug or agrochemical discovery. Simultaneous generation of multiple isomeric products from a single starting material would allow rapid expansion of chemical space and its biological evaluation.[25] Such a diversification would be particularly desirable when it can furnish constitutional product isomers that conventional methods cannot provide.

I.4 References

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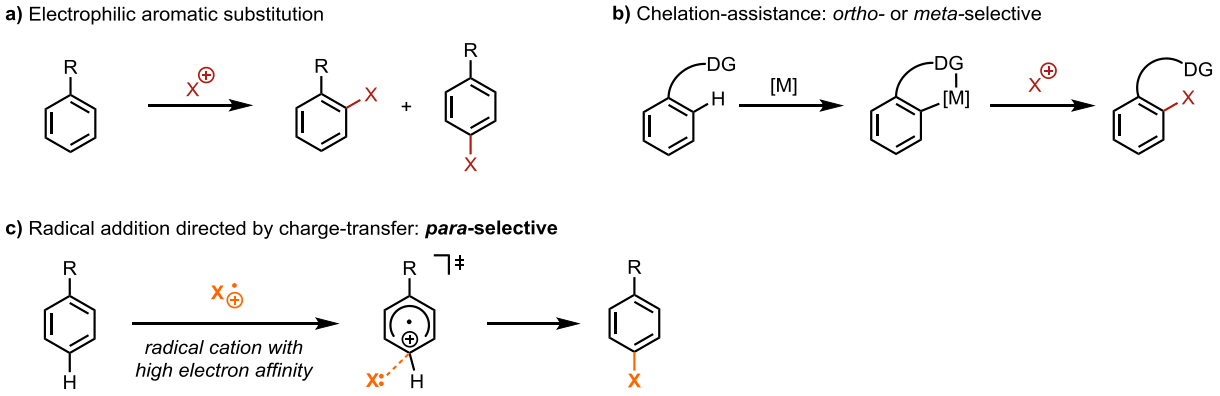
Chapter 1 – Charge-Transfer-Directed Aryl C–H Functionalization with High *para*-Selectivity

1.1 Backgrounds

As discussed in the Introduction, highly electrophilic radicals can elicit suitable polar interactions in the transition state of addition to an arene, thereby engendering a useful degree of positional selectivity due to the polarity-matching. However, an aromatic substitution reaction that consistently furnishes single constitutional product isomer based on the charge-transfer-directed reactivity principle had not been disclosed. In this chapter, we describe a highly *para*-selective radical aromatic substitution reaction that was reported in *Nature Chemistry* in June 2016.[1] We show that radical aromatic substitution can furnish novel, useful products with high chemo- and positional selectivity when an appropriately electrophilic radical is used. For most substrates, including mono-substituted arenes, only one of the possible constitutional isomers is observed in significant amounts.

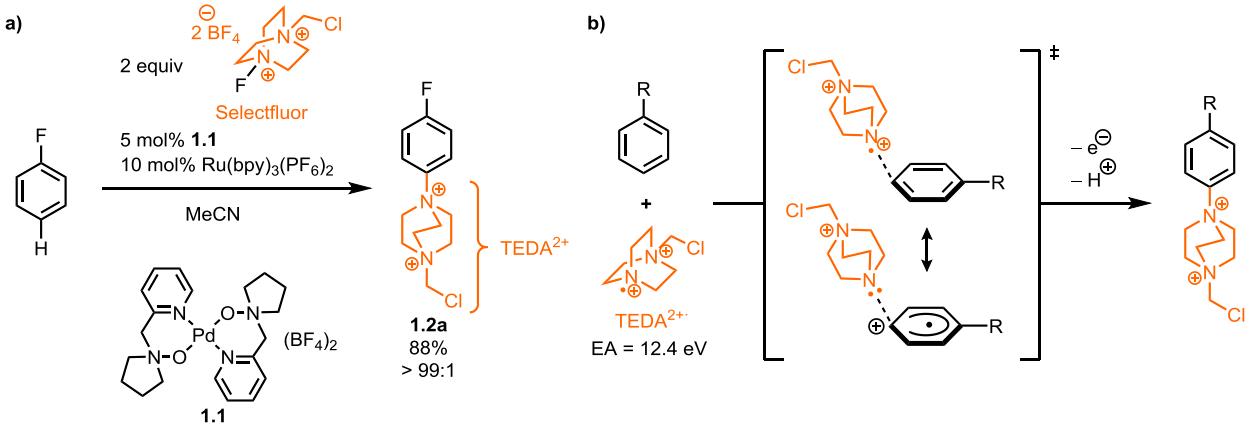


Scheme 1.1. Strategies for selective aromatic C–H substitution.

The charge-transfer-directed concept (Scheme 1.1) does not require a coordinating DG, as do chelation-assisted C–H functionalization reactions, because selectivity is determined by the electronic structure in the transition state as opposed to enforced proximity of the catalyst.

1.2 Aryl C–H Substitution by the Doubly Cationic TEDA Radical

The doubly cationic radical $TEDA^{2+\bullet}$ (TEDA, *N*-(chloromethyl)triethylenediamine), derived from a single-electron reduction of Selectfluor, is capable of engaging in radical aromatic substitution to yield *N*-aryl-*N′*-chloromethyldiazoniabicyclo[2.2.2]octane salts, which we term Ar–TEDA compounds (Scheme 1.2) (see Section 1.5.8 for evidence that implicates $TEDA^{2+\bullet}$ as the C–N bond-forming species). The reaction is enabled by a dual catalyst combination: Pd catalyst **1.1**, which we introduced in a previous report, and $Ru(bpy)_3(PF_6)_2$ (Scheme 1.2a).[2] Photoirradiation is not required for the reaction, which works equally well when shielded from light. For most arenes only one of the possible positional isomers of the Ar–TEDA product is observed as judged by NMR spectroscopy; fluorobenzene, for example, yields the *para*-substituted product in >99:1 positional selectivity (see Section 1.5.4). All mono-substituted arenes tested gave the *para*-substituted product as the only significant isomer. Di-substituted arenes and some heteroarenes similarly undergo clean substitution at the position *para* to the group with the strongest directing effect. Thus, the synthesis of the Ar–TEDA compounds described here constitutes a general non-chelation-assisted C–H functionalization reaction, with the arene as the limiting reagent and with nearly exclusive positional selectivity across a broad range of substitution patterns.



Scheme 1.2. Charge-transfer-directed aromatic substitution. a) Conversion of fluorobenzene into the corresponding Ar–TEDA compound. b) Positional selectivity of $TEDA^{2+\bullet}$ substitution results from the stabilizing effect of the arene-to-radical charge-transfer in the transition state of the addition. EA refers to the gas-phase adiabatic electron affinity calculated by DFT.

The $TEDA^{2+\bullet}$ radical is electrophilic, with an electron affinity of 12.4 eV, calculated by density functional theory (DFT). The high electron affinity of $TEDA^{2+\bullet}$ should favor a large contribution of charge transfer in the transition state of addition (Scheme 1.2b), which in turn leads to a high selectivity for aromatic substitution at the position from which the charge transfer is the greatest.[3–5] Therefore, a predictive tool for the positional selectivity of the reaction would be a metric that indicates the greatest extent of charge transfer that can be expected on attack at a given position. We found Fukui nucleophilicity indices to be well suited to this purpose. The Fukui nucleophilicity index of an atom, determined by simple quantum chemical calculations, is a measure of how readily electron density is transferred to an incoming electrophilic species attacking at the relevant atom.[6,7] Fukui indices are especially convenient as a predictive tool because the Fukui nucleophilicity index of all the atoms in a given molecule is determined by a pair of simple calculations on the arene itself; there is no need to map the potential-energy surface of the reaction by computing the transition states of various pathways.

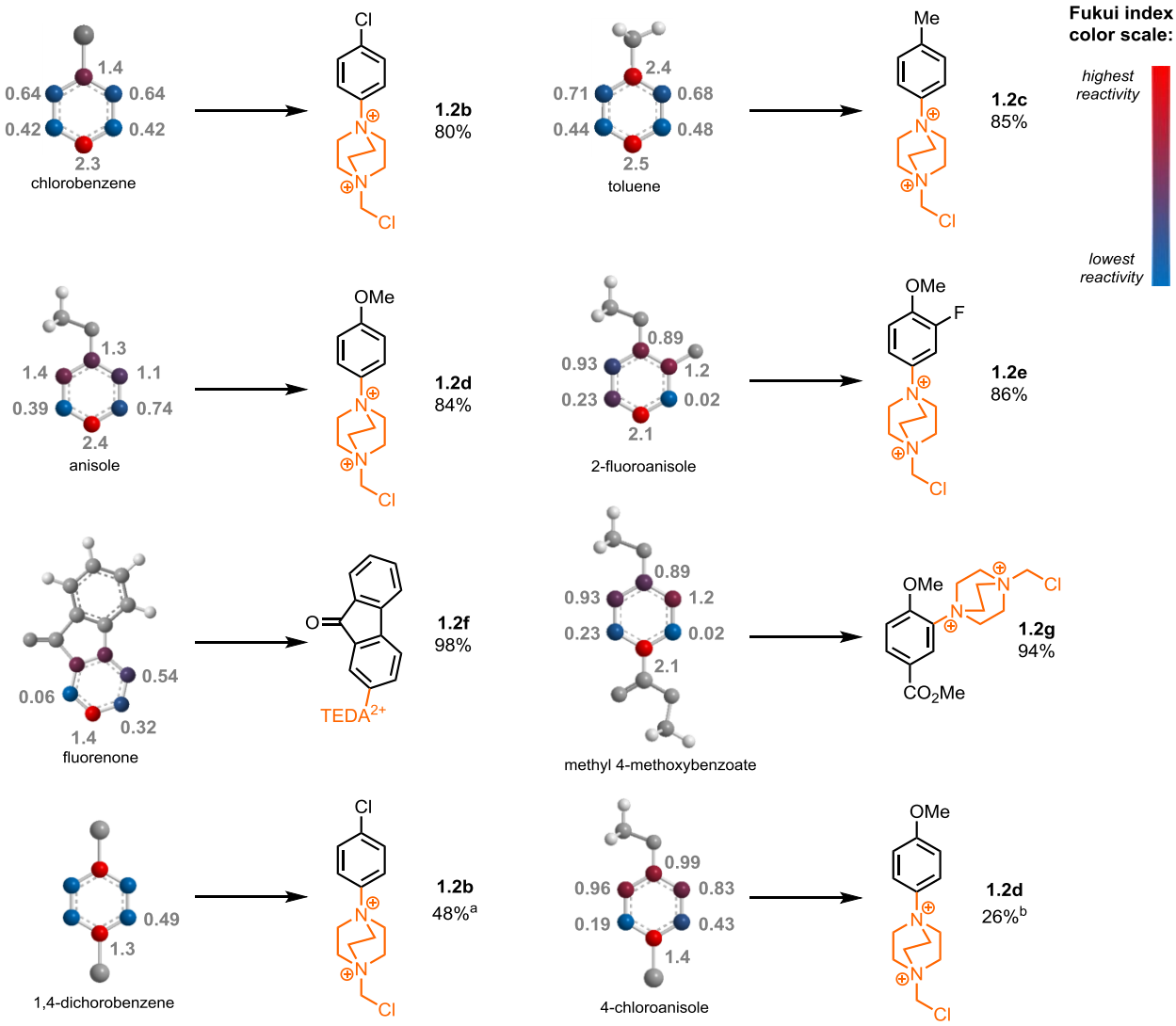


Figure 1.1. Prediction of the position of substitution by $TEDA^{2+\bullet}$ by Fukui indices. The Fukui indices depicted are multiplied by ten for simplicity of presentation. DFT computations of the Fukui indices and the electron affinity of $TEDA^{2+\bullet}$ were performed at the (U)B3LYP/6-311G(d) level of theory, with a continuum polarization solvent model for the Fukui index calculations. The Fukui indices are computed for one conformation of the molecule, so indices of positions that are symmetrically disposed about a substituent need not be equal. [a]Substitution in the 2-position was observed in 11% yield in addition to the *ipso* substitution. [b]Substitution in the 2-position was observed in 10% yield in addition to the *ipso* substitution.

Figure 1.1 shows several Ar–TEDA products and the corresponding starting material, with each aromatic carbon atom of the starting material labelled with its Fukui nucleophilicity index. This index successfully predicts the site of substitution by $TEDA^{2+\bullet}$ in almost all cases. Certain 1,4-disubstituted arenes, including 1,4-dichlorobenzene and 4-chloroanisole, yield *ipso* substitution

of the halogen as the primary product.[8] Gratifyingly, Fukui nucleophilicity indices correctly predict even the observed *ipso* substitution in these cases. If a non-substitutable functional group is present at the site with the highest Fukui index, substitution at the site with the next-highest Fukui index is observed, as for methyl 4-methoxybenzoate (**1.2g**). Although steric hindrance to an *ortho* attack may serve to augment further the *para* selectivity of the reaction, the fact that even fluorobenzene, with a single small substituent, gives >99:1 selectivity renders steric hindrance unlikely as the primary factor governing selectivity.

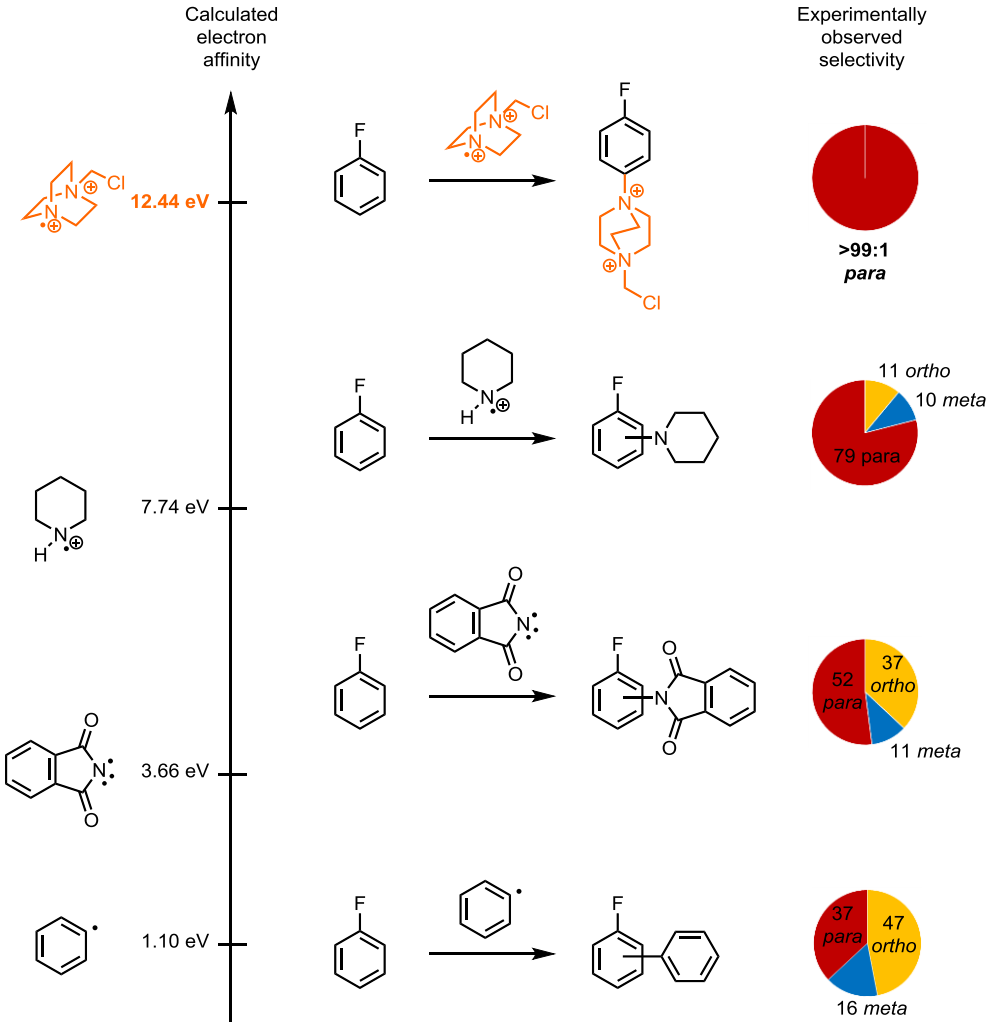


Figure 1.2. Selectivity for *para* substitution increases with increasing electron affinity of the radical. Electron affinities refer to the gas-phase adiabatic electron affinity calculated at the (U)B3LYP/6-311G(d) level of theory.

The high degree of positional selectivity we report here is unusual, especially in the context of radical aromatic substitution. A reason may be the lack of studies of substitution reactions with radicals of high electron affinity. Although the $TEDA^{2+\bullet}$ radical di-cation has been proposed as an intermediate in recently reported aliphatic C–H oxidation methodologies that utilize Selectfluor,[9–11] to our knowledge the addition of this radical to unsaturated systems has not been investigated. The radicals employed most commonly in a synthetic context are uncharged carbon-, oxygen-, nitrogen- and halogen-based radicals, which have electron affinities in the range 0.8–3.6 eV, far below the value for $TEDA^{2+\bullet}$ (12.4 eV (Figure 1.2)). Aromatic substitution reactions of most neutral radicals are known to proceed with low selectivity[12]. For example, the phenyl radical has an electron affinity of 1.1 eV and, under the conditions reported by Li and co-workers,[13] undergoes aromatic substitution with fluorobenzene to give an *ortho*:*meta*:*para* (*o*:*m*:*p*) ratio of 47:16:37. The neutral phthalimide radical has a higher electron affinity (3.7 eV). We found that the phthalimide radical, when generated under conditions reported by Sanford and co-workers,[14] undergoes aromatic substitution with fluorobenzene in an *o*:*m*:*p* ratio of 37:11:52; the selectivity for the *para* position is higher, although the other isomers still abound.

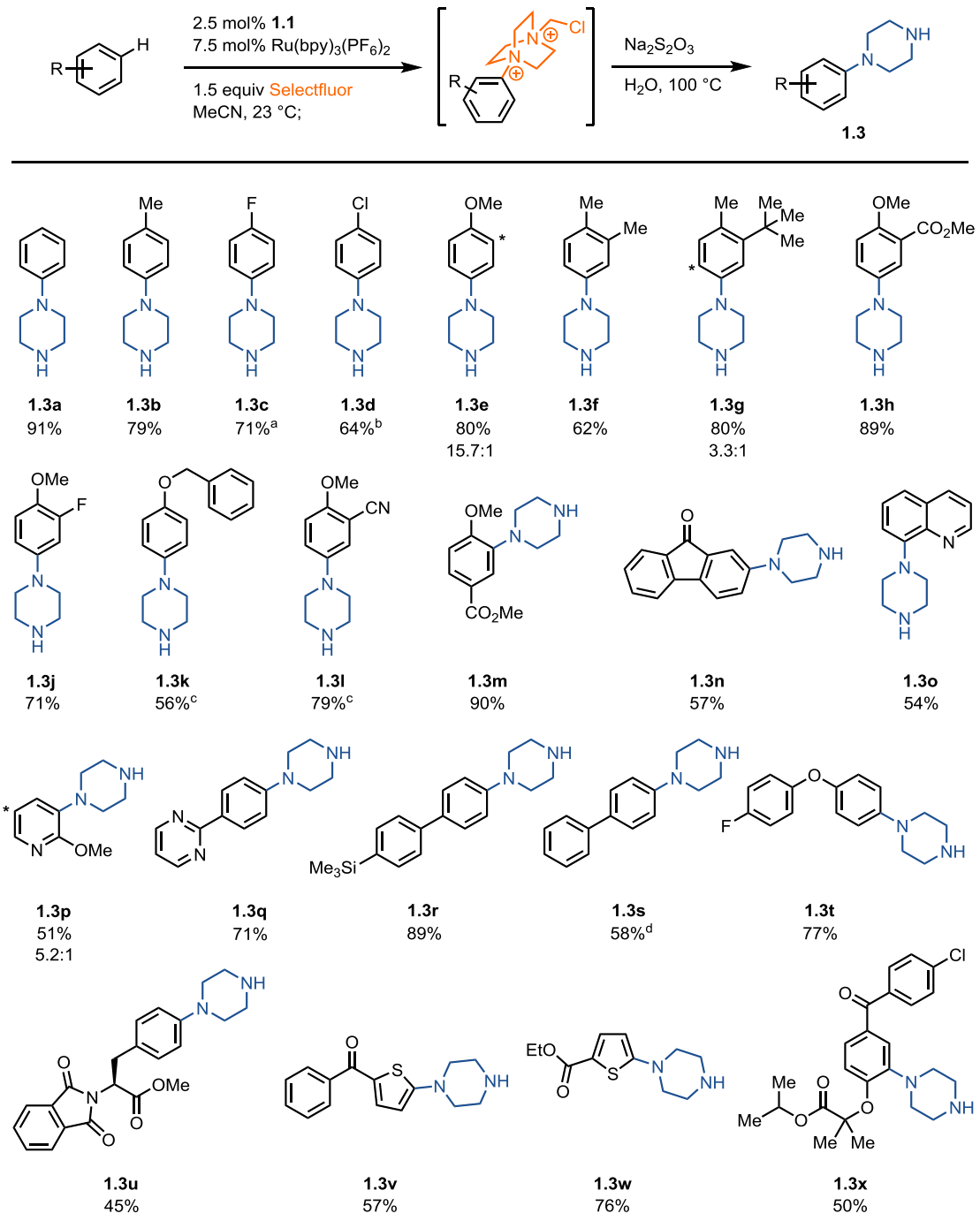
Positive charge increases electron affinity and, based on our findings and proposal, positively charged radicals should result in more-selective arene substitution reactions. Mono-cationic aminium radicals have electron affinities in the range 7–8 eV, and their aromatic substitution reactivity was investigated thoroughly in seminal work by Minisci and co-workers, who noted the higher selectivity of aminium radical addition compared with that of less-electrophilic radicals.[15–17] Under Minisci's conditions, the mono-cationic aminium radical derived from piperidine (electron affinity of 7.7 eV) adds to fluorobenzene more selectively than the neutral phthalimide radical, to afford an *o*:*m*:*p* ratio of 11:10:79. Minisci described the selectivity of

mono-cationic aminium radicals as similar to the selectivity of electrophilic aromatic substitution, affording products of *ortho* and *para* substitution of mono-substituted arenes that bear electron-donating groups.[15–17] We discovered that for sufficiently electrophilic radicals, charge transfer in the transition state of addition can lead to a high selectivity for the *para* position over the *ortho* one. We rationalized the phenomenon in terms of charge transfer in the transition state, and introduced Fukui indices as a tool for predicting the site of substitution. The second positive charge of the $TEDA^{2+\bullet}$ aminium radical increases the electron affinity to 12.4 eV and, at this level, nearly absolute selectivity for the *para* position is observed for mono-substituted arenes.

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

1.3 C–H Piperazination of (Hetero)Arenes *via* Aryl TEDA

As one synthetic application of the concept of charge-transfer-directed radical substitution, we developed a two-step, one-pot synthesis of aryl piperazines from the corresponding aryl C–H compounds (Scheme 1.3). The procedure involves the reduction of the aryl–TEDA compounds by sodium thiosulfate, which converts the TEDA moiety into a piperazine heterocycle.



Scheme 1.3. Two-step, one-pot synthesis of aryl piperazines by charge-transfer-directed C–H functionalization. *Site of piperazination of the other constitutional isomer. [a]Reaction temperature of 40 °C. [b]Reaction temperature of 45 °C in the first step. [c]For the first step, 2.5 equiv Selectfluor, 5.0 mol% **1.1** and 10 mol% $Ru(bpy)_2(PF_6)_2$. [d]For the first step, 1.0 equiv Selectfluor.

Piperazines are a common motif in pharmaceuticals and other materials; they constitute the third most-common heterocycle present in the small-molecule pharmaceuticals listed in the US Food and Drug Administration Orange Book.[18] Aryl piperazines are commonly synthesized by Buchwald–Hartwig cross-coupling reactions of aryl electrophiles with piperazine derivatives.[19] The direct synthesis of aryl piperazines reported here is advantageous because it does not require a pre-functionalized substrate, such as an aryl halide. Importantly, this advantage relies on the high and predictable positional selectivity of the reaction, which enables the high-yield synthesis of a single desired positional isomer. The reaction is operationally simple, and can be performed under air with commercial-quality solvent. Furthermore, the piperazine moiety is obtained with an unprotected secondary amine, ready for subsequent manipulation.

A variety of arenes, including five- and six-membered heteroarenes, undergo piperazination. Generally, the attack of $TEDA^{2+\bullet}$ *ortho* to the substituents is unfavourable, and occurs only for arenes in which the preferred *para* position for substitution is blocked by a group that cannot undergo *ipso* substitution. This observation can be applied to block piperazination of certain positions, or even entire arene rings, as in substrates **1.3r** and **1.3t**. Product **1.3g** demonstrates the limits of the positional selectivity of the reaction: the two substituents in 2-methyl-*tert*-butylbenzene differ only slightly in their electron-donating ability and the product was isolated as a 3.3:1 mixture of isomers. Although $TEDA^{2+\bullet}$ is known to engage in sp^3 C–H bond cleavage, we observed no evidence of such side reactions in our investigations, even though several substrates contain weak C–H bonds adjacent to aromatic rings (for example, **1.3f**) or ether oxygen atoms (for example, **1.3e** and **1.3k**); the addition of $TEDA^{2+\bullet}$ to the unsaturated aromatic system outcompetes C–H bond cleavage.

For most substrates, nearly full conversion into the Ar–TEDA compound is observed, and in several cases the yield of the piperazine after the thiosulfate-mediated stage is lower. For example, the anticholesterol drug fenofibrate undergoes Ar–TEDA formation in 88% yield, but on treatment with sodium thiosulfate at 100 °C the yield of piperazine **1.3x** is 51%. The Ar–TEDA formation reaction exhibits significant functional group tolerance, despite the highly reactive and electrophilic nature of the $TEDA^{2+\bullet}$ radical intermediate; for most substrates in Scheme 1.3, the majority of mass balance is lost in the piperazine formation step, not in the Ar–TEDA formation step.

1.4 Conclusion

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

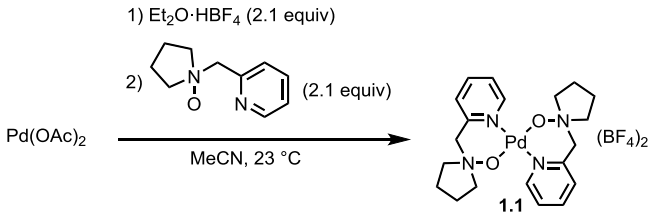
1.5 Experimental Details

1.5.1 Materials and Methods

All air- and moisture-insensitive reactions were carried out under an ambient atmosphere, magnetically stirred, and monitored by thin layer chromatography (TLC) using EMD TLC plates

pre-coated with 250 μm thickness silica gel 60 F254 plates and visualized by fluorescence quenching under UV light. Flash chromatography was performed on Dynamic Adsorbents Silica Gel 40–63 μm particle size using a forced flow of eluent at 0.3–0.5 bar pressure.[20] All air- and moisture-sensitive manipulations were performed using oven-dried glassware, including standard Schlenk and glovebox techniques under an atmosphere of nitrogen. Acetonitrile and acetonitrile-d_3 were dried over P_2O_5 and vacuum-distilled. Methanol was degassed at –30 °C under dynamic vacuum (10^{-4} Torr) for one hour and stored over 3Å sieves. All chemicals were used as received. All deuterated solvents were purchased from Cambridge Isotope Laboratories. NMR spectra were recorded on either a Varian Unity/Inova 600 spectrometer operating at 600 MHz for ^{1}H acquisitions, a Varian Unity/Inova 500 spectrometer operating at 500 MHz and 125 MHz for ^{1}H and ^{13}C acquisitions, respectively, or Varian Mercury 400 spectrometer operating at 375 MHz and 101 MHz for ^{19}F and ^{13}C acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (^{1}H: $CDCl_3$, δ 7.26; $(CD_3)_2SO$, δ 2.50; $(CD_3)_2CO$, δ 2.05; CD_3CN, δ 1.94), (^{13}C: $CDCl_3$, δ 77.16; $(CD_3)_2SO$, δ 39.52; $(CD_3)_2CO$, δ 29.84; CD_3CN, δ 1.32),[21] or added 3-nitrofluorobenzene (–112.0 ppm) for ^{19}F spectra. Signals are listed in ppm, and multiplicity identified as s = singlet, br = broad, d = doublet, t = triplet, q = quartet, quin = quintet, sep = septet, m = multiplet; coupling constants in Hz; integration. High-resolution mass spectra were obtained using an Agilent ESI-TOF (6210) mass spectrometer or a Bruker q-TOF Maxis Impact mass spectrometer. Concentration under reduced pressure was performed by rotary evaporation at 25–30 °C under appropriate pressure. Purified compounds were further dried under high vacuum (0.01–0.05 Torr). Yields refer to purified and spectroscopically pure compounds, unless otherwise noted. Experimental details of DFT calculations can be found in our group's previous publication.[1]

1.5.2 Procedure for Preparation of Complex 1.1



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

NMR Spectroscopy:

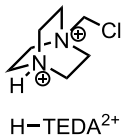
^{1}H NMR (600 MHz, DMSO, 23 °C, δ): 8.50 (dd, *J* = 5.8, 1.2 Hz, 2H), 8.30 (ddd, *J* = 7.7, 7.7, 1.5 Hz, 2H), 7.86 (ddd, *J* = 7.5, 5.8, 1.4 Hz, 2H), 7.79 (dd, *J* = 7.8, 1.2 Hz, 2H), 5.35 (s, 4H), 3.56–3.46 (m, 4H), 3.45–3.36 (m, 4H), 2.26–2.15 (m, 4H), 2.10–1.99 (m, 4H).

^{13}C NMR (125 MHz, DMSO, 23 °C, δ): 149.2, 148.2, 142.0, 128.2, 126.5, 70.1, 67.2, 21.3.

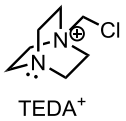
HRMS-FIA(m/z) calc'd for $C_{20}H_{28}N_4O_2Pd$ $[M]^{2+}$, 231.0622; found, 231.0632.

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

1.5.3 General Considerations for Aromatic C–H TEDAylation Reactions



H–TEDA^{2+}



TEDA^{+}

The Aryl–TEDA products are doubly cationic compounds, and similar cationic compounds are formed as byproducts of the reaction, including H–TEDA^{2+} and TEDA^{+}. Therefore, it is difficult to fully isolate the Aryl–TEDA products from the reaction mixture. We have found that performing the reaction with an excess (at least five equivalents) of the arene substrate minimizes formation of H–TEDA^{2+} and TEDA^{+} byproducts. Upon reaction completion, evaporation of the solvent, followed by trituration of the residue with DCM/MeOH mixtures to remove the excess arene, and the palladium and ruthenium catalysts, results in material that is sufficiently clean for characterization, albeit still contaminated to varying degrees with H–TEDA^{2+} and TEDA^{+}. Therefore, we have performed the Ar–TEDA formation reactions twice for each of the Ar–TEDA products **1.2a-g**: once utilizing the arene as limiting reagent (with yield determined by NMR integration relative to an internal standard), and once with excess arene (for characterization purposes). For Ar–TEDA compounds synthesized through the use of excess arene, yields of Ar–TEDA, H–TEDA^{2+}, and TEDA^{+} are calculated relative to Selectfluor, and were determined via NMR analysis of a known amount of the mixture by integrating against an internal standard.

The Ar–TEDA products may be fully isolated from H–TEDA^{2+}, and TEDA^{+} by repeated recrystallization. The Ar–TEDA product derived from fluorenone (**1.2f**) was isolated in this way and characterized as a pure compound.

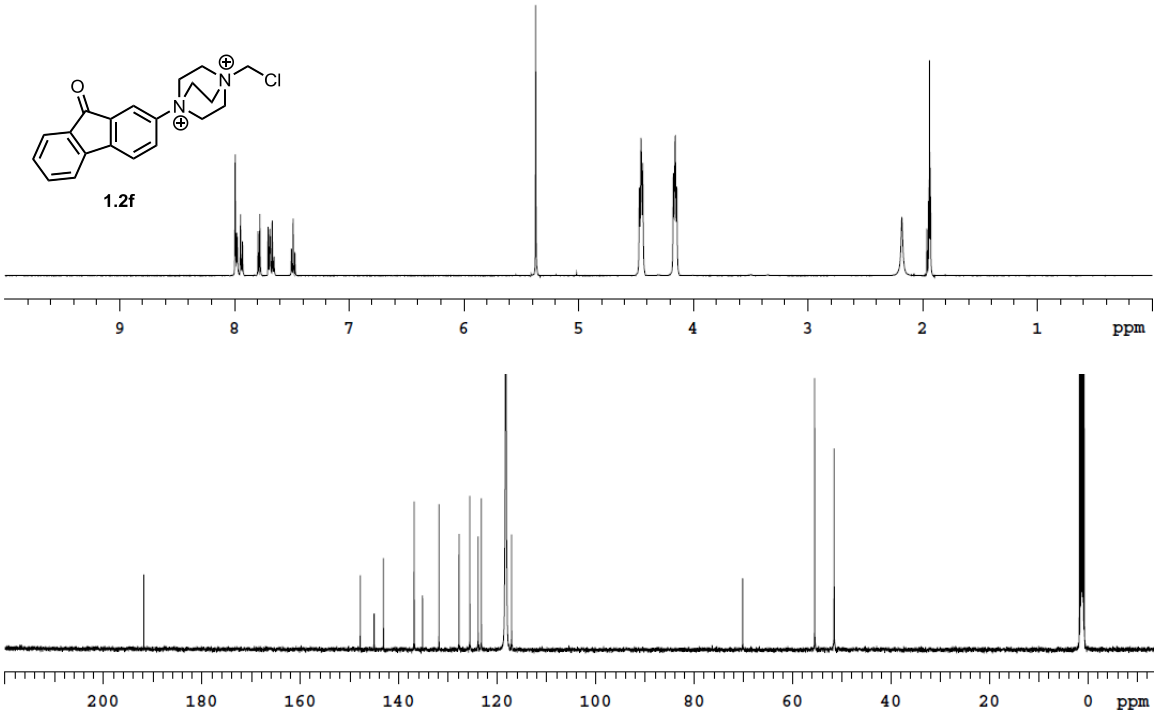
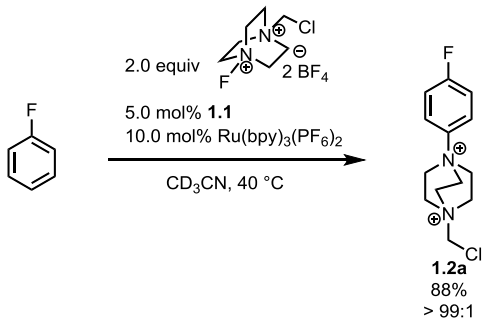


Figure 1.5. ^{1}H and ^{13}C NMR of pure Ar–TEDA **1.2f**

1.5.4 Procedure for Aromatic C–H TEDAylation Reactions (1 Equiv Arene)

1-(Chloromethyl)-4-(4-fluorophenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2a)



A 4 mL vial was charged with Selectfluor (70.9 mg, 0.200 mmol, 2.00 equiv), **1.1** (3.2 mg, 5.0 µmol, 5.0 mol%), and $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 10 µmol, 10. mol%), and 0.50 mL CD_3CN. and finally fluorobenzene (9.4 µL, 0.10 mmol, 1.0 equiv). The vial was sealed and the mixture stirred at 40 °C for 36 h. The reaction mixture was diluted with 0.25 mL CD_3CN and filtered through a

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

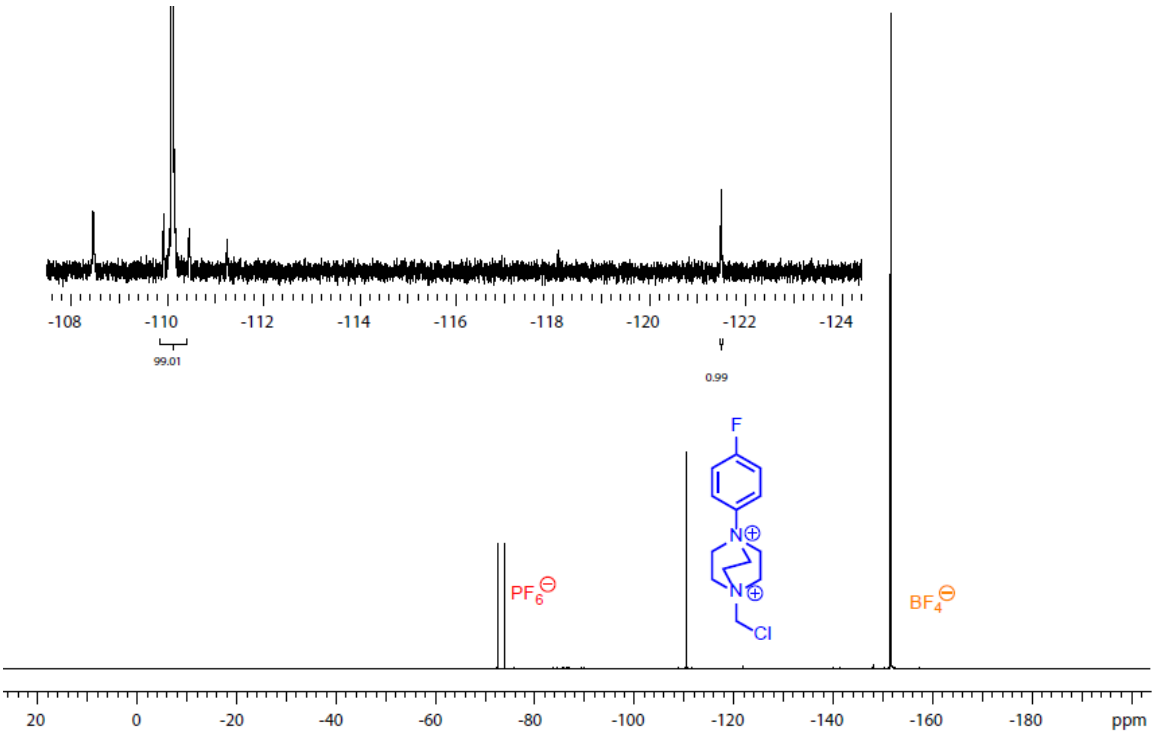


Figure 1.6. ^{19}F NMR evaluation of positional selectivity

Only one significant aryl fluoride peak was observed in ^{19}F NMR, corresponding to the title compound. After 24 scans with a relaxation delay of 20 s, another peak in the aromatic region was observed at –121.5 ppm, at a ratio of 0.99:99.1 relative to the peak corresponding to **1.2a**. The ratio between the Ar–F signal and the rms noise over a 100 Hz range was measured to be 1286 (command 'dsnmax(100)' in VNMR), implying that any other products have a maximum concentration of 0.08% of the title compound. Given that the next largest peak in the aromatic region had an intensity of below 1% of the signal of **1.2a**, and given the magnitude of the noise level, we conclude that the positional selectivity of the TEDAylation reaction of fluorobenzene is >99:1 in favor of *para* substitution.

The product mixture of the reaction to form **1.2a** was analyzed by ^{19}F NMR in several different solvents in order to rule out coincidental overlap with any peaks corresponding to positional isomers of **1.2a**. This was carried out by evaporating the acetonitrile solvent from the completed reaction mixtures and dissolving the residue in 5:1 CD_3CN:C_6D_6, d_6-DMSO, and d_5-pyridine. In each of these cases, only one aryl fluoride signal was observed by ^{19}F NMR:

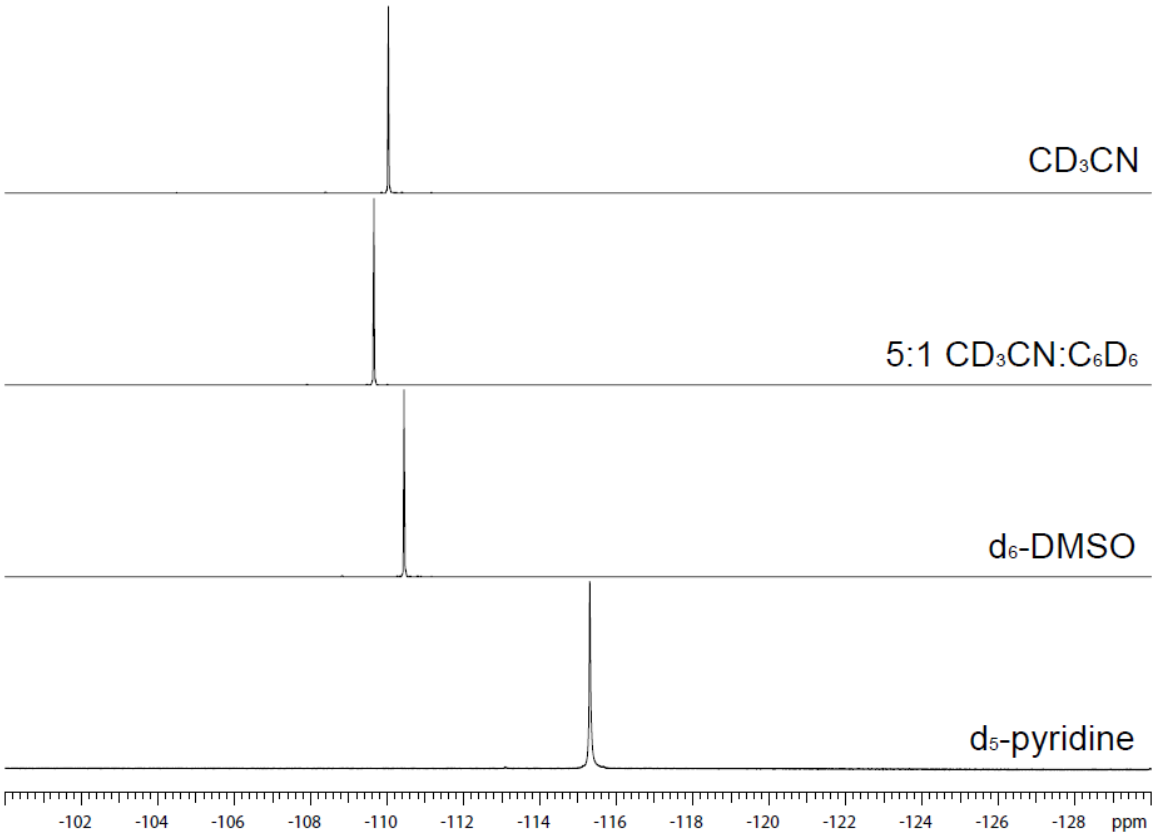
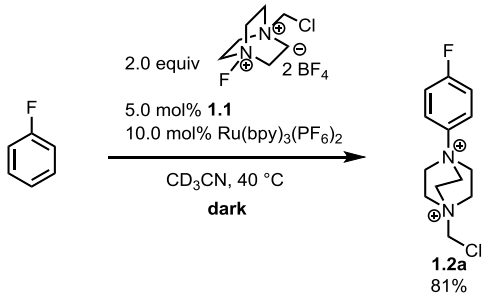


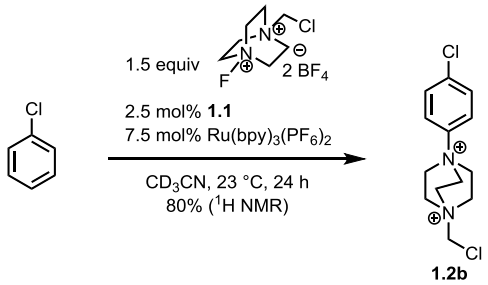
Figure 1.7. ^{19}F NMR evaluation of positional selectivity in different solvents

Formation of 1.2a in the absence of light



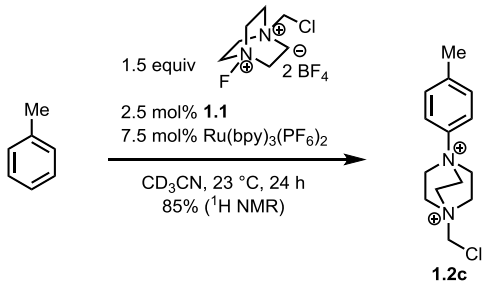
A 4 mL vial, completely covered with aluminum foil, was charged with Selectfluor (70.9 mg, 0.200 mmol, 2.00 equiv), **1.1** (3.2 mg, 5.0 μmol, 5.0 mol%), and $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 10 μmol, 10. mol%), and 0.50 mL CD_3CN. and finally fluorobenzene (9.4 μL, 0.10 mmol, 1.0 equiv). The vial was sealed and the mixture stirred in the dark at 40 °C for 24 h, after which 2.0 μL of 3-fluoronitrobenzene was added as an internal standard. The reaction mixture was diluted with 0.50 mL CD_3CN, and passed through a 0.22 μm PVDF syringe filter. The resulting solution was analyzed by ^{19}F NMR, and comparison to the internal standard revealed a yield of 81% of **1.2a**.

1-(Chloromethyl)-4-(4-chlorophenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2b)



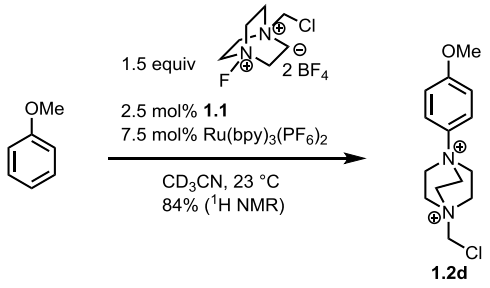
Palladium complex **1.1** (10.3 mg, 16.2 μmol) and $Ru(bpy)_3(PF_6)_2$ (41.9 mg, 48.8 μmol) were dissolved in d_3-acetonitrile (3.25 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (52.2 mg, 0.147 mmol, 1.50 equiv). The stock solution (491. μL, c = 0.20 M) containing **1.1** (2.45 μmol, 2.50 mol%) and $Ru(bpy)_3(PF_6)_2$ (7.37 μmol, 7.50 mol%) was added, followed by chlorobenzene (10.0 μL 98.2 μmol, 1.00 equiv) via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (3.0 mL). The yield of **1.2b** was determined via ^1H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **1.2b** at 7.78–7.81 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 80% yield of **1.2b**.

1-(Chloromethyl)-4-(4-methylphenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2c)



Palladium complex **1.1** (10.3 mg, 16.2 μmol) and $Ru(bpy)_3(PF_6)_2$ (41.9 mg, 48.8 μmol) were dissolved in d_3-acetonitrile (3.25 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (49.9 mg, 0.141 mmol, 1.50 equiv). The stock solution (469. μL, c = 0.20 M) containing **1.1** (2.34 μmol, 2.50 mol%) and $Ru(bpy)_3(PF_6)_2$ (7.04 μmol, 7.50 mol%) was added, followed by toluene (10.0 μL, 93.9 μmol, 1.00 equiv) via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (3.0 mL). The yield of **1.2c** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **1.2c** at 7.67–7.65 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 85% yield of **1.2c**.

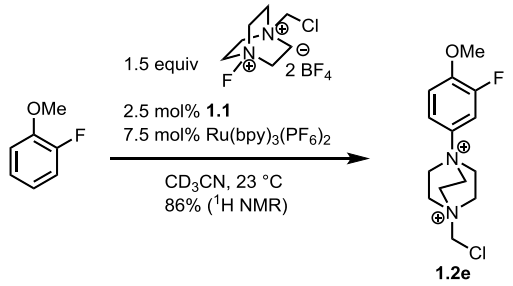
1-(Chloromethyl)-4-(4-methoxyphenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2d)



Palladium complex **1.1** (10.3 mg, 16.2 μmol) and $Ru(bpy)_3(PF_6)_2$ (41.9 mg, 48.8 μmol) were dissolved in d_3-acetonitrile (3.25 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (48.9 mg, 0.138 mmol, 1.50 equiv). The stock solution (460. μL, c = 0.200 M) containing **1.1** (2.34 μmol, 2.50 mol%) and $Ru(bpy)_3(PF_6)_2$ (7.04 μmol, 7.50 mol%) was added, followed by anisole (10.0 μL, 92.0 μmol, 1.00 equiv) via syringe. After stirring at 23 °C for 24 h,

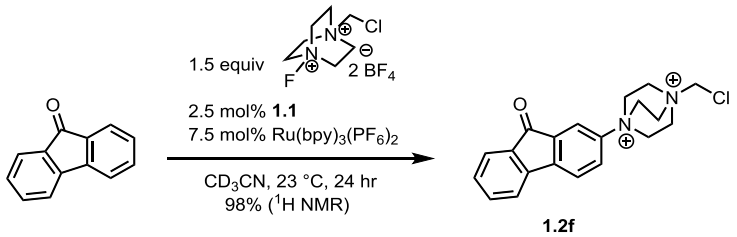
the reaction mixture was diluted with d_3-acetonitrile (3.0 mL). The yield of **1.2d** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **1.2d** at 7.72–7.69 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 84% yield of **1.2d**.

1-(Chloromethyl)-4-(3-fluoro-4-methoxyphenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2e)



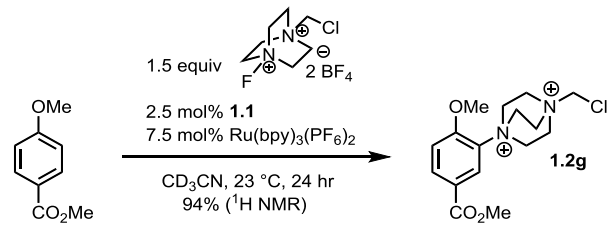
Palladium complex **1.1** (11.3 mg, 17.8 μmol) and Ru(bpy)$_3$(PF$_6$)$_2$ (45.9 mg, 53.4 μmol) were dissolved in d_3-acetonitrile (3.56 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (47.3 mg, 0.134 mmol, 1.50 equiv). The stock solution (445. μL, c = 0.200 M) containing **1.1** (2.23 μmol, 2.50 mol%) and Ru(bpy)$_3$(PF$_6$)$_2$ (6.68 μmol, 7.50 mol%) was added, followed by 2-fluoroanisole (10.0 μL, 89.0 μmol, 1.00 equiv) via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.5 mL). The yield of **1.2e** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **1.2e** at 7.34 ppm (aromatic C–H, 1H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 86% yield of **1.2e**.

1-(Chloromethyl)-4-(fluorenon-2-yl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2f)



Palladium complex **1.1** (11.3 mg, 17.8 μmol) and $Ru(bpy)_3(PF_6)_2$ (45.9 mg, 53.4 μmol) were dissolved in d_3-acetonitrile (3.56 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (47.3 mg, 0.134 mmol, 1.50 equiv) and fluorenone (16.0 mg, 89.0 μmol, 1.00 equiv). The stock solution (445. μL, c = 0.200 M) containing **1.1** (2.23 μmol, 2.50 mol%) and $Ru(bpy)_3(PF_6)_2$ (6.68 μmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.0 mL). The yield of **1.2f** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **1.2f** at 7.94–7.93 ppm (aromatic C–H, 1H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 98% yield of **1.2f**.

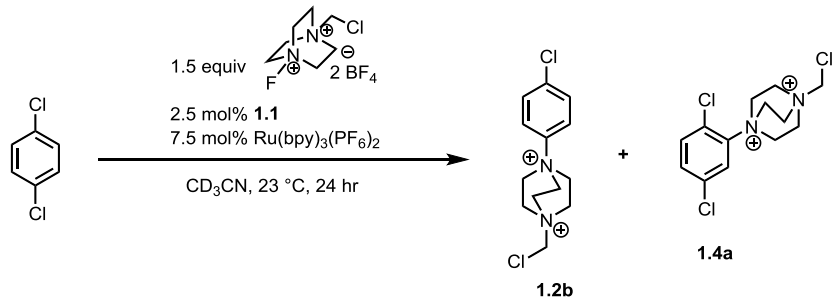
1-(Chloromethyl)-4-(2-methoxy-5-(methoxycarbonyl)phenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2g)



Palladium complex **1.1** (10.3 mg, 16.2 μmol) and $Ru(bpy)_3(PF_6)_2$ (41.9 mg, 48.8 μmol) were dissolved in d_3-acetonitrile (3.25 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (53.1 mg, 0.150 mmol, 1.50 equiv) and methyl 4-methoxybenzoate (16.6 mg, 100. μmol, 1.00 equiv). The stock solution (500. μL, c = 0.200 M) containing **1.1** (2.50 μmol, 2.50 mol%) and $Ru(bpy)_3(PF_6)_2$ (7.50 μmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (3.0 mL). The yield of **1.2g** (94 %) was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard.

The yield of **1.2g** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **1.2g** at 7.46 ppm (aromatic C–H, 1H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed a 94% yield of **1.2g**.

1-(Chloromethyl)-4-(4-chlorophenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2b) from 1,4-dichlorobenzene



Palladium complex **1.1** (11.3 mg, 17.8 μmol) and $Ru(bpy)_3(PF_6)_2$ (45.9 mg, 53.4 μmol) were dissolved in d_3-acetonitrile (3.56 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (47.3 mg, 0.134 mmol, 1.50 equiv) and 1,4-dichlorobenzene (13.1 mg, 89.0 μmol, 1.00 equiv). The stock solution (445 μL, c = 0.200 M) containing **1.1** (2.23 μmol, 2.50 mol%) and $Ru(bpy)_3(PF_6)_2$ (6.68 μmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.0 mL).

The yield of **1.2b** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **1.2b** at 7.74–7.72 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 48% yield of **1.2b**.

Another compound, consistent with structure **1.4a**, was observed in 11% yield:

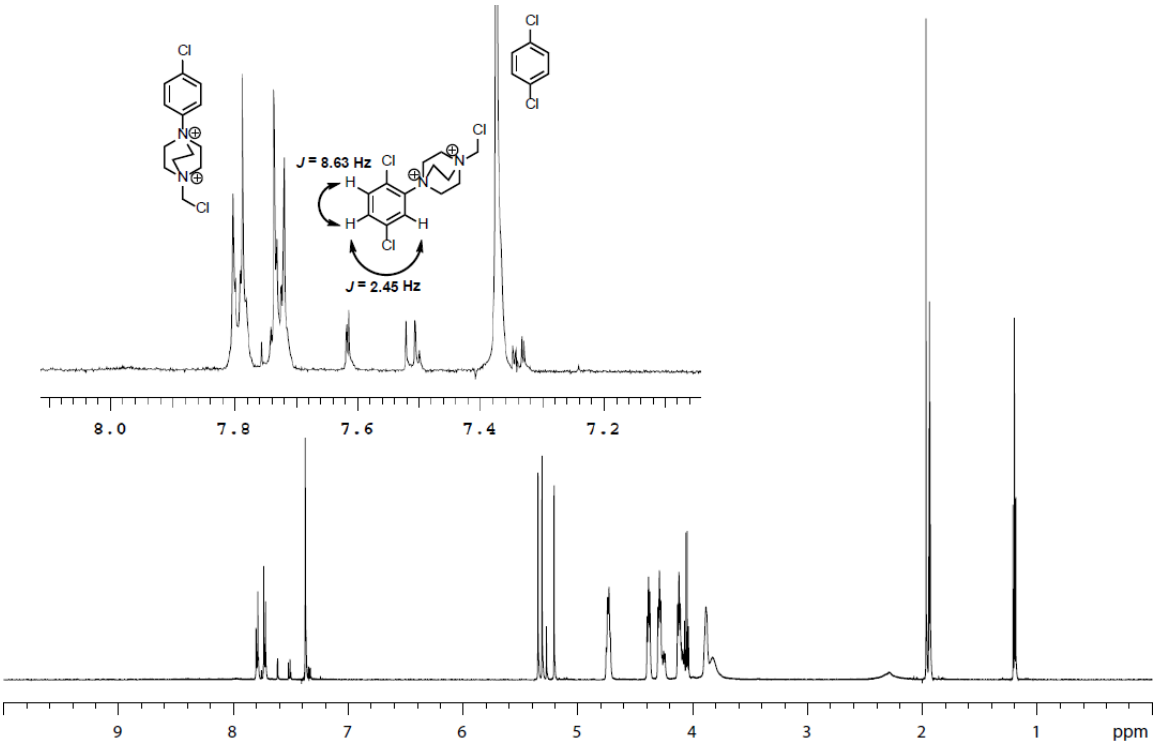
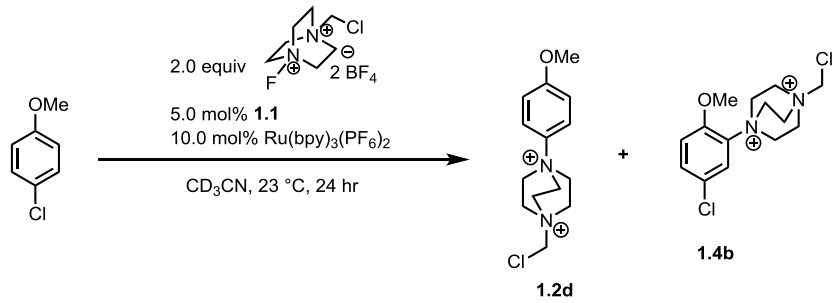


Figure 1.8. Products of TEDAylation of 1,4-dichlorobenzene

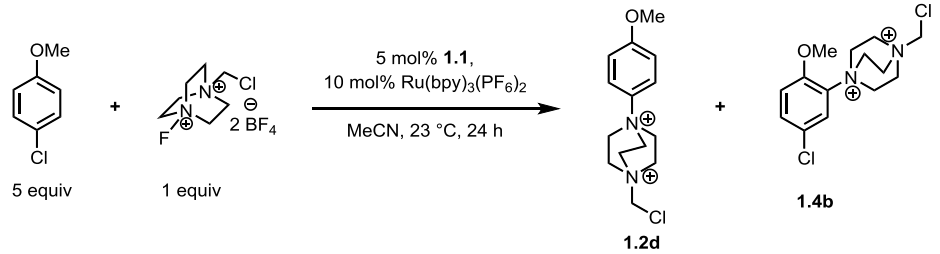
1-(Chloromethyl)-4-(4-methoxyphenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2d) from 4-chloroanisole



A stock solution was prepared, containing **1.1** (11.4 mg, 15.0 μmol) and $Ru(bpy)_3(PF_6)_2$ (25.8 mg, 30.0 μmol) were dissolved in d_3-acetonitrile (1.50 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (35.4 mg, 0.100 mmol, 2.0 equiv) and 4-chloroanisole (6.1 μL, 0.050 mmol, 1.0 equiv). The stock solution (250 μL, c = 0.20 M) containing **1.1** (2.5 μmol, 5.0 mol%) and $Ru(bpy)_3(PF_6)_2$ (5.00 μmol, 10.0 mol%) was added via syringe. After stirring at

23 °C for 48 h, the reaction mixture was diluted with d_3-acetonitrile (0.50 mL). The yield of **1.2d** (26 %) was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 µL, 51. µmol) as an internal standard.

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



To a 20 mL vial were weighed **1.1** (31.8 mg, 50.0 µmol, 5.00 mol%), $Ru(bpy)_3(PF_6)_2$ (86.0 mg, 0.100 mmol, 10.0 mol%), and Selectfluor (354. mg, 1.00 mmol, 1.00 equiv). Acetonitrile was added (5.0 mL, c = 0.20 M), followed by 4-chloroanisole (612. µL, 5.00 mmol, 5.00 equiv). The mixture was stirred for 24 hours at room temperature, after which the mixture was diluted with 10 mL acetonitrile, then filtered through celite. The filtrate was concentrated, and the residue was triturated with 20 mL of 9:1 DCM:MeOH. The solid was collected by filtration, then washed with 10 mL 9:1 DCM:MeOH, then DCM (3 × 10 mL). The solid was dried in vacuo to yield 316. mg of a tan solid. ^{1}H NMR analysis revealed **1.2d** as the dominant Ar–TEDA product, along with ca. 29% of **1.4b**:

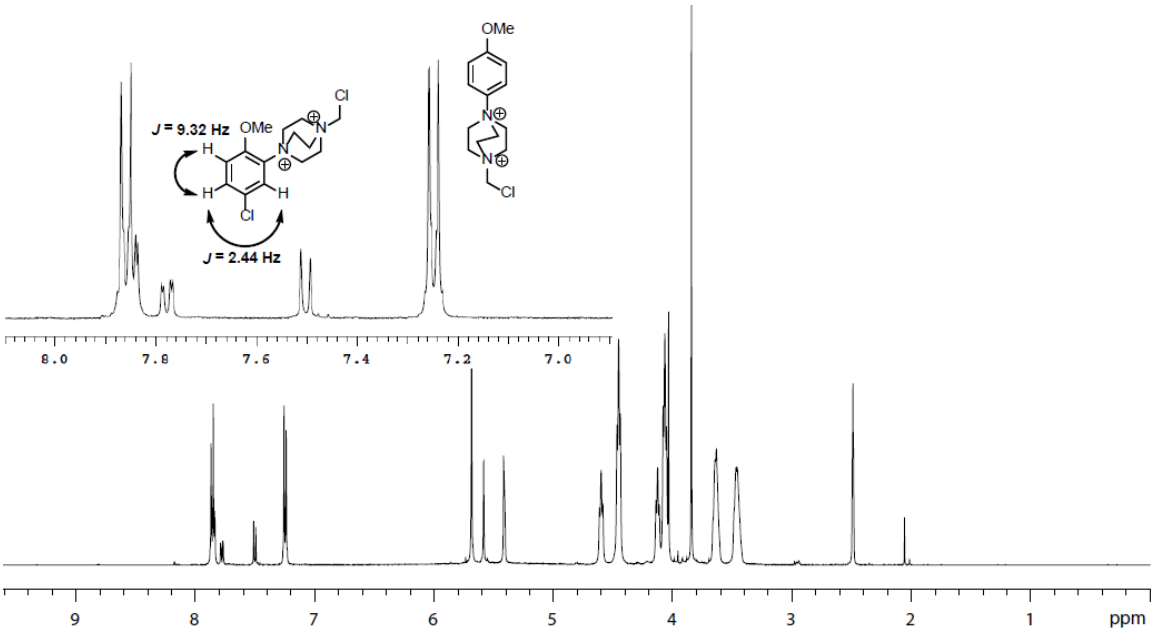
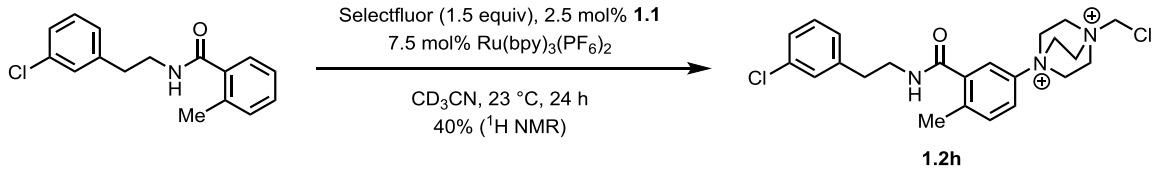


Figure 1.9. Products of TEDAylation of 4-chloroanisole

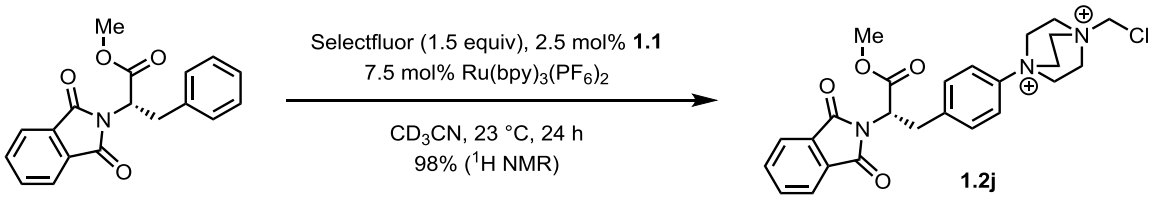
1-(Chloromethyl)-4-(3-((3-chlorophenethyl)carbamoyl)-4-methylphenyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium (1.2h)



Palladium complex **1.1** (7.2 mg, 11. µmol) and $Ru(bpy)_3(PF_6)_2$ (29.0 mg, 33.8 µmol) were dissolved in d_3-acetonitrile (2.25 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (26.6 mg, 75.0 µmol, 1.50 equiv) and *N*-(3-chlorophenethyl)-2-methylbenzamide (13.7 mg, 50.0 µmol, 1.00 equiv). The stock solution (0.25 mL, c = 0.20 M) containing **1.1** (1.2 µmol, 2.5 mol%) and $Ru(bpy)_3(PF_6)_2$ (3.75 µmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.0 mL). The yield of **1.2h** was determined via ^{1}H NMR spectroscopy using N,N-dimethylformamide (2.0 µL, 26. µmol) as an internal standard. Comparison of the integral of the peak of **1.2h** at 7.66 ppm

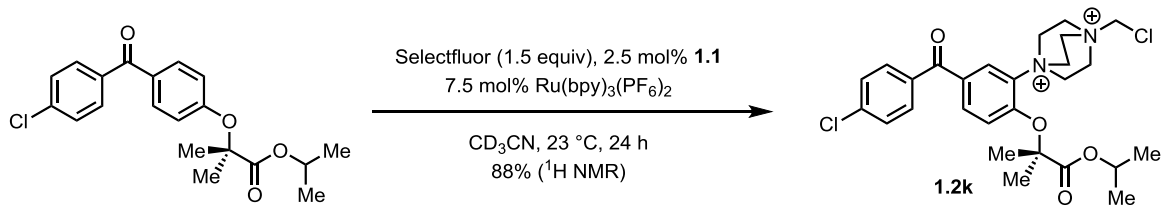
(aromatic C–H, 1H) with that of the peak of N,N-dimethylformamide (CH, 1H) revealed an 40% yield of **1.2h**.

(*S*)-1-(Chloromethyl)-4-(4-(2-(1,3-dioxoisoindolin-2-yl)-3-methoxy-3-oxopropyl)phenyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium (1.2j)



Palladium complex **1.1** (3.5 mg, 5.5 μmol) and $Ru(bpy)_3(PF_6)_2$ (14.2 mg, 16.5 μmol) were dissolved in d_3-acetonitrile (1.10 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (53.1 mg, 0.150 mmol, 1.50 equiv) and methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (30.9 mg, 0.100 mmol, 1.00 equiv). The stock solution (1.0 mL, c = 0.20 M) containing **1.1** (2.5 μmol, 2.5 mol%) and $Ru(bpy)_3(PF_6)_2$ (7.50 μmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.0 mL). The yield of **1.2j** was determined via 1H NMR spectroscopy using N,N-dimethylformamide (5.0 μL, 64. μmol) as an internal standard. Comparison of the integral of the peak of **1.2j** at 4.28–4.30 ppm (alkyl C–H, 6H) with that of the peak of N,N-dimethylformamide (CH_3, 3H) revealed an 98% yield of **1.2j**.

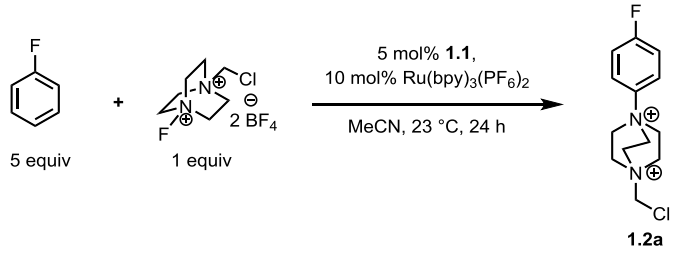
1-(5-(4-Chlorobenzoyl)-2-((1-isopropoxy-2-methyl-1-oxopropan-2-yl)oxy)phenyl)-4-(chloromethyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium (1.2k)



Palladium complex **1.1** (3.5 mg, 5.5 μmol) and $Ru(bpy)_3(PF_6)_2$ (14.2 mg, 16.5 μmol) were dissolved in d_3-acetonitrile (1.10 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (53.1 mg, 0.150 mmol, 1.50 equiv) and fenofibrate (36.1 mg, 0.100 mmol, 1.00 equiv). The stock solution (1.0 mL, c = 0.20 M) containing **1.1** (2.5 μmol, 2.5 mol%) and $Ru(bpy)_3(PF_6)_2$ (7.50 μmol, 7.50 mol%) was added via syringe. After stirring at 23 °C for 24 h, the reaction mixture was diluted with d_3-acetonitrile (2.0 mL). The yield of **1.2k** was determined via ^{1}H NMR spectroscopy using N,N-dimethylformamide (5.0 μL, 64. μmol) as an internal standard. Comparison of the integral of the peak of **1.2k** at 4.61–4.64 ppm (alkyl C–H, 6H) with that of the peak of N,N-dimethylformamide (CH_3, 3H) revealed an 88% yield of **1.2k**.

1.5.5 Procedure for Aromatic C–H TEDAylation Reactions (Excess Arene)

1-(Chloromethyl)-4-(4-fluorophenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2a)



To a 20 mL vial were added palladium complex **1.1** (31.8 mg, 50.0 μmol, 5.00 mol%), $Ru(bpy)_3(PF_6)_2$ (86.0 mg, 100. μmol, 10.0 mol%), Selectfluor (354. mg, 1.00 mmol, 1.00 equiv), and fluorobenzene (0.530 mL, 5.00 mmol, 5.00 equiv), and acetonitrile (2.5 mL, c = 0.20 M). The reaction mixture was stirred at 40 °C for 48 h. The reaction mixture was diluted with acetonitrile, filtered through celite, and the filtrate was concentrated *in vacuo*. The residue was triturated with 20 mL MeOH:DCM. The solid was collected by filtration on a glass frit, washed with 10 mL 1:9 MeOH:DCM, followed by 3 × 10 mL DCM, then dried *in vacuo* to afford 341. mg of a tan powder. For yield determination, an NMR sample in d_3-acetonitrile was prepared

containing 10.0 mg of the product mixture and 5.0 μL of ethyl acetate (51. μmol) as internal standard. Comparison of the integral of the peak of **1.2a** at 4.45–4.37 ppm (3 × CH_2, 6H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.60 mmol of Ar–TEDA (60% yield). Also present was 0.18 mmol H–$TEDA^{2+}$ (18%), measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H).

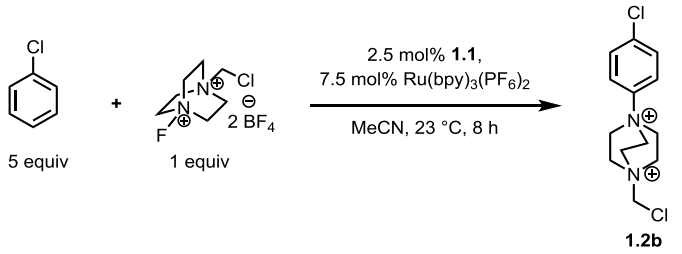
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.91–7.84 (m, 2H), 7.49–7.42 (m, 2H), 5.36 (s, 2H), 4.45–4.37 (m, 6H), 4.18–4.11 (m, 6H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 163.4 (d, *J* = 252.4 Hz), 140.7 (s), 123.8 (d, *J* = 9.6 Hz), 118.9 (d, *J* = 24.0 Hz), 70.1 (s), 55.6 (s), 51.6 (s). ^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –110.0.

HRMS-FIA(m/z) calc'd for C13H17ClFN2 [M–H]+, 255.1059; found, 255.1061.

1-(Chloromethyl)-4-(4-chlorophenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2b)



A 50 mL round-bottom flask was charged with palladium complex **1.1** (31.8 mg, 50.0 μmol. 5.00 mol%), $Ru(bpy)_3(PF_6)_2$ (86.0 mg, 0.100 mmol, 10.0 mol%), and Selectfluor (354. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added, followed by chlorobenzene (509 μL, 5.00 mmol, 5.00 equiv) via syringe. After stirring at 23 °C for 19 h, the reaction mixture was filtered through celite and concentrated *in vacuo*. The residue was triturated with a solvent mixture of DCM/MeOH (9/1 (v/v), 10 mL) and DCM (5 × 10 mL) at 23 °C to afford 463 mg of the title compound as a light yellow solid. For yield determination, an NMR sample in *d*3-

acetonitrile was prepared containing 20.0 mg of the product mixture and 3.0 µL of ethyl acetate (31. µmol) as internal standard. Comparison of the integral of the peak of **1.2b** at 7.79–7.77 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.80 mmol of Ar–TEDA (80% yield). Also present was 0.14 mmol H–$TEDA^{2+}$ (14%), measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H).

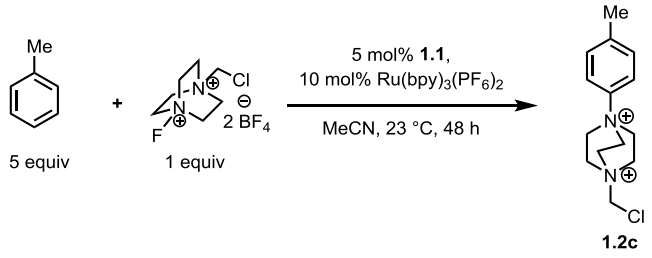
NMR Spectroscopy:

^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.79–7.82 (m, 2H), 7.70–7.73 (m, 2H), 5.36 (s, 2H), 4.40–4.43 (m, 6H), 4.13–4.15 (m, 6H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 142.9, 137.9, 131.6, 122.9, 69.7, 55.1, 51.2.

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

1-(Chloromethyl)-4-(4-methyl-phenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2c)



To a 20 mL vial were added palladium complex **1.1** (31.8 mg, 50.0 µmol, 5.00 mol%), $Ru(bpy)_3(PF_6)_2$ (86.0 mg, 100. µmol, 10.0 mol%), Selectfluor (354. mg, 1.00 mmol, 1.0 equiv), and toluene (0.530 mL, 5.00 mmol, 5.00 equiv), and acetonitrile (2.5 mL, c = 0.20 M). The reaction mixture was stirred at 23 °C for 48 h. The reaction mixture was concentrated *in vacuo*, then triturated with DCM to afford 324 mg of a tan powder. For yield determindation, an NMR sample in d_3-acetonitrile was prepared containing 10.0 mg of the product mixture and 5.0 µL of ethyl acetate (51. µmol) as internal standard. Comparison of the integral of the peak of **1.2c** at 4.37–4.32 ppm (3 × CH_2, 6H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H)

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

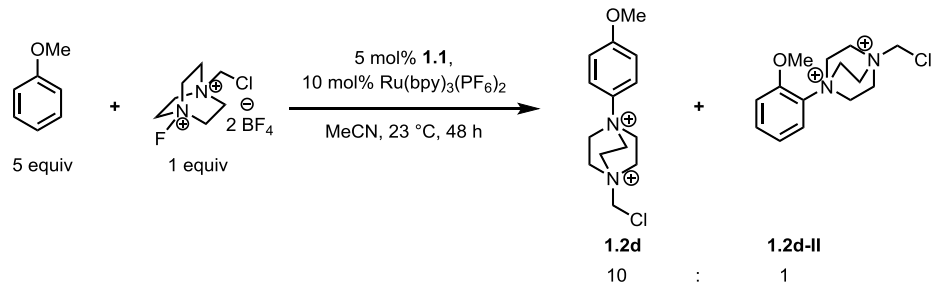
NMR Spectroscopy:

^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.67–7.63 (m, 2H), 7.54–7.00 (m, 2H), 5.33 (s, 2H), 4.37–4.32 (m, 6H), 4.11–4.07 (m, 6H), 2.44 (s, 3H).

^{13}C NMR (125 MHz, DMSO, 23 °C, δ): 142.1, 141.4, 131.0, 120.3, 68.2, 53.94, 50.4, 20.3.

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

1-(Chloromethyl)-4-(4-methyl-phenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2d)



To a 20 mL vial were added palladium complex **1.1** (31.8 mg, 50.0 μmol, 5.00 mol%), $Ru(bpy)_3(PF_6)_2$ (86.0 mg, 100. μmol, 10.0 mol%), Selectfluor (354. mg, 1.00 mmol, 1.0 equiv), and anisole (0.544 mL, 5.00 mmol, 5.0 equiv), and acetonitrile (2.5 mL, c = 0.20 M). The reaction mixture was stirred at 23 °C for 48 h. The reaction mixture was concentrated *in vacuo*, then triturated with DCM to afford 324. mg of a tan powder. For yield determination, an NMR sample in d_3-acetonitrile was prepared containing 10.0 mg of the product mixture and 5.0 μL of ethyl acetate (51. μmol) as internal standard. Comparison of the integral of the peak of **1.2d** at 4.36–4.31 ppm (3 × CH_2, 6H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.43 mmol of **1.2d** (43% yield). An additional compound

was observed in 4.3% yield, assignable to **1.2d-II**. Also present was 0.31 mmol H–TEDA^{2+} (31%), measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H).

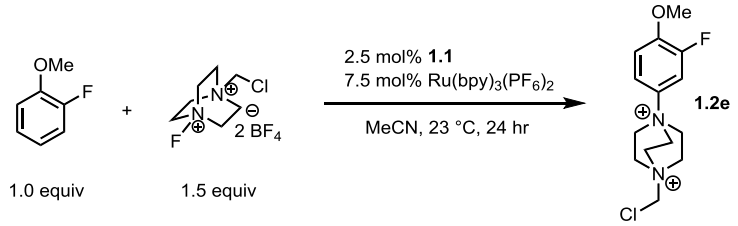
NMR Spectroscopy:

^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.72–7.67 (m, 2H), 7.21–7.17 (m, 2H), 5.33 (s, 2H), 4.36–4.31 (m, 6H), 4.20–4.15 (m, 6H), 3.88 (s, 3H).

^{13}C NMR (125 MHz, DMSO, 23 °C, δ): 160.5, 137.0, 122.1, 115.5, 68.2, 54.1, 50.4, 43.4.

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

1-(Chloromethyl)-4-(3-fluoro-4-methoxyphenyl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2e)



A 50 mL round-bottom flask was charged with palladium complex **1.1** (31.8 mg, 50.0 μmol. 5.00 mol%), $Ru(bpy)_3(PF_6)_2$ (86.0 mg, 0.100 mmol, 10.0 mol%), and Selectfluor (531. mg, 1.50 mmol, 1.50 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added, followed by 2-fluoroanisole (112 μL, 1.00 mmol, 1.00 equiv) via syringe. After stirring at 23 °C for 24 h, the reaction mixture was filtered through celite and concentrated *in vacuo*. The residue was triturated with a solvent mixture of DCM/MeOH (9/1 (v/v), 10 mL) and DCM (5 × 10 mL) at 23 °C to afford 573 mg of a orange solid. The solid was triturated with a solvent mixture of DCM/MeOH (9/1 (v/v), 10 mL) and DCM (5 × 10 mL) at 23 °C to afford 562 mg of the title compound as a light orange solid. For yield determination, an NMR sample in *d*3-acetonitrile was prepared containing 20.0 mg of the product mixture and 3.0 μL of ethyl acetate (3.1×10^{-5} mol) as internal standard. Comparison of the integral of the peak of **1.2e** at 7.34 ppm (aromatic C–H, 1H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.76 mmol of

Ar–TEDA (76% yield). Also present was 0.42 mmol H–$TEDA^{2+}$ (42%) measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H).

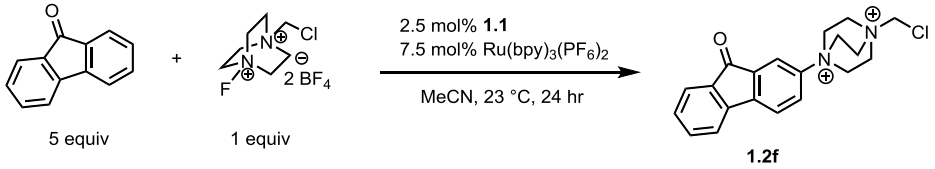
NMR Spectroscopy:

^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.67 (dd, *J* = 12.2, 3.3 Hz, 1H), 7.59 (ddd, *J* = 9.3, 3.3, 1.6 Hz, 1H), 7.34 (dd, *J* = 9.3, 9.3 Hz, 1H), 5.36 (s, 2H), 4.36–4.38 (m, 6H), 4.11–4.13 (m, 6H), 3.96 (s, 3H).

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

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

1-(Chloromethyl)-4-(fluorenon-2-yl)-1,4-diazabicyclo[2.2.2]octane^{2+} (1.2f)



A 50 mL round-bottom flask was charged with palladium complex **1.1** (31.8 mg, 50.0 μmol. 5.00 mol%), $Ru(bpy)_3(PF_6)_2$ (86.0 mg, 0.100 mmol, 10.0 mol%), Selectfluor (354. mg, 1.00 mmol, 1.00 equiv), and 9*H*-fluoren-9-one (901 mg, 5.00 mmol, 5.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. After stirring at 23 °C for 16 h, the reaction mixture was filtered through celite and concentrated *in vacuo*. The residue was triturated with a solvent mixture of DCM/MeOH (9/1 (v/v), 10 mL) and DCM (5 × 10 mL) at 23 °C to afford 559. mg of a yellow solid. The solid was triturated with a solvent mixture of DCM/MeOH (9/1 (v/v), 10 mL) and DCM (5 × 10 mL) at 23 °C to afford 468. mg of a bright yellow solid. The solid was triturated with a solvent mixture of DCM/MeOH (9/1 (v/v), 10 mL) and DCM (5 × 10 mL) at 23 °C to afford 453. mg of the title compound as a bright yellow solid. For yield determination, an NMR

sample in d_3-acetonitrile was prepared containing 20.0 mg of the product mixture and 3.0 µL of ethyl acetate (3.1×10^{-5} mol) as internal standard. Comparison of the integral of the peak of **1.2f** at 5.36 ppm (CH_2Cl, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.77 mmol of Ar–TEDA (77% yield). Also present was 0.069 mmol H–$TEDA^{2+}$ (7%), measured by integration of the peak at 3.85–3.81 ppm ($3 \times CH_2$, 6H).

The product mixture of **1.2f** obtained above (50 mg) was further purified through repeated recrystallization by vapor diffusion of diethyl ether into an acetonitrile solution. Pure product **1.2f** (15 mg) was obtained as yellow crystals and characterized.

Note: Compound **1.2f** exhibits concentration-dependent chemical shifts. The chemical shifts listed below were recorded from a sample of 12 mg **1.2f** in 7.5 mL CD_3CN.

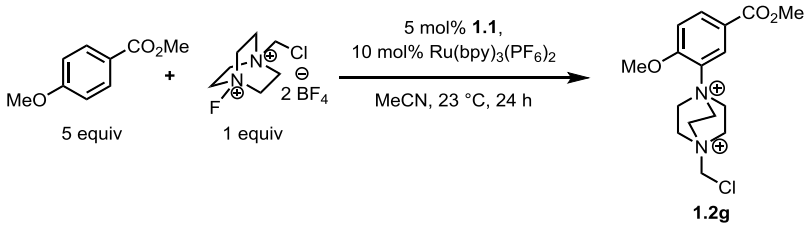
NMR Spectroscopy:

^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 8.00–7.97 (m, 2H), 7.95–7.92 (m, 1H), 7.80–7.77 (m, 1H), 7.71–7.65 (m, 2H), 7.51–7.47 (m, 1H), 5.38 (s, 2H), 4.45–4.47 (m, 6H), 4.15–4.18 (m, 6H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 191.7, 147.7, 145.0, 143.0, 136.8, 136.7, 135.0, 131.7, 127.7, 125.4, 123.8, 123.1, 116.9, 70.0, 55.4, 51.5.

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

1-(Chloromethyl)-4-(5-methoxy-2-(methoxycarbonyl)phenyl)$^{2+}$ (1.2g)



To a 20 mL vial were added palladium complex **1.1** (19.0 mg, 25.0 µmol, 5.00 mol%), $Ru(bpy)_3(PF_6)_2$ (43.0 mg, 5.00 µmol, 10.0 mol%), Selectfluor (177. mg, 0.500 mmol, 1.00 equiv),

and methyl 4-methoxybenzoate (416 mg, 2.50 mmol, 5.00 equiv), and acetonitrile (2.5 mL, c = 0.20 M). The reaction mixture was stirred at 23 °C for 48 h. The reaction mixture was concentrated *in vacuo*, then triturated with DCM to afford 191. mg of a tan powder. ^{1}H NMR shows ca. 35% contamination by H–TEDA^{2+}.

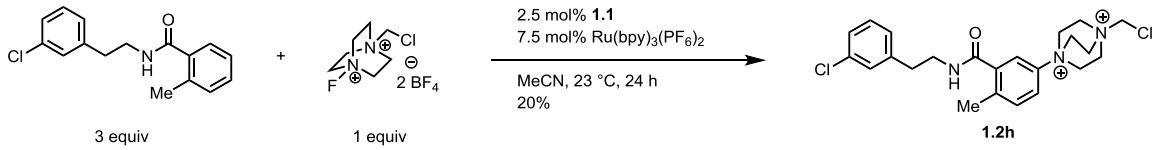
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 8.27 (dd, *J* = 8.9, 1.8 Hz, 1H), 8.21 (d, *J* = 1.8 Hz, 1H), 7.46 (d, *J* = 8.9 Hz, 1H), 5.33 (s, 2H), 4.62–4.54 (m, 6H), 4.15–4.09 (m, 6H), 4.14 (s, 3H), 3.92 (s, 3H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 165., 156.51, 135.4, 130.8, 124.7, 124.3, 116.6, 70.4, 58.4, 53.7, 51.6, 45.1.

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

1-(Chloromethyl)-4-(3-((3-chlorophenethyl)carbamoyl)-4-methylphenyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium (1.2h)



A 4 mL vial was charged with palladium complex **1.1** (3.2 mg, 5.0 μmol. 2.5 mol%), $Ru(bpy)_3(PF_6)_2$ (12.9 mg, 15.0 μmol, 7.50 mol%), Selectfluor (70.9 mg, 0.200 mmol, 1.00 equiv), and *N*-(3-chlorophenethyl)-2-methylbenzamide (164. mg, 0.600 mmol, 3.00 equiv). Acetonitrile (1.0 mL, c = 0.20 M) was added via syringe, and the reaction mixture was stirred at 23 °C for 24 h. The reaction mixture was concentrated *in vacuo* to afford a red heterogeneous solid mixture. The solid was triturated with DCM to afford 62 mg of the title compound as a light yellow solid (20% yield). ^{1}H NMR shows ca. 49% contamination by 1-(chloromethyl)-1,4-diazabicyclo[2.2.2]octane-1,4-diium (H–TEDA^{2+}).

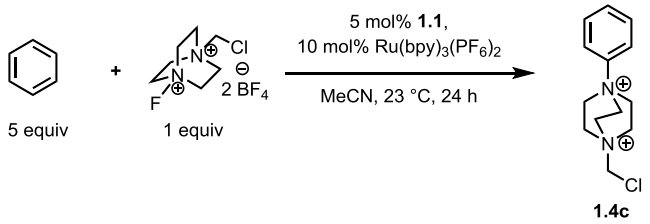
NMR Spectroscopy:

^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.71 (dd, *J* = 8.8, 2.9 Hz, 1H), 7.67 (d, *J* = 2.9 Hz, 1H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.30–7.33 (m, 2H), 7.23–7.25 (m, 2H), 6.99 (bs, 1H), 5.36 (s, 2H), 4.38–4.40 (m, 6H), 4.12–4.15 (m, 6H), 3.61–3.64 (m, 2H), 2.91 (t, *J* = 6.9 Hz, 2H), 2.34 (s, 3H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 168.2, 142.9, 142.0, 141.3, 140.1, 134.6, 134.1, 131.0, 129.9, 128.6, 127.3, 121.9, 120.0, 70.1, 55.4, 51.6, 41.4, 35.8, 19.3.

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

1-(Chloromethyl)-4-phenyl-1,4-diazabicyclo[2.2.2]octane^{2+} (1.4c)



To a 20 mL vial were added palladium complex **1.1** (31.8 mg, 50.0 μmol, 5.00 mol%), $Ru(bpy)_3(PF_6)_2$ (86.0 mg, 100. μmol, 10.0 mol%), Selectfluor (354. mg, 1.00 mmol, 1.00 equiv), and benzene (0.446 mL, 5.00 mmol, 5.0 equiv), and acetonitrile (2.5 mL, c = 0.20 M). The reaction mixture was stirred at 23 °C for 48 h. The reaction mixture was concentrated *in vacuo*, then triturated with DCM to afford 360 mg of a tan powder. For yield determination, an NMR sample in d_3-acetonitrile was prepared containing 10.0 mg of the product mixture and 5.0 μL of ethyl acetate (51. μmol) as internal standard. Comparison of the integral of the peak of **1.4c** at 4.41–4.36 ppm (3 × CH_2, 6H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed the bulk mixture to contain 0.67 mmol of Ar–TEDA (67% yield). Also present was 0.15 mmol H–TEDA^{2+} (15%), measured by integration of the peak at 3.85–3.81 ppm (3 × CH_2, 6H).

NMR Spectroscopy:

^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.82–7.77 (m, 2H); 7.75–7.69 (m, 3H), 5.35 (s, 2H), 4.41–4.36 (m, 6H), 4.41–4.09 (m, 6H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 144.4, 131.3, 130.8, 120.7, 68.2, 53.9, 50.4

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

1.5.6 Aromatic TEDAylation Trials with 1.05 Equivalents of Selectfluor

For the aromatic TEDAylation reaction, we have generally used 1.5–2.0 equivalents of Selectfluor, as we have found that the excess is required to push most substrates to completion. To probe the tolerance of the reaction to a reduction in the loading of Selectfluor, we have attempted the TEDAylation of toluene and anisole with 1.05 equivalents of Selectfluor, and compared the results to the standard conditions with 1.5 equivalents of Selectfluor. We have found only minor diminution of yield for these substrates with the reduced loading of Selectfluor:

Substrate	Selectfluor Loading	Yield
anisole	1.05 equivalents	85%
	1.50 equivalents	89%
toluene	1.05 equivalents	83%
	1.50 equivalents	92%

Toluene substrate, 1.05 equivalents Selectfluor

Palladium complex **1.1** (13.4 mg, 21.1 μmol) and $Ru(bpy)_3(PF_6)_2$ (36.1 mg, 42.0 μmol) were dissolved in d_3-acetonitrile (2.1 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (37.2 mg, 0.105 mmol, 1.05 equiv), followed by 0.50 mL of the stock solution containing **1.1** (5.0 μmol, 5.0 mol%) and $Ru(bpy)_3(PF_6)_2$ (10. μmol, 10. mol%). Finally, 10.7 μL toluene (0.10 mmol, 1.0 equiv) was added, and the solution was stirred at 23 °C for 48 h. The

reaction mixture was diluted with d_3-acetonitrile (0.25 mL), passed through a 0.2 μm PVDF syringe filter, and analyzed by ^{1}H NMR.

The yield of **1.2c** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **1.2c** at 7.67–7.65 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 85% yield of **1.2c**.

Toluene substrate, 1.50 equivalents Selectfluor

Palladium complex **1.1** (13.4 mg, 21.1 μmol) and $Ru(bpy)_3(PF_6)_2$ (36.1 mg, 42.0 μmol) were dissolved in d_3-acetonitrile (2.1 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (53.1 mg, 0.150 mmol, 1.50 equiv), followed by 0.50 mL of the stock solution containing **1.1** (5.0 μmol, 5.0 mol%) and $Ru(bpy)_3(PF_6)_2$ (10. μmol, 10. mol%). Finally, 10.7 μL toluene (0.10 mmol, 1.0 equiv) was added, and the solution was stirred at 23 °C for 48 h. The reaction mixture was diluted with d_3-acetonitrile (0.25 mL), passed through a 0.2 μm PVDF syringe filter, and analyzed by ^{1}H NMR.

The yield of **1.2c** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **1.2c** at 7.67–7.65 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 89% yield of **1.2c**.

Anisole substrate, 1.05 equivalents Selectfluor

Palladium complex **1.1** (13.4 mg, 21.1 μmol) and $Ru(bpy)_3(PF_6)_2$ (36.1 mg, 42.0 μmol) were dissolved in d_3-acetonitrile (2.1 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (37.2 mg, 0.105 mmol, 1.05 equiv), followed by 0.50 mL of the stock solution containing **1.1** (5.0 μmol, 5.0 mol%) and $Ru(bpy)_3(PF_6)_2$ (10. μmol, 10. mol%). Finally, 10.9 μL

anisole (0.10 mmol, 1.0 equiv) was added, and the solution was stirred at 23 °C for 48 h. The reaction mixture was diluted with d_3-acetonitrile (0.25 mL), passed through a 0.2 μm PVDF syringe filter, and analyzed by ^{1}H NMR.

The yield of **1.2d** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **1.2d** at 7.72–7.69 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 83% yield of **1.2d**.

Anisole substrate, 1.50 equivalents Selectfluor

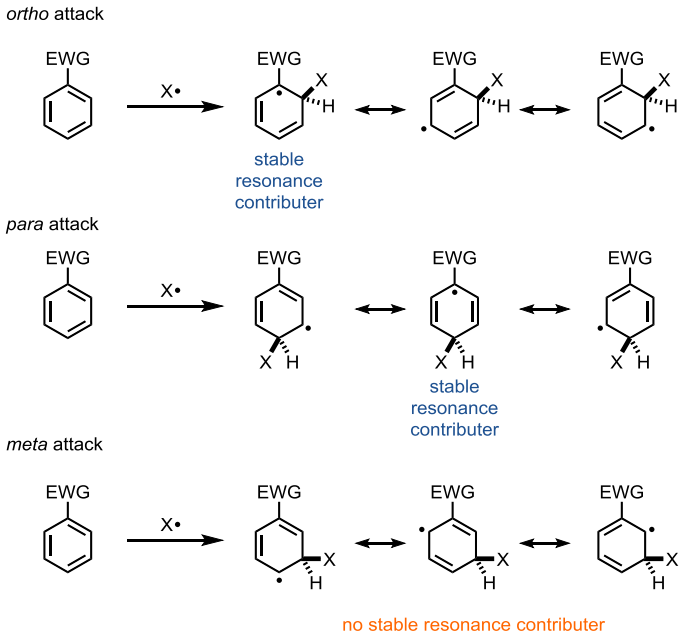
Palladium complex **1.1** (13.4 mg, 21.1 μmol) and $Ru(bpy)_3(PF_6)_2$ (36.1 mg, 42.0 μmol) were dissolved in d_3-acetonitrile (2.1 mL) to afford a stock solution. A 4 mL vial was charged with Selectfluor (53.1 mg, 0.150 mmol, 1.50 equiv), followed by 0.50 mL of the stock solution containing **1.1** (5.0 μmol, 5.0 mol%) and $Ru(bpy)_3(PF_6)_2$ (10. μmol, 10. mol%). Finally, 10.9 μL anisole (0.10 mmol, 1.0 equiv) was added, and the solution was stirred at 23 °C for 48 h. The reaction mixture was diluted with d_3-acetonitrile (0.25 mL), passed through a 0.2 μm PVDF syringe filter, and analyzed by ^{1}H NMR.

The yield of **1.2d** was determined via ^{1}H NMR spectroscopy using ethyl acetate (5.0 μL, 51. μmol) as an internal standard. Comparison of the integral of the peak of **1.2d** at 7.72–7.69 ppm (aromatic C–H, 2H) with that of the peak of ethyl acetate at 1.20 ppm (CH_3, 3H) revealed an 92% yield of **1.2d**.

1.5.7 Selectivity of TEDAylation with Resonance Electron-Withdrawing Substituents

Radicals are stabilized both by electron-donating and electron-withdrawing substituents. Therefore, in radical aromatic substitution of arenes bearing electron-withdrawing groups,

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



We have found that upon reaction with $TEDA^{2+\cdot}$, benzonitrile yields the *para* substituted Ar–TEDA isomer in ca. 10% conversion. No other isomer is observable. This result can be understood by considering the resonance stabilization effect described above. For arenes substituted with electron-donating groups, attack at the *ortho* and *para* positions are favored by resonance considerations, while attack at the *para* position is further favored by charge transfer in the transition state of addition. In the case of arenes bearing resonance electron-withdrawing groups, we rationalize that attack is constrained to the *ortho* and *para* positions by resonance

stabilization considerations. Thus, attack occurs at the *para* position, even though the *meta* position may be capable of greater charge-transfer stabilization.

TEDAylation of benzonitrile

In a 4 mL vial, palladium complex **1.1** (3.2 mg, 5.0 μmol, 5.0 mol%), $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 10. μmol, 10.0 mol%), and Selectfluor (70.9 mg, 0.200 mmol, 2.00 equiv) were dissolved in d_3-acetonitrile (0.50 mL). Finally, 10.2 μL benzonitrile (0.100 mmol, 1.00 equiv) was added, and the solution was stirred at 40 °C for 48 h. The reaction mixture was diluted with d_3-acetonitrile (0.25 mL), passed through a 0.2 μm PVDF syringe filter, and analyzed by ^{1}H NMR:

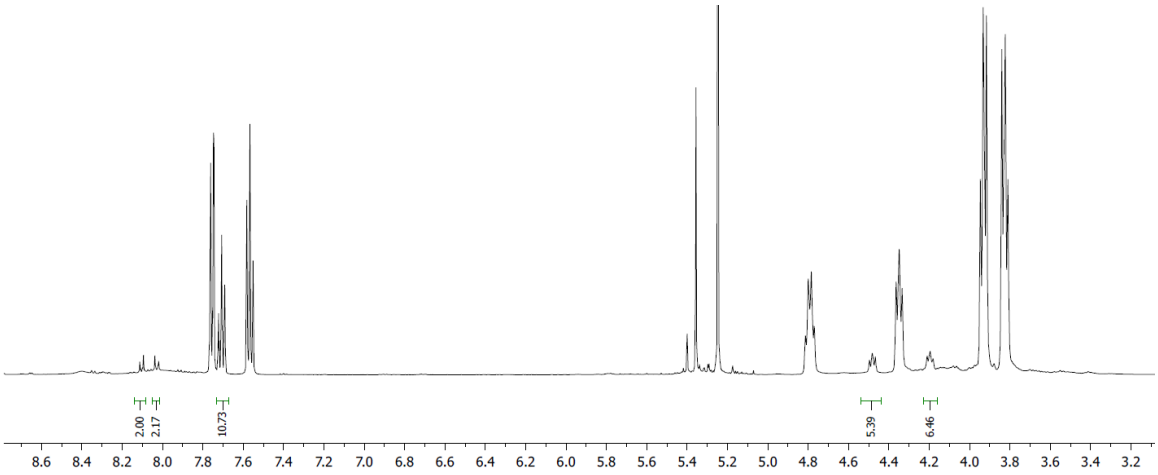


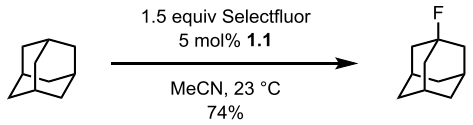
Figure 1.10. TEDAylation of benzonitrile

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

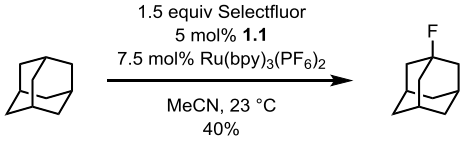
Lectka has reported that treatment of adamantane with Selectfluor in the presence of various radical initiators leads to C–H fluorination.[9,10] It was proposed that such reactions proceed through the intermediacy of $TEDA^{2+}$, which abstracts a hydrogen atom from the substrate. We have observed aliphatic C–H fluorination in the presence of Selectfluor and **1.1**, which is consistent with the formation of $TEDA^{2+\cdot}$ through the action of **1.1** on Selectfluor. We propose that the yield is diminished in the presence of $Ru(bpy)_3(PF_6)_2$ due to oxidation by Ru^{III} of the alkyl radical generated upon hydrogen atom abstraction, leading to non-fluorinated products.

We have furthermore observed the formation of **1.2a** from fluorobenzene via copper catalysis, under conditions similar to those reported by Baran.[35] This finding indicates that neither **1.1** or $Ru(bpy)_3(PF_6)_2$ is uniquely effective catalyst for Ar–TEDA formation, and is consistent with the free $TEDA^{2+\cdot}$ radical as the C–N bond forming species.

Observation of aliphatic C–H fluorination under TEDAylation conditions

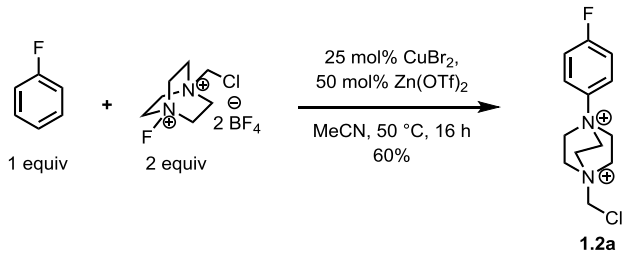


To a 4 mL vial were added adamantane (13.6 mg, 0.100 mmol, 1.00 equiv), Selectfluor (53.2 mg, 0.150 mmol, 1.50 equiv), **1.1** (3.2 mg, 5.0 μmol, 5.0 mol%), and CD_3CN (0.70 mL). The reaction was stirred for 16 hours at room temperature, after which 2.0 μL of 3-fluoronitrobenzene was added as an internal standard, and the solution was analyzed by ^{19}F NMR. 1-Fluoroadamantane was observed in 74% yield.



To a 4 mL vial were added adamantane (13.6 mg, 0.100 mmol, 1.00 equiv), Selectfluor (53.2 mg, 0.150 mmol, 1.50 equiv), **1.1** (3.2 mg, 5.0 μmol, 5.0 mol%), $Ru(bpy)_3(PF_6)_2$ (6.4 mg, 7.5 μmol, 7.5 mol%) and CD_3CN (0.70 mL). The reaction was stirred for 16 hours at room temperature, after which 2.0 μL of 3-fluoronitrobenzene was added as an internal standard, and the solution was analyzed by ^{19}F NMR. 1-Fluoroadamantane was observed in 40% yield.

Observation of Aryl–TEDA formation under copper catalysis



To a 4 mL vial were added cupric bromide (7.3 mg, 33. μmol, 25 mol%), zinc triflate (23.6 mg, 64.9 μmol, 50.0 mol%), and Selectfluor-PF_6 (135. mg, 0.286 mmol, 2.00 equiv). Acetonitrile-d_3 (1.0 mL) was then added, followed by fluorobenzene (12.0 μL, 0.128 mmol, 1.00 equiv). The reaction mixture was stirred for 16 hours at 50 °C. The mixture was allowed to cool to room temperature, 2.0 μL of 3-fluoronitrobenzene was added as internal standard. The mixture was filtered through a PVDF syringe filter to remove insoluble materials, and the filtrate was analyzed by ^{1}H and ^{19}F NMR. Compound **1.2a** was observed in 60% yield, along with ca. 32% of 4-fluorobromobenzene.

The NMR sample was concentrated by rotary evaporation, and the residue was triturated with DCM (3 × 1 mL), then tetrahydrofuran (2 × 2 mL) to yield a tan powder. Analysis by ^{1}H and ^{19}F NMR shows **1.2a** is the only Ar–TEDA product formed in significant amounts:

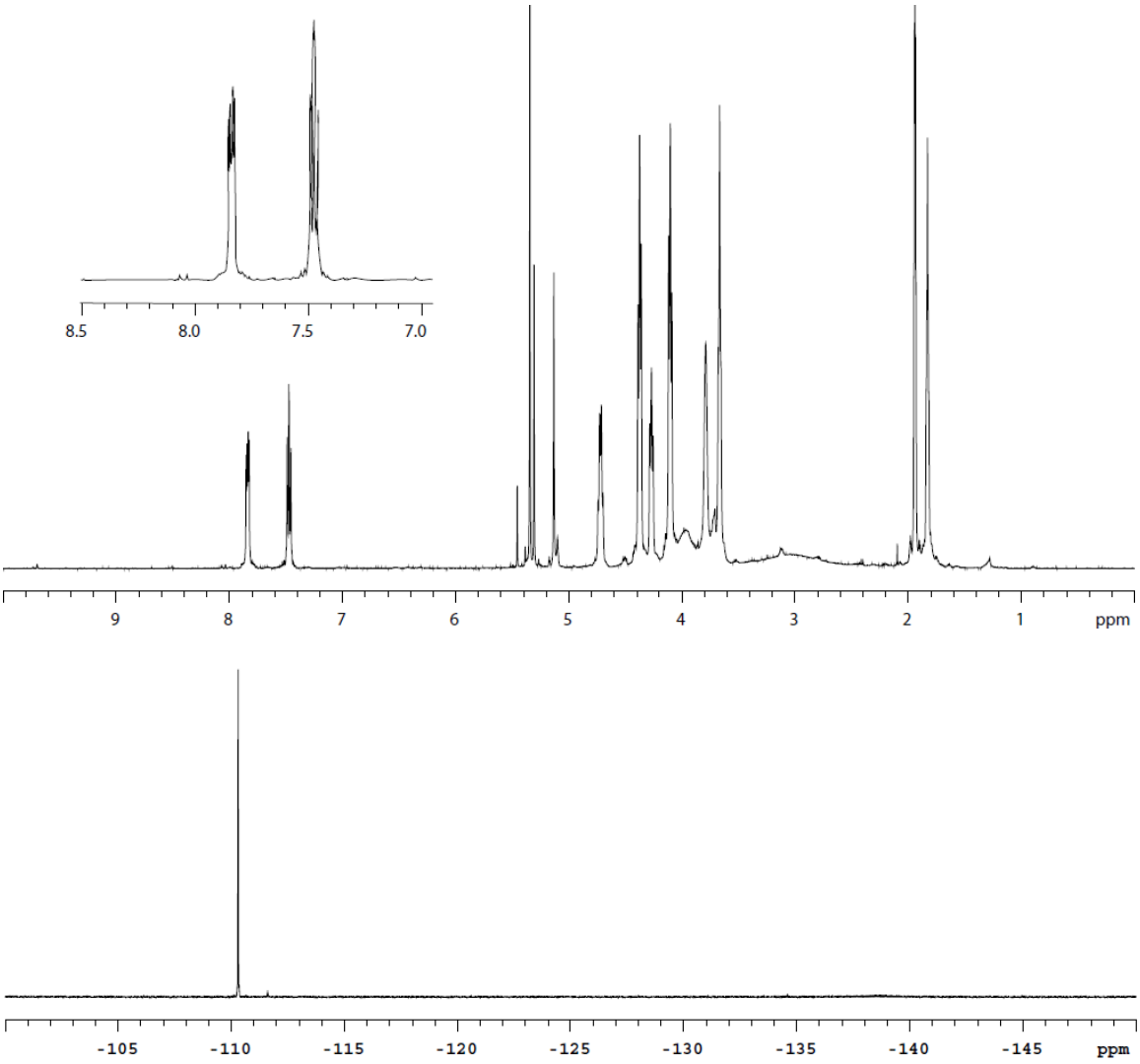


Figure 1.11. ^{1}H and ^{19}F NMR of **1.2a** synthesized via copper catalysis (CD_3CN, 23 °C)

1.5.9 Positional Selectivity as a Function of Electron Affinity: A Discussion

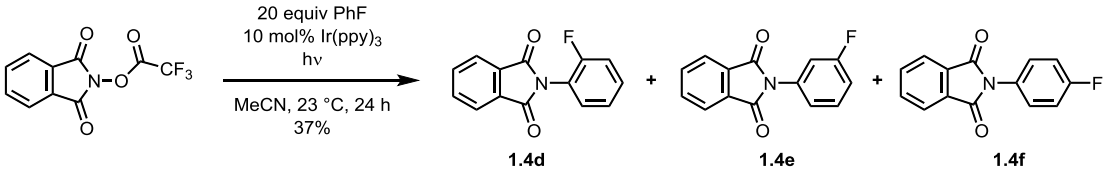
We argue in this work that the electron affinity of a radical has a strong effect on the positional selectivity exhibited by the radical in aromatic substitution, with higher electron affinity leading to higher selectivity for the *para* position of monosubstituted arenes. To illustrate this trend, we compare the selectivity of several radicals across a range of electron affinities in their aromatic substitution with fluorobenzene. It should be noted that electron affinity is not the only factor influencing positional selectivity. Different radicals with similar electron affinities may yield

differing positional selectivity due to the influence of other factors, such as differing degrees of steric hinderance. Furthermore, the same radical may exhibit somewhat differing positional selectivities with the same substrate under varying experimental conditions.[17] Thus, to illustrate the general trend, we have chosen four radicals with widely varying electron affinities, so that the influence of confounding factors is minimized:

- Phenyl radical: data taken from the work of Li *et al*[13]
- Phthalimidyl radical: aromatic substitution carried out based on conditions reported by Sanford *et al*[14]
- Piperidine aminium radical: aromatic substitution carried out based on conditions reported by Minsci *et al*[15–17]
- $TEDA^{2+\cdot}$: the subject of this work

Full experimental procedures and characterization of products for the reactions of phthalimidyl radical and piperidine aminium radical are found in the sections below.

1.5.10 Aromatic Substitution of Fluorobenzene by Phthalimidyl Radical



In an N_2-filled glovebox, into a 4 mL vial were weighed N-trifluoroacetoxy phthalimide (13.0 mg, 50.2 μmol, 1.00 equiv) and tris(2-phenylpyridyl)iridium(III) (3.3 mg, 5.0 μmol, 10. mol%). Acetonitrile (1.0 mL) was then added, followed by fluorobenzene (94. μL, 1.0 mmol, 20 equiv). The vial was sealed, removed from the glovebox, and stirred magnetically for 24 hours at room temperature under irradiation by a 60 W desk lamp. The volatile components were removed by rotary evaporation. The residue was taken up in CD_3CN, and 2.0 μL (18.8 μmol) of 3-

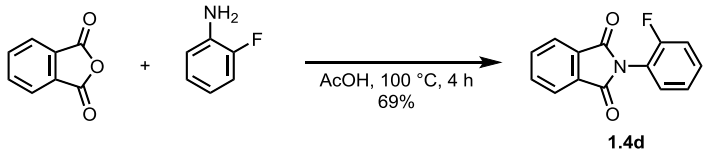
fluoronitrobenzene was added as internal standard. The mixture was filtered through a PVDF syringe filter to remove all insoluble materials, and the filtrate was analyzed by ^{19}F NMR. The following amounts of **1.4d**, **1.4e**, and **1.4f** were observed:

N-(2-fluorophenyl)phthalimide (**1.4d**)	7.1 μmol
N-(3-fluorophenyl)phthalimide (**1.4e**)	1.9 μmol
N-(4-fluorophenyl)phthalimide (**1.4f**)	9.7 μmol

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

1.5.11 Synthesis of Authentic Samples of 1.4d, 1.4e, and 1.4f

N-(2-Fluorophenyl)-phthalimide (1.4d)



1.4d

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

NMR Spectroscopy:

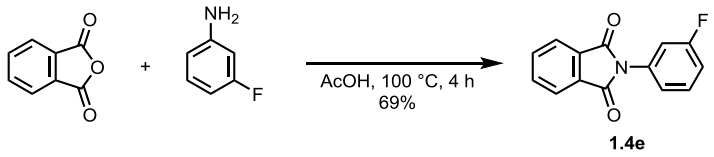
^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.97–7.93 (m, 2H), 7.90–7.86 (m, 2H), 7.57–7.51 (m, 1H), 7.49–7.44 (m, 1H), 7.39–7.32 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 166.4 (s), 157.8 (d, *J* = 252.7 Hz), 134.4 (s), 131.8 (s), 130.7 (d, *J* = 8.0 Hz), 129.8 (d, *J* = 0.9 Hz), 124.6 (d, *J* = 4.0 Hz), 123.8 (s),

119.3 (d, J = 13.2 Hz), 116.7 (d, J = 19.5 Hz). ^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –113.9.

HRMS-FIA(m/z) calc'd for $C_{14}H_9FNO_2$ $[M+H]^+$, 242.0612; found, 242.0613.

***N*-(3-Fluorophenyl)-phthalimide (1.4e)**



1.4e

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

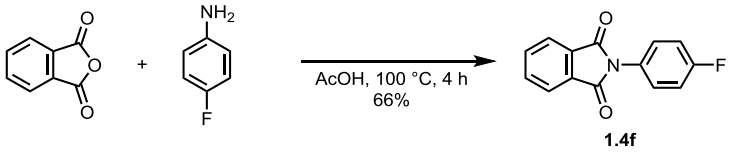
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.96–7.92 (m, 2H), 7.89–7.85 (m, 2H), 7.55 (ddd, J = 14.7, 8.3, 6.4 Hz, 1H), 7.32 (ddd, J = 8.0, 1.9, 0.9 Hz, 1H), 7.28–7.24 (m, 1H), 7.21 (ddd, J = 8.7, 2.6, 0.9 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 166.8 (s), 162.6 (d, J = 246.7 Hz), 134.6 (s), 133.0 (d, J = 10.3 Hz), 131.5 (s), 130.2 (d, J = 9.0 Hz), 123.9 (s), 122.0 (d, J = 3.5 Hz), 115.0 (d, J = 21.1 Hz), 113.9 (d, J = 24.7 Hz). ^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –121.5.

HRMS-FIA(m/z) calc'd for $C_{14}H_9FNO_2$ $[M+H]^+$, 242.0612; found, 242.0611.

***N*-(4-Fluorophenyl)-phthalimide (1.4f)**



1.4f

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

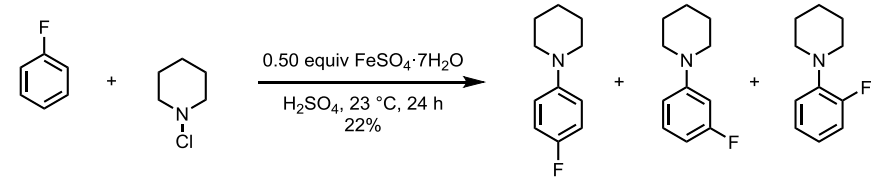
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.94–7.90 (m, 2H), 7.88–7.84 (m, 2H), 7.48–7.43 (m, 2H), 7.30–7.25 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 167.1 (s), 161.8 (d, *J* = 247.6 Hz), 134.4 (s), 131.5 (s), 128.3 (d, *J* = 8.7 Hz), 127.5 (d, *J* = 3.2 Hz), 123.7 (s), 116.1 (d, *J* = 22.5 Hz). ^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –115.3.

HRMS-FIA(m/z) calc'd for $C_{14}H_9FNO_2$ $[M+H]^+$, 242.0612; found, 242.0615.

1.5.12 Aromatic Substitution of Fluorobenzene by Piperidinium radical



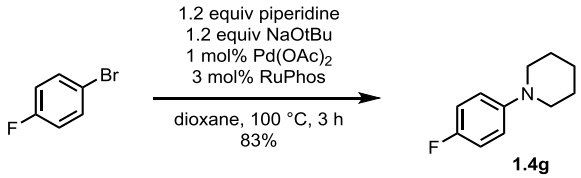
2.0 equiv 1.0 equiv **1.4g** **1.4h** **1.4j**

To 2.00 g of concentrated sulfuric acid in a 20 mL vial at 0 °C were added 188. µL of fluorobenzene (2.00 mmol, 2.00 equiv), 120. mg of N-chloropiperidine (1.00 mmol, 1.00 equiv), and finally 139. mg of pulverized ferrous sulfate heptahydrate (0.500 mmol, 0.500 equiv). The

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

1.5.13 Synthesis of Authentic Samples of 1.4g, 1.4h, and 1.4j

1-(4-Fluorophenyl)piperidine (1.4g)



To a flame-dried 50 mL Schlenk flask were added 22.5 mg palladium acetate (22.5 mg, 0.100 mmol, 1.00 mol%), 140 mg RuPhos (0.300 mmol, 3.00 mol%), and 1.153 g of sodium tert-butoxide (12.00 mmol, 1.20 equiv). The flask was sealed with a septum, then evacuated and refilled with N_2 three times. Anhydrous dioxane (10.0 mL) was added via syringe through the septum, followed by 1.75 g 4-fluorobromobenzene (10.0 mmol, 1.00 equiv) and 1.19 mL piperidine (12.0 mmol, 1.20 equiv). The mixture was degassed via N_2 sparge for 10 minutes, then heated at 100 °C for 3 hours. The reaction mixture was diluted with ethyl acetate to 50 mL, and filtered through celite to remove the precipitated palladium metal. The filtrate was washed with water (3 × 50 mL) and brine (2 × 50 mL), dried over $NaSO_4$, and concentrated. The residue

was purified by flash chromatography on silica gel (hexanes → 19:1 hexanes:EtOAc) to yield 1.48 g of the title compound as a brown oil (8.28 mmol, 83%).

NMR Spectroscopy:

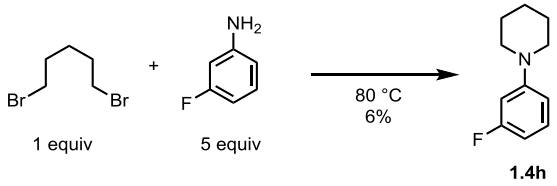
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.94–7.90 (m, 2H), 7.88–7.84 (m, 2H), 7.48–7.43 (m, 2H), 7.30–7.25 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 167.1 (s), 161.8 (d, *J* = 247.6 Hz), 134.4 (s), 131.5 (s), 128.3 (d, *J* = 8.7 Hz), 127.5 (d, *J* = 3.2 Hz), 123.7 (s), 116.1 (d, *J* = 22.5 Hz).

^{19}F NMR (470 MHz, $CDCl_3$, 23 °C, δ): –128.1.

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

1-(3-Fluorophenyl)piperidine (1.4h)



To a 20 mL vial were added 0.55 mL 1,5-dibromopentane (4.0 mmol, 1.0 equiv) and 1.92 mL 3-fluoroaniline (20.0 mmol, 5.0 equiv). The vial was sealed, and the mixture was heated with stirring at 80 °C for 4 hours, after which the mixture was allowed to come to room temperature, and 10 mL of 6 M NaOH was added. The mixture was then extracted with diethyl ether (3 × 10 mL), and the combined organic layers were concentrated. To the residue was added 10 mL Ac_2O, and the mixture was stirred for 30 minutes at room temperature. To the mixture was added 20 mL of 1 M HCl and 10 mL water. The mixture was extracted with DCM (2 × 20 mL), then basified to pH 14 with 6 M NaOH. The basic mixture was extracted with DCM (3 × 20 mL). The combined organic layers were dried over Na_2SO_4, and concentrated to give a brown oil. The brown oil was distilled with a Hickmann still to give 126. mg of a colorless oil.

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

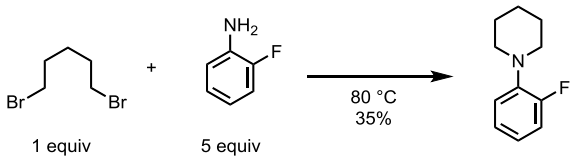
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.20–7.14 (m, 1H), 6.71–6.68 (m, 1H), 6.64–6.59 (m, 1H), 6.52–6.47 (m, 1H), 3.20–3.16 (m, 4H), 1.74–1.68 (m, 4H), 1.63–1.58 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 163.9 (d, *J* = 242.6 Hz), 153.6 (d, 10.9 Hz), 129.9 (d, *J* = 10.1 Hz), 111.4 (d, *J* = 2.2 Hz), 105.1 (d, *J* = 21.6 Hz), 102.8 (d, *J* = 24.8 Hz), 50.0 (s), 25.5 (s), 24.2 (s). ^{19}F NMR (470 MHz, $CDCl_3$, 23 °C, δ): –115.6.

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

1-(2-Fluorophenyl)piperidine (1.4j)



To a 20 mL vial were added 2.20 mL 1,5-dibromopentane (16.2 mmol, 1.00 equiv) and 7.80 mL 3-fluoroaniline (80.8 mmol, 5.00 equiv). The vial was sealed, and the mixture was heated with stirring at 80 °C for 24 hours, after which the mixture was allowed to come to room temperature, and 20 mL of 1 M NaOH was added. The mixture was then extracted with DCM (3 × 20 mL), and the combined organic layers were dried over Na_2SO_4, then concentrated. To the residue was added 50 mL Ac_2O, and the mixture was stirred for 2 hours at room temperature. To the solution was added 50 mL of 1 M HCl and ice. The mixture was extracted with DCM (5 × 25 mL), then

basified to pH 14 with 6 M NaOH. The basic mixture was extracted with DCM (5 × 25 mL). The combined organic layers were dried over Na_2SO_4, and concentrated to give 994. mg of the title compound as a yellow oil (5.55 mmol, 35%).

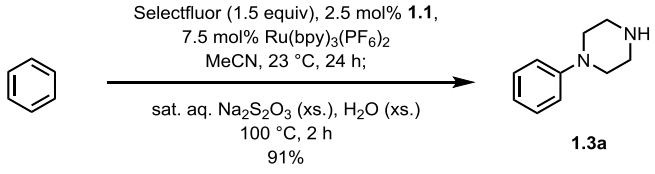
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.09–6.97 (m, 3H), 6.95–6.90 (m, 1H), 3.07–3.04 (m, 4H), 1.81–1.76 (m, 4H), 1.64–1.58 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 155.8 (d, *J* = 245.6 Hz), 141.3 (d, *J* = 8.4 Hz), 124.2 (d, *J* = 3.6 Hz), 121.9 (d, *J* = 7.9 Hz), 119.1 (d, *J* = 3.2 Hz), 115.8 (d, *J* = 21.1 Hz), 52.0 (s), 26.1 (s), 24.2 (s). ^{19}F NMR (470 MHz, $CDCl_3$, 23 °C, δ): –125.7.

1.5.14 Procedures for the Preparation of Aryl Piperazines

1-Phenylpiperazine (1.3a)



A 100 mL pressure tube was charged with palladium complex **1.1** (17.8 mg, 28.0 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (72.1 mg, 83.9 μmol, 7.50 mol%), and Selectfluor (595. mg, 1.68 mmol, 1.50 equiv). Acetonitrile (5.6 mL, c = 0.20 M) was added, followed by benzene (100. μL, 1.12 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (11 mL) and water (11 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. DCM (20 mL) and ethylenediamine (1.5 mL) were added and the organic layer was washed with 6 M aq. sodium hydroxide (5 mL). The aq. layer was extracted with DCM (2 × 10 mL). The combined organic layers were extracted with 1 M aq.

hydrochloric acid (2 × 10 mL). Ethylenediamine (6.5 mL) was added to the combined acidic aq. layers, followed by basification with 6 M aq. sodium hydroxide (5 mL). The basic aq. layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (190. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (95.5/4.0/0.5 (v/v/v)) to afford 163. mg of the title compound as a yellow oil (91% yield).

R_f = 0.32 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

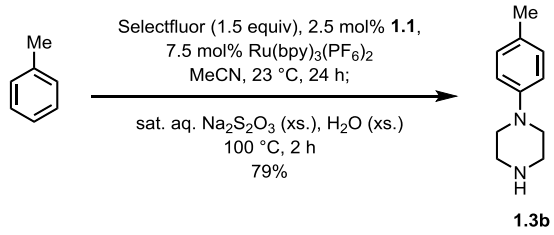
NMR Spectroscopy:

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

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 151.9, 129.2, 119.9, 116.3, 50.5, 46.3.

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

1-(*p*-Tolyl)piperazine (1.3b)



1.3b

A 100 mL pressure tube was charged with palladium complex **1.1** (13.6 mg, 21.4 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (55.2 mg, 64.2 μmol, 7.50 mol%), and Selectfluor (455. mg, 1.28 mmol, 1.50 equiv). Acetonitrile (4.3 mL, c = 0.20 M) was added, followed by toluene (91.1 μL, 0.856 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (8.6 mL) and water (8.6 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture

was transferred to a separatory funnel. DCM (20 mL) and ethylenediamine (1.5 mL) were added and the organic layer was washed with 6 M aq. sodium hydroxide (5 mL). The aq. layer was extracted with DCM (2 × 10 mL). The combined organic layers were extracted with 1 M aq. hydrochloric acid (2 × 15 mL). Ethylenediamine (5.0 mL) was added to the combined acidic aq. layers, followed by basification with 6 M aq. sodium hydroxide (8 mL). The basic aq. layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (143. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (97.5/2.0/0.5 (v/v/v)) to afford 119. mg of the title compound as a yellow oil (79% yield).

R_f = 0.35 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

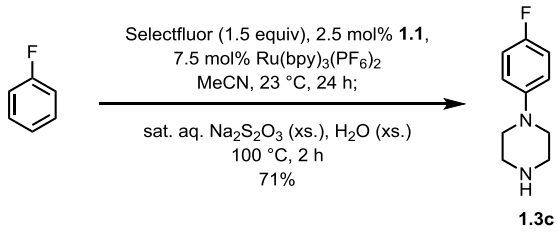
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.07–7.09 (m, 2H), 6.84–6.86 (m, 2H), 3.07–3.10 (m, 4H), 3.01–3.04 (m, 4H), 2.28 (s, 3H), 1.68 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 149.7, 129.7, 129.3, 116.5, 50.9, 46.1, 20.5.

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

1-(4-Fluorophenyl)piperazine (1.3c)



1.3c

A 100 mL pressure tube was charged with palladium complex **1.1** (17.0 mg, 26.6 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (68.7 mg, 80.0 μmol, 7.50 mol%), and Selectfluor (566. mg, 1.60 mmol, 1.50 equiv). Acetonitrile (11 mL, c = 0.10 M) was added, followed by fluorobenzene (100. μL,

1.06 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (21 mL) and water (21 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. DCM (30 mL) and ethylenediamine (1.5 mL) were added and the organic layer was washed with 6 M aq. sodium hydroxide (5 mL). The aq. layer was extracted with DCM (2 × 15 mL). The combined organic layers were extracted with 1 M aq. hydrochloric acid (2 × 15 mL). Ethylenediamine (6.5 mL) was added to the combined acidic aq. layers, followed by basification with 6 M aq. sodium hydroxide (5 mL). The basic aq. layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (160. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (91.5/8.0/0.5 (v/v/v)) to afford 136. mg of the title compound as a yellow oil (71% yield).

R_f = 0.14 (DCM/MeOH/28% aq. ammonium hydroxide 91.5:8.0:0.5 (v/v/v)).

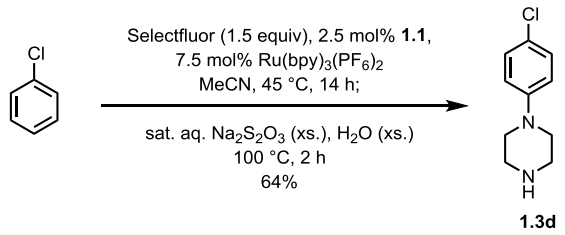
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 6.94–6.96 (m, 2H), 6.85–6.87 (m, 2H), 3.03–3.07 (m, 8H), 2.45 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 157.3 (d, *J* = 238.8 Hz), 148.5 (d, *J* = 2.8 Hz), 118.0 (d, *J* = 7.7 Hz), 115.6 (d, *J* = 22.0 Hz), 51.4 (s), 46.1 (s). ^{19}F NMR (500 MHz, $CDCl_3$, 23 °C, δ): –127.4.

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

1-(4-Chlorophenyl)piperazine (1.3d)



1.3d

A 100 mL pressure tube was charged with palladium complex **1.1** (15.6 mg, 24.6 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (63.3 mg, 73.7 μmol, 7.50 mol%), and Selectfluor (522 mg, 1.47 mmol, 1.50 equiv). Acetonitrile (4.9 mL, c = 0.20 M) was added, followed by chlorobenzene (100. μL, 0.982 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 45 °C for 14 h. Saturated aq. sodium thiosulfate (9.8 mL) and water (9.8 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. DCM (20 mL), ethylenediamine (0.5 mL), and 6 M aq. sodium hydroxide (5 mL) were added and the organic layer was separated. The aq. layer was extracted with DCM (2 × 15 mL). The combined organic layers were extracted with 1 M aq. hydrochloric acid (3 × 10 mL). Ethylenediamine (5.0 mL) was added to the combined acidic aq. layers, followed by basification with 6 M aq. sodium hydroxide (5 mL). The basic aq. layer was extracted with DCM (4 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (180. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (94.5/5.0/0.5 (v/v/v)) to afford a yellow solid (171. mg). The residue was further purified by preparatory HPLC with a solvent mixture of water/acetonitrile/trifluoroacetic acid (89.9/10.0/0.1 to 49.9/50.0/0.1 (v/v/v)) to afford 125. mg of the title compound as a bright yellow solid (64% yield).

$\mathbf{R}_f$ = 0.26 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

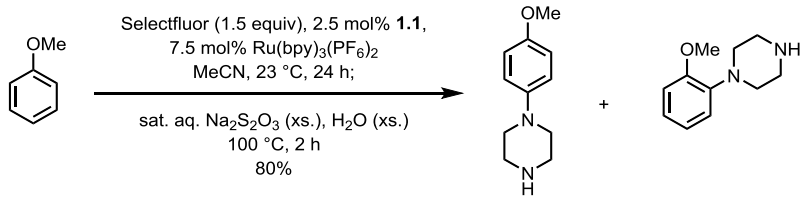
NMR Spectroscopy:

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

^{13}C NMR (500 MHz, $CDCl_3$, 23 °C, δ): 150.6, 129.0, 124.6, 117.4, 50.5, 46.2.

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

1-(4-Methoxyphenyl)piperazine (1.3e)



A 100 mL pressure tube was charged with palladium complex **1.1** (14.6 mg, 23.0 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (59.3 mg, 69.0 μmol, 7.50 mol%), and Selectfluor (489. mg, 1.38 mmol, 1.50 equiv). Acetonitrile (4.6 mL, c = 0.20 M) was added, followed by anisole (100. μL, 0.920 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (9.2 mL) and water (9.2 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. DCM (25 mL) and ethylenediamine (3.0 mL) were added and the organic layer was washed with 6 M aq. sodium hydroxide (5 mL). The aq. layer was extracted with DCM (2 × 15 mL). The combined organic layers were extracted with 1 M aq. hydrochloric acid (2 × 15 mL). Ethylenediamine (6.5 mL) was added to the combined acidic aq. layers, followed by basification with 6 M aq. sodium hydroxide (5 mL). The basic aq. layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (170. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium

hydroxide (93.0/6.5/0.5 (v/v/v)) to afford 152. mg of the title compound as a light yellow solid (80% yield), containing 1-(2-methoxyphenyl)piperazine (6%). For characterization, 35. mg of the mixture was further purified by preparatory HPLC with a solvent mixture of water/acetonitrile/trifluoroacetic acid (89.9/10.0/0.1 to 69.9/30.0/0.1 (v/v/v)) to afford 23. mg of the title compound as an off-white solid.

R_f = 0.46 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

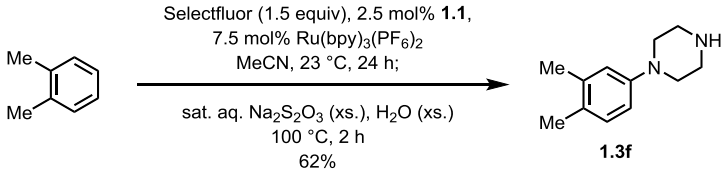
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 6.86–6.89 (m, 2H), 6.81–6.84 (m, 2H), 3.74 (s, 3H), 3.03 (s, 8H), 2.74 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 153.9, 146.1, 118.4, 114.5, 55.6, 51.7, 46.1.

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

1-(3,4-Dimethylphenyl)piperazine (1.3f)



A 100 mL pressure tube was charged with palladium complex **1.1** (13.2 mg, 20.7 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (53.4 mg, 62.1 μmol, 7.50 mol%), and Selectfluor (440. mg, 1.24 mmol, 1.50 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added, followed by *o*-xylene (100. μL, 1.00 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (8.3 mL) and water (8.3 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, ethylenediamine (5.0 mL) and water (15 mL) were added, and the mixture was stirred for 1 h further. The reaction mixture was transferred to a separatory funnel. DCM (20 mL) was added and the organic layer was separated. The aq. layer was extracted with DCM (2 × 15 mL). The combined organic layers

were extracted with 1 M aq. hydrochloric acid (3 × 10 mL). Ethylenediamine (2.0 mL) was added to the combined acidic aq. layers, followed by basification with 6 M aq. sodium hydroxide (6 mL). The basic aq. layer was extracted with DCM (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (117. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (97.5/2.0/0.5 (v/v/v)) to afford 97.0 mg of the title compound as a yellow solid (62% yield).

R_f = 0.32 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

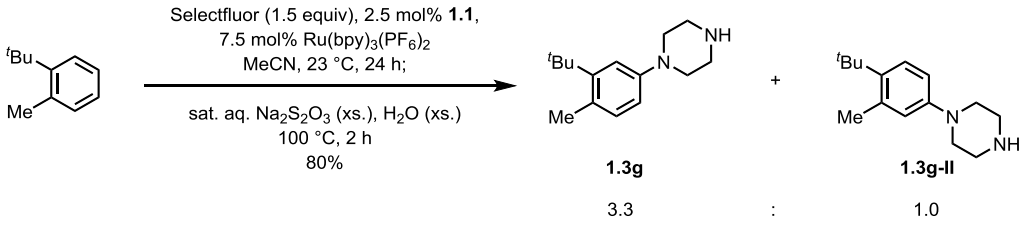
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.03 (d, *J* = 8.2 Hz, 1H), 6.76 (d, *J* = 2.6 Hz, 1H), 6.69 (dd, *J* = 8.2, 2.6 Hz, 1H), 3.09 (m, 4H), 3.03 (m, 4H), 2.24 (s, 3H), 2.19 (s, 3H), 1.72 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 150.3, 137.2, 130.2, 128.2, 118.2, 114.0, 51.2, 46.4, 20.3, 18.9.

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

1-(3-(*tert*-Butyl)-4-methylphenyl)piperazine (1.3g), 1-(4-(*tert*-Butyl)-3-methylphenyl)piperazine (1.3g-II)



A 100 mL pressure tube was charged with palladium complex **1.1** (7.16 mg, 11.2 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (29.0 mg, 33.8 μmol, 7.50 mol%), and Selectfluor (239. mg, 0.675 mmol, 1.50 equiv). Acetonitrile (2.2 mL, c = 0.20 M) was added, followed by 1-(*tert*-butyl)-2-

methylbenzene (75.0 µL, 0.450 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (4.5 mL) and water (4.5 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. DCM (20 mL), ethylenediamine (0.5 mL), water (5 mL) and 6 M aq. sodium hydroxide (0.5 mL) were added and the organic layer was separated. The aq. layer was extracted with DCM (2 × 15 mL). The combined organic layers were extracted with 1 M aq. hydrochloric acid (3 × 10 mL). Ethylenediamine (2.0 mL) was added to the combined acidic aq. layers, followed by basification with 6 M aq. sodium hydroxide (5 mL). The basic aq. layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (91.4 mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (96.5/3.0/0.5 (v/v/v)) to afford 83.5 mg of the title compounds (**1.3g**:**1.3g-II** = 3.3 : 1.0) as a yellow oil (80% yield).

R_f = 0.25 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

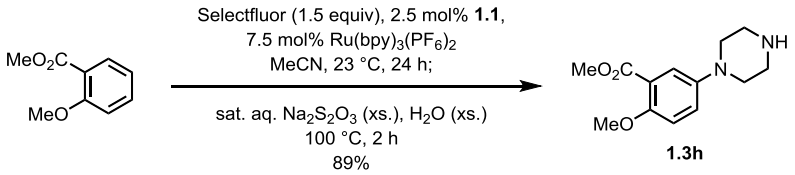
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): **1.3g** 7.01–7.03 (m, 2H), 6.68 (dd, *J* = 8.3, 2.6 Hz, 1H), 3.09–3.13 (m, 4H), 3.01–3.06 (m, 4H), 2.46 (s, 3H), 1.88 (s, 1H), 1.40 (s, 9H). **1.3g-II** 7.26 (d, *J* = 8.7 Hz, 1H), 6.67–6.72 (m, 2H), 3.09–3.13 (m, 4H), 3.01–3.06 (m, 4H), 2.51 (s, 3H), 1.38 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 150.0, 149.6, 148.6, 139.5, 137.1, 133.4, 128.0, 126.9, 120.6, 115.6, 113.6, 113.0, 51.3, 50.4, 46.4, 46.3, 36.2, 35.2, 31.2, 30.8, 23.6, 22.5.

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

Methyl 2-methoxy-5-(piperazin-1-yl)benzoate (1.3h)



A 100 mL pressure tube was charged with palladium complex **1.1** (11.1 mg, 17.4 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (44.9 mg, 52.2 μmol, 7.50 mol%), and Selectfluor (370. mg, 1.04 mmol, 1.50 equiv). Acetonitrile (3.5 mL, c = 0.20 M) was added, followed by methyl 2-methoxybenzoate (100. μL, 0.700 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (7.0 mL) and water (7.0 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. DCM (20 mL) and ethylenediamine (0.3 mL) were added and the organic layer was separated. The aq. layer was extracted with DCM (2 × 15 mL). The combined organic layers were extracted with 10% aq. glacial acetic acid (2 × 15 mL). The combined acidic aq. layers were basified with ethylenediamine (4.0 mL). The basic aq. layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (175. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (96.5/3.0/0.5 (v/v/v)) to afford 155. mg of the title compound as a yellow oil (89% yield).

$\mathbf{R_f}$ = 0.16 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

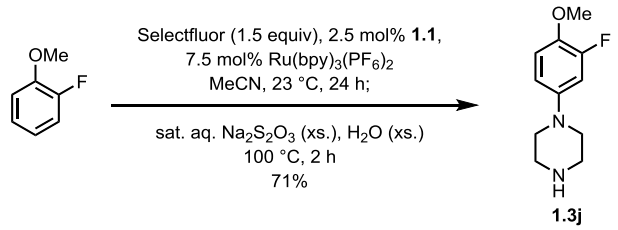
NMR Spectroscopy:

^{1}H NMR (125 MHz, $CDCl_3$, 23 °C, δ): 7.35 (d, *J* = 3.0 Hz, 1H), 7.03 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.88 (d, *J* = 9.0 Hz, 1H), 3.85 (s, 3H), 3.82 (s, 3H), 2.98–3.03 (m, 8H), 1.67 (s, 1H).

^{13}C NMR (500 MHz, $CDCl_3$, 23 °C, δ): 166.9, 153.2, 145.6, 122.1, 120.3, 119.8, 113.5, 56.6, 52.1, 51.5, 46.2.

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

1-(3-Fluoro-4-methoxyphenyl)piperazine (1.3j)



A 100 mL pressure tube was charged with palladium complex **1.1** (15.9 mg, 25.0 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor (531.5 mg, 1.500 mmol, 1.50 equiv), and 2-fluoroanisole (112 μL, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 1 h. After cooling to 23 °C, the reaction mixture was filtered through celite, and the filter cake was extracted with 5 × 15 mL acetonitrile and 2 × 15 mL water. The acetonitrile was removed from the filtrate by rotary evaporation. To the remaining aq. mixture 0.50 mL ethylene diamine was added, and the aq. mixture was basified to pH 14 with 6 M NaOH, then transferred to a separatory funnel. The aq. layer was extracted with DCM (5 × 15 mL). The combined organic layers were extracted with 1 M HCl (5 × 15 mL). To the combined acidic aq. layers was added ethylene diamine (0.5 mL), and the mixture was basified to pH 14 with 6 M NaOH. The basic aq. layer was extracted with DCM (5 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The residue was purified by chromatography on silica gel eluting with DCM/MeOH 9:1 (v/v) to afford 150. mg of the title compound as a brown oil (71% yield).

$\mathbf{R_f}$ = 0.28 (DCM/MeOH 9:1 (v/v)).

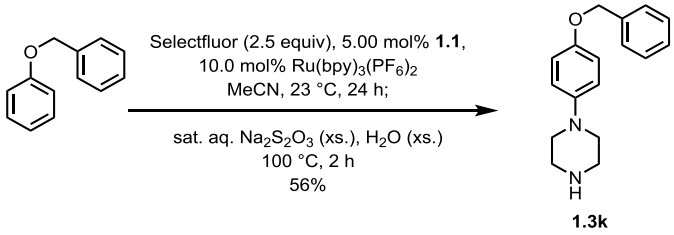
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 6.86 (dd, *J* = 9.1, 9.1 Hz, 1H), 6.69 (dd, *J* = 14.0, 2.8 Hz, 1H), 6.59 (m, 1H), 3.81 (s, 4H), 3.63 (br, 1H), 3.05 (s, 4H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 152.8 (d, *J* = 243.7 Hz), 146.3 (d, *J* = 7.8 Hz), 141.3 (d, *J* = 10.6 Hz), 114.6 (d, *J* = 2.9 Hz), 111.6 (d, *J* = 3.5 Hz), 105.7 (d, *J* = 21.1 Hz), 56.9 (s), 50.5 (s), 45.5 (s).

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

1-(4-(Benzyloxy)phenyl)piperazine (1.3k)



1.3k

A 100 mL pressure tube was charged with palladium complex **1.1** (31.8 mg, 50.0 μmol. 5.00 mol%), $Ru(bpy)_3(PF_6)_2$ (86.0 mg, 100. μmol, 10.0 mol%), Selectfluor (886. mg, 2.50 mmol, 2.50 equiv), and benzyl phenyl ether (184. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, 0.5 mL ethylene diamine was added and the reaction mixture was basified to pH 14 with 6 M NaOH, then filtered through celite. The filter cake was extracted with acetonitrile (5 × 15 mL). The acetonitrile was removed from the filtrate by rotary evaporation. The remaining aq. mixture was transferred to a separatory funnel and extracted with DCM (5 × 15 mL). The combined organic layers were extracted with 1 M HCl (5 × 15 mL). To the combined acidic aq. layers was added ethylene diamine (0.5 mL),

and the mixture was basified to pH 14 with 6 M NaOH. The basic aq. layer was extracted with DCM (5 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The residue was purified by chromatography on silica gel eluting with DCM/MeOH 19:1 → 9:1 (v/v) to afford 151. mg of the title compound as an off-white powder (56% yield).

R_f = 0.35 (DCM/MeOH 9:1 (v/v)).

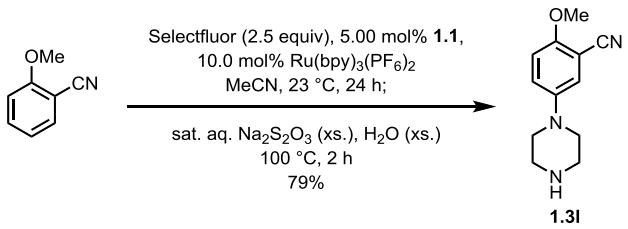
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.44–7.41 (m, 2H), 7.40–7.33 (m, 2H), 7.34–7.30 (m, 1H), 6.94–6.88 (m, 4H), 5.02 (s, 2H), 3.07 (s, 8H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 153.1, 146.2, 137.3, 128.5, 127.8, 127.5, 118.3, 115.6, 70.5, 51.4, 46.0.

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

2-Methoxy-5-(piperazin-1-yl)benzonitrile (1.3l)



1.3l

A 100 mL pressure tube was charged with palladium complex **1.1** (31.8 mg, 50.0 μmol. 5.00 mol%), $Ru(bpy)_3(PF_6)_2$ (86.0 mg, 100. μmol, 10.0 mol%), Selectfluor (886. mg, 2.50 mmol, 2.50 equiv), and 2-methoxybenzonitrile (122. μL, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, 0.5 mL ethylene diamine was added and the reaction mixture was basified to pH 14 with 6 M NaOH, then filtered through

celite. The filter cake was extracted with acetonitrile (5 × 15 mL). The acetonitrile was removed from the filtrate by rotary evaporation. The remaining aq. mixture was transferred to a separatory funnel and extracted with DCM (5 × 15 mL), then 9:1 DCM/MeOH (v/v) (3 × 15 mL). The combined organic layers were extracted with 1 M HCl (5 × 15 mL). To the combined acidic aq. layers was added ethylene diamine (0.5 mL), and the mixture was basified to pH 14 with 6 M NaOH. The basic aq. layer was extracted with 9:1 DCM/MeOH (v/v) (6 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The residue was purified by chromatography on silica gel eluting with DCM/MeOH 9:1 (v/v) to afford 190. mg of the title compound as a brown oil (79% yield).

R_f = 0.31 (DCM/MeOH 9:1 (v/v)).

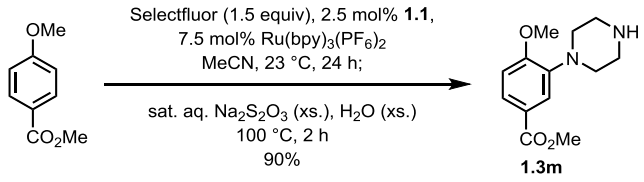
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.12 (dd, *J* = 9.1, 3.1 Hz, 1H), 7.07 (d, *J* = 3.1 Hz, 1H), 6.88 (d, *J* = 9.1 Hz, 1H), 3.86 (s, 4H), 3.04 (s, 4H), 2.56 (br, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 155.2, 145.8, 123.2, 121.1, 116.7, 112.3, 101.7, 56.2, 50.9, 40.8.

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

Methyl 4-methoxy-3-(piperazin-1-yl)benzoate (1.3m)



A 100 mL pressure tube was charged with palladium complex **1.1** (15.9 mg, 25.0 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor (531. mg, 1.50 mmol, 1.50 equiv), and methyl 4-methoxybenzoate (166. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated

aq. sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, ethylenediamine (1.5 mL) and water (15 mL) were added, and the mixture was stirred for 1 h further. The reaction mixture was transferred to a separatory funnel. DCM (20 mL) was added and the organic layer was separated. The aq. layer was extracted with DCM (2 × 15 mL). The combined organic layers were extracted with 10% aq. glacial acetic acid (2 × 15 mL). The combined acidic aq. layers were basified with ethylenediamine (4.5 mL). The basic aq. layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (252. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (91.5/8.0/0.5 (v/v/v)) to afford 226. mg of the title compound as a yellow solid (90% yield).

R_f = 0.16 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

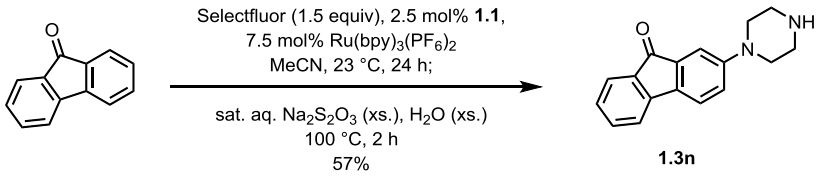
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.74 (dd, *J* = 8.1, 2.1 Hz, 1H), 7.61 (d, *J* = 2.4 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 3.92 (s, 3H), 3.88 (s, 3H), 3.09–3.11 (m, 8H), 1.67 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 167.1, 156.2, 141.3, 125.6, 122.9, 119.7, 110.5, 55.8, 52.0, 51.6, 46.0.

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

2-(Piperazin-1-yl)-9*H*-fluoren-9-one (1.3n)



1.3n

A 100 mL pressure tube was charged with palladium complex **1.1** (8.83 mg, 13.9 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (35.8 mg, 41.6 μmol, 7.50 mol%), Selectfluor (295. mg, 0.832 mmol,

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

R_f = 0.34 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

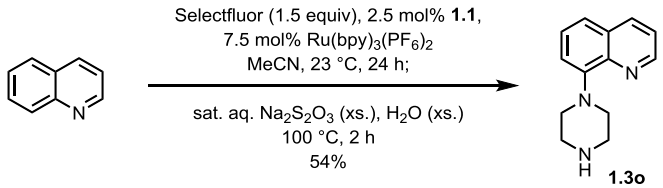
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.57 (d, *J* = 7.3 Hz, 1H), 7.40 (td, *J* = 7.4, 1.1 Hz, 1H), 7.34–7.36 (m, 2H), 7.23 (d, *J* = 2.4 Hz, 1H), 7.15 (td, *J* = 7.4, 1.1 Hz, 1H), 6.93 (dd, *J* = 8.2, 2.4 Hz, 1H), 3.19–3.21 (m, 4H), 3.02–3.04 (m, 4H), 1.74 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 194.6, 152.9, 145.4, 135.7, 135.1, 134.9, 134.4, 127.6, 124.3, 121.2, 120.5, 119.5, 111.9, 50.1, 46.1.

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

8-(Piperazin-1-yl)quinoline (1.3o)



A 100 mL pressure tube was charged with palladium complex **1.1** (13.5 mg, 21.2 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (54.6 mg, 63.5 μmol, 7.50 mol%), and Selectfluor (450. mg, 1.27 mmol, 1.50 equiv). Acetonitrile (4.2 mL, c = 0.20 M) was added, followed by quinoline (100. μL, 84.6 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (8.5 mL) and water (8.5 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. DCM (20 mL) and ethylenediamine (2.5 mL) were added and the organic layer was washed with 6 M aq. sodium hydroxide (5 mL). The aq. layer was extracted with DCM (2 × 15 mL). The combined organic layers were extracted with 1 M aq. hydrochloric acid (2 × 15 mL). Ethylenediamine (5.0 mL) was added to the combined acidic aq. layers, followed by basification with 6 M aq. sodium hydroxide (5 mL). The basic aq. layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (137. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (91.5/8.0/0.5 (v/v/v)) to afford 98.2 mg of the title compound as a yellow oil (54% yield).

$\mathbf{R_f}$ = 0.18 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

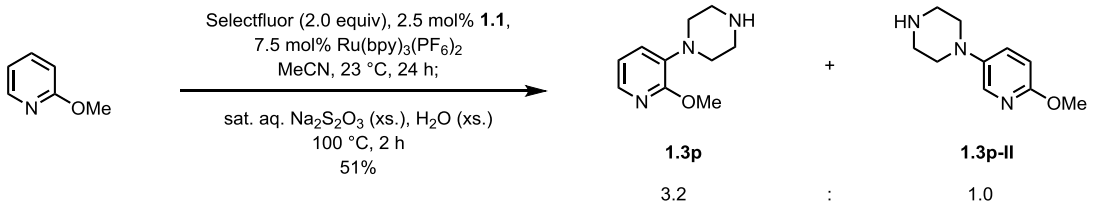
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 8.86 (dd, *J* = 4.1, 1.8 Hz, 1H), 8.08 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.42–7.44 (m, 2H), 7.34 (dd, *J* = 8.2, 4.1 Hz, 1H), 7.12 (dd, *J* = 6.5, 2.4 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 149.8, 148.3, 142.8, 136.6, 129.7, 126.8, 121.8, 120.9, 116.1, 53.2, 46.2.

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

1-(2-Methoxypyridin-3-yl)piperazine (1.3p), 1-(6-methoxypyridin-3-yl)piperazine (1.3p-II)



A 100 mL pressure tube was charged with palladium complex **1.1** (15.1 mg, 23.8 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (61.3 mg, 71.3 μmol, 7.50 mol%), and Selectfluor (674. mg, 1.90 mmol, 2.00 equiv). Acetonitrile (4.8 mL, c = 0.20 M) was added, followed by 2-methoxypyridine (100. μL, 0.951 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (9.5 mL) and water (9.5 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. DCM (15 mL) and ethylenediamine (2.5 mL) were added and the organic layer was washed with 6 M aq. sodium hydroxide (5 mL). Volume of the aq. layer was reduced by half and then the aq. layer was extracted with DCM (2 × 15 mL) and then mixture of DCM/MeOH (9.0/1.0 (v/v), 3 × 15 mL). The combined organic layers were extracted with 1 M aq. hydrochloric acid (3 × 15 mL). Ethylenediamine (5.0 mL) was added to the combined acidic aq. layers, followed by basification with 6 M aq. sodium hydroxide (5 mL). The basic aq. layer was extracted with DCM (2 × 15 mL) and then mixture of DCM/MeOH

(9.0/1.0 (v/v), 3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (120. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (96.0/3.5/0.5 (v/v/v)) to afford 94.5 mg of the title compounds (**1.3p**:**1.3p-II** = 3.2:1.0) as a yellow oil (51% yield).

$\mathbf{R_f}$ = 0.16 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

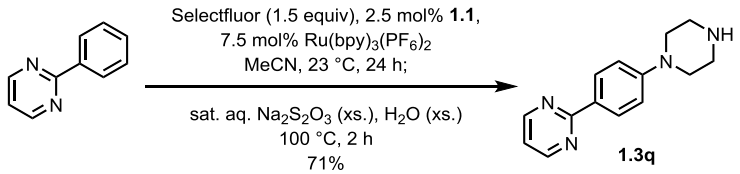
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): **1.3p** 7.76 (dd, *J* = 4.9, 1.7 Hz, 1H), 7.05 (dd, *J* = 7.7, 1.7 Hz, 1H), 6.80 (dd, *J* = 7.7, 4.9 Hz, 1H), 3.95 (s, 3H), 2.98–3.02 (m, 8H), 2.19 (s, 1H). **1.3p-II** 7.74 (d, *J* = 3.0 Hz, 1H), 7.24 (dd, *J* = 8.9, 3.0 Hz, 1H), 6.64 (d, *J* = 8.9 Hz, 1H), 3.84 (s, 3H), 2.98-3.02 (m, 8H), 2.19 (s, 1H).

^{13}C NMR (500 MHz, $CDCl_3$, 23 °C, δ): **1.3p** 156.9, 139.0, 136.6, 124.7, 117.1, 53.4, 51.3, 46.1. **1.3p-II** 158.9, 142.9, 134.6, 129.8, 110.7, 53.4, 51.6, 46.1.

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

2-(4-(Piperazin-1-yl)phenyl)pyrimidine (1.3q)



A 100 mL pressure tube was charged with palladium complex **1.1** (15.9 mg, 25.0 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor (531. mg, 1.50 mmol, 1.50 equiv), and 2-phenylpyrimidine (156. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was

basified with aq. 6 M sodium hydroxide solution (10 mL) and ethylenediamine (0.5 mL), filtered through celite rinsing with acetonitrile (5 × 15 mL), and acetonitrile removed *in vacuo* to afford a brown aq. solution. The aq. layer was transferred to a separatory funnel and extracted with a solvent mixture of MeOH/DCM (1/9 (v/v), 5 × 15 mL). The combined organic layers were extracted with aq. 1M hydrochloric acid solution (3 × 15 mL). The combined acidic aq. layers were basified to pH 14 with aq. 6M sodium hydroxide solution and ethylenediamine (0.5 mL). The basic aq. layer was extracted with a solvent mixture of MeOH/DCM (1/9 (v/v), 5 × 15 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH (9/1 (v/v)) to to afford 171. mg of the title compound as an off-white solid (71% yield).

R_f = 0.08 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

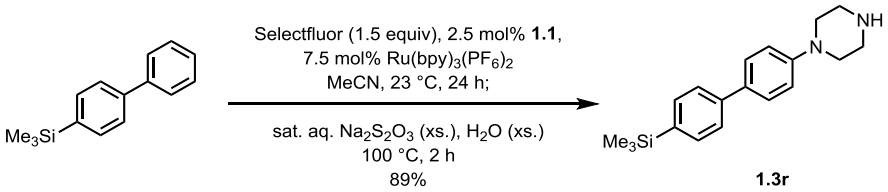
NMR Spectroscopy:

^{1}H NMR (500 MHz, DMSO-d_6, 23 °C, δ): 8.77 (d, *J* = 5.0 Hz, 2H), 8.23 (d, *J* = 9.5 Hz, 2H), 7.27 (t, *J* = 4.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz, 2H), 3.21 (t, *J* = 5.0 Hz, 4H), 2.86 (t, *J* = 5.0 Hz, 4H).

^{13}C NMR (125 MHz, DMSO-d_6, 23 °C, δ): 163.5, 157.4, 153.0, 128.8, 126.7, 118.4, 114.1, 47.9, 45.2.

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

1-(4'-(Trimethylsilyl)-[1,1'-biphenyl]-4-yl)piperazine (1.3r)



1.3r

A 100 mL pressure tube was charged with palladium complex **1.1** (7.03 mg, 11.0 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (28.5 mg, 33.1 μmol, 7.50 mol%), Selectfluor (235. mg, 0.662 mmol, 1.50 equiv), and [1,1'-biphenyl]-4-yltrimethylsilane (100. mg, 0.442 mmol, 1.00 equiv). Acetonitrile (2.2 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, ethylenediamine (2.5 mL) and water (20 mL) were added, and the mixture was stirred for 1 h further. The reaction mixture was transferred to a separatory funnel. DCM (20 mL) was added and the organic layer was separated. The aq. layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (220. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (97.5/2.0/0.5 (v/v/v)) to afford 122. mg of the title compound as a yellow solid (89% yield).

$\mathbf{R_f}$ = 0.31 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

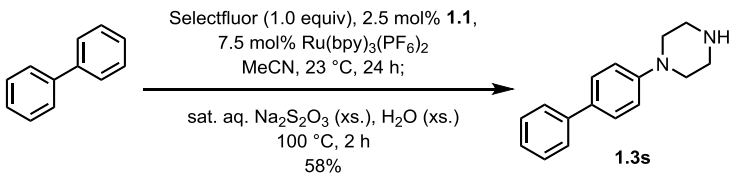
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.56–7.60 (m, 4H), 7.53–7.55 (m, 2H), 6.99–7.02 (m, 2H), 3.21–3.23 (m, 4H), 3.06–3.08 (m, 4H), 2.16 (s, 1H), 0.31 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 151.2, 141.4, 138.2, 133.9, 132.3, 127.8, 125.9, 116.2, 50.2, 46.2, -0.9.

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

1-([1,1'-Biphenyl]-4-yl)piperazine (1.3s)



A 100 mL pressure tube was charged with palladium complex **1.1** (15.9 mg, 25.0 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor (531. mg, 1.00 mmol, 1.00 equiv), and 1,1'-biphenyl (154. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. An aliquot was removed, concentrated, redissolved in CD_3CN, and analyzed by ^1H NMR, which showed a 9:1 mixture of biphenyl–TEDA:biphenyl, with no significant double TEDAylation product:

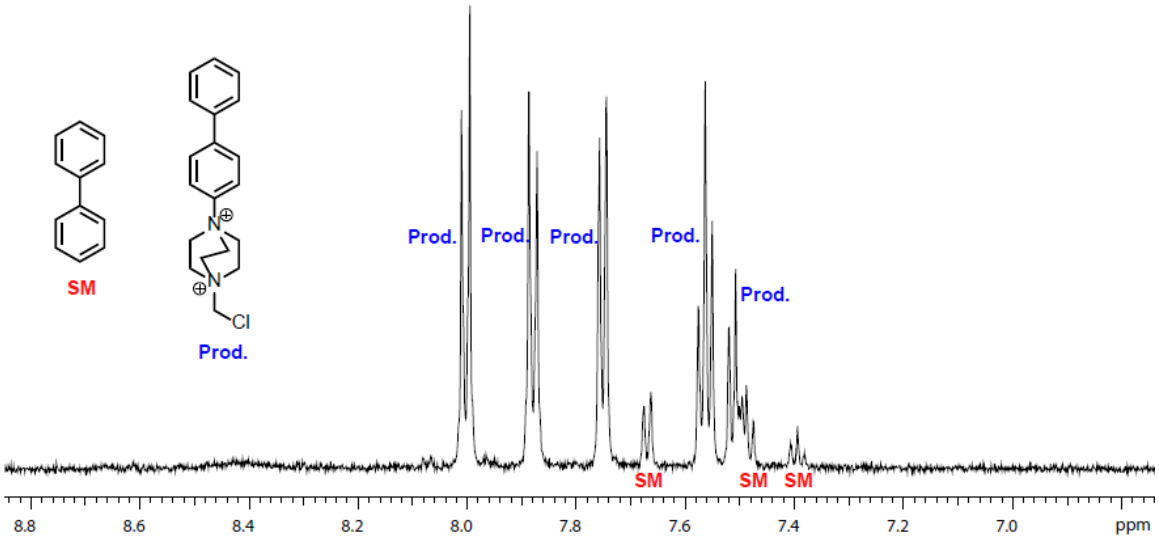


Figure 1.12. ^1H NMR of biphenyl TEDAylation reaction mixture

Saturated aq. sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was basified with aq. 6 M sodium hydroxide solution (10 mL) and ethylenediamine (0.5 mL), filtered through celite rinsing with acetonitrile (5 × 15 mL), and acetonitrile removed *in vacuo* to afford a brown aq. solution. The aq. layer was transferred to a separatory funnel and extracted with a solvent mixture of MeOH/DCM (1/9 (v/v), 5 × 15 mL). The combined organic layers were extracted with aq. 1M hydrochloric acid solution (3 × 15 mL). The combined acidic aq. layers were basified to pH 14 with aq. 6M sodium hydroxide solution and ethylenediamine (0.5 mL). The basic aq. layer was extracted with a solvent mixture of MeOH/DCM (1/9 (v/v), 5

× 15 mL). The organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH (9/1 (v/v)) to to afford 138. mg of the title compound as an off-white solid (58% yield).

R_f = 0.10 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

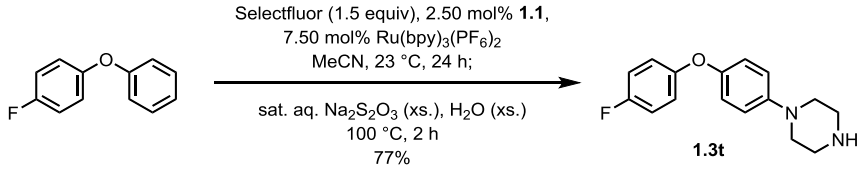
NMR Spectroscopy:

^{1}H NMR (600 MHz, F_3CO_2D, 23 °C, δ): 7.83 (m, 2H), 7.65 (m, 2H), 7.53 (m, 2H), 7.41 (m, 2H), 7.36 (m, 1H), 4.31 (s, 4H), 4.15 (s, 4H).

^{13}C NMR (125 MHz, F_3CO_2D, 23 °C, δ): 149.6, 141.4, 133.0, 132.2, 132.0, 130.1, 123.6, 55.9, 45.8.

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

1-(3-Fluoro-4-methoxyphenyl)piperazine (1.3t)



A 100 mL pressure tube was charged with palladium complex **1.1** (15.9 mg, 25.0 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor (532. mg, 1.50 mmol, 1.50 equiv), and phenyl 4-fluorophenyl ether (188. mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (10 mL) and water (10 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was filtered through celite, and the filter cake was extracted with 5 × 15 mL acetonitrile and 2 × 15 mL water. The acetonitrile was removed from the filtrate by rotary evaporation. To the remaining aq. mixture 0.50 mL ethylene diamine was added, and the aq. mixture was basified to

pH 14 with 6 M NaOH, then transferred to a separatory funnel. The aq. layer was extracted with DCM (7 × 30 mL). The combined organic layers were extracted with 1 M HCl (5 × 30 mL). To the combined acidic aq. layers was added ethylene diamine (0.5 mL), and the mixture was basified to pH 14 with 6 M NaOH. The basic aq. layer was extracted with DCM (5 × 30 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil (220. mg). The residue was purified by chromatography on silica gel eluting with DCM/MeOH 19:1 → 9:1 (v/v) to afford 190. mg of the title compound as an off-white powder (77% yield).

R_f = 0.35 (DCM/MeOH 9:1 (v/v)).

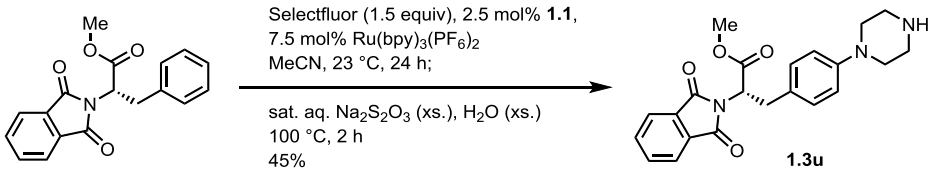
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.00–6.95 (m, 2H), 6.94–6.88 (m, 6H), 3.74 (br, 1H), 3.19–3.12 (m, 4H), 3.12–3.06 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 158.3 (d, *J* = 240.4 Hz), 154.1 (d, *J* = 2.5 Hz), 156.6 (s), 147.9 (s), 119.8 (s), 119.2 (d, *J* = 8.1 Hz), 117.9 (s), 116.0 (d, *J* = 23.2 Hz), 50.6 (s), 45.7 (s).

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

Methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-(4-(piperazin-1-yl)phenyl)propanoate (1.3u)



A 100 mL pressure tube was charged with palladium complex **1.1** (5.9 mg, 9.3 μmol. 2.5 mol%), $Ru(bpy)_3(PF_6)_2$ (24.0 mg, 27.9 μmol, 7.50 mol%), and Selectfluor (198 mg, 0.558 mmol, 1.50 equiv). Solution of methyl (*S*)-2-(1,3-dioxoisoindolin-2-yl)-3-phenylpropanoate (115 mg, 0.372 mmol, 1.00 equiv) in dry acetonitrile (1.9 mL, c = 0.20 M) was added via syringe. The reaction

mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (3.8 mL) and water (3.8 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, water (5 mL) and saturated aq. sodium carbonate (1 mL) were added, and the mixture was filtered over a glass frit with a filter paper. The filtrate was transferred to a separatory funnel. DCM (30 mL) was added and the organic layer was separated. The aq. layer was extracted with DCM (2 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (123 mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (93.7/6.0/0.3 (v/v/v)) to afford 66.3 mg of the title compound as a yellow solid (45% yield).

R_f = 0.76 (DCM/MeOH/28% aq. ammonium hydroxide 93.7:6.0:0.3 (v/v/v)).

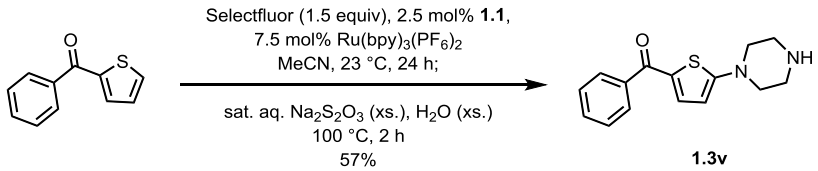
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.76–7.79 (m, 2H), 7.68–7.70 (m, 2H), 7.04–7.07 (m, 2H), 6.72–6.75 (m, 2H), 5.12 (dd, *J* = 11.0, 5.7 Hz, 1H), 3.77 (s, 3H), 3.46–3.53 (m, 2H), 3.08–3.11 (m, 4H), 3.04–3.06 (m, 4H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 169.6, 167.6, 150.1, 134.2, 131.8, 129.7, 128.4, 123.6, 116.7, 53.5, 53.0, 49.4, 45.5, 33.8.

HRMS-FIA(m/z) calc'd for $C_{22}H_{23}N_3O_4$ $[M+H]^+$, 394.1761; found, 394.1760.

Phenyl(5-(piperazin-1-yl)thiophen-2-yl)methanone (1.3v)



1.3v

A 100 mL pressure tube was charged with palladium complex **1.1** (8.5 mg, 13. μmol. 2.5 mol%), $Ru(bpy)_3(PF_6)_2$ (34.2 mg, 40.0 μmol, 7.50 mol%), Selectfluor (282. mg, 0.800 mmol, 1.50 equiv),

and phenyl(thiophen-2-yl)methanone (100. mg, 0.530 mmol, 1.00 equiv). Acetonitrile (2.6 mL, c = 0.20 M) was added via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (5.3 mL) and water (5.3 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. DCM (20 mL), ethylenediamine (0.5 mL) and saturated aq. sodium carbonate (5 mL) were added and the organic layer was separated. The aq. layer was extracted with DCM (3 × 15 mL). The combined organic layers were extracted with 1 M aq. hydrochloric acid (3 × 10 mL). Ethylenediamine (6.0 mL) was added to the combined acidic aq. layers, followed by basification with 3 M aq. sodium hydroxide (6 mL). The basic aq. layer was extracted with DCM (4 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (126. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (95.5/4.0/0.5 (v/v/v)) to afford 82. mg of the title compound as a yellow solid (57% yield).

$\mathbf{R_f}$ = 0.38 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

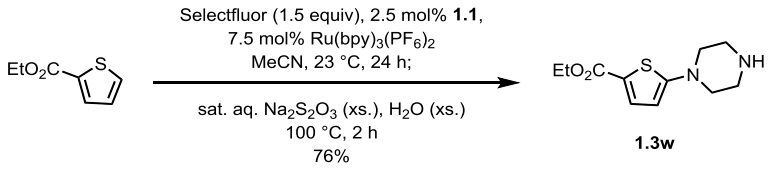
NMR Spectroscopy:

^{1}H NMR (600 MHz, $CDCl_3$, 23 °C, δ): 7.73 (d, *J* = 7.5 Hz, 2H), 7.49 (t, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 2H), 7.36 (d, *J* = 4.3 Hz, 1H), 6.03 (d, *J* = 4.3 Hz, 1H), 3.30 (t, *J* = 4.9 Hz, 4H), 2.99 (t, *J* = 4.9 Hz, 4H), 2.00 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 186.7, 167.8, 139.0, 138.3, 131.1, 128.7, 128.3, 127.5, 104.4, 50.6, 45.2.

HRMS-FIA(m/z) calc'd for $C_{15}H_{17}N_2OS$ $[M+H]^+$, 273.1056; found, 273.1046.

Ethyl 5-(piperazin-1-yl)thiophene-2-carboxylate (1.3w)



1.3w

A 100 mL pressure tube was charged with palladium complex **1.1** (11.8 mg, 18.6 μmol. 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (47.9 mg, 55.7 μmol, 7.50 mol%), and Selectfluor (395. mg, 1.11 mmol, 1.50 equiv). Acetonitrile (3.7 mL, c = 0.20 M) was added, followed by ethyl thiophene-2-carboxylate (100. μL, 0.743 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (7.4 mL) and water (7.4 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. DCM (20 mL) and ethylenediamine (0.5 mL) were added and the organic layer was separated. The aq. layer was extracted with DCM (2 × 15 mL). The combined organic layers were extracted with 10% aq. glacial acetic acid (3 × 10 mL). The combined acidic aq. layers were basified with ethylenediamine (4.5 mL). The basic aq. layer was extracted with DCM (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (156. mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (95.5/4.0/0.5 (v/v/v)) to afford 135. mg of the title compound as a yellow solid (76% yield).

$\mathbf{R_f}$ = 0.52 (DCM/MeOH/28% aq. ammonium hydroxide 90.5:9.0:0.5 (v/v/v)).

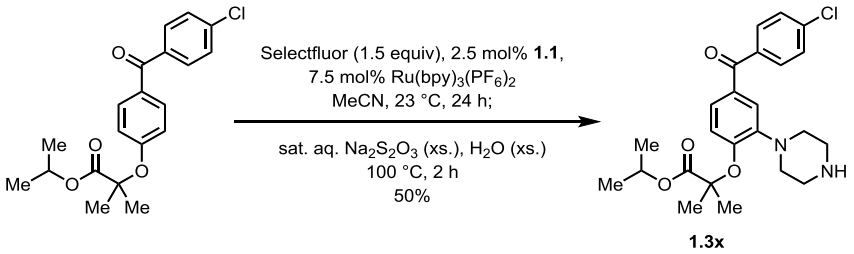
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.52 (d, *J* = 4.3 Hz, 1H), 6.00 (d, *J* = 4.3 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 3.19–3.20 (m, 4H), 2.98–2.99 (m, 4H), 2.17 (s, 1H), 1.30 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 165.2, 162.9, 134.9, 116.9, 104.1, 60.5, 50.8, 45.2, 14.5.

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

Isopropyl 2-(4-(4-chlorobenzoyl)-2-(piperazin-1-yl)phenoxy)-2-methylpropanoate (1.3x)



1.3x

A 100 mL pressure tube was charged with palladium complex **1.1** (4.4 mg, 6.9 μmol. 2.5 mol%), $Ru(bpy)_3(PF_6)_2$ (17.9 mg, 20.8 μmol, 7.50 mol%), Selectfluor (147 mg, 0.416 mmol, 1.50 equiv), and fenofibrate (100 mg, 0.277 mmol, 1.00 equiv). Acetonitrile (1.4 mL, c = 0.20 M) was added via syringe, and the reaction mixture was stirred at 23 °C for 24 h. Saturated aq. sodium thiosulfate (2.8 mL) and water (2.8 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, water (10 mL), saturated aq. sodium carbonate (0.25 mL), and ethylenediamine (70 μL) were added, and the mixture was filtered over a glass frit with a filter paper. The filtrate was transferred to a separatory funnel. DCM (40 mL) was added and the organic layer was separated. The aq. layer was extracted with DCM (3 × 20 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red solid (146 mg). The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/MeOH/28% aq. ammonium hydroxide (96.5/3.0/0.5 to 94.5/5.0/0.5 (v/v/v)) to afford 62 mg of the title compound as a yellow solid (50% yield).

$\mathbf{R_f}$ = 0.11 (DCM/MeOH/28% aq. ammonium hydroxide 95.5:4.0:0.5 (v/v/v)).

NMR Spectroscopy:

^{1}H NMR (600 MHz, CD_3CN, 23 °C, δ): 7.69–7.71 (m, 2H), 7.51–7.53 (m, 2H), 7.37 (d, *J* = 2.2 Hz, 1H), 7.31 (dd, *J* = 8.4, 2.2 Hz, 1H), 6.73 (d, *J* = 8.4 Hz, 1H), 5.02 (hept, *J* = 6.2 Hz, 1H), 3.01–3.06 (m, 8H), 2.68 (bs, 1H), 1.65 (s, 6H), 1.18 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 195.0, 173.7, 153.4, 144.4, 138.6, 137.8, 132.2, 131.4, 129.4, 126.4, 121.1, 116.7, 80.8, 70.2, 51.7, 46.5, 25.6, 21.7.

HRMS-FIA(m/z) calc'd for $C_{24}H_{29}ClN_2O_4$ $[M+H]^+$, 445.1889; found, 445.1888.

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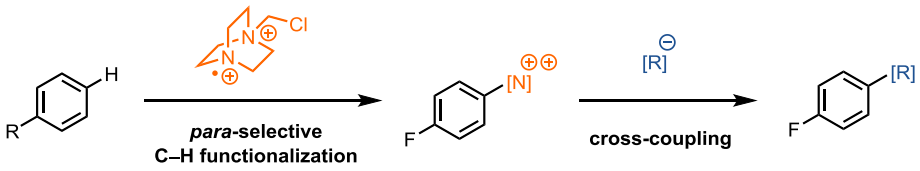
Chapter 2 – Transition-Metal-Catalyzed Cross-Coupling of Aryl TEDA Derivatives

2.1 Backgrounds

Non-chelation-assisted, *para*-selective aryl C–H substitution by the doubly cationic TEDA radical,[1] described in Chapter 1, may function as a branch point for installation of a variety of functional groups on the position of the initial substitution (Scheme 2.1). The structure of aryl TEDA is analogous to aryl trimethylammonium cation, which has been shown to participate in a number of transition-metal-catalyzed cross-coupling reactions as the electrophilic coupling partner.[2–11]

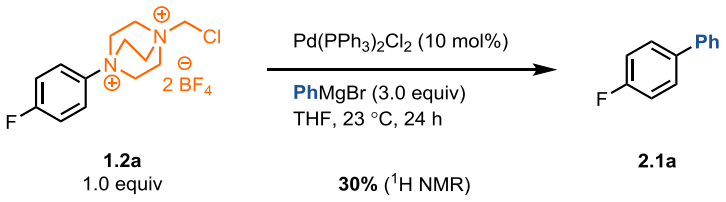


Scheme 2.1. Potential synthetic utility of aryl TEDA as a cross-coupling electrophile.

In this chapter, we describe cross-coupling reactions of aryl TEDA derivatives, including the nickel-catalyzed methylation of aryl TEDA II that was reported in *Angewandte Chemie* in June 2018.[12] Aryl C–H TEDAylation with Selectfluor II, an N–F reagent analogous to Selectfluor, is followed by efficient installation of a methyl group, constituting together a non-chelation-assisted, *para*-selective C–H methylation of arenes. Selectivity remains high, and the absence of the chloromethyl substituent of Selectfluor enables successful methylation of the unusual dicationic aryl electrophile. To the best of our knowledge, *para*-selective C–H methylation of carboarenes had not been reported.

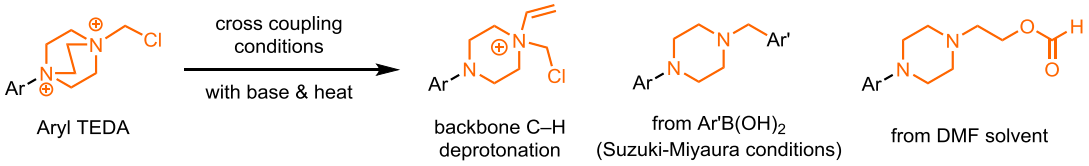
2.2 Preliminary Cross-Coupling Reactivity of Aryl TEDA

Initially, we found out that an aryl TEDA **1.2a** could undergo palladium-catalyzed Kumada-type arylation (Scheme 2.3), employing a procedure slightly modified from that for the coupling of aryl trimethylammonium triflate reported by Reeves.[4]



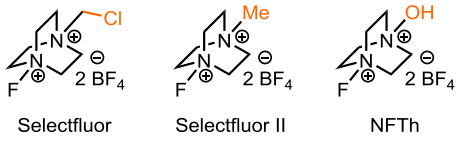
Scheme 2.2. Kumada arylation of aryl TEDA **1.2a**.

While the analogous reactivity of the aryl TEDA compound was promising, we were unable to further optimize the reaction yield, mainly due to the side reactions on the electrophilic TEDA backbone (Scheme 2.4).



Scheme 2.3. Side-reactivity of aryl TEDA with the *N*-chloromethyl substituent.

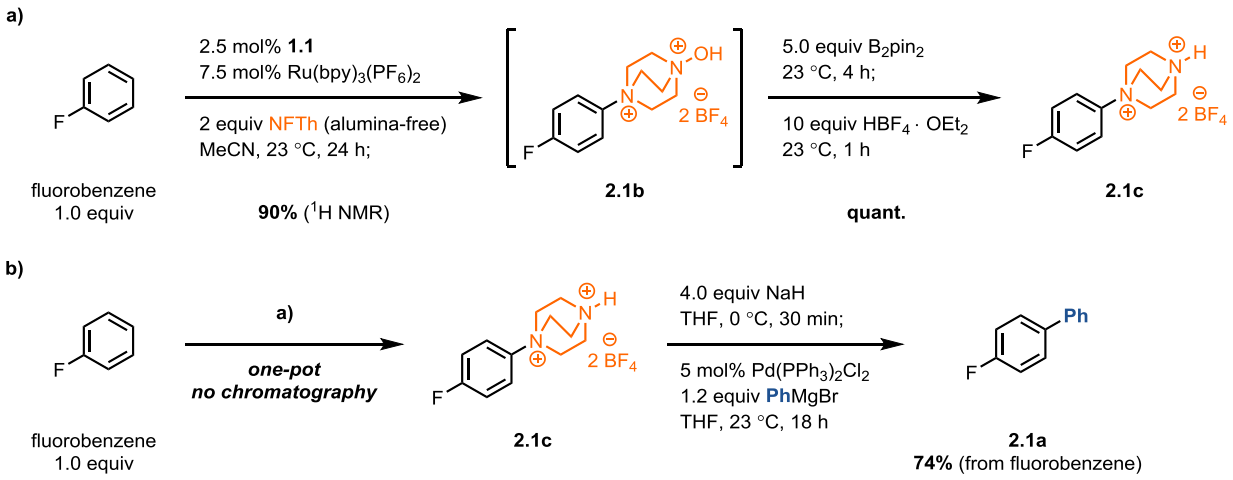
Having reasoned that the undesired reactivity may be attenuated by removing the chloromethyl substituent in the aryl TEDA structure, we turned our attention to other N-fluoro compounds that were expected to undergo aryl functionalization analogous to what Selectfluor does (Scheme 2.5).



Scheme 2.4. Three related N-fluoro compounds with analogous di-cationic TEDA structures.

NFTh, the N-oxyl analog of Selectfluor, also participates in the C–H TEDAylation of fluorobenzene under the same reaction condition, described in Chapter 1, and affords an aryl

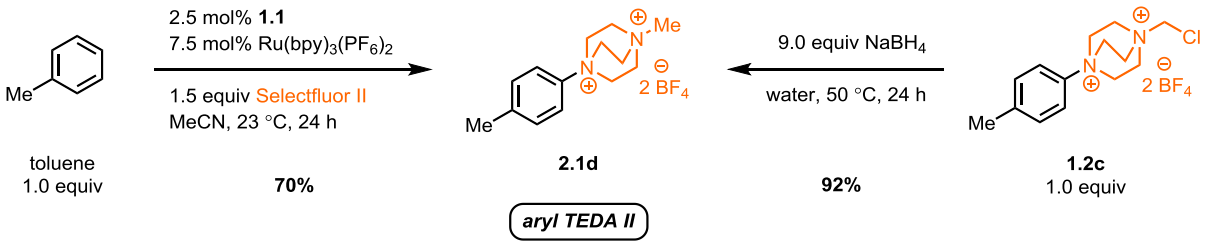
OxyTEDA compound **2.1b**. We found that the N-oxyl group can be reduced by a diboron reagent to furnish a free amine, which was subsequently protonated and isolated by trituration from DCM (Scheme 2.6a).



Scheme 2.5. *Para*-selective C–H arylation of fluorobenzene via aryl DABCOnium. A) One-pot synthesis of aryl DABCOnium **2.1c** using NFTh reagent. B) Palladium-catayzed arylation of **2.1c** with a high yield.

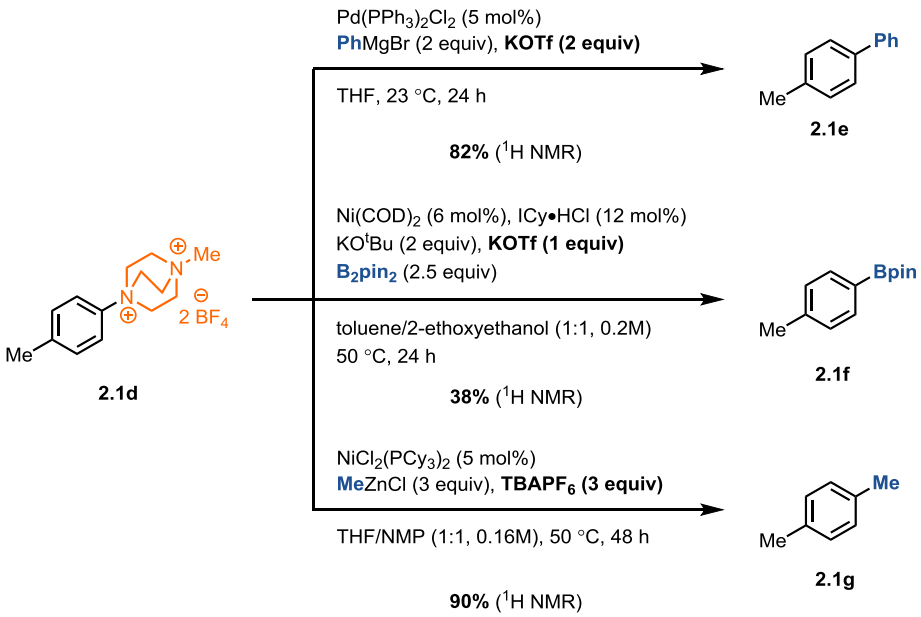
Gratifyingly, the readily isolated aryl DABCOnium compound is a much more efficient electrophile for Kumada arylation than the original aryl TEDA (Scheme 2.6b), and an overall yield of 74% based on the amount of fluorobenzene was observed.

However, the reactive N-fluoro reagent NFTh is a potential explosive, and is no longer commercially available to organic chemists. With the knowledge that the absence of chloromethyl substituent on the TEDA backbone contributes to the superior cross-coupling reactivity, we instead investigated the performance of Selectfluor II, the N-methyl analog of Selectfluor, towards C–H functionalization and cross-coupling reactions.



Scheme 2.6. Synthesis of aryl TEDA II **2.1d** via TEDAylation of toluene with Selectfluor and reduction of aryl TEDA **1,2c**.

Selectfluor II is a safer, less reactive reagent, while it still participated in the analogous TEDAylation reaction with a satisfactory yield from toluene. Moreover, it can alternatively be prepared by facile reduction of carbon-chlorine bond in the aryl TEDA obtained from Selectfluor (Scheme 2.7).



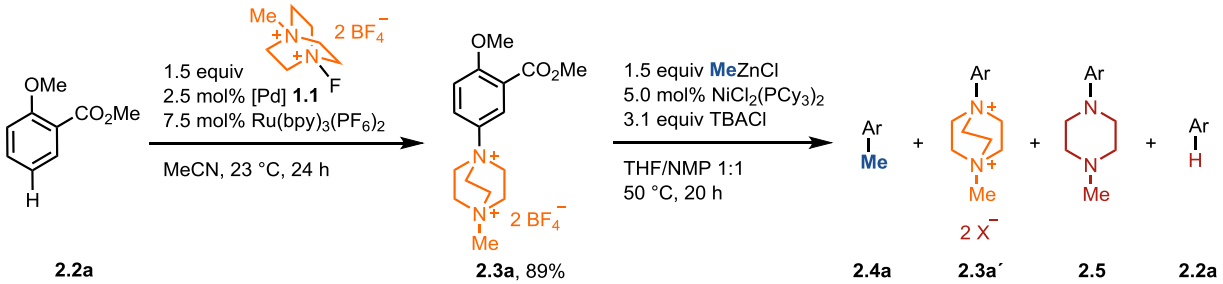
Scheme 2.7. Transition-metal catalyzed arylation, borylation, and methylation reactions of aryl TEDA II **2.1d**.

As expected, the aryl TEDA II compound also exhibited cross-coupling reactivity superior to that of the original aryl TEDA. In addition to the Kumada-type arylation reaction, we found out that **2.1d** can undergo two different cross-coupling reactions, borylation and methylation, again using procedures adapted from the reported coupling reactions of aryl trimethylammonium salts (Scheme 2.8).[5,9] Moreover, we discovered that anionic additives play significant roles in improving the reaction yields; the yield of arylation of **2.1d** was increased from 60% to 82% by adding 2 equivalence of potassium triflate. Importantly, addition of tetrabutylammonium hexafluorophosphate was crucial for suppressing the decomposition of **2.1d** to a number of

unidentified aryl piperazine derivatives and achieving the 90% yield; without the additive, only 25% of the desired methylarene **2.1g** was observed.

2.3 C–H Methylation of (Hetero)Arenes *via* Aryl TEDA–II

With the preliminary results on the desirable reactivity of aryl TEDA II, we conducted further optimization of the Negishi-type methylation reaction. We found that, the required anionic additive for efficient cross-coupling differs depending on specific arene substrates, and the additive compatible with most substrates was actually TBACl, instead of $TBAPF_6$ (Scheme 2.8). The addition of organic or inorganic halide sources is known to promote the *in situ* formation of higher-order zincates $RZnX_3^{2-}$ (R = alkyl, X = halide), which facilitate the transmetalation.[13–15] Among the tested halide sources, however, only TBACl furnished the corresponding methylated arene in high yield from **2.3a**, and suppressed the formation of byproducts. Addition of other halides resulted in precipitates, which we believe to be Ar-TEDA complexes **2.3a´** that may exit the catalytic cycle *via* counteranion exchange (some unreacted Ar-TEDA was observed by ^1H NMR spectroscopy only after addition of DMSO.), or by formation of aryl piperazine **2.5**. Expansions to other alkyl cross-coupling reactions, for example *n*-butylation, were not promising.

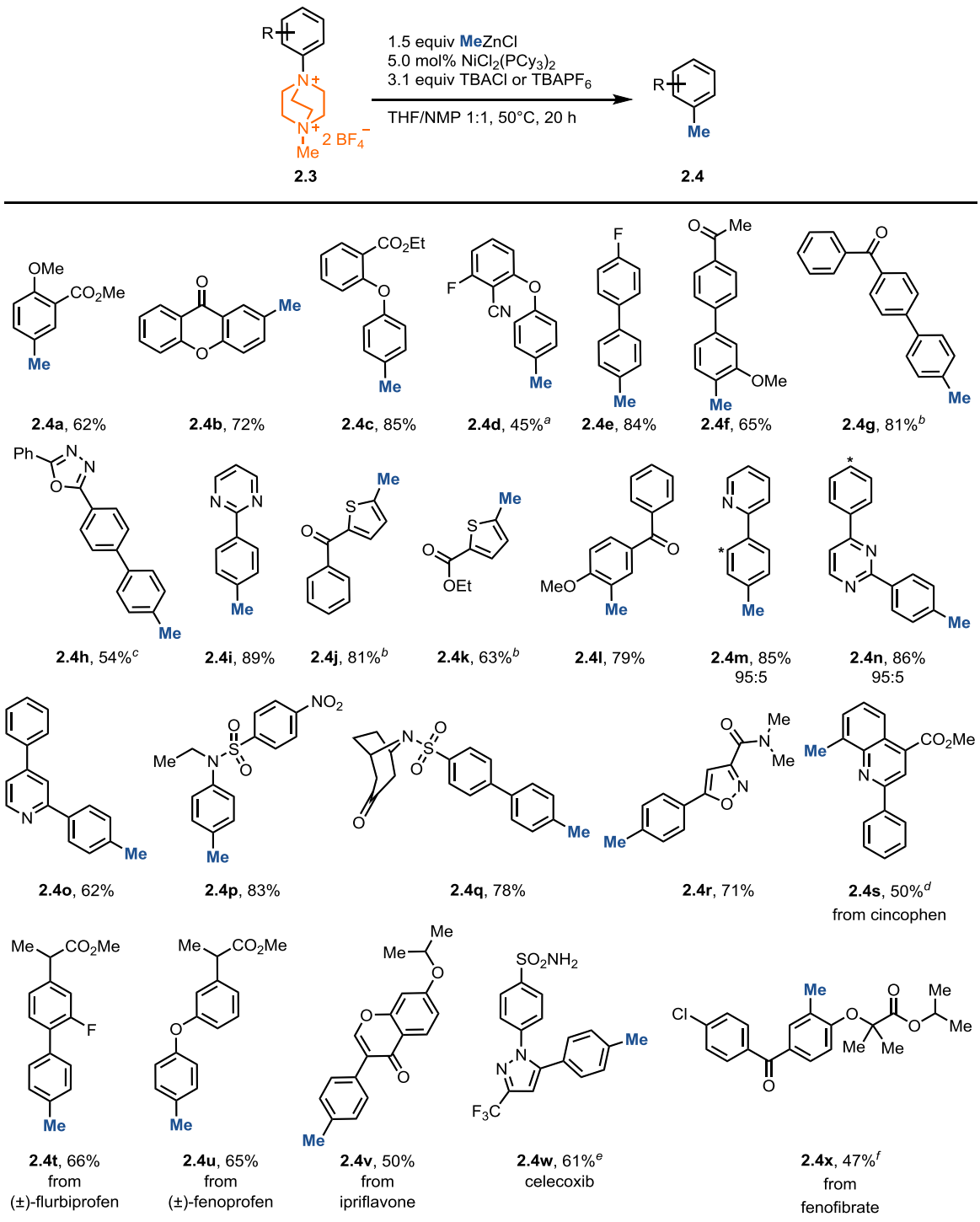


2.2a **2.3a**, 89% **2.4a** **2.3a´** **2.5** **2.2a**

Change of reaction conditions	Yield (%)[b]			
none	71	8	<1	<1
no additive	8	90	<1	<1
TBABr instead of TBACl	33	43	13	<1
$TBAPF_6$ instead of TBACl	14	85	<1	<1
LiCl instead of TBACl	<5	18	<1	<1
Me_2Zn instead of MeZnCl	40	<1	10	<1
nBuZnCl instead of MeZnCl	<1[c]	<5	<1	21

Scheme 2.8. Optimization[a] of Negishi-type methylation of aryl TEDA II **2.2a**. [a]Reaction conditions: **2.3 a** (0.05 mmol), $NiCl_2(PCy_3)_2$ (5 mol %), TBACl (3.1 equiv), and MeZnCl (1 M in THF; 1.5 equiv) in THF/NMP (1:1, c = 0.17 M) at 50 °C for 20 h. [b]Yield determined by ^{1}H NMR spectroscopy. [c]*n*-Butyl rather than methyl.

Functional groups including esters (**2.4a**, **2.4c**), nitrile (**2.4d**), ethers (**2.4b**–**d**), ketones (**2.4b**, **2.4l**), sulfonamides (**2.4p**, **2.4q**), amide (**2.4r**) and chloro (**2.4x**) are tolerated in the C–H methylation of arenes (Scheme 2.9). Several electron-rich amines, however, are not suitable due to their incompatibility with Selectfluor. The two-step transformation proved to be compatible with *N*-heteroaromatic compounds (**2.4h**, **2.4i**, **2.4m**–**o**, **2.4v**) as well as thiophenes (**2.4j**, **2.4k**). In a small number of cases, lower yields were obtained due to the low solubility of certain Ar-TEDA compounds in the THF/NMP mixture. The issue was addressed by replacement of TBACl with $TBAPF_6$ (**2.4g**, **2.4h**, **2.4k**). Both electron- rich and -neutral substrates reacted smoothly in the C–H methylation reaction. When more than one arene is present, the most electron-rich arene is methylated in preference, often in remarkable selectivity (**2.4n**, **2.4o**), and always with perfect positional selectivity within the limits of detection. Electron-deficient arenes, such as methyl benzoate, are insufficiently reactive and undergo low or no conversion in the first step. The methylation of 2,4-diphenylpyridine was successfully performed on gram-scale, with no notable decrease in yield. We further demonstrated the utility of the transformation through late-stage functionalization of small molecule pharmaceuticals (**2.4s-x**). For example, the 4' position of flurbiprofen methyl ester (**2.4t**) was methylated selectively in 66% yield. The position, susceptible to metabolic oxidation,[16] can be protected by the introduction of the methyl group.[17] Our approach was also applied to the synthesis of celecoxib (**2.4w**).[18]



Scheme 2.9. Methylation of aryl TEDA II´s. Reactions performed with Ar-TEDA (0.25 mmol), $NiCl_2(PCy_3)_2$ (5 mol %), TBACl (3.1 equiv), and MeZnCl (1 M in THF; 1.5 equiv) in THF/NMP (1:1, c = 0.17 M) at 50 °C for 20 h. Yields refer to analytically pure compounds. [a]TBACl (4 equiv) was used, with $NiCl_2(PCy_3)_2$ (10 mol %) and MeZnCl (1 M in THF, 2 equiv). [b]$TBAPF_6$ (3.1 equiv) was used instead of TBACl. [c]$TBAPF_6$ (4 equiv) was used instead of TBACl, with $NiCl_2(PCy_3)_2$ (10 mol %) and MeZnCl (1 M in THF, 2 equiv). [d]Major isomer (7:2:1 ratio).

[e]$NiCl_2(PCy_3)_2$ (10 mol %), TBACl (4 equiv) and MeZnCl (1 M in THF, 4 equiv) were used. [f]$NiCl_2(PCy_3)_2$ (5 mol %), TBACl (4 equiv), and MeZnCl (1 M in THF, 1.0 equiv) were used.

2.4 Conclusion

In conclusion, we have developed a new selective methylation of arenes based on a C–H functionalization–cross-coupling sequence. Our transformation does not require a pre-installed coordinating group on the starting materials, and therefore allows access to an enlarged substrate scope in comparison to previously reported methods. The addition of the TEDA–II radical to arenes led successfully to both high selectivity and reactivity in cross-coupling. We anticipate that the concept of using electrophilic radicals for subsequent cross-coupling will encourage further development of desirable C–H functionalization reactions.

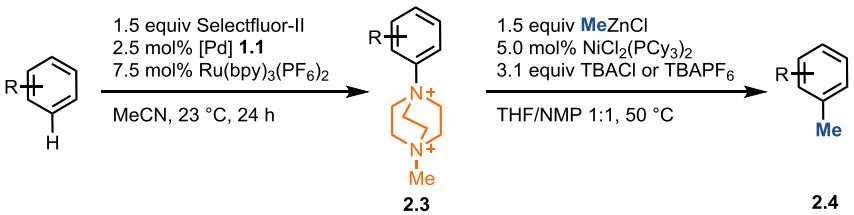
2.5 Experimental Details

2.5.1 Materials and Methods

All air- and moisture-insensitive reactions were carried out under an ambient atmosphere, magnetically stirred, and monitored by thin layer chromatography (TLC) using EMD TLC plates pre-coated with 250 μm thickness silica gel 60 F_{254} plates and visualized by fluorescence quenching under UV light and $KMnO_4$ stain. Flash chromatography was performed on Geduran® Silica Gel 40–63 μm particle size using a forced flow of eluent at 0.3–0.5 bar pressure. All air- and moisture-sensitive manipulations were performed using oven-dried glassware, using standard Schlenk line or dry, nitrogen-filled glovebox techniques. The reactions using a microwave were performed in a Biotage® Initiator+. Anhydrous solvents were obtained from Phoenix Solvent Drying Systems. Acetonitrile and NMP (N-methyl-2-pyrrolidone) were purchased from Sigma-Aldrich® and used as received. All arene substrates were used as received from commercial suppliers, unless otherwise stated. 2,4-Diphenylpyridine[19] and 2,4-

diphenylpyrimidine[20] were prepared according to procedures reported in the literature. 1-(Pyridine-2-ylmethyl)pyrrolidine 1-oxide was prepared according to the literature.[21] Selectfluor II was purchased from Sinojie hanson Ltd, and was used as received. The tetra-*n*-butylammonium salt, LiCl and $MgCl_2$ were purchased from commercial suppliers, and dried for 12 h under high vacuum (0.1–0.2 mbar) at 80°C. $Ru(bpy)_3(PF_6)_2$ and $Ni(PCy_3)_2Cl_2$, were purchased from Sigma-Aldrich® and were used as received. MeZnCl 2M in THF was purchased from Acros Organics. *n*BuZnCl was prepared according to the literature.[22] All deuterated solvents were purchased from Euriso-Top®. NMR spectra were recorded on a Bruker 500 spectrometer operating at 500 MHz and 125 MHz for ^1H and ^{13}C acquisitions, respectively. Chemical shifts were referenced to the residual proton solvent peaks (^1H: $CDCl_3$, δ 7.26; DMSO-d_6, δ 2.50; CD_3CN, δ 1.94; acteone-d_6, δ 2.05), solvent ^{13}C signals ($CDCl_3$, δ 77.2; DMSO-d_6 δ 40.2; CD_3CN, δ 118.7, 1.4; acteone-d_6, δ 29.84). ^{19}F NMR spectra were referenced using a unified chemical shift scale based on the ^1H resonance of tetramethylsilane (1% v/v solution in the respective solvent).[23] Signals are listed in ppm, and multiplicity identified as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants in Hz; integration. All HRMS data were recorded on Q Exactive Plus from Thermo. Concentration under reduced pressure was performed by rotary evaporation at 40 °C under appropriate pressure. Purified compounds were further dried under high vacuum (0.1–0.2 mbar). Yields refer to purified and spectroscopically pure compounds, unless otherwise noted.

2.5.2 General Procedure for the C–H Functionalization-Methylation Sequence



2.3 **2.4**

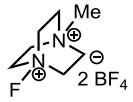
To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 mg, 1.50 mmol, 1.50 equiv), and an arene (1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 x 2 mL). The resulting pure Ar-TEDA **2.3** was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours.

An oven-dried, argon-filled Schlenk tube was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), Ar-TEDA **2.3** (0.250 mmol, 1.00 equiv), and $n Bu_4N^+Cl^-$ (TBACl) (215 mg, 0.775 mmol, 3.10 equiv) or $n Bu_4N^+PF_6^-$ ($TBAPF_6$) (300 mg, 0.775 mmol, 3.10 equiv). The Schlenk flask was capped with a rubber septum, then evacuated and back-filled with argon. This evacuation/back-filling process was repeated three times. NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added to the reaction mixture. The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL), with brine (5 mL), then dried over

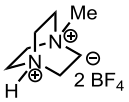
Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel to give the title product.

Note 1: the purification procedure for Ar-TEDAs presented above is general and more efficient that the previously reported one. Combination of Et_3N and MeCN/DCM allowed to purge the remaining TEDA-H^{2+} and/or $TEDA^+$ formed in the course of the reaction. The purging efficiency is comparable when Selectfluor is used instead of Selectfluor II.

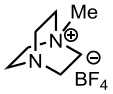
Note 2: when the Ar–TEDAs were contaminated with remaining TEDA-H^{2+} and/or $TEDA^+$, a second purification was performed as described below.



Selectfluor II



TEDA-H^{2+}



$TEDA^+$

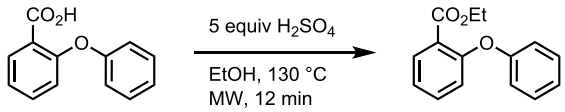
In a 20 mL-vial, acetonitrile (2 mL) was added to the solids, followed by Et_3N (excess, V = 0.3 mL) was added and the resulting mixture was stirred for 2 min at 23 °C. DCM (10 mL) was then added, and the precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial and MeOH (5 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting solid was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours.

Note 3: The Ar–TEDA compounds have been purified and characterized by NMR and HRMS. However, in some cases, due to a low solubility of the isolated compounds in deuterated solvents (Acetone-d_6, DMSO-d_6, CD_3CN), the signal to noise ratio of the recorded ^{13}C-NMR spectra is low.

Note 4: We appreciate that, generally, for practical use, many scientists prefer not to use a glovebox. The transformation, as reported in this general procedure, was carried out conveniently without the use of a glovebox. For simplicity, in our own research, we have opted to execute the transformation for most compounds by using a glovebox. Control experiments showed that yields were within error of measurement if the reaction was carried out using a glovebox or not.

2.5.3 Preparation of Starting Materials

Ethyl 2-phenoxybenzoate (2.2c)



2.2c, 87%

A 10 mL microwave vial equipped with a magnetic stirring bar was charged 2-phenoxybenzoic acid (320 mg, 1.49 mmol, 1.00 equiv). EtOH (2.5 mL) and concentrated H_2SO_4 (0.40 mL) were then added to the vial. The vial was sealed with a cap and placed in the microwave. The reaction mixture was stirred for 12 minutes at 130 °C under microwave irradiation. After cooling to 23 °C, the pH was adjusted to 7–8 by addition of a saturated aq. solution of sodium bicarbonate. The solution was then transferred to a separatory funnel, and extracted three times with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (1 × 5 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.2c** (310 mg, 87%) as a colorless liquid.

$\mathbf{R_f}$ = 0.52 (EtOAc/pentane 1:9 (v/v)).

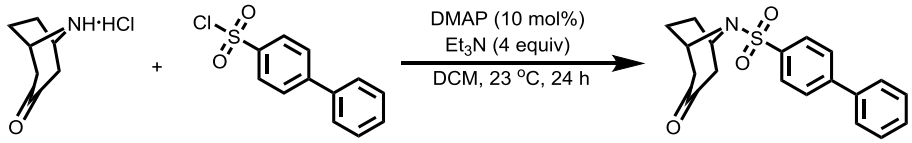
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.92 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.47 (ddd, *J* = 8.2, 7.3, 1.8 Hz, 1H), 7.34–7.28 (m, 2H), 7.20 (td, *J* = 7.7, 1.2 Hz, 1H), 7.06 (tt, *J* = 7.3, 1.1 Hz, 1H), 7.02 (dd, *J* = 8.2, 1.2 Hz, 1H), 6.96–6.92 (m, 2H), 4.26 (q, *J* = 7.2 Hz, 2H), 1.21 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 165.9, 158.0, 155.8, 133.6, 131.9, 129.8, 124.1, 123.8, 122.9, 121.5, 117.8, 61.2, 14.2.

HRMS-FIA(m/z) calc'd for $C_{15}H_{14}O_3Na^+$ $[M+Na]^+$, 265.0835; found, 265.0837.

***N*-(Biphenyl-4-sulfonyl)nortropinone (2.2q)**



2.2q, 66%

A 50 mL round bottom flask was charged with nortropinone hydrochloride (0.808 g, 5.00 mmol, 1.00 equiv), DCM (25 mL, c = 0.2 M), biphenyl-4-sulfonyl chloride (1.26 g, 5.00 mmol, 1.00 equiv), triethylamine (2.0 g, 2.8 mL, 20 mmol, 4.0 equiv) and 4-dimethylamino pyridine (61 mg, 0.50 mmol, 0.10 equiv). After stirring for 24 hours at 23 °C, the reaction mixture was diluted with DCM (100 mL) and washed with 0.5 M aq. HCl (150 mL). The aq. layer was extracted with DCM (3 × 50 mL), and the combined organic phases were dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel, eluting with DCM/ethyl acetate (90:10 (v/v)) to afford *N*-(biphenyl-4-sulfonyl)nortropinone **2.2q** (1.12 g, 3.28 mmol, 66%) as a colorless solid.

R_f = 0.40 (ethyl acetate/DCM, 10:90 (v/v)).

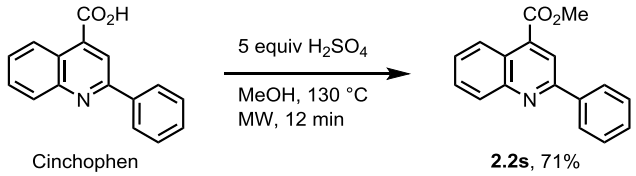
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.97 (m, 2H), 7.73 (m, 2H), 7.61 (m, 2H), 7.48 (m, 2H), 7.43 (m, 1H), 4.55 (m, 2H), 2.82 (dd, *J* = 16.4, 4.5 Hz, 2H), 2.39 (dd, *J* = 17.1, 1.5 Hz, 2H), 1.78 (m, 2H), 1.62 (m, 2H) ppm.

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): δ 206.9, 146.2, 139.1, 138.4, 129.2, 128.8, 127.943, 127.936, 127.4, 56.2, 50.4, 29.5 ppm.

HRMS-ESI (m/z) calculated for $C_{19}H_{19}SNO_3Na^+$ $[M+Na]^+$, 364.0978; found, 364.0981

Methyl 2-phenylquinoline-4-carboxylate (2.2s)



A 20 mL microwave vial equipped with a magnetic stirring bar was charged with Cinchophen (1.99 g, 8.00 mmol, 1.00 equiv). MeOH (8.3 mL) and concentrated H_2SO_4 (2.0 mL) were then added to the vial. The vial was sealed with a cap and placed in the microwave. The reaction mixture was stirred for 12 minutes at 130 °C under microwave irradiation. After cooling to 23 °C, the pH was adjusted to 7–8 by addition of aq. solution of sodium hydroxide 1M. The solution was then transferred to a separatory funnel, and extracted three times with EtOAc (1 × 40 mL, 2 × 20 mL). The combined organic layer was washed with brine (1 × 10 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:9 (v/v) to afford the desired product **2.2s** (1.50 g, 71%) as a colorless solid.

$\mathbf{R_f}$ = 0.43 (EtOAc/pentane 1:9 (v/v)).

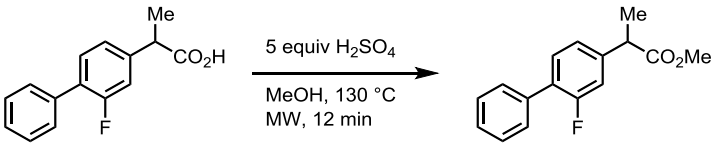
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.75 (dd, *J* = 8.4, 1.3 Hz, 1H), 8.42 (s, 1H), 8.27–8.18 (m, 3H), 7.78 (ddd, *J* = 8.4, 6.9, 1.4 Hz, 1H), 7.64 (ddd, *J* = 8.3, 6.9, 1.3 Hz, 1H), 7.59–7.53 (m, 2H), 7.52–7.47 (m, 1H), 4.08 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 167.0, 156.9, 149.4, 139.0, 135.8, 130.5, 130.1, 129.9, 129.1, 128.0, 127.6, 125.6, 124.1, 120.5, 52.9.

These spectroscopic data correspond to those reported in the literature.[24]

(±)-Flurbiprofen methyl-ester (2.2t)



2.2t, 93%

A 20 mL microwave vial equipped with a magnetic stirring bar was charged with (±)-Flurbiprofen (1.63 g, 6.67 mmol, 1.00 equiv). MeOH (7.0 mL) and concentrated H_2SO_4 (1.8 mL) were then added to the vial. The vial was sealed with a cap and placed in the microwave. The reaction mixture was stirred for 12 minutes at 130 °C under microwave irradiation. After cooling to 23 °C, the pH was adjusted to 7–8 by addition of aq. solution of sodium hydroxide 1M. The solution was then transferred to a separatory funnel, and extracted three times with EtOAc (1 × 40 mL, 2 × 20 mL). The combined organic layer was washed with brine (1 × 10 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.2t** (1.68 g, 93%) as a colorless liquid.

R_f = 0.49 (EtOAc/pentane 1:9 (v/v)).

NMR Spectroscopy:

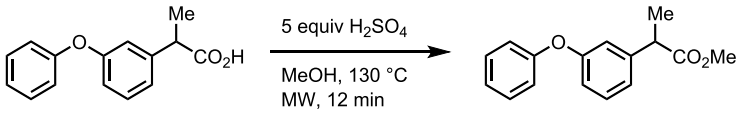
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.56–7.51 (m, 2H), 7.47–7.42 (m, 2H), 7.42–7.32 (m, 2H), 7.19–7.10 (m, 1H), 3.77 (q, *J* = 7.2 Hz, 1H), 3.71 (s, 3H), 1.54 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 174.6, 159.8 (d, *J* = 248 Hz), 141.9 (d, *J* = 7.7 Hz), 135.6, 131.0 (d, *J* = 4.0 Hz), 129.08 (d, *J* = 2.9 Hz), 128.6, 128.0 (d, *J* = 13.6 Hz), 127.8, 123.7 (d, *J* = 3.4 Hz), 115.4 (d, *J* = 24.3 Hz), 52.4, 45.1, 18.6.

^{19}F NMR (470 MHz, $CDCl_3$, 23 °C, δ): –117.6.

These spectroscopic data correspond to those reported in the literature.[25]

(±)-Fenoprofen methyl-ester (2.2u)



2.2u, 99%

A 10 mL microwave vial equipped with a magnetic stirring bar was charged with (±)-Fenoprofen (485 mg, 2.00 mmol, 1.00 equiv). MeOH (2.1 mL) and concentrated H_2SO_4 (0.53 mL) were then added to the vial. The vial was sealed with a cap and placed in the microwave. The reaction mixture was stirred for 12 minutes at 130 °C under microwave irradiation. After cooling to 23 °C, the pH was adjusted to 7–8 by addition of a saturated aq. solution of sodium bicarbonate. The solution was then transferred to a separatory funnel, and extracted three times with EtOAc (3 × 10 mL). The combined organic layer was washed with brine (1 × 5 mL), dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.2u** (507 mg, 99%) as a colorless liquid.

$\mathbf{R_f}$ = 0.49 (EtOAc/pentane 1:9 (v/v)).

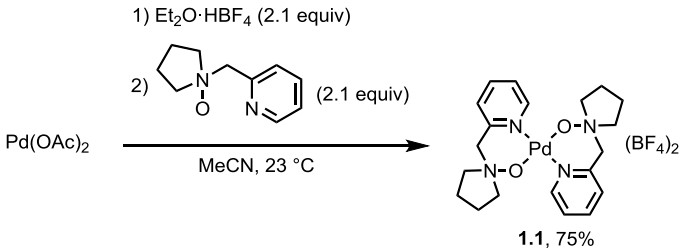
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.38–7.30 (m, 2H), 7.27 (t, *J* = 7.9 Hz, 1H), 7.13–7.08 (m, 1H), 7.06–6.97 (m, 4H), 6.88 (dd, *J* = 8.1, 2.2 Hz, 1H), 3.70 (q, *J* = 7.2 Hz, 1H), 3.67 (s, 3H), 1.49 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 174.8, 157.6, 157.1, 142.6, 130.0, 129.9, 123.5, 122.4, 119.1, 118.3, 117.4, 52.2, 45.4, 18.6.

These spectroscopic data correspond to those reported in the literature.[26]

2.5.4 Procedure for Preparation of Palladium Complex 1.1[1]



A flame-dried, 250 mL 2-neck flask under nitrogen was charged with $Pd(OAc)_2$ (5.00 g, 22.3 mmol, 1.0 equiv), and the flask was evacuated and refilled with N_2. Through a septum was added dry acetonitrile (50 mL, Aldrich Sure/Seal^{TM}), followed by $Et_2O{\cdot}HBF_4$ (6.4 mL, 47 mmol, 2.1 equiv). The resulting suspension was stirred at 23 °C for 30 min, after which 1-(pyridine-2-ylmethyl)pyrrolidine 1-oxide (8.334 g, 46.77 mmol, 2.1 equiv) was added as a solution in dry acetonitrile (40 mL, Aldrich Sure/Seal^{TM}). The resulting mixture was stirred for 1 h, after which the reaction mixture was diluted with 100 mL acetonitrile to dissolve the precipitated product, and the resulting solution was filtered through celite, and the filtrate was concentrated by rotary evaporation. The resulting brown solid was triturated with DCM (40 mL) by sonication. The product was collected by filtration on a glass frit, then washed with DCM (40 mL) followed by tetrahydrofuran (40 mL), then allowed to dry on the frit with applied suction to yield 10.61 g of a yellow powder (16.66 mmol, 75%).

NMR Spectroscopy:

^{1}H NMR (600 MHz, DMSO-d_6,, 23 °C, δ): 8.50 (dd, *J* = 5.8, 1.2 Hz, 2H), 8.30 (ddd, *J* = 7.7, 7.7, 1.5 Hz, 2H), 7.86 (ddd, *J* = 7.5, 5.8, 1.4 Hz, 2H), 7.79 (dd, *J* = 7.8, 1.2 Hz, 2H), 5.35 (s, 4H), 3.56–3.46 (m, 4H), 3.45–3.36 (m, 4H), 2.26–2.15 (m, 4H), 2.10–1.99 (m, 4H).

^{13}C NMR (125 MHz, DMSO-d_6, 23 °C, δ): 149.2, 148.2, 142.0, 128.2, 126.5, 70.1, 67.2, 21.3.

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

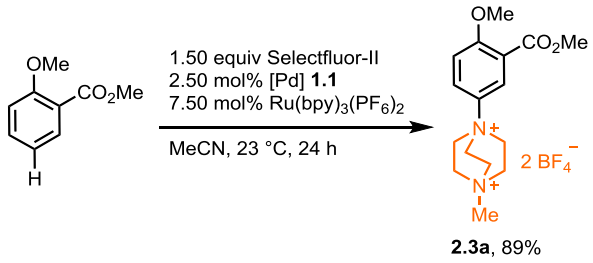
Elemental anal. calc'd for $C_{20}H_{28}B_2F_8N_4O_2Pd$: C, 37.74; H, 4.43; N, 8.80. Found: C, 37.83; H, 4.14; N, 9.04.

These spectroscopic data correspond to those reported in the literature.[1]

2.5.5 Procedures for C–H TEDAylation of Arenes

The isolated Ar–TEDA^{+} BF_4^{-} compounds may contain trace PF_6^{-} anions instead of the BF_4^{-} anions, as observed by a doublet in the ^{19}F NMR at –72.3 ppm with a coupling constant of *J* = 707 Hz. The counterion has no dramatic effect on the reaction; we have made no attempt to obtain material free of PF_6^{-}, and for stoichiometry calculations have assumed the BF_4 to be the sole counteranion.

Methyl 5-TEDA-2-methoxybenzoate (2.3a)



2.3a, 89%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 mg, 1.50 mmol, 1.50 equiv), and methyl-2-methoxybenzoate (166 mg, 107 μL, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried undervacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 414 mg of the desired product **2.3a** as a colorless solid (89%).

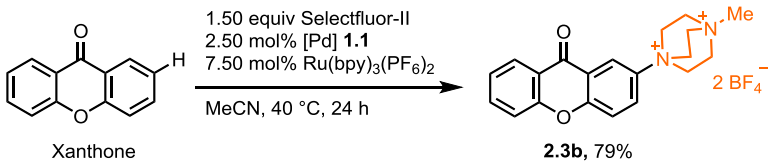
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.36 (d, *J* = 3.5 Hz, 1H), 8.28 (dd, *J* = 9.5, 3.5 Hz, 1H), 7.51 (d, *J* = 9.5 Hz, 1H), 4.94–4.85 (m, 6H), 4.58–4.48 (m, 6H), 4.01 (s, 3H), 3.87 (s, 3H), 3.75 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6, 23 °C, δ): 164.9, 158.9, 136.3, 126.0, 123.4, 121.0, 114.2, 56.8, 54.2, 52.8, 52.6, 51.5.

HRMS-ESI (m/z) calc'd for $C_{16}H_{24}N_2O_3BF_4^+$ $[M\text{-}BF_4]^+$, 379.1811; found, 379.1813.

2-TEDA-xanthone (2.3b)



To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and Xanthone (192 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (10 mL, c = 0.10 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 40 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 392 mg of the desired product **2.3b** as a beige solid (79%).

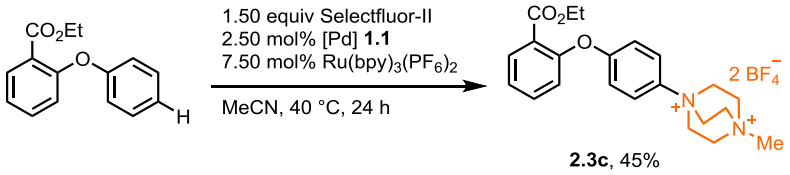
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.84 (d, *J* = 3.4 Hz, 1H), 8.63 (dd, *J* = 9.5, 3.4 Hz, 1H), 8.29 (dd, *J* = 7.9, 1.7 Hz, 1H), 8.04 (d, *J* = 9.5 Hz, 1H), 7.97 (ddd, *J* = 8.7, 7.2, 1.7 Hz, 1H), 7.71 (d, *J* = 8.7 Hz, 1H), 7.60–7.56 (m, 1H), 5.08–5.02 (m, 6H), 4.66–4.60 (m, 6H), 3.80 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6, 23 °C, δ): 175.4, 155.7, 155.6, 140.1, 136.6, 127.7, 126.2, 125.3, 121.5, 121.2, 120.8, 119.5, 118.5, 54.3, 52.9, 51.6.

HRMS-ESI (m/z) calc'd for $C_{20}H_{22}N_2O_2BF_4^+$ $[M\text{-}BF_4]^+$, 409.1705; found, 409.1706.

Ethyl 2-(4-TEDAphenoxy)benzoate (2.3c)



2.3c, 45%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and ethyl 2-phenoxybenzoate (242 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 40 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). A second purification was performed to eliminate the remaining impurities. The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 245 mg of the desired product **2.3c** as a colorless solid (45%).

NMR Spectroscopy:

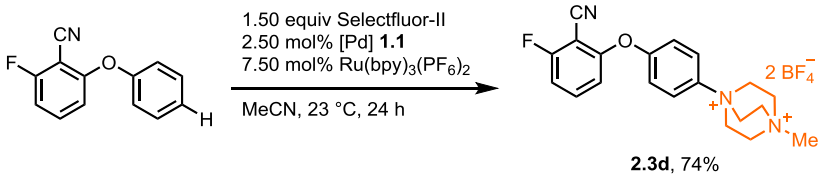
^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.10–8.05 (m, 2H), 8.00 (dd, *J* = 7.8, 1.8 Hz, 1H), 7.72 (ddd, *J* = 8.1, 7.4, 1.8 Hz, 1H), 7.45 (td, *J* = 7.6, 1.1 Hz, 1H), 7.26 (dd, *J* = 8.1,

1.1 Hz, 1H), 7.19–7.13 (m, 2H), 4.85–4.79 (m, 6H), 4.52–4.45 (m, 6H), 4.16 (q, *J* = 7.1 Hz, 2H), 3.72 (s, 3H), 1.12 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 176.2, 165.6, 161.5, 154.1, 135.4, 133.0, 127.0, 125.6, 124.1, 123.0, 118.7, 62.0, 55.6, 54.3, 53.6, 14.2.

HRMS-ESI (m/z) calc'd for $C_{22}H_{28}N_2O_3BF_4^+$ $[M\text{-}BF_4]^+$, 455.2124; found, 455.2119.

2-(4-TEDAphenoxy)-6-fluorobenzonitrile (2.3d)



2.3d, 74%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and 2-Fluoro-6-phenoxybenzonitrile (213 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and transferred to an Erlenmeyer flask. DCM (25 mL) was added, followed by pentane (50 mL), and the mixture was stirred for 5 min at room temperature. The solids were collected by filtration on a glass frit, washed two times with pentane (2 × 2 mL), then two times with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 379 mg of the desired product **2.3d** as an orange solid (74%).

NMR Spectroscopy:

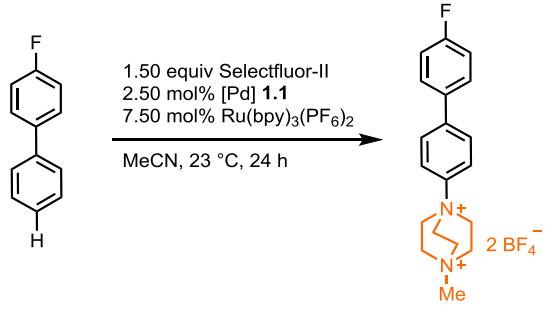
^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.30–8.21 (m, 2H), 7.80 (td, *J* = 8.5, 6.6 Hz, 1H), 7.60–7.52 (m, 2H), 7.29 (td, *J* = 8.7, 0.9 Hz, 1H), 7.03 (dd, *J* = 8.5, 0.9 Hz, 1H), 4.93–4.87 (m, 6H), 4.58–4.50 (m, 4H), 3.76 (s, 3H).

^{13}C NMR (125 MHz, Acetone-d_6, 23 °C, δ): 164.8 (d, *J* = 257.5 Hz), 159.5 (m), 158.2, 137.3 (d, *J* = 10.5 Hz), 124.2, 121.8, 115.8 (m), 112.7 (d, *J* = 19.7 Hz), 111.3, 56.1, 54.6, 53.4.

^{19}F NMR (470 MHz, Acetone-d_6, 23 °C, δ): –107.1, –150.7.

HRMS-ESI (m/z) calc'd for $C_{20}H_{22}N_3OBF_5^+$ $[M\text{-}BF_4]^+$, 426.1770; found, 426.1776.

4-TEDA-4'-fluoro-[1,1'-biphenyl] (2.3e)



2.3e, 93%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and 4-fluoro-1,1'-biphenyl (172 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL),

then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 439 mg of the desired product **2.3e** as a colorless solid (93%).

NMR Spectroscopy:

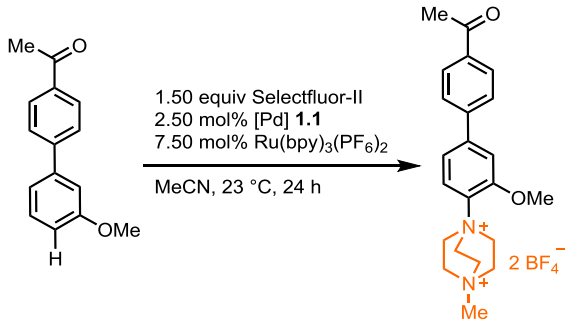
^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.28–8.17 (m, 2H), 8.09–8.01 (m, 2H), 7.90–7.77 (m, 2H), 7.38–7.26 (m, 2H), 5.00–4.87 (m, 6H), 4.63–4.48 (m, 6H), 3.76 (s, 3H).

^{13}C NMR (125 MHz, Acetone-d_6, 23 °C, δ): 164.1 (d, J = 246.5 Hz), 144.47, 143.72, 135.4 (d, J = 3.3 Hz), 130.2 (d, J = 8.4 Hz), 129.9, 122.13, 116.9 (d, J = 21.9 Hz), 55.9, 54.7, 53.4.

^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –115.1, –151.4.

HRMS-ESI (m/z) calc'd for $C_{19}H_{23}N_2BF_5^+$ $[M\text{-}BF_4]^+$, 385.1869; found, 385.1866.

1-(3'-Methoxy-4´-TEDAbiphenyl-4-yl)ethanone (2.3f)



2.3f, 67%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and 1-(3'-methoxy[1,1'-biphenyl]-4-yl)ethan-1-one (226 mg,

1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). A second purification was performed to eliminate the remaining impurities. The resulting pure Ar-TEDA was dried undervacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 354 mg of the desired product **2.3f** as a beige solid (67%).

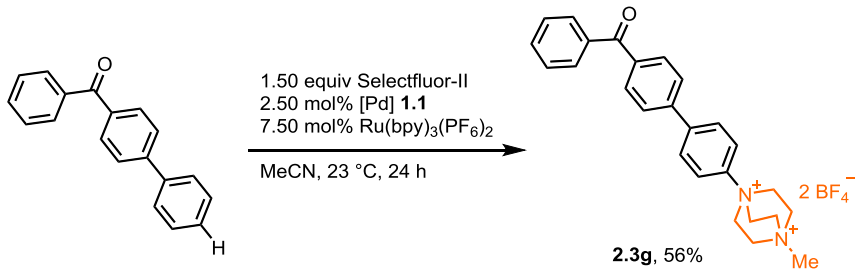
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.16–8.09 (m, 2H), 8.04 (d, *J* = 8.9 Hz, 1H), 7.97–7.90 (m, 2H), 7.82 (d, *J* = 2.1 Hz, 1H), 7.62 (dd, *J* = 8.8, 2.1 Hz, 1H), 5.09–4.95 (m, 6H), 4.60–4.47 (m, 6H), 4.31 (s, 3H), 3.70 (s, 3H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 198.5, 153.2, 145.7, 143.2, 138.3, 129.9, 128.6, 123.2, 123.0, 121.2, 115.00, 57.9, 54.31, 53.8, 27.1.

HRMS-ESI (m/z) calc'd for $C_{22}H_{28}N_2O_2BF_4^+$ $[M\text{-}BF_4]^+$, 439.2174; found, 439.2171.

(4'-TEDA-[1,1'-biphenyl]-4-yl)(phenyl)methanone (2.3g)



To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and 4-benzoylbiphenyl (258 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 310 mg of the desired product **2.3g** as a colorless solid (56%).

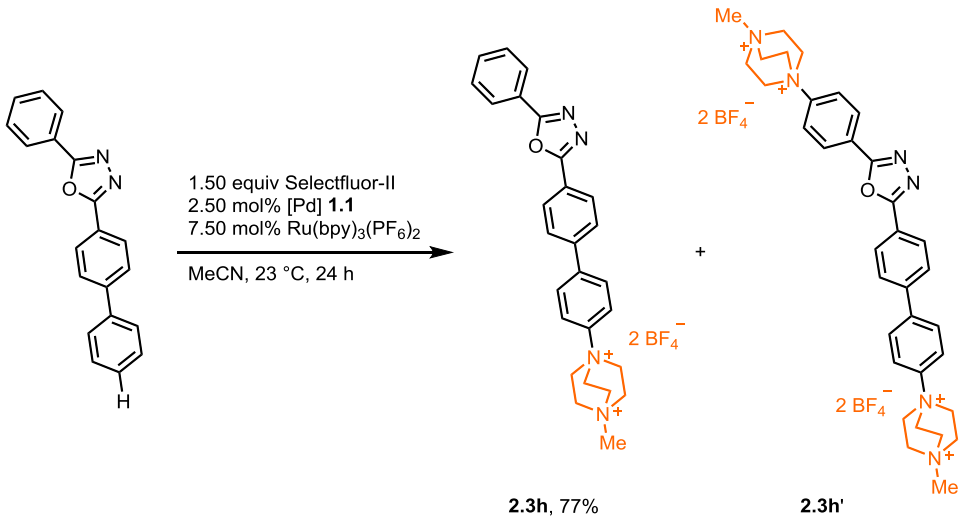
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.31–8.26 (m, 2H), 8.19–8.15 (m, 2H), 7.99–7.96 (m, 2H), 7.95–7.91 (m, 2H), 7.84–7.81 (m, 2H), 7.72–7.68 (m, 1H), 7.63–7.57 (m, 2H), 5.00–4.91 (m, 6H), 4.63–4.45 (m, 6H), 3.78 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6, 23 °C, δ): 195.3, 144.2, 141.5, 141.3, 136.9, 136.9, 132.9, 130.5, 129.6, 128.8, 128.7, 127.3, 121.7, 54.1, 52.8, 51.6.

HRMS-ESI (m/z) calc'd for $C_{26}H_{28}N_2OBF_4^+$ $[M\text{-}BF_4]^+$, 471.2225; found, 471.2222.

2-(4'-TEDA-[1,1'-biphenyl]-4-yl)-5-phenyl-1,3,4-oxadiazole (2.3h)



To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and 2-(4-biphenylyl)-5-phenyl-1,3,4-oxadiazole (298 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). A

second purification was performed to eliminate the remaining impurities. The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 469 mg of the desired product **2.3h** as a colorless solid (77%).[a]

[a]The compound **2.3h** is isolated in mixture with the bis-functionnalized arene **2.3h´**. The ratio **2.3h**/**2.3h´** calculated by ^{1}H-NMR is 85:15.

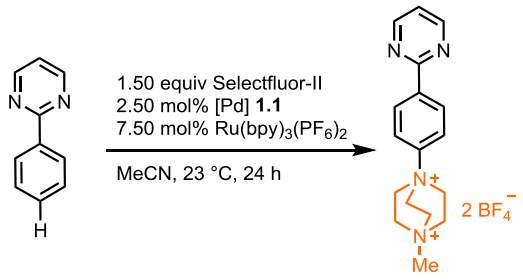
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.34–8.32 (m, 2H), 8.31–8.27 (m, 2H), 8.25–8.17 (m, 4H), 8.07–8.03 (m, 2H), 7.71–7.63 (m, 3H), 5.01–4.92 (m, 6H), 4.63–4.55 (m, 6H), 3.79 (s, 3H).

^{13}C NMR (125 MHz, Acetone-d_6, 23 °C, δ): 164.8, 164.3, 144.8, 142.2, 141.5, 132.4, 129.7, 129.3, 128.5, 128.5, 127.9, 127.1, 124.2, 122.2, 55.0, 53.7, 52.3.

HRMS-ESI (m/z) calc'd for $C_{27}H_{28}N_4OBF_4^+$ $[M\text{-}BF_4]^+$, 511.2287; found, 511.2286.

2-(4-TEDAphenyl)pyrimidine (2.3i)



2.3i, 65%

To a 4 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (8.4 mg, 13 μmol, 2.5 mol%), $Ru(bpy)_3(PF_6)_2$ (34.1 mg, 39.7 μmol, 7.50 mol%), Selectfluor II (254 g, 794 μmol, 1.50 equiv), and 2-phenylpyrimidine (82.7 mg, 529 μmol, 1.00 equiv). Acetonitrile (2.6 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The solvent was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.2 mL) was added to the vial. The resulting

mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (5 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). A second purification was performed to eliminate the remaining impurities. The resulting solid was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 155 mg of the desired product **2.3i** as a colorless solid (65%).

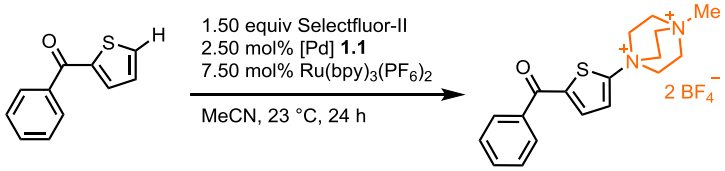
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.96 (d, J = 4.9 Hz, 2H), 8.81–8.70 (m, 2H), 8.37–8.20 (m, 2H), 7.52 (t, J = 4.9 Hz, 1H), 4.98–4.88 (m 6H), 4.62–4.50 (m, 6H), 3.77 (s, 3H).

^{13}C NMR (125 MHz, Acetone-d_6, 23 °C, δ): 162.9, 158.9, 141.6, 136.7, 131.1, 122.1, 121.8, 56.1, 54.8, 53.5.

HRMS-ESI (m/z) calc'd for $C_{17}H_{22}N_4BF_4^+$ $[M\text{-}BF_4]^+$, 369.1868; found, 369.1870.

(5-TEDAthiophen-2-yl)(phenyl)methanone (2.3j)



2.3j, 42%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and 2-benzoylthiophene (231 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with

a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (5 mL) and EtOAc (10 mL) were added to the vial. The precipitate was collected by filtration on a glass frit, washed with EtOAc (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 204 mg of the desired product **2.3j** as a beige solid (42%).

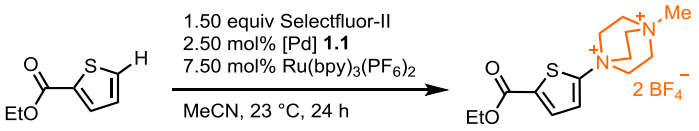
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.00 (d, J = 4.4 Hz, 1H), 7.96–7.91 (m, 2H), 7.86 (d, J = 4.4 Hz, 1H), 7.78–7.71 (m, 1H), 7.68–7.54 (m, 2H), 5.08–4.97 (m, 6H), 4.61–4.52 (m, 6H), 3.77 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6, 23 °C, δ): 186.9, 151.9, 142.2, 135.7, 134.2, 133.6, 129.2, 129.0, 125.0, 56.7, 52.7, 51.7.

HRMS-ESI (m/z) calc'd for $C_{18}H_{22}N_2OSBF_4^+$ $[M\text{-}BF_4]^+$, 401.1476; found, 401.1474.

Ethyl 5-TEDAthiophene-2-carboxylate (2.3k)



2.3k, 47%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and ethyl 2-thiophenecarboxylate (156 mg, 135 μL, 1.00 mmol,

1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (5 mL) and EtOAc (10 mL) were added to the vial. The precipitate was collected by filtration on a glass frit, washed with EtOAc (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). A second purification was performed to eliminate the remaining impurities. The resulting pure Ar-TEDA was dried undervacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 215 mg of the desired product **2.3k** as a beige solid (47%).

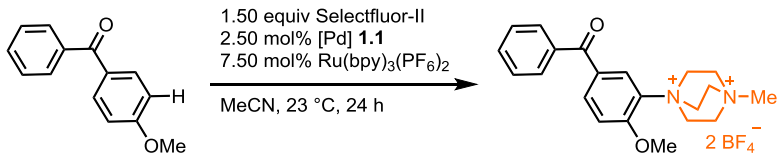
NMR Spectroscopy:

^{1}H NMR (500 MHz, DMSO-d_6, 23 °C, δ): 7.91 (d, J = 4.1 Hz, 1H), 7.84 (d, J = 4.4 Hz, 1H), 4.65–4.49 (m, 6H), 4.36 (q, J = 7.1 Hz, 2H), 4.12–3.98 (m, 6H), 3.38 (s, 3H), 1.31 (t, J = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, DMSO-d_6, 23 °C, δ): δ 160.2, 150.2, 132.7, 132.6, 124.8, 62.2, 56.7, 52.7, 51.7, 14.1.

HRMS-ESI (m/z) calc'd for $C_{14}H_{22}N_2O_2S^{2+}$ $[M]^{2+}/2$, 141.0695; found, 141.0696.

(3-TEDA-4-methoxyphenyl)(phenyl)methanone (2.3l)



2.3l, 57%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and 4-methoxybenzophenone (212 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 294 mg of the desired product **2.3l** as a beige solid (57%).

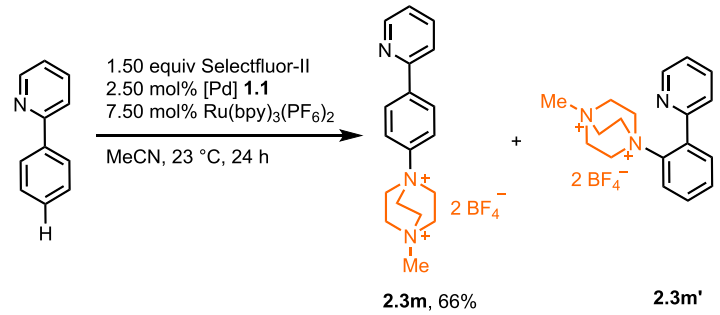
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6), 23 °C, δ 8.30 (d, *J* = 1.9 Hz, 1H), 8.12 (dd, *J* = 8.7, 1.9 Hz, 1H), 7.84– 7.79 (m, 2H), 7.72–7.68 (m, 2H), 7.62–7.55 (m, 2H), 5.10–5.02 (m, 6H), 4.58–4.50 (m, 6H), 4.30 (s, 3H), 3.69 (s, 3H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 194.3, 156.0, 137.6, 136.1, 133.9, 131.8, 130.9, 130.9, 130.7, 129.7, 124.6, 116.2, 58.3, 54.3, 54.2, 54.2, 53.8.

HRMS-ESI (m/z) calc'd for $C_{21}H_{26}N_2O_2BF_4^+$ $[M\text{-}BF_4]^+$, 425.2018; found, 425.2019.

2-(4-TEDAphenyl)pyridine (2.3m)



To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 µmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 µmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and 2-phenylpyridine (155 mg, 143 µL, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). A second purification was performed to eliminate the remaining impurities. The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 302 mg of the desired product **2.3m** as a brown solid (66%)[a].

[a]The compound **2.3m** is isolated in mixture with the isomer **2.3m'**. The ratio **2.3m/2.3m'** calculated by ^{1}H-NMR is 95:5.

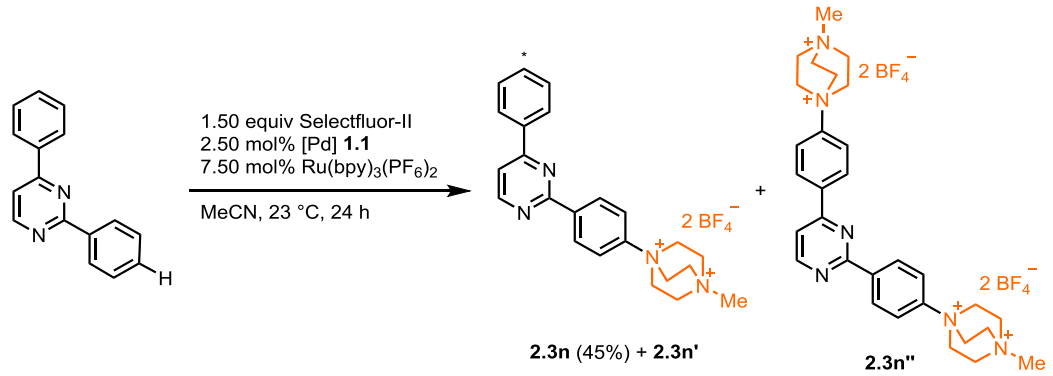
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.74 (ddd, J = 4.8, 1.8, 0.9 Hz, 1H), 8.53–8.43 (m, 2H), 8.29–8.21 (m, 2H), 8.10 (dt, J = 8.0, 1.0 Hz, 1H), 8.00–7.91 (m, 1H), 7.44 (ddd, J = 7.6, 4.8, 1.1 Hz, 1H), 4.97–4.87 (m, 6H), 4.61–4.52 (m, 6H), 3.77 (s, 3H).

^{13}C NMR (125 MHz, DMSO-d_6, 23 °C, δ): 154.1, 150.4, 145.1, 141.4, 138.1, 128.7, 124.3, 121.9, 121.52, 54.5, 53.3, 52.1.

HRMS-ESI (m/z) calc'd for $C_{18}H_{23}N_3BF_4^+$ $[M\text{-}BF_4]^+$, 368.1916; found, 368.1912.

2-(4-TEDAphenyl)-4-phenylpyrimidine (2.3n)



To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and 2,4-diphenylpyrimidine (232 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass

frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). A second purification was performed to eliminate the remaining impurities. The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 320 mg of a mixture of isomers as a colorless solid (60%) that contains the major isomer **2.3n** (45%). The compound **2.3n** contains about 14 % of the mono-functionnalized 2,4-phenylpyrimidine **2.3n´** (other isomer) and 11 % of the compound **2.3n´´** (percentages estimated by ^{1}H-NMR). These compounds were not purged before the methylation step.

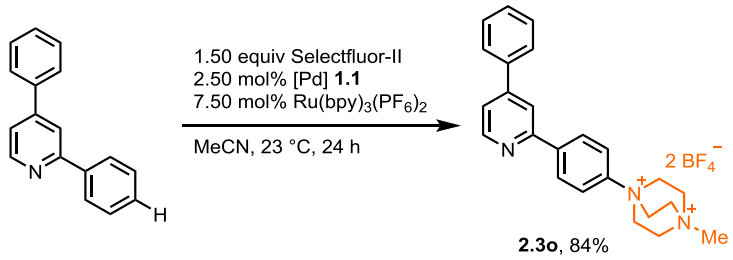
NMR Spectroscopy:

1H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 9.01 (d, J = 5.3 Hz, 1H), 8.94–8.88 (m, 2H), 8.40–8.36 (m, 2H), 8.34–8.31 (m, 2H), 8.05 (d, J = 5.3 Hz, 1H), 7.63–7.59 (m, 3H), 5.02–4.92 (m, 6H), 4.64–4.53 (m, 6H), 3.78 (s, 3H).

^{13}C NMR (125 MHz, CD_3CN , 23 °C, δ): 164.7, 162.4, 159.2, 141.7, 136.9, 133.9, 132.0, 131.0, 129.7, 127.8, 121.3, 116.6, 55.2, 54.0, 53.3.

HRMS-ESI (m/z) calc'd for $C_{23}H_{26}N_4^{2+}$ $[M]^{2+}/2$, 179.1073; found, 179.1074.

2-(4-TEDAphenyl)-4-phenylpyridine (2.3o)



2.3o, 84%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 µmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 µmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and 2,4-diphenylpyridine (231 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with

a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 448 mg of the desired product **2.3o** as a colorless solid (84%).

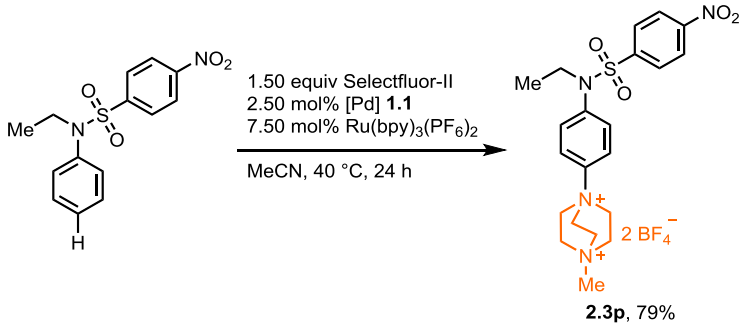
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.80 (br d, *J* = 5.1 Hz, 1H), 8.65–8.59 (m, 2H), 8.39–8.37 (m, 1H), 8.30–8.24 (m, 2H), 7.94–7.88 (m, 2H), 7.75 (dd, *J* = 5.1, 1.7 Hz, 1H), 7.62–7.49 (m, 3H), 5.03–4.92 (m, 6H), 4.65–4.55 (m, 6H), 3.79 (s, 3H).

^{13}C NMR (125 MHz, Acetone-d_6, 23 °C, δ): 155.7, 151.5, 150.4, 145.7, 143.1, 138.8, 130.3, 130.2, 130.1, 128.1, 122.3, 122.0, 119.6, 56.0, 54.8, 53.5.

HRMS-ESI (m/z) calc'd for $C_{24}H_{27}N_3^{2+}$ $[M]^{2+}/2$, 178.6097; found, 178.6098.

***N*-ethyl-4-nitro-N-(4-TEDAphenyl)benzenesulfonamide (2.3p)**



2.3p, 79%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and *N*-ethyl-4-nitro-N-phenylbenzenesulfonamide (306 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (10 mL, c = 0.10 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 40 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 479 mg of the desired product **2.3p** as a colorless solid (79%).

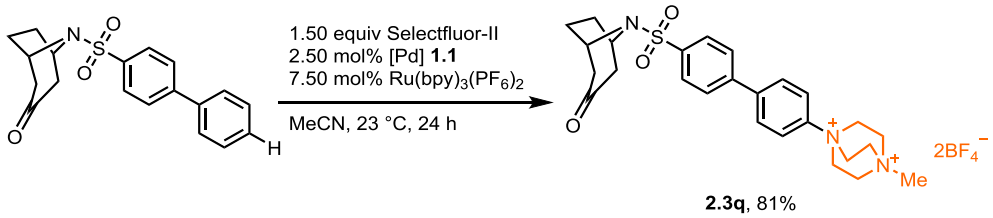
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetonitrile-d_3, 23 °C, δ): 8.44-8.19 (m, 2H), 7.88-7.65(m, 4H), 7.57-7.36 (m, 2H), 4.35-4.30 (m, 6H), 4.06-4.01 (m, 6H) 3.68 (q, *J* = 7.1 Hz, 2H), 3.37 (s, 3H), 1.06 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, Acetonitrile-d_3, 23 °C, δ): 151.2, 143.5, 143.3, 141.8, 131.3, 129.5, 125.1, 122.1, 55.2, 53.9, 53.3, 46.2, 13.7.

HRMS-ESI (m/z) calc'd for $C_{21}H_{28}N_4O_4S^+$ $[M\text{-}BF_4]^+$, 432.1820; found, 432.1821.

***N*-(4-TEDAphenyl-4-sulfonyl)nortropinone (2.3q)**



2.3q, 81%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 mg, 1.50 mmol, 1.50 equiv), and *N*-(Biphenyl-4-sulfonyl)nortropinone (341 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (10.0 mL, c = 0.10 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried undervacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 519 mg of the desired product **2.3q** as a colorless solid (81%).

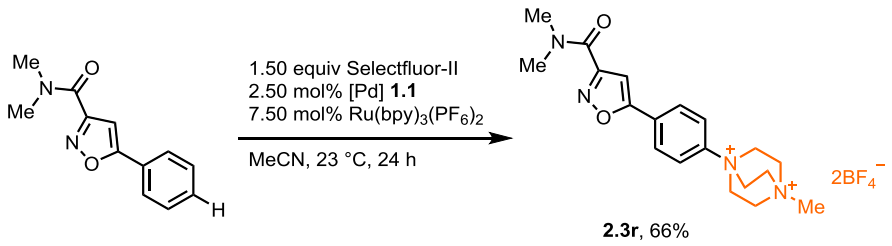
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetonitrile-d_3, 23 °C, δ): 8.13-7.99 (m, 4H), 7.97-7.86 (m, 4H), 4.60-4.48 (m, 2H), 4.38 (t, *J* = 7.4 Hz, 6H), 4.06 (t, *J* = 7.4 Hz, 6H), 3.40 (s, 3H), 2.77 (dd, *J* = 16.6, 4.6 Hz, 2H), 2.44-2.28 (m, 2H), 1.44-1.15 (m, 2H), 0.91 (dd, *J* = 6.6, 2.5 Hz, 3H).

^{13}C NMR (125 MHz, Acetonitrile-d_3, 23 °C, δ): 207.0, 144.2, 143.0, 142.8, 140.6, 130.1, 128.9, 128.6, 121.7, 56.9, 55.2, 54.0, 53.3, 50.5, 29.4.

HRMS-ESI (m/z) calc'd for $C_{26}H_{23}N_3O_3S^+$ $[M\text{-}BF_4]^+$, 467.2231; found, 467.2232.

***N*,*N*-dimethyl-5-(4-TEDAphenyl)isoxazole-3-carboxamide (2.3r)**



To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 mg, 1.50 mmol, 1.50 equiv), and *N*,*N*-dimethyl-5-phenylisoxazole-3-carboxamide (216 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (10.0 mL, c = 0.10 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried undervacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 341 mg of the desired product **2.3r** as a colorless solid (66%).

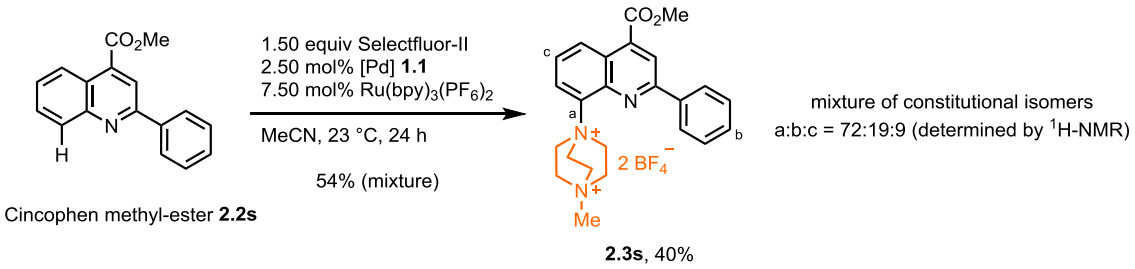
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetonitrile-d_3, 23 °C, δ): 8.29-8.08 (m, 2H), 8.03-7.78 (m, 2H), 7.09 (s, 1H), 4.38-4.33 (m, 6H), 4.07-4.01 (m, 6H), 3.37 (s, 3H), 3.17 (s, 3H), 3.08 (s, 3H).

^{13}C NMR (125 MHz, Acetonitrile-d_3, 23 °C, δ): 206.8, 146.0, 138.8, 136.1, 129.8, 127.8, 127.5, 127.1, 56.1, 50.3, 29.4, 21.2, 14.2.

HRMS-ESI (m/z) calc'd for $C_{19}H_{26}N_4O_2^+$ $[M\text{-}BF_4]^+$, 342.2045; found, 342.2045.

Methyl 8-TEDA-2-phenylquinoline-4-carboxylate (2.3s)



To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and Cincophen methyl-ester (263 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). A second purification was performed to eliminate the remaining impurities. The resulting Ar-TEDA was dried under

vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 309 mg of a mixture of constitutional isomers as a yellow solid (54%) that contains the major isomer **2.3s** (40% yield).

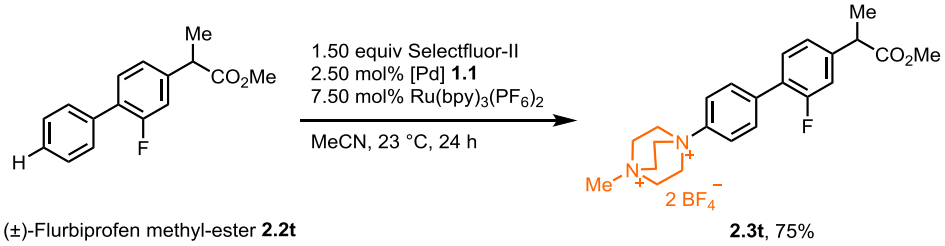
NMR Spectroscopy:

^{1}H NMR (400 MHz, DMSO-d_6, 23 °C, δ): 8.79 (d, J = 8.5 Hz, 1H), 8.71 (s, 1H), 8.39 (d, J = 8.2 Hz, 1H), 8.34–8.26 (m, 2H), 7.98 (t, J = 8.3 Hz, 1H), 7.72–7.65 (m, 3H), 5.04–4.94 (m, 6H), 4.27–4.18 (m, 6H), 4.06 (s, 3H), 3.43 (s, 4H).

^{13}C NMR (101 MHz, acetone-d_6, 23 °C, δ) 167.1, 154.5, 149.9, 146.2, 142.2, 137.9, 131.4, 131.2, 130.5, 129.5, 126.4, 125.1, 122.2, 120.4, 56.0, 54.7, 53.4, 53.3.

HRMS-ESI (m/z) calc'd for $C_{24}H_{27}N_3O_2BF_4^+$ $[M\text{-}BF_4]^+$, 476.2127; found, 476.2130.

(±)-Methyl 2-(4'-TEDA-2-fluoro-[1,1'-biphenyl]-4-yl)propanoate (2.3t)



(±)-Flurbiprofen methyl-ester **2.2t** — **2.3t**, 75%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and (±)-Flurbiprofen methyl-ester (258 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and transferred to an Erlenmeyer flask. DCM (30mL) was added, followed by pentane (60 mL), and the mixture was stirred for 5 min at room temperature. The solids were collected by filtration on a glass frit, washed two times with pentane (2 × 2 mL), then two times with diethyl ether (2 × 2 mL). Recrystallizations in

MeOH afforded the pure Ar-TEDA,[a] subsequently dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 300 mg of the desired product **2.3t** as a colorless solid (75%).

[a]The recrystallization was performed to purge the remaining $TEDA^{2+}$ and $TEDA\text{-}H^{+}$ side-products. No other isomer was eliminated during this process, as the reaction is >98% selective to the para-position of the arene (amination monitored by ^{1}H-NMR).

NMR Spectroscopy:

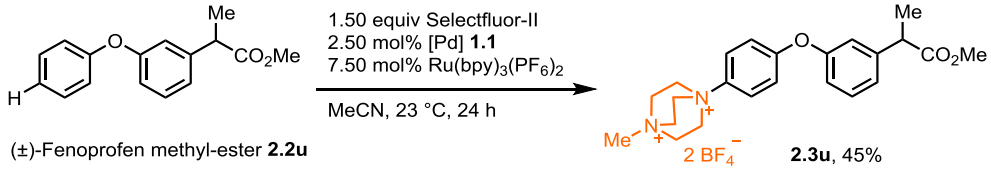
^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.27–8.21 (m, 2H), 8.01–7.91 (m, 2H), 7.59 (t, *J* = 8.1 Hz, 1H), 7.35–7.24 (m, 2H), 5.01–4.88 (m, 6H), 4.63–4.50 (m, 6H), 3.91 (q, *J* = 7.2 Hz, 1H), 3.76 (s, 3H), 3.67 (s, 3H), 1.50 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 175.0, 160.4 (d, *J* = 247.7 Hz), 145.4 (d, *J* = 8.0 Hz), 143.9, 139.7, 132.2 (d, *J* = 3.4 Hz), 131.8 (d, *J* = 3.3 Hz), 125.6 (d, *J* = 13.3 Hz), 125.3 (d, *J* = 3.3 Hz), 121.49, 116.3 (d, *J* = 23.5 Hz), 55.50, 54.32, 53.61, 52.69, 45.46, 18.70.

^{19}F NMR (470 MHz, CD_3CN,, 23 °C, δ): –119.3, –151.4.

HRMS-ESI (m/z) calc'd for $C_{23}H_{29}N_4O_2F^{2+}$ $[M]^{2+}/2$, 192.1101; found, 192.1101.

(±)-Methyl 2-(3-(4-TEDAphenoxy)phenyl)propanoate (2.3u)



(±)-Fenoprofen methyl-ester **2.2u** — **2.3u**, 45%

To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and (±)-Fenoprofen methyl-ester (256 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was

concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and transferred to an Erlenmeyer flask. DCM (50 mL) was added, followed by pentane (100 mL), and the mixture was stirred for 5 min at room temperature. The solids were collected by filtration on a glass frit, washed two times with pentane (2 × 2 mL), then two times with diethyl ether (2 × 2 mL). Recrystallizations in MeOH afforded the pure Ar-TEDA,[a] subsequently dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 251 mg of the desired product **2.3u** as a colorless solid (45%).

[a]The recrystallization was performed to purge the remaining $TEDA^{2+}$ and $TEDA\text{-}H^{+}$ side-products. No other isomer was eliminated during this process, as the reaction is >98% selective to the para-position of the arene (amination monitored by ^{1}H-NMR).

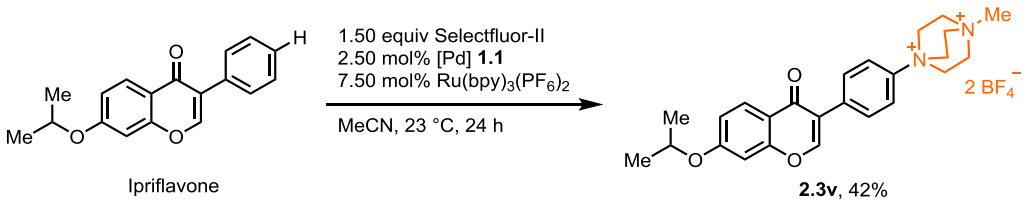
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.17–8.07 (m, 2H), 7.44 (t, *J* = 8.0 Hz, 1H), 7.31–7.25 (m, 2H), 7.24–7.20 (m, 1H), 7.11 (t, *J* = 2.3 Hz, 1H), 7.02 (dd, *J* = 8.0, 2.3 Hz, 1H), 5.93–4.79 (m, 6H), 4.58–4.44 (m, 6H), 3.83 (q, *J* = 7.2 Hz, 1H), 3.74 (s, 3H), 3.63 (s, 3H), 1.45 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 175.2, 160.6, 156.2, 144.7, 131.5, 125.3, 123.2, 120.1, 120.1, 119.5, 55.6, 54.3, 53.6, 52.6, 45.7, 18.8.

HRMS-ESI (m/z) calc'd for $C_{23}H_{30}N_4O_3^{2+}$ $[M]^{2+}/2$, 191.1123; found, 191.1123.

3-(4-TEDAphenyl)-7-isopropoxy-4H-chromen-4-one (2.3v)



To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and Ipriflavone (280 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (5.0 mL, c = 0.20 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 23 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and transferred to an Erlenmeyer flask. DCM (25 mL) was added, followed by pentane (50 mL), and the mixture was stirred for 5 min at room temperature. The solids were collected by filtration on a glass frit, washed two times with pentane (2 × 2 mL), then two times with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL). The resulting pure Ar-TEDA was dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 244 mg of the desired product **2.3v** as a colorless solid (42%).

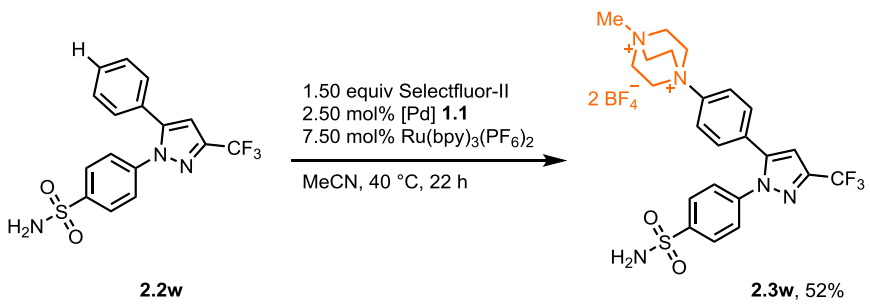
NMR Spectroscopy:

^{1}H NMR (500 MHz, Acetone-d_6, 23 °C, δ): 8.50 (s, 1H), 8.21–8.15 (m, 2H), 8.14–8.09 (m, 1H), 8.06–8.01 (m, 2H), 7.13–7.04 (m, 2H), 4.91 (m, 6H), 4.94–4.87 (d, *J* = 6.0 Hz, 1H), 4.58–4.51 (m, 6H), 3.76 (s, 3H), 2.82 (s, 3H), 1.39 (d, *J* = 6.0 Hz, 6H).

^{13}C NMR (125 MHz, Acetone-d_6, 23 °C, δ): 175.1, 163.9, 159.0, 155.7, 144.7, 137.0, 132.1, 128.3, 123.2, 121.4, 118.8, 116.9, 102.8, 71.8, 56.1, 54.8, 53.5, 22.1.

HRMS-ESI (m/z) calc'd for $C_{25}H_{30}N_2O_3BF_4^+$ $[M\text{-}BF_4]^+$, 493.2280; found, 493.2283.

4-(5-(4-TEDAphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl)benzenesulfonamide (2.3w)



To a 50 mL-round bottomed flask equipped with a magnetic stirring bar were added palladium complex **1.1** (43.3 mg, 68.1 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (176 mg, 204 μmol, 7.50 mol%), Selectfluor II (1.31 g, 4.08 mmol, 1.5 equiv), and **2.2t** (1.00 g, 2.72 mmol, 1.00 equiv). Acetonitrile (11 mL, [**2.2t**] = 0.25 M) was added via syringe to the mixture, the flask was capped with a rubber septum and the reaction mixture was stirred at 40 °C for 22 h. Et_3N (excess, V = 0.8 mL) was added dropwise to the flask at room temperature. The resulting mixture was stirred for 2 min at 23 °C, and DCM (70 mL) was added to the flask. After being stirred for 5 min, the precipitate was collected by filtration on a glass frit. The residue remaining in the reaction flask was dissolved in acetonitrile (10 mL), DCM (50 mL) was then added to the flask, and the resulting precipitate was collected by filtration on the glass frit. The solids were washed with DCM (2 × 15 mL), affording a resin containing the Ar-TEDA, TEDA-H^{2+} and $TEDA^{+}$. A purification by prep-HPLC (YMC-Pack Triart C18 (30x150 mm: 5 μm), MeOH/H_2O = 40:60 (v/v), injection volume V_{inj} = 400 μL (m = 40 mg), flow rate = 30.0 mL/min, 35 °C, retention time; 3.3 min) afforded a solid, which was subsequently stirred in Et_2O for 30 min, filtered on a glass frit and dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 954 mg of the desired product **2.3w** as an orange solid (52%). The resonance of the $–CF_3$ substituent could not be clearly identified in the ^{13}C NMR, but the corresponding ^{19}F NMR resonance was identified.

NMR Spectroscopy:

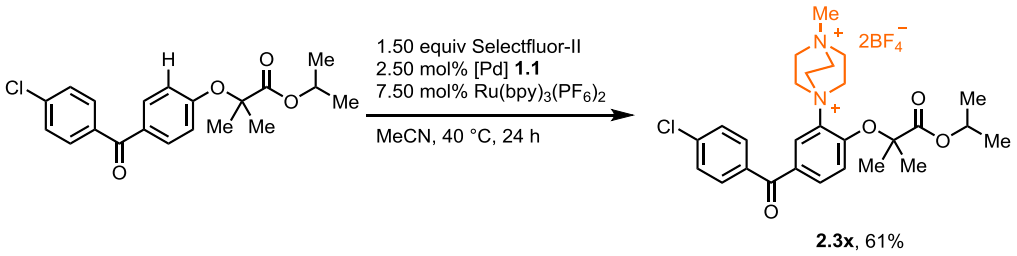
^{1}H NMR (500 MHz, CD_3CN, 23 °C, δ): 7.97–7.88 (m, 2H), 7.81–7.75 (m, 2H), 7.64–7.59 (m, 2H), 7.54–7.47 (m, 2H), 7.11 (s, 1H), 5.79 (br s, 2H), 4.34–4.27 (m, 6H), 4.05–3.97 (m, 6H), 3.36 (s, 3H).

^{13}C NMR (125 MHz, CD_3CN, 23 °C, δ): 145.0, 144.4, 144.1, 143.8, 142.4, 133.1, 132.4, 55.6, 54.3, 53.7.

^{19}F NMR (470 MHz, CD_3CN, 23 °C, δ): –62.9, –151.3.

HRMS-ESI (m/z) calc'd for $C_{23}H_{26}N_5O_2SF_3^{2+}$ $[M]^{2+}/2$, 246.5874; found, 246.5875.

Isopropyl 2-(4-(4-chlorobenzoyl)-2-TEDAphenoxy)-2-methylpropanoate (2.3x)



To a 20 mL-vial equipped with a magnetic stirring bar were added palladium complex **1.1** (15.9 mg, 25.5 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (64.5 mg, 75.0 μmol, 7.50 mol%), Selectfluor II (480 g, 1.50 mmol, 1.50 equiv), and Fenofibrate (361 mg, 1.00 mmol, 1.00 equiv). Acetonitrile (10 mL, c = 0.10 M) was added via syringe to the mixture, the vial was sealed with a Teflon cap, and the reaction mixture was stirred at 40 °C for 24 h. The mixture was concentrated *in vacuo* to half of its original volume, and Et_3N (excess, V = 0.3 mL) was added to the vial. The resulting mixture was stirred for 2 min at 23 °C, and DCM (18 mL) was added to the vial. The precipitate was collected by filtration on a glass frit, washed with DCM (2 × 2 mL), then with diethyl ether (2 × 2 mL). The remaining solid was transferred to a glass vial, and MeOH (10 mL) was added. The vial was sealed with a Teflon cap and the resulting mixture was stirred at 70 °C for 1 h. After cooling to 23 °C, the solids were collected by filtration on a glass frit, washed with MeOH (2 × 2 mL), then with diethyl ether (2 × 2 mL), affording a resin. A purification by prep-HPLC

(YMC-Pack Triart C18 (30x150 mm: 5 µm), MeOH/H_2O = 70:30 (v/v), injection volume V_{inj} = 400 µL (m = 40 mg), flow rate = 42.5 mL/min, 35 °C, retention time; 3.1 min) afforded a solid, which was subsequently stirred in Et_2O for 30 min, filtered on a glass frit and dried under vacuum (P < 0.1 mbar) at 70 °C for 3 hours to afford 403 mg of the desired product **2.3x** as an orange solid (61%).

NMR Spectroscopy:

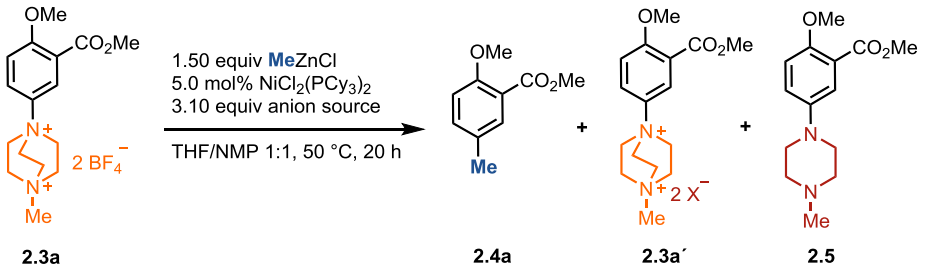
^{1}H NMR (500 MHz, Acetonitrile-d_6, 23 °C, δ): 8.04 (d, *J* = 1.9 Hz, 1H), 7.94 (dd, *J* = 8.8, 1.8 Hz, 1H), 7.82-7.65 (m, 2H), 7.63-7.48 (m, 2H), 7.14 (d, *J* = 8.7 Hz, 1H), 5.01 (p, *J* = 6.2 Hz, 1H), 4.56 (t, *J* = 7.2 Hz, 6H), 4.08 (t, *J* = 7.2 Hz, 6H), 3.35 (s, 3H), 1.88 (s, 6H), 1.15 (d, *J* = 6.2 Hz, 6H).

^{13}C NMR (125 MHz, Acetonitrile-d_6, 23 °C, δ): 192.6, 171.1, 152.0, 135.6, 134.9, 131.9, 131.2, 130.9, 129.3, 124.7, 118.2, 84.2, 70.9, 53.6, 53.5, 53.1, 25.2, 21.0.

HRMS-ESI (m/z) calc'd for $C_{27}H_{25}N_2O_4Cl^+$ $[M\text{-}BF_4]^+$, 486.2274; found, 486.2277.

2.5.6 Optimization of the Negishi Cross-Coupling

Optimization of the halide source



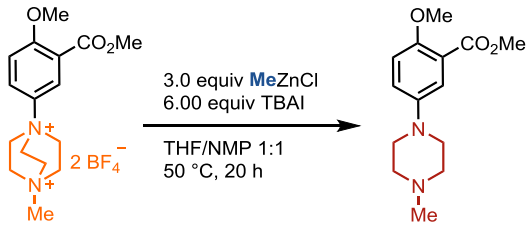
In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (1.7 mg, 2.5 µmol, 5.0 mol%), **2.3a** (23.3 mg, 50.0 µmol, 1.00 equiv), and the anion source (155 µmol, 3.10 equiv). NMP (0.15 mL), THF (0.15 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.15 mL, 0.15 mmol, 1.50 equiv) were then added successively to the reaction mixture. The vial was

sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 48 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, followed by acetonitrile (0.5 mL), and DCM (10 μmol) via syringe. The closed vial was sonicated for 1 minute, and an aliquot of the resulting mixture was taken with a pipette, transferred to an NMR tube and the pipette was rinced with CD_3CN.

anion source	yield (%)[a]		
	2.4a	**2.3a´**	**2.5**
none	8	90	<1
TBAI	9	52	17
TBABr	33	43	10
TBACl	**71**	**8**	**<1**
$TBAPF_6$	14	85	<1
$MgCl_2$	<1	23	<1
LiCl	<5	18	<1

[a]Yield determined by ^{1}H NMR spectroscopy; the resonance at 8.24 ppm (**2.3a´**, aromatic C–H), the resonance at 7.47 ppm (**2.4a**, aromatic C–H), and the resonance at 7.21 ppm (**2.5**, aromatic C–H) were compared to the resonance at 5.48 ppm (DCM).

Characterization of methyl 2-methoxy-5-(4-methylpiperazin-1-yl)benzoate (2.5)



2.3a **2.5**, 6%

A 4 mL vial was charged with **2.3a** (55.0 mg, 120 μmol, 1.00 equiv), and tetra-*n*-butylammonium iodide (266 mg, 720 μmol, 6.00 equiv). NMP (0.55 mL) a solution of MeZnCl in THF (c = 1.0 M, 0.45 mL, 0.35 mmol, 3.0 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and placed on a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C,

MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL), with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with DCM/MeOH 95:5 (v/v) to afford the desired product **2.5** (4 mg, 6%) as a colorless liquid.

R_f = 0.20 (DCM/MeOH 95:5 (v/v)).

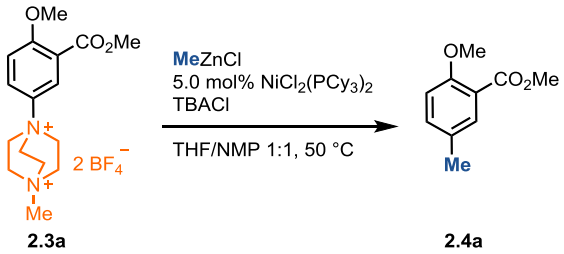
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.38 (d, *J* = 3.2 Hz, 1H), 7.07 (dd, *J* = 9.0, 3.2 Hz, 1H), 6.91 (d, *J* = 9.0 Hz, 1H), 3.89 (s, 3H), 3.85 (s, 3H), 3.18–3.11 (m, 4H), 2.64–2.55 (m, 4H), 2.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$,, 23 °C, δ): 167.0, 153.3, 145.2, 122.1, 120.5, 119.9, 113.6, 56.7, 55.3, 52.2, 50.2, 46.3.

HRMS-ESI (m/z) calc'd for $C_{14}H_{21}N_2O_3^+$ $[M+H]^+$, 265.1549; found, 265.1547.

Optimization of the MeZnCl/TBACl ratio



2.3a **2.4a**

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (1.7 mg, 2.5 μmol, 5.0 mol%), **2.3a** (23.3 mg, 50.0 μmol, 1.00 equiv), and $n$$Bu_4N^+Cl^-$ (TBACl) (various equiv). NMP (0.15 mL), THF (amount needed to obtain c = 0.17 M), and a solution of 1.0 M MeZnCl in THF (various equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block

(50 °C). The reaction mixture was then stirred at 50 °C for 48 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, followed by acetonitrile (0.5 mL), and DCM (10 μmol) via syringe. The closed vial was sonicated for 1 minute, and an aliquot of the resulting mixture was taken with a pipette, transferred to a NMR tube and the pipette was rinced with CD_3CN.

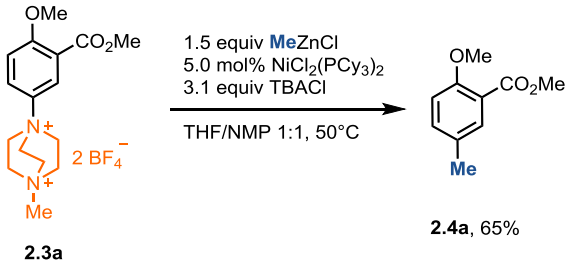
equivalence		yield (%)[a]	
MeZnCl	TBACl	**2.4a**	**2.3a**
1.5	0.75	21	77
1.5	1.6	20	35
1.5	**3.1**	**71**	**8**
1.5	4.5	32	<1
3	1.6	18	29
3	3.2	15	14
3	6.1	68	<1

[a]Yield determined by ^{1}H NMR spectroscopy; the resonance at 8.24 ppm (**2.3a**, aromatic C–H) and the resonance at 7.47 ppm (**2.4a**, aromatic C–H) were compared to the resonance at 5.48 ppm (DCM).

The experiments on the ratio MeZnCl/TBACl revealed that excess of TBACl was required to obtain high yield of the methylarene **2.4a**. With a 1:1 ratio or lower, less than 30% yield was obtained. Starting material accounted for the remainder of the mass balance.

2.5.7 Procedures for the Methylation of Ar-TEDA

Methyl 2-methoxy-5-methylbenzoate (2.4a)



2.3a

2.4a, 65%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3a** (117 mg, 0.250 mmol, 1.00 equiv), and $nBu_4N^+Cl^-$ (TBACl) (215 mg, 0.775 mmol, 3.10 equiv), NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.4a** (28 mg, 62%) as a colorless liquid.

R_f = 0.27 (EtOAc/pentane 1:9 (v/v)).

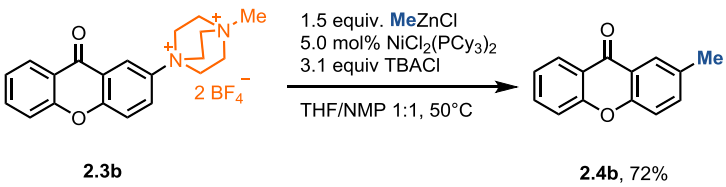
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.61–7.58 (m, 1H), 7.57–7.23 (m, 1H), 6.87 (d, *J* = 8.5 Hz, 1H), 3.88 (s, 3H), 3.87 (s, 3H), 2.29 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 167.0, 157.2, 134.1, 132.1, 129.6, 119.8, 112.2, 56.2, 52.1, 20.4.

HRMS-EI (m/z) calc'd for $C_{10}H_{12}O_3^+$ $[M]^+$, 180.0781; found, 180.0783.

2-Methyl-9*H*-xanthen-9-one (2.4b)



2.3b **2.4b**, 72%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3b** (124 mg, 0.250 mmol, 1.00 equiv), and $nBu_4N^+Cl^-$ (TBACl) (215 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.4b** (38 mg, 72%) as a colorless solid.

R_f = 0.46 (EtOAc/pentane 1:9 (v/v)).

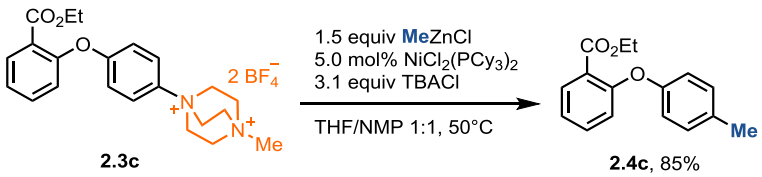
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.24–8.20 (m, 1H), 8.00 (br s, 1H), 7.61–7.56 (m, 1H), 7.42–7.38 (m, 1H), 7.35 (br d, *J* = 8.4 Hz, 1H), 7.28–7.21 (m, 2H), 2.35 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 177.4, 156.3, 154.5, 136.2, 134.7, 133.8, 126.8, 126.1, 123.8, 121.9, 121.6, 118.1, 117.8, 21.0.

HRMS-ESI (m/z) calc'd for $C_{14}H_{11}O_2^+$ $[M+H]^+$, 211.0753; found, 211.0754.

Ethyl 2-(p-tolyloxy)benzoate (2.4c)



In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3c** (136 mg, 0.250 mmol, 1.00 equiv), and $n Bu_4N^+Cl^-$ (TBACl) (215 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.4c** (55 mg, 85%) as a colorless oil.

$\mathbf{R_f}$ = 0.58 (EtOAc/pentane 1:9 (v/v)).

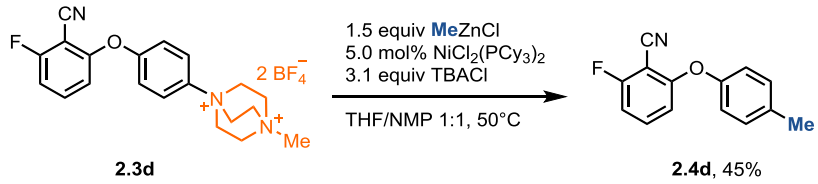
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.89 (dd, *J* = 7.7, 1.8 Hz, 1H), 7.43 (ddd, *J* = 8.3, 7.4, 1.8 Hz, 1H), 7.16 (td, *J* = 7.7, 1.1 Hz, 1H), 7.13 – 7.09 (m, 2H), 6.96 (dd, *J* = 8.3, 1.1 Hz, 1H), 6.88–6.84 (m, 2H), 4.28 (q, *J* = 7.2 Hz, 2H), 2.32 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 166.0, 156.5, 155.5, 133.5, 132.6, 131.8, 130.3, 123.7, 123.3, 120.7, 118.2, 61.2, 20.8, 14.3.

HRMS-ESI (m/z) calc'd for $C_{16}H_{17}O_3^+$ $[M+H]^+$, 257.1172; found, 257.1174.

2-Fluoro-6-(p-tolyloxy)benzonitrile (2.4d)



2.3d **2.4d**, 45%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3d** (128 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+Cl^-$ (TBACl) (215 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:99 (v/v) to afford the desired product **2.4d** (26 mg, 45%) as a colorless solid.

R_f = 0.45 (EtOAc/pentane 1:9 (v/v)).

NMR Spectroscopy:

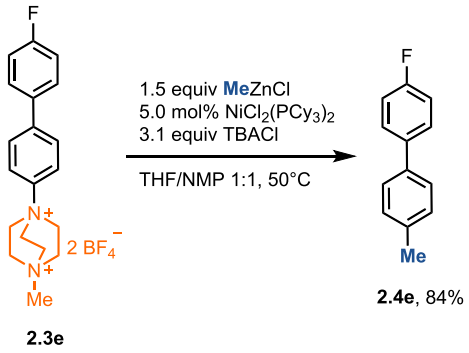
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.39 (td, *J* = 8.5, 6.5 Hz, 1H), 7.24–7.20 (m, 2H), 7.02–6.97 (m, 2H), 6.85 (td, *J* = 8.4, 0.8 Hz, 1H), 6.59–6.55 (m, 1H), 2.37 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 164.2 (d, *J* = 259.3 Hz), 161.7 (d, *J* = 4.3 Hz), 152.2, 135.6, 134.9 (d, *J* = 10.7 Hz), 130.9, 120.5, 111.5 (d, *J* = 3.8 Hz), 111.4, 109.4 (d, *J* = 19.7 Hz), 20.98.

^{19}F NMR (470 MHz, $CDCl_3$, 23 °C, δ): –105.0.

HRMS-ESI (m/z) calc'd for $C_{14}H_{10}ONFNa^+$ $[M+Na]^+$, 250.0638; found, 250.0639.

4-Fluoro-4'-methyl-1,1'-biphenyl (2.4e)



In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3e** (118 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+Cl^-$ (TBACl) (215 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:100 (v/v) to afford the desired product **2.4e** (39 mg, 84%) as a colorless solid.

$\mathbf{R_f}$ = 0.84 (EtOAc/pentane 1:9 (v/v)).

NMR Spectroscopy:

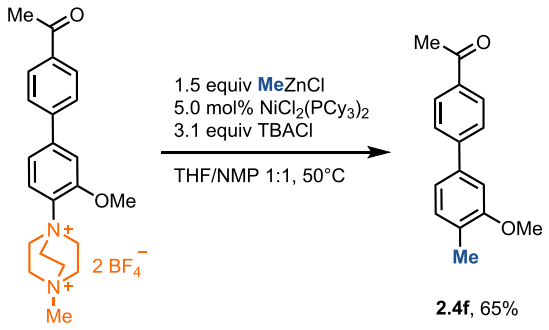
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.58–7.53 (m, 2H), 7.50–7.45 (m, 2H), 7.30–7.25 (m, 1H), 7.17–7.11 (m, 2H), 2.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 162.4 (d, *J* = 245.8 Hz), 137.5, 137.4 (d, *J* = 3.1 Hz), 137.2, 129.7, 128.6 (d, *J* = 8.1 Hz), 127.0, 115.7 (d, *J* = 21.3 Hz), 21.2.

^{19}F NMR (470 MHz, $CDCl_3$, 23 °C, δ): –116.2.

HRMS-EI (m/z) calc'd for $C_{13}H_{11}F^+$ $[M]^+$, 186.0839; found, 186.0841.

1-(3'-Methoxy-4´-methylbiphenyl-4-yl)ethanone (2.4f)



In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3f** (132 mg, 0.250 mmol, 1.00 equiv), and nBu$_4$N$^+$Cl$^-$ (TBACl) (215 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered, and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.4f** (39 mg, 65%) as a colorless solid.

$\mathbf{R}_f$ = 0.3 (EtOAc/pentane 1:9 (v/v)).

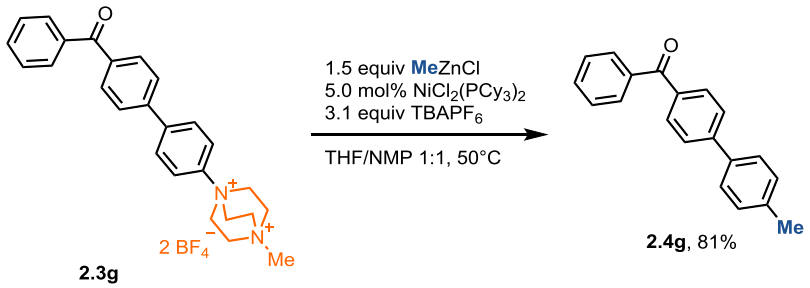
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.06–7.99 (m, 2H), 7.70–7.66 (m, 2H), 7.23 (br d, *J* = 7.6 Hz, 1H), 7.13 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.07 (br d, *J* = 1.7 Hz, 1H), 3.92 (s, 3H), 2.64 (s, 3H), 2.28 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 197.9, 158.3, 146.2, 139.0, 135.8, 131.2, 129.0, 127.2, 127.2, 119.4, 109.0, 55.5, 26.8, 16.2.

HRMS-ESI (m/z) calc'd for $C_{16}H_{16}O_2Na^+$ $[M+Na]^+$, 263.1042; found, 263.1044.

(4'-Methyl-[1,1'-biphenyl]-4-yl)(phenyl)methanone (2.4g)



In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3g** (140 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+PF_6^-$ ($TBAPF_6$) (300 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by

flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.4g** (55 mg, 81%) as a colorless solid.

$\mathbf{R_f}$ = 0.49 (EtOAc/pentane 1:9 (v/v)).

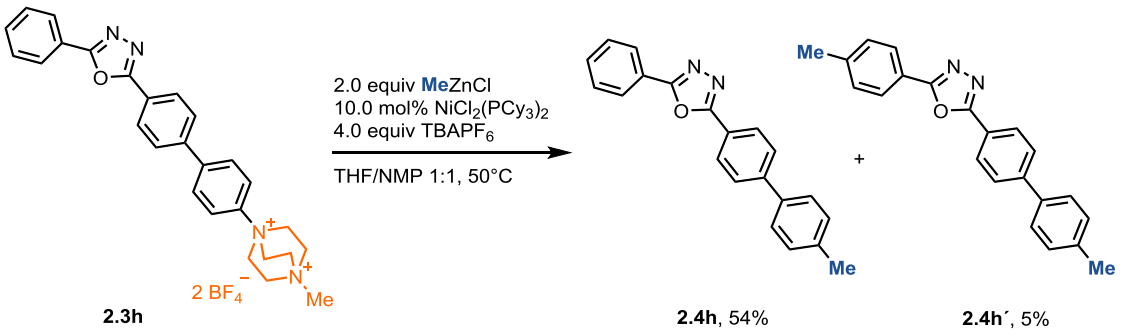
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.91–7.86 (m, 2H), 7.86–7.82 (m, 2H), 7.72–7.67 (m, 2H), 7.62–7.58 (m, 1H), 7.57–7.54 (m, 2H), 7.53–7.48 (m, 2H), 7.31–7.28 (m, 2H), 2.42 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 196.5, 145.3, 138.3, 137.98, 137.2, 136.1, 132.5, 130.9, 130.1, 129.9, 128.4, 127.3, 126.9, 21.3.

HRMS-ESI (m/z) calc'd for $C_{20}H_{17}O^+$ $[M+H]^+$, 273.1274; found, 273.1275.

2-(4'-Methyl-[1,1'-biphenyl]-4-yl)-5-phenyl-1,3,4-oxadiazole (2.4h)



2.3h **2.4h**, 54% **2.4h´**, 5%

In an anhydrous, nitrogen-filled glovebox, a 4 mL-vial was charged with $Ni(PCy_3)_2Cl_2$ (17.2 mg, 25.0 μmol, 10.0 mol%), **2.3h** (150 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+PF_6^-$ ($TBAPF_6$) (387 mg, 1.00 mmol, 4.00 equiv). NMP (0.75 mL), THF (0.25 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.50 mL, 0.50 mmol, 2.0 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in*

vacuo, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford a mixture of products **2.4h** and **2.4h´** (48 mg) in a 88:12 ratio (determined by ^{1}H-NMR). Further purification by prep-HPLC (YMC-Pack Triart C18 (30x150 mm: 5 μm), MeCN/H_2O = 90:10 (v/v), injection volume V_{inj} = 600 μL (m = 6 mg), flow rate = 42.5 mL/min, 35 °C, retention time; 4.45 min (**2.4h**), 5.22 min (**2.4h´**) provided the title compound **2.4h** (40 mg, 54%) and **2.4h´** (4 mg, 5%).

The following data was obtained for the mixture:

R_f = 0.28 (EtOAc/pentane 1:9 (v/v)).

The following data were obtained for the pure products:

2-(4'-Methyl-[1,1'-biphenyl]-4-yl)-5-phenyl-1,3,4-oxadiazole (**2.4h**)

NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.22–8.19 (m, 2H), 8.18–8.14 (m, 2H), 7.78–7.73 (m, 2H), 7.60–7.53 (m, 5H), 7.30 (d, *J* = 7.8 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 164.7, 164.6, 144.5, 138.3, 137.0, 131.8, 129.8, 129.2, 127.5, 127.5, 127.1, 127.0, 124.1, 122.4, 21.3.

HRMS-EI (m/z) calc'd for $C_{21}H_{16}N_2O^+$ $[M]^+$, 312.1257; found, 312.1259.

2-(4'-methyl-[1,1'-biphenyl]-4-yl)-5-(p-tolyl)-1,3,4-oxadiazole (**2.4h´**)

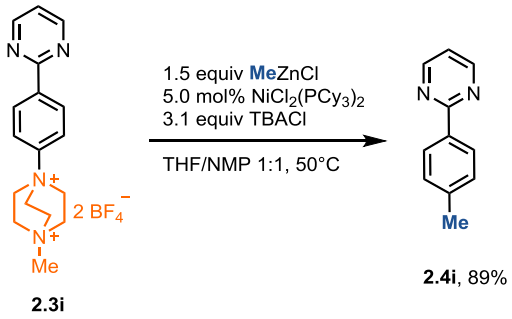
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.25–8.14 (m, 2H), 8.09–8.01 (m, 2H), 7.78–7.72 (m, 2H), 7.59–7.55 (m, 2H), 7.37–7.33 (m, 2H), 7.31–7.28 (m, 2H), 2.45 (s, 1H), 2.42 (s, 2H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 164.7, 164.3, 144.3, 142.3, 138.2, 137.0, 129.8, 129.7, 127.5, 127.3, 127.0, 126.9, 122.5, 121.2, 21.7, 21.2.

HRMS-ESI (m/z) calc'd for $C_{22}H_{18}N_2ONa^+$ $[M+Na]^+$, 349.1311; found, 349.1312.

2-(p-Tolyl)pyrimidine (2.4i)



2.3i

2.4i, 89%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3i** (114 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+Cl^-$ (TBACl) (215 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.4i** (38 mg, 89%) as a beige solid

$\mathbf{R_f}$ = 0.3 (EtOAc/pentane 1:9 (v/v)).

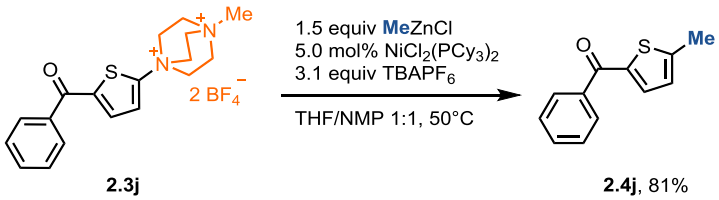
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.77 (d, *J* = 4.8 Hz, 2H), 8.36–8.32 (m, 2H), 7.32–7.28 (m, 2H), 7.12 (t, *J* = 4.8 Hz, 1H), 2.42 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 164.9, 157.3, 141.1, 135.0, 129.5, 128.2, 118.9, 21.6.

HRMS-EI (m/z) calc'd for $C_{11}H_{10}N_2^+$ $[M]^+$, 170.0838; found, 170.0838.

5-Methylthiophen-2-yl)(phenyl)methanone (2.4j)



2.3j **2.4j**, 81%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3j** (122 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+PF_6^-$ ($TBAPF_6$) (300 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:99 (v/v) to afford the desired product **2.4j** (41 mg, 81%) as a colorless liquid.

R_f = 0.5 (EtOAc/pentane 1:9 (v/v)).

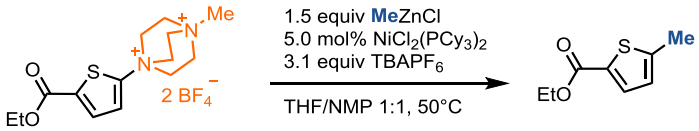
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.85–7.80 (m, 2H), 7.58–7.54 (m, 1H), 7.50–7.44 (m, 3H), 6.84–6.81 (m, 1H), 2.57 (br d, *J* = 1.0 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 188.0, 150.5, 141.6, 138.4, 135.8, 132.1, 129.1, 128.4, 126.8, 16.2.

HRMS-EI (m/z) calc'd for $C_{12}H_{10}OS^+$ $[M]^+$, 202.0447; found, 202.0449.

(5-Methylthiophen-2-yl)(phenyl)methanone (2.4k)



2.3k **2.4k**, 63%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3k** (114 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+PF_6^-$ ($TBAPF_6$) (300 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:99 (v/v) to afford the desired product **2.4k** (27 mg, 63%) as a colorless liquid.

$\mathbf{R_f}$ = 0.68 (EtOAc/pentane 1:9 (v/v)).

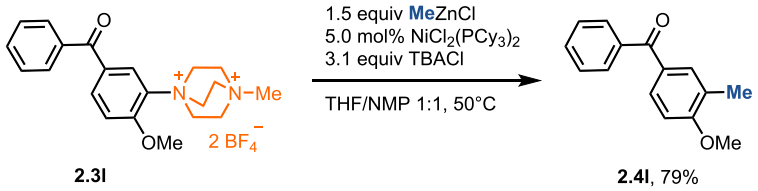
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.60 (d, *J* = 3.7 Hz, 1H), 6.75 (dq, *J* = 3.7, 1.1 Hz, 1H), 4.32 (q, *J* = 7.1 Hz, 2H), 2.51 (d, *J* = 1.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 162.4, 147.7, 133.8, 131.5, 126.4, 61.0, 15.9, 14.5.

HRMS-ESI (m/z) calc'd for $C_{12}H_{10}O_2SNa^+$ $[M+Na]^+$, 193.0294; found, 193.0293.

(4-Methoxy-3-methylphenyl)(phenyl)methanone (2.4l)



2.3l **2.4l**, 79%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3l** (132 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+Cl^-$ (TBACl) (215 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.4l** (45 mg, 79%) as a colorless oil.

$\mathbf{R_f}$ = 0.35 (EtOAc/pentane 1:9 (v/v)).

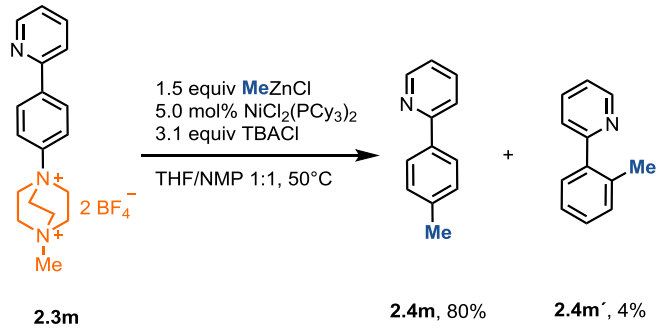
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.78–7.73 (m, 2H), 7.70–7.66 (m, 2H), 7.59–7.53 (m, 1H), 7.49–7.44 (m, 2H), 6.86 (d, *J* = 8.3 Hz, 1H), 3.90 (s, 3H), 2.25 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 195.9, 161.6, 138.6, 132.8, 131.8, 130.7, 129.8, 129.7, 128.2, 126.8, 109.1, 55.6, 16.3.

HRMS-ESI (m/z) calc'd for $C_{15}H_{15}O_2^+$ $[M+H]^+$, 227.1066; found, 227.1066.

2-(*p*-Tolyl)pyridine (2.4m)



2.3m **2.4m**, 80% **2.4m´**, 4%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3m** (114 mg, 0.250 mmol, 1.00 equiv), and nBu$_4$N$^+$Cl$^-$ (TBACl) (215 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash

column chromatography on silica gel eluting with EtOAc/pentane 1:99 (v/v) to afford a mixture of products **2.4m** and **2.4m´** (39 mg) in a 94:6 ratio. Further purification by prep-HPLC (YMC-Pack Triart C18 (30x150 mm: 5 µm), MeOH/H_2O (0.1% trifluoroacetic acid) = 40:60 (v/v), injection volume V_{inj} = 500 µL (m = 10 mg), flow rate = 42.5 mL/min, 35 °C, retention time; 4.08 min (**2.4m´**), 4.82 min (**2.4m**)) provided the title compound **2.4m** (34 mg, 80%) and **2.4m´** (2 mg, 4%) as a colorless liquids.

The following data was obtained for the mixture:

R_f = 0.44 (EtOAc/pentane 1:9 (v/v)).

The following data were obtained for the pure products:

2-(p-tolyl)pyridine (**2.4m**):

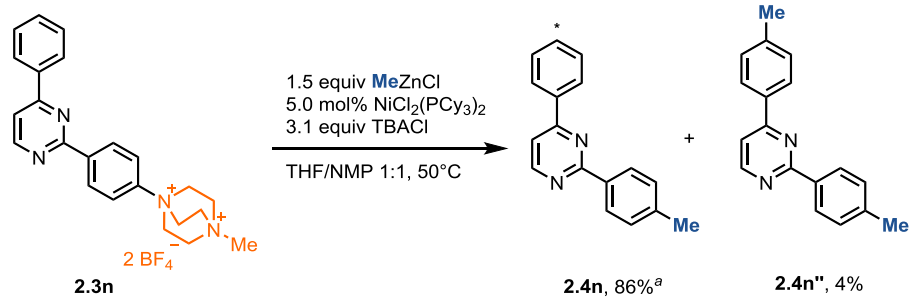
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.70–8.66 (m, 1H), 7.93–7.88 (m, 2H), 7.74–7.68 (m, 2H), 7.31–7.27 (m, 2H), 7.19 (ddd, *J* = 6.3, 4.8, 2.2 Hz, 1H), 2.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 157.6, 149.7, 139.0, 136.8, 136.7, 129.6, 126.9, 121.9, 120.3, 21.4.

HRMS-EI (m/z) calc'd for $C_{12}H_{11}N^+$ $[M]^+$, 169.0886; found, 169.0886.

4-Phenyl-2-(*p*-tolyl)pyrimidine (2.4n)



2.3n **2.4n**, 86%[a] **2.4n"**, 4%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 µmol, 5.0 mol%), **2.3n** (133 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+Cl^-$ (TBACl) (215 mg,

0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford a mixture of products **2.4n** and **2.4n´´** (60 mg) in a 97:3 ratio (determined by ^{1}H-NMR). Further purification by prep-HPLC (YMC-Pack Triart C18 (30x150 mm: 5 μm), MeCN/H_2O = 90:10 (v/v), injection volume V_{inj} = 600 μL (m = 6 mg), flow rate = 42.5 mL/min, 35 °C, retention time; 4.34 min (**2.4n**), 5.20 min (**2.4n´´**)) provided the title compounds **2.4n** (53 mg, 86%)[a] and **2.4n´´** (3 mg, 4%) as a colorless liquids.

[a]the compound **2.4n** contains 5% of the mono-methylated 2,4-phenylpyridine **2.4n´** (other isomer, measured by ^{1}H-NMR).

The following data was obtained for the mixture:

R_f = 0.43 (EtOAc/pentane 1:9 (v/v)).

The following data were obtained for the pure products:

4-Phenyl-2-(p-tolyl)pyrimidine (**2.4n**)

NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.82 (d, *J* = 5.3 Hz, 1H), 8.50–8.46 (m, 2H), 8.26–8.22 (m, 2H), 7.58 (d, *J* = 5.3 Hz, 1H), 7.56–7.49 (m, 3H), 7.36–7.30 (m, 2H), 2.45 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 164.8, 163.9, 157.9, 141.1, 137.2, 135.3, 131.0, 129.4, 129.0, 128.4, 127.3, 114.4, 21.7.

HRMS-EI (m/z) calc'd for $C_{17}H_{14}N_2^+$ $[M]^+$, 246.1151; found, 246.1153.

2,4-di-*p*-tolylpyrimidine (**2.4n´**)

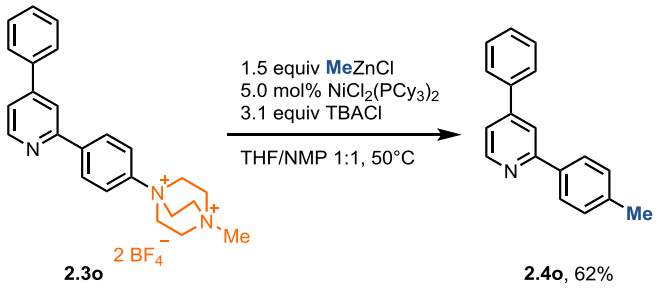
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.79 (d, *J* = 5.3 Hz, 1H), 8.49–8.43 (m, 2H), 8.17–8.08 (m, 2H), 7.55 (d, *J* = 5.3 Hz, 1H), 7.36–7.30 (m, 4H), 2.45 (s, 3H), 2.44 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$, 23 °C, δ): 164.7, 163.9, 157.8, 141.4, 141.0, 135.4, 134.4, 129.8, 129.4, 128.4, 127.3, 114.1, 21.7, 21.6.

HRMS-ESI (m/z) calc'd for $C_{18}H_{17}N_2^+$ $[M+H]^+$, 261.1386; found, 261.1388.

4-Phenyl-2-(*p*-tolyl)pyridine (2.4o)



2.3o **2.4o**, 62%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3o** (133 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+Cl^-$ (TBACl) (215 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating

block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.4o** (32 mg, 62%) as a pale yellow liquid.

R_f = 0.36 (EtOAc/pentane 1:9 (v/v)).

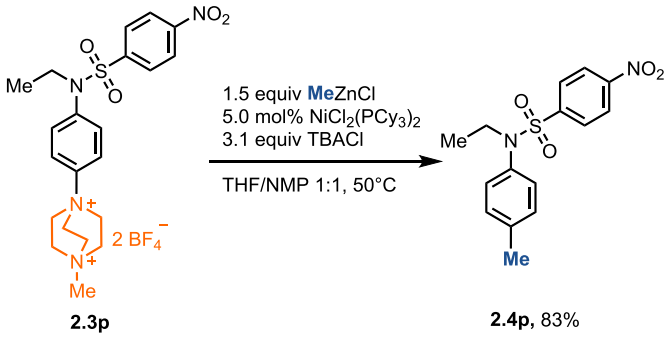
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.72 (dd, *J* = 5.2, 0.8 Hz, 1H), 7.99–7.93 (m, 2H), 7.91 (dd, *J* = 1.7, 0.8 Hz, 1H), 7.73–7.68 (m, 2H), 7.55–7.49 (m, 2H), 7.49–7.44 (m, 1H), 7.42 (dd, *J* = 5.2, 1.7 Hz, 1H), 7.34–7.29 (m, 2H), 2.43 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 158.2, 150.2, 149.4, 139.2, 138.8, 136.9, 129.7, 129.3, 129.1, 127.2, 127.0, 120.1, 118.6, 21.4.

HRMS-EI (m/z) calc'd for $C_{18}H_{15}N^+$ $[M]^+$, 243.1203; found, 245.1199.

***N*-ethyl-4-nitro-*N*-(*p*-tolyl)benzenesulfonamide (2.4p)**



In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3p** (152 mg, 0.250 mmol, 1.00 equiv), and nBu$_4$N$^+$Cl$^-$ (TBACl) (215 mg,

0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:99 (v/v) to afford the desired product **2.4p** (66.4 mg, 83%) as a colorless solid.

R_f = 0.61 (EtOAc/pentane 1:9 (v/v)).

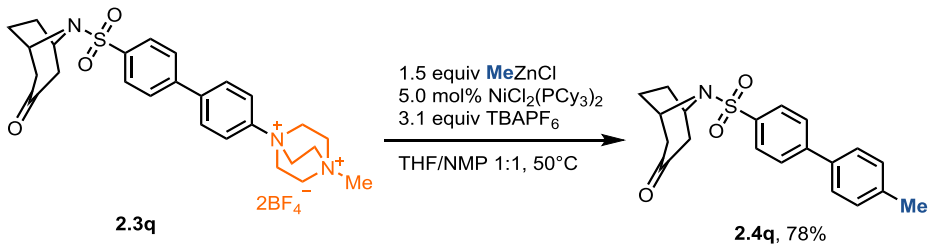
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.33-8.22 (m, 2H), 7.95-7.69 (m, 2H), 7.16–7.05 (m, 2H), 6.96–6.77 (m, 2H), 3.63 (q, *J* = 7.1 Hz, 2H), 2.36 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 149.9, 144.4, 138.6, 135.1, 130.0, 128.7, 128.6, 124.0, 46.1, 21.1, 14.1.

HRMS-EI (m/z) calc'd for $C_{15}H_{16}N_2O_4SNa^+$ $[M+Na]^+$, 343.0723; found, 343.0723.

8-((4'-methyl-[1,1'-biphenyl]-4-yl)sulfonyl)-8-azabicyclo[3.2.1]octan-3-one (2.4q)



2.3q **2.4q**, 78%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3q** (160 mg, 0.250 mmol, 1.00 equiv), and $n Bu_4N^+PF_6^-$ ($TBAPF_6$) (300 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:99 (v/v) to afford the desired product **2.4q** (69 mg, 81%) as a colorless liquid.

R_f = 0.5 (EtOAc/pentane 1:9 (v/v)).

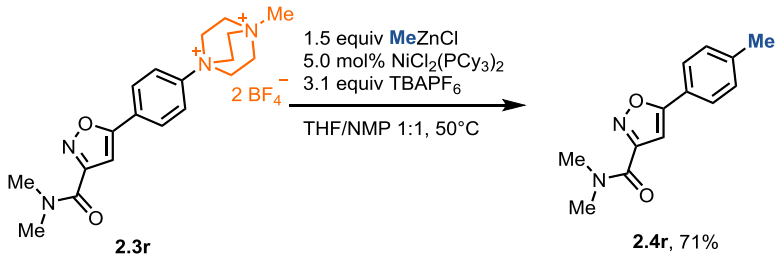
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.04-7.89 (m, 2H), 7.81-7.64 (m, 2H), 7.63–7.45 (m, 2H), 7.36–7.27 (m, 2H), 4.55 (tt, *J* = 4.7, 2.3 Hz, 2H), 2.93-2.72 (m, 2H), 2.41 (s, 3H), 2.40 (d, *J* = 6.3 Hz, 2H), 2.37 (d, *J* = 1.7 Hz, 2H), 1.86-1.72 (m, 2H) , 1.62 (t, *J* = 7.3 Hz, 2H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 188.0, 150.5, 141.6, 138.4, 135.8, 132.1, 129.1, 128.4, 126.8, 16.2.

HRMS-EI (m/z) calc'd for $C_{20}H2_1NO_3SNa^+$ $[M+Na]^+$, 378.1134; found, 378.1134.

***N*,*N*-dimethyl-5-(*p*-tolyl)isoxazole-3-carboxamide (2.4r)**



In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3r** (122 mg, 0.250 mmol, 1.00 equiv), and $n Bu_4N^+PF_6^-$ ($TBAPF_6$) (300 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:99 (v/v) to afford the desired product **2.4r** (41 mg, 81%) as a colorless liquid.

R_f = 0.5 (EtOAc/pentane 1:9 (v/v)).

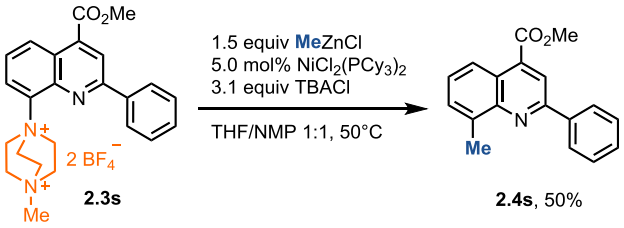
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.73–7.64 (m, 2H), 7.36-7.27 (m, 2H), 6.77 (s, 1H), 3.33 (s, 3H), 3.15 (s, 3H), 2.41 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 170.3, 161.1, 159.4, 141.0, 129.8, 125.9, 124.1, 100.1, 38.8, 36.0, 21.5.

HRMS-EI (m/z) calc'd for $C_{13}H_{14}N_2O_2Na^+$ $[M+Na]^+$, 253.0947; found, 253.0947.

Methyl 8-methyl-2-phenylquinoline-4-carboxylate (2.4s)



In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), Ar-TEDAs mixture (141 mg, 0.250 mmol, 1.00 equiv) including **2.3s** (72 mol%), and nBu$_4$N$^+$Cl$^-$ (215.4 mg, 0.77 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.375 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.375 mL, 0.37 mmol, 1.5 equiv) were then added to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23°C, the reaction was quenched by addition of MeOH (0.1 mL), the volatiles but the NMP were evaporated on a rotary evaporator, and the resulting mixture dissolved in MTBE (20 mL). Transferred to a separatory funnel, the organic layer was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with MTBE/pentane 2:98 (v/v) to afford the desired product **2.4s** (34 mg, 68%) as a colorless solid.

R$_f$ = 0.54 (EtOAc/pentane 1:9 (v/v)).

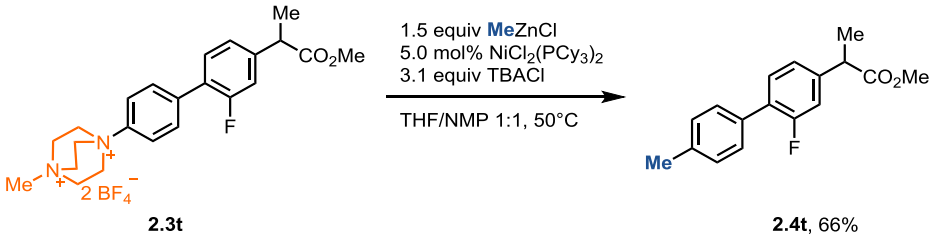
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.58–8.52 (br d, J = 8.6 Hz, 1H), 8.40 (s, 1H), 8.32–8.26 (m, 2H), 7.63–7.59 (m, 1H), 7.58–7.46 (m, 4H), 4.07 (s, 3H), 2.92 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 167.3, 154.8, 148.2, 139.1, 138.2, 136.0, 130.1, 129.7, 129.0, 127.6, 127.5, 124.0, 123.3, 119.5, 52.8, 18.6.

HRMS-ESI (m/z) calc'd for $C_{18}H_{16}N_2O^+$ $[M+H]^+$, 278.1175; found, 278.1176.

(±)-4´-Methyl-flurbiprofen methyl-ester (2.4t)



2.3t **2.4t**, 66%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3t** (140 mg, 0.250 mmol, 1.00 equiv), and nBu$_4$N$^+$Cl$^-$ (215.4 mg, 0.77 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:100 (v/v) to afford the desired product **2.4t** (45 mg, 66%) as a colorless liquid.

$\mathbf{R_f}$ = 0.52 (EtOAc/pentane 1:9 (v/v)).

NMR Spectroscopy:

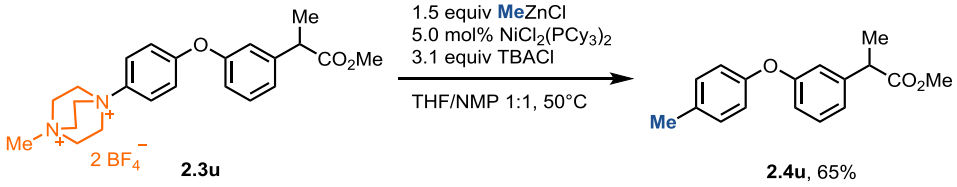
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.46–7.41 (m, 2H), 7.38 (t, J = 8.0 Hz, 1H), 7.27–7.23 (m, 2H), 7.17–7.09 (m, 2H), 3.76 (q, J = 7.2 Hz, 1H), 3.70 (s, 3H), 2.40 (s, 3H), 1.54 (d, J = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 174.6, 159.9 (d, *J* = 249.3 Hz), 141.6 (d, *J* = 8.0 Hz),137.6, 132.7, 130.8 (d, *J* = 4.4 Hz), 129.3, 128.9 (d, *J* = 3.2 Hz), 128.0 (d, *J* = 14.0 Hz), 123.6 (d, *J* = 3.5 Hz), 115.33 (d, *J* = 23.8 Hz), 52.4, 45.1, 21.3, 18.6.

^{19}F NMR (470 MHz, $CDCl_3$, 23 °C, δ): –117.6.

HRMS-EI (m/z) calc'd for $C_{17}H_{17}O_2F^+$ $[M]^+$, 272.1207; found, 272.1205.

(±)-Methyl 2-(3-(*p*-tolyloxy)phenyl)propanoate (2.4u)



In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3u** (139 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+Cl^-$ (215.4 mg, 0.77 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:99 (v/v) to afford the desired product **2.4u** (44 mg, 65%) as a colorless liquid.

$\mathbf{R_f}$ = 0.54 (EtOAc/pentane 1:9 (v/v)).

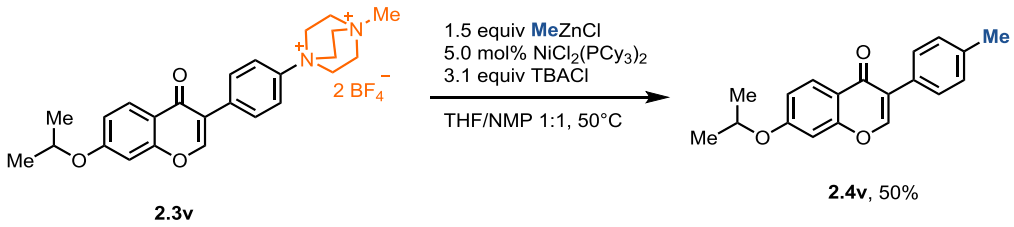
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.31–7.27 (m, 1H), 7.20–7.13 (m, 2H), 7.05–7.01 (m, 1H), 6.99–6.97 (m, 1H), 6.97–6.91 (m, 2H), 6.87 (ddd, *J* = 8.2, 2.5, 1.0 Hz, 1H), 3.72 (q, *J* = 7.2 Hz, 1H), 3.69 (s, 3H), 2.37 (s, 3H), 1.51 (d, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 174.8, 158.1, 154.6, 142.5, 133.2, 130.4, 129.9, 122.0, 119.3, 117.7, 116.9, 52.2, 45.4, 20.9, 18.7.

HRMS-EI (m/z) calc'd for $C_{17}H_{18}O_3^+$ $[M]^+$, 270.1250; found, 270.1252.

7-Isopropoxy-3-(p-tolyl)-4H-chromen-4-one (2.4v)



2.3v **2.4v**, 50%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3v** (145 mg, 0.250 mmol, 1.00 equiv) and $n$$Bu_4N^+Cl^-$ (215.4 mg, 0.77 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.37 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.37 mL, 0.37 mmol, 1.5 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL)and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:9 (v/v) to afford the desired product **2.4v** (37 mg, 50%) as a colorless solid.

$\mathbf{R}_f$ = 0.31 (EtOAc/pentane 1:9 (v/v)).

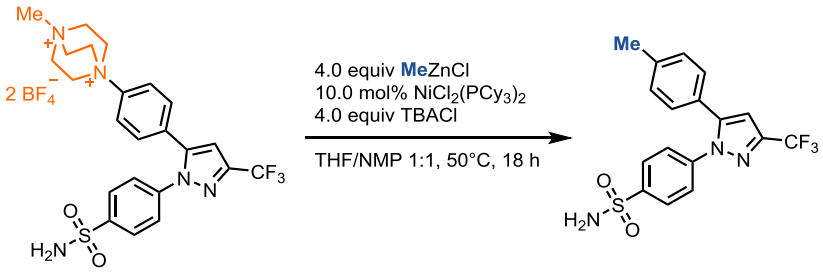
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 8.20 (dd, *J* = 9.0, 1.1 Hz, 1H), 7.92 (d, *J* = 1.1 Hz, 1H), 7.49–7.43 (m, 2H), 7.29–7.21 (m, 2H), 6.95 (ddd, *J* = 9.0, 2.4, 1.0 Hz, 1H), 6.86–6.81 (m, 1H), 4.67 (hept, *J* = 6.0, 1H), 2.39 (s, 3H), 1.43–1.39 (m, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 175.9, 162.5, 158.1, 152.4, 138.0, 129.3, 129.2, 129.0, 128.0, 125.3, 118.3, 115.6, 101.7, 70.9, 22.0, 21.4.

HRMS-ESI (m/z) calc'd for $C_{19}H_{19}O_3^+$ $[M+H]^+$, 295.1329; found, 295.1328.

Celecoxib (2.4w)



2.3w **2.4w**, 61%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial (vial n°1) was charged with nBu$_4$N$^+$Cl$^-$ (277.9 mg, 1.00 mmol, 4.00 equiv), then NMP (0.50 mL) and a solution of MeZnCl in THF (c = 1.0 M, 0.50 mL, 0.50 mmol, 2.0 equiv) were successively added to the vial. The resulting mixture was stirred at 23 °C for 15 min. A second 4 mL vial (vial n°2) was charged with $Ni(PCy_3)_2Cl_2$ (17.2 mg, 25.0 μmol, 10.0 mol%) and **2.3w** (167 mg, 0.250 mmol, 1.00 equiv). A solution of MeZnCl in THF (c = 1.0 M, 0.50 mL, 0.50 mmol, 2.0 equiv) and NMP (0.50 mL) were then added to the vial. The resulting solution was stirred at 23 °C for 10 min, before being transferred to the vial n°1 using a pipette. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 18 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture was diluted with

water (10 mL). The aq. layer was extracted with MTBE (3 × 20 mL), and the combined organic layers were washed with water (2 × 10 mL) andwith brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The crude material was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:4 (v/v) to afford the desired product **2.4w** (58 mg, 61%) as a colorless solid.

R_f = 0.14 (EtOAc/pentane 1:9 (v/v)).

NMR Spectroscopy:

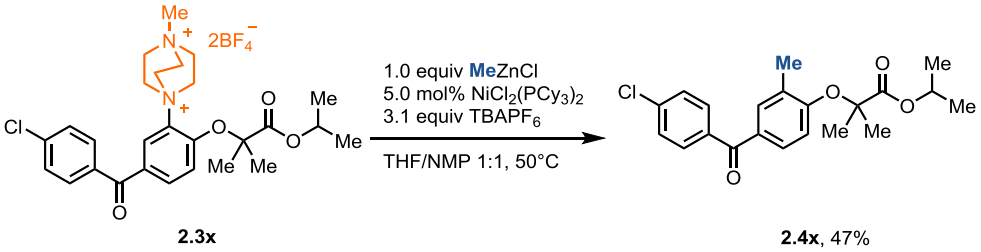
^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.96–7.87 (m, 2H), 7.51–7.44 (m, 2H), 7.21–7.16 (m, 2H), 7.14–7.08 (m, 2H), 6.74 (s, 1H), 4.95 (br s, 2H), 2.38 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 145.4, 144.3 (q, *J* = 38.4 Hz), 142.7, 141.4, 140.0, 129.9, 128.9, 127.7, 125.8, 125.6, 121.2 (d, *J* = 269.3 Hz), 106.5, 21.5.

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

HRMS-ESI (m/z) calc'd for $C_{17}H_{15}N_3O_2SF_3^+$ $[M+H]^+$, 382.0831; found, 382.0382.

Isopropyl 2-(4-(4-chlorobenzoyl)-2-methylphenoxy)-2-methylpropanoate (2.4x)



2.3x **2.4x**, 47%

In an anhydrous, nitrogen-filled glovebox, a 4 mL vial was charged with $Ni(PCy_3)_2Cl_2$ (8.6 mg, 12 μmol, 5.0 mol%), **2.3x** (165 mg, 0.250 mmol, 1.00 equiv), and $n$$Bu_4N^+PF_6^-$ ($TBAPF_6$) (300 mg, 0.775 mmol, 3.10 equiv). NMP (0.75 mL), THF (0.50 mL), and a solution of MeZnCl in THF (c = 1.0 M, 0.25 mL, 0.25 mmol, 1.0 equiv) were then added successively to the reaction mixture. The vial was sealed with a Teflon cap and moved from the glovebox to a preheated metal heating block (50 °C). The reaction mixture was then stirred at 50 °C for 20 hours. After

cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (20 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 10 mL) and with brine (1 × 5 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 5:95 (v/v) to afford the desired product **2.4x** (44 mg, 47%) as a colorless solid.

R_f = 0.64 (EtOAc/pentane 1:9 (v/v)).

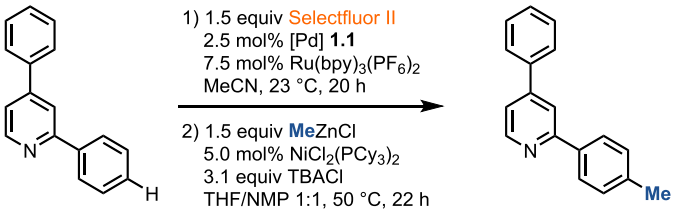
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 °C, δ): 7.71–7.68 (m, 2H), 7.65 (dd, *J* = 2.3, 0.9 Hz, 1H), 7.51 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.46–7.42 (m, 2H), 6.65 (d, *J* = 8.6 Hz, 1H), 5.08 (p , *J* = 6.3 Hz, 1H), 2.27 (s, 3H), 1.66 (s, 6H), 1.20 (d, *J* = 6.3 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$, 23 °C, δ): 194.5, 173.2, 158.1, 138.2, 136.6, 133.0, 131.2, 129.8, 129.3, 129.0, 128.5, 114.1, 79.4, 69.2, 25.5, 21.5, 16.8.

HRMS-ESI (m/z) calc'd for $C_{21}H_{23}O_4ClNa^+$ $[M+Na]^+$, 397.1177; found, 397.1178.

2.5.8 Gram-Scale Methylation of 2,4-Diphenylpyridine



1.05 g

2.4o, 50%

To a 100 mL-round bottomed flask equipped with a magnetic stirring bar were added palladium complex **1.1** (72.2 mg, 113 μmol, 2.50 mol%), $Ru(bpy)_3(PF_6)_2$ (293 mg, 340 μmol, 7.50 mol%), Selectfluor II (2.18 g, 6.81 mmol, 1.5 equiv), and a solution of 2,4-diphenylpyridine (1.05 g, 4.54 mmol, 1.00 equiv) in MeCN (10 mL). Additionnal acetonitrile (13 mL) was added via syringe to

the mixture, the flask was capped with a rubber septum and the reaction mixture was stirred at 23 °C for 20 h. Et_3N (excess, V = 1.5 mL) was added dropwise to the flask at room temperature. The resulting mixture was stirred for 2 min at 23 °C, and DCM (75 mL) was added to the flask. After being stirred for 5 min, the precipitate was collected by filtration on a glass frit, washed with DCM (2 × 15 mL), then with diethyl ether (2 × 15 mL). The resulting Ar-TEDA was dried under vacuum (P < 0.1 mbar) at room temperature for 1 hour. In an oven-dried argon-filled Schlenck flask was charged with $Ni(PCy_3)_2Cl_2$ (157 mg, 227 μmol, 5.44 mol%), **2.3o** (2.27 g, 4.17 mmol, 1.00 equiv), and $n Bu_4N^+Cl^-$ (TBACl) (3.91 g, 14.1 mmol, 3.38 equiv). The Schlenk flask was capped with a rubber septum, then evacuated and back-filled with argon. This evacuation/back-filling process was repeated three times. NMP (13.6 mL), THF (6.80 mL), and a solution of MeZnCl in THF (c = 1.0 M, 6.81 mL, 6.81 mmol, 1.63 equiv) were then added successively to the reaction mixture. The Schlenck was moved to a preheated oil bath (50 °C) and the reaction mixture was then stirred at 50 °C for 20 hours. After cooling to 23 °C, MeOH (0.1 mL) was added to the mixture, the volatiles except the NMP were removed *in vacuo*, and the resulting mixture dissolved in MTBE (120 mL). The solution was then transferred to a separatory funnel and was washed with water (4 × 50 mL) and with brine (1 × 50 mL), then dried over Na_2SO_4, filtered and concentrated to dryness. The residue was purified by flash column chromatography on silica gel eluting with EtOAc/pentane 1:100 (v/v) to afford the desired product **2.4o** (562 mg, 50% over two steps) as a pale yellow liquid.

2.6 References

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Chapter 3 – Enthalpy-Governed Cationic Radical Aromatic Substitution with Low Substrate and Positional Selectivity

3.1 Backgrounds

Radical reactivity towards unsaturated systems can be governed by polar- and/or enthalpic effects. Contrary to a common notion, a highly electrophilic radical such as ammonia radical cation can exhibit an apparent non-electrophilic behavior due to enthalpic effects (see Section I.2.3).[1] It is not completely evident in which situations will the polar effects dominate over the enthalpic effects, and vice versa. Conventionally, it is suggested that the enthalpic effects will mainly govern the radical reactivity when a radical is weakly nucleophilic or electrophilic, and, on the contrary, that the polar effects will dominate for highly polar radicals.[2] Such rationale may succeed to explain why, for example, the weakly polar phenyl radical is generally unselective. However, the electron affinity of ammonia radical cation is 10 eV,[3] which is the highest among simple aminium radicals. Enthalpy-controlled aromatic substitution by a high-electron-affinity-radical is rare, perhaps because there has been a lack of synthetic interests to develop methods that generate such a radical. The data of homolytic amination may be interpreted as an alternative possibility that, when appropriately designed to elicit a large enthalpy gain upon addition to an arene, the reactivity and selectivity of a radical with high electron affinity can be controlled by enthapic effects. Such a highly reactive radical may potentially engender a synthetically useful transformation with an extremely broad substrate scope and an ability to generate a diverse spectrum of constitutional product isomers from a single starting material.

In this chapter, we describe a divergent, late-stage (hetero)aryl C–H amination reaction that was reported in *Angewandte Chemie* in November 2018.[4] A novel 2-ethylpyridine N–OTf (**3.1**)

fragments into a pyridinium radical cation upon reduction by a photo-excited ruthenium complex. The pyridinium radical cation, with an electron affinity value of 9 eV,[5] substitutes both electron-rich and -poor C–H bonds with low selectivity, due to significant enthalpic effects. We apply the broad substrate scope of the aryl C–H pyridination reaction towards direct conversion of structurally complex aromatic molecules into primary (hetero)arylamines, thereby addressing the long-standing limitations of currently employed aryl C–H amination methodology.

Late-stage aryl C–N bond formation is desirable in small molecule discovery because a quarter of the top 200 pharmaceuticals by US retail sales in 2015 contain (hetero)arylamines.[6] However, broadly applicable C–H amination of complex aromatic compounds has yet to be achieved. Two challenges exist: Limitations with respect to functional-group-tolerance and limitations with respect to the electronic substrate scope. Electrophilic aromatic nitration with the reactive NO_2^+ electrophile is able to functionalize both electron-rich and -poor arenes, but the high reactivity of NO_2^+ limits the functional-group-tolerance of nitration.[7] Modern amination reactions exhibit improved functional-group-tolerance, but the electrophilic aminating reagents[8–16] are no longer sufficiently reactive to react with electron-deficient arenes such as methyl benzoate. One–electron oxidation of the arene to an arene radical cation with subsequent nucleophilic attack by a nitrogen nucleophile has been successfully established *via* both electrochemical- and photooxidation.[17,18] However, in both cases, the arene must be sufficiently electron-rich for the oxidation to occur, which limits the substrate scope also to electron-rich arenes.[19]

The limitations of the known amination reactions with respect to their reactivity profiles can be understood in light of well-appreciated polarity matching in the transition state (Figure 3.1a), as discussed in the Introduction (see Section I.1 and I.2). The more the polarity preference is pronounced, the more challenging it becomes to reach a large electronic substrate scope. In other

words, for each approach, whether oxidized nitrogen-based reagent or arene oxidation, the reactive aminating species is intrinsically limited to react with a subset of substrates that can elicit suitable polar interactions.

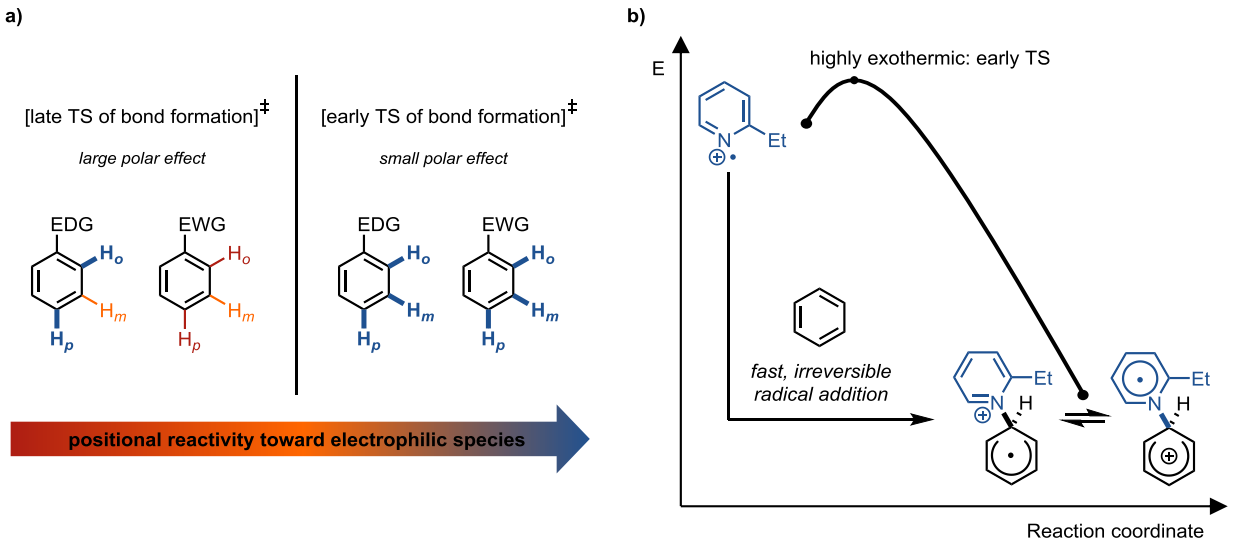


Figure 3.1. Strategy for general, diversifying aryl C–H amination. a) Polarity-matching-dependent aromatic reactivity toward electrophilic bond-forming species. b) Conceptual energy diagram of cationic pyridinium σ-radical's addition.

In addition to the consequence on substrate scope, polarity matching results in the predictable positional selectivity of most aryl C–H amination reactions. For example, with electron-rich substrates the NO_2^+ electrophile has a bias for the *ortho*- and *para*- positions, whereas electron-withdrawing substituents will primarily direct the electrophile to the *meta*- position (see Section I.1.1).[20] Modern amination reactions also provide product mixtures reminiscent of polarity matching. Reactions based on one-electron arene oxidation exhibit *para*-selectivity, due to the electronic population in the arene radical cation[17]. If other isomers are desired, a different synthesis must be designed.

An early transition state of bond formation would involve small polar interactions between the reactants, and therefore, would minimize substrate/positional bias with respect to electronic structure. Characteristics of such a transition state would manifest themselves in kinetic isotope

effects (KIEs) close to unity for an aromatic C–H substitution reaction as well as a small Hammett ρ value, ideally as close to zero as possible. One approach to achieve an early transition state is to select a suitably reactive radical aminating species that can undergo a highly exothermic addition to an arene, yet remain tolerant of a large variety of functional groups (Figure 3.1b). Minisci demonstrated that the high exothermicity of ammonium radical addition to an arene can engender low positional selectivity (see Section I.2.3),[1] but reactivity towards electron-poor substrates was not synthetically useful (5% yield for functionalization of benzonitrile) and the reaction requires an acidic solvent. We rationalized that the cationic pyridinium σ-radical should be more reactive than conventional nitrogen-based radicals because its unpaired electron is located in an sp^2-hybridized orbital.[21–23] As a simple surrogate, we have calculated the bond dissociation energy (BDE) of the N–H bond in the pyridinium ion to be 88 $kJmol^{-1}$ higher relative to the dimethylammonium ion (see Section 3.6.10). Charge delocalization in the ensuing cyclohexadienyl radical upon C–N bond formation would contribute to a larger enthalpy gain, when compared to additions of aliphatic aminium radicals, for which delocalization may not be possible in a large extent. A catalytic system that generates the pyridinium radical cation would be able to access a large substrate scope with constitutional diversity in a synthetically useful transformation.

3.2 Aryl C–H Substitution by the Pyridinium Radical Cation

The pyridinium radical cation shown in Figure 3.2a, generated through reduction of an activated pyridine *N*-oxide by a visible-light-excited metal catalyst, adds to both phenyl acetate and nitrobenzene, in contrast to other known amination reactions, to provide products in a 1:1:1 and 1:2:1 mixture, respectively. Conventional nitration provides products in ratios to be expected for electrophilic substitution reactions, whereas nitrogen-based radical addition, as a surrogate for

modern methodology, has as of yet not been observed for electron-poor arenes at all. For sufficiently electron-rich arenes, modern amination reactions proceed with the expected regioselectivity. As shown in Figure 3.2a, amination with the pyridinium radical cation can also provide late-stage access to complex arylamines that other methods cannot. Various nitration reaction attempts either failed to achieve conversion or led to substrate decomposition into an intractable mixture, while modern methodology is not compatible with the electronic structure in the example shown.

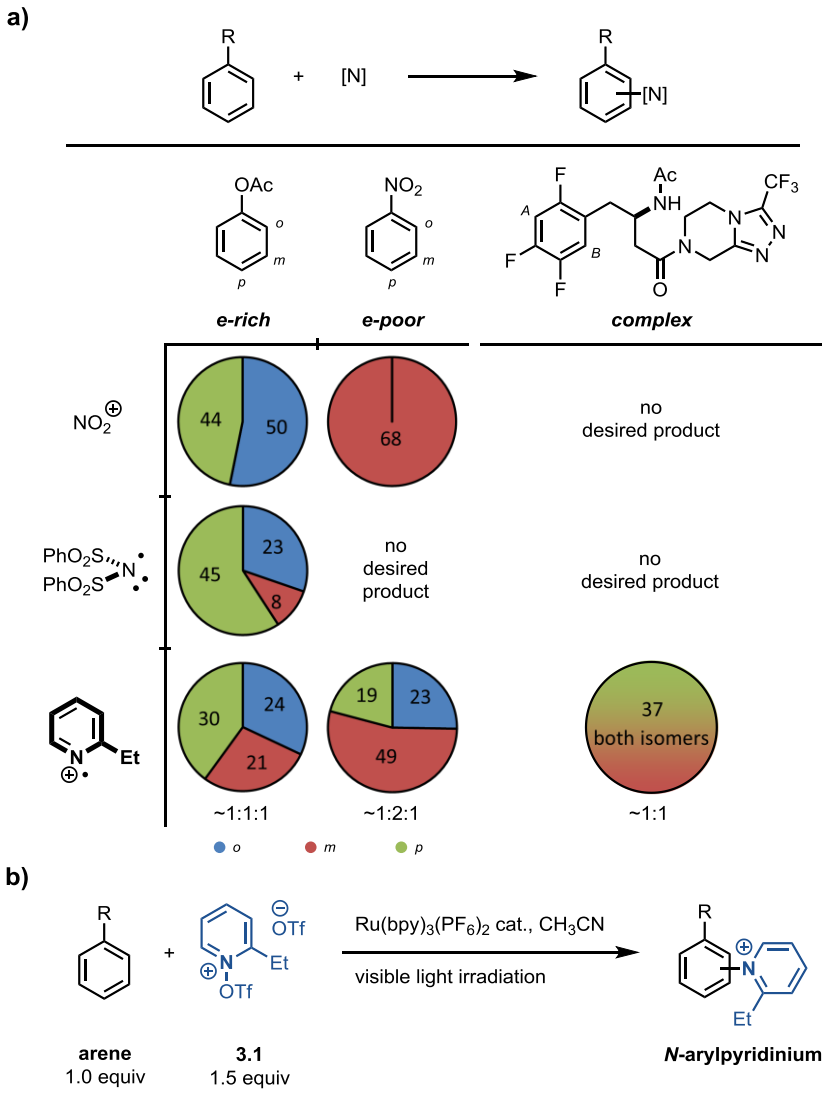
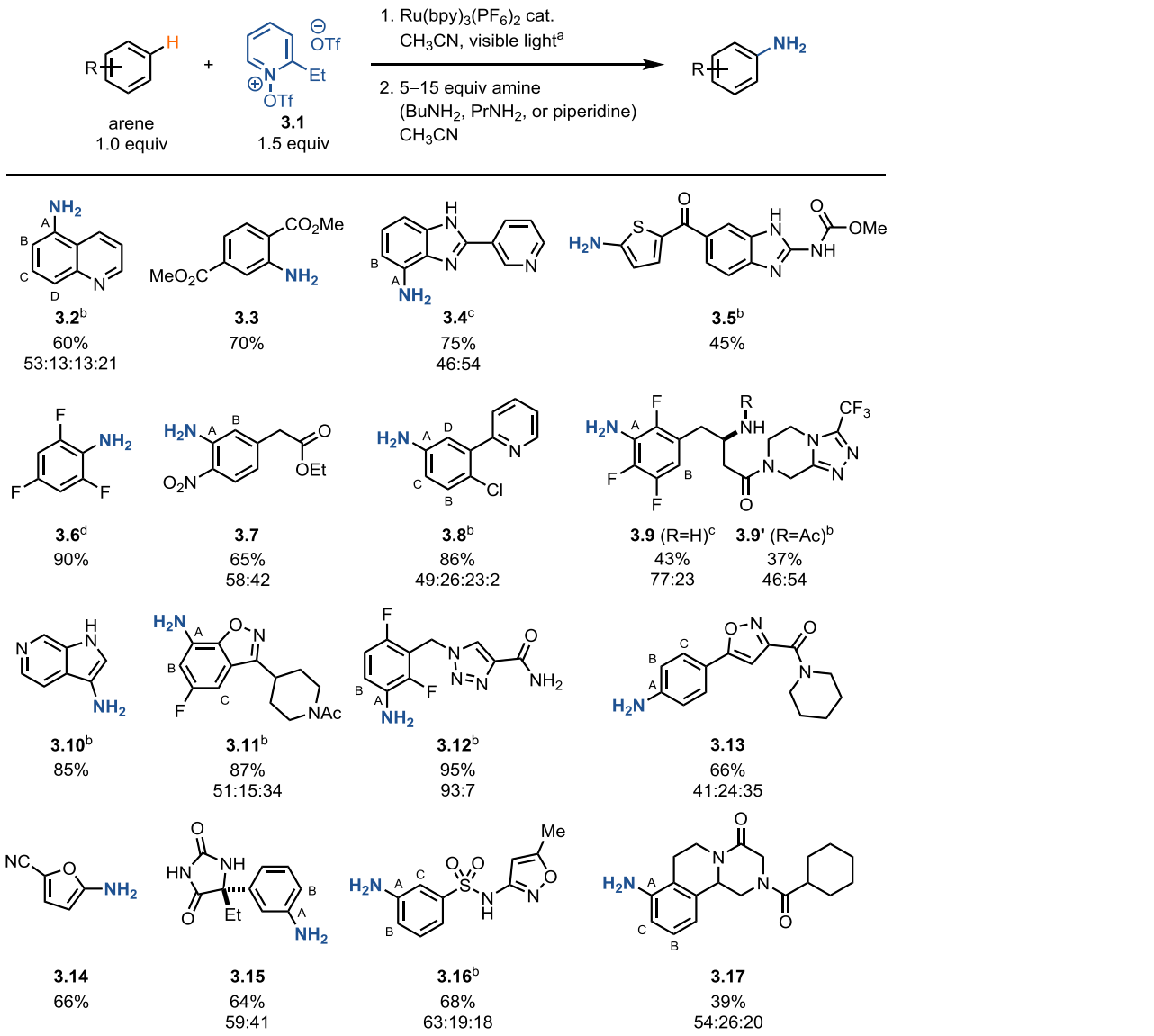


Figure 3.2. a) Selectivity profiles and % yields of aromatic substitution reactions with indicated aminating species. b) Diversity-generating aryl C–H pyridination using reagent **3.1**.

We prepared 2-ethylpyridine *N*–OTf (**3.1**) by triflation of commercially available 2-ethylpyridine *N*-oxide.[24] Other evaluated pyridine derivatives afforded aminated products but in lower yields. Irradiation of a solution containing arene, the photoredox catalyst $Ru(bpy)_3(PF_6)_2$, and reagent **3.1** in acetonitrile affords *N*–arylpyridinium salts (Figure 3.2b). Irradiation with a 70 W blue LED with 2 mol% catalyst loading led to complete benzene conversion within as short as 30 seconds (see Section 3.6.2), while more structurally complex substrates were converted over 15–90 minutes; the reaction can also be performed with a 23 W compact fluorescent lamp (CFL), in which case the reaction time increases to up to 24 h, and the catalyst loading for electron-poor substrates must be increased to 5 mol%. Reagent **3.1** can be prepared *in situ*, or synthesized independently and stored for at least 6 months under inert atmosphere; it can be used for a short period of time in air, which facilitates a practical reaction setup. Both the ruthenium catalyst and irradiation are crucial for the reaction to occur, although upon initiation, the reaction does proceed in the dark, albeit less efficiently, presumably through a chain transfer process.

3.3 Divergent, Late-Stage (Hetero)Aryl C–H Amination

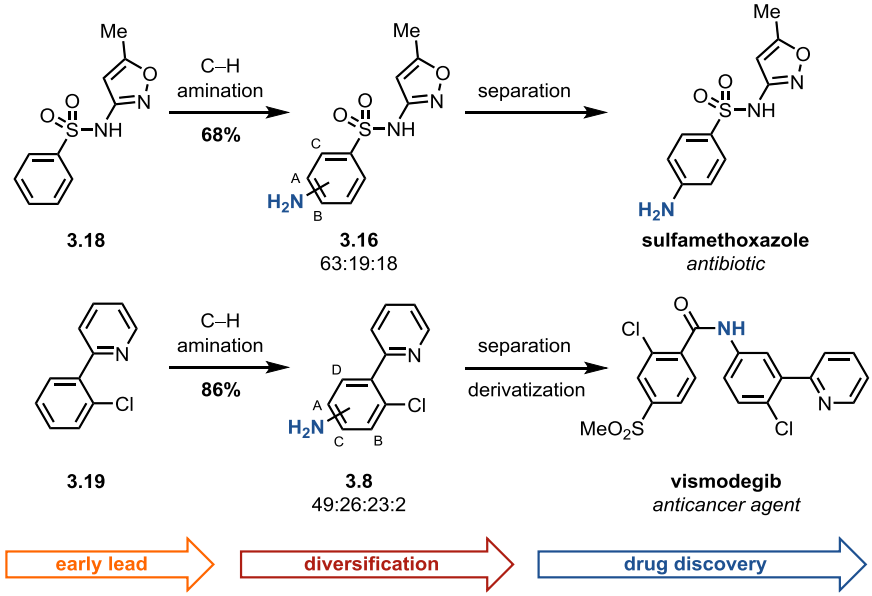
Subsequent *in situ* aminolysis of the *N*–arylpyridinium salts with butylamine, propylamine, or piperidine, reminiscent of the electrophilic reactivity of Zincke salts,[25] liberates (hetero)arylamines. We combined the aromatic pyridination reaction and the arylpyridinium aminolysis into a one-pot procedure for late-stage C–H amination of arenes and heteroarenes.



Scheme 3.1. Late-stage direct arene C–H amination. [a]Reaction conditions with blue LED: 2 mol% $Ru(bpy)_3(PF_6)_2$, 40 W or 70 W blue LED, 30 °C, 15–90 min; Reaction conditions with CFL: 5 mol% $Ru(bpy)_3(PF_6)_2$, 23 W CFL, 23–25 °C, 24 h; see Section 3.6.2 for details. [b]1.0 equivalent TfOH. [c]2.0 equivalent TfOH. [d]Derivatized due to volatility of the product

The demonstrated substrate scope of the cationic pyridinium radical substitution (Scheme 3.1) exceeds that of modern aryl C–H amination reactions previously reported (see Section 3.6.4), and also tolerates functional complexity that is not tolerated by conventional nitration. A majority of the substrates presented are marketed drug molecules and common pharmacophores, whose aminated analogues are often challenging to access by other transformations, especially at

a late stage of a synthesis. Substrates containing basic *N*-heterocycles were protonated with a stoichiometric amount of trifluoromethanesulfonic acid to suppress reagent decomposition, in which case those heterocycles became deactivated toward functionalization (**3.2**, **3.4**, **3.5**, **3.8**, **3.10**, **3.12**). With the exception of certain five-membered heteroarenes that have a strong electronic bias (**3.5**, **3.10**, **3.14**) and arenes that bear a bulky functional group (**3.13**, **3.15**, **3.16**, **3.17**), a large set of positional isomers was accessed. Each constitutional product isomer was isolated by chromatographic separation, based on standard and/or C18-reversed phase silica gel, and characterized as analytically pure compound. The ability to deliver diversified products from biologically privileged structures in pure form renders the late-stage amination relevant and promising toward streamlined exploration of chemical space for pharmaceutical innovations.

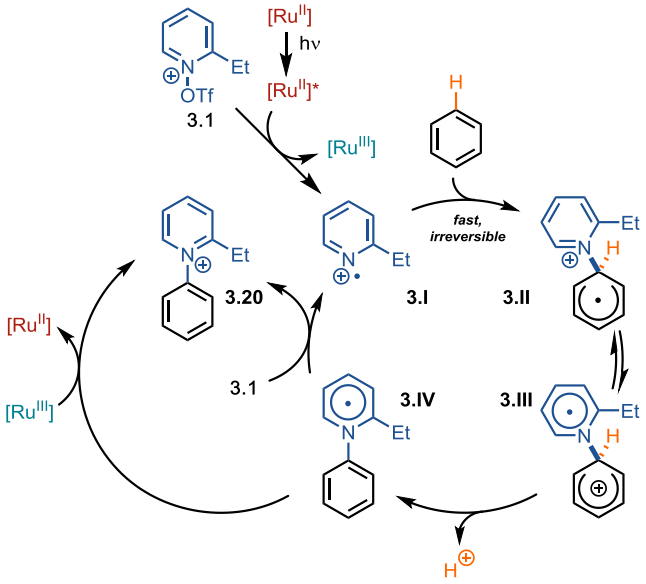


Scheme 3.2. Synthetic utility of late-stage amination for streamlined drug discovery.

We demonstrate the utility of the diversifying aryl C–H amination by simulating the discovery of two marketed drugs (Scheme 3.2). Amination of **3.18** and **3.19** afforded multiple aminated products through carboarene functionalization. After purification and/or derivatization,[26] the antibiotic sulfamethoxazole and the anticancer agent vismodegib are quickly accessible,

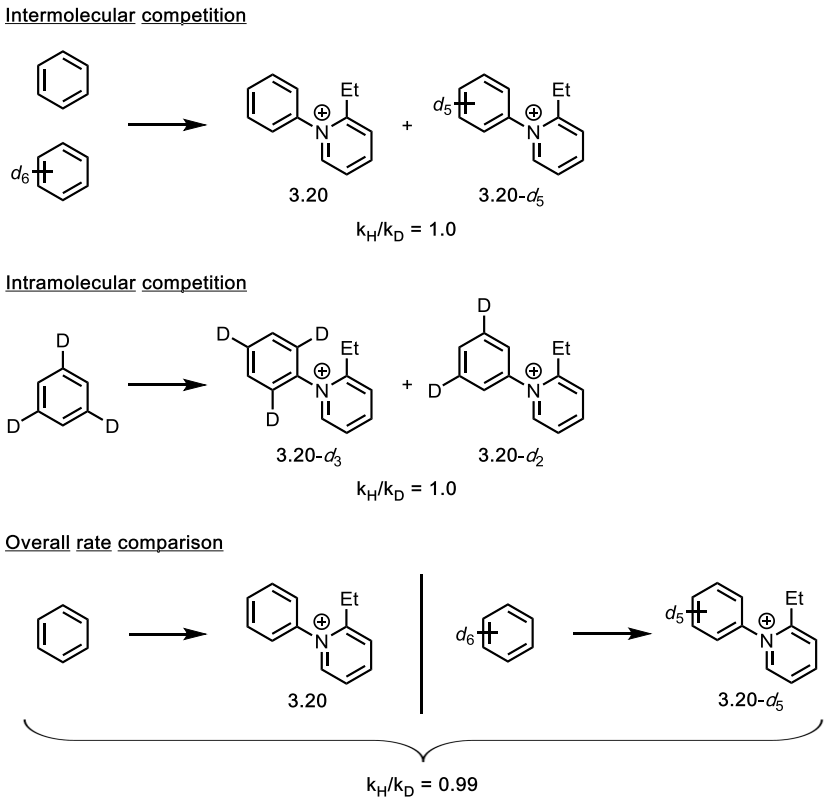
respectively. We point out that, in a hypothetical drug discovery scenario, our method provides access to several constitutional isomers, of which the isomer with the best biological activity could then be identified, without the need for independent *ab initio* syntheses.

3.4 Mechanistic Features of the Pyridinium Radical Substitution



Scheme 3.3. Plausible reaction mechanism. The two depicted pathways for the single-electron oxidation of **3.IV** are, presumably, both operative at the same time.

We propose the mechanism for aryl pyridination shown in Scheme 3.3. Reduction of the reagent **3.1** by the photo-excited ruthenium catalyst generates the pyridinium σ-radical cation (**3.I**), which adds to an arene; the early transition state of addition is proposed to be the origin of both the broad substrate scope and the constitutional diversity. The early transition state should result in a small, if any, secondary kinetic isotope effect (KIE). When measured, both the inter- and the intramolecular competition resulted in KIE of 1.0 (Scheme 3.4). The KIE value of unity in nitrogen radical aromatic substitution is unusual, and reflects a transition state of addition that is insensitive to the re-hybridization of the carbon atom on which the substitution occurs.



Scheme 3.4. Kinetic isotope effect measurements; see Section 3.6.7 for details.

The small electronic bias of the radical addition is quantified as a Hammett ρ value of –0.81 (Figure 3.3a), which was compared to those of substitution by ammonium and dimethylaminium radical cations, generated *via* analogous redox catalysis[1,27,28] (see Section 3.6.8). These more conventional aminium radicals have ρ values of –2.7 and –5.2, respectively, significantly larger in magnitude, in agreement with a smaller electronic substrate scope. The extreme metrics of the presented amination reaction with respect to constitutional diversity are best illustrated when they are compared in a Brown-Stock correlation diagram (Figure 3.3b) to other electrophilic and radical aromatic substitution reactions.[29] Brown-Stock analysis describes a linear free-energy relationship with respect to substrate- and positional selectivity. In this analysis, arene functionalization by the pyridinium radical cation emerges as the transformation with the

smallest bias for constitutional selectivity, at least among the practically useful reactions for which Brown-Stock data are available (see Section 3.6.9).

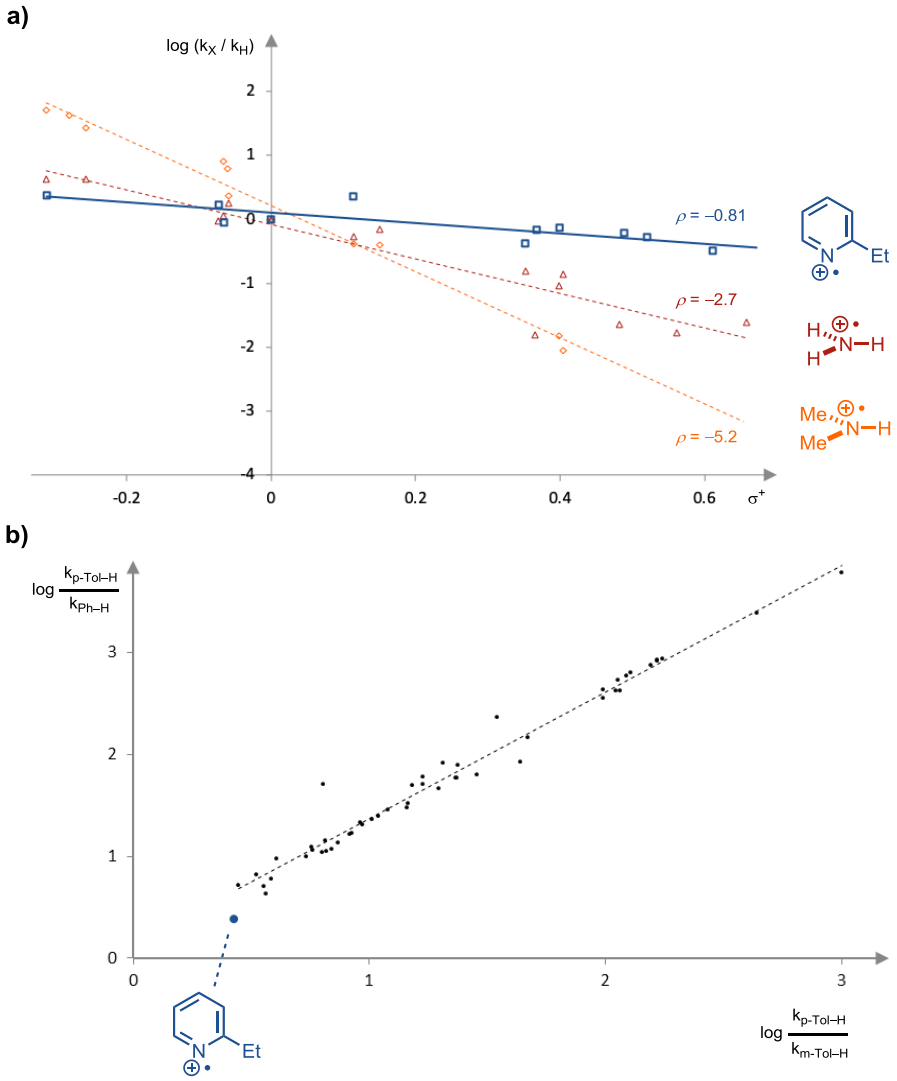


Figure 3.3. Linear free-energy relationship analysis; see Section 3.6.8 and 3.6.9 for details. a) Comparison of Hammett plots for radical substitution of mono-substituted arenes (PhX, X = Me, ^{i}Pr, ^{t}Bu, H, F, Cl, Br, CO_2Et, CO_2Me, CF_3, CN). b) Fitting of the pyridinium radical cation into the Brown-Stock diagram, which plots the substrate selectivity ($k_{p\text{-tol–H}}$ vs. $k_{Ph–H}$) against the positional selectivity ($k_{p\text{-tol–H}}$ vs. $k_{m\text{-tol–H}}$). The black points represent data for aliphatic aminium radical substitution and electrophilic substitution.

The distonic radical cations **3.II** and/or **3.III**, resulting from the radical addition, would undergo facile deprotonation to afford the arylpyridine radical **3.IV**, from which single-electron oxidation by the oxidized ruthenium complex or by **3.1** would afford the arylpyridinium salt **3.20**. The

absence of a significant overall rate difference (KIE of 0.99) between the pyridination reactions of benzene and perdeuterated benzene (Scheme 3.4) is in agreement with a fast C–H bond cleavage event.

3.5 Enthalpic Effects on the Selectivity of the Pyridinium Radical

The pyridinium radical cation exhibits substrate- and positional selectivity significantly lower than those of ammonium radical cation. The two cationic nitrogen radicals possess similar electron affinity values (9 eV for pyridinium and 10 eV for ammonium)[3,5] and presumably also form C–N bonds with similar dissociation energy values (N–H BDE´s of pyridinium and ammonium are 122 kcal/mol and 127 kcal/mol, respectively. See Section 3.6.10).[30] The electron affinity and the expected energy gain from bond formation with the pyridinium radical are both slightly lower than those of the ammonium, but the information of these two measures appears to be insufficient to account for the experimental results described herein.

One aspect of the pyridinium radical that may contribute to the more pronounced enthalpic effect is, as suggested in Section 3.1, the aromatic nature of the σ-radical cation. The aromatic π-system of the pyridinium radical could accept electron density from the cyclohexadienyl radical addition intermediate, and therefore facilitate the re-aromatizing deprotonation that may provide an additional driving force to furnish the substitution product.

Moreover, it is worth noting the hybridization of the nitrogen atoms in the two radical species. The nitrogen atom of the pyridinium radical is sp^2-hybridized both before and after the radical addition. On the other hand, the nitrogen atom of the planar ammonium radical cation would undergo re-hybridization from sp^2 to sp^3 upon C–N bond formation, during which reorganization of the bonded hydrogen atoms is required. The non-necessity of such reorganization may also contribute to the earlier transition state of addition by the pyridinium radical cation.

3.6 Conclusion

We demonstrate that the reactivity of the sp^2-hybridized, aromatic pyridinium radical cation is, despite its very high electron affinity, largely governed by enthalpic effects. The resulting C–N bond forming reaction illustrates a synthetic strategy of how to access structural complexity that goes beyond the scope accessible through conventional amination reactions. The reaction is expected to expedite discovery of biologically active small molecules *via* late-stage functionalization. Other reagents that would elicit early transition states of bond formation between reactive species and π-systems may access molecular diversity for other carbon–heteroatom bond forming reactions beyond what we have shown here. It has not escaped our attention that, in principle, the analysis provided here should also enable the design of highly regio-selective aromatic C–H functionalization reactions.

3.6 Experimental Details

3.6.1 Materials and Methods

All air- and moisture-insensitive reactions were carried out under an ambient atmosphere and monitored by thin-layer chromatography (TLC). High-resolution mass spectra were obtained using Q Exactive Plus from Thermo. Concentration under reduced pressure was performed by rotary evaporation at 25–40 °C at an appropriate pressure. Purified compounds were further dried under high vacuum (0.008–0.5 Torr). Yields refer to purified and spectroscopically pure compounds, unless otherwise stated. All air- and moisture-sensitive manipulations were performed using oven-dried glassware (130 °C for a minimum of 12 hours), including standard Schlenk and glove-box techniques under an atmosphere of argon, although they can operate equally under an atmosphere of nitrogen. Irradiation of photochemical reactions were carried out

using a 23 W CFL (OSRAM Dulux Twist), a 40 W blue LED (Kessil A 160WE Tuna Blue), or a 5–100 W blue LED (KT-elektronic Power LED blue 450 nm Aquarium, variable power). The photochemical reactions using the Power LED blue 450 nm Aquarium were cooled by an electric cooler (Thermoelectric cooler Peltier element).

Solvents

Acetonitrile, DCM, and methanol were purchased from Sigma-Aldrich and used as received. Anhydrous solvents were obtained from Phoenix Solvent Drying Systems. 2,2,2-Trifluoroethanol (TFE) was purchased from Sigma-Aldrich and dried by distillation over $CaSO_4$. All deuterated solvents were purchased from Euriso-Top. Anhydrous acetonitrile-d_3 was dried by distillation over P_2O_5.

Chromatography

Thin layer chromatography (TLC) was performed using EMD TLC plates pre-coated with 250 μm thickness silica gel 60 F_{254} plates and visualized by fluorescence quenching under UV light. Flash chromatography was performed using silica gel (40–63 μm particle size) purchased from Geduran. Preparatory high-performance liquid chromatographic separation was executed on Shimadzu Prominence Preparative HPLC system with an YMC-Triart C18 HPLC column.

Spectroscopy and Instruments

NMR spectra were recorded on a Bruker Ascend^{TM} 500 spectrometer operating at 500 MHz, 125 MHz, and for ^{1}H, ^{13}C, and ^{19}F acquisitions, respectively. Chemical shifts are reported in ppm with the solvent resonance as the internal standard. For ^{1}H NMR: $CDCl_3$, δ 7.26; CD_3CN, δ 1.94; CD_2Cl_2, δ 5.32; $(CD_3)_2SO$, δ 2.50. For ^{13}C NMR: $CDCl_3$, δ 77.16; CD_3CN, δ 1.32; CD_2Cl_2, δ 53.84; $(CD_3)_2SO$, δ 39.52. ^{19}F NMR spectra were referenced using a unified chemical shift scale based on the ^{1}H resonance of tetramethylsilane (1% v/v solution in the respective solvent).[31]

Data is reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad; coupling constants in Hz; integration. Liquid chromatography-coupled mass spectroscopic data were obtained on Agilent 1260 Infinity Automated LC/MS Purification System. Cyclic voltammetry measurements were performed with an Epsilon EClipse^{TM} Potentiostat/Galvanostat.from BASi.

Starting materials

All substrates were used as received from commercial suppliers, unless otherwise stated. 2-Ethylpyridine 1-oxide and (±)-nirvanol were purchased from Enamine. Quinoline, dimethyl terephthalate, 2-(pyridine-3-yl)-benzimidazole, 1,3,5-trifluorobenzene, ethyl 4-nitrophenyl acetate, sitagliptin phosphate, rufinamide, methyl 5-phenylisoxazole-3-carboxylate, 2-furonitrile, praziquantel, N-fluorobenzenesulfonimide, 9-mesityl-3,6-di-*tert*-butyl-10-phenylacridinium tetrafluoroborate, TEMPO, ammonium carbamate, $Rh_2(esp)_2$, $Fe(SO_4)_2{\cdot}7H_2O$, aniline, *o*-toluidine, *m*-toluidine, *p*-toluidine, 2-fluoroaniline, 3-fluoroaniline, 4-fluoroaniline, 2-chloroaniline, 3-chloroaniline, 4-chloroaniline, methyl 2-aminobenzoate, methyl 3-aminobenzoate, methyl 4-aminobenzoate, 2-(trifluoromethyl)aniline, 3-(trifluoromethyl)aniline, 4-(trifluoromethyl)aniline, 2-nitroaniline, 3-nitroaniline, and 4-nitroaniline were purchased from Sigma-Aldrich. Nocodazole and N-(5-methyl-3-isoxazolyl)benzenesulfonamide were purchased from Toronto Research Chemicals. 6-Azaindole and 3-(1-acetyl-4-piperidinyl)-5-fluoro-1,2-benzisoxazole were purchased from Alfa Aesar. *Tert*-butyl(mesitylsulfonyl)oxycarbamate was purchased from Combi-Blocks. 2-(2-Chlorophenyl)pyridine was prepared according to a reported procedure.[32] Sitagliptin was prepared by washing a suspension of sitagliptin phosphate monohydrate in DCM with saturated aqueous $NaHCO_3$ solution. Palladium complex **3.22** and

$Ag(bpy)_2ClO_4$ were prepared according to reported procedures.[8] $MsONH_3OTf$ was prepared according to a reported procedure.[15] $Fe(SO_4)_2 \cdot 7H_2O$ was ground into fine powders prior to use.

3.6.2 Experimental Procedures and Compound Characterization

Representative procedure of amination of (hetero)arenes

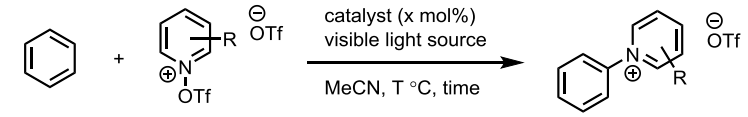
Under inert atmosphere, an oven-dried 20 mL vial was charged with a stirring bar and dry acetonitrile (1.5 mL). The stirred liquid was cooled to –40 °C, and then trifluoromethanesulfonic anhydride (88 µL, 0.15 g, 0.52 mmol, 1.3 equiv) was added via glass syringe. Under inert atmosphere, an oven-dried 4 mL vial was charged with 2-ethylpyridine 1-oxide (65 µL, 64 mg, 0.52 mmol, 1.3 equiv) and dry acetonitrile (0.5 mL), and the mixture was briefly swirled. The solution of 2-ethylpyridine 1-oxide was added to the solution of trifluoromethanesulfonic anhydride dropwise via syringe. The mixture was stirred at –40 °C for 1 min, and then warmed to 23 °C over 5 min. After 14 min, the vial was briefly opened to air, and $Ru(bpy)_3(PF_6)_2$ (17 mg, 20 µmol, 5.0 mol%) and an arene (0.40 mmol, 1.0 equiv) were added. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 30 °C, irradiated with two 40 W blue LEDs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 30 min, butylamine (0.40 mL, 4.0 mmol, 10 equiv) was added, and the mixture was stirred at 23 °C for 16 h. The reaction mixture was concentrated *in vacuo*. Preparatory chromatography based on standard and/or C18-reversed phase silica gel achieved separation of each constitutional isomer for all compounds reported here.

When the mixture of arylamines was difficult to purify by standard separation techniques, the arylpyridinium salts were first separated by high-performance liquid chromatography.

For operational convenience, the amination of the (hetero)arenes reported here was conducted with isolated 2-ethylpyridine *N*–OTf (**3.1**).

Optimization of reaction conditions

An oven-dried 4 mL vial was charged with a stirring bar, a photoredox catalyst (x mol%), and a pyridine *N*–OTf reagent (y equiv). Dry acetonitrile-d_3 (0.50 mL, c = 0.20 M) was added via syringe. To the stirred mixture, benzene (8.9 µL, 7.8 mg, 1.0 mmol, 1.0 equiv) was added via glass syringe. The vial was sealed with a plastic cap, and the reaction mixture was stirred at T °C and irradiated with a visible light source. After the specified reaction time, deuterium oxide (10 µL) was added to quench the reaction. Ethyl acetate (10 µL, 9.0 mg, 0.10 mmol) was added as an internal standard, and the reaction mixture was analyzed *via* ^{1}H NMR spectroscopy.

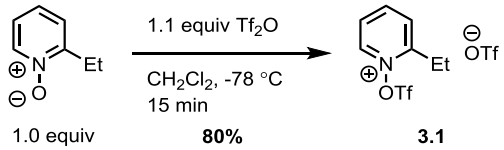


catalyst	x	R	y	T (°C)	light source	time	yield (%)
$Ru(bpy)_3(PF_6)_2$	5.0	H	2.0	23–25	2 × 23 W CFL	24 h	57
$Ru(bpm)_3(PF_6)_2$	5.0	H	2.0	23–25	2 × 23 W CFL	24 h	0
$Ir\{dF(CF_3)ppy\}_2(dtbpy)(PF_6)$	5.0	H	2.0	23–25	2 × 23 W CFL	24 h	54
$Ir(dtbpy)(ppy)_2(PF_6)$	5.0	H	2.0	23–25	2 × 23 W CFL	24 h	53
$Ru(bpy)_3(PF_6)_2$	5.0	4-Me	2.0	23–25	2 × 23 W CFL	24 h	52
$Ru(bpy)_3(PF_6)_2$	5.0	4-^{t}Bu	2.0	23–25	2 × 23 W CFL	24 h	52
$Ru(bpy)_3(PF_6)_2$	5.0	4-CF_3	2.0	23–25	2 × 23 W CFL	24 h	0
$Ru(bpy)_3(PF_6)_2$	5.0	4-OMe	2.0	23–25	2 × 23 W CFL	24 h	52
$Ru(bpy)_3(PF_6)_2$	5.0	3,5-Me_2	2.0	23–25	2 × 23 W CFL	24 h	53
$Ru(bpy)_3(PF_6)_2$	5.0	2,4-Me_2	2.0	23–25	2 × 23 W CFL	24 h	69
$Ru(bpy)_3(PF_6)_2$	5.0	2-Et	1.5	23–25	2 × 23 W CFL	24 h	39 (40% di-)[a]
$Ru(bpy)_3(PF_6)_2$	5.0	2-Et	1.1	23–25	2 × 23 W CFL	24 h	79
none		2-Et	1.1	23–25	2 × 23 W CFL	24 h	0

$Ru(bpy)_3(PF_6)_2$	5.0	2-Et	1.1	23–25	none	24 h	0
$Ru(bpy)_3(PF_6)_2$	1.5	2-Et	1.1	23–25	2 × 23 W CFL	24 h	77
$Ru(bpy)_3(PF_6)_2$	5.0	2-Et	1.1	23–25	2 × 23 W CFL	5 min	10
$Ru(bpy)_3(PF_6)_2$	5.0	2-Et	1.1	23–25	2 × 23 W CFL	24 h	28[b]
$Ru(bpy)_3(PF_6)_2$	5.0	2-Et	1.1	30	70 W blue LED	5 min	78
$Ru(bpy)_3(PF_6)_2$	2.0	2-Et	1.1	30	70 W blue LED	30 s	80

Table 3.1. Optimization data of aryl C–H pyridination. The positional selectivities of different pyridine N–OTf derivatives towards substituted arenes were practically similar. [a]Overfunctionalization yielded 40% of bis-pyridinated benzene. [b]Light irradiation was halted at t = 5 min.

2-Ethylpyridine *N*–OTf (3.1)



Under inert atmosphere, an oven-dried 100 mL round-bottom flask was charged with 2-ethylpyridine 1-oxide (3.695 g, 30.00 mmol, 1.0 equiv) and dry DCM (10 mL, c = 3.0 M). Under inert atmosphere, an oven-dried 250 mL two-neck round-bottom flask, equipped with a stirring bar, was charged with trifluoromethanesulfonic anhydride (6.1 mL, 9.3 g, 33 mmol, 1.1 equiv) and dry DCM (30 mL, c = 1.1 M). The solution of Tf_2O was cooled to –78 °C. The solution of 2-ethylpyridine 1-oxide was added, under inert atmosphere, to the stirred solution of Tf_2O via syringe, dropwise over 5 min. The round-bottom flask containing 2-ethylpyridine 1-oxide was rinsed with 5 mL of dry DCM and the resulting solution was added to the reaction mixture. The resulting suspension was stirred at –78 °C for 15 min. Dry diethyl ether (10 mL) was added via syringe, and the white precipitate **3.1** was isolated via Schlenck filtration (9.7 g, 80% yield). 2-Ethylpyridine *N*–OTf (**3.1**) is moisture-sensitive, and was stored in a glove-box.

For performing aryl C–H pyridination reactions, a desired amount of **3.1** was weighed in a 4 mL vial inside the glove-box. The sealed vial was brought out of the glove-box, and **3.1** was poured into an open reaction vessel containing a solution of the rest of the reaction components.

NMR Spectroscopy:

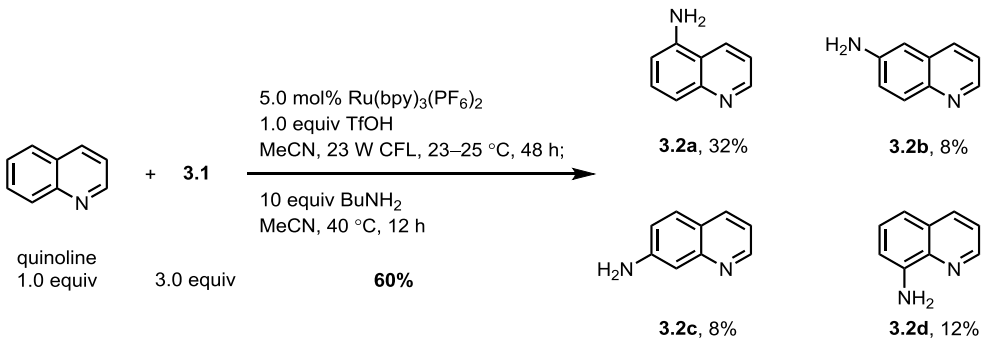
^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 8.94 (dd, *J* = 7.0, 1.2 Hz, 1H), 8.72 (ddd, *J* = 8.0, 8.0, 1.2 Hz, 1H), 8.25 (dd, *J* = 8.0, 2.0 Hz, 1H), 8.17–8.12 (m, 1H), 3.26 (q, 2H), 1.46 (t, 3H).

^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –69.2, –79.4.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 160.4, 150.5, 142.9, 131.7, 129.5, 25.9, 11.4.

HRMS-FIA(m/z) calc'd for $C_8H_9F_3NO_3S^+$ $[M]^+$, 256.0250; found, 256.0250.

Aminoquinolines 3.2



An oven-dried 20 mL vial was charged with a stirring bar, quinoline (47 µL, 52 mg, 0.40 mmol, 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (17 mg, 20 µmol, 5.0 mol%). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe. To the stirred mixture, trifluoromethanesulfonic acid (35 µL, 60 mg, 0.40 mmol, 1.0 equiv) was added via glass syringe, and then **3.1** (243 mg, 0.600 mmol, 1.5 equiv) was added. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, **3.1** (243 mg, 0.600 mmol, 1.5 equiv) was added. After 24 h, the

reaction mixture was concentrated *in vacuo*, and the residue was purified by preparatory high-performance liquid chromatography with a solvent mixture of water (0.1% TFA)/acetonitrile (80/20 (v/v)) to afford 65 mg of fraction **a**, 71 mg of fraction **b**, 42 mg of fraction **c**, and 24 mg of fraction **d** as red oils.

To a 20 mL vial, charged with the fraction **a** and a stirring bar, butylamine (0.40 mL, 4.0 mmol) was added, and the mixture was stirred at 40 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/methanol (98/2 to 96/4 (v/v)) to afford 18 mg of **3.2a** (32% yield).

To a 20 mL vial, charged with the fraction **b** and a stirring bar, butylamine (0.40 mL, 4.0 mmol) was added, and the mixture was stirred at 40 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/methanol (98/2 to 94/6 (v/v)) to afford 5 mg of **3.2b** (8% yield).

To a 20 mL vial, charged with the fraction **c** and a stirring bar, butylamine (0.40 mL, 4.0 mmol) was added, and the mixture was stirred at 40 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/methanol (97/3 to 92/8 (v/v)) to afford 5 mg of **3.2c** (8% yield).

To a 20 mL vial, charged with the fraction **d** and a stirring bar, butylamine (0.40 mL, 4.0 mmol) was added, and the mixture was stirred at 40 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (20/80 to 70/30 (v/v)) to afford 7 mg of **3.2d** (12% yield).

5-Aminoquinoline (**3.2a**):

$\mathbf{R_f}$ = 0.26 (DCM/methanol/28% aqueous ammonium hydroxide (96.5/3.0/0.5 (v/v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 8.80 (dd, *J* = 4.1, 1.6 Hz, 1H), 8.29 (ddd, *J* = 8.5, 1.6, 0.9 Hz, 1H), 7.46 (dd, *J* = 8.3, 7.6 Hz, 1H), 7.38–7.34 (m, 2H), 6.79 (dd, *J* = 7.5, 0.9 Hz, 1H), 4.81 (br, 2H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 151.1, 150.2, 145.2, 131.1, 131.0, 120.2, 119.2, 119.1, 109.6.

HRMS-FIA(m/z) calc'd for $C_9H_9N_2^+$ $[M+H]^+$, 145.0760; found, 145.0755.

6-Aminoquinoline (**3.2b**):

R_f = 0.21 (DCM/methanol/28% aqueous ammonium hydroxide (96.5/3.0/0.5 (v/v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 8.54 (dd, *J* = 4.2, 1.6 Hz, 1H), 7.94–7.91 (m, 1H), 7.77 (d, *J* = 9.0 Hz, 1H), 7.26 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.17 (dd, *J* = 8.9, 2.5 Hz, 1H), 6.88 (d, *J* = 2.5 Hz, 1H), 4.52 (br, 2H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 147.3, 147.0, 143.9, 134.2, 131.0, 130.9, 122.4, 122.3, 107.0.

HRMS-FIA(m/z) calc'd for $C_9H_9N_2^+$ $[M+H]^+$, 145.0760; found, 145.0762.

7-Aminoquinoline (**3.2c**):

R_f = 0.15 (DCM/methanol/28% aqueous ammonium hydroxide (96.5/3.0/0.5 (v/v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 8.64 (dd, *J* = 4.3, 1.8 Hz, 1H), 8.02–7.99 (m, 1H), 7.62 (d, *J* = 8.7 Hz, 1H), 7.11 (dd, *J* = 8.1, 4.3 Hz, 1H), 7.05 (d, *J* = 2.3 Hz, 1H), 7.02 (dd, *J* = 8.7, 2.3 Hz, 1H), 4.65 (br, 2H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 151.4, 151.2, 150.4, 136.4, 129.8, 122.5, 119.6, 118.2, 108.5.

HRMS-FIA(m/z) calc'd for $C_9H_9N_2^+$ $[M+H]^+$, 145.0760; found, 145.0753.

8-Aminoquinoline (**3.2d**):

R_f = 0.54 (DCM/methanol/28% aqueous ammonium hydroxide (96.5/3.0/0.5 (v/v/v)))

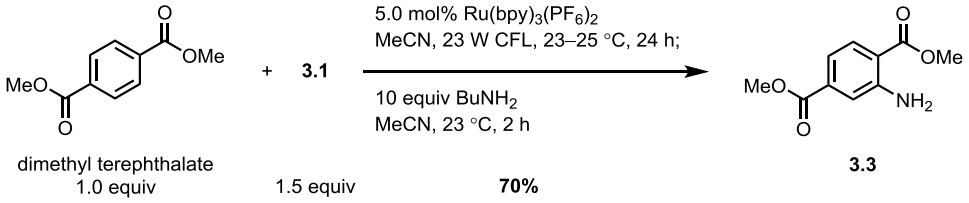
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 8.72 (dd, *J* = 4.1, 1.7 Hz, 1H), 8.13 (dd, *J* = 8.3, 1.7 Hz, 1H), 7.41 (dd, *J* = 8.3, 4.1 Hz, 1H), 7.32 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.13 (dd, *J* = 8.1, 1.2 Hz, 1H), 6.91 (dd, *J* = 7.5, 1.2 Hz, 1H), 5.26 (br, 2H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 148.4, 145.8, 138.9, 136.8, 129.8, 128.5, 122.4, 115.9, 110.1.

HRMS-FIA(m/z) calc'd for $C_9H_9N_2^+$ $[M+H]^+$, 145.0760; found, 145.0755.

Dimethyl 2-aminoterephthalate (3.3)



An oven-dried 20 mL vial was charged with a stirring bar, dimethyl terephthalate (78 mg, 0.40 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (17 mg, 20 µmol, 5.0 mol%), and **3.1** (243 mg, 0.600 mmol, 1.5 equiv). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, butylamine (0.40 mL, 4.0 mmol, 10 equiv) was added, and the mixture was stirred at 23 °C for 2 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by

chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (95/5 to 85/15 (v/v)) to afford 58 mg of **3.3** as a yellow solid (70% yield).

$\mathbf{R_f}$ = 0.71 (2-methylpentane/ethyl acetate (55/45 (v/v)))

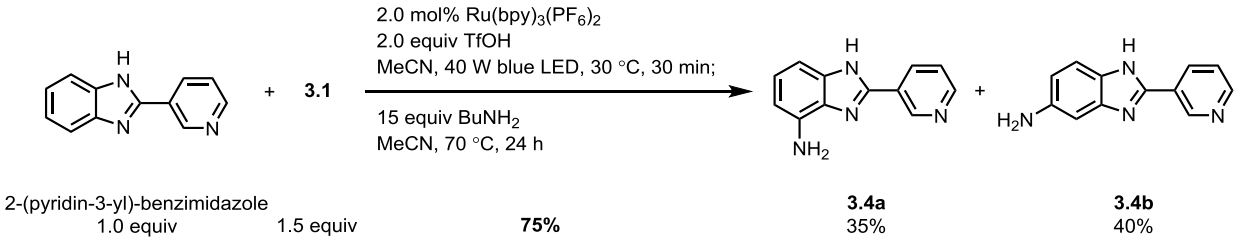
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 ºC, δ): 7.89 (d, 1H), 7.34 (d, 1H), 7.23 (dd, 1H), 5.82 (br, 2H), 3.89 (s, 3H), 3.88 (s, 3H).

^{13}C NMR (124 MHz, $CDCl_3$, 23 ºC, δ): 168.1, 166.7, 150.2, 134.9, 131.5, 118.1, 116.6, 113.9, 52.4, 51.9..

HRMS-FIA(m/z) calc'd for $C_{10}H_{12}NO_4^+$ $[M+H]^+$, 210.0761; found, 210.0767.

2-(Pyridin-3-yl)-benzimidazole analogues 3.4



An oven-dried 4 mL vial was charged with a stirring bar, 2-(pyridine-3-yl)-benzimidazole (39 mg, 0.20 mmol, 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (3.4 mg, 4.0 µmol, 2.0 mol%). Dry acetonitrile (1.0 mL, c = 0.20 M) was added via syringe. To the stirred mixture, trifluoromethanesulfonic acid (35 µL, 60 mg, 0.40 mmol, 1.0 equiv) was added via glass syringe, and then **3.1** (122 mg, 0.300 mmol, 1.5 equiv) was added. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 30 °C, irradiated with two 40 W blue LEDs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 30 min, butylamine (0.30 mL, 3.0 mmol, 15 equiv), and the mixture was stirred at 70 °C for 24 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent

mixture of DCM/methanol/28% aqueous ammonium hydroxide (97.5/2/0.5 to 95.5/4/0.5 (v/v/v)) to afford 15 mg of **3.4a** (35%) and 17 mg of **3.4b** (40%) as yellow solids (75% total yield).

2-(Pyridin-3-yl)-benzimidazole-4-amine (**3.4a**):

R_f = 0.30 (DCM/2-propanol/28% aqueous ammonium hydroxide (91.5/8.0/0.5 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3OD, 23 ºC, δ): 9.21 (d, *J* = 1.7 Hz, 1H), 8.60 (dd, *J* = 4.8, 1.6 Hz, 1H), 8.42 (ddd, *J* = 8.0, 2.1, 1.6 Hz, 1H), 7.56 (ddd, *J* = 8.0, 4.9, 0.8 Hz, 1H), 7.04 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.90 (d, *J* = 7.9 Hz, 1H), 6.56 (dd, *J* = 7.7, 0.8 Hz, 1H).

^{13}C NMR (124 MHz, CD_3OD, 23 ºC, δ): 150.8, 148.2, 148.0, 139.8, 139.4, 135.6, 132.5, 128.2, 125.8, 125.6, 108.2, 102.7.

HRMS-FIA(m/z) calc'd for $C_{12}H_{11}N_4^+$ $[M+H]^+$, 211.0978; found, 211.0982.

2-(Pyridin-3-yl)-benzimidazole-5-amine (**3.4b**):

R_f = 0.20 (DCM/2-propanol/28% aqueous ammonium hydroxide (91.5/8.0/0.5 (v/v)))

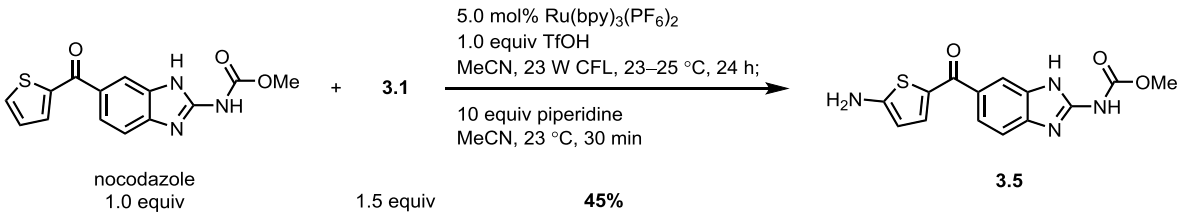
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3OD, 23 ºC, δ): 9.16 (dd, *J* = 2.3, 0.9 Hz, 1H), 8.56 (dd, *J* = 4.9, 1.6 Hz, 1H), 8.36 (ddd, *J* = 8.0, 2.3, 1.6 Hz, 1H), 7.50 (ddd, *J* = 8.0, 4.9, 0.9 Hz, 1H), 7.39 (dd, *J* = 8.6, 0.7 Hz, 1H), 6.91 (dd, *J* = 2.1, 0.6 Hz, 1H), 6.76 (dd, *J* = 8.6, 2.1 Hz, 1H).

^{13}C NMR (124 MHz, CD_3OD, 23 ºC, δ): 150.6, 148.7, 148.0, 145.7, 140.1, 135.5, 135.4, 128.2, 125.3, 117.7, 115.1, 99.8.

HRMS-FIA(m/z) calc'd for $C_{12}H_{11}N_4^+$ $[M+H]^+$, 211.0978; found, 211.0984.

Nocodazole analogue 3.5



An oven-dried 20 mL vial was charged with a stirring bar, nocodazole (120. mg, 0.400 mmol, 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (17 mg, 20 µmol, 5.0 mol%). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe. To the stirred mixture, trifluoromethanesulfonic acid (35 µL, 60 mg, 0.40 mmol, 1.0 equiv) was added via glass syringe, and then **3.1** (243 mg, 0.600 mmol, 1.5 equiv) was added. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, the reaction mixture was concentrated *in vacuo*, and the residue was triturated with DCM (2 × 5 mL). To the residue, acetonitrile (2.0 mL) and piperidine (0.40 mL, 4.0 mmol, 10 equiv) were added, and the mixture was stirred at 23 °C for 30 min. The reaction mixture was concentrated *in vacuo*, and the residue was purified by preparatory high-performance liquid chromatography with a solvent mixture of water (0.1% TFA)/acetonitrile (80/20 (v/v)) to afford 56 mg of **3.5·TFA** (45% yield) as a white solid. In the NMR sample preparation, a molar equivalent of trifluoromethanesulfonic acid was added to improve solubility. Protonated nocodazole analogue **3.5·TFA**:

R_f = 0.22 (DCM/methanol/trifluoroacetic acid (90/9.9/0.1 (v/v)))

NMR Spectroscopy:

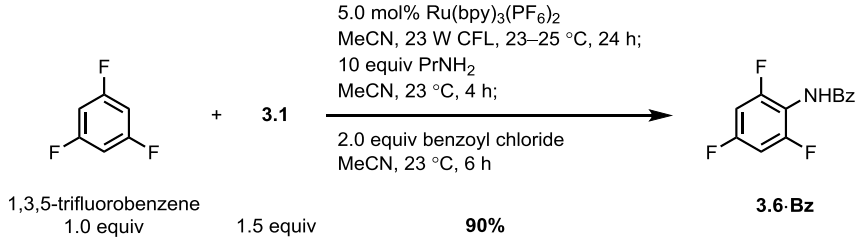
^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 12.15 (br, 2H), 10.91 (s, 1H), 7.99 (d, *J* = 1.4 Hz, 1H), 7.86 (d, *J* = 8.5 Hz, 1H), 7.79–7.73 (m, 2H), 6.92 (d, *J* = 5.3 Hz, 1H), 3.95 (s, 3H).

^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –77.8.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 181.9, 158.5, 158.2, 153.4, 149.5, 147.0, 132.1, 130.3, 129.3, 128.1, 123.1, 121.5 (q, triflate), 116.2 (q, TFA trifluoromethyl), 115.9, 114.7.

HRMS-FIA(m/z) calc'd for $C_{14}H_{13}N_4O_3S^+$ $[M+H]^+$, 317,0703; found, 317,0697.

***N*-(2,4,6-Trifluorophenyl)benzamide (3.6·Bz)**



An oven-dried 20 mL vial was charged with a stirring bar, $Ru(bpy)_3(PF_6)_2$ (17 mg, 20 µmol, 5.0 mol%), and **3.1** (243 mg, 0.600 mmol, 1.5 equiv). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe, and then 1,3,5-trifluorobenzene (41 µL, 53 mg, 0.40 mmol, 1.0 equiv) was added via glass syringe. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, propylamine (0.32 mL, 4.0 mmol, 10 equiv) were added, and the mixture was stirred at 23 °C for 4 h. The reaction mixture was concentrated *in vacuo*. To the residue, acetonitrile (2.0 mL) and benzoyl chloride (93 µL, 110 mg, 0.80 mmol, 2.0 equiv) were added, and the mixture was stirred at 23 °C for 6 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (20/80 (v/v)) to afford 90 mg of **3.6·Bz** as a yellow solid (90% yield).

$\mathbf{R_f}$ = 0.71 (2-methylpentane/ethyl acetate (55/45 (v/v)))

NMR Spectroscopy:

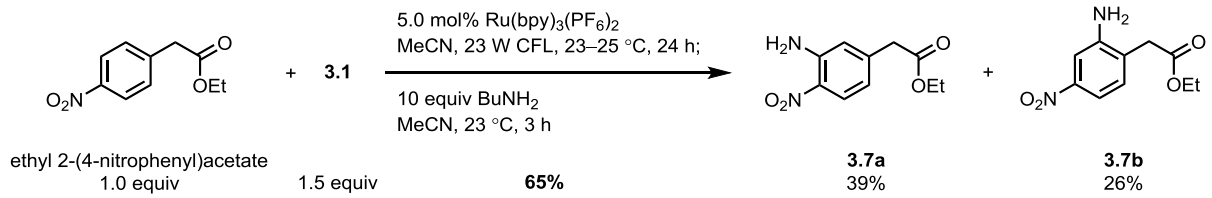
^{1}H NMR (500 MHz, CD_2Cl_2, 23 ºC, δ): 7.94–7.85 (m, 2H), 7.65 (br, 1H), 7.62–7.56 (m, 1H), 7.52–7.46 (m, 2H), 6.82–6.74 (m, 2H).

^{19}F NMR (500 MHz, CD_2Cl_2, 23 ºC, δ): –109.9, –115.0.

^{13}C NMR (124 MHz, CD_2Cl_2, 23 ºC, δ): 166.2, 161.2 (ddd, *J* = 249, 14.8, 14.8 Hz), 158.7 (ddd, *J* = 251, 15.3, 7.5 Hz), 133.6, 132.7, 129.1, 127.9, 111.3 (ddd, *J* = 16.5, 16.5, 4.9 Hz,), 101.2–100.6 (m).

HRMS-FIA(m/z) calc'd for $C_{13}H_9F_3NO^+$ $[M+H]^+$, 252,0631; found, 252,0624.

Ethyl 2-(4-nitrophenyl)acetate analogues 3.7



An oven-dried 20 mL vial was charged with a stirring bar, ethyl 2-(4-nitrophenyl)acetate (84 mg, 0.40 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (17 mg, 20 µmol, 5.0 mol%), and **3.1** (243 mg, 0.600 mmol, 1.5 equiv). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, butylamine (0.40 mL, 4.0 mmol, 10 equiv) was added, and the mixture was stirred at 23 °C for 3 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (90/10 to 70/30 (v/v)) to afford 35 mg of **3.7a** (39%) and 23 mg of **3.7b** (26%) as yellow solids (65% total yield).

Ethyl 2-(3-amino-4-nitrophenyl)acetate (**3.7a**):

R_f = 0.55 (2-methylpentane/ethyl acetate (55/45 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 7.54 (d, *J* = 2.3 Hz, 1H), 7.46 (dd, *J* = 8.3, 2.3 Hz, 1H), 7.22 (d, *J* = 8.3 Hz, 1H), 4.66 (br, 2H), 4.12 (q, 2H), 3.64–3.56 (m, 2H), 1.22 (t, 3H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 171.3, 149.2, 148.5, 132.7, 127.0, 112.8, 110.2, 62.0, 38.1, 14.4.

HRMS-FIA(m/z) calc'd for $C_{10}H_{12}N_2O_4Na^+$ $[M+Na]^+$, 247.0689; found, 247.0690.

Ethyl 2-(2-amino-4-nitrophenyl)acetate (**3.7b**):

R_f = 0.50 (2-methylpentane/ethyl acetate (55/45 (v/v)))

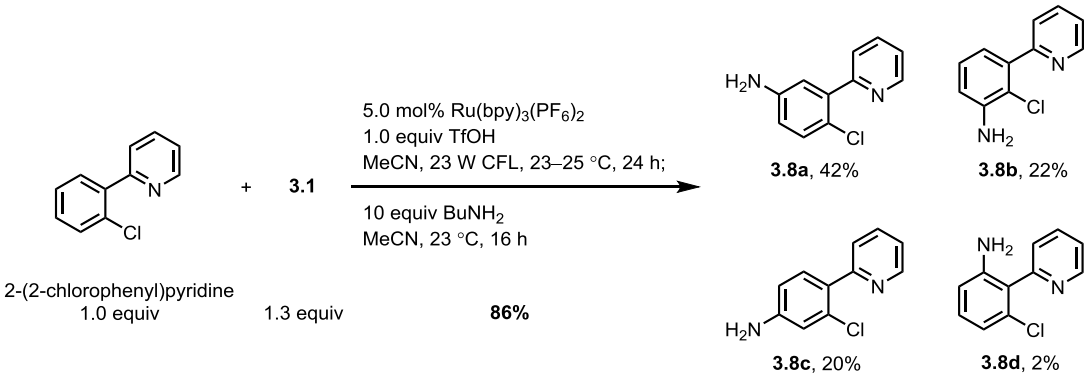
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3OD, 23 ºC, δ): 7.98 (d, *J* = 8.8 Hz, 1H), 6.84 (d, *J* = 1.8 Hz, 1H), 6.57 (dd, *J* = 8.8, 1.8 Hz, 1H), 6.50 (br, 2H), 4.12 (q, 2H), 3.60–3.52 (m, 2H), 1.22 (t, 3H).

^{13}C NMR (124 MHz, CD_3OD, 23 ºC, δ): 171.4, 146.6, 144.0, 131.6, 126.8, 120.1, 118.6, 61.8, 41.4, 14.5.

HRMS-FIA(m/z) calc'd for $C_{10}H_{13}N_2O_4^+$ $[M+H]^+$, 225.0870; found, 225.0870.

2-(2-Chlorophenyl)pyridine analogues 3.8



An oven-dried 20 mL vial was charged with a stirring bar, 2-(2-chlorophenyl)pyridine (76 mg, 0.40 mmol, 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (17 mg, 20 µmol, 5.0 mol%). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe. To the stirred mixture, trifluoromethanesulfonic acid (35

μL, 60 mg, 0.40 mmol, 1.0 equiv) was added via glass syringe, and then **3.1** (211 mg, 0.521 mmol, 1.3 equiv) was added. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, the reaction mixture was concentrated *in vacuo*, and the residue was purified by preparatory high-performance liquid chromatography with a solvent mixture of water (0.1% TFA)/acetonitrile (80/20 (v/v)) to afford 80 mg of fraction **a**, 55 mg of fraction **b**, 31 mg of fraction **c**, and 7 mg of fraction **d** as yellow oils.

To a 20 mL vial, charged with the fraction **a** and a stirring bar, butylamine (0.40 mL, 4.0 mmol) was added, and the mixture was stirred at 23 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (80/20 to 20/80 (v/v)) to afford 34 mg of **3.8a** (42% yield).

To a 20 mL vial, charged with the fraction **b** and a stirring bar, butylamine (0.40 mL, 4.0 mmol) was added, and the mixture was stirred at 23 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (80/20 to 20/80 (v/v)) to afford 18 mg of **3.8b** (22% yield).

To a 20 mL vial, charged with the fraction **c** and a stirring bar, butylamine (0.40 mL, 4.0 mmol) was added, and the mixture was stirred at 23 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (80/20 to 20/80 (v/v)) to afford 16 mg of **3.8c** (20% yield).

To a 20 mL vial, charged with the fraction **d** and a stirring bar, butylamine (0.40 mL, 4.0 mmol) was added, and the mixture was stirred at 23 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (80/20 to 20/80 (v/v)) to afford 2 mg of **3.8d** (2% yield).

2-(2-Chlorophenyl)pyridine analogue **3.8a**:

R_f = 0.14 (2-methylpentane/ethyl acetate (55/45 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_2Cl_2, 23 ºC, δ): 8.66 (ddd, *J* = 4.8, 1.7, 0.9 Hz, 1H), 7.75 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.62 (ddd, *J* = 7.8, 1.0, 1.0 Hz, 1H), 7.28 (ddd, *J* = 7.4, 4.8, 1.0 Hz, 1H), 7.21 (d, *J* = 8.5 Hz, 1H), 6.89 (d, *J* = 2.9 Hz, 1H), 6.67 (dd, *J* = 8.5, 2.9 Hz, 1H), 2.99 (br, 2H).

^{13}C NMR (124 MHz, CD_2Cl_2, 23 ºC, δ):157.4, 149.8, 146.2, 140.1, 136.1, 130.9, 125.1, 122.7, 120.9, 118.0, 116.5.

HRMS-FIA(m/z) calc'd for $C_{11}H_{10}ClN_2^+$ $[M+H]^+$, 205.0527; found, 205.0526.

2-(2-Chlorophenyl)pyridine analogue **3.8b**:

R_f = 0.32 (2-methylpentane/ethyl acetate (55/45 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_2Cl_2, 23 ºC, δ): 8.67 (ddd, *J* = 4.8, 1.8, 0.9 Hz, 1H), 7.76 (ddd, *J* = 7.7, 7.7, 1.8 Hz, 1H), 7.54 (ddd, *J* = 7.8, 1.0, 1.0 Hz, 1H), 7.29 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 7.15 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.87 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.84 (dd, *J* = 7.9, 1.5 Hz, 1H), 4.25 (br, 2H).

^{13}C NMR (124 MHz, CD_2Cl_2, 23 ºC, δ): 158.0, 149.7, 144.2, 140.6, 136.1, 127.5, 125.0, 122.6, 121.0, 117.5, 115.8.

HRMS-FIA(m/z) calc'd for $C_{11}H_{10}ClN_2^+$ $[M+H]^+$, 205.0527; found, 205.0525.

2-(2-Chlorophenyl)pyridine analogue **3.8c**:

R_f = 0.21 (2-methylpentane/ethyl acetate (55/45 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_2Cl_2, 23 ºC, δ): 8.64 (d, *J* = 4.8 Hz, 1H), 7.72 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.62 (d, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 8.3 Hz, 1H), 7.22 (ddd, *J* = 7.4, 4.8, 1.0 Hz, 1H), 6.77 (d, *J* = 2.3 Hz, 1H), 6.66 (dd, *J* = 8.3, 2.3 Hz, 1H), 3.65 (br, 2H).

^{13}C NMR (124 MHz, CD_2Cl_2, 23 ºC, δ): 157.3, 149.6, 148.4, 136.0, 132.9, 132.8, 129.3, 125.0, 122.0, 115.8, 113.9.

HRMS-FIA(m/z) calc'd for $C_{11}H_{10}ClN_2^+$ $[M+H]^+$, 205.0527; found, 205.0527.

2-(2-Chlorophenyl)pyridine analogue **3.8d**:

R_f = 0.25 (2-methylpentane/ethyl acetate (55/45 (v/v)))

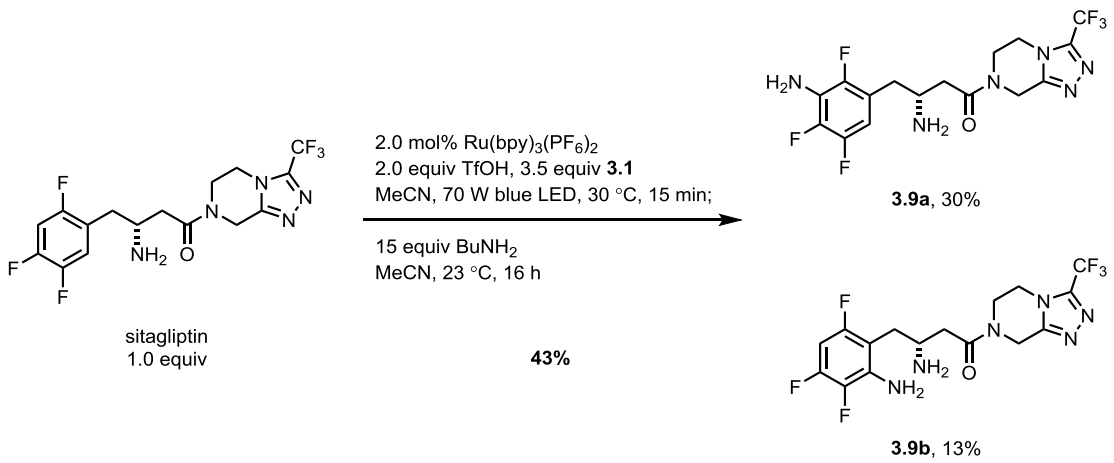
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_2Cl_2, 23 ºC, δ): 8.70 (ddd, *J* = 4.8, 1.8, 1.0 Hz, 1H), 7.83 (ddd, *J* = 7.8, 7.8, 1.8 Hz, 1H), 7.50 (ddd, *J* = 7.8, 7.8, 1.0 Hz, 1H), 7.30 (ddd, *J* = 7.6, 4.8, 1.1 Hz, 1H), 7.09 (dd, *J* = 8.0, 8.0 Hz, 1H), 6.85 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.69 (dd, *J* = 8.1, 1.1 Hz, 1H).

^{13}C NMR (124 MHz, CD_2Cl_2, 23 ºC, δ): 156.0, 149.9, 147.4, 137.1, 133.5, 130.1, 127.1, 124.6, 122.9, 119.4, 114.9.

HRMS-FIA(m/z) calc'd for $C_{11}H_{10}ClN_2^+$ $[M+H]^+$, 205.0527; found, 205.0530.

Sitagliptin analogues 3.9



An oven-dried 4 mL vial was charged with a stirring bar, sitagliptin (122 mg, 0.300 mmol, 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (5.2 mg, 6.0 μmol, 2.0 mol%). Dry acetonitrile (1.5 mL, c = 0.20 M) was added via syringe. To the stirred mixture, trifluoromethanesulfonic acid (53 μL, 90 mg, 0.60 mmol, 2.0 equiv) was added via glass syringe, and then **3.1** (182 mg, 0.450 mmol, 1.5 equiv) was added. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 30 °C, irradiated with a 70 W blue LED (2 cm away from the vial), and cooled with an electric cooler (surrounding the vial). After 5 min, **3.1** (122 mg, 0.300 mmol, 1.0 equiv) was added and the mixture was stirred with irradiation. After 5 min, **3.1** (122 mg, 0.300 mmol, 1.0 equiv) was added again and the mixture was stirred with irradiation. After 5 min, butylamine (0.45 mL, 4.5 mmol, 15 equiv) was added, and the mixture was stirred at 23 °C for 16 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparatory high-performance liquid chromatography with a solvent mixture of water (0.1% TFA)/acetonitrile (60:40 (v/v)) to afford 55 mg and 26 mg of **3.9a·TFA** and **3.9b·TFA**, respectively, containing unidentified impurities. The fraction containing **3.9a·TFA** was further purified by preparatory high-performance liquid chromatography with a solvent mixture of water (0.1% TFA)/methanol (60/40 (v/v)) to afford 48 mg of **3.9a·TFA** as a yellow solid (30% yield). The fraction containing **3.9b·TFA** was further

purified by preparatory high-performance liquid chromatography with a solvent mixture of water (0.1% TFA)/methanol (60/40 (v/v)) to afford 21 mg of **3.9b·TFA** as a yellow solid (13% yield).

Sitagliptin analogue **3.9a·TFA**:

$\mathbf{R_f}$ = 0.11 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 7.00 (br, 3H), 6.52–6.45 (m, 1H), 5.05–4.75 (m, 2H), 4.28–4.10 (m, 2H), 4.06–3.94 (m, 1H), 3.93–3.75 (m, 2H), 3.07–2.83 (m, 3H), 2.82–2.67 (m, 1H).

^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –65.1, –77.9, –142.1, –146.2, –159.5.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 171.3/171.2 (rotameric), 160.3 (q, *J* = 37.9 Hz), 151.9/151.4 (rotameric), 148.2 (ddd, *J* = 239, 11.3, 2.7 Hz), 147.3 (dd, *J* = 235, 5.0 Hz), 144.2 (q, *J* = 40.3 Hz), 140.2 (ddd, *J* = 238, 15.9, 7.7 Hz), 128.3–128.0 (m), 120.5, 116.7 (q, *J* = 288 Hz), 105.2 (ddd, *J* = 20.2, 4.7, 4.7 Hz), 50.8/50.7 (rotameric), 44.5/44.1 (rotameric), 42.9/39.7 (rotameric), 42.1/38.7 (rotameric), 34.1/33.9 (rotameric), 32.1/32.0 (rotameric).

HRMS-FIA(m/z) calc'd for $C_{16}H_{17}F_6N_6O^+$ $[M+H]^+$, 423.1363; found, 423.1364.

Sitagliptin analogue **3.9b·TFA**:

$\mathbf{R_f}$ = 0.15 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

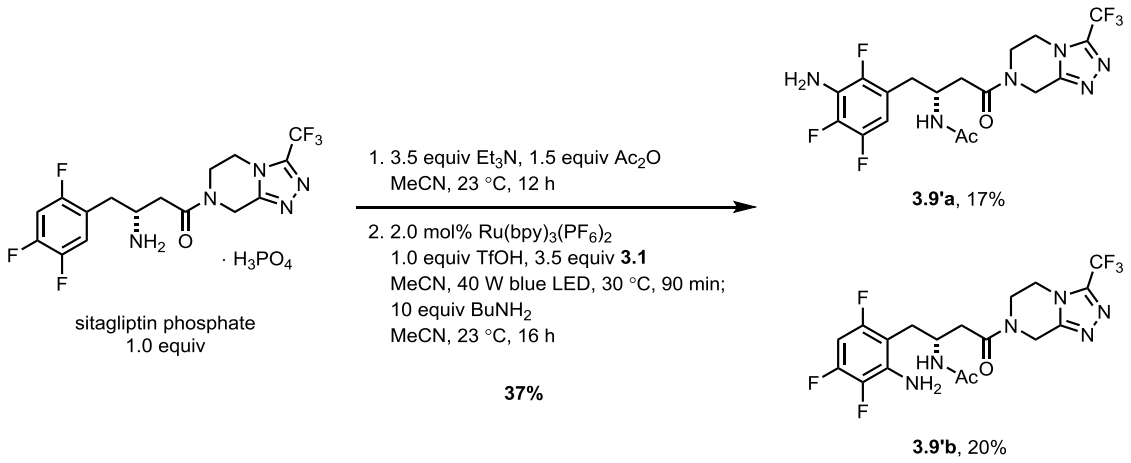
^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 7.53 (br, 3H), 6.44–6.34 (m, 1H), 4.99–4.78 (m, 2H), 4.20–4.07 (m, 2H), 4.04–3.95 (m, 1H), 3.89–3.74 (m, 2H), 3.08–2.94 (m, 2H), 2.92–2.80 (m, 2H).

^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –65.2, –77.9, –121.6, –140.8, –167.2.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 171.2/171.1 (rotameric), 160.7 (q, *J* = 36.7 Hz), 158.0 (dd, *J* = 238, 14.5 Hz), 151.7/151.2 (rotameric), 150.6 (ddd, *J* = 242, 15.6, 11.2 Hz), 144.2 (q, *J* = 39.6 Hz), 138.7–138.4 (m), 137.4 (dd, *J* = 233, 13.9 Hz), 119.6 (q, *J* = 268 Hz), 105.0 (ddd, *J* = 21.2, 2.5, 2.5 Hz), 93.1 (dd, *J* = 29.9, 22.2 Hz), 49.3, 44.3/44.0 (rotameric), 43.0/39.8 (rotameric), 42.2/38.7 (rotameric), 34.2/34.0 (rotameric), 27.1.

HRMS-FIA(m/z) calc'd for $C_{16}H_{17}F_6N_6O^+$ $[M+H]^+$, 423.1363; found, 423.1370.

***N*-Ac-Sitagliptin analogues 3.9'**



An oven-dried 4 mL vial was charged with a stirring bar and sitagliptin phosphate (104 mg, 0.200 mmol, 1.0 equiv). Dry acetonitrile (1.0 mL, c = 0.20 M) was added via syringe. Triethylamine (98 µL, 71 mg, 0.7 mmol, 3.5 equiv) and acetic anhydride (28 µL, 31 mg, 0.30 mmol, 1.5 equiv) were consecutively added via glass syringe. The vial was sealed with a plastic cap, and the mixture was stirred at 23 °C. After 12 h, saturated aqueous sodium bicarbonate (5 mL) and water (5 mL) were added, and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*.

The residue was transferred to an oven-dried 4 mL vial charged with a stirring bar and $Ru(bpy)_3(PF_6)_2$ (3.4 mg, 4.0 µmol, 2.0 mol%). Dry acetonitrile (1.0 mL, c = 0.20 M) was added via syringe. To the stirred mixture, trifluoromethanesulfonic acid (18 µL, 30 mg, 0.20 mmol, 1.0

equiv) was added via glass syringe, and then **3.1** (122 mg, 0.300 mmol, 1.5 equiv) was added. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 30 °C, irradiated with two 40 W blue LEDs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 30 min, **3.1** (81 mg, 0.20 mmol, 1.0 equiv) was added and the mixture was stirred with irradiation. After 30 min, **3.1** (81 mg, 0.20 mmol, 1.0 equiv) was added again and the mixture was stirred with irradiation. After 30 min, butylamine (0.20 mL, 2.0 mmol, 10 equiv) was added, and the mixture was stirred at 23 °C for 16 h. The reaction mixture was concentrated *in vacuo*. The residue was purified by preparatory high-performance liquid chromatography with a solvent mixture of water/acetonitrile (60:40 (v/v)) to afford 21 mg and 22 mg of **3.9'a** and **3.9'b**, respectively, containing unidentified impurities. The fraction containing **3.9'a** was further purified by preparatory high-performance liquid chromatography with a solvent mixture of water (0.1% TFA)/methanol (50/50 (v/v)) to afford 16 mg of **3.9'a** as a white solid (17% yield). The fraction containing **3.9'b** was further purified by preparatory high-performance liquid chromatography with a solvent mixture of water/methanol (40/60 (v/v)) to afford 19 mg of **3.9'b** as a white solid (20% yield).

N-Ac-Sitagliptin analogue **3.9'a**:

$\mathbf{R_f}$ = 0.36 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 6.60/6.54 (d, *J* = 8.1 Hz, 1H, rotameric), 6.46–6.38 (m, 1H), 4.93–4.81 (m, 2H), 4.59–4.21 (m, 3H), 4.21–4.03 (m, 2H), 4.01–3.84 (m, 2H), 2.89–2.72 (m, 2H), 2.72–2.53 (m, 2H), 1.76/1.71 (s, 3H, rotameric).

^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –64.6, –142.4, –147.1, –160.8.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 170.7/170.6 (rotameric), 170.3, 152.0/151.6 (rotameric), 147.9 (ddd, *J* = 238, 10.6, 3.0 Hz), 145.2 (d, *J* = 234 Hz), 142.3 (q, *J* = 38 Hz), 137.6 (ddd, *J* = 238, 16.5, 7.6 Hz), 125.5 (ddd, *J* = 19.1, 12.9, 3.1 Hz), 120.1–119.7 (m), 117.8 (q, *J* = 269 Hz), 103.2 (dd, *J* = 19.6, 4.8 Hz), 47.6/47.5 (rotameric), 44.6/44.1 (rotameric), 43.3/39.6 (rotameric), 42.3/38.6 (rotameric), 38.2/37.7 (rotameric), 33.8/33.6 (rotameric), 23.1/23.0 (rotameric).

HRMS-FIA(m/z) calc'd for $C_{18}H_{19}F_6N_6O_2^+$ $[M+H]^+$, 465.1468; found, 465.1472.

N-Ac-Sitagliptin analogue **3.9'b**:

R_f = 0.42 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

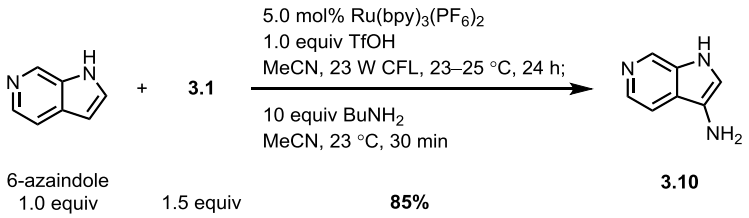
^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 6.68 (d, *J* = 8.0 Hz, 1H), 6.33–6.23 (m, 1H), 5.44 (br, 2H), 4.97–4.83 (m, 2H), 4.28–4.18 (m, 1H), 4.18–4.06 (m, 2H), 4.04–3.81 (m, 2H), 2.76–2.56 (m, 4H), 1.82/1.80 (s, 3H, rotameric).

^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –64.6, –122.9, –141.8, –168.1.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 171.4, 171.2, 157.5 (dd, *J* = 239, 13.6 Hz), 152.0/151.5 (rotameric), 149.9 (ddd, *J* = 241, 16.6, 11.6 Hz), 144.1 (q, *J* = 38.9 Hz), 138.4 (ddd, *J* = 9.6, 9.6, 4.0 Hz), 136.9 (ddd, *J* = 233, 14.4, 3.6 Hz), 119.7 (q, *J* = 269 Hz), 107.7 (ddd, *J* = 21.5, 2.8, 2.8 Hz), 92.0 (dd, *J* = 30.4, 21.9 Hz), 46.7, 44.4/44.1 (rotameric), 43.0/39.7 (rotameric), 42.2/38.6 (rotameric), 37.4/37.1 (rotameric), 29.2, 25.0.

HRMS-FIA(m/z) calc'd for $C_{18}H_{19}F_6N_6O_2^+$ $[M+H]^+$, 465.1468; found, 465.1473.

1*H*-Pyrrolo[2,3-*c*]pyridine-3-amine (3.10)



An oven-dried 20 mL vial was charged with a stirring bar, 6-azaindole (47 mg, 0.40 mmol, 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (17 mg, 20 µmol, 5.0 mol%). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe. To the stirring mixture, trifluoromethanesulfonic acid (35 µL, 60 mg, 0.40 mmol, 1.0 equiv) was added via glass syringe, and then **3.1** (243 mg, 0.600 mmol, 1.5 equiv) were added. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, the reaction mixture was concentrated *in vacuo*, and the residue was triturated with DCM (2 × 5 mL). To the residue, acetonitrile (2.0 mL) and butylamine (0.40 mL, 4.0 mmol, 10 equiv) was added, and the mixture was stirred at 23 °C for 30 min. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-propanol/28% aqueous ammonium hydroxide (99.5/0.5 (v/v)) to afford 45 mg of **3.10** as a yellow solid (85% yield).

R_f = 0.72 (DCM/2-propanol (20/80 (v/v)))

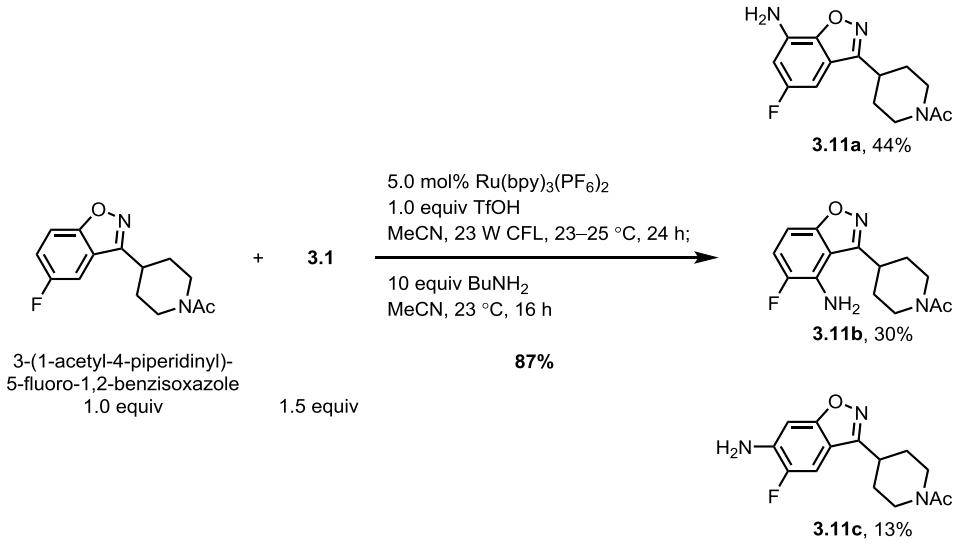
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 8.29 (dd, *J* = 0.9, 0.9 Hz, 1H), 7.91 (d, *J* = 5.4 Hz, 1H), 7.10 (dd, *J* = 5.4, 0.9 Hz, 1H), 5.42 (d, *J* = 0.9 Hz, 1H), 4.86 (bs, 2H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 150.6, 139.3, 137.0, 131.6, 130.8, 112.2, 80.6.

HRMS-FIA(m/z) calc'd for $C_7H_8N_3^+$ $[M+H]^+$, 134.0713; found, 134.0706.

Fluorobenzisoxazole analogues 3.11



An oven-dried 20 mL vial was charged with a stirring bar, 3-(1-acetyl-4-piperidinyl)-5-fluoro-1,2-benzisoxazole (105 mg, 0.400 mmol, 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (17 mg, 20 µmol, 5.0 mol%). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe. To the stirred mixture, trifluoromethanesulfonic acid (35 µL, 60 mg, 0.40 mmol, 1.0 equiv) was added via glass syringe, and then **3.1** (243 mg, 0.600 mmol, 1.5 equiv) was added. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, butylamine (0.40 mL, 4.0 mmol, 10 equiv) was added, and the mixture was stirred at 23 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/methanol (99/1 to 95/5 (v/v)) to afford 45 mg of a yellow mixture that contains **3.11a**, **3.11b**, and **3.11c**. The mixture was purified by preparatory high-performance liquid chromatography with a solvent mixture of water (0.1% TFA)/acetonitrile (60:40 (v/v)) to afford 48 mg of **3.11a** (44%), 33 mg of **3.11b** (30%), and 14 mg of **3.11c** (13%) as white solids (87% total yield).

Fluorobenzisoxazole analogue **3.11a**:

$\mathbf{R_f}$ = 0.25 (DCM/methanol (94/6 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_2Cl_2, 23 ºC, δ): 6.75 (dd, *J* = 8.3, 2.3 Hz, 1H), 6.59 (dd, *J* = 11.0, 2.3 Hz, 1H), 4.86 (br, 2H), 4.57–4.48 (m, 1H), 3.98–3.88 (m, 1H), 3.32–3.18 (m, 2H), 2.83–2.72 (m, 1H), 2.12–1.99 (m, 5H), 1.90–1.79 (m, 1H), 1.76–1.64 (m, 1H).

^{19}F NMR (500 MHz, CD_2Cl_2, 23 ºC, δ): –121.0.

^{13}C NMR (124 MHz, CD_2Cl_2, 23 ºC, δ): 169.5, 162.8 (d, *J* = 4.7 Hz), 161.1 (d, *J* = 236 Hz), 150.8, 134.1 (d, *J* = 13.1 Hz), 121.8 (d, *J* = 12.8 Hz), 101.8 (d, *J* = 30.7 Hz), 94.2 (d, *J* = 26.3 Hz), 46.9, 41.8, 35.0, 31.2, 30.7, 21.7.

HRMS-FIA(m/z) calc'd for $C_{14}H_{17}FN_3O_2^+$ $[M+H]^+$, 278.1299; found, 278.1304.

Fluorobenzisoxazole analogue **3.11b**:

R_f = 0.25 (DCM/methanol (94/6 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 7.24 (dd, *J* = 11.5, 8.8 Hz, 1H), 6.77 (dd, *J* = 8.8, 3.0 Hz, 1H), 4.75 (br, 2H), 4.56–4.48 (m, 1H), 3.99–3.89 (m, 1H), 3.45–3.36 (m, 1H), 3.33–3.24 (m, 1H), 2.89–2.80 (m, 1H), 2.19–2.09 (m, 2H), 2.04 (s, 3H), 1.89–1.77 (m, 1H), 1.72–1.59 (m, 1H).

^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –148.4.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 169.5, 162.1 (d, *J* = 4.9 Hz), 161.6, 147.2 (d, *J* = 227 Hz), 130.7 (d, *J* = 16.6 Hz), 118.9 (d, *J* = 23.9 Hz), 111.4 (d, *J* = 5.3 Hz), 97.7 (d, *J* = 8.0 Hz), 46.7, 41.6, 35.3, 31.6, 31.2, 21.7.

HRMS-FIA(m/z) calc'd for $C_{14}H_{17}FN_3O_2^+$ $[M+H]^+$, 278.1299; found, 278.1302.

Fluorobenzisoxazole analogue **3.11c**:

R_f = 0.25 (DCM/methanol (94/6 (v/v)))

NMR Spectroscopy:

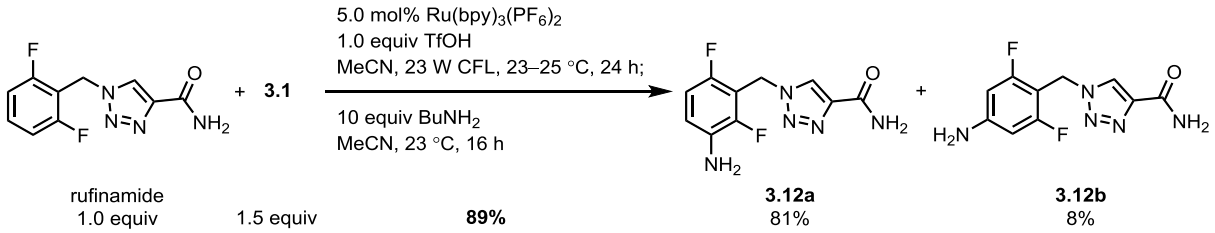
^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 7.24 (d, *J* = 10.2 Hz, 1H), 6.85 (d, *J* = 6.9 Hz, 1H), 4.63–4.56 (m, 1H), 4.31 (br, 2H), 3.96–3.90 (m, 1H), 3.29–3.14 (m, 2H), 2.85–2.76 (m, 1H), 2.12–2.00 (m, 5H), 1.96–1.74 (m, 2H).

^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –143.6.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 169.0, 161.4, 161.0 (d, *J* = 4.3 Hz), 149.7 (d, *J* = 237 Hz), 138.9 (dd, *J* = 16.2, 6,1 Hz), 110.9 (d, *J* = 9.6 Hz), 106.0 (d, *J* = 22.6 Hz), 94.9–94.8 (m), 46.6, 41.5, 34.7, 31.0, 30.5, 21.7.

HRMS-FIA(m/z) calc'd for $C_{14}H_{17}FN_3O_2^+$ $[M+H]^+$, 278.1299; found, 278.1304.

Rufinamide analogues 3.12



An oven-dried 20 mL vial was charged with a stirring bar, rufinamide (95 mg, 0.40 mmol, 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (17 mg, 20 µmol, 5.0 mol%). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe. To the stirred mixture, trifluoromethanesulfonic acid (35 µL, 60 mg, 0.40 mmol, 1.0 equiv) was added via glass syringe, and then **3.1** (243 mg, 0.600 mmol, 1.5 equiv) was added. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, butylamine (0.40 mL, 4.0 mmol, 10 equiv) was added, and the mixture was stirred at 23 °C for 16 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/methanol/28% aqueous ammonium hydroxide (95.5/4.5/0.5 (v/v)) to afford 45 mg of a red

solid that contains **3.12a** and **3.12b**. The mixture was purified by preparatory high-performance liquid chromatography with a solvent mixture of water/acetonitrile (60:40 (v/v)) to afford 82 mg of **3.12a** (81%) and 8 mg of **3.12b** (8%) as white solids (89% total yield).

Rufinamide analogue **3.12a**:

R_f = 0.69 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, $(CD_3)_2SO$, 23 ºC, δ): 8.47 (s, 1H), 7.85 (br, 1H), 7.46 (br, 1H), 6.86 (ddd, *J* = 9.1, 9.1, 1.3 Hz, 1H), 6.79 (ddd, *J* = 9.7, 9.7, 5.8 Hz, 1H), 5.65 (s, 2H), 5.13 (s, 2H).

^{19}F NMR (500 MHz, $(CD_3)_2SO$, 23 ºC, δ): –132.6 (dd, *J* = 7.0, 7.0 Hz), –135.7 (d, *J* = 9.5 Hz).

^{13}C NMR (124 MHz, $(CD_3)_2SO$, 23 ºC, δ): 161.3, 151.2 (dd, *J* = 236, 5.7 Hz), 148.1(dd, *J* = 243, 6.7 Hz), 142.8, 133.3 (dd, *J* = 13.0, 2.4 Hz), 126.7, 116.2 (dd, *J* = 8.6, 6.2 Hz), 111.0 (dd, *J* = 22.0, 3.6 Hz), 110.5 (dd, *J* = 20.2, 16.7 Hz), 41.6 (dd, *J* = 3.8, 3.8 Hz).

HRMS-FIA(m/z) calc'd for $C_{10}H_{10}F_2N_5O^+$ $[M+H]^+$, 254.0848; found, 254.0844.

Rufinamide analogue **3.12b**:

R_f = 0.67 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

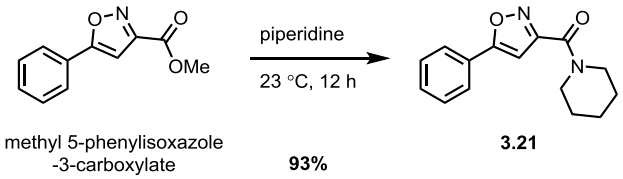
^{1}H NMR (500 MHz, $(CD_3)_2SO$, 23 ºC, δ): 8.37 (s, 1H), 7.82 (br, 1H), 7.44 (br, 1H), 6.26–6.19 (m, 2H), 5.95 (s, 2H), 5.47 (s, 2H).

^{19}F NMR (500 MHz, $(CD_3)_2SO$, 23 ºC, δ): –116.6 (m).

^{13}C NMR (124 MHz, $(CD_3)_2SO$, 23 ºC, δ): 161.8 (dd, *J* = 244, 11.3 Hz), 161.4, 152.0 (dd, *J* = 14.8, 14.8 Hz), 142.8, 126.1, 96.5 (dd, *J* = 20.3, 20.3 Hz), 96.1–95.8 (m), 41.2 (dd, *J* = 3.6, 3.6 Hz).

HRMS-FIA(m/z) calc'd for $C_{10}H_{10}F_2N_5O^+$ $[M+H]^+$, 254.0848; found, 254.0849.

(5-Phenylisoxazol-3-yl)(piperidin-1-yl)methanone (3.21)



methyl 5-phenylisoxazole -3-carboxylate

93%

3.21

A 4 mL vial was charged with a stirring bar, methyl 5-phenylisoxazole-3-carboxylate (305 mg, 1.50 mmol, 1.0 equiv), and piperidine (0.59 mL, 508 mg, 6.0 mmol, 4.0 equiv). The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23 °C for 12 h. The reaction mixture was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (75/25 (v/v)) to afford 357 mg of **3.21** as a yellow solid (93% yield).

$\mathbf{R_f}$ = 0.26 (2-methylpentane/ethyl acetate (80/20 (v/v)))

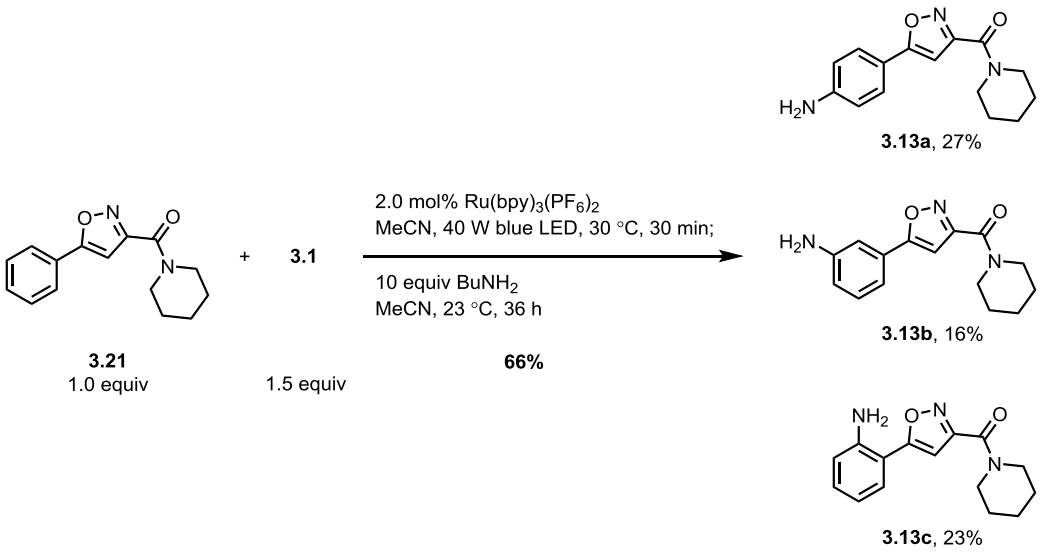
NMR Spectroscopy:

^{1}H NMR (500 MHz, $CDCl_3$, 23 ºC, δ): 7.67–7.62 (m, 2H), 7.34–7.27 (m, 3H), 6.67 (s, 1H), 3.60 (t, 4H), 1.60–1.44 (m, 6H).

^{13}C NMR (124 MHz, $CDCl_3$, 23 ºC, δ): 169.7, 159.1, 159.0, 130.2, 128.7, 126.4, 125.5, 100.1, 47.8, 43.2, 26.4, 25.3, 24.1.

HRMS-FIA(m/z) calc'd for $C_{15}H_{17}N_2O_2^+$ $[M+H]^+$, 257.1285; found, 257.1286.

(5-Phenylisoxazol-3-yl)(piperidin-1-yl)methanone analogues 3.13



An oven-dried 4 mL vial was charged with a stirring bar, **3.21** (51 mg, 0.20 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (3.4 mg, 4.0 µmol, 2.0 mol%), and **3.1** (122 mg, 0.300 mmol, 1.5 equiv). Dry acetonitrile (1.0 mL, c = 0.20 M) was added via syringe. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 30 °C, irradiated with two 40 W blue LEDs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 30 min, butylamine (0.30 mL, 2.0 mmol, 10 equiv) was added, and the mixture was stirred at 23 °C for 36 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/methanol (99/1 to 95/5 (v/v)) to afford a mixture containing **3.13a**, **3.13b**, and **3.13c**. The mixture was further purified by preparatory high-performance liquid chromatography with a solvent mixture of water (0.1% TFA)/acetonitrile (50/50 (v/v)) to afford 15 mg of **3.13a** (27% yield), 8.9 mg of **3.13b** (16% yield), and 12 mg of **3.13c** (23% yield) as white solids (total 66% yield).

(5-Phenylisoxazol-3-yl)(piperidin-1-yl)methanone analogue **3.13a**:

$\mathbf{R_f}$ = 0.22 (2-methylpentane/ethyl acetate (55/45 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3OD, 23 ºC, δ): 7.84–7.79 (m, 2H), 7.20–7.16 (m, 2H), 6.85 (s, 1H), 3.73 (t, 2H), 3.63 (t, 2H), 1.78–1.60 (m, 6H).

^{13}C NMR (124 MHz, CD_3OD, 23 ºC, δ): 171.6, 161.6, 160.4, 142.9, 128.6, 122.9, 120.6, 99.7, 49.5, 44.6, 27.7, 26.7, 25.3.

HRMS-FIA(m/z) calc'd for $C_{15}H_{18}N_3O_2^+$ $[M+H]^+$, 272.1394; found, 272.1388.

(5-Phenylisoxazol-3-yl)(piperidin-1-yl)methanone analogue **3.13b**:

R_f = 0.18 (2-methylpentane/ethyl acetate (55/45 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3OD, 23 ºC, δ): 7.80 (ddd, *J* = 7.9, 1.7, 1.0 Hz, 1H), 7.74 (dd, *J* = 1.9, 1.9 Hz, 1H), 7.60 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.38 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 1H), 7.04 (s, 1H), 3.74 (t, 2H), 3.66 (t, 2H), 1.80–1.60 (m, 6H).

^{13}C NMR (124 MHz, CD_3OD, 23 ºC, δ): 170.6, 161.3, 160.6, 137.4, 132.0, 129.6, 124.8, 124.4, 119.4, 101.8, 49.5, 44.6, 27.7, 26.7, 25.3.

HRMS-FIA(m/z) calc'd for $C_{15}H_{18}N_3O_2^+$ $[M+H]^+$, 272.1394; found, 272.1390.

(5-Phenylisoxazol-3-yl)(piperidin-1-yl)methanone analogue **3.13c**:

R_f = 0.33 (2-methylpentane/ethyl acetate (55/45 (v/v)))

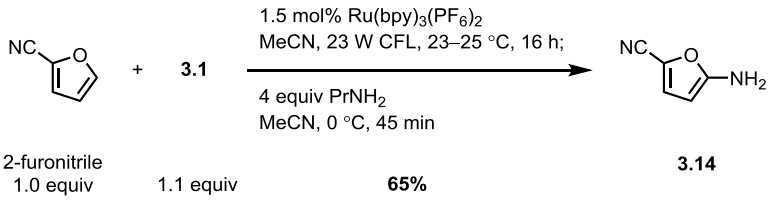
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 7.54 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.23 (ddd, *J* = 8.3, 7.2, 1.6 Hz, 1H), 6.84 (dd, *J* = 8.3, 1.2 Hz, 1H), 6.76 (ddd, *J* = 8.3, 7.2, 1.2 Hz, 1H), 6.71 (s, 1H), 4.89 (bs, 2H), 3.67 (t, 2H), 3.56 (t, 2H), 1.72–1.53 (m, 6H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 171.1, 160.6, 160.2, 146.6, 132.6, 129.7, 118.4, 117.9, 111.9, 101.3, 48.8, 43.8, 27.4, 26.4, 25.1.

HRMS-FIA(m/z) calc'd for $C_{15}H_{18}N_3O_2^+$ $[M+H]^+$, 272.1394; found, 272.1390.

5-Aminofuran-2-carbonitrile (3.14)



An oven-dried 20 mL vial was charged with a stirring bar, $Ru(bpy)_3(PF_6)_2$ (5.2 mg, 6.0 µmol, 1.5 mol%), and **3.1** (178 mg, 0.440 mmol, 1.1 equiv). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe, and then 2-furonitrile (35 µL, 37 mg, 0.40 mmol, 1.0 equiv) was added via glass syringe. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 16 h, the reaction mixture was cooled to 0 °C, and then propylamine (0.13 mL, 1.6 mmol, 4.0 equiv) was added. The reaction mixture was stirred at 0 °C for 45 min. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (80/20 to 60/40 (v/v)) to afford 28 mg of **3.14** as a yellow solid (65% yield).

R_f = 0.48 (2-methylpentane/ethyl acetate (55/45 (v/v)))

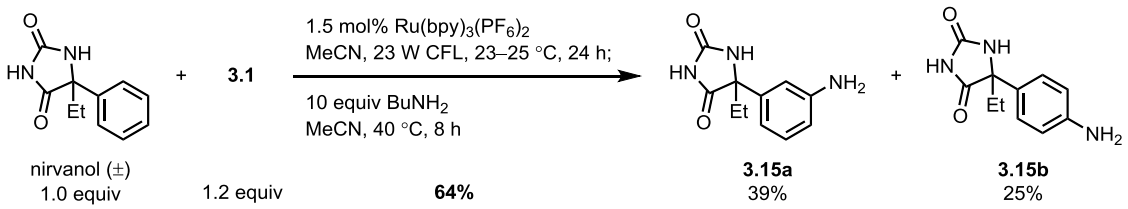
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 7.11 (d, *J* = 3.7 Hz, 1H), 5.18 (d, *J* = 3.7 Hz, 1H), 5.16 (br, 2H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 161.7, 128.0, 116.1, 114.2, 85.3.

HRMS-FIA(m/z) calc'd for $C_{11}H_{14}N_3O_2^+$ $[M+H]^+$, 220.1081; found, 220.1077.

Nirvanol analogues 3.15



An oven-dried 20 mL vial was charged with a stirring bar, nirvanol (±) (82 mg, 0.40 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (5.2 mg, 6.0 µmol, 1.5 mol%), and **3.1** (194 mg, 0.480 mmol, 1.2 equiv). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, butylamine (0.40 mL, 4.0 mmol, 10 equiv) was added, and the mixture was stirred at 40 °C for 8 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/2-propanol/28% aqueous ammonium hydroxide (95/4.5/0.5 (v/v/v)) to afford 34 mg of **3.15a** (39%) and 22 mg of **3.15b** (25%) as yellow solids (64% total yield).

Nirvanol analogue **3.15a**:

R_f = 0.38 (DCM/methanol (92/8 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 7.10 (dd, *J* = 7.8, 7.8 Hz, 1H), 6.90 (dd, *J* = 2.0, 2.0 Hz, 1H), 6.82 (ddd, *J* = 7.8, 1.8, 0.9 Hz, 1H), 6.67 (ddd, *J* = 7.9, 2.2, 0.9 Hz, 1H), 2.23–2.13 (m, 1H, diastereotopic), 2.05–1.96 (m, 1H, diastereotopic), 0.92 (t, 3H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 175.4, 156.6, 147.6, 139.2, 130.0, 115.4, 115.2, 112.2, 69.6, 31.7, 8.25

HRMS-FIA(m/z) calc'd for $C_{11}H_{14}N_3O_2^+$ $[M+H]^+$, 220.1081; found, 220.1077.

Nirvanol analogue **3.15b**:

$\mathbf{R_f}$ = 0.40 (DCM/methanol (92/8 (v/v)))

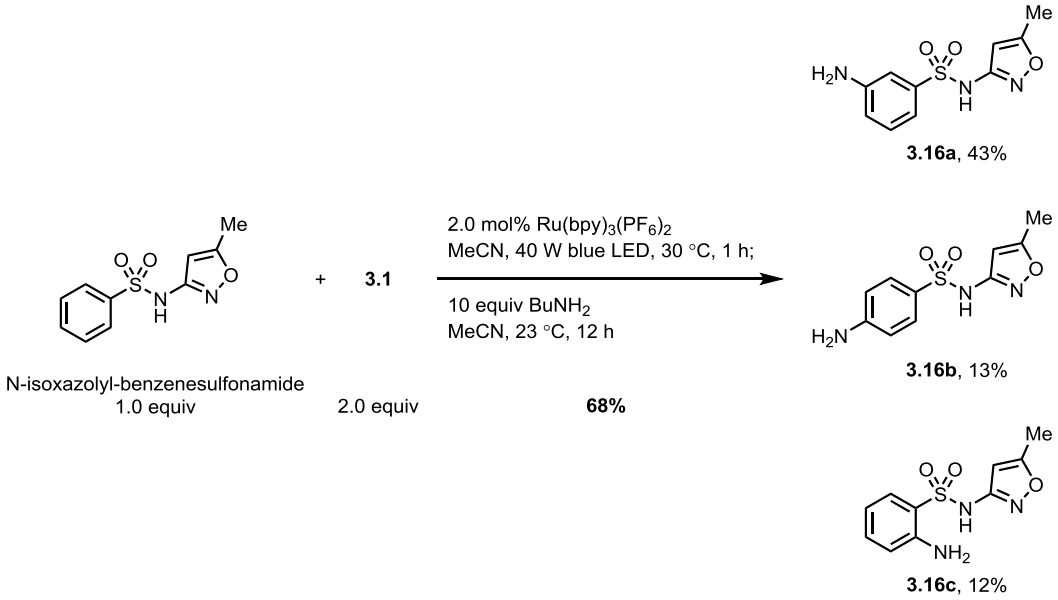
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 7.25–7.21 (m, 2H), 6.73–6.69 (m, 2H), 2.20–2.10 (m, 1H, diastereotopic), 2.01–1.92 (m, 1H, diastereotopic), 0.91 (t, 3H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 179.2, 159.4, 148.9, 128.9, 127.3, 116.3, 70.0, 32.2, 8.4.

HRMS-FIA(m/z) calc'd for $C_{11}H_{14}N_3O_2^+$ $[M+H]^+$, 220.1081; found, 220.1079.

Sulfamethoxazole and its analogues 3.16



An oven-dried 4 mL vial was charged with a stirring bar, N-(5-methyl-3-isoxazolyl)benzenesulfonamide (48 mg, 0.20 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (3.4 mg, 4.0 µmol, 2.0 mol%), and **3.1** (122 mg, 0.300 mmol, 1.5 equiv). Dry acetonitrile (1.0 mL, c = 0.20 M) was added via syringe. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 30 °C, irradiated with two 40 W blue LEDs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 30 min, **3.1** (41 mg, 0.10 mmol, 0.50 equiv) was added and the mixture was stirred with irradiation. After 30 min, the reaction mixture was concentrated

in vacuo, and the residue was purified by preparatory high-performance liquid chromatography with a solvent mixture of water (0.1% TFA)/acetonitrile (70/30 (v/v)) to afford 44 mg of fraction **a**, 16 mg of fraction **b**, and 17 mg of fraction **c** as white solids.

To a 20 mL vial, charged with the fraction **a** and a stirring bar, butylamine (0.20 mL, 2.0 mmol) was added, and the mixture was stirred at 23 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (70/30 to 20/80 (v/v)) to afford 22 mg of **3.16a** (43% yield).

To a 20 mL vial, charged with the fraction **b** and a stirring bar, butylamine (0.20 mL, 2.0 mmol) was added, and the mixture was stirred at 23 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (70/30 to 20/80 (v/v)) to afford 6.9 mg of **3.16b** (13% yield).

To a 20 mL vial, charged with the fraction **c** and a stirring bar, butylamine (0.20 mL, 2.0 mmol) was added, and the mixture was stirred at 23 °C for 12 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (70/30 to 20/80 (v/v)) to afford 6.1 mg of **3.16c** (12% yield).

Sulfamethoxazole analogue **3.16a**:

$\mathbf{R_f}$ = 0.2 (2-methylpentane/ethyl acetate (50/50 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3OD, 23 ºC, δ): 7.20 (dd, *J* = 7.9, 7.9 Hz, 1H), 7.15 (dd, *J* = 2.0, 2.0 Hz, 1H), 7.10 (ddd, *J* = 7.8, 1.7, 0.9 Hz, 1H), 6.86 (ddd, *J* = 7.9, 2.3, 0.8 Hz, 1H), 6.12 (q, *J* = 0.7 Hz, 1H), 2.31 (d, *J* = 0.7 Hz, 3H).

^{13}C NMR (124 MHz, CD_3OD, 23 ºC, δ): 171.8, 159.6, 150.3, 141.7, 130.7, 120.1, 116.2, 113.4, 96.5, 12.3.

HRMS-FIA(m/z) calc'd for $C_{10}H_{12}N_3O_3S^+$ $[M+H]^+$, 254.0594; found, 254.0598.

Sulfamethoxazole (**3.16b**):

R_f = 0.16 (2-methylpentane/ethyl acetate (50/50 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3OD, 23 ºC, δ): 7.57–7.53 (m, 2H), 6.66–6.62 (m, 2H), 6.09 (q, *J* = 0.8 Hz, 1H), 2.30 (d, *J* = 0.8 Hz, 3H).

^{13}C NMR (124 MHz, CD_3OD, 23 ºC, δ): 171.7, 159.6, 154.8, 130.2, 126.4, 114.2, 96.4, 12.2.

HRMS-FIA(m/z) calc'd for $C_{10}H_{12}N_3O_3S^+$ $[M+H]^+$, 254.0594; found, 254.0597.

Sulfamethoxazole analogue **3.16c**:

R_f = 0.32 (2-methylpentane/ethyl acetate (50/50 (v/v)))

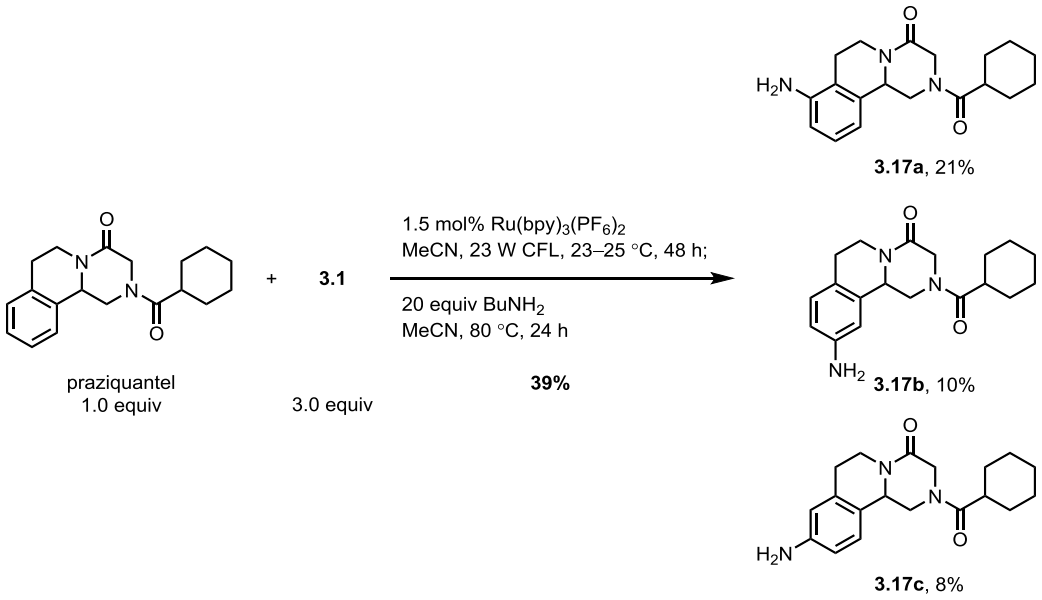
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3OD, 23 ºC, δ): 7.63 (dd, *J* = 8.1, 1.5 Hz, 1H), 7.25 (ddd, *J* = 8.6, 7.1, 1.6 Hz, 1H), 6.79 (dd, *J* = 8.3, 0.9 Hz, 1H), 6.63 (ddd, *J* = 8.1, 7.1, 1.1 Hz, 1H), 6.05 (q, *J* = 0.8 Hz, 1H), 2.28 (d, *J* = 0.8 Hz, 3H).

^{13}C NMR (124 MHz, CD_3OD, 23 ºC, δ): 171.7, 159.3, 148.1, 135.5, 130.8, 120.7, 118.4, 116.9, 96.2, 12.2.

HRMS-FIA(m/z) calc'd for $C_{10}H_{12}N_3O_3S^+$ $[M+H]^+$, 254.0594; found, 254.0592.

Praziquantel analogues 3.17



An oven-dried 20 mL vial was charged with a stirring bar, praziquantel (125 mg, 0.400 mmol, 1.0 equiv), $Ru(bpy)_3(PF_6)_2$ (5.2 mg, 6.0 µmol, 1.5 mol%), and **3.1** (243 mg, 0.600 mmol, 1.5 equiv). Dry acetonitrile (2.0 mL, c = 0.20 M) was added via syringe. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, **3.1** (243 mg, 0.600 mmol, 1.5 equiv) was added and the mixture was stirred with irradiation. After 24 h, butylamine (0.80 mL, 8.0 mmol, 20 equiv) were added, and the mixture was stirred at 80 °C for 24 h. The reaction mixture was concentrated *in vacuo*, and the residue was purified by preparatory high-performance liquid chromatography with a solvent mixture of water/acetonitrile (60/40 (v/v)) to afford 27 mg of **3.17a** (21%), 13 mg of **3.17b** (10%), and 10 mg of **3.17c** (8%) as white solids (39% total yield).

Praziquantel analogue **3.17a**:

R_f = 0.64 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 7.08–6.96 (m, 1H), 6.70–6.53 (m, 2H), 4.91/4.37 (dd, *J* = 13.2, 2.8 Hz, 1H, rotameric), 4.86/4.70 (dd, *J* = 10.1, 3.2 Hz, 1H, rotameric), 4.80–4.73 (m, 1H), 4.54/4.35 (d, *J* = 18.3 Hz, 1H, rotameric), 4.12 (br, 2H), 3.99/3.64 (d, *J* = 17.4 Hz, 1H, rotameric), 3.20/2.75 (dd, *J* = 13.3, 10.8 Hz, 1H, rotameric), 2.79–2.70 (m, 1H), 2.79–2.70/2.60–2.52 (m, 1H, rotameric), 2.52–2.45 (m, 2H), 1.84–1.62 (m, 5H), 1.54–1.16 (m, 5H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 175.3, 165.9/165.1 (rotameric), 146.7/146.6 (rotameric), 135.2/134.7 (rotameric), 128.0, 120.7/120.5 (rotameric), 115.6/115.5 (rotameric), 115.6/115.4 (rotameric), 114.0/113.9 (rotameric), 56.5/55.6 (rotameric), 49.9/46.0 (rotameric), 49.5/46.6 (rotameric), 40.9/40.7 (rotameric), 38.8/38.7 (rotameric), 30.4/30.1 (rotameric), 30.2/29.9 (rotameric), 26.7, 26.3, 24.3.

HRMS-FIA(m/z) calc'd for $C_{19}H_{26}N_3O_2^+$ $[M+H]^+$, 328.2020; found, 328.2016.

Praziquantel analogue **3.17b**:

R_f = 0.64 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 6.94–6.88 (m ,1H), 6.56 (s, 1H), 6.55–6.50 (m, 1H), 4.95–4.72 (m, 1H), 4.67–4.44 (m, 2H), 4.41–4.28 (m, 1H), 4.11 (br, 2H), 4.04–3.97/3.74–3.65 (m, 1H, rotameric), 3.28–3.17/2.79–2.67 (m, 1H, rotameric), 2.79–2.67/2.65–2.52 (m, 4H, rotameric), 1.83–1.63 (m, 5H), 1.56–1.17 (m, 5H).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 175.3/175.2 (rotameric), 166.1/165.2 (rotameric), 147.6, 134.9/134.4 (rotameric), 130.8/130.7 (rotameric), 124.8/124.5 (rotameric), 115.1/114.9 (rotameric),, 112.1/111.9 (rotameric), 56.3/55.6 (rotameric), 50.0/46.0

(rotameric), 49.6/46.8 (rotameric), 40.9/40.8 (rotameric), 39.9/39.8 (rotameric), 30.4/29.9 (rotameric), 30.1, 28.5, 26.7, 26.3/26.2 (rotameric), 26.3.

HRMS-FIA(m/z) calc'd for $C_{19}H_{26}N_3O_2^+$ $[M+H]^+$, 328.2020; found, 328.2022.

Praziquantel analogue **3.17c**:

$\mathbf{R_f}$ = 0.67 (DCM/methanol (90/10 (v/v)))

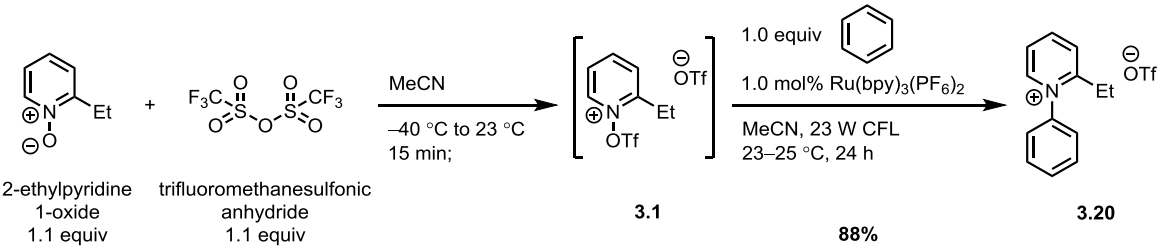
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3OD, 23 ºC, δ): 7.01 (dd, *J* = 23.5, 8.3 Hz, 1H), 6.60–6.51 (m, 1H), 6.44 (s, 1H), 4.94–4.75 (m, 1H), 4.69–4.46 (m, 2H), 4.41–4.32 (m, 1H), 4.17 (br, 2H), 4.07–3.98/3.77–3.67 (m, 1H, rotameric), 3.26–3.15/2.92–2.69 (m, 1H, rotameric), 2.92–2.69/2.69–2.51 (m, 4H, rotameric), 1.86–1.65 (m, 5H), 1.57–1.19 (m, 5H).

^{13}C NMR (124 MHz, CD_3OD, 23 ºC, δ): 175.2, 166.1/165.2 (rotameric), 148.0/147.9 (rotameric),137.4/137.1 (rotameric),127.5/127.2 (rotameric),123.0/122.4 (rotameric), 115.0, 114.2, 55.9/55.1 (rotameric), 50.2/46.1 (rotameric), 49.5/46.7 (rotameric), 40.9/40.7 (rotameric), 39.6/39.4 (rotameric), 30.3, 30.1, 29.9, 29.5/29.4 (rotameric), 26.7, 26.3.

HRMS-FIA(m/z) calc'd for $C_{19}H_{26}N_3O_2^+$ $[M+H]^+$, 328.2020; found, 328.2013.

2-Ethyl-1-phenylpyridin-1-ium trifluoromethanesulfonate (3.20)



Under inert atmosphere, an oven-dried 20 mL vial was charged with a stirring bar and dry acetonitrile (1.5 mL). The stirred liquid was cooled to –40 °C, and then trifluoromethanesulfonic anhydride (74 µL, 120 mg, 0.44 mmol, 1.1 equiv) was added dropwise via glass syringe. Under

inert atmosphere, an oven-dried 4 mL vial was charged with 2-ethylpyridine 1-oxide (55 µL, 54 mg, 0.44 mmol, 1.1 equiv) and dry acetonitrile (0.5 mL), and the mixture was briefly swirled. The solution of 2-ethylpyridine 1-oxide was added to the solution of trifluoromethanesulfonic anhydride dropwise via syringe. The mixture was stirred at –40 °C for 1 min, and then slowly warmed to 23 °C. After 14 min, the vial was briefly opened to air, and $Ru(bpy)_3(PF_6)_2$ (3.4 mg, 4.0 µmol, 1.0 mol%) and benzene (36 µL, 32 mg, 0.40 mmol, 1.0 equiv) were added. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, the reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/methanol (93/7 (v/v)) to afford 117 mg of **3.20** (88% yield) as a yellow oil.

$\mathbf{R_f}$ = 0.41 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 8.64–8.58 (m, 2H), 8.10 (d, *J* = 8.1 Hz, 1H), 8.00–7.95 (m, 1H), 7.77–7.67 (m, 3H), 7.60–7.54 (m, 2H), 2.78 (q, 2H), 1.23 (t, 3H).

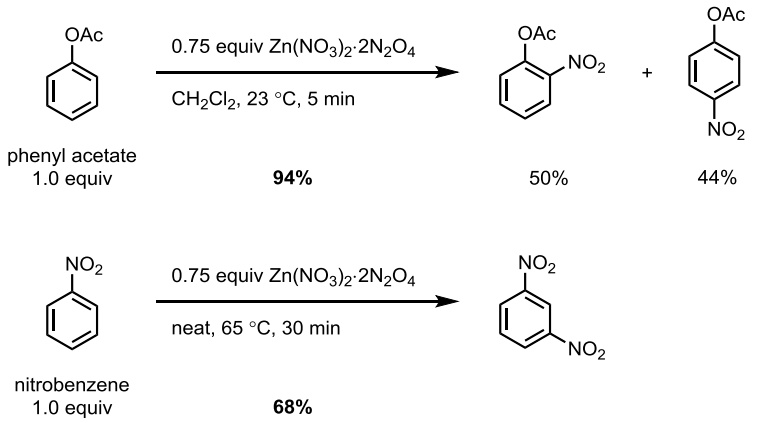
^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –79.2.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 161.9, 147.9, 146.8, 141.7, 132.5, 131.3, 129.0, 126.6, 126.2, 122.0 (q, J = 320 Hz), 27.8, 12.6.

HRMS-FIA(m/z) calc'd for $C_{13}H_{14}N^+$ $[M]^+$, 184.1121; found, 184.1124.

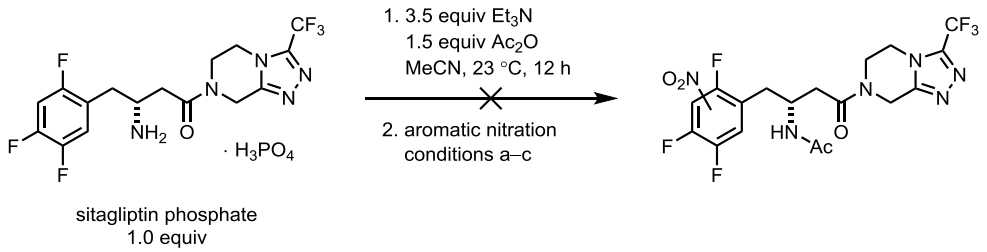
3.6.3 Comparative Analysis of Nitration, Imidation,[8] and Pyridination

Nitration of phenyl acetate and nitrobenzene



The data above were obtained from the literature.[20]

Attempts of nitration of *N*-acetyl-sitagliptin



An oven-dried 4 mL vial was charged with a stirring bar and sitagliptin phosphate (52 mg, 0.10 mmol, 1.0 equiv). Dry acetonitrile (0.50 mL, c = 0.20 M) was added via syringe. Triethylamine (49 µL, 36 mg, 0.35 mmol, 3.5 equiv) and acetic anhydride (14 µL, 15 mg, 0.15 mmol, 1.5 equiv) were consecutively added via glass syringe. The vial was sealed with a plastic cap, and the mixture was stirred at 23 °C. After 12 h, saturated aqueous sodium bicarbonate (5 mL) and water (5 mL) were added, and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was subjected to 3 different conditions of aromatic nitration, see below.

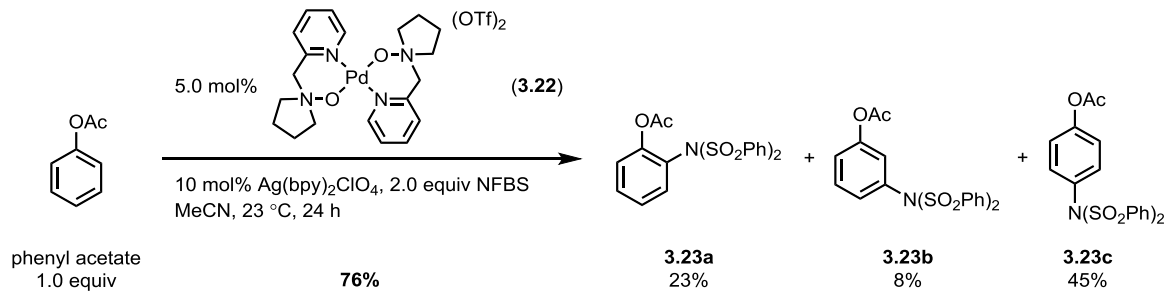
Condition a: The residue was transferred to a 4 mL vial charged with a stirring bar. Concentrated sulfuric acid (0.50 mL) and concentrated nitric acid (0.50 mL) were consecutively added via syringe. The vial was sealed with a plastic cap, and the mixture was stirred at 60 °C. After 24 h,

the reaction mixture was poured onto ice. Saturated aqueous sodium carbonate (20 mL) was added, and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue did not contain any desired nitrated product according to ^{1}H NMR and LCMS analyses.

Condition b: The residue was transferred to an oven-dried 4 mL vial charged with a stirring bar. Dry DCM (0.30 mL) was added via syringe. To the stirred mixture, trifluoromethanesulfonic acid (8.9 µL, 15 mg, 0.10 mmol, 1.0 equiv) was added via glass syringe. An oven-dried 4 mL vial was charged with nitronium tetrafluoroborate (40 mg, 0.30 mmol, 3.0 equiv) and dry acetonitrile (0.30 mL). The solution of nitronium tetrafluoroborate was added dropwise to the stirred solution of the N-acetyl-sitagliptin via syringe. The vial was sealed with a plastic cap, and the mixture was stirred at 60 °C. After 24 h, the reaction mixture was concentrated *in vacuo*. The residue did not contain any desired nitrated product according to ^{1}H NMR and LCMS analyses.

Condition c: The residue was transferred to an oven-dried 4 mL vial charged with a stirring bar and nitronium tetrafluoroborate (40 mg, 0.30 mmol, 3.0 equiv). Trifluoromethanesulfonic acid (0.50 mL) was added. The vial was sealed with a plastic cap, and the mixture was stirred at 23 °C. After 24 h, the reaction mixture was poured onto ice. Saturated aqueous sodium carbonate (20 mL) was added, and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue did not contain any desired nitrated product according to ^{1}H NMR and LCMS analyses.

C–H imidation of phenyl acetate



In a glove-box, a 4 mL vial was charged with a stirring bar, palladium complex **3.22** (7.6 mg, 10 μmol, 5.0 mol%), $Ag(bpy)_2ClO_4$ (10.4 mg, 20.0 μmol, 10 mol%), and N-fluorobenzenesulfonimide (126 mg, 0.400 mmol, 2.0 equiv). Dry acetonitrile (0.50 mL, c = 0.40 M) was added via syringe. The vial was sealed with a PTFE/Silicone septum, and brought out of the glove-box. Under inert atmosphere, phenyl acetate (25 μL, 27 mg, 0.20 mmol, 1.0 equiv) was added to the stirred mixture via glass syringe, and the mixture was stirred at 23 °C. After 24 h, the reaction mixture was concentrated *in vacuo*, and the residue was purified by chromatography on silica gel eluting with a solvent mixture of 2-methylpentane/ethyl acetate (5/95 to 50/50 (v/v)) to afford 66 mg of a white solid as a mixture of **3.23a**, **3.23b**, and **3.23c** (76% total yield). ^{1}H NMR integral analysis revealed a 23% yield of **3.23a**, an 8% yield of **3.23b**, and a 45% yield of **3.23c**.

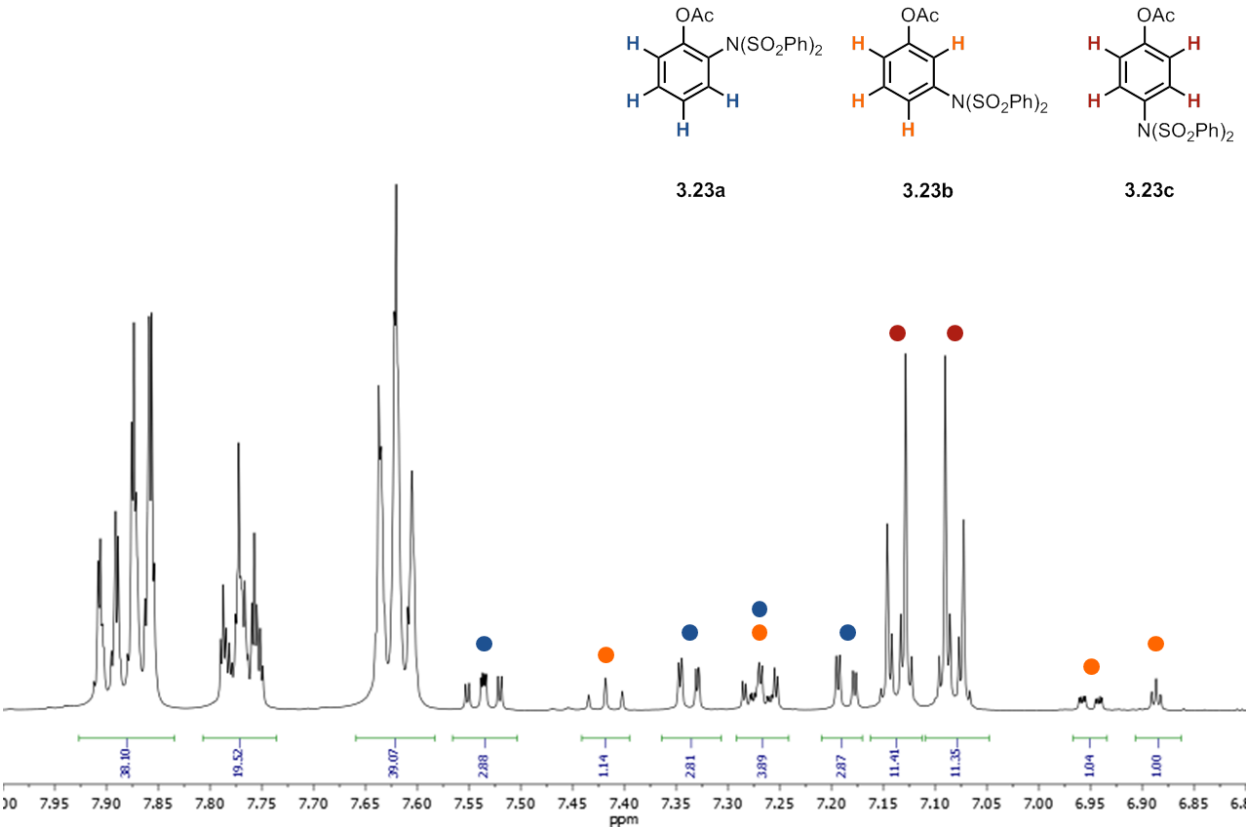


Figure 3.4. Assignment of ^{1}H NMR peaks corresponding to **3.23a**, **3.23b**, and **3.23c**.

R$_f$ = 0.57 (2-methylpentane/ethyl acetate (55/45 (v/v)))

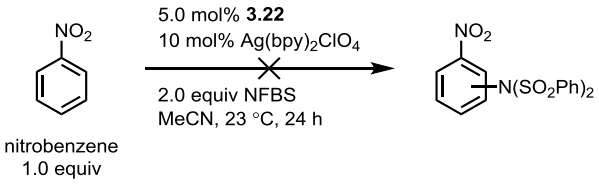
NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 7.92–7.88 (m, 4H, **3.23a**), 7.88–7.84 (m, 4H, **3.23b** + **3.23c**), 7.80–7.74 (m, 2H, **3.23a** + **3.23b** + **3.23c**), 7.65–7.59 (m, 4H, **3.23a** + **3.23b** + **3.23c**), 7.54 (ddd, *J* = 9.0, 7.4, 1.6 Hz, 1H, **3.23a**), 7.42 (dd, *J* = 8.1, 8.1 Hz, 1H, **3.23b**), 7.34 (dd, *J* = 8.2, 1.3 Hz, 1H, **3.23a**), 7.29–7.25 (m, 1H, **3.23a** + **3.23b**), 7.19 (dd, *J* = 7.9, 1.6 Hz, 1H, **3.23a**), 7.16–7.11 (m, 2H, **3.23c**), 7.11–7.06 (m, 2H, **3.23c**), 6.95 (ddd, *J* = 7.9, 2.0, 1.0 Hz, 1H, **3.23b**), 6.89 (dd, *J* = 2.1, 2.1 Hz, 1H, **3.23b**), 2.26 (s, 3H, **3.23c**), 2.23 (s, 3H, **3.23b**), 1.87 (s, 3H, **3.23a**).

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 170.1, 170.0, 168.3, 153.3, 152.1, 150.1, 140.2, 139.9, 139.8, 135.7, 135.6, 135.5, 135.4, 133.9, 133.7, 132.4, 132.3, 130.9, 130.4, 130.3, 130.2, 130.0, 129.5, 129.3, 126.9, 126.6, 126.3, 125.2, 125.1, 123.8, 21.3, 21.2, 21.1.

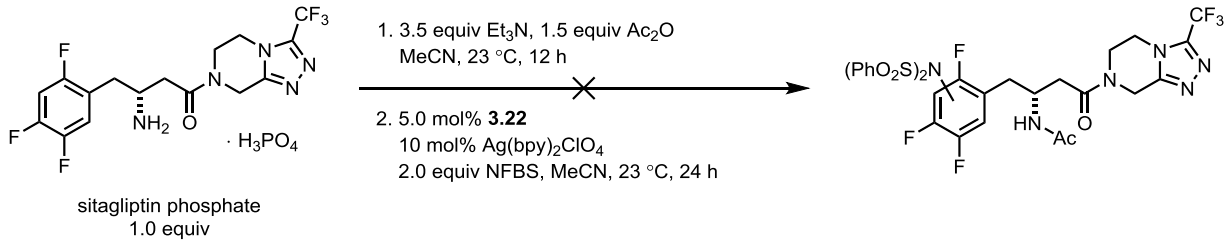
HRMS-FIA(m/z) calc'd for $C_{20}H_{17}NO_6S_2Na^+$ $[M+Na]^+$, 454.0389; found, 454.0392.

Attempt of C–H imidation of nitrobenzene



In a glove-box, a 4 mL vial was charged with a stirring bar, palladium complex **3.22** (7.6 mg, 10 µmol, 5.0 mol%), $Ag(bpy)_2ClO_4$ (10.4 mg, 20.0 µmol, 10 mol%), and N-fluorobenzenesulfonimide (126 mg, 0.400 mmol, 2.0 equiv). Dry acetonitrile (0.50 mL, c = 0.40 M) was added via syringe. The vial was sealed with a PTFE/Silicone septum, and brought out of the glove-box. Under inert atmosphere, nitrobenzene (21 µL, 25 mg, 0.20 mmol, 1.0 equiv) was added to the stirred mixture via glass syringe, and the mixture was stirred at 23 °C. After 24 h, the reaction mixture was concentrated *in vacuo*. The residue did not contain any desired imidated product according to ^{1}H NMR and LCMS analyses.

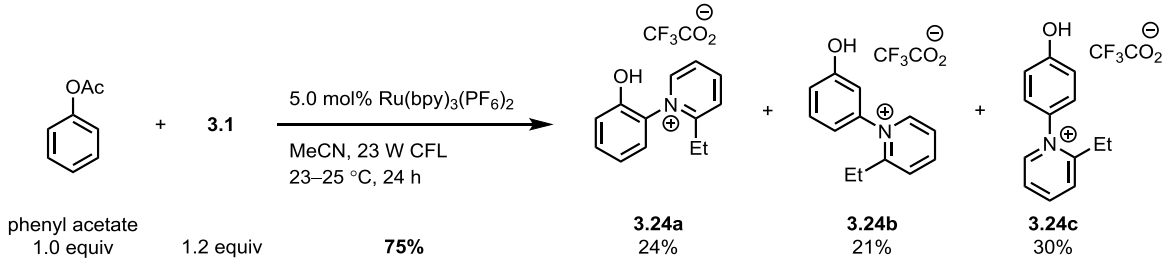
Attempt of C–H imidation of *N*-acetyl-sitagliptin



An oven-dried 4 mL vial was charged with a stirring bar and sitagliptin phosphate (52 mg, 0.10 mmol, 1.0 equiv). Dry acetonitrile (0.50 mL, c = 0.20 M) was added via syringe. Triethylamine (49 µL, 36 mg, 0.35 mmol, 3.5 equiv) and acetic anhydride (14 µL, 15 mg, 0.15 mmol, 1.5 equiv)

were consecutively added via glass syringe. The vial was sealed with a plastic cap, and the mixture was stirred at 23 °C. After 12 h, saturated aqueous sodium bicarbonate (5 mL) and water (5 mL) were added, and the mixture was extracted with DCM (3 × 10 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo*. The residue was brought into a glove-box, and was transferred to a 4 mL vial charged with a stirring bar, palladium complex **3.22** (3.2 mg, 5.0 μmol, 5.0 mol%), $Ag(bpy)_2ClO_4$ (5.2 mg, 10.0 μmol, 10 mol%), and N-fluorobenzenesulfonimide (63 mg, 0.20 mmol, 2.0 equiv). Dry acetonitrile (0.25 mL, c = 0.40 M) was added via syringe. The vial was sealed with a plastic cap, and brought out of the glove-box. The mixture was stirred at 23 °C. After 24 h, the reaction mixture was concentrated *in vacuo*. The residue did not contain any desired imidated product according to ^{1}H NMR and LCMS analyses.

C–H pyridination of phenyl acetate



An oven-dried 4 mL vial was charged with a stirring bar, $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 10 μmol, 5.0 mol%), and **3.1** (97 mg, 0.24 mmol, 1.2 equiv). Dry acetonitrile (1.0 mL, c = 0.20 M) was added via syringe, and then phenyl acetate (25 μL, 27 mg, 0.20 mmol, 1.0 equiv) was added via glass syringe. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, the reaction mixture was concentrated *in vacuo*, and the residue was purified by preparatory high-performance liquid chromatography with a solvent mixture of water

(0.1% TFA)/methanol (80/20 (v/v)) to afford 15 mg of **3.24a** (24%), 13 mg of **3.24b** (21%), and 19 mg of **3.24c** (30%) as yellow solids (75% total yield).

Ortho-pyridinated phenol (**3.24a**):

R_f = 0.22 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 8.58 (ddd, *J* = 8.1, 8.1, 1.3 Hz, 1H), 8.54 (dd, *J* = 6.2, 1.0 Hz, 1H), 8.07 (d, *J* = 8.1 Hz, 1H), 7.95 (ddd, *J* = 7.4, 6.1, 0.9 Hz, 1H), 7.56 (ddd, *J* = 7.4, 7.4, 1.4 Hz, 1H), 7.42 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.23 (d, *J* = 8.2 Hz, 1H), 7.15 (dd, *J* = 7.7 Hz, 1H), 2.89–2.70 (m, 2H), 1.23 (t, 3H).

^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –77.6.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 162.7, 151.5, 148.1, 147.9, 147.5, 134.0, 129.1, 128.8, 127.5, 126.4, 121.8, 27.2, 12.2.

HRMS-FIA(m/z) calc'd for $C_{13}H_{14}NO^+$ $[M]^+$, 200.1070; found, 200.1069.

Meta-pyridinated phenol (**3.24b**):

R_f = 0.15 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 8.58 (dd, *J* = 6.2, 1.0 Hz, 1H), 8.54 (ddd, *J* = 8.0, 8.0, 1.4 Hz, 1H), 8.03 (d, *J* = 8.0 Hz, 1H), 7.91 (m, 1H), 7.47 (dd, *J* = 8.0, 8.0 Hz, 1H), 7.20 (dd, *J* = 8.3, 1.8 Hz, 1H), 7.06 (dd, *J* = 2.1, 2.1 Hz, 1H), 6.93 (dd, *J* = 7.8, 1.5 Hz, 1H), 2.88–2.78 (m, 2H), 1.25 (t, 3H).

^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –77.0.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 162.0, 160.3, 147.7, 146.6, 142.4, 132.1, 128.9, 126.0, 119.6, 116.7, 113.7, 27.6, 12.7.

HRMS-FIA(m/z) calc'd for $C_{13}H_{14}NO^+$ $[M]^+$, 200.1070; found, 200.1070.

Para-pyridinated phenol (**3.24c**):

$\mathbf{R_f}$ = 0.10 (DCM/methanol (90/10 (v/v)))

NMR Spectroscopy:

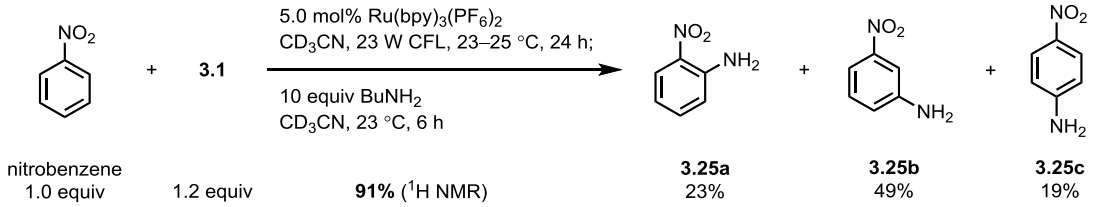
^{1}H NMR (500 MHz, CD_3CN, 23 ºC, δ): 8.57 (dd, *J* = 6.1, 1.0 Hz, 1H), 8.52 (ddd, J = 8.0, 8.0, 1.3 Hz, 1H), 8.02 (d, *J* = 8.0 Hz, 1H), 7.92–7.87 (m, 1H), 7.35–7.30 (m, 2H), 7.15–7.09 (m, 2H), 2.80 (q, 2H), 1.22 (t, 3H).

^{19}F NMR (500 MHz, CD_3CN, 23 ºC, δ): –76.9.

^{13}C NMR (124 MHz, CD_3CN, 23 ºC, δ): 162.6, 161.2, 147.5, 147.3, 133.2, 128.8, 127.7, 126.0, 117.6, 27.8, 12.6.

HRMS-FIA(m/z) calc'd for $C_{13}H_{14}NO^+$ $[M]^+$, 200.1070; found, 200.1069.

C–H pyridination/amination of nitrobenzene



An oven-dried 4 mL vial was charged with a stirring bar, $Ru(bpy)_3(PF_6)_2$ (8.6 mg, 10 µmol, 5.0 mol%), and **3.1** (97 mg, 0.24 mmol, 1.2 equiv). Dry acetonitrile-d_3 (1.0 mL, c = 0.20 M) was added via syringe, and then nitrobenzene (21 µL, 25 mg, 0.20 mmol, 1.0 equiv) was added via glass syringe. The vial was sealed with a plastic cap, and the reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, butylamine (0.10 mL, 75 mg, 1.0 mmol, 5.0 equiv) was added, and the mixture was stirred at 40 °C. After 18 h, the yields of **3.25a**, **3.25b**, and **3.25c** were determined via ^{1}H NMR spectroscopy using ethyl acetate (20 µL, 0.20 mmol) as an internal

standard. Comparison of the integrals of the peak at 6.95 ppm (**3.25a** aromatic C–H, 1H), the peak at 7.44–7.41 ppm (**3.25b** aromatic C–H, 2H), the peak at 8.00–7.96 ppm (**3.25c** aromatic C–H, 2H) , and the peak of ethyl acetate at 4.06 ppm (CH_2, 2H) revealed a 23% yield of **3.25a**, a 49% yield of **3.25b**, and a 19% yield of **3.25c**.

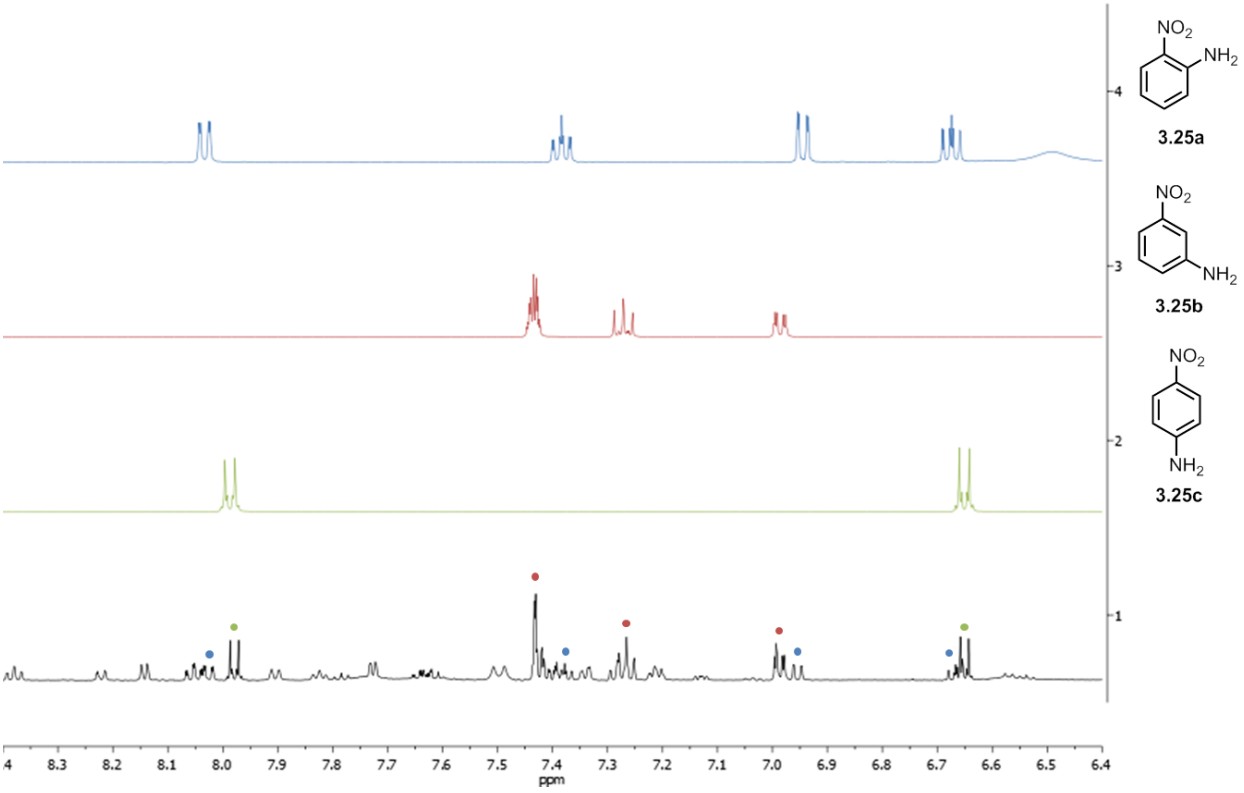


Figure 3.5. Assignment of ^{1}H NMR peaks corresponding to **3.25a**, **3.25b**, and **3.25c**.

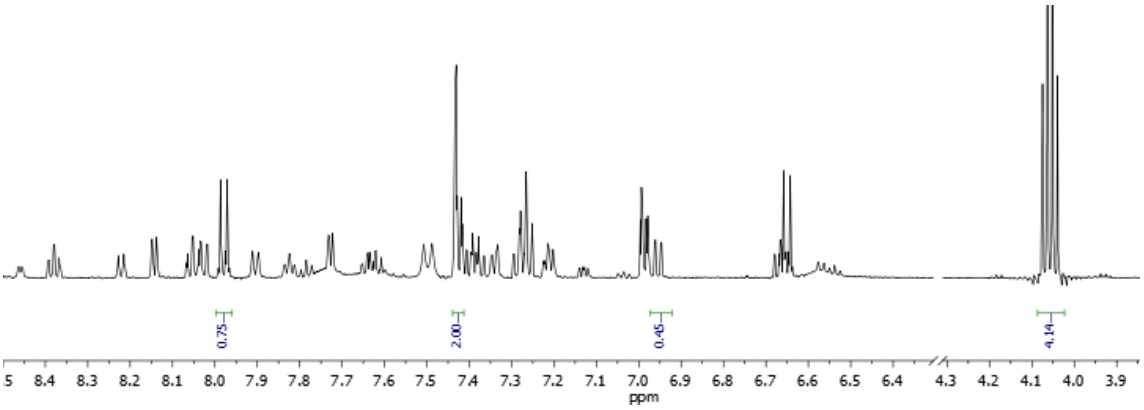
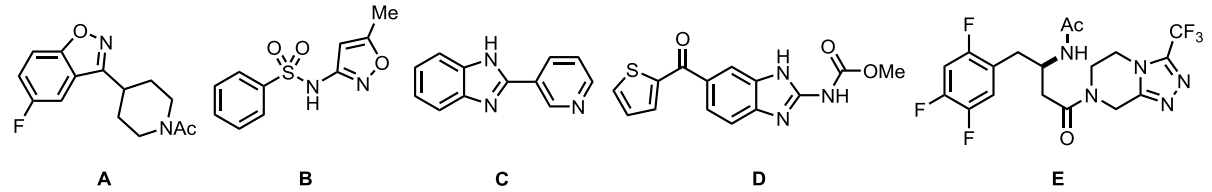


Figure 3.6. Integrals of selected peaks for ^{1}H NMR yield measurement.

3.6.4 Comparative Analysis of Modern Amination Reactions and Amination by the Pyridinium Radical Cation

Procedures of selected state-of-the-art amination methods



Five compounds in our substrate table were selected (depicted above) for comparison of four modern amination methods that we consider currently the best amination reactions published, reported by Nicewicz,[18] Falck,[16] Ritter,[8] and Morandi[15]. While, of course, there are other protocols available, any reported modern aryl C–H amination reaction, to our best knowledge falls into one of the four mechanistic scenarios that the selected methods represents: 1) addition of a nitrogen nucleophile to an arene radical cation, 2) electrophilic addition of a nitrenoid species to an arene, 3) addition of a protected aminyl radical to an arene, and 4) addition of an aminium radical cation to an arene.

Condition **1**[18]: A 4 mL vial was charged with a stirring bar, an arene (0.10 mmol, 1.0 equiv), 9-mesityl-3,6-di-*tert*-butyl-10-phenylacridinium tetrafluoroborate (5.0 mol%), ammonium carbamate (4.0 equiv), and TEMPO (20 mol%). A 10:1 mixture of 1,2-dichloroethane/water (1.0 mL, c = 0.1 M) was added *via* syringe. The vial was sealed with a PTFE/Silicone septum, and the reaction mixture was sparged with O_2 for 5 min. The reaction mixture was then stirred at 30 °C for 24 h, irradiated with a 40 W blue LED (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). The reaction mixture was then concentrated *in vacuo*.

Condition **2**[16]: Under Ar atmosphere, an oven-dried 4 mL vial was charged with a stirring bar, an arene (0.10 mmol, 1.0 equiv), and *tert*-butyl(mesitylsulfonyl)oxycarbamate (1.5 equiv). Dry TFE

(1 mL, c = 0.1 M) was added *via* syringe, and the stirred mixture was cooled to 0 °C. To the stirred mixture, trifluoroacetic acid (2.0 equiv) was added *via* glass syringe, and then $Rh_2(esp)_2$ (2.0 mol%) was added. After warming to 23 °C over 30 min, the reaction mixture was stirred at 23 °C for 24 h. The reaction mixture was then concentrated *in vacuo*.

Condition **3**[8]: Under Ar atmosphere, an oven-dried 4 mL vial was charged with an arene (0.10 mmol, 1.0 equiv), palladium complex **3.22** (5.0 mol%), $Ru(bpy)_3(PF_6)_2$ (2.5 mol%), and N-fluorobenzenesulfonimide (2.0equiv). Dry acetonitrile (0.5 mL, c = 0.20 M) was added and the reaction mixture was stirred in a sealed vial at 50°C for 24h. The reaction mixture was then concentrated *in vacuo*.

Condition **4**[15]: A 4 mL vial was charged with an arene (0.10 mmol, 1.0 equiv), $Fe(SO_4)_2{\cdot}7H_2O$ (5.0 mol%), and $MsONH_3OTf$ (1.5 equiv). The vial was sealed with a PTFE/Silicone septum. The vial was evacuated and refilled with Ar for 3 times, and then was equipped with an Ar-filled balloon. A 2:1 mixture of acetonitrile/water (0.3 mL, c = 0.33 M) was degassed through Ar purging for 5 min, and then added *via* syringe. The reaction mixture was stirred at 23 °C for 16 h. The reaction mixture was then concentrated *in vacuo*.

Comparison of reaction outcomes of the selected amination methods

The 20 reaction mixtures obtained from the combinations of the substrates **A**–**E** and the conditions **1**–**4** were analyzed by NMR spectroscopy, the results of which are shown below.

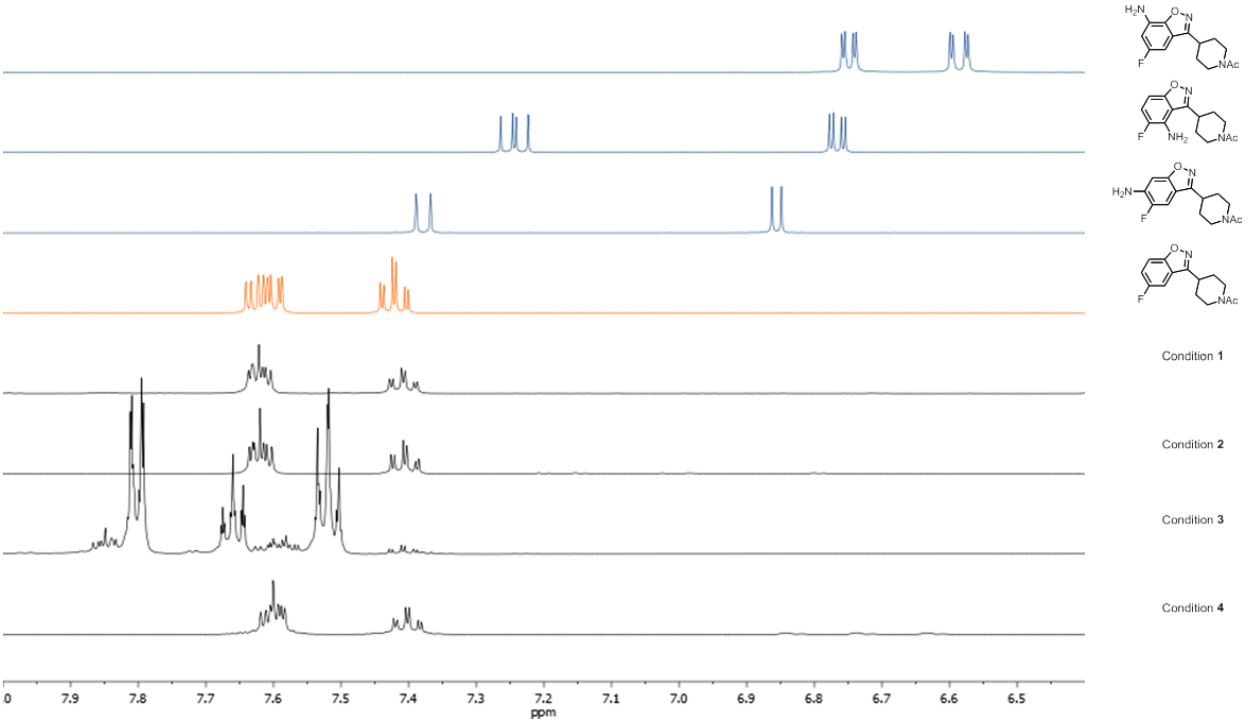


Figure 3.7. ^{1}H NMR spectra of the reaction mixtures (in CD_3CN) from the attempts to aminate the substrate **A**.

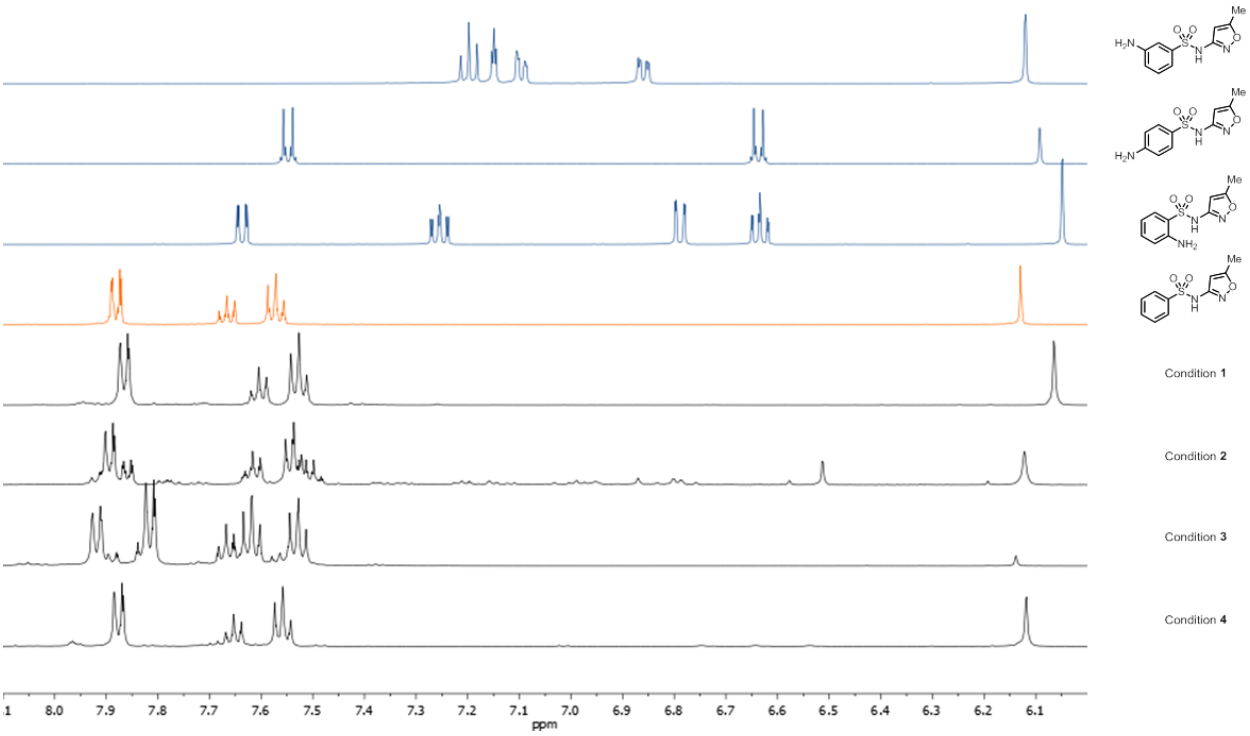


Figure 3.8. ^{1}H NMR spectra of the reaction mixtures (in CD_3OD) from the attempts to aminate the substrate **B**.

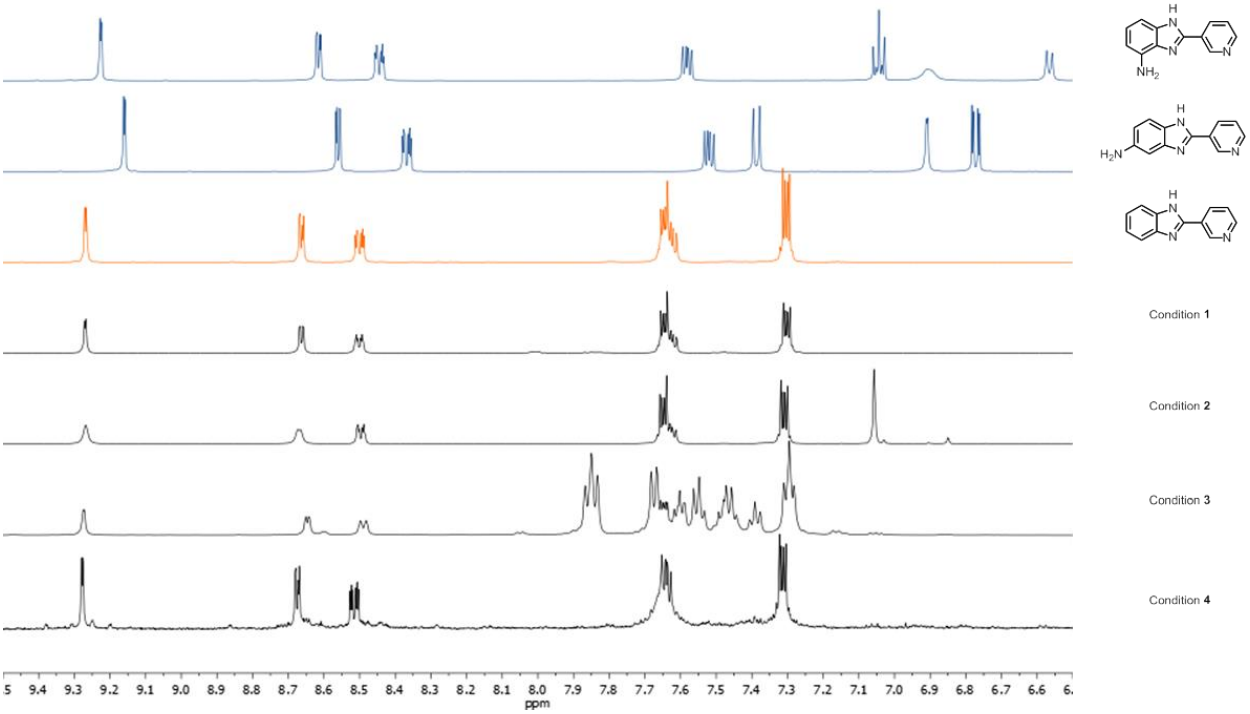


Figure 3.9. ^{1}H NMR spectra of the reaction mixtures (in CD_3OD) from the attempts to aminate the substrate **C**.

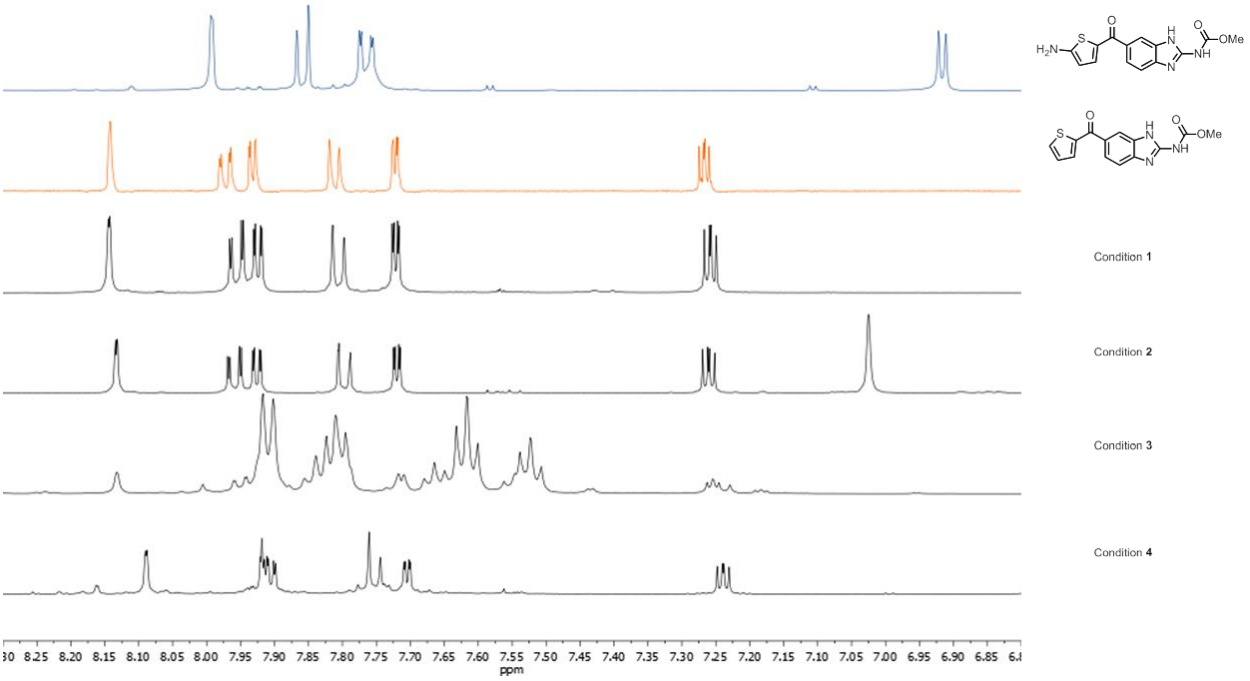


Figure 3.10. ^{1}H NMR spectra of the reaction mixtures (in CD_3CN) from the attempts to aminate the substrate **D**.

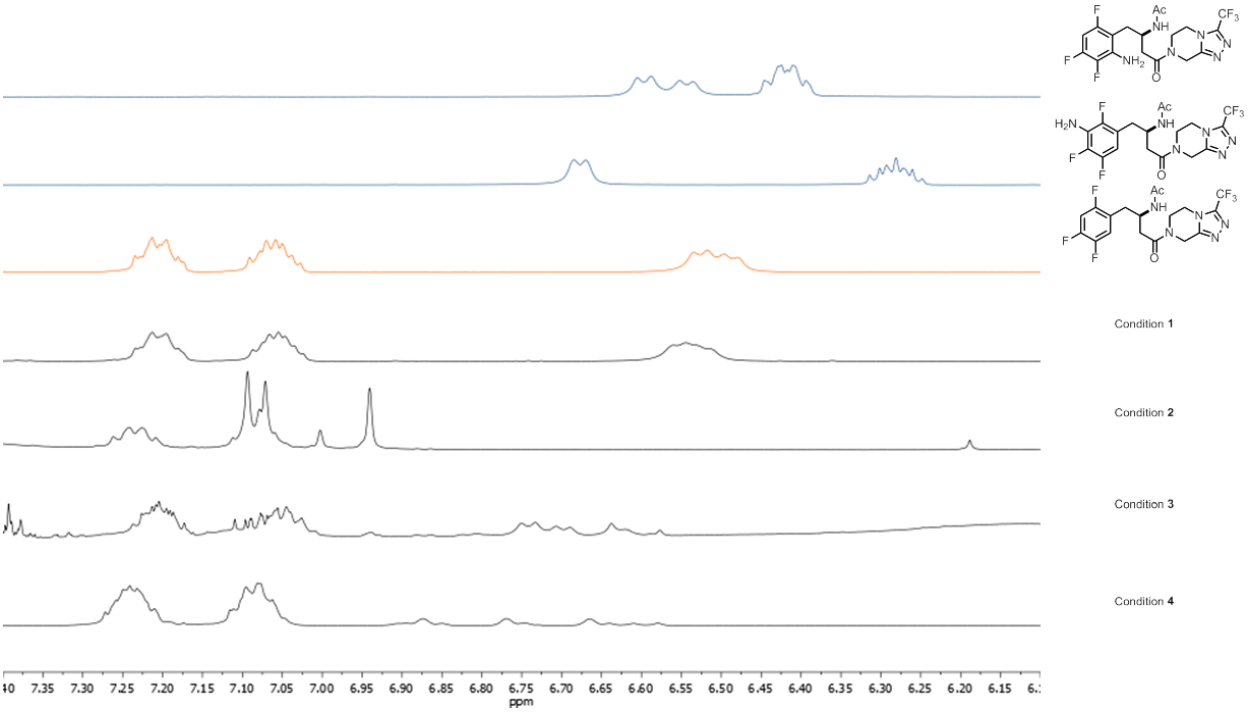


Figure 3.11. ^{1}H NMR spectra of the reaction mixtures (in CD_3CN) from the attempts to aminate the substrate **E**.

The reaction outcomes are summarized in the table below.

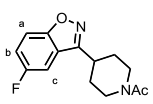
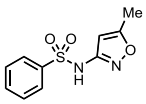
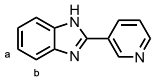
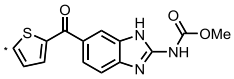
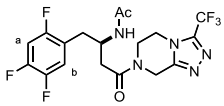
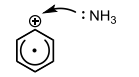
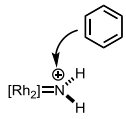
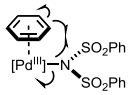
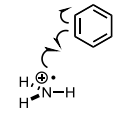
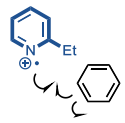
C-H amination mechanism \ arene substrate	 A	 B	 C	 D	 E
	No desired pdt	No desired pdt	No desired pdt	No desired pdt	No desired pdt
	No desired pdt	No desired pdt	No desired pdt	No desired pdt	No desired pdt
	No desired pdt	No desired pdt	No desired pdt	No desired pdt	No desired pdt
	No desired pdt	No desired pdt	19% (a:b=95:5)	No desired pdt	No desired pdt
	87% (a:b:c=51:15:34)	68% (*o*:*m*,*p*=18:63:19)	75% (a:b=54:46)	45%	37% (a:b=46:54)

Table 3.2. Comparison of reaction outcomes of four modern amination methods with the pyridination reaction.

3.6.5 Cyclic Voltammetry

Determination of the reduction potential of 2-ethylpyridine *N*–OTf (3.1)

Cyclic voltammetry measurements of **3.1** were performed with a Pt working electrode, Pt auxiliary electrode, $Ag/AgNO_3$ reference electrode (0.01 M $AgNO_3$, 0.1 M Bu_4NClO_4), Bu_4NOTf electrolyte (0.1 M in MeCN), and analyte (2-ethylpyridine *N*–OTf, 1 mM) with a sweep rate of 400 mV/s. The electrode potential of the $Ag/AgNO_3$ reference electrode was measured to be 288 mV vs. SCE.

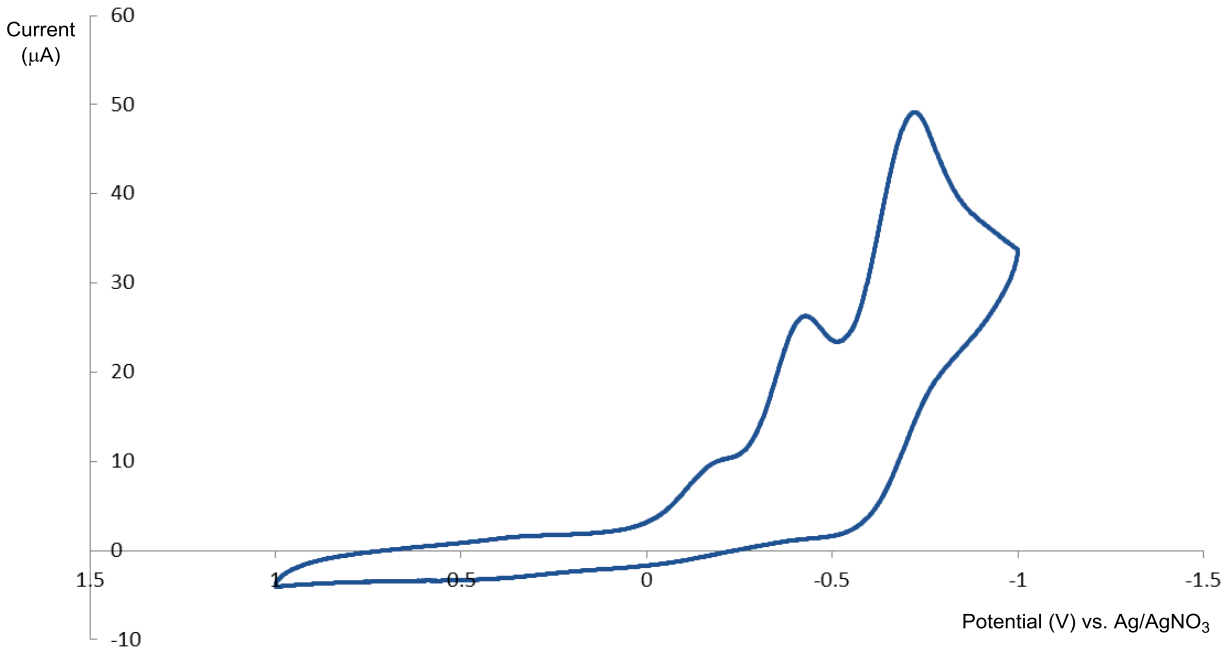
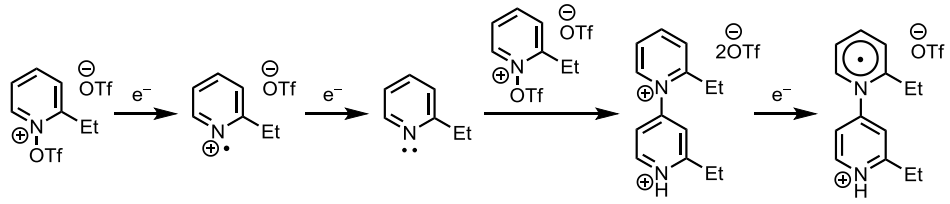


Figure 3.12. Voltammetry measurements.

An irreversible reduction is observed at $E_{1/2}^{red}$ = –0.14 V vs. SCE. An additional irreversible reduction at $E_{1/2}^{red}$ = –0.43 V vs. SCE was observed, which, we postulate, arises from the single-electron reduction of a bispyridinium compound (see below).



3.6.6 Quantum Yield Measurement

Determination of the light intensity of the blue LED photolysis setup

The photon flux of the Power LED blue 450 nm Aquarium photolysis setup was determined by standard ferrioxalate actinometry.[33–35] Potassium ferrioxalate trihydrate was prepared according to literature[36] and recrystallized three times from water. A buffered solution of 1,10-

phenanthroline was prepared by dissolving 68 mg of 1,10-phenanthroline (0.37 mmol) and 308 mg of sodium acetate (3.75 mmol) in 0.2 M aqueous sulfuric acid (5 mL, c = 0.075 M).

A 4 mL vial was charged with a stirring bar and potassium ferrioxalate trihydrate (368 mg, 0.750 mmol). 0.2 M aqueous sulfuric acid (0.50 mL, c = 1.5 M) was added via syringe. The vial was sealed with a plastic cap, and the solution was stirred at 23 °C, irradiated with a 5 W blue LED (2 cm away from the vial), and cooled with an electric cooler (surrounding the vial). Irradiation was halted after 30.0 s, and 0.2 M aqueous sulfuric acid (1.5 mL) and the buffered solution of 1,10-phenanthroline (2 mL) were added consecutively via syringe. The resulting solution was kept in the dark for 5 min, and then 0.1 mL of the solution was taken as an aliquot and diluted with 0.2 M aqueous sulfuric acid (1.9 mL). The absorbance of the resulting solution in a cuvette (l = 1.0 cm) at 510 nm was measured by UV-Vis spectrometer. A non-irradiated sample was also prepared in the same manner otherwise, and the absorbance at 510 nm was measured.

The amount of ferrous ion formed was calculated as following:

$$\text{mol } Fe^{2+} = \frac{V \times \Delta A}{l \times \varepsilon} = 1.47 \times 10^{-5} \text{ mol}$$

where V is the total volume (0.0800 L) of the solution that was analyzed, ΔA is the difference in absorbance (2.043) at 510 nm between the irradiated and non-irradiated samples, l is the path length (1.000 cm), and ε is the molar absorptivity at 510 nm (11,100 L/mol·cm).[37]

The photon flux was calculated as follows:

$$\text{photon flux} = \frac{\text{mol } Fe^{2+}}{\Phi \times t \times f} = 5.85 \times 10^{-7} \text{ mol photon/s}$$

where Φ is the quantum yield for the ferrioxalate actinometer (approximated as 0.845, which was reported for a 0.15 M solution at λ = 457.9 nm),[37] t is the time (30.0 s), and f is the fraction of

light absorbed at 450 nm (0.9926). The fraction of light absorbed was determined by the following equation:

$$f = 1.0000 - 10^{-A} = 0.9926$$

where A is the measured absorbance (2.130) of the 0.15 M solution of potassium ferrioxalate at 450 nm.

Determination of quantum yield

In a glove-box, a 4 mL vial was charged with a stirring bar, $Ru(bpy)_3(PF_6)_2$ (1.3 mg, 1.5 μmol, 1.5 mol%), and **3.1** (44 mg, 0.11 mmol, 1.1 equiv). Dry acetonitrile-d_3 (0.50 mL, c = 0.20 M) was added via syringe. The vial was sealed with a PTFE/Silicone septum, and brought out of the glove-box. Under inert atmosphere, benzene (8.9 μL, 7.8 mg, 0.10 mmol, 1.0 equiv) was added to the stirred mixture via glass syringe. The reaction mixture was stirred at 23 °C, irradiated with a 5 W CFLs (2 cm away from the vial), and cooled with an electric cooler (surrounding the vial). After 3 min, ethyl acetate (10 μL, 9.0 mg, 0.10 mmol) was added as an internal standard, and the reaction mixture was analyzed *via* ^{1}H NMR spectroscopy. Comparison of the integral of the peak of **3.20** at 2.76 ppm (CH_2, 2H) with that of the peak of ethyl acetate at 4.06 ppm (CH_2, 2H) revealed a 53% yield of **3.20** (5.3×10^{-5} mol).

A 3×10^{-3} M solution of $Ru(bpy)_3(PF_6)_2$ in acetonitrile was prepared, and the absorbance of the solution at 450 nm was measured (A > 3). The fraction of light absorbed at 450 nm was calculated as described above (f > 0.999).

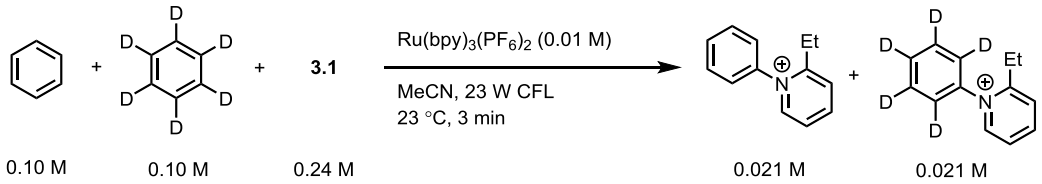
The quantum yield was calculated as follows:

$$\Phi = \frac{\text{mol } \mathbf{20}}{\text{flux} \times t \times f} = 0.505$$

where flux is the photon flux determined by ferrioxalate actinometry (5.85×10^{-7} mol photon/s), t is the time (180 s), and f is the fraction of light absorbed by [Ru] at 450 nm (1.00).

3.6.7 Kinetic H/D Isotope Effect Analysis

Intermolecular competition



In a glove-box, a 4 mL vial was charged with a stirring bar, $Ru(bpy)_3(PF_6)_2$ (1.7 mg, 2 μmol, 10 mol%), and **3.1** (30 mg, 0.075 mmol, 3.0 equiv). Dry acetonitrile-d_3 (0.25 mL, c = 0.10 M) was added via syringe. The vial was sealed with a PTFE/Silicone septum, and brought out of the glove-box. Under inert atmosphere, benzene (2.2 μL, 2.0 mg, 0.025 mmol, 1.0 equiv) and benzene-d_6 (2.2 μL, 2.1 mg, 0.025 mmol, 1.0 equiv) were added to the stirred mixture via glass syringe. The reaction mixture was stirred at 23 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 3 min, ethyl acetate (5.0 μL, 4.5 mg, 0.051 mmol) was added as an internal standard, and the reaction mixture was analyzed *via* ^{1}H NMR spectroscopy. For ^{1}H NMR integral analysis (Supplementary Fig. 9), we selected the multiplet peak at 8.62–8.56 ppm, corresponding to the hydrogen atoms on **b** and **c** in both **3.20** and **3.20**-d_5, and the multiplet peak at 7.57–7.52 ppm, corresponding to the hydrogen atom on **a** in **3.20**. Comparison of the integrals of those peaks with that of the peak of ethyl acetate at 4.06 ppm (CH_2, 2H) revealed a 21% yield of **3.20** and a 21% yield of **3.20**-d_5.

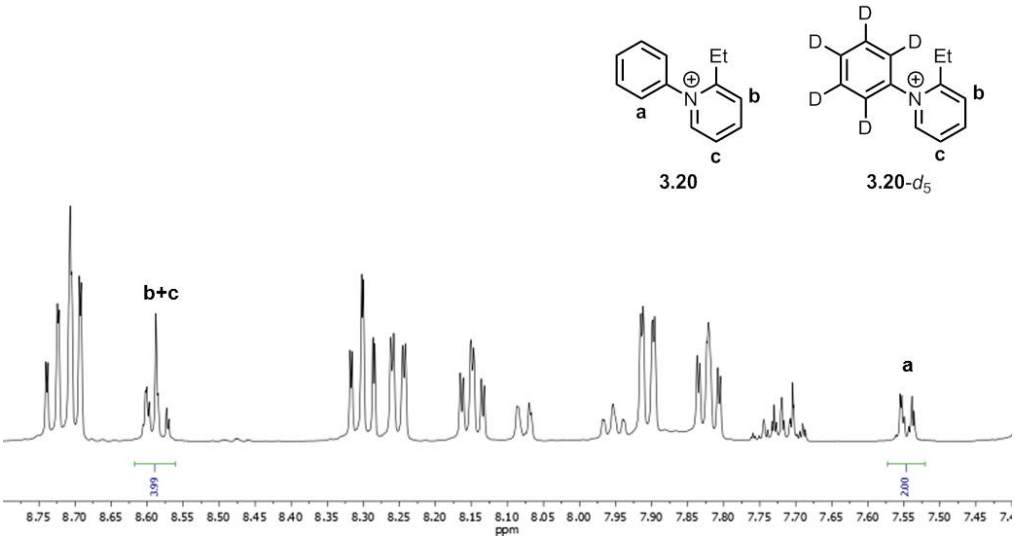
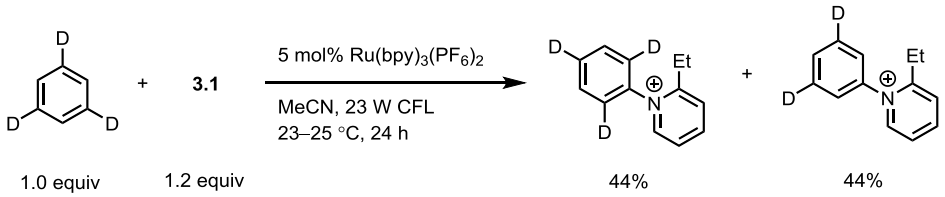


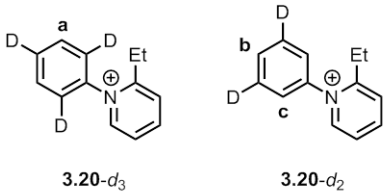
Figure 3.13. Quantification of **3.20** and **3.20**-d_5.

Intramolecular competition



In a glove-box, a 4 mL vial was charged with a stirring bar, Ru(bpy)$_3$(PF$_6$)$_2$ (2 mg, 2 µmol, 5 mol%), and **3.1** (30 mg, 0.075 mmol, 1.5 equiv). Dry acetonitrile-d_3 (0.25 mL, c = 0.20 M) was added via syringe. The vial was sealed with a PTFE/Silicone septum, and brought out of the glove-box. Under inert atmosphere, benzene-1,3,5-d_3 (4.5 µL, 4.0 mg, 0.050 mmol, 1.0 equiv) was added to the stirred mixture via glass syringe. The reaction mixture was stirred at 23–25 °C, irradiated with two 23 W CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 24 h, ethyl acetate (5.0 µL, 4.5 mg, 0.051 mmol) was added as an internal standard, and the reaction mixture was analyzed *via* ^{1}H NMR spectroscopy. For ^{1}H NMR integral analysis (Supplementary Fig. 10), we selected the multiplet peaks at 7.76–7.73 ppm, 7.73–7.68 ppm, and 7.56–7.52 ppm, corresponding to the hydrogen atoms on **a**, **b**, and **c**,

respectively. Comparison of the integrals of those peaks with that of the peak of ethyl acetate at 4.06 ppm (CH_2, 2H) revealed a 44% yield of **3.20**-d_3 and a 44% yield of **3.20**-d_2.



3.20-d_3 **3.20**-d_2

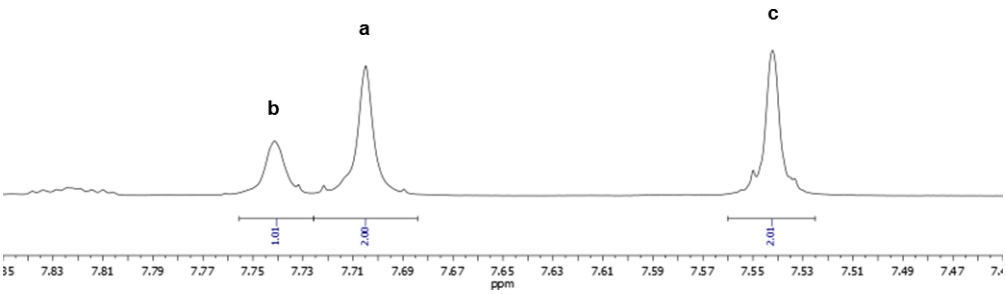
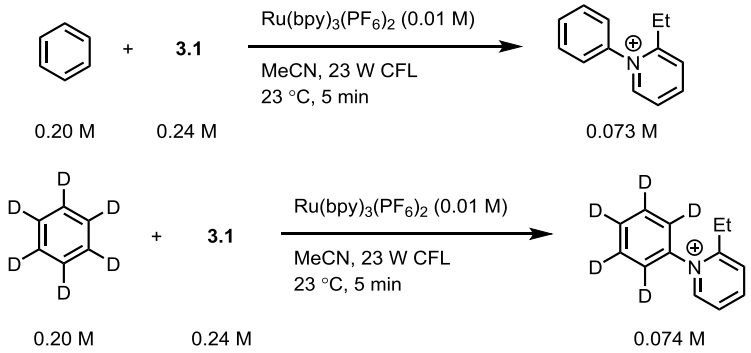


Figure 3.14. Quantification of **3.20**-d_3 and **3.20**-d_2.

Overall rate comparison



In a glove-box, each of two 4 mL vials was charged with a stirring bar, $Ru(bpy)_3(PF_6)_2$ (2 mg, 2 μmol, 5 mol%), and **3.1** (30 mg, 0.075 mmol, 1.5 equiv). Dry acetonitrile-d_3 (0.25 mL, c = 0.20 M) was added to each vial via syringe. The vials were sealed with a PTFE/Silicone septum, and brought out of the glove-box. Under inert atmosphere, benzene (2.2 μL, 2.0 mg, 0.025 mmol, 1.0 equiv) and benzene-d_6 (2.2 μL, 2.1 mg, 0.025 mmol, 1.0 equiv) were separately added to the two vials via glass syringe. The reaction mixtures were stirred at 23 °C, irradiated with two 23 W

CFLs (3 cm away from the vial), and cooled with a fan (6 cm away from the vial). After 5 min, ethyl acetate (5.0 µL, 4.5 mg, 0.051 mmol) was added, to each vial, as an internal standard, and the two reaction mixtures were analyzed *via* ^{1}H NMR spectroscopy. For ^{1}H NMR integral analysis (Supplementary Fig. 11, Supplementary Fig. 12), we selected the quartet peaks at 2.77 ppm, corresponding to the hydrogen atoms on **a**. Comparison of the integrals of those peaks with that of the peak of ethyl acetate at 4.06 ppm (CH_2, 2H) revealed a 36% yield of **3.20** and a 37% yield of **3.20**-d_5.

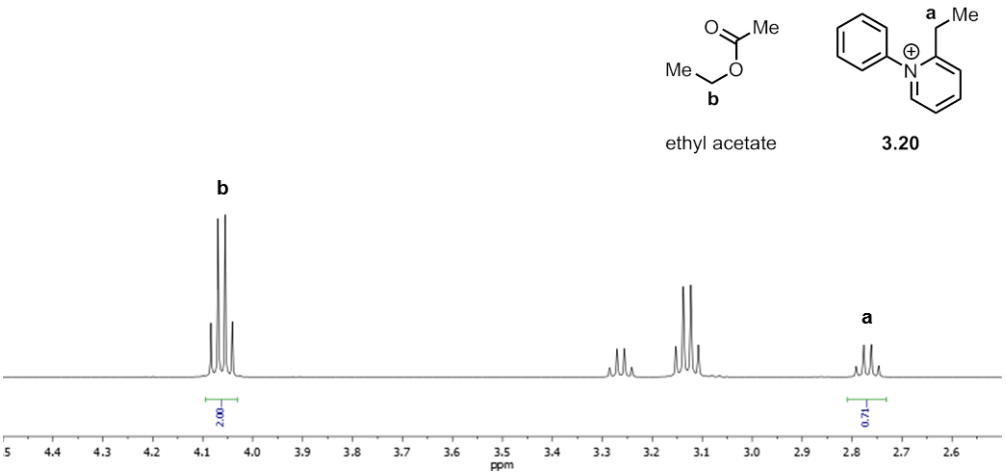


Figure 3.15. Quantification of **3.20**.

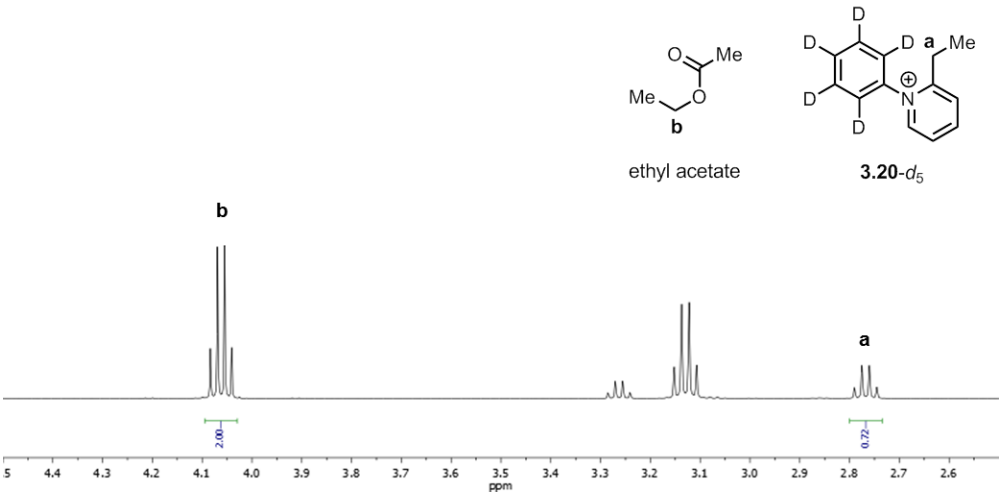
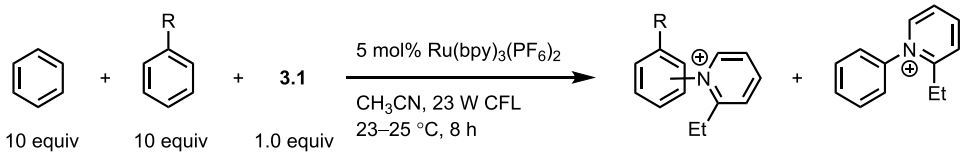


Figure 3.16. Quantification of **3.20**-d_5.

3.6.8 Hammett Analysis

Measurement of relative rates of arene substrates toward C–H pyridination



In a glove-box, a 4 mL vial was charged with a stirring bar, **3.1** (20 mg, 0.050 mmol, 1.0 equiv), and $Ru(bpy)_3(PF_6)_2$ (2 mg, 2 µmol, 5 mol%). The vial was sealed with a PTFE/Silicone septum, and brought out of the glove-box. Dry acetonitrile (0.25 mL, c = 0.20 M), benzene (45 µL, 39 mg, 0.50 mmol, 10 equiv), and a mono-substituted arene (0.50 mmol, 10 equiv) were added via glass syringe, consecutively. The reaction mixture was stirred at 23–25 °C and irradiated for 8 h with two 23 W CFLs (3 cm away from the vial) with a fan placed for cooling. The reaction mixture was concentrated *in vacuo*. The residue was purified by chromatography on silica gel eluting with a solvent mixture of DCM/methanol (99/1 to 90/10 (v/v)) to afford a mixture of arylpyridinium salts.

To a 4 mL vial, charged with the product mixture and a stirring bar, butylamine (50 µL, 37 mg, 0.50 mmol) was added, and the mixture was stirred at 23 °C for 12 h. The reaction mixture was concentrated *in vacuo* (40 °C, 100 mbar), and analyzed *via* ^{1}H NMR spectroscopy for determination of the relative concentrations of the arylamine products.

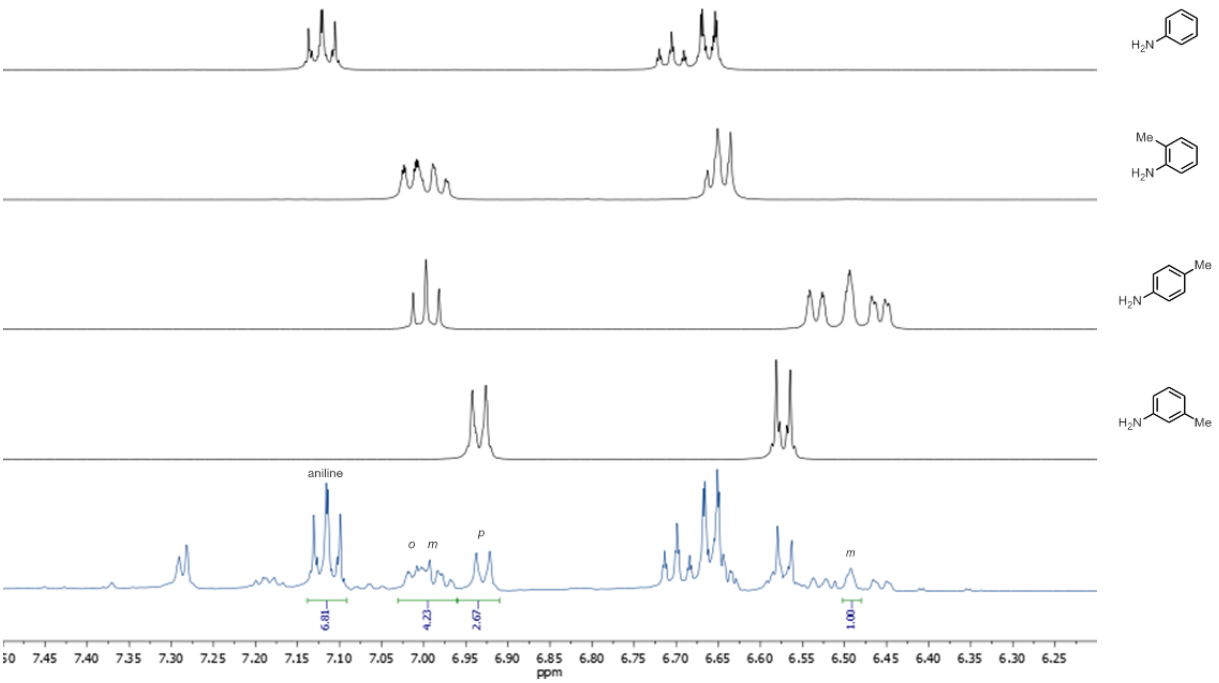


Figure 3.17. Competition between toluene and benzene ([o-toluidine] : [m-toluidine] : [p-toluidine] : [aniline] = 1.0 : 0.62 : 0.83 : 2.1). The 1H NMR spectra were measured in CD2Cl2.

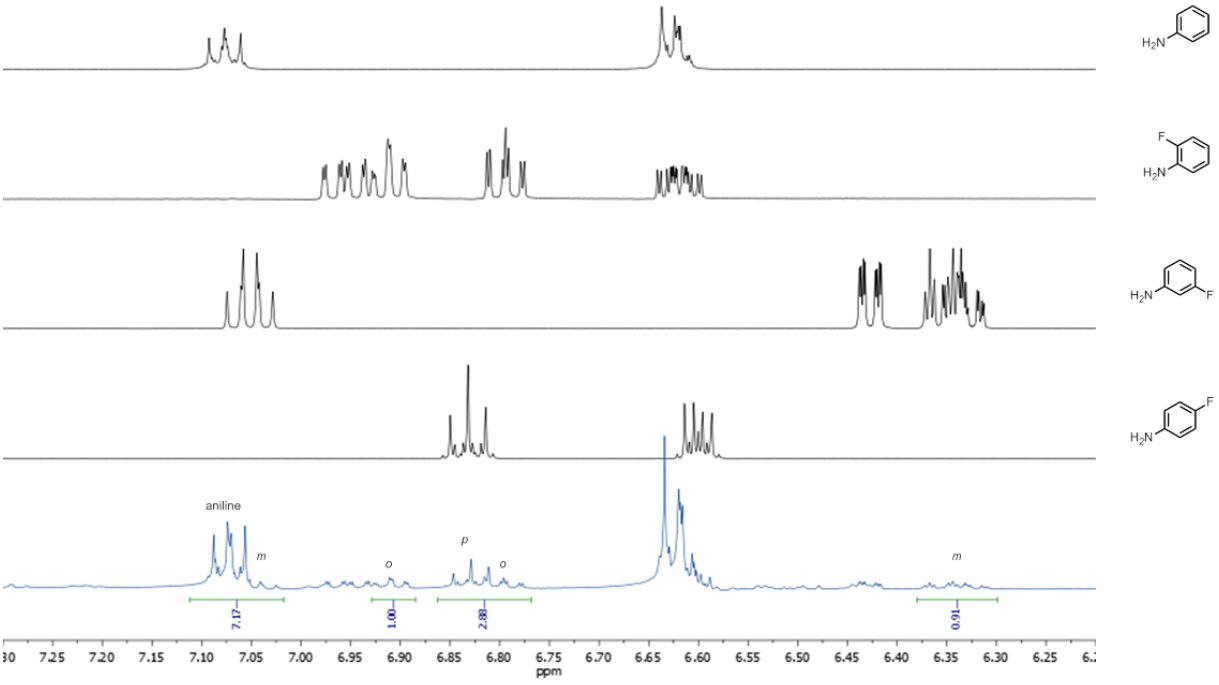


Figure 3.18. Competition between fluorobenzene and benzene ([2-fluoroaniline] : [3-fluoroaniline] : [4-fluoroaniline] : [aniline] = 1.0 : 0.45 : 0.94 : 3.4). The 1H NMR spectra were measured in CD3CN.

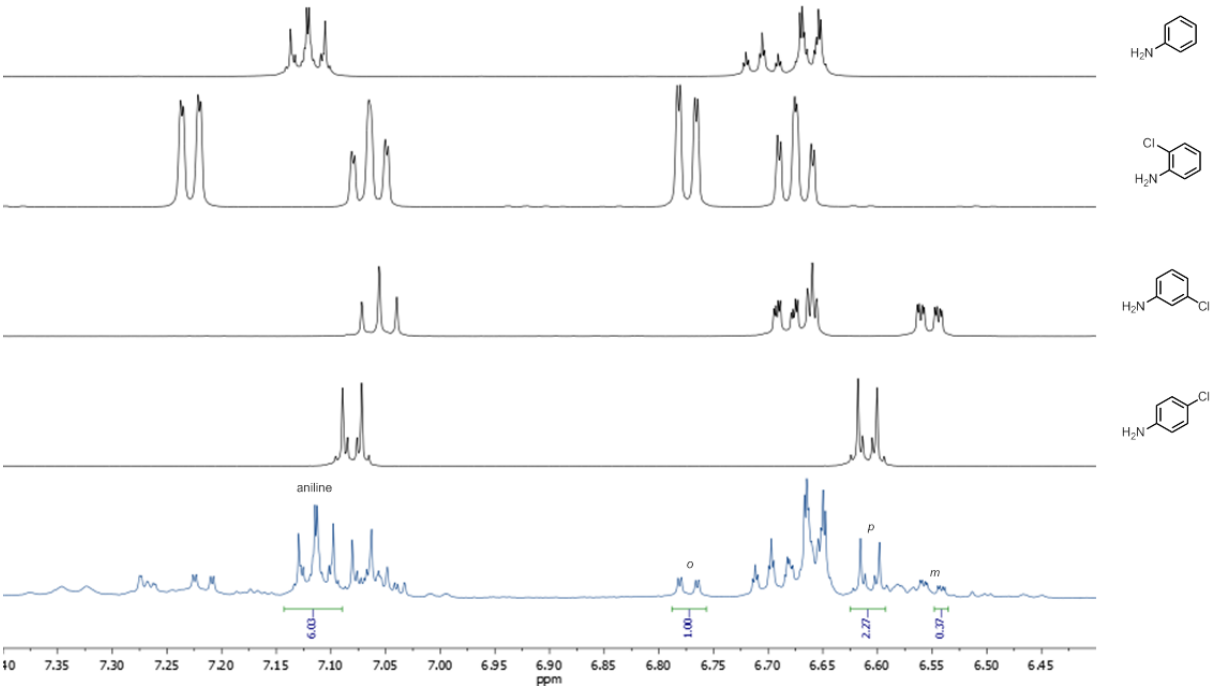


Figure 3.19. Competition between chlorobenzene and benzene ([2-chloroaniline] : [3-chloroaniline] : [4-chloroaniline] : [aniline] = 1.0 : 0.74 : 1.1 : 3.0). The 1H NMR spectra were measured in CD2Cl2.

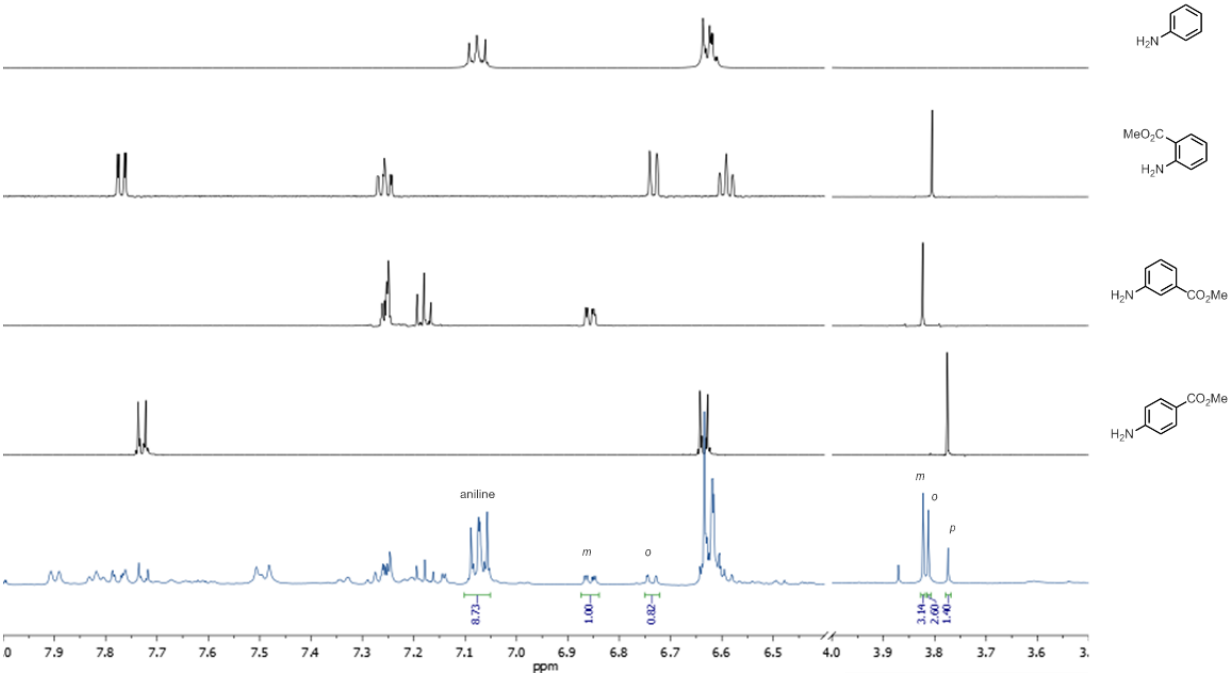


Figure 3.20. Competition between methyl benzoate and benzene ([methyl 2-aminobenzoate] : [methyl 3-aminobenzoate] : [methyl 4-aminobenzoate] : [aniline] = 1.0 : 1.2 : 0.54 : 5.3). The 1H NMR spectra were measured in CD3CN.

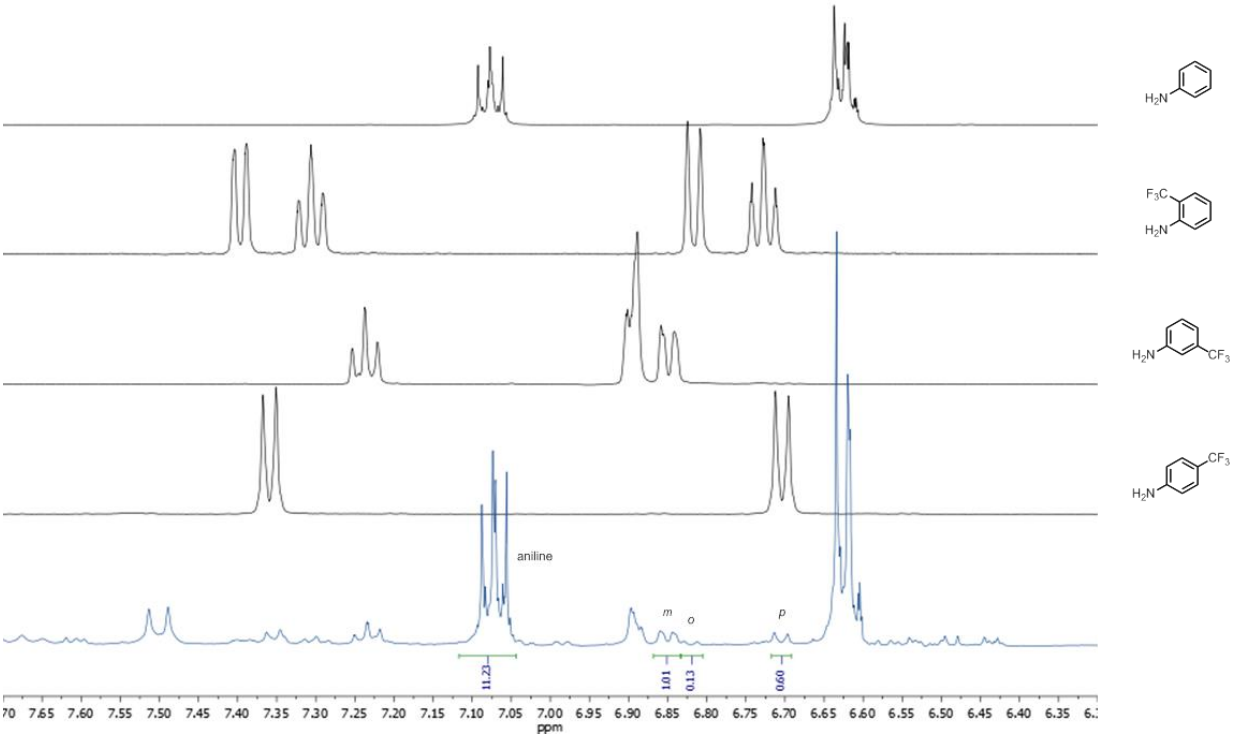


Figure 3.21. Competition between α,α,α -trifluorotoluene and benzene ([2-(trifluoromethyl)aniline] : [3-(trifluoromethyl)aniline] : [4-(trifluoromethyl)aniline] : [aniline] = 1.0 : 7.8 : 2.3 : 43). The 1H NMR spectra were measured in CD3CN.

Hammett plots

We compared the reaction rates of mono-substituted arenes with three different cationic nitrogen radical species, dimethylaminium ($Me_2HN^{\bullet+}$), ammonium ($H_3N^{\bullet+}$), and pyridinium (2-Et-$Pyr^{\bullet+}$), by Hammett analysis. We employed electrophilic substituent constants[38] because addition reactions of the cationic nitrogen radicals introduce partial cationic charges into an arene π-system. Relative rates of arene C–H substitution by ammonium radical cation and dimethylaminium radical cation were obtained from literature.[1,27,28] The $H_3N^{\bullet+}$ radical is generated from hydroxylamine O-sulfonic acid by ferrous sulfate catalyst in aqueous acetic acid,[1] while the $Me_2HN^{\bullet+}$ radical is generated from N-chlorodimethylamine by ferrous lactate catalyst in nitroethane/concentrated sulfuric acid,[27] both *via* redox cycles analogous to that of the

pyridination reaction. Linear least squares regression analyses of the plots yield the electrophilic Hammett reaction constants (ρ values) of the selected radical aromatic substitution reactions.

For a mono-substituted arene PhX, the partial rate factors F_m and F_p are defined as follows:

$$F_m = \frac{k_{m\text{-XPh–H}}}{k_{\text{Ph–H}}} = \frac{d[m\text{-XPh–NR}_2] / dt}{d[\text{Ph–NR}_2] / dt} \times 3$$

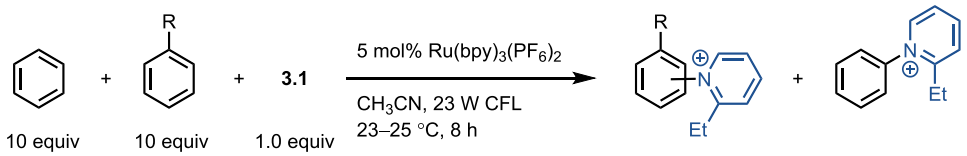
$$F_p = \frac{k_{p\text{-XPh–H}}}{k_{\text{Ph–H}}} = \frac{d[p\text{-XPh–NR}_2] / dt}{d[\text{Ph–NR}_2] / dt} \times 6$$

where the ratio of the concentrations of the different C–H bonds ([*m*-XPh–H] : [*p*-XPh–H] : [Ph–H] = 2 : 1 : 6) in the competition experiments was taken into account.

In each Hammett plot that corresponds to each of the nitrogen radical species, log values of the partial rate factors were plotted against the electrophilic substituent constants.

Substituent	Hammett constants		Partial rate factors (F)					
			$Me_2HN^{\bullet+}$		$H_3N^{\bullet+}$		2-Et-$Pyr^{\bullet+}$	
	σ_m^+	σ_p^+	F_m	F_p	F_m	F_p	F_m	F_p
Me	–0.066	–0.31	8.0	51	1.2	4.2	0.88	2.4
^{i}Pr	–0.060	–0.28	6.2	42				
^{t}Bu	–0.059	–0.26	2.3	27	1.8	4.3		
H	0		1		1		1	
F	0.35	–0.073			0.15	0.93	0.41	1.7
Cl	0.40	0.11	0.015	0.41	0.093	0.53	0.74	2.3
Br	0.40	0.15	0.009	0.40	0.14	0.69		
CO_2Et	0.37	0.48			0.016	0.023		
CO_2Me	0.37	0.49					0.69	0.62
CF_3	0.52	0.61					0.53	0.32
CN	0.56	0.66			0.017	0.025		

Table 3.3. Tabulated electrophilic Hammett constants and partial rate factors of three radical aromatic substitution reactions.



Scheme 3.5. Reaction scheme of arene C–H substitution by the pyridinium radical cation.

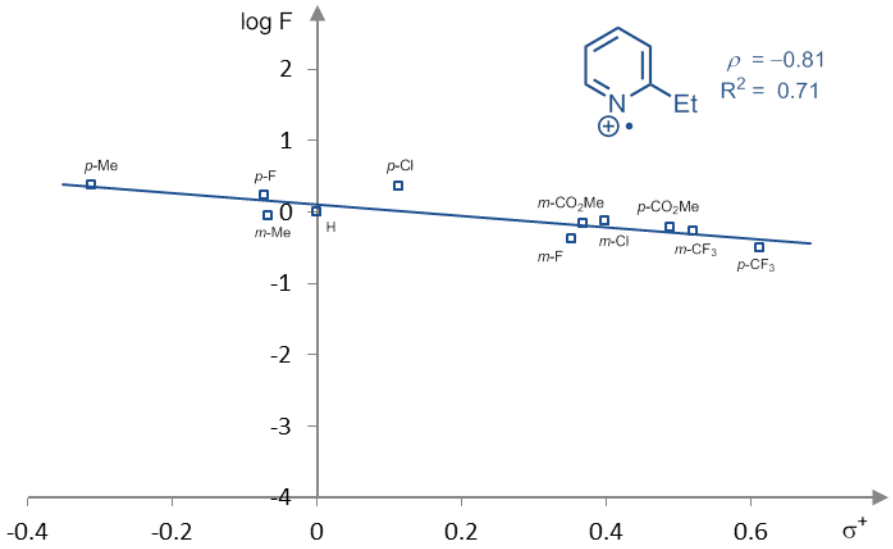
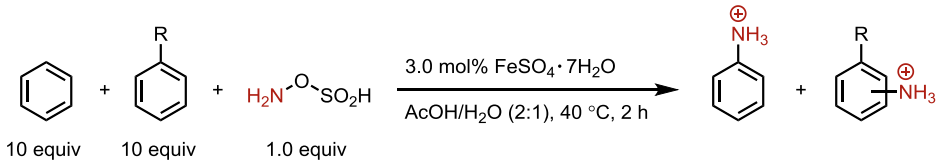


Figure 3.22. Hammett plot of the pyridinium radical cation toward arene substitution.



Scheme 3.6. Reaction scheme of arene C–H substitution by the ammonium radical cation.

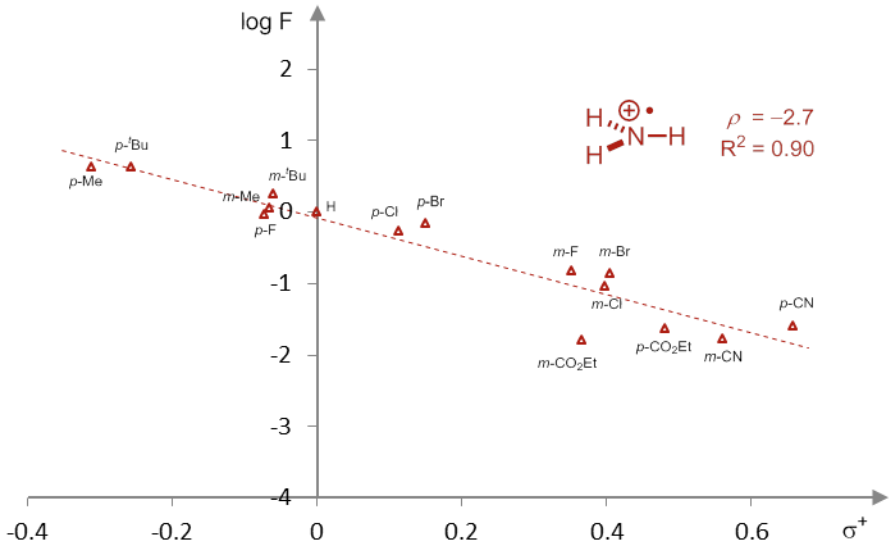
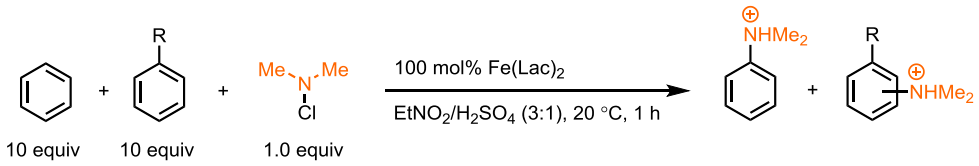


Figure 3.23. Hammett plot of the ammonium radical cation toward arene substitution.



Scheme 3.7. Reaction scheme of arene C–H substitution by the dimethylaminium radical cation.

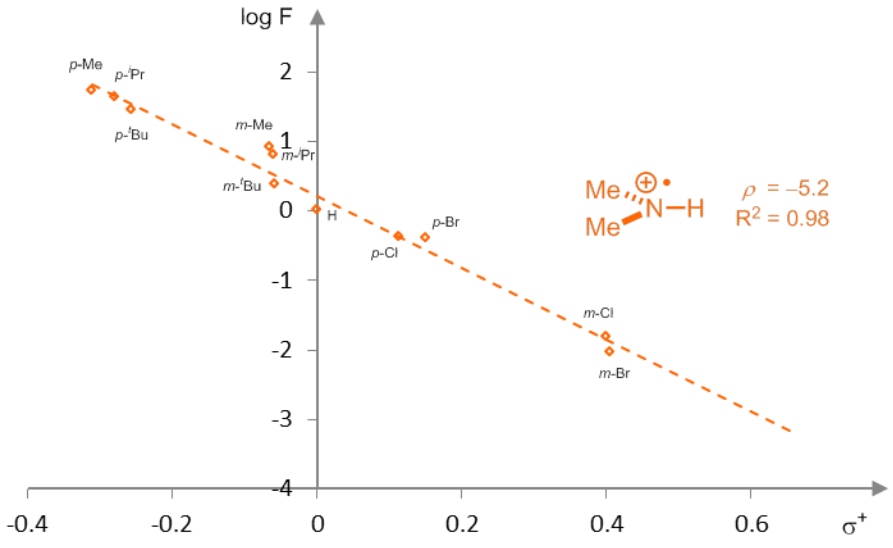


Figure 3.24. Hammett plot of the dimethylaminium radical cation toward arene substitution.

3.6.9 Comparison of the Pyridinium Radical Cation and other Electrophilic Bond-Forming Species Based on Brown-Stock Analysis

Tabulation of selectivity relationship data

As originally described by Brown and Stock,[29] a linear free energy relationship between the relative rate of *p*-Tol–H versus Ph–H and the relative rate of *p*-Tol–H versus *m*-Tol–H is generally observed for electrophilic aromatic substitution. We compared the selectivity relationship data of pyridinium, ammonium, and dimethylaminium radical cations with those of the 47 electrophilic aromatic substitution reactions (halogenation, acylation, proton exchange, nitration, sulfonylation, protodesilylation, mercuration, and alkylation; see ref 29 for details) that were tabulated by Brown and Stock.

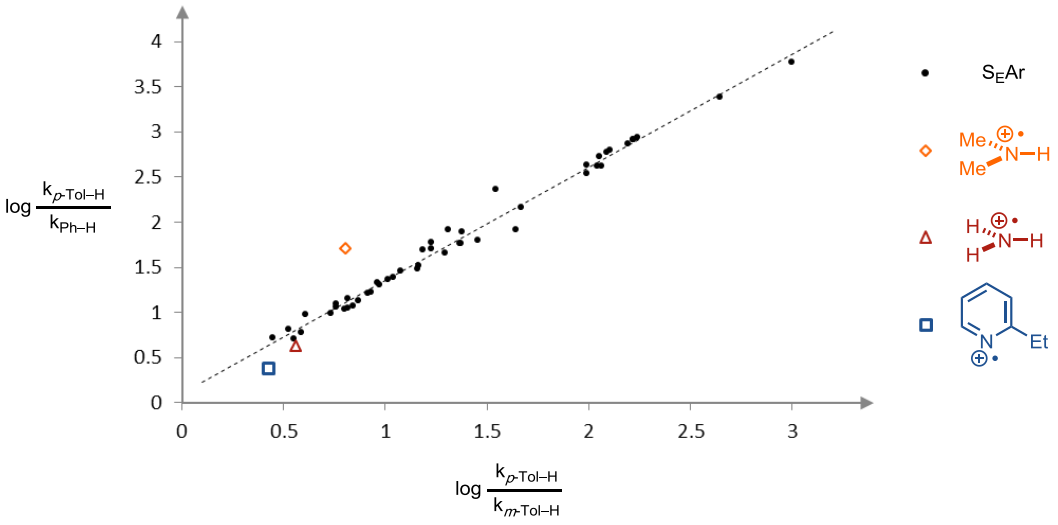


Figure 3.25. Original Brown-Stock diagram with three cationic nitrogen radicals.

An extended diagram with more tabulated data[39] is depicted below (data of gas-phase reactions were omitted).

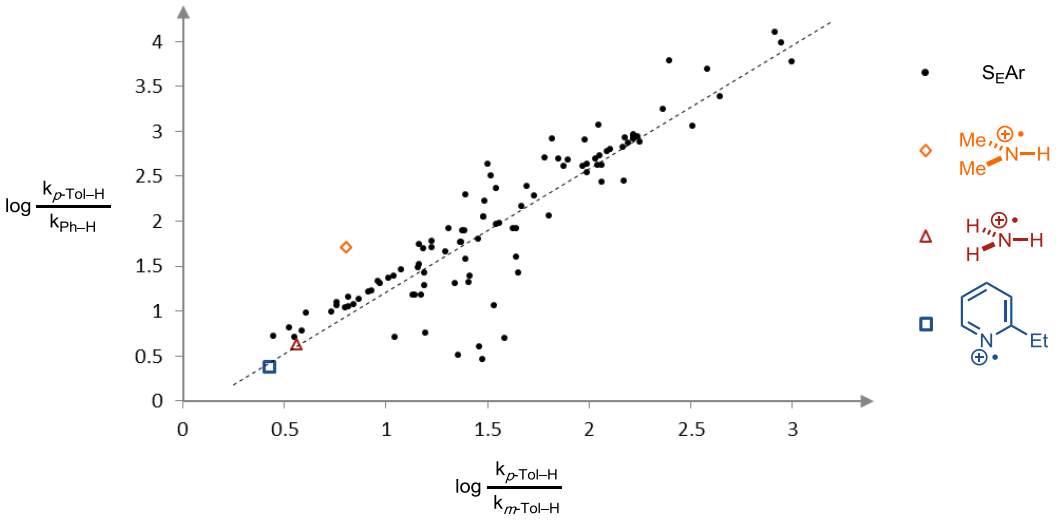


Figure 3.26. Extended Brown-Stock diagram with three cationic nitrogen radicals.

The pyridinium radical cation exhibits the smallest selectivity profile among the tabulated bond-forming species with electrophilic characters. The location of an aromatic substitution reaction on the Brown-Stock diagram is interpreted as an indicator of how advanced the transition state of bond formation is.

Discussion on aromatic substitution by neutral radicals

We extended the Brown-Stock diagram by tabulating the selectivity relationship data of neutral radical species. Radical aromatic substitution reactions that exhibit negative Hammett ρ values were selected, including arylation,[40] acyloxylation,[41,42] perfluoroalkylation,[43] cyanation,[44] alkynylation,[45] and dinitromethylation.[46]

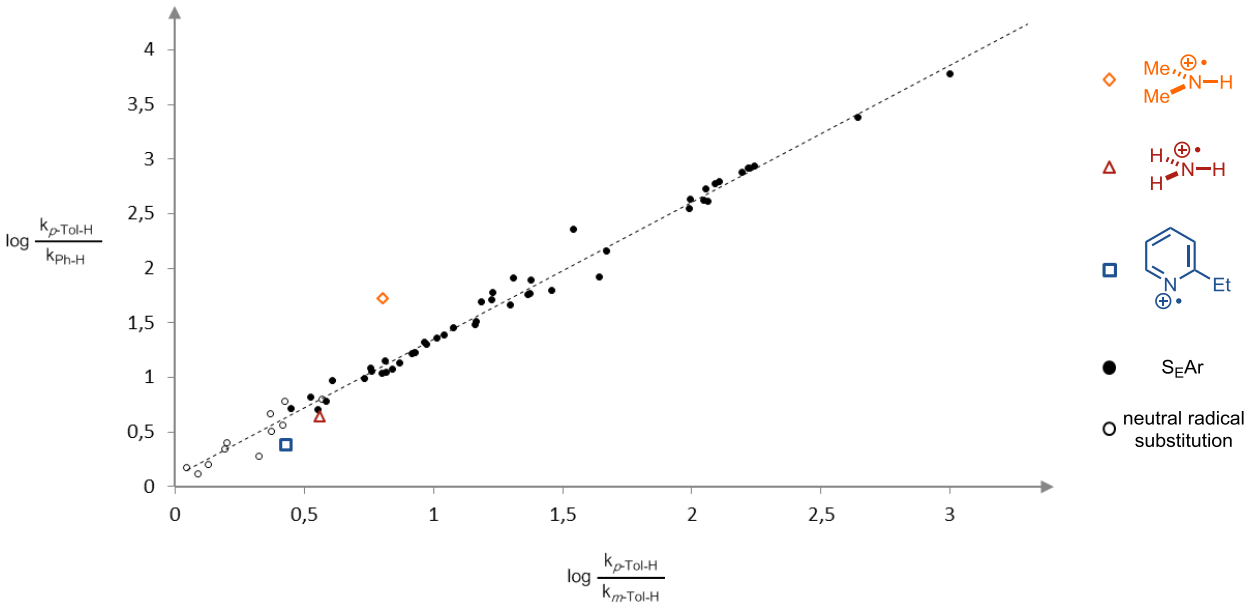


Figure 3.27. Plot of radical aromatic substitution reactions on the Brown-Stock diagram.

The data of arene substitution by neutral radicals (with electrophilic characters) also satisfy the linear free energy relationship as illustrated in the Brown-Stock diagram that was originally described only for electrophilic aromatic substitution. As is well appreciated, the neutral radicals exhibit low selectivity. However, those neutral radicals cannot be used for synthetically useful arene functionalization with one equivalent of arene. To the best of our knowledge, no neutral radical aromatic substitution reaction has been reported to be practically effective with less than 5 equivalents of a carboarene relative to the radical species. The neutral radicals with high reactivity are prone to a number of undesired pathways, such as H atom abstraction and fragmentation. The data of the neutral radicals are therefore omitted in Figure 3.3b in order to compare reactions with practical synthetic values, of which the pyridination is the least biased with respect to constitutional bias.

3.6.10 Comparison of N–H Bond Dissociation Energies of 2-Ethylpyridinium and Dimethylammonium Ions

Calculation of N–H BDE of pyridinium ion

Aue et al.[30] defined the N–H BDE of a protonated amine, in other words, hydrogen affinity of the corresponding amine radical cation, as following:

$HA([N]^{\bullet+}) = PA([N]) + IP([N]^{\bullet+}) - IP(H\bullet)$

where HA is hydrogen affinity, PA is proton affinity, and IP is ionization potential. Hydrogen affinity of dimethylamine radical cation was reported, by using this equation, to be 101.3 $kcalmol^{-1}$. We adopted the equation, using reported thermodynamic parameters of 2-ethylpyridine.[47] IP value of 2-ethylpyridine was approximated as that of 2-picoline.[5]

$HA(pyr^{\bullet+}) = PA(pyr) + IP(pyr^{\bullet+}) - IP(H\bullet)$

$= 228\ kcalmol^{-1} + 208\ kcalmol^{-1} - 314\ kcalmol^{-1}$

$= 122\ kcalmol^{-1}$

$HA(pyr^{\bullet+}) - HA(Me_2NH^{\bullet+}) = 122\ kcalmol^{-1} - 101.3\ kcalmol^{-1}$

$= 21\ kcalmol^{-1}$

$= 88\ kJmol^{-1}$

3.7 References

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