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Charge Transfer Directed Radical Substitution Enables *para*-Selective C–H Functionalization

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Abstract

Efficient C–H functionalization requires selectivity for specific C–H bonds. Progress has been made for directed aromatic substitution reactions to achieve *ortho*- and *meta*- selectivity, but a general strategy for *para*-selective C–H functionalization has remained elusive. Herein, we introduce a previously unappreciated concept which enables nearly complete *para* selectivity. We propose that radicals with high electron affinity elicit areneto-radical charge transfer in the transition state of radical addition, which is the factor primarily responsible for high positional selectivity. We demonstrate that the selectivity is predictable by a simple theoretical tool and show the utility of the concept through a direct synthesis of aryl piperazines. Our results contradict the notion, widely held by organic chemists, that radical aromatic substitution reactions are inherently unselective. The concept of charge transfer directed radical substitution could serve as the basis for the development of new, highly selective C–H functionalization reactions.

Historically, electrophilic aromatic substitution is perhaps the most important reaction class for the functionalization of aromatic C–H bonds, but typically affords mixtures of products (Figure 1a).[1] Transition-metal catalyzed reactions have generally struggled with the same limitations in positional selectivity, except when a coordinating directing group on the arene substrate is utilized to position the catalyst within close proximity to a specific C–H bond.[2,3] This chelation-assisted approach has been successful in enabling C–H functionalization *ortho*,[4,5] and in some cases *meta*,[6] to the coordinating directing group (Figure 1b). Steric hindrance has been explored as a strategy to control positional selectivity in C–H functionalization, but product mixtures still result, particularly for monosubstituted arenes.[7-9] There have been isolated reports of nonchelation-assisted aromatic C–H

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G.B.B., W.H., and A.R.M. designed and performed the experiments and analyzed the data. G.B.B. discovered the Ar–TEDA formation reaction and conceived of the mechanistic proposal and explanation for the positional selectivity. A.R.M. discovered the reduction of Ar-TEDA compounds to aryl piperazines. G.B.B. and T.R. prepared the manuscript with input from W.H. and A.R.M.

Full experimental and computational details, and characterization of new compounds are available in the supplemental online information.

functionalization reactions with anomalously high *para* selectivity for monosubstituted arenes; however, these reactions either require solvent quantities of arene or work only on activated arenes, and the origin of their *para* selectivity is unknown, precluding generalization to the design of other *para* selective functionalization reactions.[10-12] Thus, no general strategy currently exists for highly *para* selective C–H functionalization. Such a strategy would constitute a novel complement to the classical electrophilic aromatic substitution paradigm, especially if no particular directing group is required.

Herein, we describe how aromatic substitution by highly electrophilic radicals, which are capable of eliciting significant charge transfer from the arene in the transition state of addition, exhibits high selectivity for positions *para* to substituents on the arene (Figure 1c). Radical aromatic substitution reactions normally do not proceed with synthetically useful positional selectivity on substituted arenes. For example, in the 2007 edition of *Advanced Organic Chemistry* by Carey and Sundberg, it is claimed that "there are some inherent limits to the usefulness of such reactions. Radical Substitutions are only moderately sensitive to substituent directing effects, so that substituted reactants usually give a mixture of products. This means that the practical utility is limited to symmetrical reactants, such as benzene, where the position of attack is immaterial."[13] The results reported herein demonstrate that, contrary to prior assumptions, radical aromatic substitution can furnish novel, useful products with high chemo- and positional selectivity when an appropriately electrophilic radical is used. We show that for most substrates, including monosubstituted arenes, only one of the possible positional isomers is observed in significant amounts. The charge transfer directed concept does not require a coordinating directing group as do chelation-assisted C–H functionalization reactions because selectivity is determined by the electronic structure in the transition state as opposed to enforced proximity of the catalyst.

Results and Discussion

Charge Transfer Directed Radical Substitution

The doubly cationic radical $TEDA^{2+\bullet}$, derived from single electron reduction of Selectfluor, is capable of engaging in radical aromatic substitution to yield *N*-aryl-*N'*-chloromethyldiazoniabicyclo[2.2.2]octane salts, which we have termed Ar–TEDA compounds (Figure 2, see page S25–S27 in Supporting Information for evidence implicating $TEDA^{2+\bullet}$ as C–N bond forming species). The reaction is enabled by a dual catalyst combination: Pd catalyst **1**, which we have introduced in a previous report, and $Ru(bipy)_3(PF_6)_2$ (Figure 2a).[14] Photoirradiation is not required for reaction, which works equally well when shielded from light. For most arenes only one of the possible positional isomers of the Ar–TEDA product is observed as judged by nuclear magnetic resonance spectroscopy; fluorobenzene, for example, yields the *para* substituted product in >99:1 positional selectivity (Supplementary Figure S2). All monosubstituted arenes tested give the *para* substituted product as the only significant isomer. Disubstituted arenes and some heteroarenes likewise undergo clean substitution at the position *para* to the group with the strongest directing effect. Thus, the synthesis of Ar–TEDA compounds described here constitutes a general non-chelation-assisted C–H functionalization reaction, with the arene

as the limiting reagent, with nearly exclusive positional selectivity across a broad range of substitution patterns.

The $TEDA^{2+\bullet}$ radical is an electrophilic radical, with an electron affinity of 12.4 eV, calculated by DFT. The high electron affinity of $TEDA^{2+\bullet}$ should favor a large contribution of charge-transfer in the transition state of addition (Figure 2B), which in turn leads to high selectivity for aromatic substitution at the position from which charge transfer is the greatest.[15-17] Therefore, a predictive tool for the positional selectivity of the reaction would be a metric which indicates the greatest extent of charge transfer that can be expected upon attack at a given position. We found Fukui nucleophilicity indices to be well-suited to this purpose. The Fukui nucleophilicity index of an atom, determined by simple quantum chemical calculations, is a measure of how readily electron density is transferred to an incoming electrophilic species attacking at the relevant atom.[18-20] Fukui indices are especially convenient as a predictive tool because the Fukui index for all atoms in a given molecule are determined by a pair of simple calculations on the arene itself; there is no need to map the potential energy surface of the reaction by computing the transition states of various pathways.

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

The high degree of positional selectivity we report here is unusual, especially in the context of radical aromatic substitution. A reason may be a lack of studies of substitution reactions by radicals of high electron affinity. While the $TEDA^{2+\bullet}$ radical dication has been proposed as an intermediate in recently reported aliphatic C–H oxidation methodologies utilizing Selectfluor,[22-24] to our knowledge addition of this radical to unsaturated systems has not been investigated. The most commonly employed radicals in a synthetic context are uncharged carbon-, oxygen-, nitrogen-, and halogen-based radicals, which have electron affinities in the range of 0.8–3.6 eV, far below the value for $TEDA^{2+\bullet}$ (12.44 eV, Figure 3). Aromatic substitution reactions of most neutral radicals are known to proceed with low selectivity.[13] For example, the phenyl radical has an electron affinity of 1.1 eV, and under conditions reported by Li, undergoes aromatic substitution with fluorobenzene to give an *ortho*:*meta*:*para* ratio of 47:16:37.[25] The neutral phthalimide radical has a higher electron affinity (EA = 3.66 eV). We have found that the phthalimide radical, when generated under conditions reported by Sanford,[26] undergoes aromatic substitution with fluorobenzene in a

37:11:52 ratio of *ortho*, *meta*, and *para* isomers; the selectivity for the *para* position is higher, though the other isomers still abound.

Positive charge increases electron affinity, and based on our findings and proposal, positively charged radicals should result in more selective arene substitution reactions. Monocationic aminium radicals have electron-affinities in the range of 7–8 eV, and their aromatic substitution reactivity was thoroughly investigated in seminal work by Minisci, who noted the higher selectivity of aminium radical addition compared to less electrophilic radicals. Under Minisci's conditions, the monocationic aminium radical derived from piperidine (EA = 7.74 eV) adds to fluorobenzene more selectively than the neutral phthalimide radical to afford an *o*:*m*:*p* ratio of 11:10:79. Minisci described the selectivity of monocationic aminium radicals as similar to the selectivity of electrophilic aromatic substitution, affording products of *ortho* and *para* substitution of monosubstituted arenes bearing electron donating groups.[27-29] We have discovered that, for sufficiently electrophilic radicals, charge transfer in the transition state of addition can lead to high selectivity for the *para* position over *ortho*; we have rationalized the phenomenon in terms of charge transfer in the transition state, and have introduced Fukui indices as a tool for predicting the site of substitution. The second positive charge of the $TEDA^{2+\bullet}$ aminium radical increases the electron affinity to 12.44 eV, and at this level, nearly absolute selectivity for the *para* position is observed for monosubstituted arenes.

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

We furthermore note that radicals of electron affinity comparable to $TEDA^{2+\bullet}$ need not in principle be based on cationic aminium radicals. For example, DFT calculations indicate that alkoxyl radicals exhibit a similar trend with increasing positive charge, though the septet oxygen atom itself lacks a formal charge (Supplementary Figure S11). Thus, in principle, highly electrophilic radicals could be designed for the installation of a variety of functional groups, not just C–N bonds.

Application to the synthesis of aryl piperazines

As one synthetic application of the charge transfer directed radical substitution concept, we have developed a two-step, one-pot synthesis of aryl piperazines from the corresponding aryl C–H compounds (Table 1). The procedure involves reduction of the Aryl–TEDA compounds by sodium thiosulfate, which converts the TEDA moiety into a piperazine heterocycle. Piperazines are a common motif in pharmaceuticals and materials; they constitute the third most common heterocycle present in the small molecule pharmaceuticals listed in the FDA Orange Book.[30] Aryl piperazines are commonly synthesized by Buchwald-Hartwig cross coupling reactions of aryl electrophiles with piperazine derivatives.[31] The direct synthesis of

aryl piperazines reported here is advantageous because it does not require a pre-functionalized substrate, such as an aryl halide. Importantly, this advantage relies on the high and predictable positional selectivity of the reaction, which enables the high-yield synthesis of a single desired positional isomer. The reaction is operationally simple, and can be performed under air with commercial-quality solvent. Furthermore, the piperazine moiety is obtained with an unprotected secondary amine, ready for subsequent manipulation.

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

For most substrates, nearly full conversion to the Ar–TEDA compound is observed, and in several cases the yield of the piperazine following the thiosulfate-mediated stage is lower. For example, the anti-cholesterol drug Fenofibrate undergoes Ar–TEDA formation in 88% yield, but upon treatment with sodium thiosulfate at 100 °C the yield of piperazine **3x** is 51%. The Ar–TEDA formation reaction exhibits significant functional group tolerance, despite the highly reactive and electrophilic nature of the $TEDA^{2+\bullet}$ radical intermediate; for most substrates in Table 1, the majority of mass balance is lost in the piperazine formation step, not the Ar–TEDA formation step.

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

Methods

Representative C–H piperazination procedure: 1-(p-Tolyl)piperazine (3b)

A 100 mL pressure tube was charged with palladium complex **1** (13.6 mg, 21.4 μmol. 2.50 mol%), $Ru(bipy)_3(PF_6)_2$ (55.2 mg, 64.2 μmol, 7.50 mol%), and Selectfluor (455. mg, 1.28 mmol, 1.50 equiv). Acetonitrile (4.3 mL, c = 0.20 M) was added, followed by toluene (91.1 μL, 0.856 mmol, 1.00 equiv) via syringe. The reaction mixture was stirred at 23 °C for 24 h.

Saturated aqueous sodium thiosulfate (8.6 mL) and water (8.6 mL) were added, the pressure tube was sealed, and the reaction mixture was stirred at 100 °C for 2 h. After cooling to 23 °C, the reaction mixture was transferred to a separatory funnel. Dichloromethane (20 mL) and ethylenediamine (1.5 mL) were added and the organic layer was washed with 6 M aqueous sodium hydroxide (5 mL). The aqueous layer was extracted with dichloromethane (2 × 10 mL). The combined organic layers were extracted with 1 M aqueous hydrochloric acid (2 × 15 mL). Ethylenediamine (5.0 mL) was added to the combined acidic aqueous layers, followed by basification with 6 M aqueous sodium hydroxide (8 mL). The basic aqueous layer was extracted with dichloromethane (3 × 15 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a red oil. The residue was purified by chromatography on silica gel eluting with a solvent mixture of dichloromethane/methanol/28% aqueous ammonium hydroxide (97.5/2.0/0.5 (v/v/v)) to afford 119. mg of the title compound as a yellow oil (79% yield).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Summary sentence

Exceptional positional selectivity in aromatic substitution is achievable through a previously unappreciated phenomenon: radicals with high electron affinity undergo radical aromatic substitution with nearly exclusive *para* selectivity by eliciting significant arene-to-radical charge transfer in the transition state of addition.

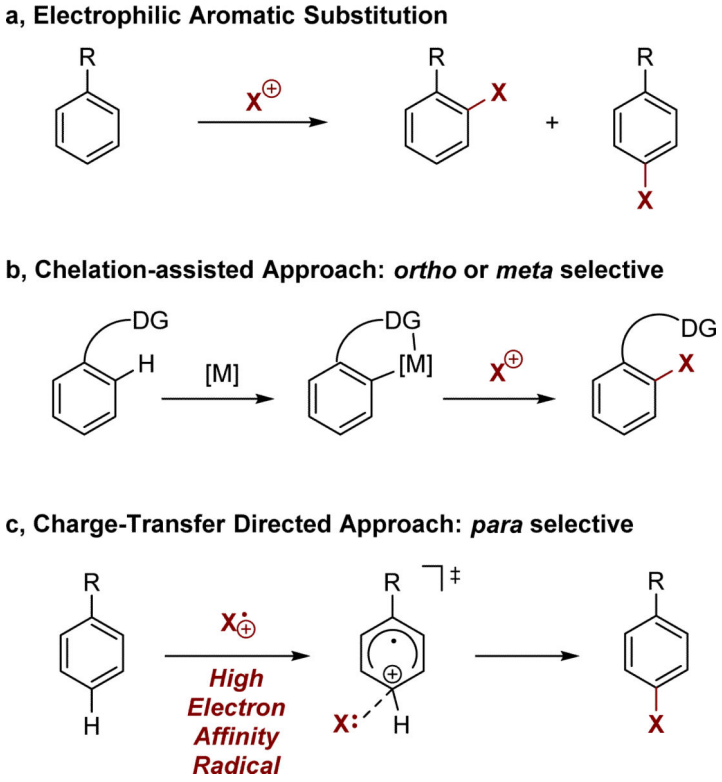


Figure 1. Selective C–H functionalization

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

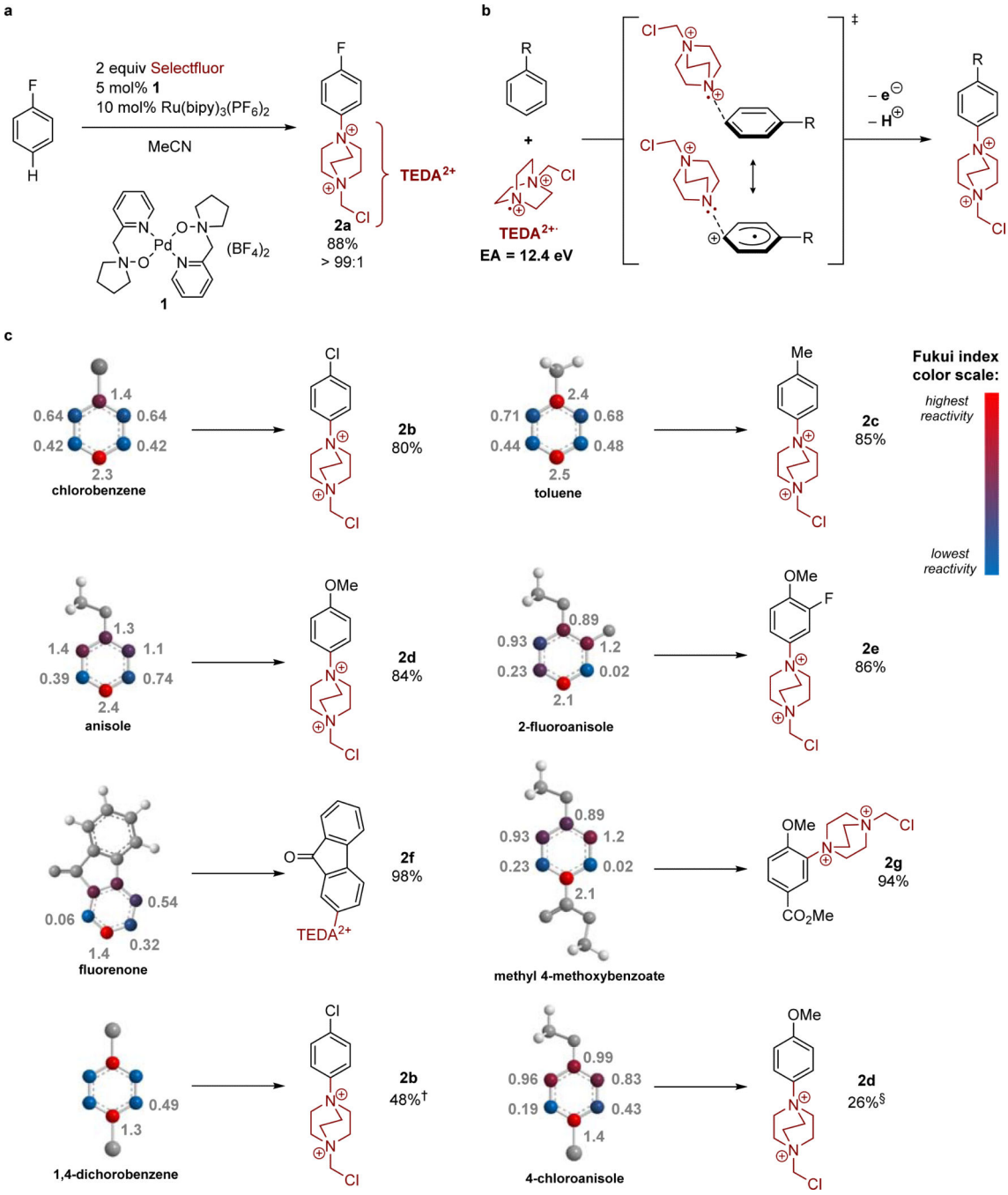


Figure 2. Charge transfer directed aromatic substitution

a, Conversion of fluorobenzene to the corresponding Ar–TEDA compound **2a**. **b,** Positional selectivity of $TEDA^{2+\cdot}$ substitution is due to the stabilizing effect of arene-to-radical charge transfer in the transition state of addition. EA = Electron Affinity, refers to gas phase adiabatic electron affinity calculated by DFT. **c,** The position of substitution by $TEDA^{2+\cdot}$ is predictable by Fukui indices. Fukui indices depicted are multiplied by ten for simplicity of presentation. DFT computations of Fukui indices and electron affinity of $TEDA^{2+\cdot}$ performed at the (U)B3LYP/6-311G(d) level of theory, with continuum polarization solvent

model for Fukui index calculations. Note that Fukui indices are computed for one conformation of the molecule, so indices of positions that are symmetrically disposed about a substituent need not be equal. See Supplemental Information for full computational details. † Substitution in the 2-position was observed in 11% yield in addition to *ipso* substitution (Supplemental Information). § Substitution in the 2-position was observed in 10% yield in addition to *ipso* substitution (Supplemental Information).

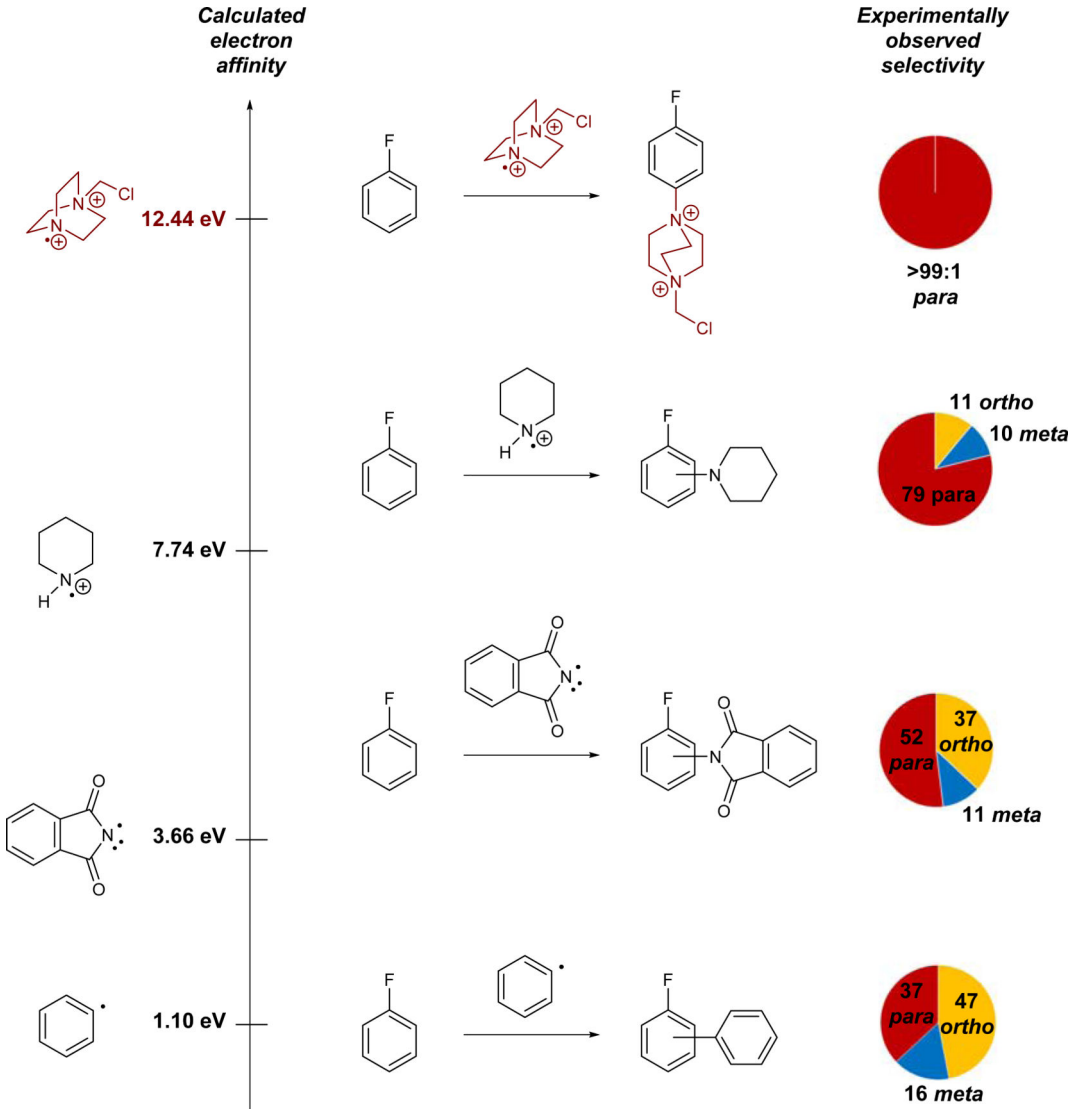
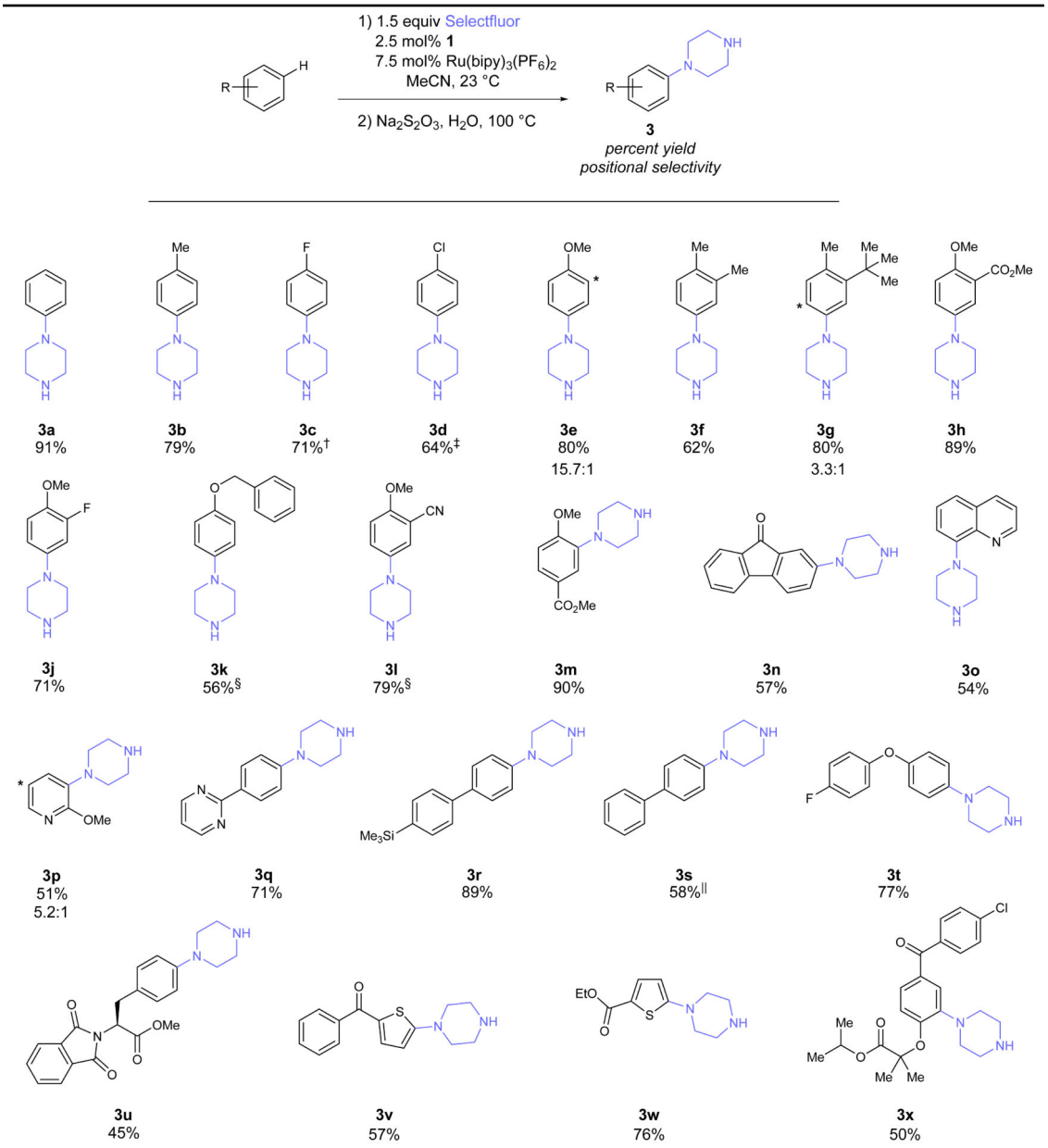


Figure 3. Selectivity for *para* substitution increases with increasing electron affinity of the radical

Electron affinities refer to gas phase adiabatic electron affinity calculated at the (U)B3LYP/6-311G(d) level of theory.

Table 1

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



† 40 °C reaction temperature in the first step. ‡ 45 °C reaction temperature in the first step. § 2.5 equiv Selectfluor, 5.0 mol% **1**, and 10 mol% $Ru(bipy)_2(PF_6)_2$ in first step. 1.0 equiv Selectfluor used in first step. * denotes the site of piperazination of the other constitutional isomer.