nature chemistry

ARTICLES

PUBLISHED ONLINE: 6 JUNE 2016 | DOI: 10.1038/NCHEM.2529

Charge-transfer-directed radical substitution enables *para*-selective C–H functionalization

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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 that enables nearly complete *para* selectivity. We propose that radicals with high electron affinity elicit arene-to-radical charge transfer in the transition state of radical addition, which is the factor primarily responsible for high positional selectivity. We demonstrate with a simple theoretical tool that the selectivity is predictable 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 radical substitution directed by charge transfer 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 (Fig. 1a)[1]. Reactions catalysed by transition metals have generally struggled with the same limitations in positional selectivity, except when a coordinating directing group (DG) on the arene substrate is utilized to position the catalyst within close proximity of 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 DG (Fig. 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 are isolated reports of non-chelation-assisted aromatic C–H functionalization reactions with anomalously high *para* selectivity for monosubstituted arenes; however, these reactions either require solvent quantities of arene or work only on activated arenes, and the origin of their *para* selectivity is unknown, which precludes 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 classic electrophilic aromatic substitution paradigm, especially if no particular DG 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 (Fig. 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 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.

Results and discussion

Radical substitution directed by charge transfer. 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 (Fig. 2) (see pages S25–S27 in the Supplementary Information 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**, which we introduced in a previous report, and $Ru(bipy)_3(PF_6)_2$ (bipy, bipyridine) (Fig. 2a)[14]. 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 (Supplementary Fig. 2). All monosubstituted arenes tested gave the *para*-substituted product as the only significant isomer. Disubstituted 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.

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 favour a large contribution of charge transfer in the transition state of addition (Fig. 2b), which in turn leads to a high selectivity for aromatic substitution at the

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position from which the charge transfer is the greatest[15–17]. 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[18–20]. 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 2c 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[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 for methyl 4-methoxybenzoate (**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.

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 dication has been proposed as an intermediate in recently reported aliphatic C–H oxidation methodologies that utilize Selectfluor[22–24], 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 (Fig. 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 the conditions reported by Li and co-workers, undergoes aromatic substitution with fluorobenzene to give an *ortho*:*meta*:*para* (*o*:*m*:*p*) ratio of 47:16:37 (ref. 25). 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[26], 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. Monocationic 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[27–29]. Under Minisci's conditions, the monocationic 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 monocationic aminium radicals as similar to the selectivity of electrophilic aromatic substitution, affording products of *ortho* and *para*

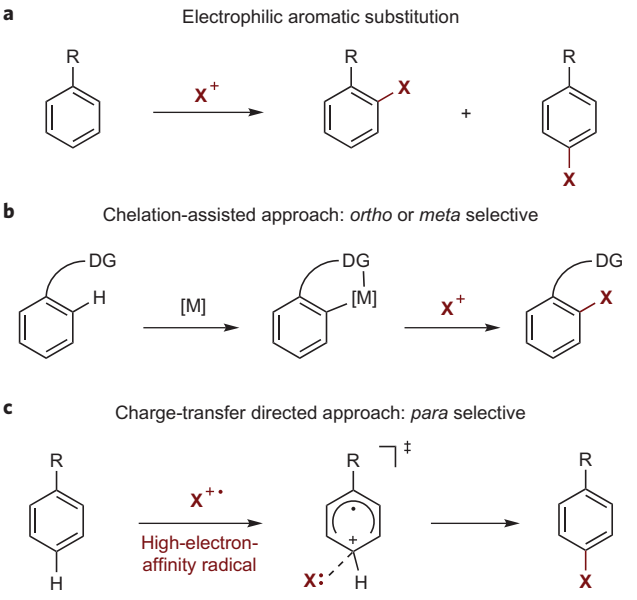

Figure 1 | Selective C–H functionalization. a, Electrophilic aromatic substitution generally yields mixtures of isomers. **b**, Lewis basic DGs direct functionalization to proximal bonds by chelation assistance. **c**, Charge-transfer-directed approach: arene-to-radical charge transfer, elicited by highly electrophilic radicals, leads to a high *para* selectivity.

substitution of monosubstituted arenes that bear electron-donating groups[27–29]. 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 monosubstituted 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.

Furthermore, radicals of electron affinity comparable to that of $TEDA^{2+\bullet}$ 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, although the septet oxygen atom itself lacks a formal charge (Supplementary Fig. 11). 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 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 (Fig. 4). The procedure involves the 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 other materials; they constitute the

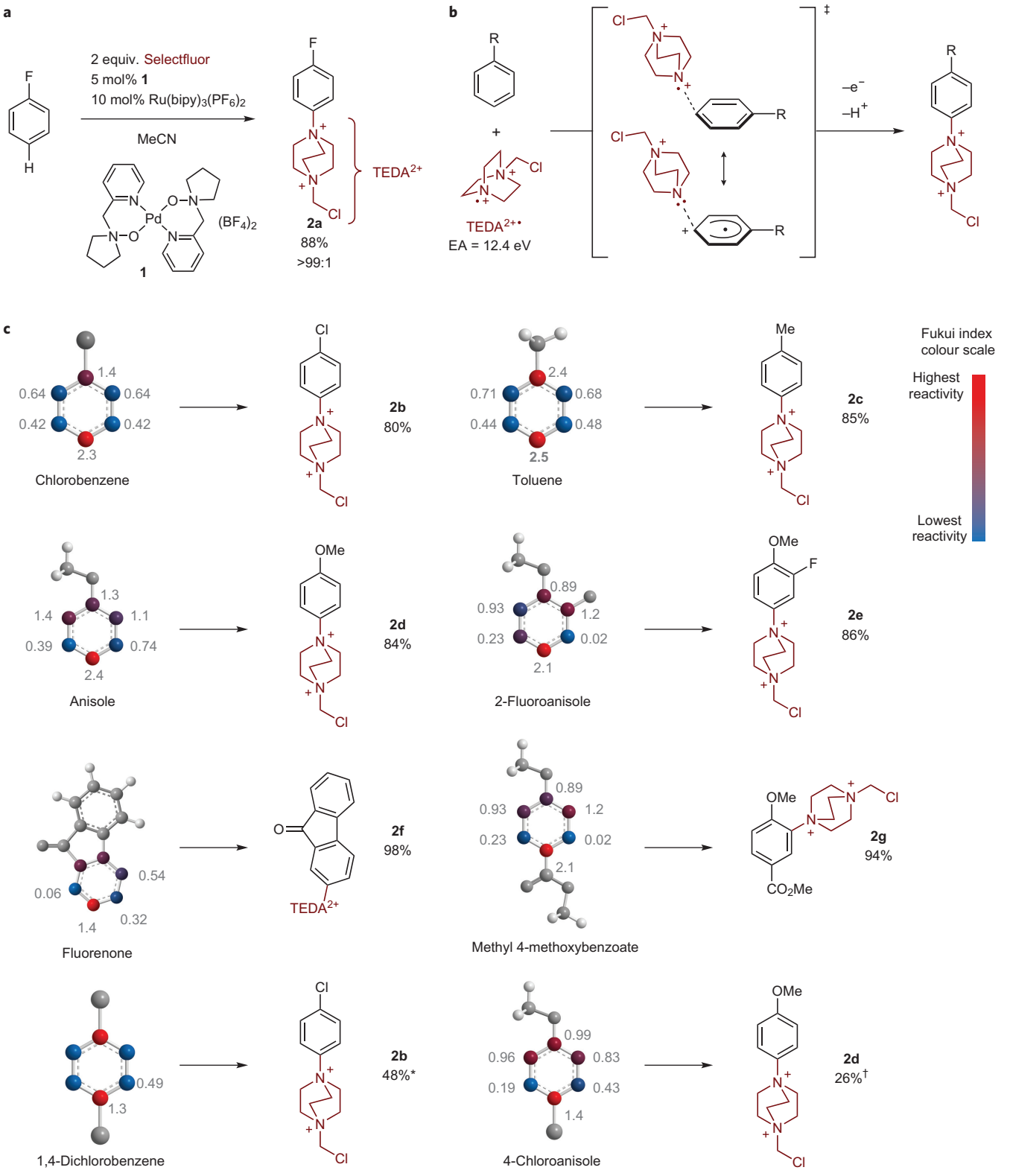

Figure 2 | Charge-transfer-directed aromatic substitution. a, Conversion of fluorobenzene into the corresponding Ar–TEDA compound. **b**, Positional selectivity of $TEDA^{2+\bullet}$ substitution results from the stabilizing effect of the arene-to-radical charge transfer in the transition state of the addition. EA refers to the gas-phase adiabatic electron affinity calculated by DFT. **c**, The position of substitution by $TEDA^{2+\bullet}$ is predictable 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 (see the Supplementary Information for full computational details). *Substitution in the 2-position was observed in 11% yield in addition to the *ipso* substitution (see the Supplementary Information). †Substitution in the 2-position was observed in 10% yield in addition to the *ipso* substitution (see the Supplementary Information).

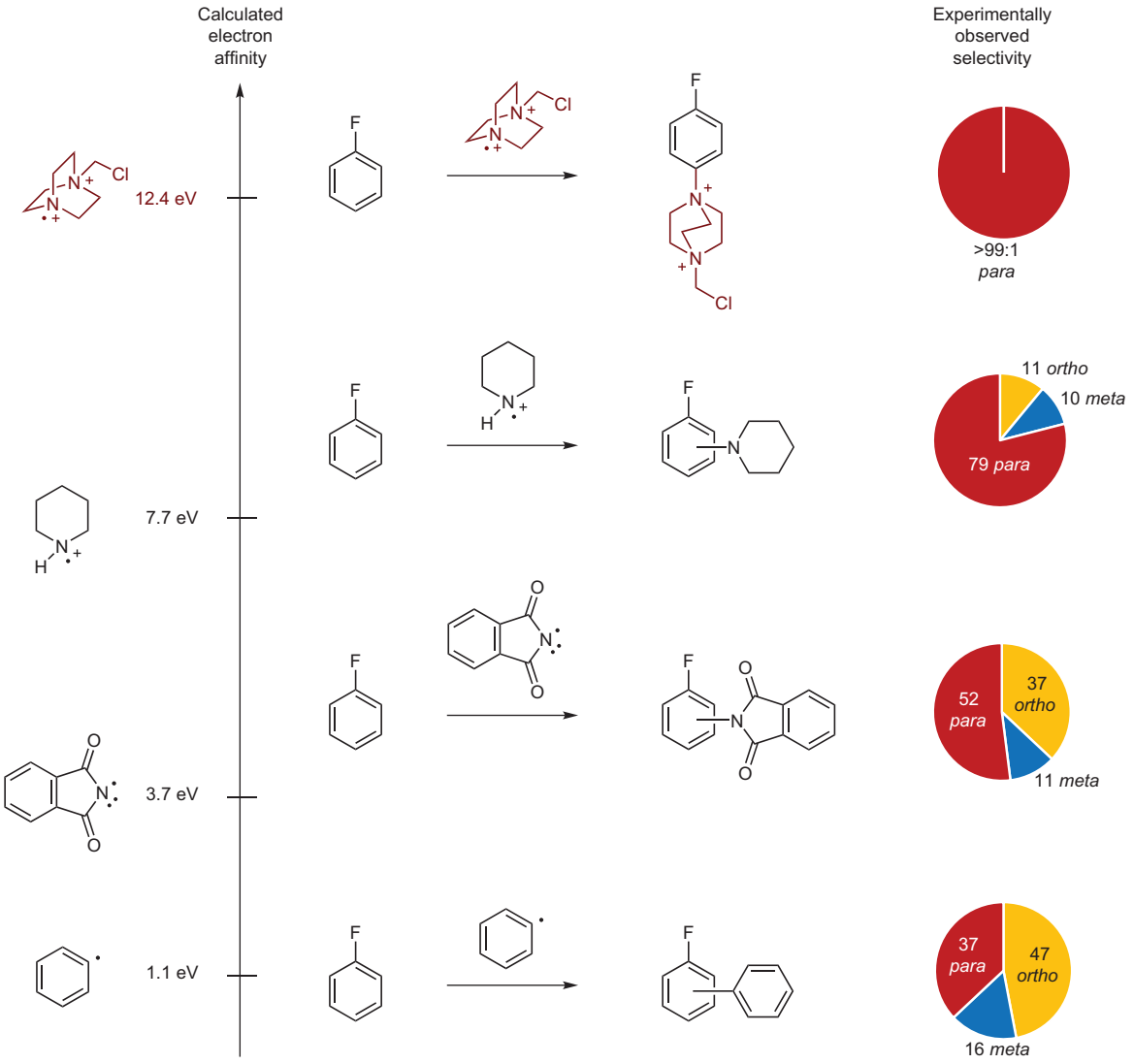

Figure 3 | Selectivity for *para* substitution increases with increasing electron affinity of the radical. Electron affinities refer to the gas-phase adiabatic electron affinity calculated at the (U)B3LYP/6-311G(d) level of theory.

third most-common heterocycle present in the small-molecule pharmaceuticals listed in the US Food and Drug Administration 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 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 **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 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, **3f**) or ether oxygen atoms (for example, **3e** and **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 **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 Fig. 4, the majority of mass balance is lost in the piperazine formation step, not in the Ar–TEDA formation step.

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 selectivities in charge-transfer-directed

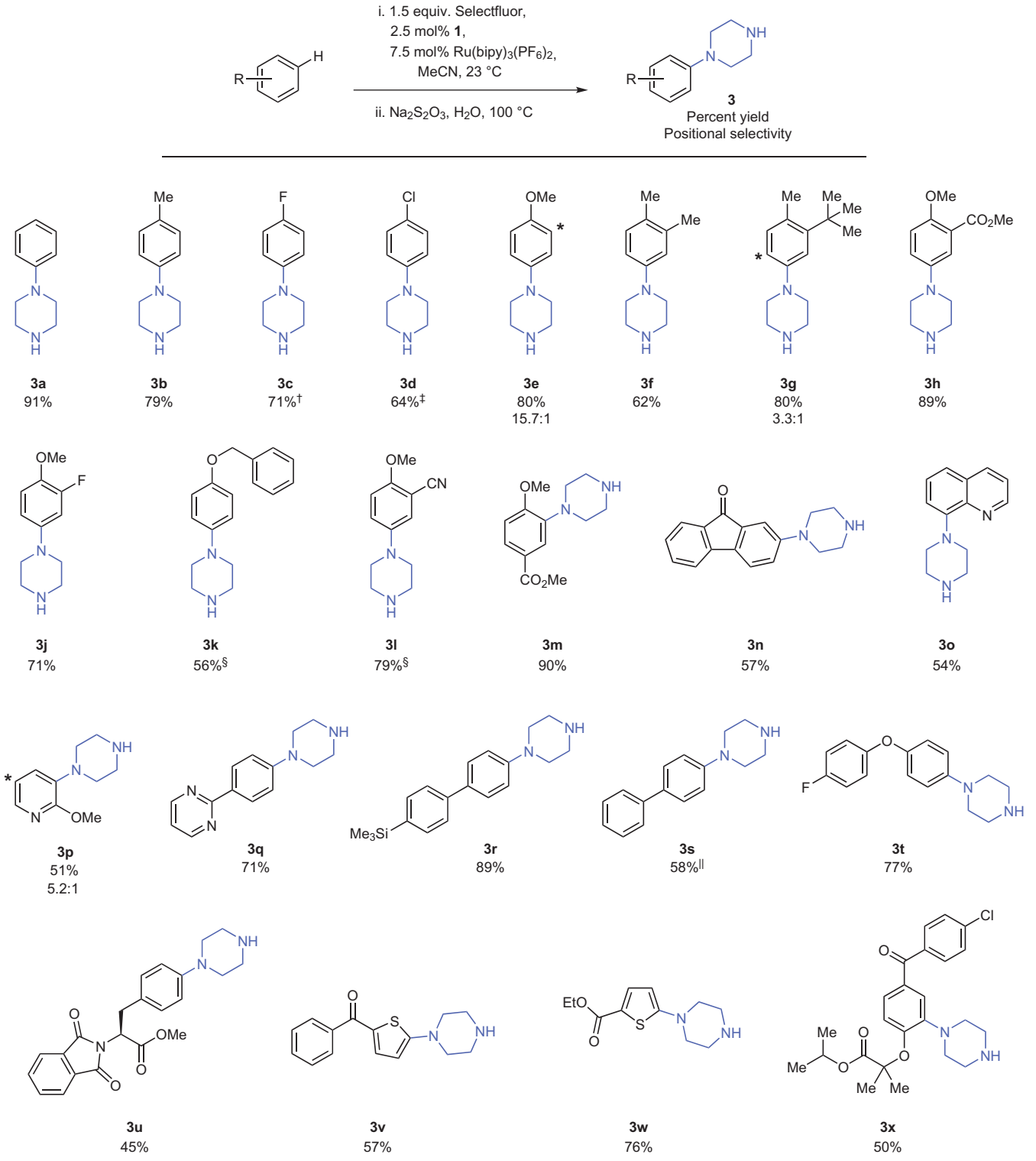

Figure 4 | Two-step, one-pot synthesis of aryl piperazines by charge-transfer-directed C–H functionalization. *Site of piperazination of the other constitutional isomer. †Reaction temperature of 40 °C. ‡Reaction temperature of 45 °C in the first step. §For the first step, 2.5 equiv. Selectfluor, 5.0 mol% **1** and 10 mol% $Ru(bipy)_2(PF_6)_2$. ‖For the first step, 1.0 equiv. Selectfluor.

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.

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, 0.20 M) was added, followed by toluene (91.1 μl, 0.856 mmol, 1.00 equiv.) via a syringe. The reaction mixture was stirred at 23 °C for 24 hours. 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 two hours. 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).

Full experimental and computational details and the characterization of new compounds are available in the Supplementary Information.

Received 14 January 2016; accepted 5 April 2016; published online 6 June 2016

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Acknowledgements

The authors thank the National Institute of General Medical Sciences (GM088237), the National Institute of Biomedical Imaging and Bioengineering (EB013042), UCB Pharma and Kwanjeong Educational Foundation for funding. The authors further thank J. McClean (Harvard University) for helpful discussions.

Author contributions

G.B.B., W.S.H. and A.R.M. designed and performed the experiments and analysed the data. G.B.B. discovered the Ar–TEDA formation reaction and conceived 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.S.H. and A.R.M.

Additional information

Supplementary information and chemical compound information are available in the online version of the paper. Reprints and permissions information is available online at www.nature.com/reprints. Correspondence and requests for materials should be addressed to T.R.

Competing financial interests

The authors declare no competing financial interests.