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Regiodivergent Aromatic Electrophilic Substitution Using Nitrosoarenes in Hexafluoroisopropanol: A Gateway for Diarylamines and *p*-Iminoquinones Synthesis

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Abstract. A metal-free aromatic electrophilic substitution reaction using nitrosoarenes as the electrophile in 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) is reported. HFIP activates nitrosoarene towards the electrophilic C–H amination followed by a concomitant N–O bond cleavage to deliver diarylamines without requiring any extra reagent or further treatment. The dual electrophilic nature of nitrosoarene permits a switchover of selectivity to C–H oxygenation furnishing dearomatized *p*-iminoquinones following a unique mechanistic rationale of two consecutive [2,3] sigmatropic rearrangement in nitroso-chemistry.

Keywords: Aromatic electrophilic substitution; hexafluoroisopropanol; nitrosoarenes; C–H amination; C–H oxygenation

Introduction

Functionalization of native C–H bonds represents one of the central goals in advanced organic synthesis. In this regard, the Lewis acid-mediated or catalyzed Friedel-Crafts (FC) reactions constitute a conventional route to deliver industrially relevant functionalized arenes with structural diversity *via* C–C bond formation.[1] Recently, in search of a milder, efficient and benign activator, fluorinated alcohol 1,1,1,3,3,3-hexafluoro-isopropanol (HFIP) has emerged as a potential alternative to promote intra- and intermolecular FC acylation as well as FC alkylation with large set of electrophiles, such as acid chlorides,[2] allylic alcohols,[3] benzyl alcohols/halides,[4] epoxides,[5] and even cyclopropane[6] via ring-opening (Scheme 1, *left side*). The exotic reactivity of HFIP has been ascribed to its mild acidity, low nucleophilicity, the high dielectric constant for cation stabilization and moreover, strong hydrogen-bond donor ability.[7] When the HFIP is studied significantly for forging C–C bonds (Scheme 1, *top left*), the HFIP-mediated C–X (X = N or O) bond formation remains rarely explored except recent reports on C–H amination of free anilines using azodicarboxylic esters as electrophiles and C–H oxygenation of arenes using methanesulfonic peroxyanhydride (Scheme 1, *top right*).[8],[9], [10]

In this line, developing a C–H bond functionalization using nitrosoarenes as an electrophile in HFIP (a strong hydrogen-bond donor solvent as well as a mild Brønsted acid) will be highly fascinating, yet regiochemically challenging.[11] If possible, HFIP will activate the heteroatoms of nitroso-functionality and consequently provide an avenue for regiochemically divergent electrophilic C–N bond formation along with the construction of C–O bond. The dual electrophilic nature of nitroso-functionality and unique features of HFIP have prompted us to devise a mild, regioselective and straightforward method en route to various diarylamines via C–H amination and *p*-iminoquinones via C–H oxygenation of arenes (Scheme 1, *bottom, this work*). Both the diarylamines and iminoquinones are ubiquitous motifs in several natural products such as marine-alkaloids, pharmaceuticals, agrochemicals and materials.[12],[13] While diarylamines are synthesized by transition-metal catalyzed C–N coupling[14] or radical-based direct C–H aminations including photoredox catalysis,[15] iminoquinones are usually obtained via oxidation of aniline derivatives.[16] However, this metal-free approach is portrayed by: (1) direct synthesis of diarylamines without requiring additional reagent or treatment for N–O bond cleavage (*step-economic*); (2) rarely explored HFIP-activated double C–H oxidation of arene *via* two consecutive [2,3] sigmatropic rearrangement in nitroso-chemistry for the direct synthesis of *p*-iminoquinones; (3) switching of regioselectivity by altering reactants and imperative role of HFIP in the activation of nitrosoarene (sometimes, the catalytic amount of TfOH is needed for *p*-iminoquinones); (4) easy recovery *via* rotary evaporator and reuse of HFIP solvent.

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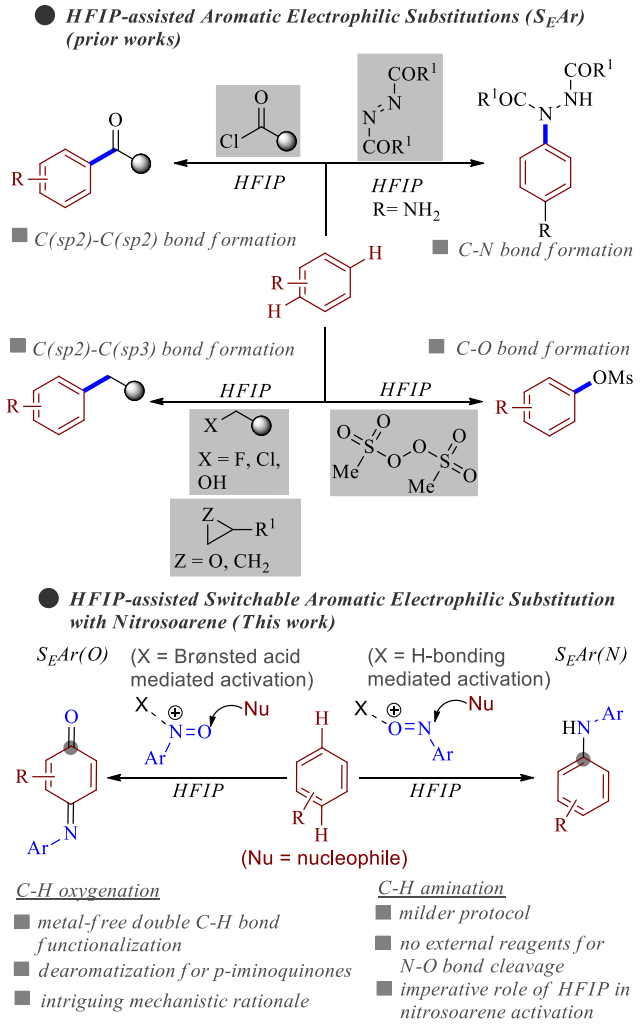
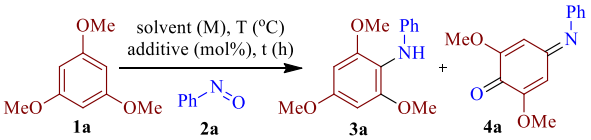


Scheme 1. HFIP-mediated aromatic electrophilic substitution reactions.

Results and Discussion

We initiated our investigation by reacting 1,3,5-trimethoxybenzene (**1a**, 3.0 equiv) as the model substrate with nitrosobenzene (**2a**, 1.0 equiv) as the electrophilic reagent in a series of solvents (0.75 M) at 55 °C (Table 1, entries **1-6**). While most of the solvents provided a little or no conversion, HFIP surprisingly, promoted the reaction significantly delivering diarylamine (**3a**) as the major product via C–H amination along with the additional formation of *p*-iminoquinone (**4a**) as minor product via C–H oxygenation. We attribute this regioselectivity due to the dual nature of HFIP. HFIP activates nitrosobenzene through H-bonding with more electronegative *O*-atom delivering **3a** via C–H amination, whereas mild Brønsted acidity of HFIP results in the protonation of the more basic *N*-atom of nitrosobenzene that leads to the attack of the arene at the nitroso *O*-atom for the C–H oxygenation. Guided by the notion to suppress the side reactions of reactive nitrosobeneze, the lowering of reaction temperature (55 °C to 25 °C) remained detrimental to the overall reactivity (Table 1, entries **7–8**). However, monitoring the concentration (0.75 to 0.15 M) resulted in a drastic improvement of the reactivity, delivering the desired diarylamine product (**3a**) in 47% isolated yield and good selectivity (10:1) (Table 1, entry **9**).[17] Excess of **1a** is necessary to achieve acceptable yield. Nevertheless, the presence of *p*-iminoquinone (**4a**) in a tiny amount in the reaction mixture encouraged us to develop an alternative set of conditions for its exclusive formation. Since the Brønsted acidity of HFIP promotes the C–H oxygenation, we envisioned that an acid additive might selectively protonate *N*-atom of nitrosobenzene for the C–H oxygenation. Indeed, this switchover of selectivity was feasible in the presence of catalytic amount of TfOH (20 mol%) and by the reversal of stoichiometry of 1,3,5-trimethoxybenzene (**1a**, 1.0 equiv) and nitrosobenzene (**2a**, 3.0 equiv) affording *p*-iminoquinone (**4a**) as sole product (47%) (Table 1, entry **12**).[18] All the components and parameters, such as the utilization of HFIP, the stoichiometry of reactants and concentration, remain crucial in achieving the desired reactivity and selectivity. Notably, this method is distinguished by the imperative role of HFIP in the activation of nitrosoarene through H-bonding and furthermore, in situ N–O bond cleavage without requiring an additional reagent to deliver direct C–H amination product. Additionally, later, the C–H oxygenation followed by the shifting of nitrogen counterpart to provide *p*-iminoquinone is excelled by the presence of HFIP.

Table 1. Optimization study and reaction set up.



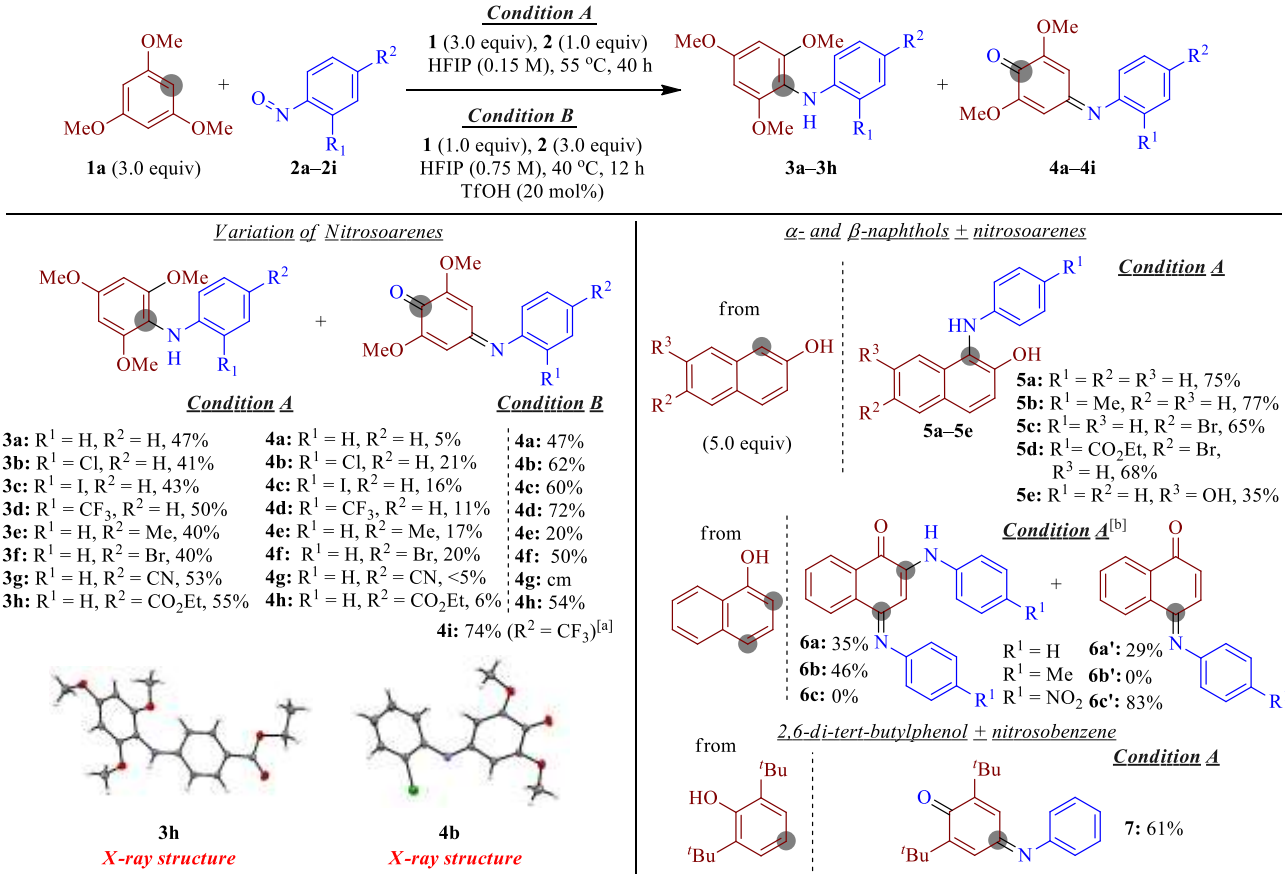
Entry	**1a**/**2a** (equiv)	Solvent (M)	T (°C)	t (h)	Yield **3a**/**4a**(%)[a]
1	3/1	MeCN (0.75)	55	40	<5/—
2	3/1	THF (0.75)	55	40	<1/—
3	3/1	$MeNO_2$ (0.75)	55	40	<1/—
4	3/1	EtOH (0.75)	55	40	<1/—
5	3/1	TFE (0.75)	55	40	<5/—
6	3/1	HFIP (0.75)	55	40	37/5
7	3/1	HFIP (0.75)	45	40	30/5
8	3/1	HFIP (0.75)	25	40	25/5
9[b]	**3/1**	**HFIP (0.15)**	**55**	**40**	**51(47)/5**
10	1/3	HFIP (0.15)	55	40	20/13
11[c]	1/3	HFIP (0.75)	25	12	—/40
12[d, e]	**1/3**	**HFIP (0.75)**	**40**	**12**	**—/49(47)**

[a] Reaction condition A (entry 1-9): **1a** (3.0 equiv, 0.45 mmol) and **2a** (1.0 equiv, 0.15 mmol) stirred in solvent; condition B (entry 10-12): **1a** (1.0 equiv, 0.15 mmol) and **2a** (3.0 equiv, 0.45 mmol) stirred in HFIP in the presence of TfOH (0-20 mol%); yield determined by ^{1}H NMR using CH_2Br_2 as internal standard; isolated yields in parentheses.

[b] 1 mmol scale reaction provided 52% isolated yield of **3a**. [c] 15 mol% TfOH as additive. [d] 20 mol% TfOH as additive. [e] 1 mmol scale reaction provided 40% isolated yield of **4a**.

With these two different sets of optimized conditions, we set out to explore the scope and limitations of C–H amination as well as C–H oxygenation protocols with several arene partners and variety of nitrosoarenes decorated with diverse functionality, as summarized in Scheme 2. Initially, various nitrosoarenes with different functional groups such as halide, (trifluoro)methyl, nitrile, ester (**2a**–**2h**) reacted well with 1,3,5-trimethoxy benzene (**1a**) to afford corresponding diarylamines (**3a**–**3h**) in 40-55% yields (*under condition A*), accompanied by the formation of *p*-iminoquinones as side products, albeit in lower amounts. Nitrosoarenes featuring electron-withdrawing nitrile and ester groups delivered the corresponding diarylamines (**3g** and **3h**) almost exclusively. However, to our delight, the reaction of β-naphthol derivatives with nitrosoarenes resulted in various aminonaphthols (**5a**–**5e**) as sole products in good yields. Interestingly, while α-naphthol was employed as a substrate, the amination products (even more electron-rich) preceded further reaction, delivering *N*-arylamine functionalized *p*-iminoquinone derivatives (Scheme 2, **6a**–**6c**). C–H amination at 4-position of α-naphthol led to the formation of *p*-iminoquinones **6a'**–**6c'**. With phenol and thioanisole, we obtained colored complex reaction mixture without detecting any isolable desired product. To our delight, 2,6-di-tert-butylphenol afforded *p*-iminoquinone **7** in 61% yield. When electron-rich heterocyclic compounds indole and benzothiophene were tested, no desired product was detected instead a colored complex reaction mixture was obtained.

Contrastingly, the presence of TfOH (20 mol%) and switching the stoichiometry of reactants at a slightly reduced temperature in HFIP, *p*-iminoquinones were obtained in complete regioselectivity via C–H oxygenation (*under condition B*) (Scheme 2, **4a**–**4i**). The nitrosoarenes decorated with electron-withdrawing groups worked well yielding corresponding *p*-iminoquinones in excellent yields, such as furnishing **4d** and **4i** in 72% and 74% respectively.



Scheme 2. HFIP-assisted C–H amination and C–H oxygenation of arenes with nitrosoarenes.

Condition A for diarylamine synthesis: **1a** or **β-naphthol** (0.45-0.75 mmol) and **2a–h** (0.15 mmol) HFIP (0.15 M), 55 °C, 40 h (10 h for **β-naphthol**); condition B for *p*-iminoquinone synthesis: **1a** (0.15 mmol) and **2a–i** (0.45 mmol), TfOH (20 mol%), HFIP (0.75 M), 40 °C, 12 h; isolated yields unless otherwise mentioned. [a] using condition B. [b] using **α-naphthol** (0.15 mmol) and nitrosoarene (0.30 mmol) for 10 h. cm = complex mixture. X-ray structure of **3h** and **4b**. [19]

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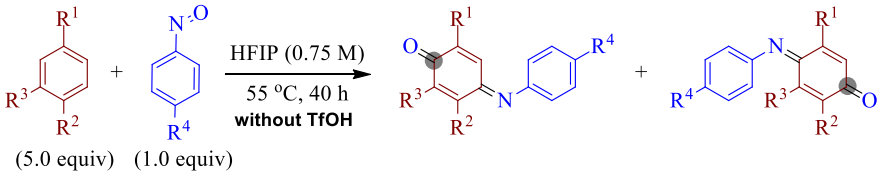
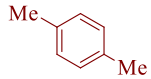
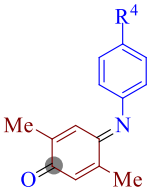
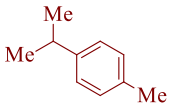
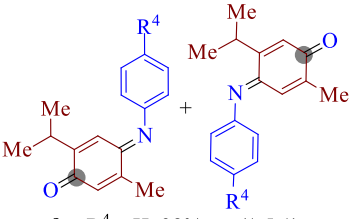
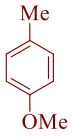
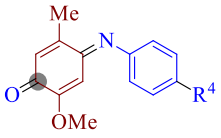
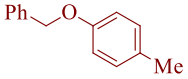
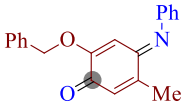
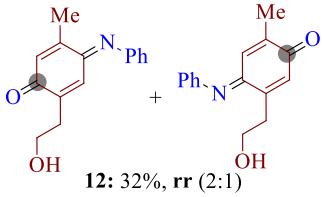
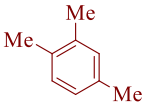
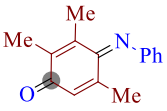
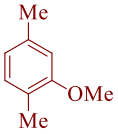
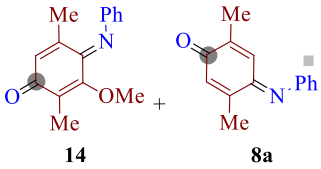
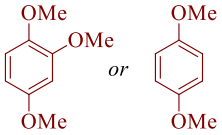
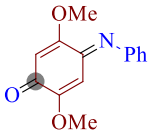
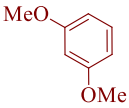
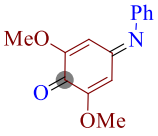
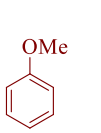
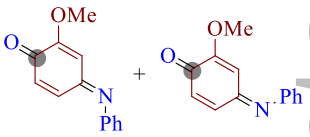
Aside from 1,3,5-trimethoxybenzene and naphthols, other electron-rich alkylated arenes remained competent for the synthesis of *p*-iminoquinones via C–H oxygenation with exquisite selectivity (Scheme 3). Interestingly, the reaction could be performed in the absence of TfOH, since its utilization was found to be deleterious for this set of arenes. We reason that, it is due to the Brønsted acidity of HFIP that protonates *N*-atom of nitrosoarene for the C–H oxygenation. It is notable to mention that according to our mechanistic rationale, two equivalents of nitrosoarene were consumed to construct one equivalent of *p*-iminoquinone via double C–H bond functionalization, thus obtaining the product in 50% yield (based on nitrosoarene) would reveal for achieving the highest efficiency. Taking it into account, at first, *p*-xylene was tested for the formation of the iminoquinone **8a** and **8b** as sole regioisomer. Furthermore, the unsymmetrical di-substituted arenes appeared to be viable substrates delivering product **9a**–**9b** and **12** as regioisomeric mixtures in moderate to good yields. The exclusive regiochemical outcome was obtained for *p*-iminoquinone **10a**–**10b**, and **11.** In this regard, the site selectivity of oxygenation event was dictated by the more electron-donating substituent to its *ortho*-position. However, moving to tri-substituted arenes for the formation of the products **13**–**14**, the regioselectivity is found to be controlled by the steric factor irrespective of substitution at *para*-position. Interestingly, **8a** was formed together with **14** from 2-methoxy-1,4-dimethylbenzene via the C–H oxygenation at the *para*-position of the OMe group followed by the shifting of nitrogen counterpart and release of methanol. While *o*-xylene and *m*-xylene remained unreacted under this condition, to our delight, 1,2,4-trimethoxybenzene and 1,4-dimethoxybenzene delivered the identical *p*-iminoquinone **15**. It was surprising to find this different reactivity between 1,2,4-trimethoxybenzene and 1,3,5-trimethoxybenzene. We think it was the nucleophilicity of the reactive carbons of the substrates as mentioned above that was highly influenced by the characteristic of HFIP (H-bonding vs. Brønsted acidity). Importantly, 1,3-dimethoxybenzene provides *p*-iminoquinone **4a**, and even anisole were converted to corresponding *p*-iminoquinone **16** without detecting any diarylamine formation. Interestingly, as such, this external oxidant-free protocol offers the first example of metal-free dearomatization of arenes via double C–H bond functionalization.



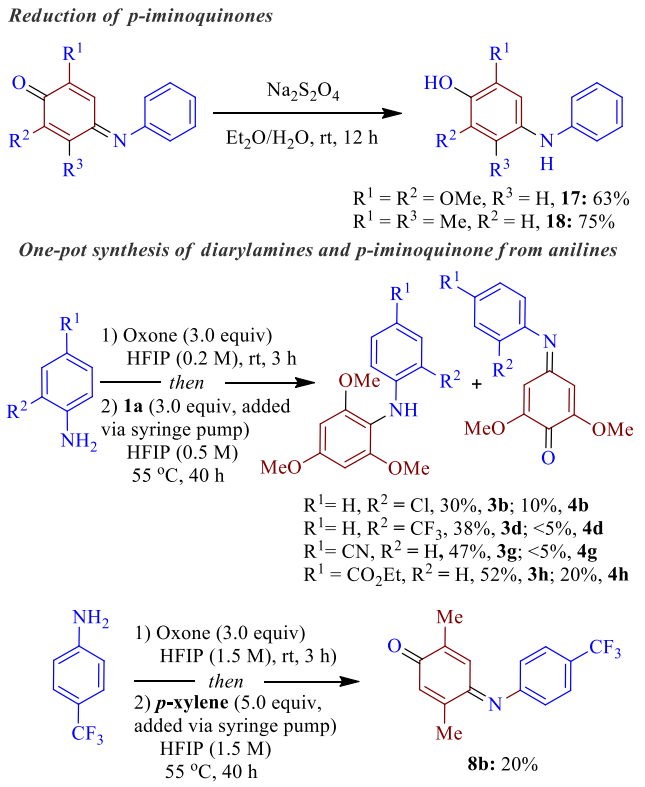
Starting Materials	Products
	 **8a:** R^4 = H, 25% **8b:** R^4 = CF_3, 30%
	 **9a:** R^4 = H, 28%, **rr** (1.5:1) **9b:** R^4 = CF_3, 31%, **rr** (2:1)
	 **10a:** R^4 = H, 30% **10b:** R^4 = CF_3, 34%
	 **11:** 32%
	 **12:** 32%, **rr** (2:1)

Starting Materials	Products
	 **13:** 30%
	 **14** **8a** 30%, **rr** (2:1)
	 **15:** 43%[a]
	 **4a:** 32%[a]
	 **16:** 31% (*E*/*Z* = 1.25:1)[a]

Scheme 3. C–H oxygenation for the synthesis of *p*-iminoquinone.

Reaction conducted on 0.15 mmol scale using 1.0 equiv of nitrosoarene, 5.0 equiv of arene in HFIP (0.75 M) at 55 °C, 40 h. isolated yields unless otherwise mentioned. (maximum expected yield = 50%). rr = regioisomeric ratio determined by ^{1}H NMR analysis of crude reaction mixture.[a] Performed at 80 °C.

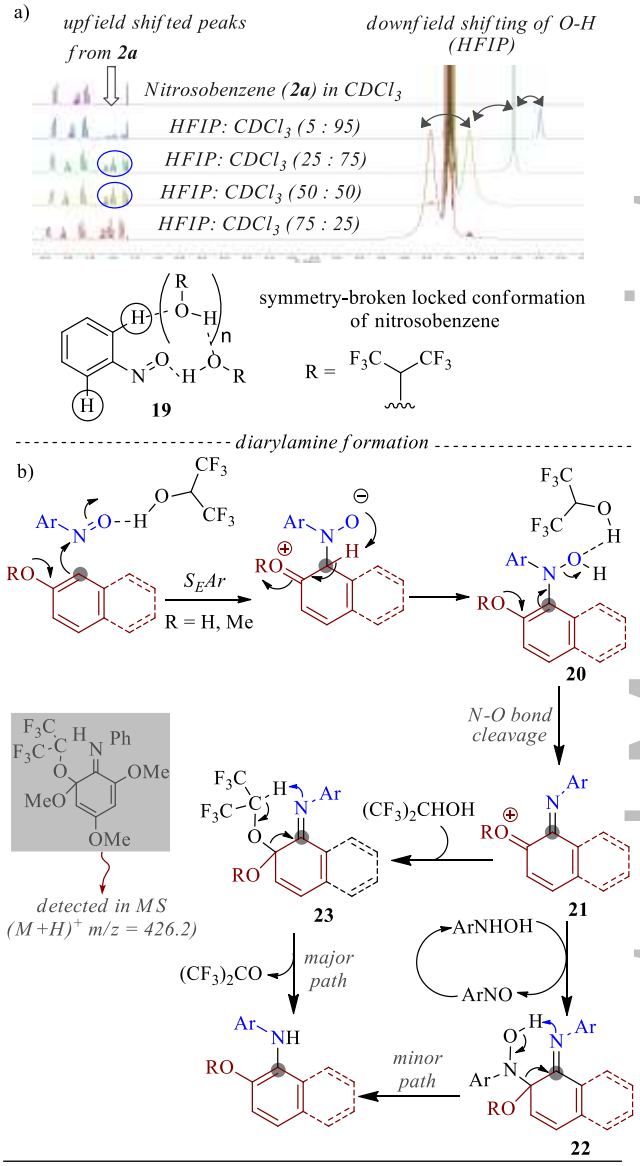
Additionally, the synthetic potential of this methodology was demonstrated by converting *p*-iminoquinone to *p*-aminophenol by the reduction with $Na_2S_2O_4$ in good yield (Scheme 4, *top*). As proof of practicability, the nitrosoarenes were generated in situ from anilines and transformed into the desired amination as well as *p*-iminoquinone products via a one-pot sequential operation (Scheme 4, *bottom*).



Scheme 4. Synthetic application of the developed methodology: Reduction of *p*-iminoquinones (*top*); one-pot sequential synthesis of diarylamines and *p*-iminoquinones (*bottom*).

Based on the experimental evidence and previous reports, [2,4,8a] we propose tentative mechanisms for the formation of both diarylamine and *p*-iminoquinone. At first, the *O*-atom of nitrosobenzene is activated by the H-bonding interaction with HFIP as corroborated by recording ^{1}H NMR spectra of nitrosobenzene in the presence of variable amounts of HFIP exhibiting an apparent shift of O–H signal of HFIP and a new set of aromatic signals (Scheme 5a). We believe that two or higher number of HFIP molecules engage in activation of nitroso moiety through H-bonding with *O*-atom. We presume the formation of 9- or higher-membered ring system **19** involving *o*-hydrogen of nitrosobenzene (the identical structure was previously proposed by Yamamoto and his group).[20] This solvation cluster breaks the symmetry of nitrosobenzene (through locked conformation) and displays chemically distinguished two sets of aromatic protons (*o*, *m* and *p*) of nitrosobenzene. The aforementioned interpretation supports the shifting of aromatic protons towards upfield in ^{1}H NMR.

For the diarylamine synthesis, a nucleophilic attack by the highly electron-rich arenes (1,3,5-trimethoxybenzene and naphthol derivatives) onto the *N*-center of activated nitrosoarene generates hydroxylamine intermediate **20** (Scheme 5b), which is further activated by HFIP making the N–O bond cleavage facile to deliver iminoquinone intermediate **21**. The trapping of intermediate **21** by HFIP generates intermediate **23** as detected in MS and GCMS analysis.[21] The release of hexafluoroacetone (not able to detect) from the intermediate **23** results the formation of diarylamine. However, the involvement of arylhydroxylamine formed via auto reduction-oxidation of nitrosoarenes cannot be ruled out in the reduction process through the intermediate **22**.

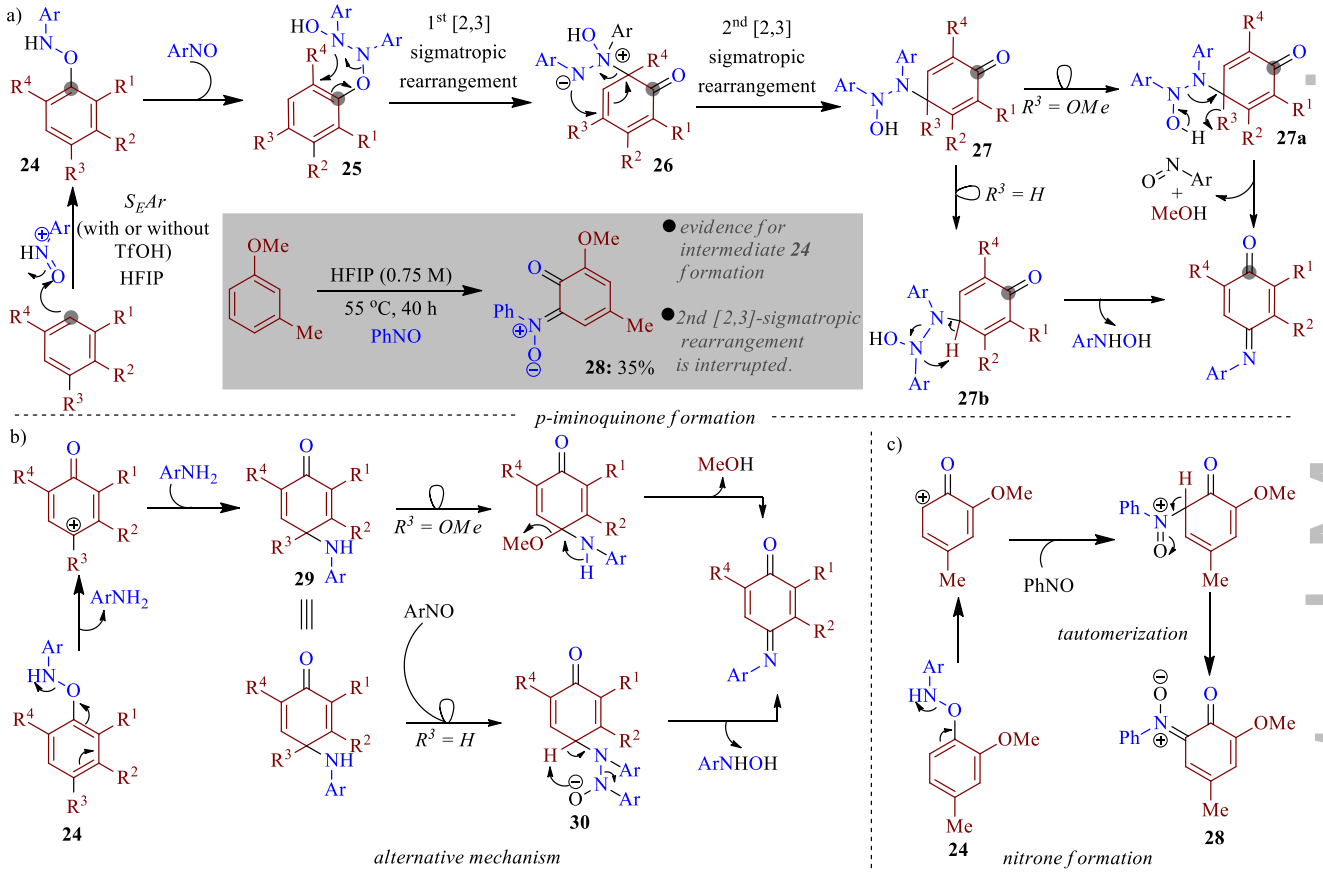


Scheme 5. a) ^{1}H NMR experiment for the activation of nitrosobenzene in HFIP. b) Plausible mechanism for C–H amination.

While the H-bond drives the C–N bond formation, the generation of iminoquinone is triggered by the protonation of the *N*-atom of nitrosoarene either by TfOH or by HFIP alone (pK_a = 9.3)[22] for the C–O bond formation (Scheme 6a). A nucleophilic attack by the arenes onto the *O*-center of *N*-protonated nitrosoarene generates hydroxylamine intermediate **24** (detected in MS and GCMS analysis, see SI), which readily reacts with another molecule of nitrosoarene to form intermediate **25**. At this stage, two successive [2,3] sigmatropic rearrangements of

this intermediate **25** furnish the intermediate **27** via the formation of intermediate **26**.[23] When the *para*-position is substituted with a methoxy group, the intermediate **27a** releases methanol providing *p*-iminoquinone. On the other hand, when the *para* position is free, the intermediate **27b** liberates a molecule of hydroxylamine delivering the dearomatized *p*-iminoquinone product. The formation of nitrone **28** from 3-methylanisole reinforces the involvement of intermediate **26** via the C–H oxygenation followed by the first [2,3] sigmatropic rearrangement.

Alternatively, hydroxylamine intermediate **24** can undergo N–O bond cleavage by the involvement of the electron-rich arene. This creates a partial positive charge on the *para*-position of the arene to which the aniline released in the previous step can add to form intermediate **29** (Scheme 6b). When the *para*-position is substituted with methoxy group (R^3 = OMe), intermediate **29** can release methanol to furnish *p*-iminoquinone. Whereas, when R^3 = H, intermediate **29** can react with another molecule of nitrosoarene forming **30**, which eventually liberates hydroxyamine providing the *p*-iminoquinone product. The same hydroxylamine intermediate **24** can undergo N–O bond cleavage, generating a partial positive charge on the *ortho*-carbon followed by the attack of another molecule of nitrosoarene, delivering the nitrone **28** after tautomerization (Scheme 6c).



Scheme 6. a) Mechanistic proposal for the formation of *p*-iminoquinone via two consecutive [2,3] sigmatropic rearrangement. b) An alternative mechanism for the formation of *p*-iminoquinone. c) An alternative mechanism for the nitrone formation.

Conclusion

We have depicted a rarely explored metal-free aromatic C–H bond functionalization utilizing nitrosoarenes as dual electrophiles and conducting the reaction in HFIP, which serves as an activator for nitroso-functionality. Notably, nitrosoarene, being a single entity, can deliver regioselective divergent C–H amination and/or C–H oxygenation outcome. While the C–H amination directly affords diarylamines via the scission of N–O bond without any external reagent, the C–H oxygenation results in the dearomatizing difunctionalization of arenes to furnish *p*-iminoquinones, where consecutive [2,3] sigmatropic rearrangements remain mechanistically intriguing in nitroso-regime. Furthermore, the significant characteristics of HFIP meticulously guide the regioselectivity of an aromatic C–H bond functionalization in a metal-free pathway.

Experimental Section

Representative procedure for the synthesis of diarylamines from 1,3,5-trimethoxybenzene and nitrosobenzene: An oven-dried glass vial is charged with a magnetic stir bar, **1a** (75.0 mg, 0.45 mmol, 3.0 equiv), and **2a** (16.0 mg, 0.15 mmol, 1.0 equiv). 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) (0.2 mL, 0.15 M) is added to the mixture in argon atmosphere. The vial is maintained for 40 h at 55ºC. The reaction mixture is then passed through a plug of silica. The vial is rinsed with CH_2Cl_2 (2 X 2 mL), and the collected organic phases are evaporated under reduced pressure. The analytically pure product **3a** is obtained by column chromatography on silica gel using petroleum ether and ethyl acetate (20:1, v/v) as eluent.

Representative procedure for the synthesis of iminoquinone from 1,3,5-trimethoxybenzene, nitrosobenzene and TfOH as an additive: An oven-dried glass vial is charged with a magnetic stir bar, **1a** (25.0 mg, 0.15 mmol, 1.0 equiv), and **2a** (48.0 mg, 0.45 mmol, 3.0 equiv). A solution of TfOH (150.0 µl, 20 mol%, 0.2 M in HFIP) in 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) (50.0 µl, 0.75 M) is added to the mixture. The vial is maintained for 12 h at 40 ºC.The reaction mixture is then passed through a plug of silica. The vial is rinsed with CH_2Cl_2 (2 X 2mL), and the collected organic phases are evaporated under reduced pressure. The analytically pure product **4a** is obtained by column chromatography on silica gel using petroleum ether and ethylacetate (1:1, v/v) as eluent.

Representative procedure for the synthesis of iminoquinone from *p-xylene* and nitrosobenzene: An oven-dried glass vial is charged with a magnetic stir bar, ***p-xylene*** (90.0µl, 0.75 mmol, 5.0 equiv), and **2a** (16.0 mg, 0.15 mmol, 1.0 equiv). 1,1,1,3,3,3-Hexafluoro-2-propanol (HFIP) (0.2 mL, 0.75 M) is added to the mixture in argon atmosphere. The vial is maintained for 40 h at 55ºC. The reaction mixture is then passed through a plug of silica. The vial is rinsed with CH_2Cl_2 (2 X 2 mL), and the collected organic phases are evaporated under reduced pressure. The analytically pure product **8a** is obtained by column chromatography on silica gel using petroleum ether and ethyl acetate (40:1, v/v) as eluent.

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FULL PAPER

Regiodivergent Aromatic Electrophilic Substitution Using Nitrosoarenes in Hexafluoroisopropanol: A Gateway for Diarylamines and *p*-Iminoquinones Synthesis

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Suman Pradhan, Sourav Roy, Soumen Ghosh, and Indranil Chatterjee*