

Controllable Selective Oxidation of Anilines to Azoxybenzenes and Nitrobenzenes by Regulating the Base

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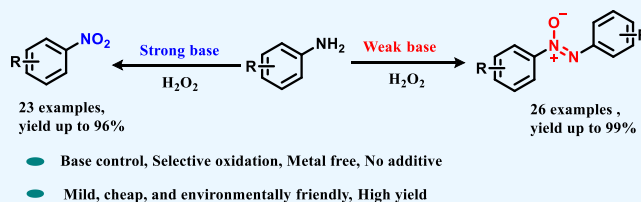


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ABSTRACT: The importance of selectively oxidizing aniline into value-added chemicals azoxybenzene and nitrobenzene is well-recognized in organic synthesis. However, the lack of control over selectivity and the complex synthesis of costly catalysts significantly hinder these reactions' industrial applications. In this work, an environmentally friendly approach was developed for the selective oxidation of substituted anilines. This method involves adjusting the strength of alkalinity with peroxide as the oxidant, without the addition of any metals or additives. A mild base (NaF) facilitated azoxybenzene formation, while a stronger base (NaOMe) enabled the synthesis of nitroaromatics. These protocols are user-friendly and scalable, accommodating various substitution patterns and functional groups, yielding products with high to excellent yields. The findings of this work present a framework for investigating base catalysis in organic synthesis and provide a viable and effective approach for selectively oxidizing aniline.



INTRODUCTION

Oxidation of readily available and cheap anilines to produce high-value products like azoxybenzene and nitrobenzene holds pivotal importance in both industrial and academic domains owing to the unique properties of these compounds. Nitroarenes play a pivotal role as versatile building blocks in the synthesis of a wide array of compounds, including pharmaceuticals, explosives, dyes, and materials.¹ Nitro derivatives also hold particular importance in developing mechanistic concepts.² Moreover, azoxybenzenes possess considerable value and find extensive applications in various industries such as reducing agents, polymerization inhibitors, drug intermediates, energetic materials, dyes, and therapeutic agents.³ Further, electronic displays employ certain azoxybenzene derivatives as liquid crystals.⁴ Moreover, the azoxy group finds utility in the C–H functionalization of arenes as an *ortho*-directing group and serves as a precursor for the Wallach rearrangement.⁵ Furthermore, the azoxy group, viewed as a bioisostere of amide and alkene functionalities, exhibits promising anticancer properties.⁶

The traditional approach to synthesizing Nitroarenes usually involves directly nitrating aromatic compounds under harsh reaction conditions. Yet, this method faces significant challenges due to limited functional group tolerance and inadequate regioselectivity, marking its primary limitations.⁷ Consequently, various alternative protocols have been established, such as the oxidative transformation of arylamines to nitroarenes (Scheme 1). Various oxidizing agents have been utilized for the transformation, including H₂O₂, peracetic acid, *m*-CPBA, tert-butyl hydroperoxide (TBHP) with KI, HOF-CAN, nonanebis, sodium perborate with cetyl-trimethylammonium bromide and tungstophosphoric acid, H₂O₂ with

CaWO₄, H₂O₂ with diphenyl diselenide, TBHP with Rh₂(cap)₄, and TBHP with CrS-2.⁸ However, the majority of documented approaches exhibit limitations, including unregulated oxidation, reliance on harsh reaction conditions, low yields, extended reaction durations, and subpar selectivity. Employing H₂O₂ as an oxidative agent has been acknowledged for its cost-effectiveness and eco-friendly nature, generating only water as a byproduct. Yet, due to the relatively weak oxidizing attributes of H₂O₂, it necessitates pairing with a catalyst or reagent to induce oxidation by activating reactive intermediates. Therefore, the development of a mild and effective oxidation protocol in this field is highly desirable.

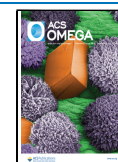
Conversely, the production of azoxybenzene can occur via both reduction and oxidation processes. For instance, a reduction approach involved the utilization of organocatalytic reduction of aromatic nitro compounds.⁹ In contrast, alternative oxidation routes using stoichiometric oxidants, such as peracetic acid, BaMnO₄, TBHP, Pb(OAc)₄, Hg(OAc)₂, and oxone, have been reported for arylamine oxidation.¹⁰ Nevertheless, the aforementioned oxidants have a more pronounced environmental footprint compared to H₂O₂ and oxygen (O₂).¹¹ As of now, several heterogeneous catalysts have undergone extensive investigation for aniline oxidation utilizing H₂O₂ as an environmentally friendly oxidant. Notably, Ti-

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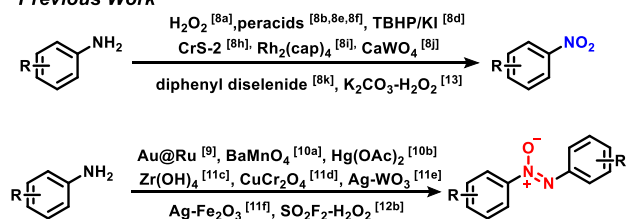
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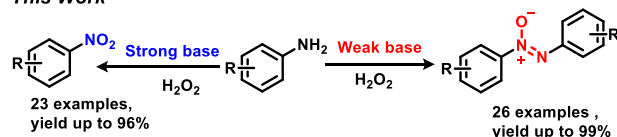


Scheme 1. Synthetic Approaches for Aniline Oxidation to Azoxy and Nitro Compounds

Previous Work

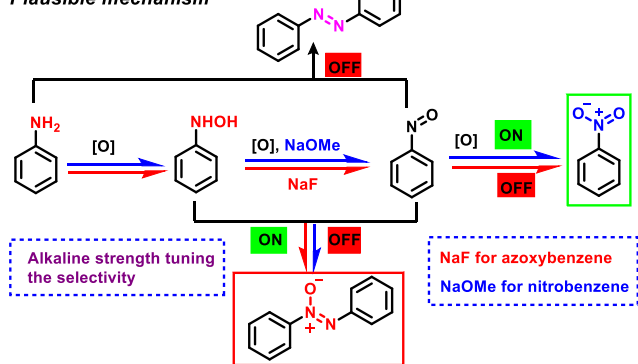


This Work



- Base control, Selective, Metal free, No additive
- Mild, cheap, and environmentally friendly, High yield

Plausible mechanism



based materials, $\text{Zr}(\text{OH})_4$, spinel CuCr_2O_4 , Ag-WO_3 , $\text{Ag-Fe}_2\text{O}_3$, and Nb_2O_5 have demonstrated potential in selectively oxidizing arylamines to azoxybenzenes.¹² Additionally, other homogeneous catalysts, such as SeO_2 and 2,2,2-trifluoroaceto-phenone, have also been studied.¹³

However, these systems employ complex catalysts that produce unpredictable selectivity, leading to azoxybenzene being the primary product. There have been reports indicating that the oxidizing potency of peroxides can be enhanced in a basic environment. The $\text{K}_2\text{CO}_3\text{-H}_2\text{O}_2$ system exhibits the ability to efficiently convert anilines into nitrobenzenes at room temperature, yielding moderate to high percentages (ranging from 65 to 95%).¹⁴ In another part of this work, benzylamines were successfully converted into benzamides in the presence of TBHP/ CS_2CO_3 at 80 °C.¹⁴ Additionally, the Tamao–Fleming oxidation is an important reaction that uses a Lewis base-KF- H_2O_2 system to transform organosilanes into alcohols.¹⁵ These results suggest the development of a strategy based on adjusting the strength of the alkalinity in the H_2O_2 oxidation system. Such modifications hold the potential to establish a selective, eco-friendly procedure that could yield either the nitro compound or the azoxy compound. Fortunately, aniline's oxidation can be controlled to produce azoxybenzene by employing weak or Lewis bases, while strong bases facilitate its transformation into nitrobenzene. This selective oxidation process presents a promising methodology for synthesizing these two compounds.

RESULTS AND DISCUSSION

Aniline (**1a**) was utilized as a model substrate along with various weak bases at 80 °C, including general weak bases and Lewis bases (Table 1), using MeCN as the solvent and H_2O_2 as the green oxidant. Encouragingly, in a preliminary experiment using NaOAc as the weak base, it was found that the aniline (**1a**) was rapidly oxidized to azoxybenzene (**2a**) with 78% yield and nitrobenzene (**3a**) with 21% yield in 1 h (Table 1, entry 1). To enhance the selectivity and yield of the reaction, an investigation was conducted into the dosage of NaOAc, H_2O_2 , and various solvents. Subsequently, a decrease in both the reaction's conversion and the yield of azoxybenzene (**2a**) was observed (Table S1). Additionally, further screening of additional weak bases revealed that the yield of azoxybenzene (**2a**) was reduced by sodium formate and K_2CO_3 . However, the conversion rate and selectivity of Na_2CO_3 were similar to NaOAc (Table 1, entries 2–4). Based on these results, other weak bases, including Lewis bases, were screened. Among them, potassium fluoride and potassium fluoride dihydrate can increase the yield to 87% and 89%, respectively (Table 1, entries 5 and 6). Fortunately, when sodium fluoride was present, aniline smoothly reacted with H_2O_2 , yielding azoxybenzene (**2a**) in high yields, reaching up to 99% with exceptional selectivity (Table 1, entry 7). Subsequently, solvent compatibility was examined, revealing lower yields in *N,N*-dimethylformamide (DMF) and dichloroethane (DCE), while no product was obtained using water as a solvent (Table 1, entries 8–10). It has been reported that MeCN reacts with H_2O_2 to afford peroxy-carboximidic acid, with a highly reactive character to be involved in oxidative processes.⁸ Moreover, reducing the H_2O_2 quantity decreased the yield of azoxybenzene (Table 1, entries 11–12, Table S1). Subsequent reactions investigated the impact of NaF quantity, where a slight decrease in both yield and selectivity of azoxybenzene (**2a**) was observed upon reducing NaF from 2.0 to 1.0, 0.5, and 0.2 equivalents, producing yields of up to 96, 92, and 89%, respectively (Table 1, entries 13–15 and Table S1). Increasing the amount of NaF to 3 equivalents can reduce the reaction time to 0.5 h without affecting the yield, whereas omitting the NaF from the reaction system altogether significantly changes the reaction outcome (Table 1, entry 16). There is only a limited amount of product and the reaction system is messy, indicating that NaF acts as a catalyst to accelerate the reaction rate (Table S1 and Figure S1).

Subsequently, strong bases were screened under these standard conditions. When strong bases such as K_3PO_4 , tBuOK, NaOH, NaOMe, and NaOEt were used, an exothermic reaction took place, accompanied by the decomposition of H_2O_2 ; hence, the reaction was conducted at room temperature. The reaction resulted in a substantial shift in the reaction outcome, with nitrobenzene (**3a**) being the predominant product, nevertheless with a minimal yield. Among them, NaOMe has the highest yield, precisely, 12% (Table 1, entries 17–20, Table S1). The above experimental results suggest that it may be possible to selectively synthesize nitrobenzene (**3a**) and azoxybenzene (**2a**) by regulating the strength of alkalinity. Strong bases favor the formation of nitrobenzene, and weak bases favor the formation of azoxybenzene. The next series of reactions was carried out to investigate the amount of NaOMe required for the reaction. The yield of nitrobenzene (**3a**) was noted to initially rise before declining, whereas the overall selectivity showed a

Table 1. Optimization of the Reaction Conditions^a

Reaction scheme: Aniline (1a) reacts with H₂O₂ and base in a solvent at 80 °C for 1 h to produce azoxybenzene (2a) and nitrobenzene (3a).

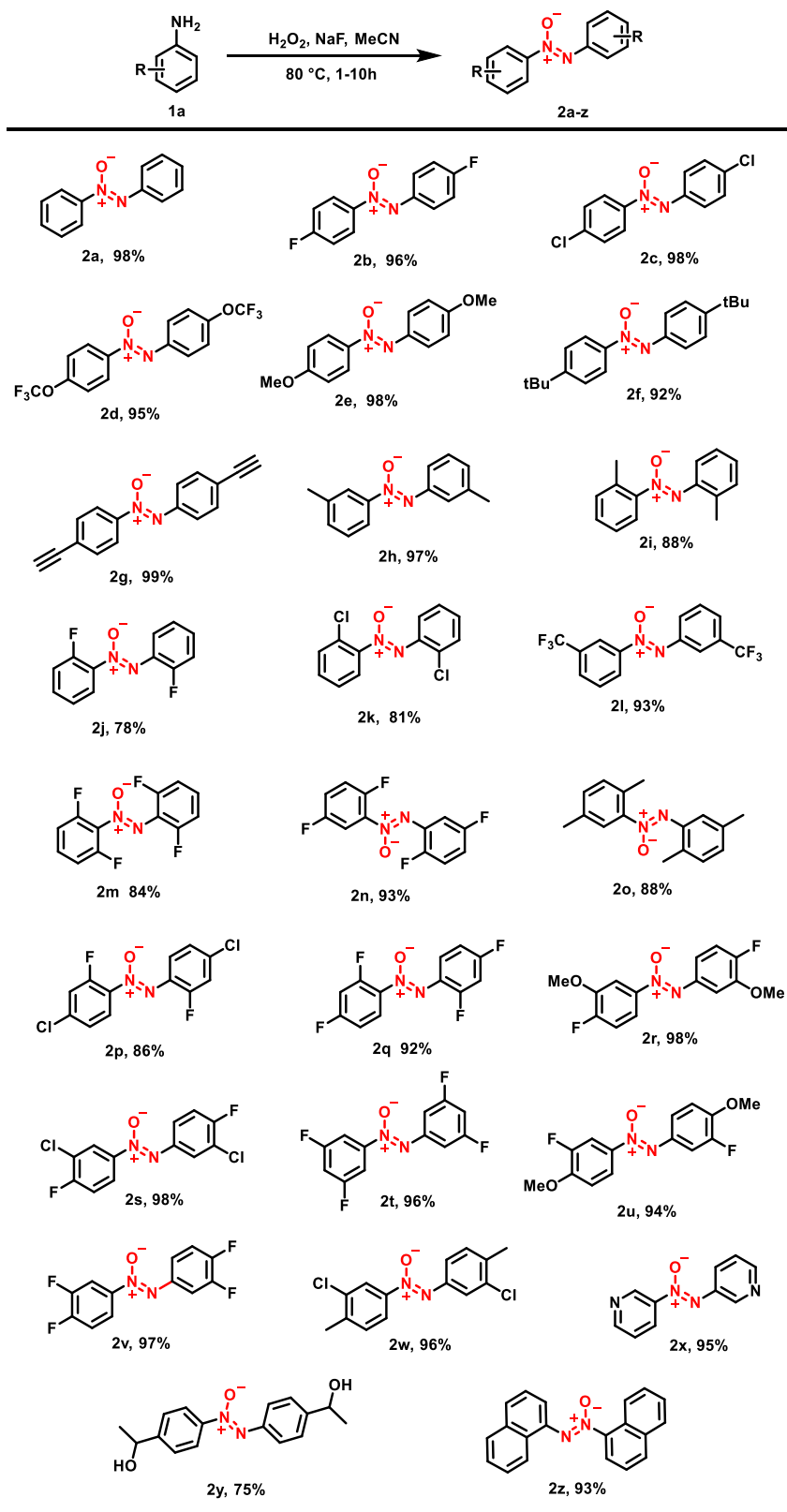
entry	base (2 equiv)	H ₂ O ₂ (equiv)	T (°C)	time (h)	solvent	yield 2a ^b (%)	yield 3a ^b (%)
1	NaOAc	10	80	1	MeCN	78	22
2	HCOONa	10	80	1	MeCN	47	49
3	K ₂ CO ₃	10	80	1	MeCN	21	34
4	Na ₂ CO ₃	10	80	1	MeCN	78	23
5	KF	10	80	1	MeCN	87	12
6	KF·2H ₂ O	10	80	1	MeCN	89	10
7	NaF	10	80	1	MeCN	>99	
8	NaF	10	80	1	DMF	90	
9	NaF	10	80	1	DCE	20	8
10	NaF	10	80	1	H ₂ O		
11	NaF	5	80	1	MeCN	50	
12	NaF	5	80	8	MeCN	96	
13 ^c	NaF	10	80	2	MeCN	89	8.6
14 ^d	NaF	10	80	2	MeCN	92	6
15 ^e	NaF	10	80	2	MeCN	96	trace
16 ^f	NaF	10	80	0.5	MeCN	>99	
17	K ₃ PO ₄	10	rt	1	MeCN		6
18	tBuOK	10	rt	1	MeCN		3
19	NaOH	10	rt	1	MeCN		4
20	NaOMe	10	rt	1	MeCN		12
21 ^g	NaOMe	10	rt	1	MeCN	10	89
22 ^h	NaOMe	10	rt	1	EtOH/MeCN	3	96

^aAniline (2.00 mmol) in solvent (4 mL), base (2 equiv), and 30% aqueous H₂O₂ (10 equiv) were added consecutively. The reaction mixture was left stirring for 1 h at 80 °C. ^bYield determined by GC. ^cNaF (0.2 equiv). ^dNaF (0.5 equiv). ^eNaF (1.0 equiv). ^fNaF (3.0 equiv). ^gNaOMe (0.4 equiv). ^hMixture solvent EtOH/MeCN (4 mL:1 mL).

general decrease (Table S2 and Figure S2). When the amount of NaOMe is 0.4 equivalents, the yield of nitrobenzene is the highest (Tables S2 and 1, entry 21). To enhance the yield of nitrobenzene, various solvent combinations were screened. Notably, a 96% yield of nitrobenzene was achieved with an ethanol/acetonitrile volume ratio of 4:1 (Table 1, entry 22, Table S3). However, reducing the amount of H₂O₂ leads to a decrease in both the yield and selectivity of nitrobenzene (Table S2).

Having established the optimal reaction conditions for facilitating aniline oxidation to azoxybenzenes, the versatility and scope of this methodology were assessed. Various substituted anilines were subjected to hydrogen peroxide in the presence of NaF under standard conditions (Scheme 2). This approach accommodated both electron-rich and electron-poor anilines, enabling the synthesis of a broad array of substituted azoxybenzenes. Initial oxidation using aniline produced azoxybenzene (2a) in a high yield (96% isolated yield). Subsequent oxidations of substrates carrying electron-withdrawing groups at diverse positions on the aromatic ring, such as *p*-fluoroaniline (2b), *p*-chloroaniline (2c), *p*-trifluoromethoxyaniline (2d), and *m*-trifluoromethylaniline (2p), resulted in the respective products in high yields. However, like *o*-fluoroaniline, *o*-chloroaniline resulted in slightly lower yields of the isolated product (2j and 2k). A range of azoxybenzenes featuring electron-donating groups were successfully derived from their respective anilines. The presence of diverse alkyl groups in the *meta* and *para* positions resulted in high yields for products 2e–i. Notably, *m*-toluidine

exhibited better yield than *o*-toluidine in producing the corresponding product (2h vs 2i), attributed to steric effects. Moreover, disubstituted anilines containing either electron-donating or electron-withdrawing groups were amenable to oxidative dehydrogenation, yielding the desired azoxyaromatic products in excellent yields (2m–2w). Fluorine atoms have special chemical properties and are widely used in the pharmaceutical, materials, printing, and dyeing industries.¹⁶ However, there are few reports on the synthesis of polyfluorinated azoxybenzenes. Fortunately, difluoro-substituted azoxyaromatics can be obtained via this method from the corresponding aniline in excellent yields (2m, 2n, 2q, 2t, and 2v). In addition, the heterocyclic azoxy compound 2x can also be synthesized using this method. It is worth noting that the conversion of 1-(4-aminophenyl)ethan-1-ol and 1-naphthylamine into the corresponding azoxybenzene (2y, 2z) can be achieved with high efficiency, but in which the hydroxyl groups are partially oxidized to aldehydes or ketones. However, substrates containing phenol and carboxyl groups led to the corresponding azoxy product in low yields; this may be because the phenol group is oxidized to benzoquinone and carboxylic acid group to consume the base. Unfortunately, the aliphatic amines cannot be oxidized to corresponding azoxyarenes. In addition, the synthesis of asymmetric azoxybenzene was investigated by combining 4-chloroaniline and aniline. However, GC analysis demonstrated the detection of four azoxy products, none of which was particularly dominant (Figure S3). Consequently, it appears that the

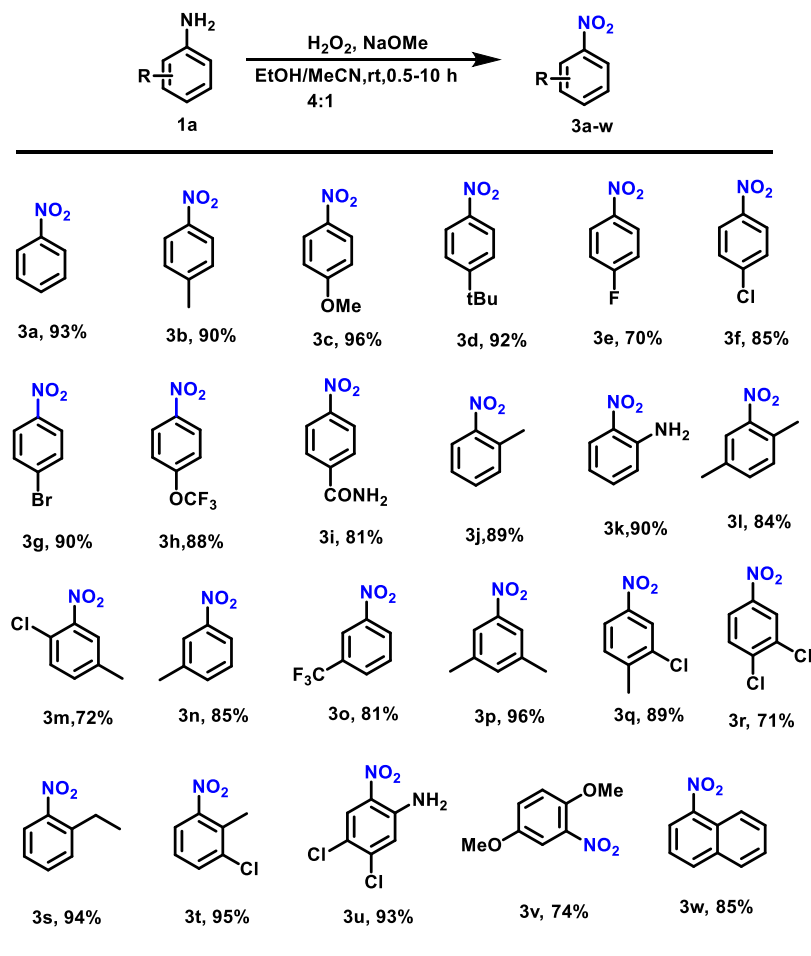
Scheme 2. Substrate Scope of the Oxidation of Substituted Anilines to Azoxyarenes^a

^aReaction condition: 1a (2 mmol), NaF (4 mmol, 168 mg), H_2O_2 (20 mmol, 2 mL), MeCN (4 mL), 80 °C, 1–10 h.

$\text{H}_2\text{O}_2/\text{NaF}$ oxidation system may not be ideally suited for the synthesis of asymmetric azoxybenzenes.

Based on the outcomes from investigating various quantities of NaOMe and different ratios of mixed solvents (Tables S2

and S3), the oxidation of substituted anilines to nitro compounds was subsequently investigated (Scheme 3). A comprehensive investigation was undertaken to examine the scope of NaOMe-mediated oxidation of anilines to Nitro-

Scheme 3. Substrate Scope of the Oxidation of Substituted Anilines to Nitroarenes^a

^aReaction condition: 1a (2 mmol), NaOMe (0.8 mmol, 43 mg), H₂O₂ (20 mmol, 2 mL), MeCN (4 mL), EtOH (1 mL), rt, 1–10 h.

Scheme 4. Gram-Scale Oxidations of Aniline 1a to Azoxybenzene 2a and Nitrobenzene 3a

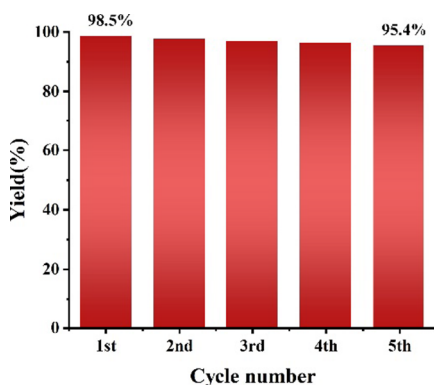
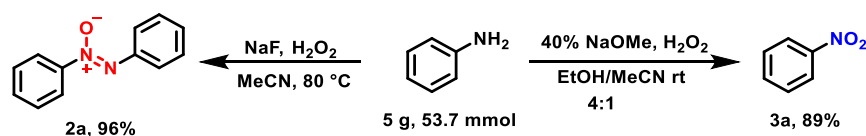
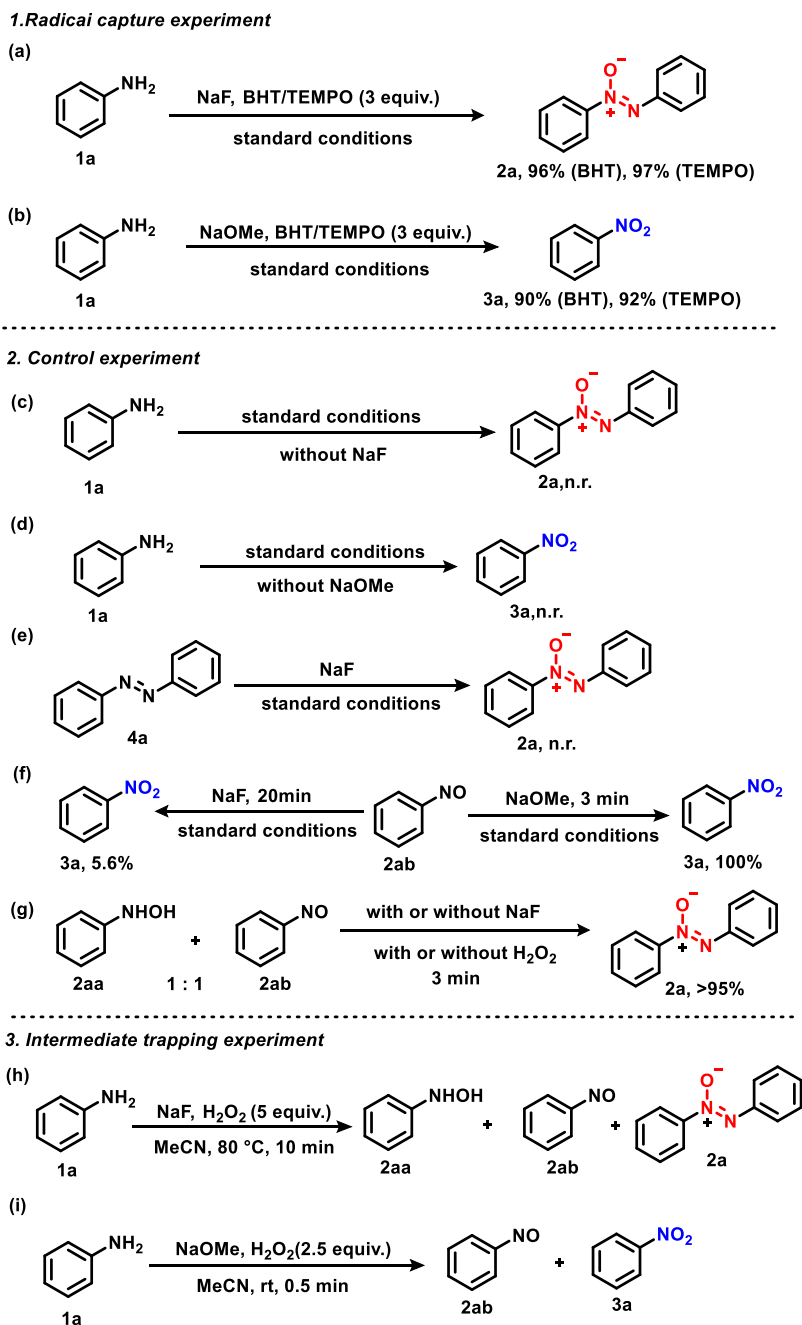


Figure 1. Yields of azoxybenzene in five recycle runs with NaF. Reaction condition: aniline (2 mmol), NaF (4 mmol, 168 mg), H₂O₂ (20 mmol, 2 mL), MeCN (4 mL), 80 °C, 1 h; the reaction mixture was extracted three times with ethyl acetate, and then the aqueous phase was evaporated and NaF was recycled for reuse.

arenes, utilizing anilines as substrates, along with EtOH and MeCN (4:1, 5 mL) as the mixture solvent, and H₂O₂ as the terminal green oxidant, conducted at room temperature for durations ranging from 0.5 to 10 h. Anilines containing electron-donating groups such as methyl, methoxy, and *tert*-butyl in *ortho*, *meta*, and *para* positions were well accommodated, yielding the respective nitroaromatics in high yields (3b–3d, 3j, 3n, and 3s). In addition, a variety of Nitroarenes bearing electron-withdrawing groups were easily obtained from the corresponding anilines. Halo-substituted anilines performed well, allowing the formation of 4-fluoronitrobenzene (3e), 4-chloronitrobenzene (3f), and 4-bromonitrobenzene (3g) in fairly good yields. 4-(Trifluoromethoxy)aniline, 4-aminobenzamide, and 3-(trifluoromethyl)aniline were also subjected to the NaOMe-mediated oxidation method reported here to afford 4-trifluoromethoxynitrobenzene (3h), 4-nitrobenzamide (3i), and 3-(trifluoromethyl)nitrobenzene (3o). The oxidation of multisubstituted anilines has also been investigated. Various

Scheme 5. Mechanism Exploration Experiments



substrates with electron-donating or -withdrawing groups positioned at diverse sites on the aromatic ring were employed, resulting in the formation of the respective multisubstituted Nitroarenes with moderate to high yields (**3l**, **3m**, **3p–3r**, **3t**, and **3v**). Intriguingly, *o*-phenylenediamines generated 2-nitroanilines (**3k**, **3u**); however, the subsequent oxidation to 1,2-dinitrobenzene did not occur. This could be attributed to the robust electron-withdrawing effect of the nitro group in 2-nitroaniline, hindering further oxidation. Additionally, 1-nitronaphthalene (**3w**) can also be successfully converted using this methodology. In summary, anilines carrying both electron-donating and electron-withdrawing groups underwent conversion to the respective nitrobenzenes, yielding moderate to high yields. Unfortunately, 3-aminopyridine and 4-ethynylaniline gave low yields (40% and 30%, respectively),

while 4-aminophenol, 4-aminobenzoic acid, 1*H*-pyrrol-3-amine, and aliphatic amines did not lead to the desired product.

The gram-scale oxidation of aniline was then executed to demonstrate the utility of these established methodologies (Scheme 4). Comparable efficiency to the smaller scale was observed in the NaF-mediated oxidation, resulting in azoxybenzene (**2a**). Furthermore, the successful oxidation of aniline (**1a**) into nitrobenzene (**3a**) via NaOMe indicated the potential suitability of these methods for large-scale production.

A study was conducted to investigate the reusability of NaF by extracting the reaction mixture, evaporating the aqueous phase, and recycling NaF. The recovered NaF was tested directly under optimized reaction conditions, showing no

significant decline in activity after five consecutive runs in terms of the reaction yield and selectivity of the desired azoxybenzene (Figure 1). Since NaOMe hydrolyzes to form NaOH in the presence of water, no recycle experiment was carried out.

Two established mechanisms are believed to govern the oxidation of anilines: the nitrosobenzene intermediate mechanism and the aniline radical mechanism (Figure S4).¹⁷ To gain insight into the mechanism underlying the oxidation of primary amines, control reactions were conducted. When radical scavengers such as 2,6-ditert-butyl-4-methylphenol (BHT) and 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) were separately introduced into the reaction system of aniline (1a) with NaF/H₂O₂ and NaOMe/H₂O₂, the yields of 2a and 3a exhibited no noticeable change (Scheme 5a,b). These results confirm that the reactions are unlikely to proceed through a radical process. Under the respective reaction conditions, the reactions of 1a with H₂O₂ did not proceed in the absence of NaF and NaOMe (Scheme 5c,d). Meanwhile, there was no oxidation of azobenzene to azoxybenzene under standard conditions, indicating that the formation of azoxybenzene did not occur via the oxidation pathway of azobenzene (Scheme 5e).¹² In addition, an oxidation experiment of nitrosobenzene was conducted, revealing that nitrosobenzene can be rapidly oxidized into nitrobenzene under strong base conditions, while the conversion under weak base conditions is significantly slower (Scheme 5f). Interestingly, phenylhydroxylamine and nitrosobenzene can be quickly converted into azoxybenzene with or without hydrogen peroxide in the presence or absence of NaF (Scheme 5g). These results demonstrate that hydrogen peroxide exhibits a stronger oxidizing capacity in a strong base but a weaker oxidizing capacity in a mild base, which is also the reason for the controllable selective oxidation of aniline by regulating the strength of alkalinity. Additionally, we conducted the intermediate trapping experiment by GCMS. In the NaF-mediated oxidation system, the detection of intermediate phenylhydroxylamine (2aa) and nitrosobenzene (2ab) suggests consistency with the reaction pathway outlined in Scheme 1 (refer to Figures S5 and S6 in the Supporting Information for additional details); however, only nitrosobenzene (2ab) intermediates were trapped in the NaOMe-mediated oxidation system (Scheme 5h,i).

Therefore, on the basis of the above studies, a plausible mechanism for the controllable selective oxidation of aniline to azoxybenzene and nitrobenzene by regulating the strength of alkalinity is illustrated in Scheme 1 and Figure S7. In the NaF-mediated oxidation system, the oxidation of aniline to phenylhydroxylamine (2aa) was found to be rapid (Step I). Therefore, no azobenzene (4a) was detected (step V). Simultaneously, the oxidizing of phenylhydroxylamine (2aa) to nitrosobenzene (2ab) was relatively rapid (step II); therefore, these two intermediates could condense rapidly to form azoxybenzene (2a) (step IV, Figure S7a). However, only nitrosobenzene (2ab) intermediates were trapped in the NaOMe-mediated oxidation system, indicating that the oxidation process of steps I to III was very fast (Scheme 1 and Figure S7b). The mechanism study shows that hydrogen peroxide has a weak oxidizing ability in a mild base but a stronger oxidizing ability in a strong base.

CONCLUSIONS

In conclusion, a mild, highly efficient, and selective method has been developed for oxidizing primary amines into azoxybenzenes and nitrobenzenes. This process involves utilizing the eco-friendly oxidant H₂O₂ in the presence of either the strong base NaOMe or the weak base NaF. The selectivity of these reactions can be easily modified by adjusting the alkalinity strength, eliminating the need for metal or organic compounds. This method serves as an alternative to traditional techniques relying on heterogeneous systems that predominantly produce azoaromatics. Notably, this work represents the first instance of regulating aniline oxidation by manipulating alkalinity strength. These findings establish a foundational framework for investigating base catalysis and broadening its applications within the realm of organic synthesis.

ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at <https://pubs.acs.org/doi/10.1021/acsomega.4c04820>.

General remarks; experimental procedures; synthesis of asymmetric azoxybenzenes; mechanism exploration experiment; reference; and NMR spectra of compounds (PDF)

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Notes

The authors declare no competing financial interest.

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