ORGANIC CHEMISTRY

Nitrate reduction enables safer aryldiazonium chemistry

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Aryldiazonium salts remain a staple in organic synthesis and are still prepared largely in accord with the protocol developed in the 19th century. Because of the favorable reactivity that often cannot be achieved with other aryl(pseudo)halides, diazonium chemistry continues to grow. Facile extrusion of dinitrogen contributes to the desired reactivity but is also reason for safety concerns. Explosions have occurred since the discovery of these reagents and still result in accidents. In this study, we report a diazonium chemistry paradigm shift based on nitrate reduction using thiosulfate or dihalocuprates as electron donors that avoids diazonium accumulation. Because nitrate reduction is rate-limiting, aryldiazoniums are produced as fleeting intermediates, which results in a safer and often more efficient deaminative halogenation in a single step from anilines.

Sandmeyer used aryldiazonium salts 140 years ago to achieve the oxidative addition to d^{10} metals for the synthesis of aryl halides (Fig. 1A) (*1*). The reactivity of diazonium salts often surpasses that of other (pseudo)halides and is based on their high electrophilicity, low reduction potential of −0.16 V versus standard calomel electrode (SCE) (*2*), and formation of dinitrogen as a leaving group that enables challenging transformations such as single-electron transfer (SET)–initiated oxidative addition to main-group elements (*3*, *4*). Therefore, diazonium salts are still prepared routinely both on laboratory scale and in industrial plants (*5*, *6*), and aryl halides are still commonly prepared from aryldiazonium salts (*7*, *8*). Since the first report on aryldiazonium salt synthesis with nitrous acid (*9*), little has changed in their preparation. Nitrosonium (NO^+) ions, formed through acidic degradation of nitrite-based reagents such as sodium ($NaNO_2$) or isoamylnitrite (*10*), react with anilines at low temperature, which is commonly required owing to the instability of aryldiazonium salts above 5°C (*11*). The resulting salts are either isolated or accumulate for subsequent treatment with nucleophiles, sometimes at higher temperatures, in a separate second step (*10*). Reaction enthalpies of up to $\Delta H = -84$ kcal mol^{-1} are common for diazonium decomposition reactions and can result in violent exothermic reactions that arise from rapid energy release with concomitant gas evolution (*12*). The often unpredictable instability of aryldiazonium salts can result in detonation upon contact with air (*13*) and even in solution (*14*), which has led to many severe accidents in undergraduate lab courses (*15*), academic research (*16*), and industry, with fatal consequences at times (*17*). The persistent assumption in the community that the tetrafluoroborate (BF_4^-) counterion prevents explosions of diazonium salts has been proven to be incorrect because BF_4^- salts have also been reported to explode (*18*). To attenuate the risks associated with aryldiazonium batch processes, continuous-flow setups (*19*, *20*) can be used. Although several large-scale processes are in place, such as the Balz-Schiemann reaction for the synthesis of fluorobenzene (*21*), small changes in the protocol, small quantities of impurities, and mechanical force can result in unexpected detonations, and every new aryldiazonium salt should be considered dangerous and explosive until proven otherwise (*18*). To mitigate the dangers associated with diazonium chemistry, alternative deamination protocols have been developed that, for example, use pyridines as leaving groups (*22*) or diazenes as intermediates (*23*, *24*); however, those reactions typically do not achieve the broad utility and high atom economy of the parent diazotization methods.

Although nitrate (NO_3^-) is thermodynamically a stronger oxidant [NO_3^-/N_2, pH =14, 0.25 V versus standard hydrogen electrode (SHE)] than nitrite (NO_2^-/N_2, pH =14, 0.41 V versus SHE) (*25*), it has not been used in diazotization processes, likely because it is considered an inert oxidant because of its high kinetic stability toward reduction (*26*). In acidic conditions, NO_3^- and nitrate esters do not produce nitrosonium cation (NO^+), which is used for diazotization, but instead form nitronium ions (NO_2^+) that react as electrophiles for arene nitration, not diazotization (Fig. 1A) (*27*). Several microorganisms are able to reduce nitrate by using it as the terminal electron acceptor for respiration. For example, chemolithotrophic *Thiobacilus denitrificans* uses thiosulfate ($S_2O_3^{2-}$) to produce dinitrogen (N_2) and sulfate (SO_4^{2-}) as NO_3^- reduction by-products (*28*). In plants, nitrate reduction is performed with nitrate reductase metalloenzymes (Fig. 1B). Eukaryotic nitrate reductases operate by an oxygen atom transfer mechanism carried out in the molybdenum-based active site with hydrogen-bonding assistance (*29*). Synthetic nitrate reduction approaches are still challenging and a subject of ongoing research: On the basis of initial discoveries of Holm's group (*30*, *31*), who reported bioinspired oxomolybdenum transition metal complexes, several research groups have developed Fe- and Cu-based nitrate reduction catalysts (*26*, *32*).

Design of a nitrate reduction strategy

The formation of NO_2^+ in acidic conditions and the kinetic stability of NO_3^- may be the reasons that nitrate salts and their esters have been ignored as diazotization reagents for more than a century. The conversion of NO_2^- to NO^+ and of NO_3^- to NO_2^+ with acid are redox-neutral processes. Use of nitrate (N oxidation state = +V) as a diazotization reagent therefore requires a reductive pathway in the absence of strong acid for the generation of NO^+ (N oxidation state = +III). Single-electron reduction to nitrogen dioxide (NO_2, N oxidation state = +IV) allows the formation of NO^+ through disproportionation of dinitrogen tetroxide (N_2O_4, Fig. 1C) (*33*). Our protocol relies on thiosulfate or dihalocuprates as electron donors for nitrate reduction and can use readily available potassium nitrate or nitrate esters. Although NO_3^- is thermodynamically strong enough to oxidize nucleophiles such as bromide and iodide (*34*) on the basis of reduction potentials, it is kinetically compatible with various nucleophiles in the same reaction mixture, including bromide, iodide, and thiosulfate. By contrast, the previously used nitrite and alkyl nitrites are incompatible with several nucleophiles because they react through kinetically facile oxidation (*35*). Therefore, such nucleophiles cannot be present during diazotization with nitrites, and diazoniums accumulate or must be isolated, which results in the safety issues of global diazonium chemistry. Because the process of nitrate reduction is the rate-limiting step in our strategy, diazoniums are produced as fleeting intermediates in only minute concentrations, which results in several fundamental advantages when compared with conventional diazonium chemistry: (i) Thermal runaway reactions are avoided because nitrate reduction has a higher Gibbs free energy of activation (e.g., $\Delta G^\ddagger = 26.7$ kcal·mol^{-1} for iodination, fig. S71) than does aryldiazonium halogenation ($\Delta G^\ddagger = 15.8$ kcal·mol^{-1} for iodination, fig. S72); (ii) anilines are used as starting

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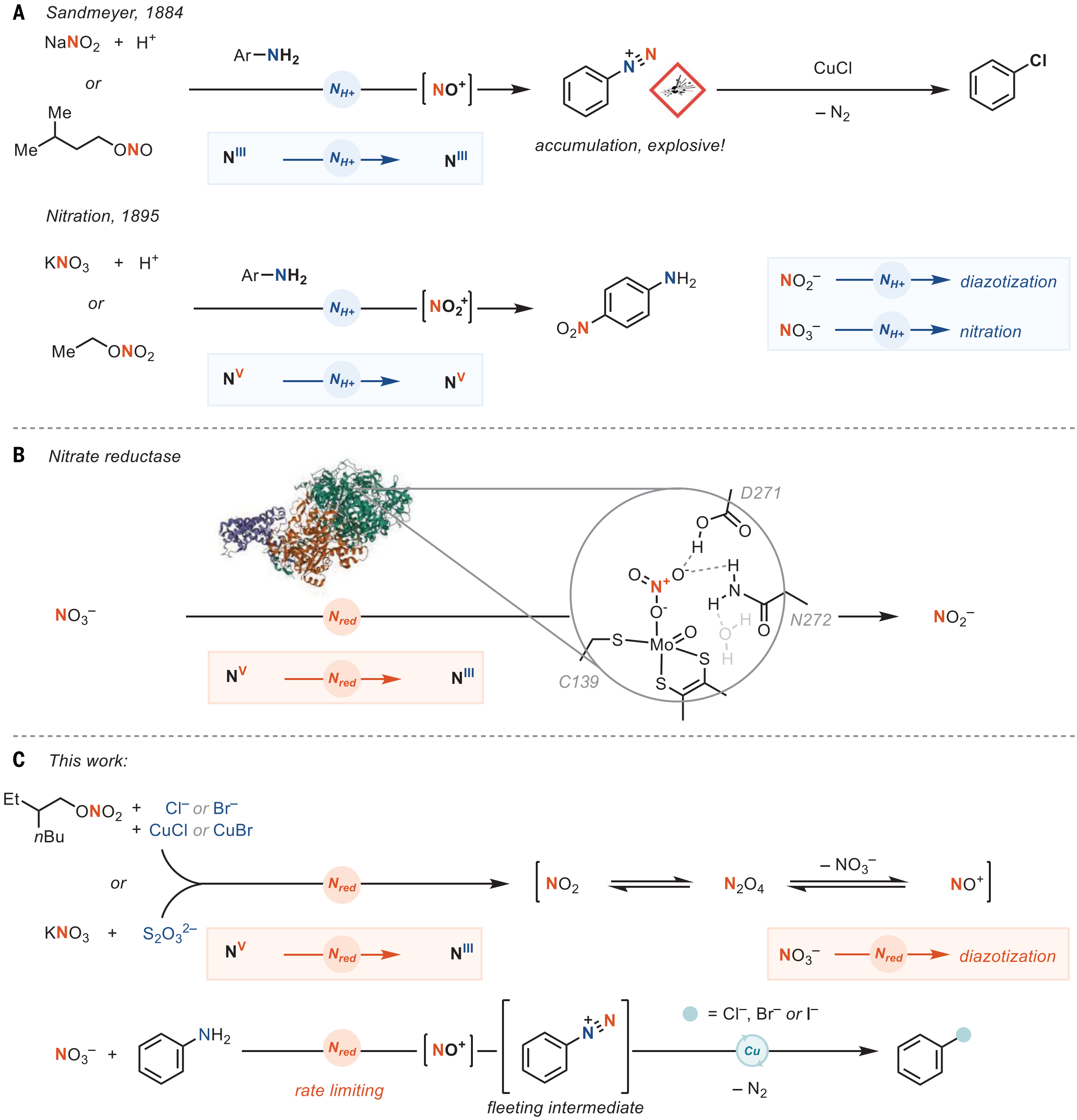


Fig. 1. Diazonium salts as fleeting intermediates. (**A**) (Top) Acidic activation of nitrite and alkyl nitrites leads to accumulation of aryldiazonium salts. (Bottom) Acidic activation of nitrate and nitrate esters leads to nitration. (**B**) Nitrate reductase (1Q16) metalloenzymes use nitrate as terminal electron acceptor for respiration. (**C**) This work: Nitrate reduction with thiosulfate or cuprates as rate-limiting step enables direct functionalization of anilines. Me, methyl; Ar, aryl; N_{H+}, nitrogen oxyanion protonation; N_{red}, nitrate reduction.

materials directly, which avoids a two-step sequence with isolation or storage of diazonium salts; (iii) whereas most aryldiazoniums are unstable above 5°C, restricting conventional reactions to low temperatures, our protocol is not so constrained and may access reaction chemistry beyond traditional diazonium reactions; and (iv) nitrate and its esters are more readily available and less expensive than alkyl nitrites. In addition, diazotization and functionalization of diazoniums produce H_2O and N_2 as by-products, as compared with other modern deaminative strategies with pyridines, carboxylates, or esters as side products.

Here we detail the organic and inorganic chemistry involved in the direct deaminative halogenation of anilines through aryldiazoniums as fleeting intermediates, using abundant nitrate salts and nitrate esters, readily available reductants, and common halide sources. All three deaminative halogenation reactions reported in this study can be carried out using both nitrate salts and nitrate esters under the same reaction conditions, although chlorination delivered higher yields with 2-ethylhexyl nitrate (**2**), whereas bromination and iodination gave higher yields with nitrate salts (tables S1 to S6). In conventional diazotization methods, halides are oxidized by nitrites when mixed simultaneously (*34*–*36*), whereas the use of nitrates allows the presence of nucleophiles to deliver aryl halides in a single step from anilines such as **1** shown in Fig. 2A. Cu^I salts can facilitate both the reduction of nitrate esters and the conversion of aryl diazoniums to aryl halides by conventional Sandmeyer-type reactivity. The combination of nitrate esters and Cu(I)halides enables the deaminative chlorination, bromination, and iodination of anilines and aminoheterocycles. Deaminative iodination can also be performed in the absence of copper. Without copper, sulfur-based reagents such as thiosulfate allow for nitrate-salt reduction, whereas iodide directly converts aryldiazoniums to aryl iodides. Chlorination was achieved using tetrabutylammonium chloride (TBACl), CuCl, and nitrate esters such as 2-ethylhexyl nitrate (**2**), which is obtained from 2-ethylhexanol, a common plasticizer alcohol produced on a multimillion-ton scale every year by the Guerbet reaction (*37*). Bromination is performed using $TBANO_3$, $Na_2S_2O_3{\cdot}5H_2O$, 1,2-dibromoethane (**4**) (DBE) as bromine source, and CuBr. Iodination is carried out using KNO_3, sodium thiosulfate pentahydrate ($Na_2S_2O_3 \cdot 5H_2O$) as reductant, and 1,2-diiodoethane (DIE) as iodine source. Refluxing acetonitrile (MeCN) was chosen as the reaction medium; aprotic polar solvents, such as MeCN, minimized the amount of protodeaminated side products (figs. S17 to S24), yet can solubilize the ionic species involved in the reaction.

Mechanistic investigation

Although the conditions of the reaction shown in Fig. 2A differ substantially from a conventional diazotization, all mechanism-based experiments are in agreement with the intermediacy of aryldiazonium salts, with subsequent reaction progress analogous to a Sandmeyer reaction. Observation of unlabeled, partially labeled, and fully labeled dinitrogen (N_2) as reaction product by gas chromatography–mass spectrometry (GC-MS) is consistent with the formation of aryldiazoniums and their subsequent conversion to product. Labeled ^{15}N-dinitrogen could also be observed by in situ ^{15}N nuclear magnetic resonance (NMR) spectroscopy, yet no diazonium salt was detected within error of measurement in any experiment throughout the reaction by proton (^{1}H) or ^{15}N NMR spectroscopy, which established that no aryldiazonium salts accumulate in substantial quantity and supports the claim that they form as short-lived intermediates only (figs. S70 and S73). To access the diazonium intermediate, nitrate may be ultimately converted to NO^+ in a two-electron reduction (Fig. 1C).

Although aryl halide formation from aryldiazonium intermediates is anticipated to follow the conventional Sandmeyer mechanism, including redox-active copper participation, the nitrate reduction step as reported here is conceptually different. We describe two related but distinct pathways for nitrate reduction, one for nitrate esters and one for nitrate salts (fig. S15). In conventional diazotization reactions, NO^+ is formed by acidic degradation of either nitrite salts or alkyl nitrites. Guided by density functional theory (DFT) calculations, we posited that alkyl nitrates would be reduced by SET from dihalocuprates such as $Cu(I)Cl_2^-$ (figs. S91 and S93). In the case of chlorination, CuCl reacts with TBACl to form $[CuCl_2]^-$ (**7**), which can reduce 2-ethylhexylnitrate **2** to form NO_2 and **8** (Fig. 2B). Cuprate **8** and NO_2 could further react to form CuCl and nitryl chloride (NO_2Cl), which can undergo homolytic N–Cl bond cleavage to form NO_2 and chlorine radical (*38*) (Fig. 2B, orange box). The NO_2 formed from NO_2Cl degradation produces the aryldiazonium through dimerization to N_2O_4 and subsequent disproportionation to NO^+ NO_3^- (*39*). The aryl chloride is subsequently formed from the diazonium intermediate through conventional Sandmeyer-type reactivity with CuCl. The intermediacy of NO_2Cl is in agreement with the formation of the deaminative chlorination product **3** when NO_2Cl was used directly in the reaction in the absence of **2** (table S11). Higher yields of halodeaminated products were observed when the chlorine radical scavenger 2-methyl-2-butene was added. Its chlorine adduct was observed experimentally, which in addition to higher yield, further supports the proposed mechanism (figs. S50 to S53). In the absence of Cu^I, nitrate ester **2** is converted through nucleophilic substitution with chloride to form 2-ethylhexyl chloride and nitrate as leaving group (figs. S46 to S49; for DFT calculations see fig. S92). For bromination, nitrate ester **2** delivered aryl bromides in the presence of CuBr and TBABr (Fig. 2C). The combination of $TBANO_3$ and **4** resulted in improved reaction outcomes (77% yield with $TBANO_3$ and **4** versus 63% yield with **2**, CuBr and TBABr). Dibromoethane **4** is converted to nitrate ester **9** by nucleophilic displacement of bromide (fig. S54). The liberated bromide can be trapped by CuBr to produce $CuBr_2^-$ (**10**), which subsequently reduces the formed nitrate ester **9** to give NO_2 and **11** (figs. S55 to S57). Slow in situ formation of nitrate ester **9** affords a higher yield than adding a stoichiometric amount of **9** or **2** at the beginning of the reaction, presumably because of competing side reactions that occur in the presence of a higher concentration of nitrate esters in this case (Fig. 2C, table). Analogously to chlorination, electrophilic bromine species are formed during the bromination reaction. The addition of $Na_2S_2O_3{\cdot}5H_2O$ as a scavenger suppresses dibromination of **1** (figs. S58 to S61) and allows the isolation of arylbromides in higher yields—49% in the absence of thiosulfate versus 77% with 20 mol % of thiosulfate.

Deaminative iodination with nitrate ester **2**, CuI, and TBAI delivered **6** in 68% yield (fig. S15). In the absence of Cu^I, **1** was converted to **6** in 98% yield when thiosulfate was used as stoichiometric reductant instead of cuprates. Thiosulfate ($S_2O_3^{2-}$) itself does not reduce NO_3^- below 140°C (table S13). Hence, a chemically competent reductant must be formed in situ in the reaction shown in Fig. 2A, possibly from $S_2O_3^{2-}$. Thiosulfate forms tetrathionate ($S_4O_6^{2-}$) by oxidation with iodine, which is formed in equilibrium with ethylene from 1,2-diiodoethane; ethylene was observed with in situ NMR spectroscopy (fig. S63) (*40*, *41*). But tetrathionate ($S_4O_6^{2-}$) is kinetically also not competent to reduce NO_3^- (table S13). However, we found that tetrathionate conversion to sulfur dioxide (SO_2), sulfate (SO_4^{2-}), and sulfur (S_8) (*42*) can be catalyzed by I_2 as redox mediator (table S14). When SO_2 was used directly as nitrate reductant (Fig. 2D), the reaction proceeded productively, yet in lower yield as compared with the reaction with thiosulfate (table S13). We concluded that the slow release of the effective nitrate reductant SO_2 from $S_2O_3^{2-}$ through $S_4O_6^{2-}$ is critical for a high yield (*43*); stoichiometric addition of SO_2 at the beginning of the reaction resulted in a less-efficient process (table S15). Likewise, initial excess of SO_2 further reduces the yield, presumably because of a competing Lewis acid–Lewis base adduct with the aniline—which was observed experimentally (fig. S69) to suppress productive diazotization (*44*)—or because of undesired side reactivity, such as the reduction of iodine by SO_2 (*45*). Gas-phase electron paramagnetic resonance (EPR) experiments of the reaction headspace confirmed the formation of NO_2 (Fig. 2D) from NO_3^- and SO_2. When aniline **1** reacted with NO_2, formed by the reaction of nitrate with SO_2, in the absence of a copper redox mediator, the corresponding diazonium salt was observed experimentally and could be trapped with nucleophiles to further substantiate the proposed mechanism (table S16). Iodide that is formed during the thiosulfate oxidation is a suitable nucleophile for the aryl iodide formation from the diazonium intermediate (table S15).

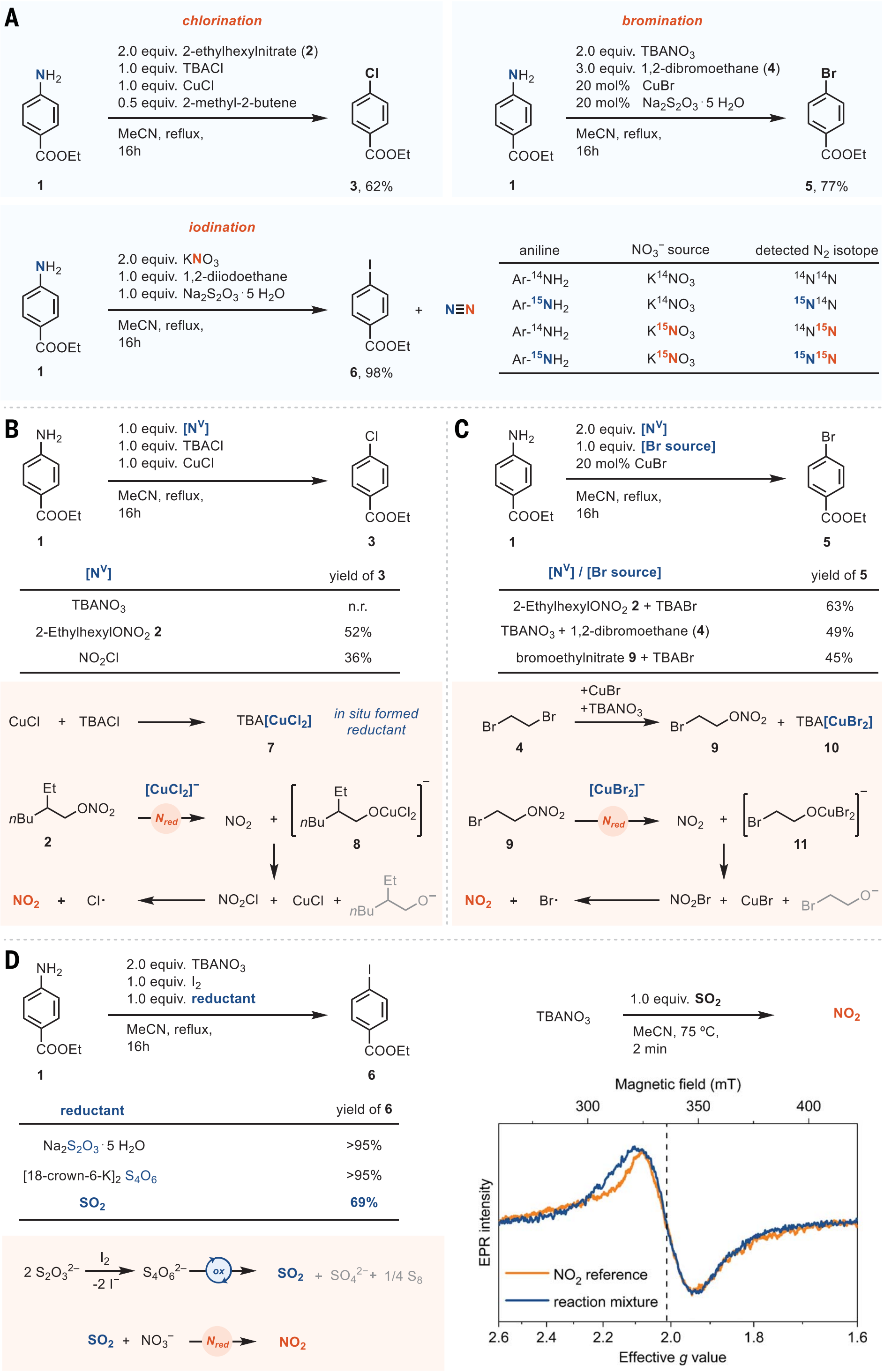


Fig. 2. Mechanistic insights for direct deaminative halogenations by nitrate reduction. (**A**) Optimized conditions for chlorination, bromination, and iodination of **1**; nitrogen detection by GC-MS and isotopic labeling. (**B**) Control experiments with different N^V reagents. (Orange box, left) Proposed mechanism based on the control experiments and figs. S43 to S53. Nitrate ester reduction in deaminative chlorination proceeds by single-electron transfer (SET) from in situ formed dichlorocuprate **7**. (**C**) Control experiments with different N^V reagents and Br sources. (Orange box, right) Proposed mechanism based on the control experiments and figs. S54 to S62. Formation of nitrate ester **9** from 1,2-dibromoethane **4**, followed by SET from dibromocuprate **10** in deaminative bromination. (**D**) (Left) Control experiments with different sulfur-based reductants. (Orange box) Proposed mechanism based on the control experiments and figs. S62 to S80. For the deaminative iodination reaction, SO_2 is responsible for nitrate reduction, which is formed from thiosulfate. (Right) Detection of NO_2 radical with EPR spectroscopy; for spectroscopic details and EPR parameters, see fig. S62. Me, methyl; Et, ethyl; Ph, phenyl; TBA, tetrabutylammonium; MeCN, acetonitrile; 18-crown-6, 1,4,7,10,13,16-hexaoxacyclooctadecane (18-crown-6 ether); ox, oxidant; N_{red}, nitrate reduction (n.r. = <5% product detected by ^1H NMR spectroscopy).

aniline	NO_3^- source	detected N_2 isotope
Ar-$^{14}NH_2$	$K^{14}NO_3$	$^{14}N^{14}N$
Ar-$^{15}NH_2$	$K^{14}NO_3$	$^{15}N^{14}N$
Ar-$^{14}NH_2$	$K^{15}NO_3$	$^{14}N^{15}N$
Ar-$^{15}NH_2$	$K^{15}NO_3$	$^{15}N^{15}N$

$[N^V]$	yield of 3
$TBANO_3$	n.r.
2-EthylhexylONO_2 **2**	52%
NO_2Cl	36%

$[N^V]$ / [Br source]	yield of 5
2-EthylhexylONO_2 **2** + TBABr	63%
$TBANO_3$ + 1,2-dibromoethane (**4**)	49%
bromoethylnitrate **9** + TBABr	45%

reductant	yield of 6
$Na_2S_2O_3 \cdot 5\ H_2O$	>95%
[18-crown-6-K]$_2$ S_4O_6	>95%
SO_2	69%

Scope and comparison with conventional diazonium chemistry

A variety of structurally and electronically diverse arenes and hetarenes can participate in the nitrate reduction–based deaminative halogenation (Fig. 3). Substrate-dependent optimization of the reaction conditions was not required during the preparation of the substrate scope. The reactions were set up with technical-grade solvents, commercially available starting materials, and reagents, and without the need for flow equipment. An inert atmosphere was not required; the reactions were conducted under air, and 50 vol % of water content in the solvent still resulted in 70% yield versus 98% yield with ~5 vol % water content (table S2). The nitrogen-based species that are formed during the reaction and that are responsible for the generation of NO^+, such as NO_2, are gaseous, therefore the reactions were carried out in closed systems. However, the use of sealed vessels is not a requirement for deaminative chlorination (75% yield in closed system versus 64% yield at reflux for **19**) and bromination (67% yield in closed system versus 78% yield at reflux for **27**). Deaminative iodination requires a closed

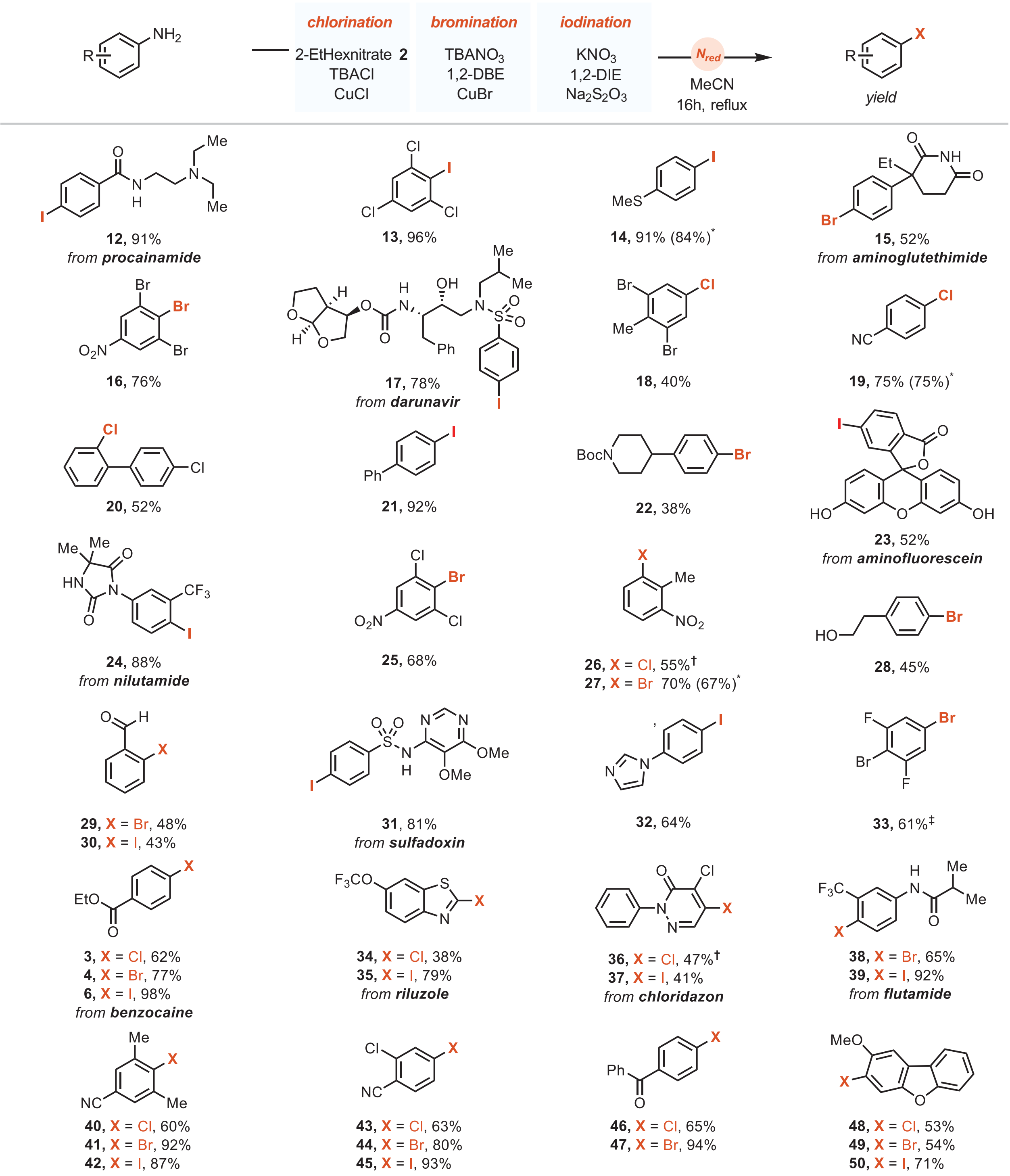
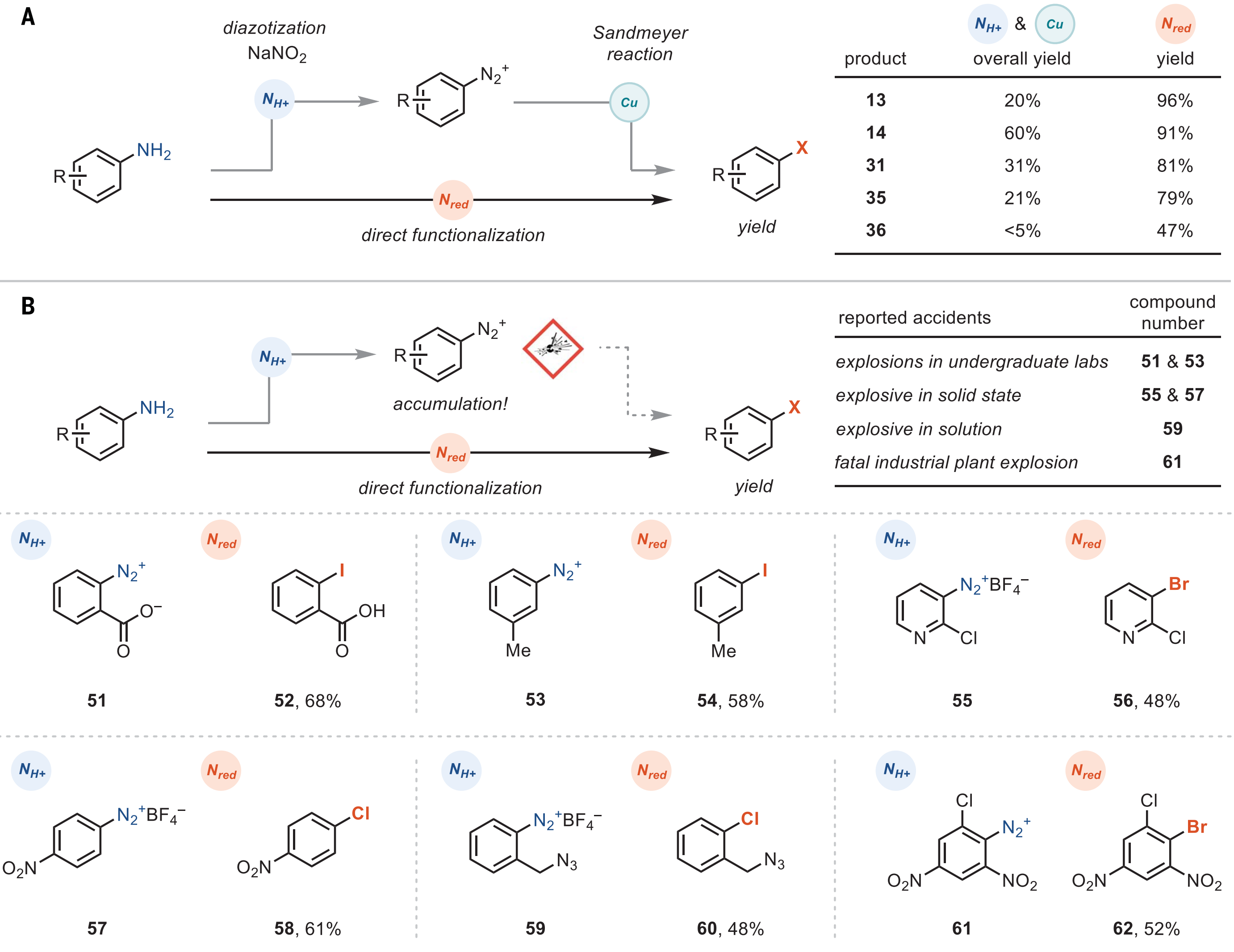


Fig. 3. Substrate scope of anilines. Reaction conditions are as follows. Chlorination: 0.500 mmol aniline, 1.00 mmol **2**, 0.500 mmol CuCl, 0.500 mmol TBACl, 0.250 mmol 2-methyl-2-butene in 1.25 ml of acetonitrile, reflux, 16 hours. Bromination: 0.500 mmol aniline, 1.00 mmol $TBANO_3$, 0.100 mmol CuBr, 0.100 mmol $Na_2S_2O_3 \cdot 5H_2O$, 1.50 mmol 1,2-dibromoethane in 1.25 ml of acetonitrile, reflux, 16 hours. Iodination: 0.500 mmol aniline, 1.00 mmol KNO_3, 0.600 mmol $Na_2S_2O_3 \cdot 5H_2O$, 0.600 mmol 1,2-diiodoethane in 1.25 ml of acetonitrile, reflux, 16 hours. *10.0 mmol scale. †2.00 mmol **2** and 1.00 mmol CuCl. ‡yield determined by ^1H NMR spectroscopy because of the volatility of compound **33**. Supplementary materials provide detailed experimental procedures. Me, methyl; Et, ethyl; Ph, phenyl; TBA, tetrabutylammonium; N_{red}, nitrate reduction.

system—possibly because of the diminished solubility of SO_2 in acetonitrile at elevated temperatures (*46*)—but can proceed at pressures lower than 3.1 bars (fig. S29); variation of the reactor size and headspace volume did not change the reaction yield appreciably (table S8 to S10). The distinct mechanism of diazotization through nitrate reduction can address several limitations of conventional



product	N_{H+} & Cu overall yield	N_{red} yield
13	20%	96%
14	60%	91%
31	31%	81%
35	21%	79%
36	<5%	47%

reported accidents	compound number
explosions in undergraduate labs	**51** & **53**
explosive in solid state	**55** & **57**
explosive in solution	**59**
fatal industrial plant explosion	**61**

Fig. 4. Direct halogenation of anilines of which diazonium salt was reported to cause an explosion. (**A**) Comparison of two-step synthesis of aryl halides with the nitrate-based protocol. (**B**) Direct halogenation of anilines of which accumulated diazonium salts are reported explosives. Reaction conditions are as follows. Chlorination: 0.500 mmol aniline, 1.00 mmol **2**, 0.500 mmol CuCl, 0.500 mmol TBACl, 0.250 mmol 2-methyl-2-butene in 1.25 ml of acetonitrile, reflux, 16 hours. Bromination: 0.500 mmol aniline, 1.00 mmol TBANO$_3$, 0.600 mmol CBr$_4$ and 0.400 mmol Na$_2$S$_2$O$_3$·5H$_2$O in 1.25 ml of ethyl acetate, reflux, 16 hours. Iodination: 0.500 mmol aniline, 1.00 mmol KNO$_3$, 0.600 mmol Na$_2$S$_2$O$_3$·5H$_2$O, 0.600 mmol 1,2-diiodoethane in 1.25 ml of acetonitrile, reflux, 16 hours. Supplementary materials provide detailed experimental procedures. Me, methyl; TBA, tetrabutylammonium; N_{H+}, nitrogen oxyanion protonation; N_{red}, nitrate reduction.

diazonium chemistry that include undesired oxidation of functional groups (*46*); failure to efficiently functionalize sterically hindered anilines (*47*) and aminoheterocycles (*22*); low product yield because of competing biaryl and phenol formation through radical dimerization and addition of water, respectively (*48*); and undesired protodeaminations (*49*). Those disadvantages result from the use of nitrites and the high concentration of the reactive diazonium salt that lead to side reactions, which is not the case when diazoniums are produced as fleeting intermediates in the absence of strong, kinetically reactive oxidants such as nitrite. With nitrate salts and nitrate ester **2**, oxidant-labile thioethers are tolerated (**14**); functionalization of *ortho* and *ortho,ortho*–disubstituted anilines (**13**) proceeds in up to 96% yield; and aminoheterocycles or anilines with heterocyclic substituents (**31**, **35**, **36**) can participate (Fig. 4A). Improvement over conventional diazonium chemistry becomes even more apparent in a comparison of severely dangerous, explosive diazonium salts (Fig. 4B). Anthranilic acid and *meta*-toluidine are substrates for diazonium preparation in undergraduate labs, although both diazonium salts have detonated (*15*, *50*). Pyridine-based diazoniums are often unstable in the solid state (*51*). Aryldiazoniums that are classified as potentially explosive by the rule of six (*52*)—because they contain more than one energetic functional group per six carbon atoms—have caused explosions when dry and even in solution, as for example, nitroarene **57** (*53*) or azide **59** (*14*). In the case of dinitro-substituted diazonium salt **61**, a fatal explosion killed three and injured 31 individuals in a Ciba AG plant (*17*). The nitrate reduction strategy avoids accumulation of the explosive diazonium salts and gives direct access to the aryl halides without observation of any violent reaction from rapid gas evolution or uncontrolled energy release.

Outlook

Nitrate reduction of inexpensive and readily available nitrate salts and nitrate esters allows the direct deaminative functionalization of anilines and aminoheterocycles without the need for modern, specialized reagents. The fundamentally different mechanism of nitrate reduction over nitrite protonation allows diazonium chemistry at elevated temperatures and the functionalization of substrates bearing energetic or sensitive functional groups. The immediate consequence reported here is a safer and higher-yielding halogenation, yet the mechanistic manifold may also provide a more general platform for the development of diazonium chemistry beyond current reach, thanks to the lack of required high-energy intermediate accumulation, as has been the case since the 19th century.

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SUPPLEMENTARY MATERIALS

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Materials and Methods
Figs. S1 to S93
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