JOC The Journal of Organic Chemistry

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Ipso Nitration of Aryl Boronic Acids Using Fuming Nitric Acid

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Cite This: https://doi.org/10.1021/acs.joc.1c00886 Read Online

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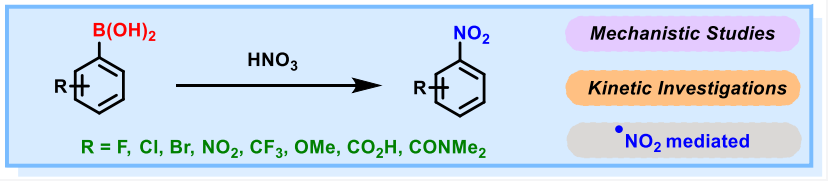


ABSTRACT: The *ipso* nitration of aryl boronic acid derivatives has been developed using fuming nitric acid as the nitrating agent. This facile procedure provides efficient and chemoselective access to a variety of aromatic nitro compounds. While several activating agents and nitro sources have been reported in the literature for this synthetically useful transformation, this report demonstrates that these processes likely generate a common active reagent, anhydrous HNO_3. Kinetic and mechanistic studies have revealed that the reaction order in HNO_3 is >2 and indicate that the $^{\bullet}NO_2$ radical is the active species.

INTRODUCTION

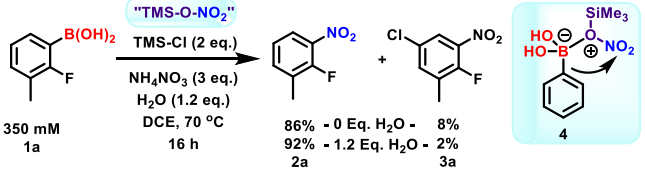
Nitration of aromatic species *via* electrophilic aromatic substitution is one of the most widely studied organic transformations in the chemical literature.[1,2] This processes typically uses the "mixed-acid" method, a combination of nitric and sulfuric acids for the *in situ* generation of active electrophilic nitronium (NO_2^+) species.[3,4] For more than a century, this classical approach has been adopted across the entire chemical industry for commercial production of a plethora of products, ranging from pharmaceutical agents to explosives and plastics.[1,2,5] Despite the wide use and economical nature of this methodology, there are important synthetic limitations associated with this process. Regioselectivity issues commonly result in the formation of difficult to remove isomeric byproducts which are of particular importance in a regulated commercial environment. Susceptibility of substrates to hydrolysis and oxidation under these conditions also leads to generally poor functional group compatibility.

To address these challenges, methodologies for the *ipso* substitution of a variety of functional groups have been developed to access nitroaromatics in a more selective manner.[6,7] In relation to an ongoing late-stage program, our group has a particular interest in the use of boronic acids as precursors to nitroaromatics *via ipso* substitution. The seminal work in this field was conducted by Olah *et al.* demonstrating the *ipso* substitution of boronic acids with NH_4NO_3 and trifluoroacetic anhydride (TFAA)[8] or trimethylsilyl chloride (TMS-Cl)[9] as activating agents. Since these initial reports, several groups have demonstrated the use of alternative nitrate sources (MNO_3) or the combination of a nitrite (MNO_2) in conjunction with an oxidant for the *ipso* nitration of boronic acids.[6,7] Of particular note are $Bi(NO_3)_5$,[10] $Fe(NO_3)_3$,[11] and $AgNO_3$[9] which demonstrate good chemoselectivity but require heterogeneous reaction conditions and extended reaction times. *tert*-Butyl nitrite has also been utilized for this transformation;[12] however, moderate yields and the requirement of air as an external oxidant limit the scalability of this methodology.

RESULTS AND DISCUSSION

In the context of one of our programs, we pursued the efficient and scalable conversion of boronic acid **1a** to the corresponding nitroaromatic **2a** (Scheme 1). Initial investigations quickly led us to pursue the conditions first reported by Olah *et al.* for further optimization (for details of complete screening conditions see the Supporting Information).[8,9] While the reported room-temperature procedure in CH_2Cl_2 required >72 h to obtain meaningful conversion, we demonstrated that

Scheme 1. Optimal Conditions for Nitration of Boronic Acid 1 Using NH_4NO_3/TMS-Cl



Special Issue: Excellence in Industrial Organic Synthesis 2021

Received: April 16, 2021

simply using 1,2-dichloroethane (DCE) and increasing the reaction temperature to 70 °C provided 86% yield of the desired product **2a** in 16 h. To our surprise the inclusion of H_2O (1.2 equiv) was found to improve the purity profile of the reaction and increased the isolated yield to 92%.

Despite our best efforts, however, we were unable to suppress formation of chlorinated byproduct **3** in this process. This species could not be removed via distillation nor crystallization, rendering this procedure unsuitable for obtaining the high-purity material required for our purposes. Olah *et al.* also observed chlorinated byproducts in their original procedure (up to 25%).[8,9] They proposed that chlorination was a result of the active reagent, TMS-O-NO_2, reacting with excess TMS-Cl to form the highly reactive species nitryl chloride (NO_2Cl).

To address formation of chlorinated byproduct **3** we investigated the use of alternative activated silyl species for generation of the proposed active nitrating agent TMS-O-NO_2 and silyl boronate intermediate **4** (Table 1). Several such reagents exhibited good reactivity in this process, and nitrated product **2** could be isolated in the high purity required to meet the required specifications. Despite providing an excellent alternative to TMS-Cl for laboratory-scale synthesis, the high cost and difficulty in sourcing large quantities of these reagents rendered this approach untenable for large-scale production.

Table 1. Reactivity of Activated Silyl Species[a]

Entry	TMS-X, X =	Product **2** (%)[b]	pKa Conjugate acid of X[c]
1	O-$SiMe_3$	0	19.0
2	O-$B(OSiMe_3)_2$	0	9.0
3	N-imidazole	0	6.9
4	O-$P(O)(OSiMe_3)_2$	0	2.1[e]
	TMS-O-NO_2 - Proposed Active Species		-1.3
5	O-SO_2Me	79	-2.6
6	O-SO_2-O-$SiMe_3$	89 (81)[d]	-3.0[e]
7	Cl	92 (86)[d]	-8.0
8	O-SO_2CF_3	87 (43)[d]	-14.7

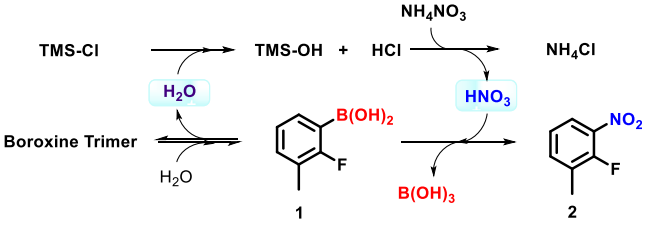
[a]Reaction and conditions as shown in Scheme 1 using TMS-X. [b]Determined by ^{19}F NMR spectroscopy of crude reaction mixture. [c]From Evans *et al.*[13] in H_2O. [d]Yield in parentheses refers to reaction without H_2O additive. [e]pK_a H_3PO_4 and H_2SO_4 respectively.

We were particularly intrigued by the clear distinction in the reactivity of the silyl reagents studied (Table 1); those with a conjugate acid pK_a < HNO_3 exhibited excellent reactivity, whereas no reaction was detected for those with a conjugate acid pK_a > HNO_3. Counterintuitively, the addition of H_2O again resulted in an increased yield of desired product even when using notoriously water-sensitive reagents (entries 6–8 in Table 1).

To further interrogate the mechanism of this transformation we turned to *in situ* multinuclear CryoFree NMR spectroscopy for continuous monitoring of reaction progress.[14−17] This technique allowed monitoring of boronic acid **1a** and nitrated product **2a** using ^{19}F NMR and simultaneous monitoring of TMS-Cl consumption using ^{1}H NMR. Because of the heterogeneous nature of the reaction mixture the reaction concentration was significantly reduced to prevent mass-transfer-limited kinetics.

These studies rapidly revealed several interesting mechanistic features of this reaction (Figure 1 and Scheme 2). Under standard reaction conditions, in the absence of H_2O, a significant induction period (~5 h) was observed. During induction, the boronic acid starting material undergoes condensation to the boroxine trimer and TMS-Cl is concurrently hydrolyzed to TMS-OH. Interestingly, nitration to form product **2** does not initiate until TMS-Cl has been consumed.

Scheme 2. Proposed Mechanism of Nitration with HNO_3 as Reactive Species



In contrast, inclusion of H_2O in the system instigates rapid hydrolysis of TMS-Cl, and upon complete consumption, the reaction initiates (~1 h). During reaction progress the boroxine trimer maintains a low equilibrium concentration.

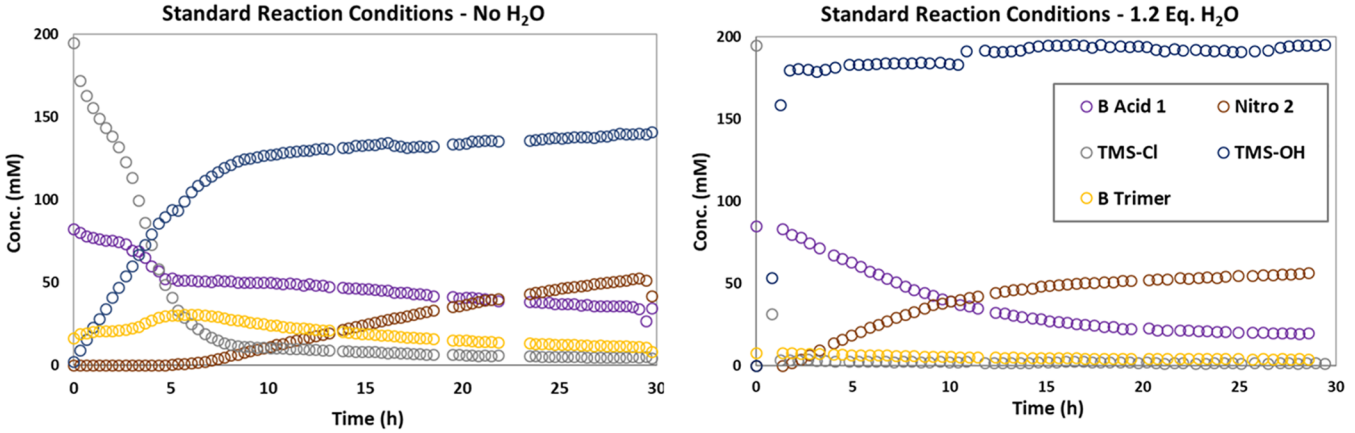


Figure 1. CryoFree NMR of Standard Reactions Conditions with and without H_2O additive. Reaction conditions: $[\mathbf{1a}]_0$ = 90 mM, $[\text{TMS-Cl}]_0$ = 198 mM, $[NH_4NO_3]$ = 270 mM, $[H_2O]$ = 108 mM. Reactions conducted in d_4-1,2-DCE at 70 °C.

https://doi.org/10.1021/acs.joc.1c00886
J. Org. Chem. XXXX, XXX, XXX−XXX

Importantly, these observations draw into question the proposal that TMS-O-NO_2 is the active reagent in this process. Both reaction systems demonstrate complete conversion of TMS-Cl to TMS-OH prior to nitration of boronic acid **1**. Alternatively, the HCl byproduct of TMS-Cl hydrolysis may protonate NH_4NO_3 to form an anhydrous source of HNO_3 to act as the nitrating agent (Scheme 2). This proposal is consistent with the observation that activated silyl species with a conjugate acid $pK_a <$ HNO_3 were efficient in this transformation. Through a series of control experiments HNO_3 was identified as the active nitrating agent (Table 2)

Table 2. Nitration of Boronic Acid 1 Using Nitric Acid[a]

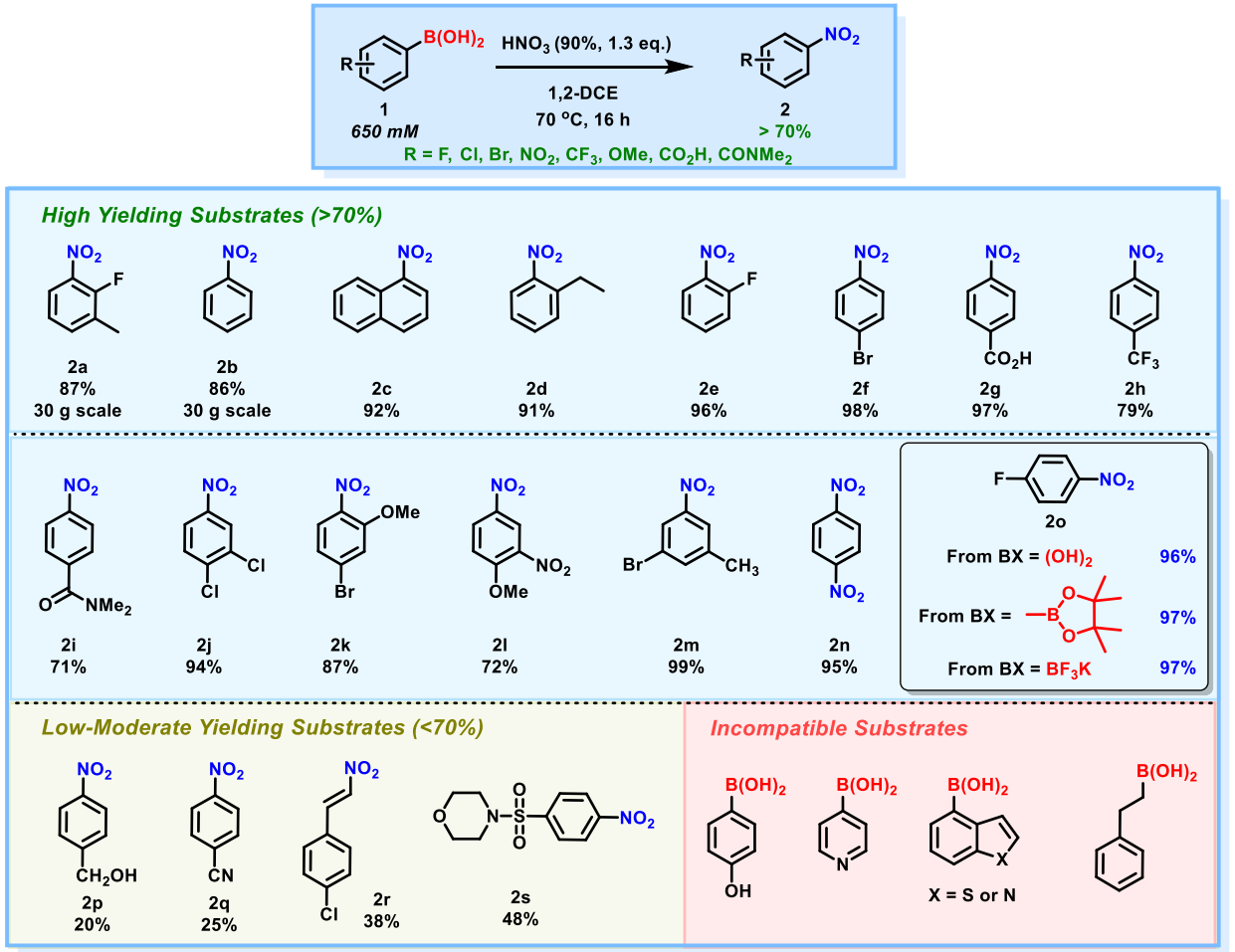
entry	NH_4NO_3 equiv	TMS-OH equiv	acid[b] (equiv)	product **2** (%)[c]
1	3	2.5	HCl (5)	43
2	3	2.5	HNO_3 (5)	89
3	3	2.5	HNO_3 (2)	89
4	3	0	HNO_3 (2)	88
5	**0**	**0**	**HNO_3 (2)**	**85**

[a]Reaction and conditions as shown in Scheme 1. [b]HCl (37% Aq.) and HNO_3(90%, fuming) were used. [c]Determined by ^{19}F NMR spectroscopy of crude reaction mixture.

Intrigued by the generality of this approach to access nitrated species from boronic acids, we subjected a series of aryl boronic acids to the optimized reaction conditions (Scheme 3). Despite the apparently harsh reaction conditions, we were pleased to demonstrate that a variety of functional groups were well tolerated under reaction conditions (Scheme 3). Alkyl/halo substituted aryl boronic acids were converted cleanly to the corresponding nitroaromatics in good to excellent yield (**2a**−**2f**). Aryl boronic acids containing carboxyl (**2g**), trifluoromethyl (**2h**), and tertiary amide (**2l**) functionalities as well as disubstituted species (**2m**−**2p**, including nitro and methyoxy) also undergo efficient HNO_3-mediated *ipso* substitution. Double *ipso* substitution of benzene-1,4-diboronic acid to 1,4-dinitrobenzene was also achieved in high yield (**2q**). Furthermore, it was demonstrated that this methodology could be utilized for nitration of boronic acid pinacol ester and trifluoroborate salt substrates in identical yields to the corresponding boronic acid (**2r**). It should be noted that substrates containing functionalities that undergo facile oxidation suffer from low yields (**2s** and **2t**) or are incompatible with reaction conditions. We were pleased to demonstrate that a vinyl boronic acid (**2u**) could also undergo this transformation albeit in lower yield. Heteroaryl boronic acids were not suitable substrates for this process.

Importantly, this process is not only highly yielding but, in many cases, also provides high-purity crude material (>97 wt %), and therefore, for many applications further purification is not required (see the Supporting Information). We were also able to demonstrate the scalability of this process conducting

Scheme 3. Substrate Scope for HNO_3-Mediated Nitration of Boronic Acids



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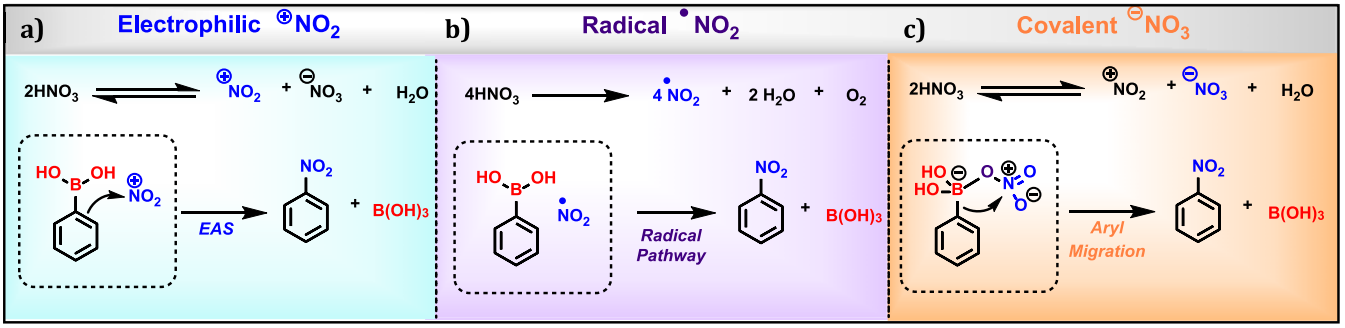

Figure 2. Plausible reaction mechanisms for HNO_3-mediated nitration of boronic acids.

ipso nitration of boronic acids **1a** and **1b** on 30 g scale in good and reproducible yield.

It should be noted that prior to scaling this process that appropriate safety testing and hazard evaluation should be conducted for the appropriate substrate and that accurate volumetric titration should be used to evaluate the concentration of HNO_3 (see the Supporting Information). These safety considerations are the subject of a concurrent report from our laboratories.[18]

We next sought to investigate possible mechanistic pathways for this synthetically useful transformation and primarily considered three possibilities. In analogy to the mechanism proposed by Olah *et al.* using TMS-Cl, HNO_3 may generate an active electrophilic nitronium species and form product via electrophilic aromatic substitution (EAS, Figure 2a).[8,9] Alternatively, HNO_3 may act as a source of the highly reactive $^{\bullet}NO_2$ radical and react in a radical substitution with the boronic acid substrate (Figure 2b). Finally, nitrate (NO_3^-) formed from HNO_3 dissociation may react with the boronic acid to form a boronate which undergoes aryl migration in the product-forming step (Figure 2c).

The former was ruled out through the use of nitronium tetrafluoroborate as mechanistic probe to interrogate the efficacy of the reactive nitronium cation (NO_2^+) in this process. Under standard reaction conditions no product formation was observed (entry 2, Table 3). These results imply that the nitronium cation is unlikely to be the active species in this transformation and that electrophilic substitution is not the productive pathway. To investigate the possibility of a radical-mediated transformation, TEMPO and hydroquinone were used as radical scavengers and resulted in complete inhibition of the desired reaction (entries 3 and 4 in Table 3). Inactivation of this process by radical scavengers strongly implies the presence and importance of these species in the product mechanistic pathway. Several radical mechanisms have been proposed previously for analogous nitration of aryl/vinyl boronic and carboxylic acids, including direct radical substitution[19,20] and via H atom abstraction to form benzoic nitric anhydrides followed by fragmentation.[21]

Table 3. Mechanistic Probes[a]

entry	reagent (equiv)	additive (equiv)	SM 1 (equiv)[b]	product 2 (%)[b]
1	HNO_3 (2)	none	0	87
2	NO_2BF_4 (2)	none	79	0
3	HNO_3 (2)	TEMPO (2.2)	61	0
4	HNO_3 (2)	hydroquinone (2.2)	68	4

[a]Reaction and conditions as shown in Scheme 3 using boronic acid **1a**. [b]Determined by ^{19}F NMR of crude reaction mixture.

To gain further insight into the mechanism of this transformation, we considered the reaction of boronate ester **1r-b** and trifluoroborate **1r-c** utilizing CryoFree NMR spectroscopy for continuous *in situ* monitoring of the reaction progress (Figure 3a–c). This study demonstrated the absence of any observable intermediates during nitration of these substrates, and the increased reaction rate for trifluoroborate **1r-c** precluded product formation *via* the boronic acid intermediate **1r-a**. While direct nitration of pinacol ester **1r-b** may occur via a nitrate intermediate (Figure 2c), trifluoroborate salt **1r-c** is unable to form such an intermediate. Furthermore, the distinct absence of any observable intermediates by both ^{19}F and ^{11}B NMR spectroscopy render sequential formation of product *via* a boronate species highly unlikely (see the Supporting Information for ^{11}B spectra). ^{11}B NMR spectroscopy also demonstrated that consumption of the starting material was accompanied solely by formation of boric acid. These studies indicate the likely productive mechanistic pathway occurs *via* radical substitution.

CryoFree NMR spectroscopy was also employed to gain insight into the reaction progress kinetics.[22,23] Variable time normalization analysis (VTNA)[24−27] was used to interrogate the order in boronic acid SM **1a** and nitric acid. These studies revealed that the reaction is negative order in boronic acid **1**, and VTNA indicated a reaction order of −0.5 (Figure 4a). This indicates reversible formation of an inactive species and is consistent with the observation that the reaction rate *increases* as boronic acid is consumed. In contrast to the TMS-Cl-mediated process (Scheme 2) no dimerized species were observable by *in situ* ^{19}F NMR. The addition of H_2O (0.5 equiv) with the aim of inhibiting a condensation-induced dimerization had no effect on the reaction rate, and the order in boronic acid remained −0.5, indicating that the inactive species was not a result of self-condensation of the boronic acid. This was corroborated using boronic acid pinacol ester **1r-b**; VTNA revealed the order in the pinacol ester **1r-b** was also −0.5, where condensation-induced dimerization is not possible (see the Supporting Information).

While less definitive, VTNA of the order in HNO_3 indicated that the order in HNO_3 was ∼2.5−4.0 (Figure 4b, order shown = 3.0). While HNO_3 is involved in nonproductive equilibrium processes that may affect the observed order, we believe that the higher order in HNO_3 implies that multiple HNO_3 entities are involved in the rate-determining step (RDS) of this process. As such, the RDS is likely generation of the highly reactive $^{\bullet}NO_2$ resulting from the autocatalytic dissociation of HNO_3 (Figure 4b).[28−32] The less definitive reaction order in

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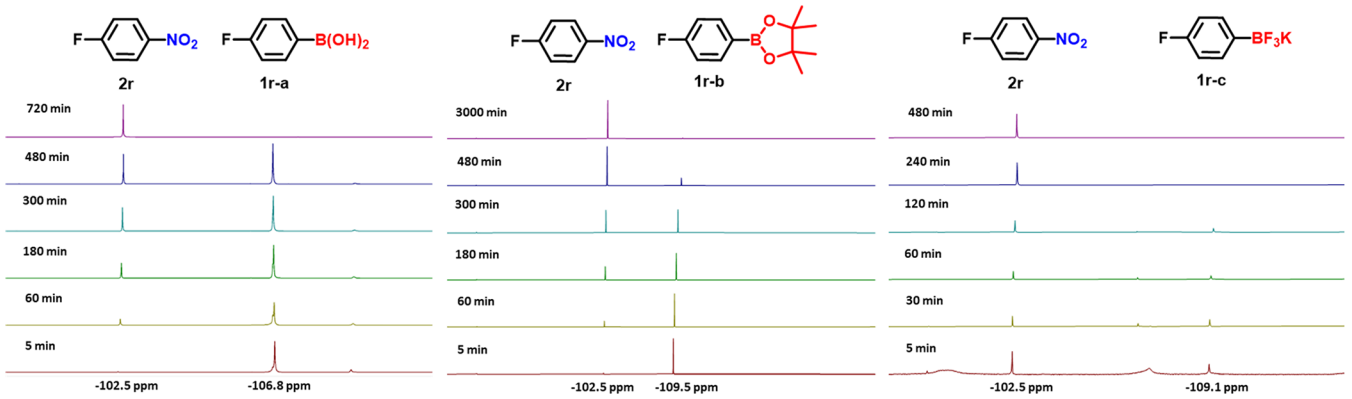

Figure 3. Comparison of *in situ* CryoFree ^{19}F NMR analysis HNO_3-mediated nitration of (a) boronic acid (**1r-a**), boronate ester (**1r-b**), and trifluoroboronate salt (**1r-c**).

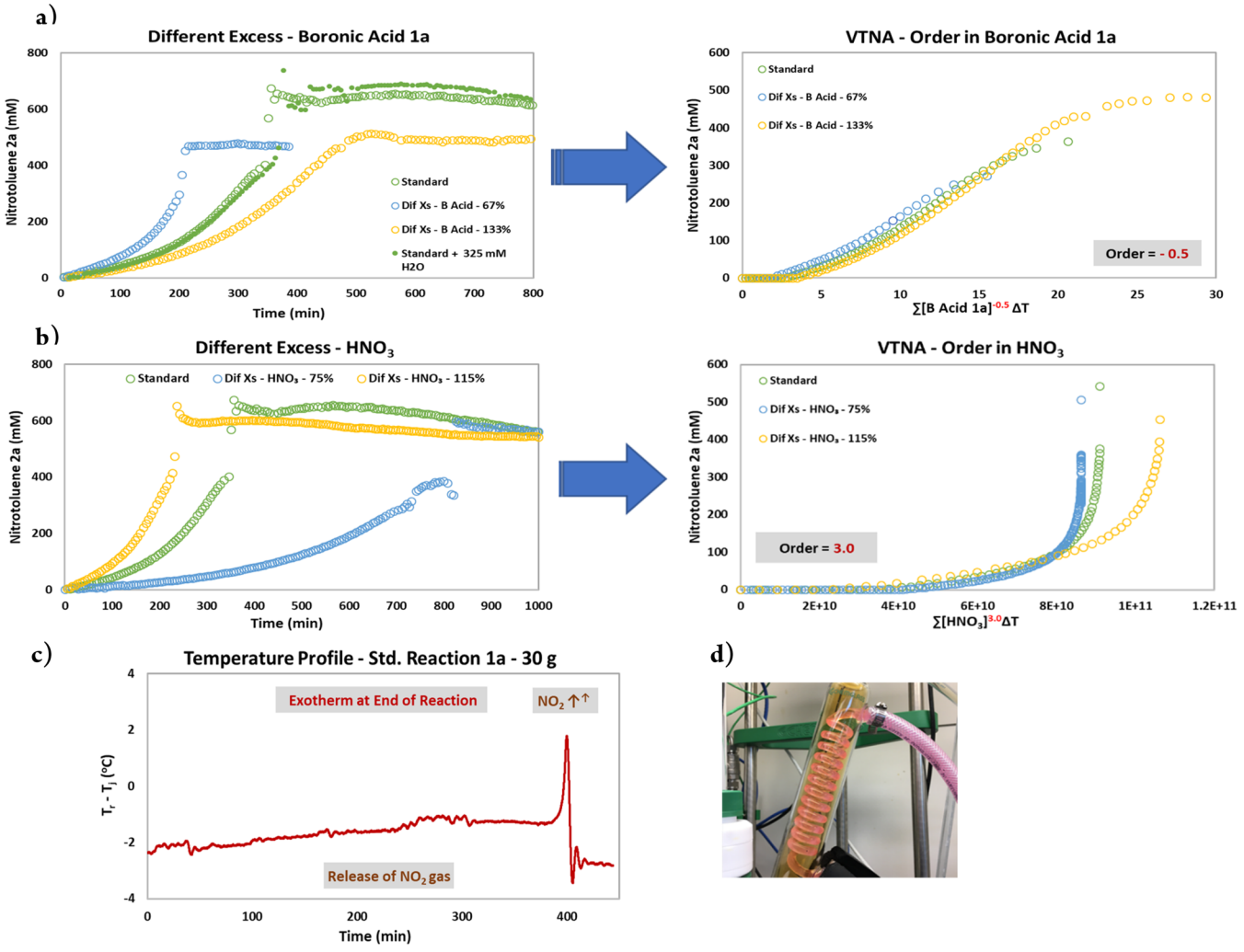

Figure 4. Reaction progress kinetics and variable time normalization for (a) different excess boronic acid and (b) different excess HNO_3. (c) Temperature profile of standard reaction. (d) Release of NO_x(g) upon reaction completion.

HNO_3 is a result of reversible and nonproductive interaction of HNO_3 with the boronic acid acting to sequester HNO_3 dissociation and is in agreement with the negative order observed in boronic acid. While we have been unable to observe this species *in situ*, our kinetic studies demonstrate its presence.

The combination of negative order substrate kinetics with elevated order and autocatalytic dissociation of (HNO_3) leads to an unusual reaction profile. The overall reaction rate *increases* as the reaction proceeds with the maximal reaction rate at the end of the reaction. Importantly, it should be noted that completion of the reaction is *accompanied by a moderate but* ***significant exothermic release of brown*** NO_x ***gas*** *which*

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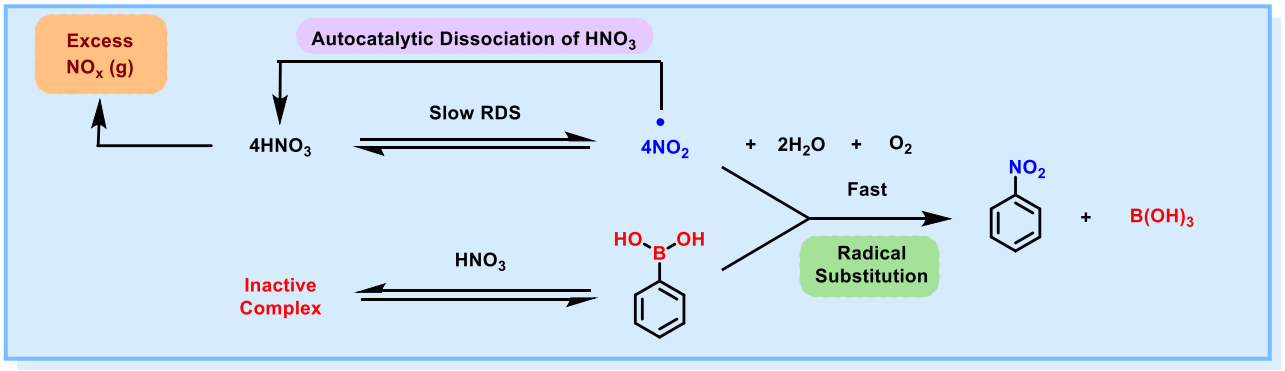
Scheme 4. Proposed Mechanism of HNO_3-Mediated Nitration of Aryl Boronic Acids



should be accounted for when considering scaling this process (Figure 4c,d).[18]

Consideration of the mechanistic and kinetic information gained from these studies allows proposal of a plausible reaction mechanism (Scheme 4). These experimental observations are consistent with slow, rate-determining dissociation of HNO_3 to produce the active $^{\bullet}NO_2$ radical which can either react with the boronic acid substrate to form the desired nitration product or catalyze further dissociation of HNO_3. As boronic acid is consumed, $^{\bullet}NO_2$ increasingly acts to catalyze further HNO_3 dissociation, accelerating the reaction rate. Upon complete consumption of substrate, excess $^{\bullet}NO_2$ promotes autocatalytic HNO_3 dissociation, ultimately resulting in evolution of excess NO_x gas.[18]

CONCLUSION

In conclusion, we have demonstrated the use of fuming HNO_3 for the highly efficient nitration of aryl boronic acids. This discovery resulted from investigations into a previously reported TMS-Cl/NH_4NO_3-mediated nitration for which we revealed HNO_3 to be the active nitrating agents.[8,9] Mechanistic and kinetic studies were utilized to interrogate the nature of the productive reaction pathway and indicate that a $^{\bullet}NO_2$ radical substitution is the likely mechanism of this synthetically useful transformation. A variety of functional groups are well-tolerated under these apparently harsh reaction conditions and the chemoselectivity of this process is exemplified by the high purity of the crude material obtained. While caution should be exerted prior to use of this methodology, we have demonstrated the scalability of this process in a safe and efficient manner.

EXPERIMENTAL SECTION

General Methods. All reactions were performed under anhydrous conditions and an atmosphere of nitrogen in pressure release vials, a 100 mL Mettler-Toledo Easymax reactor, or in a 500 mL ChemGlass reactor. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials, unless otherwise indicated. Solvents and reagents: anhydrous 1,2-dichloroethane, ethyl acetate, and heptanes were obtained commercially from Sigma-Aldrich. ^{1}H NMR spectra were recorded on a Bruker AV-400 instrument. Chemical shifts (δ_H) are quoted in parts per million (ppm), referenced to the appropriate residual solvent peak. Coupling constants (J) are reported to the nearest 0.1 Hz. All starting materials, additional reagents, solvents, and deuterated solvents for NMR spectra were obtained commercially and used without further purification.

General Procedure for HNO_3-Mediated *Ipso* Nitration of Boronic Acids. Boronic acid solid (final conc. 650 mM) was added to a pressure release vial equipped with a magnetic stirrer bar. 1,2-Dichloroethane (1 mL) was added followed by HNO_3 (90%, fuming, 1.2 equiv, 37 μL). The reaction mixtures were heated to 70 °C on a heating mantle for 16 h. After cooling to RT, the reaction mixtures were diluted with 1,2-dichloroethane (1 mL) and water (2 mL) was added. The resulting heterogeneous biphasic mixture was filtered through a syringe filter. The organic phase was then washed with sat. sodium bicarbonate (2 × 2 mL) and filtered through a thin silica plug before being concentrated *in vacuo*. For several substrates this resulted in analytically pure material. Where further purification was required, flash chromatography was conducted using EtOAc/heptanes and the desired fractions were concentrated *in vacuo* to afford the product.

*2-Fluoro-1-methyl-3-nitrobenzene (**2a**).* 2-Fluoro-3-methylboronic acid (100 mg, 0.65 mmol) was employed to afford product as a low melting white solid (88 mg, 0.57 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.82 (ddd, J = 8.5, 6.9, 1.8 Hz, 1H), 7.52−7.43 (m, 1H), 7.17 (td, J = 8.5, 2.7 Hz, 1H), 2.37 (d, J = 2.7 Hz, 3H). ^{19}F NMR (376 MHz, CDCl3): δ −122.45. Spectral data are in agreement with the literature.[17]

*Nitrobenzene (**2b**).* Phenylboronic acid (80 mg, 0.65 mmol) was employed to afford product as a light green oil (69 mg, 0.56 mmol, 86%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.25 (d, J = 6.4 Hz, 2H), 7.72 (t, J = 7.4 Hz, 2H), 7.57 (s, 1H). Spectral data are in agreement with the literature.[33]

*1-Nitronapthalene (**2c**).* Napthalene -1-boronic acid (112 mg, 0.65 mmol) was employed. Flash chromatography (eluent: 5−25% EtOAc/heptanes) was conducted, and the appropriate fractions were concentrated *in vacuo* to afford product as a yellow solid (92 mg, 0.53 mmol, 92%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.59 (d, J = 7.7 Hz, 1H), 8.26 (dd, J = 7.6, 1.2 Hz, 1H), 8.15 (d, J = 9.3 Hz, 1H), 7.99 (d, J = 7.7 Hz, 1H), 7.75 (t, J = 8.5 Hz, 1H), 7.68−7.62 (m, 1H), 7.57 (t, J = 7.9 Hz, 1H). Spectral data are in agreement with the literature.[34]

*1-Ethyl-2-nitrobenzene (**2d**).* (2-Ethylphenyl)boronic acid (98 mg, 0.65 mmol) was employed to afford product as light yellow solid (89 mg, 0.59 mmol, 91%). ^{1}H NMR (400 MHz, CDCl3): δ 7.89 (dd, J = 8.1, 1.4 Hz, 1H), 7.54 (td, J = 7.6, 1.4 Hz, 1H), 7.43−7.30 (m, 2H), 2.94 (q, J = 7.5 Hz, 2H), 1.31 (t, J = 7.5 Hz, 3H). Spectral data are in agreement with the literature.[34]

*1-Fluoro-2-nitrobenzene (**2e**).* 2-Fluorophenylboronic acid (91 mg, 0.65 mmol) was employed to afford product as light green liquid (88 mg, 0.62 mmol, 96%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23−7.32 (m, 2H), 7.60−7.63 (m, 1H), 8.04−8.07 (m, 1H). Spectral data are in agreement with the literature.[34]

*1-Bromo-4-nitrobenzene (**2f**).* 4-Bromophenylboronic acid (105 mg, 0.51 mmol) was employed to afford product as white solid (100 mg, 0.50 mmol, 98%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.12 (d, J = 7.8 Hz, 2H), 7.70 (d, J = 7.9 Hz, 2H). Spectral data are in agreement with the literature.[36]

*4-Nitrobenzoic Acid (**2g**).* 4-Carboxyphenylboronic acid (108 mg, 0.65 mmol) was employed to afford product as an off-white solid by direct filtration of the reaction mixture followed by washing with dichloroethane (105 mg, 0.63 mmol, 97%). ^{1}H NMR (400 MHz,

https://doi.org/10.1021/acs.joc.1c00886
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$CDCl_3$): δ 8.35 (d, J = 9.1 Hz, 2H), 8.29 (d, J = 9.2 Hz, 2H). Spectral data are in agreement with the literature.[37]

*4-Benzonitrotrifluoride (**2h**).* 4-(trifluoromethyl)phenylboronic acid (124 mg, 0.65 mmol) was employed to afford product as an off-white solid (98 mg, 0.51 mmol, 79%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.46−8.19 (m, 2H), 7.94−7.68 (m, 2H). Spectral data are in agreement with the literature.[38]

*N,N-Dimethyl-4-nitrobenzamide (**2i**).* (4-(Dimethylcarbamoyl)-phenyl)boronic acid (125 mg, 0.65 mmol) was employed. Flash chromatography (eluent: 5−50% EtOAc/heptanes) was conducted, and the appropriate fractions were concentrated *in vacuo* to afford product as a yellow solid (89 mg, 0.46 mmol, 71%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.29 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.8 Hz, 2H), 3.17 (d, J = 11.6 Hz, 6H), 2.99 (d, J = 6.6 Hz, 6H). Spectral data are in agreement with the literature.[39]

*1,2-Chloro-4-nitrobenzene (**2j**).* 3,4-Dichlorophenylboronic acid (123 mg, 0.65 mmol) was employed to afford product as light yellow oil (117 mg, 0.61 mmol, 94%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (d, J = 2.6 Hz, 1H), 8.11 (dd, J = 8.8, 2.6 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H). Spectral data are in agreement with the literature.[40]

*4-Bromo-2-methoxy-1-nitrobenzene (**2k**).* 4-Bromo-2-methoxy-phenylboronic acid (231 mg, 0.65 mmol) was employed to afford product as an off-white solid (130 mg, 0.56 mmol, 87%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77 (d, J = 8.6 Hz, 1H), 7.27 (d, J = 8.6 Hz, 1H), 7.20 (dd, J = 8.6, 1.9 Hz, 1H), 3.99 (s, 3H). Spectral data are in agreement with the literature.[41]

*1-Methoxy-2,4-dinitrobenzene (**2l**).* 4-Methoxyl-3-nitrophenylboronic acid (128 mg, 0.65 mmol) was employed. Flash chromatography (eluent: 5−25% EtOAc/heptanes) was conducted, and the appropriate fractions were concentrated *in vacuo* to afford product as an off-white solid (93 mg, 0.47 mmol, 72%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.76 (d, J = 2.8 Hz, 1H), 8.47 (dd, J = 9.3, 2.8 Hz, 1H), 7.25 (d, J = 9.3 Hz, 1H), 4.12 (s, 3H). Spectral data are in agreement with the literature.[35]

*1-Bromo-3-methyl-5-nitrobenzene (**2m**).* 3-Bromo-5-methylphenylboronic acid (100 mg, 0.44 mmol) was employed to afford product as white solid (95 mg, 0.44 mmol, 99%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.19 (br s, 1H), 7.99 (br s, 1H), 7.67 (br s, 1H), 2.47 (s, 3H). Spectral data are in agreement with the literature.[42]

*1,4-Dinitrobenzene (**2n**).* 1,4-benzenedibronic acid (100 mg, 0.58 mmol) was employed with HNO_3 (2.6 equiv) to afford product as pale yellow solid (92 mg, 0.55 mmol, 95%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.44 (s, 4H). Spectral data are in agreement with the literature.[43]

*4-Fluoronitrobenzene (**2o**).* 4-Fluorophenylboronic acid (90 mg, 0.65 mmol), 4-fluorophenylboronic acid pinacol ester (145 mg, 0.65 mmol), or potassium 4-fluorophenltricluoroborate (130 mg, 0.65 mmol) was employed to afford product as a colorless oil in 96−97% yield. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.28 (dd, J = 9.2, 4.7 Hz, 2H), 7.23 (dd, J = 9.3, 7.7 Hz, 2H). Spectral data are in agreement with the literature.[44]

*(4-Nitrophenyl)methanol (**2p**).* (4-(Hydroxymethyl)phenyl)-boronic acid (99 mg, 0.65 mmol) was employed. Flash chromatography (eluent: 5−50% EtOAc/heptanes) was conducted, and the appropriate fractions were concentrated *in vacuo* to afford product as an off-white solid (20 mg, 0.013 mmol, 20%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.23 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 4.89 (s, 2H). Spectral data are in agreement with the literature.[45]

*4-Nitrobenzonitrile (**2q**).* 4-Cyanophenylboronic acid (105 mg, 0.68 mmol) was employed to provide the product as white solid (25 mg, 0.17 mmol, 25%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.37 (dt, J = 9.0 Hz, 2H), 7.90 (dt, J = 9.0 Hz, 2H). Spectral data are in agreement with the literature.[46]

*Chloro-4-(2-nitrovinyl)benzene (**2r**).* (4-Chlorostyryl)boronic acid (176 mg, 0.65 mmol) was employed. Flash chromatography (eluent: 5−50% EtOAc/heptanes) was conducted, and the appropriate fractions were concentrated *in vacuo* to afford product as a yellow solid (45 mg, 0.025 mmol, 38%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (d, J = 13.7 Hz, 1H), 7.58 (d, J = 13.7 Hz, 1H), 4.12−3.59 (m, 4H), 7.54−42 (m, 4H). Spectral data are in agreement with the literature.[33]

*4-((4-Nitrophenyl)sulfonyl)morpholine (**2s**).* (4-(Morpholinosulfonyl)phenyl)boronic acid (128 mg, 0.65 mmol) was employed to afford product as an off-white solid (85 mg, 0.31 mmol, 48%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.43 (d, J = 8.8 Hz, 2H), 7.97 (d, J = 8.8 Hz, 2H), 4.12−3.59 (m, 4H), 3.32−2.85 (m, 4H). Spectral data are in agreement with the literature.[47]

*5-Chloro-2-fluoro-1-methyl-3-nitrobenzene (**3**).* 5-Chloro-2-fluoro-3-methylphenylboronic acid (500 mg, 2.7 mmol), ammonium nitrate (3 equiv, 640 mg, 8.0 mmol) were loaded into a pressure release vial (20 mL) and 1,2-dichloroethane (10 mL) added followed by H_2O (60 μL, 1.2 equiv, 3.2 mmol). The reaction mixture was heated to 70 °C for 16 h on a heating mantle before being allowed to cool to RT. The organic phase was diluted with 1,2-dichloroethane (10 mL) and washed with NaOH (1 M, 10 mL) and water (10 mL) and concentrated *in vacuo* to afford crude oil. Crude product was purified by flash chromatography (eluent: 100% heptanes) to afford product as a light yellow solid (90 mg, 18%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (ddd, J = 6.0, 2.7, 0.8 Hz, 1H), 7.49 (ddd, J = 6.0, 2.7, 0.8 Hz, 1H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −128.82. ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$): δ 152.9, 150.3, 135.3 (d, J = 5.3 Hz), 129.2 (d, J = 18.2 Hz), 127.9 (d, J = 4.7 Hz), 122.3 (d, J = 2.8 Hz), 13.7 (d, J = 4.0 Hz). HRMS (m/z + ES): Found 188.9996 (M^+ $C_7H_5ClFNO_2$ Requires: 188.9992).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.1c00886.

Full details of CryoFree NMR spectroscopy experiments including all raw data used in kinetic analysis and variable time normalization (PDF)

Protocol for scale up of HNO_3-mediated nitration process including description of HNO_3 titration (PDF)

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https://doi.org/10.1021/acs.joc.1c00886
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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The authors acknowledge highly stimulating and insightful discussions with Michal Achmatowicz (formerly of Amgen) during the progression of this work.

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