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Recent advances in *ipso*-nitration reactions

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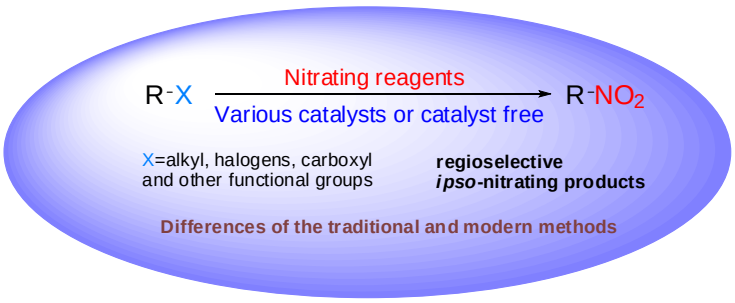
Abstract

In the present review the various types of *ipso*-nitration reactions, in particular those advances in *ipso*-nitration reactions that have been reported since the beginning of this century (i.e., from 2000-2015) are discussed. The review highlights the recent developments of the *ipso*-nitration reactions, a variety of the differences between traditional and modern methods for performing *ipso*-nitration reactions, as well as the most novel approaches to performing these reactions. In addition, the proposed mechanisms of *ipso*-nitration reactions are discussed.



Keywords: *ipso*-Nitration, calixarenes, arylboronic acids

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1. Introduction

The nitration[1,2] of organic compounds (aliphatic, aromatic, heterocyclic, and others) is one of the key reactions of both organic synthesis and organic chemistry in general.[3,4] Moreover, nitro compounds are actually used by pharmacists and medicinal chemists in their investigations, most commonly as building blocks, lead compounds, and intermediates for drug discovery efforts.[5-7] The functional groups (methyl, ethyl, propyl, butyl, halogens, hydroxyl, carbonyl, carboxyl, and others) that are attached to aliphatic chains or to aromatic rings can be converted to the nitro (NO_2) group in a nitrating mixture, and this type of nitration is called *ipso*-nitration.[8-10] A key difference between ordinary nitration and *ipso*-nitration is described in Figure 1.

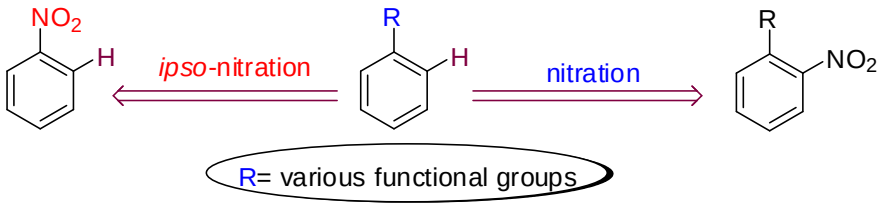


Figure 1. The key difference between nitration and *ipso*-nitration.

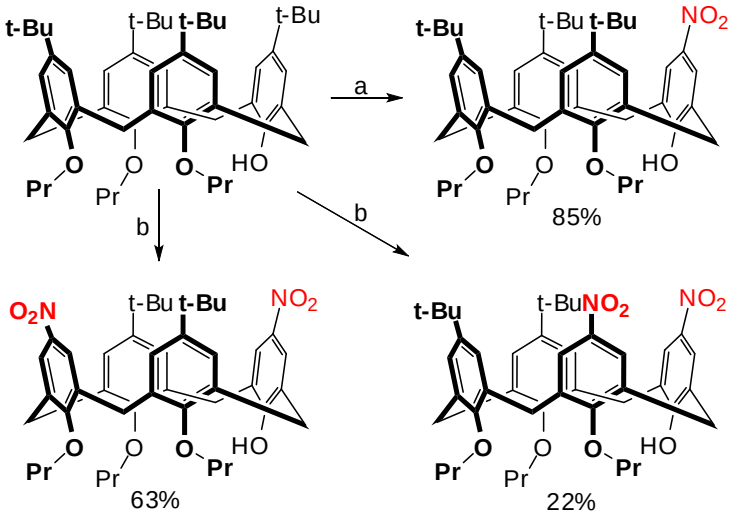
The *ipso*-nitration of organic compounds was initially developed with the use of nitric acid (HNO_3) or nitrating mixtures (HNO_3/AcOH or HNO_3/H_2SO_4), approaches which are now referred to as traditional or classical methods. However, there are several problems with these traditional methods when it comes to forming regioselective nitro products. However, in spite of these problems, researchers have nonetheless tried, in the hope of obtaining selective nitro products, to refine these nitrating mixtures by increasing or decreasing the levels of nitric acid in the mixtures, by using catalysts or non-catalytic methods and various metal salts in making the mixtures, and by bypassing poor regioselectivity, low yields, and the formation of undesired by-products.

In recent years, several literature investigations have focused on such reported developments of *ipso*-nitration reactions. In this review, we provide a general overview of recent advances and developments in *ipso*-nitration reactions that have been reported since the beginning of this century *(i.e.*, in the period 2000-2015).

2. Developments in traditional *ipso*-nitration

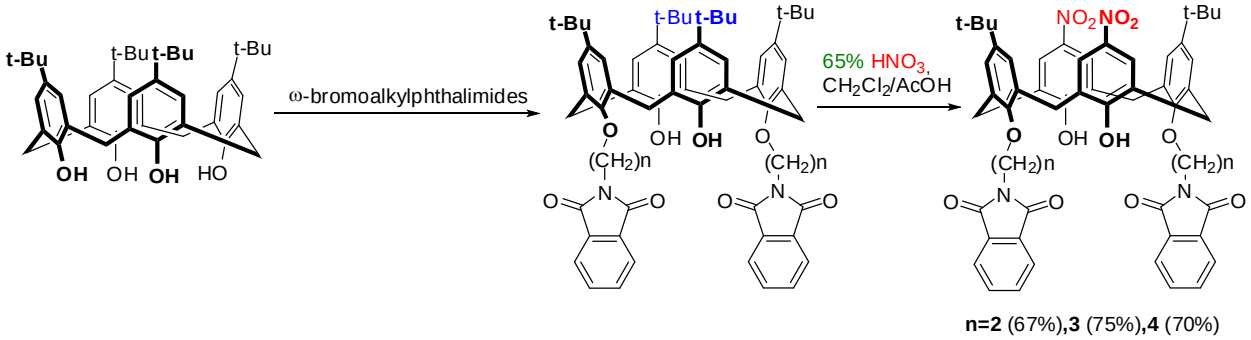
2.1 *ipso*-Nitration of macromolecules (calixarenes)

The most commonly used *ipso*-nitration reaction is one that is widely used in calixarene chemistry.[11-13] If *tert*-butylcalix[4]arene is reacted with 63% HNO_3 in a mixture of dichloromethane (DCM) and glacial acetic acid at -15 °C, it was observed the formation of a selective mono *ipso*-nitrated compound in 85% yield (Scheme 1). In addition, if acetic anhydride is used instead of glacial acetic acid at -10 °C, *tert*-butylcalix[4]arene generates dinitro products.[14]



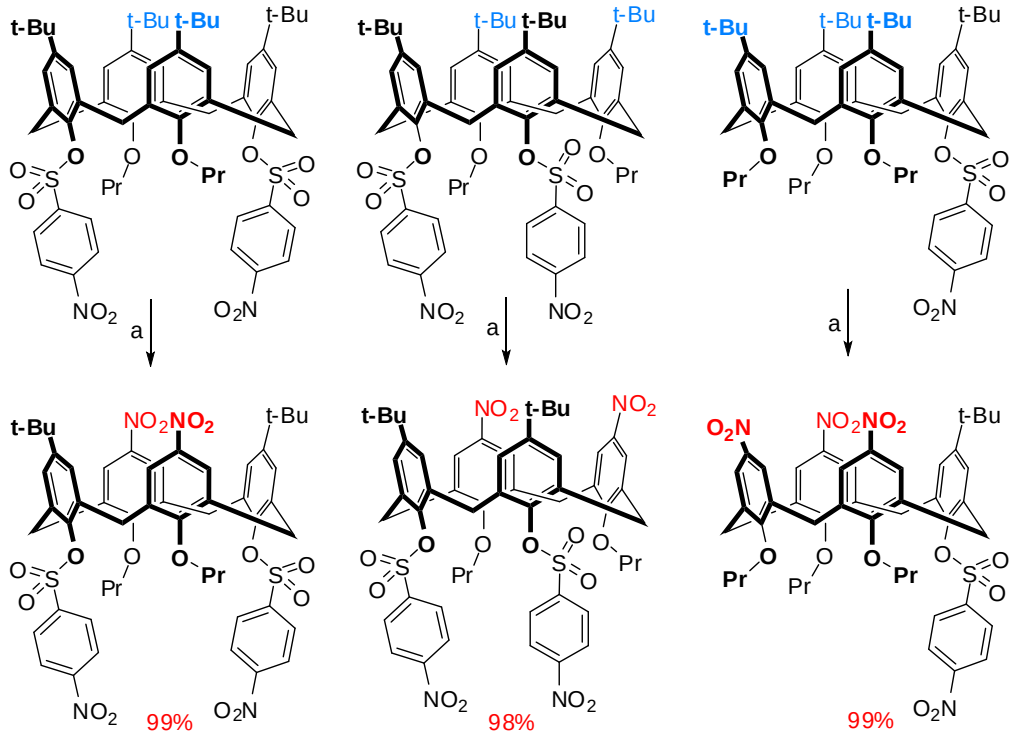
Scheme 1. *ipso*-Nitration of *tert*-butylcalix[4]arene.

In 2005, Böhmer and colleagues reported the selective *ipso*-nitration of a *tert*-butylcalix[4]arene,[15] following the by *O*-alkylation with ω-bromoalkylphthalimides or ω-bromonitriles (for *n* = 2 *N*-(β-hydroxyethylphthalimide, triphenylphosphine/Cs_2CO_3) to obtain 5,17-di-*tert*-butyl-11,23-dinitro-26,28-diphthalimidoethoxycalix[4]arenes and the corresponding derivatives for *n* = 2 or 4 (*n* = 2,3,4) in good yields (67-75%) (Scheme 2). In this approach, 65% HNO_3 in DCM/acetic acid was used as the nitrating agent.



Scheme 2. Selective *ipso*-nitration of *tert*-butylcalix[4]arene.

Hudecek *et al*. investigated a simple regioselective *ipso*-nitration of the nosyl-substituted calix[4]arenes.[16] In their approach, they used 100% HNO_3 in an AcOH/DCM mixture at room temperature. In the resulting *ipso*-nitration of calix[4]arenes, selective *ipso* products were formed in yields of 99, 98, and 99%, respectively (Scheme 3). In addition, the ^1H NMR spectrum of 11,23-di-*tert*-butyl-5,17-dinitro-25,27-bis(*p*-nitrobenzenesulfonyloxy)-26,28-dipropoxycalix[4]arene (cone) clearly proves the regioselective formation of a distal *p*-nitro-substituted product, where both NO_2 groups are on the alkyloxylated rings.



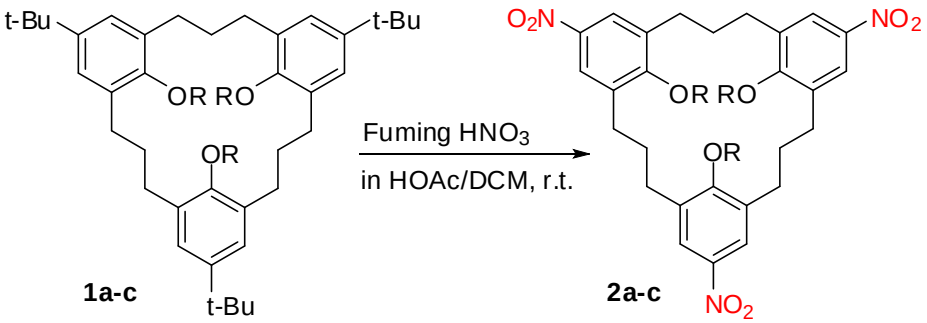
Scheme 3. Regioselective *ipso*-nitration of calix[4]arenes.

Another selective *ipso*-nitration of calix[6]azacryptands involving tosyl, nosyl, and acetyl fragments, was also recently presented.[17] In experiments following the traditional method, calix[6]arene derivatives were dissolved in DCM and then a mixture of fuming nitric acid/glacial acetic acid (1:1) at 0 °C was added, which finally resulted in the production of the selective nitro products in high yields (Scheme 4). The authors of this investigation utilized a classical approach to achieve an *ipso*-nitration reaction; however, they also observed that the electronic connection between the two rims is not the only factor that influences the selectivity. Rather, they noted that the conformational properties of the small rim part can also orient the selectivity of the *ipso*-nitration and influence the reaction rate. In order to achieve hexa-substitution, the reagent to substrate ratio (acid/calix) had to be increased ten-fold above that of the optimization condition.[18]

Scheme 4. *ipso*-Nitration reactions of *N*-sulfonamido and *N*-acetamido calix[6]arenes.

Yamato *et al*. investigated the *ipso*-nitration of [3$_n$]metacyclophanes (MCPs) with "cone" and "partial-cone" conformations.[19] The introduction of three nitro groups through the direct replacement of *tert*-butyl groups via *ipso*-nitration of 6,15,24-tri-*tert*-butyl-9,18,27-trimethoxy[3.3.3]MCP (**1a**) (Table 1) with fuming HNO_3 for 0.5 h at room temperature formed 9,18,27-trimethoxy-6,15,24-trinitro[3.3.3]MCP (**2a**) in a 95% yield. In contrast, if the *ipso*-nitration of *O*-(*N*,*N*-diethylacetamide) derivative (**1b**) was attempted under these conditions, no reaction was observed.

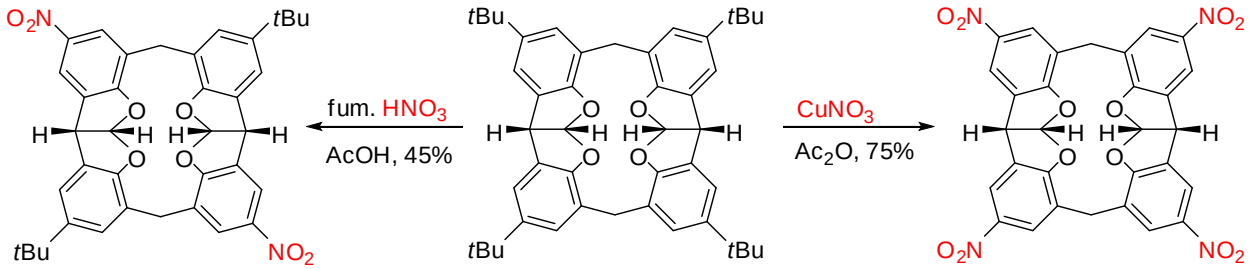
Table 1. *ipso*-Nitration of **1c**



Entry	Nitration reagents	Time (h)	Products (Yield %)		
			3c	**4c**	**2c**
1	$CuNO_3/Ac_2O$	24	0	86	14
2	Fuming HNO_3/HOAc	0.5	0	75	25
3	Fuming HNO_3/HOAc	1	0	52	48
4	Fuming HNO_3/HOAc	2	0	0	100

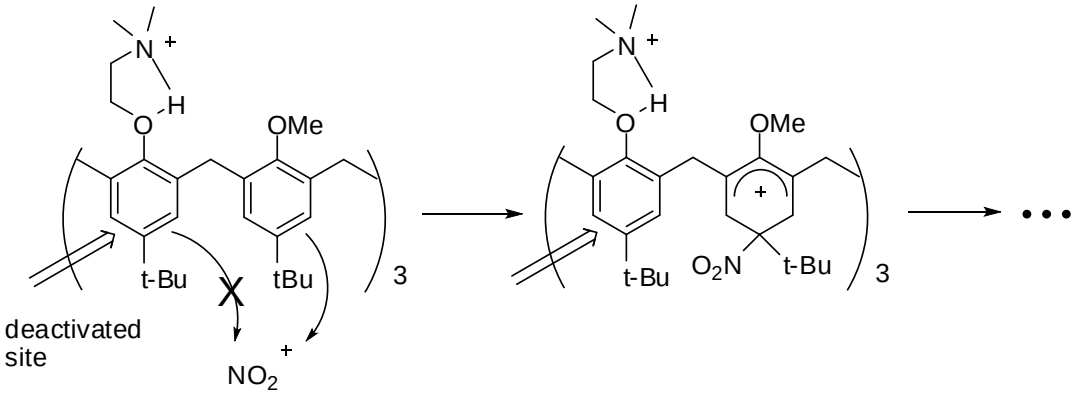
In addition, they used copper(II)nitrate in an acetic anhydride solution for the screening of cone-6,15,24-tri-*tert*-butyl-9,18,27-tris[(ethoxycarbonyl)methoxy]-[3.3.3]MCP (cone-**1c**). After 24 h, they obtained a mixture of the dinitration product cone-**4c** and the trinitration product cone-**2c** in 86 and 14% yields, respectively (Table 1). The mononitration product (cone-**3c**) was not obtained under any of the conditions they tested.[19]

The selective *ipso*-nitration of *tert*-butyl[2.2.2]MCP through the use of fuming nitric acid or copper nitrate was reported in 2011 by Sawada *et al*.[20] As detailed in that report, when 2,2',9,9'-tetra-*t*-butyl-5a,10b-dihydro-[1,1](4,7)benzofuro[2,3-*b*]benzofuranophane interacted with fuming nitric acid, it was observed formation of selective dinitro product, if copper nitrate was used as nitrating agent, it was obtained tetranitro compound in 75% yield (Scheme 5). With regard to selective dinitro products, a ^{1}H NMR signal for *tert*-butyl protons was observed at 1.26 ppm with an intensity ratio of 18 protons. This indicates that two *tert*-butyl groups are substituted by two nitro groups.



Scheme 5. *ipso*-Nitration of *tert*-butyl[2.2.2]MCP.

Obviously, the nature of the various substituents (R) plays a key role in the determination of the nitration positions in the *ipso*-nitration of calixarenes in traditional methods, when used nitric acid as nitrating agent. Redon *et al*. explained a possible mechanism for this in their report.[21] In brief, the mechanism is related to the presence of a protonable site at the γ-position of the phenolic oxygen atom. Due to the basic character of calixarenes, all of their nitrogenous arms must be protonated under strongly acidic reaction conditions. This protonated nitrogen group is in an ideal position for hydrogen bonding to the phenolic oxygen atom, and thus deactivating the whole aromatic cycle toward electrophilic attack by removing the electron density (Scheme 6).



Scheme 6. Proposed mechanism for the selective *ipso*-nitration with calix[6]arenes.

In general, a more suitable condition or nitrating agent for the conversion of calixarenes in good yields into nitrocalixarenes is to use nitric acid in acetic acid at lower (*i.e.* 0-5 °C) temperatures. Chawla and co-

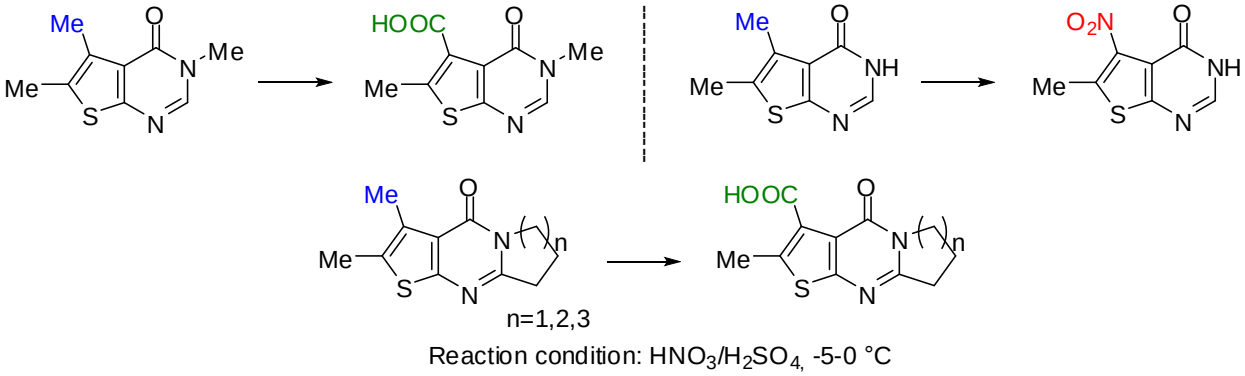
workers[22] showed this by applying a comparative analysis to a variety of reaction conditions (Table 2). As indicated, *ipso*-nitration with acetic anhydride/nitric acid ensures a good yield of *p*-nitrocalix[n]arenes; however, a similar reaction with *p-tert*-butylcalix[n]arenes leads to a mixture from which nitrocalix[n]arenes can only be separated in lower yields due to acetylation. Similarly, the use of CAN/acetic acid also produces lower yields due to the oxidation of substrates.

Table 2. *ipso*-Nitration of *p-tert*-butylcalix[*n*]arenes using different nitrating reagents

Calix[*n*]arene	Nitrating mixture	Temperature (°C)	Time (h)	Yield (%)
Calix[4]	CH_3COOH/HNO_3	0–5	4	76
Calix[6]	CH_3COOH/HNO_3	0–5	4	79
Calix[8]	CH_3COOH/HNO_3	0–5	4	70
Calix[4]	Ac_2O/HNO_3	0	5	75
Calix[6]	Ac_2O/HNO_3	0	5	78
Calix[8]	Ac_2O/HNO_3	0	5	76
Calix[4]	CAN/acetone/AcOH	Reflux	8	50
Calix[6]	CAN/acetone/AcOH	Reflux	8	55
Calix[8]	CAN/acetone/AcOH	Reflux	8	55

2.2 *ipso*-Nitration of heterocycles

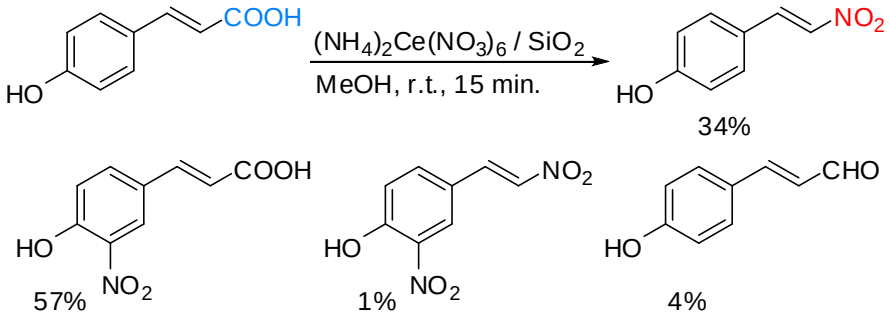
Our own research group reported for the first time that, depending on the presence of substituents in positions 2 and 3 of the pyrimidine and thiophene rings, *ipso*-nitration or oxidation proceeds in various directions, either by the electrophilic *ipso*-substitution of methyl groups at C-5 by nitro groups or by their oxidation to carboxyl groups with the formation of the corresponding 5-carboxy derivatives (Scheme 7).[23-26] This research also revealed that, in the absence of a substituent in position 3, the electrophilic *ipso*-substitution of the methyl group by a nitro group with the formation of a 5-nitro derivative would take place. Thus, we found that, when the interaction of the compounds with electron-donating groups at N-3 position of the thienopyrimidine molecule was conducted with a nitrating mixture (HNO_3/H_2SO_4 at 0-5 °C), instead of the *ipso*-nitration of methyl groups at C-5 the reaction proceeded in an unexpected direction, *i.e.*, there was oxidation of the methyl groups.



Scheme 7. *ipso*-Nitration of thienopyrimidines.

2.3 Cerium (IV) ammonium nitrate (CAN) as nitrating agent

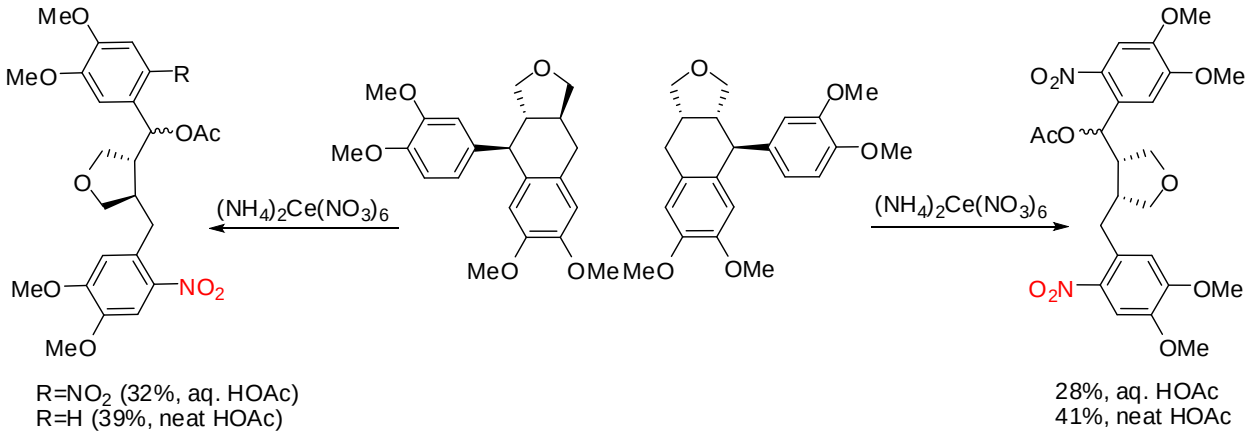
Messere *et al*. described the *ipso*-nitration reaction of substituted cinnamic acids with cerium (IV) ammonium nitrate (CAN) with the support of silica in a solid-phase approach.[27] In their work, substituted-hydroxycinnamic acids were selected as substrates, and among them, only 4-hydroxycinnamic acid, when reacted under the above conditions for 15 min. in methanol, produced an *ipso*-nitration product in a yield as high as 34%. It was observed, that during the reaction process formed nitration products (57%) and 4-hydroxycinnamaldehyde (4%) as a side product in low yields (Scheme 8). When cinnamic acid was reacted with CAN/SiO_2, it failed to produce any *ipso*-nitration product; rather, the retention of the carboxylic functional group was observed.



Scheme 8. *ipso*-Nitration of 4-hydroxycinnamic acid with CAN/SiO_2.

On the other hand, the *ipso*-nitration of a vinyl carboxyl group with HNO_3 is unusual. Probably, the *ipso*-nitrated product and 4-hydroxycinnamic acid go through hydrolysis and oxidation to yield benzoic acid, which is then susceptible to *ipso*-nitration with decarboxylation.[28,29]

LaLonde and colleagues discovered that the use of CAN in acetic acid/water (9:1) results in the conversion of (3a*R*,4*S*,9a*R*) and (3a*R*,4*S*,9a*S*) tetrahydrofurans into *ipso*-products via simultaneous *ipso*-nitration and oxidation through the opening of the B-ring of the tetrahydrofurans (Scheme 9).[30]



Scheme 9. *ipso*-Nitration of (3a*R*,4*S*,9a*R*) and (3a*R*,4*S*,9a*S*) tetrahydrofurans with CAN

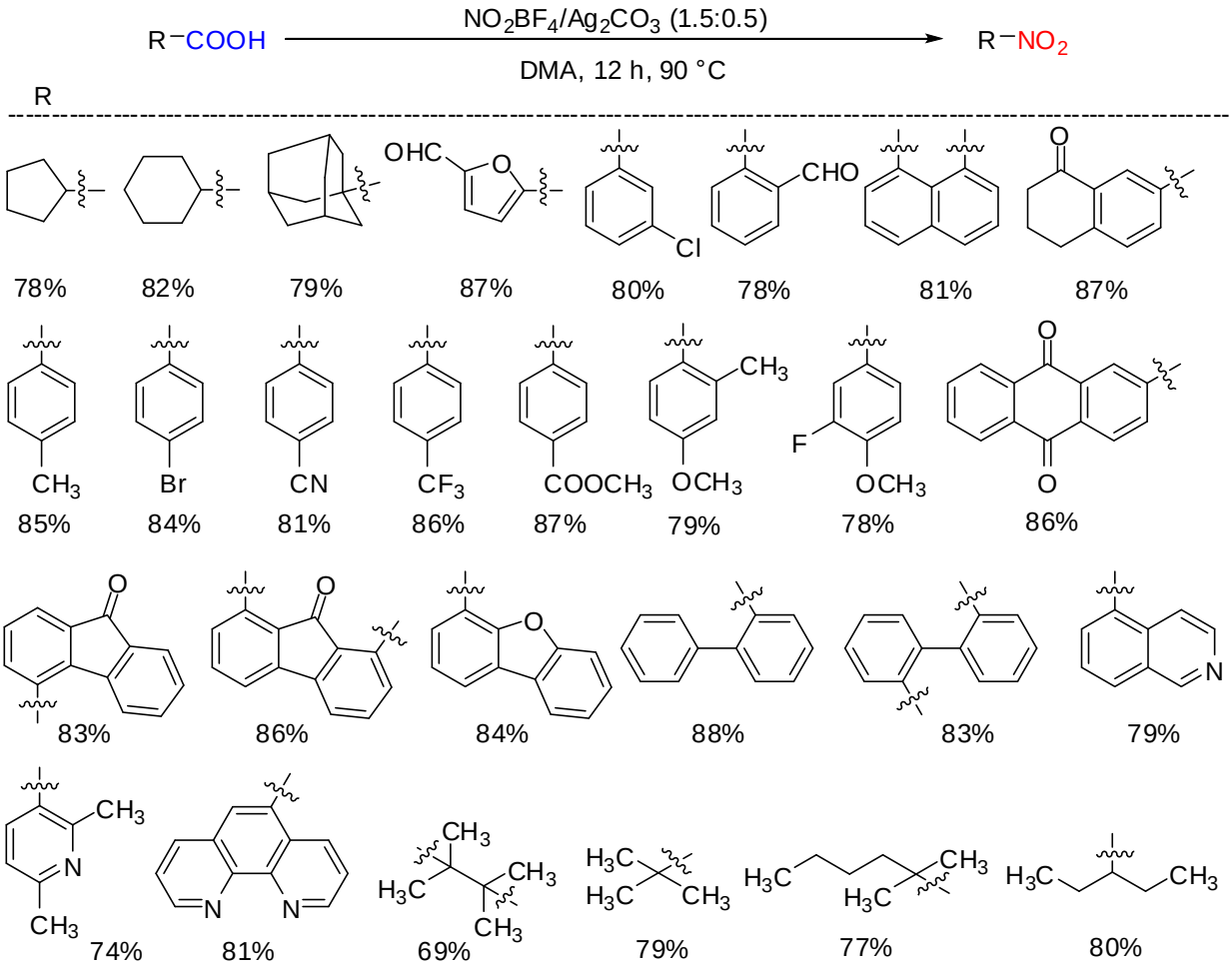
When the (3a*R*,4*S*,9a*S*) derivative was treated with CAN in neat acetic acid, the yield of the final product rose to 41%, whereas the treatment of (3a*R*,4*S*,9a*R*) derivative under the same conditions resulted in a similar yield of mononitroburseran (39%) favoring one of two diastereomeric acetates.

3. Modern Approaches to *ipso*-Nitration

3.1 *ipso*-Nitration of carboxylic groups

It has previously been proven that various silver salts can be employed as catalysts for decarboxylative carbon-carbon, carbon-silicon, carbon-oxygen, carbon-boron, carbon-sulfur, carbon-phosphorus, and carbon-halogen bond-forming reactions. Proceeding from these facts, Natarajan *et al*. described a novel and efficient approach for the *ipso*-nitration of a broad range of carboxylic acids with nitronium tetrafluoroborate (NO_2BF_4) as a nitrating agent and silver carbonate (Ag_2CO_3) as a decarboxylation reagent in dimethylacetamide (DMA) (Table 3).[31]

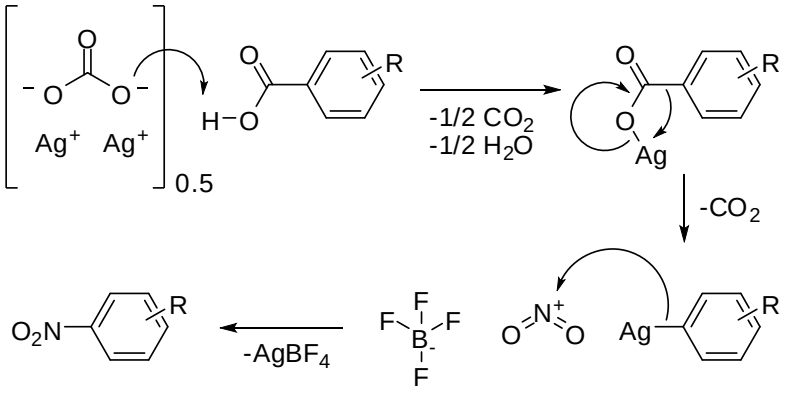
Table 3. *ipso*-Nitration of alkyl and aryl carboxylic acids



Reactions in various anhydrous solvents including acetonitrile, chloroform, DCM, dichloroethane, DMA, tetrahydrofuran, and tetrachloroethane suggested that anhydrous DMA was the best medium for the *ipso*-nitration of aliphatic and aromatic carboxylic acids. Furthermore, this research group demonstrated the generality of this new protocol by applying it to a series of electronically diversified aliphatic and aromatic carboxylic acids (Table 3). In those reactions, aryl-/heteroaryl-/polyaryl carboxylic acids with electron donating (CH_3, OCH_3, C_6H_5) and withdrawing (F, Cl, Br, CN, CF_3, CHO, $COOCH_3$) groups afforded moderate to good yields

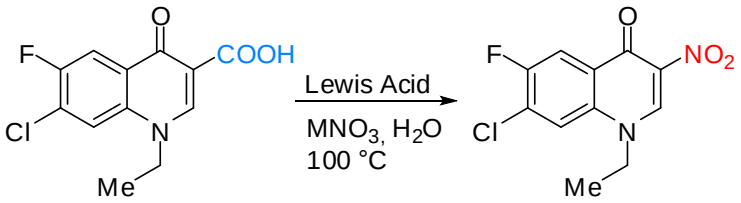
of corresponding nitroarenes. The reactions were all complete within 12 h, affording the desired products in 74–88% yields.

Thus, the proposed mechanism (Scheme 10) starts with an anion exchange at the silver center to produce the metal carboxylate, which in turn provides an arylmetal species through the extrusion of carbon dioxide. A subsequent reaction with nitronium ion results in the formation of the desired nitro compound, leaving silver tetrafluoroborate as a byproduct. It is noteworthy to mention that, in the absence of NO_2BF_4, only the decarboxylated compound was detected, which indicates the formation of an aryl-silver species as an intermediate.



Scheme 10. Proposed mechanism for the decarboxylative *ipso*-nitration.

Table 4. Effect of copper salts and nitrating agents on *ipso*-nitration



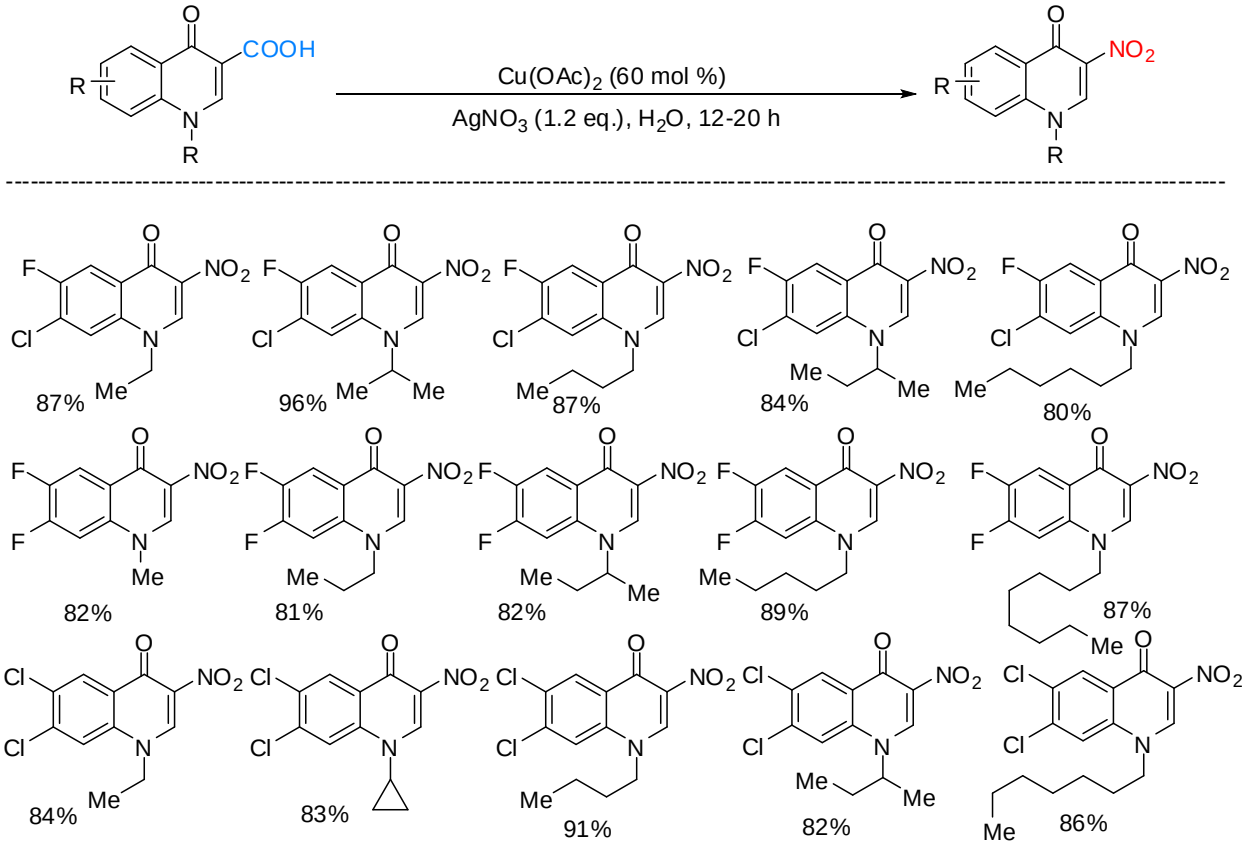
Entry	Lewis acid	Amount (mol%)	MNO_3	Yield (%)	Entry	Lewis acid	Amount (mol%)	MNO_3	Yield (%)
1	$Cu(OAc)_2$	40	$AgNO_3$	65	6	$Cu(OAc)_2$	60	$La(NO_3)_3$	66
2	$Cu(OAc)_2$	50	$AgNO_3$	87	7	$Cu(OAc)_2$	60	$Ca(NO_3)_2$	59
3	$Cu(OAc)_2$	60	$AgNO_3$	92	8	$Cu(OAc)_2$	100	$AgNO_3$	90
4	CuOAc	60	$AgNO_3$	72	9	—		$AgNO_3$	—
5	$Cu(OAc)_2$	60	$NaNO_3$	72				$La(NO_3)_3$	66

In 2015, Azad *et al*. developed an efficient, cost-effective, and green methodology for the *ipso*-nitration of 3-carboxy-4-quinolones via the quantitative use of copper acetate and silver nitrate in water.[32] The effect of the metal nitrating agent, catalyst, and solvent was investigated under the conditions of an open atmosphere and a temperature of 100 °C over 24 h, with 7-chloro-1-ethyl-6-fluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid used as the substrate. Copper (II) acetate was selected for the condition screening with AgNO3 as a nitrating agent, and water as the solvent. The results indicated that 60 mol% $Cu(OAc)_2$ converted the substrate

into a nitro product at 92% yield (Table 4). When $NaNO_3$ and $La(NO_3)_3$ were each used as the nitrating agent, the nitro products were formed at yields of 72 and 66%, respectively. The reaction did not proceed at all if no catalysts were used. Copper (I) was also effective, albeit affording lower yields.

Further, the same researchers used dihalo (F/Cl, F/F, and Cl/Cl) quinolones related with various alkyl groups at the N1 position for *ipso*-nitration. *Ipso* products were obtained in yields 80-96%, when the relevant reactions were allowed proceeded for 12–20 hrs (Table 5).

Table 5. *ipso*-Nitration of dihalo-3-carboxy-4-quinolones



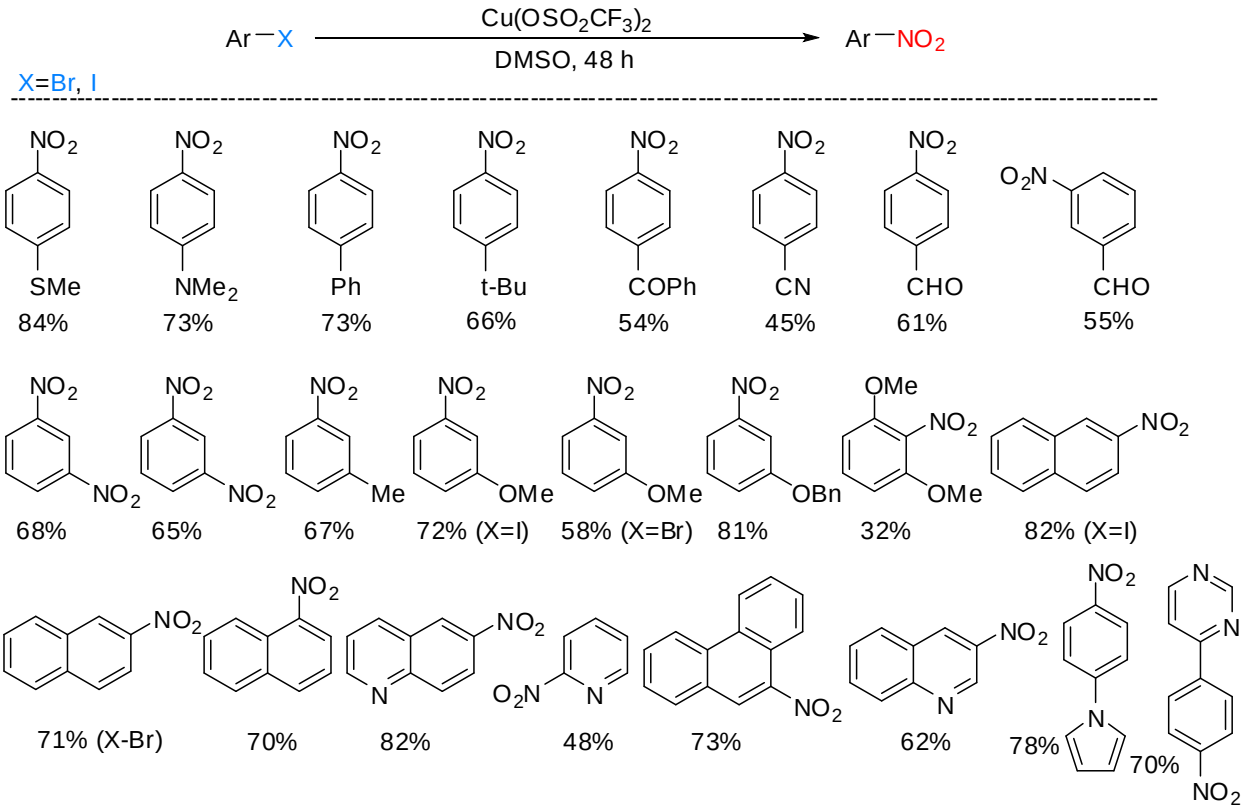
3.2 *ipso*-Nitration of halogens

In order to circumvent the need for a phase transfer catalyst, Lakshmi Kantam and colleagues studied the copper catalyzed *ipso*-nitration of iodoarenes, bromoarenes, and heterocyclic haloarenes under ligand-free conditions.[33] In their experiments, 4-bromothioanisole was initially selected as the substrate for performing the optimization reaction, while 25 mol% copper salts and 3 equiv of KNO_2 were selected as the catalysts and nucleophile, respectively. Among the various optimization studies for the *ipso*-nitration of 4-bromothioanisole, the most promising result (an 84% yield) was obtained using 25 mol% of $Cu(OSO_2CF_3)_2$ and 3 equiv of KNO_2 in 0.6 mL of DMSO at 130 °C.

A wide variety of electron-rich and electron-deficient iodoarenes and bromoarenes were then studied for *ipso*-nitration after the optimization. It was observed that a lot of electron-rich haloarenes reacted smoothly, irrespective of the nature and orientation of the functional groups present, to produce the nitro products in good yields (Table 6). It is important to note that several functional groups, including NO_2, CHO, CN, COPh, NMe_2, OCH_2Ph, OMe, SMe, Ph, and Me, were tolerated in this condition, except for 4-bromoaniline and 4-iodophenol. In addition, this method could be carried out for the *ipso*-nitration of heterocycles such as 2-

bromopyridine, 3-bromoquinoline, 6-bromoquinoline, 1-(4-iodophenyl)-1*H*-pyrrole, and 4-(4-bromophenyl)pyrimidine.

Table 6. Copper catalyzed *ipso*-nitration of haloarenes

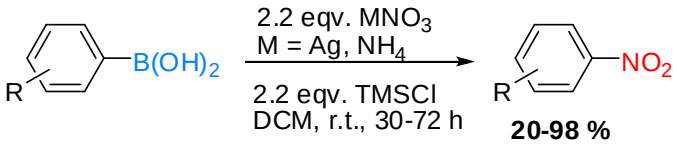


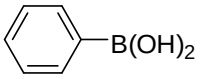
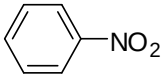
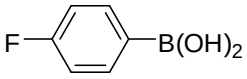
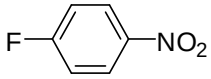
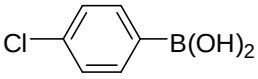
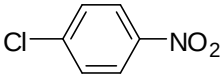
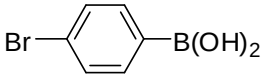
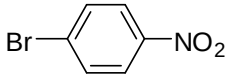
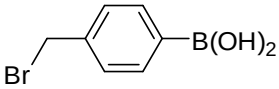
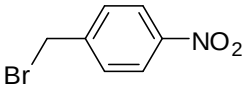
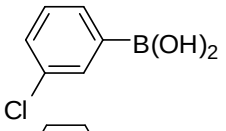
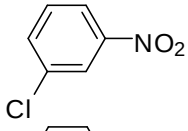
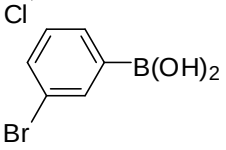
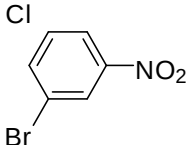
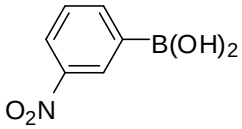
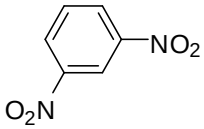
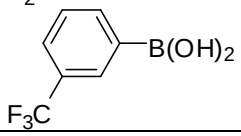
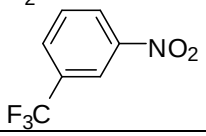
3.3 *ipso*-Nitration of arylboronic acids

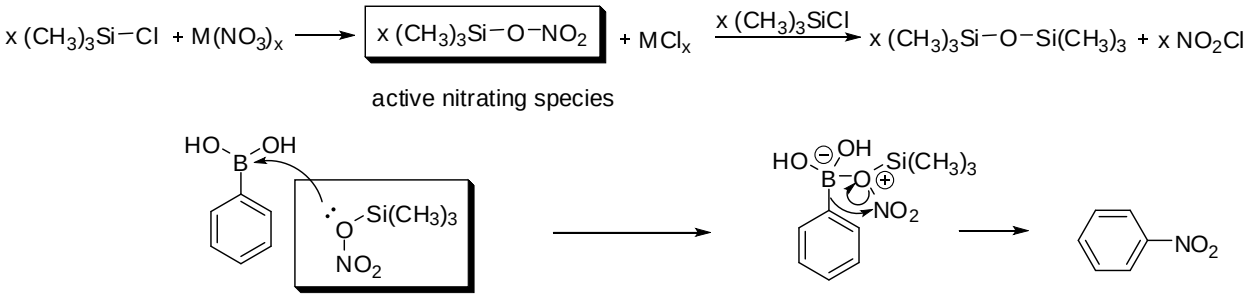
Surya Prakash and co-workers have reported a simple, convenient, and mild method for the *ipso*-nitration of arylboronic acids using inorganic nitrate salt and chlorotrimethylsilane (TMSCl) (Table 7).[34] In this type of *ipso*-nitration, 2-10% nitrochlorination was observed in certain cases. It was found that when $AgNO_3$ was used instead of NH_4NO_3 as the nitrate salt, the extent of chlorination was significantly decreased. In addition, it was investigated the effect of various nitrate salts and solvents on *ipso*-nitration reactions and it was observed that $AgNO_3$ and DCM provided the best results, respectively.

TMSCl reacts with nitrate salts to generate TMS-O-NO_2 species. The dinitro product, however, was not observed in any such reactions; it is likely that there exists a prominent electronic interaction between the boronic acid group and the intermediate active nitrating agent TMS-O-NO_2 species via the boron and the siloxy group due to the high oxophilicity of boron (Scheme 11). This would help the nitration to occur at the ipso position. TMS-O-NO_2 can then undergo further reaction with excess TMSCl to produce hexamethyldisiloxane and nitryl chloride, which can also act as the nitrating species. For the generation of nitryl chloride, an excess of TMSCl is required, but it was observed that phenylboronic acid can undergo nitration completely with 1 equiv of TMSCl. Generally, this reaction takes 72 h for completion. It should be noted, that this method was found more selective than the method in which Crivello's reagent[35] were used to provide the *ipso*-nitration products in moderate to high yields. Another significant feature of this method is the complete absence of dinitro product.

Table 7. *ipso*-Nitration of arylboronic acids using TMSCl/nitrate salts

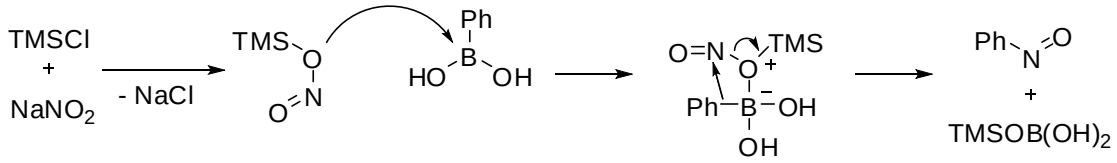


Entry	Arylboronic acid	Nitrate salt	Time (h)	Products	Yield (%)
1		$AgNO_3$	30		98
2		NH_4NO_3	48		75
3		NH_4NO_3	48		92
4		NH_4NO_3	48		96
5		NH_4NO_3	30		75
6		$AgNO_3$	72		90
7		$AgNO_3$	72		88
8		$AgNO_3$	18		45
9		$AgNO_3$	72		20



Scheme 11. Proposed mechanism for *ipso*-nitration of arylboronic acid.

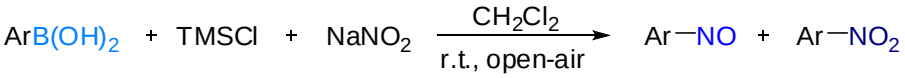
Based on this result, the same group studied the interaction of arylboronic acids with a $NaNO_2$-TMSCl system, and ultimately observed *ipso*-nitrosation reactions in most cases.[36] Initially, 4-methoxyphenylboronic acid was selected for optimization, and was then added to a stirred mixture of $NaNO_2$ (2.2 equiv) and TMSCl (2.2 equiv) in anhydrous dichloromethane under argon at room temperature for 72 h. However, as the initial results proved to be unsuccessful, the conditions of an open-air atmosphere and the addition of 0.5 equiv of water were applied for a reaction time of 3 h., all of which appeared to be suitable conditions for the reaction. The mechanism of the *ipso*-nitrosation reaction of arylboronic acids with sodium nitrite and TMSCl (Scheme 12) is similar to the mechanism illustrated above in Scheme 12, the key difference being the formation of TMS-O-NO species instead of TMS-O-NO_2 species.



Scheme 12. Proposed mechanism of *ipso*-nitrosation of phenylboronic acid with $NaNO_2$ and TMSCl.

If arylboronic acids with various substituents in the aromatic portion react under the above conditions, *ipso*-nitrosation and *ipso*-nitration products in different ratios can be observed as the final resulting compounds (Table 8). It was observed, for example, that 4-alkoxy- and 4-phenoxyphenylboronic acids underwent the reaction smoothly to produce the corresponding nitrosoarenes in both high yields and good chemoselectivities.

Table 8. *ipso*-Nitrosation of arylboronic acids



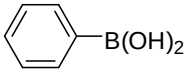
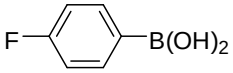
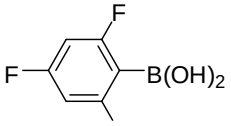
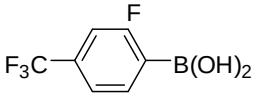
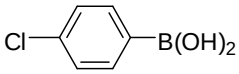
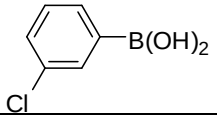
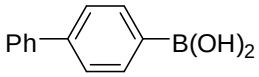
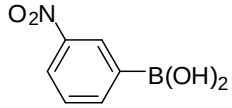
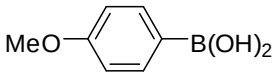
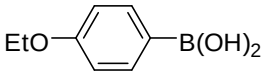
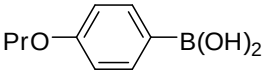
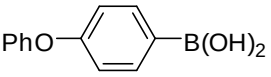
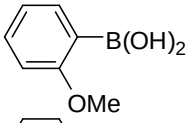
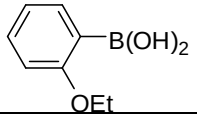
Entry	Substrate	Conversion (%)	Time (h)	Yield (%)	
				Ar—NO	Ar—NO_2
1		>99	12	2	97
2		>99	12	59	41
3		0	12	–	–
4		>99	12	10	85
5		>99	12	14	65
6		>99	12	28	64

Table 8. Continued

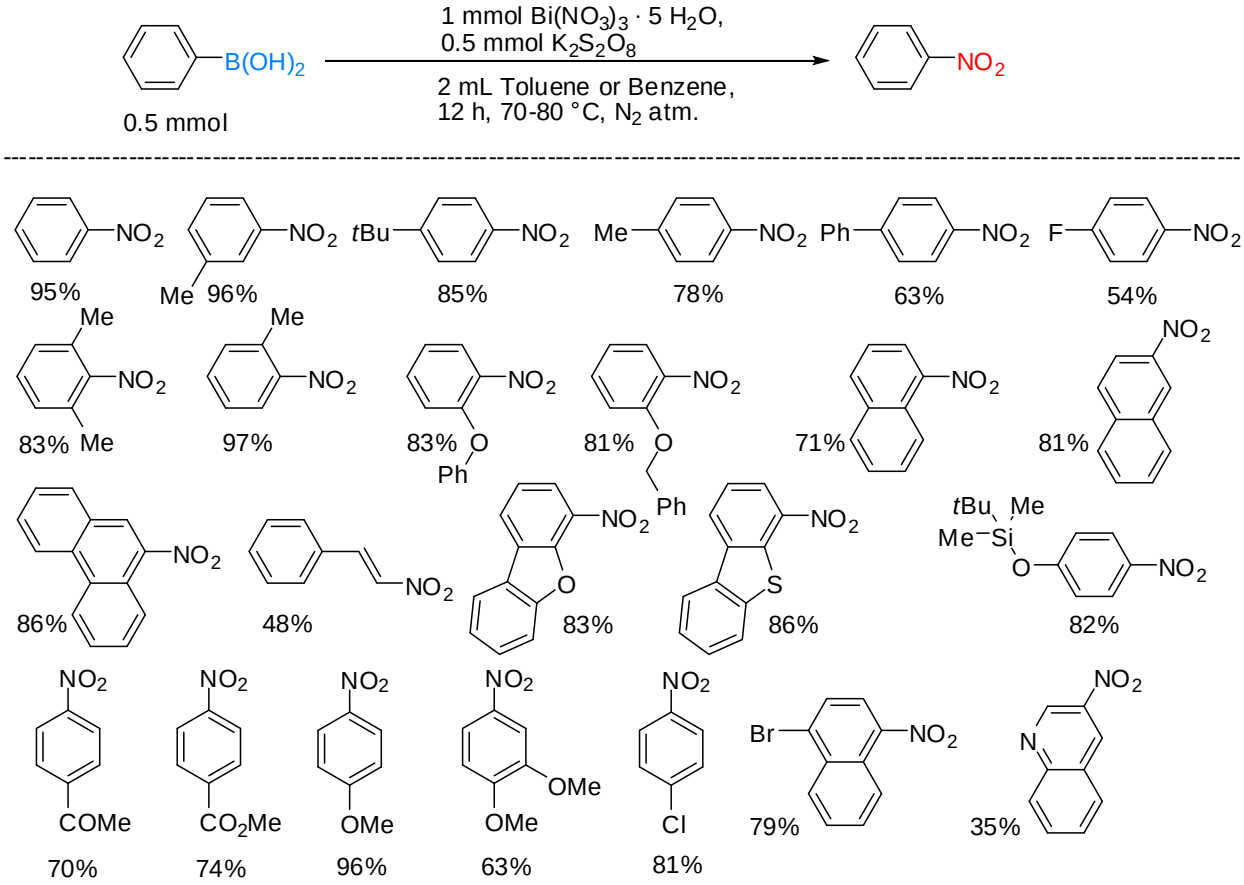
Entry	Substrate	Conversion (%)	Time (h)	Yield (%)	
				Ar—NO	Ar—NO_2
7		0	12	0	0
8		>99	12	0	95
9		>99	12	96	1
10		>99	2	87	12
11		>99	2	94	1
12		>99	4	60	36
13		>99	2	12	7
14		>99	12	12	38

On the whole, the amount of nitro products was found to decrease with the increasing electron donating ability of the substituents. However, electron-rich 2-alkoxy substituted phenylboronic acids produce relatively low yields with these substrates, apparently because the inductive effect of oxygen may also play a pivotal role in the reaction yield (Table 8).

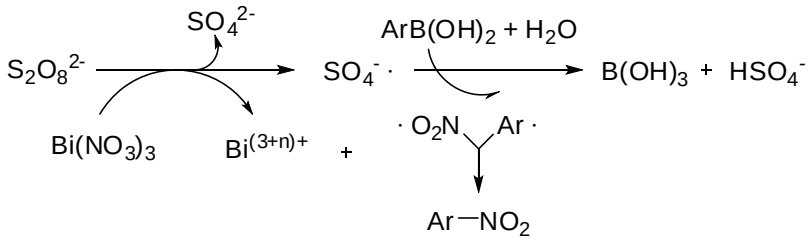
A simple and convenient method for the conversion of arylboronic acid to nitroarenes using $Bi(NO_3)_3{\cdot}5H_2O/K_2S_2O_8$ as the nitrating agent was reported by Manna *et al*. in 2012.[37] In their research, this *ipso*-nitration protocol was investigated in the context of reactions of phenylboronic acid with different nitrate sources in various solvents. The best result was achieved with 1 mmol of $Bi(NO_3)_3{\cdot}5H_2O$ with 0.5 mmol of the arylboronic acids at 80 °C. Other nitrate sources such as NaNO3, Pb(NO3)2, NaNO2, and AgNO2 failed to yield the nitro products. However, if Cd(NO3)2 was used as the nitrating agent at 100°C, nitro products was formed in a yield of 51%, while a better result was obtained with AgNO3 under the same reaction conditions. Herein, *ipso*-nitration proceed successfully in solvents such as toluene, o-xylylene, benzene, and trifluorotoluene, but it was observed that temperatures higher than 80 °C led to lower conversion due to increased protodeboronation reactions, therefore, only toluene and benzene were used in further investigations. Furthermore, the $Bi(NO_3)_3 \cdot 5H_2O/K_2S_2O_8$ catalyzed transformation of arylboronic acids to nitroaromatics has also been studied (Table 9).

ipso-Nitration of the heterocyclic, alkyl, and aryl substituted arylboronic acids formed products in good to excellent yields (63-96%), including with base-sensitive functional groups such as keto with an acidic alkyl and ester group (Table 9).

Table 9. *ipso*-Nitration of arylboronic acids



The mechanism of *ipso*-nitration of arylboronic acid (Scheme 13) is believed to be akin to the radical-based mechanisms like those involving the use of 2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO), hydroquinone, and thiourea. The addition of hydroquinone or TEMPO with $PhB(OH)_2$ resulted in the formation of the desired $PhNO_2$ product. In such a reaction, in the presence of bismuth (III) salts, persulfate anion disproportionates into sulfate dianion and sulfate radical anion. This radical could then react with the boronic acid through an unexplored process (which is expected to be the subject of future investigations), providing an aryl radical.

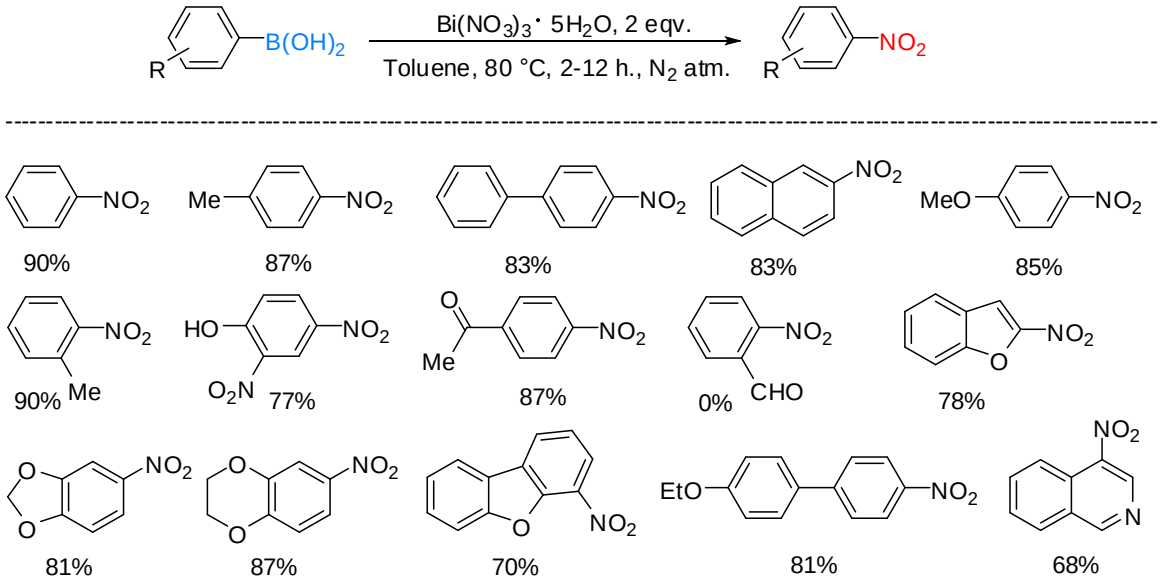


Scheme 13. Proposed mechanism for *ipso*-nitration of arylboronic acid.

Yadav *et al*. developed a catalyst-free *ipso*-nitration of the phenyl boronic acids using different nitrate sources such as zirconium nitrate, potassium nitrate, sodium nitrate, cerric ammonium nitrate, silver nitrate, bismuth subnitrate, and bismuth (III) nitrate.[38] Toluene was chosen as the reaction medium for the related

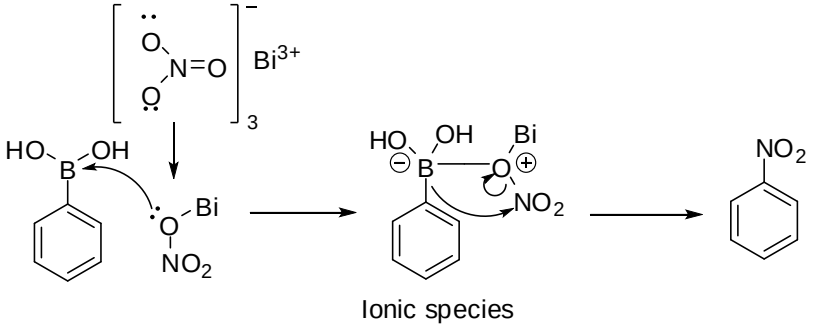
optimization studies. Formed nitroarenes from various substituted phenyl and heteroaryl boronic acids are shown in Table 10.

Table 10. Nitroarenes synthesized from arylboronic acids.



It was observed that $Bi(NO_3)_3{\cdot}5H_2O$ was the best nitrating agent for *ipso*-nitration, and 2 equiv of $Bi(NO_3)_3{\cdot}5H_2O$ in toluene as a solvent, as well as reflux at 80°C for 2 h, were chosen as the conditions for further studies.

The mechanism of *ipso*-nitration by $Bi(NO_3)_3{\cdot}5H_2O$ is illustrated in Scheme 14. At first, the researchers investigated whether the catalyst-free *ipso*-nitration occurs via a free-radical mechanism; the reaction of phenylboronic acid was performed in the presence of the free-radical scavengers TEMPO and thiourea. The reaction took place smoothly in the presence of TEMPO and thiourea, thus ruling out the possibility of a free-radical mechanism. The fact that aliphatic boronic acid did not participate in this reaction indicates that the aromatic ring plays an important electronic role in the *ipso*-nitration and that bismuth nitrate is presumably responsible for the *in situ* production of Bi–O–NO_2 species. Insofar as boron is highly oxophilic, it is likely that through electronic interactions between the boronic acid group and the species of Bi–O–NO_2, be formed an ionic species, which helps to occur the *ipso*-nitration reactions.

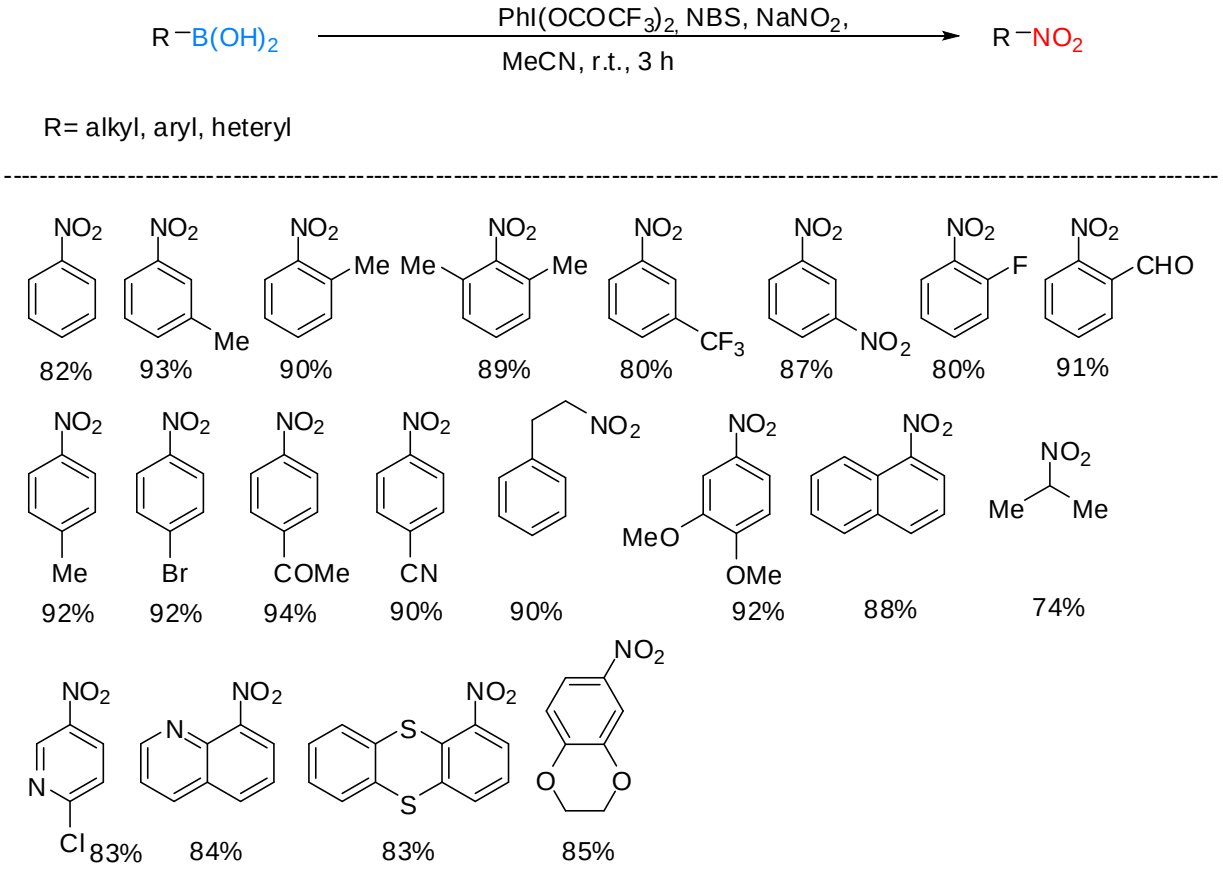


Scheme 14. Proposed mechanism for *ipso*-nitration of arylboronic acids by $Bi(NO_3)_3{\cdot}5H_2O$.

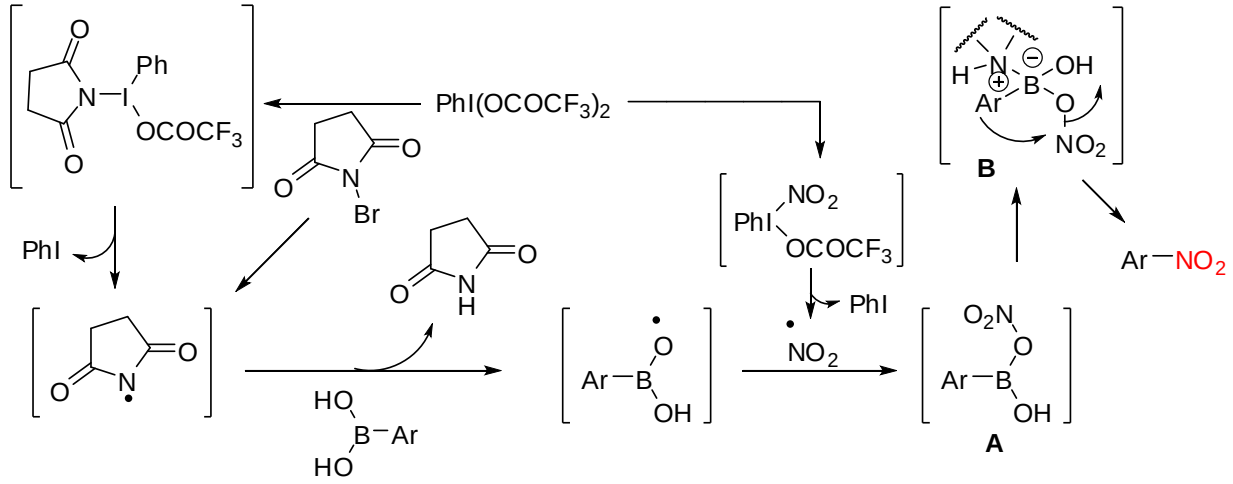
Chatterjee *et al*. reported a highly efficient [bis-(trifluoroacetoxy)]iodobenzene (PIFA)-mediated oxidative regioselective nitration of aryl-, alkyl- and heteroarylboronic acids, with their first example being the use of a PIFA–NBS–$NaNO_2$ combination to generate nitroarenes under transition metal-free conditions.[39] In their study, it was observed that the presence as well as the amount of an additive (NBS) is important for better conversion of the organoboronic acids to the nitroarenes. Increasing the amount of NBS to 2.1 eq. and that of PIFA to 3.0 eq. resulted in quantitative *ipso*-nitration of the *m*-tolylboronic acid. In addition, the PIFA-mediated *ipso*-nitration of aryl-, alkyl- and heteroarylboronic acids with either an electron donating or withdrawing group, which was investigated in their work, was found to generate nitro compounds in excellent yields (74-94%) (Table 11).

The preliminary mechanism of these previously investigated reactions probably takes place via the generation of an O-centered radical in the presence of NBS and PIFA; this further reacts with the nitro radical, which itself is formed through the one-electron oxidation of $NaNO_2$ in the presence of PIFA, to form the metastable species A.

Table 11. *ipso*-Nitration of aryl-, alkyl- and heteroarylboronic acids



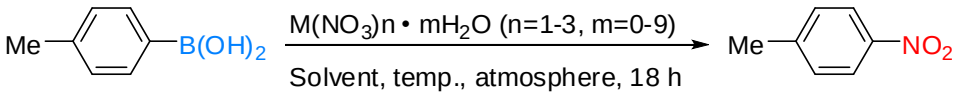
After all, as shown in Scheme 15, the nitroarenes are formed via nitro transfer to the aryl moiety through 1,3-aryl migration from the tetra-coordinated species B, which is itself produced from A through coordination by the succinimide.



Scheme 15. Mechanism of the *ipso*-nitration of organoboronic acids in the presence of NBS.

Recently, Yang and colleagues reported a simple, efficient, and practical *ipso*-nitration of arylboronic acids with 0.5 equiv. of iron nitrate without the addition of any additive.[40] At first, 4-methylboronic acid was selected as a substrate and the reaction conditions were studied systematically with a variety of nitrate salts and solvents; in addition, various reaction temperatures and atmospheres were also screened (Table 12).

Table 12. *ipso*-Nitration of 4-methylboronic acid with various nitrate salts



Entry	$M(NO_3)_n \cdot mH_2O$ (equiv.)	Solvent	Temp. (°C)	Yield (%)
1	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	Toluene	80	93
2	$Cu(NO_3)_2 \cdot 3H_2O$ (1.5 eq.)	Toluene	80	75
3	$Ni(NO_3)_2 \cdot 6H_2O$ (1.5 eq.)	Toluene	80	20
4	$Mg(NO_3)_2$ (1.5 eq.)	Toluene	80	0
5	$Co(NO_3)_2 \cdot 6H_2O$ (1.5 eq.)	Toluene	80	70
6	$Zn(NO_3)_2 \cdot 6H_2O$ (1.5 eq.)	Toluene	80	10
7	NH_4NO_3 (3 eq.)	Toluene	80	Trace
8	$AgNO_3$ (3 eq.)	Toluene	80	74
9	KNO_3 (3 eq.)	Toluene	80	Trace
10	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	Toluene	80	50[a]
11	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	Toluene	80	40[b]
12	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	MeCN	80	20
13	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	*c*-Hexane	80	78
14	$Fe(NO_3)_3 \cdot 9H_2O$ (1 eq.)	MeOH	80	16

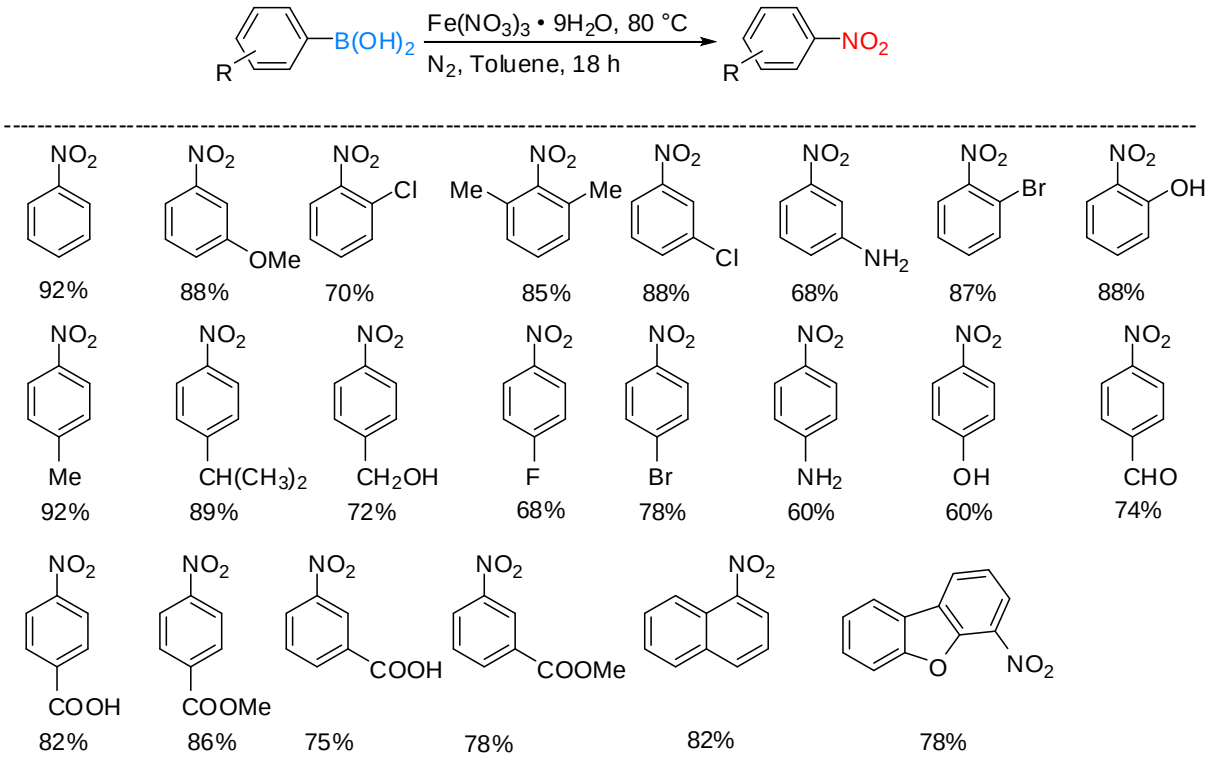
Table 12. Continued

Entry	M(NO3)n·mH2O (equiv.)	Solvent	Temp. (°C)	Yield (%)
15	$Fe(NO_3)_3·9H_2O$ (1 eq.)	H_2O	80	0
16	$Fe(NO_3)_3·9H_2O$ (1 eq.)	Toluene	100	89
17	$Fe(NO_3)_3·9H_2O$ (1 eq.)	Toluene	60	24
18	$Fe(NO_3)_3·9H_2O$ (0.5 eq.)	Toluene	80	92
19	$Fe(NO_3)_3·9H_2O$ (0.3 eq.)	Toluene	80	68

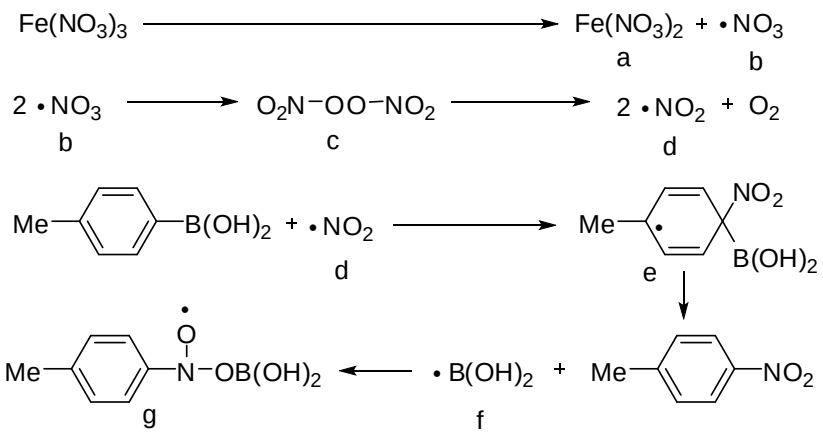
[a] Under air. [b] Under oxygen atmosphere.

If the reaction was performed under air or oxygen atmosphere, the final product yields were reduced. When 4-methylboronic acid was reacted with $Fe(NO_3)_3·9H_2O$ under a nitrogen atmosphere in toluene (at 80 °C), however, nitro products were obtained at a yield of 93%. Therefore, it was selected as the optimal conditions for further *ipso*-nitration reaction. For instance, screening of the *ipso*-nitration of arylboronic acids with electron-donating and electron-withdrawing groups indicated that final products were obtained in higher yields with the arylboronic acids with electron-donating groups than with those containing electron-withdrawing groups (Table 13).

Table 13. *ipso*-Nitration of arylboronic acids with iron nitrate



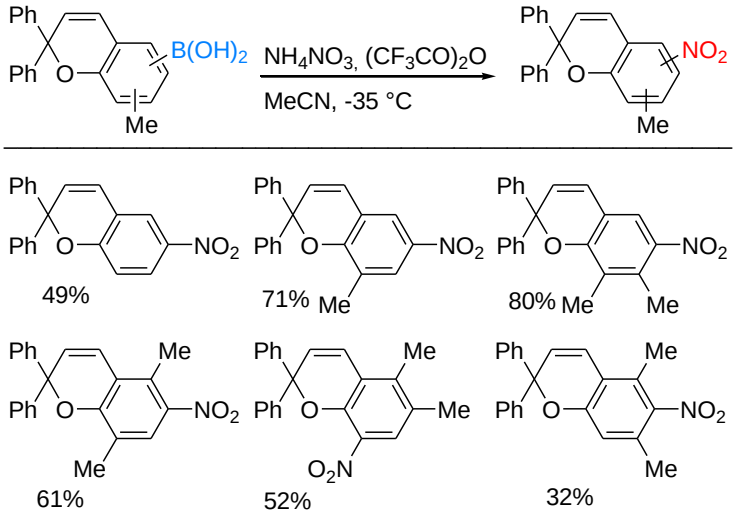
A possible mechanism for the *ipso*-nitration of arylboronic acids with iron nitrate, probably follows a path similar to the following: under heating $Fe(NO_3)_3$ produces $Fe(NO_3)_2$ (**a**) and the radical NO_3 (**b**) that dimerizes to **c**, which then decomposes to NO_2 (**d**) releasing oxygen (Scheme 16).



Scheme 16. Possible mechanism for *ipso*-nitration of arylboronic acids with iron nitrate.

Next NO_2 (**d**) reacts with 4-methylphenylboronic acid to produce the cyclohexadienyl (**e**) radical, that loses the radical $B(OH)_2$ (**f**), affording the reaction product. The interaction of radical $B(OH)_2$ (**f**) with the reaction product, would then lead to the detected boroxynitroxide (**g**) (Scheme 16).

In 2007, Bougdid *et al*. presented the first *ipso*-nitration of 2,2-diphenyl-2*H*-1-benzopyrans.[41] They selected Crivello's reagent (NH_4NO_3/$(CF_3CO)_2O$) as the nitrating agent. At first, trifluoroacetic anhydride was slowly added to a mixture of NH_4NO_3 (1.1 equiv) in acetonitrile. Thereafter, boronic acid (1 equiv) was reacted with the prepared nitrating agent at -35 °C, forming only selective mono nitro products (Scheme 17).



Scheme 17. *ipso*-Nitration of 2,2-diphenyl-2*H*-1-benzopyrans.

Conclusions

In summary, the recent advances in *ipso*-nitration reactions, including those carried out via both classical and modern methods have been highlighted in this review. The most commonly used traditional *ipso*-nitration reaction involves the synthesis of nitrocalixarenes, whereas arylboronic acids are preferred in the more modern approaches using various metal salts and mild nitrating agents. In the 1990s, it was observed that, in a

lot of experimental investigations, only alkyl groups were transformed into nitro groups by *ipso*-nitration. However, this type of reaction has been noticeably developed in more recent years, and now various functional groups, such as hydroxyl, carbonyl, carboxyl, cycloalkane, and halo-derivatives, can be converted into selective nitro products, whereby can be used as building blocks in organic synthesis. Thus, our research group believes that, in organic synthesis methodology, the conversion of any functional group into a nitro group will always be an important point to consider, which is why perspectives on *ipso*-nitration will continue to develop in the future.

Acknowledgments

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