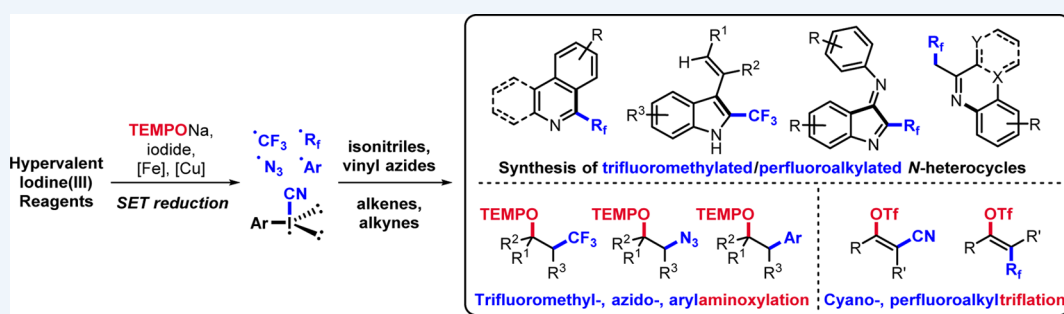


# Iodine(III) Reagents in Radical Chemistry

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**CONSPECTUS:** The chemistry of hypervalent iodine(III) compounds has gained great interest over the past 30 years. Hypervalent iodine(III) compounds show valuable ionic reactivity due to their high electrophilicity but also express radical reactivity as single electron oxidants for carbon and heteroatom radical generation. Looking at ionic chemistry, these iodine(III) reagents can act as electrophiles to efficiently construct C–CF<sub>3</sub>, X–CF<sub>3</sub> (X = heteroatom), C–R<sub>f</sub> (R<sub>f</sub> = perfluoroalkyl), X–R<sub>f</sub>, C–N<sub>3</sub>, C–CN, S–CN, and C–X bonds. In some cases, a Lewis or a Bronsted acid is necessary to increase their electrophilicity. In these transformations, the iodine(III) compounds react as formal “CF<sub>3</sub><sup>+</sup>”, “R<sub>f</sub><sup>+</sup>”, “N<sub>3</sub><sup>+</sup>”, “Ar<sup>+</sup>”, “CN<sup>+</sup>”, and “X<sup>+</sup>” equivalents. On the other hand, one electron reduction of the I(III) reagents opens the door to the radical world, which is the topic of this Account that focuses on radical reactivity of hypervalent iodine(III) compounds such as the Togni reagent, Zhdankin reagent, diaryliodonium salts, aryliodonium ylides, aryl(cyano)iodonium triflates, and aryl(perfluoroalkyl)iodonium triflates. Radical generation starting with I(III) reagents can also occur via thermal or light mediated homolysis of the weak hypervalent bond in such reagents. This reactivity can be used for alkane C–H functionalization. We will address important pioneering work in the area but will mainly focus on studies that have been conducted by our group over the last 5 years.

We entered the field by investigating transition metal free single electron reduction of Togni type reagents using the readily available sodium 2,2,6,6-tetramethylpiperidine-1-oxyl salt (TEMPONa) as an organic one electron reductant for clean generation of the trifluoromethyl radical and perfluoroalkyl radicals. That valuable approach was later successfully also applied to the generation of azidyl and aryl radicals starting with the corresponding benziodoxole (Zhdankin reagent) and iodonium salts. In the presence of alkenes as radical acceptors, vicinal trifluoromethyl-, azido-, and arylaminoxylation products result via a sequence comprising radical addition to the alkene and subsequent TEMPO trapping. Electron-rich arenes also react with I(III) reagents via single electron transfer (SET) to give arene radical cations, which can then engage in arylation reactions. We also recognized that the isonitrile functionality in aryl isonitriles is a highly efficient perfluoroalkyl radical acceptor, and reaction of R<sub>f</sub>-benziodoxoles (Togni type reagents) in the presence of a radical initiator provides various perfluoroalkylated *N*-heterocycles (indoles, phenanthridines, quinolines, etc.). We further found that aryliodonium ylides, previously used as carbene precursors in metal-mediated cyclopropanation reactions, react via SET reduction with TEMPONa to the corresponding aryl radicals. As a drawback of all these transformations, we realized that only one ligand of the iodine(III) reagent gets transferred to the substrate. To further increase atom-economy of such conversions, we identified cyano or perfluoroalkyl iodonium triflate salts as valuable reagents for stereoselective vicinal alkyne difunctionalization, where two ligands from the I(III) reagent are sequentially transferred to an alkyne acceptor.

Finally, we will discuss alkynyl-benziodoxoles as radical acceptors for alkynylation reactions. Similar reactivity was found for the Zhdankin reagent that has been successfully applied to azidation of C-radicals, and also cyanation is possible with a cyano I(III) reagent. To summarize, this Account focuses on the design, development, mechanistic understanding, and synthetic application of hypervalent iodine(III) reagents in radical chemistry.

## 1. INTRODUCTION

Since the early 1990s, chemistry with I(III) compounds has witnessed significant advances in organic chemistry, due to their strong electrophilicity and valuable oxidizing properties, combined with their environment-friendly nature and in many cases commercial availability. The list of useful reactions

applying I(III) reagents is meanwhile long.<sup>1</sup> They have been used for oxidative I-ligand transfer to transition metals, for electrophilic functionalization, for electrophilic iodonium

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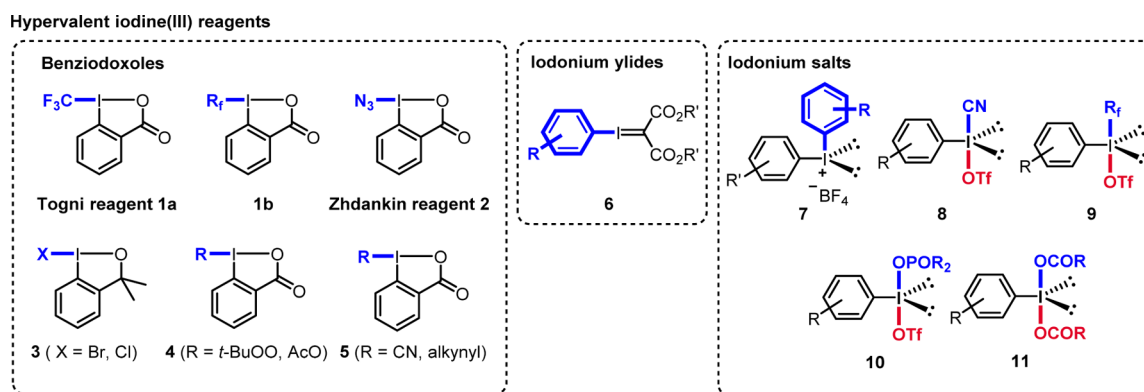
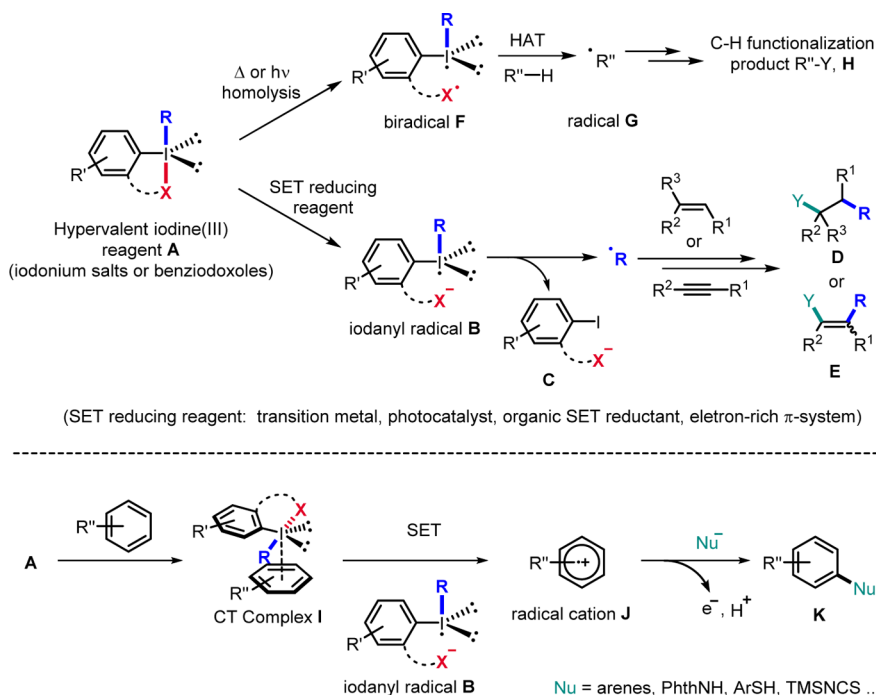
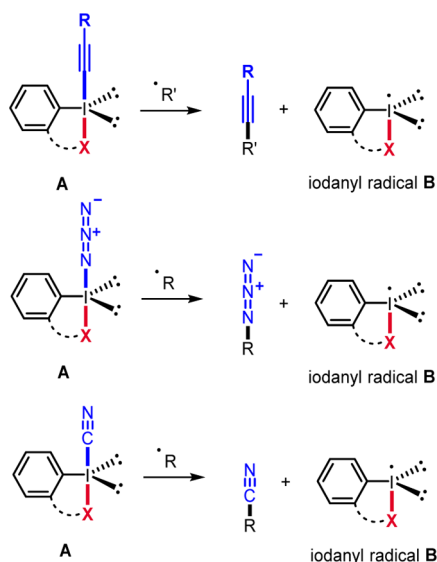


Figure 1. I(III) reagents used in radical chemistry.

## Scheme 1. Generation of Radicals Using I(III) Reagents



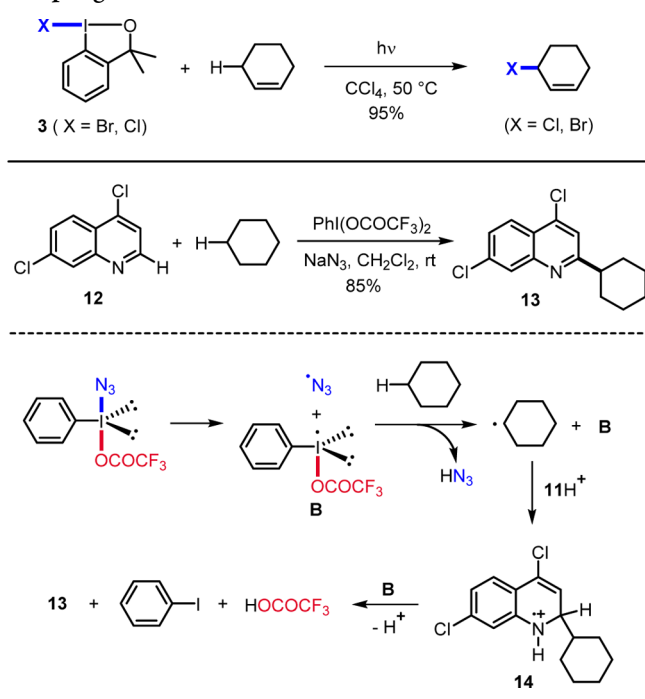
## Scheme 2. I(III) Reagents as Radical Acceptors



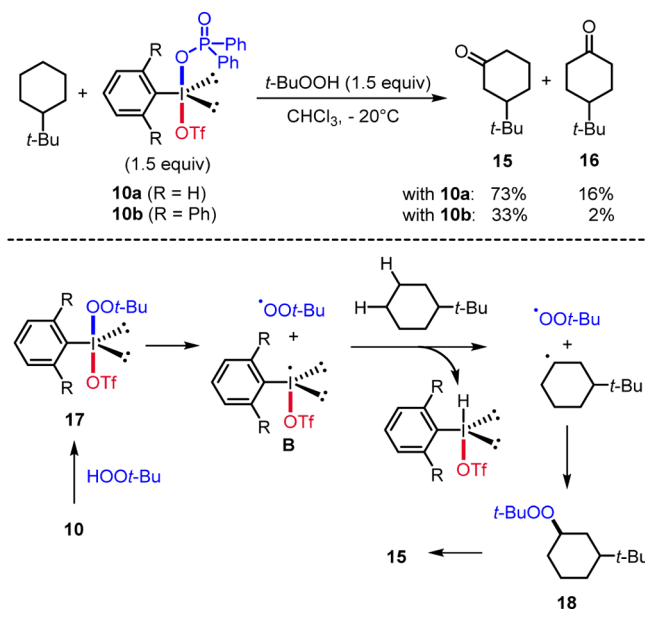
activation of carbon–carbon  $\pi$ -bonds, for direct C–H functionalization, for conducting iodonium ylide chemistry, as chiral I(III) compounds in enantioselective synthesis, as carbon and heteroatom radical precursors, and as radical acceptors.<sup>1</sup> The purpose of this Account is to give an overview on radical chemistry with I(III) reagents focusing on recent work from our group. It covers literature on the use of the I(III) compounds 1–11 up to March 2017 (Figure 1).

The synthesis of I(III) reagents has been reviewed<sup>1b,e,f</sup> and will therefore not be further discussed herein. Compared to regular covalent I–R and I–X bonds, the R–I–X bond in I(III) compounds **A**, which is termed the “hypervalent bond”, is a three-atom–four-electron bond that is highly polarized, significantly longer, and also weaker than the corresponding I–R and I–X bonds in regular iodides.<sup>1b,e</sup> Homolytic cleavage of the weak I–X bond in an I(III) reagent **A** is achieved thermally or by irradiation to provide the biradical **F** (Scheme 1). If  $\text{X}^\bullet$  and  $\text{aryl-I}^\bullet\text{-R}$  are not covalently linked, X–I homolysis results in the generation of two heteroatom centered radicals. These radicals can react with a substrate  $\text{R}''\text{-H}$  via H-abstraction to generate the C-radical **G**, which upon further reaction

Scheme 3. C–H Halogenation and Oxidative Cross-Coupling



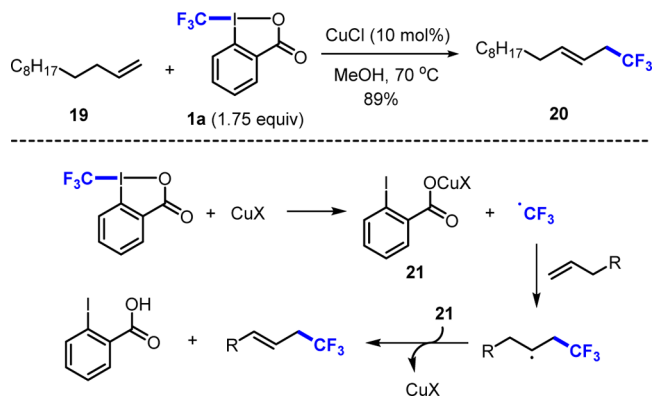
Scheme 4. C–H Abstraction by Iodanyl Radicals



(mostly oxidation and trapping) provides the C–H functionalization product **H**.<sup>2</sup> The iodanyl radical (aryl–I<sup>•</sup>–R) and also the X<sup>•</sup> radical can undergo H abstraction.<sup>2fg,i–m</sup> However, iodanyl radicals can only express radical chemistry at the I atom if they are longer lived, which is the case if  $\alpha$ -fragmentation would lead to a high energy radical R<sup>•</sup>. For such a system (R = CN), we showed that iodanyl radicals efficiently add to alkynes (see section 7).<sup>3</sup>

More abundant in radical chemistry of I(III) reagents is the one electron reduction of compounds **A**. To this end, various single electron transfer (SET) reducing reagents, such as transition metals,<sup>4</sup> photocatalysts,<sup>5</sup> organic reductants,<sup>6</sup> and electron-rich  $\pi$ -systems<sup>7</sup> have been used. SET reduction of **A**

Scheme 5. Cu-Catalyzed Allylic Trifluoromethylation



first leads to radical **B**, which fragments to the radical R<sup>•</sup> and anion C. R<sup>•</sup> can engage in typical addition reactions to (hetero)arenes, alkenes, and alkynes. The adduct radicals are then oxidized and trapped to afford compounds **D** and **E** (for alkene/alkyne additions). If a transition metal is used for SET reduction, oxidation and trapping is often mediated by the oxidized transition metal complex. Alternatively, the SET reduction of iodine(III) by arenes can occur via preformation of a charge-transfer (CT) complex **I**. SET then provides the radical cation intermediate **J**, which can be trapped by various carbon or heteroatom type nucleophiles to form after renewed SET oxidation and deprotonation the corresponding arylation products **K**.<sup>7</sup>

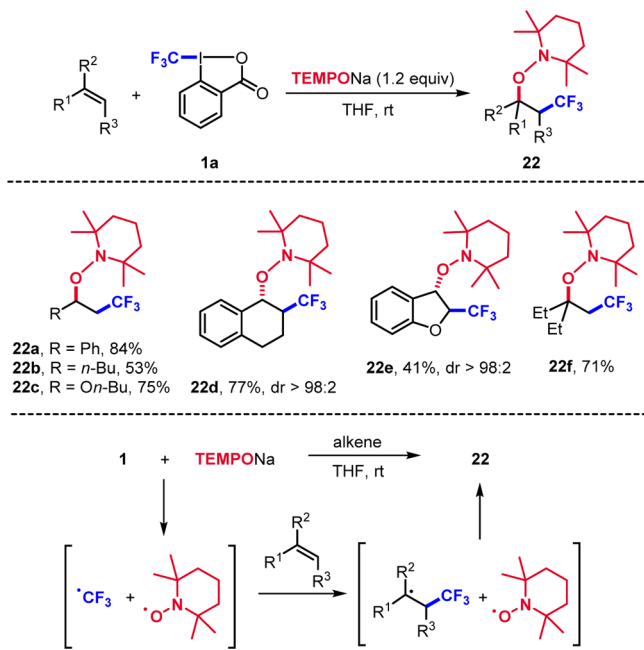
I(III) reagents were also shown to act as radical acceptors. This is the case for arylalkynyl compounds **A** where radicals R<sup>•</sup> react with **A** to the iodanyl radical **B** and the alkynylated product (Scheme 2).<sup>8a–c</sup> Similar radical group transfer also occurs with azidyl derivatives **A** (R = N<sub>3</sub>) to give alkyl azides,<sup>9</sup> and also cyanide transfer to C-radicals with reagents **A** (R = CN) is possible.<sup>8f</sup> The following sections give an overview on all these different transformations.

## 2. RADICAL C–H FUNCTIONALIZATION USING I(III) REAGENTS

In 1979, Martin reported the benzylic and allylic radical C–H chlorination and bromination with halobenziodoxoles of type **3**.<sup>2i</sup> These reactions likely proceed as chain processes where iodanyl radicals derived from **3** undergo C–H abstraction and the thus generated C-radicals are halogenated by reagents **3** to give the halogenated products along with the corresponding iodanyl radicals thereby sustaining the chain (see Scheme 3, exemplified for halogenation of cyclohexane).<sup>2i</sup> In analogy, radical C–H iodination by the I(III) reagent **4** was disclosed by Barluenga.<sup>2a</sup> With I<sub>2</sub>, **4**, and TMSN<sub>3</sub> (10 mol %), cyclohexane was transformed to iodocyclohexane. The iodanyl radical **B** (Scheme 1, X = OCO) derived from **4** abstracts a H atom from cyclohexane to generate the cyclohexyl radical that gets iodinated with I<sub>2</sub>.

Antonchik showed that *in situ* generated PhI(OCOCF<sub>3</sub>)N<sub>3</sub> can be used for transition metal free cross-dehydrogenative coupling of heterocycles with aldehydes<sup>2b</sup> and alkanes.<sup>2c,d</sup> For example, quinoline **12** reacts with PhI(OCOCF<sub>3</sub>)N<sub>3</sub>, readily generated from PhI(OCOCF<sub>3</sub>)<sub>2</sub> with NaN<sub>3</sub>, and cyclohexane to **13** (85%, Scheme 3).<sup>2c</sup> Homolysis of the weak I–N<sub>3</sub> bond generates an N<sub>3</sub>-radical and **B** (X = OCOCF<sub>3</sub>). The N<sub>3</sub>-radical abstracts a H atom from cyclohexane to give the cyclohexyl radical, which adds to protonated **12** to radical cation **14**.

Scheme 6. Trifluoromethylaminoxylation of Alkenes



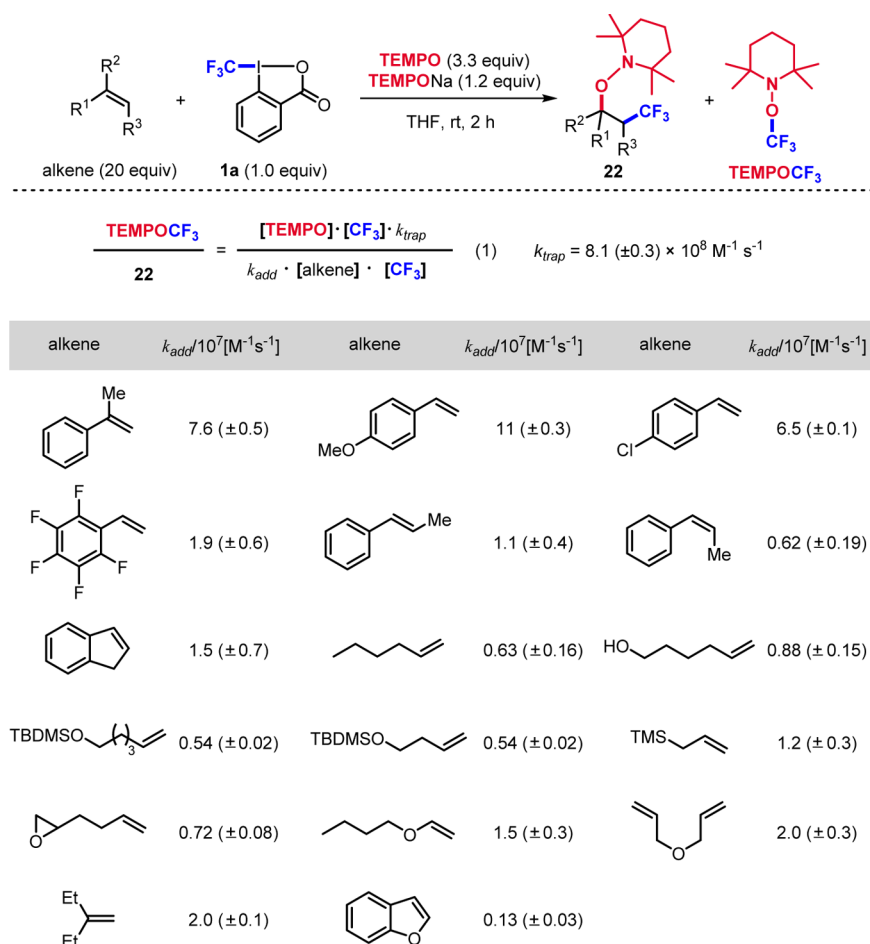
Deprotonation and oxidation with **B** lead to **13**, iodobenzene, and trifluoroacetic acid. Note that azido-I(III) reagents derived from PhIO/TMSN<sub>3</sub> were previously used by Magnus for radical

C–H azidation.<sup>2k</sup> In these transformations, the C-radical generated by H-transfer is trapped (azidated) by the azido-I(III) reagent (see also section 8).<sup>2k</sup> Similar reactivity was reported by Kita using PhI(OCOCF<sub>3</sub>)<sub>2</sub>/TMSN<sub>3</sub> as reagent couple.<sup>2l</sup>

Support for iodanyl radicals acting in H-abstraction reactions was provided by Maruoka.<sup>2e</sup> Reagents **10** were applied to the oxidation of *t*-Bu-cyclohexane with *t*-BuOOH as a cooxidant to give the regioisomeric ketones **15** and **16** (Scheme 4). Reagent **10** first reacts with *t*-BuOOH to the I(III) intermediate **17**. I–O bond homolysis in **17** generates **B** and *t*-BuOO•. H-abstraction from *t*-Bu-cyclohexane by **B** provides a cyclohexyl radical. As compared to **B** (R = H) derived from **10a**, for the bulkier radical **B** (R = Ph) derived from **10b**, selectivity for C(3)–H abstraction is higher. Cross-coupling of the C-radical with the peroxy radical<sup>10</sup> gives **18**. Finally, ionic β-fragmentation affords *t*-BuOH and the target ketone. Similar reactivity was also noted for alkane C–H functionalization with PhI(OOt-Bu)<sub>2</sub>.<sup>2h</sup> Notably, oxidation of benzylic C–H bonds to ketones via iodanyl radicals was already reported by Ochiai in 1992.<sup>2j</sup>

### 3. TRIFLUOROMETHYLATION VIA SET REDUCTION OF THE TOGNI REAGENT

The CF<sub>3</sub> group is a valuable substituent for modulation of chemical and physical properties of drug candidates, agrochemicals, and polymers.<sup>11</sup> CF<sub>3</sub>-bearing benziodoxoles **1a**, introduced by Togni, have been intensively used for electrophilic

Scheme 7. Rate Constants for CF<sub>3</sub> Radical Addition to Alkenes



trifluoromethylation of carbon and heteroatom based nucleophiles.<sup>12</sup> This chemistry has been reviewed<sup>12</sup> and we will only address examples on radical transformations focusing on our own contributions. In 2011, Buchwald and Wang described allylic trifluoromethylation of alkenes with reagent **1a** (Scheme 5).<sup>4a,b</sup> For example, reaction of **19** with **1a** using catalytic CuCl provided trifluoromethylated alkene **20**. Mechanistically, radical generation occurs by reduction of **1a** with CuCl to give the CF<sub>3</sub>-radical and **21**. CF<sub>3</sub>-radical addition to the alkene leads to the adduct radical that is finally oxidized by the Cu-complex **21**. Numerous papers on radical trifluoromethylation with **1a** using redox catalysis have appeared since.<sup>12,13</sup>

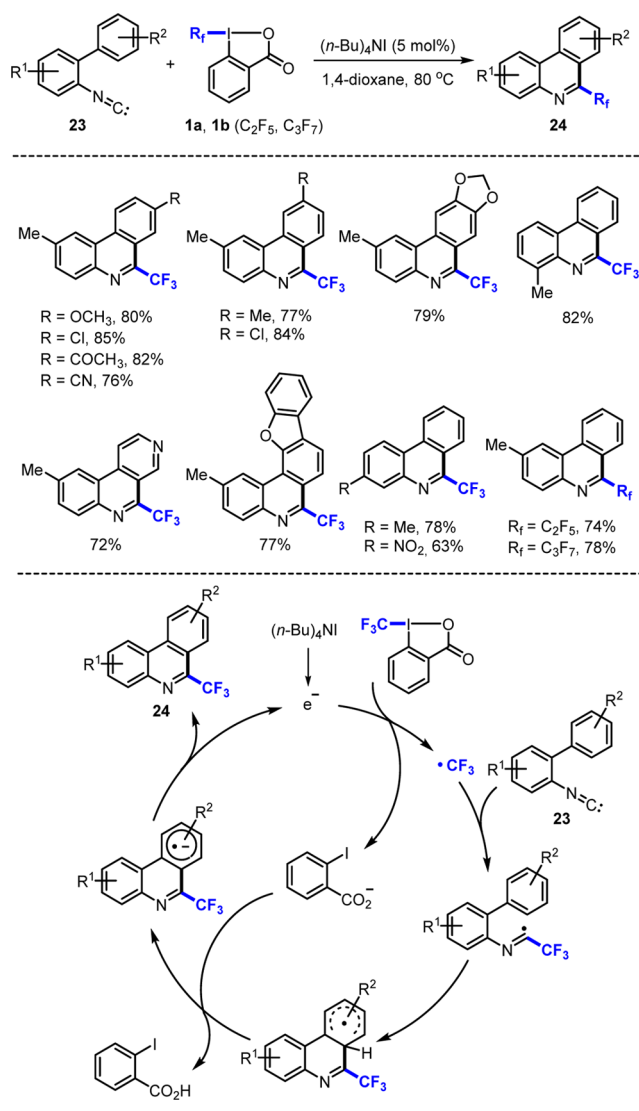
We assumed that the I(III)–CF<sub>3</sub> bond in **1a** can be reduced with the sodium 2,2,6,6-tetramethylpiperidine-1-oxyl salt (TEMPONa) salt. Indeed, reaction of **1a** with TEMPONa cleanly generates the CF<sub>3</sub>-radical and TEMPO.<sup>6</sup> In the presence of a reactive alkene, alkene CF<sub>3</sub>-radical addition and trapping by TEMPO provide **22** (Scheme 6). Not only activated styrene derivatives (**22a**) but also nonactivated aliphatic alkenes were successfully converted (**22b**). Reactions were less efficient with electron-poor alkenes but provided good results with electron-rich vinyl ethers (**22c**). Trifluoromethylaminoxylation of cyclic alkenes (**22d**) and of benzofuran (**22e**) afforded the products with excellent stereo- and regioselectivity. This cascade also worked on  $\beta$ -disubstituted alkenes to give tertiary alkoxyamines (**22f**).

Despite the many contributions toward radical trifluoromethylation, only few studies on the determination of rate constants for CF<sub>3</sub>-radical addition to alkenes appeared.<sup>14</sup> The TEMPONa mediated CF<sub>3</sub>-radical addition was identified as a tool to estimate such rate constants.<sup>15</sup> If the addition of the CF<sub>3</sub>-radical to the alkene is slow, trapping of the CF<sub>3</sub>-radical by TEMPO that is concomitantly formed in the initial SET step (see Scheme 6) to form TEMPO–CF<sub>3</sub> occurs as a side reaction. The rate constant for trapping of TEMPO by the CF<sub>3</sub>-radical ( $k_{\text{trap}} = (8.1 \pm 0.3) \times 10^8 \text{ M}^{-1} \text{ s}^{-1}$ ) was determined and used as a radical clock for estimation of all other rate constants (Scheme 7). Product ratio of TEMPO trapping versus trifluoromethylaminoxylation was used to calculate the rate constant  $k_{\text{add}}$  for CF<sub>3</sub>-radical addition according to eq 1.<sup>15</sup> CF<sub>3</sub>-radical addition to styrene and its derivatives is fast and lies in the order of  $10^7$  to  $10^8 \text{ M}^{-1} \text{ s}^{-1}$ . Additions proceed faster for electron-rich styrene derivatives and steric effects play a role.

Trifluoromethylated *N*-heterocycles are prevalent in many drugs or drug candidates.<sup>11</sup> Traditionally, the introduction of the CF<sub>3</sub> group into an *N*-heteroarene is achieved by reaction of a halogenated or borylated heteroarene with a trifluoromethylating reagent catalyzed by a transition metal.<sup>11</sup> Direct C–H trifluoromethylation of a heteroarene can be achieved by using either radical chemistry or transition metal based processes.<sup>11</sup> As an alternative, we chose *ortho*-isocyanobiaryls **23** as acceptors using reagents **1a** and **1b** as trifluoromethyl and perfluoroalkyl radical precursors to give **24** (Scheme 8).<sup>16,17</sup> The cascade works best in 1,4-dioxane at 70 °C with (*n*-Bu)<sub>4</sub>Ni as a radical initiator (Scheme 8). Mechanistically, chain initiation occurs by reduction of **1** by the iodide to generate a CF<sub>3</sub>-radical and *ortho*-iodobenzoate. CF<sub>3</sub>-radical addition to the isonitrile generates an imidoyl radical, which undergoes intramolecular base promoted homolytic aromatic substitution to afford **24** formally liberating an electron to close the catalytic cycle.<sup>18,19</sup>

The aryl isonitrile approach is general for the preparation of perfluoroalkylated heteroarenes.<sup>20–23</sup> The concept was also used for preparation of isoquinolines **26** from  $\alpha$ -isocyno

## Scheme 8. Reaction of 2-Isocyanobiaryls with I(III) Reagents



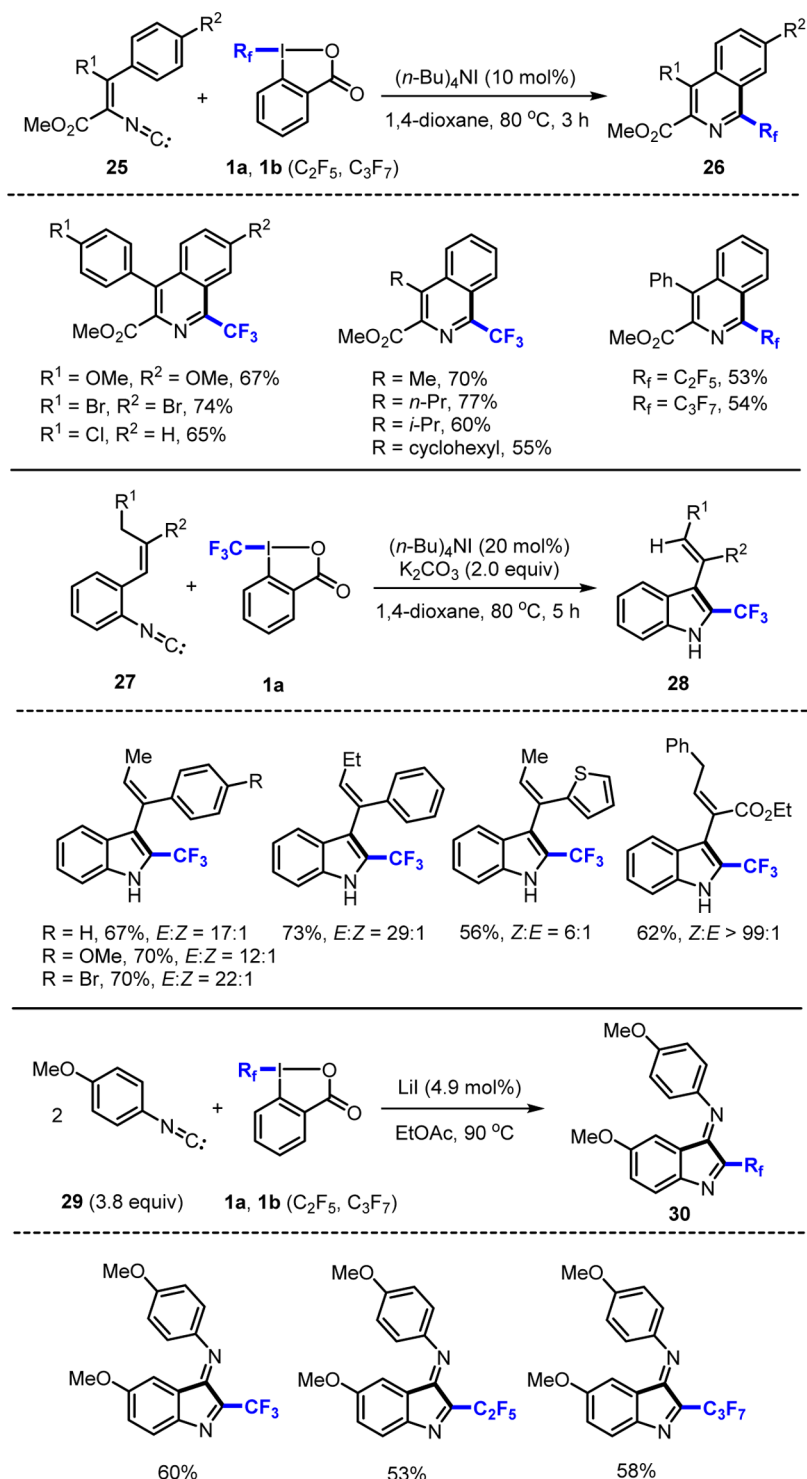
cinnamic esters **25** and I(III) reagents **1a** and **1b** (Scheme 9).<sup>21</sup> In analogy, indoles **28** were prepared from isonitriles **27**,<sup>22</sup> and we found that electron-rich isonitriles **29** react with **1a** and **1b** via two sequential radical additions to indole-3-imines **30**.<sup>23</sup>

Guided by Chiba who used vinyl azides as CF<sub>3</sub>-radical acceptors,<sup>24</sup> we reacted azides **31** with **1a** or **1b** ( $R_f = \text{C}_2\text{F}_5$ ) in the presence of (*n*-Bu)<sub>4</sub>Ni and Cs<sub>2</sub>CO<sub>3</sub> to give the phenanthridines **32** (X = C, Y = CH) (Scheme 10).<sup>25</sup> Quinoxalones **32** (X = N, Y = N) are also accessible by such cascades. The chain is initiated by SET reduction of **1a** generating the CF<sub>3</sub>-radical and the *ortho*-iodobenzoate anion. Addition of the CF<sub>3</sub>-radical to the vinyl group followed by N<sub>2</sub>-fragmentation affords an iminyl radical, which undergoes base promoted homolytic aromatic substitution<sup>19</sup> to give the 2,2,2-trifluoroethyl phenanthridines and quinoxalones **32**. In the product forming step, an electron is formally liberated<sup>18a</sup> closing the catalytic cycle.

## 4. ALKENE AZIDATION WITH AZIDYL RADICALS

N<sub>3</sub>-radical generation is achieved by homolysis of the I–N<sub>3</sub> bond in azido I(III) reagents. Antonchick generated bis(azido)iodobenzene **35** *in situ* by reacting phenyliodine bis(trifluoroacetate) **11** with

Scheme 9. Perfluoroalkylated Heteroarenes from Aryl Isonitriles

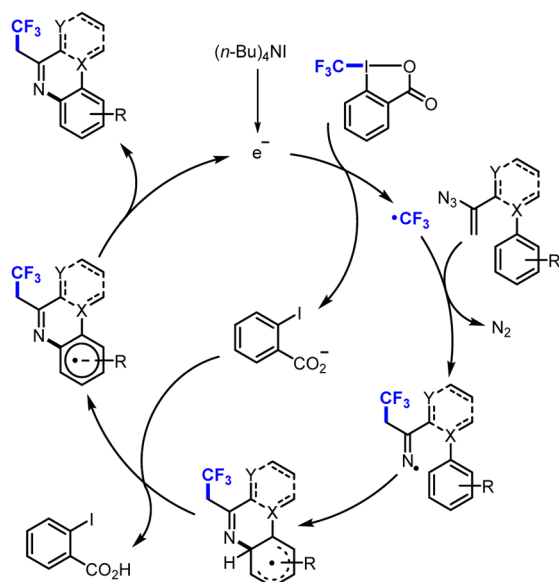
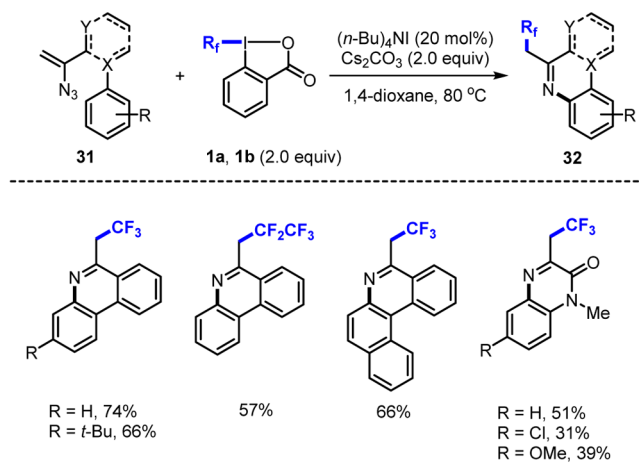


TMSN<sub>3</sub>.<sup>26</sup> Reagent **35** reacts with acrylamides **33** to  $\alpha$ -oxindoles **34** (Scheme 11). Cascades proceed by addition of the N<sub>3</sub>-radical to **33** to give the radical **36**, which cyclizes to the arene to **37**. Oxidation by the azidoiodanyl radical generated in the initial homolysis and deprotonation give **34**. Amidinyl radicals can also be generated by homolysis of amidinyl I(III) reagents that are easily prepared *in situ* upon reaction of bezamidines with PhI(OAc)<sub>2</sub>.<sup>27</sup>

The Zhdankin reagent **2**<sup>28</sup> can be SET reduced for clean N<sub>3</sub>-radical generation. Loh disclosed that styrene derivatives

react with **2** under Cu-catalysis to provide the azidoxygenation products **38**.<sup>9d</sup> SET reduction of **2** by a Cu(I)-complex gives the N<sub>3</sub>-radical that adds to the styrene derivative to provide a benzylic radical and a Cu(II)-complex. Oxygenation to **38** is assisted by the Cu(II)-complex generated in the initial SET step.

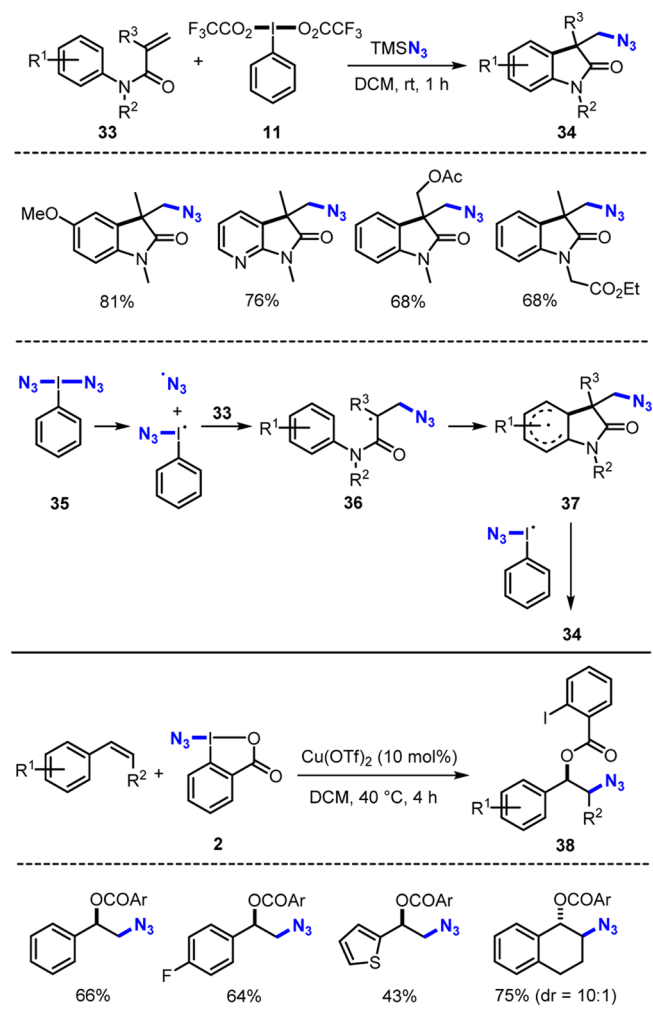
Recognizing the similarity of the Togni and Zhdankin reagents, we explored radical azidoxygenation of alkenes with TEMPO<sub>Na</sub> and found that alkenes react with **2** and TEMPO<sub>Na</sub> to products **39** (Scheme 12).<sup>29</sup> Styrene derivatives, enol ethers,

Scheme 10. Vinyl Azides as CF<sub>3</sub>-Radical Acceptors

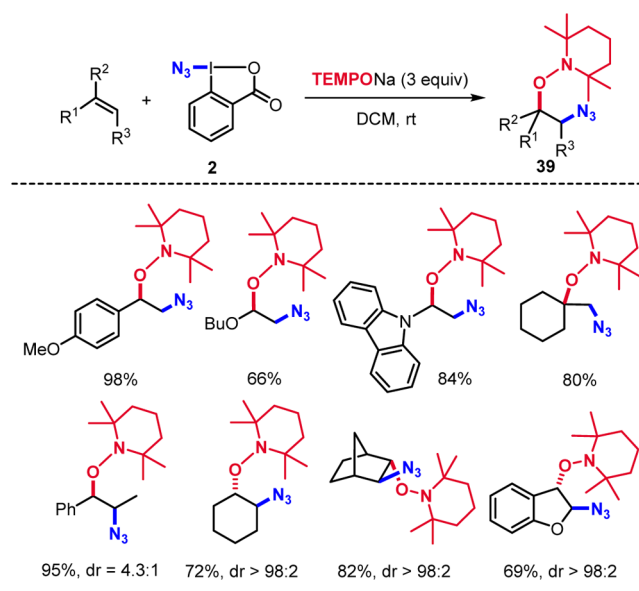
enamines, aliphatic alkenes, and benzofurans were substrates for this transformation. The mechanism resembles that for the trifluoromethylaminoxylation discussed in [Scheme 6](#).

## 5. BIARYL FORMATION VIA ARENE RADICAL CATIONS

Kita showed that electron-rich arenes are SET oxidized by Lewis acid activated  $\text{PhI}(\text{OCOCF}_3)_2$  to arene radical cations that react intra-<sup>30a</sup> or intermolecularly<sup>7a,b</sup> with an arene to give biaryls after one-electron oxidation and deprotonation. For example, reaction of a bibenzyl ether with  $\text{PhI}(\text{OCOCF}_3)_2$  and a B-Lewis acid provided **40** ([Scheme 13](#)). SET oxidation occurs via formation of a charge transfer complex between the I(III) reagent and the arene with subsequent electron transfer to form an arene radical cation. Intramolecular electrophilic aromatic substitution followed by a renewed SET oxidation and deprotonation lead to **40**. Cross dehydrogenative coupling can be achieved using two different arenes with different oxidation potential:<sup>7a</sup> Reaction of naphthalene and pentamethylbenzene with  $\text{PhI}(\text{OCOCF}_3)_2$  provided the cross coupling product **41**. More general is the cross coupling between heteroaryl I(III) reagents and electron-rich arenes. As shown for the reaction of I-species **42** with 1,3-dimethoxybenzene to give biaryl **43**, the

Scheme 11. Cascades Involving N<sub>3</sub>-Radicals

Scheme 12. Azidoaminoxylation of Alkenes

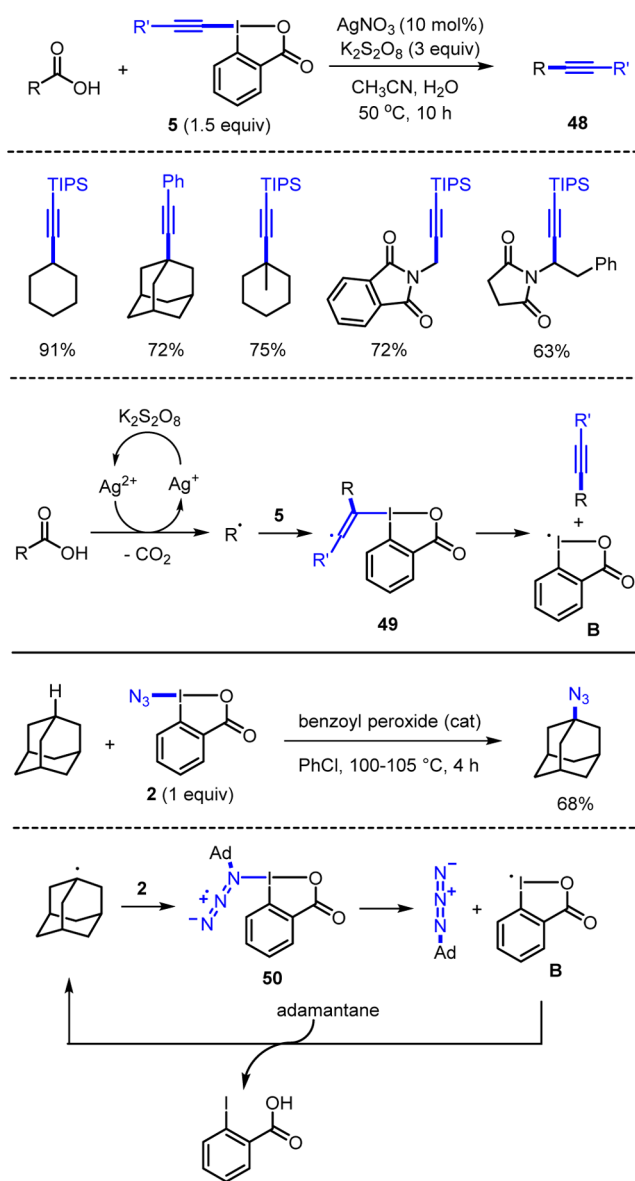


I(III) reagent acts as SET oxidant and aryl donor.<sup>7b</sup> Likely, C–C bond formation occurs directly from the charge transfer complex. It was also found that arene azidation can be obtained by reaction of intermediately generated arene radical cations





Scheme 17. C-Radical Alkynylation and Azidation

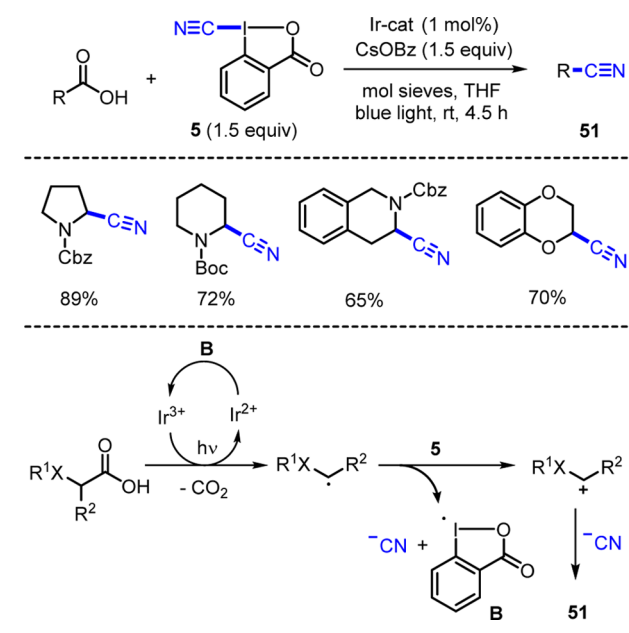


that internal and terminal alkenes are suitable substrates to provide the arylaminoxylated products 45. Mechanistically, these transformations resemble the trifluoromethylaminoxylations discussed in Scheme 6. We also tested diaryliodonium salts as aryl radical precursors,<sup>31</sup> which have been applied to electrophilic arylation,<sup>35</sup> cross-coupling reactions,<sup>36</sup> C–H arylations,<sup>37</sup> and for benzyne generation.<sup>38</sup> Aryl radical generation was clean upon treatment of the salt 7 with TEMPONa.<sup>34</sup> In the presence of a styrene derivative, radical addition and subsequent TEMPO trapping give products 45. Both symmetric and nonsymmetric diaryliodonium tetrafluoroborates were tested showing that SET reduction of electronically different diaryl I(III) reagents occurs with low selectivity. Moreover, steric effects do not play an important role for aryl radical generation (Scheme 14).

## 7. TRANSFER OF TWO LIGANDS FROM HYPERVALENT I(III) REAGENTS

In most transformations, only one ligand of the I(III) reagent gets transferred to the substrate. We were intrigued by the

Scheme 18. Cyanation of Carboxylic Acids



challenge of sequentially transferring two ligands from an I(III) reagent to an alkyne<sup>39</sup> and found that aryl(cyano)iodonium triflates 8<sup>40</sup> can be applied to stereo- and regioselective alkyne cyanotriflation.<sup>3</sup> This transformation is best conducted with Fe(OAc)<sub>2</sub>, 1,10-phenanthroline, and triflate 8 (Scheme 15). Cyanotriflation works on alkyl aryl alkynes with complete regiochemistry and excellent *Z/E*-stereoselectivity to provide 46. Mechanistically, SET-reduction of 8 by the Fe(II)–phen complex generates radical A, which adds to the alkyne to give vinyl radical B. SET oxidation of B by the Fe(III)-complex leads to cation C regenerating the Fe(II)-complex. Reductive elimination at the I(III) center provides the cationic acrylonitrile, which gets trapped by the triflate anion *syn* to the sterically less shielding cyano group.

We also applied aryl(perfluoroalkyl)iodonium triflates 9 for alkyne perfluoroalkyltriflation. Reactions proceed using CuCl initiation and 9 to provide 47 with excellent regio- and stereoselectivity (Scheme 16).<sup>41</sup> The perfluoroalkyltriflation works for internal and terminal aryl alkynes. Initiation of the chain occurs by SET reduction of 9 with CuCl to generate the R<sub>F</sub>-radical, Cu(II)ClOTf, and iodobenzene. R<sub>F</sub>-radical addition to the alkyne leads to a vinyl radical, which is oxidized by 9 in an electron-catalyzed<sup>18a</sup> process to give a vinylic cation that is stereoselectively trapped by the triflate anion to 47. The high *E*-stereoselectivity can be explained considering steric shielding and also electrostatic repulsion by the R<sub>F</sub>-substituent. Reactions can also be initiated by (*n*-Bu)<sub>4</sub>N<sup>+</sup>I<sup>-</sup> supporting that perfluoroalkyltriflation proceeds via a chain process. However, since reactions are more efficiently initiated by the Cu(I)-salt, in some cycles the vinylic radical gets oxidized by Cu(II)ClOTf regenerating the initiator, featuring smart initiation.<sup>18b</sup>

## 8. I(III) REAGENTS AS RADICAL ACCEPTORS

Li and co-workers showed that alkynyl I(III) reagents 5 act as C-radical acceptors.<sup>8a</sup> They chose carboxylic acids as substrates that are oxidatively decarboxylated to C-radicals using catalytic AgNO<sub>3</sub> and K<sub>2</sub>S<sub>2</sub>O<sub>8</sub> (Scheme 17). Secondary and tertiary carboxylic acids were converted to the alkynylated products 48. Xiao<sup>8c</sup> and Waser<sup>8d</sup> conducted similar transformations under

photoredox catalysis to convert carboxylic acids with **5** to products **48**, and Chen used alkyl trifluoroborates as C-radical precursors in combination with **5** (R = alkynyl) and a photoredox catalyst.<sup>8b</sup> Li suggested that Ag-catalyzed decarboxylation of the acid leads to a C-radical that adds to reagent **5** to form radical **49**.  $\beta$ -Fragmentation provides radical **B** and the target **48**.<sup>8a</sup> Notably, computational studies by Waser revealed that **49** might not be an intermediate and that the alkynyl transfer might occur by a direct substitution.<sup>8f</sup>

Early studies on radical azidation with azido-I(III) reagents were disclosed by Magnus showing that the PhIO in combination with TMSN<sub>3</sub> allows for direct radical C–H azidation.<sup>2k</sup> In analogy, Ph(OCOCF<sub>3</sub>)<sub>2</sub>/TMSN<sub>3</sub> can be used for this purpose.<sup>2l</sup> C-radical azidation can also be achieved with reagent **2** under radical conditions, as first reported by Zhdankin.<sup>9b</sup> For example, adamantane reacts with **2** in chlorobenzene at 105 °C using dibenzoyl peroxide as an initiator to azidoadamantane. Initiation occurs by thermal decomposition of the peroxide to give a carboxyl radical, which abstracts a H atom from adamantane to generate the adamantyl radical, which adds to **2** leading to adduct **50**, which fragments to azidoadamantane and radical **B**. **B** abstracts a H atom from adamantane to sustain the chain. Several groups reported successful C-radical azidation with reagent **2** since.<sup>9c–g</sup>

Waser showed that the carboxylic group in acids can be substituted by the cyano group with reagent **5** (R = CN) using photoredox catalysis (Scheme 18).<sup>8f</sup> Oxidative decarboxylation by a photoexcited Ir(III) complex gives a C-radical that reacts with **5** to the cyano transfer product **51**. Calculations reveal that the C-radical generated after oxidative decarboxylation likely reduces **5** to form an iminium cation, an iodanyl radical **B**, and cyanide. The iminium ion is eventually trapped by the cyanide to **51**. Iodanyl radical **B** is reduced by the Ir(II)-catalyst to regenerate the Ir(III)-complex closing the catalytic cycle. As a byproduct, 2-iodobenzoate is formed.

## 9. SUMMARY AND PERSPECTIVE

We showed that I(III) compounds are valuable reagents to conduct diverse radical chemistry. The hypervalent bond in these reagents is weak so that thermal homolysis or irradiation leads to reactive intermediates that can be used for direct C–H functionalization. A large body of work deals with single electron reduction of I(III) reagents to provide carbon or heteroatom centered radicals. Radical generation by SET-reduction of I(III) reagents has emerged as a versatile tool for reliable functionalization of  $\pi$ -systems, allowing access to synthetically valuable structures. Notably, often transformations can be conducted in the absence of any transition metal catalyst or toxic reagent. These reactions show high efficiency, and selectivity and often good atom economy, starting materials are easily accessed, and waste handling is not a problem. Further, it is discussed that selected I(III) reagents can also act as radical acceptors for alkynylation, azidation, and cyanation. As can be extracted from the many recent contributions, radical chemistry using I(III) compounds is a timely and active research field. Considering the current ongoing renaissance of radical chemistry, it is obvious that novel interesting applications of I(III) reagents in synthetic radical chemistry will appear in the future.

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## Notes

The authors declare no competing financial interest.

## Biographies

**Xi Wang** was born in Changsha, China, in 1985. He received his B.S. from Hunan University in 2006 and joined the group of Professor Zhangjie Shi at Peking University in 2008. He moved to the laboratory of Professor Jianbo Wang at Peking University in 2010 and obtained his Ph.D. in 2013. Since 2014, he has conducted postdoctoral studies as an Alexander von Humboldt Fellow in the Studer group at the Westfälische Wilhelms-Universität in Münster. His research focuses on trifluoromethylation, cross-coupling reactions involving metal carbenes, and SET reduction of hypervalent iodine(III) reagents.

**Armido Studer** received his Diploma in 1991 and his Ph.D. in 1995 from ETH Zürich with Prof. Dieter Seebach. He then did postdoctoral studies at the University of Pittsburgh with Prof. Dennis P. Curran. In 1996, he started his independent career at the ETH Zürich. In 2000, he was appointed Associate Professor of Organic Chemistry at the Philipps-University in Marburg, and in 2004 Professor of Organic Chemistry at the Westfälische Wilhelms-University in Münster. In 2006, he received the Novartis Young Investigator Award in Chemistry, in 2007 the Solvias Ligand Contest Award, in 2014 the Research Award of the WWU Münster, and an ERC Advanced Grant in 2016. His research focuses on the development of new synthetic methods in radical chemistry, NHC catalysis, and transition metal catalysis. Polymer chemistry and surface chemistry are other research areas of interest.

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