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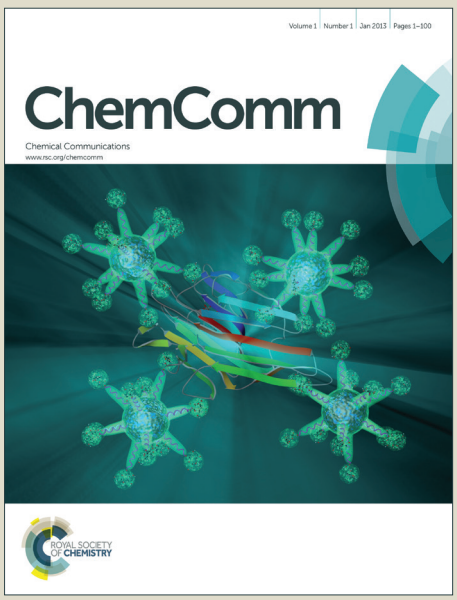

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Halocarbocyclization versus Dihalogenation: Substituent Directed Iodine(III) Catalyzed Halogenations

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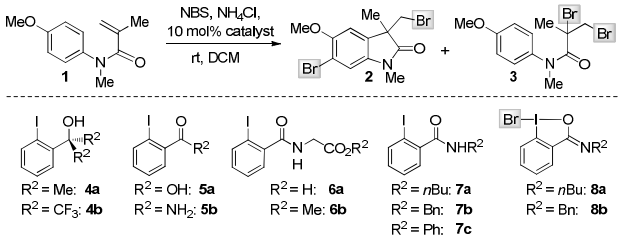
The substituents' nucleophilicity in iodobenzene pre-catalysts have a huge impact on product selectivity in iodine(III) triggered halogenations, steering the reactivity from solely carbocyclizations towards dihalogenations. Utilizing this catalyst-dependent reactivity a diastereo- and chemoselective dihalogenation method was established allowing the conversion of structurally and electronically diverse unsaturated compounds in excellent yields.

(λ3)-Iodanes recently advanced to valuable and reliable reagents due to their low toxicity, mild reactivity, and ease of handling.[1] Besides their broad application as oxidants iodine(III) compounds have also entered other fields of organic chemistry, in particular atom transfer reactions.[1-2] Hypervalent iodine-halogen reagents are frequently used in fluorinations[1c,g,3] and chlorinations,[1c-e,g,4,5] while the installation of bromine or iodine into carbon frameworks using such reagents is less common. The latter may be attributed to the instability, especially of non-cyclic I(III)-X compounds, making studies towards the in-situ generation of cyclic reagents and/or their involvement in catalytic processes highly desirable. The only isolable bromo iodine(III) compounds known so far are Martin's bromoiodinanes.[6] These representatives were applied in radical brominations by Martin in 1979[6a] and later studied by Braddock in more detail.[6b,c,7]

In this paper we describe the decisive impact of the structure of iodobenzene pre-catalysts **4**-**7** on product selectivity, allowing a change in the reaction course from halocarbocyclization to dihalogenation. This *ortho*-substituent dependent reactivity is closely connected to the *trans* effect exhibited by the nearly linear disposed ligands at the iodine atom in the putatively in-situ formed iodine(III) species, such as **8** (Table 1). Exploiting these properties of **4**-**7** has led to the development of a reliable, easy to handle, and safe catalytic *anti*-selective dibromination and dichlorination method.

During our studies on iodine(III)-mediated cyclization reactions, we realized that the structure of the employed iodobenzene catalyst has a significant effect on the reaction outcome. Catalysts equipped with less nucleophilic groups at C-2, like, e.g., the hydroxy methylene function in **4**, did not trigger any reaction at all (Table 1, entry 1). Bromocarbocyclization to **2** proceeded upon replacement of these alcohol moieties by more Lewis basic groups such as an acid or amide function in **5**, but only slowly and with activated substrates such as **1** (entry 2). In the next step we further enhanced the nucleophilicity of the carboxyl oxygen in order to accelerate product formation.[7] Therefore, we screened a series of iodobenzamides with various substituents at the nitrogen atom. To our surprise, small structural variations even in the periphery of the *N*-substituents in our catalysts accounted for dramatic changes in overall reactivity and chemoselectivity. Replacing the carboxyl containing side chain in **6** (entry 3) by a substituent exhibiting purely electron-donating properties (+I and/or +M), such as the alkyl, benzyl, or phenyl moiety in **7**, gave rise not only to oxoindole **2**, but also to a significant amount of dibrominated product **3** under the same reaction conditions (entry 4).

Table 1 Influence of the *ortho*-substituents in pre-catalyst **4**-**7** on the bromination of amides **1**



Entry[a]	catalyst	time	ratio of **2**:**3**[b]	yield[c]
1	**4a**/**4b**	24 h	-	-
2	**5a**/**5b**	6 h	1:0	30%/74%
3	**6a**/**6b**	3 h	1:0	96%/94%[8]
4	**7a**/**7b**/**7c**	3 h	~3:1	89%/92%/85%

[a]The reactions were carried out using **1** (1.00 mmol), NBS (2.20 mmol.), catalyst (10 mol%), and 1 drop NH_4Cl_{aq} in DCM (0.2M) at rt. [b]Determined by ^1H NMR from the crude mixture. [c]Isolated yield.

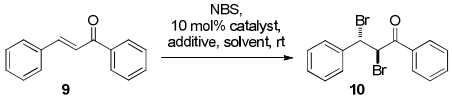
The structure-dependent reactivity can be traced back to the *trans* influence[9] of the ligands in the putative intermediate **8**. This mutual effect[10] has a tremendous impact on the in-situ formed iodine(III) compounds **8**, thus resulting in the formation of more instable and consequently more reactive iodine(III) species with increasing donor ability of the ligand *trans* to the bromine atom. In addition to the observed rate acceleration (see ESI), the chemoselectivity was significantly altered by the *trans* effect exhibited by the different *ortho* substituents in iodobenzenes **4**-**7**, shifting the reactivity from

bromocarbocyclization to dibromination. This variation in selectivity has to be accompanied with a change in reaction mechanism, as dibromination does not occur in the presence of an electrophilic bromination reagent alone, such as NBS, without an inorganic bromide salt added.[11] Our initial studies suggest that the strong *trans* effect exhibited by the *N*-substituents in **7** leads to the facial in-situ generation of bromine, as indicated by the brown-orange color that appears upon addition of catalyst **7** to the reaction mixtures and that vanishes during the transformation. As I(III)-species, in general, are prone to radical reactions, we propose that in the highly reactive intermediates **8** the weak Br-I(III) bond is cleaved homolytically. The resulting bromine radical then reacts with another equivalent of NBS or intermediate **8** giving bromine that in turn triggers a classical electrophilic bromination of alkene **2**.[12] The exclusive formation of *trans*-vicinal dibromo compounds (Figure 1) strongly indicates such an electrophilic mechanism via a bromonium ion. Control experiments with chalcone (**9**, see ESI) as starting material showed a significantly hampered or even completely abolished dibromination activity when the reaction was conducted in the dark or if TEMPO was added as a radical scavenger.[13] Such an influence of reactivity was not observed during bromocarbocyclization reactions of **2**.[8] This further supports our hypothesis that the iodine(III) reagents **8**, which bear *ortho* groups with a strong *trans* effect, are involved in a radical generation of Br_2, while I(III) intermediates originating from pre-catalysts with less nucleophilic substituents next to iodine, such as **5** and **6**, act as electrophilic bromination agents.

The catalyst-dependent dibromination pathway opens the possibility to develop a reliable, ecologically benign, and safe dibromination method. Electrophilic halogenations are typically performed using Br_2,[14] which poses difficulties in handling, as well as from synthetic and environmental considerations. In order to provide safer, more selective, and 'greener' alternatives, especially suitable for large-scale applications, this research area has become a vital and intensively studied field.[6c,15,16] However, only recently the first organocatalytic approaches to vicinal dibrominated alkanes have been described. These strategies utilize either sub-stoichiometric quantities of pyrrolidine together with NBS[17] or a thiourea-derived catalyst in combination with dibromohydantoin,[18] both producing the respective *anti* addition products.

With this in mind, we further advanced our organocatalytic system and introduced it as a versatile alternative for the direct application of Br_2. Using chalcone (**9**) as our model substrate, the best results were obtained employing 10 mol% of catalyst **7a** in the presence of 2.2 equiv. NBS, selectively giving the *trans*-dibrominated compound **10** in 98% yield (Table 2, entry 1). Only little conversion of **9** (12%) was observed without catalyst **7a** (entry 2). As already observed earlier,[8] addition of an acidic additive was necessary to obtain sufficient turnover (entry 3-4).

Table 2 Selected examples for the optimization of the reaction conditions in iodine(III)-mediated dibrominations[a]

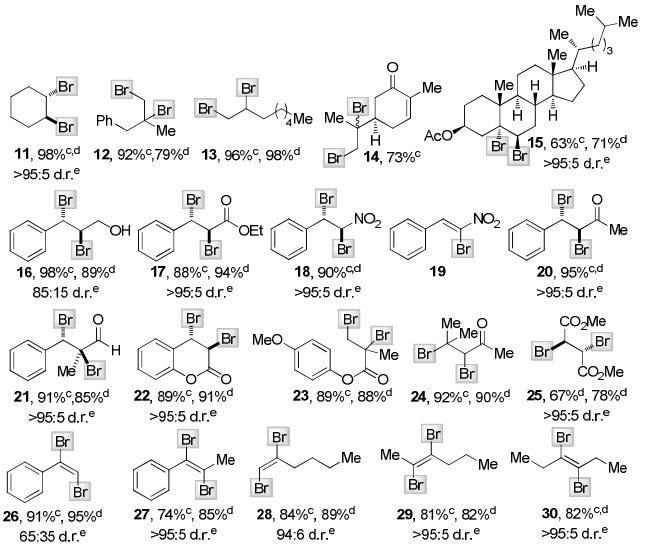


Entry	catalyst	additive (10 mol%)	time	conversion[b]
1	**7a**	NH_4Cl	2 h	>99% (98%)[c]
2	-	NH_4Cl	5 h	12%
3	**7a**	-	5 h	<5%
4	**7a**	TFA	1 h	>99%

[a]The reactions were carried out using **9** (1.00 mmol), NBS (2.20 mmol.), catalyst (10 mol%), and 1 drop NH_4Cl_{aq} in DCM (0.2M) at rt. [b]Determined by HPLC from the crude mixture. [c]Isolated yield. For more entries with **9** as substrate and further examples as well as control experiments see ESI.

Under these conditions, a multitude of different unsaturated compounds (Figure 1), ranging from simple hydrocarbons, like e.g., cyclohexene, methallylbenzene, and 1-octene (→11-13) to structurally highly complex molecules such as carvone and cholesterol (→14, 15), were efficiently converted in 63%-98% yield and complete diastereoselectivity. One exception constituted the use of cinnamyl alcohol, where an isomeric mixture of **16** (85:15 d.r.) was isolated favoring the *anti* product (98% yield). Transformation of electron-poor and thus deactivated olefins was also easily performed, affording products **17**-**25**. Due to the mild reaction conditions, no elimination of HBr was observed, except for nitrophenylethane **18**, which was slowly converted into its addition-elimination product **19** upon work-up. When the double-bond was replaced by an alkyne moiety, the reaction also occurred smoothly, selectively giving the *trans*-dibromo alkenes **26**-**30** with no tetrabromo derivatives detectable. Only substrates bearing a terminal triple bond, such as phenyl acetylene and 1-hexyne, gave diastereomeric mixtures of **26** and **29** (65:35 and 94:6), respectively. It is noteworthy that the dibromination of both alkenes and alkynes proceeded chemoselectively with no aromatic bromination being observed, even if highly activated aryl moieties were present, such as in the 4-OMe phenyl ester **23**.

Figure 1 Substrate scope for the dibromination.[a,b]



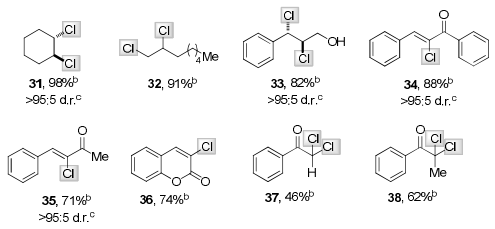
[a]**Procedure A:** The reactions were carried out using alkene or alkyne (1 eq.), NBS (2.2 eq.), catalyst **7a** (10 mol%), and 1 drop NH_4Cl_{aq} in DCM (0.2M) at rt. [b]**Procedure B:** The reactions were carried out using alkene or alkyne (1 eq.), KBr (3.0 eq.), oxone (1.1 eq.), and catalyst **7a** (10 mol%) in DCM (0.2M) at rt or 0 °C. [c]Isolated yield obtained using procedure A. [d]Isolated yield obtained using procedure B. [e] d.r. determined by ^1H NMR.

To make the method even more environmentally friendly, we attempted to replace the electrophilic bromination agent NBS, which produces succinimide as a waste product, by KBr/oxone.[19,20] Under these conditions the yields remained excellent while the reaction times for the conversion of all substrates employed were significantly shorter (down to 5 min). Although oxidative halogenations employing inorganic salts and oxone are literature-known,[15c,21] our catalytic procedure constitutes a significant improvement, as it avoids the often needed harsh conditions. Even substrates bearing oxidatively sensitive functionalities, like, e.g. hydroxy or aldehyde groups, were smoothly transformed into their dibromo products (**16** and **21**) in very good yields and selectivities. Also seemingly inert starting materials, like, e.g. coumarin (**35**),

which showed no reaction without catalyst **7a** at all (see ESI), were easily converted into **22** using the described protocol.

The switch to dichlorinations[22] was done by simple replacing KBr by its corresponding chloride salt (KCl) affording the desired *trans* dichlorocyclohexane (**31**) and 1,2-dichlorooctane (**32**) in 98% and 91% yield, respectively (Figure 2). Surprisingly, alcohol **33** was obtained as a single diastereomer upon chlorination, in contrast to the generation of its dibromo analog **16** (c.f. Figure 1). Compounds bearing electron-deficient double bonds also reacted under these conditions, providing the α-chlorinated products **34**-**36** in good yields (71%-88%).[23] Application of alkynes produced the geminal dichlorinated ketones **37** and **38**. The corresponding dibromo carbonyl compounds were found only in traces when KBr was used which may be due to the fact that chloride is less nucleophilic and thus less reactive compared to bromide.

Figure 2 Oxidative chlorination of alkenes and alkynes[a]



[a]The reactions were carried out using alkene or alkyne (1 eq.), KCl (5.0 eq.), oxone (1.1 eq.), and catalyst **7a** (10 mol%) in DCM (0.2M) at rt or 0 °C. [b]Isolated yields. [c]d.r. determined by ^{1}H NMR.

In summary, we showed that subtle variations of the electronic properties of the *ortho* substituents in iodobenzene pre-catalysts **4**-**7** do not only affect the reaction rate, but also significantly influence the chemoselectivity in iodine(III) mediated halogenations. This catalyst-dependent reactivity clearly correlates with the nucleophilicity and thus with the strength of the *trans* effect exhibited by the *ortho* substituent in the I(III) intermediates **8**. In-depth studies of the observed structure-reactivity relationship together with detailed investigations of the alterations in the mechanisms addressed by structurally diverse I(III) catalysts are part of ongoing studies in our group and will help to further extend the concept of iodine(III)-triggered halogen-induced reactions.

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Notes and references

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† Electronic Supplementary Information (ESI) available: Experimental procedures, supplementary data, and the ^{1}H-, ^{13}C-NMR spectra, see DOI: 10.1039/c000000x/

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