Asymmetric Synthesis

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Asymmetric Hydroxylative Phenol Dearomatization Promoted by Chiral Binaphthylic and Biphenylic Iodanes**

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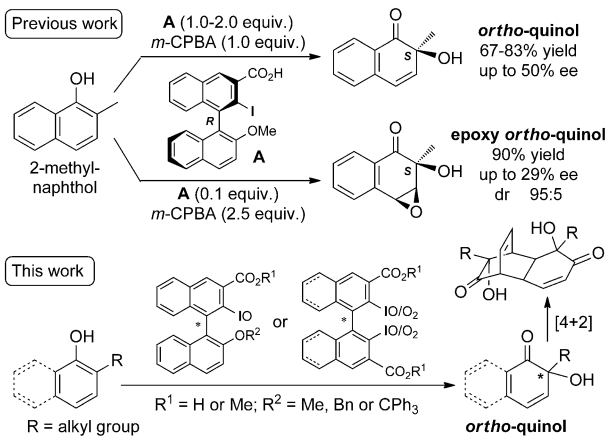
Abstract: *The long-standing quest for chiral hypervalent organoiodine compounds (i.e., iodanes) as metal-free reagents for asymmetric synthesis continues. Although remarkable progress has recently been made in organoiodine-catalyzed reactions using a terminal oxidant in stoichiometric amounts, there is still a significant need for "flaskable" chiral iodane reagents. Herein, we describe the synthesis of new iodobinaphthyls and iodobiphenyls, their successful and selective DMDO-mediated oxidation into either λ^3- or λ^5-iodanes, and the evaluation of their capacity to promote asymmetric hydroxylative phenol dearomatization (HPD) reactions. Most notably, a C_2-symmetrical biphenylic λ^5-iodane promoted the HPD-induced conversion of the monoterpene thymol into the corresponding ortho-quinol-based [4+2] cyclodimer (i.e., bis(thymol)) with enantiomeric excesses of up to 94%.*

The chemistry of hypervalent organoiodine compounds, also referred to as iodanes, has unarguably experienced an impressive development since the early 1990s, as evidenced by both the diversity of iodane reagents that are available today and the number of chemical transformations that these reagents can promote.[1,2] The initial incitement to the development of λ^3- and λ^5-iodanes (i.e., I^{III}- and I^{V}-based compounds), which was mainly due to their useful oxidizing properties and capacity to replace toxic heavy-metal-based reagents in dehydrogenating and oxygenative reactions, has paved the way to the exploitation of iodanes in various metal-free reactions.[1,2] Major current and competing research efforts focus on the design of chiral iodane structures for asymmetric synthesis and organoiodine-catalyzed versions thereof.[3] While remarkable progress has notably been made in intramolecular asymmetric oxygenative reactions, such as phenol dearomatizing spirolactonization[3b,c] and alkene oxy-lactonization[3d] with enantiomeric excesses (*ee*) above 90%, the quest for novel chiral iodanes continues.

Our own contribution to this area of research led to the identification of iodobinaphthyl **A** as a promising scaffold for more challenging intermolecular asymmetric oxygenative reactions, such as the hydroxylative phenol dearomatization (HPD reaction), which we could accomplish with up to 50% *ee* through the in situ generation of the chiral iodane using *meta*-chloroperbenzoic acid (*m*-CPBA) as the oxidant (Scheme 1).[4] We were however unsatisfied with the difficulties we encountered in the attempt to cleanly oxidize **A** ex situ, because this prevented us from isolating and characterizing the reacting iodane species. Mass spectrometric analysis of the reaction medium indicated the possible implication of a λ^5-iodane species, but an asymmetric oxygen-transfer from a corresponding λ^3-iodane species could not be entirely disregarded on the sole basis of this analysis.[4a] Moreover, the efficient epoxidation of the primary *ortho*-quinol product that was observed when using *m*-CPBA in excess cast some doubts on its abilities to be used as a general and chemoselective terminal oxidant in organo-iodine-catalyzed variants of such reactions with oxygenation-sensitive substrates (Scheme 1).[4a,c] We thus decided to generate several chiral iodobiaryls to find a convenient solution for their ex situ oxidation into iodanes and to



Scheme 1. Asymmetric hydroxylative phenol dearomatization (HPD reaction) using chiral biarylic iodanes generated in situ[4a] or ex situ (this work).

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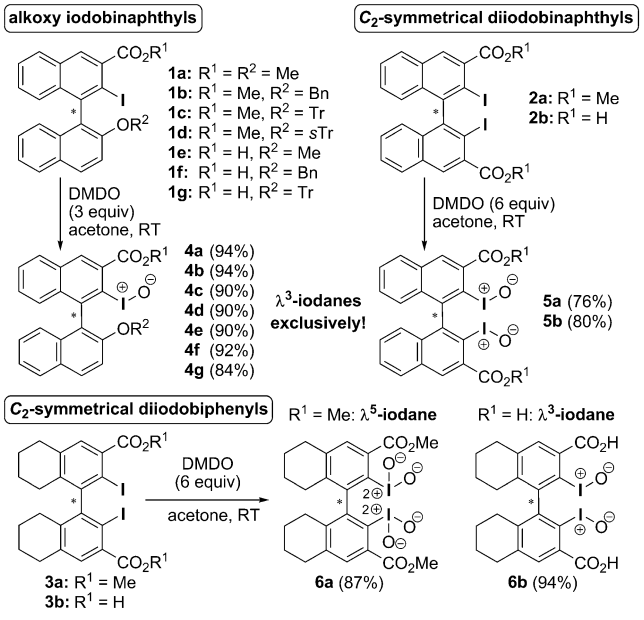
evalutate the performance of these "flaskable" iodanes in asymmetric HPD reactions.

This investigation commenced with the oxidation of 3-iodo-2-naphthoic acid, a simple iodonaphthyl species chosen as a model compound to identify suitable conditions for its conversion into its corresponding λ^3- or λ^5-iodane (see the Supporting Information). The screening of oxidizing systems that were selected among those classically used in hypervalent iodine chemistry[1,5] showed that effective oxygenation could be achieved with either oxone in water/acetonitrile (1:1), *m*-CPBA in dichloromethane, or 3,3-dimethyldioxirane (DMDO) in acetone. In all three cases, the single iodane that precipitated from the reaction mixture was identified as an iodosyl derivative by ^{13}C NMR analysis[6] and isolated in 83, 90, and 91% yields, respectively. X-ray analysis of the translucent needles obtained by crystallization from DMSO revealed the cyclic benziodoxole structure of this λ^3-iodane (CCDC-953640, see the Supporting Information).[7] No iodyl variant was detected in any of these oxidations, even when using DMDO, which is usually used to generate such λ^5-iodanes.

In light of these successful and selective oxidations of a iodonaphthyl substrate into its corresponding λ^3-iodane, we next decided to reconsider the ex situ oxidation of our iodobinaphthyl **A**. We thus synthesized a series of structurally related alkoxy iodobinaphthyls **1a–g** (i.e., R^2 = Me, Bn, trityl (Tr), or supertrityl (*s*Tr)) bearing either a methyl ester or a carboxylic acid function in *ortho* position to the iodine center (i.e., R^1 = Me or H, Scheme 2; see also the Supporting Information).[4a] Atropisomeric resolution was achieved by semipreparative HPLC separation of their common racemic binaphthylamine intermediate on a chiral stationary phase. The absolute configuration of the (*S*)-atropisomer was confirmed by X-ray analysis (CCDC-989094).[7] The absence of racemization during the subsequent chemical steps was controlled by HPLC analysis on a chiral stationary phase (see the Supporting Information). The C_2-symmetrical diiodobinaphthyls **2a/b** were similarly prepared, and partial hydrogenation of the binaphthyl core gave access to the diiodobiphenyl analogues **3a/b** (Scheme 2, see the Supporting Information). Atropisomeric resolution of compounds **2** and **3** was achieved using (*S*)-mandelic acid as chiral auxiliary. The absolute configuration of (*R*)-**2a** and (*R*)-**3a** was confirmed by X-ray analysis (CCDC-989095 and CCDC-989096).[7]

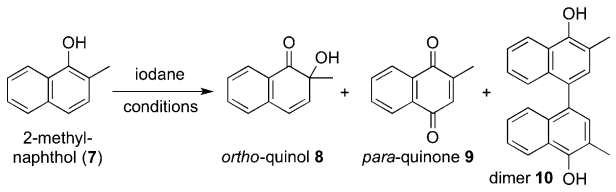


Scheme 2. Selective DMDO-mediated oxidation of alkoxy and C_2-symmetrical iodobiaryls to their corresponding λ^3- or λ^5-iodanes. *s*Tr = supertrityl = C(4-*t*Bu-C_6H_4)$_3$, Tr = trityl = CPh_3.

The benzyloxy iodobinaphthyl methyl ester **1b** was then chosen to identify an appropriate oxygenating reagent and was thus subjected to all the oxidizing conditions previously screened (see above). Only freshly prepared DMDO cleanly oxidized **1b**. The use of three equivalents of DMDO in acetone at room temperature for 6 hours was necessary to reach complete conversion of **1b** into the iodosyl derivative **4b**, which was isolated as a white powder in 94% yield (Scheme 2). ^{13}C NMR analysis was used to confirm the oxidation state of its iodine center on the basis of the chemical shift of the aromatic ipso carbon atom (C_{ipso}-I^{III}) at 114.9 ppm (see the Supporting Information).[6] Again, no λ^5-iodane was detected, even when a longer reaction time (up to 24 hours) or additional equivalents of DMDO were used. This surprisingly selective DMDO-mediated oxygenation was next applied to the other alkoxy iodobinaphthyls **1a**,**c–g**, and again full conversion into the corresponding iodosyl derivatives **4a**,**c–g** was achieved in very good to excellent yields (Scheme 2). The iodosyl carboxylic acids **4e–g** were characterized by NMR analyses as isomeric mixtures, which were probably due to the co-existence in solution of their open and benziodoxole cyclic forms (see the Supporting Information). The C_2-symmetrical diiodobinaphthyls **2a/b** were similarly oxidized upon treatment with six equivalents of DMDO to afford the corresponding bis(λ^3-iodanes) **5a/b** in good yields. The diiodobiphenyl analogues **3a/b** behaved differently under these conditions. In contrast to the binaphthyl ester variants **1a–d** and **2a**, the bis(ester) **3a** was cleanly converted into the bis(λ^5-iodane) **6a**, whereas the oxidation of bis(carboxylic acid) **3b** stopped at the bis(λ^3-iodane) stage **6b**, as it is usually observed with 2-iodobenzoic/3-iodonaphthoic acids under these DMDO-mediated oxidation conditions (Scheme 2, see the Supporting Information).

The capacity of these biarylic iodanes to deliver an oxygen atom was next evaluated in the context of our benchmark reaction, that is, the hydroxylative dearomatization of 2-methylnaphthol (**7**).[4a] The most revealing experiments that we conducted using the racemic alkoxybinaphthylic λ^3-iodanes (±)-**4a/b** and **4e/f** are summarized in Table 1. The conversion of **7** into *ortho*-quinol **8**, with the concomitant formation of the undesired *para*-quinone **9** and dimer **10**,[8] was examined by ^{1}H NMR analysis of the clean product mixtures. Using one equivalent of the methoxybinaphthylic iodane methyl ester (±)-**4a** in CH_2Cl_2, **7** was converted into the *ortho*-quinol **8** and the *para*-quinone **9** in about 40% yield each, together with only 10% of dimer **10** (Table 1, entry 1). The lower solubility of **4b** in CH_2Cl_2 led us to add 2,2,2-trifluoroethanol (TFE), a fluorinated solvent commonly used in iodane-mediated reactions.[9] A good compromise between

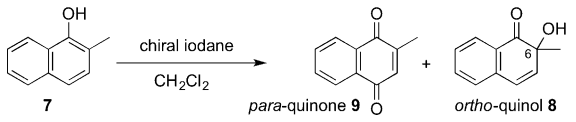
Table 1: Preliminary evaluation of reaction conditions for hydroxylative dearomatization of 2-methylnaphthol (**7**) mediated by binaphthylic λ^3-iodane.



Ent.	Iodane [equiv]	Conditions[a]	Conv. [%][b]	Yield [%][b] 8	9	10
1	(±)-**4a** [1.0]	CH_2Cl_2, 24 h	91	40	41	10
2	(±)-**4b** [1.0]	CH_2Cl_2/TFE (95:5), 24 h	88	40	20	28
3	(±)-**4b** [2.0]	CH_2Cl_2/TFE (95:5), 48 h	100	51	49	n.d.
4[c]	(±)-**4b** [1.2]	CH_2Cl_2, 24 h	100	48	35	12
5	(±)-**4e** [1.0]	CH_2Cl_2, 24 h	35	5	n.d.	30
6	(±)-**4f** [1.0]	CH_2Cl_2/TFE (95:5), 48 h	41	n.d.	n.d.	41

[a] Reactions run at room temperature using [**7**] = 70 mM in the indicated solvent. [b] Determined by ^{1}H NMR analysis. [c] [**7**] = 25 mM. n.d. = not detected, TFE = 2,2,2-trifluoroethanol.

Table 2: Asymmetric hydroxylative dearomatization of 2-methylnaphthol (**7**) mediated by biarylic λ^3- or λ^5-iodanes.[a]



Entry	Iodane [equiv]	*T* [°C]	*t* [h]	Yield [%][b] 9	8	*ee* [%][c]
1	(*R*)-**4a** [1.2]	RT	24	25	55	3 (*6S*)[d]
2	(*R*)-**4a** [1.2]	−40	48	25	50	19 (*6S*)
3	(*S*)-**4b** [1.2]	RT	24	35	46	15 (*6R*)
4	(*S*)-**4b** [1.2]	−40	48	25	41	35 (*6R*)
5	(*S*)-**4c** [1.2]	RT	24	30	40	36 (*6R*)
6	(*S*)-**4c** [1.2]	−40	48	25	40	45 (*6R*)
7	(*S*)-**4c** [1.2]	−80	72	25	35	53 (*6R*)
8	(*R*)-**4d** [1.2]	RT	18	30	33	17 (*6S*)
9	(*R*)-**6a** [0.6]	RT	18	25	55	50 (*6S*)
10	(*R*)-**6a** [0.6]	−80	72	15	40	73 (*6S*)

[a] Reactions run using [**7**] = 25 mM in CH_2Cl_2. [b] Determined by ^{1}H NMR analysis; for clarity, formation of **10** (ca. 5–10% at RT and up to 40% at −80°C) is not shown. [c] Enantiomeric excesses determined by HPLC analysis of pure *ortho*-quinol **8** using a chiral stationary phase. [d] Absolute configuration at C6 of the major enantiomer.

the solubility of **4b**, the extent of conversion of **7** into **8**–**10** (88–100%), and the yield of **8** (40–51%) was found using a 95:5 mixture of CH_2Cl_2/TFE (Table 1, entries 2 and 3). Moreover, dimer **10** was not detected when a two-fold excess of **4b** was used (entry 3). Higher dilutions in pure CH_2Cl_2 were also tested, and comparable performances were obtained when the reaction was run using a 25 mM (instead of 70 mM) solution of **7** in CH_2Cl_2 and 1.2 equivalent of **4b** (Table 1, entry 4). The use of the carboxylic acid analogues (±)-**4e**/**f**, which in solution adopt at least in part a cyclic benziodoxole structure (see above), was unsatisfactory, as less than 10% of *ortho*-quinol **8** was detected when the reaction was performed in CH_2Cl_2 (Table 1, entry 5), CH_2Cl_2/TFE (95:5; entry 6), or in other solvents such as TFE, DMF, or DMSO. In particular, the lack of reactivity of **4e** is somewhat surprising, as the in situ *m*-CPBA-mediated oxidation of its iodobinaphthyl precursor **A** (herein **1e**) afforded an iodane species that converted **7** into **8** in good to high yields (up to 83%).[4a] These observations led us to use the methyl ester series of our alkoxybiarylic iodanes in the following study of the asymmetric version of this HPD reaction.

The atropisomerically pure versions of the biarylic iodane methyl esters **4**–**6** were thus next evaluated for their capacity to convert **7** into an enantioenriched *ortho*-quinol **8**. All reactions were run using a 25 mM solution of **7** in CH_2Cl_2 and a slight excess of iodane (i.e., 1.2 equiv of the alkoxybinaphthyls **4**, and 0.6 equiv of the C_2-symmetrical biaryls **5** and **6**). The most significant results are summarized in Table 2. The oxygen transfer was effective in all cases, and led to the formation of **8** in acceptable yields of up to 55% and the *para*-quinone **9** as by-product in 15–30% yield. An increasing steric demand of the alkoxy group (i.e., OMe, OBn, and OTr) of the binaphthylic λ^3-iodanes **4a**–**c** positively influenced their induction of asymmetry, up to an encouraging *ee* value of 36% at room temperature (Table 2, entries 1, 3, and 5). This influence showed its limitation with the supertrityloxybinaphthylic iodane (*R*)-**4d**, the use of which led to a lower yield of **8** with only 17% *ee* (Table 2, entry 8), probably because this highly bulky alkoxy group blocks the approach of the substrate toward the hypervalent iodine center. A decrease of the temperature down to −40°C expectedly increased the *ee* value for **4a**–**c** to 19, 35, and 45%, respectively (Table 2, entries 2, 4, and 6). At −80°C, (6*R*)-**8** was obtained with 53% *ee* using the λ^3-iodane (*S*)-**4c** at the expense of the reaction time and yield (Table 2, entry 7).

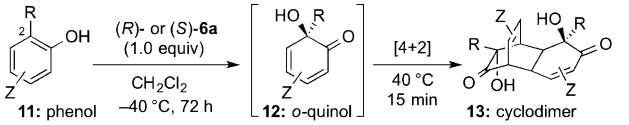
The C_2-symmetrical binaphthylic bis(λ^3-iodane) (*R*)-**5a** afforded **8** in only about 30% yield and with *ee* values of only 25–30%, even at −40°C (see the Supporting Information). We were however gratified by the performances of the C_2-symmetrical biphenylic bis(λ^5-iodane) (*R*)-**6a**, which furnished (6*S*)-**8** in acceptable yields (40–55%) with *ee* values of 50% at room temperature, and 73% at −80°C (Table 2, entries 9 and 10). The modulation of the dihedral angle around the chiral biaryl axis, probably resulting from the partial reduction of the binaphthylic core, and the I^V-type geometry (and reactivity) of the hypervalent iodine centers of **6a** are plausible key factors of its better ability to induce asymmetry.

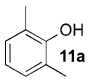
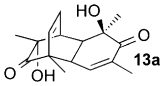
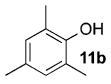
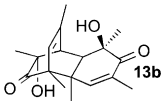
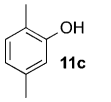
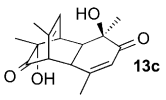
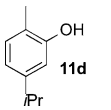
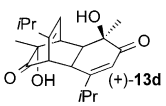
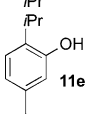
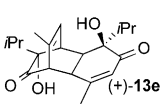
Overall, the results of these model reactions enabled us to identify a new chiral λ^5-iodane reagent that is capable of reaching asymmetric inductions comparable with the best results previously reported for such a challenging iodane-mediated intermolecular oxygenative dearomatizing reaction.[4a,10a] The yields of the transformation of 2-methylnaphthol (**7**) into an enantioenriched *ortho*-quinol **8** are lower than those we previously observed in the case of the in situ generation of iodane species using *m*-CPBA,[4a] but this oxidant alone, as well as DMDO, mediates the partial conversion of **7** into (±)-**8** (see the Supporting Information).[4c] Chiral iodanes, such as ex situ generated **6a**, should thus find valuable applications in asymmetric HPD reactions of 2-alkylarenols.

A series of 2-alkylphenols **11** was thus selected as starting materials to evaluate the scope of the asymmetric oxygen-transfer aptitude of **6a**. Such alkylphenols are commonly used test substrates in HPD/[4+2] cyclodimerization cascade reactions that aim at the construction of the bicyclo-[2.2.2]octenone framework.[10] Although reactions run with **6a** in CH_2Cl_2 at −80 °C did not give any product, even after four days, complete consumption of **11** was achieved at −40 °C for 72 h, affording the corresponding *ortho*-quinol **12**, which spontaneously started to dimerize. Heating the reaction mixture at 40 °C for 15 minutes permitted the completion of this dimerization in the expected regio- and stereoselective homochiral fashion.[10d,f] Upon treatment with (*R*)-**6a**, the symmetrical 2,6-dimethyl- and 2,4,6-trimethylphenols (**11a/b**) furnished the corresponding cyclodimers **13a** and **13b** in fair yields and *ee* values (Table 3, entries 1 and 2). The nonsymmetrical 2,3-dimethyl- and 2,3,5-trimethylphenols gave complex mixtures of products that resulted from the formation of *ortho*-quinones and/or nondimerizing 5-methylated *ortho*-quinol intermediates (not shown).[10d,f] However, the treatment of 2,5-dimethylphenol (**11c**) furnished the expected cyclodimer **13c**, which was isolated in 68% yield with 84% *ee* using (*R*)-**6a**, and again with 84% *ee*, but in a reversed ratio using (*S*)-**6a** (Table 3, entries 3 and 4). In the same fashion, the conversion of the natural 2-methyl-5-isopropylphenol (carvacrol, **11d**) with (*R*)-**6a** afforded bis(carvacrol) as the sole product in 71% yield with 68% *ee* in favor of the natural dimer (+)-**13d**.[11a,b] The treatment of **11d** with (*S*)-**6a** furnished (−)-**13d** in 68% yield with 74% *ee* (Table 3, entries 5 and 6). An even better induction of asymmetry was observed by subjecting the regioisomer 5-methyl-2-isopropylphenol (thymol, **11e**) to (*R*)-**6a**. The cyclodimer bis(thymol) (+)-**13e** was indeed obtained in 75% yield with 92% *ee*. A five-fold scale-up of this reaction confirmed this remarkable result with the production of (+)-**13e** in 77% yield with 94% *ee* (Table 3, entries 7 and 8). The structure of (+)-**13e** was established by X-ray analysis and by comparison with data reported for racemic **13e**[10d,e,11c] (see the Supporting Information). In none of these three 2,5-dialkylphenol cases (**11c–e**) were detected products that could have resulted from the oxygenation at the unsubstituted *ortho* position or from other modes of dimerization. This λ^5-iodane-induced asymmetric synthesis of terpenoid bicyclo[2.2.2]octenones constitutes an efficient metal-free alternative to the enantioselective HPD approach mediated by the copper-sparteine-dioxygen complex.[10b]

In conclusion, we have prepared a series of rare chiral biarylic iodanes[12] in high yields by a selective ex situ DMDO-mediated oxidation of alkoxylated iodobinaphthylic and C_2-symmetrical diiodobinaphthylic and diiodobiphenylic compounds into either iodosyl or iodyl reagents. Evaluation of these λ^3- and λ^5-iodanes for their capacity to promote the enantioselective oxygen transfer in phenol dearomatization reactions led to the identification of a novel biphenylic C_2-symmetrical bis(λ^5-iodane) as a highly efficient metal-free reagent for asymmetric intermolecular oxygenative phenol dearomatization reactions. Further studies toward its application to the synthesis of other *ortho*-quinol-based natural products and to other oxygen-transfer reactions, as well as mechanistic experiments, are currently in progress and will be reported in due course.

Table 3: Enantioselective hydroxylative dearomatization of 2-alkylphenols **11** mediated by biphenylic λ^5-iodane **6a**.[a]



Entry	Phenol	Iodane	Cyclodimer	Yield [%][b]	*ee* [%][c]
1	 **11a**	(*R*)-**6a**	 **13a**	52	40
2	 **11b**	(*R*)-**6a**	 **13b**	41	58
3	 **11c**	(*R*)-**6a**	 **13c**	68	84
4		(*S*)-**6a**		47	84
5	 **11d**	(*R*)-**6a**	 (+)-**13d**	71	68 (+)[d]
6		(*S*)-**6a**		68	74 (−)
7	 **11e**	(*R*)-**6a**	 (+)-**13e**	75	92 (+)
8[e]		(*R*)-**6a**		77	94 (+)

[a] Reactions run using [**11**] = 30 mM in CH_2Cl_2. [b] Isolated yield. [c] Enantiomeric excesses determined by HPLC analysis of pure cyclodimer **13** using a chiral stationary phase. [d] Optical rotation of the major enantiomer. [e] Five-fold scale up (5 days).

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[1] For a selection of recent books and reviews on hypervalent iodine chemistry, see: a) V. V. Zhdankin, *Hypervalent Iodine Chemistry—Preparation, Structure, and Synthetic Applications of Polyvalent Iodine Compounds*, Wiley, Chichester, **2013**; b) M. S. Yusubov, V. V. Zhdankin, *Curr. Org. Synth.* **2012**, *9*, 247; c) A. Duschek, S. F. Kirsch, *Angew. Chem.* **2011**, *123*, 1562; *Angew. Chem. Int. Ed.* **2011**, *50*, 1524; d) V. V. Zhdankin, *J. Org. Chem.* **2011**, *76*, 1185; e) A. Varvoglis, *Tetrahedron* **2010**, *66*, 5739; f) E. A. Merritt, B. Olofsson, *Angew. Chem.* **2009**, *121*, 9214; *Angew. Chem. Int. Ed.* **2009**, *48*, 9052; g) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299; h) R. M. Moriarty, *J. Org. Chem.* **2005**, *70*, 2893; i) *Hypervalent Iodine Chemistry—Modern Developments in Organic Synthesis* in *Topics Curr. Chem.*, *Vol. 224* (Ed.: T. Wirth), Springer, Berlin, **2003**.

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[8] The *para*-quinone **9** is probably derived from **8** through an allylic shift, followed by the oxidation of the resulting *para*-quinol or the rearomatized *para*-hydroquinone. Dimer **10** is also a contaminant of commercially available **7**, which is highly sensitive to this oxidative dimerization.

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