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Diastereoselective IBX Oxidative Dearomatization of Phenols by Remote Induction: Towards the Epicocconone Core Framework**

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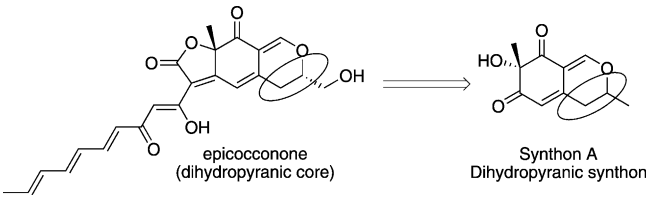
Pyranic azaphilones are cytotoxic natural products that have been extensively studied recently.[1] However, no synthesis of dihydro-product, such as epicocconone,[2] has been reported so far. In this line, a convergent synthesis of epicocconone from synthon A was engaged (Scheme 1). During these studies, we came across a highly diastereoselective IBX-mediated double deprotection–dehydration–oxidative dearomative one-pot process.

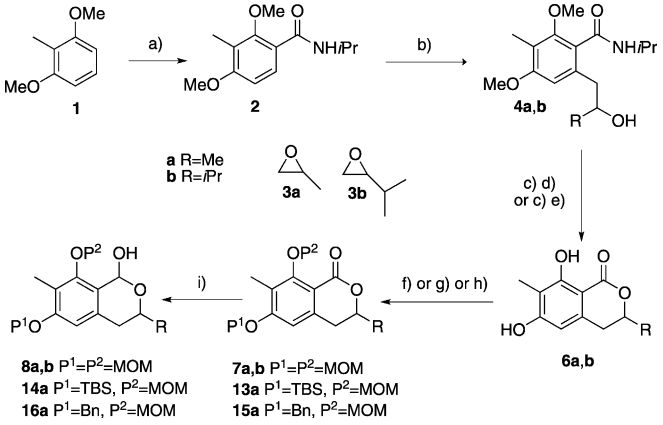


Scheme 1. Retrosynthetic pathways: dihydropyranic azaphilones.

Organohypervalent iodine reagents have attracted growing interest for decades as versatile and environmentally benign oxidants. Among them, IBX (2-iodoxybenzoic acid, λ5-iodane) is used in numerous classical oxidation reactions, but a particular case is the oxidative dearomatization, which almost only hypervalent iodine reagents can perform (less used reagents are: $Pb(OAc)_4$, $Ph_2Se_2O_3$, $NaIO_4$ and Cu^I/O_2). Although the mechanism of oxidative dearomatization is still unclear and depends on the oxidant, hypervalent iodine reagents are nowadays commonly used.[1,2]

λ3-iodane-mediated diastereoselective oxidative dearomatizations of phenols have been reported in the case in which the nucleophile is present on a substituent of the aromatic ring and intramolecularly attacks at either the *ortho*- or *para* positions of the phenol.[3c] Quideau reported the S-IBX (λ5-iodane)-mediated oxidative dearomatization of a *para*-substituted phenol with a stereogenic center on the α-position of the substituent, but the dearomatization was not diastereoselective.[5] We wish now to report on the first diastereoselective IBX-mediated oxidative *ortho*-dearomatization of phenols with a remote stereogenic center, in which the nucleophile is not part of the starting phenol.

The synthesis of protected phenols **8** (Scheme 2) began with 1,3-dimethoxytoluene **1**, which reacts with *i*PrNCO in the presence of $AlCl_3$ to give the amide **2** required for or-



Scheme 2. Synthesis of lactols **8**, **14**, and **16**. Reaction conditions: a) *i*PrNCO, $AlCl_3$, 95%; b) *t*BuLi/TMEDA then **3a** or **3b** (**4a**, 82%; **4b**, 52%); c) CSA/toluene reflux; d) $AlCl_3$ (**6a**, 95%, 2 steps); e) BBr_3 (**6b**, 68%, 2 steps); f) NaH/MOMCl (2 equiv), (**7a**, 98; **7b**, 91%); g) TBSCl/Et_3N then NaH/MOMCl (**13a**, 89%); h) $BnBr/K_2CO_3$ then NaH/MOMCl (**15a**, 83%); i) DIBAL-H, toluene, −78°C.

thometallation and the subsequent trapping of the organometallic species with either epoxide **3a** or **3b**. The resulting alcohols (**4a** and **4b**) were subjected to lactonisation by simply heating to reflux in toluene in the presence of camphorsulfonic acid (CSA, 1.1 equiv), leading to **5a** and **5b**. Diphenol **6a** was obtained quantitatively after treatment with $AlCl_3$ and heating to reflux in dichloromethane, however, **6b** required BBr_3 to be prepared cleanly. Compounds **6a** and **6b** were subsequently re-protected as MOM ethers **7** by treatment with methyl chloromethyl ether (MOMCl) and NaH. Lactones **7** were then cleanly reduced to lactols **8** by diisobutylaluminum hydride (DIBAL-H) in toluene. Lactol **14a** and **16a** were also prepared with different protecting groups from **6a**, by using TBS (Et_3N/TBSCl) or Bn (BnBr/K_2CO_3) regioselective monoprotections at position 6, then MOM protection (NaH/MOMCl) of the phenol at position

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[**] IBX = 2-iodoxybenzoic acid.

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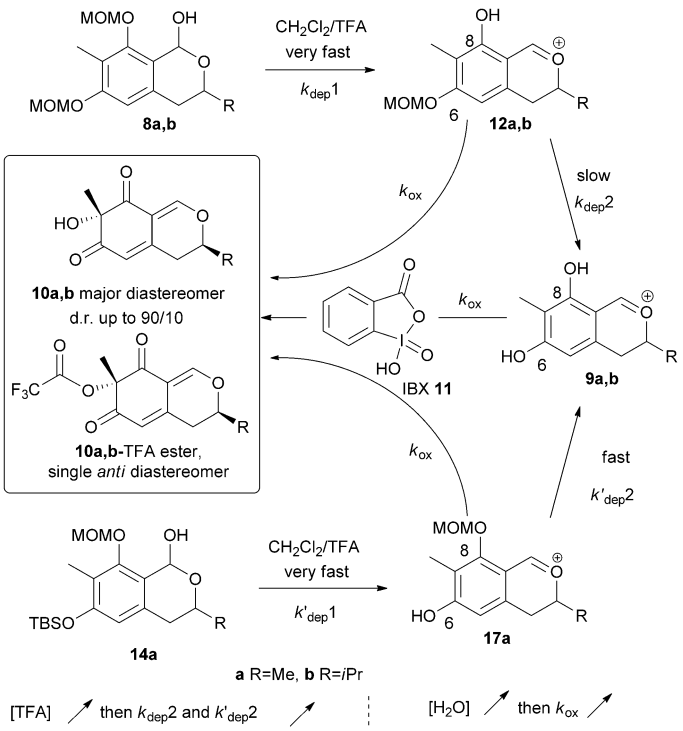
8, followed by a DIBAL reduction. Lactols **8**, **14**, and **16** were obtained as single diastereomers.

Oxidative dearomatization on **8a** and **8b** was then performed with IBX **11** in the presence of different amounts of trifluoroacetic acid (TFA, Scheme 3 and Table 1). TFA was selected because it rapidly generates oxonium ions from lactols and should deprotect MOM ethers. Furthermore, it has been reported that TFA accelerates IBX oxidations.[6] The oxidation of hemiketal **8a** afforded alcohol **10a** in 32% yield with no diastereoselectivity when 20 equiv of TFA was used (IBX was added at the same time, Table 1, entry 1). Surprisingly, **10a**-TFA ester was isolated with 12% yield as a single *anti* diastereomer (Figure 1).[7a] Lowering the amount of TFA to 7 equiv resulted in a moderate diastereoselective formation of **10a** (60/40) along with 10% of **10a**-TFA ester, as a single diastereomer (Table 1, entry 2). Adding a catalytic amount of tetrabutylammonium iodide (TBAI)[8] resulted in a lower yield, without affecting the diastereoselectivity significantly (Table 1, entry 4). However, adding water (2 or 20 equiv) resulted in an increase of both yield and diastereoselectivity (up to 90/10), compared with the same anhydrous conditions (also lowers the amount of TFA ester, compare Table 1, entries 2, 5, and 6). Furthermore, adding 20 equiv of water also afforded a cleaner and faster reaction. If only 2 equiv of TFA are added, without water, the diastereoselectivity is maintained but the yield is less than with water (Table 1, entry 7).[9]



Scheme 3. Diastereoselective oxidative dearomatization.

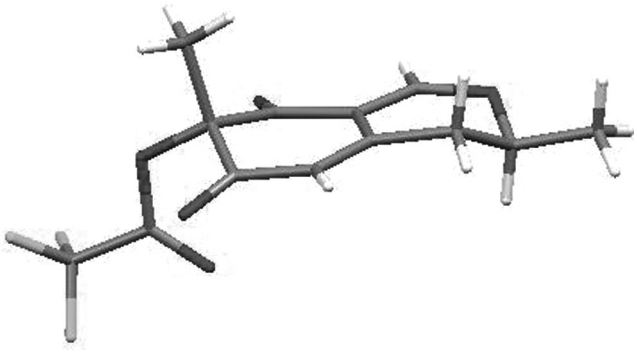


Figure 1. X-ray of **10a**-TFA ester.

The influence of the protecting group at position 6 was then studied. Dearomatization of **14a**, bearing an acid-labile TBS group at position 6, yielded **10a** with either no or low diastereoselectivity in either anhydrous or aqueous conditions, respectively (Table 1, entries 8 and 9). Treatment of **16a**, bearing a benzyl protecting group, with TFA and IBX, resulted also in low diastereoselective oxidative dearomatization (Table 1, entry 10).

In the case of the oxidation of hemiketal **8b** bearing the isopropyl side chain (Table 1, entries 11–15), **10b** was obtained in a similar diastereomeric ratio (d.r.) than with **8a** (up to 89/11). Only when the reaction was performed with 20 equiv of TFA, a moderate increase to 60:40 d.r. was observed (compared with 50/50 with **8a**; compare Table 1, en-

Table 1. Diastereoselective oxidative dearomatization.[a]

Entry	Phenol	TFA [equiv]	Additive	[equiv]	**10**	Yield [%]	d.r. **10**[b]	Yield [%] TFA ester	d.r. TFA ester [b]
1	**8a**	20	–	–	**10a**	32	50/50	12	100/0
2	**8a**	7	–	–	**10a**	32	60/40	10	100/0
3[c]	**8a**	7	–	–	**10a**	30	50/50	–	–
4	**8a**	7	TBAI	0.1	**10a**	22	62/38	10	100/0
5	**8a**	7	H_2O	2	**10a**	42	85/15	2	100/0
6	**8a**	7	H_2O	20	**10a**	48	90/10	–	–
7	**8a**	2	–	–	**10a**	34	83/17	4	100/0
8	**14a**	2	–	–	**10a**	43	50/50		–
9	**14a**	7	H_2O	20	**10a**	47	60/40	–	–
10	**16a**	7	–	–	**10a**	32	65/35	–	–
11	**8b**	20	–	–	**10b**	35	60/40	6	100/0
12	**8b**	7	–	–	**10b**	37	60/40	2	100/0
13[c]	**8b**	7	–	–	**10b**	41	61/39	–	–
14	**8b**	7	H_2O	20	**10b**	42	89/11	–	–
15	**8b**	2	–	–	**10b**	41	82/18	–	–

[a] Typical procedure: **8a** was dissolved in CH_2Cl_2 before adding TFA, additive (when noted) and IBX (2 equiv). The solution was stirred until complete conversion. [b] Measured by ^1H NMR spectroscopy. [c] **8a** (entry 3) or **8b** (entry 13) in CH_2Cl_2 + 7 equiv of TFA, stirred overnight before adding IBX.

tries 1 and 11); **10b**-TFA ester was also isolated as a single diastereomer.

The oxidative dearomatization of in situ generated **9a** or **9b** was performed after TFA treatment of **8a** or **8b** and overnight stirring (for complete deprotection of both MOM groups), before addition of IBX. In these cases, **10a** was obtained with no diastereoselectivity (Table 1, entry 3) whereas **10b** was obtained with a moderate 61/39 d.r. (Table 1, entry 13). These two results show the lack of or low diastereoselectivity of the oxidation of free diphenols **9a** or **9b**; they also show that *i*Pr substitution induces a better, although to a moderate extent, diastereoselectivity. These results are also consistent with the d.r. observed in the presence of 20 equiv of TFA (Table 1, entries 1 and 11), in which free diphenols are formed very quickly (vide infra, Figure 2).

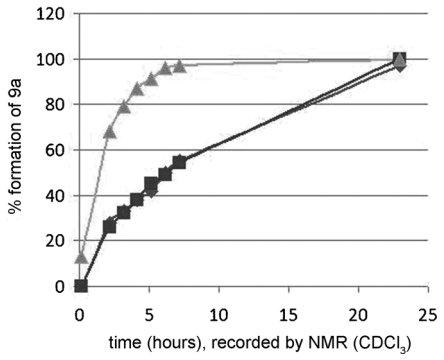


Figure 2. Kinetics of formation of **9a** from **8a** in various conditions. ◆ = TFA (7 equiv); ■ = TFA (7 equiv) + H_2O (2 equiv); ▲ = TFA (20 equiv).

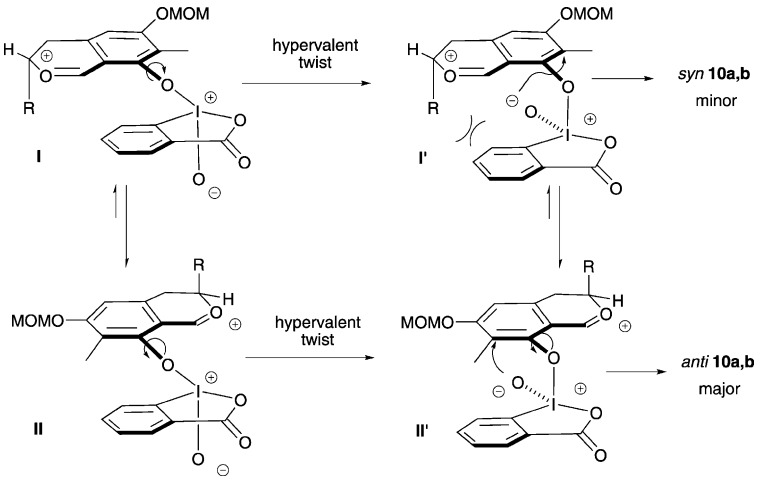
Importantly, the formation of TFA esters do not arise from esterification of the corresponding alcohols in the reaction medium but certainly during dearomatization by TFA transfer from TFA–IBX esters.[10] Moderate yields may be explained by the high sensitivity of **10** on silica and aqueous conditions, due to Michael addition of water on the enone moiety. The use of SIBX instead of IBX did not allow us to increase the yield.[11]

The sequential, but different, deprotection of protecting groups on lactols **8a** and **14a** has been observed (Scheme 3). Treatment of either **8a** or **14a** with TFA very quickly (minutes) yielded the oxonium ion **12a** (MOM cleavage at position 8), or **17a** (TBS cleavage at position 6), respectively. Then, **12a** slowly evolved to diphenol **9a** ($k_{dep}2$), whereas **17a** more rapidly evolved to diphenol **9a** ($k'_{dep}2$). The kinetics of these second deprotections ($k_{dep}2$ and $k'_{dep}2$) were shown to be [TFA] dependent because the greater the number of equivalents of TFA, the faster the deprotection occurs (Figure 2). These kinetics are correlated with the observed diastereoselectivity of **10a** (Table 1, compare entries 1, 2, and 7) and we propose that the oxidative dearomatization of either monophenol **12a** or **17a** is diastereoselective, whereas the oxidation of **9a** is not. Furthermore, we have shown that adding water dramatically accelerated the reaction. In this case, the kinetics of oxidation (k_{ox}) increase but do not affect the kinetics of deprotection significantly ($k_{dep}2$ and $k'_{dep}2$). Therefore, in the presence of water, the oxidation of **12a** and **17a** takes place before the second deprotection and results in high diastereoselectivity. The water–TFA combination presumably depolymerizes IBX and allows for a more favorable liquid–liquid interaction instead of a solid–liquid interaction, with IBX being poorly soluble in dichloromethane. In the case of **14a**, the observed diastereoselectivity was lower than with **8a** (Table 1, compare entries 6 and 9). This is due to the faster deprotection of **17a**, compared with **12a** ($k'_{dep}2 > k_{dep}2$), which increases the amount of **9a**, for which the oxidation is not diastereoselective.

In the case of **16a**, NMR studies in the presence of TFA only showed that the benzyl protecting group tolerated acidic conditions (since only the MOM at position 8 was cleaved). Accordingly, a high diastereoselectivity was expected but, to our surprise, low diastereoselectivity was observed. This can be explained by the IBX-mediated deprotection and oxidation of the benzyl group,[12] generating diphenol **9a**, in which oxidative dearomatization is not diastereoselective.

To summarize, the obtained diastereoselectivity of **10** is a combination of the highly diastereoselective oxidation of **12a**, **12b**, or **17a**, counterbalanced by the non- or low-diastereoselective oxidation of **9a** or **9b**.

We can then postulate that diastereoselective oxidation takes place when IBX coordinates to the phenol in position 8 or 6 (the other phenol still being protected) and delivers oxygen on one side preferentially, *anti* to the methyl of the dihydropyran ring (Scheme 4). Indeed, ligand exchange be-

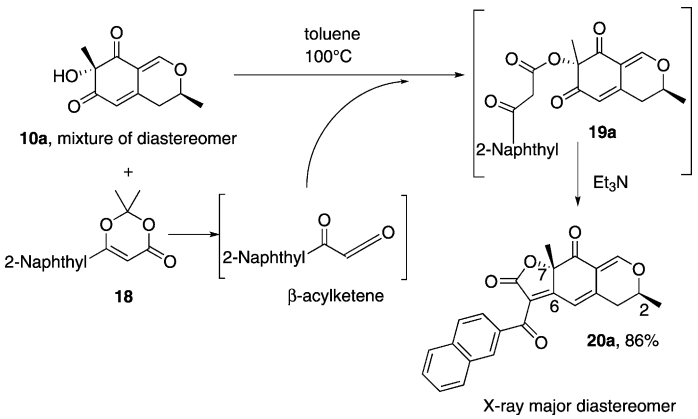


Scheme 4. Proposed mechanism for diastereoselectivity.

tween IBX and monophenol **12** leads to conformer **I**, which can evolve through a hypervalent twist[4f,13] to **I′** in which the aryl moiety of IBX is on the same face as the methyl of the oxonium ion. On the other hand, **I** can also rotate around the aryl–O bond to give rise to conformer **II**, which can evolve through a sterically more favorable hypervalent twist to **II′** in which the aryl moiety of IBX is opposite to the anomeric methyl. This leads preferentially to anti-oxidation and explains the observed diasteroselectivity. In the case of **10**-TFA ester, we propose that in situ formation of the TFA ester of IBX is responsible for the oxidation and that the corresponding *O*-TFA-substituted conformers **I**, **I′**, **II** and **II′** are more sensitive to steric hindrance, giving rise to complete *anti* diastereoselectivity

The next challenge towards the epicocconone core was bypassed using dioxin-4-ones for the one-pot access to acylfuranone derivatives.

Lactol **8a**, as a mixture of diastereomers, was then heated with dioxin-4-one **18** (in the presence of Et_3N), leading to acylfuranone **20a**, after conversion to β-keto-ester **19a** and completely regioselective cyclization with 6-carbonyl in 86% yield (Scheme 5). Diastereomers of acylfuranone **20a**



Scheme 5. Derivatization of **10a** and introduction of the furanone ring.

could be separated and the major diastereomer was crystallized,[7b] allowing us to evidence the *anti* relationship between 6-O and 2-Me, thus validating the *anti* oxidative dearomatization (Figure 3).

To conclude, we report the first IBX-mediated diastereoselective oxidative dearomatization with remote induction (over 5 bonds) and show the dramatic effect of water on this reaction. We also shed light on the mechanism of the IBX oxidative dearomatization, by validating the hypervalent twist with an internal delivery of the oxygen atom. Although remote stereocontrol has been known for decades, induction based on hypervalent twisting is a new concept that could be applied for diastereoselective oxidations. Theoretical studies on the origin of the diastereoselectivity are in progress. Dearomatized alcohols were then regioselectively transformed into acylfuranones leading to the core structure of epicocconone in a one pot sequence. Application of

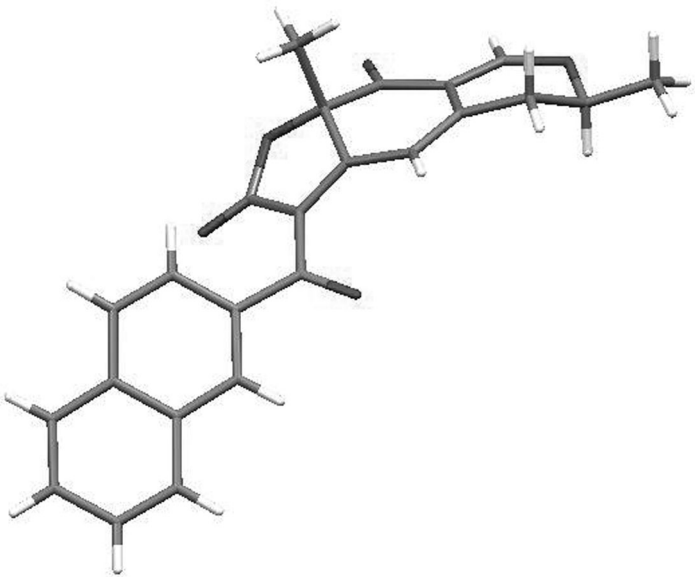


Figure 3. X-ray of major diastereomer **20a**.

this methodology to the yet never synthesized natural product and analogues is under investigation and results will be reported in due course.

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Keywords: diastereoselectivity · iodine · lactones · natural products · oxidative dearomatization

[1] For recent references, see a) N. Osmanova, W. Schultze, N. Ayoub, *Phytochem. Rev.* **2010**, *9*, 315–342; b) R. C. Clark, S. Y. Lee, D. L. Boger, *J. Am. Chem. Soc.* **2008**, *130*, 12355–12369; c) W.-J. Qian, W.-G. Wei, Y.-X. Zhang, Z.-J. Yao, *J. Am. Chem. Soc.* **2007**, *129*, 6400–6401; d) J. Zhu, J. A. Porco, *Org. Lett.* **2006**, *8*, 5169–5171; e) M. A. Marsini, K. M. Gowin, T. R. R. Pettus, *Org. Lett.* **2006**, *8*, 3481–3483.

[2] P. J. Bell, P. Karuso, *J. Am. Chem. Soc.* **2003**, *125*, 9304–9305.

[3] a) J. P. Brand, D. Fernández González, S. Nicolai, J. Waser, *Chem. Commun.* **2011**, *47*, 102–115; b) A. Duschek, S. F. Kirsch, *Angew. Chem. Int. Ed.* **2011**, *50*, 1524–1552; c) L. Pouységu, D. Deffieux, S. Quideau, *Tetrahedron* **2010**, *66*, 2235–2261; d) V. Satam, A. Harad, R. Rajule, H. Pati, *Tetrahedron* **2010**, *66*, 7659–7706; e) M. Uyanik, K. Ishihara, *Chem. Commun.* **2009**, 2086–2099; f) V. V. Zhdankin, P. J. Stang, *Chem. Rev.* **2008**, *108*, 5299–5358.

[4] For chiral IBX derivatives, see: a) M. Fujita, Y. Yoshida, K. Miyata, A. Wakisaka, T. Sugimura, *Angew. Chem.* **2010**, *122*, 7222–7225; *Angew. Chem. Int. Ed.* **2010**, *49*, 7068–7071; b) S. Altermann, S. Schäfer, T. Wirth, *Tetrahedron* **2010**, *66*, 5902–5907; c) M. Uyanik, T. Yasui, K. Ishihara, *Tetrahedron* **2010**, *66*, 5841–5851; d) M. Uyanik, T. Yasui, K. Ishihara, *Angew. Chem.* **2010**, *122*, 2221–2223; *Angew. Chem. Int. Ed.* **2010**, *49*, 2175–2177; e) J. K. Boppisetti, V. D. Birman, *Org. Lett.* **2009**, *11*, 1221–1223; f) S. Quideau, G. Ly-

vinec, M. Marguerit, K. Bathany, A. Ozanne-Baudenon, T. Buffeteau, D. Cavagnat, A. Chénédé, *Angew. Chem.* **2009**, *121*, 4675–4679; *Angew. Chem. Int. Ed.* **2009**, *48*, 4605–4609; g) T. Dohi, A. Maruyama, N. Takenaga, K. Senami, Y. Minamitsuji, H. Fujioka, S. B. Caemmerer, Y. Kita, *Angew. Chem.* **2008**, *120*, 3847–3850; *Angew. Chem. Int. Ed.* **2008**, *47*, 3787–3790; h) U. Ladziata, J. Carlson, V. V. Zhdankin, *Tetrahedron Lett.* **2006**, *47*, 6301–6304; i) V. V. Zhdankin, J. T. Smart, P. Zhao, P. Kiprof, *Tetrahedron Lett.* **2000**, *41*, 5299–5302.

[5] a) L. Pouységu, M. Marguerit, J. Gagnepain, G. Lyvinec, A. J. Eatherton, S. Quideau, *Org. Lett.* **2008**, *10*, 5211–5214; b) J. Gagnepain, F. Castet, S. Quideau, *Angew. Chem.* **2008**, *120*, 638; *Angew. Chem. Int. Ed.* **2008**, *47*, 628.

[6] N. Lebrasseur, J. Gagnepain, A. Ozanne-Beaudenon, J.-M Léger, S. Quideau, *J. Org. Chem.* **2007**, *72*, 6280–6283.

[7] Cambridge crystallographic data base access for **10a**-TFA ester; a) CCDC-818701; b) major diastereomer of **18a**: CCDC-765697. This data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[8] J. Zhu, A. R. Germain, J. A. Porco, *Angew. Chem.* **2004**, *116*, 1259–1263; *Angew. Chem. Int. Ed.* **2004**, *43*, 1239–1243.

[9] Water has been used as solvent (or co-solvent) with a sometimes beneficial effect for diverse IBX oxidations. To the best of our knowledge, this beneficial effect has never been reported for oxidative dearomatization a) J. S. Yadav, B. V. Subba Reddy, A. P. Singh, A. K. Basak, *Tetrahedron Lett.* **2008**, *49*, 5880–5882; b) A. Kommreddy, M. S. Bowsher, M. R. Gunna, K. Botha, T. K. Vinod, *Tetrahedron Lett.* **2008**, *49*, 4378–4382; c) K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *Angew. Chem.* **2003**, *115*, 4211–4216; *Angew. Chem. Int. Ed.* **2003**, *42*, 4077–4082; d) K. Surendra, N. S. Krishnaveni, M. A. Reddy, Y. V. D. Nageswar, K. Rama Rao, *J. Org. Chem.* **2003**, *68*, 9119–9121; e) N. Srilakshmi Krishnaveni, K. Surendra, Y. V. D. Nageswar, K. Rama Rao, *Synthesis* **2003**, 2295–2297; for effect of water on Dess–Martin oxidation see f) S. D. Meyer, S. L. Schreiber, *J. Org. Chem.* **1994**, *59*, 7549–7552.

[10] Compound **10a** stirred with TFA and IBX did not afford **10a**-TFA ester.

[11] A. Ozanne, L. Pouysegu, D. Depernet, B. François, S. Quideau, *Org. Lett.* **2003**, *5*, 2903–2906.

[12] Nicolaou reported that IBX can oxidize benzylic positions by SET. K. C. Nicolaou, T. Montagnon, P. S. Baran, Y.-L. Zhong, *J. Am. Chem. Soc.* **2002**, *124*, 2245–2258.

[13] a) J. Y. Su, W A. Goddard, *J. Am. Chem. Soc.* **2005**, *127*, 14146–14147; b) M. Uyanik, M. Akakura, K. Ishihara, *J. Am. Chem. Soc.* **2009**, *131*, 251–262.

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