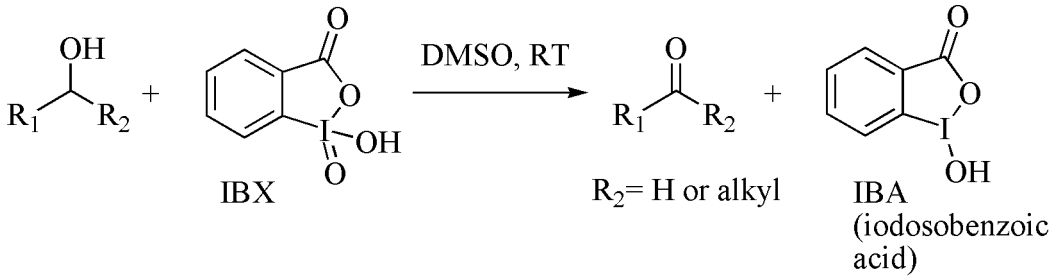
IBX: an old reagent……

In 1893, the 2-iodoxybenzoic acid (1-hydroxy-1,2-benziodoxol-3(1*H*)-one 1-oxide, usually abbreviated as IBX, see Figure 1) was discovered by Hartmann and Meyer[1], and was forgotten during almost one century, probably due to its remarkable insolubility in most organic solvents and water. In 1983, Dess and Martin[2] used it to prepare the 1,1,1-triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1*H*)-one 1-oxide (see Figure 1) another hypervalent iodine reagent. This more soluble oxidative reagent known as Dess-Martin periodinane (DMP) became very popular in organic synthesis, as one of the most convenient reagents available for oxidation of alcohols.[3]

Figure 1

Frigerio and Santagostino[4] reported in 1994 the first successful oxidation of a variety of alcohols with IBX in DMSO, the only solvent in which its solubility is appreciable. IBX is easily accessible, non-toxic and insensitive to the presence of air or moisture (see Scheme 1).[5] IBX is commercially available but could be prepared by oxidation of 2-iodoxybenzoic acid (2IBAcid) with oxone®.[6] Unfortunately, DMP and IBX decompose violently under impact and/or heating (>200°C), clearly limiting industrial applications.[7] However, as we will see, SIMAFEX a French company developed and patented a non-explosive white-powder formulation of IBX composed of a mixture of IBX itself (49%), isophthalic acid (29%) and benzoic acid (22%).[8]

Scheme 1

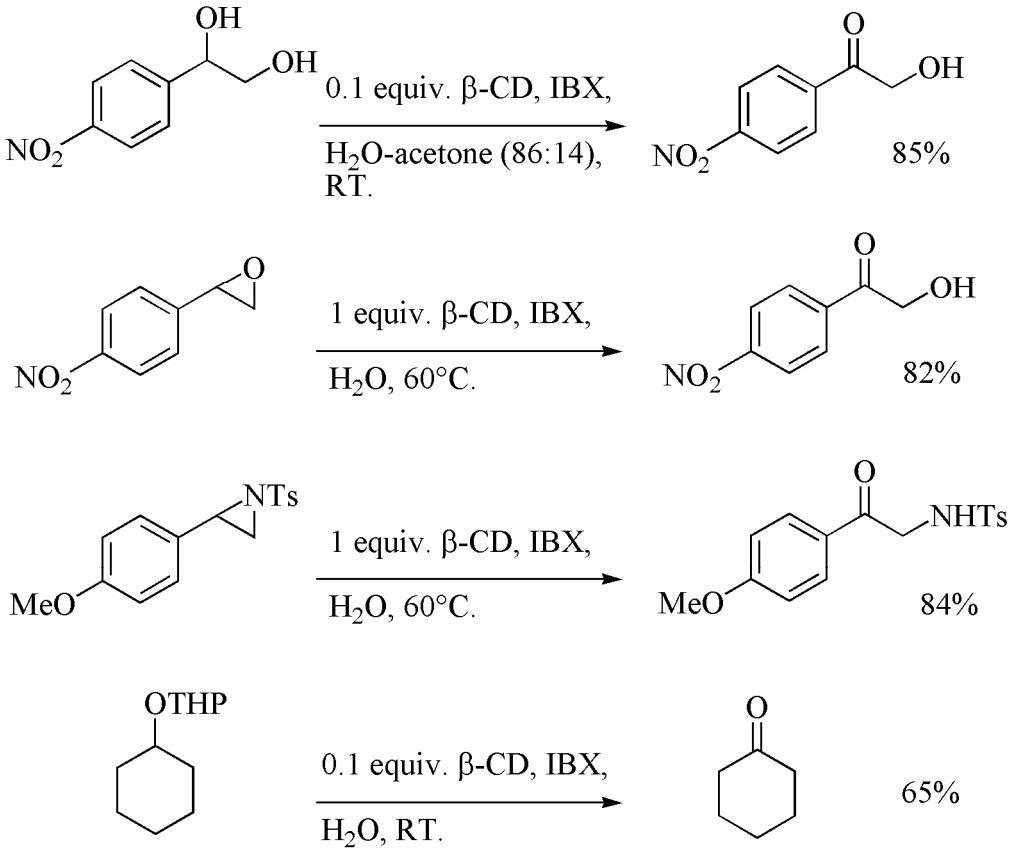


[1] C. Hartmann, V. Meyer, *Chem. Ber.* **1893**, *26*, 1727-1732.
[2] D. B. Dess, J. C. Martin, *J. Org. Chem.* **1983**, *48*, 4155-4156.
[3] D. B. Dess, J. C. Martin, *J. Am. Chem. Soc.* **1991**, *113*, 7277-7278. For an excellent recent review on this field, see: V. V. Zhdankin, *Curr. Org. Synt.,* **2005**, *2*, 121-145.
[4] M. Frigerio, M. Santagostino, *Tetrahedron Lett.* **1994**, *35*, 8019-8022.
[5] For reviews on IBX, see: T. Wirth, *Angew. Chem., Int. Ed.* **2001**, *40*, 2812-2814, V. V. Zhdankin, P. J. Stang, *Chem. Rev.*, **2002**, *102*, 2523-2584.
[6] M. Frigerio, M. Santagostino, S. Sputore, *J. Org. Chem.* **1999**, *64*, 4537-4538.
[7] J. B. Plumb, D. J. Harper, *Chem. Eng. News* **1990**, *68*(29), 3.

In one decade, many synthetically useful transformations, including oxidation reactions, accomplished by IBX have been published and the most recent are summarized in this note.

At first, the limited solubility of IBX has prompted many researchers to reach more practical experimental conditions. Rao *and Coll.*[9] published a set of papers using IBX in aqueous medium with □-cyclodextrine (□-CD) as catalyst through the formation of host-guest complexes by noncovalent bonding as seen in enzymes. Some pertinent applications are outlined in Scheme 2.

Scheme 2



At elevated temperature, IBX is soluble in most solvents to carry on oxidation of alcohols.[10,11] Best results were obtained with EtOAc or DCE as solvent: byproducts are insoluble at RT and therefore removed by simple filtration (see Scheme 3). It should be pointed out that in these conditions, toluene (*vide infra*) and THF used as solvent are oxidized in benzaldehyde and □-butyrolactone respectively!

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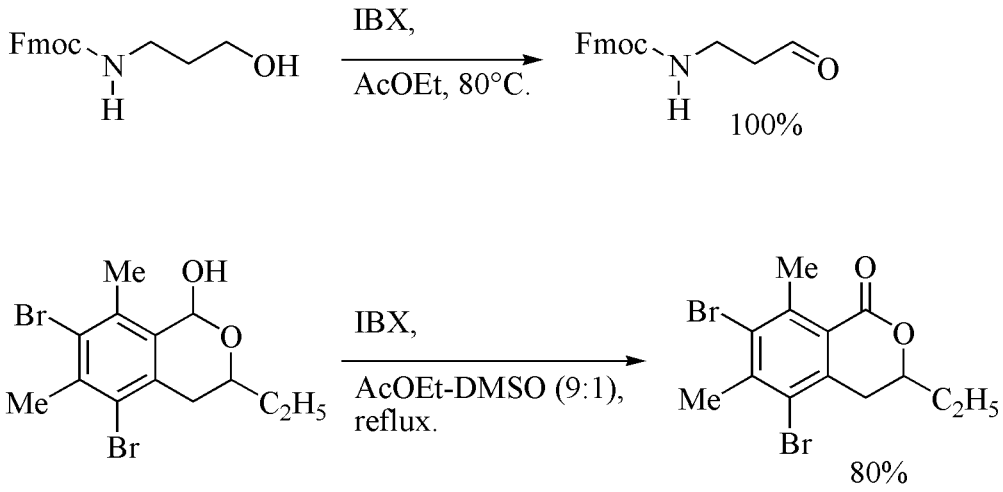
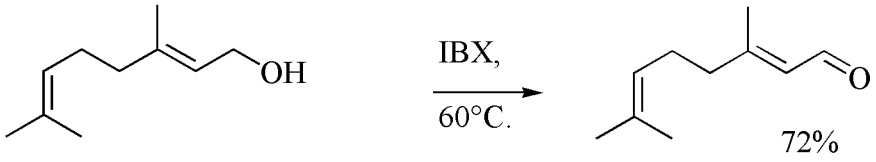
[8] D. Depernet,; B. François, WO 02/057210 A1, PCT/FR02/00189, US 2002/0107416 or C.A.. **2002**, 137, 109123.
[9] (a) K. Surendra, N. Srilakshmi Krishnavent, M. Arjun Reddy, Y. V. D. Nageswar, K. Rama. Rao, *J. Org. Chem.* **2003**, *68*, 2058-2059. (b) K. Surendra, N. Srilakshmi Krishnavent, M. Arjun Reddy, Y. V. D. Nageswar, K. Rama. Rao, *J. Org. Chem.* **2003**, *68*, 9119-9121. (c)) M. Narender, M. Somi Reddy, V. Pavan Kumar, Y. V. D. Nageswar, K. Rama. Rao, *Tetrahedron Lett.* **2005**, *46*, 1971-1975.
[10] J. D. More, N. S. Finney, *Org. Lett.* **2002**, *4*, 3001-3003.
[11] J. N. Moorthy, N. Singhal, P. Mal, *Tetrahedron Lett.* **2004**, *45*, 309-312.

Scheme 3



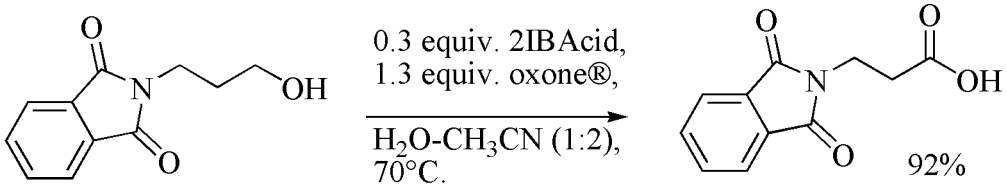
Oxidation of allylic and benzylic alcohols to corresponding carbonyl compounds have been efficiently achieved under solvent-free conditions at elevated temperature, as well as oxidation of aromatic aldehydes to acids (see Scheme 4).[12]

Scheme 4



Vinod *and Coll.*[13] published very recently an efficient protocol for oxidation of alcohols by *in situ* generation of IBX from catalytic amounts of 2IBAcid in the presence of oxone® as co-oxidant. In these conditions, oxone® oxidizes not only IBA (the reduced formed of IBX), but also the aldehyde intermediates into acids (see Scheme 5).

Scheme 5



[12] J. N. Moorthy, N. Singhal, P. Venkatakrishnan, *Tetrahedron Lett.* **2004**, *45*, 5419-5424.
[13] A. P. Thottumkara, M. S. Bowsher, T. K. Vinod, *Org. Lett.* **2005**, *7*, 2933-2936.

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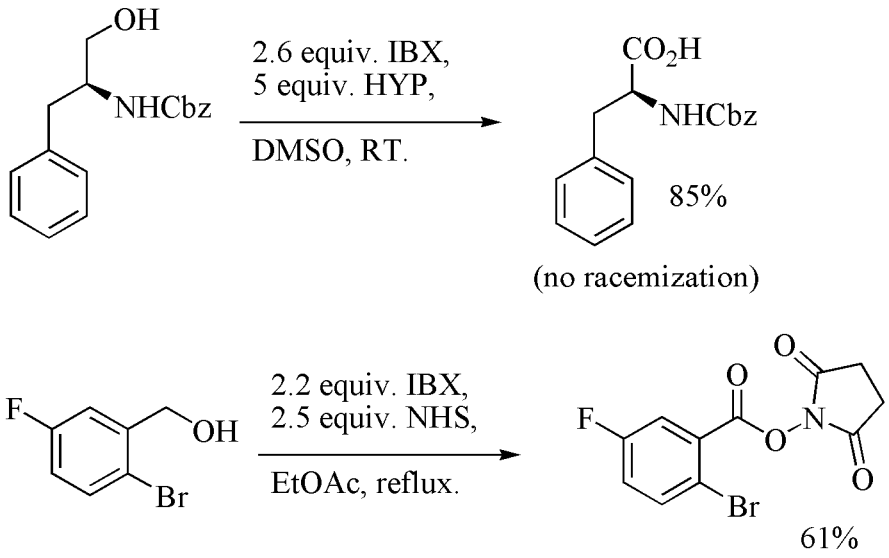
Polymers supported IBX were also prepared. These reagents were easily separated by filtration and IBA could be regenerated by oxidation with oxone®.[14] Also, ionic liquids have been used efficiently as polar solvents for oxidation of alcohols using IBX.[15]

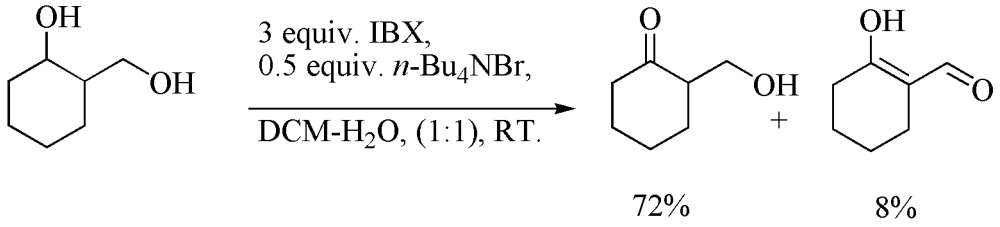
Oxidation of primary alcohols and aldehydes to carboxylic acids using an excess of IBX in the presence of *O*-nucleophiles such as 2-hydroxypyridine (HYP) or *N*-hydroxysuccinimide (NHS) *via* the corresponding activate esters was described by Giannis *and Coll.* (see Scheme 6).[16] Performing this reaction in EtOAc instead of DMSO led to the isolation of the corresponding active esters in good yield (see Scheme 6).[17]

Scheme 6



A good chemoselective oxidation of secondary alcohol to ketone in the presence of primary alcohol was observed with **1** IBX and *n*-Bu_4NBr as a phase transfer catalyst in the DCM-water mixture (see Scheme 7).[18]

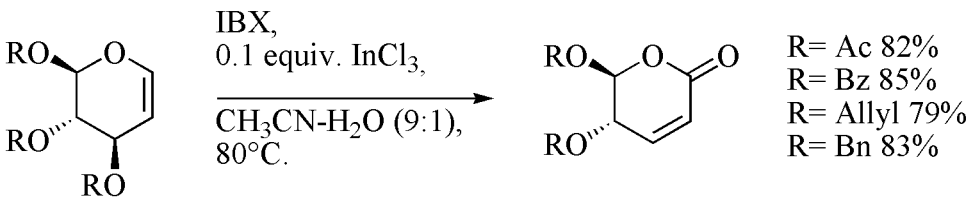
Scheme 7



[14] W.-J. Chung, D.-K. Kim, Y.-S. Lee, *Tetrahedron Lett.* **2003**, *44*, 9251-9254 and cited literature.
[15] (a) G. Karthikeyan, P. T. Perumal, Synthesis, 2003, 2249-2251. (b) J. S. Yadav, B. V. S. Reddy, A. K. Basak, A. Venkat Narsaiah, *Tetrahedron* **2004**, *60*, 2131-2135 and cited literature.
[16] R. Mazitschek, M. Mülbaier, A. Giannis, *Angew. Chem., Int. Ed.* **2002**, *41*, 4059-4061.
[17] A. Schulze, A. Giannis, *Adv. Synth. Catal.* **2004**, *346*, 252-256.
[18] C. Kuhakarn, K. Kittigowittana, M. Pohmakotr, V. Reutrakul, *Tetrahedron* **2005**, *61*, 8995-9000.

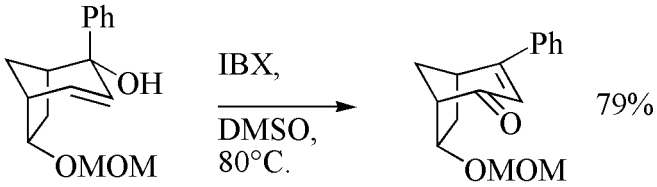
Conversion of glycals into □□□-unsaturated □-lactones was efficiently carried out using IBX with a catalytic amount of $InCl_3$ (see Scheme 8).[19]

Scheme 8



Oxidative rearrangement of five- and six-membered cyclic tertiary allylic alcohols was performed with IBX (see Scheme 9).[20]

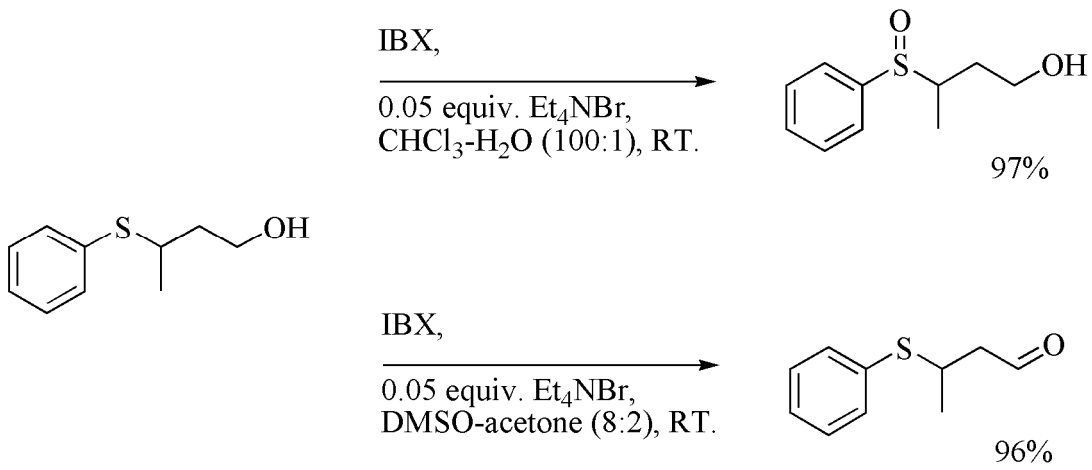
Scheme 9



Sulfides could be chemoselectively oxidized to their corresponding sulfoxides with IBX and a catalytic amount of Et_4NBr (see Scheme 10).[21] In this protocol, the chemoselectivity could moved from sulfide to alcohol oxidation by simply changing the solvent.

Scheme 10

[19] J. S. Yadav, B. V. Subba. Reddy, Ch. Suresh Reddy, *Tetrahedron Lett.* **2004**, *45*, 4583-4585.
[20] M. Shibuya, S. Ito, M. Takahashi, Y. Iwabuchi, *Org. Lett.* **2004**, *6*, 4303-4306.
[21] V. G. Shukla, P. D. Salgaonkar, K. G. Akamanchi, *J. Org. Chem.* **2003**, *68*, 5422-5425.



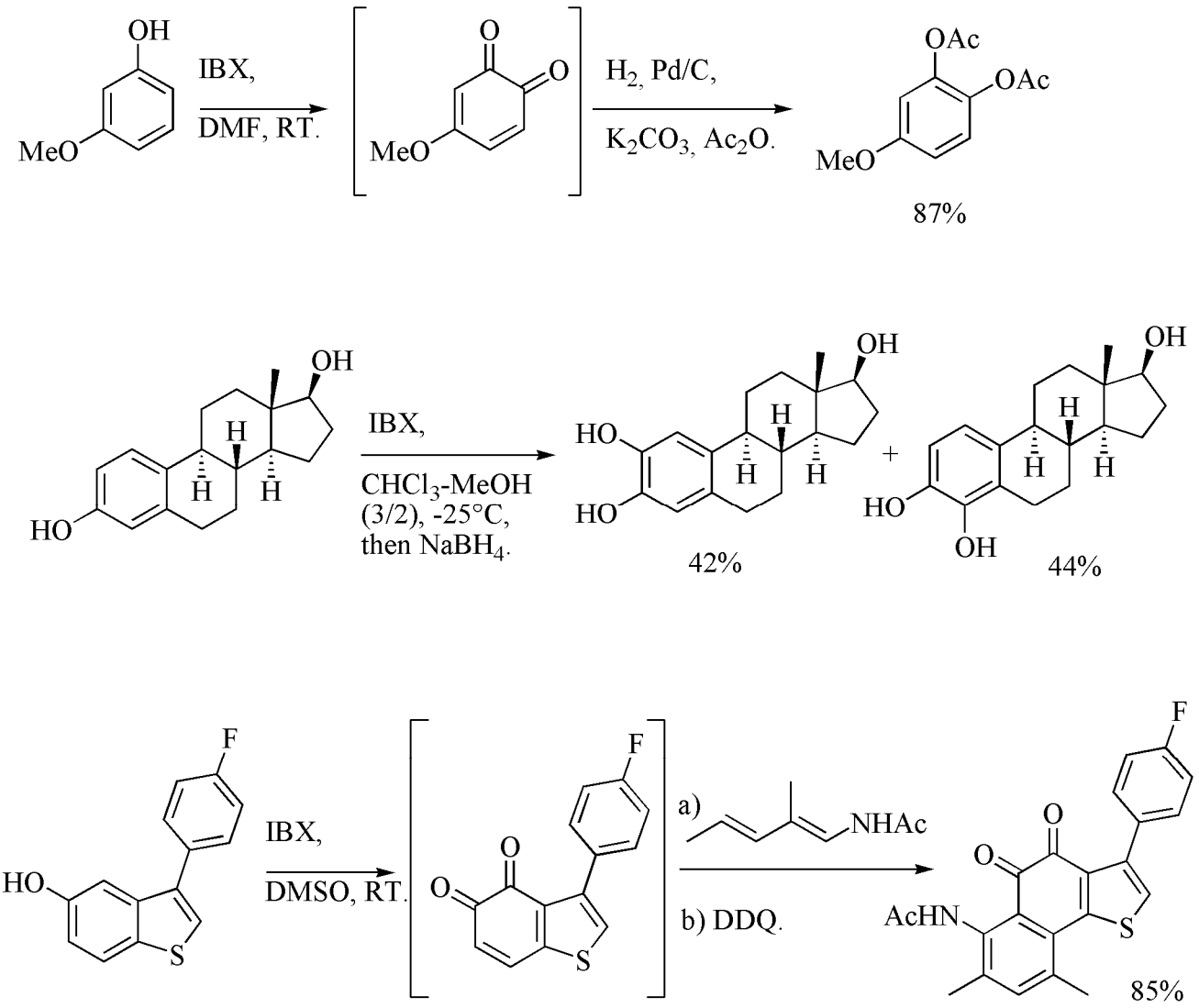
Oxidation of various phenolic compounds to *o*-quinone intermediates were reported with IBX. In DMF at RT, phenols containing at least one electron-donating group led regioselectively to *o*-quinones, which were reduced *in situ* to the corresponding catechols (see Scheme 11).[22] In a $CHCl_3$/MeOH mixture at low temperature, the phenolic oxidation was found to be less regioselective but could be expanded to phenol itself (see Scheme 11).[23] Synthesis of *o*-benzothiophenquinones has been also reported using IBX.[24]

[22] D. Magdziak, A. A. Rodriguez, R. W. Van De Water, T. R. R. Pettus, *Org. Lett.* **2002**, *4*, 285-288.

[23] A. Pezzella, L. Lista, A. Napolitano, M. d'Ischia, *Tetrahedron Lett.* **2005**, *46*, 3541-3544.

[24] Y.-D. Shen, H.-Q. Wu, S.-L. Zhang, X.-Z. Bu, L.-K. An, Z.-S. Huang, P.-Q. Liu, L.-Q. Gu, Y.-M.. Li, A. S. C. Chan, *Tetrahedron* **2005**, *61*, 9097-9101.

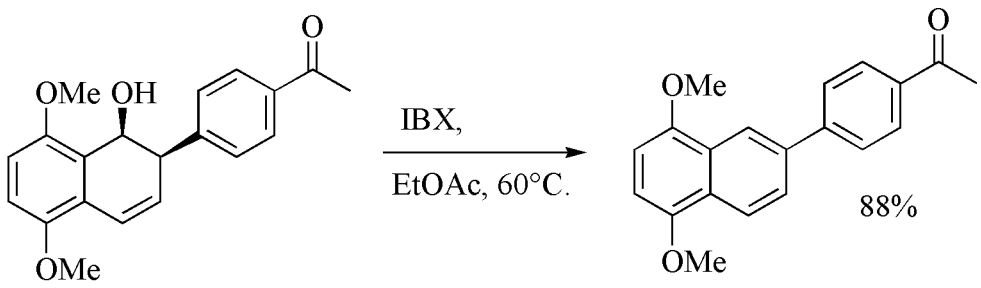
Scheme 11



2-Substituted *cis*-1,2-dihydronaphthols were oxidized to their corresponding naphthols with IBX in EtOAc or acetone as outlined in Scheme 12, this transformation was examined without success with numerous oxidants.[25]

[25] C.-L. Chen, S. F. Martin, *Org. Lett.* **2004**, *6*, 3581-3584.

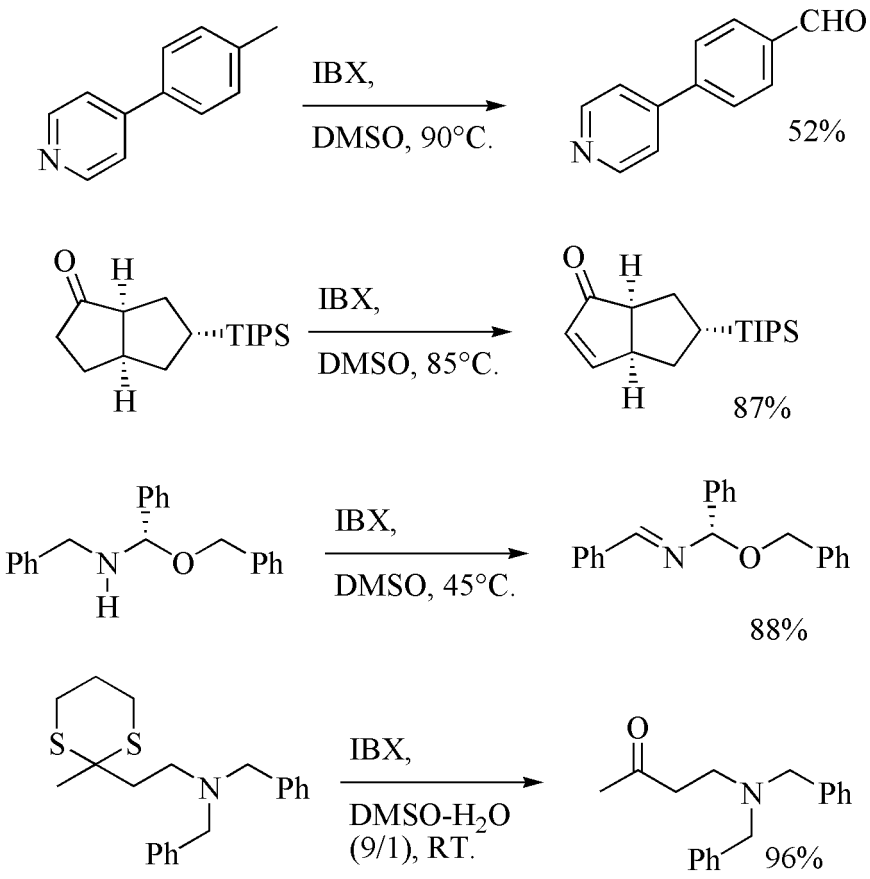
Scheme 12



Nicolaou *and coll.* have discovered a plethora of remarkable new synthetic transformation based on the reactivity of IBX. A selection of some of the most pertinent examples is outlined in scheme 13: oxidation of the benzylic position into aldehydes and oxidation of saturated ketones to the corresponding □,□-unsaturated compounds.[26] Dehydrogenation of amines and cleavage of dithioacetals and dithioketals are also included (See Scheme 13).[27]

Scheme 13

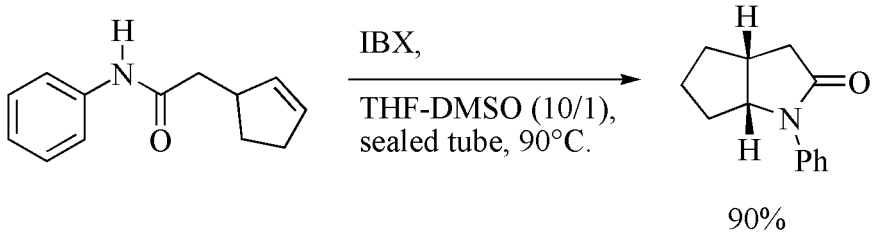
[26] K. C. Nicolaou, T. Montagnon, P. S. Baran, Y.-L. Zhong, *J. Am. Chem. Soc.* **2002**, *124*, 2245-2258.
[27] K. C. Nicolaou, C. J. N. Mathison, T. Montagnon, *J. Am. Chem. Soc.* **2004**, *126*, 5192-5201 and cited literature.



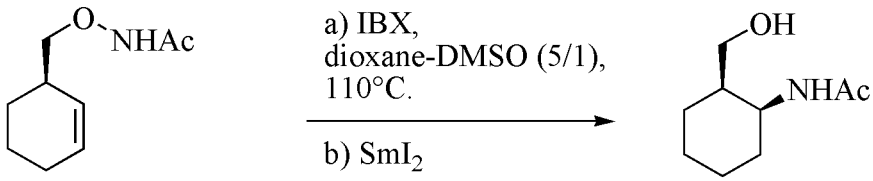
Also, IBX-mediated radical cyclisation of unsaturated *N*-aryl amides and unsaturated alkoxyamine via *N*-centered radicals have been described (See Scheme 14).[28] This methodology has been used for the preparation of various compounds such as □-lactams, cyclic urethanes, aminosugars, 1,3 and 1,2-aminoalcohols.[29] This transformation is consistent with a single electron transfer (SET) mechanism.

[28] K. C. Nicolaou, P. S. Baran, Y.-L. Zhong, S. Barluenga, K. W. Hunt, R. Kranich, J. A. Vega, *J. Am. Chem. Soc.* **2002**, *124*, 2233-2244.
[29] B. Janza, A. Studer, *J. Org. Chem.* **2005**, *70*, 6991-6994 and cited literature.

Scheme 14



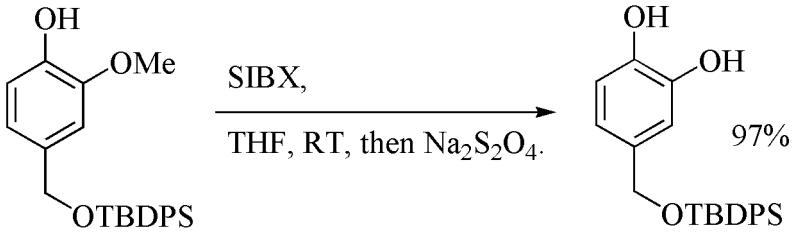
90%



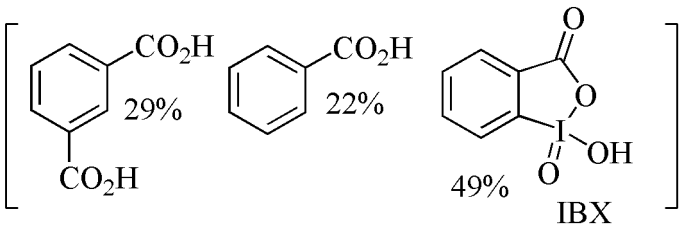
37%, dr>98:2

Stabilized IBX (abbreviated as SIBX) has been developed by SIMAFEX as a non explosive version of IBX. This new formulation was found to be as effective and selective as IBX in various solvents in different transformations.[30] SIBX is able to perform oxygenative demethylation of 2-methoxyphenols (see Scheme 15).

Scheme 15



SIBX =



IBX a reagent which will continue to surprise us!

[30] A. Ozanne, L. Pouységu, D. Depernet, B. Francois, S. Quideau, *Org. Lett.* **2003**, *5*, 2903-2906.