Graphical Abstract

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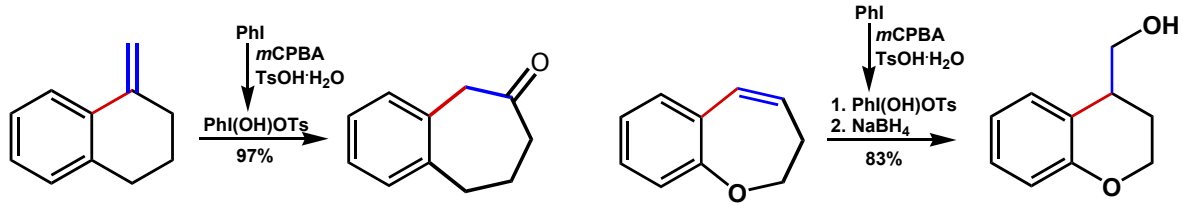

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Oxidative Rearrangement of Alkenes using *In Situ* Generated Hypervalent Iodine(III)

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ABSTRACT

A novel protocol for the oxidative rearrangement of alkenes using *in situ* generated hypervalent iodine(III) was developed. This approach uses inexpensive, readily available, and stable chemicals (PhI, *m*CPBA, TsOH) giving rearrangement products in yields comparable to those obtained using the more expensive commercially available [hydroxy(tosyloxy)iodo]benzene [HTIB or Koser's reagent]. Additionally, an alternative protocol for the synthesis of 1-methyl-2-tetralone through the one-step epoxidation/rearrangement of 4-methyl-1,2-dihydronaphthalene using *m*CPBA and TsOH was developed.

Hypervalent iodine reagents are extensively used in chemical synthesis[1] for various carbon-carbon bond formations,[2] rearrangements[3] and functional group transformations.[4] The inherent low toxicity, high stability and ready availability of the hypervalent iodine reagents together with their fascinating reactivity make them superior to the toxic heavy metal-based oxidants, such as lead(IV), mercury(II) and thallium(III).[1] The development of reactions using *in situ* generated hypervalent iodine species is one of the most notable achievements in the area, especially for asymmetric reactions.[3e, 5] Of the various hypervalent iodine(III) reagents, [hydroxy(tosyloxy)iodo]benzene [HTIB or Koser's reagent] is one of the most popular.[6] HTIB is used for a variety of useful transformations, such as rearrangement of alkenes[7] (including ring contraction[8] and expansion[9]), electrophilic cyclization,[10] α-functionalization of carbonyl compounds,[11] tosyloxylation of aromatic rings[12] and oxidative biaryl couplings.[13] Herein we describe a flexible and general strategy for *in situ* generation of HTIB and its use in the oxidative rearrangement of alkenes. HTIB is formed from the inexpensive reagents iodobenzene, *m*-chloroperoxybenzoic acid (*m*CPBA), and *p*-toluene sulfonic acid ($TsOH.H_2O$).

Fluoroalcohols, like 2,2,2-trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoroisopropanol (HFIP), exhibit unique properties like high polarity, low nucleophilicity, high ionizing power and exceptional hydrogen-bond donor ability. Moreover, TFE and HFIP have the capability to stabilize reactive cationic intermediates which are produced by the action of hypervalent iodine species.[14] Using the cyclic alkene **1** as substrate, several alternatives to perform an oxidative rearrangement were investigated using TFE and HFIP as solvents. The reaction is performed in three steps. First step, HTIB was generated *in situ* by treating iodobenzene with *m*CPBA and $TsOH.H_2O$ at room temperature in a mixture of TFE and CH_2Cl_2.[15] Second step involve the addition of the appropriate solvent for the oxidative rearrangement HFIP/CH_2Cl_2 followed by addition of substrate **1**.[8d, 8e] The presence of a small amount of water minimizes the formation of undesired acetal-like product.[8d, 8e] The aldehyde formed in this process was reduced *in situ* adding $NaBH_4$, delivering the corresponding hydroxy ring contraction product **2** in 63% yield (Table 1, entry 1). Removal of the solvent after formation of the iodine(III), gave the desired product **2** in a similar yield (entry 2). The effect of solvents on the model reaction was further examined. Using a 1:1 mixture of TFE/CH_2Cl_2 and different amounts of H_2O afforded the desired alcohol **2** in low to moderate yield (entries 3-6). However, using a smaller amount of TFE gave alcohol **2** in 56% yield (entry 7). The use of the highly polar and low nucleophilic solvent HFIP[14] in different mixtures with CH_2Cl_2 and H_2O gave the ring contraction product **2** in good yields (entries 8-11). The best yield was obtained when 1:6 ratio of HFIP/ CH_2Cl_2 was used, in the presence of H_2O. This yield is comparable to that obrained using commercially available HTIB (entry 11). The desired reaction failed to take place when CH_2Cl_2/H_2O was used (entry 12). We also considered the use of other oxidants, like Oxone® ($KHSO_5$),[3a, 16] hydrogen peroxide (H_2O_2),[5f] and potassium persulfate ($K_2S_2O_8$).[17] Oxone was tested using different solvents (CH_3CN, TFE/ CH_2Cl_2 and $CHCl_3$) without success (entries 13-15). The

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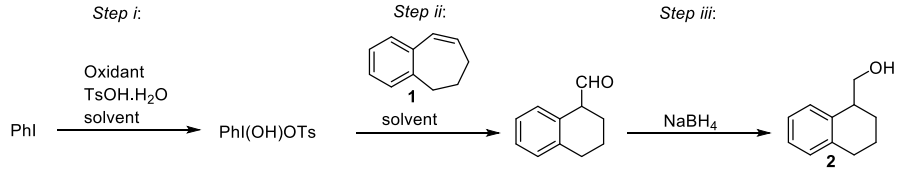
starting material was recovered when $K_2S_2O_8$ and H_2O_2 were used as oxidants (entries 16 and 17).

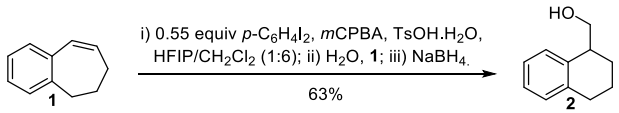
Table 1. Rearrangement Reactions of Cyclic Alkene **1** Using *In Situ* Generated HTIB



Entry	Oxidant	Solvent step i	Solvent step ii	Yield of **2** (%)
1	*m*CPBA	TFE/CH_2Cl_2 (1:1)	HFIP/CH_2Cl_2 (1:4), 22 equiv H_2O	63
2	*m*CPBA	TFE/CH_2Cl_2 (1:1) (solvent evaporated)	HFIP/CH_2Cl_2 (1:4), 22 equiv H_2O	64
3	*m*CPBA	TFE/CH_2Cl_2 (1:1)	22 equiv H_2O	48
4	*m*CPBA	TFE/CH_2Cl_2/H_2O (1:1:1)	-	23
5	*m*CPBA	TFE/CH_2Cl_2 (1:1)	H_2O (1 mL)	57
6	*m*CPBA	TFE/CH_2Cl_2 (1:1)	H_2O (2 mL)	31
7	*m*CPBA	TFE/CH_2Cl_2 (1:6)	22 equiv H_2O	56
8	*m*CPBA	HFIP/CH_2Cl_2/H_2O (1:3:3)	-	47
9	*m*CPBA	HFIP/CH_2Cl_2 (1:1)	22 equiv H_2O	61
10	*m*CPBA	HFIP/CH_2Cl_2/H_2O (1:6:6)		54
11	*m*CPBA	HFIP/CH_2Cl_2 (1:6)	22 equiv H_2O	71(65)[b]
12	*m*CPBA	CH_2Cl_2/H_2O (1:1)	-	-[b]
13	Oxone	CH_3CN	HFIP/CH_2Cl_2 (1:4), 22 equiv H_2O	-[b]
14	Oxone	TFE/CH_2Cl_2 (1:1)	HFIP/CH_2Cl_2 (1:4), 22 equiv H_2O	27
15	Oxone	$CHCl_3$	HFIP/CH_2Cl_2 (1:4), 22 equiv H_2O	11[c]
16	$K_2S_2O_8$	TFE/CH_2Cl_2 (1:6)	22 equiv H_2O	-[b]
17	H_2O_2	H_2O_2, TFE/CH_2Cl_2 (1:1),	22 equiv H_2O	-[b]

[a] Isolated yields.
[b] Reaction carried out with commercially available Koser's reagent.
[c] Starting material recovered.

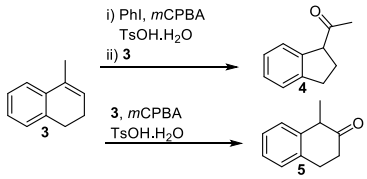
The use of 1,4-diiodobenzene instead of iodobenzene was also investigated. When the oxidative rearrangement of **1** was carried out with this new Koser`s reagent derivative, the rearrangement product **2** was obtained in 63% yield (Scheme 1).



Scheme 1 Koser's reagent derivative from 1,4-diiodobenzene

Based on previous work, we know that alkyl substituted double bonds can have a different reactivity in rearrangements.[8f, 18] Thus, a second screening was performed with alkene **3**. Under the optimized reaction conditions for **3**, the desired ring contraction product **4** was obtained in only 41% yield (Table 2, entry 1). Using a mixture of TFE/CH_2Cl_2 as a solvent enhanced the yield to 73% (entry 2). However, if the substrate is added together with *m*CPBA, another rearrangement product, 1-methyl-2-tetralone (**5**), was obtained presumably through epoxidation by *m*CPBA followed by acid-catalyzed rearrangement (entry 3). This transformation was also took place in the presence of a catalytic amount of PhI (entry 4) or even without it (entry 5). This one step transformation of **3** into **5** is fast, convenient, high yielding and uses readily available chemicals, constituting a useful method to obtain 2-tetralones. Analogous two-steps protocols were also reported.[19] Additionally, compounds like **5** can be obtained by the rearrangement of epoxides using lewis acids.[19b, 20] Another route to transform **3** into **5** is through a hydrobration/oxidation sequence.[21]

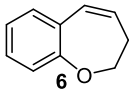
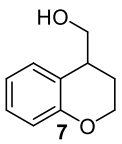
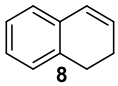
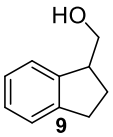
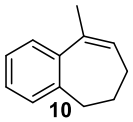
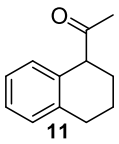
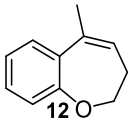
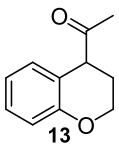
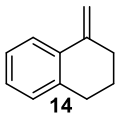
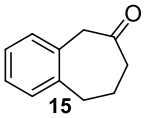
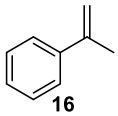
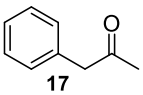
Table 2. Rearrangement Reactions of 1,2-dihydro-4-methylnaphthalene (**3**)



Entry	Reagents and Conditions	Product
1	i) PhI, *m*CPBA, TsOH.H_2O, HFIP/CH_2Cl_2 (1:6); ii) **3**	**4** (41%)
2	i) PhI, *m*CPBA, TsOH.H_2O TFE/CH_2Cl_2 (1:1); ii) **3**	**4** (73%)
3	**3**, PhI, *m*CPBA, TsOH.H_2O TFE/CH_2Cl_2 (1:4)	**5** (73%)
4	**3**, PhI (30 mol%), *m*CPBA, TsOH.H_2O, TFE/CH_2Cl_2 (1:4)	**5** (75%)
5	**3**, *m*CPBA, TsOH.H_2O, TFE/CH_2Cl_2 (1:4)	**5** (81%)

Having established the optimal reaction conditions for the *in situ* generation of HTIB, the scope and generality of the oxidative rearrangement of alkenes was systematically examined. As shown in Table 3, the reaction conditions were found to be very general. Dihydrobenzo[*b*]oxepine **6** afforded the corresponding chromane **7** in 83% yield (entry 1). A smooth oxidation took place with 1,2-dihydronaphthalene (**8**) leading to the indane **9** (entry 2). The methyl substituted olefins **10** and **12** were successfully transformed into the corresponding rearrangement products **11** and **13**, respectively (entries 3 and 4). The exocyclic alkene **14** gave the corresponding ring expansion product **15** in nearly quantitative yield (entry 5). The generality of methodology was further demonstrated by the oxidative rearrangement of α-methylstyrene into the corresponding α-aryl ketone **17** in 81% yield (entry 6). It is impotant to note that all yields are in the same range of that obtained using commercially available HTIB.

Table 3. Oxidative Rearrangement of Alkenes using *in situ* Generated Iodine(III)

Entry	Substrate	Product	Yield
1			83[a] (87)[d,8e]
2			65[a] (74)[d,8d]
3			79[b] (62)[d,8d]
4			61[b] (58)[d,8e]
5			97[c] (99)[d,9a]
6			81[c] (84)[d,7]

a) i) PhI, *m*CPBA, $TsOH{\cdot}H_2O$, HFIP/CH_2Cl_2 (1:6), 30 min; ii) 22 equiv H_2O, substrate; iii) $NaBH_4$.
b) i) PhI, *m*CPBA, $TsOH{\cdot}H_2O$, TFE/CH_2Cl_2 (1:1), 30 min; ii) substrate.
c) i) PhI, *m*CPBA, $TsOH{\cdot}H_2O$, HFIP/CH_2Cl_2 (1:6), 30 min; ii) 22 equiv H_2O, substrate.
d) Reported yield when reaction carried out with commercially available Koser's reagent.

In conclusion, a new method for the oxidative rearrangement of alkenes using *in situ* generated iodine(III) was developed. The protocol uses inexpensive and stable chemicals, furnishing rearrangement products in yields comparable to those obtained using commercially available iodine(III).

Acknowledgments

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Supplementary Material

Supplementary data (spectroscopic data and experimental procedures) associated with this article can be found, in the online version.

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