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Chiral hypervalent iodine compounds

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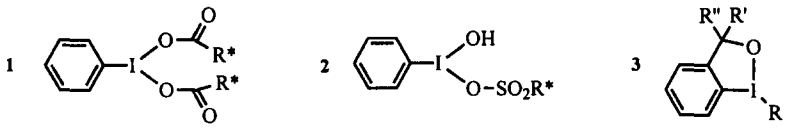
Abstract: The synthesis of non-racemic chiral hypervalent iodine reagents is described together with the first application of these reagents in asymmetric functionalizations of ketones and alkenes. © 1997, Elsevier Science Ltd. All rights reserved.

Recently hypervalent iodine compounds have attracted much interest in organic synthesis.[1] They are often used as mild and selective oxidants e.g. Dess–Martin periodinane,[2] or as reagents for oxygenation reactions e.g. the Koser reagent {PhI(OH)OTos}.[3] Only a few chiral hypervalent iodine compounds have been synthesized to date.[4] Some are chiral binaphthyl compounds,[4d] but most of them are derivatives of chiral carboxylic acids (type **1**) or chiral sulfonic acids (type **2**). These molecules have been used only in oxidation reactions to convert sulfides into sulfoxides. Very recently compounds of type **3** were described[5] also in optically active form,[5b] and we would like to communicate the results of our investigations in this area.



Hypervalent iodine compounds can not only be used as oxidants, but also as electrophilic reagents. Iodine lactonisations, α-oxytosylations of ketones or dioxytosylations of alkenes can be performed with these reagents.[3] Because new asymmetric centers are created during these reactions, chiral hypervalent iodine compounds should be promising reagents for asymmetric variants of these reactions.

In our work with chiral selenium electrophiles we found that selenium cations, which are coordinated to the oxygen atom of a chiral alcohol, perform addition reactions to various alkenes with high diastereoselectivities.[6] The formation of a five-membered ring with a close proximity to the asymmetric center and the selenium electrophile was found to be advantageous. The stereogenic centers in compounds **1** and **2** are, however, far away from the iodine atom. Therefore we planned the synthesis of hypervalent iodine compounds, where the stereogenic center is closer to the iodine atom as in **3**.[7]

The chiral hypervalent iodine compounds are used in stoichiometric amounts in the reactions described above. Therefore they must be accessible in a short synthetic sequence. The synthesis of **6** starts with the chiral alcohol **4**. Compound **4** is commercially available or can be prepared by addition of diethylzinc to benzaldehyde in the presence of chiral catalysts (>98% *ee*).[8] After *ortho*-lithiation[9] of **4**, iodine is introduced and the secondary alcohol is converted to the methyl ether **5**. The oxidation is performed with sodium perborate in glacial acetic acid[10] and leads to the (diacetoxy)iodobenzene derivative. Subsequent treatment with *para*-toluenesulfonic acid monohydrate yields the hydroxy(tosyloxy)iodobenzene compound **6**. Although the yield from the introduction of iodine in **4** is only 40%, the subsequent formation of the ether and the synthesis of the diacetate are reactions with very good yields. The hypervalent iodine compound **6** can be purified by crystallization and is obtained in 68% yield.[11] The benzyl protected compound **6b** is less stable than **6a** while the *tert*-butyl protected compound decomposed during purification.

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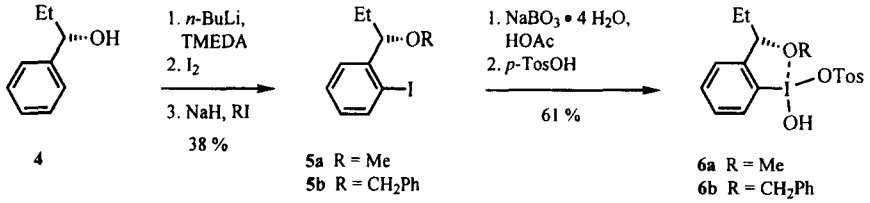
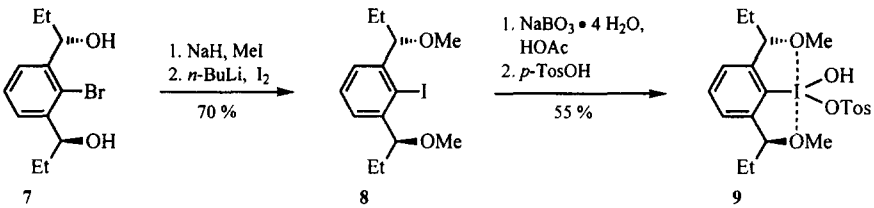
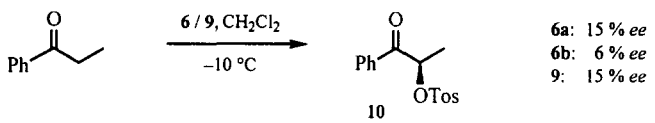


The X-ray analysis of **6a**[12] shows a similar T-shaped structure like the Koser reagent[13] with an oxygen–iodine–oxygen angle of 167.3° (Koser reagent 178.8°). Interestingly the oxygen of the methoxy-group replaces the tosylate. We observed a short distance from the oxygen atom of the methoxy-group to the iodine of about 2.47 Å and a longer (tosylate)–oxygen iodine distance of 2.91 Å. The bond length of the (hydroxy)–oxygen atom to iodine is 1.94 Å and of the iodine–carbon bond 2.08 Å and therefore similar in both structures.

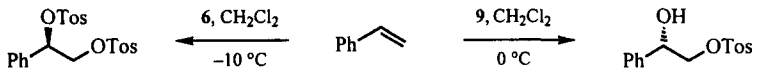
The synthesis of the C_2-symmetric hypervalent iodine compound **9** is achieved in a similar way. Because the iodine cannot be introduced *via* an *ortho*-deprotonation, the synthesis starts with a brominated compound. The addition reaction of diethylzinc to 2-bromoisophthalaldehyde[14] in the presence of a chiral catalyst leads to the chiral alcohol **7**.[15] The hydroxy groups of the diol **7** are methylated and after lithiation the bromine is replaced by iodine yielding compound **8** in 70% yield. After oxidation with sodium perborate in glacial acetic acid and reaction with *para*-toluenesulfonic acid monohydrate the hypervalent iodine compound **9** is isolated in 55% yield. The purification is difficult because of the high polarity of **9** but can done by repeated washing with pentane.



Oxytosylations of ketones in the α-position can be performed with the Koser reagent. This reaction can be described mechanistically by an electrophilic attack of the iodine at the double bond of the enolate with subsequent S_N2 substitution of the iodine by the tosylate. Therefore we investigated the hypervalent iodine compounds **6** and **9** in this reaction. The hypervalent iodine compound is dissolved in acetonitrile and treated with an excess of propiophenone. The enantiomeric excess of the product **10** is determined by HPLC after purification on silica gel (40–70% yield). The oxytosylated compound **10** shows an enantiomeric excess up to 15%.[16]



With hypervalent iodine compounds the functionalization of alkenes is also possible. During the reaction with an alkene an iodonium intermediate is formed which then reacts twice with a tosylate to yield the dioxytosylated compound. Because in reactions with asymmetrically substituted alkenes a stereogenic center is formed we investigated the reaction of styrene with the hypervalent iodine compounds **6a** and **6b**. The dioxytosylate **11** was isolated in 30–70% yield with an enantiomeric excess up to 21%. Compound **11** was found to possess the *R*-configuration.[17] The reaction of **6** with styrene therefore proceeds with the same facial selectivity as the reaction with analogous chiral selenium compounds.[6a] The reaction of **9** with styrene yields compound **12** with 17% *ee*. The reaction path to this compound as well as the inversion of the configuration is not clear. Like the corresponding selenium compounds the C_2-symmetric hypervalent iodine compound **9** shows no advantage over compound **6**.



11
with **6a**: 21 % *ee*
with **6b**: 16 % *ee*

12
17 % *ee*

Iodine lactonisations with allylacetic acid and sulfide oxidations to sulfoxides were investigated. Although the products were isolated in good yields, the use of the hypervalent iodine compounds **6** and **9** resulted in very low enantiomeric excesses (up to 5% *ee*). The investigations presented herein describe the synthesis of chiral hypervalent iodine compounds as well as their first use in asymmetric synthesis. The synthesis of other chiral hypervalent iodine compounds as asymmetric electrophilic reagents is currently under investigation.

Acknowledgements

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11. (*S*)-1-(*I*-Hydroxy-*I*-tosyloxy)-iodo-2-(1-methoxypropyl)-benzene **6a**: (*S*)-1-Iodo-2-(1-methoxypropyl)benzene **5a** (478 mg, 1.73 mmol) is dissolved in 20 mL glacial acetic acid and treated with sodium perborate (2.66 g, 17.3 mmol). After stirring for 3 hours at 60°C the glacial acetic acid

is removed under reduced pressure, the residue diluted with water and extracted three times with $CHCl_3$. The solvent is removed and the residue dried in vacuum at 50°C. The diacetoxyiodo compound is obtained in 87% yield (592 mg, 1.50 mmol). The diacetoxyiodo compound (394 mg, 1 mmol) and *para*-toluenesulfonic acid monohydrate (190 mg, 1 mmol) are dissolved in acetonitrile (5 mL) and stirred for 1 hour at room temperature. The solvent is distilled off and the residue recrystallized from acetonitrile and product **6a** obtained (317 mg, 68%). Selected spectroscopic data for **6a**: $[\alpha]_D^{25}$=+38.2 (c=0.76, $CHCl_3$); ^{1}H-NMR (300 MHz, $CDCl_3$) δ=0.93 (t, *J*=7.4 Hz, 3H), 1.81 (m, 2H), 2.33 (s, 3H), 3.69 (s, 3H), 4.53 (t, *J*=6.1 Hz, 1H), 7.12 (d, *J*=8.0 Hz, 2H), 7.27 (d, *J*=7.4 Hz, 1H), 7.45 (t, *J*=7.4 Hz, 1H), 7.53 (t, *J*=7.4 Hz, 1H), 7.76 (d, *J*=8.0 Hz, 2H), 7.84 (d, *J*=7.4 Hz, 1H), 8.30–9.20 (s, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ=9.0 (q), 21.3 (q), 28.1 (t), 60.7 (q), 87.6 (d), 113.4 (s), 126.1 (d, 2C), 127.4 (d), 128.5 (d), 128.7 (d, 2C), 130.7 (d), 131.2 (d), 138.7 (s), 140.1 (s), 141.6 (s); mp. 137–139°C; correct elemental analysis for $C_{17}H_{21}ISO_5$.

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