Stereoselective Synthesis

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Highly Stereoselective Metal-Free Oxyaminations Using Chiral Hypervalent Iodine Reagents**

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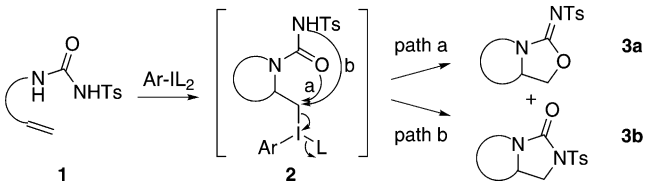
Hypervalent iodine reagents are frequently used and have found wide applications in synthesis.[1,2] They are used in a wide range of transformations as environmentally friendly, mild and highly selective oxidants because they avoid the issues of toxicity or the complicated ligands of many transition-metal-based systems. They can also be employed as electrophilic reagents for the functionalization of alkenes in halolactonizations[3] and dioxytosylations,[4] for the oxidative dearomatization of phenols,[5] and the α-functionalization of ketones.[6,7] In this context, the use of chiral hypervalent iodine reagents for asymmetric transformations has emerged as an interesting area of research in recent years.[8] Only recently the catalytic use of iodine compounds in synthesis has been developed.[9] We reported the first catalytic use of enantiomerically pure iodoarenes in asymmetric reactions,[10] which opened the possibility to employ a wide range of such compounds with various structural features as catalysts.[11]

The 1,2-difunctionalization of alkenes is a very important transformation as is illustrated by the occurrence of the 1,2-amino alcohol moiety in a huge range of bioactive compounds, natural products, and chiral reagents for stereoselective synthesis. Transition-metal-catalyzed oxidative amination reactions are established methods for the synthesis of new carbon–nitrogen and carbon–oxygen bonds through the functionalization of alkenes.[12] The osmium-based catalytic aminohydroxylation is an early efficient route developed by Sharpless et al.,[13] but other metal catalysts, such as palladium and platinum, have also been used for intramolecular aminations.[14] The use of bifunctional nucleophiles together with hypervalent iodine reagents in additions to alkenes can lead to versatile building blocks as shown in the aminohydroxylations of alkenes.[15]

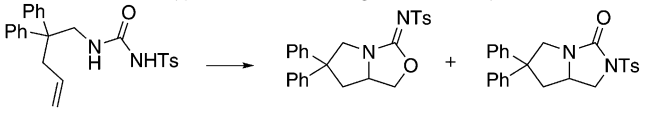
Herein we describe the first efficient stereoselective oxyaminations using chiral hypervalent iodine compounds. For these reactions we have investigated sulfonyl-substituted homoallylic urea derivatives of type **1** (Scheme 1). After the activation of the double bond with the hypervalent iodine reagent, the first nucleophile reacts to give intermediate **2**. The hypervalent iodine moiety is then attached to an sp^3-hybridized carbon atom and is therefore an excellent leaving group, several orders of magnitude more reactive than triflates or tosylates.[16] The subsequent substitution reaction directly yields bicyclic compounds **3**. It has already been shown that, depending on the reaction conditions, such cyclizations can lead either to isoureas **3a** or to the formation of diamination products **3b** (Scheme 1).[15c,17]



Scheme 1. Cyclization of urea bisnucleophiles with alkenes using hypervalent iodine reagents (Ar-IL_2) for the synthesis of isoureas **3a** (path a) or of cyclic ureas **3b** (path b).

Initial cyclizations of substrate **4** were performed by modifying literature procedures.[15c] [Bis(trifluoroacetoxy)iodo]benzene led to the reaction products **5a** and **5b** in low yields in a very slow reaction (Table 1, entry 1). Also the addition of catalytic amounts of diphenyl diselenide, a catalyst which was successful in a series of other cyclization–elimination sequences,[18] did not provide a substantial improvement as reaction time is still long (entry 2). The addition of *tert*-butyldimethylsilyl triflate (TBDMSOTf, Table 1, entries 3 and 4) or trimethylsilyl triflate (TMSOTf) to (diacetoxyiodo)benzene generates in situ, as evidenced by NMR spectroscopic investigations (see the Supporting Infor-

Table 1: Different hypervalent iodine reagents for the cyclization of **4**.



4 **5a** **5b**

Entry	Reagents	Solvent, Conditions	Yield [%] 5a	5b
1	$PhI(OCOCF_3)_2$	CH_2Cl_2, RT, 120 h	26	28
2	$PhI(OCOCF_3)_2$, 5 mol% $(PhSe)_2$	CH_2Cl_2, RT, 72 h	62	6
3	$PhI(OAc)_2$, TBDMSOTf	CH_2Cl_2, −78 to RT, 8 h	48	20
4	$PhI(OCOCF_3)_2$, TBDMSOTf	CH_2Cl_2, −78 to RT, 3 h	50	22

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mation), the more reactive $PhI(OTf)_2$.[19] This step leads to a mixture of **5a** and **5b** (ratio approx. 2:1) in a much faster reaction with improved combined yields of 72% (Table 1, entry 4).

Lactate-based hypervalent iodine compounds have been synthesized by Fujita et al.[20] and reagent **6a** has been introduced by Ishihara et al. for a highly enantioselective spirolactonizations.[21] As the products **5a** and **5b** contain stereogenic centers, substrate **4** was cyclized using the different chiral hypervalent iodine reagents **6** (Figure 1). Under various reaction conditions, only isourea compound **5a** was obtained with all reagents **6** and the cyclic urea derivative **5b** could not be detected.

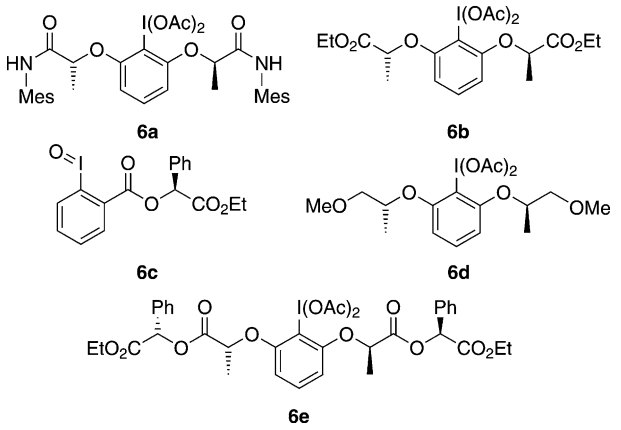


Figure 1. Enantiomerically pure lactate- and mandelate-derived hypervalent iodine reagents **6**.

As shown in Table 2, the hypervalent iodine reagent **6a** has been investigated together with different acids for its activation (Table 2, entries 1–3). The highest selectivities are obtained with trimethylsilyl triflate (TMSOTf) leading to the reaction product **5a** with an enantiomeric excess of 61% *ee* (Table 2, entry 3).[22] Slightly higher reaction temperatures led to lower selectivities (Table 2, entry 4), as did other solvents (Table 2, entries 5 and 6). The hypervalent iodine compounds **6b** and **6d**, which are also derived from lactic acid, were less efficient in the stereoselective cyclization of **4** (Table 2, entries 7 and 8). In these experiments, stoichiometric amounts of the hypervalent iodine reagents **6** are being used. About 80–85% of the reduced aryl iodides are recovered after the reaction without loss of optical purity and can be reused by oxidation. Previous research by our group using selenium electrophiles revealed that styrene derivatives are potential substrates for cyclizations with high selectivities.[23] We therefore prepared and investigated compound **7** in stereoselective cyclizations leading to isourea **8** containing a stereogenic tetrasubstituted carbon atom.

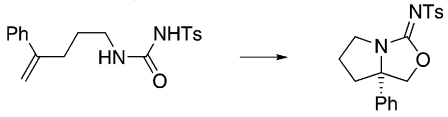
All the chiral hypervalent iodine reagents **6** shown in Figure 1 have been used for the cyclization of compound **7** (Table 3, entries 1–5). Highest selectivities have been obtained with reagent **6a**, probably because of its ability to coordinate through the amide nitrogen atoms to the iodine atom.[21] Also reagent **6e**, containing lactic acid and mandelic acid moieties, led to a good selectivity for product **8** (Table 3, entry 5). The addition of trifluoroethanol, which can strongly influence reactions with hypervalent iodine compounds,[24] did not have a pronounced effect in this case (Table 3, entry 6). The use of other solvent mixtures increased selectivities and yields. Experiments with **7** containing small amounts of *para*-toluenesulfonamide ($TsNH_2$) as a result of the preparation procedure gave variable results. Addition of $TsNH_2$ to the reagent **6a** together with an excess of TMSOTf, led to reproducible results and to synthetically very attractive selectivities, especially if **6a** is allowed to react first with TMSOTf (Table 3, entries 9 and 10).

Table 2: Conditions for the stereoselective cyclization to **5a**.

Entry	Reagents[a]	Solvent	Yield [%]	*ee* [%]
1	**6a**, TBDMSOTf	CH_2Cl_2	50	40
2	**6a**, TfOH	CH_2Cl_2	58	40
3	**6a**, TMSOTf	CH_2Cl_2	48	61
4	**6a**, TMSOTf	CH_2Cl_2	61	57[b]
5	**6a**, TMSOTf	toluene	0	–
6	**6a**, TMSOTf	THF	34	10
7	**6b**, TMSOTf	CH_2Cl_2	30	12
8	**6d**, TMSOTf	CH_2Cl_2	50	0

[a] Reaction temperature −78 °C, reaction time 14 h. [b] Reaction temperature −78 °C to room temperature.

Table 3: Stereoselective cyclization of **7** to isourea derivative **8**.



7 **8**

Entry	Reagents[a]	Solvent	Yield [%]	*ee* [%][b]
1	**6a**, 1.5 equiv TMSOTf	CH_2Cl_2	40	78
2	**6b**, 1.5 equiv TMSOTf	CH_2Cl_2	35	69
3	**6c**, 1.5 equiv TMSOTf	CH_2Cl_2	34	50
4	**6d**, 1.5 equiv TMSOTf	CH_2Cl_2	20	50
5	**6e**, 1.5 equiv TMSOTf	CH_2Cl_2	40	75
6	**6a**, 1.5 equiv TMSOTf	CH_2Cl_2/CF_3CH_2OH (1:1)	43	81
7[c,d]	**6a**, 2 equiv TMSOTf	CH_2Cl_2/Et_2O (3:1)	48	88
8[c]	**6a**, 2 equiv TMSOTf, 0.5 equiv $TsNH_2$	CH_2Cl_2/Et_2O (1:3)	76	90
9[c,e]	**6a**, 2 equiv TMSOTf, 0.5 equiv $TsNH_2$	CH_2Cl_2/Et_2O (1:3)	60–71	92–96
10[c,e,f]	**6a**, 3 equiv TMSOTf, 0.5 equiv $TsNH_2$	CH_2Cl_2:Et_2O (1:3)	–	>99

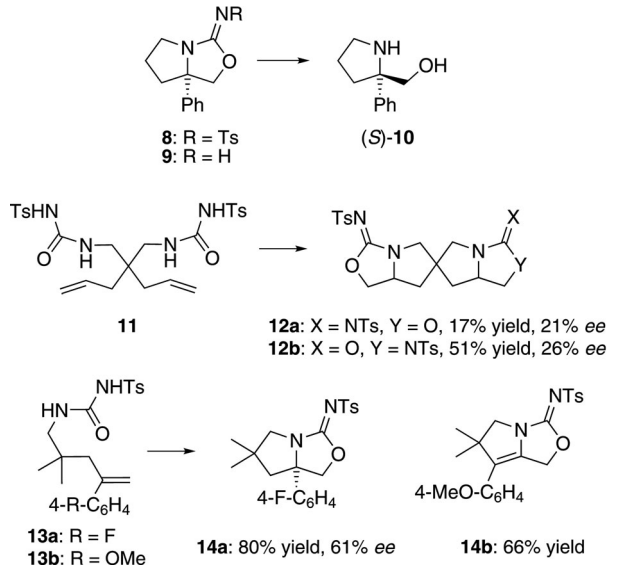
[a] Reaction temperature −78 °C, reaction time 14–18 h. [b] The major enantiomer has *S* configuration. [c] Reaction time 3 h. [d] Reaction temperature −100 °C. [e] Addition of **7** after reaction of **6a** with TMSOTf. [f] Reaction performed on analytical scale.

Owing to large signal broadening and decomposition above −40 °C, the structure of **6a** after the addition of TMSOTf and $TsNH_2$ could not be examined by NMR spectroscopy. Compound **8** was obtained enantiomerically pure (> 99 % *ee*) on an analytical-scale reaction (Table 3, entry 10), however, the selectivity dropped slightly on larger scale (Table 3, entry 9). The absolute configuration of the major isomer of **8** was found to be *S* by anomalous dispersion scattering by X-ray crystallography[25] and the refined Flack parameter[26] was 0.11(11). This allowed the rapid synthesis of (*S*)-2-phenylprolinol [(*S*)-**10**] by acidic cleavage of the tosylated derivative **8** to give the isourea compound **9** and subsequent basic cleavage to form the amino alcohol **10**.[15c] As a result of the tetrasubstituted carbon atom in **8**, all one-step deprotection attempts were unsuccessful. Despite the importance of proline-based catalysts in organocatalysis, 2-phenylprolinol **10** has not yet been prepared enantiomerically pure because α-aryl proline derivatives are very difficult to synthesize in optically pure form.[27]

This method was then also applied to substrates **11** and **13** demonstrating that other compounds are also accessible in good enantioselectivities (Scheme 2). Products **12a** and **12b** are formed as single diastereomers as judged from their NMR spectra but with low selectivities. Electron-withdrawing substituents on the aryl moiety in **13a** (R = F) led to the expected amino oxygenated product **14a**, whereas the electron-rich derivative **13b** (R = OMe) undergoes, after cyclization, further oxidation and rearrangement, probably through a reaction between the hypervalent iodine reagent and the methoxy-substituted aryl moiety.

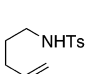
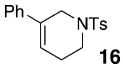
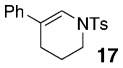
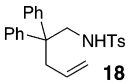
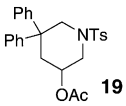
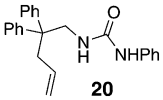
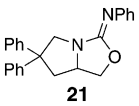
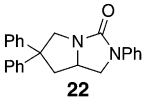
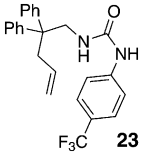
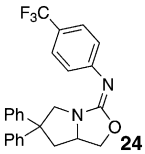
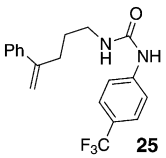
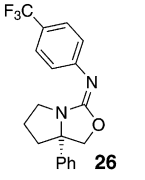
Apart from the N-tosylated urea derivatives shown above, substrates with other substituents on the nitrogen atom were investigated. The cyclization of tosylamide derivative **15** did result in the formation of achiral six-membered ring systems with elimination whereas the direction of elimination was found to be dependent on the Lewis acid used in the reaction (Table 4, entries 1 and 2). The addition of TBDMSOTf led to the elimination product **16** while with $BF_3{\cdot}OEt_2$ enamine **17** was isolated. The cyclization of tosylamide **18** also resulted in a 6-*endo* cyclization product with the acetate added as an external nucleophile. In this reaction the use of **6a** as chiral reagent led to an enantiomeric excess of only 27 % in product **19** (Table 4, entry 3). Similar reactions have already been described using gold catalysis.[28] The variation of the tosyl substituent on the urea moiety leads to altered nucleophilicities of the nitrogen moiety. A phenyl (Table 4, entries 4 and 5) or trifluoromethylphenyl substituent (entries 6 and 7) resulted in substrates with generally lower reactivity as seen by the lower yields in these reactions. Also the solvents used in the reactions had to be adjusted to ensure the solubility of the starting materials. With substrate **20** the use of $PhI(OTf)_2$ as the achiral reagent led to the expected isourea derivative **21**, whereas the chiral reagent **6a** yielded the cyclic urea **22** as the product of a diamination reaction. Good enantioselectivity (79 % *ee*) was obtained in product **26** (Table 4, Entry 7) and the absolute configuration was assigned in analogy to the results shown above.

The addition of nitrogen nucleophiles to alkenes using hypervalent iodine reagents is known and we have inves-



Scheme 2. Application of the hypervalent-iodine-mediated oxyamination of alkenes: Synthesis of (*S*)-2-phenylprolinol **10** and other oxyaminations.

Table 4: Other substrates in stereoselective cyclization reactions using **6a** and TMSOTf.

Entry	Substrate	Product	Yield [%]	*ee* [%][b]
1	 **15**	 **16**	48[a]	–
2		 **17**	42[b]	–
3	 **18**	 **19**	54	27
4	 **20**	 **21**	31[c]	0
5		 **22**	15[d]	42
6	 **23**	 **24**	45	39
7	 **25**	 **26**	30	79

[a] $PhI(OAc)_2$, TBDMSOTf, AcOH. [b] $PhI(OAc)_2$, $BF_3{\cdot}OEt_2$, AcOH. [c] $PhI(OAc)_2$, TMSOTf. [d] solvent: CH_3CN, no reaction occurred in CH_2Cl_2.

tigated aziridinations in detail, but stoichiometric amounts of the reagents were always necessary.[29] The requirement for a catalytic reaction is an oxidant that can convert iodoarenes into the iodine(III) reagents but that does not oxidize the alkene substrates. We are still investigating if such an oxidant exists for the aminohydroxylation described herein which would allow a catalytic asymmetric, metal-free aminohydroxylation.

These results demonstrate the large potential of chiral hypervalent iodine reagents in oxyaminations in place of metal-based methods together with a rapid access to unusual amino acid derivatives.

Experimental Section

General procedure for cyclizations: TMSOTf was added slowly to a solution of the urea-tethered alkene (1 equiv) and the hypervalent iodine compound **6** (1.2 equiv) in the solvent/solvent mixture (2 mL/0.1 mmol alkene) at −78 °C. The dry ice/acetone bath was removed and the reaction was allowed to warm to room temperature. The reaction was stirred overnight. The reaction was quenched with saturated aqueous $NaHCO_3$ (2 mL/0.1 mmol alkene), and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 5 mL/0.1 mmol alkene) and combined with the organic layer, dried over $MgSO_4$, filtered and concentrated in vacuo. The products were purified by chromatography (silica gel, ethyl acetate/hexane 3:5). Product yields are given in Tables 1–4 and Scheme 2. Typically, 80–85 % of the reduced aryl iodide are isolated without loss of optical purity.

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