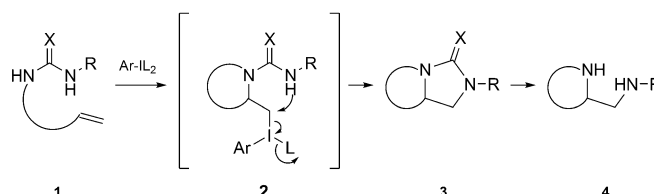


Diamination

Enantioselective Diamination with Novel Chiral Hypervalent Iodine Catalysts

Pushpak Mizar, Aragorn Laverny, Mohammad El-Sherbini, Umar Farid, Michael Brown, Florence Malmedy, and Thomas Wirth^{*[a]}

Abstract: Vicinal diamines constitute one of the most important functional motifs in organic chemistry because of its wide occurrence in a variety of biological and pharmaceutical molecules. We report an efficient metal-free, highly stereoselective intramolecular diamination using a novel chiral hypervalent iodine reagent together with its application as an efficient catalyst for the synthesis of diamines.



Scheme 1. Intramolecular diamination with hypervalent iodine reagents.

Hypervalent iodine reagents have found broad application in organic chemistry and are nowadays frequently used in synthesis.^[1,2] It is of great interest to investigate their ability as highly selective oxidants,^[3] electrophilic reagents,^[4] to improve known reactions like the α -functionalizations of ketones^[5] and to develop new reactions such as rearrangements^[6] using hypervalent iodine compounds. Oxidative transformations are of particular interest and a great challenge for organocatalytic processes. The requirement of developing new catalytic reactions with metal-free reagents such as iodine is considerable as efficient procedures of this type are still immature.^[7]

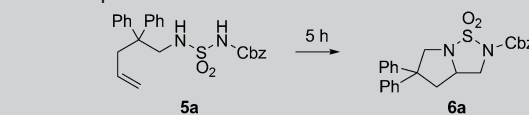
The addition of nitrogen nucleophiles to alkenes using hypervalent iodine reagents is known and aziridinations of alkenes,^[8] aminohydroxylations^[9] and aminofluorinations^[10] have already been carried out using stoichiometric amounts of either achiral or chiral reagents. Bifunctional nucleophiles can lead to interesting building blocks as shown in Scheme 1. After the activation of the double bond in compound 1 with the hypervalent iodine reagent, the first nucleophile attacks to give intermediate 2. The hypervalent iodine moiety in 2 is attached to a sp^3 -hybridized carbon atom and is therefore an excellent leaving group, several orders of magnitude more reactive than triflates or tosylates.^[11] Products of type 3 are formed which can be transformed into 1,2-diamines 4. There are various metal-catalyzed methods available to carry out vicinal diamination of alkenes,^[12] but only a few reports in which stoi-

chiometric amounts of hypervalent iodine reagents have been used for diaminations to generate racemates^[13] and also enantiomerically enriched products.^[14] However, there are hardly any methods available to carry out the reaction stereoselectively using chiral metal-free catalysts.^[15]

Herein, we report the application of novel chiral iodine catalysts for stereoselective intramolecular diamination reactions using various homoallylic guanidine and diaminosulfone derivatives. Initial investigations were carried out using substrate 5a. It was observed that (diacetoxyiodo)benzene and [bis(trifluoroacetoxy)iodo]benzene led to a sluggish reaction at 0 °C affording a very low yield of product 6a. As reported in other reactions,^[16] we tried to activate the reagents with a Lewis acid and observed that, upon addition of $BF_3 \cdot OEt_2$, TMSOTf, or a 1:1 mixture of $BF_3 \cdot OEt_2$ and TMSOTf (Table 1, entries 2–5), the reaction proceeded faster with decent yields for the product. The nature of the solvent and also the reaction temperature have a strong influence on the overall yield as summarized in Table 1.

For homoallylic guanidine derivatives 7 (Table 2), the nature of the N-protecting group had a dominant effect on the cycli-

Table 1. Optimization of reaction conditions.



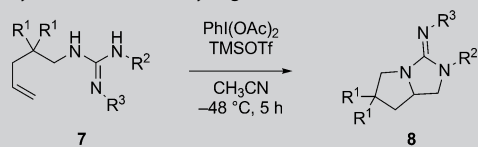
Entry	Reagent(s)	Solvent	Temp [°C]	6a: Yield [%]
1 ^[a]	PhI(OCOCF ₃) ₂	MeCN	0	29
2	PhI(OAc) ₂ , TMSOTf	CH ₂ Cl ₂	–78	12
3	PhI(OAc) ₂ , TMSOTf	MeCN	–48	87
4	PhI(OAc) ₂ , BF ₃ · OEt ₂	MeCN	–48	81
5	PhI(OAc) ₂ , BF ₃ · OEt ₂ and TMSOTf (1:1)	MeCN	–48	85

[a] Reaction time 24 h.

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Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201403891>.

Table 2. Cyclization of homoallylic guanidine derivatives **7**.

						
Entry	Alkene	Product	R ¹	R ²	R ³	8 : Yield [%]
1	7a		Ph	Boc	Boc	traces
2	7b	8a	Ph	Cbz	Cbz	82
3	7c	8b	Ph	H	Ts	84
4	7d		Me	Boc	Boc	traces
5	7e	8c	Me	Cbz	Cbz	14
6	7f	8d	Me	H	Ts	21

zation. When *tert*-butyl oxycarbonate (Boc) was used as the protecting group, only traces of the product **8** were observed (Table 2, entries 1 and 4). However, with carboxybenzoyl (Cbz) or tosylate (Ts) protecting groups, the products were obtained in reasonable yields. Studies have shown that the final carbon–nitrogen bond formation usually proceeds via an S_N2-type transition state with inversion of configuration and, hence, the nucleophilicity of the participating nitrogen moiety has a major influence.^[17] In addition, methyl substituents on the backbone of the alkene **7** (R¹=Me) are less efficient in directing the cyclization as with phenyl substituents in that place (R¹=Ph) where the yields are much higher.

To develop a stereoselective method for diamination reactions, the reaction **5a** → **6a** was performed using lactate-based chiral hypervalent iodine reagents **9** (Figure 1) under the optimized reaction conditions (Table 1, entry 3). Reagents **9** have been very successful in stereoselective reactions with alkenes^[9,10,14,18] and also other substrates,^[19,20] but here it was observed that only minor stereoselectivities could be obtained

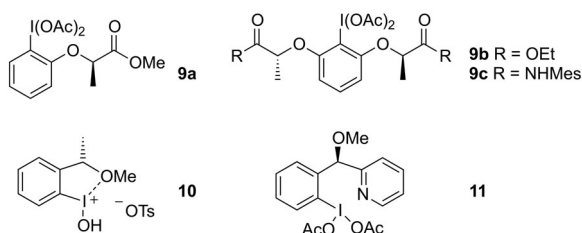
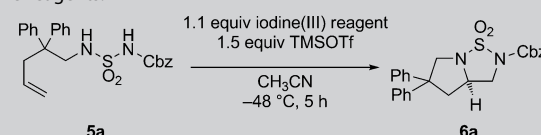


Figure 1. Chiral hypervalent iodine reagents.

Abstract in German: Durch die weite Verbreitung in einer Vielzahl von biologischen und pharmazeutischen Molekülen stellen vicinale Diamine eine der wichtigsten Funktionalitäten in der organischen Chemie dar. Wir berichten über eine effiziente metallfreie, hochstereoselektive intramolekulare Diaminierung unter Verwendung eines neuartigen chiralen hypervalenten Iod-Reagenz zusammen mit seinem Einsatz als effizienter Katalysator für die Synthese von Diaminen.

Table 3. Enantioselective reaction **5a** → **6a** with chiral hypervalent iodine reagents.

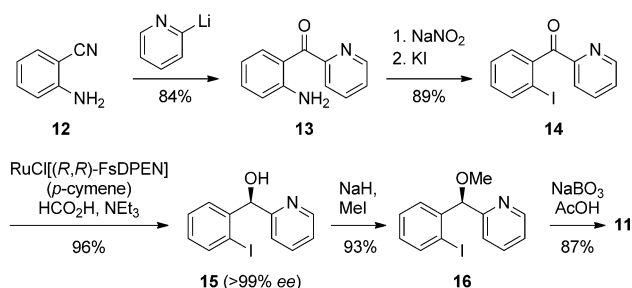
			
Entry	Reagent (1.1 equiv)	6a : Yield [%]	6a : ee [%]
1	9a	21	0
2	9b	24	0
3	9c	20	10
4	10	45	52
5	11	52	72
6 ^[a]	11	21	32
7 ^[b]	11	43	24
8 ^[c]	11	traces	–
9 ^[d]	11	60	82
10 ^[e]	11	70	92

[a] BF₃ · OEt₂ used instead of TMSOTf. [b] Reaction temperature: 0 °C. [c] Reaction temperature: 25 °C. [d] 3 equiv TMSOTf. [e] 1 equiv TMSOTf and 1 equiv BF₃ · OEt₂.

(Table 3, entries 1–3). The relatively large conformational flexibility in these reagents causes a weaker interaction of oxygen or nitrogen heteroatoms of the lactate moieties with the iodine which could also potentially be replaced by interactions with nitrogen atoms of the substrate **5a**. Reagent **10** has much less conformational flexibility with a strong interaction of the methoxy oxygen atom with the iodine established by X-ray analysis.^[21] With this simple chiral hypervalent iodine reagent **10**, much better selectivities (52% ee) were observed in the cyclization of **5a** to **6a** (Table 3, entry 4).

Based on this observation, we designed a novel hypervalent reagent with a pyridine moiety attached to a chiral benzylic center, which should allow an efficient coordination of the pyridine nitrogen to the iodine atom. It is well known that pyridines are good ligands for iodine(III), the close proximity to the stereogenic center should allow high selectivities to be obtained.^[22] This was indeed observed when the reaction was carried out using the novel hypervalent iodine reagent **11**, which led to the product **6** in 72% ee (Table 3, entry 5). NMR evidence suggests that it is indeed the nitrogen that is coordinating to the iodine, but the instability of the reagent **11** prevents further investigation and we cannot exclude that also the oxygen atom of the methoxy moiety coordinates. Reagent **11** is prepared directly before use and has been investigated with various Lewis acids for its activation, using different solvents and reaction temperatures. It was observed that the highest selectivity (92% ee) could be obtained with a 1:1 mixture of trimethylsilyl triflate (TMSOTf) and boron trifluoride etherate (BF₃ · OEt₂) at –48 °C using acetonitrile as solvent (Table 3, entry 10). Under these reaction conditions BF₂OTf · OEt₂ is acting as the Lewis acid.^[23]

The synthesis of reagent **11** is straightforward and is shown in Scheme 2. The aniline derivative **13**, obtained by the addition of 2-lithiopyridine to 2-cyanoaniline **12**, is iodinated to **14**



Scheme 2. Synthesis of the novel chiral hypervalent iodine(III) reagent **11**.

and reduced by using a chiral ruthenium catalyst.^[24] The alcohol **15**, obtained in >99% ee, is methylated to **16** and oxidized with sodium perborate to reagent **11** in 87% yield. The absolute configuration of **15** was determined to be (*R*) by deiodination of **15** and comparison of the optical rotation with a literature reference (see the Supporting Information).^[25]

The reagent **11** was then used in the diamination of various substrates. It was again observed that diphenyl-substituted substrates led to the cyclized products in good yields and with high enantioselectivities. Independent of the linker between the two nitrogen nucleophiles, the cyclization occurred with selectivities at or above 90% ee using either sulfonamides **5** (Table 4, entries 5 and 6) or guanidine derivatives **7** (Table 4, entries 2 and 4), whereas dimethyl-substituted, dimethyl ester-substituted or unsubstituted substrates showed almost no reaction (Table 4, entries 1, 3, 7, 9–12). Also a substituent *R*¹ on the alkene moiety is tolerated leading to chiral products containing a tetrasubstituted stereocenter with a nitrogen substituent. The absolute stereochemistry of the product **6a** has been determined to be (*R*) by independent synthesis of **17a**

Table 4. Stereoselective cyclization to bicyclic products.

5 (X: SO₂) or 7 (X: C=NR) 6 (X: SO₂) or 8 (X: C=NR)								
Entry	Alkene	Product	R ¹	R ²	R ³	X	Yield [%]	ee [%]
1	5d		H	Me	Cbz	SO ₂	traces	–
2	7c	8b	H	Ph	H	C=NTs	75	91
3	7f		H	Me	H	C=NTs	traces	–
4	7b	8a	H	Ph	Cbz	C=NCbz	71	92
5	5b	6b	Ph	Ph	Cbz	SO ₂	75	94
6	5c	6c	Me	Ph	Cbz	SO ₂	68	90
7	5e		H	H	Cbz	SO ₂	n.r. ^[a]	–
8	5a	6a	H	Ph	Cbz	SO ₂	70	92
9	5f		H	CO ₂ Me	Cbz	SO ₂	n.r. ^[a]	–
10	7e		H	Me	Cbz	C=NCbz	traces	–
11	7g		H	H	Cbz	C=NCbz	n.r. ^[a]	–
12	7h		H	H	H	C=NTs	n.r. ^[a]	–

[a] n.r.: no reaction.

(*R*=H) (see the Supporting Information). By analogy it can therefore be assumed that the products **6** and **8** (and **17**) have (*R*) absolute stereochemistry for *R*¹=H, Me and (*S*) for *R*¹=Ph when using reagent **11**. The new reagent **11** was also found to show promising selectivities in other stereoselective reactions.^[26]

All reactions shown in Table 4 were performed with stoichiometric amounts of hypervalent iodine(III) reagent **11** and the optical pure, reduced iodine(I) compound **16** was recovered after the reaction.

We then investigated the possibility of an in situ formation of the hypervalent iodine species by using the iodine(I) catalyst **16** together with stoichiometric amounts of an oxidant. The reaction occurred when 20 mol% of the iodine(I) catalyst **16** was used together with 2.2 equivalents *meta*-chloroperbenzoic acid (*m*CPBA) at –48 °C in acetonitrile. However, the yield was low and the enantioselectivity only moderate. Upon changing the oxidant to sodium perborate and after addition of three equivalents of acetic acid at room temperature, much higher yields and selectivities were obtained. There are reactions reported for the oxidation of alkenes to oxiranes or vicinal acetoxy alcohols using sodium perborate, but these reactions usually take about 24 h for completion and at higher temperatures under highly acidic reaction conditions.^[27] In the reaction described in Table 5 almost no competing reactions are observed and the

Table 5. Stereoselective catalytic cyclizations.

Entry	Alkene	Product	R	X	Yield [%]	ee [%]
1	7b	8a	H	C=NCbz	69	76
2	5a	6a	H	SO ₂	45	80
3	5b	6b	Ph	SO ₂	72	86
4	5c	6c	Me	SO ₂	67	83

desired products **6** can be obtained in reasonable yields with good selectivities. A removal of 'X' and the Cbz protecting group is possible by reduction using lithium aluminum hydride, and the free diamines **17** are easily obtained. The Cbz protecting group has to be removed by hydrogenation (Pd/C) prior to reduction.

In summary, we present a highly stereoselective intramolecular diamination of alkenes using a novel, simple hypervalent

iodine(III) reagent. This metal-free method provides rapid access to bicyclic molecules and to diamines in a fast synthetic sequence. Using these results, the first catalytic protocol for a stereoselective diamination of alkenes has been developed.

Experimental Section

All synthetic methods including spectroscopic and analytical data are included in the Supporting Information.

Acknowledgements

This project was supported by an EU Marie Curie fellowship to P.M. (DIALMEC, No. 298642) and by support from ENCPB to A. L. Support from the School of Chemistry, Cardiff University is also gratefully acknowledged. We thank the EPSRC National Mass Spectrometry Facility, Swansea, for mass spectrometric data.

Keywords: cyclization • diamination • hypervalent iodine • organocatalysis • stereoselective synthesis

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Received: June 10, 2014

Published online on July 17, 2014