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Efficient Synthesis of Chiral 2,2′-Bipyrrolidines by an *anti*-Selective Alkene Diamination

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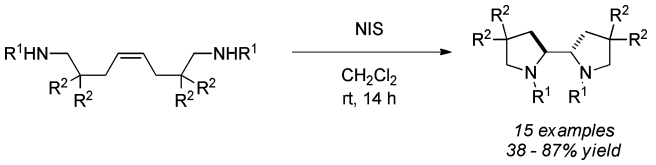
ABSTRACT



The rapid and efficient construction of complex chiral bicyclic amines is possible using a novel alkene diamination reaction. Electrophilic iodinating agents promote the intramolecular *anti*-selective diamination of alkenes and allow the efficient synthesis of chiral amines such as *trans*-bipyrrolidines.

Vicinal (1,2-) diamines are important building blocks of natural products and biologically active compounds.[1] Chiral vicinal diamines are widely employed as a backbone for the construction of reagents and catalysts in asymmetric synthesis.[2] A particularly interesting class of 1,2-diamines are *trans*-2,2′-bipyrrolidines, sterically demanding chiral diamines with applications in organocatalysis and asymmetric synthesis (Figure 1).[3] In many cases 2,2′-bipyrrolidines have shown properties superior to the more commonly used diamines such as *trans*-1,2-diamino cyclohexane.[4] One particularly interesting bipyrrolidine-based ligand is the *trans*-bpbp ligand **1** which was shown to be the preferred ligand for biomimetic C−H-bond oxidation reactions.[5] In iron-catalyzed asymmetric alkene dihydroxylations, the use of a *trans*-bpbp derivative as a metal ligand was again the key to reaching high enantioselectivities.[6] However, despite their advantages the general use of 2,2′-bipyrrolidines as building blocks for organocatalysts and chiral ligands has been limited most likely due to their difficult accessibility.[7] The preparation of unsubstituted 2,2′-bipyrrolidine is possible by the unselective photochemical dimerization of pyrrolidine followed by extensive recrystallization to separate the isomers.[7d] However, reliable procedures for the synthesis of substituted derivatives are missing.

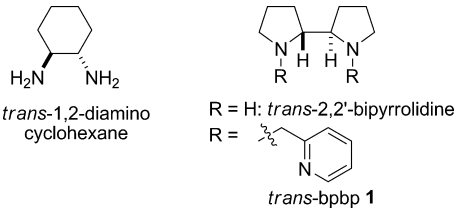


Figure 1. Important chiral diamines for asymmetric catalysis.

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One of the most attractive routes for the synthesis of 1,2-diamines is the direct diamination of alkenes.[8] Efficient methods for inter- and intramolecular alkene diaminations with urea- or sulfonamide-protected precursors and stoichiometric oxidants have been developed using transition metal catalysts.[9−11] These methods have in common the fact that the amino functionalities are usually introduced to the alkene via a formal *syn*-addition. Recently, transition-metal-free procedures for alkene diaminations have emerged employing environmentally friendly hypervalent iodine or electrophilic halogen reagents.[12] Again, these diaminations employ amines with electron-deficient protecting groups (urea, sulfonates) and proceed with *syn*-selectivity. However, *anti*-selective diaminations are rare.[13] Recently, Muñiz et al. reported an intermolecular *anti*-diamination of styrene derivatives using hypervalent iodine reagents.[14] Herein, we present a generally applicable method for the synthesis of bipyrrolidines starting from simple linear precursors using an intramolecular *anti*-diamination of alkenes promoted by electrophilic halogenating agents.

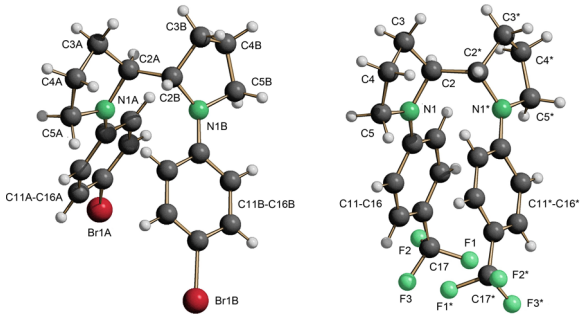
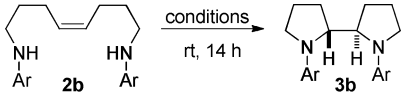


Figure 2. Crystal structures of diamines **3b** (left) and **3h** (right).

During our investigations on asymmetric halocyclization reactions[15] we observed an unusual halogen-induced intramolecular diamination reaction. When (*Z*)-*N*,*N*′-(4-bromophenyl)-1,8-diaminooct-4-ene **2b** was treated with *N*-iodosuccinimide (1.2 equiv) at rt a clean alkene diamination reaction to give *N*,*N*′-di(4-bromophenyl)-2,2′-bipyrrolidine **3b** was observed. The product **3b** was isolated as a single diastereomer indicating a stereospecific reaction. Single crystal X-ray structure analysis revealed the product to be *trans*-configured at the newly formed stereocenters suggesting an *anti*-addition of the amino groups onto the alkene (Figure 2).

Table 1. Electrophilic Iodine-Induced Diamination of (*Z*)-*N*,*N*′-(4-Bromophenyl)-1,8-diaminooct-4-ene **2b**



Ar = 4-BrPh

entry	reagent[a]	solvent	additive	yield (%)[b]
1	NIS	CH_2Cl_2	–	82
2	NIS	CH_2Cl_2	$NaHCO_3$	61
3	NIS	CH_2Cl_2	$NaHCO_3$[c]	63
4	NIS	THF	–	81
5	NIS	MeCN	–	70
6	I_2	CH_2Cl_2	$NaHCO_3$[c]	68
7	ICl	CH_2Cl_2	–	40
8	$BnMe_3NICl_2$	CH_2Cl_2	–	25
9	NBS	CH_2Cl_2	–	~20
10	NCS	CH_2Cl_2	–	–[d]

[a] 1.2 equiv. [b] Isolated yield. [c] Saturated solution in H_2O. [d] Less than 5% conversion after 18 h at rt.

The reaction conditions were carefully optimized, and the application of *N*-iodosuccinimide (1.2 equiv)

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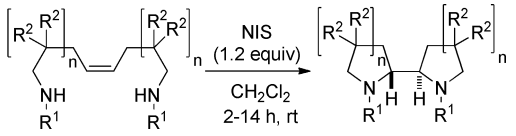
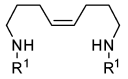
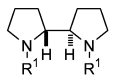
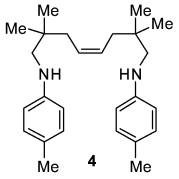
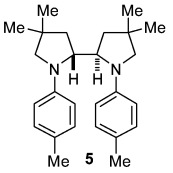
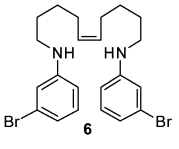
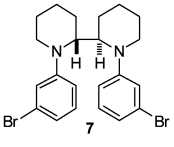
in dichloromethane proved to be optimal (Table 1, entry 1). The addition of base led to significantly decreased yields (entries 2 and 3). Iodine also induced the diamination reaction, but lower yields were obtained (entry 6). Other electrophilic iodine sources such as $BnMe_3NICl_2$ or ICl proved to be inferior (entries 7 and 8). *N*-Bromosuccinimide led to a complex reaction mixture containing several monocyclization products and only about 20% of **3b** (entry 9). Using *N*-chlorosuccinimide, no conversion of the starting material could be observed (entry 10). The reaction could be efficiently conducted in several solvents, but the use of dichloromethane provided the highest yields (entries 1, 4, and 5).

Table 2. Reaction Scope

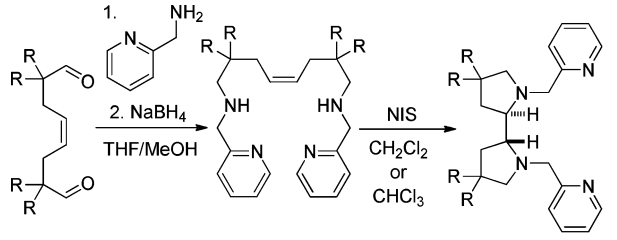


entry	starting material	product	yield (%)[a]
			
1	**2a**, R^1 = Ph	**3a**, R^1 = Ph	67
2	**2b**, R^1 = 4-BrPh	**3b**, R^1 = 4-BrPh	82
3	**2c**, R^1 = 3-BrPh	**3c**, R^1 = 3-BrPh	86
4	**2d**, R^1 = 2-BrPh	**3d**, R^1 = 2-BrPh	65
5	**2e**, R^1 = 2-IPh	**3e**, R^1 = 2-IPh	82
6	**2f**, R^1 = 4-MePh	**3f**, R^1 = 4-MePh	87
7	**2g**, R^1 = 2-MePh	**3g**, R^1 = 2-MePh	46
8	**2h**, R^1 = 4-CF_3Ph	**3h**, R^1 = 4-CF_3Ph	75
9	**2i**, R^1 = 4-CNPh	**3i**, R^1 = 4-CNPh	65
10	**2j**, R^1 = 4-NO_2Ph	**3j**, R^1 = 4-NO_2Ph	45
11	**2k**, R^1 = 4-OMePh	**3k**, R^1 = 4-OMePh	38[b]
12	**2l**, R^1 = *t*Bu	**3l**, R^1 = *t*Bu	65[c]
13	**2m**, R^1 = Bn	**3m**, R^1 = Bn	72[c]
14			57[d]
15			62

[a] Isolated yield. [b] I_2 (2.5 equiv) was used instead of NIS; reaction conducted in THF at −78 °C. [c] 2.4 equiv of NIS were used. [d] Reaction conducted at 0 °C.

Under optimized conditions the scope of the reaction was investigated (Table 2). A wide variety of aryl groups at the nitrogen atoms containing electron-donating and -neutral substituents were tolerated (entries 1−7). Yields were generally good to very good, and sterically demanding aryl groups with substituents at the ortho position caused only slightly lower yields (entries 4, 5, and 7). Even with electron-deficient substituents (−CF_3, −NO_2, −CN; entries 8, 9, and 10) selective *anti*-addition was observed (crystal structure of **3h**, Figure 1, and **3j**, SI). With strongly electron-donating groups (R = 4-OMe, PMP protecting group, entry 11), a complex reaction mixture was obtained. However, under modified conditions (I_2, −78 °C) the *anti*-addition product was isolated in moderate yield.[16] Alkyl substituents such as *tert*-butyl and benzyl groups at nitrogen were tolerated as well (entries 12 and 13). The efficient cyclization of the benzyl protected diamine **2m** makes the benzyl group the protection group of choice if *N*,*N*′-unsubstituted bipyrrolidines are targeted. The diamination reaction is not limited to cyclizations of unsubstituted 1,8-diaminooct-4-enes such as **2**. Diamine **4** was cyclized to give a chiral 2,2′-bipyrrolidine **5** with a tetramethyl substituted backbone (entry 14). Likewise, 1,10-diaminodec-5-ene **6** underwent 6-*exo* cyclizations to yield *N*,*N*′-(3-bromophenyl)-2,2′-bipiperidine **7**.

Scheme 1. Synthesis of *trans*-bpbp Ligands



8: R = H
10: R = Ph

9: R = H, 73%
11: R = Ph, 74%

1: R = H, 60% (from **8**)
12: R = Ph, 77%

Probably the most important bipyrrolidine-based ligand is the *trans*-bpbp ligand.[5] The method presented here allows a simple and diastereoselective synthesis of this ligand starting from dialdehyde **8** (easily available from 1,5-cyclooctadiene by selective oxidation of one double bond[17]). Reductive amination with 2-picolyl amine provided diamine **9** which upon treatment with 2 equiv of NIS yielded the desired bpbp-ligand **1** with complete diastereoselectivity and good yield (60% over two steps, Scheme 1). Moreover, our method is also suitable for the synthesis of backbone-substituted *trans*-bpbp ligands. Reductive amination of tetraphenyl-substituted dialdehyde **10** with 2-picolyl amine yields diamine **11** which again can be cyclized to give **12**, a sterically demanding 4,4,4′,4′-tetraphenyl-substituted *trans*-bpbp ligand (Scheme 1).

The unexpected *anti*-selectivity observed in this diamination reaction is best explained by the neighboring group

(16) It seems that NIS and I_2 induce the partial decomposition of **2k**/**3k** to unidentified oxidation products (aromatic iodination was not observed). For the oxidative deprotection of PMP groups by NIS and I_2: Verkade, J. M. M.; von Hemert, L. J. C.; Quaedflieg, P. J. L. M.; Alsters, P. L.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron Lett.* **2006**, *47*, 8109.

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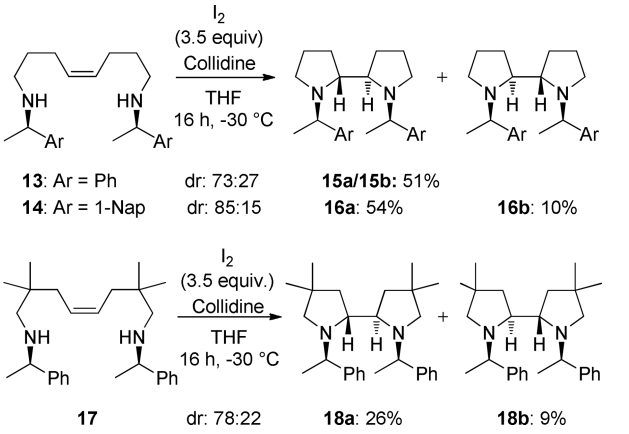
effect of the electron-rich amine after an initial halocyclization reaction.[18] Upon treatment of diamine **2** with an electrophilic iodine source, an *anti*-selective iodocyclization to an intermediate occurs. With electron-withdrawing groups at the nitrogen atom such as the often used tosyl protecting group, the reaction stops at this point and the iodocyclization product can be isolated. However, if the substituent on nitrogen is rather electron rich (as in this case alkyl or aryl groups), an aziridinium ion can be formed which is subsequently opened from the backside leading to the *anti*-diamination product. The involvement of azirdinium ions has also been suggested by Muñiz in his hypervalent iodine mediated diamination reaction to explain the observed *anti*-selectivity.[13,14]

Resolution of racemic 2,2′-bipyrrolidines is in principle possible using tartaric acid as a resolving agent, but an asymmetric synthesis would be clearly more attractive. One way to achieve this goal would be the use of a chiral auxiliary at nitrogen. Diastereoselective halocyclizations are well-known and often proceed with high selectivities.[19] However, this case represents a very special situation, as the presumed halonium ion intermediate would be a (pseudo) *meso*-halonium ion and diastereoselective cyclizations of such *meso*-type intermediates are uncommon.[15] As a chiral auxiliary we chose 1-(phenyl)ethylamine derivatives which are easily available and well-known for high stereoinduction.[20] Reductive amination of dialdehyde **8** with 1-(phenyl)- or 1-(naphthyl)ethylamine provided the diamines **13** and **14**. Upon treatment with iodine (which led to better selectivities than NIS) **13** cyclized to give the diastereomeric products **15a** and **15b** as an inseparable mixture with moderate diastereoselectivity (dr 73:27, Scheme 2). Using the more sterically demanding 1-naphthylethyl group, much better induced diastereoselectivities were obtained. Under optimized reaction conditions (I_2, THF, −30 °C), diamine **14** cyclized to bipyrrolidines **16a** and **16b** with high diastereoselectivity (dr 85:15). The diastereomers **16a** and **16b** were easily separable by column chromatography, and the major diastereomer **16a** was isolated in 54% yield. After removal of the 1-(naphthyl)ethyl auxiliary, which is possible under reductive conditions ($Pd(OH)_2$/C, HCOOH), and acylation with benzoyl chloride, *N*,*N*′-dibenzoyl-2,2′-bipyrrolidine was obtained in diastereo- and enantiopure form. Comparison of the optical rotation with literature values[21] established the configuration of the major diastereomer **16a** at the 2,2′-carbon atoms to be *R*,*R*. The chiral auxiliary approach is also viable for substituted bipyrrolidines. Cyclization of diamine **17** with a tetramethyl-substituted carbon chain using iodine proceeded with moderate induced diastereoselectivitiy (dr 78:22). After column chromatography tetramethyl bipyrrolidine **18a** was isolated in 26% yield in diastereomerically pure form. This represents the first selective synthesis of a chiral substituted bipyrrolidine.

Scheme 2. Chiral-Auxiliary-Based Asymmetric Synthesis of Bipyrrolidines



In conclusion, we present herein an efficient method for the selective synthesis of substituted bipyrrolidines and bipiperidines starting from cheap and readily available starting materials. The method employs an intramolecular *anti*-selective diamination reaction of alkenes which proceeds under very practical reaction conditions (NIS, rt) without the need for protecting groups. This is a clear advantage over many other diamination methods which require amine derivatives with electron-withdrawing protecting groups (ureas, sulfonamides) that are often difficult to remove. Our method allows for the efficient and diastereoselective synthesis of substituted bipyrrolidines which are of great interest in asymmetric synthesis and biomimetic C−H oxidation reactions.

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Supporting Information Available. Experimental details, characterization data for all starting materials and products, and X-ray crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.

(18) A mechanistic scheme can be found in the Supporting Information.

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