ORGANIC LETTERS

2008
Vol. 10, No. 2
329−332

Synthesis of 2,6-Disubstituted Piperazines by a Diastereoselective Palladium-Catalyzed Hydroamination Reaction

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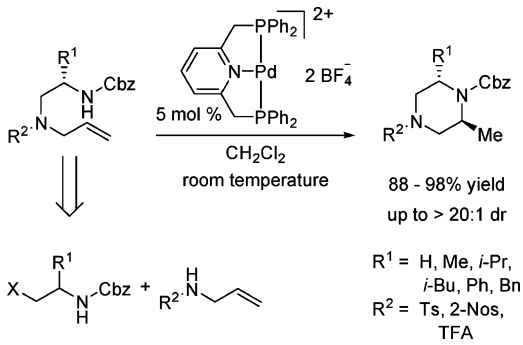
Received November 30, 2007

ABSTRACT



A highly diastereoselective intramolecular hydroamination is the key step in a modular synthesis of 2,6-disubstituted piperazines. The requisite hydroamination substrates were prepared in excellent yields by nucleophilic displacement of cyclic sulfamidates derived from amino acids. A variety of alkyl and aryl substituents at the 2-position were tolerated. The stereochemistry of the piperazines was determined to be *trans* by X-ray crystallography, which also showed the preferred conformation of the 2,6-disubstituted piperazine to be a twist-boat due to $A_{1,3}$ strain.

Piperazines are an important class of nitrogen-containing heterocycles that are common in pharmaceutical agents. The 1,4-diazacyclohexane ring provides a convenient core from which many compounds can be derived through convergent synthesis. This feature makes piperazines great templates for generating libraries of compounds for the study of structure−activity relationships (SAR). Piperazine nuclei are found in a range of biologically active compounds, including 5HT-anxiolytics,[1] dopamine D_3 agents,[2] Bcl-2 inhibitors,[3] cytochrome *c* inhibitor,[4] CNS compounds,[5] and HIV protease inhibitors.[6]

One significant drawback to using piperazines as biological scaffolds is the difficulty of introducing substituents on its carbon backbone, thus limiting SAR studies to substitution at the two nitrogen atoms. Although a variety of methods are suitable for the synthesis of substituted 2,5-diketopiperazines,[7] leading to the 2,5-substitution pattern, the synthesis of chiral 2,6-disubstituted piperazines has been relatively unexplored.[8] Jacobsen has successfully synthesized chiral 2,6-disubstituted piperazines by setting the stereocenters of

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(4) Bombrun, A.; Gerber, P.; Casi, G.; Terradillos, O.; Antonsson, B.; Halazy. *J. Med. Chem.* **2003**, *46*, 4365−4368.

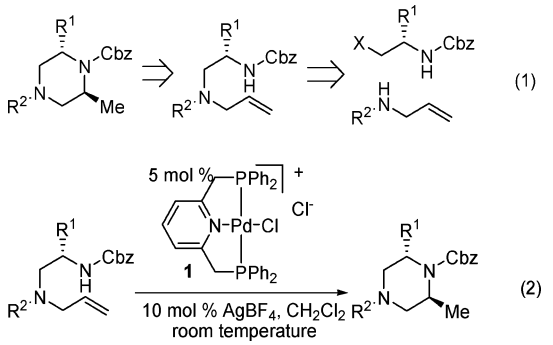
(5) Jacobsen, E. J.; Stelzer, L. S.; TenBrink, R. E.; Belonga, K. L.; Carter, D. B.; Im, H. K.; Im, W. B.; Sethy, V. H.; Tang, A. H.; VonVoigtlander, P. F.; Petke, J. D.; Zhong, W.-Z.; Mickelson, J. W. *J. Med. Chem.* **1999**, *42*, 1123−1144.

10.1021/ol702891p CCC: $40.75
Published on Web 12/22/2007

the piperazine precursor prior to ring closure.[9] Conversely, Quirion used a chiral auxiliary to direct the stereoselective addition of both the 2- and 6-substituents onto a preformed piperazine ring in a diastereoselective fashion.[10] Unfortunately, both synthetic routes are long, and the yields are moderate to low. Very recently, Wolfe and co-workers reported a synthesis of 2,6-disubstituted piperazines that was highly selective for the *cis* product.[11]

We recently reported an intramolecular palladium-catalyzed hydroamination of alkenes that is broadly tolerant of useful functional groups.[12] By taking advantage of this reaction, a modular and efficient route to enantiopure 2,6-disubstituted piperazines should be feasible (Scheme 1). In

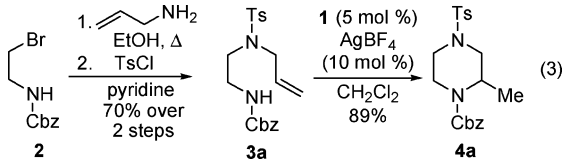
Scheme 1. Modular Piperazine Synthesis via Intramolecular Hydroamination



a retrosynthetic sense, disconnection of two diametrically opposed C−N bonds via hydroamination and substitution effectively cuts the piperazine nucleus into two equal halves: an allylic amine and an enantiopure aminoalcohol-derived fragment. In the forward sense, coupling of the two starting materials would give the appropriate hydroamination substrate, which can then be cyclized using palladium catalyst **1** to provide the desired piperazine (eq 2).

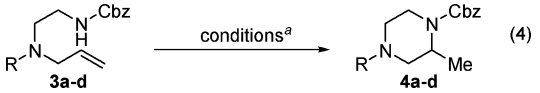
To test the tolerance of Pd catalyst **1** for a substrate with an additional nitrogen in the backbone, model substrate **3a** was chosen for initial studies. Compound **3a** was synthesized by substitution of bromide **2** with allylamine, followed by protection of the free amine with *p*-toluenesulfonyl chloride.[13] Subjecting compound **3a** to standard hydroamination conditions resulted in clean formation of differentially protected piperazine **4a** in 89% yield (Scheme 2).

Scheme 2. Synthesis of Aminoalkene **3** Followed by Hydroamination



With this promising result, the effects of other protecting groups at the 4-position were examined (Table 1). When the

Table 1. Effect of the Protecting Group at the 4-position



entry	R	additive	% conversion[b]	% yield[c]
1	Ts (**3a**)	none	100	89
2	2-Nos (**3b**)	none	100	97
3	TFA (**3c**)	none	33	ND
4	TFA (**3c**)	$HBF_4{\cdot}OEt_2$	100	99
5	Boc (**3d**)	none	0	ND
6	Boc (**3d**)	$HBF_4{\cdot}OEt_2$	20[d]	ND

[a] 5 mol % **1**, 10 mol % $AgBF_4$, $MgSO_4$, CH_2Cl_2, 20 h. [b] Determined by ^1H NMR. [c] Isolated yields. [d] The remaining material was Boc-deprotected aminoalkene. ND = not determined, 2-Nos = 2-nitrobenzenesulfonamide.

internal nitrogen was protected as a sulfonamide (entries 1 and 2), the aminoalkenes readily underwent hydroamination to give piperazines **4a** and **4b** in excellent yields. When the protecting group was changed to a trifluoroacetamide (TFA, **3c**), however, the reaction did not go to completion even after 2 days. Mechanistic studies of this hydroamination reaction suggest that mildly basic substituents can slow the reaction rate by inhibiting the protonolysis step.[14] The TFA protecting group is slightly more basic than the sulfonamides and could be slowing the reaction in a similar manner. The addition of cocatalytic acid to the reaction mixture should help overcome this inhibitory effect and restore catalytic reactivity. Indeed, when compound **3c** was treated under standard reaction conditions with the addition of tetrafluoroboric acid ($HBF_4{\cdot}Et_2O$), piperazine **4c** was formed nearly quantitatively. In the absence of the palladium catalyst, the acid failed to promote formation of **4c**. When Boc-protected substrate **4d** was used, no reaction was observed under standard reaction conditions. Addition of acid to the reaction mixture did result in some conversion to desired product (entry 6); however, competitive deprotection of the Boc group also occurred.

To synthesize 2,6-disubstituted piperazines, a route to the appropriate hydroamination substrate **7** was required. Ini-

(6) Askin, D.; Eng, K. K.; Rossen, K.; Purick, R. M.; Welss, K. M.; Volante, R. P.; Reider, P. J. *Tetrahedron Lett.* **1994**, *35*, 673−676.
(7) For a review on diketopiperazine synthesis, see: Dinsmore, C. J.; Beshore, D. C. *Tetrahedron* **2002**, *58*, 3297−3312.
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(9) Mickelson, J. W.; Belonga, K. L.; Jacobsen, E. J. *J. Org. Chem.* **1995**, *60*, 417−4183.
(10) Schanen, V.; Cherrier, M.-P.; de Melo, S. J.; Quirion, J.-C.; Husson, H.-P. *Synthesis* **1996**, *7*, 833−837.
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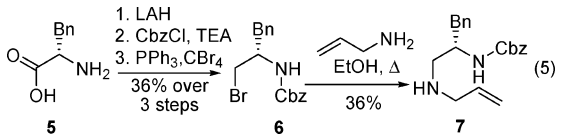
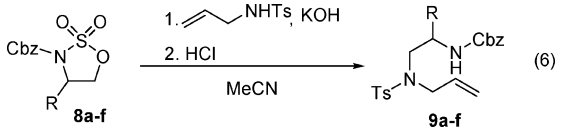
tially, enantiopure protected bromoamine **6** was synthesized from L-phenylalanine **5** using known methods (Scheme 3).[15]

Scheme 3. Initial Synthesis of Aminoalkene **7**



Unfortunately, treatment of compound **6** with allylamine afforded only poor yields of substrate **7**. Multiple byproducts resulting from attack on the Cbz protecting group by allylamine were detected. Poor yields were also obtained when *N*-allyltoluenesulfonamide was used as a nucleophile under basic conditions.

Table 2. Synthesis of Aminoalkenes **9a**−**f** from Cyclic Sulfamidates **8a**−**f**



R	% yield[a]	configuration
Me (**9a**)	95	*S*
*i*Pr (**9b**)	81	*R*
*i*Bu (**9c**)	74	*S*
Bn (**9d**)	94	*S*
Ph (**9e**)	89	*R*
*t*Bu (**9f**)	89	*S*

[a] Isolated yields.

An improved route to aminoalkene **7**, or a protected version thereof, was required. Cyclic sulfamidates **8a**−**f** were readily synthesized from the corresponding enantiopure amino alcohols[16] in good yields using a modification of literature conditions.[17] Treatment of **8a**−**f** with *N*-allyltoluenesulfonamide and KOH in acetonitrile resulted in clean displacement to give the desired aminoalkenes **9a**−**f** in good yields after acidic work up (Table 2).

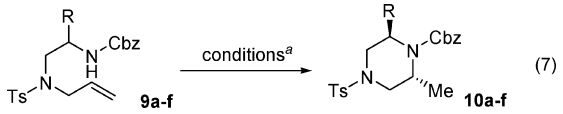
These substituted aminoalkene precursors (**9a**−**f**) were then subjected to standard hydroamination conditions (Table 3). Substrates **9a**−**d** readily cyclized to the corresponding piperazines **10a**−**d** in high yields and with excellent diastereoselectivities. Phenyl-substituted piperazine **10e** was also formed in high yield, although the diastereoselectivity of the

(15) (a) Piper, J. R.; Stringfellow, C. R., Jr.; Johnston, T. P. *J. Med. Chem.* **1966**, *9*, 911−920. (b) Kano, S.; Yokomatsu, T.; Iwasawa, H.; Shibuya, S. *Heterocycles* **1987**, *26*, 2805−2809. (c) Han, M. S.; Oh, D. J.; Kim, D. H. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 701−705.

(16) The amino alcohols were derived from enantiopure amino acids by methods described in ref 15.

(17) Posakony, J. J.; Grierson, J. R.; Tewson, T. J. *J. Org. Chem.* **2002**, *67*, 5164−5169.

Table 3. Hydroamination of Aminoalkenes **9a-f**



R	% yield[b]	configuration	dr[c]
Me (**10a**)	98	(*S*,*S*)	>20:1
*i*Pr (**10b**)	95	(*R*,*R*)	>20:1
*i*Bu (**10c**)	94	(*S*,*S*)	19:1
Bn (**10d**)	93	(*S*,*S*)	>20:1
Ph (**10e**)	88	(*R*,*R*)	5:1
*t*Bu (**10f**)	NR[d]	–	–

[a] 5 mol % **1**, 10 mol % $AgBF_4$, $MgSO_4$, CH_2Cl_2, 20 h. [b] Isolated yields. [c] Determined by ^1H NMR. [d] No Reaction. Only starting material **9f** was isolated.

product was slightly diminished. Surprisingly, *tert*-butyl-substituted aminoalkene **9f** failed to produce any of the desired product, most likely due to the steric bulk of the *tert*-butyl group.

The relative stereochemistry of the piperazine product was determined to be *trans* by single-crystal X-ray diffraction of **10a** (Figure 1a). Unexpectedly, the preferred conformation

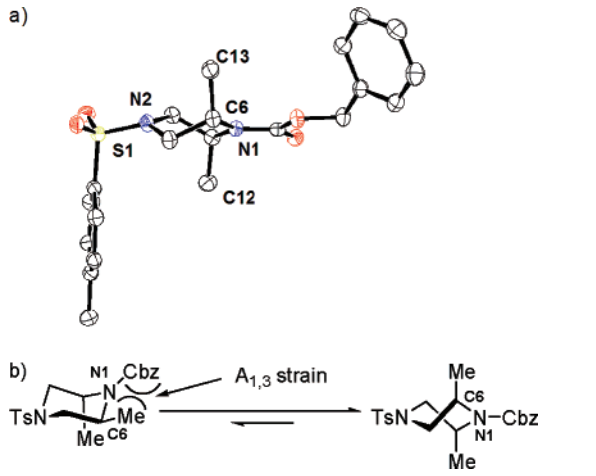


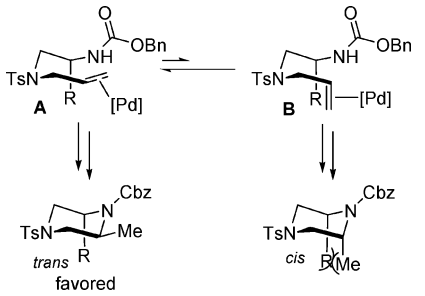
Figure 1. (a) ORTEP of **10a**. Thermal ellipsoids shown at 50% probability. (b) Ring flip from chair to boat.

of the piperazine ring is a twist-boat, rather then the typical chair conformation. This preference is a result of allylic strain between the alkyl substituents and the carbamate protecting group. In the chair conformation, one of the two alkyl substituents is forced to adopt an equatorial position adjacent to the carbamate protecting group, which would result in a strong $A_{1,3}$-interaction (Figure 1b). In the twist-boat conformation, however, both alkyl groups can adopt axial conformations to avoid allylic strain with the carbamate moiety. Typical values for the cost of adopting a twist-boat confor-

mation (5.3 kcal/mol in cyclohexane)[18] and the magnitude of $A_{1,3}$-strain (~3.4−4.7 kcal/mol)[19] would indicate that this tradeoff should be slightly unfavorable. However, in this system the twist-boat conformation is likely to be more stable due to the presence of two sp^2-hybridized nitrogen atoms in the ring, reducing the torsional strain. Excluding ketopiperazines, this is the first report of a 2,6-disubstituted piperazine that prefers a boat conformation to our knowledge.[20] By analogy, the major diastereomers of piperazines **10b**−**e** are also presumed to be *trans* isomers adopting twist-boat confomations.[21]

A model that correctly predicts the diastereoselectivity and reactivity of aminoalkenes **9a**−**f** is illustrated in Scheme 4.

Scheme 4. Model for the Diastereoselectivity and Reactivity of Aminoalkenes **9a**−**f**



The palladium catalyst binds to the alkene, thereby activating it toward attack by the carbamate, generating a palladium-alkyl intermediate. In the chairlike transition state for the cyclization, the substituent in the 2-position will adopt a pseudoaxial orientation to avoid allylic strain with the carbamate group. Cyclization will preferentially occur with the alkenyl group in a pseudo-equatorial (**A**) position, rather than in a pseudoaxial (**B**) position, leading to selective formation of the *trans* diastereomer. Additionally, when the substituent at the 2-position is too large, as in compound **9f** (R = *tert*-butyl), the group cannot be accommodated in either the pseudoequatorial position or the pseudoaxial position. Hence, **9f** fails to cyclize at all.[22] After protonolysis of the palladium−carbon bond of the alkyl complex, the piperazine is released from the catalytic cycle, and in the case of the *trans*-substituted piperazine, the chair conformation flips to the thermodynamically more favorable twist-boat conformation. It is worth noting that, in both the piperazine cyclization reported by Wolfe[11] and the lanthanide-catalyzed hydroaminations[23] to give piperidines, the *cis* isomers were favored, whereas this system affords preferentially the *trans* isomers. This difference in selectivity likely arises from the presence of an aryl group or a hydrogen on the cyclizing nitrogen rather than a carbamate, which therefore avoids the possibility of allylic strain.

In conclusion, a short, high-yielding, and stereoselective route to enantiopure *trans*-2,6-disubstituted piperazines with differentially protected nitrogen atoms has been developed. Both sulfonamide and TFA protecting groups at N-4 as well as a variety of alkyl and aryl-substituents at C-2 were tolerated. An improved synthesis of the requisite 2-substituted aminoalkenes was developed using cyclic sulfamidates derived from enantiopure amino acids. Hydroamination of these aminoalkenes gave excellent yields of the desired piperazines with good to excellent diastereoselectivity for the *trans* isomer. The *trans*-substituted piperazines adopt an unusual twist-boat conformation both in solution and in the solid state.

Acknowledgment. Werner Kaminsky and John Freudenthal (University of Washington) are acknowledged for X-ray crystallography, and the University of Washington is acknowledged for financial support.

Supporting Information Available: Detailed reaction conditions and experimental data for synthesis of all new starting materials and products, details of the X-ray crystal structure of **10a**, and a detailed analysis of the ^{1}H NMR spectrum of compound **10d**. This material is available free of charge via the Internet at http://pubs.acs.org.

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