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Stereoselective Synthesis of Trisubstituted Aziridines with *N*-α-Diazoacyl Camphorsultam

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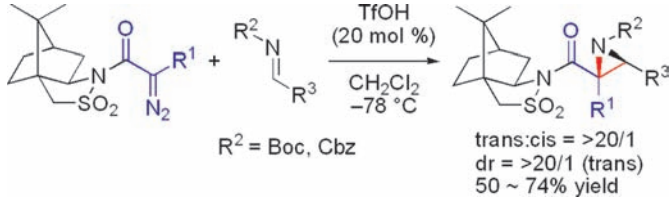
ABSTRACT



A Brønsted acid-catalyzed reaction of α-substituted α-diazocarbonyl compounds bearing camphorsultam as a chiral auxiliary and *N*-alkoxycarbonyl imines was implemented as an unprecedented means to provide trisubstituted aziridines in a highly stereodefined manner.

As enantiomerically pure aziridines can serve as chiral building blocks in the preparation of nitrogen-containing complex molecules,[1,2] considerable efforts have been devoted to the development of reliable methods to access chiral aziridines stereoselectively.[1,3]

Originating from Brookhart and Templeton's discovery,[4] acid-catalyzed reaction of imines and α-unsubstituted α-diazocarbonyl compounds (Figure 1, $R^1 = H$) has increasingly been studied as a unique and promising tool for the stereoselective synthesis of aziridines and has already culminated in the establishment of catalytic asymmetric methods affording either cis or trans 2,3-disubstituted aziridines with high enantioselectivities, using chiral Lewis acids or Brønsted acids.[5−9] However, when it comes to the stereoselective synthesis of trisubstituted aziridines, neither this method nor most of the other existing aziridinations provide a general solution. To the best of our knowledge, the only successful method reported to date is the aza-Darzens reaction with chiral *N*-sulfinyl imines and α-halo enolates by Davis and co-workers.[10]

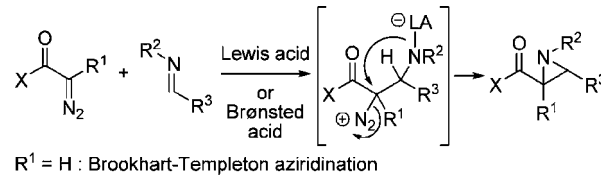


Figure 1. Acid-catalyzed aziridination of α-diazocarbonyl compounds and imines.

(1) *Aziridines and Epoxides in Organic Synthesis*; Yudin, A. K., Ed.; Wiley-VCH: Weinheim, Germany, 2006.

(2) (a) McCoull, W.; Davis, F. A. *Synthesis* **2000**, 1347. (b) Hu, X. E. *Tetrahedron* **2006**, *60*, 2701.

(3) (a) Jacobsen, E. N. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, Germany, 1999; Vol. 2, p 607. (b) Müller, P.; Fruit, C. *Chem. Rev.* **2003**, *103*, 2905. (c) Sweeney, J. *Eur. J. Org. Chem.* **2009**, 4911.

(4) Casarrubios, L.; Pérez, J. A.; Brookhart, M.; Templeton, J. L. *J. Org. Chem.* **1996**, *61*, 8358. See also the references included in ref 6.

(5) (a) Antilla, J. C.; Wulff, W. D. *J. Am. Chem. Soc.* **1999**, *121*, 5099. For a recent review, see: (b) Zhang, Y.; Lu, Z.; Wulff, W. D. *Synlett* **2009**, 2715.

(6) For other chiral Lewis acid-catalyzed reactions, see: (a) Juhl, K.; Hazell, R. G.; Jørgensen, K. A. *J. Chem. Soc., Perkin Trans. 1* **1999**, 2293. (b) Redlich, M.; Hossain, M. M. *Tetrahedron Lett.* **2004**, *45*, 8987. (c) Wipf, P.; Lyon, M. A. *ARKIVOC* **2007**, *xii*, 91.

(7) Hashimoto, T.; Uchiyama, N.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *130*, 14380.

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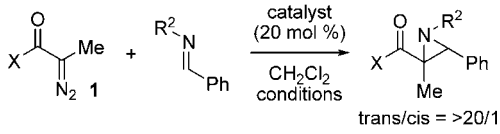
In this context, we communicate herein the modification of Brookhart and Templeton's aziridination to include the asymmetric synthesis of trisubstituted aziridines. This goal was accomplished by use of *N*-Boc imines and α-alkyl-α-diazocarbonyl compounds which bear a camphorsultam as a key combination of substrates.[11] Furthermore, by taking advantage of thus-obtained *N*-Boc protected aziridines, a ring rearrangement was conducted to provide stereodefined α,α-disubstituted *β*-hydroxy-α-amino acid derivatives.

We commenced our study by systematically investigating the influence of the *N*-substituent of imines derived from benzaldehyde and the substituent attached to the carbonyl carbon of the diazo compound, using BF_3•Et_2O as a common Lewis acid catalyst (Table 1). This study clearly demonstrated the difficulty to simply extend the Brookhart and Templeton method to the synthesis of trisubstituted aziridines. Namely, attempts to use *N*-phenyl or *N*-benzyl imines with ethyl α-methyl-α-diazoacetate **1a**, which only differ from their original procedure in that the methyl group is attached at the α-position of the diazoacetate (see Figure 1), gave no or a trace amount of aziridines, respectively (entries 1 and 2). We then turned our attention to screen other imines having *tert*-butoxycarbonyl, diphenylphosphonyl, or *N*-tosyl moieties, respectively. Although the imines with the two latter *N*-substituents remained intact (entries 4 and 5), use of the *N*-Boc imine at low temperature afforded the desired aziridine, albeit in low yield (entry 3).

Table 1. Preliminary Exploration of Aziridinations with Various α-Methyl-α-diazocarbonyl Compounds and Benzaldehyde-Derived Imines[a,b]



entry	X	R^2	catalyst	conditions °C, time	yield[c] (%)
1	EtO (**1a**)	Bn	BF_3·Et_2O	rt, 2.5 h	–
2		Ph	BF_3·Et_2O	rt, 20 min	<9
3		Boc	BF_3·Et_2O	–78, 30 min	<17
4		$Ph_2P(O)$	BF_3·Et_2O	–78, 30 min	–
5		Ts	BF_3·Et_2O	–78, 30 min	–
6		Boc	$TiCl_4$	–50, 1.5 h	<16
7		Boc	CF_3SO_3H	–78, 10 min	19
8	 **1b**	Boc	BF_3·Et_2O	–78, 10 min	52
9	 **1c**	Boc	BF_3·Et_2O	–78, 1 h	56

[a] Reactions were performed with **2** (0.10 mmol) and imine (0.15 mmol) in the presence of 20 mol % of catalyst in CH_2Cl_2 for 5−20 min. [b] Trans/cis ratio was determined by ^{1}H NMR of the crude material. [c] Isolated yield.

As the use of other strong Lewis and Brønsted acids aimed at increasing the efficiency was found to be unfruitful (entries 6 and 7),[12] we set out to examine the effect of the template attached to the carbonyl carbon of the diazo compounds in view of its drastic influence on the reaction pathway observed in our related studies.[7,11d] Accordingly, two sets of α-diazocarbonyl compounds **1b** and **1c** having oxazolidin-2-one and 1,3-propanesultam substituents were examined in combination with benzaldehyde *N*-Boc imine under the influence of a catalytic amount of BF_3•Et_2O (entries 8 and 9). Gratifyingly, the outcome of the reaction was dramatically varied in both cases, giving the aziridines as a major product. Irrespective of the substituents attached to the carbonyl carbon, the *trans*-aziridine was solely obtained, probably circumventing the steric repulsion between the hindered carbonyl moiety and the aryl group in the course of the aziridine ring-closure step.

At this stage, the focus was set on the development of an asymmetric variant of this unprecedented trisubstituted aziridine synthesis. Since the high stereochemical fidelity of the camphorsultam as a chiral auxiliary of α-diazocarbonyl compounds in acid catalysis has been recently established in our laboratory,[11d,13] asymmetric aziridination was then implemented with use of *N*-α-diazoacyl (−)-camphorsultam

(8) (a) Akiyama, T.; Suzuki, T.; Mori, K. *Org. Lett.* **2009**, *11*, 2445. (b) Zeng, X.; Zeng, X.; Xu, Z.; Lu, M.; Zhong, G. *Org. Lett.* **2009**, *11*, 3036. (c) Hu, G.; Huang, L.; Huang, R. H.; Wulff, W. D. *J. Am. Chem. Soc.* **2009**, *131*, 15615.

(9) For asymmetric aziridination with diazoalkanes and imines mediated by chiral sulfur ylides, see: (a) Aggarwal, V. K.; Thompson, A.; Jones, R. V. H.; Standen, M. C. H. *J. Org. Chem.* **1996**, *61*, 8368. (b) Aggarwal, V. K.; Alonso, E.; Fang, G.; Ferrara, M.; Hynd, G.; Porcelloni, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 1433.

(10) (a) Davis, F. A.; Liu, H.; Reddy, G. V. *Tetrahedron Lett.* **1996**, *37*, 5473. (b) Davis, F. A.; Liu, H.; Zhou, P.; Fang, T.; Reddy, G. V.; Zhang, Y. *J. Org. Chem.* **1999**, *64*, 7559. (c) Davis, F. A.; Deng, J.; Zhang, Y.; Haltiwanger, R. C. *Tetrahedron* **2002**, *58*, 7135. (d) Davis, F. A.; Deng, J. *Org. Lett.* **2007**, *9*, 1707.

(11) For the use of α-substituted α-diazocarbonyl compounds in acid-catalyzed stereoselective synthesis, see: (a) Hashimoto, T.; Naganawa, Y.; Kano, T.; Maruoka, K. *Chem. Commun.* **2007**, 5143. (b) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2008**, *131*, 2434. (c) Hashimoto, T.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *130*, 6614. (d) Hashimoto, T.; Miyamoto, H.; Naganawa, Y.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 11280.

(12) Williams, A. L.; Johnston, J. N. *J. Am. Chem. Soc.* **2004**, *126*, 1612.

(13) Ma, M.; Peng, L.; Li, C.; Zhang, X.; Wang, J. *J. Am. Chem. Soc.* **2005**, *127*, 15016.

(14) The reaction was quenched after the complete consumption of the diazo compound. Several unidentified materials were observed by ^{1}H NMR of the crude material in small quantities which could be easily removed by column chromatography on silica gel.

(15) A catalytic amount of camphorsulfonic acid indeed facilitated the reaction of **1b** and *N*-Boc imine smoothly, although the aziridine was obtained in a racemic form. In our preliminary experiments, neither chiral phosphoric acid nor dicarboxylic acid (see refs 6 and 7) promoted the reaction even at room temperature.

(16) For reviews on Brønsted acid catalysis, see: (a) Akiyama, T. *Chem. Rev.* **2007**, *107*, 5744. (b) Terada, M. *Chem. Commun.* **2008**, 4097.

(17) Hasegawa, T.; Yamamoto, H. *Synlett* **1998**, 882.

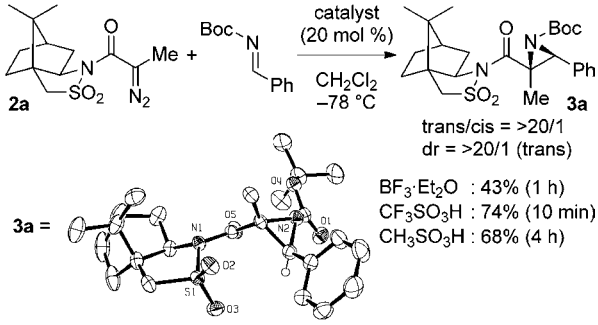
(18) The reaction provided a mixture of the corresponding aziridine, oxazolidin-2-one, and 2-benzyloxyoxazoline.

(19) (a) Tomasini, C.; Vecchione, A. *Org. Lett.* **1999**, *1*, 2153. (b) Lu, Z.; Zhang, Y.; Wulff, W. D. *J. Am. Chem. Soc.* **2007**, *129*, 7185, and references cited therein.

(20) For recent reviews on asymmetric synthesis of α,α-disubstituted α-amino acids, see: (a) Ohfune, Y.; Shinada, T. *Eur. J. Org. Chem.* **2005**, 5127. (b) Vogt, H.; Bräse, S. *Org. Biomol. Chem.* **2007**, *5*, 406. (c) Cativiela, C.; Díaz-de-Villegas, M. D. *Tetrahedron: Asymmetry* **2007**, *18*, 569. (d) Mosey, R. A.; Fisk, J. S.; Tepe, J. J. *Tetrahedron: Asymmetry* **2008**, *19*, 2755.

2a (Scheme 1). As anticipated, the desired *trans*-aziridine **3a** could be obtained as a single stereoisomer in 43% yield

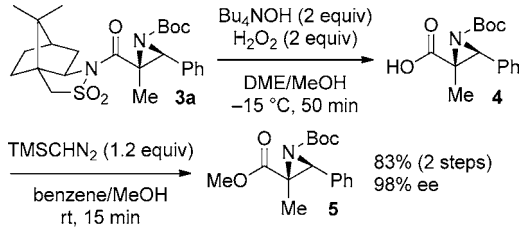
Scheme 1. Asymmetric Aziridination with *N*-α-Diazoacyl (−)-Camphorsultam



by use of $BF_3{\cdot}Et_2O$.[21] Further investigation revealed the high efficiency of a strong Brønsted acid, triflic acid, with which the reaction led to completion within 10 min giving the aziridine in 74% yield.[14] It is also worth mentioning that the use of a weaker acid, methanesulfonic acid, with longer reaction times was equally effective.[15,16]

The chiral auxiliary of the so-obtained aziridine could easily be removed by treatment with tetrabutylammonium hydroxide and hydrogen peroxide as shown in Scheme 2.[17]

Scheme 2. Removal of the Chiral Auxiliary

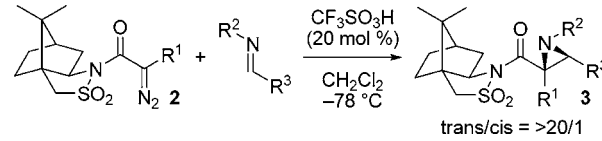


Esterification of the crude acid **4** with $TMSCHN_2$ furnished the aziridine carboxylate **5** in 83% yield. The enantiomeric purity of this material was determined to be 98% ee by chiral HPLC analysis.

With these fundamental results in hand, the scope of this asymmetric trisubstituted aziridine synthesis was investigated in detail (Table 2). Irrespective of the substituent pattern and electronic property of the aromatic ring of *N*-Boc imines, the reactions generally proceeded uneventfully, furnishing the corresponding *trans*-aziridines with high stereoselectivity (entries 2−8). Although the incorporation of methoxy or

(21) CCDC 710136 (**3a**) and CCDC 750124 (**6**) contain the supplementary crystallographic data for this paper. The crystallographic coordinates have been deposited with the Cambridge Crystallographic Data Centre; deposition nos. 710136 and 750124. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre, 12 Union Rd., Cambridge CB2 1EZ, UK or via www.ccdc.cam.ac.uk/conts/retrieving.html.

Table 2. Brønsted Acid-Catalyzed Asymmetric Aziridination[a,b]



entry	R^1	R^2	R^3	yield[c] (%)	dr[d] (trans)
1	Me (**2a**)	Boc	Ph	74 (**3a**)	>20/1
2			2-tolyl	60 (**3b**)	>20/1
3			3-tolyl	63 (**3c**)	>20/1
4[e]			4-tolyl	59 (**3d**)	>20/1
5			2-Np	54 (**3e**)	>20/1
6			4-ClC_6H_4	62 (**3f**)	>20/1
7			4-$PivOC_6H_4$	56 (**3g**)	>20/1
8			3-$MeOC_6H_4$	62 (**3h**)	>20/1
9			Cy		
10	Et (**2b**)		Ph	50 (**3i**)	>20/1
11[f]	Me (**2a**)	Cbz	Ph	61 (**3j**)	>20/1
12[f]			2-tolyl	64 (**3k**)	>20/1
13[f]			3-tolyl	66 (**3l**)	>20/1
14			4-BrC_6H_4	55 (**3m**)	>20/1
15[f]			3-$MeOC_6H_4$	56 (**3n**)	>20/1

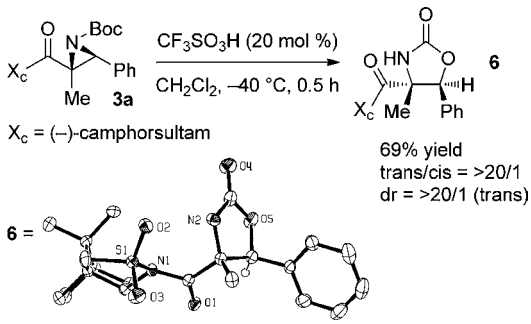
[a] Reactions were performed with **2** (0.10 mmol) and imine (0.15 mmol) in the presence of 20 mol % of catalyst in CH_2Cl_2 for 5−20 min. [b] Trans/cis ratio was determined by ^1H NMR of the crude material. [c] Isolated yield. [d] Determined by ^1H NMR of the crude material. [e] Performed with 3 equiv of imine. [f] Performed with 20 mol % of CH_3SO_3H for 1−4 h under otherwise identical conditions.

acyloxy group as the 4-substituent of the imine was proven to be intolerant, use of 4-pivaloyloxybenzaldehyde *N*-Boc imine as their surrogate provided the aziridine in reasonable yield (entry 7). At present, this method is not applicable to the reaction of *N*-Boc imines derived from aliphatic aldehydes (entry 9). α-Ethyl-substituted diazo compound **2b** could be utilized as well, giving the corresponding aziridine in 50% yield with equally high stereoselectivity (entry 10).

Considering the practicality of the benzyloxycarbonyl (Cbz) group as a protective group of amines, this newly developed aziridination was then applied to the reactions with *N*-Cbz imines (entries 11−15). As it became obvious that triflic acid was too strong as catalyst to stop the reaction at the stage of the aziridine,[18] we opted for the use of methanesulfonic acid as a milder acid in anticipation of the attenuation of undesired overreactions. Consequently, *N*-Cbz aziridines could be obtained in yields ranging from 56% to 66% with uniformly high diastereoselectivities. The only exception was the aziridination with 4-bromobenzaldehyde *N*-Cbz imine, wherein the reaction was very sluggish probably due to the lower affinity of this imine for the acid catalyst. This issue could be solved by returning to the catalytic use of triflic acid, giving the aziridine in 55% yield (entry 14).

With the enantioenriched *N*-Boc protected aziridines in hand, we became interested in the acid-catalyzed rearrangement of *N*-Boc aziridines to the corresponding oxazolidin-2-ones[19] as a means of generating α,α-disubstituted β-hydroxy-α-amino acid derivatives (Scheme 3).[20] Accordingly, the aziridine **3a** was subjected to an acidic condition that was

Scheme 3. Acid-Catalyzed Ring Rearrangement of Aziridine to Oxazolidin-2-one



only slightly different from the above aziridination condition in that a higher reaction temperature was employed. As anticipated, triflic acid facilitated the reaction to give the corresponding oxazolidin-2-one **6a** in 69% yield. This rearrangement proceeded with the retention of the configuration at the β-carbon, and gave the trisubstituted *trans*-oxazolidin-2-one as an essentially single isomer.[21]

In conclusion, we developed herein an unprecedented protocol for the stereoselective synthesis of trisubstituted aziridines, building on the judicious combination of imines and α-substituted α-diazocarbonyl compounds bearing camphorsultam as a chiral auxiliary. Research is currently underway to develop a catalytic enantioselective version of this aziridination with use of chiral Lewis acid or Brønsted acid, and will be reported in due course.

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Supporting Information Available: Experimental details, characterization data for new compounds, and crystal data for compounds **3a** and **6a**. This material is available free of charge via the Internet at http://pubs.acs.org.

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