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Chiral Brønsted Acid-Catalyzed Asymmetric Trisubstituted Aziridine Synthesis Using α-Diazoacyl Oxazolidinones

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Supporting Information

ABSTRACT: Despite the remarkable advances in catalytic asymmetric aziridinations over the past decades, establishing a general procedure for the stereoselective synthesis of trisubstituted aziridines has remained an elusive goal. Chiral *N*-triflyl phosphoramide-catalyzed reactions of *N*-α-diazoacyl oxazolidinones and *N*-Boc imines were developed as a solution to this unmet challenge.

Catalytic asymmetric aziridination has been extensively studied as a viable means of producing strained three-membered azacycles, which are valuable synthetic building blocks for the synthesis of chiral amines.[1] However, despite steady progress over the last two decades, almost all of the research reported to date is applicable only to the synthesis of mono- or disubstituted aziridines, and no general catalytic asymmetric methods to provide trisubstituted aziridines in a highly stereoselective manner have been offered.

Acid-catalyzed aziridination of α-diazoacetates and imines, first reported by Brookhart, Templeton and co-workers,[2,3] has attracted the attention of synthetic chemists as a promising strategy to give enantiomerically enriched disubstituted aziridines in a catalytic manner. These efforts, pioneered by Wulff[4] and further developed by our group[5] and others[6] using chiral Brønsted acids,[7] have now become sophisticated enough to give rise to either cis- or trans-disubstituted aziridines with high stereoselectivities (Figure 1). However, none of these studies has been successful in finding a way to synthesize trisubstituted aziridines, despite the expectation that extrusion of nitrogen would provide a strong thermodynamic driving force for the generation of such congested stereocenters.

Meanwhile, we have been intensively working on the use of α-substituted α-diazocarbonyl compounds in various acid catalyses for the past several years.[8] In the course of these studies, we realized the acid-catalyzed diastereoselective synthesis of trisubstituted aziridines by using *N*-α-diazocarbonyl compounds having camphorsultam as a chiral auxiliary and *N*-Boc imines.[9] The important lesson we learned in achieving the trisubstituted aziridine synthesis was the need for a judicious choice of the template attached to the carbonyl carbon of α-diazocarbonyl compound and the N-protecting group of the imine as well as the use of a strong Lewis or Brønsted acid as the catalyst.

We report herein the first general procedure for the catalytic asymmetric synthesis of trisubstituted aziridines using α-diazocarbonyl compounds bearing oxazolidinones as key templates and *N*-Boc imines in the presence of a strong chiral Brønsted acid. The notable feature of this catalytic system is its applicability to two possible substrate combinations: α-substituted α-diazocarbonyl compounds/aldimines and α-unsubstituted α-diazocarbonyl compound/ketimines (Figure 1). In addition, an unprecedented chiral Brønsted acid-catalyzed hydrolytic kinetic resolution of the trisubstituted aziridines will be described briefly.

On the basis of our early observations, the combination of the *N*-Boc imine derived from benzaldehyde and *N*-α-diazopropionyl oxazolidinone (**4a**) was selected as a model reaction for the discovery of a suitable catalyst (Table 1).[10] In contrast to the chiral Brønsted acid-catalyzed disubstituted aziridination, wherein an axially chiral dicarboxylic acid and a chiral monophophoric acid worked efficiently,[5,6] this reaction could not be facilitated by these catalysts even at room temperature (entries 1 and 2). Meanwhile, the strongly acidic *N*-triflyl phosphoramide (*S*)-**3a** developed by Yamamoto and co-workers was found to be exceptionally reactive and gave the desired trisubstituted aziridine as a single trans isomer in 66% yield with 23% ee at −78 °C (entry 3).[11,12] Attachment of phenyl groups at the 3 and 3′ positions of the catalyst [(*S*)-**3b**] led to a dramatic increase in the enantioselectivity to 81% ee (entry 4). Although the additional effort to improve the selectivity by tuning the catalyst was unfruitful, we found that the use of hexane as a cosolvent had a substantial positive effect on the enantioselectivity (entry 5). The importance of the oxazolidinone moiety attached to the diazo compound was affirmed by the fact that the use of the corresponding ethyl ester gave the aziridine in only poor yield (entry 6).

With the optimal catalyst and reaction conditions in hand, we investigated the substrate scope with regard to *N*-Boc imines and the α-substituent of α-diazocarbonyl compounds **4** (Table 2). Whereas the 2-tolaldehyde-derived imine was unreactive, other imines bearing substituents at the 3 or 4 positions could be converted to the trisubstituted aziridines with good enantioselectivities (entries 2−4). A 2-naphthyl-substituted aziridine was obtained with comparable enantioselectivity (entry 5). This asymmetric aziridination worked particularly well for *N*-Boc imines bearing an electron-withdrawing group, furnishing trisubstituted arizidines with high enantioselectivities ranging from 89 to 95% ee (entries 6−13). In the case of an *N*-Boc imine bearing an electron-donating methoxy group, the aziridination was slowed considerably, and the aziridine was obtained with slightly lower enantioselectivity by carrying out the reaction at −60 °C (entry 14). Importantly, the chain length of the α-substituent of α-diazoacyl oxazolidinone **4** did not affect the yield or stereoselectivity of the product (entries 15 and 16).

Received: May 9, 2011
Published: May 31, 2011

dx.doi.org/10.1021/ja203901h | *J. Am. Chem. Soc.* 2011, 133, 9730–9733

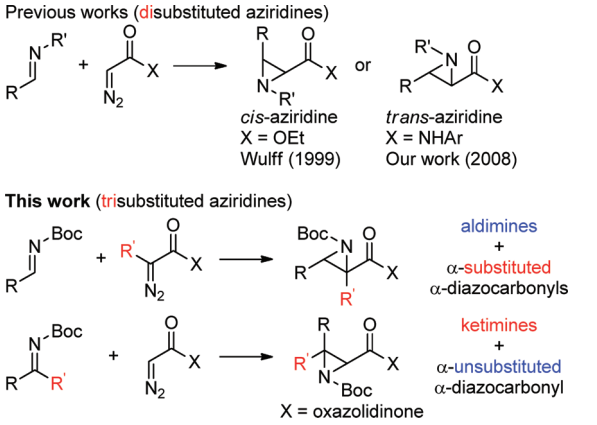
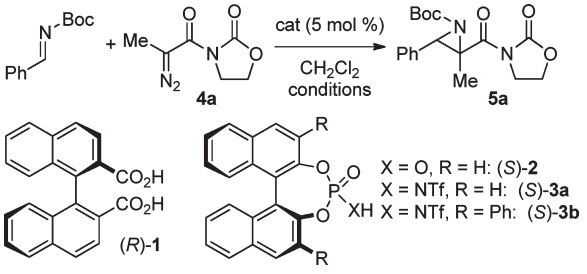


Figure 1. Strategies for the acid-catalyzed asymmetric syntheses of disubstituted and trisubstituted aziridines.

Table 1. Optimization of the Reaction Conditions[a]

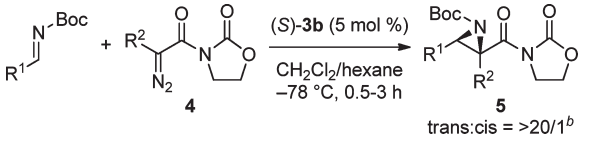


entry	cat	conditions	% yield[b]	trans:cis[c]	% ee[d]
1	(*R*)-**1**	rt, 24 h	nr	–	–
2	(*S*)-**2**	rt, 24 h	nr	–	–
3	(*S*)-**3a**	−78 °C, 4 h	66	>20:1	23
4	(*S*)-**3b**	−78 °C, 1 h	94	>20:1	81
5[e]	(*S*)-**3b**	−78 °C, 1 h	86	>20:1	83
6[f]	(*S*)-**3b**	−78 °C, 5 h	11	>20:1[g]	–

[a] Reactions were performed with benzaldehyde *N*-Boc imine (0.10 mmol) and **4a** (0.13 mmol) in the presence of 5 mol % catalyst (0.005 mmol). [b] Isolated yield. [c] Determined by ^{1}H NMR analysis of the crude material. [d] Determined by chiral HPLC analysis. [e] Performed in 1:1 CH_2Cl_2/hexane. [f] Ethyl α-diazopropionate was used instead of **4a**. [g] The relative configuration was not determined.

As an alternative option for the construction of trisubstituted aziridines via Brookhart−Templeton aziridination, a substrate combination of ketimines and α-unsubstituted α-diazocarbonyl compounds can also be conceived.[9] To determine the viability of this strategy, we further examined the reaction of *N*-Boc α-ketimino esters **6** and *N*-α-diazoacetyl oxazolidinone **7** (Table 3).[13] After some additional experiments, we reached the optimal reaction conditions for implementation of this aziridination, which used the same catalyst, *N*-triflyl phosphoramide (*S*)-**3b**, in toluene at −40 °C. α-Phenyl-α-ketimino esters **6a**−**c** having different ester moieties could be converted to the corresponding trisubstituted aziridines as essentially the single trans isomers with more than 90% ee (entries 1−3). With this method, a variety of aziridines having sterically and electronically modified aryl groups could be obtained with enantioselectivities ranging from 84 to 98% ee (entries 4−8).

Table 2. Catalytic Asymmetric Aziridination of α-Substituted α-Diazocarbonyl Compounds and Aldimines[a]



entry	R^1	R^2	% yield[c]	% ee[d]
1	Ph	Me (**4a**)	86 (**5a**)	83
2	2-tolyl	Me	low	–
3	3-tolyl	Me	77 (**5b**)	80
4	4-tolyl	Me	69 (**5c**)	77
5	2-Np	Me	81 (**5d**)	81
6	4-FC_6H_4	Me	71 (**5e**)	88
7[e]	3-ClC_6H_4	Me	76 (**5f**)	90
8[e]	4-ClC_6H_4	Me	80 (**5g**)	92
9[e]	3-BrC_6H_4	Me	74 (**5h**)	95
10[e]	4-BrC_6H_4	Me	76 (**5i**)	92
11	3-$NO_2C_6H_4$	Me	80 (**5j**)	89
12	4-$NO_2C_6H_4$	Me	78 (**5k**)	90
13	4-$MeO_2CC_6H_4$	Me	91 (**5l**)	87
14[e,f]	3-$MeOC_6H_4$	Me	80 (**5m**)	74
15[e]	4-ClC_6H_4	Et (**4b**)	83 (**5n**)	91
16	4-ClC_6H_4	Pr (**4c**)	79 (**5o**)	89

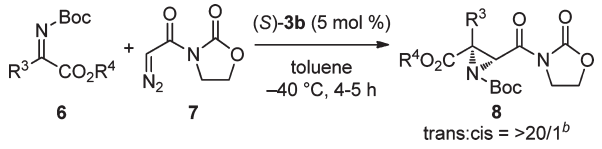
[a] Reactions were performed with aromatic aldehyde *N*-Boc imine (0.10 mmol) and *N*-α-diazoacyl oxazolidinone **4** (0.13 mmol) in the presence of 5 mol % (*S*)-**3b** (0.005 mmol). [b] Determined by ^{1}H NMR analysis of the crude material. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] Performed in CH_2Cl_2. [f] Performed at −60 °C.

In the course of these experiments, we were intrigued by the fact that the enantioselectivity of the reaction of *N*-Boc aldimines and *N*-α-diazoacyl oxazolidinones was increased by extending the reaction time, even though the yield was compromised to some extent. For example, the result shown in entry 1 of Table 2 shifted to 58% yield and 87% ee after 15 h of stirring. Scrutiny of the remaining byproduct identified the formation of a compound that showed the mass spectrum derived from hydrolytic ring opening of the aziridine. This observation prompted us to examine the possibility of hydrolytic kinetic resolution of the trisubstituted aziridines in situ with adventitious water by the action of the catalyst (*S*)-**3b** (Scheme 1). To gain insight into this experimental observation, the racemic trisubstituted aziridine *rac*-**5a** was treated with 0.55 equiv of water in the presence of 5 mol % (*S*)-**3b**. After the mixture was stirred at −78 °C for 2 h, the trisubstituted aziridine was recovered in 63% yield with 23% ee, showing the apparent involvement of the kinetic resolution.[14,15] At the same time, the hydrolyzed product **9**, which was assumed to be generated by the hydrolysis and successive ring reconstruction, was isolated in 26% yield with 54% ee as a single diastereomer. X-ray crystallographic analysis of **9** revealed that the hydrolysis of the aziridine proceeded via an S_N2 mechanism to give an *anti*-β-hydroxy-α-amino carbonyl compound.[16] This kinetic resolution could also be extended to ethanolysis, with which **10** was obtained in 27% yield with 59% ee while **5a** was recovered in 59% yield with 37% ee.[17]

In conclusion, we have succeeded in opening a way for the catalytic preparation of stereodefined trisubstituted aziridines

dx.doi.org/10.1021/ja203901h | *J. Am. Chem. Soc.* 2011, 133, 9730–9733

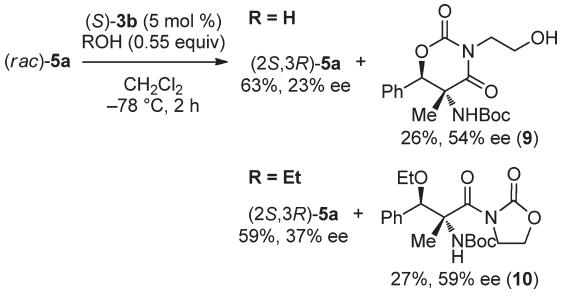
Table 3. Catalytic Asymmetric Aziridination of an α-Unsubstituted α-Diazocarbonyl Compound and Ketimines[a]



entry	R^3	R^4		% yield[c]	% ee[d]
1	Ph	^{t}Bu	**6a**	89 (**8a**)	95
2	Ph	Et	**6b**	88 (**8b**)	92
3	Ph	Me	**6c**	81 (**8c**)	90
4	3-tolyl	^{t}Bu	**6d**	86 (**8d**)	90
5	4-tolyl	^{t}Bu	**6e**	89 (**8e**)	98
6[e]	3-MeOC$_6$H$_4$	^{t}Bu	**6f**	80 (**8f**)	91
7	4-ClC$_6$H$_4$	^{t}Bu	**6g**	92 (**8g**)	92
8	2-Np	^{t}Bu	**6h**	74 (**8h**)	84

[a] Reactions were performed with *N*-Boc α-ketimino ester **6** (0.10 mmol) and **7** (0.13 mmol) in the presence of 5 mol % (*S*)-**3b** (0.005 mmol). [b] Determined by ^{1}H NMR analysis of the crude material. [c] Isolated yield. [d] Determined by chiral HPLC analysis. [e] Performed at −20 °C.

Scheme 1. Hydrolytic Kinetic Resolution of the Trisubstituted Aziridine



bearing three different substituents,[18] which had rarely been accessible directly by any kind of catalytic asymmetric transformation. The proper choice of substrates, namely, *N*-α-diazoacyl oxazolidinones and *N*-Boc imines, along with *N*-triflyl phosphoramide as the catalyst, was critical to implemention of this strategy. The synthetic diversity of this aziridination could be broadened by applying two substrate combinations having a complementary set of substituents. In addition, hydrolytic kinetic resolution of the aziridines was revealed, and this will be of interest for future elaboration.[19]

■ ASSOCIATED CONTENT

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

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■ ACKNOWLEDGMENT

This work was partially supported by a Grant-in-Aid for Scientific Research from the MEXT, Japan. T.H. is thankful for a Grant-in-Aid for Young Scientists (B).

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(16) See the Supporting Information for details.

(17) Hydrolyzed products were not observed in the results showcased in Tables 2 and 3.

(18) During the preparation of this manuscript, Antilla and coworkers reported a catalytic asymmetric two-step aza-Darzens reaction to give trisubstituted aziridines having two identical acetyl groups. See: Larson, S. E.; Li, G.; Rowland, G. B.; Junge, D.; Huang, R.; Woodcock, H. L.; Antilla, J. C. *Org. Lett.* **2011**, *13*, 2188.

(19) After the submission of this manuscript, Huang and Wulff reported the catalytic asymmetric synthesis of trisubstituted aziridines using identical reactions. See: Huang, L.; Wulff, W. D. *J. Am. Chem. Soc.* **2011**, *133*, 8892 .