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Catalytic Asymmetric Diaziridination

Lennart Lykke, Kim Søholm Halskov, Bjørn Dreiø Carlsen, Victor X. Chen, and Karl Anker Jørgensen*

Center for Catalysis, Department of Chemistry, Aarhus University, DK-8000 Aarhus C, Denmark

Supporting Information

ABSTRACT: The first catalytic enantio- and diastereoselective synthesis of diaziridines is presented. Aziridination of *N*-tosyl aldimines applying modified hydroxylamine under asymmetric phase-transfer catalysis furnished optically active diaziridines. The diaziridines are formed as a single diastereomer in up to 96% ee, containing two orthogonal *N*-protecting groups, which can be deprotected selectively.

The development of new efficient and highly selective methodologies for the construction of heterocyclic structures is a cornerstone in organic synthesis.[1] Small heterocyclic molecules have found applications as reagents or reactants, as well as have become an essential part of the scaffold of natural compounds or pharmaceuticals.[2] Diaziridines are an interesting class of strained heterocycles, but surprisingly their asymmetric synthesis has only been scarcely studied.

Diaziridines[3] are heterocyclic compounds containing two N-atoms and one C-atom in a three-membered ring; as such the diaziridine ring is both a hydrazine and an aminal. This duality is reflected in the reactivity of this class of compounds.[4] These structures were first reported in the late 1950s by three groups concurrently.[5] Owing to the strained nature of this family of compounds, the weak N−N bond, and the hydrazine−aminal duality, these compounds exhibit unusual and interesting reactivity.[6] A remarkable property of diaziridines is that the N-atoms due to ring stain and lone-pair repulsion are configurationally stable;[7] consequently the diaziridine ring possesses three stereogenic centers. Nevertheless, to the best of our knowledge no catalytic asymmetric protocol leading to optically active diaziridines has been reported.

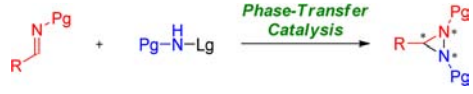
N-Monosubstituted diaziridines have found application as a *N*-transfer agent to α,β-unsaturated amides, forming diastereo- and enantioenriched aziridines.[8] Interestingly, depending on the structure of the diaziridine, the *cis*- and *trans*-selectivity could be controlled. Additionally, diaziridines have found use as 1,3-dipolar precursors by ring opening in the reaction with various π-systems.[9] Depending on the nature of the diaziridine system it opens in either a C−N or N−N fashion. Furthermore, diaziridines have found applications as a protected analog of a diazine which is used as a carbene precursor.[10]

The formation of diaziridines in general proceeds by N−N bond formation, thus coupling two heteroatoms. Imines can be oxidized by hydroxylamine *O*-sulfonic acids or *O*-esters in an organic or inorganic base-mediated reaction affording racemic *trans*-1,3-substituted diaziridines in excellent yields.[11] The reaction is a two-step sequence initiated by 1,2-addition of the derivatized hydroxylamine to the imine; the resulting aminal collapses via an intramolecular, nucleophilic substitution reaction furnishing the diaziridine ring.

The use of chiral auxiliary based imines is the only existing procedure for the synthesis of optically active diaziridines.[12] More recently, a catalytic enantioselective amidation of acylimines to give the open aminals was reported.[13]

Recently, the aziridination of electron-deficient C=C double bonds, applying acylated hydroxycarbamates or *N*-protected *O*-tosyl hydroxylamines as *N*-transfer agents, has been achieved for the formation of optically active aziridines.[14] We envisioned that this type of *N*-transfer agents might react with C=N double bonds for the asymmetric synthesis of diaziridines. We now report the first catalytic asymmetric formation of diaziridines applying a chiral phase-transfer catalyst (Scheme 1).

Scheme 1. Strategy for the Synthesis of Optically Active Diaziridines



Our studies were initiated by examining the diaziridination of *N*-tosyl benzaldimine **1a** applying the *N*-transfer agents **2a** and **2b** (Table 1), which have been successfully applied for the aziridination of electron-deficient olefins. The reaction was subjected with various organic and inorganic bases, but disappointingly no reactivity was observed. Addition of a catalytic amount of tetrabutylammonium bromide (TBAB) as a phase-transfer reagent did not promote reactivity (Tabel 1, entries 1 and 2). We considered that the nucleophilicity of the carbamate or sulfonamide N-atom might not be sufficient to undergo addition to **1a**. In order to test this hypothesis, we synthesized *N*-benzyl *O*-benzoyl hydroxylamine (**2c**) which is a more electron-rich and hence a more nucleophilic *N*-transfer agent.[15] To our delight, applying *N*-transfer agent **2c** under phase-transfer conditions using potassium carbonate as a base afforded 1-benzyl-3-phenyl-2-tosyldiaziridine (**4a**) in full conversion (entry 3). Throughout the present work, the synthesized diaziridines were formed as a single diastereomer. The reaction is performed as a solid base/organic solvent two-phase system; hence an aqueous base hydrolyzes the imine. It should be noted that the reaction also takes place using an organic base (DBU); however, as stoichiometric amounts of a chiral base would be required, we decided to follow the phase-transfer catalysis (PTC) strategy.[16]

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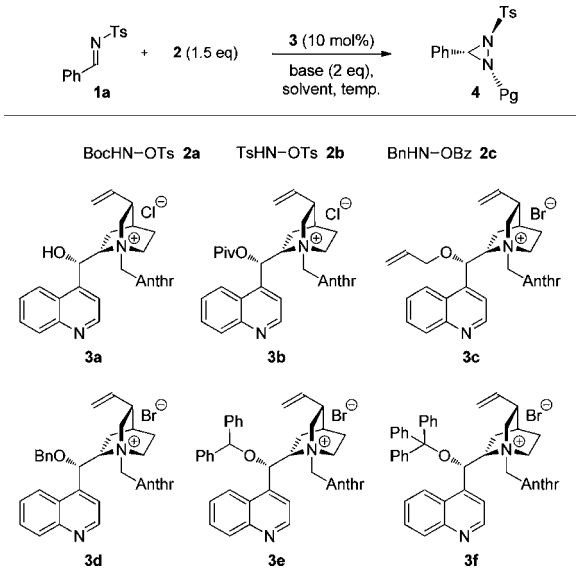
Table 1. Selected Screening Results for Reaction Conditions for the Enantioselective Diaziridination of *N*-Tosyl Benzaldimine 1a



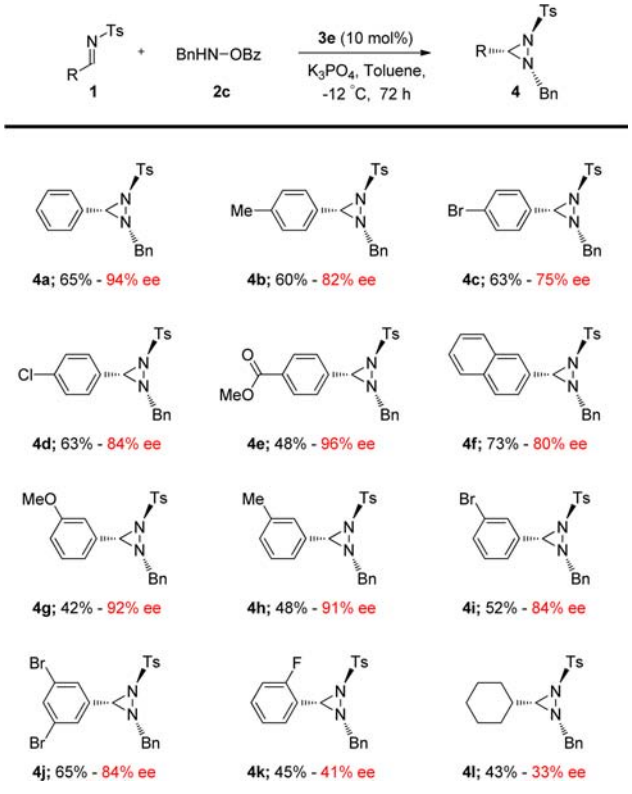
entry[a]	cat.	*N*-donor	solvent	base	temp (°C)	conv (%)	ee[b] (%)
1	TBAB	**2a**	toluene	K_2CO_3	4	–	nd
2	TBAB	**2b**	toluene	K_2CO_3	4	–	nd
3	TBAB	**2c**	toluene	K_2CO_3	4	>95	nd
4	**3a**	**2c**	toluene	K_2CO_3	4	>95	6
5	**3b**	**2c**	toluene	K_2CO_3	4	>95	17
6	**3c**	**2c**	toluene	K_2CO_3	4	>95	15
7	**3d**	**2c**	toluene	K_2CO_3	4	>95	35
8	**3d**	**2c**	CH_2Cl_2	K_2CO_3	4	30	nd
9	**3d**	**2c**	*m*-xylene	K_2CO_3	4	72	19
10	**3d**	**2c**	*o*-xylene	K_2CO_3	4	77	26
11	**3d**	**2c**	Ph–Cl	K_2CO_3	4	77	32
12	**3d**	**2c**	Ph–CF_3	K_2CO_3	4	>95	32
13	**3d**	**2c**	toluene	$KHCO_3$	4	–	nd
14	**3d**	**2c**	toluene	Cs_2CO_3	4	>95	27
15[c]	**3d**	**2c**	toluene	K_3PO_4	4	>95	34
16	**3e**	**2c**	toluene	K_3PO_4	4	>95	57
17	**3f**	**2c**	toluene	K_3PO_4	4	>95	0
18[d]	**3e**	**2c**	toluene	K_3PO_4	−12	84	94

[a]All reactions performed on a 0.05 mmol scale using **1a** (0.05 mmol), **2** (0.075 mmol), **3** (0.005 mmol), and base (0.1 mmol) in 0.5 mL of anhydrous solvent for 24 h at 4 °C. [b]Determined by chiral stationary phase HPLC. [c]Reaction time 4 h. [d]Reaction time 72 h.

We initiated a screening protocol by surveying asymmetric phase-transfer catalysts and were pleased that cinchonine quaternized with a 9-methyleneanthracene at the quinuclidine N-atom, indicating a promising skeleton for catalyst development (entries 4–7). It was discovered that the *O*-benzylated catalyst **3d** catalyzed the reaction in full conversion and up to 35% ee (entry 7). With a promising catalyst in hand we performed a solvent screening (entries 8–12) and observed that the reaction only furnished the desired diaziridine to a significant degree in aromatic solvents; disappointingly, no enhancement was achieved with regards to conversion or enantioselectivity when compared to toluene. We then turned our attention to the base. It was recognized that potassium bicarbonate was too weak to mediate the reaction (entry 13). When employing cesium carbonate the reaction proceeded in full conversion to the product diaziridine **4a** but with inferior enantioselectivity compared to potassium carbonate (entry 14 vs 7). When potassium phosphate was used the product diaziridine was afforded with similar selectivity as with potassium carbonate; however, the reaction rate was significantly enhanced (entry 15 vs 7). Employing the novel *O*-diphenylmethylene-modified catalyst **3e** using potassium phosphate afforded the diaziridine **4a** with the enantioselectivity increased to 57% ee (entry 16). Surprisingly, increasing the bulky nature of the *O*-substituent further by *O*-tritylation **3f** depleted the enantioselectivity completely (entry 17). Applying catalyst **3e** at a lowered temperature (−12 °C) furnished the diaziridine product **4a** with an excellent enantiomeric excess of 94% ee (entry 18); however, further cooling prolonged the reaction time significantly giving no additional improvement in enantioselectivity. It should be noted that the reaction time was increased to 72 h for the reaction to reach acceptable conversion (84%), while the remaining material was the uncyclized aminal intermediate.

Encouraged by this result, a representative selection of *N*-tosyl aldimines was prepared in order to investigate the generality of the reaction (Scheme 2). We were pleased to find that the high efficiency demonstrated by catalyst **3e** for the model reaction could be sustained for the diaziridination of a broad range of imines. Generally, aromatic imines having substituents in the *meta*- and *para*-positions furnished the optically active diaziridine

Scheme 2. Scope for the Enantioselective Diaziridination of *N*-Tosyl Aldimines[a]



[a]All reactions performed using **1** (0.05 mmol), **2c** (0.075 mmol), **3e** (0.005 mmol), and K_3PO_4 (0.1 mmol) in 0.5 mL of anhydrous toluene for 72 h at −12 °C. Isolated yields by FC. Ee determined by chiral stationary phase HPLC.

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products in acceptable to high yields with high to excellent enantioselectivities (products **4b**–**e**,**g**–**j**). Imines with aromatic substituents having an electronic nature ranging from electron-donating to -withdrawing participated successfully in the enantioselective diaziridination; however, when aromatic imines having electron-rich substituents, which are able to conjugate a lone pair of electrons to the imine, were employed (e.g., *p*-MeO-C_6H_4 or 2-furanyl), no product formation was observed. Interestingly, a disubstituted aromatic imine was employed in the reaction affording diaziridine **4j** in high yield and enantioselectivity. Additionally, a 2-naphthyl-based imine also gave rise to the corresponding diaziridine **4f** in high yield and enantioselectivity. In general *ortho*-substituted aromatic imines performed sluggishly in the reaction, probably owing to steric reasons, although an *o*-fluoro substituted imine afforded the product **4k**, albeit in a moderate yield and enantioselectivity. Having surveyed the diaziridination of aromatic aldimines, we considered the possibility of expanding the developed methodology to aliphatic *N*-tosyl aldimines. Indeed catalyst **3e** furnished cyclohexyl-substituted optically active diaziridine **4l**; disappointingly a moderate yield and enantioselectivity were obtained.

Determination of the relative and absolute configuration of the optically active diaziridines was carried out by X-ray analysis of **4c**, which proved to be the (1*R*,2*R*,3*S*)-1-benzyl-3-aryl-2-tosyldiaziridine as shown in Figure 1.[17] Hence, the remaining diaziridines **4** were assigned by analogy assuming a common reaction pathway.

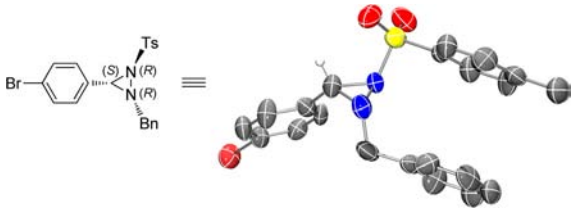


Figure 1. Single crystal X-ray structure of **4c**.

A computational study (M06-2X/6-31+G(d,p))[18,19] was employed to examine the inversion barriers for diaziridine **4a**. Our studies predicted structure **A** (Figure 2) to be the lowest

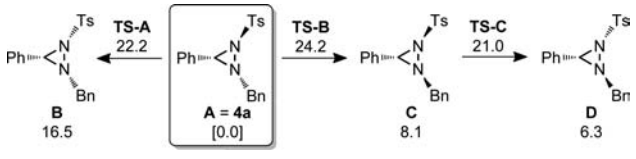


Figure 2. Calculated inversion barriers and relative energies of the diaziridine **4a**. Energies are reported in kcal/mol and are relative to the energy of **A**.

energy diastereomer and conformer, in agreement with the X-ray structure of **4c**. Consistent with the experimental and theoretical findings,[20] the favored isomer places the two *N*-substituents *trans* to one another. Structure **A** also takes advantage of a favorable π-stacking interaction between the two *N*-substituents (see Figure 1). Conversion of **A** to **C**, in which the Ts- and Bn-groups on the N-atoms have a *cis*-relationship, proceeds with a barrier of 24.2 kcal/mol. Inversion of the Ts-group in **A** occurs with a barrier of 22.2 kcal/mol and leads to the all cis-isomer of **4a**, which is 16.5 kcal/mol higher in energy than **A**.[21] Inversion of the Ts-group in **C** proceeds with a barrier of 21.0 kcal/mol. It should also be noted that all diastereoisomers of **A** are higher in energy than **A**. These data suggest that the diaziridine should exclusively exist as diastereoisomer **A**, which is consistent with the experimental findings.

Based on experimental observations, we propose a mechanistic pathway for the catalytic enantio- and diastereoselective diaziridination of *N*-tosyl aldimines as outlined in Figure 3.

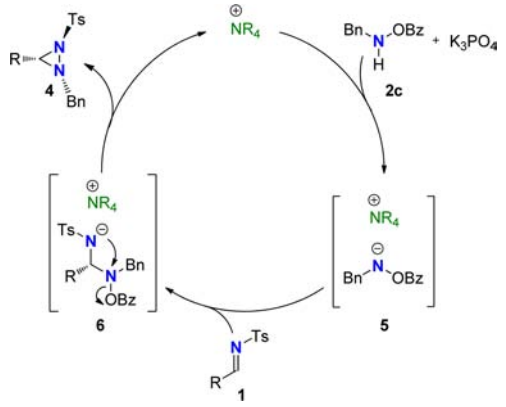
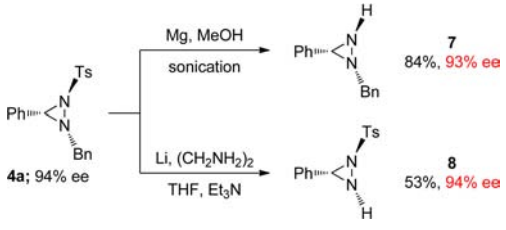


Figure 3. Mechanistic proposal of the asymmetric diaziridination of *N*-tosyl aldimines.

Upon filtration of the reaction mixture (removal of catalyst and base), prior to reaction completion, the uncyclized aminal adduct **6** was observed in a significant amount by ^{1}H NMR spectroscopy, and this adduct did not cyclize furnishing the diaziridine **4** in the absence of the catalyst, even at elevated temperatures. We propose that the first step is the formation of a contact ion-pair **5**, by reaction of the deprotonated hydroxylamine with the phase-transfer catalyst, which undergoes an enantioselective addition to the *N*-tosyl aldimine. Based on the experimental observations, we suggest a stepwise reaction mechanism, in which the rate-determining step consists of an ammonium-ion catalyzed diastereoselective N–N bond forming cyclization of **6** affording the diaziridine **4**.

To demonstrate the utility of the optically active diaziridines, we set out to investigate whether the two *N*-protection groups could be removed in an orthogonal fashion. To remove the tosyl moiety, we decided to follow the Ragnarsson procedure,[22] which is a mild and effective Mg-mediated reductive cleavage. The detosylated diaziridine **7** was isolated in an unoptimized 84% yield as the *cis*-isomer without racemization (Scheme 3). Deprotection of the benzyl-moiety proved much more challenging, as both benzylamine and the N–N bond of the diaziridine underwent hydrogenation even when very mild hydrogenation methodologies were applied. Chloroformate dealkylation reactions failed to afford any desired product. We circumvented this challenge by employing the mild dissolved

Scheme 3. Orthogonal Deprotection of the Two *N*-Protection Groups



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metal-reduction conditions developed by Angle.[23] Treatment of **4a** with lithium using a solvent mixture of ethylenediamine, triethylamine, and THF afforded the debenzylated diaziridine **8** in 53% yield (unoptimized).

In conclusion, this work constitutes the first example of a catalytic asymmetric diaziridination. The developed methodology takes advantage of a phase-transfer catalyzed nitrogen insertion into the π-system of *N*-tosyl aldimines facilitated by *N*-benzyl-*O*-benzoyl hydroxylamine as the *N*-transfer agent affording *N*-tosyl-*N*′-benzyl-diaziridines as a single diastereomer in up to high yields (up to 75%) with high to excellent enantioselectivity (up to 96% ee) and with absolute diastereocontrol. Experimental observations indicate a stepwise mechanism in which the rate-determining step is an ammonium-ion catalyzed N−N bond forming cyclization of an aminal intermediate. Furthermore, orthogonal *N*-deprotections have been demonstrated.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, analytical data, and NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

kaj@chem.au.dk

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

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■ REFERENCES

(1) *Asymmetric Synthesis of Nitrogen Heterocycles*; Royer, J., Ed.; Wiley-VCH: Wienheim, 2009.

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

(3) Reference 1, Chapter 5.

(4) (a) Schmitz, E. *Adv. Heterocycl. Chem.* **1979**, *24*, 63. (b) Schmitz, E. In *Diaziridines, 3H-Diazirines, Diaziridinones and Diaziridinimines, Small Ring Heterocycles*, Vol. *1*; Lowowski, W., Ed.; Pergamon Press: Oxford, 1983; p 195.

(5) (a) Schmitz, E. *Angew. Chem.* **1959**, *71*, 127. (b) Abendroth, H. J.; Henrich, G. *Angew. Chem.* **1959**, *71*, 283. (c) Paulsen, S. R. *Belg. Pat.* **1959**, 588352.

(6) For reviews on diaziridine reactivity, see: (a) Kostyanovsky, R. G., Murugan, R.; Sutharchanadevi, M. In *Comprehensive Heterocyclic Chemistry II*, Vol. *1A*; Padwa, A., Ed.; Elsevier: Oxford, 1996; p 347. (b) McAllister, G. D.; Perry, A.; Taylor, R. J. K. In *Comprehensive Heterocyclic Chemistry III*, Vol. *1*; Padwa, A., Ed.; Elsevier: New York, 2008; p 539. (c) Makhova, N. N.; Shevtsov, A. V.; Petukhova, V. Y. *Russ. Chem. Rev.* **2011**, *80*, 1035.

(7) Jennings, W. B.; Boyd, D. R. In *Cyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi, Y., Eds.; VCH: New York, 1992; Chapter 5.

(8) Ishihara, H.; Hori, K.; Sugihara, H.; Ito, Y. N.; Katsuki, T. *Helv. Chim. Acta* **2002**, *85*, 4272.

(9) (a) Komatsu, M.; Nishikaze, N.; Sakamoto, M.; Oshihiro, Y.; Agawa, T. *J. Org. Chem.* **1974**, *39*, 3198. (b) Shevtsov, A. V.; Kuznetsov, V. V.; Kislukhin, A. A.; Petukhova, V. Y.; Strelenko, Y. A.; Makhova, N. N. *J. Heterocycl. Chem.* **2006**, *43*, 881. (c) Syroeshkina, Y. S.; Kuznetsov, V. V.; Lyssenko, K. A.; Makhova, N. N. *Mendeleev Commun.* **2008**, *18*, 207. (d) Alper, H.; Delledonne, D.; Kameyama, M.; Roberto, D. *Organometallics* **1990**, *9*, 762. (e) Du, H.; Zhao, B.; Shi, Y. *J. Am. Chem. Soc.* **2007**, *129*, 762. (f) Zhao, B.; Du, H.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 3523. (g) Zhao, B.; Peng, X.; Cui, S.; Shi, Y. *J. Am. Chem. Soc.* **2010**, *132*, 11009. (h) Capretto, D. A.; Brouwer, C.; Poor, C. B.; He, C. *Org. Lett.* **2011**, *13*, 5842.

(10) (a) Moss, R. A. *Acc. Chem. Res.* **2006**, *39*, 267. (b) Hashimoto, M.; Hatanaka, Y. *Eur. J. Org. Chem.* **2008**, 2513.

(11) For a review of the synthesis of diaziridines, see: Makhova, N. N.; Petukhova, V. Y.; Kuznetsov, V. V. *ARKIVOC* **2008**, 128.

(12) (a) Fioravanti, S.; Olivieri, L.; Pellacani, L.; Tardella, P. A. *Tetrahedron Lett.* **1998**, *39*, 6391. (b) Carroccia, L.; Fioravanti, S.; Pellacani, L.; Sadun, C.; Tardella, P. A. *Tetrahedron* **2011**, *67*, 5375. (c) Carroccia, L.; Delfini, M.; Fioravanti, S.; Pellacani, L.; Sciubba, F. *J. Org. Chem.* **2012**, *77*, 2069.

(13) Rowland, G. B.; Zhang, H.; Rowland, E. B.; Chennamadhavuni, S.; Wang, Y.; Antilla, J. C. *J. Am. Chem. Soc.* **2005**, *127*, 15696.

(14) (a) Vesely, J.; Ibrahem, I.; Zhao, G.-L.; Rios, R.; Córdova, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 778. (b) Deiana, L.; Dziedzic, P.; Zhao, G.-L.; Vesely, J.; Ibrahem, I.; Rios, R.; Sun, J.; Córdova, A. *Chem.—Eur. J.* **2011**, *17*, 7904. (c) Pesciaioli, F.; Vincentiis, F. D.; Galzerano, P.; Bencivenni, G.; Bartoli, G.; Mazzanti, A.; Melchiorre, P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8703. (d) Arai, H.; Sugaya, N.; Sasaki, N.; Makino, K.; Lectard, S.; Hamada, Y. *Tetrahedron Lett.* **2009**, *50*, 3329. (e) Jiang, H.; Holub, N.; Jørgensen, K. A. *Proc. Natl. Acad. Sci. U.S.A.* **2010**, *107*, 20630. (f) Albrecht, L.; Jiang, H.; Dickmeiss, G.; Geschwend, B.; Hansen, S. G.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2010**, *132*, 9188. (g) Jiang, H.; Halskov, K. S.; Johansen, T. K.; Jørgensen, K. A. *Chem.—Eur. J.* **2011**, *17*, 3842.

(15) The synthesis of *N*-benzyl-*O*-tosyl hydroxylamine was also attempted; however, this compound was unstable under basic conditions.

(16) For reviews on phase-transfer catalysis, see: (a) Ooi, T.; Maruoka, K. *Angew. Chem., Int. Ed.* **2007**, *46*, 4222. (b) Hashimoto, T.; Maruoka, K. *Chem. Rev.* **2007**, *107*, 5656. (c) Brak, K.; Jacobsen, E. N. *Angew. Chem., Int. Ed.* **2013**, *52*, 534. (d) *Asymmetric Phase Transfer Catalysis*; Maruoka, M., Ed.; Wiley-VCH: Wienheim, 2008. For recent examples, see: (e) He, R.; Shirakawa, S.; Maruoka, K. *J. Am. Chem. Soc.* **2009**, *131*, 16620. (f) Ma, T.; Fu, X.; Kee, C. W.; Zong, L.; Pan, Y.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2011**, *133*, 2828. (g) Shirakawa, S.; Liu, K.; Maruoka, K. *J. Am. Chem. Soc.* **2012**, *134*, 916. (h) Hong, S.; Lee, J.; Kim, M.; Park, Y.; Park, C.; Kim, M.-H.; Jew, S.-S.; Park, H.-G. *J. Am. Chem. Soc.* **2011**, *133*, 4924. (i) Qi, J.; Beeler, A. B.; Zhang, Q.; Porco, J. A. *J. Am. Chem. Soc.* **2010**, *132*, 13642.

(17) For X-ray analysis details, see Supporting Information. Ortep-3 was used for the X-ray plot: Farrugia, L. J. *J. Appl. Crystallogr.* **1997**, *30*, 565.

(18) Calculations were performed with *GAUSSIAN09*. Geometries were optimized without symmetry constraints at the M06-2X/6-31+G(d,p) level of theory (Zhao, Y.; Truhlar, D. *Theor. Chem. Acc.* **2008**, *120*, 215) in the gas phase. See Supporting Information for the details and references for theoretical methods.

(19) The inversion barriers and relative free energies of the intermediates were also calculated at MP2/cc-pVDZ//M06-2X/6-31+G(d,p). With this method, the same energetic trends are observed as with M06-2X/6-31+G(d,p). Barriers for inversion ranged from 26 to 28 kcal/mol, and **A** is favored over all other isomers by 3−8 kcal/mol. For details, see Supporting Information.

(20) (a) Nielsen, I. M. B. *J. Phys. Chem. A* **1998**, *102*, 3193. (b) Alkorta, I.; Elguero, J.; Zborowski, K. *J. Phys. Chem. A* **2007**, *111*, 1096.

(21) It should be noted that TS-D does not directly connect **A** to **D**. Due to steric crowding, no transition state connecting **A** to **D** could be located. The conformer of **A** leading to TS-D is 2.5 kcal/mol higher in energy.

(22) Nyasse, B.; Grehn, L.; Ragnarsson, U. *Chem. Commun.* **1997**, 1017.

(23) Angle, S. R.; Henry, R. H . *J. Org. Chem.* **1998**, *63*, 7490.