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(5*S*)-1,3-Diaza-2-imino-3-phenylbicyclo[3.3.0]octane: first example of guanidine based in situ recyclable chiral catalytic source for borane-mediated asymmetric reduction of prochiral ketones

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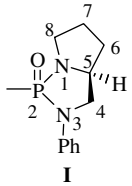
Abstract—(5*S*)-1,3-Diaza-2-imino-3-phenylbicyclo[3.3.0]octane has been synthesized and successfully employed, for the first time, as a chiral catalytic source for the borane-mediated asymmetric reduction of prochiral α-halo ketones to provide the corresponding secondary alcohols in high enantiomeric purity. The potential of this guanidine as an in situ recyclable chiral catalytic source for the borane-mediated chiral reduction processes has also been demonstrated.

1. Introduction

The development of useful and practical chiral catalysts for the borane-mediated asymmetric reduction of prochiral ketones for obtaining enantiomerically pure (enriched) secondary alcohols has been, and continues to be, an area of interest in chiral chemistry because of the challenges involved in such endeavors and also due to the applications of homochiral secondary alcohols in organic and medicinal chemistry.[1–6] In fact, after ingenious utilization of oxazaborolidines, by Corey et al.,[6,7] as chiral catalysts for the borane-mediated asymmetric reduction of prochiral ketones, there has been much activity in designing and developing various kinds of oxazaborolidine-based chiral catalysts. Several efforts have also been made in developing chiral catalysts based on titanium,[8,9] sulfonamide,[10,11] and phosphorus[12–14] derivatives for this purpose. To the best of our knowledge, there is no report in the literature on the application of chiral guanidine as a chiral catalyst/catalytic source for the borane-mediated asymmetric reduction of prochiral ketones. We herein report (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo[3.3.0]octane as the first example of guanidine based in situ recyclable chiral catalytic source for the borane-mediated asymmetric reduction of representative prochiral ketones.

We have been working for the last few years on the development of useful chiral catalysts containing the N–P=O structural framework for the borane-mediated asymmetric reduction of prochiral ketones,[15–19] actually inspired by the elegant work of Wills and co-workers.[12–14] In this direction, we have designed and synthesized a number of chiral catalysts having N–P=O structural framework built mainly on (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo[3.3.0]-octane framework **I** and examined their applications.[15–19]



I

2. Results and discussion

During these studies we have also, to some extent, established that the group on the phosphorus in (5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo[3.3.0]octane skeleton **I** has no significant role to play in chiral induction process[18] and also the stereochemistry on the phosphorus stereogenic center does not play any role in directing the

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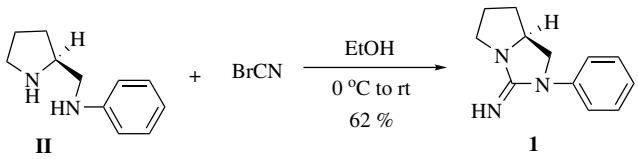
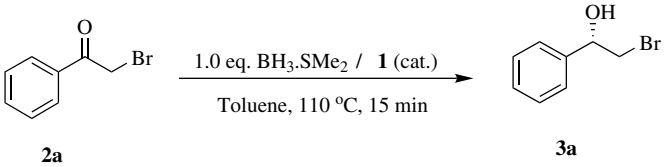
stereoselectivity of the reduction process.[19] On the basis of these results, it appeared to us that real chiral director in all these studies is the chiral diamine (2*S*)-2-anilinomethylpyrrolidine **II** from which actually all our catalysts were derived. It, therefore, occurred to us that guanidine derivative **1**, derived from this wonderful diamine **II**, might provide some interesting guidelines/directions so as to understand the applicability of molecules, containing chiral guanidine framework as possible chiral catalysts or catalytic sources for the borane-mediated asymmetric reduction of prochiral ketones. Accordingly, we have synthesized the desired (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo[3.3.0]octane **1**[20] via the reaction of the chiral diamine **II** with cyanogen bromide according to the general literature procedure (Eq. 1).[21] The structure of this compound was also established by the single crystal X-ray data (Fig. 1).[22]



(1)

We first examined the reduction of phenacyl bromide **2a** with different catalytic amounts of guanidine derivative **1** (Table 1, Eq. 2). The best results were obtained when phenacyl bromide **2a** was subjected to the borane-mediated chiral reduction under the influence of **1** (5 mol %) in refluxing toluene for 15 min, thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol **3a** in 81% yield with 83% enantiomeric excess (Table 1, entry 3).[23]

Table 1. Asymmetric reduction of phenacyl bromide **2a** at 110 °C[a]



(2)

Entry	Catalyst **1** (mol %)	Yield[b] (%) **3a**	Enantiomeric excess[c] (%) **3a**
1	2	82	74
2	4	84	81
3	**5**	**81**	**83**
4	6	86	79
5	8	88	78
6	10	80	80

[a] All reactions were carried out on a 1 mM scale of phenacyl bromide with 1 mM of $BH_3{\cdot}SMe_2$ in the presence of **1** in toluene for 15 min at 110 °C.
[b] Isolated yields of alcohol after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c] Determined by HPLC analysis using the chiral column, Chiralcel-OD-H.

Encouraged by this result and also with a view to understand the generality, we extended this methodology to a representative prochiral α-halo ketones **2b–h**. The resulting secondary alcohols **3b–h** were obtained in 72–83% enantiomeric excesses (Table 2, Eq. 3).

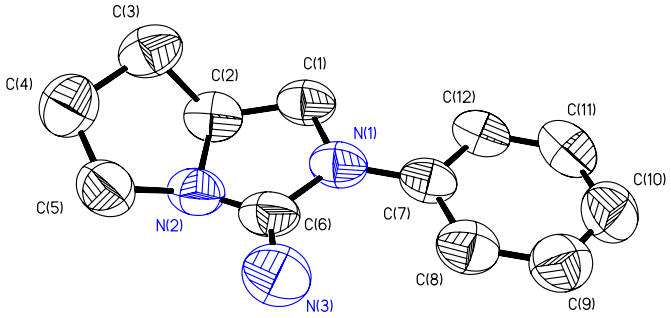


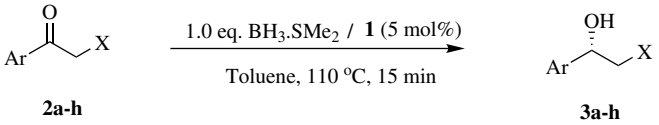
Figure 1. ORTEP diagram of **1** (*Hydrogen atoms were omitted for clarity*).

2.1. Towards understanding catalytic process

With a view to understand the nature of the actual chiral catalyst/catalytic source, we carried out the following experiments: (i) We performed the reaction between guanidine derivative **1** (0.25 mM) and $BH_3{\cdot}SMe_2$ (5 mM, 5 mL, 1 M solution in toluene) in refluxing toluene (25 mL) for 15 min (in the ratio of 1:20 as in the case of reaction conditions), and recorded the ^1H, ^{13}C, ^{11}B NMR[27] spectra of this crude mixture (after removal of excess $BH_3{\cdot}SMe_2$ and toluene under vacuum). Although ^1H and ^{13}C NMR spectral data did not provide any indication about the exact structure of the actual catalyst, the presence of a peak at δ 85.02 ppm (along with other peaks) and also the absence of a peak at δ 161.69 ppm (present in spectrum of original guanidine **1**) in the ^{13}C NMR spectrum indicate the possible reduction of C=N of the guanidine, probably leading to the formation of compound **III** (*possibly complexing with borane*) having *CH* attached to three different nitrogens (Scheme 1).

(ii) With a view to understand the stability of guanidine moiety in the presence of $BH_3{\cdot}SMe_2$ at room temperature, we have treated guanidine derivative **1** (0.25 mM) and $BH_3{\cdot}SMe_2$ (5 mM, 5 mL, 1 M solution in toluene) in toluene (25 mL) at room temperature (≈30 °C) for 15 min (in the ratio of 1:20 as in the case of reaction conditions) and recorded ^1H, ^{13}C, ^{11}B NMR[28] spectra of this crude compound (after removal of excess $BH_3{\cdot}SMe_2$ and toluene under vacuum). ^{13}C NMR spectrum indicated that the guanidine moiety is more or less intact as evidenced by the absence of any peak in the region δ 70–110 ppm (due to the absence of carbon attached to three nitrogens) and the presence of a peak at δ 161.02 ppm (as there is no reduction of C=N). The ^{13}C NMR spectrum also showed the presence of all the peaks that are originally present in starting guanidine **1** (with little difference in the chemical shift values) along with the minor peaks (probably arising due to the complexation with borane). We then performed the asymmetric reduction of phenacyl bromide under the influence of **1** (5 mol %) at room temperature (≈30 °C) in order to understand its efficiency as a catalyst. The resulting secondary alcohol was obtained with 32% enantiomeric excess, and more interestingly with an (*R*)-configuration (opposite to the configuration of the alcohol obtained under reflux conditions). Although enantioselectivity is low, this interested us

Table 2. Asymmetric reduction of prochiral α-halo ketones[a]



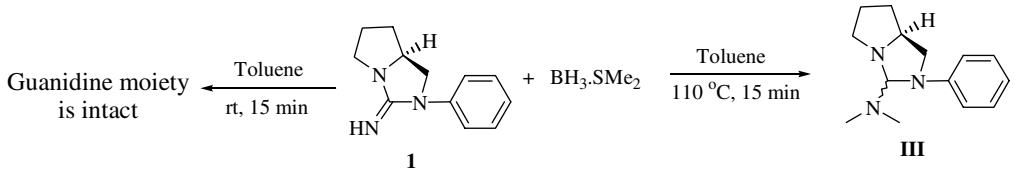
2a-h **3a-h** (3)

X = Br, Cl

Ar = Ph, 4-MePh, 4-BrPh, 4-ClPh, 4-NO_2Ph, Naphth-2-yl

Substrate	Ar	X	Product	Yield[b] (%)	$[\alpha]_D^{25}$	Conf.[c]	ee (%)
2a	Phenyl	Br	**3a**	81	+36.5 (*c* 1.1, $CHCl_3$)	*S*[24]	83[d]
2b	Phenyl	Cl	**3b**	80	+40.7 (*c* 1.3, C_6H_{12})	*S*[24]	81[d]
2c	4-Methylphenyl	Br	**3c**	85	+35.3 (*c* 1.2, $CHCl_3$)	*S*[15]	82[d]
2d	4-Methylphenyl	Cl	**3d**	82	+42.0 (*c* 1.1, $CHCl_3$)	*S*[15]	83[d]
2e	4-Bromophenyl	Br	**3e**	78	+27.7 (*c* 1.1, $CHCl_3$)	*S*[25]	81[e]
2f	4-Chlorophenyl	Br	**3f**	89	+37.4 (*c* 1.2, $CHCl_3$)	*S*[15]	83[e]
2g	4-Nitrophenyl	Br	**3g**	84	+26.5 (*c* 1.2, $CHCl_3$)	*S*[16]	78[f]
2h	Naphth-2-yl	Br	**3h**	86	+21.6 (*c* 1.0, EtOH)	*S*[26]	72[e]

[a] All reactions were carried out on 1 mM scale of α-halo ketone with 1 mM of BH_3·SMe_2 in the presence of **1** (5 mol %) in toluene for 15 min at 110 °C.
[b] Isolated yields of alcohols after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecules.
[d] Determined by HPLC analyses using the chiral column, Chiralcel-OD-H.
[e] Determined by HPLC analyses using the chiral column, Chiralcel-OJ-H.
[f] Determined by HPLC analysis of the corresponding acetate using the chiral column, Chiralcel-OD-H.



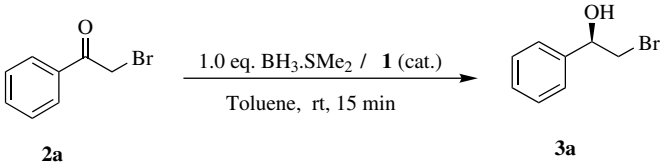
Scheme 1.

because of the reversal of stereoselection from room temperature to 110 °C. Thus the same catalytic source operates in two different stereodirections in the reduction of phenacyl bromide, providing the resulting alcohol with opposite configurations at room temperature and high temperature (110 °C) due to two different catalytic species actually involved in the reduction pathway. We also carried out the same reaction with different catalytic amounts in order to study the influence of the amount of catalyst on the asymmetric induction at room temperature (Table 3, Eq. 4).

(iii) With a view to understand the stereoselection of reduced catalytic species **III**, at room temperature, we carried out the reduction of phenacyl bromide under the influence of catalytic species **III** (5 mol %) (generated in situ by the reaction of guanidine moiety **1** with BH_3·SMe_2 at 110 °C and cooling back to room temperature) for 30 min at room temperature and obtained the corresponding (*S*)-2-bromo-1-phenylethanol in 44% ee (Scheme 2).

This study demonstrates that there is a remarkable difference in the levels of stereoselectivity from the same catalytic species from 110 °C to room temperature probably due to two different pathways of reduction processes.

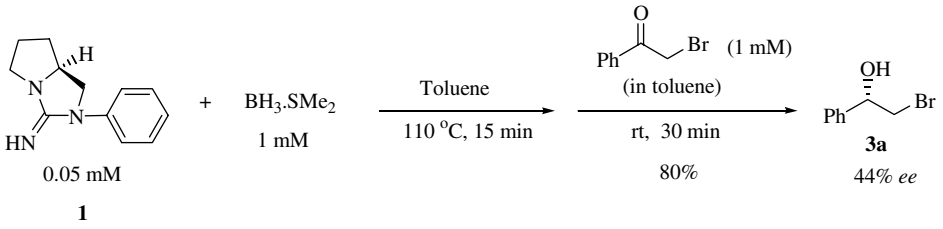
Table 3. Asymmetric reduction of phenacyl bromide **2a** at room temperature[a]



2a **3a** (4)

Entry	Catalyst **1** (mol %)	Yield[b] (%) **3a**	Enantiomeric excess[c] (%) **3a**	Configuration[d]
1	5	87	32	*R*
2	6	85	31	*R*
3	8	85	36	*R*
4	10	84	36	*R*
5	15	83	37	*R*

[a] All reactions were carried out on a 1 mM scale of phenacyl bromide with 1 mM of BH_3·SMe_2 in the presence of **1** in toluene for 15 min at ≈30 °C.
[b] Isolated yields of alcohol after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).
[c] Determined by HPLC analysis using the chiral column, Chiralcel-OD-H.
[d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that in the literature.[24]



Scheme 2.

2.2. Recyclable potential of in situ generated catalyst/ catalytic species

With a view to examine the in situ recyclable potential of the catalytic species **III**, we first carried out the reduction of phenacyl bromide (1 mM) in a usual way at 110 °C (run 1). $BH_3{\cdot}SMe_2$ (1 mM) (for run 2) was added to this reaction flask (without work-up) and heated at 110 °C for 15 min, and then a solution of phenacyl bromide (1 mM) in toluene was slowly added drop-wise and stirring was continued at 110 °C for further 15 min as usual (run 2). We were pleased to obtain the resulting secondary alcohol (after work-up and purification as usual) in almost the same enantioselectivity. In a similar way, we have also examined the recyclability of this catalytic species for a further two times (total four times); the enantioselectivity remained almost the same (Table 4).

Table 4. Recyclable ability of catalytic species **III** in the asymmetric reduction of phenacyl bromide **2a**

Number of runs	Enantiomeric excess[a] (%) **3a**
1	83
2	79
3	78
4	79

[a] Determined by HPLC analysis using the chiral column, Chiralcel-OD-H.

3. Conclusion

In conclusion, we have, for the first time, developed a novel and in situ recyclable chiral catalytic source **1** based on a guanidine framework for the borane-mediated asymmetric reduction of prochiral α-halo ketones, thus providing the secondary alcohols with reasonably high enantiomeric excesses. Our study also demonstrates a remarkable reversal of stereoselectivity going from room temperature (≈30 °C) to high temperature (110 °C) during the borane-mediated reduction of phenacyl bromide using guanidine **1** as a chiral catalytic source, probably due to two different catalytic species actually involved in the transition state of the reduction process. We also observed interesting temperature dependant levels of stereoselectivity from the same catalytic species **III**, probably due to different pathways involved in the reduction process. This study also, to some extent, indicates that it would in principle be possible to obtain both enantiomers of the secondary alcohols in homochiral form with appropriate chiral guanidine derivative as a chiral catalytic source. Work towards this direction is underway in our laboratory.

Acknowledgments

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20. Chiral guanidine, (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo-[3.3.0]octane **1**, is a new molecule. This was synthesized following the general procedure described by Ma and Cheng.[21] Spectral data for the chiral source **1**: mp: 58 °C; $[\alpha]_D^{25} = -48.7$ (*c* 1.1, $CHCl_3$); ^1H NMR (400 MHz/$CDCl_3$): δ 1.42–1.54 (m, 1H), 1.84–1.98 (m, 1H), 1.99–2.10 (m, 2H), 3.22–3.29 (m, 1H), 3.50–3.61 (m, 1H), 3.68–3.73 (m, 1H), 3.77–3.86 (m, 1H), 3.91–3.98 (m, 1H), 5.09 (b, 1H), 7.02–7.10 (m, 1H), 7.32–7.56 (m, 4H); ^{13}C NMR (100 MHz/$CDCl_3$): δ 25.92, 31.37, 48.14, 51.60, 57.48, 120.32, 123.09, 129.09, 141.32, 161.69; IR (KBr): 3316, 1630, 1593 cm^{-1}; LCMS (*m*/*z*): 202 $(M+H)^+$; Anal. Calcd for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.66; H, 7.47; N, 20.86.
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22. Crystal data for (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo[3.3.0]-octane **1**: The single crystal X-ray structure revealed the presence of two molecules in the asymmetric unit. For clarity we have shown one molecule in the ORTEP diagram (Fig. 1). Empirical formula, $C_{12}H_{15}N_3$; formula weight, 201.27; colorless, rectangular crystals; crystal dimensions, $0.45 \times 0.32 \times 0.14$ mm^3; monoclinic, lattice type, primitive; $a = 9.5937$ (13) Å, $b = 11.6631$ (16) Å, $c = 9.6206$ (13) Å; $\alpha = 90.00$; $\beta = 91.683$ (2); $\gamma = 90.00$; $V = 1076.0$ (3) $Å^3$; space group, $P2_1$ (International Table No. 14); $Z = 4$; $D_{calcd} = 1.242$ g/cm^3; $F_{000} = 432$; $\lambda(Mo\ K_\alpha) = 0.71073$ Å; $R(I \geqslant 2\sigma_1) = 0.0378$; $wR^2 = 0.0923$. Detailed X-ray crystallographic data are available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC No. 299827). Although the sample is enantiomerically pure, with an (*S*)-configuration, the asymmetric unit consists of two molecules related by a pseudo-center of symmetry. For similar literature reports please see: (a) Bats, J. W.; Grundl, M. A.; Hashmi, A. S. K. *Acta Crystallogr.* **2001**, *C57*, 208–210; (b) Pradeep, C. P. *Acta Crystallogr.* **2005**, *E61*, o3825–o3827.
23. *Asymmetric reduction of phenacyl bromide* **2a**: *Synthesis of (S)-2-bromo-1-phenylethanol* **3a**: *Representative procedure*: To a stirred solution of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo[3.3.0]octane **1** (0.05 mM, 10.1 mg) in toluene (5 mL) was added $BH_3{\cdot}SMe_2$ (1 mM, 1 mL, 1 M solution in toluene) at room temperature, and the reaction mixture heated at 110 °C for 15 min. A solution of phenacyl bromide **2a** (1 mM, 199 mg) in toluene (2 mL) was added slowly drop-wise and heating was continued for further 15 min. The reaction mixture was then cooled to room temperature and quenched with MeOH. The solvent was removed under reduced pressure, and the residue thus obtained was purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*S*)-2-bromo-1-phenylethanol **3a** in 81% (163 mg) yield as a colorless oil.
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27. ^{11}B NMR spectrum showed a broad peak at δ 31.7 ppm (in addition to other peaks in the region δ −32 to 3 ppm), probably indicating the presence of N–B–N (diazaborolidine moiety). For similar ^{11}B NMR chemical shifts see: Cruz, A.; Geniz, E.; Contreras, R. *Tetrahedron: Asymmetry* **1998**, *9*, 3991–3996.
28. ^{11}B NMR spectrum did not show any peak in the region δ 15–40 ppm, thus indicating the absence of N–B–N and ^{11}B NMR spectrum showed peaks at δ −20.3, −21.4, −29.9 ppm and a minor peak at δ −11.3 ppm, indicating the presence of the tetra-coordinated boron (ate complexes). *However, it needs more studies to understand the actual nature of the boron present in the catalytic cycle.*