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(5*S*)-1-Aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane: a novel chiral catalytic source containing the N–(C=NH)–O moiety for the borane-mediated asymmetric reduction of prochiral ketones

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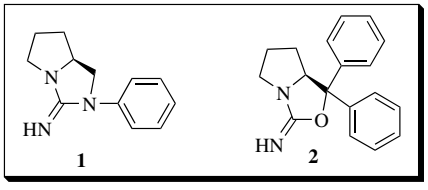
Abstract—(5*S*)-1-Aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane, a novel chiral catalytic source containing the N–(C=NH)–O moiety, has been synthesized and successfully utilized, for the first time, as a chiral catalytic source in the borane-mediated asymmetric reduction of prochiral ketones in refluxing toluene, to provide the corresponding secondary alcohols with up to 93% enantiomeric excess.

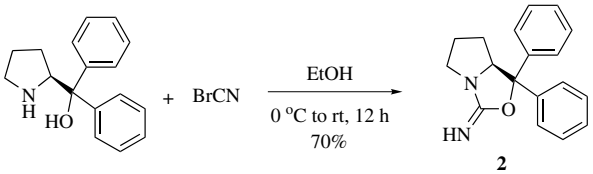
1. Introduction

Boron based chiral reducing agents/catalysts occupy a special place in the history of asymmetric reduction of prochiral ketones for providing secondary alcohols in high enantiomeric purities.[1–8] We have recently reported, for the first time, the application of chiral guanidine, (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane **1**, as a novel, in situ recyclable chiral catalytic source for the borane-mediated asymmetric reduction of prochiral α-halo ketones.[9] During this study, we have also noticed that this catalytic source has remarkable potential in directing the borane-mediated reduction of phenacyl bromide at high temperature (110 °C) (in refluxing toluene) providing (*S*)-2-bromo-1-phenylethanol in 83% ee, while at room temperature (30 °C) producing (*R*)-2-bromo-1-phenylethanol in 37% ee.[9] This remarkable temperature dependant reversal of stereoselectivity exhibited by compound **1**, containing the N–(C=NH)–N framework in the borane-mediated asymmetric reduction of phenacyl bromide, prompted us to examine whether similar closely related chiral catalytic source (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo-(3.3.0)octane **2**, with an N–(C=NH)–O moiety, would also exhibit such kind of temperature dependant reversal of stereoselectivity in similar reduction processes. In continuation of our studies[9–15] in the search of efficient and practical chiral catalysts, we herein report the synthesis and application of (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane **2**, which contains the N–(C=NH)–O moiety, as a novel chiral catalytic source for the borane-mediated asymmetric reduction of prochiral ketones in refluxing toluene, to provide the resulting secondary alcohols in up to 93% enantiomeric excess.



2. Results and discussion

The desired chiral catalyst, (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane **2** has been synthesized via the reaction of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine with cyanogen bromide according to Eq. 1. The structure of this compound was also established by single crystal X-ray data (Fig. 1).



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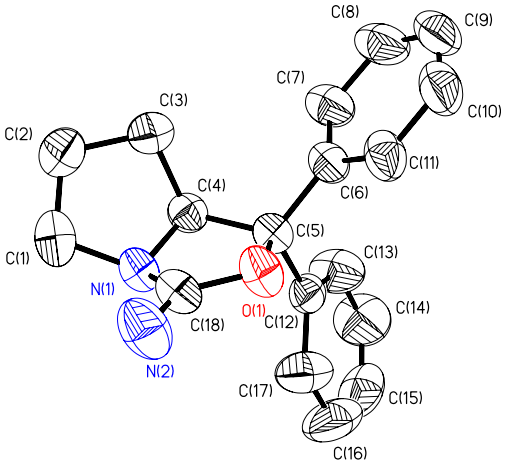


Figure 1. ORTEP diagram of **2** (hydrogen atoms were omitted for clarity).

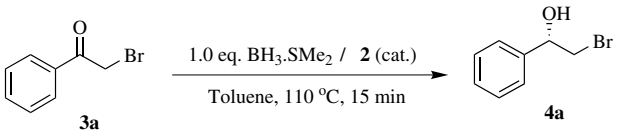
We then performed the asymmetric reduction of phenacyl bromide **3a** with varying catalytic amounts of (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane **2** with a view to understand the requirement of minimum amount of the catalyst for obtaining highest selectivity (Eq. 2, Table 1). The best results were obtained when phenacyl bromide **3a** was treated with $BH_3{\cdot}SMe_2$ under the influence of **2** (2 mol %) in refluxing toluene for 15 min, thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol **4a** in 85% yield with 92% enantiomeric excess (Table 1, entry 3).

With a view to examine the generality of this methodology, we have subjected representative prochiral α-halo ketones **3b–e** to the borane-mediated asymmetric reduction using this catalytic source. The resulting secondary alcohols **4b–e** were obtained in 88–93% enantiomeric excess (Eq. 3, Table 2).

Encouraged by these results and also with a view to examine the level of selectivity in the case of aryl alkyl ketones, we have extended this methodology for the borane-mediated asymmetric reduction of representative aryl alkyl ketones **3f–j**. The resulting secondary alcohols **4f–j** were obtained in 70–87% enantiomeric excess (Eq. 4, Table 3).

With a view to further understand the efficiency of this molecule **2** as a chiral catalytic source and also to examine the possible reversal of stereoselectivity at room temperature, we have carried out the borane-mediated asymmetric reduction of phenacyl bromide **3a** at room temperature under the influence of **2** (2 mol %). The resulting 2-bromo-1-phenylethanol was obtained in very low (5%) enantiomeric purity, interestingly, with an opposite configuration, that

Table 1. Standardization: asymmetric reduction of phenacyl bromide **3a** at 110 °C[a]

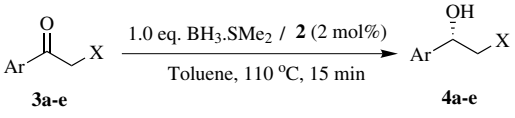


3a **4a** (2)

Entry	Catalyst **2** (mol %)	Yield[b] (%) **4a**	Enantiomeric excess[c] (%) **4a**	Configuration[d]
1	0.5	80	87	(*S*)
2	1	81	90	(*S*)
3	**2**	**85**	**92**	**(*S*)**
4	3	82	90	(*S*)
5	4	82	91	(*S*)
6	5	81	92	(*S*)
7	10	82	92	(*S*)
8	15	80	92	(*S*)

[a] All reactions were carried out on 1 mM scale of phenacyl bromide **3a** with $BH_3{\cdot}SMe_2$ (1 mM) in the presence of **2** 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] 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 of reported molecule.[16]

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



3a-e **4a-e** (3)

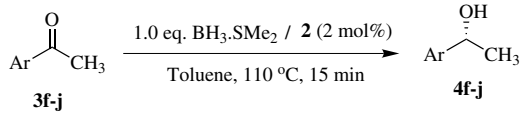
X = Br, Cl

Ar = Phenyl, 4-Bromophenyl, 4-Chlorophenyl, 4-Nitrophenyl

Substrate	Ar	X	Product	Yield[b] (%)	$[\alpha]_D^{25}$	Configuration[c]	ee (%)
3a	Phenyl	Br	**4a**	85	+40.1 (*c* 1.8, $CHCl_3$)	(*S*)[16]	92[d]
3b	Phenyl	Cl	**4b**	87	+44.7 (*c* 1.1, C_6H_{12})	(*S*)[16]	91[d]
3c	4-Bromophenyl	Br	**4c**	86	+31.9 (*c* 1.2, $CHCl_3$)	(*S*)[17]	92[e]
3d	4-Chlorophenyl	Br	**4d**	85	+39.3 (*c* 1.0, $CHCl_3$)	(*S*)[15]	93[e]
3e	4-Nitrophenyl	Br	**4e**	84	+32.3 (*c* 1.3, $CHCl_3$)	(*S*)[14]	88[f]

[a] All reactions were carried out on 1 mM scale of α-halo ketone with $BH_3{\cdot}SMe_2$ (1 mM) in the presence of **2** (2 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 specific rotation with that of the 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.

Table 3. Asymmetric reduction of aryl alkyl ketones[a]



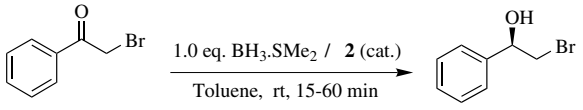
3f-j 4f-j (4)

Ar = Phenyl, 4-Methylphenyl, 4-Bromophenyl, 4-Chlorophenyl, 4-Nitrophenyl

Substrate	Ar	Product	Yield[b] (%)	$[\alpha]_D^{25}$	Configuration[c]	ee (%)
3f	Phenyl	**4f**	77	+35.5 (*c* 1.2, MeOH)	(*R*)[18]	80[d]
3g	4-Methylphenyl	**4g**	82	+29.2 (*c* 1.5, MeOH)	(*R*)[19]	70[e]
3h	4-Bromophenyl	**4h**	85	+27.5 (*c* 1.1, $CHCl_3$)	(*R*)[19]	73[e]
3i	4-Chlorophenyl	**4i**	84	+38.5 (*c* 1.3, Et_2O)	(*R*)[19]	78[e]
3j	4-Nitrophenyl	**4j**	82	+27.2 (*c* 1.2, EtOH)	(*R*)[20]	87[f]

[a] All reactions were carried out on 1 mM scale of aryl alkyl ketone with $BH_3{\cdot}SMe_2$ (1 mM) in the presence of **2** (2 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 specific rotation with that of the reported molecules.
[d] Determined by HPLC analysis 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.

Table 4. Asymmetric reduction of phenacyl bromide **3a** at room temperature[a]



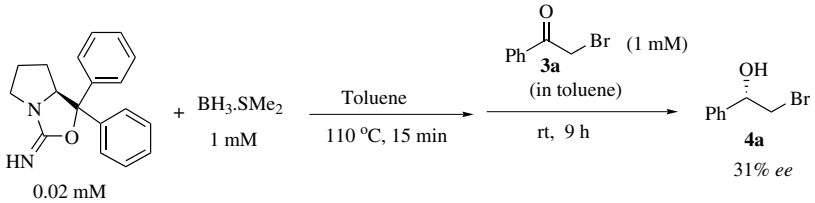
3a 4a (5)

Entry	Catalyst **2** (mol %)	Time (min)	Yield[b] (%)	Enantiomeric excess[c] (%) **4a**	Configuration[d]
1	2	60	86	5	(*R*)
2	5	15	81	7	(*R*)
3	10	15	82	5	(*R*)
4	15	15	80	4	(*R*)

[a] All reactions were carried out on 1 mM scale of phenacyl bromide **3a** with $BH_3{\cdot}SMe_2$ (1 mM) in the presence of **2** in toluene at room temperature.
[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] The absolute configuration was assigned by the comparison of the sign [(−) i.e., (levo rotatory)] of the specific rotation with that of reported molecule.[16] Also the intensities of enantiomeric (*R*) and (*S*) peaks in HPLC confirm the assignment of configuration.

is, an (*R*)-configuration (Eq. 5, Table 4). In order to improve the enantioselectivity, we performed the same reaction with varying amounts of the catalytic source. However the enantioselectivity remains almost the same (Table 4). Although the enantioselectivity is not that impressive, this result is still interesting in the sense that compound **2**, containing the N–(C=NH)–O moiety, shows a potential for exhibiting a temperature dependant reversal of stereoselectivity in borane-mediated reduction processes.

Next, we directed our studies to examine the potential of the chiral species, generated in situ by the reaction of **2** with $BH_3{\cdot}SMe_2$ in refluxing toluene, in asymmetric reductions at room temperature. Thus, we have treated compound **2** (2 mol %, 0.02 mM) with $BH_3{\cdot}SMe_2$ (1 mM) for 15 min in refluxing toluene and cooled to room temperature and performed the reduction of phenacyl bromide **3a** (1 mM) at room temperature to provide the corresponding 2-bromo-1-phenylethanol **4a** in 31% enantiomeric purity with an (*S*)-configuration (Scheme 1). This is an interesting result



Scheme 1.

as it clearly indicates that enantioselectivities are better at higher temperature (110 °C) than at room temperature probably due to better coordination of borane and ketone with the catalyst at high temperature than at room temperature. This result is, in fact, consistent with our earlier result with a chiral guanidine, that is, (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo(3.3.0)octane **1**.[9]

Since the level of reversal of stereoselectivity exhibited by catalyst/catalytic source **2** at room temperature in the borane-mediated reduction of phenacyl bromide **3a** is not impressive, we did not make any attempt towards understanding the nature of catalyst generated in situ by the reaction of **2** with $BH_3{\cdot}SMe_2$ in refluxing toluene.

3. Conclusion

We have developed a novel chiral catalytic source (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane **2**, containing an N–(C═NH)–O moiety for the borane-mediated asymmetric reduction of prochiral ketones, which provides the corresponding secondary alcohols with up to 93% enantiomeric purity. Although this chiral source **2** provides inferior (negligible) enantioselectivities at room temperature when compared to our earlier catalyst, chiral guanidine **1**,[9] with respect to the reversal of stereoselectivity, it does give clear indication that an appropriate chiral catalytic source containing the N–(C═NH)–O moiety might provide high levels of temperature dependant stereodirectionality thus leading to the production of both the enantiomers in high enantioselectivities in the borane-mediated reduction of prochiral ketones. Work is currently in progress towards the development of such a suitable chiral catalytic source.

4. Experimental

4.1. Synthesis of (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane 2

This molecule was prepared following the literature procedure for the preparation of guanidines via the reaction of diamines with cyanogen bromide, with some modification.[21] To a stirred solution of (*S*)-2-(diphenylhydroxymethyl)pyrrolidine (8 mM, 2.02 g) in EtOH (18 mL) was carefully added a solution of cyanogen bromide (16 mM, 1.694 g) in EtOH (2 mL) at 0 °C. After stirring the reaction mixture for 12 h at room temperature, it was heated at 100 °C (about 2 h) to completely remove the boiling solvents. The residue thus obtained was diluted with EtOH (16 mL) and 1 M NaOH (16 mL) and was extracted with CH_2Cl_2 (3×30 mL). The combined organic layer was dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the residue thus obtained, crystallized (hexanes–EtOAc = 9:1) to provide the desired (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane **2** in 70% (1.56 g) yield. MP: 94–96 °C; $[\alpha]_D^{25} = -221.9$ (*c* 1.14, $CHCl_3$); IR (KBr): 3341, 1676 cm^{-1}; ^1H NMR (400 MHz/$CDCl_3$): δ 1.04–1.16 (m, 1H), 1.58–1.69 (m, 1H), 1.74–1.96 (m, 2H), 3.23–3.34 (m, 1H), 3.57–3.68 (m, 1H), 4.48 (dd, 1H, $J = 5.6$ Hz and 10.4 Hz), 5.12 (br s, 1H), 7.21–7.37 (m, 8H), 7.45–7.51 (m, 2H); ^{13}C NMR (50 MHz/$CDCl_3$): δ 25.35, 28.82, 48.52, 70.93, 87.26, 125.66, 126.07, 127.48, 128.06, 128.13, 128.40, 140.70, 143.61, 163.89; LC–MS (*m*/*z*): 279 $(M+H)^+$; Anal. Calcd for $C_{18}H_{18}N_2O$: C, 77.67; H, 6.52; N, 10.06. Found: C, 77.89; H, 6.53; N, 10.05. Crystal data: Empirical formula, $C_{18}H_{18}N_2O$; formula weight, 278.34; colorless, rectangular crystal; crystal dimensions, $0.35 \times 0.30 \times 0.28$ mm^3; orthorhombic, lattice type, primitive; $a = 8.5608(5)$ Å, $b = 10.1884(6)$ Å, $c = 16.9703(10)$ Å; $\alpha = 90.00$; $\beta = 90.00$; $\gamma = 90.00$; $V = 1480.16(15)$ $Å^3$; space group, $P2_12_12_1$ (International Table No. 19); $Z = 4$; $D_{calcd} = 1.249$ g/cm^3; $F_{000} = 592$; $\lambda(Mo\,K_\alpha) = 0.71073$ Å; $R(I \geqslant 2\sigma_1) = 0.0549$; $wR^2 = 0.1275$. Detailed X-ray crystallographic data is available from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK (CCDC No. 635393).

4.2. Asymmetric reduction of phenacyl bromide 3a: synthesis of (*S*)-2-bromo-1-phenylethanol 4a: representative procedure

To a stirred solution of (5*S*)-1-aza-2-imino-3-oxa-4,4-diphenylbicyclo(3.3.0)octane **2** (0.02 mM, 0.4 mL, 0.05 M solution in toluene) in toluene (4 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 reflux for 15 min. A solution of phenacyl bromide **3a** (1 mM, 199 mg), in toluene (2 mL), was added slowly drop-wise and heated at reflux for a further 15 min. The reaction mixture was cooled to room temperature and quenched with MeOH. The solvent was removed under a reduced pressure and the residue thus obtained, purified by column chromatography (silica gel, 5% ethyl acetate in hexanes) to provide the desired (*S*)-2-bromo-1-phenylethanol **4a** in 85% (171 mg) yield as a colorless oil.

All alcohols **4a**–**j** are known in the literature.[12–20] In fact, we have also prepared alcohols **4a**–**i** and reported their spectral data.[12,13,15] The present spectral data (IR, ^1H and ^{13}C NMR) of **4a**–**i** are in agreement with the earlier data. The spectral data (IR, ^1H and ^{13}C NMR) of **4j** is reported in the literature[20] and our data is in agreement with the reported data.

Acknowledgments

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