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Tetrahedron: Asymmetry
Tetrahedron: *Asymmetry* 17 (2006) 1041–1044

(2*S*)-2-Anilinomethylpyrrolidine: an efficient in situ recyclable chiral catalytic source for the borane-mediated asymmetric reduction of prochiral ketones in refluxing toluene

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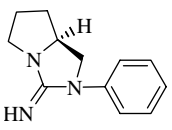
Received 16 March 2006; accepted 23 March 2006
Available online 27 April 2006

Abstract—(2*S*)-2-Anilinomethylpyrrolidine was successfully utilized as a chiral catalytic source in the borane-mediated asymmetric reduction of prochiral ketones in refluxing toluene to provide the corresponding secondary alcohols with enantiomeric excesses up to 91%. The potential of (2*S*)-2-anilinomethylpyrrolidine as an in situ recyclable chiral catalytic source in the borane-mediated chiral reduction processes has also been demonstrated.

1. Introduction

In the preceding paper, we described the application of (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo[3.3.0]octane **1** as the first example of guanidine based chiral catalytic source for the borane-mediated asymmetric reduction of representative prochiral ketones.[1] In continuation of our studies[2–6] in the search for suitable, practical and recyclable chiral catalysts for the borane-mediated asymmetric reduction processes, we herein report (2*S*)-2-anilinomethylpyrrolidine **2** as an efficient in situ recyclable chiral catalytic source for the asymmetric reduction of prochiral ketones in refluxing toluene, thus providing the desired secondary alcohols in high enantioselectivities.



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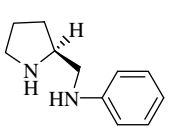

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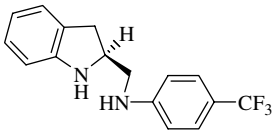

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2. Results and discussion

During our work on the borane-mediated asymmetric reduction of representative prochiral ketones using the chiral guanidine, that is, (5*S*)-1,3-diaza-2-imino-3-phenylbicyclo[3.3.0]octane **1** built on the (2*S*)-2-anilinomethylpyrrolidine **2** framework, as an in situ recyclable catalytic source, we observed a remarkable reversal of stereoselectivity from room temperature (≈30 °C) to high temperature (110 °C), probably due to two different catalytic species actually involved in the transition state of the reduction process. We also observed interesting temperature dependent levels of stereoselectivity from the same catalytic species due to the different pathways involved in the reduction process.[1] This temperature dependent direction and levels of stereoselectivity have attracted our attention, and based on this fact it occurred to us that (2*S*)-2-anilinomethylpyrrolidine[7] itself might offer promising enantioselectivities at higher temperature, that is, at 110 °C in toluene. Asami et al.[8,9] reported during their elegant work on the applications of various chiral diamines as possible catalysts for the borane- mediated asymmetric reduction of prochiral keotnes that chiral diamine **3**, as a catalyst, provides high enantioselectivities in the reduction of prochiral ketones at room temperature and at low temperatures (up-to −15 °C) (they studied up-to −30 °C), while catalyst **2** provides inferior selectivities (14% ee) at room temperature in the reduction of acetophenone. However, to the best of our knowledge, they did not examine the effect of high temperature on the enantioselectivity using those chiral diamines, and also there is no report in the literature in this regard.

Accordingly, we have performed the reduction of phenacyl bromide **4a** using 5 mol % (2*S*)-2-anilinomethylpyrrolidine

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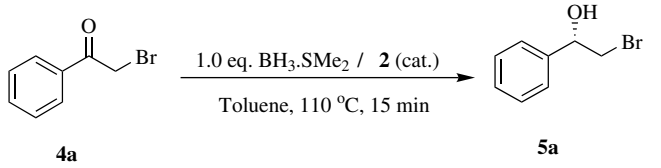
doi:10.1016/j.tetasy.2006.03.021

in the presence of $BH_3{\cdot}SMe_2$ at 110 °C. The reduction went to completion within 15 min, and more interestingly the desired secondary alcohol **5a** was obtained in 91% enantiomeric excess. As a result, we thought it would be appropriate to investigate the minimum levels of the catalyst required for the reduction process to achieve maximum possible induction. We, therefore, performed the reduction of phenacyl bromide using different quantities of catalyst (from 0.25 to 10 mol %), and noticed that 2 mol % catalyst also offers almost the same selectivity as that of 3, 4, 5 and 10 mol % catalyst (Eq. 1, Table 1).[10]

Table 1. Asymmetric reduction of phenacyl bromide with different quantities of the catalyst[a]



4a **5a** (1)

Entry	Catalyst **2** (mol %)	Yield[b] (%) **5a**	Enantiomeric excess[c] (%) **5a**	Configuration[d]
1	0.25	82	69	*S*
2	0.5	80	86	*S*
3	1	82	86	*S*
4	**2**	**82**	**91**	***S***
5	3	80	90	*S*
6	4	78	91	*S*
7	5	79	91	*S*
8	10	82	89	*S*

[a] All reactions were carried out on 1 mM scale of phenacyl bromide with 1 mM of $BH_3{\cdot}SMe_2$ in the presence of **2** 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.
[d] Absolute configuration was assigned by comparison of the sign of the specific rotation with that reported.[11]

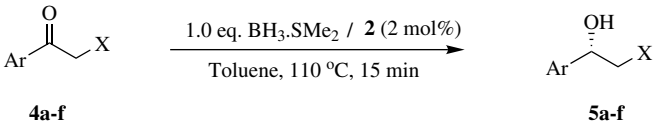
In order to understand the generality of this methodology, we have then carried out the reduction of representative prochiral α-halo ketones **4b–f** using 2 mol % catalyst to provide the resulting secondary alcohols **5b–f** in 84–90% enantiomeric excesses (Eq. 2, Table 2).

With a view to extend the scope of the application of this catalyst, we have also examined the reduction of representative class of aryl alkyl ketones **4g–k** using 2 mol % (2*S*)-2-anilinomethylpyrrolidine **2**. The resulting secondary alcohols **5g–k** were obtained in 74–78% enantiomeric excesses (Eq. 3, Table 3).

2.1. Towards understanding the nature of the catalytic species

In order to understand the effect of temperature on the enantioselectivity, we examined the efficiency of this diamine **2** (2 mol %) as a chiral source in the asymmetric reduction of phenacyl bromide **4a** with $BH_3{\cdot}SMe_2$ at room temperature (≈30 °C) for 7 h and obtained the resulting secondary alcohol **5a** in 8% enantiomeric excess. In an attempt to understand the nature of the catalyst/catalytic species generated in situ, we carried out the reaction between **2** (0.2 mM, 4 mL, 0.05 M solution in toluene) and $BH_3{\cdot}SMe_2$ (10 mM, 10 mL, 1 M solution in toluene) in refluxing toluene (40 mL) for 15 min (in the ratio of 1:50 as in the case of reaction conditions), and recorded the ^{11}B NMR spectrum of this crude mixture (after removal of excess $BH_3{\cdot}SMe_2$ and toluene under vacuum) and observed a broad peak at δ 33.2 ppm[16] [in addition to other peaks between δ −10 and −30 ppm, arising most likely due to tetra-coordinated boron species (ate-complexes)]. This probably indicates the presence of diazaborolidine moiety in the catalyst/catalytic species. However, we did

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



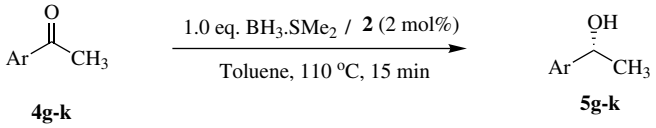
4a-f **5a-f** (2)

X = Cl, Br
Ar = phenyl, 4-methylphenyl, 4-bromophenyl, 4-chlorophenyl, 4-nitrophenyl

Substrate	Ar	X	Product	Yield[b] (%)	$[\alpha]_D^{25}$	Conf.[c]	ee (%)
4a	Phenyl	Br	**5a**	82	+39.8 (*c* 1.2, $CHCl_3$)	*S*[11]	91[d]
4b	Phenyl	Cl	**5b**	80	+43.8 (*c* 1.0, C_6H_{12})	*S*[11]	87[d]
4c	4-Methylphenyl	Cl	**5c**	88	+43.1 (*c* 0.8, $CHCl_3$)	*S*[6]	84[d]
4d	4-Bromophenyl	Br	**5d**	85	+30.5 (*c* 1.0, $CHCl_3$)	*S*[12]	90[e]
4e	4-Chlorophenyl	Br	**5e**	83	+38.9 (*c* 0.9, $CHCl_3$)	*S*[6]	90[e]
4f	4-Nitrophenyl	Br	**5f**	84	+29.9 (*c* 0.8, $CHCl_3$)	*S*[5]	86[f]

[a] All reactions were carried out on 1 mM scale of α-halo ketone with 1 mM of $BH_3{\cdot}SMe_2$ 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 reported.
[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]



4g-k **5g-k** (3)

Ar = phenyl, 4-methylphenyl, 4-bromophenyl, 4-chlorophenyl, 4-nitrophenyl

Substrate	Ar	Product	Yield[b] (%)	$[\alpha]_D^{25}$	Conf.[c]	ee (%)
4g	Phenyl	**5g**	79	+35.2 (*c* 0.9, MeOH)	*R*[13]	76[d]
4h	4-Methylphenyl	**5h**	79	+33.1 (*c* 0.7, MeOH)	*R*[14]	74[e]
4i	4-Bromophenyl	**5i**	87	+30.6 (*c* 1.0, $CHCl_3$)	*R*[14]	78[e]
4j	4-Chlorophenyl	**5j**	78	+37.5 (*c* 0.7, Et_2O)	*R*[14]	77[e]
4k	4-Nitrophenyl	**5k**	83	+22.2 (*c* 0.5, EtOH)	*R*[15]	78[f]

[a] All reactions were carried out on 1 mM scale of aryl alkyl ketone with 1 mM of $BH_3{\cdot}SMe_2$ 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 reported.
[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.

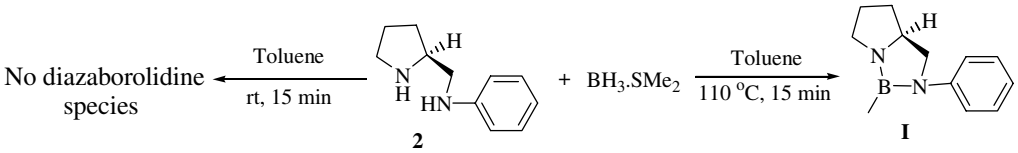
not observe any peak in the region δ 20–40 ppm [but contains peaks between δ −10 and −30 ppm, probably due to tetra-coordinated boron species (ate-complexes), that is, due to complexation of borane with diamine] in the ^{11}B NMR spectrum of the crude compound, when a similar reaction was carried out at room temperature (≈30 °C) (Scheme 1). These results suggest the formation of diazaborolidine species at 110 °C, while such a species is not formed at room temperature.

In order to understand the potential of the diazaborolidine species as a catalyst at room temperature, we performed the asymmetric reduction of phenacyl bromide under the influence of catalytic species **I** (2 mol %) (generated in situ by the reaction of diamine **2** with $BH_3{\cdot}SMe_2$ at reflux temperature and cooling back to room temperature) at room temperature for 6 h and obtained the resulting (*S*)-2-bromo-1-phenylethanol with 33% ee (Scheme 2).

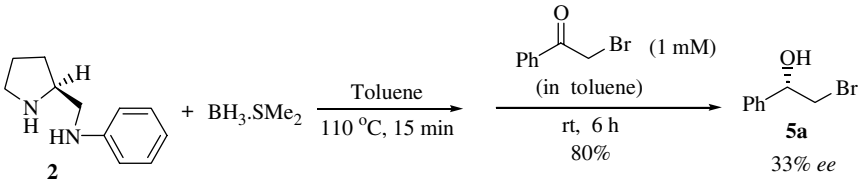
These results possibly suggest that different pathways of reduction processes may be operating at high temperature (110 °C) and at room temperature with the same catalytic species. We are now, in fact, in the process of understanding these aspects.

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

With a view to understand the in situ recyclable nature of the catalytic species **I**, we have first performed the reduction of phenacyl bromide (1 mM scale) in the usual way at 110 °C (run 1). To this reaction flask (without work-up), $BH_3{\cdot}SMe_2$ (1 mM) (for run 2) was added and heated at 110 °C for 15 min, and then a solution of phenacyl bromide (1 mM) in toluene was slowly added dropwise 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 examined the recyclable ability of this catalyst for two more times (total four times) and noticed that the enantioselectivity remained almost the same (Table 4).



Scheme 1.



Scheme 2.

Table 4. Recyclable ability of catalyst **I** in the asymmetric reduction of phenacyl bromide **4a**

Number of runs	Enantiomeric purity (%)[a] **5a**
1	91
2	89
3	88
4	88

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

In order to examine (rule out) the possible auto-catalytic potential of the alkoxyborane, generated in the reaction medium, in inducing the chirality in the asymmetric reduction of phenacyl bromide, we have conducted the reduction of phenacyl bromide with $BH_3{\cdot}SMe_2$ (1 equiv and also with 2 equiv) under the influence of (*S*)-2-bromo-1-phenylethanol (1 equiv, 84% ee) (for 30 and 15 min, respectively). In both cases, we obtained (*S*)-2-bromo-1-phenylethanol in 42% enantiomeric purity (i.e., enantiomeric purity of the alcohol obtained by the reduction is ≈0%). These experiments clearly indicate that there is no auto-catalysis, and (*S*)-2-bromo-1-phenylethanol (as boron species) has no role in the chiral induction process. Thus, these experiments clearly demonstrate the recyclable potential of the diamine as the chiral catalytic source in the asymmetric reduction processes.

3. Conclusion

In conclusion, we have developed a simple, convenient and practical methodology for the borane-mediated asymmetric reduction of prochiral ketones employing (2*S*)-2-anilinomethylpyrrolidine **2** as an efficient in situ recyclable chiral catalytic source in refluxing toluene, thus providing the secondary alcohols with high enantiomeric purities. Although our methodology did not provide 100% enantioselectivities, this study has shown the hidden potential of chiral diamines in directing the enantioselective processes in the borane-mediated asymmetric reduction of prochiral ketones at high temperature, and also emphasizes the need for the design of appropriate chiral diamines for achieving 100% enantioselectivities. Work towards the design of different chiral diamines in achieving complete enantioselectivities is currently underway in our laboratory.

Acknowledgements

We thank CSIR (New Delhi), for funding this project. We thank the UGC (New Delhi), for recognizing our University of Hyderabad as 'University with Potential for Excellence (UPE)' and also recognizing the School of Chemistry as a 'Center for Advanced Studies in Chemistry' and providing some instrumental facilities. K.V.R. and B.S.R. thank CSIR (New Delhi), for their research fellowships.

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