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TETRAHEDRON: *ASYMMETRY*

(2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo[3.3.0]octane: a novel chiral source for borane-mediated catalytic chiral reductions†

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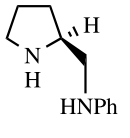
Abstract—(2*S*,5*S*)-1,3-Diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo[3.3.0]octane has been successfully employed as a chiral catalytic source for the borane mediated asymmetric reductions of prochiral α-halo ketones to provide the desired (*S*)-secondary alcohols in 81–91% enantiomeric purities, thus for the first time demonstrating the potential of the *N-P(=O)Cl* structural framework to generate a recoverable, reusable and air stable catalyst for the asymmetric reduction processes.

Brown's outstanding contributions to chiral borane chemistry and Corey's elegant utilization of oxazaborolidines as chemzymes for the asymmetric reduction of prochiral ketones to afford secondary alcohols with high enantiomeric purities have indeed provided a new outlook and direction to synthetic processes in chiral chemistry, particularly in chiral reduction methodologies.[1–7] Recently Wills et al. have introduced an ingenious class of novel chiral catalysts containing the *N-P=O* structural framework for borane-mediated asymmetric reduction of prochiral ketones.[8–14] Very recently we have demonstrated the application of 1,4-bis[(5*S*)-1,3-diaza-2-phospha-2-oxo-3-phenylbicyclo-[3.3.0]octan-2-yl]piperazine **2** (derived from the chiral diamine, (*S*)-2-anilinomethylpyrrolidine, **1**) containing the *N-P=O* structural framework, as a catalyst for the borane-mediated asymmetric reduction of prochiral α-halo ketones.[15] This methodology requires 30 mol% catalyst for reduction of prochiral α-halo ketones to afford the resulting (*S*)-configured 2-halo-1-arylethanols with high enantiomeric purities. We felt that a loading of 30 mol% catalyst was too large an amount, rendering the methodology expensive. Thus, we decided to develop new frameworks and/or molecules able to catalyze the reaction even when used in very small amounts. We also felt that it would be highly useful if such molecules could be easily accessible in large amounts. A literature survey revealed that (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo[3.3.0]-octane **3**, which is readily available in large quantities,[16] has not been examined for catalytic chiral reduction processes. We envisaged that **3**, containing the *N-P(=O)Cl* framework, might offer promise as a catalytic chiral source for borane-mediated catalytic chiral reductions. To this end, we now report the borane-mediated reduction of prochiral α-halo ketones in the presence of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo-(3.3.0)octane **3** (5 mol%) to provide the resulting (*S*)-secondary alcohols with high enantiomeric purities.



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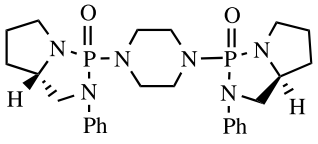

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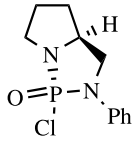

3

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† Dedicated to Professor Herbert C. Brown, an outstanding organic chemist, on the occasion of his 90th birthday.

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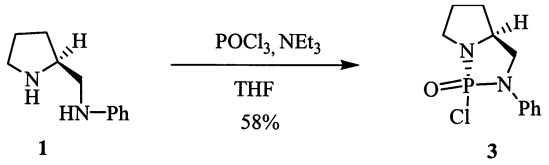
The required catalyst (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo[3.3.0]octane **3** was synthesized according to the procedure reported by Fiaud and co-workers via the reaction of (*S*)-2-anilinomethylpyrrolidine **1** (obtained from inexpensive and commercially available (*S*)-glutamic acid following the literature procedure[17,18]) with $POCl_3/NEt_3$ in THF (Eq. (1)).[16,19]

(1)

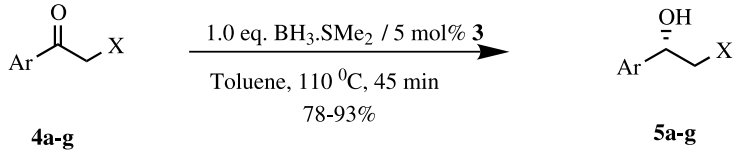


1 **3**

We first examined the borane-mediated asymmetric reduction of phenacyl bromide in the presence of varying amounts of catalyst **3**. The best results were obtained when phenacyl bromide **4a** (1 mmol) was treated with borane–dimethyl sulfide (1 mmol) under the influence of **3** (5 mol%, 12.8 mg) in refluxing toluene for 45 min, thus providing the desired alcohol (*S*)-2-bromo-1-phenylethanol **5a** in 89% yield with enantiomeric purity of 87% (after usual work-up and purification by column chromatography).[15] This was indeed a very encouraging result. We then extended the same reaction to a representative class of prochiral α-halo ketones (aryl halomethyl ketones) **4b–g** to provide the resulting secondary alcohols **5b–g** with high enantiomeric purities (81–91%) (Eq. (2), Table 1). The enantiomeric purities of the chiral alcohols **5a–d** were determined by HPLC analysis using a Chiralcel-OD chiral column with reference to the corresponding racemic alcohols. The enantiomeric purities of alcohols **5e–g** were determined by ^1H NMR spectral analysis of their acetate derivatives in the presence of the chiral shift reagent, $Eu(hfc)_3$, with reference to their corresponding racemic acetates.

In order to understand the nature of the catalyst we treated the molecule **3** (0.2 mmol, 51.4 mg) with $BH_3{\cdot}SMe_2$ (0.3 mmol, 1.5 equiv.) in toluene for 10 min under reflux (Eq. (3)). The excess borane was destroyed by addition of methanol and the resulting solid was filtered, washed with ether and dried under reduced pressure to provide a light yellow solid **A** (41 mg).[22] We have carried out the reductions of phenacyl bromide **4a** (1 mmol) and phenacyl chloride **4b** (1 mmol) in the presence of catalytic amounts of this solid **A** (12.8 mg) to provide the resulting secondary alcohols **5a** and **5b** with enantiomeric purities of 82 and 81%, respectively (determined by HPLC analysis using the chiral column, Chiralcel-OD) (Eq. (4)). With a view to recovering and reusing the chiral source we carried out the reduction of phenacyl bromide on 4 mmol scale with borane–dimethyl sulfide in the presence of **3** (5 mol%, 51.4 mg) and recovered the chiral source (40 mg) as a solid **B**.[23] With a view to understanding reusability of the recovered chiral source **B** we performed the reductions of phenacyl bromide **4a** (1 mmol) and phenacyl chloride **4b** (1 mmol) with borane–dimethyl sulfide in the presence of catalytic amounts of the recovered chiral source **B** (12.8 mg). The resulting secondary alcohols **5a** and **5b** were obtained in enantiomeric purities of 85 and 78%, respectively (determined by HPLC analysis using a Chiralcel-OD chiral column) (Eq. (4)). These results clearly indicate that the solids **A** and **B** have almost the same chiral directing efficiency as the original chiral source i.e. molecule **3**. Both the prepared (**A**) and

Table 1. Asymmetric reduction of α-halo ketones[a]



4a-g **5a-g**

X = Br, Cl

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

81-91% ee

(2)

Substrate	Ar	X	Product	Yield (%)[b]	$[\alpha]_D^{25}$	Conf.[c]	E.e (%)[d]
4a	Phenyl	Br	**5a**	89	+39.0 (*c* 1.0, $CHCl_3$)	*S*[21]	87
4b	Phenyl	Cl	**5b**	93	+40.0 (*c* 1.0, cyclohexane)	S[21]	81
4c	4-Methylphenyl	Br	**5c**	87	+37.5 (*c* 1.0, $CHCl_3$)	*S*[15]	83
4d	4-Methylphenyl	Cl	**5d**	91	+42.0 (*c* 1.0, $CHCl_3$)	*S*[15]	82
4e	4-Bromophenyl	Br	**5e**	88	+30.7 (*c* 2.4, $CHCl_3$)	*S*[20]	86[e]
4f	4-Chlorophenyl	Br	**5f**	80	+37.9 (*c* 1.2, $CHCl_3$)	*S*[15]	88[e]
4g	4-Nitrophenyl	Br	**5g**	78	+32 (*c* 1.0, $CHCl_3$)	*S*[f]	91[e]

[a] All reactions were carried out on 1 mmol scale with respect to α-halo ketone with $BH_3{\cdot}SMe_2$ (1 mmol) in the presence of **3** (5 mol%) in toluene for 45 min at 110°C.

[b] Yields of pure alcohol after purification by column chromatography (silica gel, 5% ethyl acetate in hexanes).

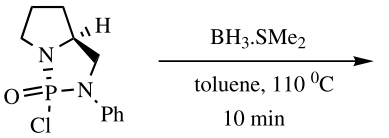
[c] Absolute configuration was assigned by comparison of the sign of the specific rotation with that of reported molecules.[15,20,21]

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

[e] Enantiomeric purities were determined by ^1H NMR (200 MHz) spectral analysis of the acetates in the presence of the chiral shift reagent, $Eu(hfc)_3$, with reference to the corresponding racemic acetates.

[f] Absolute configuration was tentatively assigned by analogy with **5a–f**.

recovered (**B**) catalysts are air stable, recoverable and reusable. A comparison of ^{1}H and ^{13}C NMR spectral studies of the original chiral source **3** with that of **A** and **B** clearly indicates that they may have similar structural organization (the chiral diamine moiety is intact).[19,22] The IR, ^{1}H, ^{13}C and ^{31}P NMR spectral studies of **A** and **B** indicate that these solids may have the same structure (while determining the melting points we also found that both **A** and **B** decompose at 126–129°C).[22]

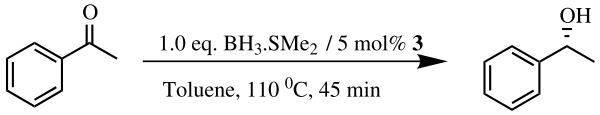


(3)

3

The most striking difference between the chiral source **3** and the solids **A** and **B** is their solubility profile (the solids **A** and **B** are insoluble in most organic solvents including hexanes, ether, chloroform, dichloromethane, ethyl acetate, THF, methanol and water, while the original chiral source **3** is soluble in ether, chloroform and dichloromethane etc.). In both cases (solids **A** and **B**), the ^{11}B NMR spectrum shows a very weak broad signal at δ 2.80 indicating that the actual catalyst (solids **A** or **B**), may not contain any boron species. This weak signal may be attributed to the presence of minor amounts of some boron species in the actual catalysts (**A** or **B**). On the basis of these preliminary studies, we assume that the catalyst (**A** or **B**) may not be monomeric in nature.

It is worth mentioning here the interesting work of Asami and co-workers[24] who reported the use of chiral β-diamines as catalysts for borane-mediated chiral reductions of prochiral ketones. During this study they reported that the reduction of acetophenone with BH_3·THF in the presence of (*S*)-2-anilinomethylpyrrolidine **1** (10 mol%) provided the desired secondary alcohol in 14% enantiomeric purity. With a view to understanding the mechanism and examining other applications of the *NP(=O)Cl* framework we performed the borane-mediated reduction of acetophenone in the presence of (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo(3.3.0)octane **3** (5 mol%). The requisite secondary alcohol was obtained with enantiomeric purity of 62% [(determined by HPLC analysis using a Chiralcel-OD chiral column) $[\alpha]_D^{25}$ +27.5 (*c* 0.4, MeOH) [lit.[25] $[\alpha]_D^{25}$ +37.7 (*c* 3.81, MeOH) (*R*)-configuration 84% e.e.] (Eq. (5)). This experiment demonstrates that the diazaborolidine is not generated in our reaction and also indicates that the *NP(=O)N* framework has a considerable effect on the stereodirection in comparison with that of the chiral diamine **1**.



(5)

62% ee

In conclusion, we have successfully carried out the borane-mediated asymmetric reduction of prochiral α-halo ketones using (2*S*,5*S*)-1,3-diaza-2-phospha-2-oxo-2-chloro-3-phenylbicyclo[3.3.0]octane **3** as a chiral catalytic source. Although the exact structure of the catalyst is not known at the moment, this work demonstrates for the first time, the potential of *N-P(=O)Cl* framework as a chiral source to generate a recoverable, reusable and air stable catalyst for the borane-mediated enantioselective reduction processes. Further work in the development of new chiral molecules based on the *N-P(=O)Cl* framework with a view to understanding the actual structure of the catalyst and the mechanism of this catalytic reduction process is now in progress in our laboratory.

Acknowledgements

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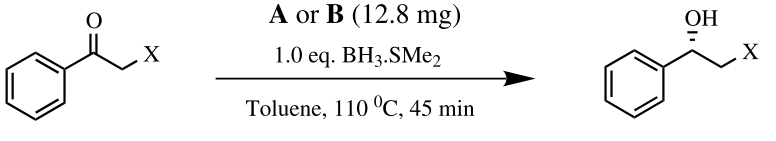

	Enantiomeric purity with **A**	with **B**
X=Br	*82%*	*85%*
X=Cl	*81%*	*78%*

(4)

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19. Spectral data for the chiral source **3**: mp: 138–140°C [lit.[16] 135°C]; $[\alpha]_D^{25}$ +127.2 (*c* 2.1, $CHCl_3$); ^1H NMR (200 MHz) ($CDCl_3$): δ 1.51–1.79 (m, 1H), 1.92–2.25 (m, 3H), 3.08–4.28 (m, 5H), 7.01–7.42 (m, 5H); ^{13}C NMR (50 MHz) ($CDCl_3$): δ 27.03 (d, $J=4.15$ Hz), 30.98, 44.73, 50.75 (d, $J=18.6$ Hz), 58.58 (d, $J=9.45$ Hz), 117.85 (d, $J=3.95$ Hz), 123.22, 129.16, 140.01 (d, $J=4.95$ Hz); ^{31}P NMR (81 MHz): δ 18.47 ($CDCl_3$); 20.88 (DMSO-d_6); MS (*m*/*z*): 257 (M^+).
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22. Spectral data for catalyst **A**: mp: 126–129°C (dec.); ^1H NMR (200 MHz) (DMSO-d_6): δ 1.52–2.22 [m, (4×*n*)H], 3.01–3.94 [m, (5×*n*)H], 6.52–6.73 [m, (3×*n*)H], 7.07–7.23 [m, (2×*n*)H] [(*n* can be 1 or any integer greater than 1) the proton count has been written as (×*n*) as the exact structure is not known]; ^{13}C NMR (50 MHz) (DMSO-d_6): δ 23.02, 27.66, 43.99, 44.52, 58.41, 112.56, 116.71, 129.10, 148.03; ^{31}P NMR (81 MHz) (DMSO-d_6): δ 0.01, 2.37. We have also recorded the ^{11}B NMR (64 MHz) spectrum (DMSO-d_6), which showed a very weak broad signal at δ 2.80. The solid **B** has similar spectral and physical data.
23. To recover the chiral source **B**: the reaction mixture was quenched with excess methanol (to destroy the excess borane). The solvent was evaporated and the residue was diluted with ether. The solid thus obtained was collected by filtration, washed with ether and dried under reduced pressure.
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