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Chiral ferrocenyl amino alcohols as catalysts for the enantioselective borane reduction of ketones

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Abstract—The catalytic asymmetric borane reduction of prochiral ketones was examined in the presence of chiral oxazaborolidine catalysts prepared in situ from chiral ferrocenyl amino alcohols. The corresponding chiral secondary amino alcohols were obtained with modest to high enantiomeric excesses (up to 90%) using (1*S*,2*S*)-2-amino-1-ferrocenyl-3,3-dimethyl-1-butanol **5c**.

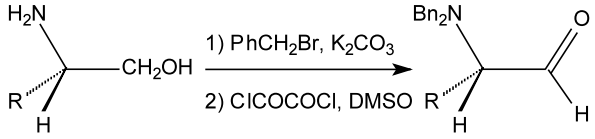
1. Introduction

Enantiomerically pure secondary alcohols are important intermediates for various other functionalities such as halides, amines, esters, and ethers. Hence, the asymmetric synthesis of enantiomerically enriched secondary alcohols has been extensively studied. Among the variety of asymmetric reactions leading to enantiomerically pure alcohols, the enantioselective reduction of prochiral ketones with borane in presence of a chiral ligand has received considerable attention.[1] Following on from the original work of Itsuno[2] and Corey,[3] a great number of studies have been reported over the last decade and many new compounds, derived from naturally occurring and unnatural starting materials, have been prepared in order to find more effective and economically attractive catalysts.[4] However, to our knowledge, the use of ferrocenyl amino alcohols in the reduction of ketones has not been reported so far. Thus, it should be of interest to investigate the catalytic ability of such ligands. We have an ongoing interest in the synthesis and application of chiral ferrocenyl amino alcohols in enantioselective alkylation of aldehydes by diethylzinc[5] and we thought to evaluate the effect resulting from the introduction of a ferrocenyl moiety onto the catalysts. In this communication, we report the synthesis of enantiomerically pure ferrocenyl amino alcohols and their application as ligands in the reduction of ketones by borane.

2. Results and discussion

The amino aldehydes **2a**–**c** were obtained in two steps. The amino functions of natural L-alaninol **1a**, L-valinol **1b** and L-*tert*-leucinol **1c** were first protected with two benzyl groups and the resulting *N*,*N*-dibenzylamino alcohols were transformed into the amino aldehydes by Swern oxidation. Compounds **2a**–**c** were isolated in 97, 83, and 78% isolated overall yields, respectively (Scheme 1).

Ferrocenyllithium, prepared by reaction of *t*-BuLi with ferrocene in THF at −78°C, was added to the amino aldehydes **2a**–**c** providing a mixture of diastereomeric compounds **3a**/**4a**, **3b**/**4b** and **3c**/**4c** in 61, 51 and 50% overall yield, respectively (Scheme 2). In agreement with the literature,[6] the 'erythro' isomer was the major amino alcohol obtained: **3a**/**4a**: 92/8, **3b**/**4b**: 91/9. The diastereomeric ratios were determined by HPLC analysis of the crude isolated product and the diastereomers were separated by silica gel column chromatography. The coupling constant values $J_{1,2}$ (Scheme 2) allowed to



1a R = CH_3 **2a**
1b R = $CH(CH_3)_2$ **2b**
1c R = $C(CH_3)_3$ **2c**

Scheme 1.

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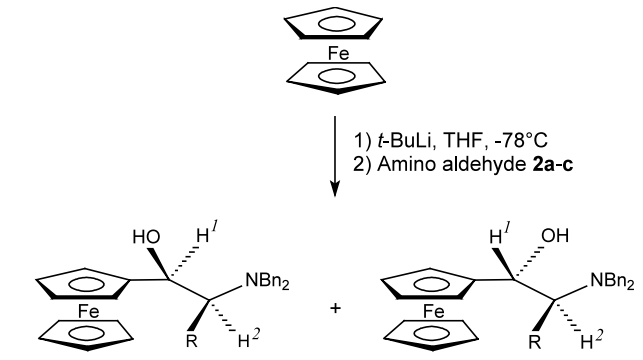


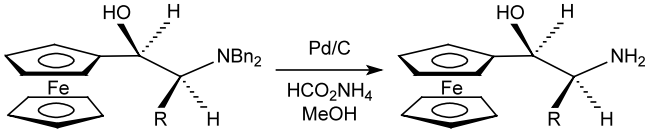
$R = CH_3$	**3a**	**4a**
$R = CH(CH_3)_2$	**3b**	**4b**
$R = C(CH_3)_3$	**3c**	**4c**

Scheme 2.

establish unambiguously the stereochemistry of the diastereomers (**3a**: $J_{1,2}=6$ Hz, **4a**: $J_{1,2}=9.5$ Hz, **3b**: $J_{1,2}=5$ Hz, **4b**: $J_{1,2}=8.5$ Hz). The determination of the ratio of diastereomers **3c**/**4c** was not possible because of the instability of the products and the absence of separation by column chromatography and HPLC analysis. Thus, the crude product was used in the next step without purification and separation.

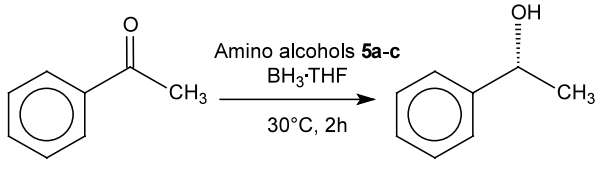
The primary amino alcohols were obtained by deprotection of the amino function. Thus, the two benzyl groups of the ferrocenylamino alcohol **3a** and **3b** were cleaved in the presence of a mixture of ammonium formate and Pd–C in methanol providing **5a** and **5b** in 80 and 70% isolated yield, respectively (Scheme 3).[7] The same experimental procedure was applied to the mixture **3c**/**4c** leading to the diastereomer **5c** in 52% yield.[8] It has to be mentioned that attempts to deprotect the minor diastereomers led to decomposition products.

The primary ferrocenyl amino alcohols **5a–c** were then evaluated in the enantioselective reduction of acetophenone (Scheme 4). The reaction was carried out in THF at 30°C with in situ generated oxazaborolidines using



3a **5a**
3b **5b**
3c **5c**

Scheme 3.



Scheme 4.

BH_3 and the amino alcohols.[9] The results are summarised in Table 1.

In order to evaluate the catalytic behaviour of the ligands, two levels of loading (10 and 100 mol%) were utilised. In all cases, 1-phenylethanol with the (*R*)-enantiomer predominating was obtained quantitatively. We observed a decrease in the enantioselectivity with decreasing reaction temperature, as has already been reported in the literature[10] (compare entries 3 and 4).

The results show that the enantioselectivity of the reaction is very sensitive to the structure of the chiral ligand. Increasing the bulkiness of the alkyl group on the carbon bearing the amino function induces an increase in the enantioselectivity when the amino alcohols were used at 10 mol% (entries 1, 4 and 6). However, this effect is less important when using stoichiometric conditions (entries 2, 5 and 7). The presence of a *tert*-butyl group on the carbon bearing the amino function for **5c** gives the most satisfactory results (entries 6 and 7). The enantioselectivities were 84% using 10 mol% of **5c** and 90% using 100 mol% of **5c**. Moreover, the difference between the enantiomeric excesses obtained under the catalytic and stoichiometric conditions for **5c** is not important (Δe.e. = 6%) in comparison with **5a** (Δe.e. = 59%) and **5b** (Δe.e. = 34%).

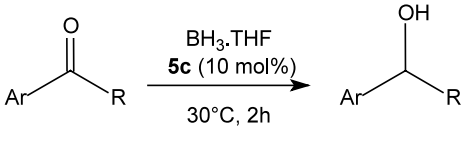
We observed a beneficial effect of the presence of the ferrocenyl moiety in the amino alcohol: the replacement of the phenyl group of norephedrine with a ferrocenyl moiety for **5a** provided higher enantioselectivity in the respective reduction reaction (74.5% for norephedrine and 81% for ferrocenyl ligand **5a**).[11]

Finally, we investigated the efficiency of ligand **5c** in the reduction of four representative aromatic ketones

Table 1. Enantioselective reduction of acetophenone with BH_3·THF using ferrocenyl amino alcohols **5a–c**[a]

Entry	Auxiliary (mol%)	E.e. (%)[b]	Conf.[c]
1	**5a** (10)	20	*R*
2	**5a** (100)	81	*R*
3	**5b** (10)[d]	45	*R*
4	**5b** (10)	54	*R*
5	**5b** (100)	88	*R*
6	**5c** (10)	84	*R*
7	**5c** (100)	90	*R*

[a] The chemical yields of isolated products were 95–100%.
[b] The e.e. values were determined by capilliary GC analysis with a FC-cyclodex (0.24 mm×30 m) column.
[c] The absolute configuration of the product was determined by comparison of the sign of the specific rotation to the literature data.
[d] The reaction was carried out at 20°C.



Scheme 5.

Table 2. Reduction of aromatic ketones with BH_3·THF using ferrocenyl amino alcohol **5c** as catalyst (10 mol%)[a]

Entry	Ketone	E.e. (%)[b]	Conf.[c]
1	1-Tetralone	83	*R*
2	Propiophenone	74	*R*
3	4-Chloroacetophenone	77	*R*
4	ω-Bromoacetophenone	82	*S*

[a] The chemical yields of isolated products were 100%. The reactions were carried out at 30°C.

[b] The e.e. values were determined by capilliary GC analysis with a FC-cyclodex (0.24 mm×30 m) column.

[c] The absolute configuration of the product was determined by comparison of the sign of the specific rotation with the literature data.

(Scheme 5) and these results are reported in Table 2. Thus, the reduction of ketones using 10 mol% of **5c** gave excellent chemical yields and enantioselectivities from 74 to 83%.

3. Conclusion

A series of enantiomerically pure ferrocenyl amino alcohols was prepared by stereoselective routes and applied as catalytic ligands in the enantioselective reduction of prochiral ketones, giving chiral alcohols with modest to high enantioselectivities. Further investigations are in progress regarding the amelioration of the design of ferrocenyl ligands of this type.

Acknowledgements

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References

1. For reviews, see: (a) Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763–784; (b) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 1986–2012; (c) Itsuno, S. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley: New York, 1998; Vol. 52, pp. 395–576.
2. Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469–470.
3. Corey, E.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
4. For recent examples, see: (a) Sato, S.; Watanabe, H.; Asami, M. *Tetrahedron: Asymmetry* **2000**, *11*, 4329–4340; (b) Fiaud, J.-C.; Mazé, F.; Kagan, H. B. *Tetrahedron: Asymmetry* **1998**, *9*, 3647–3655; (c) Pinho, P.; Guijarro, D.; Andersson, P. G. *Tetrahedron* **1998**, *54*, 7897–7906; (d) Zhou, H.-B.; Zhang, J.; Lü, S.-M.; Xie, R.-G.; Zhou, Z.-Y.; Choi, M. C. K.; Chan, A. S. C.; Yang, T.-K. *Tetrahedron* **2001**, *57*, 9325–9333.
5. (a) Bastin, S.; Agbossou-Niedercorn, F.; Brocard, J.; Pélinski, L. *Tetrahedron: Asymmetry* **2001**, *12*, 2399–2408; (b) Bastin, S.; Brocard, J.; Pélinski, L. *Tetrahedron Lett.* **2000**, *41*, 7303–7307.
6. Reetz, M. T. *Chem. Rev.* **1999**, *99*, 1121–1162.
7. Compound **5a**: $[\alpha]_D^{20}=+74.0$ (*c* 1.04, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.98 (d, $J=6.5$ Hz, 3H), 2.97 (qd, $J=4.8$ and 6.5 Hz, 1H), 4.15–4.22 (m, 4H), 4.22 (s, 5H), 4.25 (d, $J=4.8$ Hz, 1H). Compound **5b**: $[\alpha]_D^{20}=+93.4$ (*c* 0.54, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (d, $J=6.5$ Hz, 3H), 0.96 (d, $J=6.5$ Hz, 3H), 1.56–1.62 (m, 1H), 2.53 (dd, $J=6.5$ and 6.5 Hz, 1H), 4.18 (m, 2H), 4.21 (m, 1H), 4.24 (s, 5H), 5.27 (m, 1H), 4.33 (d, $J=5.5$ Hz, 1H).
8. Compound **5c**: $[\alpha]_D^{20}=+173.7$ (*c* 0.244, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ 0.83 (s, 9H), 2.68 (d, $J=4.5$ Hz, 1H), 4.15–4.30 (m, 4H), 4.24 (s, 5H), 4.39 (d, $J=4.5$ Hz, 1H).
9. **Typical procedure for the reduction of prochiral ketones**: Under nitrogen, BH_3·THF (473 μL, 1 M) was added to a solution of chiral ligand (0.236 mmol or 0.019 mmol) in dry THF (10 mL) at 30°C. A solution of acetophenone (473 μL, 0.189 mmol), in dry THF (5 mL), was added dropwise over a period of 50 min at 30°C. After stirring for 2 h at 30°C, MeOH (5 mL) and then HCl (5 mL, 3 M) were added to the reaction mixture. The alcohol product was isolated by extraction with diethyl ether. The organic layer was dried over Na_2SO_4. After concentration by rotary evaporation, the product was analysed by chiral GC.
10. (a) Brunel, J.-M.; Maffei, M.; Buono, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2255–2260; (b) Stone, B. J. *Tetrahedron: Asymmetry* **1994**, *5*, 465–472.
11. Didier, E.; Loubinoux, B.; Ramos Tombo, G. M.; Rihs, G. *Tetrahedron* **1991**, *47*, 4941–4958.