Pergamon

Tetrahedron: *Asymmetry* 11 (2000) 3221–3225

TETRAHEDRON: *ASYMMETRY*

Study of asymmetric reduction of 1-substituted fluorenone with borane in the presence of several chiral amino alcohols

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Received 29 June 2000; accepted 12 July 2000

Abstract

The enantioselective reduction of 1-bromofluorenone by borane in the presence of different chiral amino alcohols has been studied. The alcohol obtained has the (*S*) or (*R*) configuration depending on the nature of the substitution of the amino alcohol. The experimentally determined absolute configuration can be explained when a four-center cyclic transition state consisting of the oxazaborolidine and fluorenone compound is considered.

1. Introduction

Synthesis of enantiomerically pure compounds from achiral starting materials, using easily recoverable chiral auxiliaries, has been a major focus in organic chemistry in recent years. Enantiomerically pure alcohols are particularly useful as building blocks for the synthesis of natural products and pharmaceutical chemicals since a large number of synthetic methods have been developed to transform this functionality into other organic functions like amines, halogens etc. During our search for new materials,[1] we faced the problem of the formation of a stereogenic center at the 9-position of the fluorenyl system. One of the plausible ways is the synthesis of chiral alcohols via asymmetric reduction of prochiral polysubstituted ketones.[2] Although many reports describe the asymmetric reduction of ketones by either enzymatic reductions,[3] or a wide variety of modified organometallic reagents prepared by mixing aluminum hydride or borane with various chiral diols or amino alcohols,[4,5] they usually refer to methylalkyl or arylalkyl ketones, mainly acetophenone.[6] To our knowledge, very little attention has been paid to diarylketones, especially to the fluorenone system. Its structural rigidity has prevented its study. In order to distinguish the two aromatic rings in the fluorenone system electronically and sterically, we chose a 1-substituted fluorenone to be reduced. Substitution in other positions of the aromatic ring were not expected

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0957-4166/00/$ - see front matter
PII: S0957-4166(00)00275-5

to affect the course of the reaction in a significant way, nor the enantiomeric excess or the absolute configuration. 1-Bromofluorenone was selected as a model not only because it is easy to synthesize,[7] but also because it can be dehalogenated by hydrogenolysis, after the induction of chirality, when reduction is performed on multiple substituted fluorenones.[2]

2. Results and discussion

We describe our studies on the asymmetric reduction of 1-bromofluorenone with borane in the presence of chiral amino alcohols with different substitution patterns (Fig. 1) chosen to elucidate the importance of the presence of phenyl substitution to establish a π–π interaction with the fluorenone molecule in the transition state. Factors such as temperature, ratio between chiral amino alcohol and hydride, etc. which affect the course of the reaction, have been considered.

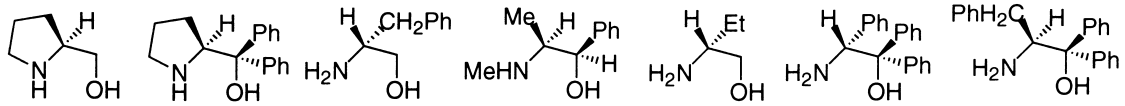


Figure 1. Chiral amino alcohols used to the preparation of chiral oxazaborolidines

Table 1 shows the results obtained in the reduction process. Poor chemical yields were obtained as expected due to the structural rigidity of the fluorenone system, which can produce high sterical hindrance to the approach of the chiral reductor (Table 1). The effect of the solvent on the reductions was examined. The highest enantiomeric excess was found with toluene (84%) and benzene (68%) when the amino alcohol **2** was used as chiral modifier (entries 4 and 2).

Table 1
Reduction of 1-bromofluorenone with chiral modified borane

Entry	AA[a]	Solvent	Ratio[b]	Temp (°C)	Time (h)	Conf.[c]	e.e.	Yield (%)
1	1	benzene	1 : 1 :1	rt	14	R	51	16
2	2	benzene	1 : 1 :1	rt	14	S	68	22
3	2	benzene	1 : 1 :1	reflux	8	S	50	34
4	2	toluene	1 : 1 :1	-30	168	S	84	13
5	2	toluene	1:1.75:1[d]	-30	240	S	12	14
6	3	benzene	1 : 1 :1	rt	14	S	15	45
7	4	THF	1 : 1 :1	rt	14	R	12	12
8	5	THF	1 : 1 :1	rt	14	S	13	21
9	6	benzene	1 : 1 :1	rt	12	R	41	13
10	7	benzene	1 : 1 :1	rt	14	S	5	12

Note: [a] chiral amino alcohol used in the oxazaborolidine preparation. [b] Molar ratio of chiral modifier, borane and 1-bromofluorenone. [c] The configuration of 1-bromofluorenol was related to the sign of its optical rotation as described elsewhere.[10] [d] 0.75 mmol of more borane was added to the solution of fluorenone and the oxazaborolidine.

Nevertheless, all the chemical yields obtained were very low, between 13 and 45%. Higher reaction temperatures gave slightly better yields, but also lower e.e. (entry 3). The main effect on the chemical yield and the enantiomeric excess was produced by the steric hindrance due to the substitution on the C-1 of the amino alcohol. Amino alcohols with a substituted amino group give better chemical yields and enantiomeric excesses than those not substituted.[8] Of all the amino alchohols tested **1**–**7**, the best e.e. corresponds to **2**, the Corey's auxiliary (*S*)-α,α-diphenyl-2-pyrrolidine methanol.[9] The other chiral amino alcohols used in the complex formation with borane improved neither the chemical yields nor the enantiomeric excess. The presence of at least one phenyl group in the amino alcohol increases the chemical yield of the product, perhaps because of the π–π-interaction of these phenyl groups with the fluorenone system. However, an excess of phenyl groups (three groups in amino alcohols **6** and **7**, entries 9 and 10) slightly decreases the chemical yield presumably because of steric hindrance. Amino alcohols **1** and **2** with a pyrrolidine nitrogen gave better e.e.s. The absolute configuration of the 1-bromofluoren-9-ol[10] obtained depended on the chiral amino alcohol used. Entry 5 shows that the addition of more borane to the reaction mixture, after formation of the oxazaborolidine complex, did not increase either the enantiomeric excess or the chemical yield. All comparisons between the different amino alcohols were then performed using an equimolecular ratio between borane and the chiral modifier.

The hypothesis of a transition state of six centers was proposed[11,12] to explain the absolute configuration of the new stereogenic center, where the oxazaborolidine is coordinated with the ketone and a molecule of free borane. To explain our own results, when no more borane was added, the six-ring nature of the transition state cannot be applied. Nevertheless, if this model is considered, the results expected for the absolute configuration are not coincident with those determined experimentally. The small enantiomeric excesses obtained do not warrant structural interpretations. However, the absolute configuration of the chiral 1-bromofluoren-9-ol obtained in all the experiments can be justified as a result of a transition state with a four-center ring (O–B–H–C). In the absence of other types of interactions this should be, together with the minimal sterical hindrance, what determines the approximation pattern of the two substrates (Fig. 2). For this reason, when the amino alcohols **1**-(*S*) and **5**-(*R*) were used, the configuration found for the 1-bromofluoren-9-ol was (*S*) and (*R*), respectively (entries 1 and 8). Molecular orbital calculations were carried out using the semiempirical AM1[13] Hamiltonian of the MOPAC 93[14] program on a Silicon Indigo 2 computer with full optimization of all bond lengths, angles and torsion angles. They were performed to elucidate the direction of the dipole moment of the B–H bond, in the oxazaborolidine compound, and that of the C–O bond of the fluorenone compound. The B and C nuclei are the most electron-deficient nuclei in these bonds from the net atomic charges calculated (B = 0.164, H = 0.069; C = 0.316, O = –0.242). An approximation of the two molecules to give a four-center ring, as proposed, is then feasible.

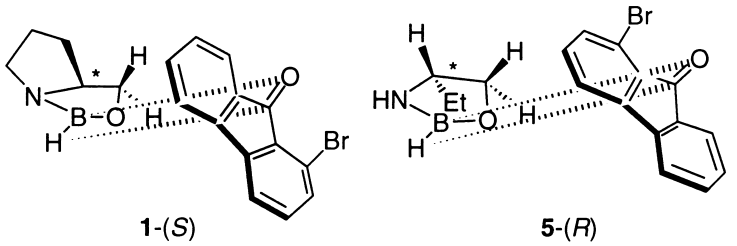
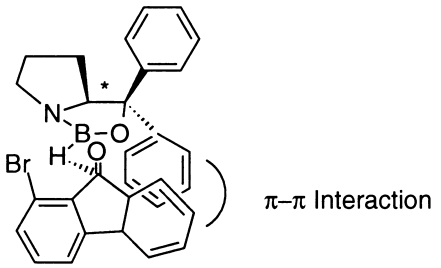


Figure 2. Four-center ring approximation

With the other amino alcohols assayed (entries 6–10) an additional interaction should be considered: the π–π interaction between the benzene ring of the fluorenone system and those of the amino alcohols, which favors the approach of the oxazaborolidine and the prochiral ketone (Fig. 3). The chiral amino alcohol represented is Corey's auxiliary (Fig. 3). When this type of transition state model is applied in all the experiments of Table 1 the absolute configuration of the emerging stereogenic center is concordant with the experimental data.



2-(*S*)

Figure 3. Four-center ring approximation with additional π–π interaction

3. Experimental

As a typical procedure, first the oxazaborolidine compound was formed from a stirred suspension of chiral amino alcohol in toluene, to which an equimolar of 1 M solution of borane in THF was added at room temperature. After stirring for a further 10 min, the mixture was heated under reflux (110°C) for 30 min. The reductor, oxazaborolidine was formed after removal of solvent in vacuum. It was dissolved and transferred into a solution of 1-bromofluoren-9-one in the corresponding solvent at the reaction temperature. The reaction was monitored by TLC or GC and quenched with a saturated NH_4Cl solution. General work-up was as follows: methylene chloride was used to extract the reaction mixture. The organic phase was washed successively in aqueous 1N HCl and 1N NaOH, then with water until neutral pH, and was finally dried with $MgSO_4$, filtered and evaporated, affording the crude alcohol, which was purified by a flash chromatography with methylene chloride as eluent.

Acknowledgements

Financial support from the Comisión Interministerial de Ciencia y Tecnología and from the Generalitat de Catalunya (Project n. QFN94–4612) of Spain is acknowledged.

References

1. Dobarro, A.; Velasco, D.; Arnim, V. v.; Finkelmann, H. *Macromol. Chem. Phys.* **1997**, *198*, 2563–2581.
2. Yu, Z.; Velasco, D. *Tetrahedron Lett.* **1999**, *40*, 3229–3232.

3. Nakamura, R.; Matsuda, T. *J. Org. Chem.* **1998**, *63*, 8957–8964.
4. Deloux, L.; Srebnik, M. *Chem. Rev.* **1993**, *93*, 763–784.
5. Brunel, J. M.; Maffei, M.; Buono, G. *Tetrahedron: Asymmetry* **1993**, *4*, 2255–2260.
6. Brown, E.; Lézé, A.; Touet, J. *Tetrahedron: Asymmetry* **1992**, *3*, 841–844.
7. Huntress, E. H.; Pfister, K.; Pfister, K. H. T. *J. Am. Chem. Soc.* **1942**, *64*, 2845–2849.
8. Itsuno, S.; Ito, K.; Hirao, A.; Nakahama, S. *J. Chem. Soc., Chem. Commun.* **1983**, 469–470.
9. Corey, E. J.; Bakshi, R. K.; Shibata, S. *J. Am. Chem. Soc.* **1987**, *109*, 5551–5553.
10. Darby, A. C.; Hargreaves, M. K.; Raval, D. A. *J. Chem. Soc., Chem. Commun.* **1970**, 1554–1555.
11. Corey, E. J.; Link, J. O.; Bakshi, R. K. *Tetrahedron Lett.* **1992**, *33*, 7107–7110.
12. Quallich, G. C.; Blake, J. F.; Woodall, T. M. *J. Am. Chem. Soc.* **1994**, *116*, 8516–8525.
13. Stewart, J. J. P. *J. Comput. Chem.* **1989**, *10*, 209–220; *ibid.* 221–264.
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