Pergamon

Tetrahedron Letters, Vol. 38, No. 29, pp. 5193-5196, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)01125-8

Stereodivergent Approach to *syn*- and *anti*-2-Amino-1,2-diarylethanols Using Oxazaborolidine-Mediated Asymmetric Reduction

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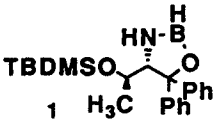
Abstract: Highly enantioselective reduction of 1,2-diaryl-2-benzyloxyiminoethanones was conducted using oxazaborolidine derived from L-threonine and BH_3• SMe_2 to give β-imino alcohols in high enantiomeric purity. Subsequent reduction of the imino functionality afforded either *syn*- or *anti*-2-amino-1,2-diarylethanols in high enantiomeric purity by choosing appropriate reduction conditions.

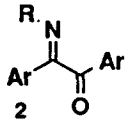
The importance of homochiral 2-amino-1,2-diarylethanol **3** is increasing in connection with the widespread use of its derivatives as chiral auxiliaries in many useful asymmetric reactions.[1] For the preparation of this highly useful class of compounds, the resolution of racemic amino alcohols with mandelic acid[2] or preferential crystallization[3] has been most often used. However, there have not been many reports which deal with asymmetric synthesis of 2-amino-1,2-diarylethanol **3**. Transformation of chiral 1,2-diol,[4,15] enzyme-catalyzed cyanohydrin formation-arylation,[5] and asymmetric aminohydroxylation[6] are the only examples. We have previously reported that the oxazaborolidine-catalyzed reduction of 1,2-diimine provides a short efficient route to homochiral (*R,R*)-1,2-diphenylethylenediamine in good overall yield.[7] Considering the ability of the oxazaborolidine **1** derived from L-threonine to offer high enantiofacial discrimination, we conducted the reduction of α-imino ketones **2** under the oxazaborolidine-BH_3 conditions for the synthesis of *syn*- and *anti*-2-amino-1,2-diarylethanol **3**. This paper describes an efficient approach to both *syn*- and *anti*-2-amino-1,2-diarylethanols **3** in high enantiomeric excess.

In contrast to the previous result on the stereoselective reduction of 1,2-bis(*p*-anisylimino)-1,2-diphenylethane,[7] initial examination into bis-reduction of *p*-anisylimino ketone **2a** in the presence of 20 mol% of the catalyst **1** with a stoichiometric amount of BH_3•THF in THF met with low enantio- and diasteoselectivity, and a mixture of *syn*-(1*S*,2*S*)-**3a** and *anti*-(1*S*,2*R*)-**3a** was obtained in 88% yield with a ratio of *syn* : *anti* = 58 : 42, where the enantiomeric purity of the product was less than 14% ee. This may be due to the low reactivity of the anisylimino functionality towards the present reduction. The produced imino alcohol **4a** or amino alcohols **3a** would act as precursors of oxazaborolidine to participate in the present reduction cycle as a ligand, which

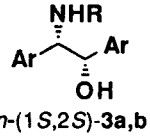


1

a: R = *p*-$MeOC_6H_4$, Ar = Ph
b: R = *p*-Ts, Ar = Ph
c: R = BnO, Ar = Ph

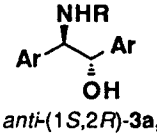


2



syn-(1*S*,2*S*)-**3a,b**

d: R = BnO, Ar = *p*-$MeOC_6H_4$
e: R = BnO, Ar = *p*-MeC_6H_4



anti-(1*S*,2*R*)-**3a,b**

f : R = BnO, Ar = *p*-BrC_6H_4
g: R = BnO, Ar = 2-Furyl

4

could also cause the low enantioselectivity. Although a more reactive derivative, *p*-tosylimino analogue **2b** was subjected to the same reduction conditions, only a slight increase in the enantiofacial selectivity was observed, *i.e.*, 38% ee for the *syn*-isomer **3b**. Switching the substrate to oxime ether **2c** improved the enatioselectivity up to 88% ee. Among the oxime derivatives examined, benzyloxyimino analogue **2c**[8] recorded good results, where the addition of a Lewis acid, $Al(O^iPr)_3$, in the presence of 100 mol% of the oxazaborolidine considerably improved the enantiofacial selectivity, and a mixture of *syn*-(1*S*,2*S*)-**3c** (R = H) and *anti*-(1*S*,2*R*)-**3c** (R = H) was obtained in 54% yield with a ratio of *syn* : *anti* = 47 : 53 in 90 and 94% ee, respectively. However, the diastereoselectivity was not improved despite the addition of a variety of Lewis acids. These results indicated that, although the initial mono-reduction proceeded in a highly enantioselective fashion, the second step involved a non-stereoselective pathway without the influence of the oxazaborolidine **1**-BH_3•THF system. Among the reducing agents in the present reaction medium, BH_3•THF itself might effect the second reduction in a non-stereoselective fashion. In fact, the reduction of β-imino alcohol (*S*)-**4c** prepared as described below with BH_3•THF in THF gave a mixture of *syn*-**3c** (R = H) and *anti*-**3c** (R = H) with a 69 : 31 ratio in 54% yield. Therefore, sequential reduction was next investigated. Reduction using BH_3•THF as the stoichiometric reducing agent previously reported[7] gave only bis-reduction product **3** regardless of the amount of borane and the reaction time. However, the reduction of ketone was much faster than that of imine in the presence of a modifier such as *tert*-amine, and the β-imino alcohol **4** was obtained as the sole product. The results of mono-reduction are summarized in Table 1.

As shown in Table 1, the reduction in the presence of 1 eq of DBU gave the β-imino alcohol **4c** with 90% ee (entry 1), whereas the yield was improved using catecholborane as a stoichiometric reductant (entry 2). The best result was obtained when the reduction was conducted with 1.5 eq of BH_3•SMe_2 (78% yield, 98% ee). However, this reduction was sensitive to the amount of oxazaborolidine **1**, and the reaction in the presence of a catalytic amount of **1** gave β-imino alcohol **4c** in moderate yields (entries 4 & 5). Under the best conditions found for the reduction of **2c**, other benzil derivatives gave 71-83% yields of the mono-reduction products with 96-98% ee (entries 6~9). In all the cases examined in the present study, over-reduction producing amino alcohol **3** was not observed. The high enantioselectivity observed in the present reduction may be explained in terms of

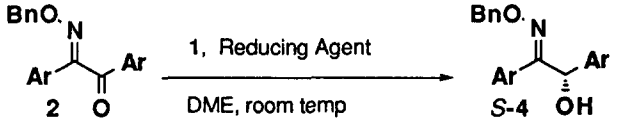


Table 1. Reduction of Imino Ketone 2.[a]

Entry	2	1(mol%)	Reduction Agent (eq)	Time (h)	%yield of 4[b]	% ee[c]
1	**2c**	100	BH_3•THF (3.0)/DBU (1.0)	11	40	90
2	**2c**	100	Cathecolborane (5.0)	22	66	90
3	**2c**	100	BH_3•SMe_2 (1.5)	24	78	98
4	**2c**	20	BH_3•SMe_2 (5.8)	40	25	56
5	**2c**	50	BH_3•SMe_2 (2.5)	75	43	90
6	**2d**	100	BH_3•SMe_2 (1.5)	3	80	98
7	**2e**	100	BH_3•SMe_2 (1.5)	25	83	98
8	**2f**	100	BH_3•SMe_2 (1.5)	14	71	98[d]
9	**2g**	100	BH_3•SMe_2 (1.5)	15	78	96

[a] The reaction was carried out according to the typical experimental procedure.[9] [b] Isolated yield. [c] Determined by HPLC analysis using a chiral stationary column (Daicel OJ). [d] Determined by ^1H NMR (500MHz) analysis of the corresponding MTPA ester.

the six-membered cyclic transition state which is similar to the one proposed by Corey et al.[10]

We next investigated the diastereoselective reduction of β-benzyloxyimino alcohols **4** into either *syn*- or *anti*-amino alcohol **3** under a variety of chelation or non-chelation conditions. In principle, the reduction which is explained in terms of a non-chelation or Felkin-Anh model produces *syn*-product *syn*-**3**, whereas a certain chelation between the hydroxy oxygen and the imino nitrogen effects the formation of *anti*-product *anti*-**3**. Under the hydrogenation conditions the reduction of β-imino alcohol was reported to give *anti*-amino alcohol.[2,11] Using 10% Pd-C / H_2, β-imino alcohol **4** was transformed into *anti*-amino alcohol **3** in good yield with good diastereomeric excess, whereas reduction with $LiAlH_4$ or $Na[AlH_2(OCH_2CH_2OCH_3)_2]$ afforded the *syn*-isomer as a major product. Representative examples are listed in Table 2.

In all the cases examined, the diastereoselectiviy was good to excellent, giving either the *syn*- or *anti*-isomer with high diastereomeric excess, and the stereochemical integrity of the starting material was remained almost unaffected. The cases where $LiAlH_4$ was used as a reducing reagent were mainly due to the reaction rate; the use of $Na[AlH_2(OCH_2CH_2OCH_3)_2]$ sometimes did not reach completion of the reduction, where the N-O bond remained intact. However, the use of $LiAlH_4$ caused racemization (entries 5 & 7) to some extent maybe due to the more forced reduction conditions. For isolation of the reduction product, in particular, from the $LiAlH_4$ or $Na[AlH_2(OCH_2CH_2OCH_3)_2]$ mediated reduction of the substituted aryl derivatives, acetylation of the resulting amino moiety was found to be useful in terms of purity of the product.

In conclusion, the present two-step procedure for (1*S*,2*S*)- or (1*S*,2*R*)-2-amino-1,2-diarylethanol realizes the power of oxazaborolidine-mediated reduction of poly-functionalized molecules, giving rapid access to a highly useful class of compounds in a diastereo- and enantioselective manner. Since a variety of benzil derivatives are readily available and transformation into mono-imino compounds is straightforward in good overall yields, the present procedure may be applied to the preparation of a variety of 1,2-amino alcohols. Moreover, the benzyl ether protecting group at the nitrogen atom was removed during the second reduction step, eliminating an otherwise tedious deprotection sequence.

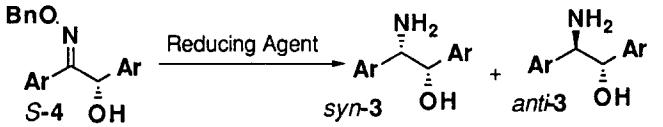


Table 2. Diastereoselective Reduction of β-Imino Alcohol 4.[a]

Entry	4	Reduction Agent	Solv.	Temp. (°C)	%yield[b]	*syn* : *anti* [c]	% ee[d]
1	**4c**	$Na[AlH_2(OCH_2CH_2OCH_3)_2]$	THF	-30~refl	59	98 : 2	98
2	**4c**	10% Pd-C / H_2	EtOH	rt	96	5 : 95	94
3	**4d**	$Na[AlH_2(OCH_2CH_2OCH_3)_2]$	THF	-30~refl	58[e]	>99 : <1	>99
4	**4d**	10% Pd-C / H_2	EtOH	rt	57	<1 : >99	98
5	**4e**	$LiAlH_4$	DME	0~refl	56[e]	88 : 12	82
6	**4e**	10% Pd-C / H_2	EtOH	rt	52	6 : 94	98
7	**4f**	$LiAlH_4$	DME	0~refl	49[e]	90 : 10	88
8	**4f**	10% Pd-C / H_2	EtOH	rt	56	<1 : >99	96

[a] The reaction was carried out according to the typical experimental procedure.[12] [b] Isolated yield. [c] Determined by ^1H NMR (270 MHz) analysis. [d] The enantiomeric purity of the major isomer. Determined by HPLC analysis (Merk Hibar column) of the corresponding mono- or bis-MTPA derivative. [e] The product was isolated as acetamide after treatment with Ac_2O.

Acknowledgment: This work was supported by the Grant-in-Aid for Scientific Research on Priority Area No. 08245104 from the Ministry of Education, Science, Sports, and Culture, of Japanese Government.

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8. The starting materials, 1,2-diaryl-2-benzyloxyiminoethanones **2c-g**, were prepared readily from mono-imination of benzil derivatives in yields ranging from 46 ~ 99%.
9. A typical procedure for the mono-reduction: To a solution of (2*S*,3*R*)-2-amino-3-(*t*-butyldimethylsiloxy)-1,1-diphenylbutanol (371.7 mg, 1.0 mmol) in 15.0 mL of DME was added BH_3•SMe_2 complex (0.24 mL, 2.5 mmol), and the mixture was stirred for 20 min at room temperature. A solution of **2c**, (315.4 mg, 1.0 mmol) in DME (2.5 mL) was added dropwise during 30 min. After stirring for 24 h at rt, usual work-up followed by purification on TLC gave β-imino alcohol **4c** as a colorless oil (246.2 mg, 78 %). The ee was determined to be 98% ee by HPLC (Daicel OJ). The absolute configuration was assigned to be *S* by transforming into **3c** (R = H).[12] The parent diketone of **2g** was mono-reduced with **1** and BH_3•THF to give the known β-keto alcohol,[14] which was benzyloxyiminated to afford **4g** and compared using HPLC.
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12. Typical procedures for *syn*-**3** and *anti*-**3**: *syn*-(1*S*,2*S*)-**3c** (R = H): To a solution of Red-Al® (481 mg, 70% in toluene, 1.7 mmol) in THF (5 mL) was added a solution of *S*-**4c** (98% ee, 122.4 mg, 0.39 mmol) in THF (2 mL) at -30 °C for 10 min. The mixture was allowed to stand at -30 °C for 2 h and then heated at reflux for 3 h. Usual work-up followed by purification on TLC gave *syn*-(1*S*,2*S*)-**3c** (R = H) (49.0 mg, 59%) as a white powder. The ratio was determined by ^{1}H NMR (270 MHz) to be *syn* : *anti* = 98 : 2, and the ee of *syn*-**3c** (R = H) by HPLC of the corresponding bis-MTPA derivative to be 98% ee. *anti*-(1*S*,2*R*)-**3c** (R = H): A solution of *S*-**4c** (98% ee, 41.0 mg, 0.13 mmol) in EtOH (3 mL) was stirred under H_2 (1 atm) in the presence of 10% Pd-C (13.8 mg) at rt for 25 h. Filtration of the crude mixture through a celite pad followed by concentration gave a crude oil, which was purified by Florisil® column chromatography to give **3c** (R = H) (26.9 mg, 96%) as a colorless oil with a ratio of *syn* : *anti* = 5 : 95 with 94% ee of *anti*-isomer. The optical rotation values obtained for the former reduction product ($[\alpha]_D^{23}$ = -106.7 (c 0.72, EtOH)) and for the latter ($[\alpha]_D^{23}$ = -5.58 (c 0.54, EtOH)) indicted that the absolute stereochemistry of *syn*-**3c** (R = H) and *anti*-**3c** (R = H) was (1*S*,2*S*) and (1*S*,2*R*), respectively.[2,3,13] The absolute stereochemistry of **3d** and **3e** was determined by comparison with the authentic samples prepared from the known (1*S*,2*S*)-diols.[14,15] **3f** was transformed into **3c** (R = H) by reduction with *n*-BuLi, and analyzed by its specific rotation.
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(*Received in Japan* 19 *May* 1997; *accepted* 4 *June* 1997)