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Single Route to Chiral *syn*- and *anti*-2-Amino-1,2-diphenylethanols via a New Stereodivergent Opening of *trans*-1,2-Diphenyloxirane

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Abstract: Oxiranyl ring opening of *trans*-stilbene oxide gave rise to *anti*- or *syn*-2-bromo-1,2-diphenylethanols, using either $MgBr_2 \cdot Et_2O$ or $MgBr_2 \cdot Et_2O$, NaBr, and KBr with Amberlyst 15, respectively. Starting from optically pure (*R*,*R*)-*trans*-stilbene oxide, (1*R*,2*R*)- and (1*R*,2*S*)-2-amino-1,2-diphenylethanols were obtained in high yield and ee.

β-Amino alcohol subunits, since their discovery in many biologically active compounds, especially as α-amino-*β*-hydroxy or α-hydroxy-*β*-amino acids,[1] have attracted the attention of synthetic chemists, and several approaches to the synthesis of these units have now been developed.[2] Among this class of compounds, the 2-amino-1,2-diphenylethanols, with both syn and anti relative configurations (compounds **1** and **2**, respectively, in Figure 1), have recently received great attention due to their use, in optically active forms, as chiral auxiliaries in asymmetric synthesis,[3] chiral stationary phases for HPLC,[4] and chiral ligands in asymmetric catalysis.[5]

Due to their important use, they are now commercially available, although expensive.[6] Several syntheses of both antipodes and diastereomeric couples have been reported such as the early resolution[7] of benzoin derivatives, which was recently performed via biocatalysis.[7b] More recent approaches employed the asymmetric reduction of 1,2-diaryl-2-benzyloxyiminoethanones[8] or the asymmetric enolate oxidation of deoxybenzoin.[9] Direct asymmetric aminohydroxylation on *trans*-stilbene[10] gave a modest yield and ee. To date, the most straightforward synthesis of these optically active compounds employed the Sharpless AD of *trans*-stilbene to the corresponding *syn*-1,2-diphenylethanediol, followed by nucleophilic amination of the corresponding cyclic sulfate with inversion[11] or retention of configuration.[12] Although the AD and subsequent elaborations to syn or anti diols allow the preparation of **1** and **2** from the same chiral precursor, the synthetic sequence to the syn compound **1**[12] appears to be complicated by the several steps to deprotect the intermediate 2-benzyloxazilidinone.

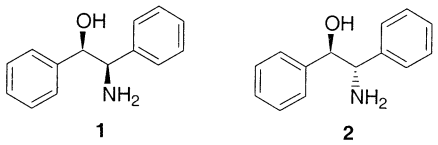

FIGURE 1.

On the other hand, despite its easy availability in the optically active form,[13] the 1,2-diphenyl epoxide **3** has never been utilized as a starting chiral synthon for the obtaining compounds **1** and **2**, despite the developed methodologies for stereocontrol in the ring opening of the oxirane ring.

Herein we present a simple and straightforward synthesis of both **1** and **2** starting from the same chiral compound **3** and employing a new stereodivergent opening of the oxirane ring.

Due to our experience in the regio and stereoselective opening of three-membered heterocyclic rings such as epoxides and aziridines with metal halides,[2c,14] we envisaged a possible route to the synthesis of **1** and **2** (Scheme 1).

The success of the synthesis in affording both diastereoisomers would depend mainly on a diastereoselective and divergent opening of the oxirane ring, which would be followed by standard nitrogen substitution, already utilized for the preparation of 1,2 amino-alcohol subunits.[15] Our study and other studies have mainly revealed that the oxirane opening by metal halides cleanly follows the S_N2 replacing mechanism with inversion of configuration. Only more recently, in the case of special

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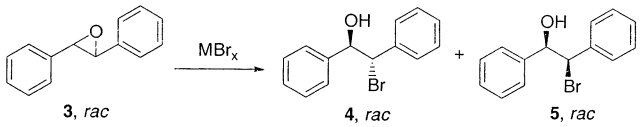
TABLE 1. Opening of *trans*-Stilbene Epoxide with Metal Halides

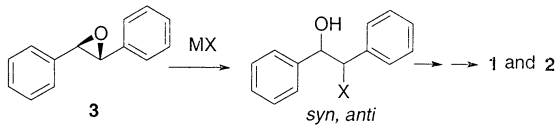


3, *rac* **4**, *rac* **5**, *rac*

entry	bromides	bromide/substrate	reaction conditions	conversion[a] (%)	yield[b] (%)	diasteromeric ratio[a] **4**	**5**
1	$MgBr_2 \cdot Et_2O$	4/1	Et_2O, 0 °C, 4 h	95	90	80	20
2	$MgBr_2 \cdot Et_2O$/Amberlyst 15[c]	3/1	CH_3CN, 0 °C, 2 h	95	90	10	90
3	NaBr/Amberlyst 15[c]	3/1	acetone, −30 °C, 12 h	90	60[d]	10	90
4	NaBr/Amberlyst 15[c]	3/1	CH_3CN, from −30 to 0 °C, 6 h	95	80[e]	10	90
5	LiBr/Amberlyst 15[c]	4/1	acetone, −30 °C, 6 h	70	65[d]	80	20
6	LiBr/Amberlyst 15[c]	4/1	CH_3CN, −30 °C, 6 h	90	85	80	20
7	KBr/Amberlyst 15[c]	3/1	CH_3CN, rt, 3 h	95	90	25	75

[a] Calculated by ^{1}H NMR analysis of the crude mixture. [b] Isolated. [c] Amberlyst 15/substrate = 220 mg/mmol. [d] Side products were observed. [e] 2,2-Diphenylacetaldehyde (10%) was also obtained.

SCHEME 1



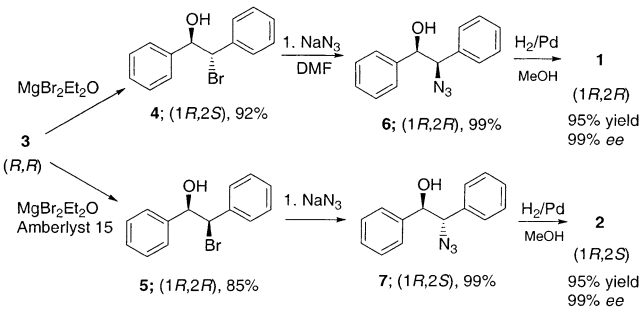
diphenyl epoxides such as pyridyl or fluoro-phenyl,[16] we found that the metal halide opening could be observed with some retention of configuration, probably due to the benzylic character of the carbon involved, although the observed opening was poorly stereoselective for useful synthetic purposes.

In search of appropriate experimental conditions for the success of the planned synthetic strategy (Scheme 1), the opening of the oxirane ring of *rac-trans*-stilbene oxide **3** was then attempted with the use of different metal halide systems. We turned out our attention to the use of a MX/Amberlyst 15 system[17] and to a frequently utilized $MgBr_2$ opening reaction, already successfully employed by us in the opening of epoxy and aziridine alcohols and derivatives.[15,18] The results in Table 1 show different levels of diastereoselectivity with the use of different systems and reaction conditions.

First, it is noteworthy as a unique case that the use of magnesium bromide alone allowed the opening of the oxiranyl ring without the need of the Amberlyst 15 (entry **1**).

Then, obtaining the anti diastereoisomer **4**,[19] as the main product in many of the reported reactions (see entries 1, 5, and 6) was not surprising. On the other hand,

SCHEME 2



we were quite delighted to observe that, using Amberlyst 15 and, alternatively, $MgBr_2$, NaBr, or KBr, we could smoothly obtain the *syn*-bromohydrin **5** in good yields and high syn/anti ratio.

Switching from acetone to acetonitrile as the reaction solvent, we observed a noteworthy enhancement of yield (entry **4** and **6**). From a synthetic point of view, the best results, in terms of overall yield and diastereoselectivity, were obtained with the use of $MgBr_2 \cdot Et_2O$ alone for the *anti*- (entry **1**) and $MgBr_2 \cdot Et_2O$/Amberlyst 15 for the *syn*-halohydrin (entry **2**).

Therefore, with these results in hand, we could follow the synthetic sequence planned in Scheme 1. The two diastereoisomers **4** and **5** were smoothly obtained using the developed procedures (see Scheme 2), starting from optically pure *trans*-epoxide **3**, in excellent overall yield and good diastereomeric ratio (compounds **4** and **5** are easily separated by standard chromatography; see Experimental Section).

The two diastereoisomers **4** and **5** were transformed, by direct S_N2-type replacement of the bromine with sodium azide, to the corresponding azido alcohols **6** and **7** in high yield and without traces of racemization. Standard catalytic hydrogenation finally afforded optically active **1** and **2**, whose analytical and physical data were in complete agreement with those of commercial samples. In conclusion, we have shown a new and easy synthetic sequence to important chiral diphenyl amino alcohols via a new stereodivergent opening of the oxirane ring. Studies on the generalization of such a stereodivergent ring opening of differently functionalized diaryl

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(19) Relative configuration of the two diastereoisomers was determined by alkaline ring closure (NaH, THF, rt) of the mixture of bromohydrins and ^{1}H NMR analysis of the mixture of the epoxides obtained.

epoxides and on its application to the synthesis of important chiral amino alcohols are currently underway.

Experimental Section

General Methods. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Commercially available reagents were used without further purification. All reactions were monitored by TLC with silica gel-coated plates. Column chromatography was carried out using 60−260 mesh silica gel at atmospheric pressure.

General Procedure for the Metal Bromide Opening of *trans*-Stilbene Epoxide 3. To a solution of *trans*-stilbene epoxide (**3**) (100 mg, 0.52 mmol) in the appropriate solvent (10 mL, see Table 1), maintained at the desired temperature, were added solid metal bromide (3−4 equiv) and Amberlyst 15 (120 mg, when needed) consecutively, in single portions. The mixture was stirred at the desired temperature, and the reaction was monitored by TLC until complete. The mixture was filtered and the filtrate evaporated under vacuum. The residue was dissolved in EtOAc, and the resulting organic layer was dried with Na_2SO_4; the solvent was evaporated under vacuum, and the crude product was analyzed by ^{1}H NMR.

anti-2-Bromo-1,2-diphenylethanol (**4**) was obtained in 92% yield after purification by silica gel chromatography (eluent: hexane/Et_2O 4/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.40 (brs, 1H), 5.12 (A part of AB system, $^3J_{AB}$ = 6.6 Hz, 1H), 5.22 (B part of AB system, $^3J_{AB}$ = 6.6 Hz, 1H), 7.30−7.50 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 58.9, 78.1, 127.0, 128.2, 128.3, 128.4, 128.7, 128.9, 137.6, 139.7. MS (*m*/*z* %): 276 $[M]^+$ (1), 278 $[M + 2]^+$ (1), 165 (5), 167 (5), 107 (100).

(1*R*,2*S*)-**4** was obtained from (1*R*,2*R*)-**3**[13b] in 92% yield (99% ee; HPLC Chiralcel OJ, *n*-hexane/2-propanol 90/10, 1.0 mL/min; $[\alpha]^{25}_D$ +16 (*c* 0.5, $CHCl_3$)) using the procedure of entry 1 (Table 1).

syn-2-Bromo-1,2-diphenylethanol (**5**) was obtained in 85% yield after purification by silica gel chromatography (eluent: hexane/Et_2O 4/1). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 3.30 (brs, 1H), 5.08 (A part of AB system, $^3J_{AB}$ = 9.0 Hz, 1H), 5.19 (B part of AB system, $^3J_{AB}$ = 9.0 Hz, 1H), 7.20−7.40 (m, 10H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 63.9, 78.1, 126.8, 128.0, 128.3, 129.4, 138.2, 138.7. MS (*m*/*z* %): 276 $[M]^+$ (1), 278 $[M + 2]^+$ (1), 165 (5), 167 (5), 107 (100).

(1*R*,2*R*)-**5** was obtained from (1*R*,2*R*)-**3**[13b] in 85% yield (99% ee, HPLC Chiralcel OJ, *n*-hexane/2-propanol 90/10, 1.0 mL/min; $[\alpha]^{25}_D$ −60 (*c* 1, $CHCl_3$)) using the procedure of entry 2 (Table 1).

(1*R*,2*R*)-2-Azido-1,2-diphenylethanol (6). To a solution of (1*R*,2*S*)-2-bromo-1,2-diphenylethanol (**4**) (100 mg, 0.36 mmol), in DMF (15 mL) at room temperature, was added solid sodium azide (1.2 equiv). After 12 h, the mixture was diluted in H_2O and extracted with Et_2O. The organic layer was dried over Na_2SO_4, and the solvent was evaporated under vacuum, yielding 82 mg (95%) of **6**. ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.89 (brs, 1H), 4.65 (A part of AB system, $^3J_{AB}$ = 7.5 Hz, 1H), 4.77 (B part of AB system, $^3J_{AB}$ = 7.5 Hz, 1H), 7.12 (brs, 3H), 7.20−7.40 (m, 7H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 72.9, 77.9, 126.9, 127.8, 128.1, 129.4, 136.0, 139.2. (1*R*,2*R*)-**6**: 99% ee; HPLC Chiralcel OJ, *n*-hexane/2-propanol 90/10, 1.0 mL/min; $[\alpha]^{25}_D$ + 76 (*c* 1, $CHCl_3$).

(1*R*,2*S*)-2-Azido-1,2-diphenylethanol (7). Using the above procedure, **7** was obtained in 95% yield from (1*R*,2*R*)-2-bromo-1,2-diphenylethanol (**5**). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.17 (X part of ABX system, $^3J_{BX}$ = 2.4 Hz, 1H), 4.72 (A part of AB system, $^3J_{AB}$ = 6.6 Hz, 1H), 4.95 (B part of ABX system, $^3J_{AB}$ = 6.6 Hz, $^3J_{BX}$ = 2.4 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 71.3, 77.4, 127.0, 128.0, 128.3, 128.3, 128.6, 128.7, 135.9, 139.7. (1*R*,2*S*)-**7**: 99% ee; HPLC Chiralcel OJ, *n*-hexane/2-propanol 90/10, 1.0 mL/min; $[\alpha]^{25}_D$ +44 (*c* 1, $CHCl_3$).

(1*R*,2*R*)-2-Amino-1,2-diphenylethanol (1). A solution of 50 mg (0.21 mmol) of **6** in 10 mL of methanol was hydrogenated at room temperature and atmospheric pressure, using Pd/C 5% (5 mg) as a catalyst, within 12 h. After filtration of the catalyst and evaporation of the solvent, 43 mg of **1** (>95% yield) was obtained.

(1*R*,2*S*)-2-Amino-1,2-diphenylethanol (2). Using the above procedure, **2** was quantitatively obtained from **7**.

Both **1** and **2** possessed ^{1}H and ^{13}C NMR spectra and optical rotation values identical to those of commercial samples.

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