Does a Chiral Alcohol Really Racemize when Its OH Group Is Protected with Boyer's Reaction?

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ABSTRACT Chiral reactants have been employed for assessing the real stereochemistry of the $BiBr_3$-catalyzed synthesis of benzylic ethers, a very useful reaction for protecting alcoholic groups. The results of this investigation are in clear contrast with the conclusions of previous studies (Boyer et al., Tetrahedron 2001;57:1917–1921). Indeed, chiral GC-MS analysis of the ethereal products gives unequivocal evidence of the complete racemization of the benzylic moiety and the complete retention of configuration of the protected alcoholic substrate. Such findings make $BiBr_3$ a powerful and stereochemically preservative catalyst for benzylation of chiral alcohols, and a potential candidate for orthogonal protecting group strategies applicable to polyhydroxy compounds. *Chirality 22:88–91, 2010.*

KEY WORDS: bismuth bromide; chiral alcohols; configuration determination; heterogeneous catalysis; benzylic ethers; protecting groups

INTRODUCTION

Benzyl groups are frequently used as protecting agents of hydroxyl functions in multistep organic syntheses. The reaction of the alcoholic substrate with benzyl bromide and a strong base, such as sodium hydride, is the most common method to obtain benzyl ethers.[1] Alcohols sensitive to basic conditions can be treated with a benzyl imidate (e.g., trichloroacetimidate) in the presence of trifluoromethanesulfonic acid.[2] A recent study employs a benzyl pyridinium salt as a benzyl donor for alcohols.[3]

The success of benzyl ethers as protective synthetic intermediates of alcoholic groups mainly lies in their aptitude to release the benzyl moiety under the action of different reagents, which can be chosen depending on the sensitivity of the molecule to reaction conditions.[4] The presence of suitable functional groups on the phenyl ring of benzylic reagents can modulate their protecting/deprotecting features toward different OH groups and, therefore, enhance their applicability as orthogonal protecting groups for polyhydroxy compounds.[5] However, it would be highly desirable to obtain benzyl ethers (**BnOR**) from alcoholic substrates (**ROH**) by using the corresponding benzyl alcohols (**BnOH**), which are the most convenient sources of benzyl groups.[6] To this end, Boyer et al. proposed $BiBr_3$ as a catalyst for a very simple and efficient etherification reaction (eq. 1),[7] specific for benzylic alcohols and occurring under mild conditions (room temperature (RT) and CCl_4 as a neutral solvent).

$$\mathbf{BnOH} + \mathbf{ROH} \xrightarrow[CCl_4\ RT]{BiBr_3} \mathbf{BnOR} \qquad (1)$$

Boyer et al. investigated the stereochemistry of eq. 1 by using several mixtures of enantiopure and racemic alcohols (**BnOH** = (*R*)- or *rac*-1-phenylethanol (**1**); **ROH** = (*S*)- or *rac*-2-butanol, (*S*)- or *rac*-2-octanol) and by monitoring the reaction by standard GC analysis and optical rotation measurements.[8] On these grounds, they concluded that the aliphatic **R** moiety in the **BnOR** product is completely (**ROH** = 1-phenylethanol, 2-octanol) or almost completely (**ROH** = 2-butanol) racemized, whereas the configuration of the benzylic carbon atom of **Bn** is completely retained (Table 1 in Ref. 8). The loss of stereochemical integrity of the C—O bond of **ROH** deprives Boyer's reaction of any real synthetic application and benzyl alcohols of any use as protecting reactant in multistep procedures involving chiral alcohols. Indeed, to the best of our knowledge, the reaction has never been reported in literature after Boyer's work.[7,8]

RESULTS AND DISCUSSION

The above stereochemical pattern is completely reversed by our results. Indeed, in the course of a study on the gas-phase behavior of protonated chiral ethers, we had to synthesize small amounts of diastereoisomeric 1-(2-butyloxy)ethylbenzenes (**2**). Strictly following Boyer's procedure,[7] (+)-(*R*)-1-phenylethanol ($\mathbf{1_R}$; FLUKA *R/S* > 99/1 –1.25 mmol in 2 ml of CCl_4) was added to a stirred solution of (−)-(*R*)-2-butanol (ALDRICH *R/S*∼92/8 –1.25 mmol) and $BiBr_3$ (ALDRICH ≥98% –1.25 mmol) in 3 ml of

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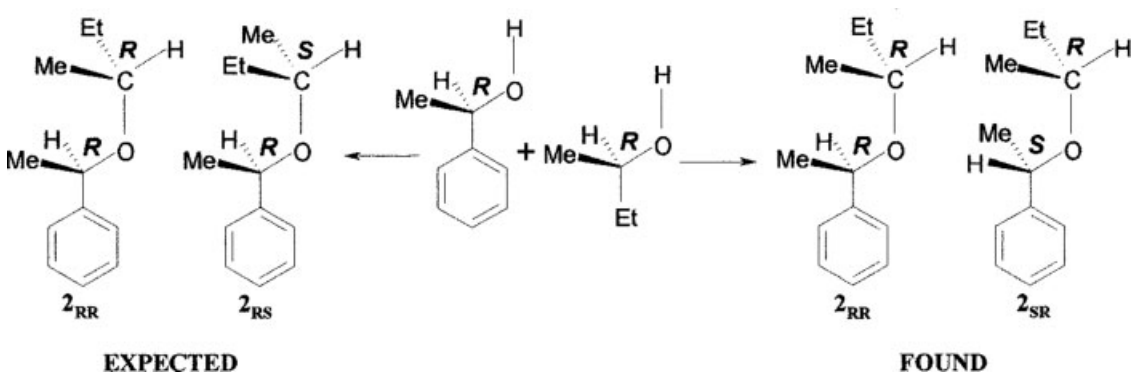
TABLE 1. GC-MS monitoring of the reaction using 1-phenylethanol and 2-butanol

Alcoholic reagents	Entry	Time (min)	$\mathbf{1_R}$ (%)	$\mathbf{1_S}$ (%)	1_{total} (a.u.)[a]	$\mathbf{2_{SR}}$ (%)	$\mathbf{2_{RS}}$ (%)	$\mathbf{2_{RR}}$ (%)	$\mathbf{2_{SS}}$ (%)	2_{total} (a.u.)[a]
R-1-Phenylethanol ($\mathbf{1_R}$)	1	<1	49.9	50.1	460	47.2		52.8		290
						93.8	6.2	93.8	6.2	
2-Butanol (R:S~ 92:8)	2	25	48.8	51.2	20	47.7		52.3		830
						93.1	6.9	93.1	6.9	
R-1-Phenylethanol ($\mathbf{1_R}$)	3	<1	50.4	49.6	300	43.9		56.1		290
						8.9	91.1	8.0	92.0	
2-Butanol (R:S~ 8:92)	4	25	51.6	48.4	22	51.2		48.8		790
						7.3	92.7	6.7	93.3	
S-1-Phenylethanol ($\mathbf{1_S}$)	5	<1	6.3	93.7	590	46.2		53.8		30
						100.0	n.d.[b]	100.0	n.d.[b]	
2-Butanol (R:S~ 92:8)	6	25	47.7	52.3	10	49.4		50.6		800
						93.0	7.0	93.0	7.0	
R-1-Phenylethanol ($\mathbf{1_R}$)	7	<1	69.3	30.7	770	50.8		49.2		980
						48.0	52.0	51.5	48.5	
rac-2-Butanol	8	25	50.2	49.8	15	48.9		51.1		910
						51.1	48.9	49.6	50.4	

The GC signals of the diastereomeric ethers **2** have been assigned by comparison with authentic standard compounds.* Uncertainty ca. 5%.
[a]GC peak area (Arbitrary Units).
[b]Not detectable.



Scheme 1. Expected vs. found stereochemical results for entries 1 and 2 in Table 1.

CCl_4 at RT. Surprisingly enough, we did not find the expected almost equimolar mixture of the (*R*)-1-((*R*)-2-butyloxy)ethylbenzene ($\mathbf{2_{RR}}$) and (*R*)-1-((*S*)-2-butyloxy) ethylbenzene ($\mathbf{2_{RS}}$) diastereoisomers (left side of Scheme 1).*[8]

Indeed, after the complete addition of the $\mathbf{1_R}$ reactant to $BiBr_3$/**ROH**, a small sample of the reaction mixture was analyzed by GC-MS using a chiral column (CHROMPACK CP-Chirasil-Dex CB, L 25 m, ID 0.25 mm, d_f 0.25 μm).† The analysis revealed that, after less than 1 min, the $\mathbf{1_R}$ reactant was completely racemized ($\mathbf{1_R}$ and $\mathbf{1_S}$ in Fig. 1 and entry 1 in Table 1). At the same time, the predominant formation of $\mathbf{2_{RR}}$ was accompanied by an equimolar amount of the (*S*)-1-((*R*)-2-butyloxy)ethylbenzene ($\mathbf{2_{SR}}$) diastereoisomer (right side of Scheme 1), instead of the expected (*R*)-1-((*S*)-2-butyloxy)ethylbenzene ($\mathbf{2_{RS}}$) one.

It is worth noting that the yield ratios $\mathbf{2_{RR}/2_{RS}}$~$\mathbf{2_{SR}/2_{SS}}$ closely resemble that of the starting 2-butanol even after 25 min reaction time, when the racemic benzylic alcohol **1** has almost completely reacted (Fig. 2 and entry 2 in Table 1).

The procedure was repeated by using (+)-(*S*)-2-butanol (ALDRICH *R/S*~8/92). The results, summarized in entries 3 and 4 of Table 1, fully conform to those reported in entries 1 and 2, the only obvious differences being the consequence of the opposite configuration of the starting 2-butanol (i.e., $\mathbf{2_{RR}/2_{RS}}$~$\mathbf{2_{SR}/2_{SS}}$~8:92).*

Of course, when the (*S*)-enantiomer of 1-phenylethanol ($\mathbf{1_S}$; FLUKA *S/R*>99/1) and the (−)-(*R*)-2-butanol (*R/S*~92/8) are used as reagents (entries 5 and 6 in Table 1), the stereochemical results for products **2** closely resemble those reported in entries 3 and 4 in Table 1, even if in this case the racemization of the benzylic reactant $\mathbf{1_S}$ is not as

*For ethers $\mathbf{2_{XY}}$ and $\mathbf{3_{XY}}$, the X label refers to the chirality of the benzylic carbon atom, whereas the Y one indicates the stereochemistry of the 2-alkyl moiety.
†Twenty microliters of the reaction mixture was diluted in 1 ml of CCl_4 containing 1-ethylnaphtalene as an internal standard, and the resulting solution was analyzed without any further manipulation.

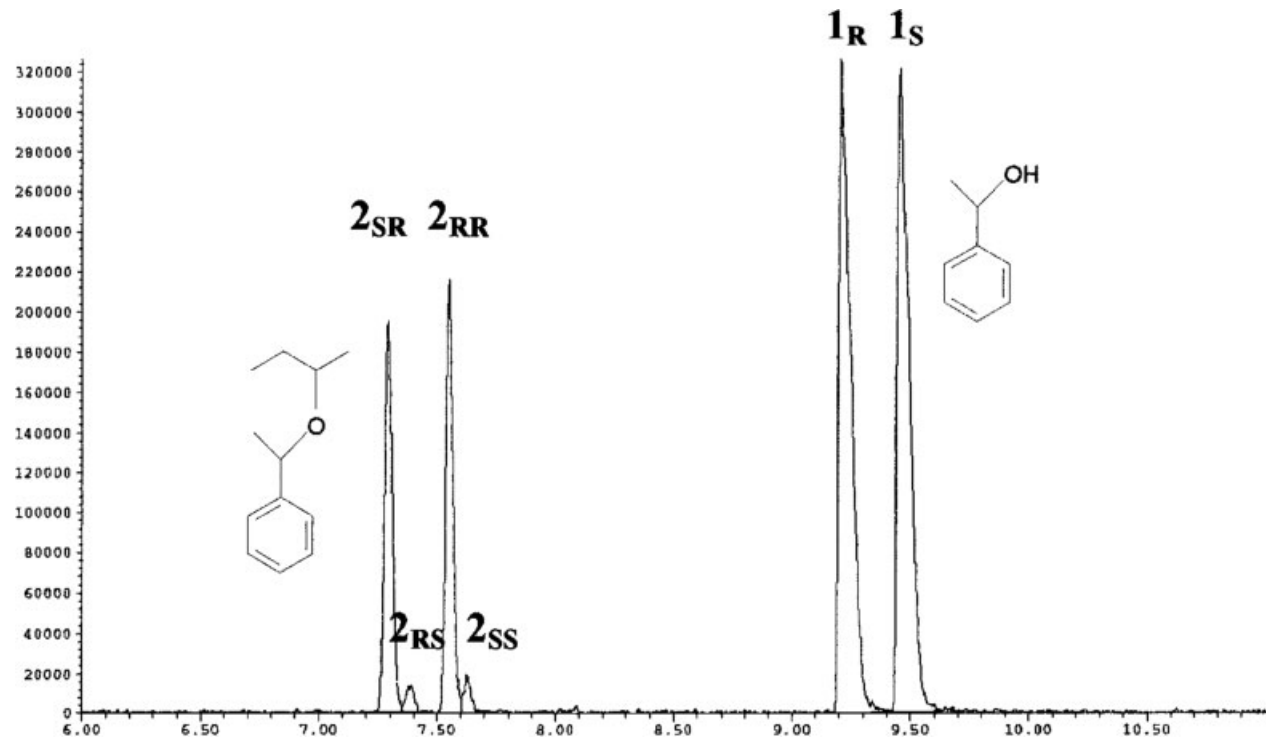


Fig. 1. GC chromatogram relative to entry 1 in Table 1.

fast as the previous cases (cf. entry 5 with entries 1 and 3 in Table 1).

Finally, a product ratio $\mathbf{2_{RR}}$:$\mathbf{2_{RS}}$:$\mathbf{2_{SR}}$:$\mathbf{2_{SS}}$ = 1:1:1:1 was found from the reaction of (+)-(*R*)-1-phenylethanol ($\mathbf{1_R}$) and *rac*-2-butanol (entries 7 and 8 in Table 1) under the same conditions.

These findings unequivocally point to the complete racemization of the benzylic carbon atom and the complete

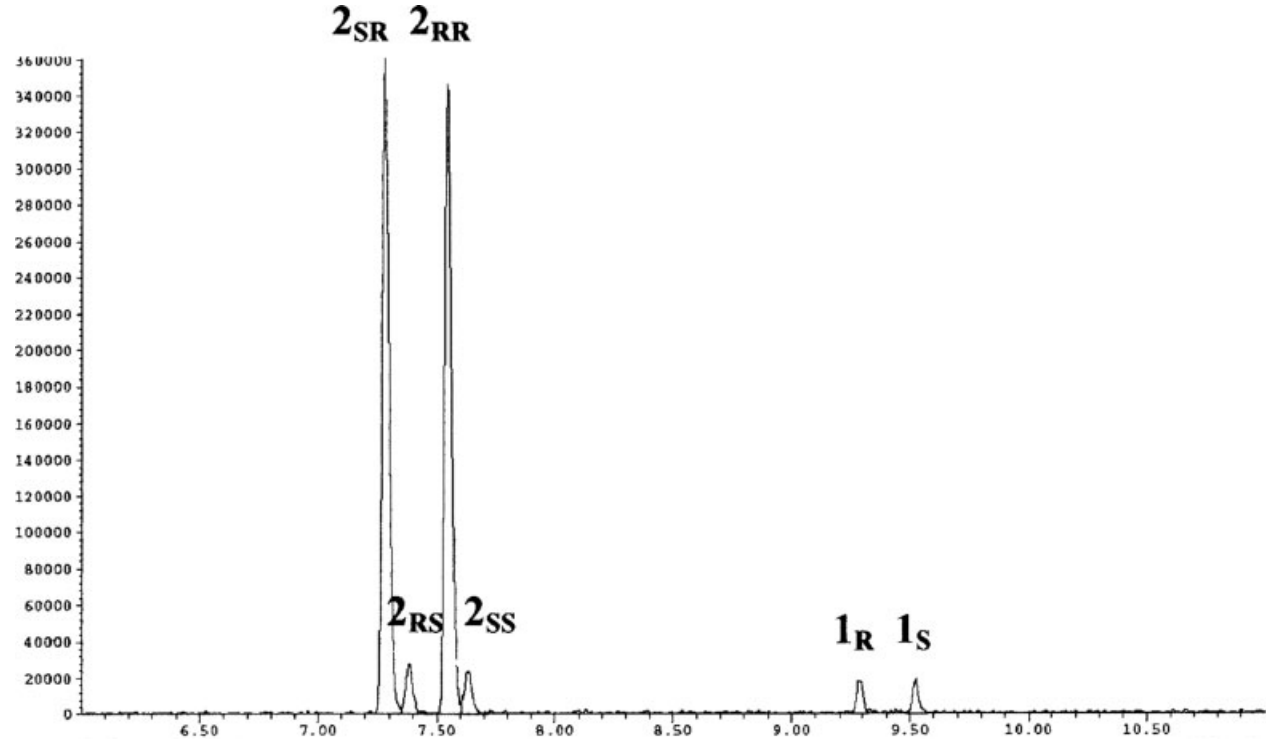


Fig. 2. GC chromatogram relative to entry 2 in Table 1.

TABLE 2. GC-MS monitoring of the reaction using 1-phenylethanol and 2-octanol

Alcoholic reagents	Entry	Time (min)	$\mathbf{1_R}$ (%)	$\mathbf{1_S}$ (%)	1_{total} (a.u.)[a]	$\mathbf{3_{SR}}$ (%)	$\mathbf{3_{RS}}$ (%)	$\mathbf{3_{RR}}$ (%)	$\mathbf{3_{SS}}$ (%)	3_{total} (a.u.)[a]
R-1-phenylethanol ($\mathbf{1_R}$)	1	<1	54.2	45.8	560	56.5	n.d.[b]	43.5	n.d.[b]	50
R-2-octanol (e.e. 98%)	2	25	54.3	45.7	90	50.4	n.d.[b]	49.6	n.d.[b]	910
R-1-phenylethanol ($\mathbf{1_R}$)	3	<1	50.0	50.0	530	n.d.[b]	57.6	n.d.[b]	42.4	110
S-2-octanol (e.e. 98%)	4	25	53.0	47.0	50	n.d.[b]	54.3	n.d.[b]	45.7	940

The GC signals of the diastereomeric ethers **3** have been assigned assuming the same elution order for these compounds and for the corresponding **2** analogues on the same chiral column.* Uncertainty ca. 5%.
[a]GC peak area (Arbitrary Units).
[b]Not detectable.

retention of configuration of the 2-butyl moiety in the formation of products **2**, which is in marked contrast with Boyer's conclusions.[8]

To gather further confirmation of our unexpected results, we decided to repeat Boyer's synthesis using 2-octanol instead of 2-butanol as the **ROH** substrate.[8] The results, reported in Table 2, show that the formed 1-(2-octyloxy)ethylbenzene isomers (3)* exhibit a stereochemistry that is consistent with the fast racemization of the starting chiral 1-phenylethanol and the complete retention of configuration of the 2-octyl moiety. This, a stereochemical result, is opposite again to that of Boyer!

CONCLUSIONS

Boyer et al. proposed an efficient method for the synthesis of benzylic ethers under mild conditions, but their conclusions about the stereochemistry of the reaction appear wrong. The results of our preliminary work enhance the applicability of the method for protecting chiral alcoholic groups. Indeed, a protecting agent preserving the configuration of the protected group is of great value for synthetic purposes. In this context, the potential of $BiBr_3$ as a catalyst for protection of chiral alcoholic functionalities (e.g., in oligosaccharides chemistry) with easily accessible reactants (i.e., substituted benzylic alcohols) deserves more attention.

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