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Boyer's Reaction and Transetherification: Mechanism and New Perspectives

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ABSTRACT The progress and stereochemistry of Boyer's reaction were analyzed using several simple, chiral, alcoholic substrates, a variable amount of $BiBr_3$ and different solvents. Basic solvents inhibit the reaction, while cyclohexane works very well; thus, it was our choice for the present study. In contrast to previous works, $BiBr_3$ behaves as a true catalyst, being not consumed during the reaction. Although poisoning of the catalyst occurs to some extent, it does not prejudice the reaction yields (>90%). Gas chromatography/mass spectrometry (GC–MS) monitoring of the reaction revealed that, for example, in the presence of alcohol **rac-1**, isomeric ethers **4** transetherificate to **3**. We propose a unifying mechanistic model for both Boyer's and transetherification reactions, in which the electronic properties of n-adducts intermediates, formed by combination of bismuth(III) of $BiBr_3$ and oxygen atoms of alcohols and ethers, play the key role for both the reactivity and the stereochemical outcome of the reaction. *Chirality 28:269–275, 2016.* © 2016 Wiley Periodicals, Inc.

KEY WORDS: ethers; stereoselectivity; bismuth bromide; benzylation; Lewis acid catalysis

INTRODUCTION

After our previous work on the stereochemistry of Boyer's reaction (Eq. 1) published some years ago,[1] we now return to the same topic, because in our opinion the potentialities of the reaction has not been completely explored as a consequence of the erroneous attribution of its stereochemical outcome in the seminal work,[2] as well as in other works and reviews published in subsequent years.[3–5]

$$\mathrm{ROH} + \mathrm{R'OH} \underset{-\mathrm{H_2O}}{\overset{\mathrm{BiBr_3}}{\rightarrow}} \mathrm{ROR'} \qquad (1)$$

In fact, Boyer's reaction is relevant from a different point of view. First, the number of synthetic routes to ethers is rather low, if compared to other common functional groups; therefore, development of further synthetic approaches is highly desirable. Second, the classical methods, first of all Williamson's reaction, often need extreme environmental conditions (i.e., alkaline media, which exclude base-sensitive compounds as substrates), while Boyer's method needs only mildly acidic conditions and room temperature. Third, Boyer's reaction makes direct use of alcoholic substrates, a class of substances relatively easy to synthesize or available from commercial sources. Fourth, in Boyer's reaction several derivatives of benzylic alcohol have been used,[2,4] but if other alcoholic substrates are also effective, it is still an open question. Fifth, even limiting the reaction to benzylic substrates, these are widely employed as protecting groups of alcoholic functions,[6–9] therefore the availability of "soft" methods such as Boyer's one, where benzylic alcohols are used as reactant, appears very desirable. The erroneous conclusion of Boyer et al.[4] about the loss of configuration of chiral alcoholic substrates probably limited the application and the success of the method. The aim of this work was to investigate the mechanism of the reaction and to analyze its main potentialities. Moreover, it is not clear if a stoichiometric amount of $BiBr_3$ is really needed, which is another point we want to investigate. Finally, CCl_4 certainly is not the more desirable solvent, especially on large-scale applications; therefore, first of all, we looked for an alternative, more ecologically friendly solvent.

MATERIALS AND METHODS

All the alcoholic substrates, as well as solvents, catalyst $BiBr_3$, and internal standard were purchased from commercial sources and used without any further purification. The reaction mixture (each component 0.625 M in 4 ml closed vial) was continuously stirred and systematically sampled by taking a small amount of solution, and then analyzed by a gas chromatography/mass spectrometry (GC–MS) system equipped with a chiral column (*CP-Chirals-Dex CB*, L 25 m, ID 0.25 mm, d_f 0.25 μm) in the 40–170°C temperature range. The synthesis of an isomeric mixture of ethers **3** and **4**, not commercially available, was carried out by means of the same above simple procedure in 20-ml vials. The raw mixture of ethereal diastereoisomers was filtered, dried on anhydrous Na_2SO_4, and purified by preparative GC (provided with an OV-17 column on Chromosorb WAW 80-100 mesh) at 170°C. Control tests were performed by means of a linear ion trap mass spectrometer coupled with an electrospray source (ESI-MS-IT - Applied Biosystems, Foster City, CA, Mod. 3200Q LC/MS/MS).

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Owing to the heterogeneous nature of the catalytic process and poisoning effects (see below), the reproducibility of reaction rates of replicated experiments is rather low (relative error about 10%). Therefore, reaction kinetics cannot be evaluated and the experimental data are discussed on the grounds of reaction progress, i.e., relative increasing/decreasing trends of reagents and products along reaction time.

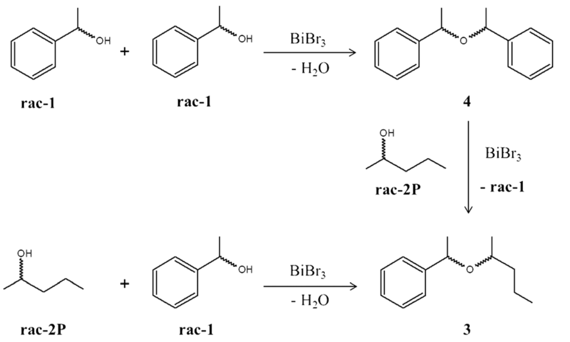
RESULTS AND DISCUSSION

Choice of an Alternative Reaction Solvent

All the experiments specifically addressed to the selection of alternative reaction solvents were performed under the same concentration (0.625 M) and temperature (25°C) conditions already employed in previous works, and using racemic mixture of reactants. In acetonitrile and in ethyl acetate, Boyer's reaction does not take place. Indeed, equimolar mixtures of the racemate of 2-pentanol (**rac-2P**) and of the racemate of 1-phenylethanol (**rac-1**)[6] in acetonitrile were completely degraded to several subproducts when $BiBr_3$ was added in an equimolar amount, while they were completely inert in ethyl acetate under the same conditions. Probably the basic nature of these solvents inhibits the acidity of bismuth in $BiBr_3$ towards alcoholic substrates. Accordingly, in CH_2Cl_2, a less basic solvent, 1-phenylethyl 2-pentyl ethers (**3**) and *di*-1-phenylethyl ethers (**4**), are promptly formed from the combination of **rac-2P** and **rac-1** and by reaction of **rac-1** with itself. Figure 1 shows the composition of the reaction mixture at the corresponding reaction time. In this figure, as well as in the other ones reported in this article and in the supporting information section, the experimental points represent mean values obtained from at least three replicated experiments. Because of the intrinsic poor reproducibility, about 10% relative error should be taken into account. In order to specify the stereochemistry of the ethereal products, a two-letter subscript (XY) was associated with the corresponding representative number, where X indicates the R/S configuration of the benzylic center, while Y states the stereochemistry of the other chiral carbon atom of the ether. Note that production of ethers **3** is not stereoselective ($\mathbf{3_{RR}}$:$\mathbf{3_{SS}}$:$\mathbf{3_{RS}}$:$\mathbf{3_{SR}}$ = 1:1:1:1). Ethers **4** are also initially formed without any significant stereoselectivity, but they seem to undergo an epimerization process ($\mathbf{4_{RR}} \leftrightarrows \mathbf{4_{RS}} \leftrightarrows \mathbf{4_{SS}}$) favoring the enantiomeric homochiral forms ($\mathbf{4_{RR}}$ e $\mathbf{4_{SS}}$) over the meso heterochiral one $\mathbf{4_{RS}}$ (inset in Fig. 1). It is also worth noting the absolute absence of *di*-2-pentyl ether among the reaction products, pointing out the inability of the aliphatic secondary alcohols **rac-2P** to self-condense to ethers, different from the "activated," benzylic alcohol **rac-1**, under the same conditions. However, after a few hours the reaction in CH_2Cl_2 stops, probably because of catalyst poisoning, as pointed out by the persistence of a substantial amount of reagents after a couple of hours, when the composition of the reaction mixture does not change any more (Fig. 1), despite an equimolar amount of $BiBr_3$ was employed.

We found that in acetonitrile, ethyl acetate, CH_2Cl_2, as well as in CCl_4,[1] the salt $BiBr_3$ disperses rather than dissolves, suggesting the occurrence of a heterogeneous catalytic process.

In passing to cyclohexane as a solvent, the general reactivity pattern observed in CH_2Cl_2 qualitatively holds (cf. Figs. 1 vs. 2), but in this apolar, hydrophobic solvent the reaction seems much more lively. In fact, reaction yields increase, as indicated either by the lower residual amount of substrate **rac-2P** at the end of the reaction, and by fast decreasing of the benzylic reagent (**rac-1**) up to its complete disappearance. At the beginning of the reaction, in cyclohexane at 25°C, besides the formation of "symmetric" ethers **4** from **rac-1**, "asymmetric" ethers **3** mainly arise from the condensation of **rac-1** with **rac-2P** (Scheme 1). However, for a reaction time longer than 2 hours (i.e., in the absence of **rac-1**): 1) the relative amount of ethers **3** *slowly* increases at the expense of both **rac-2P** and the "symmetric" ethers **4**, suggesting the occurrence of the *transetherification* reaction **4** → **3** (Scheme 1); 2) diastereomeric distribution of ethers **4** changes favoring



Scheme 1. Competitive etherification and transetherification reactions under Boyer's conditions.

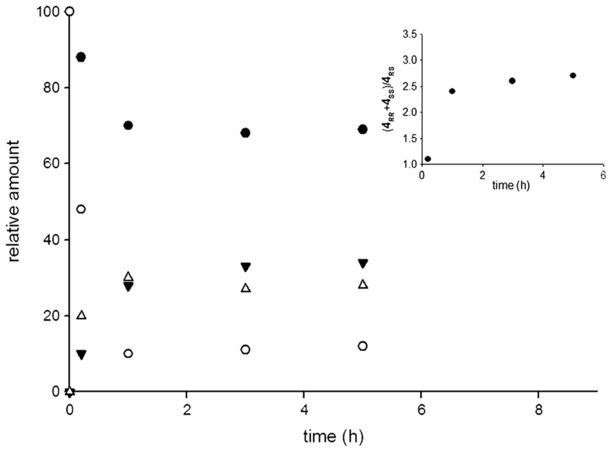


Fig. 1. Reaction in CH_2Cl_2 between the racemate of 2-pentanol (**rac-2P**) and the racemate of 1-phenylethanol (**rac-1**) in the presence of an equimolar amount of $BiBr_3$. Full circle: **rac-2P**; empty circle: **rac-1**; full triangle: **3** ($\mathbf{3_{RR}}$: $\mathbf{3_{SS}}$: $\mathbf{3_{RS}}$: $\mathbf{3_{SR}}$ = 1: 1: 1: 1); empty triangle: **4**. Inset: ($\mathbf{4_{RR}}$ + $\mathbf{4_{SS}}$)/$\mathbf{4_{RS}}$.

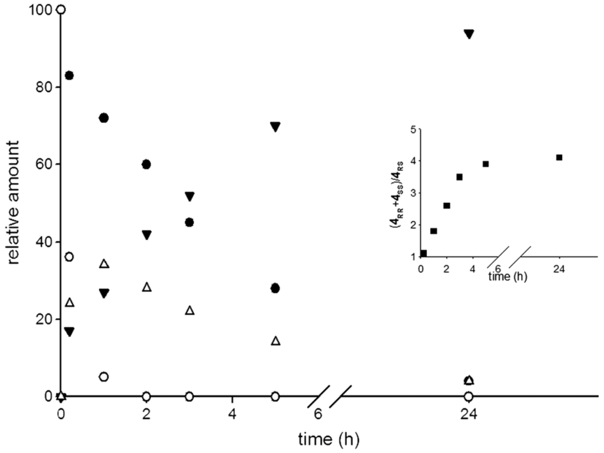


Fig. 2. Reaction in cyclohexane between the racemate of 2-pentanol (**rac-2P**) and the racemate of 1-phenylethanol (**rac-1**) in the presence of an equimolar amount of $BiBr_3$. Full circle: **rac-2P**; empty circle: **rac-1**; full triangle: **3** ($\mathbf{3_{RR}}$: $\mathbf{3_{SS}}$: $\mathbf{3_{RS}}$: $\mathbf{3_{SR}}$ = 1: 1: 1: 1); empty triangle: **4**. Inset: ($\mathbf{4_{RR}}$ + $\mathbf{4_{SS}}$)/$\mathbf{4_{RS}}$.

the homochiral forms ($\mathbf{4_{RR}}$ e $\mathbf{4_{SS}}$) over the meso heterochiral one ($\mathbf{4_{RS}}$), as already observed in CH_2Cl_2, although to a higher extent (cf. insets in Figs. 1, 2), confirming the occurrence of $\mathbf{4_{RR}}\leftrightarrows\mathbf{4_{RS}}\leftrightarrows\mathbf{4_{SS}}$ epimerization.

The residual amount of **rac-2P** and **4** after 24 h (Fig. 2) suggests that poisoning of the catalyst cannot be excluded also in cyclohexane. As in CH_2Cl_2, also in cyclohexane *di*-2-pentyl ethers are not formed at all, and $BiBr_3$ is suspended rather than dissolved in the reaction medium. Therefore, cyclohexane seems a good alternative to CCl_4, and thus we decided to carry on our work making use of cyclohexane as a solvent.

Role of BiBr$_3$

Before proceeding, control experiments were performed in order to ascertain the catalytic nature of the process in cyclohexane and the susceptibility of the alcoholic reagents to $BiBr_3$. First of all, a suspension of $BiBr_3$ in cyclohexane was stirred at room temperature for 2 h. By means of a centrifuge, the solid was separated and the liquid phase was then diluted in methanol and analyzed by ESI-MS-IT, revealing the complete lack of any signal attributable to bismuth-containing compounds. Even more, a mixture of **rac-1** and **rac-2P** dissolved in such a liquid phase does not react after more than 24 h. Similarly, the stirred 1:1 solution of **rac-1** and **rac-2P** in cyclohexane proved unreactive (even warming the solution up to 65°C), until $BiBr_3$ was added. Therefore, $BiBr_3$ is a true catalyst for the reaction of Figure 2, and in our opinion it acts in the solid state (heterogeneous catalysis), in contrast to previous conclusions.[4,5] Furthermore, a cyclohexane solution of a mixture of simple primary and secondary alcohols (1-pentanol, 1-heptanol, 2-butanol, 2-pentanol, 2-heptanol, and 2-decanol) proved completely inert, even in the presence of $BiBr_3$, pointing out that "activated" alcohols are needed for the reaction. The progressive increase of the $(\mathbf{4_{RR}} + \mathbf{4_{SS}})/\mathbf{4_{RS}}$ ratio (inset in Fig. 2) suggests that a similar reactivity check for 1-phenylethanol (**1**) deserves more attention, as shown in the next section.

Reaction of (–)-(S)-1-Phenylethanol in Cyclohexane

In order to deeply investigate the reactivity of **1** and the intrinsic behavior of "symmetric" ethers **4** (without the interference of other reactants), the chiral alcohol (–)-(*S*)-1-phenylethanol ($\mathbf{1_S}$; Fluka, Buchs, Switzerland, *R*/*S* < 1/99), instead of its racemate, was dissolved in cyclohexane. At room temperature, the inertness of this stirred solution was ascertained for 2 h by GC–MS monitoring. Then dispersing an equimolar amount of $BiBr_3$ in the same solution promptly opens a very lively reactivity scenario (Fig. 3). Indeed, the results point out the fast $\mathbf{1_S}\leftrightarrows\mathbf{1_R}$ racemization of the starting substrate and the substantial lack of diastereoselectivity in the formation of ethers **4** (open squares in the inset of Fig. 3 not far from unit within the first 1.5 h), whose subsequent $\mathbf{4_{RR}}\leftrightarrows\mathbf{4_{RS}}\leftrightarrows\mathbf{4_{SS}}$ epimerization, *after disappearance of either the starting alcohol* $\mathbf{1_S}$ *and the formed enantiomer* $\mathbf{1_R}$, goes on to make $(\mathbf{4_{RR}} + \mathbf{4_{SS}})/\mathbf{4_{RS}} = 4.2$. In the meantime, the initial enantiomeric ratio $\mathbf{4_{SS}}/\mathbf{4_{RR}} = 1.4$ decreases to 1.0 (full circles in the inset of Fig. 3).

It should also be noted that once the starting alcohol $\mathbf{1_S}$ and its enantiomer $\mathbf{1_R}$ disappear and without any other alcoholic reagent in solution, the total amount of ethers **4** do not change any more, confirming the occurrence of the abovementioned **4** → **3** transetherification when **rac-2P** is available (Fig. 2 and Scheme 1).

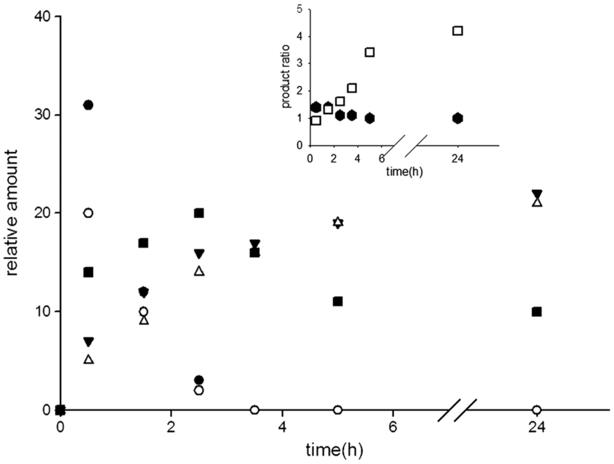


Fig. 3. Reaction of (–)-(S)-1-phenylethanol ($\mathbf{1_S}$) in the presence of an equimolar amount of $BiBr_3$ dispersed in cyclohexane. Timescale starting from the introduction of $BiBr_3$. Full circle: $\mathbf{1_S}$; empty circle: $\mathbf{1_R}$; full triangle: $\mathbf{4_{SS}}$; empty triangle: $\mathbf{4_{RR}}$; square: $\mathbf{4_{RS}}$. Inset: circle $\mathbf{4_{SS}}/\mathbf{4_{RR}}$; square $(\mathbf{4_{RR}} + \mathbf{4_{SS}})/\mathbf{4_{RS}}$.

Reaction Between (–)-(R)-2-Pentanol and the Racemate of 1-Phenylethanol in Cyclohexane

Having in mind the results of Figure 2, in the next step of our work we focused on the behavior of the other alcoholic reactant **rac-2P**. However, taking into account the fast racemization of $\mathbf{1_S}$ (Fig. 3), we decided to make direct use of the racemate **rac-1**, rather than its pure enantiomer $\mathbf{1_S}$, in all the experiments below. Moreover, being the reaction of **rac-1** with itself, to yield ethers **4**, faster than its combination with **rac-2P**, to yield ethers **3** (cf. **4** vs. **3** yields within the first hour in Fig. 2), with the aim to maintain the concentration of **rac-1** as low as possible, we also decided to modify the original Boyer's procedure as follows: **rac-1** was dissolved in cyclohexane and added dropwise to a cyclohexane solution containing the chiral alcohol (–)-(*R*)-2-pentanol ($\mathbf{2P_R}$; Aldrich, Milwaukee, WI, *R*/*S* > 98/2) in the presence of an equimolar amount of solid $BiBr_3$. As a matter of fact, such a procedure lead to a lower production of "symmetric" ethers **4** in favor of the desired "asymmetric" **3** ones (cf. Figs. 2 vs. 4). It is worth noting that: 1) ethers **3** are formed as $\mathbf{3_{RR}}$ e $\mathbf{3_{SR}}$ (in 1:1 ratio), whose 2-pentyl moiety maintains its original chirality of $\mathbf{2P_R}$; 2) $\mathbf{3_{RS}}$, $\mathbf{3_{SS}}$, as well as *di*-2-pentyl ethers, were not found among the reaction products; 3) GC–MS analysis reveal that, unlike phenylethanol (Fig. 3), the chiral aliphatic substrate $\mathbf{2P_R}$ does not undergoes any racemization process.

BiBr$_3$ as a "True" Catalyst

One more question to be addressed before a mechanistic hypothesis can be formulated is whether the catalytic process really needs an equimolar amount of $BiBr_3$, as proposed by Boyer et al.[2] To this end, several experiments were performed in cyclohexane adding **rac-1** dropwise to solutions of $\mathbf{2P_R}$ containing 10%, 20%, or 50% of $BiBr_3$ with respect to the molar concentration of the alcoholic reactants (Figs. 1-SM, 2-SM and 3-SM, respectively; Supporting Information). The results of these experiments can be summarized as follows. Within 24 h: 1) in all cases the total molar amount of ethers produced (**3** + **4**) is higher than that of the catalyst employed, 2) most of **rac-1** is consumed, but some $\mathbf{2P_R}$ remain unreacted; 3) the higher the amount of $BiBr_3$ used, the higher the reaction yield and the extent of both $\mathbf{4_{RR}} \leftrightarrows \mathbf{4_{RS}} \leftrightarrows \mathbf{4_{SS}}$ epimerization and $\mathbf{4} \rightarrow \mathbf{3}$ transetherification; 4) adding further $BiBr_3$ (30% stoichiometric) after 24 or 26 h (see footnotes in Figs. 1-SM and 2-SM, respectively), when the starting mixture practically is no more reactive, the reaction promptly restarts; 5) on the contrary, addition of further **rac-1** after 24 h does not modify the reactivity of the system (see footnote in Fig. 2-SM). This evidence point out that $BiBr_3$ behaves as a true catalyst towards alcoholic and ethereal reagents, but the incompleteness of the reaction, even when equimolar $BiBr_3$ was employed (Figs. 2, 4), suggests progressive poisoning of the catalyst, probably due to the formation of H_2O as a coproduct of the reaction.

To test this hypothesis, ancillary experiments were performed adding an equimolar amount of H_2O to the starting mixture of Figure 2 after 10 min (Fig. 4-MS) or at the beginning (Fig. 5-MS) of the reaction. Although replicated experiments provided rather scattered results (relative error about 20%), comparison of Figure 2 and Figures 4-SM/5-SM unequivocally reveals the progressive decreasing of the general reactivity pattern (namely, the lower extent of: i) $\mathbf{1_S} \leftrightarrows \mathbf{1_R}$ racemization, ii) $\mathbf{4_{RR}} \leftrightarrows \mathbf{4_{RS}} \leftrightarrows \mathbf{4_{SS}}$ epimerization, iii) $\mathbf{4} \rightarrow \mathbf{3}$ transetherification, as well as the lower absolute yields of products **3** and **4**), according to the H_2O inhibition hypothesis.

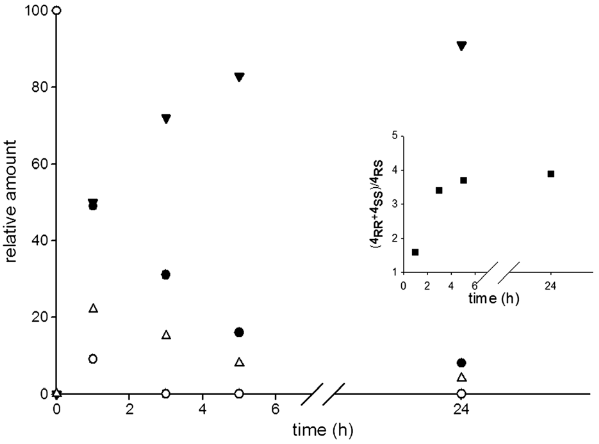


Fig. 4. Reaction between the racemate of 1-phenylethanol (**rac-1**) in cyclohexane added dropwise to a solution of (–)-(R)-2-pentanol ($\mathbf{2P_R}$) in cyclohexane containing equimolar $BiBr_3$. Full circle: $\mathbf{2P_R}$; empty circle: **rac-1** (dropwise added in about 15 minutes); full triangle: **3** ($\mathbf{3_{RR}}$:$\mathbf{3_{SR}}$ ~ 1:1); empty triangle: **4**. Inset: $(\mathbf{4_{RR}} + \mathbf{4_{SS}})/\mathbf{4_{RS}}$.

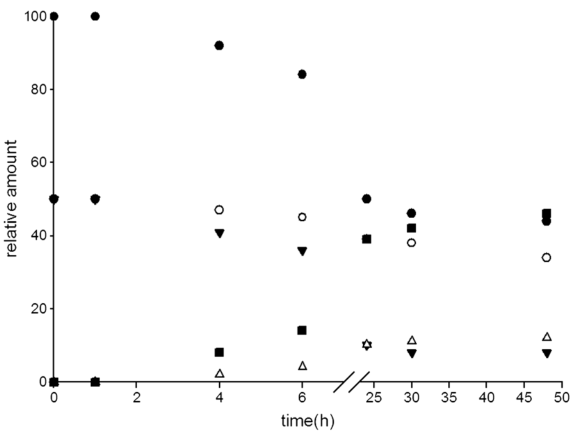


Fig. 5. $BiBr_3$ induced transetherification of diasteromeric di-1-phenylethyl ethers in cyclohexane with an equimolar mixture of 1-pentanol (**1P**) and 2-pentanol (**rac-2P**). Full circle: **4**; empty circle: **rac-2P**; full triangle: **1P**; empty triangle: **3**; square: **5**.

Other Observations

According to what Boyer et al. found in CCl_4,[2] benzyl alcohol proved less reactive than phenylethanol (**1**) in promoting the benzylation of alcohols, being about one order of magnitude slower, even increasing the temperature up to 65°C. Instead, warming the reaction mixtures containing **rac-1** lead to its substantial dehydration, yielding styrene.

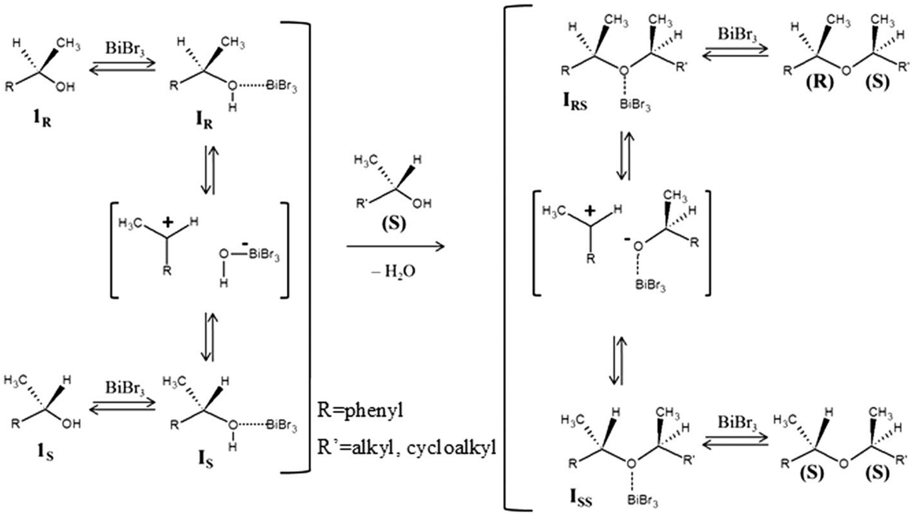
In cyclohexane, all the isomeric 1,2-, 1,3- and 1,4-metylcyclohexanols maintain their configuration at the alcoholic carbon atom when reacted with **rac-1** in the presence of $BiBr_3$ at room temperature, and the reaction is about as fast as that of simple secondary aliphatic alcohols (2-butanol, 2-pentanol, 2-eptanol, and 2-decanol), with reaction yields >90%.

Boyer's Reaction Mechanism

As a consequence of the wrong interpretation of the stereochemical outcome of the reaction, Boyer et al[2] proposed an erroneous model for the benzylation of alcohols, based on the loss of the stereochemical integrity of the substrate and the consumption of the catalyst,[4] which is in contrast to our findings. As the simplest conceivable mechanistic interpretation of our experiments, we propose that fast $\mathbf{1_S} \leftrightarrows \mathbf{1_R}$ racemization (Fig. 3) is a consequence of the reversible coordination of the acidic bismuth atom of $BiBr_3$ to the oxygen atom of $\mathbf{1_R}$ and $\mathbf{1_S}$ yielding the corresponding n-adducts $\mathbf{I_R}$ and $\mathbf{I_S}$ (left side, Scheme 2). In fact, it is well know that bismuth(III) is a *soft* Lewis acid[10–13] able to form coordination complexes with several class of basic compounds, including oxygenated substances.[14–17] Within $\mathbf{I_R}/\mathbf{I_S}$ adducts the C-O bond is weakened enough to induce the extended $\mathbf{1_S} \leftrightarrows \mathbf{1_R}$ racemization of the alcohol (Scheme 2) owing to "benzylic" stabilization of the incipient carbocation. With aliphatic or alicyclic alcohols, similar $\mathbf{I_S}$ and $\mathbf{I_R}$ intermediates (R = alkyl, cycloakyl) can also be formed, but the lack of a similar stabilizing effect makes racemization not energetically feasible under the same environmental conditions.

At room temperature, development of the positive charge at the "alcoholic" carbon atom of $\mathbf{I_R}/\mathbf{I_S}$ adducts (Scheme 2, R = phenyl) is not so extended to promote dehydration to the corresponding alkene (e.g., to obtain styrene from 1-phenylethanol, warming the solution up to refluxing is needed), but enough to allow the nucleophilic attack by any alcoholic substrate leading to the corresponding ether (right side, Scheme 2; e.g., **3** from alcohol **2**, and **4** from alcohol **1**) with retention of the configuration of the nucleophilic moiety and elimination of a molecule of water containing the oxygen atom of $\mathbf{I_R}/\mathbf{I_S}$.

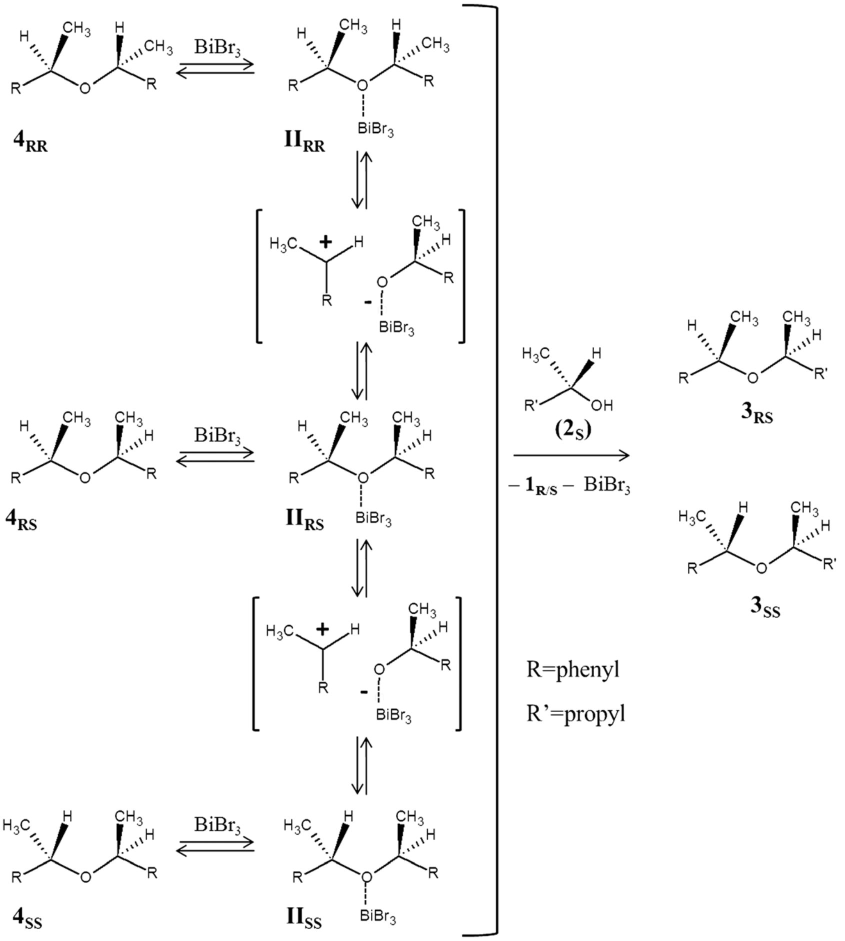
Several authors stated that the coordination number of Bi(III) complexes range from three to nine,[18–20] allowing ligand-to-ligand intermolecular interactions around the coordination sphere of Bi(III). In these optics, following the hypothesis of $\mathbf{I_R}/\mathbf{I_S}$ intermediates, preferential formation of ethers **4** over **3** ones at the beginning of the reaction (Fig. 2) could be the consequence of the greater local concentration of the aromatic alcohol **1** around adducts $\mathbf{I_R}/\mathbf{I_S}$ due to the capability of bismuth to form π-complexes



Scheme 2. Mechanism and stereochemistry of the etherification of alcohols under Boyer's conditions.

with the aromatic ring of 1-phenylethanol.[4] Of course, similar π-interactions are precluded in aliphatic and alicyclic alcohols.

The stereochemistry of the ethereal products does not allow a more intimate description of the nucleophilic step of the reaction (frontside vs. backside nucleophilic attack to I_R/I_S). Anyway, once formed, ethers **4** undergo a partial epimerization (**$4_{RR} \leftrightarrows 4_{RS} \leftrightarrows 4_{SS}$**). The simplest mechanistic interpretation of this process (left side, Scheme 3) is that the acidic bismuth atom of $BiBr_3$ coordinates the oxygen atom of **4** forming n-adduct intermediates (**II_{XY}** (X,Y = R and/or S)). The n-interaction weakens the C-O-



Scheme 3. Mechanism and stereochemistry of the transetherification reaction under Boyer's conditions.

C bonds of $\mathbf{II_{XY}}$ allowing inversion of configuration of both the X and Y benzylic moieties. Note that also "asymmetric" ethers **3** epimerize, inverting exclusively the configuration at its benzylic moiety (e.g., via $\mathbf{I_{RS}} \leftrightarrows \mathbf{I_{SS}}$ in Scheme 3), but the process (e.g., $\mathbf{3_{RR}} \leftrightarrows \mathbf{3_{SR}}$) is only barely detectable by GC–MS analysis, because epimerization does not change very much the $\mathbf{3_{RR}}:\mathbf{3_{SR}}$ = 1:1 distribution. In this view, intermediates $\mathbf{II_{XY}}$ play a key role in the mechanism of the transetherification reaction (right side, Scheme 3; next section), which is very similar to that shown in Scheme 2, with the only difference being that the leaving group is a molecule of alcohol instead of H_2O.

Transetherification Reaction

With the aim to investigate the transetherification reaction to a deeper extent, a mixture of ethers **4** (specifically synthesized, purified, and dissolved in cyclohexane) was added dropwise to a solution containing $BiBr_3$ and an equimolar mixture of 1-pentanol (**1P**) and the racemate of 2-pentanol (**rac-2P**). The results (Fig. 5) confirm the view, pointed out before, about the reaction of ethers **4** slower than that of the alcoholic substrate **1** towards the same **rac-2P** (cf. Figs. 5 vs 4). Moreover, the primary alcohol **1P** is about four times more reactive than the secondary analog **rac-2P** for the transetherification reaction under the same conditions (cf. product **3** vs. **5** in Fig. 5). Both of these results reflect the steric demand of intermediates **I** and **II** (Schemes 2 and 3) when undergoing nucleophilic attack by alcoholic reactants.

Another transetherification experiment was performed by dropwise addition of a mixture of ethers **3** (specifically synthesized, purified, and dissolved in cyclohexane) to a suspension of $BiBr_3$ in cyclohexane containing an equimolar mixture of 1-pentanol (**1P**) and the racemate of 2-hexanol. After more than 24 h, only a minor amount of 1-phenylethyl 1-pentyl ethers were formed, according to: 1) "benzylic" moiety of ethers **3** susceptible to nucleophilic reagents, in contrast to the "alkylic" 2-pentyl one; 2) primary 1-pentanol more effective than secondary 2-hexanol in promoting the transetherification reaction.

Further similar transetherification experiments using *tert*-butyl methyl ether gave more than an appreciable amount of *tert*-butyl 2-pentyl ether (about 10%, from **rac-2P**), and *tert*-butyl 1-pentyl ether (about 30%, from **1P**), showing the aptitude, under Boyer's conditions, at breaking the C-O bond of ethers bearing tertiary α-carbon atoms. In fact, under the same conditions, *di*-phenyl ether, allyl phenyl ether, and *di*-octyl ether proved completely unreactive.

Transetherification reaction, besides its growing interest for synthetic purposes,[21–24] deserves a deeper future investigation due its potential application in the production of added value chemicals from cheap, abundant, natural polysaccharides, e.g., cellulose,[25] lignin,[25–27] especially if mediated by a "green" metal like bismuth as a catalyst.

CONCLUSION

For Boyer's reaction, a useful process yielding ethers directly from alcohols under mild conditions, cyclohexane proved a solvent as good as CCl_4, in terms of reactivity and product yields, but much more convenient for both laboratory and industrial applications. Basic solvents, such as acetonitrile and ethyl acetate do not work at all, while CH_2Cl_2, a less basic solvent, ranks in the middle. In all these solvents $BiBr_3$ is not soluble, and all our experimental findings converge toward $BiBr_3$ acting as a true heterogeneous catalyst, which is not consumed during the reaction, but undergoes a poisoning process to a little extent (reaction yield >90%), probably induced by coproduced water, owing to the formation of the n-complex H_2O—$BiBr_3$. Accordingly, a general lower reactivity is observed when equimolar H_2O is added to the reaction mixture. Similar Lewis acid–base n-interactions could explain the lack of reactivity in basic media. We propose that, in cyclohexane, n-adducts ($\mathbf{I_R}/\mathbf{I_S}$) between the bismuth atom of $BiBr_3$ and the oxygen atom of alcoholic substrates play a key role in both the catalytic efficiency and the stereochemical outcome of the reaction. We guess that, within $\mathbf{I_R}/\mathbf{I_S}$ adducts, weakening of the C-O bond of "activated" alcoholic substrates (able to stabilize cationic α-carbon atom; e.g., **1**) allows both racemization of the alcoholic moiety in chiral $\mathbf{I_R}/\mathbf{I_S}$ and nucleophilic attack by another alcoholic substrate to form the corresponding ether. Self-reaction of alcohol **1** leads to isomeric ethers **4**, which partially epimerize ($\mathbf{4_{RR}} \leftrightarrows \mathbf{4_{RS}} \leftrightarrows \mathbf{4_{SS}}$) while undergoing a parallel transetherification process (e.g., **4** → **3** in the presence of 2-pentanol). Thus, it is reasonable that the "activated" benzylic carbon atoms of alcohol **1** and its symmetric ether **4** behave mechanistically similarly, the former being more reactive than the latter owing to steric factors within the corresponding n-complexes **I** and **II**, respectively.

To date, there are only a few examples of transetherification[21–24] reactions in the literature, despite that development of new strategies for the synthesis of ethers under mild conditions is highly desirable. However, in the last decade interest for this reaction has grown, mainly for its potential industrial applications.[25–27] To this end, work is in progress to investigate the efficiency of other bismuth(III)-based compounds in the transetherification reaction. Finally, the reactivity of *tert*-butyl methyl ether in the transetherification reaction also promises that other tertiary alcoholic and/or ethereal substrates (not only benzylic ones) can react under Boyer's conditions, which could be very useful in the production of high-value sugars from poor materials such as natural polysaccharides.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's web-site.

LITERATURE CITED

1. Fraschetti C, Speranza M, Filippi A. Does a chiral alcohol really racemize when its OH group is protected with Boyer's reaction? Chirality 2010;22:88–91.
2. Keramane E, Boyer B, Roque J, Pavia A. $BiBr_3$ an efficient catalyst for the benzylation of alcohols: 2-phenyl-2-propyl, a new benzyl-type protecting group. Tetrahedron Lett 2000;41:2891–2894.
3. Keramane E, Boyer B, Roque J. Reactivity of bismuth(III) halides towards alcohols. A tentative to mechanistic investigation. Tetrahedron 2001;57:1909–1916.

4. Keramane E, Boyer B, Roque J. BiBr3-catalyzed benzylation of alcohols. Stereochemistry and mechanistic investigations. Tetrahedron 2001;57:1917–1921.
5. Leonard N, Wieland C, Mohan S. Applications of bismuth(III) compounds in organic synthesis. Tetrahedron 2002;58:8373–8397.
6. David S, Hanessian S. Regioselective manipulation of hydroxyl groups via organotin derivatives. Tetrahedron 1985;41:643–663.
7. Wessel HP, Iversen T, Bundle DR. Acid-catalysed benzylation and allylation by alkyl trichloroacetimidates. J Chem Soc Perkin Trans 1985;1:2247–2250.
8. Liotta LJ, Ganem B. Selective benzylation of alcohols and amines under mild conditions. Tetrahedron Lett 1989;30:4759–4762.
9. Poon KWC, Dudley GB. Mix-and-heat benzylation of alcohols using a bench-stable pyridinium salt. J Org Chem 2006;71:3923–3927.
10. Pearson RG. Hard and soft acids and bases. J Am Chem Soc 1963;85:3533–3539.
11. Pearson RG. Recent advances in the concept of hard and soft acids and bases. J Chem Educ 1987;64:561–567.
12. Repichet S, Leroux C, Hernandez P, Dubac J, Desmurs Jr. Bismuth(III) trifluoromethanesulfonate: an efficient catalyst for the sulfonylation of arenes. J Org Chem 1999;64:6479–6482 (and references cited therein).
13. Sanderson J, Bayse CA. The Lewis acidity of bismuth(III) halides: a DFT analysis. Tetrahedron 2008;64:7685–7689.
14. Ogawa T, Yoshikawa A, Wada H, Ogawa C, Ono N, Suzuki H. Tris(2-methoxyphenyl)bismuthane as dehydrating agent with high template ability: an efficient single step synthesis of macrocycle diesters from diacid anhydrides and glycols. J Chem Soc Chem Commun 1995;1407–1408: (and references cited therein).
15. Kallal K, Coin C, Dunach E, Postel M. Bismuth(III) carboxylates as catalysts in the oxidative cleavage of epoxides and α-hydroxyketones. A tentative route to α, ω-dicarboxylic acids. New J Chem 1997;21:495–499.
16. Habata Y, Fujishiro F, Akabori S. Syntheses of crown ether-esters with (benzyloxy)methyl side arms using $SbPh_3$ and $BiPh_3$ as templates. J Chem Soc Perkin Trans 1996;1:953–957.
17. Steward CA, Calabrese JC, Arduengo AJ. Synthesis and structure of the first 20-Bi-9 system: a discrete nine-coordinate 20-electron bismuth. J Am Chem Soc 1985;107:3397–3398.
18. Briand GG, Burford N. Bismuth compounds and preparations with biological or medicinal relevance. Chem Rev 1999;99:2601–2658 (and references cited therein).
19. Lange KCH, Klapotke TM. In: Patai S, editor. The chemistry of organic arsenic, antimony and bismuth compounds. Wiley, Academic Press: New York; 1994. p315–366.
20. Genge ARJ, Levason W, Reid G. Bismuth(III) thioether chemistry: the synthesis and structure of $[Bi_4Cl_{12}(MeSCH_2CH_2CH_2SMe)_4]_n{\cdot}nH_2O$, a highly unusual network involving Bi_4Cl_4 rings and bridging dithioether ligands. Chem Commun 1998;2159–2160.
21. Salehi P, Irandoost M, Seddighi B, Behbahani FK. Tahmasebi DP. Transetherification of allylic and benzylic ethers in the presence of ferric ion Synth Commun 2000;30:1743–1747.
22. Cheun Y, Koag MC, Kou Y, Warnken Z, Lee S. Transetherification-mediated E-ring opening and stereoselective "Red-Ox" modification of furostan. Steroids 2012;77:276–281.
23. Li X, Liu B, Xu X, Chmielewski PJ. DDQ-Supported Alkoxylation of 2-Aza-21-carbaporphyrin and Noncatalyzed Transetherification of Its 3,21-Dialkoxy Derivatives. J Org Chem 2012;77:8206–8219.
24. Yang L, Seshan K, Li Y. Transetherification of guaiacol to O-ethoxyphenol with gamma Al_2O_3 as a catalyst in supercritical ethanol. Catal Commun 2013;30:36–39.
25. Karagoz S, Bhaskar T, Muto A, Sakata Y. Comparative studies of oil compositions produced from sawdust, rice husk, lignin and cellulose by hydrothermal treatment. Fuel 2005;84:875–884.
26. Yuan Z, Cheng S, Leitch M, Xu C. Hydrolytic degradation of alkaline lignin in hot-compressed water and ethanol. Biores Technol 2010;1019308–9313.
27. Gosselink, RJA. Lignin as a renewable aromatic resource for the chemical industry. PhD Thesis, Wageningen University, Wageningen, NL (2011) ISBN_: 978–94-6173-100-5.