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Highly Enantioselective Synthesis of Linear β-Amino Alcohols

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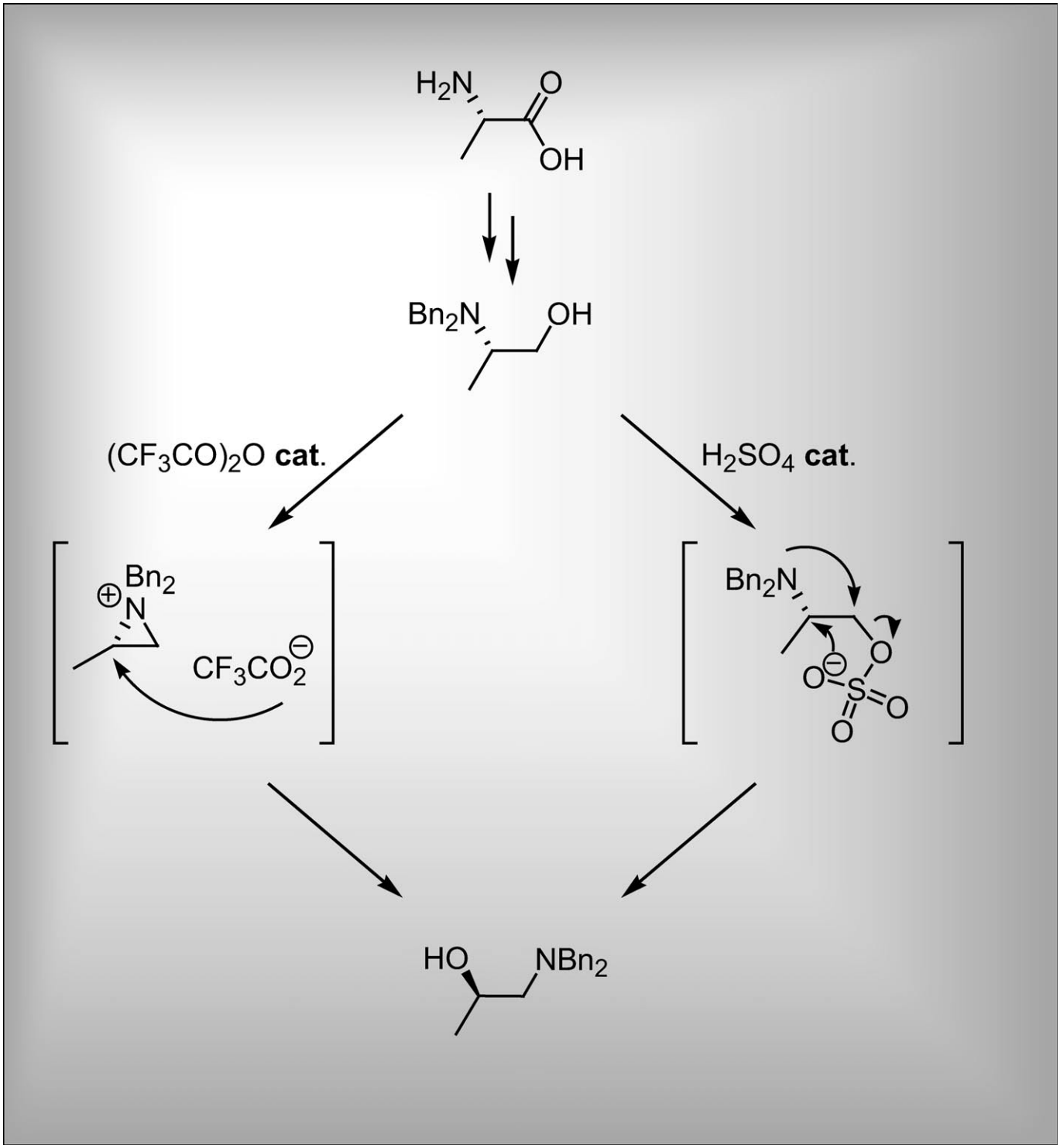
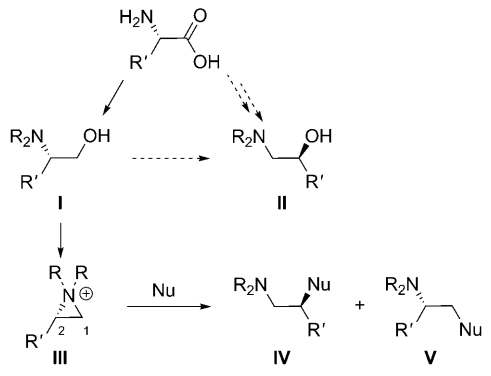


Abstract: β-Amino alcohols derived from α-amino acids have been extensively used as a powerful source of chirality. Transforming the alcohol moiety into a good leaving group has allowed the rearrangement of these β-amino alcohols and the introduction of a large number of nucleophiles through the anchimeric participation of the nitrogen atom. An overview on the recent progress realized on the rearrangement of these β-amino alcohols in the presence of $(CF_3CO)_2O$ and H_2SO_4 is reported.

Keywords: amino alcohols · aziridinium · rearrangement · sulfuric acid · trifluoroacetic anhydride

Introduction

β-Amino alcohols are present in a great variety of natural products and/or biologically active compounds.[1] Those derived from α-amino acids have been widely used in asymmetric synthesis, both as chiral auxiliaries and ligands.[2] Even though β-amino alcohols of type **I** can be easily obtained by reduction and *N*,*N*-alkylation of naturally occurring α-amino acids, β-amino alcohols of type **II** cannot be issued from α-amino acids in a straightforward manner (Scheme 1). However, it has been demonstrated in early work that transforming the alcohol moiety of β-amino alcohols of type **I** into a good leaving group led to the formation of an aziridinium intermediate of type **III**, which can be attacked by a nucleophile to produce the rearranged β-amino alcohol of type **IV**.[3] Consequently, one could perceive that β-amino alcohols of type **II** could be obtained by the rearrangement of β-amino alcohols of type **I** through the nucleophilic attack of an oxygenated nucleophile on aziridinium intermediate **III** (Scheme 1).



Scheme 1. Rearrangement of β-amino alcohols of type **I** via an aziridinium intermediate.

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As aziridinium intermediates of type **III** possesses two electrophilic positions, a nucleophilic attack on positions C1 and C2 would lead to the formation of both products **IV** and **V**. The proportions of compounds **IV** and **V** depends on the nucleophile, the R′ substituent, and, to a lesser extent, on the solvent and temperature. When oxygenated nucleophiles such as alcohols or phenols are used, a mixture of both compounds **IV** and **V** have always been observed.[4]

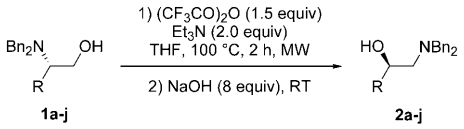
Enantioselective Rearrangement of β-Amino Alcohols of Type I to β-Amino Alcohols of Type II

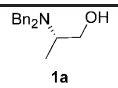
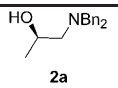
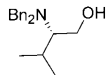
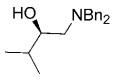
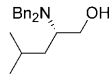
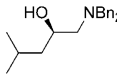
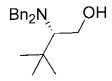
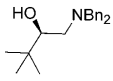
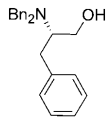
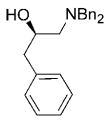
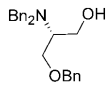
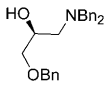
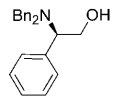
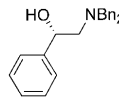
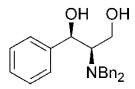
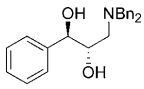
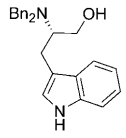
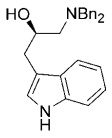
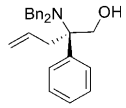
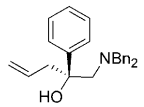
The regioselectivity of the rearrangement induced by nucleophilic attack on the aziridinium has been solved by using $(CF_3CO)_2O$ as the activating reagent. Thus, treating β-amino alcohols **I** with $(CF_3CO)_2O$ and Et_3N in THF followed by the addition of NaOH produced β-amino alcohols of type **II** in a regio-, stereo-, and enantioselective one-pot process.[5] When *N*,*N*-dibenzylamino alcohols **1a–j** were treated with $(CF_3CO)_2O$ (1.5 equiv) and Et_3N (2.0 equiv) and heated at 100 °C for a period of 2 h under microwave irradiation,[6] followed by the addition of NaOH (3.75 N), the corresponding *N*,*N*-dibenzylamino alcohols **2a–j** were isolated in good yields and *ee*′s (Table 1). It is worth noting that the rearrangement of amino-1,3-diol **1h** furnished amino-1,2-diol **2h** in 66% yield indicating that the process is very regio- and diastereoselective. Even for β-amino alcohols of type **I** possessing a quaternary center, the rearrangement was highly stereoselective as **2j** was isolated in 63% yield and 88% enantiomeric excess (*ee*) from **1j** (91% *ee*) with almost no loss of chirality.

N-Alkyl groups have almost no influence on the rearrangement, as *N*,*N*-diallylamino alcohol **1k** and *N*,*N*-dimethylamino alcohol **1l** were rearranged to β-amino alcohols **2k** and **2l** in 85% and 72% yield, and in 99% and 95% *ee*, respectively (Table 2).

The stereospecificity of this rearrangement can be explained by the formation of aziridinium intermediate **C**, which would result from an intramolecular nucleophilic attack (S_Ni) of the lone pair of the nitrogen of amino ester **B** on the carbon atom bearing the trifluoroacetate group (Scheme 2). The latter would be issued from the Et_3N deprotonation of ammonium trifluoroacetate ester **A** obtained by treatment of β-amino alcohol **I** with $(CF_3CO)_2O$. A trifluoroacetate anion could then attack the more substituted carbon atom of the aziridinium **C** to produce the rearranged β-aminoester **D**. As the formation of the aziridinium inter-

Table 1. Rearrangement of β-amino alcohols of type **I** in the presence of a stoichiometric amount of $(CF_3CO)_2O$ and Et_3N.

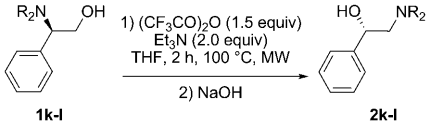


Entry	Substrates	Products	Yield [%]	*ee* [%]
1	 **1a**	 **2a**	99[a]	99
2	 **1b**	 **2b**	88	99
3	 **1c**	 **2c**	82	–
4	 **1d**	 **2d**	99	99
5	 **1e**	 **2e**	97	99
6	 **1f**	 **2f**	76	99
7	 **1g**	 **2g**	93	99
8	 **1h**	 **2h**	66[b]	99
9	 **1i**	 **2i**	97[c]	–
10	 **1j** (91% *ee*)	 **2j**	63[d]	88

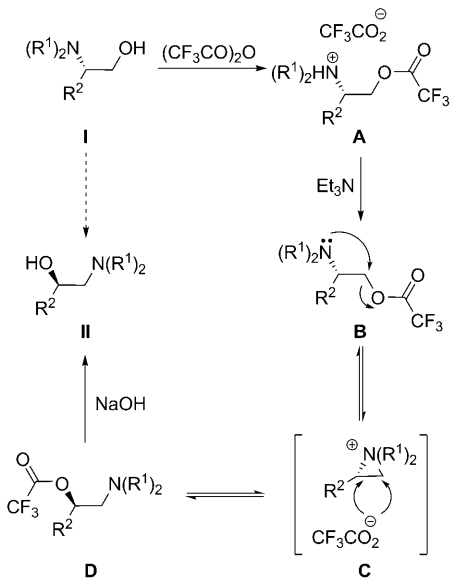
[a] $CF_3(CO)_2O$ (3.0 equiv), Et_3N (4.0 equiv), reflux , 37 h. [b] $CF_3(CO)_2O$ (1.1 equiv), Et_3N (2.0 equiv). [c] $CF_3(CO)_2O$ (3.0 equiv), Et_3N (4.0 equiv). [d] $CF_3(CO)_2O$ (2.0 equiv), Et_3N (3.0 equiv), RT, 48 h.

mediate **C** and the nucleophilic attack of the trifluoroacetate anion are reversible processes, both intermediates **B** and **D** are in equilibrium, and the secondary trifluoroacetate ester **D** is the thermodynamic product. Saponification of this ester completes the reaction, thus generating β-amino alcohol **II** (Scheme 2). As the rearranged β-amino alcohols were obtained with high *ee*'s, the formation of a planar carbocation intermediate has been excluded.

Table 2. Influence of the *N*-alkyl group on the rearrangement.

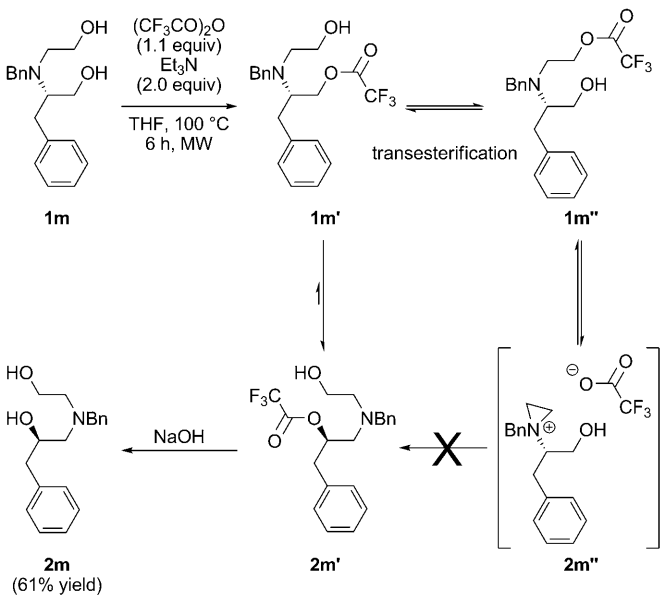


Entry	R	Yield [%]	*ee* [%] (configuration)
1	Allyl (**2k**)	85	99 (*S*)
2	Me (**2l**)	72	95 (*S*)



Scheme 2. Mechanism of the rearrangement of β-amino alcohols of type **I** in the presence of stoichiometric amounts of $(CF_3CO)_2O$ and Et_3N.

To further understand the influence of *N*-alkyl groups on the rearrangement, β-amino alcohol **1m**, possessing a 2-hydroxyethyl group fixed on the nitrogen atom, was treated with $(CF_3CO)_2O$ (1.1 equiv) and Et_3N (2.0 equiv) in THF at 100 °C for 6 h under microwave irradiation. After addition of NaOH, the rearranged β-amino alcohol **2m** was obtained in 61 % yield (Scheme 3). Although this result showed the feasibility of the rearrangement of *N*-2-hydroxyethyl β-amino alcohols, the possible mechanism of this particular case was intriguing. If the previously postulated mechanism intervened in the rearrangement, a mixture of the trifluoroacetates **1m′** and **1m″** should be formed as the two primary hydroxy groups should be esterified with similar rates (Scheme 3). Upon heating, trifluoroacetate **1m′** would rearrange into trifluoroacetate **2m′**, whereas trifluoroacetate **1m″** would form the aziridinium **2m″**. Nucleophilic attack of the aziridinium intermediate **2m″** by a trifluoroacetate anion cannot directly produce the rearranged amino ester **2m′**, but only the amino ester **1m″**, which would release the starting β-amino alcohol **1m** after saponification. As the starting β-amino alcohol **1m** was absent from the crude after saponification, this observation led us to put forward two hypotheses. First, amino esters **1m′** and **1m″** would be in equilibrium due to a transesterification reaction. Second,



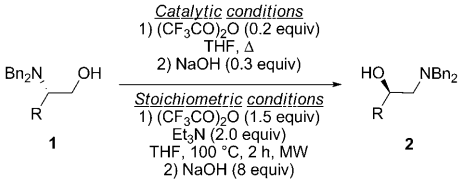
Scheme 3. Hypotheses on the rearrangement of the β-amino alcohols **1m**.

as amino esters **1m′** and **2m′** are also in equilibrium through rearrangement, amino ester **2m′** would be the more stable compound of the overall process and therefore the thermodynamic product.

If one considers that a transesterification could also take place between the rearranged amino ester **2m′** and the starting amino alcohol **1m**, the use of substoichiometric quantities of $(CF_3CO)_2O$ should be sufficient to obtain complete conversion of β-amino alcohol **1m**. Experimental conditions using $(CF_3CO)_2O$ as a catalyst were therefore devised.[7] Thus, when β-amino alcohol **1a** was treated with $(CF_3CO)_2O$ (0.2 equiv) in THF for 2 h at 180 °C under microwave irradiation, followed by the addition of NaOH (0.3 equiv), β-amino alcohol **2a** was obtained in 98 % yield and 99 % *ee*. These conditions were then applied to the β-amino alcohols **1a–h** (Table 3). The reaction proved to be general,[8] as the yields and *ee*′s of the rearranged products were very similar to those obtained when the stoichiometric conditions were used. It is worth noting that under catalytic conditions, no Et_3N is needed, avoiding possible side reactions between Et_3N and $(CF_3CO)_2O$.[9]

The formation of β-amino alcohols of type **II** from β-amino alcohols of type **I** under catalytic conditions without any Et_3N could be explained by the formation of a catalytic amount of ammonium trifluoroacetate ester **A**, which could be deprotonated by any tertiary amines present in the reaction media (and most probably compounds of type **I**, **II**, **B**, or **D**). An S_N2 intramolecular substitution by the *N*,*N*-dialkylamine functionality in **B** could form aziridinium **C**, liberating a trifluoroacetate anion in the reaction media (Scheme 4). This latter anion could attack the more substituted carbon atom of aziridinium **C**, producing amino ester **D** according to a S_N2 substitution. An intermolecular transesterification between β-amino alcohol **I** and amino ester **D**

Table 3. Rearrangement of β-amino alcohols of type **I** in the presence of $(CF_3CO)_2O$ as a catalyst.



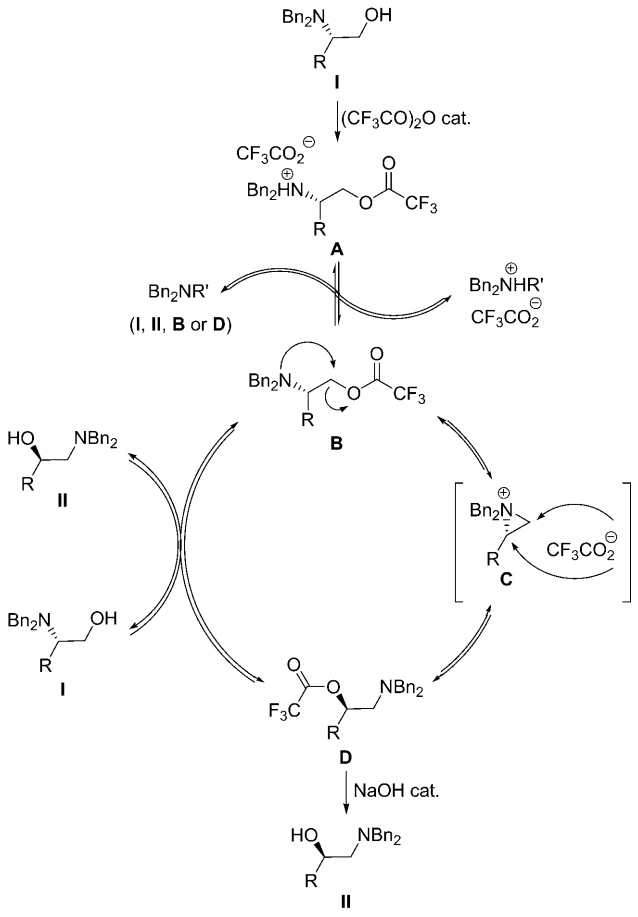
Entry	Substrates	Products	Catalytic conditions	Yield [%] (*ee* [%])[a] [yield [%] (*ee* [%])][b]
1	**1a**	**2a**	180 °C, 2 h	98 (99) [99[c] (99)]
2	**1b**	**2b**	180 °C, 2 h	93 (99) [88 (99)]
3	**1c**	**2c**	180 °C, 2 h	89 (–) [82 (–)]
4	**1d**	**2d**	100 °C, 18 h	74 (99) [99 (99)]
5	**1e**	**2e**	180 °C, 2 h	87 (99) [97 (99)]
6	**1f**	**2f**	180 °C, 2 h	96 (99) [76 (99)]
7	**1g**	**2g**	100 °C, 18 h	78 (99) [93 (99)]
8	**1h**	**2h**	100 °C, 18 h	83 (99) [66[d] (99)]

[a] Catalytic conditions. [b] Stoichiometric conditions. [c] $CF_3(CO)_2O$ (3.0 equiv), Et_3N (4.0 equiv), reflux , 37 h. [d] $CF_3(CO)_2O$ (1.1 equiv), Et_3N (2.0 equiv).

could take place to form β-amino alcohol **II** and amino ester **B**, which could in turn be transformed into aziridinium **C** again. As species **I**, **II**, **B**, and **D** are in equilibrium, both the rearranged β-amino alcoho **II** and amino ester **D** are thermodynamic products. The use of NaOH (0.3 equiv) in the second step allows the saponification of the resulting catalytic amount of amino ester **D** releasing the rearranged β-amino alcohol **II** (Scheme 4).

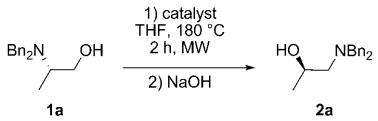
To understand the influence of the trifluoroacetate anion in the rearrangement, β-amino alcohol **1a** was treated with a catalytic amount of trifluoroacetic acid (Table 4, entry 2). After addition of NaOH, β-amino alcohol **2a** was surprisingly produced in 62 % yield. The rearrangement of β-amino alcohol **1a** was then investigated with other acids, such as AcOH, HCl, *p*-toluenesulfonic acid (PTSA), and H_2SO_4. Among these acids tested, the best yield for the rearranged product **2a** was obtained using a catalytic amount of H_2SO_4 (Table 4, entry 6). Whereas 20 mol % of $(CF_3CO)_2O$ was necessary to reach complete conversion of β-amino alcohol **1a**, not more than 5 mol % of H_2SO_4 was enough to obtain the same result.

When **1a** was heated at 180 °C for 2 h under microwave irradiation in the presence of H_2SO_4 (5 mol %), **2a** was obtained in excellent yield (97 %) and *ee* (99 %) (Table 5, entry 1). Due to this result, these latter conditions were applied to β-amino alcohols **1a–h** and **1n** (Table 5).[10] For β-amino alcohols **1a–h**, the *ee*′s of the rearranged products were excellent and the yields were in between 65–97 %, except for **1h** which was rearranged in 39 % yield. Although



Scheme 4. Mechanism of the rearrangement of β-amino alcohols of type **I** in the presence of $(CF_3CO)_2O$ as a catalyst.

Table 4. Influence of the catalyst on the rearrangement of β-amino alcohol **1a**.



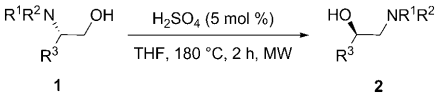
Entry	Catalyst	Mol %	Yield [%][a]
1	$(CF_3CO)_2O$	10	89
2	CF_3CO_2H	10	62
3	AcOH	10	0
4	HCl	5	0
5	PTSA	10	29
6	H_2SO_4	5	97

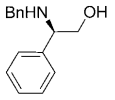
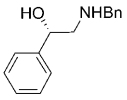
[a] Determined by ^1H NMR of the crude material.

the yield and *ee* were lower than for the corresponding *N*,*N*-dibenzyl-*β*-amino alcohol **1g** (65%, 95% *ee*), the rearrangement of compound **1n** (22% yield, 83% *ee*) has shown that the rearrangement of secondary *N*-benzyl-*β*-amino alcohols was possible.

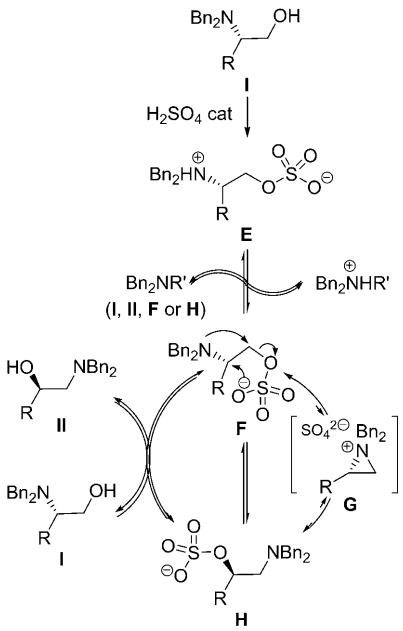
By using H_2SO_4, β-amino alcohols of type **I** could be transformed into ammonium sulfate **E** (Scheme 5), which could be deprotonated by any tertiary amine present in the

Table 5. Rearrangement of β-amino alcohols of type **I** in the presence of H_2SO_4 as the catalyst.



Entry	Substrates	Products	Yield [%]	*ee* [%]
1	**1a**	**2a**	97	99
2	**1b**	**2b**	95	99
3	**1c**	**2c**	96	–
4	**1d**	**2d**	81	99
5	**1e**	**2e**	94	99
6	**1f**	**2f**	88	99
7	**1g**	**2g**	65	95
8	**1h**	**2h**	39[a]	99
9	 **1n**	 **2n**	22[b]	83

[a] H_2SO_4 (15 mol %), THF, 180 °C, 2 h, microwave irradiation. [b] H_2SO_4 (30 mol %), THF, 180 °C, 6 h, microwave irradiation.

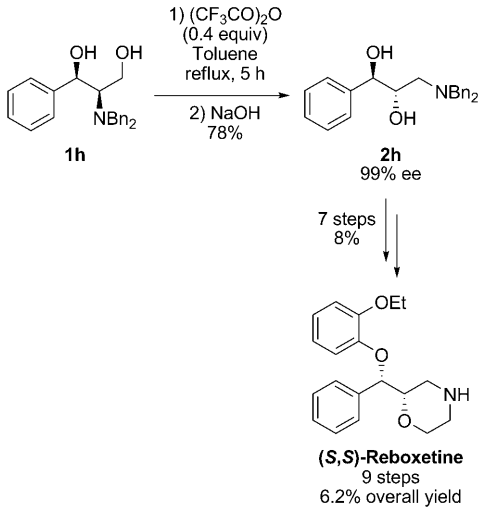


Scheme 5. Mechanism of the rearrangement of β-amino alcohols of type **I** in the presence of H_2SO_4 as the catalyst.

reaction media (and most probably compounds of type **I**, **II**, **F** or **H**). Both an intramolecular nucleophilic substitution (S_Ni) of the sulfate group by the amine functionality, and a nucleophilic attack of the sulfate group on the carbon bearing the nitrogen atom would release the rearranged amino sulfate **H**. A sulfate exchange between β-amino alcohol **I** and the rearranged amino sulfate **H** would produce the rearranged β-amino alcohol **II** and amino sulfate **F** (Scheme 5). This last sulfate would be transformed into the rearranged amino sulfate **H** until complete conversion of both β-amino alcohol **I** and amino sulfate **F**. As external nucleophiles, such as alcohols, thiols, or amines, cannot be introduced

during the process, the probability for the formation of aziridinium intermediate **G** is very low. This result seems in favor of a concerted transformation of amino sulfate **F** to amino sulfate **H**, as already described by Anker et al.[11] Besides, the formation of sulfate intermediate **E** was supported by the ability of $Py{\cdot}SO_3$ to catalyze the rearrangement, as **1a** was transformed to **2a** in 97% yield by using 5 mol% of $Py{\cdot}SO_3$.[10] The high *ee*'s obtained for the rearranged *N*,*N*-dibenzyl-β-amino alcohols allow us to exclude the formation of a planar carbocation intermediate.

The rearrangement of β-amino alcohol **1h** to **2h** under catalytic conditions has been applied to the synthesis of (*S*,*S*)-reboxetine, a selective norepinephrine reuptake inhibitor, for which an equimolar mixture of (*S*,*S*)- and (*R*,*R*)-enantiomer is actually sold as an antidepressant.[12] We have to point out that in this case, the rearrangement was achieved on a gram scale in refluxing toluene without any microwave apparatus, showing that this rearrangement could be realized at the industrial scale. β-Amino diol **2h** was then transformed into (*S*,*S*)-reboxetine in seven steps (Scheme 6).[13] By using this strategy, (*S*,*S*)-reboxetine was synthesized in nine steps with 6.2% overall yield.



Scheme 6. Application of the rearrangement of β-amino alcohols to the synthesis of (*S*,*S*)-reboxetine.

Conclusion

During our studies, the conditions allowing the rearrangement of β-amino alcohols of type **I** have been greatly improved: from stoichiometric to catalytic quantities of the major reagent [$(CF_3CO)_2O$], then from expensive $(CF_3CO)_2O$ to cheap and widely available H_2SO_4, which also allowed a reduction in the catalyst loading. Whatever the conditions used, the rearranged β-amino alcohols of type **II** were obtained in very good yields and *ee*'s. The present new conditions [catalytic quantities of $(CF_3CO)_2O$ or H_2SO_4] offer opportunities to explore the reactivity of a great variety of β-amino alcohols and to transform them into β-amino alcohols that contain biologically active compounds.

Acknowledgements

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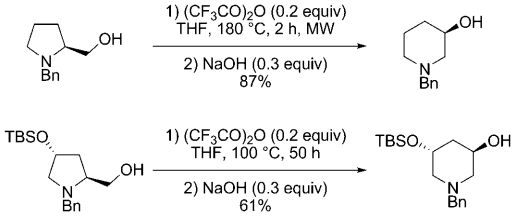

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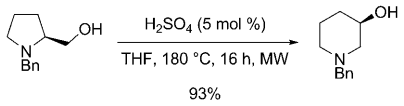

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