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Highly regioselective microwave-assisted synthesis of enantiopure C_3-symmetric trialkanolamines

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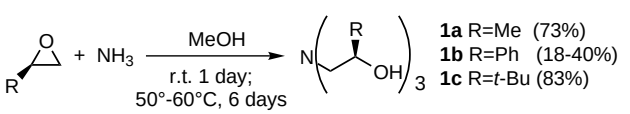
Abstract—Enantiopure, C_3-symmetric trialkanolamines can be efficiently and rapidly obtained on a gram scale via one pot or step-wise microwave-assisted epoxide ring opening with ammonia in high yields (up to 89%) and regioselectivity up to 100%.

The discovery of new stereoselective catalytic processes is a major task in chemistry and this is a field under continuous development.[1] In this context chiral ligands play a major role and many efforts have been made for finding new families of chiral ligands,[2] both via rational ligand design[3] and via combinatorial screening.[4] However, despite the intrinsic behavior of a specific ligand, its availability via simple, efficient and highly selective procedures is a necessary condition for its practical use. Therefore, the development of efficient syntheses of enantiopure ligands is of fundamental importance in stereoselective catalysis.

Recently we reported a new class of Ti(IV) and Zr(IV)/C_3 trialkanolamine complexes that efficiently catalyze stereoselective processes such as *meso*-epoxide ring opening,[5] halohydrin synthesis[6] and sulfoxidation of aryl alkyl sulfides.[7,8] The trialkanolamine ligands **1** are obtained via stereospecific ring opening of enantiopure epoxides by anhydrous ammonia (Scheme 1).[9] Nucleophilic attack of ammonia on the epoxides is a slow process and complete conversion into the products can be obtained only after 4–6 days at 50–60°C. The reaction occurs with complete control of the regiochemistry when alkyl epoxides are employed, while with aryl epoxides (e.g. styrene oxide) the regioselectivity decreases significantly and at least two of the four possible regioisomers are obtained. In the case of **1b**, chromatographic separation of the products is required.



Scheme 1. Stereospecific synthesis of enantiopure trialkanolamines.

The chromatography is not straightforward and further crystallizations are needed to obtain the pure homochiral ligands with an 18–40% yield in purified product.[9] In order to have the trialkanolamines more easily available we decided to further investigate their synthesis. An improved trialkanolamine preparation must overcome two major problems: (1) the intrinsic low reactivity of ammonia as nucleophile; and (2) the limited regioselectivity of the nucleophilic attack of the amines on 2-aryl epoxides (e.g. styrene oxide).[10] Both problems are expected to become less critical as the reaction proceeds due to the increasing reactivity of the nucleophile as well increasing steric hindrance along the series NH_3<NH_2R<NHR_2. Consequently, the first addition step (addition of ammonia to the epoxide) is the most critical.

Here we report that microwave (MW) induced heating can be effectively used for the synthesis of enantiopure C_3 trialkanolamines. Compared with traditional heating, much faster reactions (one-three hours versus six days) could be obtained affording high yields of products. Furthermore, a significant increase of the regioselectivity in the synthesis of (*R*,*R*,*R*)-tris(2-phenyl)-ethanolamine **1b** was obtained allowing a considerable

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enhancement of the chemical yields together with a much easier purification procedure.

Reactions of dry ammonia in methanol (2.0 M) with three equiv. of (*S*)-propylene oxide or (*R*)-styrene oxide were performed in closed Teflon reactors at 130°C upon irradiation with microwaves (240 W). Microwave irradiation has been applied with success in organic synthesis because reaction rates can be greatly increased by heating induced by microwaves.[11]

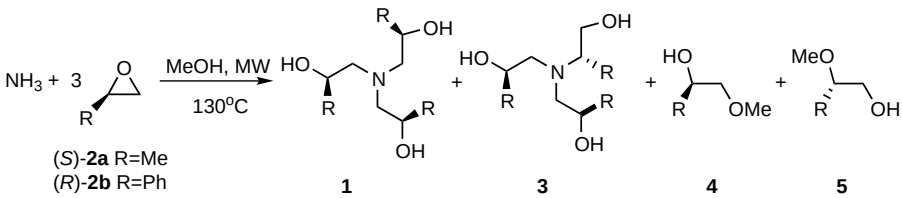
Addition of ammonia to (*S*)-propylene oxide was complete after only 90 min.[12] Not only was reaction time diminished compared with the standard procedure, but also ligand **1a** was obtained as a single regioisomer in higher yields (92%, 89% after crystallization from toluene, Table 1, entries 1 and 2). Reaction with styrene oxide required longer reaction times for completion (3 hours). Compared with the reaction of (*S*)-propylene-oxide, much lower regioselectivities were obtained [(*R*,*R*,*R*)-**1b**: (*R*,*R*,*S*)-**3b** = 58:42] and in addition to the trialkanolamines, two other products derived from solvolysis of (*R*)-styrene-oxide were also recovered: (*R*)-2-methoxy-1-phenylethanol **4b**[13] and (*S*)-2-methoxy-2-phenylethanol **5b**[14] (20%, 41:59 ratio). Purification via flash chromatography over silica gel (ethyl acetate: toluene 20:80) afforded (*R*,*R*,*R*)-**1b** in 43% yield. In the previously reported procedure, (R,R,R)-**1b** could be obtained in yields up to 40 only after more than one chromatographic separation.[9] Therefore, notwithstanding the formation of solvolysis products, a significant improvement in the regioselectivities and purification procedure of the desired C_3 trialkanolamine (*R*,*R*,*R*)-**1b** were obtained also in this case (Table 1, entries 3 and 4).

As far as the preparation of (*R*,*R*,*R*)-**1b** is concerned, a very noticeable improvement could be obtained performing the synthesis step-wise (Scheme 2).

In order to stop the synthesis at the level of amino alcohols, despite the increased nucleophilicity of the amines produced, the reactions were performed in ammonium hydroxide (28% in water) in large excess using microwave induced heating (Table 2).[12]

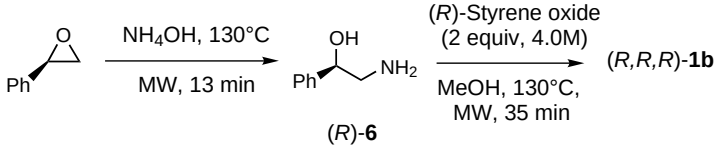
In fact, a similar approach was recently used in the vinyl epoxide ring opening by ammonium hydroxide with subsequent acceleration of the reaction and decreasing of production of side products.[15] The reaction performed under conditions comparable to the one

Table 1. One pot microwave-assisted synthesis of enantiopure (*S*,*S*,*S*)-triisopropanolamine **1a** and (*R*,*R*,*R*)-tris(2-phenyl)-ethanol amine **1b**[a]



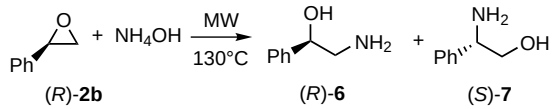
Entry	Substrate	R	Temperature (time)	Pressure (bar)	Yield,%[b]	D.e. (**1**), %[c]	1:3:4:5[d]	Yields (**1**), %[e]	Ref.
1	(*S*)-**2a**	Me	130°C (90 min)	7	92	97	>100:1:1:1	89	[f]
2	(*S*)-**2a**	Me	r.t. (1 day) then 50°C (5 days)	–	98	94	>100:1:1:1	72	9
3	(*R*)-**2b**	Ph	130°C (180 min)	4	80	n.d.	46:34:8:12	43	[f]
4	(*R*)-**2b**	Ph	r.t. (15 h) then 60°C (5 days)	–	n.d.	n.d.	n.d.	18–40	9

[a] Reaction conditions: see Ref. 12.
[b] Yields in trialkanolamines after removal of the solvent, without further purification.
[c] D.e. of (*S*,*S*,*S*)-**1a** over (*R*,*S*,*S*)-**1a** were determined on the crude reaction product via ^{13}C NMR as described in Ref. 9. The amount of diastereoselection observed depends on the enantiopurity of the reagent (*S*)-**2a**.
[d] Determined via ^{1}H NMR on the reaction mixture.
[e] Yields after purification [(*S*,*S*,*S*)-**1a** crystallization (toluene), (*R*,*R*,*R*)-**1b** chromatography (silica gel, ethyl acetate: toluene: triethylamine = 20:80:5)].
[f] Present work.



Scheme 2. Stereospecific step-wise synthesis of (*R*,*R*,*R*)-tris(2-phenyl)ethanolamine **1b**.

Table 2. Microwave-assisted synthesis of (*R*)-2-amino-1-phenylethanol **6** and (*S*)-2-amino-2-phenylethanol **7**[a]



(*R*)-**2b** (*R*)-**6** (*S*)-**7**

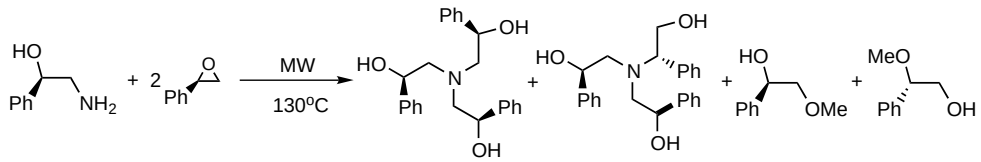
Entry	[**2b**], M	[NH_4OH]/[**2b**]	Solvent	Pressure, bar	Ratio **6**:**7**[b]	Yields, %[c]	(*R*)-**6**, %[d]	(*S*)-**7**, %[d]
1	0.03	430	–	12	80:20	>98	–	–
2	0.10	143	–	12	80:20	>98	80	20
3	0.17	86	–	12	80:20	>98	–	–
4	0.27	54	–	12	77:23	97	–	–
5	0.68	21	–	12	75:25	92	48	11
6	0.36	21	Dioxane (45%)	12	81:19	>98	60	11
7	0.18	25	Dioxane (68%)	12	91:9	>98	74	7

[a] Reaction conditions: see Ref. 12.
[b] Determined via ^1H NMR on the reaction mixture.
[c] After filtration and solvent removal.
[d] After chromatography (silica gel, ethyl acetate:methanol:triethylamine = 12:2:1).

reported in the literature for vinyl epoxides[15] afforded the two-regioisomeric alcohols (*R*)-**6** and (*S*)-**7** in good ratio (80:20) and in quantitative yield, (Table 2, entry 1).[12] Because of the very diluted reaction conditions and the high cost of ammonium hydroxide, more concentrated solutions of styrene oxide were also tested. Comparable results were obtained up to $[(R)\text{-}\mathbf{2b}]_o = 0.17$ M, while at higher concentrations (up to 0.68 M, Table 2, entry 5) a decrease of the regioselectivities (75:25) and amino diol yields (59%) was observed. The lower efficiency of the system originates from the formation of higher substitution products (amino diols) and from a partial decomposition of the reagent/products.[16] In order to verify if the decomposition was due to heterogeneous nature of the reaction mixture because styrene oxide is poorly soluble in ammonium hydroxide at such high concentrations, increasing amounts of dioxane were added to homogenize the system (Table 2, entries 6 and 7). Indeed no decomposition of the starting material was observed anymore and the formation of products of further substitution was also minimized. Under the condition reported in entry 7 a regioisomeric ratio of 91:9 was obtained and amino alcohol (*R*)-**6** was obtained in 74% yield after chromatography.[17]

The addition of amino alcohol (*R*)-**6** to (*R*)-styrene oxide was then studied. The influence of the concentration of the reagents and the nature of the solvent were explored and the reactions were performed under microwave induced heating also in this case (Table 3). Only the reactions performed in methanol and isopropanol yielded to products (Table 3, entries 1–5) and two of the three possible regioisomers were obtained. In this case the purification of the products was particularly easy and the two regioisomeric trialkanolamines **1b** and **3b** could be separated in a quantitative way by

Table 3. Microwave-assisted synthesis of (*R*,*R*,*R*)-tris(2-phenyl)ethanolamine **1b**[a]



(*R*)-**6 b** (*R*,*R*,*R*)-**1b** (*R*,*R*,*S*)-**3b** (*R*)-**4b** (*S*)-**5b**

Entry	Solvent	[(*R*)-**6**], M	Time, min	Pressure, bar	Ratio **1b**:**3b**[b]	(*R*,*R*,*R*)-**1b**, %[c]	(*R*,*R*,*S*)-**3b**, %[c]	**4b**+**5b**, %[c]
1	MeOH	0.07	95	5	89:11	55	7	39
2	MeOH	0.16	95	5	92:08	67	6	28
3	MeOH	2.00	35	5	80:20	80	20	0
4	*i*-PrOH	0.16	155	3	80:20	73	21	–
5	*i*-PrOH	2.00	125	3	73:27	72	27	–
6	*t*-BuOH	0.16	35	6	–	–	–	–
7	CH_3CN	0.16	100	2	–	–	–	–
8	THF	0.16	63	3	–	–	–	–

[a] Reaction conditions: see Refs 12 and 17.
[b] Determined via ^1H NMR on the reaction mixture.
[c] After chromatography (silica gel, ethyl acetate:toluene:triethylamine = 20:80:5).

flash chromatography over silica gel (eluent toluene: ethyl acetate: triethylamine = 80:20:5).

The reactions performed in methanol (the solvent normally used in the one pot trialkanolamine synthesis) afforded the products in very short reaction times (30–90 min) and with very good regioselectivities (Table 3, entries 1–3). The results reported indicate that the concentration of the reagents plays an important role. In fact the reactions performed at lower substrate concentrations (Table 3, entries 1 and 2) besides the trialkanolamines **1b** and **3b** afforded also the solvolysis products (*R*)-**4** and (*S*)-**5**. However, at higher reagent concentration (2.0 M) the solvent does not compete in the nucleophilic attack and (*R*,*R*,*R*)-**1** could be obtained in high yield (80%) and a good regioisomeric ratio: (*R*,*R*,*R*)-**1**: (*R*,*R*,*S*)-**3** = 80:20.

In order to overcome problems due to the solvolysis, the use of other, less nucleophilic solvents was also examined. The reactions performed in isopropanol afforded high yields of trialkanolamines but with lower regioisomeric ratio and required longer reaction times (Table 3, entries 4 and 5). Use of *tert*-butanol as solvent resulted in extensive decomposition of the reaction mixture while acetonitrile and THF did not afford any products and the starting materials were quantitatively recovered.

In conclusion an improved protocol for the regioselective and stereospecific synthesis of enantiopure, C_3-symmetric (*S*,*S*,*S*)-triisopropanolamine **1a** and (*R*,*R*,*R*)-tris(2-phenyl)-ethanol amine **1b** has been developed. Compared with the previous procedure the new method affords much faster reactions and higher chemical yields and regioselections allowing an easy preparation of the derivatives in multi-gram scale.

Acknowledgements

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10. An improved synthetic procedure for the synthesis of (*R*,*R*,*R*)-tris(2-phenyl)ethanolamine **1b** was particularly necessary because this is the ligand that affords the best performances in the Ti(IV) and Zr(IV) catalyzed stereoselective sulfoxidations (Refs 7 and 8).
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12. The reactions were performed by placing the reagents in the solvent of choice (10 ml total volume) in a close reactor (HPR-1000/10S, Milestone) equipped with pressure and temperature control units and irradiating inside the cavity of a MW Ethos-1600 Lab Station (Milestone) accordingly with the following parameters: initial power, 300 W, 5 min; final power 240 W; $T_{max} = 130$°C. After cooling the reaction to r.t., the solvent was removed under vacuum and the products were purified by chromatography or crystallization. Reactions could be run on 2.0 M scale on up to six reactors at the same time, allowing the synthesis of 0.03 mol of ligand. All the products gave satisfactory analytical data.
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16. After running the reaction under the same conditions, in the colorless reaction solution the presence of dark flakes was detected. After filtration, the usual work up was used for the isolation and purification of the products.
17. The two amino alcohols can be easily and quantitatively separated by flash chromatography on silica gel (eluent: ethyl acetate: methanol: triethylamine = 12:2:1) after removal of the solvent under vacuum. Recently (*R*)-**6** became also commercially available.