

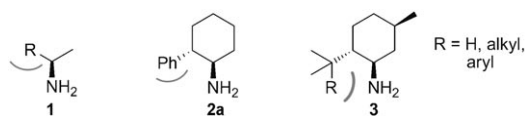
Efficient and Stereodivergent Electrochemical Synthesis of Optically Pure Menthylamines**

Jörn Kulisch, Martin Nieger, Florian Stecker, Andreas Fischer, and Siegfried R. Waldvogel*

Dedicated to Professor Dieter Hoppe on the occasion of his 70th birthday

Enantiomerically enriched amines with stereogenic information at the α position to the primary amino group represent an important class of compounds. They serve as building blocks in the synthesis of drug molecules,^[1] as auxiliaries,^[2] and as ligands for homogeneous catalysis.^[3] Many α -chiral amines are derived from the chiral pool, for example, amino alcohols, or are made synthetically, such as phenethylamines.^[1a,4] Compared to these α -chiral amines, terpene-derived primary amines have attracted little attention; only fenchyl, bornyl, and dehydroabietylamine are widely available and have been used in applications.^[5] While menthol and 8-substituted congeners play a significant role in stereoselective synthesis,^[6] the corresponding menthylamines have only rarely been utilized. Their poor availability has resulted in them being an almost neglected class of chiral amines.^[2]

The unique character of menthylamines is expressed by the strong influence of the substituent close to the amino group and leads to a superb transfer of stereogenic information. Compared to simple α -chiral amines **1**, for example, phenethylamines, a stronger steric effect on the amino moiety is created in cyclohexylamine **2** (Scheme 1). A prominent example is represented by *trans*-2-phenylcyclohexylamine (**2a**), in which a significant influence of the Ph group on the functional group exists because of the conformational rigidity. The synthesis of **2a** requires a multistep synthesis, including resolution of a racemic intermediate in most cases.^[7] Interestingly, the *cis* diastereomer of **2a** has found application in the construction of inhibitors for the glycine transporter I.^[8] The additional substituent R in **3** leads to enhanced con-

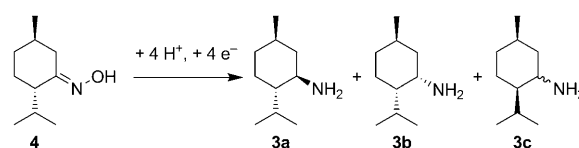


Scheme 1. Steric influence on the amino group in α -chiral primary amines.

formational stability and even stronger steric influence around the amino function. Appropriate functional groups R result in a molecular U turn.

Optically pure menthylamines have found applications as structural elements of supramolecular receptors suitable for enantiofacial discrimination^[9] and show efficient binding of electron-deficient aromatic compounds, such as caffeine and 1,3,5-trinitrotoluene (TNT).^[10,11] (+)-Neomenthylamine has been used as a building block for a stationary phase for high-performance column chromatography.^[12–15] This stationary phase was used for the racemic resolution of a cervastatin precursor.^[16,17] Some menthylamides, such as the cyclopropa-necarboxamide of (+)-neomenthylamine, also show a strong umami taste.^[18]

All the synthetic pathways to menthylamines rely on terpenoid starting materials such as (–)-menthone. Optically enriched (–)-menthone is available from natural sources and its reductive amination leads to the synthesis of menthylamines. An isomeric mixture of all the menthylamines (**3a–3c**) is obtained under Leuckart–Wallach conditions.^[19] An alternative approach is the reduction of the corresponding oxime **4** to the amine. A Bouveault–Blanc reduction was established, which led to the desired amines in good yields and suitable diastereoselectivities (Scheme 2).^[20] The drawback of this method is the necessity of 30 equivalents of sodium metal. The potential hazard and low atom efficiency thus necessitates a new and innovative approach. Furthermore, both **3a** and **3b** are needed for applications. We report here a novel electrochemical method which can be used as a stereodivergent synthesis. A related approach was demonstrated for the electrochemical reduction of isomeric menthones.^[21]



Scheme 2. Potential stereoisomers on reduction of (–)-menthone oxime.

[*] Dr. J. Kulisch, Prof. Dr. S. R. Waldvogel
Kekulé Institute for Organic Chemistry and Biochemistry
Bonn University
Gerhard-Domagk-Strasse 1, 53121 Bonn (Germany)

Dr. M. Nieger
Laboratory of Inorganic Chemistry
University of Helsinki
00014 Helsinki (Finland)

Dr. F. Stecker, Dr. A. Fischer
BASF SE, GCI/E—M311, 67056 Ludwigshafen (Germany)

Prof. Dr. S. R. Waldvogel
Institute for Organic Chemistry
Johannes-Gutenberg University Mainz
Duesbergweg 10–14, 55128 Mainz (Germany)
E-mail: waldvogel@uni-mainz.de

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Table 1: Screening for cathode materials.

Entry	Cathode	Current density [mAcm ⁻²]	Yield [%]	Faradaic yield [%]	d.r. 3a/3b
1 ^[a]	Hg	46	68	24	2.4:1
2 ^[b]	Cd	25	40	31	2.7:1
3 ^[b]	Pb	25	66	11	1.0:1
4 ^[b]	Pb/5% Cu	25	41	16	1.5:1
5 ^[b]	BDD	31	< 2	< 1	3.4:1

[a] Conditions: catholyte 0.5 M H₂SO₄ in MeOH/H₂O 1:1, 20 °C. [b] Conditions: catholyte 0.5 M H₂SO₄ in DME/H₂O 6:1, 20 °C. DME = 1,2-dimethoxyethane.

Oximes are most reliably reduced in acidic media.^[22] The cleavage of the N–O bond represents the first part of the sequence (for the mechanistic rationale, see the Supporting Information). Since the evolution of molecular hydrogen is a strongly competing reaction, specific attention was given to the cathode material. An extensive screening of potential cathode materials showed the desired transformation was only possible on metals exhibiting a high overpotential for the evolution of molecular hydrogen (see the Supporting Information). A selection of optimized conditions is displayed in Table 1. The use of mercury or cadmium as the cathodes resulted in a pronounced selectivity for (–)-menthylamine (**3a**; Table 1, entries 1 and 2), whereas lead or a copper/lead alloy gave either no selective transformation or only a slight preference for **3a** (Table 1, entries 3 and 4). Recently, boron-doped diamond (BDD) electrodes were used successfully for the reduction of oximes.^[23,24] Although a high stereoselectivity was found with the BDD cathode, only traces of menthylamines could be isolated, because of a low conversion (Table 1, entry 5). Thus, this electrode material was not considered further.

Mercury turned out to be the best cathode material in respect to stereoselectivity, but it exhibits a strong temperature dependence (Table 2). Menthylamine is favored at low temperature, but the chemical yield of the isolated product could not be increased above 76%. Only moderate current densities could be applied because of the slow mass transport between the bulk phase and the electrode surface (Table 2, entries 1 and 2). Higher temperatures resulted in the stereoselectivity for **3a** dropping; the best conversion was obtained at 0 °C (Table 2, entry 3). A further increase in the electrolysis temperature caused a decrease in the yield, since hydrolysis of the oxime occurred (Table 2, entries 4 and 5). Beckmann

Table 2: Effect of temperature on the reduction of menthone oxime on a mercury cathode.

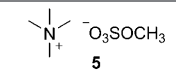
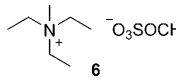
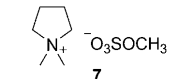
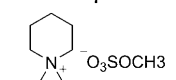
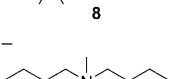
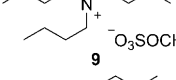
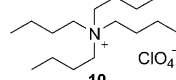
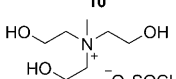
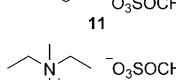
Entry	T [°C]	Current density [mAcm ⁻²]	Yield [%]	Faradaic yield [%]	d.r. 3a/3b
1 ^[a]	–14–18	23	56	34	3.8:1
2 ^[b]	–10	10	76	31	4.1:1
3 ^[a]	0	46	86	56	2.4:1
4 ^[a]	20	46	68	24	2.4:1
5 ^[a]	50	51	17	16	2.0:1

[a] Conditions: catholyte 0.5 M H₂SO₄ in DME/H₂O 1:1. [b] Conditions: catholyte 2% H₂SO₄ in DME with 10% H₂O.

rearrangement of this substrate^[25] was not detected under these conditions. The pronounced selectivity obtained by direct reduction on a metal surface can be attributed to the formation of a covalently bound intermediate in such a transformation (see the Supporting Information).^[26]

The corrosion commonly found when lead is used as the cathode material can be explained by the anticipated lead intermediates on the cathode surface. The formation of a white precipitate (PbSO₄) over the course of the electrolysis confirms this undesired side reaction. Although sulfuric acid is a strong electrolyte, the addition of a small quantity of a tetraalkylammonium salt improves the situation dramatically (Table 3). The conversions are clean and with a slight preference for the epimer **3b**. The small and relatively rigid cations **5–8** effect almost quantitative conversions (Table 3, entries 1–4). Changing the counterions had no influence on the efficiency and the stereoselectivity (see the Supporting Information). Of the additives tested, the best result was obtained with triethylmethylammonium methylsulfate (**6**), which is environmentally benign and the least expensive additive (Table 3, entry 2). The yield of the isolated product in the absence of an additive is only 88%, but it is formed with a comparable stereoselectivity (Table 3, entry 5). However,

Table 3: Quaternary ammonium salts as additives for the reduction on a lead cathode.

Entry	Additive [0.5 %]	Yield [%]	Faradaic yield [%]	d.r. 3a/3b
1 ^[a]	 5	> 99	40	0.8:1
2 ^[a]	 6	> 99	41	0.6:1
3 ^[a]	 7	> 99	40	0.7:1
4 ^[a]	 8	99	40	0.8:1
5 ^[a]	–	88	36	0.6:1
6 ^[a]	 9	78	31	0.5:1
7 ^[a]	 10	89	36	0.6:1
8 ^[a]	 11	33	14	0.9:1
9 ^[b]	 6	> 99	41	0.5:1
10 ^[c]	 6	> 99	41	0.3:1

[a] Conditions: catholyte 2% H₂SO₄ in MeOH, 20 °C. [b] Conditions: catholyte 2% H₂SO₄ in MeOH, 0 °C. [c] Conditions: catholyte 2% H₂SO₄ in MeOH, –10 °C.

preventing the undesired lead corrosion makes the use of additives attractive from a technical point of view.

The addition of either more lipophilic or hydrophilic cations does not improve the situation significantly (Table 3, entries 6–8). Small cations which are capable of forming a compact salt layer seem to efficiently block the access of protons to the cathode surface. This prevents the drain of electric current by evolution of molecular hydrogen. More lipophilic cations (**9** and **10**) might form a softer decoration (Table 3, entries 6 and 7). The strongly hydrated cation of **11** allows fast access of the protons to the lead electrode and causes inferior results (Table 3, entry 8). A further parameter for tuning the selectivity towards **3b** is the electrolysis temperature (Table 3, entries 9 and 10). Lowering the temperature to 0 °C already improves the diastereomeric ratio. When the electrolysis is performed at –10 °C the yield is still excellent, but the generated amine contains almost 75 % (+)-neomenthylamine (**3b**; Table 3, entry 10). The use of even lower temperatures results in no further benefit (see the Supporting Information).

In the absence of additive the transformation is not clean and a mixture of several products is obtained (Figure 1 a). In contrast, decoration by these additive cations results in the formation of the compact salt layer and effects a smooth electrochemical transformation (Figure 1 b). A significant amount of menthylamine is formed which can undergo hydrolysis to menthone. After the calculated current of 4 Faradays per oxime, 88 % of menthylamine is formed. The conversion is complete after an additional 2 Faradays of current, which facilitates the workup tremendously. The best results allow more than 99 % conversion to the product with a current efficiency of 66 %.

Similar to chelating effects, polycationic species should enhance the decoration of the cathode. The dicationic salt **12** obtained from the Baizer process^[27,28] shows the anticipated effect. Although **12** comprises approximately two subunits of **9**, the oxime reduction is quantitative (Table 4, entry 1). Remarkably, the electrolysis conditions result in a completely unselective menthylamine. We synthesized harder oligo(me-

Table 4: Polycationic ammonium salts as additives for the reduction on lead cathode.

Entry	Additive	Conc [%]	Yield [%]	Faradaic yield [%]	d.r. 3a/3b
1 ^[a]		0.5	> 99	40	1.0:1
2 ^[a]		< 0.1	96	39	0.6:1
3 ^[a]		0.5 + 10% H2O	> 99	40	0.6:1
4 ^[a]		< 0.1	> 99	40	0.6:1
5 ^[a]		0.5 + 10% H2O	> 99	40	0.6:1
6 ^[a]		≤ 0.1	> 99	40	0.5:1
7 ^[a]		0.5 + 20% H2O	84	34	0.6:1

[a] Conditions: catholyte 2 % H₂SO₄ in MeOH, 20 °C, 12.5 mA cm⁻².

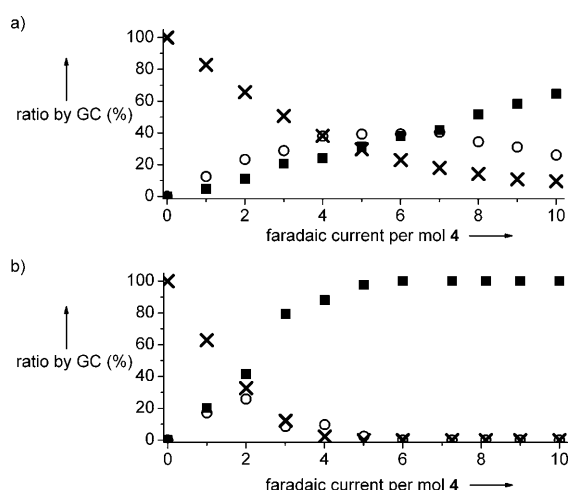
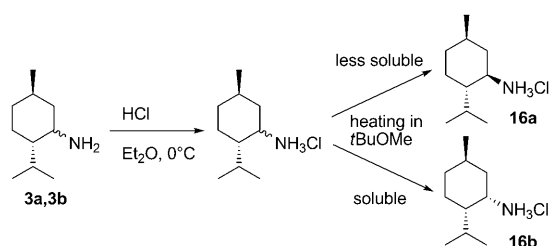


Figure 1. Menthyl derivatives monitored during the course of the electrolysis. a) Without additive; b) with 0.5 % **6** (■: menthylamines **3a** and **3b**; ○: menthylamine; ×: menthone oxime **4**).

thylammonium) derivatives by standard methods (see the Supporting Information) and tested them in this cathodic process to elucidate the power of the concept. The yield is slightly decreased, but a preference for **3b** is observed (Table 4, entry 2) when the amount of additive **13** is present in the electrolyte at less than 0.1 % by weight. The use of a little more of the additive **13** allows the electrolysis to be carried out in the presence of 10 % water without affecting the excellent performance (Table 4, entry 3). Tricationic additive **14** can be used in the presence of water or concentrations of far less than 0.1 % (Table 4, entries 4 and 5).^[29] An additive with four quaternary ammonium moieties exhibits an even higher performance. The solubility of **15** in acidic methanol is very poor but the amount is sufficient to decorate the cathode with high efficiency (Table 4, entry 6). A clear solution with 0.5 % additive is achieved with a water content of 20 %. The performance is decreased under these conditions but still much better than without additive (Table 4, entry 7).

The formation of a compact salt layer is evident from two major findings: The reduction is not stereoselective at ambient conditions since the contact to the electrode surface is missing, but, most importantly, the corrosion of the lead cathode is completely avoided. The electrodes stay intact with a shiny surface and no lead sulfate is formed.



Scheme 3. Separation of diastereomeric menthylamines by exploiting the different solubility of the hydrochlorides.

The separation of the epimers **3a** and **3b** can be performed by chromatographic means (see the Supporting Information). This is not practical since it is very time consuming and costly. After conversion into the corresponding hydrochlorides **16a** and **16b**, respectively, the different solubility in *tert*-butylmethylether can be exploited for a viable separation (Scheme 3, for details see the Supporting Information). Starting from a 1:1 ratio of diastereomers, a 35% yield of **16a** with a stereochemical purity of 90% is obtained. By this approach, **16b** can be obtained in a highly isomerically enriched manner. Both hydrochlorides are ideal derivatives for storage.

In conclusion, we have found a reliable method for the electrochemical synthesis of menthylamines from menthone oxime. The cathodic conversion on the mercury pool provides a selective reduction to (–)-menthylamine. When lead is used as the cathode material it can be decorated with a small amount of quaternary ammonium salts, which allows quantitative conversions and prevents corrosion of the toxic cathode metal. The stereoselectivity can be shifted to the technically relevant (+)-neomenthylamine by lowering the electrolysis temperature. In addition, a very practicable way for the separation of the epimeric menthylamines has been established. These unique optically pure amines are highly accessible by using this stereodivergent process and will find future applications. Moreover, a novel concept for the cathodic use of lead has been found which could eliminate concerns of employing it as an electrode material. This will open up a new possibility for sustainable reductions by electrosynthesis.

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