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Thiyl Radical Mediated Racemization of Benzylic Amines

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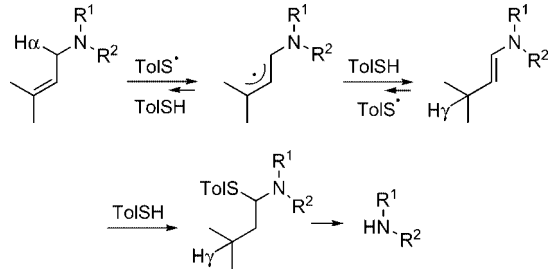
Thiyl radical mediated reversible H abstraction from the stereogenic center α to the nitrogen atom is a mild method to racemize benzylic amines. Owing to the sensitivity of atom-transfer reactions to enthalpic effects, a knowledge of both the S–H and the α-C–H bond dissociation energies is fundamental to select the thiol that is appropriate to abstract the hydrogen atom from a given amine. In the absence of experimental data, theoretical calculations supply a useful predictive tool. The experiments described here are helpful in delineating the optimal conditions that have to be fulfilled for the racemization to proceed in a reasonable time in the presence of either a stoichiometric or a catalytic amount of thiol.

Introduction

As stated by Ebbers et al. in 1997,[1] in a general review devoted to the racemization of organic compounds: "Notwithstanding the revolutionary advances in asymmetric synthesis, the resolution of racemates is still the most important approach to the industrial synthesis of optically pure compounds [...] The main disadvantage of a resolution compared to an enantioselective synthesis is the maximum theoretical yield of 50%. Therefore racemization of the unwanted isomer is of critical importance for economically and environmentally acceptable resolutions." If one ignores α-amino acid derivatives,[2] the racemization of amines is mainly performed by processes involving oxidation/reduction[1,3] (60%) or base-catalysis[1,4] (30%). The latter often necessitates rather harsh conditions, which do not tolerate additional sensitive functional groups. Redox processes going through prochiral imines or iminium ion intermediates can be performed either under heterogeneous or homogeneous catalysis. The mechanism of the ruthenium-catalyzed dehydrogenation of amines and that of the related hydrogen transfer to imines have been investigated by Bäckvall. These reactions have been applied to the racemization of benzylic amines at 110 °C in toluene.[5]

Thiols are very good hydrogen atom donors[6] and, at the same time, thiyl radicals are able to abstract hydrogen atoms from electron-rich C–H bonds.[7] They also act as efficient polar reversal catalysts in numerous radical reactions.[8] The epimerization of stereogenic centers α to an oxygen atom in cyclic systems has been reported by von Sonntag and by Roberts,[9] and we have recently shown that thiyl radicals are able to mediate the cleavage of allylic amines.[10] The reaction is likely to proceed through hydrogen abstraction from the allylic position α to the nitrogen atom, according to Scheme 1. The backward hydrogen transfer from the thiol to the carbon atom γ to the nitrogen atom in the intermediate delocalized radical leads to an enamine, which gives rise to a thioaminal under stoichiometric conditions. The latter is hydrolyzed upon acidic workup.



Scheme 1.

Following on from this study, we have investigated the thiyl radical mediated reversible H abstraction from chiral benzylic amines, since this reaction should provide an attractive methodology to racemize these activated amines under mild conditions (Scheme 2).

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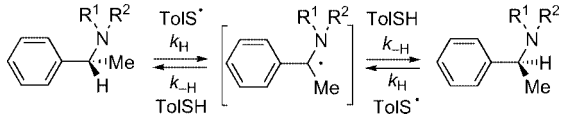


Scheme 2.

The forward hydrogen atom transfer from the amine to the electrophilic thiyl radical is particularly favored on the grounds of polar effects since it generates a strongly nucleophilic carbon-centered radical. However, the opposite polarity of the two radical species, which accelerates the hydrogen atom transfers, is not the only requirement. The S–H and the C–H bond dissociation energies (BDEs) should match each other in such a way that none of the key hydrogen transfers is too slow for the reaction to proceed in a reasonable time, and without undesired side-products being formed.

We describe herein the results obtained with α-phenethylamines **1**–**3**, amide **4**, and amines **8**–**11** (Figure 1). The influence of both experimental conditions (temperature, solvent, concentration of the reagents), and structural parameters (substitution at the nitrogen atom, nature of the thiol) has been investigated.

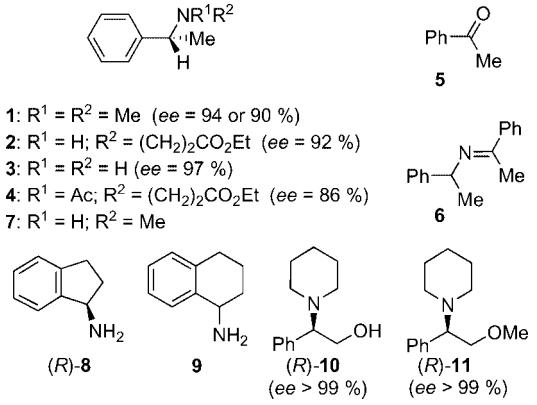


Figure 1. Structures of compounds **1**–**11**.

Results and Discussion

The racemization experiments were performed on tertiary, secondary, and primary amines **1**, **2**, and **3**. Amine **1** was obtained from the commercially available (*R*)-1-phenethylamine (**3**) in 68% yield (94–90% *ee* depending on the experiment) by an Eschweiler–Clarke methylation procedure.[11] Amine **2** was prepared in 59% yield (92% *ee*) by the addition of **3** to ethyl acrylate.[12] Amine **10** was prepared in 77% yield (*ee* > 99%) by the double alkylation of (–)-(*R*)-2-aminophenylethanol with 1,5-dibromopentane.[13] Its methylated derivative **11** was obtained in 80% yield (*ee* > 99%) upon treatment with NaH and MeI. The synthesis of these amines in racemic form was also performed according to the same protocols in order to optimize the analytical procedures.

The radical reactions were monitored and analyzed by chiral HPLC. The results are summarized in Table 1. Typical experiments were performed as follows: a benzene solution of amine (0.063–0.64 M) containing the selected thiol (1.2 or 0.2 equiv.) was heated at reflux for 6–7 h in the presence of AIBN (an overall quantity of 20 mol-% of AIBN was divided into three equal portions, which were added successively every 2 h). After concentration, the residue was diluted with HCl (1 M) and the solution was washed with Et_2O. The aqueous phase was basified with saturated sodium carbonate and extracted with Et_2O. The pure amine was isolated after drying with $MgSO_4$ and concentration. Due to the scale (approximately 100 mg of substrate), the isolated yields for the recovery of the amine after acid/base purification seldom exceeded 70%, except for the most lipophilic amine in the series (**2**). Yields determined by ^1H NMR spectroscopy using pentamethylbenzene as internal standard are given in parentheses.

As stated above, the choice of thiol is crucial. According to literature data, the α-C–H BDE is 357 kJ mol^{-1} in dibenzylaniline and 372 kJ mol^{-1} in tribenzylamine.[14] Instead of taking any of these nonbranched amines as reference, we reasoned that the α-C–H BDE in chiral benzylic amines should not be very different from the α-C–H BDE in allylic amines (the α-C–H BDE in *N*-allylic amines varies between 320 and 330 kJ mol^{-1} according to DFT calculations[10b]). This is the reason why we started studying the reactivity of thiocresol with respect to amine **1**, using the experimental conditions that had proved efficient for H abstraction from allylic amines.[10] Compound **1** was found to be almost completely racemized in 6 h (14% *ee*; Entry 1). Acetophenone (**5**) was detected in 3% yield as a side-product. The latter most probably results from oxidation of the intermediate α-amino radical. These radicals are reputedly potent one-electron reducing agents, with ionization potentials that rival those of alkali metals.[15,16]

The result reported in Entry 1 was obtained after 6 h in the presence of 1.2 equiv. of thiocresol. Reducing the number of equivalents of thiol by a factor of six (Entry 2/Entry 1) led to 28% *ee* for the recovered amine after 7 h at reflux. Multiplying the concentration by a factor of 2 or 10 did not change the results very much under stoichiometric conditions (cf. Entries 3 and 4 with Entry 1). Monitoring of the reaction by chiral HPLC led us to the conclusion that stoichiometric conditions and a concentration between 0.067 and 0.13 M was a rather good compromise.

As reported in Table 1 (Entries 6–9), the nature of the thiol was investigated with amine **1**. Racemization was completed in 6 h with both thiophenol and *n*-OctSH under stoichiometric conditions (*ee* values of 4 and 0%, respectively; Entries 6 and 8). According to enthalpic effects, going from TolS$^\cdot$ to *n*-OctS$^\cdot$ would increase k_H and conversely should decrease k_{-H}. This was clearly demonstrated by the influence of the concentration in the case of the alkanethiol: after 6 h, under catalytic conditions, the *ee* value was still 80%, whereas amine **1** was totally racemized under stoichiometric conditions (Entry 9/Entry 8). The effect was less pronounced in the case of TolSH (Entry 2/Entry 1). Thiophenol was as efficient under stoichiometric conditions as under catalytic conditions (Entry 6/Entry 7).

Table 1. Racemization of amines **1**, **2**, **3**, amide **4**, and amines **10** and **11**.

Entry	Amine (Concentration)	RSH (*n* equiv)	Reaction time (h)	Yield % Isolated (NMR)	*(R):(S)* (*ee*)	By-product (%)
1	**1** (0.067 M)[c]	TolSH (1.2)	6	30 (73)	57:43 (14)	**5** (3)
2	**1** (0.067 M)[c]	TolSH (0.2)	7	50 (84)	64:36 (28)	**5** (2)
3	**1** (0.13 M)[c]	TolSH (1.2)	6	54 (100)	54:46 (8)	**5** (6)
4	**1** (0.64 M)[c]	TolSH (1.2)	6	63 (nd[a])	58:42 (16)	**5** (5)
5	**1** (0.64 M)[c]	TolSH (0.2)	7	60 (73)	78:22 (56)	**5** (8)
6	**1** (0.067 M)[c]	PhSH (1.2)	6	70 (77)	52:48 (4)	**5** (10)
7	**1** (0.067 M)[c]	PhSH (0.2)	6[b]	60 (98)	53:47 (6)	**5** (2)
8	**1** (0.067 M)[c]	*n*-OctSH (1.2)	6	70 (75)	50:50 (0)	**5** (4)
9	**1** (0.067 M)[c]	*n*-OctSH (0.2)	6	40 (72)	90:10 (80)	**5** (6)
10	**2** (0.063 M)[d]	TolSH (1.2)	7	70 (nd)	50:50 (0)	-
11	**2** (0.063 M)[d]	TolSH (0.15)	7	80 (nd[a])	69:31 (38)	-
12	**2** (0.067 M)[d]	PhSH (1.2)	6	60 (70)	47:53 (6)	-
13	**2** (0.067 M)[d]	*n*-OctSH (1.2)	6	nd[a] (15)	90:10 (80)	-
14	**4** (0.067 M)[e]	PhSH (1.2)	6	100 (nd)	93:7 (86)	-
15	**3** (0.063 M)[f]	TolSH (1.2)	6	nd[a] (61)	80:20 (60)	**6** (14)
16	**3** (0.063 M)[f]	PhSH (1.2)	6	50 (71)	70:30 (40)	**6** (17)
17	**3** (0.063 M)[f]	PhSH (0.2)	6	30 (60)	88:12 (76)	**6** (20)
18	**3** (0.64 M)[f]	PhSH (1.2)	6	40 (72)	52:48 (4)	**6** (8)
19	**10** (0.064 M)[g]	TolSH (1.2)	6	57 (nd)	86:14 (72)	-
20	**10** (0.064 M)[g]	PhSH (1.2)	6	69 (nd)	86:14 (72)	-
21	**11** (0.064 M)[g]	TolSH (1.2)	6	70 (nd)	66:34 (32)	-
22	**11** (0.064 M)[g]	PhSH (1.2)	6	60 (nd)	71:29 (42)	-

[a] nd = not determined. [b] *ee* = 16% after 3 h. [c] $(ee)_0$ = 94%. [d] $(ee)_0$ = 92%. [e] $(ee)_0$ = 86%. [f] $(ee)_0 > 97\%$. [g] $(ee)_0 > 99\%$.

Thus, a wide range of thiols can be used to racemize tertiary benzylic amines in the presence of 1.2 equiv. of thiol. The requirement regarding the relative strength of S–H and C–H bonds is stricter when the thiol is used in catalytic amounts (0.2 equiv.) with respect to the substrate since the rate of the backward transfer is divided by a factor of six, like the thiol concentration.

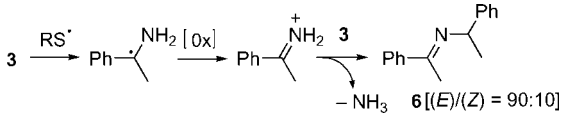
The secondary amine **2** was also racemized within 7 h using either a stoichiometric or a catalytic amount of thiocresol (0 or 38% *ee* depending on the experimental conditions; Entry 10/Entry 11). Racemization was nearly complete in 6 h with a stoichiometric amount of thiophenol. However, with octanethiol as the mediator degradation was observed. The remaining amine (15%) was not significantly racemized. This would indicate that, although *n*-OctS$^{\cdot}$ is strong enough to abstract the α-hydrogen atom, the reverse step is too slow (even in the presence of a stoichiometric amount of thiol) to prevent side reactions of the α-aminoalkyl radical.

The variation of *ee* value vs. time was also monitored. In the presence of a stoichiometric amount of thiol, the racemization proceeded slightly faster for the secondary amine **2** than for the tertiary amine **1**. The racemization of **1** proceeded slightly faster with OctSH than with TolSH (see Supporting Information).

According to literature data, acetylation strengthens the α-C–H BDE by approximately 17 kJ mol^{-1} for aliphatic amines.[17] The stereogenic center in the acetylated derivative **4** could not be epimerized whatever thiol was used (PhSH, TolSH, or even thioglycolic acid methyl ester, which has a much stronger S–H bond; see Table 3) under stoichiometric conditions (Entry 14). The absence of racemization is likely to result from the inability of any of the thiyl radical mediators used to abstract the α-hydrogen

atom because both enthalpic and polar effects are unfavorable.

The most intriguing results came from the primary amine **3**. In all cases a large amount of imine **6** was formed.[18] The oxidation of the intermediate radical leading to the corresponding carbenium ion, followed by condensation of the primary amine according to Scheme 3, might account for the formation of **6**.



Scheme 3.

When thiocresol was used as the mediator, partial racemization occurred, 61% of amine **3** (60% *ee*) was recovered, and **6** was detected in 14% yield by NMR spectroscopy (Entry 15). It should be noted that a 14% yield of imine **6** corresponds to the consumption of 28% of amine **3**. One would have expected the best hydrogen atom donor, i.e., thiocresol to give the best results. However, thiophenol gave slightly better results than thiocresol. When thiophenol was used, either in stoichiometric or catalytic amounts, the rate of recovery of amine **3** increased slightly and the recovered amine was partially racemized [40% *ee* after 6 h under stoichiometric conditions (Entry 16); 76% *ee* in the presence of a catalytic amount of PhSH (Entry 17)].

An experiment was performed using a stoichiometric amount of thiophenol at a concentration ten times higher (Entry 18/Entry 16). The higher thiophenol concentration should increase the rate of hydrogen transfer from the thiol to the intermediate α-amino radical and thus render the racemization process competitive with respect to the oxidation of the α-amino radical. Racemization was completed within 6 h and, as expected, the amount of **6** was significantly decreased. The amount of **6** was not strictly reproducible from one experiment to another, and careful degassing of the reaction medium did not affect the results.

Changing the nature of the solvent did not change the outcome of the reaction: no significant effect was registered going from benzene to toluene, heptane, or even ethyl acetate. Neither octanethiol nor methyl thioglycolate were efficient in racemizing amine **3**. When octanethiol was used, oxidative degradation of the amine was observed. In all likelihood the return hydrogen transfer (k_{-H}) is too slow, and electron transfer oxidation (possibly with the disulfide likely to be formed in the reaction medium) became the major pathway.

Theoretical Support

It long has been accepted that the α-C–H BDE increases when going from a tertiary to a secondary, and then to a primary amine.[19] However, recent data on α-C–H BDEs in aliphatic amines have shown that the degree of substitution at the nitrogen atom has little effect on the BDE.[20] To confirm or refute our mechanistic speculations, BDE calculations were undertaken. According to Guo et al.,[21] the best methods to calculate BDEs would be high-level theoretical methods such as G3 and CBS-Q; the G3B3(MP2) method also gives a quite good agreement with experimental values. However, for cost reasons, many groups have used pure DFT methods that have been shown to give reliable relative values in a series and therefore offer a good compromise.[21,22] Both S–H BDEs and α-C–H BDEs in amines **1**, **3**, and **7** (taken as a model for **2**; Figure 1) were first determined at the UB3P86/6-311++G(d,p)//UB3LYP/6-31G(d) level of theory using the Gaussian 03 program.[23] The UB3LYP/6-31G(d) basis set was used to optimize geometries. Each optimized geometry was confirmed by frequency calculations to be a real minimum. The enthalpy of each species was calculated using the UB3P86/6-311++G(d,p) electronic energy, and the zero-point vibrational energy and thermal corrections obtained at the UB3LYP/6-31G(d) level using a scale factor of 0.9804.

The energies of the frontier orbitals, i.e., the SOMOs of both the α-amino radicals and the thiyl radicals, are given in Tables 2 and 3, respectively (*n*BuSH was taken as a model for *n*-OctSH).

Table 2. Calculated α-C–H BDEs, energies of the SOMOs of α-amino radicals, and vertical ionization potentials.

Amine	**1**	**7b**	**7a**	**3**
BDE_{298K} (kJ/mol)	344.0[a]	342.5[a]	331.5[a]	327.4[a]
				347.0[b]
	371.8[c]	368.4[c]	357.5[c]	352.0[c]
α-amino radical SOMO[a] (eV)	–4.7	–4.6	–4.4	–4.6
α-amino radical vertical IP[a] (eV)	6.4			6.4

[a] UB3P86/6-311++G(d,p)//UB3LYP/6-31G(d). [b] G3B3. [c] G3B3(MP2).

It should be noted that according to the calculations reported here, the α-C–H BDE increases with substitution at the nitrogen atom, contrary to the above-mentioned general assumption. The preferred conformations of the amine and the corresponding α-amino radicals are given in Figures 2 and 3, respectively. In all cases the lowest-energy conformer of the amine corresponds to the geometry where the α-C–H bond is antiperiplanar with respect to the lone pair. According to NBO calculations,[26] the overlap between the σ^*_{C-H} orbital and the lone pair stabilizes the system by around 30–37 kJ mol^{-1} (Table 4). The interaction with the π-bonds of the aromatic ring stabilizes the ground state by less than 2.1 kJ mol^{-1}. These effects account for the variation of the C–H bond length in the series.

The case of amine **7** is somewhat special since two stable conformers were found for the ground state (their total en-

Table 3. Calculated and experimental values for S–H BDEs, and energies of the SOMOs of thiyl radicals.

Thiol	TolSH	PhSH	BuSH	MeO_2CCH_2SH
S-H BDE (kJ/mol)	322.6[a]	330.6[a]	358.2[a]	364.9[a]
	339.6[b]	346.4[b]	359.9[b]	364.4[b]
		346.0[c]	360.9[f]	
	347.5±4.1[d]	349.4±4.5[d]	370.7±8.4[e]	
$RS^{\bullet}$ SOMO[a] (eV)	–7.0	–7.2	–7.3	–7.7

[a] This work, UB3P86/6-311++G(d,p)//UB3LYP/6-31G(d). [b] This work, G3B3(MP2). [c] G3(MP2) calculated value at 298 K.[24a] [d] Experimental values.[24a] [e] Experimental value.[25] [f] G3-calculated value at 298 K for *n*BuSH.[10b]

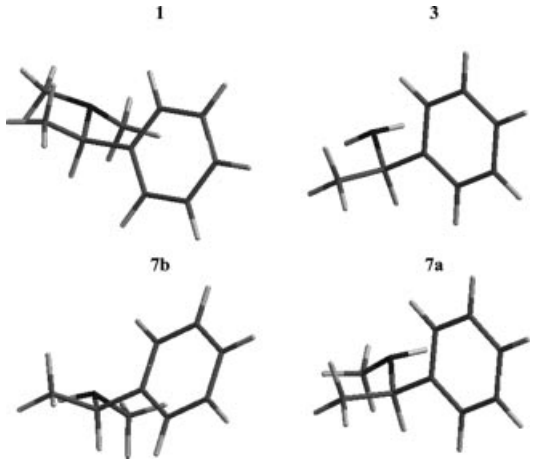


Figure 2. Preferred conformations of amines **1**, **3**, and **7**.

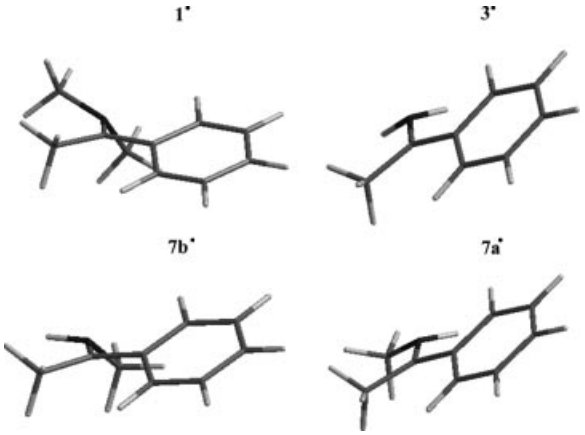


Figure 3. Preferred conformations of α-amino radicals **1**•, **3**•, and **7**•.

ergies differ by 4 kJ mol^{-1} at 298 K; at 80 °C the ratio of **7b**/**7a** would be 80:20). The most stable conformer (**7b**) corresponds to the less stable conformation of the radical (7 kJ mol^{-1} total energy difference between **7b** and **7a** at 298 K), and thus to a BDE value higher by about 11 kJ mol^{-1} (although the rotational barrier is likely to be very low). The data in Tables 2 and 4 indicate that **7** (and by extrapolation **2**) is closer to **1** than to **3**. This is in agreement with the observed reactivity.

Table 4. Hyperconjugative effects affecting the α-C–H bond determined by the NBO method for the lowest-energy conformers of amines **1**, **7a**, **7b** (models for **2a** and **2b**), **3**, **8**, **10**, and **11** calculated at the UB3P86/6-311++G(d,p)//UB3LYP/6-31+G(d) level, and bond lengths.

Amine	n -> $\sigma^*_{C\text{-}H}$[a]	$\pi_{C=Car}$ -> $\sigma^*_{C\text{-}H}$[a]	$d_{C\text{-}H}$[b]
1	37.4	< 2.1	1.110
7b	32.7	< 2.1	1.109
7a	33.3	< 2.1	1.109
3	30.3	< 2.1	1.106
8	30.7	11.6	1.109
10	26.9	< 2.1	1.105
11	35.8	< 2.1	1.108

[a] In kJ mol^{-1}. [b] C–H bond lengths in Å.

Based on the interaction of the lone pair with the σ^*_{C-H} orbital, one would expect **1** to be cleaved faster than **2**, which itself would be cleaved faster than **3**. However, the BDEs show the opposite trend. The variation of the C–H BDE in the series is well accounted for by steric interactions which prevent the radical from being planar and fully delocalized in the case of the secondary and the tertiary amines (Figure 3). If spin delocalization at the aromatic ring carbon atoms is important in all cases, the overlap between the lone pair and the singly occupied orbital is smaller when a methyl group faces the aromatic ring.

From the experimental measurements it was possible to determine how much the S–H BDEs are underestimated by the calculations (Table 3). However, the BDEs in the series were not all measured according to the same experimental method. We also had no experimental data to determine how much the C–H BDEs were underestimated. So we had in hand two independent reliable relative scales but it was not obvious to superimpose them. Owing to the accuracy of these calculations,[21] and in order to obtain more reliable absolute values for the BDEs in the series of amines for which we could not refer to any experimental measurement, G3B3(MP2) calculations were performed for both the α-C–H BDEs in amines **1**–**3** and the S–H BDEs (Tables 2 and 3). According to these data, in the case of amine **1** and, by analogy, in the case of amine **2** (closer to **1** than to **3**), the forward H transfer should be endothermic whatever the thiol is. Consequently, it should be rate-limiting. This is in agreement with the racemization of **2** proceeding slightly faster than that of **1** in the presence of a stoichiometric amount of TolSH, since the forward hydrogen transfer is less endothermic. The fact that **1** is racemized faster by *n*-OctSH than by TolSH points to the same conclusion.

Hydrogen abstraction reactions have been the object of many theoretical and empirical studies.[27] Special attention has been focused recently on hydrogen-transfer reactions from a series of aliphatic thiols to a series of carbon-centered radicals selected with respect to their polar character. High-level ab initio and DFT calculations using the curve-crossing model confirm that the activation barrier is influenced by both polar and enthalpic factors.[28,29] Unfortunately, no calculations were carried out for α-amino radicals, and the range of thiols did not include aromatic thiols.

The reduction of the hydroxymethyl radical with thiols was shown to be a reversible process. The rate constant for the reaction of the penicillamine thiyl radical with 2-propanol is $1.4 \pm (0.3) \times 10^4$ M^{-1} s^{-1}, and the rate constant for the reverse hydrogen transfer is $1.2 \pm (0.3) \times 10^8$ M^{-1} s^{-1} at 20 °C.[30,31] The rate constant for the H abstraction from peptides by the methylthiyl radical was estimated to be 3×10^5 M^{-1} s^{-1} by Rauk et al.[32]

From our estimate of the rate of racemization of amines **1** and **2** with thiocresol, one would expect the order of magnitude of k_H to be between 10^3 and 10^4 M^{-1} s^{-1} for this thiol (see Supporting Information).

The examination of the results also leads to the conclusion that the backward H transfer is critical for the efficacy of the racemization process. Only the most exothermic ones enable the racemization to proceed in the presence of a catalytic amount of thiol. As an example, in the presence of 0.2 equiv. of thiol the backward transfer would become too slow for the two-step chain mechanism to proceed with the thiol having the strongest BDE, i.e., *n*-OctSH (Entry 9). According to the calculations reported by Coote et al.,[28] the smaller the enthalpy change, the closer are the activation barriers for the forward and the backward transfers. A very narrow range between k_H and k_{-H} could be expected for the reaction of octanethiol with amine **1**. In the case of amine **2**, even in the presence of 1.2 equiv. of octanethiol, the backward hydrogen transfer would not be able to compete with oxidative degradation (Entry 13).

The least exothermic transfers from the thiol to the carbon-centered radical, i.e., those involved in the case of amine **3**, would not be fast enough to compete with the oxidation of the radical leading to the formation of acetophenone and imine **6**.

One would have expected the α-amino radical having the highest-lying SOMO to be oxidized faster. The similarity between the energies of the SOMOs of the radicals derived from **1** and **3**, as confirmed by the similarity of their non-adiabatic ionization potentials calculated at the UB3P86/6-311++G(d,p)//UB3LYP/6-31G(d) level (6.4 eV for both radicals), leads us to discard such an explanation.[33] In the case of amine **3**, the fact that PhSH is slightly more efficient than TolSH might originate from the contribution of polar effects. Since the enthalpy change is similar (based on experimental values of S–H BDEs[24a]), the hydrogen transfers involving PhS$^{\cdot}$, which is more electrophilic than TolS$^{\cdot}$ (electron affinities, *EA*, of 225.5 and 215.4 kJ mol^{-1},[24c] respectively) might be slightly faster.

Scope and Limits

The above comments should help in figuring out the scope and limits of the reaction. As stated above, the backward transfer may not be able to compete with the oxidation process when the intermediate α-amino radical is readily oxidized. In fact, this is the case for the cyclic primary benzylic amines **8** and **9**. The reaction performed with (*R*)-1-aminoindane (**8**) clearly shows that the starting material is nearly totally degraded. The remaining substrate is completely racemized. Due to favorable structural parameters, H abstraction is particularly favored and the resulting radical has a high-lying SOMO (–4.2 eV). The value for its vertical ionization potential is only 6.2 eV, therefore oxidative degradation is very fast in this case. A test was performed on racemic **9** in order to check its stability toward the reaction conditions; it was completely degraded under our standard conditions.

Beyond the previously mentioned acylation, which completely inhibits H abstraction due to the strengthening of the α-C–H BDE, we have performed some experiments on amino alcohol derivatives (**10** and **11**) in order to analyze the effect of the β-substituents. The results of the racemization experiments are also reported in Table 1. The reactions were performed under the standard conditions defined for the other amines, and the *ee* value was analyzed after 6 h at reflux in the presence of AIBN.

As shown in Figure 4, intramolecular hydrogen bonding in **10** modifies the geometry in such a way that neither the aromatic π-system nor the lone pair can fully participate in the weakening of the α-C–H bond and the stabilization of the incipient radical (Table 4). The N···H distance is 2.04 Å and the delocalization of the lone pair in the antibonding σ^*_{O-H} orbital stabilizes the system by 24.3 kJ mol^{-1}. All these effects contribute to strengthening the α-C–H bond [UB3P86/6-311++G(d,p)//UB3LYP/6-31G(d)-calculated BDE = 347.8 kJ mol^{-1}], which means that the racemization process is slowed down and the *ee* is still 72% after 6 h.

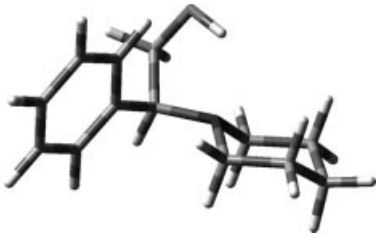


Figure 4. Influence of hydrogen bonding on the preferred conformation of amine **10**.

The results obtained with **11** as starting material suggest that the presence of the alkylated oxygen atom in the β-position still slows down the racemization process (*ee* = 42% for PhSH; Entry 22), even though there is no impediment to the antiparallel arrangement of the lone pair and the α-C–H bond (cf. Table 4). The BDE is 340.8 kJ mol^{-1} according to UB3P86/6-311++G(d,p)//UB3LYP/6-31G(d) calculations, which is slightly weaker than the α-C–H BDE in **1**.

Conclusions

We have proposed a very simple method to racemize chiral benzylic amines that is based on reversible H abstraction at the stereogenic center by a thiyl radical. The competitive oxidation of the intermediate α-amino radical makes the method less efficient for primary amines than for secondary and tertiary ones. It should be noted that in all cases, but more particularly when the carbon-centered radical is easily oxidized, the rate of H abstraction from the thiol by the carbon-centered radical is a parameter of major importance since it controls its lifetime. In this case, a stoichiometric amount of thiol is recommended in order to minimize side reactions. Since polar effects can be considered to be roughly equally favorable for all the reactions in the series, theoretical calculations of α-C–H BDEs, which enable us to quantify enthalpic factors, provide useful data to rationalize the results and can be used as a predictive tool. Further developments will be reported in due course.

Experimental Section

General: All reactions were carried out under argon. Solvents were degassed before use. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz, respectively. Chemical shifts are reported in ppm and coupling constants given in Hz. Enantiomeric excesses (*ee*) were determined by analytical chiral HPLC. The solvents for chiral chromatography (*n*-hexane, 2-PrOH, EtOH) were of HPLC grade. They were degassed and filtered through a Millipore membrane (0.45 μm) before use. Cellulose tris(3,5-dimethylphenylcarbamate), Chiralcel OD-H (250×4.6 mm), and cellulose tris(4-methylphenylcarbamate), Chiralcel OG (250×4.6 mm), chiral stationary phases are available from Chiral Technologies (Illkirch, France). The chiral HPLC analyses were performed with a screening unit composed of a Merck D-7000 system manager, a Merck–Lachrom L-7100 pump, a Merck–Lachrom L-7360 oven, a Merck–Lachrom L-7400 UV detector, and an on-line chiroptical detector (Jasco OR-1590 polarimeter or Jasco CD-1595 circular dichrometer). The sign reported in parentheses is the sign given by the on-line polarimeter in the mobile phase used for the chiral HPLC analysis. Detailed chromatographic conditions are reported below. Compounds **1**, **2**, and **10** were prepared according to literature procedures.[11–13] All other commercially available compounds were used without further purification.

(*R*)-*N*,*N*-Dimethyl-1-phenethylamine (1): *ee* = 94%. Chiral HPLC conditions for the racemic mixture: Chiralcel OD-H, hexane/2-propanol (99.8:0.2), 1 mL min^{-1}. Detector: UV (254 nm) and polarimeter. t_R (*R*, +) = 5.44, t_R (*S*, –) = 6.21, *k* (*R*, +) = 0.75, *k* (*S*, –) = 1.0, α = 1.33, R_s = 1.99.

(*R*)-Ethyl 3-(1-Phenylethylamino)propanoate (2): *ee* = 92%. Chiral HPLC conditions for the racemic mixture: Chiralcel OD-H, hexane/2-propanol (99:1), 1 mL min^{-1}. Detector: UV (254 nm) and polarimeter. t_R (*S*, –) = 8.34, t_R (*R*, +) = 9.09, *k* (*S*, –) = 1.69, *k* (*R*, +) = 1.93, α = 1.14, R_s = 0.72.

(*R*)-1-Phenethylamine (3): *ee* = 97%. Chiral HPLC conditions for the racemic mixture: Chiralcel OD-H, hexane/2-propanol (90:10), 1 mL min^{-1}. Detection: UV (220 nm) and polarimeter. t_R (*R*, +) = 6.19, t_R (*S*, –) = 7.23, *k* (*R*, +) = 1.00, *k* (*S*, –) = 1.33, α = 1.33, R_s = 1.31.

(*R*)-Ethyl 3-[*N*-(1-Phenylethyl)acetamido]propanoate (4): Acetyl chloride (186 μL, 3.28 mmol) was added to a solution of **2** (330 mg, 1.49 mmol) and Et_3N (457 μL, 3.28 mmol) in dichloromethane at 0 °C. The reaction mixture was warmed to room temperature overnight and then diluted with water and extracted twice with EtOAc. The combined organic fractions were washed with 1 N HCl, brine and dried (Na_2SO_4). The solution was concentrated to give **4** (360 mg, 1.37 mmol, 92%), which was used without further purification. *ee* = 86%. Chiral HPLC conditions for the racemic mixture: Chiralcel OD-H, hexane/ethanol (90:10), 1 mL min^{-1}. Detector: UV (254 nm) and polarimeter. t_R (*R*, +) = 11.10, t_R (*S*, –) = 13.29, *k* (*R*, +) = 2.64, *k* (*S*, –) = 3.36, α = 1.27, R_s = 2.34. ^{1}H NMR (300 MHz, $CDCl_3$, TMS; mixture of 2 rotamers in a 58:42 ratio): δ = 7.19–7.48 (m, 5 H), 6.05 (q, *J* = 7.2 Hz, 0.42 H), 5.09 (q, *J* = 7.0 Hz, 0.58 H), 4.07 (q, *J* = 7.2 Hz, 0.84 H), 4.06 (q, *J* = 7.2 Hz, 1.16 H), 3.23–3.59 (m, 2 H), 2.29–2.57 (m, 2 H), 2.25 (s, 1.74 H), 2.19 (s, 1.26 H), 1.65 (d, *J* = 7.0 Hz, 1.74 H), 1.53 (d, *J* = 7.2 Hz, 1.26 H), 1.22 (t, *J* = 7.2 Hz, 1.26 H), 1.21 (t, *J* = 7.2 Hz, 1.74 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.5 (CH_3), 16.9 (CH_3), 18.5 (CH_3), 21.1 (CH_3), 22.3 (CH_3), 22.5 (CH_3), 33.8 (CH_2), 35.6 (CH_2), 39.0 (CH_2), 40.3 (CH_2), 51.2 (CH), 56.7 (CH), 60.7 (CH_2), 61.1 (CH_2), 127.0 (CH), 127.1 (CH), 127.9 (CH), 128.2 (CH), 128.9 (CH), 129.2 (CH), 140.4 (C), 140.9 (C), 171.1 (CO), 171.3 (CO), 172.3 (CO), 174.5 (CO) ppm.

(*R*)-2-Phenyl-2-(piperidin-1-yl)ethanol (10): *ee* = 99%. Chiral HPLC conditions for the racemic mixture: Chiralcel OG, hexane/isopropanol (90:10), 1 mL min^{-1}. Detector: UV (254 nm) and polarimeter. t_R (*R*, –) = 5.28, t_R (*S*, +) = 7.36, *k* (*R*, –) = 0.70, *k* (*S*, +) = 1.38, α = 1.96, R_s = 2.10.

1-[(*R*)-2-Methoxy-1-phenylethyl]piperidine (11): NaH (60% in oil, 133 mg, 3.30 mmol) was added to a solution of **10** (454 mg, 2.20 mmol) in dry THF at 0 °C. After 20 min of stirring at 0 °C and then 20 min at room temperature, iodomethane (144 μL, 2.31 mmol) was added at 0 °C. The reaction mixture was warmed to room temperature overnight and then diluted with water and extracted twice with Et_2O. The combined organic fractions were washed with water, brine, dried (Na_2SO_4), and concentrated. The crude material was subjected to flash column chromatography on silica gel (EtOAc/Et_3N/pentane, 10:5:85) to give **11** (370 mg, 1.77 mmol, 80%). *ee* = 99%. Chiral HPLC conditions for the racemic mixture: Chiralcel OD-H, hexane, 1 mL min^{-1}. Detector: UV (254 nm) and polarimeter. t_R (*S*, +) = 8.19, t_R (*R*, –) = 10.51, *k* (*S*, +) = 1.57, *k* (*R*, –) = 2.29, α = 1.46, R_s = 3.47. ^{1}H NMR (300 MHz, $CDCl_3$, TMS): δ = 7.20–7.40 (m, 5 H), 3.78 (dd, *J* = 5.7 and 9.8 Hz, 1 H), 3.66 (dd, *J* = 5.7 and 9.8 Hz, 1 H), 3.53 (pseudo-t, *J* = 5.7 Hz, 1 H), 3.31 (s, 3 H), 2.33–2.48 (m, 4 H), 1.49–1.64 (m, 4 H), 1.30–1.43 (m, 2 H) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.0 (CH_2), 26.6 (CH_2), 52.3 (CH_2), 59.3 (CH_3), 70.1 (CH), 74.9 (CH_2), 127.5 (CH), 128.4 (CH), 128.9 (CH), 140.1 (C) ppm.

General Procedure for the Racemization: A 0.06 M solution of amine (100 mg) and thiol (1.2 equiv. or 0.2 equiv.) in benzene was refluxed for 6–7 h in the presence of AIBN (an overall quantity of 20 mol-% of AIBN was divided into three equal portions, which were added successively every 2 h). After concentration, the residue was diluted with HCl (1 M) and the solution was washed with Et_2O. The aqueous phase was basified with saturated aqueous sodium carbonate and extracted with Et_2O. The pure amine was isolated after drying with $MgSO_4$ and concentration.

Computational Details: All the calculations were performed with the Gaussian 03 software package.[24] Geometry optimizations were carried out, without constraints, at the UB3LYP/6-31G(d) level of theory. Vibrational frequencies were calculated at the UB3LYP/6-

31G(d) level to determine the nature of the located stationary points. The spin contamination was low for all radical species (maximum value for $<S^2>$ = 0.772). In all cases vibrational frequencies were scaled by a factor of 0.9804 when considering the zero-point energy.[34] The BDE values at 298 K were calculated by standard statistical thermodynamic methods using the above-mentioned frequencies. The single-point energies were then calculated at the UB3P86/6-311++G(d,p) level of theory. In order to obtain more accurate results, some BDEs were calculated using the G3B3 and G3B3(MP2) composite methods.[35] Natural bond orbital interactions were calculated using the NBO 3.1[26] method included in the Gaussian 03 package.

Supporting Information (see footnote on the first page of this article): Plot of ee/ee_0 at different concentrations for amines **1** and **2**. Plots of $\ln(ee/ee_0)$ vs. time for amines **1** and **2**. Estimated rate constants for the racemization of amines **1** and **2**.

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