Pergamon

Tetrahedron Letters 43 (2002) 4699–4702

TETRAHEDRON LETTERS

An efficient and mild ruthenium-catalyzed racemization of amines: application to the synthesis of enantiomerically pure amines

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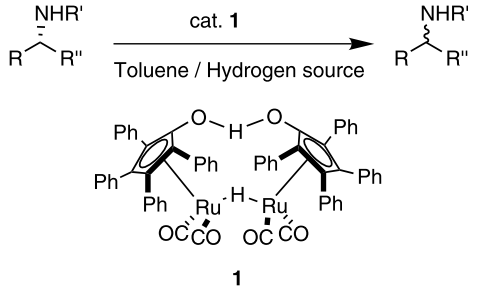
Received 4 March 2002; revised 17 April 2002; accepted 25 April 2002

Abstract—An efficient and mild Ru-catalyzed racemization of amines under transfer hydrogenation conditions is reported. A significant advantage of this new procedure is that the ruthenium hydrogen transfer catalysts allow high functional group tolerance. Interestingly, both primary and secondary amines were efficiently racemized under these conditions. We also report on the combination of this new amine racemization with an enzymatic kinetic resolution of primary amines. © 2002 Published by Elsevier Science Ltd.

The value of enantiopure amines lies mainly in their utility as building blocks for the synthesis of agrochemicals and pharmaceuticals. In recent years, many approaches for the preparation of enantiomerically pure amines have been developed.[1] Among these methods, the enzymatic kinetic resolution (KR) of the racemate still has a dominant role.[2] However, a major drawback with KR is that the yield is limited to a maximum of 50%.[3] Racemization is therefore an important tool that in combination with the KR can provide an efficient use of all racemate (after several racemization/KR repetitions the yield of the product can approach 100%).[4] However, only a few methods for racemization of amines are known in the literature.[4,5] Moreover, their potential utility is hampered by the harsh reaction conditions (high temperatures, and strong basic and/or reductive media) usually required, making these procedures incompatible with several functional groups. Therefore, it is important to develop new methods to racemize amines under conditions that can tolerate a wide number of different functional groups.

We have previously shown that low valent ruthenium complexes catalyze transfer hydrogenation of imines to amines[6] and transfer dehydrogenation of amines to imines.[7] These transformations are key steps in the racemization of amines. We now report on a ruthenium-catalyzed racemization of amines under transfer hydrogenation conditions (Eq. (1)). An important advantage of this new procedure is that the ruthenium hydrogen transfer catalysts allow high functional group tolerance.[8] We also report on the combination of this new amine racemization with an enzymatic KR of primary amines.[5d,5e,9]



1 (1)

In a first set of experiments the racemization of (*S*)-1-phenylethylamine (*S*)-**2a** using Ru-catalyst precursor **1**[10] was studied under different reaction conditions. The results are summarized in Table 1. Despite the complete racemization of (*S*)-**2a** (entry 1), the efficiency of the process was poor, since considerable amounts of imine **4a** and the corresponding amine **5a** were formed. The latter two compounds are formed via attack by **2a** on imine **3a** followed by elimination of ammonia (Scheme 1).[5a]

To increase the efficiency of the process it is necessary to decrease the amount of the side products. Three

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PII: S0040-4039(02)00817-1

different approaches were tried: (a) dilution of the reaction mixture; (b) addition of ammonia and (c) addition of a hydrogen source to increase the concentration of **1a**.

The results show that the concentration greatly affects the formation of side products **4** and **5** (entries 1–4). Thus, at low concentration the efficiency of the racemization was higher, but the side product formation was not completely inhibited. The addition of ammonia led to a significant improvement and the formation of side products **4** and **5** was effectively inhibited (entry 5). However, the scope of this procedure is limited since the use of highly basic ammonia reduces the functional group tolerance. Interestingly, we found that the addition of 0.5 or 1 equiv. of 2,4-dimethyl-3-pentanol **6** as a mild hydrogen donor successfully inhibited the formation of side products (entries 6 and 7).

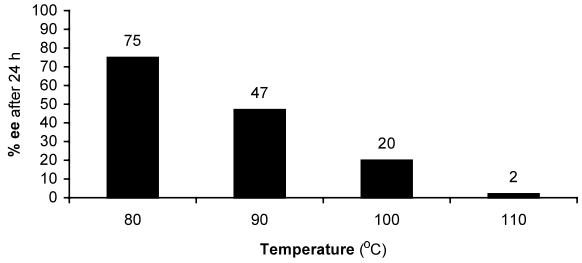
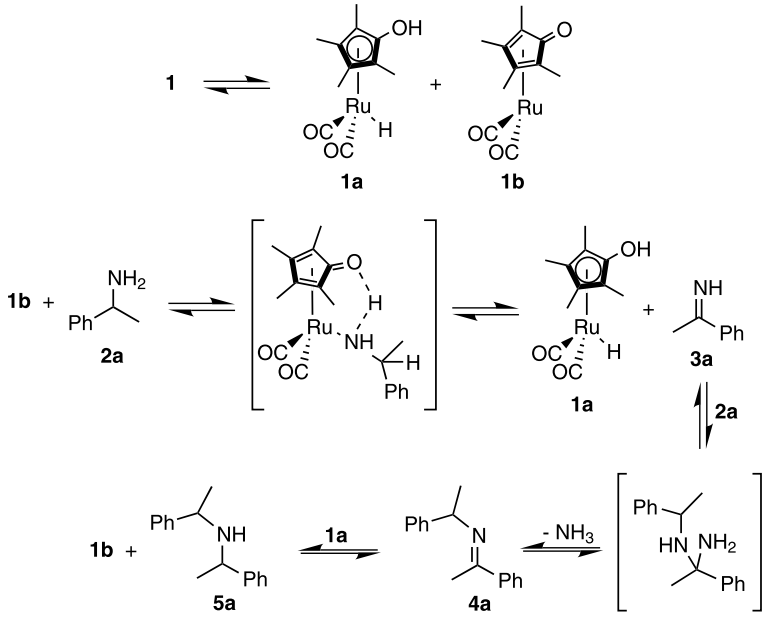
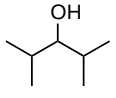


Figure 1. Temperature effect on the racemization of (*S*)-**2a**.



Scheme 1. Proposed mechanism for the formation of imine **4a** and amine **5a** (phenyl groups on cyclopentadien(yl) rings are omitted for clarity).

Table 1. Racemization of (*S*)-**2a** using catalyst precursor **1**[a]

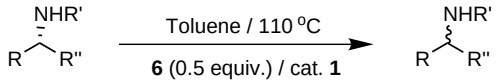


6

Entry	*t* (h)	Additive	Conc. **2a**[b]	% **2a**[c] (% ee[d])	% **4**[c]	% **5**[c]
1	48	–	1	5 (0)	12	29
2	48	–	0.5	21 (3)	8	15
3	48	–	0.25	84 (6)	5	11
4	48	–	0.125	91 (3)	3	6
5	48	1 equiv. NH_3	0.25	98 (2)	<1	<1
6	48	0.5 equiv. **6**	0.25	98 (2)	<1	<1
7	48	1 equiv. **6**	0.25	98 (2)	<1	<1

[a] Reaction conditions: (*S*)-**2a** (0.25 mmol), **1** (5 mol%) in toluene at 100°C.
[b] Concentration in M.
[c] Yield measured by GC on a CP-Chirasil-Dex CB column using pentadecane as internal standard based on the corresponding acetates after 24 h.
[d] Enantiomeric excess measured by GC on a CP-Chirasil-Dex CB column based on the corresponding acetates.

Table 2. Ru-catalyzed racemization of amines **2a**–**k**[a]



Entry	Amine	R	R′	R″	% Racemization after 1 h[b]	*t* (h)	% **2**[c] (% ee[d])
1	**2a**	Ph	H	Me	24	24	98 (3)
2	**2b**	4-OMe-Ph	H	Me	43	9	98 (3)
3	**2c**	4-F-Ph	H	Me	21	24	95 (2)
4	**2d**	4-Me-Ph	H	Me	30	9	92 (2)
5	**2e**	2-Naphthyl	H	Me	11	36	99 (5)
6	**2f**	Ph	Me	Me	100[e]	1	>99 (0[f])
7	**2g**	Ph	Ph	Me	18	24	98 (1)
8	**2h**	4-OMe-Ph	Ph	Me	44	12	>99 (3)
9	**2i**	Ph	H	CO_2Me	28	12	98 (1[g])
10	**2j**	Ph	H	$CH_2OTBDPS$	–	48	>95[h] (57[g])
11	**2k**	Ph	H	$CH_2OTBDMS$	–	48	>95[h] (32[g])

[a] Reaction conditions: (*S*)-**2** (0.25 mmol), **1** (5 mol%), **6** (0.12 mmol), toluene (2 mL).
[b] % Racemization defined as 100-% ee, measured after 1 h.
[c] Yield measured by GC on a CP-Chirasil-Dex CB column using pentadecane as internal standard.
[d] Enantiomeric excess measured by GC on a CP-Chirasil-Dex CB column based on the corresponding acetates.
[e] After 10 min, 70% racemization had occurred.
[f] Measured by GC based on the amine.
[g] Measured by HPLC on a Daicel, Chiracel OD-H column based on the amine.
[h] Yield measured by NMR.

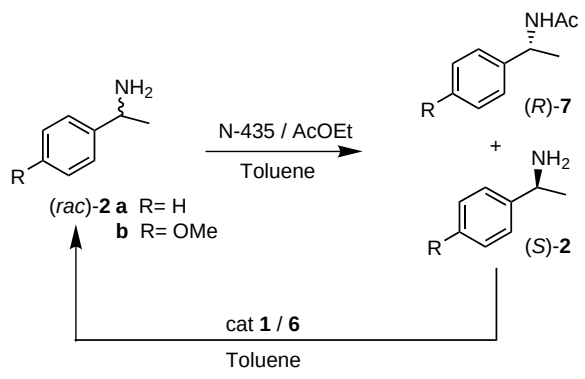
An important temperature effect was also observed (Fig. 1). Thus, as expected, the racemization efficiency is better at higher temperature.

A number of different amines **2a**–**k** were racemized employing this new procedure (Table 2).[11] Interestingly, both primary and secondary amines were efficiently racemized under these conditions. We also found that electronic variations of *para*-substituted 1-phenylethylamines have an effect on the efficiency of the racemization. Thus, the presence of electron-donating substituents increases the rate of racemization (entries 2 and 4) while electron-withdrawing substituents led to a lower reaction rate (entry 3). A similar behavior was observed in the series of secondary amines (entries 6–8). Thus, the fastest racemization was observed for the electron-rich *N*-methyl-1-phenylethylamine (entry 6). Interestingly, the α-amino ester **2i** was also efficiently racemized under these conditions (entry 9). This method can also be applied to sterically hindered protected α-amino alcohols **2j** and **2k**. However the efficiency of the process is lower. A possible explanation can be found in the high steric bulk of the silyl groups. This seems to be corroborated by the higher efficiency when the phenyl groups of the TBDPS is replaced by the less hindered methyl groups (entry 10 versus 11).

Application of catalyst **1** in a repetitive process was probed with 1-(4-methoxyphenyl)ethyl amine **2b**. Thus, after completion of the reaction from entry 2 in Table 2, the mixture was cooled and concentrated to dryness, additional aliquots of substrate, alcohol **6** and solvent were added, and racemization was continued without appreciable loss of activity. Up to three cycles were carried out without addition of more catalyst.

This new procedure was then applied to the practical synthesis of enantiomerically pure (*R*)-*N*-(1-phenylethyl) acetamide (*R*)-**7a** and (*R*)-*N*-((4-methoxyphenyl)ethyl) acetamide (*R*)-**7b** from the corresponding (*rac*)-amines **2a** and **2b**. For this purpose, the racemization procedure was combined with the enzymatic KR of primary amines in a two step manner (Scheme 2).

The enantiomerically pure acetamides (*R*)-**7a** and (*R*)-**7b** were efficiently prepared by enzymatic KR of (*rac*)-**2** using *Candida antarctica* lipase (N-435) and ethyl acetate as acyl donor at 40°C.[2b] After separation of (*S*)-**2** and (*R*)-**7** by standard extraction, (*R*)-**7** were collected and the recovered amines (*S*)-**2** were racemized at 110°C using the procedure described in Table 2. After the racemization, ethyl acetate and the recovered enzyme from the previous KR were added to the solution. After this second KR run, the corresponding acetamides **7** were isolated in good combined yield



Scheme 2.

(69% for (*R*)-**7a** and 66% for (*R*)-**7b**) in almost enantiomerically pure form (ee >98%).

In summary, we have developed a new procedure for the racemization of primary and secondary amines. The efficiency of the process together with the mild reaction conditions make the present method an attractive alternative to existing methods for racemizing amines. Further studies to investigate the scope and limitations of this procedure and to study the possibility to perform in situ DKR are under way.

Acknowledgements

Financial support from the Swedish Foundation for Strategic Research and the Swedish Research Council is gratefully acknowledged.

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10. Ru-complex **1** was prepared according to Ref. 9e and recrystallized from CH_2Cl_2/pentane prior to use.
11. In a typical experiment: To a solution of (*S*)-**2a** (32 μL, 0.25 mmol), **6** (18 μL, 0.125 mmol) and pentadecane (69 μL) in dry toluene (2 mL) under argon ruthenium catalyst **1** (13.6 mg, 0.0125 mmol) was added. The resulting reaction mixture was stirred at 110°C for 24 h under argon. To determine the yield and ee by GC, a sample (0.25 mL) was quenched with acetic anhydride (0.25 mL) and triethylamine (0.25 mL). After 5 min the sample was filtered over silica using dichloromethane as eluent.