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Recycling of pipecoloxylidide via racemization

Lisa K. Thalén [a], Martin H. Hedberg [b], Jan-E. Bäckvall [a,*]

[a] Stockholm University, Department of Organic Chemistry, Arrhenius Laboratory, SE-106 91 Stockholm, Sweden
[b] AstraZenenca Pharmaceutical Development, Department of Process Chemistry, Building 341, SE-151 85 Södertälje, Sweden

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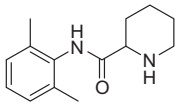
ABSTRACT

A method for the racemization of pipecoloxylidide with a ruthenium catalyst has been developed. This racemization method can be implemented in an integrated process that combines the separation of two enantiomers with racemization of the undesired enantiomer.

1. Introduction

Chiral amines are of particular interest as they are the building blocks of many pharmaceutical drugs. Several methods have been developed for the production of chiral amines, which include resolution, hydrogenation of imines and enamines,[1,2] alkylation of imines,[3] aminohydroxylation,[4] and reductive amination.[5] Resolution is a method commonly used in industrial applications due to its simplicity;[6,7] however the remaining undesired enantiomer is often discarded as waste. Therefore, it is important to have methods to racemize and then recycle the undesired enantiomer for a more efficient process. Recently, various methods for metal-catalyzed racemization of amines have been developed.[8–13] The integration of an enantiomer separation technique with racemization is one focus of work that is carried out within the INTENANT consortium.[14,15]



1, R = H, Pipecoloxylidide
2, R = Me, Mepivacaine
3, R = Pr, Ropivacaine
4, R = Bu, Bupivacaine

Pipecoloxylidide (**1**) and its derivatives (**2**–**4**) were first prepared and tested as local anesthetics in 1957.[16] Compound **1** is a useful intermediate for the synthesis of the commercial drugs Mepivacaine (**2**), Ropivacaine (**3**), and Bupivacaine (**4**), which are anesthetics of the amino amide group type. Bupivacaine [(*rac*)-**4**)] is commonly used as an anesthetic during childbirth due to its long-lasting effect. Unfortunately, there are known toxicities associated with this drug. However, the (*S*)-enantiomer of **4**, (Levobupivacaine), and **3** has a reduced level of neuro and/or cardiotoxicity in comparison with (*rac*)-**4**.[17,18] Racemic pipecoloxylidide [(*rac*)-**1**] can be prepared from picolinic acid in two steps,[19] and the (*S*)-enantiomer can then be obtained via diastereomeric salt resolution with *O*,*O*-dibenzoyl L-tartaric acid leaving the (*R*)-enantiomer as waste.[20] The objective of the present study was to develop a method for the racemization of **1**, allowing for recycling of the undesired enantiomer and increasing the overall efficiency of the process (Scheme 1).

2. Results and Discussion

The racemization of (*S*)-**1** was tested with the homogeneous ruthenium catalysts **5a**, **5b**, and **5c** (Fig. 1) and with the heterogeneous catalyst Pd/$BaSO_4$. These catalysts were chosen due to their prior success in the racemization of amines.[8–11] The racemization of (*S*)-**1** was first tested with 4 mol % **5a** at 90 °C and under these conditions an enantiomeric excess of 32% was obtained after 5 h (Table 1, entry 1). After an extended reaction time of 24 h, the ee decreased to 1% (Table 1, entry 2). The catalyst loading was then decreased to 2 mol % and by concentrating the reaction mixture and increasing the temperature to 110 °C, the racemization could be carried out with a slight increase in the rate. Upon application of these conditions, **1** could be obtained in 15% ee and 94% isolated yield after 5 h (Table 1, entry 3). The heterogeneous catalyst Pd/$BaSO_4$ used by the De Vos group was also tested.[11] However, the racemization with this catalyst was too slow for practical use (Table 1, entries 4 and 5). This could be due to either electronic effects, since the amine is not in a benzylic position, or steric effects, since the conformation of the ring could hinder binding of the substrate to the Pd-surface.

Subsequently, a comparison of catalysts **5a**, **5b**, and **5c** was carried out. The fastest racemization was observed for the electron-deficient *p*-fluoro-substituted catalyst **5b** and the slowest was observed for the electron-rich *p*-methoxy-substituted catalyst **5a** (Fig. 2). After 1 h, the enantiomeric excesses obtained using catalysts **5a**, **5b**, and **5c** were 75%, 53%, and 68%, respectively (Table 2, entries 1–3). The formation of byproducts from the reaction of the amine with the intermediate imine, as observed in previous studies,[8–10] was not seen in the racemization of (*S*)-**1** with any of these

* Corresponding author.
E-mail address: jeb@organ.su.se (Jan-E. Bäckvall).

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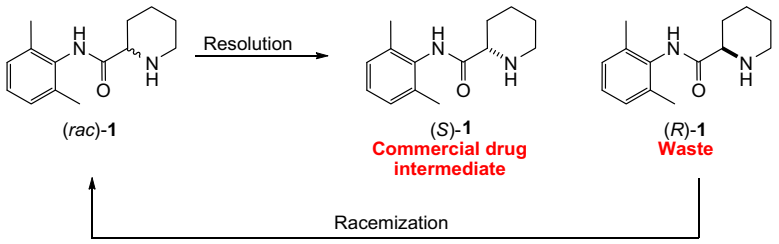


Scheme 1. Recycling of pipecoloxylidide.

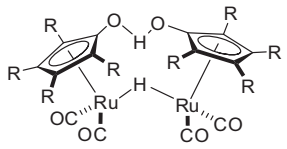
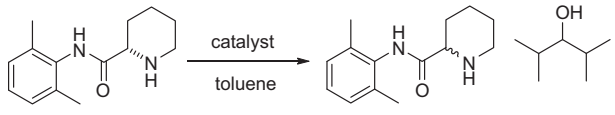


Figure 1. Ru-catalysts tested for the racemization.

Table 1
Racemization of **1**[a]



Entry	Catalyst (mol %)	Concn (M)	Temp (°C)	Time (h)	ee [b](%)
1	**5a** (4)	0.1	90	5	32
2	**5a** (4)	0.1	90	24	1
3[c]	**5a** (2)	0.25	110	5	15
4[d,e]	$Pd/BaSO_4$	0.1	110	24	96
5[e,f]	$Pd/BaSO_4$	0.1	110	24	97
6[g]	—	0.25	110	24	>99

[a] Conditions: 0.5 mmol (*S*)-**1**, toluene.
[b] Determined by HPLC.
[c] 94% Isolated yield.
[d] 10% H_2 in argon added by syringe.
[e] 0.33 mmol of (*S*)-**1**, 40 mg of 5% $Pd/BaSO_4$.
[f] 0.13 Mmol of 2-propanol.
[g] 0.25 mmol of **6**.

catalysts. This is most likely due to the cyclic motif of **1**, which makes the byproduct formation reversible.

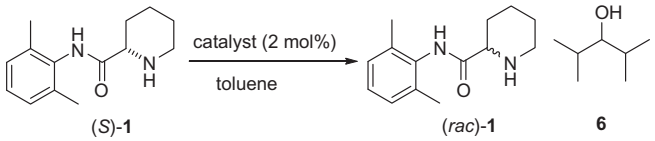
Since the rate of racemization was similar for the three Shvo analogues (**5a**, **5b**, and **5c**), and byproduct formation was not observed, catalyst **5c** was chosen for subsequent investigations due to its commercial availability.

A solvent comparison with toluene, dibutyl ether, and *t*-amyl alcohol was then carried out. The rate of racemization was the fastest in toluene, followed by dibutyl ether and *t*-amyl alcohol giving enantiomeric excess values of 68%, 75%, and 83%, respectively (Table 2, entries 3, 4, and 6). At prolonged reaction times, the rate of racemization in toluene and dibutyl ether was very similar whereas the rate in *t*-amyl alcohol was significantly lower (Fig. 3).

The effect of temperature was also evaluated and as expected, the rate of racemization increased with increasing temperature (Fig. 4). At 140 °C, the enantiomeric excess decreased to 2% within 1 h, whereas at 100 °C the enantiomeric excess was still 84% after 1 h (Table 2, entries 5 and 8).

We also investigated the racemization of the *N*-propyl derivative of pipecoloxylidide, (*S*)-Ropivacaine (**3**). The reaction of enantiomerically pure (*S*)-Ropivacaine (**3**) with catalyst **5c** (2 mol %) in dibutyl ether at 140 °C was monitored by HPLC and it was found that full racemization occurred within 40 min. Racemization of tertiary amines has previously been reported by Blacker.[21]

Table 2
Solvent, additive, and temperature evaluation



Entry	Catalyst	Solvent	Temp (°C)	Additive	ee[a] (%)
1	**5a**	Toluene	110	—	75
2	**5b**	Toluene	110	—	53
3	**5c**	Toluene	110	—	68
4	**5c**	*t*-Amyl alcohol [b]	100	—	83
5	**5c**	Dibutyl ether	100	—	84
6	**5c**	Dibutyl ether	110	—	75
7	**5c**	Dibutyl ether	120	—	44
8	**5c**	Dibutyl ether	140	—	2
9	**5c**	Dibutyl ether	120	EtOH (0.5 equiv)	44[c]
10	**5c**	Dibutyl ether	120	**6** (0.5 equiv)	46
11	**5c**	Dibutyl ether	120	EtOH (1 equiv)	44[d]
12	**5c**	Dibutyl ether	120	EtOH (10 equiv)	62[e]

Conditions: 0.5 mmol of (*S*)-**1**, Ru-catalyst, and 2 mL of solvent under argon at the indicated temperature for 1 h.
[a] Determined by HPLC.
[b] 1.5 mL of *t*-amyl alcohol.
[c] 11% of **7** (Scheme 2) after 7 h.
[d] 13% of **7** (Scheme 2) after 7 h.
[e] 89% of **7** (Scheme 2) after 7 h.

The development of an integrated system combining directly a separation technique such as chromatography or crystallization with racemization is the overall goal. Many chromatographic eluent systems and crystallization systems consist of a relatively non-polar solvent and a polar alcohol. Ideally, the racemization could be run directly following chromatography or crystallization without removal of solvent, therefore the addition of alcohols such as ethanol and 2,4-dimethyl-3-pentanol (**6**) to the racemization mixture was investigated to see if there was an effect on the racemization. The former was chosen because it is used in the chromatographic analysis of **1** and the latter was chosen due to its prior use as a hydrogen donor in the racemization of amines with **5**.[8] Addition of substoichiometric or stoichiometric amounts of ethanol (0.5 and 1 equiv) and **6** (0.5 equiv) had little or no effect on the rate of racemization whereas addition of an excess amount of ethanol (10 equiv) slowed down the racemization significantly (Table 2, entries 9–12). However, the formation of byproduct **7** (Scheme 2) was observed with as little as 0.5 equiv of ethanol and almost complete conversion into **7** was observed when 10 equiv of ethanol was added (Fig. 5).[22]

As a comparison, we also investigated the racemization of pipecoloxylidide by base. Thus, racemization of (*S*)-pipecoloxylidide with an excess sodium ethoxide (3 equiv) in refluxing ethanol was

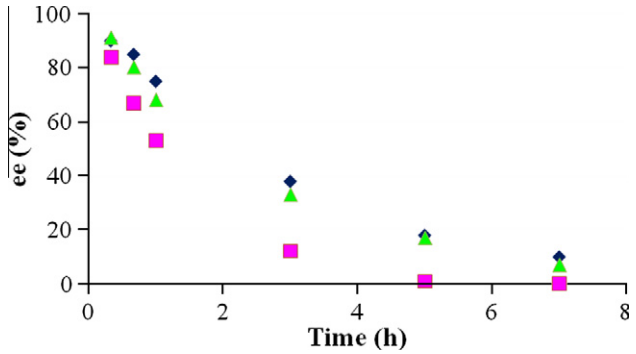


Figure 2. Racemization of **1** with catalysts **5a**, **5b**, and **5c**. ♦ **5a**, ■ **5b**, ▲ **5c**. Conditions: 0.5 mmol of (*S*)-**1**, 2 mol % of Ru-catalyst, and 2 mL of toluene under argon at 110 °C.

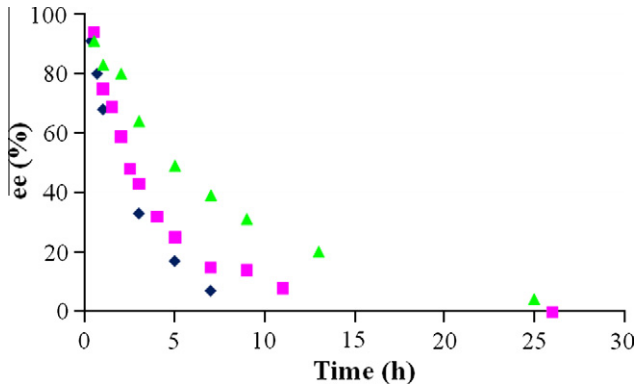


Figure 3. Solvent effects. ♦ toluene, ■ dibutyl ether, ▲ *t*-amyl alcohol (1.5 mL). Conditions: 0.5 mmol of (*S*)-**1**, 2 mol % of **5c**, and 2 mL of solvent under argon at 110 °C.

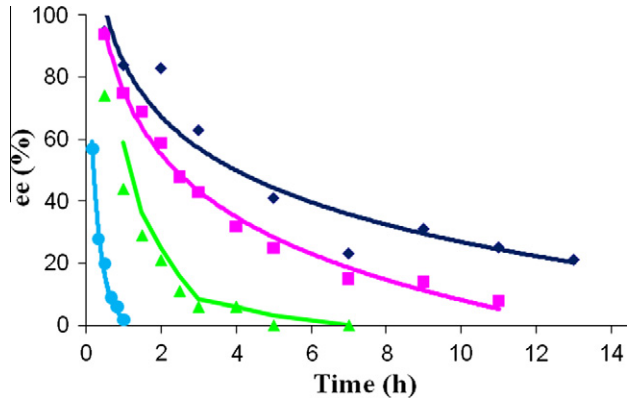


Figure 4. Temperature effect. ♦ 100 °C, ■ 110 °C, ▲ 120 °C, ● 140 °C. Conditions: 0.5 mmol of (*S*)-**1**, 2 mol % of **5c**, and 2 mL of dibutyl ether under argon at the indicated temperature. Compound **1** was not completely dissolved at 100 °C causing erratic enantiomeric excess measurements.

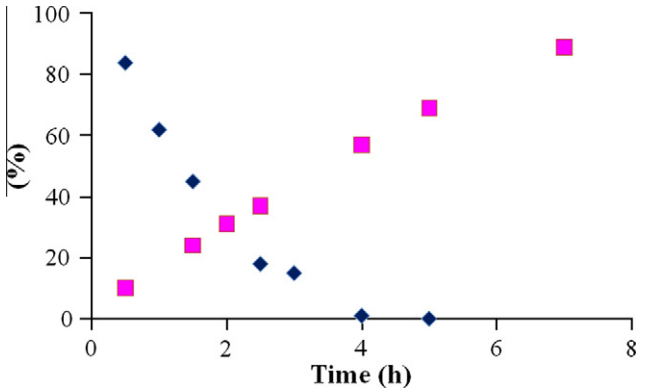


Figure 5. Formation of **7** during the racemization of **1** with catalyst **5c**. ♦ enantiomeric excess (%), ■ formation of **7** (%). Conditions: 0.5 mmol of (*S*)-**1**, 2 mol% of **5c**, 10 equiv of EtOH, and 2 mL of dibutyl ether under argon at 120 °C.

very slow and took more than three days. These conditions are much harsher than the catalytic conditions described in Tables 1 and 2.

In conclusion a method for the racemization of pipecoloxylidide (**1**) has been developed, which can be used for recycling the undesired enantiomer after the resolution of **1**. Integration of this racemization process with enantiomer separation techniques is going on within the INTENANT consortium.

3. Racemization procedure

A flame-dried 20 mL reaction vessel was charged with (*S*)-pipecoloxylidide [(*S*)-**1**] (0.5 mmol, 116.2 mg) and ruthenium catalyst **5c** (0.01 mmol, 13.3 mg). The vessel was closed, evacuated, and backfilled with argon for three times. The solvent (2 mL) and any additive were subsequently added via a syringe. The mixture was stirred at the indicated temperature. The loss of optical purity was determined by HPLC analysis (AD column, *i*-hexane/ethanol/triethylamine; 85:15:0.1, $t_r(S) = 10.33$, $t_r(R) = 12.65$ min).

3.1. *N*-(2,6-Dimethylphenyl)-1-ethylpiperidine-2-carboxamide (7)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18 (br s, 1H), 7.11–7.08 (m, 3H), 3.28–3.22 (m, 1H), 3.00–2.87 (m, 2H), 2.35–2.29 (m, 1H), 2.27 (s, 6H), 2.18–2.11 (m, 1H), 2.07–1.98 (m, 1H), 1.86–1.66 (m, 3H), 1.61–1.49 (m, 1H), 1.41–1.29 (m, 1H), 1.18 (t, J = 7.1 Hz, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 173.1, 135.3, 133.7, 128.3, 127.1, 68.7, 51.4, 51.1, 31.1, 25.1, 23.6, 18.7, 12.7. HRMS (*m*/*z*) calc for $C_{16}H_{24}N_2OH^+$ $(M+H)^{+\cdot}$ 261.1961; found 261.1970.

Acknowledgment

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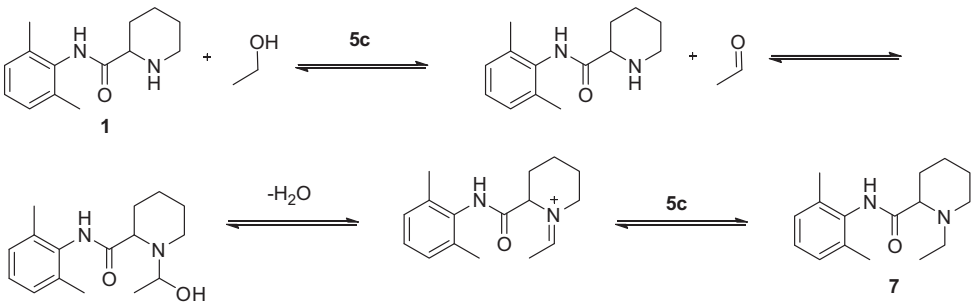

Scheme 2. Proposed mechanism for the formation of **7**.[22]

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