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ScienceDirect
Tetrahedron Letters 49 (2008) 977–979
Tetrahedron Letters

Practical chemoenzymatic dynamic kinetic resolution of primary amines via transfer of a readily removable benzyloxycarbonyl group

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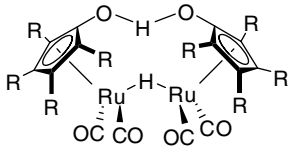
Received 30 September 2007; revised 24 November 2007; accepted 5 December 2007
Available online 8 December 2007

Abstract

A practical method for chemoenzymatic dynamic kinetic resolution of primary amines using dibenzyl carbonate as acyl donor has been developed leading to benzyl carbamates, which can be deprotected under very mild reaction conditions to give the free amine.

Chiral amines are useful synthetic intermediates and are structural elements of many biologically active compounds.[1] Commonly used methods to prepare chiral amines include hydrogenation of imines and enamines,[2] alkylation of imines,[3] and aminohydroxylation.[4] Various ligands have been utilized in these metal-catalyzed reactions to obtain high enantioselectivity. More recently, chemoenzymatic methods have been used to efficiently prepare enantiomerically pure chiral amines.[5–11] We recently reported a dynamic kinetic resolution (DKR) of primary amines using combined ruthenium (catalyst **1**) and enzyme catalysis that works on both benzylic and aliphatic amines.[6,12] Independent work by the Jacobs–de Vos group showed that a palladium/enzyme catalyst combination can be used for practical DKR of benzylic amines.[7a] Subsequent work has provided additional procedures for chemoenzymatic DKR of amines in which various racemization methods are combined with enzymatic resolution.[8–10]



1 (R = *p*-MeO-C_6H_4)

A drawback with the DKR procedures reported so far is that the product is a chiral amide, from which the free amine can only be liberated under harsh reaction conditions.[13] Therefore, there is a demand for acyl donors in the DKR of amines that transfer a readily removable protecting group. We now report on a chemoenzymatic DKR of primary amines where the products are benzyl carbamates that can be deprotected under very mild reaction conditions to give the free amine.

We first studied the use of acyl donors that transfer more electron deficient acyl groups in the DKR. This would lead to amides that can be hydrolyzed under milder conditions. Unfortunately, kinetic resolution with *Candida antarctica* lipase B (CALB) using ethyl and isopropyl trifluoroacetate as well as isopropyl chloroacetate as acyl donors resulted in significant non-catalyzed background reaction leading to low enantioselectivity under the reaction conditions required for the DKR.[14] We therefore focused our attention on acyl donors that lead to carbamates, since there is well-documented methodology to release the free amine from these compounds under mild conditions.[15] In particular, the protection of amines as allyloxy, benzyloxy, or *t*-butyloxy carbamates is popular since deprotection requires either mild Pd catalysis or weak acid catalysis.

For the enzyme-catalyzed reaction of amines to give carbamates we considered diallyl, dibenzyl, and di-*t*-butyl carbonates (**2**–**4**) as appropriate acyl donors since they gave

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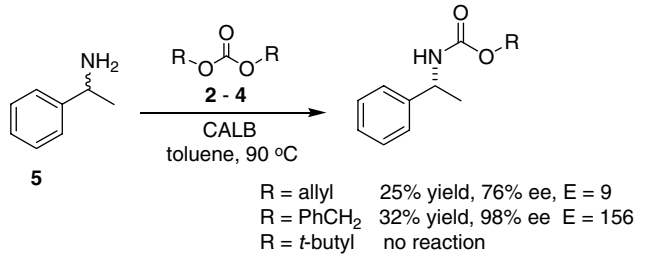
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.12.017

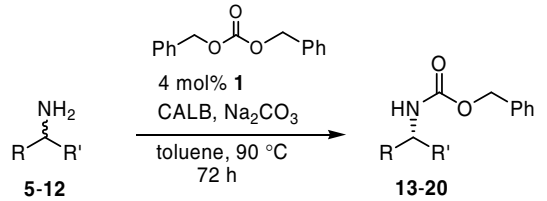
no non-catalyzed background reaction on stirring with 1-phenylethylamine (**5**) in toluene at 90 °C for 24 h. Kinetic resolution of amine **5** was carried out with CALB using carbonates **2**–**4** as acyl donors (Scheme 1). Diallyl carbonate (**2**) gave only a moderate enantioselectivity ($E = 9$)[16] whereas dibenzyl carbonate (**3**) afforded a highly enantioselective reaction ($E = 156$). The di-*t*-butyl carbonate (**4**) was completely inactive in the enzymatic reaction.

Dibenzyl carbonate (**3**) was therefore chosen as the acyl donor for the DKR reaction. We were pleased to find that carbonate **3** was compatible with the racemization catalyst **1**, and reaction of racemic **5** and carbonate **3** in the presence of Ru-catalyst **1** and CALB in toluene afforded benzyl carbamate in 90% yield and 93% ee (Table 1, entry 1). *p*-Substituted phenylethylamines (**6**–**8**) were reacted under the DKR conditions and gave the corresponding carbamates in good to high yields with high ee (97–99% ee, entries 2–4). Also aliphatic amines worked well in the chemoenzymatic DKR reaction to give the corresponding carbamates in good to high ee (entries 6–8).



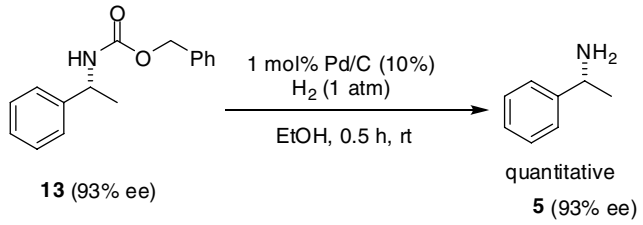
Scheme 1. CALB-catalyzed kinetic resolution of **5** with aryl alcohols.

Table 1
Dynamic kinetic resolution of primary amines with dibenzyl carbonate (**3**)[a]



Entry	Amine	R	R′	Product	Yield[b]	% ee[c]
1	**5**	Ph	Me	**13**	90	93
2	**6**	*p*-Br–Ph	Me	**14**	95	98
3	**7**	*p*-F–Ph	Me	**15**	72[d]	99
4	**8**	*p*-MeO–Ph	Me	**16**	74[d]	97
5	**9**			**17**	64	99
6	**10**	Cyclohexyl	Me	**18**	92	96
7	**11**	Heptyl	Me	**19**	89	90
8	**12**	*iso*-Propyl	Me	**20**	60[d]	99

[a] The reaction was carried out by stirring 0.5 mmol of the amine, 1.25 mmol of dibenzyl carbonate, 26.5 mg of catalyst **1** (0.02 mmol, 4 mol %), 20 mg of CALB (Novozyme-435), and 20 mg of Na_2CO_3 in dry toluene (5 ml) at 90 °C for 72 h.
[b] Isolated yield unless otherwise noted.
[c] Enantiomeric excess determined by chiral HPLC (chiralcel ODH).
[d] Determined by GC.



Scheme 2. Deprotection of carbamates obtained from DKR.

The benzyloxycarbonyl group of products **13**–**20** can be removed easily via hydrogenolytic cleavage.[15] Deprotection using 1 mol % palladium on charcoal (10%) under a hydrogen atmosphere was demonstrated with carbamate **13** where liberation of the amine was complete within half an hour at room temperature. The amine was obtained in a quantitative yield and with full retention of ee (Scheme 2). The H_2 reaction was very clean giving only CO_2 and toluene as side products. If the reaction was left too long or if a larger amount of catalyst was employed some racemization of the product was observed.

In conclusion, we have developed a practical procedure for chemoenzymatic DKR of primary amines using dibenzyl carbonate as the acyl donor, which allows release of the free amine from the carbamate products under very mild conditions.

Acknowledgments

Financial support from the Swedish Foundation for Strategic Research, the Swedish Research Council, and the German Research Foundation (DFG) is gratefully acknowledged (C.E.H.).

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13. For example, acidic hydrolysis of the acetamide of 1-phenylethylamine requires reaction at 140 °C for 48 h in concentrated hydrochloric acid.
14. The racemization with catalyst **1** under the DKR conditions requires a temperature of 90 °C (see Ref. 6).
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16. It is not clear why the allyl carbonate gives only a moderate enantioselectivity since there was no background reaction in the control reaction. A likely explanation is that the enzyme itself has some effect on the non-catalyzed reaction, increasing the reaction pathway via direct acylation.