ORGANIC LETTERS

2007
Vol. 9, No. 5
837−839

Dynamic Kinetic Resolution of Amines Involving Biocatalysis and in Situ Free Radical Mediated Racemization

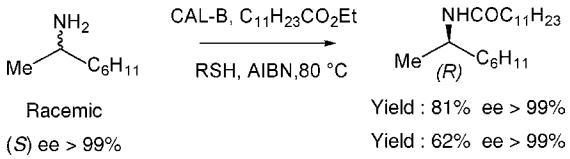
Stéphane Gastaldi,*,† Stéphanie Escoubet,† Nicolas Vanthuyne,‡ Gérard Gil,*,‡ and Michèle P. Bertrand*,†

Laboratoire de Chimie Moléculaire Organique, UMR 6517, Chimie, Biologie, et Radicaux Libres, Boite 562, Université Paul Cézanne, Aix-Marseille III, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France, and Laboratoire de Stéréochimie Dynamique et Chiralité, UMR 6180, Chirotechnologies: Catalyse et Biocatalyse, Université Paul Cézanne, Aix-Marseille III, Faculté des Sciences St Jérôme, Avenue Escadrille Normandie-Niemen, 13397 Marseille Cedex 20, France

michele.bertrand@univ-cezanne.fr

Received December 19, 2006

ABSTRACT



The association of lipase-catalyzed enzymatic resolution with in situ racemization mediated with the thiyl radical enables the dynamic kinetic resolution of non-benzylic amines. It leads to (*R*)-amides with high enantioselectivities. It can be applied either to the conversion of racemic mixtures or to the inversion of (*S*)-enantiomers.

At a time when the state of the art in asymmetric synthesis has reached an outstanding level,[1] looking for racemization processes may seem pointless. However, the resolution of racemates remains one of the main industrial routes to optically pure compounds,[2] and as a consequence, the racemization of unwanted isomers still has great economical value. The association of chemical or enzymatic resolution with an in situ racemization process (dynamic kinetic resolution (DKR))[3] is even more valuable because it allows recycling steps with a 50% maximum yield to be avoided and allows a 100% theoretical yield to be reached in one single step.[4]

Racemization of nonactivated amines often necessitates rather harsh conditions that do not tolerate the presence of additional functional groups.[2] Having elegantly solved the problem of racemization of both benzylic and non-benzylic unfunctionalized amines at 110 °C in the presence of a ruthenium catalyst[5] and taking advantage of the compatibility between the enzymatic resolution and the transition-metal-catalyzed racemization, Bäckvall and co-workers have modified the catalyst in such a way that DKR could be achieved at 90 °C.[6,7] As far as we know, there are only three other examples of DKR applied to amines. All involve transition-

† Laboratoire de Chimie Moléculaire Organique, UMR 6517, Chimie, Biologie, et Radicaux Libres.

‡ Laboratoire de Stéréochimie Dynamique et Chiralité, UMR 6180, Chirotechnologies: Catalyse et Biocatalyse.

(1) (a) Knowles, W. S. (Nobel Lecture) *Angew. Chem., Int. Ed.* **2002**, *41*, 1998−2007. (b) Noyori, R. (Nobel Lecture) *Angew. Chem., Int. Ed.* **2002**, *41*, 2008−2022. (c) Sharpless, B. K. (Nobel Lecture) *Angew. Chem., Int. Ed.* **2002**, *41*, 2024−2032.

(2) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417−9476.

(3) For a precise definition of the concept, see: Faber, K. *Chem.−Eur. J.* **2001**, *7*, 5004−5010.

(4) For general reviews, see: (a) Pellissier, H. *Tetrahedron* **2003**, *59*, 8291−8327. (b) Ward, R. S. *Tetrahedron: Asymmetry* **1995**, *6*, 1475−1490.

(5) Pàmies, O.; Ell, A. H.; Samec, J. S. M.; Hermanns, N.; Bäckvall, J.-E. *Tetrahedron Lett.* **2002**, *43*, 4699−4702.

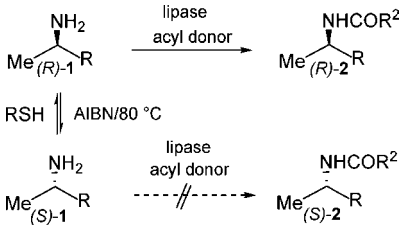
10.1021/ol063062o CCC: $37.00
Published on Web 02/06/2007

metal catalysis[8−10] and refer exclusively to the racemization of benzylic amines by catalytic Pd/C. The conceptually different chemoenzymatic deracemization using an enantioselective amine oxidase in combination with ammonia borane has also been developed.[11] In all these procedures, the racemization proceeds through an amine−imine equilibrium.

We have recently demonstrated that alkylsulfanyl radicals can mediate the racemization of amines via reversible hydrogen abstraction at the chiral center in a position α relative to nitrogen. The S−H bond dissociation enthalpy (BDE) must match the α-C−H BDE for the reversible hydrogen transfer to have some practical efficacy.[12] In the radical racemization process, the prochiral intermediate is an α-amino radical. Because the α-C−H BDE is stronger in the corresponding amide (≈17 kJ mol^{-1}), hydrogen abstraction at the chiral carbon is precluded after acylation.[12]

Having at our disposal an efficient and selective racemization process working under mild conditions at 80 °C, we investigated the possibility of devising a DKR protocol by associating enzymatic resolution and radical racemization (Scheme 1). As mentioned in our previous articles, in the

Scheme 1. Radical- and Enzyme-Catalyzed DKR



case of primary benzylic amines, the efficacy of the racemization process is limited by the competitive oxidation of the intermediate α-amino radical.[12a] Therefore, we turned our attention to non-benzylic amines all the more because only two examples of DKR of the latter had been reported in the literature.[6]

The compatibility of lipase-mediated kinetic resolution with a radical process involving a thiol was not obvious.[13] A large number of enzymes make use of radical mechanisms.[14] Furthermore, numerous studies show that proteins are degraded under radical conditions.[15]

The selection of lipase B from *Candida antartica* (CAL-B) as thermostable lipase to catalyze the aminolysis of an acyl donor was facilitated by previous work.[6−10] The commercially available polymer-supported lipase Novozym 435 is able to catalyze the amidation of primary amines under mild conditions.[16] Enzymatic resolution by lipases is usually conducted in low polarity aprotic solvents (hexane or dialkylethers). This is an advantage with regard to its compatibility with the radical reaction[12] which could easily be performed in heptane. The selection of the acyl donor was made after the resolution of amine **1a** had been tested in the presence of several acyl donors at 80 °C. Although enol esters are known to be highly efficient, irreversible acyl donors,[17] they were a priori rejected due to their capacity, as electron-rich olefins, to trap alkylsulfanyl radicals via radical addition followed by hydrogen transfer.[18] Moreover, they release carbonyl compounds that can react with the starting amine. Ethyl laurate and lauric acid turned out to be good candidates, giving satisfactory results for the resolution of amines **1** at 80 °C in 8 h.[19,20]

The next step consisted of investigating the influence of the thiol on the enzyme activity. Figure 1 shows the plots of the enantiomeric excess (ee) of the remaining amine (*S*)-**1a** vs time during the enzymatic resolution carried out at 80 °C in the presence of lauric acid and a series of thiols (1 equiv with regard to the amine). The graphs show that the enzymatic resolution is slightly more efficient in the presence of a secondary than a primary thiol ($C_6H_{11}SH$/*n*-OctSH). However, we had previously observed that the thiyl radical mediated racemization of non-benzylic primary

(6) Paetzold, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620−17621.

(7) For reviews on related topics, see: (a) Pàmies, O.; Bäckvall, J.-E. *Chem. Rev.* **2003**, *103*, 3247−3261. (b) Huerta, F. F.; Minidis, A. B. E.; Bäckvall, J.-E. *Chem. Soc. Rev.* **2001**, *303*, 321−331. (c) Pàmies, O.; Bäckvall, J.-E. *Curr. Opin. Biotechnol.* **2003**, *14*, 407−413. See also: (d) Kim, M.-J.; Ahn, Y.; Park, J. *Curr. Opin. Chem. Biol.* **2002**, *13*, 578−587.

(8) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 1211−1212.

(9) Parvulescu, A.; De Vos, D.; Jacobs, P. *Chem. Commun.* **2005**, 5307−5309.

(10) Choi, Y. K.; Kim, M. J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* **2001**, *3*, 4099−4101.

(11) Dunsmore, C. J.; Carr, R.; Fleming, T.; Turner, N. J. *J. Am. Chem. Soc.* **2006**, *128*, 2224−2225 and previous refs cited therein.

(12) (a) Escoubet, S.; Gastaldi, S.; Vanthuyne, N.; Gil, G.; Siri, D.; Bertrand, M. P. *Eur. J. Org. Chem.* **2006**, 3242−3250. (b) Escoubet, S.; Gastaldi, S.; Vanthuyne, N.; Gil, G.; Siri, D.; Bertrand, M. P. *J. Org. Chem.* **2006**, *71*, 7288−7292.

(13) Thiols might modify the enzyme through the destruction of disulfide bridges. See: Stryer, L. *Biochimie*, 4th ed.; Flammarion: Paris, 1997; Chapter 2, pp 37−39.

(14) (a) Stubbe, J.; van der Donk, W. A. *Chem. Rev.* **1998**, *98*, 705−762. (b) Frey, P. A.; Hegeman, A. D.; Reed, G. H. *Chem. Rev.* **2006**, *106*, 3302−3316.

(15) (a) Easton, C. In *Radical in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley: New York, 2001; Vol.2, Chapter 6. For the involvement of thiyl radicals, see: (b) Rauk, A.; Yu, D.; Armstrong, D. A. *J. Am. Chem. Soc.* **1998**, *120*, 8848−8855.

(16) For general reviews, see: (a) Alfonso, I.; Gotor, V. *Chem. Soc. Rev.* **2004**, *33*, 201−209. (b) Carrea, G.; Riva, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 2226−2254. (c) Turner, N. J. *Curr. Opin. Chem. Biol.* **2004**, *8*, 114−119. (d) Turner, N. J. *Curr. Opin. Biotechnol.* **2003**, *14*, 401−406. (e) Van Rantwijk, F.; Sheldon, R. A. *Tetrahedron* **2004**, *60*, 501−519. (f) Gotor-Fernandez, V.; Busto, E.; Gotor, V. *Adv. Synth. Catal.* **2006**, *348*, 797−812. (g) Koeller, K. M.; Wong, C.-H. *Nature* **2001**, *409*, 232−240.

(17) For a review, see: Hanefeld, U. *Org. Biomol. Chem.* **2003**, 2405−2415.

(18) (a) Bertrand, M. P.; Chatgilialoglu, C.; Ferreri, C. In *The Chemistry of Sulphur Radicals*; Alfassi, Z. B., Ed.; Wiley: New York, 1999; Chapter 11, pp 311−354. (b) Bertrand, M. P.; Ferreri, C. In *Radical in Organic Synthesis*; Renaud, P., Sibi, M., Eds.; Wiley: New York, 2001; Chapter 5.5, pp 485−503.

(19) The KR of amine **1a**, carried out with Novozym 435 in the presence of 1 equiv of ethyl laurate, led to (*R*)-**2a** (50% yield, ee ≥ 99%) together with the remaining amine (*S*)-**1a** (46% yield, 93% ee). Amides (*R*)-**2a** (ee ≥ 99%) and (*S*)-**1a** (99% ee) were isolated in 50% and 41% yields, respectively, in the presence of 1 equiv of lauric acid. Ethyl acetate was found to be far less selective at 80 °C than at 30 °C.

(20) The enantioselectivity for the acylation of *sec*-butyl amine by Novozym 435 was shown to increase when using esters of long-chain fatty acids. See: Goswami, A.; Guo, Z.; Parker, W. L.; Patel, R. N. *Tetrahedron: Asymmetry* **2005**, *16*, 1715−1719.

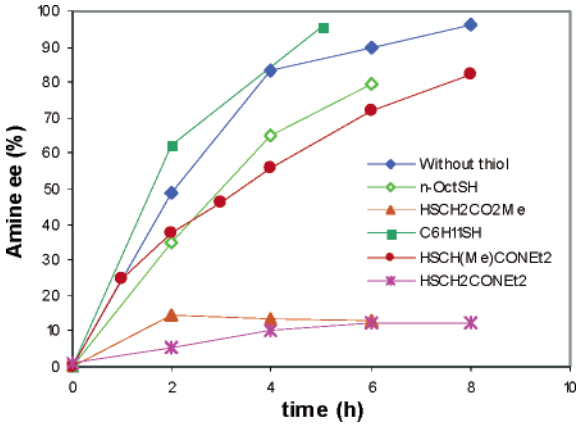
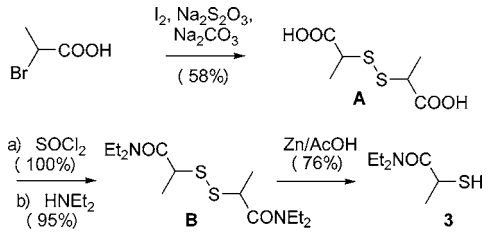


Figure 1. Plot of ee vs time, for Novozym 435 mediated enzymatic resolution of amine **1a** in the presence of thiol. Conditions: **1a** (1 mmol) in heptane (10 mL), RSH (1.2 mmol), CAL-B (Novozym 435, 200 mg), lauric acid (2 mmol), temp = 80 °C.

amines was slightly slower with cyclohexane thiol than with methyl thioglycolate. Accordingly, the latter was our first choice.[12b]

The problem was that this thiol could also play the role of an acyl donor.[21] Moreover, very low amine enantiomeric excesses were observed during the kinetic resolution of amine **1a** performed in the presence of methyl thioglycolate. The corresponding *N*,*N*-diethyl amide enabled us to overcome this problem, but this new thiol was also inhibiting the enzymatic resolution as indicated by the absence of amide and the low ee of the recovered amine (Figure 1). Its secondary analogue **3** that was prepared by reduction of the corresponding disulfide (Scheme 2) enabled us to solve both

Scheme 2. Synthesis of Thiol **3**



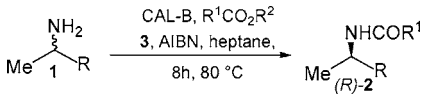
problems, while preserving the aptitude of the thiol to racemize amine **1a** within 2 h.

The conditions for the success of a DKR were optimal because we had at our disposal a highly selective resolution process compatible with the presence of a thiol at 80 °C[22] and a fast racemization process.

The results obtained for the DKR experiments performed with *N*,*N*-diethyl-2-sulfanylpropionamide (**3**) are reported in

(21) The resolution of amine **1** carried out in heptane with CALB, at 80 °C, in the presence of ethyl thioglycolate and ethyl acetate as the acyl donor, afforded the derived 2-sulfanylacetamide and the corresponding disulfide.

Table 1. Dynamic Kinetic Resolution of Amines **1a**−**e**[a]



	amines	R	$R^1CO_2R^2$	product yield (%)[b]	ee (%)
1	*rac*-**1a**	$Ph(CH_2)_2$	CH_3CO_2Et	**2a′**, 31 (95)	74
2	*rac*-**1a**	$Ph(CH_2)_2$	$C_{11}H_{23}CO_2Et$	**2a**, 70 (71)	99
3	*rac*-**1a**	$Ph(CH_2)_2$	$C_{11}H_{23}CO_2H$	**2a**, 71 (69)	>99
4	(*S*)-**1a**	$Ph(CH_2)_2$	$C_{11}H_{23}CO_2Et$	**2a**, 58 (nd)	99
5	*rac* **1b**	$Me(CH_2)_5$	$C_{11}H_{23}CO_2Et$	**2b**, 81 (nd)	>99
6	(*S*)-**1b**	$Me(CH_2)_5$	$C_{11}H_{23}CO_2Et$	**2b**, 62 (69)	>99
7	*rac*-**1c**	*t*-$BuOCOCH_2$	$C_{11}H_{23}CO_2Et$	**2c**, 47 (54)	92
8	*rac*-**1d**	$Me_2C{=}CH(CH_2)_2$	$C_{11}H_{23}CO_2Et$	**2d**, 68 (70)	94
9	*rac*-**1e**	Et	$C_{11}H_{23}CO_2H$	**2e**, 57 (nd)	86

[a] Conditions: amine (1 mmol, 0.063 M), **3** (1.2 equiv), acyl donor (1.5 equiv), Novozym 435 (200 mg). [b]Isolated yield (NMR yield). [c]EtOAc/heptane (2.6:8 in vol).

Table 1. As already noted, as an acyl donor, EtOAc was not selective for the DKR of amine *rac*-**1a** (entry 1). In all cases, the substrate was totally consumed in 8 h.

The racemic amines **1a**−**e** were transformed into the corresponding (*R*)-amides **2a**−**e** (in isolated yields ranging from 47 to 81%, with ee's varying from 86 to >99%) in the presence of either ethyl laurate or lauric acid (entries 2−9). It must be noted that good results were obtained in the presence of lauric acid, even though an equilibrium is likely to be established between the primary amine and the corresponding alkylammonium ion (entries 3 and 9). The use of 1 equiv of lauric acid only slightly slowed the radical racemization, which was completed in 5 h instead of in 2 h.

The DKR process is compatible with remote functionalities such as the trisubstituted double bond in **1d** and the sterically hindered *t*-butyl ester in **1c**. It could be tuned to achieve the complete inversion of configuration of the (*S*)-enantiomer (entries 4 and 6).

In conclusion, as far as we know, the performance of a DKR process associating lipase-catalyzed enzymatic resolution and in situ racemization involving a thiyl radical mediated process is a "premiere". This process leads to (*R*)-amides with high enantioselectivities. It can be applied either to the resolution of racemic mixtures or to the inversion of (*S*)-amines.

Acknowledgment. This work was supported by the ANR (Agence Nationale de la Recherche) (project DKR, no. Blan06-3_142460). A gift of CAL-B from Novo Nordisk A/S Denmark is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL063062O

(22) $E = k_R/k_S > 40$ in the presence of thiol **3**; 42% isolated yield and 98.5% ee for amide **2a**; 54% yield and 97.1% ee for the remaining amine for the resolution of **1a** in the presence of **3** and 1 equiv of ethyl laurate.