J|A|C|S
COMMUNICATIONS

Published on Web 11/19/2005

Chemoenzymatic Dynamic Kinetic Resolution of Primary Amines

Jens Paetzold and Jan E. Bäckvall*

Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-10691 Stockholm, Sweden

Received September 13, 2005; E-mail: jeb@organ.su.se

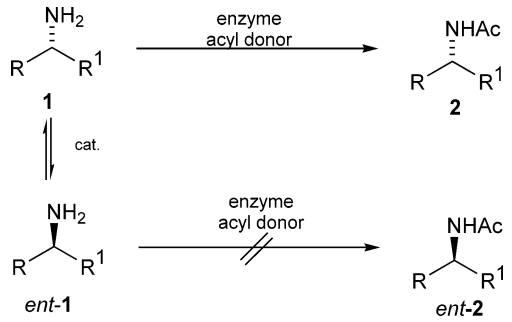
Amines are an important class of organic compounds, which can be widely used as building blocks in organic chemistry. Common methods to generate amines include electrophilic or nucleophilic addition to alkenes,[1] ring opening of aziridines,[2] reduction of amides,[2] Staudinger reaction,[2] or Buchwald−Hartwig amination.[3] Chiral amines and amides can be produced by hydrogenation of imines and enamines,[4] alkylation of imines,[5] amino hydroxylation,[6] or reductive amination.[7]

Due to its simplicity, kinetic resolution (KR) using enzymes remains one of the easiest methods to produce chiral amines out of racemic mixtures.[8] Its major drawback is the maximum yield of 50%, thus limiting this method to an early transformation in a reaction sequence. To overcome this problem, methods to racemize the nondesired enantiomer in situ have been developed (Scheme 1). This has been achieved for amino acid derivatives,[9] but unfortunately, this so-called dynamic kinetic resolution (DKR) is only suitable to substrates which have an acidic proton close to the stereogenic center.

The racemization of unfunctionalized amines is much more difficult and requires harsher reaction conditions,[10] which makes a racemization during enzymatic resolution difficult. This might be the reason only one example of DKR of amines has been reported so far, in which Pd/C was used as the racemization catalyst.[11]

In this communication, we report on a highly efficient process for DKR of amines **1** (Scheme 1). This chemoenzymatic DKR, which utilizes a ruthenium catalyst and a lipase, gives the corresponding amides **2** in high yields and high enantiomeric excess from a racemic mixture.

Scheme 1. Dynamic Kinetic Resolution of Amines



To figure out a mild racemization process, we tested a set of ruthenium catalysts **3**−**5** (Figure 1) for their ability to racemize (*S*)-1-phenylethylamine (99% ee) (**1a**) at elevated temperature and monitored the loss of optical purity over time.

The mechanism of racemization consists of a combination between dehydrogenation of the chiral amine and re-addition of the hydrogen to the imine.[12,13]

Catalysts **3** and **4**, which have given high racemization rates for secondary alcohols,[14,15] showed modest activities for racemization of (*S*)-**1a**, resulting in enantiomeric excess values of 85 and 46% after 24 h (Table 1, entries 1 and 2). Shvo's catalyst (**5a**) showed

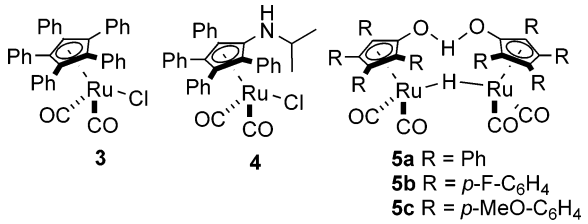
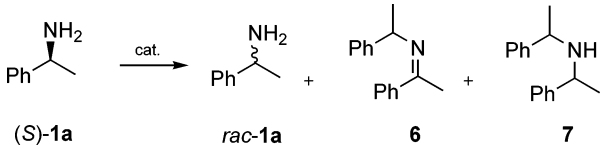


Figure 1. Racemization catalysts.

Table 1. Racemization of (*S*)-1-Phenylethylamine (**1a**)[a]



entry	catalyst	*T* (°C)	ee (%)[b]	selectivity for **1a** (%)[c]
1[d]	**3**	100	85	>98
2[d]	**4**	100	46	>98
3	**5a**	100	53	82
4	**5b**	100	36	25
5	**5c**	100	55	95
6[e]	**5c**	100	25	90
7[e]	**5c**	90	55	95
8[f]	**5c**	90	55	>98
9[f]	**5c**	80	78	>98

[a] Conditions: 0.50 mmol (*S*)-phenylethylamine, 0.02 mmol Ru source, 2 mL of toluene, 30 μL of pentadecane as internal standard, 24 h. [b] Determined as corresponding acetamides using chiral GC. [c] Determined by GC. [d] Activated with 0.02 mmol KO*t*-Bu. [e] With 0.02 mmol **5c**. [f] With 0.02 mmol **5c**, 8 mL of toluene.

an almost equal racemization rate, giving a reasonable enantiomeric excess value of 53% (entry 3). Due to its slower rate of re-addition of hydrogen, formation of condensation products **6** and **7** occurred, which lowers the selectivity of racemization (entry 3).[13]

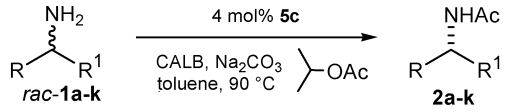
Since the racemization using Shvo's catalyst (**5a**) proceeds under more neutral conditions, we tested different variants of **5a** in order to figure out a more selective catalyst. With the fluorine-containing complex **5b**, a lower enantiomeric excess of 36% is achieved (entry 4). This indicates that, for the dehydrogenation of the amine, an electron-deficient transition metal catalyst is required. However, the selectivity of this catalyst was far lower than that of catalyst **5a**.

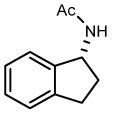
The more electron-rich catalyst **5c** showed a much more selective racemization than **5a** and **5b**, and the overall racemization rate is comparable to that of catalyst **5a** (entry 5). We consider that, although the dehydrogenation step is slowed, the rate of re-addition of hydrogen is accelerated, thus reducing the lifetime of the free imine.

To make the racemization process more efficient, we doubled the amount of catalyst (entry 6). The enantiomeric excess value dropped as expected, but the amount of the side products **6** and **7**

10.1021/ja056306t CCC: $30.25

Table 2. Dynamic Kinetic Resolution of Primary Amines[a]



entry		R / R[1]	yield (%)[b]	ee (%)[c]
1[d]	**2a**	Ph / Me	45	98
2	**2a**	Ph / Me	90	98
3[e]	**2a**	Ph / Me	85	98
4[f]	**2b**	3-Me-C_6H_4 / Me	69	98
5	**2c**	4-F-C_6H_4 / Me	83	99
6	**2d**	4-Br-C_6H_4 / Me	78	99
7[f]	**2e**	4-OMe-C_6H_4 / Me	95	99
8[f,g]	**2f**	2-Naphtyl / Me	80	>99.5
9[f,g]	**2g**	Ph / Et	85	99
10[f]	**2h**		92	95
11[f,g]	**2i**	4-CF_3-C_6H_4 / Me	91	99
12	**2j**	*n*-C_6H_{13} / Me	85	93
13[h]	**2k**	$PhCH_2CH_2$ / Me	78	95

[a] Conditions: 0.50 mmol amine, 0.02 mmol **5c**, 400 μL of isopropyl acetate, 20 mg of Novozym 435, 20 mg of Na_2CO_3, 8 mL of toluene, 90 °C, 3 days. [b] Isolated yields with >95% purity. [c] Determined by chiral GC. [d] Without Na_2CO_3. [e] With 0.02 mmol **5a**. [f] With 30 mg of CALB, 30 mg of Na_2CO_3. [g] Five days. [h] With 15 mg of enzyme, 15 mg of Na_2CO_3.

increased. This problem was solved by reducing the reaction temperature and by dilution (entries 7 and 8). In principle, the racemization is applicable even at 80 °C, but the reaction rate is too slow to be practical.

After having optimized the racemization protocol, we tried to apply a DKR using *Candida antarctica* lipase B (CALB, Novozym 435) as enzyme. Isopropyl acetate was chosen as acylating agent. Attempts to use catalysts **3** or **4**, activated by base, failed.

We next tried the combination of CALB with racemization catalyst **5c** in the presence of isopropyl acetate at 90 °C for 3 days, but only KR was observed. Surprisingly, when sodium carbonate was added to the reaction mixture, an efficient DKR process takes place (entry 2). We consider that traces of acids, originating from either the polyacrylate support, the acyl donor, or the enzyme itself, interfered with the ruthenium catalyst. Furthermore, the acyl donor releases 2-propanol, which acts as an additional hydrogen donor that can lower the amount of byproducts **6** and **7**.[13] Considering this fact, even the less selective catalyst **5a** can be used for DKR, giving (*R*)-1-phenylethylamide **2a** in 85% yield (entry 3).

Various racemic amines **1a**−**k** could be transformed into optically pure amides **2a**−**k** in high yield and high enantiomeric excess. Several functional groups, such as fluorine, bromine, ether, and trifluoromethyl, are tolerated (entries 5−7, and 11). In some cases, the reaction time was extended due to the slow rate of acylation (entries 8 and 9), whereas the reaction time of **1i** was prolonged due its slow racemization rate. The reaction also works for aliphatic amines (entries 12 and 13), making this procedure applicable for many amines which cannot be obtained in enantiomerically pure form by reduction of the corresponding imine.[4a,16]

Hydrolysis of the in situ formed imine was found to be a minor problem. The only byproduct detected was the corresponding *N*-isopropylamine. However, under dry conditions, the formation of this side product was kept below 5%.

In summary, we have developed a highly efficient protocol for DKR of amines that, for the first time, allows a variety of unfunctionalized primary amines to be transformed into one enantiomer in high yield and high enantioselectivity.

Acknowledgment. The Swedish Research Council is gratefully acknowledged for financial support. J.P. thanks the DFG for a research grant.

Supporting Information Available: Experimental procedures and analysis of the products. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) *Modern Amination Methods*; Ricci, A., Ed.; Wiley-VCH: Weinheim, Germany, 2000.
(2) *March's Advanced Organic Chemistry*, 5th ed.; Smith, M. B., March, J., Eds.; John Wiley and Sons: New York, 2001.
(3) (a) Muci, R.; Buchwald, S. L. Practical Palladium Catalysts for C−N and C−O Bond Formation. In *Topics in Current Chemistry—Cross-Coupling Reactions*; Miyaura, N., Ed.; Springer: Heidelberg, 2002; Vol. 219, pp 131−209. (b) Hartwig, J. F. Palladium-Catalyzed Amination of Aryl Halides and Related Reactions. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley and Sons: New York, 2002; Vol. 1, pp 1051−1096.
(4) (a) Blaser, H. U.; Spindler, F. Hydrogenation of Imino Groups. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 1, pp 247−265. (b) Singaram, B.; Goralski, C. T. The Reduction of Imines and Enamines with Transition Metal Hydrides. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, B., Eds.; Wiley-VCH: Weinheim, Germany, 1998; Vol. 2, pp 147−154.
(5) Denmark, S. E., Nicaise, O. J. C. Alkylation of Imino Groups. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer: Berlin, 1999; Vol. 2, pp 923−961.
(6) Bolm, C.; Hildebrand, J. P.; Muniz, K. Recent Advances in Asymmetric Dihydroxylation and Aminohydroxylation. In *Catalytic Asymmetric Synthesis*, 2nd ed.; Ojima, I., Ed.; Wiley-VCH: New York, 2000; pp 399−428.
(7) (a) Tararov, V. I.; Börner, A. *Synlett* **2005**, 203−211. (b) Tararov, V. I.; Kadyrov, R.; Riermeier, T. H.; Börner, A. *Chem. Commun.* **2000**, 1867−1868.
(8) (a) *Enzyme Catalysis in Organic Synthesis: A Comprehensive Handbook*; Drauz, K., Waldmann, H., Eds.; Wiley-VCH: Weinheim, Germany, 1995. (b) *Hydrolases in Organic Synthesis*; Bornscheuer, U. T., Kaslauskas, R. J., Eds.; Wiley-VCH: Weinheim, Germany, 1999. (c) Breuer, M.; Ditrich, K.; Habicher, T.; Hauer, B.; Kesseler, M.; Sturmer, R.; Zelinski, T. *Angew. Chem., Int. Ed.* **2004**, *43*, 788−824.
(9) (a) Turner, N. J. *Curr. Opin. Chem. Biol.* **2004**, *8*, 114−119. (b) Wegman, W. A.; Hacking, M. A. P. J.; Rops, J.; Pereira, P.; van Rantwijk, F.; Sheldon, R. A. *Tetrahedron: Asymmetry* **1999**, *10*, 1739−1750.
(10) Ebbers, E. J.; Ariaans, G. J. A.; Houbiers, J. P. M.; Bruggink, A.; Zwanenburg, B. *Tetrahedron* **1997**, *53*, 9417−9476.
(11) (a) This reference reports only one example (1-phenylethylamine) of DKR in which the reaction required 8 days and gave 64% isolated yield: Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668−669. (b) For a related paper starting from ketoximes, see: Choi, Y. K.; Kim, M. J.; Ahn, Y. *Org. Lett.* **2001**, *3*, 4099−4101.
(12) (a) Samec, J. S. M.; Ell, A. H.; Bäckvall, J. E. *Chem. Commun.* **2004**, 2748−2749. (b) Ell, A. H.; Johnson, J. B.; Bäckvall, J. E. *Chem. Commun.* **2003**, 1652−1653.
(13) Pamies, O.; Ell, A. H.; Samec, J. S. M.; Hermanns, N.; Bäckvall, J. E. *Tetrahedron Lett.* **2002**, *43*, 4699−4702.
(14) For recent reviews on DKR of alcohols, see: (a) Pamies, O.; Bäckvall, J. E. *Chem. Rev.* **2003**, *103*, 3247−3262. (b) Kim, M. J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578−587.
(15) (a) Martin-Matute, B.; Edin, M.; Bogar, K.; Bäckvall, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6535−6539. (b) Martin-Matute, B.; Edin, M.; Bogar, K.; Kaynak, F. B.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 8817−8825. (c) Csjernyik, G.; Bogar, K.; Bäckvall, J. E. *Tetrahedron Lett.* **2004**, *45*, 6799−6802. (d) Kim, M. J.; Chung, Y. I.; Choi, Y. K.; Lee, H. K.; Kim, D.; Park, J. *J. Am. Chem. Soc.* **2003**, *125*, 11494−11495. (e) Choi, J. H.; Kim, Y. H.; Nam, S. H.; Shin, S. T.; Kim, M. J.; Park, J. *Angew. Chem., Int. Ed.* **2002**, *41*, 2373−2376.
(16) Amines **2j** and **2k** cannot be obtained by asymmetric hydrogenation or transfer hydrogenation since the reported examples require an aromatic substituent: (a) Trifanova, A.; Diesen, J. S.; Chapman, C. J.; Andersson P. G. *Org. Lett.* **2004**, *6*, 3825−3927. (b) Uematsu, N.; Fujii, A.; Hashiguchi, S.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1996**, *118*, 4916−4917. (c) Mao, J.; Baker, D. C. *Org. Lett.* **1999**, *1*, 841−843.

JA056306T