Tetrahedron Letters 51 (2010) 5581–5584

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Fast racemization and dynamic kinetic resolution of primary benzyl amines

Yunwoong Kim, Jaiwook Park *, Mahn-Joo Kim *

Department of Chemistry, Pohang University of Science and Technology, San-31 Hyojadong, Pohang 790-784, Republic of Korea

ARTICLE INFO

Article history:
Received 27 July 2010
Accepted 17 August 2010
Available online 20 August 2010

ABSTRACT

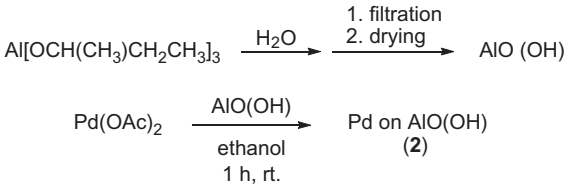
We prepared a Pd nanocatalyst (average diameter of Pd nanoparticles = 1.73 nm) displaying a remarkable activity for the racemization and dynamic kinetic resolution (DKR) of 1-methylbenzylamine. It was eight times more active than the previous best. The DKR of 1-methylbenzylamine with the Pd nanocatalyst (2 mol %) in the presence of a thermostable lipase (Novozym 435) was complete in 6 h at 70 °C. The DKRs of other benzyl amines also proceeded to completion in 6 h under similar conditions except the amount of Pd nanocatalyst.

Development of methods for the preparation of enantiomerically pure compounds is one of the important research areas due to their importance in the syntheses of natural products and chiral drugs. In the last decade, a new methodology has been intensively developed for the complete transformation of a racemic mixture into a single enantiomer: dynamic kinetic resolution (DKR) using an enzyme as the resolution catalyst together with a metal or metal complex as the racemization catalyst.[1] One of the most important factors for the successful DKR is the use of a highly efficient racemization catalyst which is compatible with enzymatic resolution. Several good racemization catalysts are now available for the DKR of secondary alcohols which can be performed at room temperature.[2] However, most racemization catalysts so far developed for the DKR of primary amines are poorly active at room temperatures. They include Pd/C,[3] $Pd/BaSO_4$,[4] Pd/AlO(OH),[5] Raney Ni and Co,[6] Ru complex,[7] and Ir complex.[8] Accordingly, the amine DKR with these catalysts should be performed at elevated temperature for long time (24 h or longer) to obtain satisfactory conversions.[9] We herein wish to report the fastest DKR of a primary amine which was completed within 6 h with a Pd nanocatalyst.

Metal nanoparticles (NPs) are attracting a great attention as efficient catalysts since they display homogeneous-like activities due to their large surface areas relative to their bulk forms.[10] We recently reported the use of a Pd nanocatalyst (**1**, Pd/AlO(OH); average diameter of Pd NPs = 2.34 nm), which is made from a Pd complex and $(sec\text{-}BuO)_3Al$ through a sol–gel process, as the racemization catalyst for the DKR of primary amines.[5] In the presence of **1** (1 mol % of Pd), the racemization of enantiopure 1-methylbenzylamine was complete in 24 h at 70 °C.[5a] Although **1** is believed to be the best among metal-based catalysts developed to date for the racemization of primary amines, it still needs further improvements for better activity. The previous studies have demonstrated that the activity of a metal nanocatalyst is dependent on the method of its preparation as well as the size of NPs.[11] Accordingly, we changed the method of preparing Pd nanocatalyst and tried to make Pd NPs smaller than those in **1**. After numerous efforts, we were able to prepare a Pd nanocatalyst which contains Pd NPs with an average diameter below 2 nm and displays a significantly enhanced racemization activity.

In a typical procedure, the Pd nanocatalyst was prepared in two steps (Scheme 1). Aluminum tri-*sec*-butoxide was reacted with water and dried to obtain AlO(OH) powder. The AlO(OH) powder was then added to a solution of $Pd(OAc)_2$ (1 wt % based on Pd) in ethanol which underwent reduction spontaneously to yield Pd NPs adsorbed on AlO(OH) (**2**; 0.85 wt % of Pd).[12] The scanning transmission electron microscopy (STEM) analysis indicated that Pd NPs of **2** had an average diameter of 1.73 ± 0.77 nm (Fig. 1).

The racemization activity of **2** was examined for optically pure 1-methylbenzylamine ((*R*)-**3a**, >99% ee). The racemization of (*R*)-**3a** was carried out in the presence of 1 mol % of Pd in toluene at 70 °C.[13] It was complete in 3 h, indicating that **2** is significantly more active than the previous catalysts (Table 1). The activation of **2** is eightfold relative to the previous best **1** (compare entries 3 and 4). The high activity of **2** enabled for the racemization at lower temperatures (entries 5 and 6). The racemization performed at 40 °C proceeded to near completion in 24 h. It is noted that the activity of **2** was reproducible from batch to batch. At this time,



Scheme 1. Preparation of Pd nanocatalyst.

* Corresponding authors. Tel.: +82 54 279 2112; fax: +82 54 279 0654.
E-mail address: mjkim@postech.ac.kr (M.-J. Kim).

0040-4039/$ - see front matter © 2010 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2010.08.050

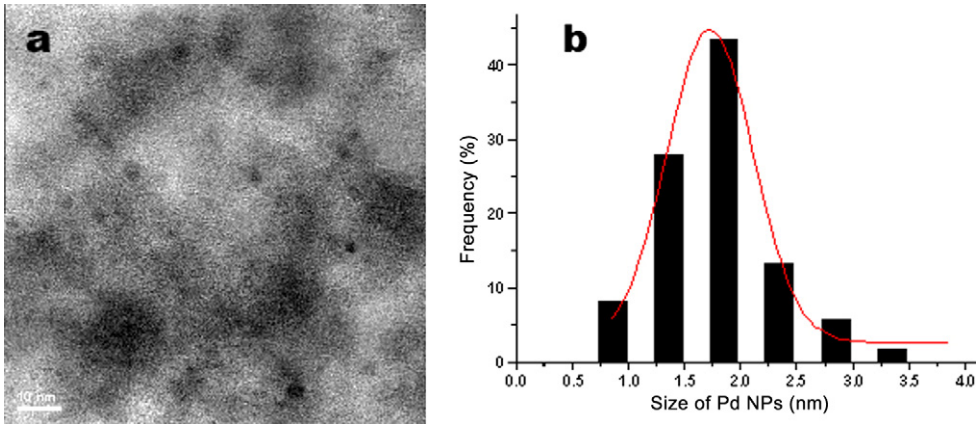
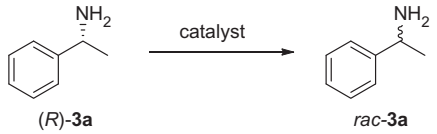


Figure 1. (a) HR STEM image of Pd on AlO(OH) (**2**). (b) Size distribution of Pd NPs obtained by HR STEM analysis.

Table 1
Racemization of (*R*)-1-methylbenzylamine (**3a**)[a]



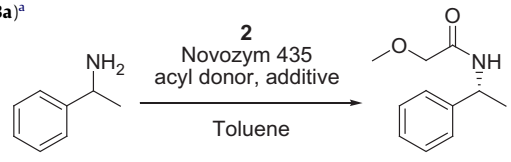
Entry	Catalyst	Amount (mol %)	Temp (°C)	Time (h)	ee[b] (%)
1[c]	Ru complex	8	90	24	55
2[d]	$Pd/BaSO_4$	5.8	70	24	2
3[e]	**1**	1	70	24	2
4	**2**	1	70	3	4
5	**2**	1	50	12	7
6	**2**	1	40	24	8

[a] Conditions: 0.1 mmol (*R*)-**3a**, 1 mL of toluene.
[b] Determined by chiral HPLC.
[c] Data from Ref. 7b. The Ru complex employed is dimeric (4 mol %) but the active species is monomeric (8 mol %).
[d] Data from Ref. 4a.
[e] Data from Ref. 5a.

no rationale is available for such a high activity of **2**. We however speculate that the smaller size and larger surface area of Pd NPs would be a major contributing factor. Also the method of preparation would affect the activity of Pd. Catalyst **2** was prepared by impregnating the dried AlO(OH) matrix with Pd NPs while **1** was prepared by entrapping Pd NPs into the AlO(OH) gel during gelation. Accordingly, the substrates would be more readily accessible to Pd NPs of the former than those of the latter.

The performance of **2** as the racemization catalyst in DKR was explored with a commercial lipase (Novozym 435) as the resolution catalyst. The DKR reactions of racemic **3a** (0.3 mmol) were performed under several different conditions for optimization (Table 2).[14] In the presence of **2** (1 mol % of Pd), Novozym 435 (25 mg/mmol of substrate), and ethyl methoxyacetate (1.7 equiv) as the acyl donor in toluene at 70 °C, the DKR took 24 h for completion but the yield (85%) was less than satisfactory (entry 1). The use of isopropyl methoxyacetate as the acyl donor improved the yield to 90% (entry 2). It is believed that isopropanol from isopropyl methoxyacetate during DKR facilitates the racemization of amines by acting as an additional hydrogen source for the returning of imines to amines.[4a,7b] A further improvement in reaction time from 24 to 12 h was achieved with the use of sodium carbonate as a base to trap any acidic species from the commercial enzyme preparation or the acyl donor hydrolyzed (entry 3). Previously, the corresponding DKR with **1** took 72 h to give similar yield and ee.[5a] Therefore, the present DKR is sixfold faster compared to the previous DKR. Finally, we were able to further reduce the reaction time to 6 h by doubling the amounts of catalysts (entry 4). The optimized DKR afforded a high yield (92%) and an excellent enantiopurity

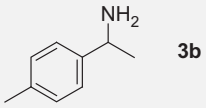
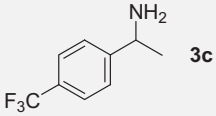
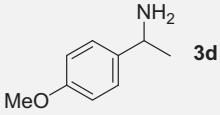
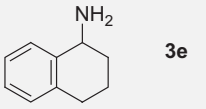
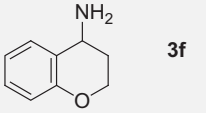
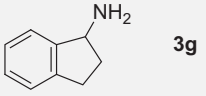
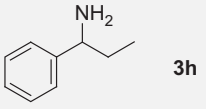
Table 2
Dynamic kinetic resolution of 1-methylbenzylamine (**3a**)[a]



Entry	Pd (mol %)	Lipase (mg/mmol)	Na_2CO_3 (mg/mmol)	Temp (°C)	Time (h)	Conv[b] (%)	Yield[c] (%)	ee[d] (%)
1[e]	1	25	0	70	24	97	85	99
2[f]	1	25	0	70	24	96	90	99
3[f]	1	25	25	70	12	97	85	99
4[f]	2	50	50	70	6	>97	92	99
5[f]	1	25	25	50	48	>97	90	98
6[f]	2	25	25	40	48	>97	98	98

[a] Conditions: 0.3 mmol **3a**, 1.7 equiv of acyl donor, 6 mL of toluene.
[b] Determined by ^1H NMR.
[c] Isolated yield.
[d] Determined by chiral HPLC.
[e] Acyl donor = ethyl methoxyacetate.
[f] Acyl donor = isopropyl methoxyacetate.

Table 3
Dynamic kinetic resolution of additional benzyl amines[a]

Entry	Substrate	Pd (mol %)	Novozym (mg/mmol)	Time (h)	yield[b] (%)	ee[c] %
1	 **3b**	5	50	6	94	98
2[d]	 **3c**	4	50	6	99	98
3	 **3d**	5	50	6	88	97
4	 **3e**	5	50	6	97	>99
5	 **3f**	5	50	6	96	>99
6	 **3g**	5	50	6	83	90
7		5	40	12	93	96
8	 **3h**	2	150	6	89	>99
9		2	150	12	97	>99

[a] Conditions: 0.3 mmol of substrate, 1.7 equiv of isopropyl methoxyacetate, 6 mL of toluene, 70 °C, 6 h.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Using methyl methoxyacetate as an acyl donor.

(99% ee). The DKR reactions at lower temperatures (40–50 °C) also proceeded smoothly within a reasonable reaction time (48 h) to provide excellent results (entries 5 and 6). This is important because the amine DKR would become possible with other enzymes, which lose their activities at 70 °C or higher but have acceptable stability at 40–50 °C.

To see the scope and generality of the DKR procedure using **2** as the racemization catalyst, we carried out the DKR reactions of additional benzyl amines **3b**–**h** (Table 3). It was found that ring-substituted benzyl amines **3b**–**g** were less prone to racemization than **3a**[15] so that they needed 4–5 mol % of **2** for the fast DKR within 6 h. Interestingly, **3b** with an electron-withdrawing substituent on benzene ring underwent its DKR with high yield (99%) and excellent ee (98%), whereas the DKR of **3d** with a strongly electron-donating substituent provided a lower yield (88%) with some byproducts[4a] resulting from the reactions of amine substrates with their racemization intermediates (imines)[16] (entries 2 and 3).

The DKRs of two six-membered alicyclic amines (**3e** and **3f**) proceeded smoothly well to afford high yields and excellent enantiopurities (entries 4 and 5). The DKR of five-membered alicyclic amine **3g**, however, was less than satisfactory in both yield and enantiopurity (entry 6). To obtain better results, the reaction time was increased to 12 h with a decrease in the amount of enzyme (entry 7). The DKR of a slow-reacting substrate (**3h**) did not proceed to completion in 6 h even though a three times larger amount of enzyme was employed (entry 8). The reaction time thus was extended to 12 h to obtain a high yield with an excellent enantiopurity (entry 9).

In summary, we have demonstrated that the fast racemization and DKR of 1-methylbenzylamine can be achieved with a Pd nanocatalyst containing Pd nanoparticles smaller than 2 nm in average diameter, and the DKR procedure is applicable to other benzyl amines. It is noteworthy that the DKR can be carried out at a mild temperature (40 °C) which is significantly lower than the previously reported cases. Thus it should be possible to use other enzymes, which are less thermostable than Novozym 435, with the Pd nanocatalyst for the DKR of amines. Further studies toward this end are under way at this laboratory.

Acknowledgments

This work was supported by the National Research Foundation of Korea (2009–0087801) and POSCO. The authors thank the Korean Government for supporting our graduate program via the BK21 project.

References and notes

1. Reviews: (a) Kim, M.-J.; Ahn, Y.; Park, J. *Curr. Opin. Biotechnol.* **2002**, *13*, 578–587; (b) Pamies, O.; Bäckvall, J. E. *Chem. Rev.* **2003**, *103*, 3247–3262; (c) Kim, M.-J.; Ahn, Y.; Park, J. *Bull. Korean Chem. Soc.* **2005**, *26*, 515–522; (d) Martin-Matute, B.; Bäckvall, J. E. *Curr. Opin. Biol.* **2007**, *11*, 226–232; (e) Ahn, Y.;

Ko, S.-B.; Kim, M.-J.; Park, J. *Coord. Chem. Rev.* **2008**, *252*, 647–658; (f) Lee, J. H.; Han, K.; Kim, M.-J.; Park, J. *Eur. J. Org. Chem.* **2010**, 999–1015.

2. (a) 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; (b) Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972–1977; (c) Martin-Matute, B.; Edin, M.; Bogar, K.; Bäckvall, J. E. *Angew. Chem., Int. Ed.* **2004**, *43*, 6535–6539; (d) Kim, N.; Ko, S.-B.; Kwon, M. S.; Kim, M.-J.; Park, J. *Org. Lett.* **2005**, *7*, 4523–4526; (e) Berkessel, A.; Sebastian-Ibarz, M. L.; Müller, T. N. *Angew. Chem., Int. Ed.* **2006**, *45*, 6567–6570; (f) Akai, S.; Tanimoto, K.; Kanao, Y.; Egi, M.; Yamamoto, T.; Kita, Y. *Angew. Chem., Int. Ed.* **2006**, *45*, 2592–2595; (g) Haak, R. M.; Berthiol, F.; Jerphagnon, T.; Gayet, J. A.; Tababiono, C.; Postema, C. P.; Ritleng, V.; Pfeffer, M.; Janssen, D. B.; Minnaard, A. j.; Feringa, B. L.; De Vries, J. G. *J. Am. Chem. Soc.* **2008**, *130*, 13508–13509; (h) Kim, M.-J.; Choi, Y. K.; Kim, S.; Kim, D.; Han, K.; Ko, S.-B.; Park, J. *Org. Lett.* **2008**, *10*, 1295–1298.
3. (a) Reetz, M. T.; Schimossek, K. *Chimia* **1996**, *50*, 668–669; (b) Choi, Y. K.; Kim, M. J.; Ahn, Y.; Kim, M.-J. *Org. Lett.* **2001**, *3*, 4099–4101.
4. (a) Parvulescu, A.; De Vos, D.; Jacobs, P. *Chem. Commun.* **2005**, 5307–5309; (b) Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Chem. Eur. J.* **2007**, *13*, 2034–2043; (c) Andrade, L. H.; Silva, A. V.; Pedrozo, E. C. *Tetrahedron Lett.* **2009**, *50*, 4331–4334.
5. (a) Kim, M.-J.; Kim, W.-H.; Han, K.; Choi, Y. K.; Park, J. *Org. Lett.* **2007**, *9*, 1157–1159; (b) Han, K.; Park, J.; Kim, M.-J. *J. Org. Chem.* **2008**, *73*, 4302–4304; (c) Choi, Y. K.; Kim, Y.; Han, K.; Park, J.; Kim, M.-J. *J. Org. Chem.* **2009**, *74*, 9543–9545.
6. Parvulescu, A. N.; Jacobs, P. A.; De Vos, D. E. *Adv. Synth. Catal.* **2008**, *350*, 113–121.
7. (a) Pamies, O.; Ell, A. H.; Samec, J. S. M.; Hermanns, N.; Bäckvall, J. E. *Tetrahedron Lett.* **2002**, *43*, 4699–4702; (b) Paetzold, J.; Bäckvall, J. E. *J. Am. Chem. Soc.* **2005**, *127*, 17620–17621; (c) Veld, M. A. J.; Hult, K.; Palmans, A. R. A.; Meijer, E. W. *Eur. J. Org. Chem.* **2007**, 5416–5421; (d) Thalén, L. K.; Zhao, D.; Sortais, J.-B.; Paetzold, J.; Hoben, C.; Bäckvall, J. E. *Chem. Eur. J.* **2009**, *15*, 3403–3410.
8. (a) Stirling, M.; Blacker, J.; Page, M. I. *Tetrahedron Lett.* **2007**, *48*, 1247–1250; (b) Blacker, A. J.; Stirling, M. J.; Page, M. I. *Org. Process Res. Dev.* **2007**, *11*, 642–648.
9. Recently, a faster amine DKR using a sulfanyl radical for racemization was reported. (a) Gastaldi, S.; Escoubet, S.; Vanthuyne, N.; Gil, G.; Bertrand, M. P. *Org. Lett.* **2007**, *9*, 837–839; (b) Routaboul, L.; Vanthuyne, N.; Gastaldi, S.; Gil, G.; Bertrand, M. P. *J. Org. Chem.* **2008**, *73*, 364–368; (c) Blidi, L. E.; Nechab, M.; Vanthuyne, N.; Gastaldi, S.; Bertrand, M. P.; Gil, G. *J. Org. Chem.* **2009**, *74*, 2901–2903.
10. Heiz, U.; Landman, U. *Nanocatalysis*; Springer: Berlin, Heidelberg, New York, 2006.
11. (a) Tsunoyama, H.; Sakurai, H.; Negishi, Y.; Tsukuda, T. *J. Am. Chem. Soc.* **2005**, *127*, 9374–9375; (b) Evans, G.; Kozhevnikov, I. V.; Kozhevnikova, E. F.; Claridge, J. B.; Vaidhyanathan, R.; Dickinson, C.; Wood, C. D.; Cooper, A. I.; Rosseinsky, M. J. *J. Mater. Chem.* **2008**, *18*, 5518–5523; (c) Beck, I. E.; Bukhtiyarov, V. I.; Pakharukov, I. Y.; Zaikovsky, V. I.; Kriventsov, V. V.; Parmon, V. N. *J. Catal.* **2009**, *268*, 60–67; (d) Wang, C.; van der Vliet, D.; Chang, K.-C.; You, H.; Strmcnik, D.; Schlueter, J. A.; Markovic, N. M.; Stamenkovic, V. R. *J. Phys. Chem. C* **2009**, *113*, 19365–19368.
12. *Preparation of AlO(OH).* (*sec*-BuO)$_3$Al (5.0 mL, 19.5 mmol) and 2-butanol (10 mL) were added to a 50 mL round-bottomed flask and then stirred at room temperature for 10 min to obtain a homogeneous solution, followed by the addition of water (3 mL). The reaction mixture was stirred at room temperature for 20 min followed by the addition of acetone (30 mL) and then stirred for additional 30 min. The mixture was filtered, washed with acetone, and dried at 150 °C under a reduced pressure to give AlO(OH) as white powder (1.54 g). *Preparation of* **2**. Pd(OAc)$_2$ (33 mg, 0.147 mmol) and ethanol (10 mL, 170 mmol) were added to a 50 mL round-bottomed flask and stirred at room temperature for 10 min followed by the addition of AlO(OH) (1.54 g).
The resultant mixture was further stirred at room temperature for 1 h to allow the spontaneous reduction of Pd(II) to Pd(0) nanoparticles adsorbed on AlO(OH) powder. The heterogeneous mixture was filtered, washed with acetone, and dried at 80 °C under a reduced pressure to give **2** as dark powder (Pd on AlO(OH); 1.46 g). The ICP analysis indicated that the Pd nanocatalyst contained 0.85 wt % of Pd.
13. *Racemization of* (*R*)-**3a**. (*R*)-**3a** (12 mg, 0.10 mmol) was added to a suspension of Pd catalyst **2** (13 mg, 1.0 mol % of Pd) in dry and degassed toluene (1 mL; 0.10 M). The reaction mixture was stirred at 70 °C under argon. After 3 h, the reaction mixture was cooled to room temperature and filtered through a glass filter (pore size: 20−30 μm). The filtrate was concentrated and analyzed by ^{1}H NMR spectroscopy and HPLC (Kromasil-5-CellCoat, *n*-hexane/2-propanol/diethyl amine = 90:10:0.1, flow rate = 1.5 mL/min, UV 220 nm): (*R*)-**3a** = 5.57 min, (*S*)-**3a** = 6.57 min.
14. *Dynamic kinetic resolution of* **3a**. A solution containing **3a** (36 mg, 0.30 mmol), Pd nanocatalyst **2** (76 mg, 2.0 mol % of Pd), Novozym 435 (15 mg), sodium carbonate (15 mg), and isopropyl methoxyacetate (71 μL, 1.7 equiv) in dry and degassed toluene (6 mL) was stirred at 70 °C under argon atmosphere. After 6 h, the reaction mixture was cooled to room temperature and filtered through a glass filter with celite pad. The filtrate was concentrated and analyzed by ^{1}H NMR spectroscopy, indicating that all of the substrate was consumed. The mixture was subjected to a flash column chromatography (silica gel, *n*-hexane/ethyl acetate = 1:1) to provide **4a** (53.6 mg, 0.277 mmol, 92%, 99% ee): mp 61−63 °C (lit.[5a] mp 59−60 °C); $[\alpha]_D^{25}$ + 90.1 (*c* 1.0, $CHCl_3$) (lit.[5a] $[\alpha]_D^{25}$ + 85.2 (*c* 0.5, $CHCl_3$)); HPLC ((*R*,*R*)Whelk−O1, *n*-hexane/2-propanol = 80:20, flow rate = 2.0 mL/min, UV 217 nm): (*S*)-**4a** = 7.06 min, (*R*)-**4a** = 17.08 min; ^{1}H and ^{13}C NMR data are in good agreement with the literature data.[5a]
15. In general, the racemization of benzyl amines takes place through a two-step process, dehydrogenation and hydrogenation via an imine intermediate. The observation that the racemizations of **3b**–**g** took place slowly relative to that of **3a** in DKR indicates that racemization is retarded by both electron-donating and electron-attracting groups on the benzene ring.
16. In racemization, the dehydrogenation step should be rate determining with electron-attracting groups while the hydrogenation step should be rate determining with electron-donating groups. Accordingly, the life time of imine intermediate in the latter case is long relative to that in the former case. This explains the reason why the amounts of byproducts resulting from the side reactions of imine intermediate (including its reaction with amine substrate) are significantly larger in the DKR of **3d** with an electron-donating group than in the DKR of **3b** with an electron-attracting group.