



<http://www.diva-portal.org>

Postprint

This is the accepted version of a paper published in *Chemistry - A European Journal*. This paper has been peer-reviewed but does not include the final publisher proof-corrections or journal pagination.

Citation for the original published paper (version of record):

Gustafson, K P., Gudmundsson, A., Lewis, K., Bäckvall, J-E. (2017)
Chemoenzymatic Dynamic Kinetic Resolution of Secondary Alcohols Using an Air- and
Moisture-Stable Iron Racemization Catalyst
Chemistry - A European Journal, 23(5): 1048-1051
<https://doi.org/10.1002/chem.201605754>

Access to the published version may require subscription.

N.B. When citing this work, cite the original published paper.

Permanent link to this version:

<http://urn.kb.se/resolve?urn=urn:nbn:se:su:diva-141286>

Chemoenzymatic Dynamic Kinetic Resolution of Secondary Alcohols using an Air and Moisture stable Iron Racemization Catalyst

Karl P. J. Gustafson,^[a] Arnar Guðmundsson,^[a] Kayla Lewis^[a] and Jan-E. Bäckvall*^[a]

Abstract: Herein, we report on a metalloenzymatic dynamic kinetic resolution of *sec*-alcohols employing an iron-based racemization catalyst together with a lipase. The iron catalyst was evaluated in racemization and then used in dynamic kinetic resolution of a number of *sec*-alcohols to give enantiomerically pure products in good to high yields. The iron catalyst is air and moisture stable and it is readily accessible.

Asymmetric synthesis is an active and important area of organic chemistry that has had a profound influence on several other fields of science.^[1] The most common method today for obtaining enantiomerically pure compounds on an industrial scale is still the resolution of a racemic mixture.^[2] Resolution protocols suffer from one major intrinsic drawback, which is that only a maximum yield of 50% of a single desired enantiomer can be obtained. To enable quantitative yield, the undesired enantiomer has to be converted into the desired one, which can be achieved by coupling the resolving protocol to a racemization. This combination leads to a so-called dynamic kinetic resolution (DKR), where an *in situ* racemization catalyst maintains the starting material racemic during the resolution.^[3]

Racemization of secondary alcohols can be achieved with different methods. One of the most studied approaches relies on a reversible transfer hydrogenation strategy, where metals such as Ru,^[4] Ir^[5] and Rh,^[6,7] and Al^[8] have been shown to catalyze the racemization. Racemization of alcohols can also be accomplished without metals, for instance with the use of acidic resins^[9] or zeolites^[10] in a dehydration/hydration mechanism. Several other substrate-specific catalysts have been reported utilizing a similar concept as the dehydration/hydration pathway (with C-O cleavage), for racemization of allylic alcohols^[11] or allylic esters.^[12]

The first practical metalloenzymatic DKR of secondary alcohols was reported in 1997,^[13] where the dimeric ruthenium Shvo catalyst^[14] and *Candida antarctica* lipase B were employed at 70 °C. Continued efforts by several groups have led to the development of a number of efficient ruthenium-based racemization catalysts compatible with enzymatic processes (see Figure 1).^[15] Several of these catalysts give a fully racemic alcohol at ambient conditions with short reaction times (<30 min). Numerous enzymes have been shown to be compatible with these Ru racemization catalysts leading to efficient DKR of a large number of substrates in high yields and excellent enantiomeric excess.^[3f]

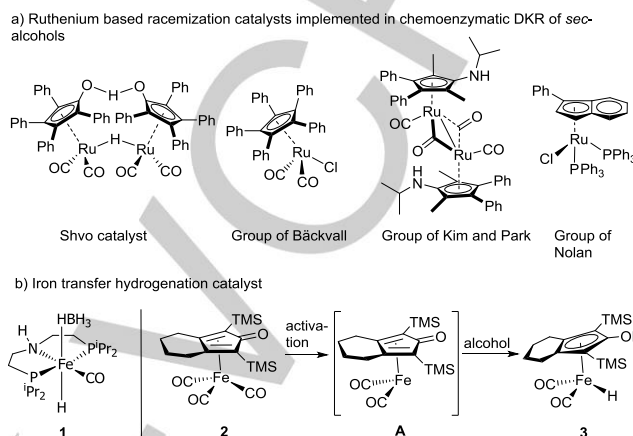


Figure 1. a) Ruthenium transfer hydrogenation catalyst used in chemoenzymatic DKR of alcohols. b) iron transfer hydrogenation catalysts.

More recently, research has been focused on the use of complexes of more non-toxic and inexpensive metals for the racemization of alcohols. Therefore, work has been dedicated towards the development of iron-based racemization catalysts. We have recently reported on a pincer type iron-based racemization catalyst **1**, being the first reported iron-based racemization catalyst.^[16] This catalyst was able to fully racemize a wide range of benzylic alcohols at 50 °C within 10-15 min. However, catalyst **1** was not able to racemize aliphatic alcohols nor was it compatible with the reaction conditions required for a chemoenzymatic DKR.

These results led us to pursue studies on other iron catalysts.^[17] Catalyst **3**, first isolated in 1999 by the group of Knölker,^[18] found its first catalytic applications when Casey and Guan demonstrated its use in hydrogenation of ketones to alcohols.^[19] More recently, several reports on *in-situ* generation of **A** and **3** by activation of precursor **2**, for dehydrogenation/hydrogenation reactions have been reported.^[20] We therefore decided to explore the use of **2** as a precursor for the potential racemization catalytic species **A** and **3**. In these racemization reactions species **A** dehydrogenates the alcohol to a ketone and hydride **3** hydrogenates the ketone back to alcohol. We now report on the use of stable catalyst precursor **2** in combination with a lipase for the chemoenzymatic DKR of alcohols. During the completion of our work the group of Rueping reported on the direct use of air- and moisture-sensitive catalyst **3** in DKR of alcohols.^[21] An advantage with our procedure over the one reported by Rueping, is that stable complex **2** can be used as pre-catalyst, which avoids handling of the highly sensitive catalyst **3**.

We commenced the screening of reaction conditions for catalyst **2** with attempts to racemize (*S*)-1-phenylethanol (**4a**) using 10 mol% of activator Me₃NO (TMANO) in toluene. To our delight, we observed racemization of the alcohol; however, the

[a] Department of Organic Chemistry, Arrhenius Laboratory, Stockholm University, SE-10691 Stockholm, Sweden
Fax: +46-8-154908; Phone: +46-8-674 7178
E-mail: jeb@organ.su.se

catalyst was not stable over more than a few minutes. This phenomenon can most likely be ascribed to that trimethylamine deactivates the catalyst, which was previously observed by Funk and Moyers.^[20c] In our recently published iron racemization protocol^[16] we observed that etheric solvents increased the stability of the catalyst. Thus, when subjecting catalyst **2** to the use in etheric solvents such as anisole or CPME an increased stability of the catalytic system was observed (Table 1, entry 1). To increase the efficiency of the system, additives were screened, and the addition of 50 mol% of ketone increased the rate of racemization dramatically (entry 2). This effect is in agreement with the observation by Casey and Guan,^[19] that the slow step in the transfer hydrogenation is the re-addition of hydrogen to ketone. Inorganic bases also had a profound effect on the system (entries 3-5), which can be explained by the fact that the iron hydride becomes more reactive in the presence of base, leading to a facilitated re-addition.^[22] We then continued to explore the ketone amount (see Supporting Information, Table S1), where 20 mol% proved to be sufficient to maintain the catalytic efficiency (entry 6). Lowering the temperature to 60 °C reduced the rate (entry 7), but the lower temperature would allow the catalyst to be compatible with a broader set of enzymes.

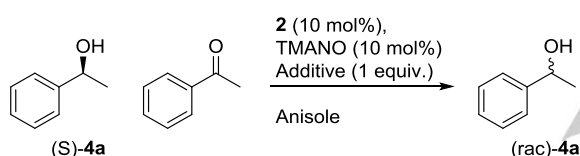


Table 1. Racemization of alcohol (S)-**4a** using catalyst **2**, screening of conditions.^{[a][b]}

Entry	T (°C)	Amount of ketone (mol%)	Additive ^[c]	ee-value of 4 ^[d]	
				30 min	60 min
1	90	-	-	76%	52%
2	90	50	-	43%	22%
3	90	50	Na ₂ CO ₃	14%	4%
4	90	50	K ₂ CO ₃	10%	2%
5	90	50	Na ₂ SO ₄	84%(62%) ^[d]	74%(32%) ^[e]
6	90	20	K ₂ CO ₃	26%	4%
7	60	20	K ₂ CO ₃	76%	58%

[a] General reaction conditions: 1.0 mmol of (S)-**4a**, 0.10 mmol of **2**, 0.1 mmol of Me₃NO, 0.2 mmol of acetophenone, 1 mL of anisole. [b] for complete optimization see Supporting Information. [c] 1 mmol of additive. [d] ee-values were determined by chiral GC. [e] 0.8 equiv. of triethylamine was added.

The catalytic activity of catalyst **2** under DKR conditions using *Candida antarctica* lipase B (CalB) was next evaluated. After accessing a set of acyl donors in the DKR it became evident that aryl acetates worked best since other activated

esters such as vinyl or isopropenyl acetate afforded acetaldehyde or acetone, respectively, which interferes with the transfer hydrogenation catalyst.²³ The DKR reaction was highly concentration dependent and using a substrate concentration of 1M in the presence of the enzyme terminated the racemization catalyst. For a successful result it was necessary to dilute the reaction mixture to a substrate concentration of 0.25 M. Na₂CO₃ was used as base to facilitate the hydride re-addition as well as to remove traces of free acid.²⁴ Simple phenyl acetate as acyl donor worked well together with CalB and iron catalyst **2** in the DKR of **4a** (Figure 2), and **5a** could be isolated in 84% yield with 98% ee. Other substrates also gave an efficient DKR, and the 4-chloro and 4-bromo substituted benzylic alcohols **4b** and **4c** afforded enantiomerically pure (>99% ee) **5b** and **5c** in 87% and 84% yield, respectively. The electron-rich substrate **4d** afforded **5d** in 89% yield (99% ee). Furthermore, the protocol tolerated the more electron rich 4-methoxy substituted benzylic alcohol **4e**, which furnished acetate **5e** in 85% yield and 97% ee. Surprisingly, for the strongly electron deficient alcohol **4f**, acetate **5f** was only isolated in 62% yield and with an ee of 96%. Naphtyl derivative **4g** furnished acetate **5g** in 93% yield and 98% ee. The DKR system also tolerated an ethyl group as the small group of the alcohol (**4h**, R' = Et) and acetate **5h** was obtained in 75% yield and 98.5% ee. For the DKR of aliphatic alcohol **4i** *Burkholderia cepacia* lipase (PS-C) was used as enzyme and acetate **5i** was isolated in 78% yield and 95% ee. The latter enzyme has proven to be versatile in the resolution of numerous *sec*-alcohols and amines.^[25]

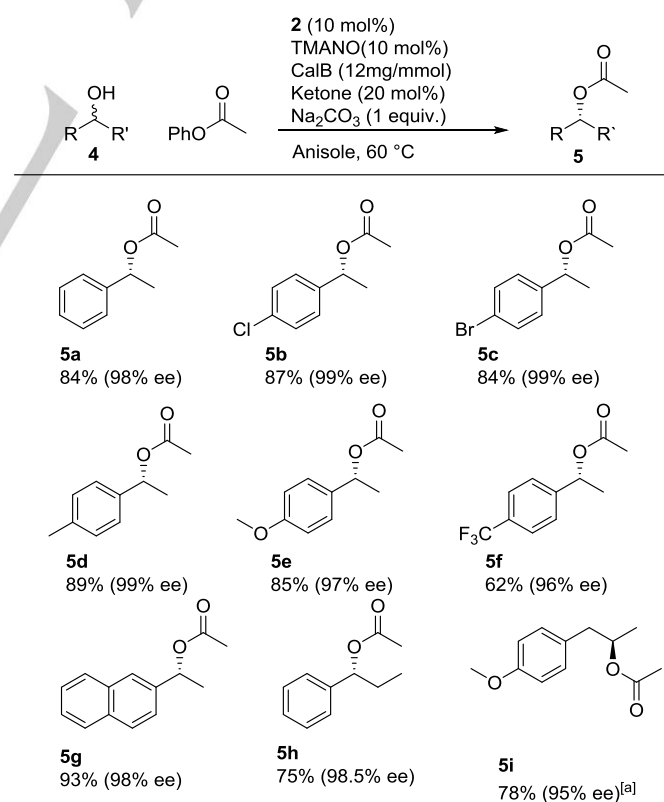


Figure 2. Substrate scope. General reaction conditions: 1.0 mmol of **4**, 0.1 mmol of **2**, 0.1 mmol of Me₃NO, 0.2 mmol of the corresponding ketone

(RCOR'), CalB (12 mg of Novozym 435) and 2.0 mmol of phenyl acetate in 4 mL of anisole [a] The lipase used was PS-C (25 mg/mmol).

To further demonstrate the practical use of the present method, the reaction of alcohol **4g** was scaled up to 10 mmol scale (Figure 3).

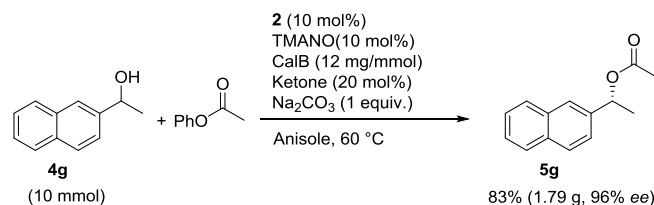


Figure 3. DKR reaction scaled up to 10 mmol.

Herein, we have reported on a chemoenzymatic dynamic kinetic resolution of secondary alcohols utilizing an air- and moisture-stable iron catalyst for the racemization of alcohols. This procedure allows a set of enantiomerically pure benzylic and aliphatic acetates to be prepared in good to high yields and with excellent ee. Two enzymes were shown to be compatible with the racemization catalyst, CalB and PS-C. It was also demonstrated that the reaction could be scaled up to 10 mmol scale. The rate of racemization was shown to be greatly influenced by the addition of inorganic bases, which helped to facilitate the hydrogen re-addition of the intermediate hydride. Continued efforts in our group will be focused on the development of more efficient and broadly applicable earth abundant metal racemization catalysts.

Experimental Section

Standard procedure for the Fe-catalyzed racemization of secondary alcohols. Into a flame dried Schlenk flask were added Fe catalyst **2** (0.1 mmol), Na₂CO₃ (1 mmol), and TMANO (0.1 mmol) and the reaction mixture was evacuated and refilled with argon repeated times. A stock solution of the alcohol and ketone was added to the mixture and the reaction was heated and monitored over time.

Standard procedure for the Fe-catalyzed dynamic kinetic resolution of secondary alcohols. Fe catalyst **2** (0.1 mmol), Na₂CO₃ (1 mmol), TMANO (0.1 mmol) and lipase (CalB as Novozyme-435 12 mg/mmol; PS-C 25 mg/mmol) were added into a flame dried Schlenk flask. The Schlenk flask was evacuated and refilled with argon repeated times. A stock solution of alcohol and ketone in anisole was added. The reaction mixture was heated and stirred for 24 h.

Acknowledgements

Financial support from the Swedish Research Council (621-2013-4653), the European Research Council (ERC AdG 247014), the Berzelii Center EXSELENT, and the Knut and Alice Wallenberg Foundation is gratefully acknowledged. K.L. thanks the IRES exchange graduate student program for a stipend.

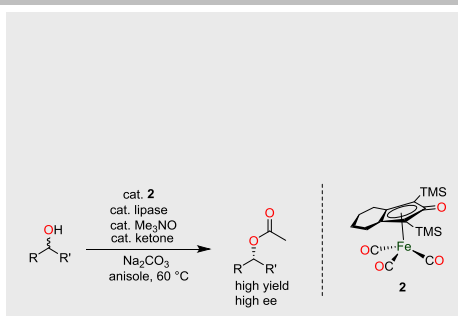
Keywords: iron catalysis • enzyme catalysis • racemization • secondary alcohols • dynamic kinetic resolution

- [1] a) E. N. Jacobsen, A. Pfaltz, H. Yamamoto, *Comprehensive Asymmetric Catalysis: I-III*, Springer, Berlin, **1999**; b) J. Clayden, N. Greeves, S. Warren, P. Wothers, *Organic Chemistry*, Oxford University Press, **2000**; c) Wolf, C. *Dynamic Stereochemistry of Chiral Compounds: Principles and Applications*, The Royal Society of Chemistry: Cambridge, **2008**.
- [2] H. Pellissier, *Chirality from Dynamic Kinetic Resolution*, RSC Publishing, **2011**.
- [3] a) O. Pamies, J.-E. Bäckvall *Chem. Rev.* **2003**, *103*, 3247-3262. b) Y. Ahn, S.-B. Ko, M.-J. Kim, J. Park, *Coord. Chem. Rev.* **2008**, *252*, 647-658; c) R. Marcos, B. Martín-Matute, *Isr. J. Chem.* **2012**, *52*, 639-652; d) A. Parvulescu, J. Janssens, J. Vanderleyden, D. De Vos, *Top. Catal.* **2010**, *53*, 931-941; e) P. Hoyos, V. Pace, A. R. Alcántara, *Adv. Synth. Catal.* **2012**, *354*, 2585-2611. f) O. Verho, Bäckvall, *J. Am. Chem. Soc.* **2015**, *137*.
- [4] a) G. Cséjnyik, K. Bogár, J.-E. Bäckvall, *Tetrahedron Lett.* **2004**, *45*, 6799-6802; b) B. Martín-Matute, M. Edin, K. Bogár, J. E. Bäckvall *Angew. Chem. Int. Ed.* **2004**, *43*, 6535 - 6539. c) J. H. Choi, Y. K. Choi, Y. H. Kim, E. S. Park, E. J. Kim, M.-J. Kim, J. Park, *J. Org. Chem.* **2004**, *69*, 1972-1977. d) N. Kim, S.-B. Ko, M. S. Kwon, M.-J. Kim, J. Park, *Org. Lett.* **2005**, *7*, 4523-4526. e) Q. Xi, W. Zhang, X. Zhang, *Synlett* **2006**, 945-947. f) S. Manzini, C. A. Urbina-Blanco, A. Poater, A. M. Z. Slawin, L. Cavallo, S. P. Nolan, *Angew. Chem. Int. Ed.* **2012**, *51*, 1042-1045;
- [5] R. M. Haak, F. Berthiol, T. Jerphagnon, A. J. A. Gayet, C. Tarabiono, C. P. Postema, V. Ritleng, M. Pfeffer, D. B. Janssen, A. J. Minnaard, B. L. Feringa, J. G. de Vries, *J. Am. Chem. Soc.* **2008**, *130*, 13508-13509.
- [6] P. M. Dinh, J. A. Howarth, A. R. Hudnott, J. M. J. Williams, W. Harris, *Tetrahedron Lett.* **1996**, *37*, 7623-7626.
- [7] For reviews see: a) J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson, P. Brandt, *Chem. Soc. Rev.* **2006**, *35*, 237-248; b) F. F. Huerta, A. B. E. Minidis, J.-E. Bäckvall, *Chem. Soc. Rev.* **2001**, *30*, 321-331.
- [8] For an Al-catalyst see: A. Berkessel, M. L. Sebastian-Ibarz, T. N. Müller, *Angew. Chem. Int. Ed.* **2006**, *45*, 6567-6570.
- [9] a) Y. Cheng, G. Xu, J. Wu, C. Zhang, L. Yang, *Tetrahedron Lett.* **2010**, *51*, 2366-2369; b) Y. Zhu, K.-L. Fow, G.-K. Chuah, S. Jaenicke, *Chem. Eur. J.* **2007**, *13*, 541-547.
- [10] a) J. Wang, D.-M. Do, G.-K. Chuah, S. Jaenicke, *ChemCatChem* **2013**, *5*, 247-254; b) S. Wuyts, K. De Temmerman, D. De Vos, P. Jacobs, *Chem. Commun.* **2003**, 1928-1929; c) X. Li, Y. Shi, Z. Wang, Y. Zhang, Y. Tang, *J. Catal.* **2012**, *288*, 24-32.
- [11] S. Akai, K. Tanimoto, Y. Kanao, M. Egi, T. Yamamoto, Y. Kita, *Angew. Chem. Int. Ed.* **2006**, *45*, 2592-2595.
- [12] J. V. Allen, J. M. J. Williams, *Tetrahedron Lett.* **1996**, *37*, 1859-1862.
- [13] a) A. L. E. Larsson, B. A. Persson, J. E. Bäckvall, *Angew. Chem., Int. Ed.* **1997**, *36*, 1211; b) B. A. Persson, A. L. E. Larsson, M. Le Ray, J.-E. Bäckvall, *J. Am. Chem. Soc.* **1999**, *121*, 1645-1650
- [14] (a) N. Menashe, Y. Shvo, *Organometallics* **1991**, *10*, 3885-3891 (b) G.-Z. Wang, U. Andreasson, J. E. Bäckvall, *J. Chem. Soc. Chem. Commun.* **1994**, 1037-1038. (c) M. L. S. Almeida, M. Beller, G.-Z. Wang and J. E. Bäckvall *Chem. Eur. J.* **1996**, *2*, 1533-1536 (d) B. L. Conley, M. K. Pennington-Boggio, E. Boz, T. J. Williams, *Chem. Rev.* **2010**, *110*, 2294-2312. (e) M. C. Warner, C. P. Casey, and J. E. Bäckvall *Topics in Organometallic Chemistry*, **2011**, *37*, 85-125.
- [15] a) M. C. Warner, J.-E. Bäckvall, *Acc. Chem. Res.* **2013**, *46*, 2545-2555. b) Y. Do, I.-C. Hwang, M.-J. Kim, J. Park, *J. Org. Chem.* **2010**, *75*, 5740-5742. c) M. Päiviö, D. Mavrynsky, R. Leino, L. T. Kanerva, *Eur. J. Org. Chem.* **2011**, 1452-1457; d) D. Mavrynsky, M. Päiviö, K. Lundell, R. Sillanpää, L. T. Kanerva, R. Leino, *Eur. J. Org. Chem.* **2009**, 1317-1320. e) S. Manzini, J. A. Fernández-Salas, S. P. Nolan, *Acc. Chem. Res.* **2014**, *47*, 3089-3101.
- [16] C. Bornschein, K. P. J. Gustafson, O. Verho, M. Beller, J. E. Bäckvall, *Chem. Eur. J.* **2016**, *22*, 11583-11586.
- [17] Recent reviews on Knölker-type iron catalyst and non-innocent ligands see: a) A. Quintard, J. Rodriguez, *Angew. Chem. Int. Ed.* **2014**, 4044-4055; *Angew. Chem.* **2014**, *126*, 4124-4136. b) R. Khusnutdinova, D. Milstein, *Angew. Chem. Int. Ed.* **2015**, *54*, 12236-12273; *Angew. Chem.* **2015**, *127*, 12406-12445. Selected examples of iron-catalyzed asymmetric hydrogenation c) W. Zuo, A. J. Lough, Y. F. Li, R. H. Morris, *Science* **2013**, *342*, 1080-1083; d) Y. Li, S. Yu, X. Wu, J. Xiao, W. Shen, Z. Dong, J. Gao, *J. Am. Chem. Soc.* **2014**, *136*, 4031-4039.
- [18] H. J. Knölker, H. Goesmann, R. Klaus, *Angew. Chem. Int. Ed.* **1999**, *38*, 2064-2066; *Angew. Chem.* **1999**, *111*, 2196-2199.
- [19] a) C. P. Casey, H. Guan, *J. Am. Chem. Soc.* **2007**, *129*, 5816-5817 b) C. P. Casey, H. Guan, *J. Am. Chem. Soc.* **2009**, *131*, 2499-2507

- c) for related oxidations, see: M. G. Coleman, A. N. Brown, B. A. Bolton, H. Guan, *Adv. Synth. Catal.* **2010**, *352*, 967-970.
- [20] a) S. Fleischer, S. S. Zhou, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2013**, *52*, 5120-5124; *Angew. Chem.* **2013**, *125*, 5224-5228; b) N. Plank, J. L. Drake, D. K. Kim, T. W. Funk, *Adv. Synth. Catal.* **2012**, *354*, 597-601; c) S. A. Moyer, T. Funk, *Tetrahedron Lett.* **2010**, *51*, 5430-5433; selected examples for reductive amination see: d) A. Pagnoux-Ozherelyeva, N. Pannetier, M. D. Mbaye, S. Gaillard, J.-L. Renaud, *Angew. Chem. Int. Ed.* **2012**, *51*, 4976-4980; *Angew. Chem.* **2012**, *124*, 5060-5064; e) S. Moulin, H. Dentel, A. Pagnoux-Ozherelyeva, S. Gaillard, A. Poater, L. Cavallo, J. -F. Lohier, J.-L. Renaud, *Chem. Eur. J.* **2013**, *19*, 17881-17890; f) T.-T. Thai, D.S. Mrel, A. Poater, S. Gaillard, J.-L. Renaud, *Chem. Eur. J.* **2015**, *21*, 7066-7070 selected examples of direct alkylation of amines with alcohols see: g) T. Yan, B. L. Feringa, K. Barta, *Nat. Commun.* **2014**, *5*, 5602-5609; h) A. J. Rawlings, L. J. Diorazio, M. Wills, *Org. Lett.* **2015**, *17*, 1086-1089; i) T. Yan, B. L. Feringa, K. Barta, *ACS. Catal.* **2016**, *6*, 381-388; selected examples of Knölker complexes in dual catalysis; see: j) S. Zhou, S. Fleischer, K. Junge, M. Beller, *Angew. Chem. Int. Ed.* **2011**, *50*, 5120-5124; *Angew. Chem.* **2011**, *123*, 5226-5230; selected examples of chiral Knölker type catalyst k) J. P. Hopewell, J. E. D. Martins, T. C. Johnson, J. Godfrey, M. Wills, *Org. Biomol. Chem.* **2012**, *10*, 134-145; l) P. Gajewski, M. Renom-Carrasco, S. V. Facchini, L. Pignataro, L. Lefort, J. G. de Vries, R. Ferraccioli, A. Forni, U. Piarulli, C. Gennari, *Eur. J. Org. Chem.* **2015**, *9*, 1887-1893; m) A. Berkessel, S. Reichau, A. von der Hçh, N. Leconte, J.-M. Neudçrfl, *Organometallics* **2011**, *30*, 3880-3887
- [21] O. El-Sepelgy, N. Alandini, M. Rueping, *Angew. Chem. Int. Ed.* **2016**, *55*, 13602–13605; *Angew. Chem.* **2016**, *128*, 13800–13803.
- [22] A. Chakraborty, R. Garrison Kinney, J. A. Krause, H. Guan, *ACS Catal.* **2016**, 7855-7864.[23]
- [23] A similar problem with these acyl donors was previously observed in DKR with the Shvo catalyst (see ref. 13)
- [24] The use of K_2CO_3 resulted in background acylation
- [25] Selected example of the use of *Burkholderia cepacia* lipase in the kinetic resolution of alcohols a) A. Horiguchi, K. Mochida *Biosci. Biotech. Biochem.* **1995**, *59*, 1287-1290. b) R. Lihammar, R. Millet, J.-E. Bäckvall *J. Org. Chem.* **2013**, *78*, 12114-12120. c) A. Träff, K. Bogar, M. Warner, J.-E. Bäckvall *Org. Lett.* **2008**, *10*, 4870-4810. (H. S. Bevianakatti, A. A. Banerji *J. Org. Chem.* **1991**, *56*, 5372-5375. An example of kinetic resolution of amines d) R. Varma, S. M. Kasture, B. G. Gaikwad, S. Nene, U. R. Kalkote, *Asian J. Biochem.* **2007**, *2*, 279-283.

Text:

Iron Thrown: Utilization of an *in-situ* activated iron complex as racemization catalyst in the chemoenzymatic dynamic kinetic resolution of *sec*-alcohols is reported. The iron catalyst was evaluated in the racemization and then used in dynamic kinetic resolution of a number of *sec*-alcohols to give enantiomerically pure products in good to high yields.



K. P. J. Gustafson, Arnar Guðmundsson, Kayla Lewis, J.-E. Bäckvall*

Page No. – Page No.

Chemoenzymatic Dynamic Kinetic Resolution of Secondary Alcohols using an Air and Moisture stable Iron Racemization Catalyst