ChemComm

COMMUNICATION

View Article Online
View Journal | View Issue



# Enantioselective hydrogenation of α,β-disubstituted nitroalkenes†‡

Cite this: *Chem. Commun.*, 2014, **50**, 8878

Received 23rd May 2014,
Accepted 16th June 2014

DOI: 10.1039/c4cc03942d

www.rsc.org/chemcomm

Shengkun Li,*[ab] Kexuan Huang[b] and Xumu Zhang*[b]

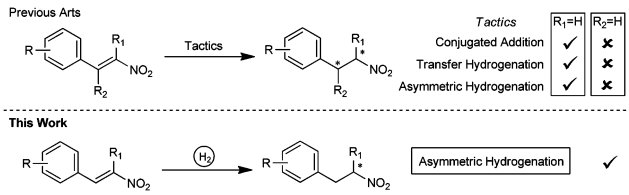
**The first highly chemo- and enantioselective hydrogenation of α,β-disubstituted nitroalkenes was accomplished with rhodium/JosiPhos-$J_2$ as a catalyst, with the yield and enantioselectivity of up to 95% and 94%, respectively. The α-chiral nitroalkanes will provide an entry to valuable chiral amphetamines which are otherwise not so easily accessed.**

Enantioenriched nitroalkanes are valuable intermediates in synthetic chemistry. It can be further converted to other versatile building blocks through simple transformation.[1] The "chameleon" property renders chiral nitroalkanes valuable to the synthesis of pharmaceuticals, agrochemicals and biologically interesting natural compounds. With nitroalkenes as starting materials, considerable progress in biocatalysis,[2] transfer hydrogenation,[3] conjugate additions[1a,4] as well as asymmetric hydrogenation[5] has been made for the synthesis of β-branched nitroalkanes. These tactics seem not to be so efficient or were not reported for the synthesis of α-branched nitroalkanes. In this protocol, synthesis of α-chiral nitroalkanes *via* asymmetric hydrogenation will be disclosed (Scheme 1).

The development of reliable methodologies for the preparation of enantiopure α-branched nitroalkanes is an attractive topic for the synthesis of chiral β-arylisopropylamines(amphetamines), which is the core scaffold of many top best-selling drugs worldwide[6] or natural products[7] (Fig. 1).

Chiral β-arylisopropylamines are conventionally produced through laborious chiral resolution or stoichiometric chiral auxiliary assisted transformation.[8] Though great progress has been made in hydrogenation of β-arylenamides to β-aryl-isopropylamines, these approaches suffer from metal-catalysis, multi-steps, and *E*/*Z* isomeric mixtures in synthesis of substrates.[9] Intensive efforts have been devoted to develop biocatalytic systems to furnish α-branched nitroalkanes.[2a,d,10] Only until recently, Hummel and Gröer disclosed an elegant procedure catalyzed by an ene reductase, which produced the enantioenriched α-chiral nitroalkanes with the enantiomeric excesses of up to 95%.[11]

Considering the environmental compatibility and atom economy, direct asymmetric hydrogenation of α,β-disubstituted nitroalkenes with $H_2$ will be a compelling method for the synthesis of chiral β-arylisopropylamines. The *trans*-nitroalkenes are easily accessible starting from readily available and economically attractive aldehydes and nitroalkanes through the Henry reaction followed by dehydration in one pot with high yields.[2d,10c] The asymmetric hydrogenation of α,β-disubstituted nitroalkenes have met limited progress so far, to the best of our knowledge, only asymmetric hydrogenation of (*E*)-(2-nitroprop-1-en-1-yl)benzene **1a** was reported with the maximum enantioselectivity of 58% under rather harsh conditions.[12] Herein, we will document that




Scheme 1 Transformation of nitroalkenes to chiral nitroalkanes.

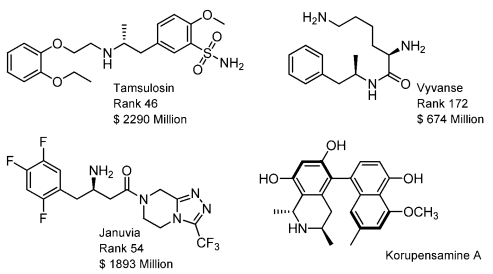
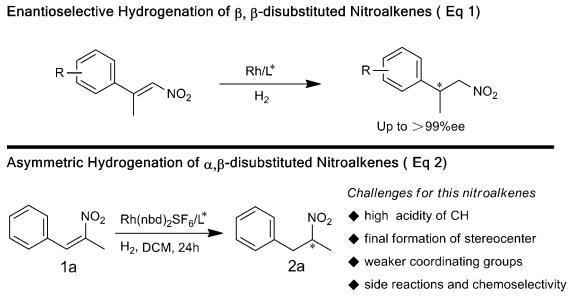



Fig. 1 Structures of drugs and natural products.

[a] *College of Plant Protection, Nanjing Agricultural University, Nanjing 210095, P.R. China. E-mail: saintkun001@njau.edu.cn; Tel: +86-025-84399753*
[b] *Department of Chemistry and Chemical Biology, and Department of Pharmaceutical Chemistry, Rutgers, the State University of New Jersey, Piscataway, New Jersey 08854, USA. E-mail: xumu@rci.rutgers.edu*

† Dedicated to Professor Wenjun Wu on the occasion of his 70th birthday.

‡ Electronic supplementary information (ESI) available: Experimental procedures and analytical data. See DOI: 10.1039/c4cc03942d




Scheme 2 Challenges of hydrogenation of α,β-disubstituted nitroalkenes.

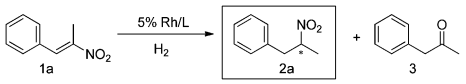
the Rh/JosiPhos-$J_2$ catalyst enables the first highly enantioselective hydrogenation of α,β-disubstituted nitroalkenes, providing α-chiral nitroalkanes with good enantioselectivity of up to 94%.

In our continuing efforts on the transition-metal-catalyzed asymmetric hydrogenation of nitroalkenes, our group reported the first asymmetric hydrogenation of β,β-disubstituted nitroalkenes with a rhodium catalyst and a base assisted practical asymmetric reduction (eqn (1), Scheme 2).[5] However, these established methodologies were not readily translated from β,β-disubstituted nitroalkenes to α,β-disubstituted nitroalkenes, with poor enantioselectivity or low reactivity even at elevated temperature and higher catalyst loading (see ESI‡).

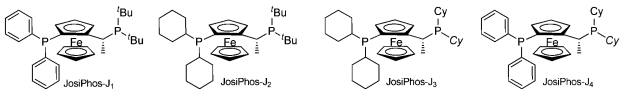
Several critical concerns have been postulated or recognized that have thus far hindered the overall efficiency in asymmetric hydrogenation of α,β-disubstituted nitroalkenes (eqn (2), Scheme 2). (1) The high acidity of the CH adjacent to the nitro group will make the resulting products to racemize easily.[10b] (2) The protonation step of α-carbon is necessary for building up the stereocenter, while it is postulated to proceed in a non-chiral environment following chiral catalyst adduct elimination.[3a] (3) Binding of coordinating groups to metals will synergize with catalysts to enhance the activity and stereocontrol, while the four-membered ring chelates from the α,β-disubstituted nitroalkenes are presumably less stable because of ring strain.[13] (4) Nef reaction, over reduction and isomerization of nitroalkenes will compete with the desired stereogenic transformation.[12,14]

Hence, exploration and progress of the asymmetric hydrogenation of α,β-disubstituted nitroalkenes will be of both fundamental and practical importance. With nitroalkene **1a** as a model substrate, our initial attempts with the previous catalysts were not so satisfying. In an effort to settle this challenging problem, a large and diverse set of chiral ligands were evaluated through a chiral toolbox approach, including both monodentate and bidentate ligands and multitudinous subspecies thereof. With the conversion <5%, the catalysts of rhodium with monodentate phosphine ligands seemed not to be so efficient (see ESI‡). Some representative results for bidentate phosphorus ligands of structure-diversity are shown in Table 1. The rigid P-chiral TangPhos only demonstrated poor enantioselectivity (7%), *albeit* with full conversion (entry 1, Table 1). 30% of the Nef product was detected in the Ph-BPE reaction system (entry 2, Table 1), and the conversion dropped dramatically when it was replaced by BDPP (6% conversion, entry 3, Table 1). The planar chiral ligand PhanePhos furnished

Table 1 Optimization for asymmetric hydrogenation of nitroalkene **1a**[a]




| Entry | Ligand | Conv.[i] | Product distribution[i] 1a | 2a | 3 | ee of 2a[j] |
|---|---|---|---|---|---|---|
| 1 | TangPhos | 95 | 0 | 100 | 0 | 7 |
| 2 | Ph-BPE | 92 | 8.5 | 63.8 | 27.7 | 35 |
| 3 | BDPP | 6 | 94.5 | 5.5 | 0 | 40 |
| 4 | Phanephos | 32 | 67.7 | 32.3 | 0 | 33 |
| 5 | Binap | 84 | 15.9 | 68.2 | 15.9 | 18 |
| 6 | MeO-Biphep | 15 | 84.7 | 15.3 | 0 | 7 |
| 7 | $C_3$-tunephos | 5 | >95 | <5 | | NA |
| 8 | Et-*f*-ketalphos | >95 | 0 | 100 | 0 | 8 |
| 9 | Josiphos-$J_1$ | >95 | 0 | 100 | 0 | 30 |
| 10 | Walphos | 7 | 92.6 | 7.3 | 0 | 42 |
| 11 | Mandyphos | 12 | 88.1 | 11.9 | 0 | 21 |
| 12 | TaniaPhos | 59 | 40.8 | 59.2 | 0 | 59 |
| 13 | Chenphos | 29 | 71.2 | 28.8 | 0 | 4 |
| 14 | Josiphos-$J_1$ | 42 | 57.7 | 42.3 | 0 | 35 |
| 15 | Josiphos-$J_2$ | 24 | 76.2 | 23.8 | 0 | 70 |
| 16 | Josiphos-$J_3$ | 21 | 79.6 | 20.4 | 0 | 33 |
| 17 | Josiphos-$J_4$ | <5 | >95 | <5 | 0 | NA |
| 18[b] | Josiphos-$J_2$ | 38 | 62.3 | 37.7 | 0 | 87 |
| 19[b,c] | Josiphos-$J_2$ | 43 | 56.5 | 43.5 | 0 | 44 |
| 20[b,d] | Josiphos-$J_2$ | <5 | >95 | <5 | 0 | NA |
| 21[b,e] | Josiphos-$J_2$ | <5 | >95 | <5 | 0 | NA |
| 22[b,f] | Josiphos-$J_2$ | 32 | 68.3 | 31.7 | 0 | 49 |
| 23[g] | Josiphos-$J_2$ | 58 | 41.9 | 58.1 | 0 | 86 |
| 24[h] | Josiphos-$J_2$ | >95 | 0 | 100 | 0 | 86 |




[a] Unless otherwise mentioned, all reactions were carried out with a $Rh(nbd)_2BF_4$/ligand/substrate ratio of 1 : 1.1 : 20, under 80 atm $H_2$ in DCM, at 50 °C for 24 h; 14–22: 60 atm, 40 °C, 36 h. [b] $Rh(nbd)_2SbF_6$ as a metal precursor. [c] With 10% $NEt_3$ as an additive. [d] With 10% PTSA as an additive. [e] With 10% L-CSA as an additive. [f] With 50% $CH_3NO_2$ as an additive. [g] 60 atm, 60 °C, 24 h, 5% $Rh(nbd)_2SbF_6$. [h] 50 atm, 70 °C, 36 h, 2.5% $Rh(nbd)_2SbF_6$. [i] The conversion and the molar ratio of product distribution were determined by $^1H$ NMR of the crude product of hydrogenation. [j] Enantiomeric excess was determined by HPLC on a chiral phase. NA: not available; Cy: cyclohexyl; *t*Bu: *tert*-butyl; DCM: dichloromethane.

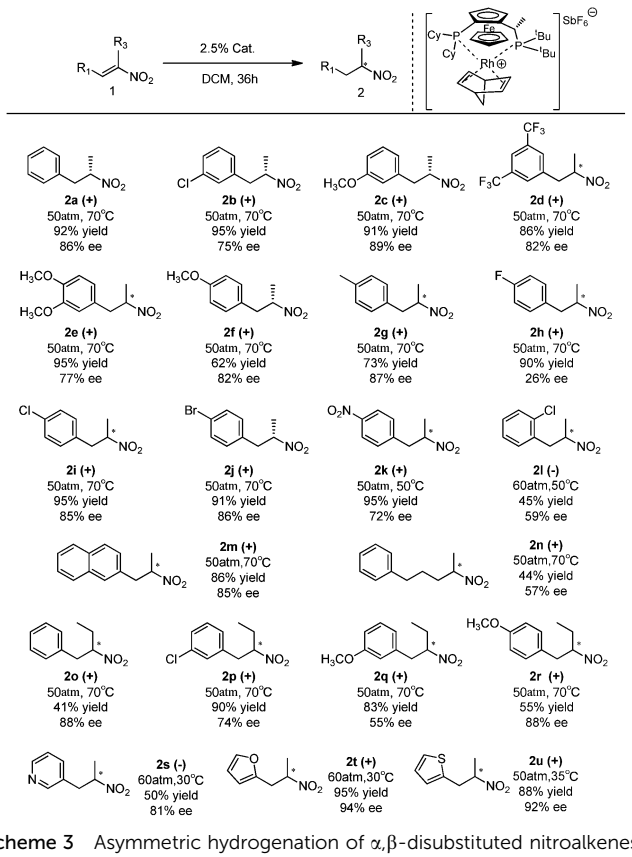
the α-chiral nitroalkane in moderate yield and enantioselectivity (entry 4, Table 1). Besides the negative effect of electron-donating substituents of the atropisomeric biaryl-bisphosphine ligands, the decrease in dihedral angle will lead to similar results on both reactivity and selectivity (entries 5–7, Table 1). The illuminating results were achieved when ferrocene-based ligands were chosen, careful screening protrudes the JosiPhos type ligands (entry 9, Table 1). The reactivity and enantioselectivity showed distinct variation with the steric and electronic factors of the substituents on the phosphorus atom of the JosiPhos ligands, while no clear trends could be concluded (entries 9–17, Table 1, for more information see ESI‡). Considering enantioselectivity and reaction efficiency, JosiPhos-$J_2$ was chosen as the optimal ligand for further optimization of other parameters. Replacement of the counterion $BF_4^-$ by the bulky and weak coordinating $SbF_6^-$ improved the enantioselectivity to 87%, which is already high for this type of reaction (entry 18, Table 1).

Since the efficiency was still not so satisfying (38% conversion), a diverse set of additives, including bases, acids and nitroethane, were evaluated. Unfortunately, no promising results were achieved; the acids can deactivate the catalyst thoroughly (entries 20–23, Table 1). After fine tuning and systematic optimization of reaction parameters, the nitroalkene **1a** was hydrogenated with 86% ee in full conversion (entry 25, Table 1).

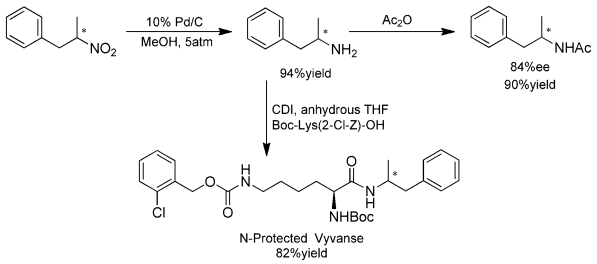
To establish the scope and limitations of this novel catalytic system, a broad range of α,β-disubstituted nitroalkenes were tested under the optimized reaction conditions. Notably, an array of *meta* and *para* substituted nitroalkenes (monosubstituted or disubstituted with electron-withdrawing or electron-donating groups) are amenable to this catalytic system to furnish the optically active nitroalkanes in useful enantioselectivities (**2a–2k**, Scheme 3). Most of the nitroalkenes were hydrogenated enantioselectively independent of the type of substituent. The sharp deterioration in the ee value was detected in the hydrogenation of **1h**, may be due to the distinctive physicochemical properties of fluorine. This process can proceed smoothly keeping the nitro group on the phenyl ring intact (**2k**, Scheme 3).

A dramatic drop in both yield and ee occurs when the *ortho*-chloro nitroalkene was used (**2l**, Scheme 3). This may be ascribed to the competing Nef reaction and the unstable coplanar arrangement of electron delocalized nitro groups, the C=C bond and the aromatic π-system.

It should be noted that 2-naphthylnitroalkene **1m** will furnish the enantioenriched nitroalkane with 86% conversion and 85% ee, respectively (**2m**, Scheme 3). Though the α,β-dialkyl-substituted nitroalkene demonstrated low reactivity, it can also furnish chiral nitroalkane in useful enantioselectivity (**2n**, Scheme 3). With the more hindered ethyl group at the α-position of the α,β-disubstituted nitroalkenes, the substrates can also be hydrogenated with moderate to good enantioselectivities (**2o–2r**, Scheme 3).




Scheme 3 Asymmetric hydrogenation of α,β-disubstituted nitroalkenes.




Scheme 4 Synthesis of chiral amphetamines.

A wide array of heterocyclic substrates are also tolerated (**2s–2u**, Scheme 3). Notably, the furyl, thiophenyl-nitroalkenes were successfully hydrogenated with the enantioselectivity of up to 94% (**2t**) and 92% (**2u**), respectively.

To further demonstrate the utility of this hydrogenation procedure, we turned our attention to scale-up hydrogenation (1.63 g scale for **1a**) and drug synthesis. Valuable chiral amphetamine can be accessed from **2a** directly with a good ee value and excellent yield (84% ee and 90% yield, Scheme 4). It can also be further converted to other drugs easily through simple transformation,[15] for example, the condensation of amphetamine with Boc-Lys(2-Cl-Z)-OH will give the *N*-protected Vyvanse in high yield.

In conclusion, we have accomplished the first rhodium catalyzed highly chemo- and enantioselective hydrogenation of a variety of α,β-disubstituted nitroalkenes. The nitroalkane products provide entry to valuable chiral amphetamine and its derivatives, which are otherwise not so easily accessed in a few steps in view of atom economy and cost-efficiency. Given the relatively high catalyst loading, further work should be carried out with the aim of better understanding the hydrogenation mechanism of this substrate, and ultimately developing catalytic systems that can lead to further improvement in reactivity as well as enantioselectivity.

This research was financially supported by National Institutes of Health (GM58832) and the Scientific Research Foundation for introduced talent of Nanjing Agricultural University for S. Li (020-80900205).

## Notes and references

1 (*a*) O. M. Berner, L. Tedeschi and D. Enders, *Eur. J. Org. Chem.*, 2002, **2002**, 1877; (*b*) O. Noboru and F. Henry, *The Nitro Group in Organic Synthesis*, 2001, pp. 231–268.

2 Representative publications: (*a*) H. S. Toogood, A. Fryszkowska, M. Hulley, M. Sakuma, D. Mansell, G. M. Stephens, J. M. Gardiner and N. S. Scrutton, *ChemBioChem*, 2011, **12**, 738; (*b*) A. Fryszkowska, H. Toogood, M. Sakuma, G. M. Stephens, J. M. Gardiner and N. S. Scrutton, *Catal. Sci. Technol.*, 2011, **1**, 948; (*c*) A. Fryszkowska, H. Toogood, M. Sakuma, J. M. Gardiner, G. M. Stephens and

N. S. Scrutton, *Adv. Synth. Catal.*, 2009, **351**, 2976; (*d*) A. Fryszkowska, K. Fisher, J. M. Gardiner and G. M. Stephens, *J. Org. Chem.*, 2008, **73**, 4295; (*e*) H. S. Toogood, a. Fryszkowska, V. Hare, K. Fisher, A. Roujeinikova, D. Leys, J. M. Gardiner, G. M. Stephens and N. S. Scrutton, *Adv. Synth. Catal.*, 2008, **350**, 2789; (*f*) K. Durchschein, W. M. F. Fabian, P. Macheroux, K. Zangger, G. Trimmel and K. Faber, *Org. Biomol. Chem.*, 2011, **9**, 3364; (*g*) H. S. Toogood, J. M. Gardiner and N. S. Scrutton, *ChemCatChem*, 2010, **2**, 892. And see more references therein.

3 (*a*) Y. Tang, J. Xiang, L. Cun, Y. Wang, J. Zhu, J. Liao and J. Deng, *Tetrahedron: Asymmetry*, 2010, **21**, 1900; (*b*) O. Soltani, M. A. Ariger and E. M. Carreira, *Org. Lett.*, 2009, **11**, 4196; (*c*) C. Czekelius and E. M. Carreira, *Org. Lett.*, 2004, **6**, 4575; (*d*) C. Czekelius and E. M. Carreira, *Angew. Chem., Int. Ed.*, 2003, **42**, 4793; (*e*) J. Xiang, E.-X. Sun, C.-X. Lian, W.-C. Yuan, J. Zhu, Q. Wang and J. Deng, *Tetrahedron*, 2012, **68**, 4609; (*f*) N. J. A. Martin, L. Ozores and B. List, *J. Am. Chem. Soc.*, 2007, **129**, 8976; (*g*) J. F. Schneider, M. B. Lauber, V. Muhr, D. Kratzer and J. Paradies, *Org. Biomol. Chem.*, 2011, **9**, 4323.

4 Representative publications: (*a*) J. Wu, D. M. Mampreian and A. H. Hoveyda, *J. Am. Chem. Soc.*, 2005, **127**, 4584; (*b*) D. M. Mampreian and A. H. Hoveyda, *Org. Lett.*, 2004, **6**, 2829; (*c*) A. Alexakis, C. Benhaim, S. Rosset and M. Humam, *J. Am. Chem. Soc.*, 2002, **124**, 5262; (*d*) A. Alexakis and C. Benhaim, *Org. Lett.*, 2000, **2**, 2579; (*e*) T. Ishii, S. Fujioka, Y. Sekiguchi and H. Kotsuki, *J. Am. Chem. Soc.*, 2004, **126**, 9558; (*f*) Z. Ye, P. M. Jeremiah and H. R. Viresh, *Angew. Chem., Int. Ed.*, 2010, **49**, 153; (*g*) Z.-Q. Wang, C.-G. Feng, S.-S. Zhang, M.-H. Xu and G.-Q. Lin, *Angew. Chem., Int. Ed.*, 2010, **49**, 5780; (*h*) C. Curti, G. Rassu, V. Zambrano, L. Pinna, G. Pelosi, A. Sartori, L. Battistini, F. Zanardi and G. Casiraghi, *Angew. Chem., Int. Ed.*, 2012, **51**, 6200; (*i*) D. Uraguchi, Y. Ueki and T. Ooi, *Chem. Sci.*, 2012, **3**, 842; (*j*) G. Rassu, V. Zambrano, L. Pinna, C. Curti, L. Battistini, A. Sartori, G. Pelosi, F. Zanardi and G. Casiraghi, *Adv. Synth. Catal.*, 2013, **355**, 1881. And see more references therein.

5 (*a*) S. Li, K. Huang, J. Zhang, W. Wu and X. Zhang, *Chem. – Eur. J.*, 2013, **19**, 10840; (*b*) S. Li, K. Huang, B. Cao, J. Zhang, W. Wu and X. Zhang, *Angew. Chem., Int. Ed.*, 2012, **51**, 8573.

6 (*a*) N. A. McGrath, M. Brichacek and J. T. Njardarson, *J. Chem. Educ.*, 2010, **87**, 1348; (*b*) Njardarson Group. Top 200 Pharmaceutical Products by Worldwide Sales in 2009. http://cbc.arizona.edu/njardarson/group/top-pharmaceuticals-poster.

7 G. Bringmann, T. Gulder, T. A. M. Gulder and M. Breuning, *Chem. Rev.*, 2011, **111**, 563.

8 A. Kleemann, J. Engel, B. Kutscher and D. Reichert, *Pharmaceutical Substances: Syntheses, Patents, Applications*, Thieme, Stuttgart, 4th edn, 2001.

9 (*a*) J. Chen, W. Zhang, H. Geng, W. Li, G. Hou, A. Lei and X. Zhang, *Angew. Chem., Int. Ed.*, 2009, **48**, 800; (*b*) S.-F. Zhu, T. Liu, S. Yang, S. Song and Q.-L. Zhou, *Tetrahedron*, 2012, **68**, 7685.

10 (*a*) K. Sakai, A. Nakazawa, K. Kondo and H. Ohta, *Agric. Biol. Chem.*, 1985, **49**, 2331; (*b*) R. R. Bak, A. F. McAnda, A. J. Smallridge and M. A. Trewhella, *Aust. J. Chem.*, 1996, **49**, 1257; (*c*) Y. Kawai, Y. Inab and N. Tokitoh, *Tetrahedron: Asymmetry*, 2001, **12**, 309; (*d*) H. Korbekandi, P. Mather, J. Gardiner and G. Stephens, *Enzyme Microb. Technol.*, 2008, **42**, 308; (*e*) Y. Yanto, C. K. Winkler, S. Lohr, M. Hall, K. Faber and A. S. Bommarius, *Org. Lett.*, 2011, **13**, 2540; (*f*) T. Classen, J. Pietruszka and S. M. Schuback, *ChemCatChem*, 2013, **5**, 711.

11 E. Burda, T. Reß, T. Winkler, C. Giese, X. Kostrov, T. Huber, W. Hummel and H. Grçger, *Angew. Chem., Int. Ed.*, 2013, **52**, 9323.

12 (*a*) Y. Li and T. Izumi, *J. Chin. Chem. Soc.*, 2002, **49**, 505; (*b*) Y. Li and T. Izumi, *J. Chem. Res., Synop.*, 2003, 128.

13 S. Khumsubdee and K. Burgess, *ACS Catal.*, 2013, **3**, 237.

14 K. Durchschein, W. M. F. Fabian, P. Macheroux, K. Zangger, G. Trimmel and K. Faber, *Org. Biomol. Chem.*, 2011, **9**, 3364.

15 P. A. Jass, T. J. Johnson, J. S. Douglas and M. W. Schiesher, US8614346, WO2010148305A1, 2010.