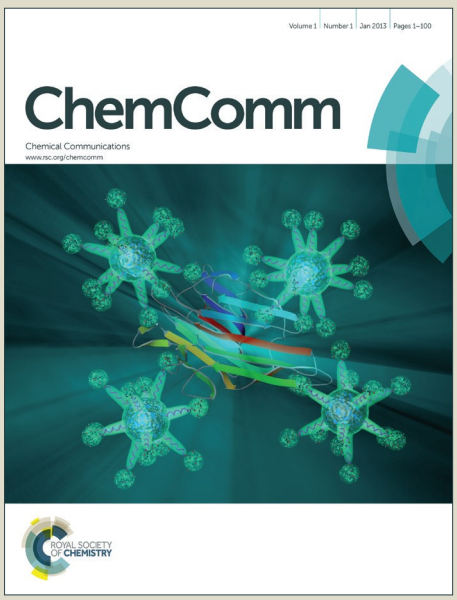
ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: L. Yao, J. Wen, S. Liu, R. Tan, N. M. Wood, W. chen, S. zhang and X. Zhang, *Chem. Commun.*, 2015, DOI: 10.1039/C5CC09089J.



ROYAL SOCIETY OF CHEMISTRY

www.rsc.org/chemcomm

View Article Online
DOI: 10.1039/C5CC09089J

Journal Name

COMMUNICATION

Highly Enantioselective Hydrogenation of α-oxy Functionalized α, β-unsaturated Acids Catalyzed by a ChenPhos-Rh Complex In CF_3CH_2OH

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Lin Yao,[a,b] Jialin Wen,[b] Shaodong Liu,[b] Renchang Tan,[b] Noel Marie Wood,[b] Weiping Chen,*[a] Shengyong Zhang,*[a] and Xumu Zhang*[b]

The rhodium complexes coordinated by Chenphos are very effective catalysts for the enantioselective hydrogenation of α-aryloxy and α-alkoxy-substituted α, β-unsaturated carboxylic acids under mild conditions in CF_3CH_2OH. The catalytic system could be successfully employed in building the core structure of a new FDA approved drug LCZ 696.

Enantiomerically pure α-oxy-functionalized carboxylic acids are useful synthetic intermediates and have important applications in the agrochemical field as crop protection reagents.[1] In addition, they exhibit important pharmacological properties, making them useful as nootropic, analgesic, hypocholesterolemic and hyperlipidemic reagents.[2] Many α-aryloxy and α-alkoxy cinnamic acid derivatives have attracted considerable attention as potential agonists against peroxisome proliferator-activated receptors (PPARs) in the treatment of type Ⅱ diabetes,[3] and several compounds of this class are now in various stages of clinical development. Figure 1 shows selected examples of bioactive compounds containing chiral α-oxy-functionalized carboxylic acids.

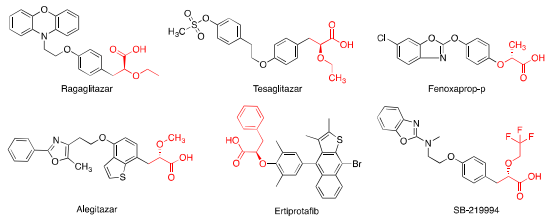


Fig. 1. Selected bioactive compounds derived from chiral α-aryloxy or alkoxy carboxylic acids.

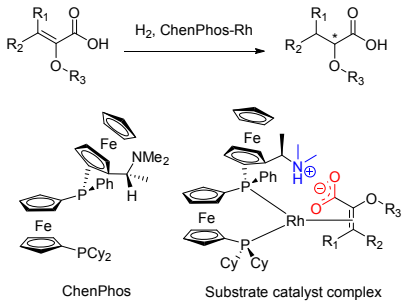
Enantioselective hydrogenation of α,β-unsaturated carboxylic acids by transition metal complexes represents a straightforward way to make these chiral carboxylic acids. Over the past decades, a variety of efficient chiral metal complexes have been developed for the hydrogenation of α-aryl- or α-alkyl-substituted α,β-unsaturated acids with excellent activities and enantioselectivities.[4] However, highly efficient catalysts for the asymmetric hydrogenation of α-aryloxy- or α-alkoxy-substituted α,β-unsaturated acids are limited. Ever since Maligres and Krska's report on the first highly enantioselective hydrogenation of α-aryloxy crotonic acids using Ru-BINAP complexes as catalysts in 2004,[5] several other catalyst systems have been developed for asymmetric hydrogenation of α-oxy-functionalized α,β-unsaturated carboxylic acids. For examples, the Ru/diphosphine complexes [$Ru(OAc)_2$/SFDP] developed by Zhou[6] for the hydrogenation of α-aryloxy crotonic acids and $Ru(OAc)_2$/(*S*)-TMBTP system reported by Puentener[7] for the hydrogenation of α-methoxy cinnamic acids. Rh/diphosphine catalysts such as the Rh-Walphos complexes developed by Houspis[8] and the Rh-Trifer developed by Chen[4p] were employed to asymmetric hydrogenation of α-ethoxy cinnamic acids. The best results were achieved by Zhou[9] with high enantioselectivities in asymmetric hydrogenation of various α-oxy-functionalized α, β-unsaturated acids utilizing a chiral spiro Ir/phosphino-oxazoline complex as catalyst, however, an external base is needed to facilitate the reaction. Thus, considering the importance of the α-oxy-functionalized carboxylic acids, development of truly effective catalysts for this transformation is still highly desirable.

In our ongoing research in asymmetric hydrogenation, we are always interested in developing a novel and highly efficient catalyst to carry out useful transformations. Previously, we reported ChenPhos as ligand in the Rh-catalysed highly efficient asymmetric hydrogenation of α-alkyl-substituted cinnamic acids[4q] and 2-substituted-2-alkenols.[10] The key to our success for ChenPhos is the activation of substrates through a secondary interaction between the ligand and the substrates.

[a] *Department of Medicinal Chemistry, School of Pharmacy, Fourth Military Medical University, 169 Changle West Road, Xi'an, 710032, PR China. Email: wpchen@fmmu.edu.cn; syzhang@fmmu.edu.cn*
[b] *Department of Chemistry & Chemical Biology, Department of Medicinal Chemistry, Rutgers, The State University of New Jersey, 610 Taylor Road, Piscataway, NJ, 08854 (USA). Email: xumu@rci.rutgers.edu*

†Electronic Supplementary Information (ESI) available: experimental procedures, analytic data of the obtained products. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C5CC09089J

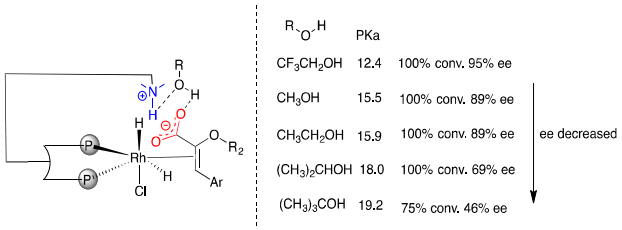


Scheme 1. Asymmetric hydrogenation of α-oxy functionalized α, β-unsaturated acid catalysed by ChenPhos-Rh complex

Following this idea, we envisioned that the metal complex of this ligand should be suitable for the asymmetric hydrogenation of α-oxy functionalized α,β-unsaturated acids (Scheme 1). Herein we document a Rh-ChenPhos complex catalyzed hydrogenation of α-aryloxy and α-alkyloxy α,β-unsaturated acids, affording the corresponding saturated carboxylic acids in high enantioselectivities. There are several advantages of this catalyst system: 1) no external base is needed to achieve high activities and enantioselectivities, comparing to Zhou's Ir catalyst system; 2) high enantioselectivities (up to 99% ee) and high TONs (up to 5000) have been achieved; 3) solvent effect plays a critical role in achieving high ees and a strong ionic interaction can dictate enantioselectivities in an appropriate solvent, such as CF_3CH_2OH.

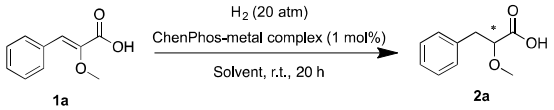
Initially, the (*Z*)-2-methoxy-3-phenylacrylic acid **1a** was chosen as a model substrate. To our delight, hydrogenation of **1a** in the presence of ChenPhos-Rh complex, generated *in situ* from $[Rh(COD)_2]BF_4$ (1.0 mol%; NBD = 2,5-norbornadiene) and ChenPhos (1.1 equivalent with respect to Rh), in methanol under 20 atm of hydrogen pressure at room temperature, gave (*S*)-**2a** with full conversion and 87% ee (Table 1, entry 1). With this encouraging result, various metal precursors were screened. All of other Rh precursors gave similar results, and $[Rh(NBD)Cl]_2$ offered up to 89% ee (entries 1-4). Although an Ir precursor $[Ir(COD)Cl]_2$ gave similar ee value (entry 5), it showed less activities comparing with the Rh species (see ESI†).

Solvent effect plays an important role in asymmetric catalysis, especially for the Rh-catalyzed asymmetric hydrogenation.[11] Firstly, several polar protic solvents MeOH, EtOH, CF_3CH_2OH, *i*-PrOH and *t*-BuOH were tested in this transformation (Scheme 2). Employing CF_3CH_2OH as the



Scheme 2. Solvent effect in the reaction

Table 1. Screening of metal precursors and solvent in asymmetric hydrogenation of α-methyloxy α, β-unsaturated acid by ChenPhos-metal complex[a]



Entry	Metal precursor	Solvent	Conv. (%)[b]	Ee (%)[c]
1	$[Rh(COD)_2]BF_4$	MeOH	100	87
2	$[Rh(NBD)_2]BF_4$	MeOH	100	88
3	$[Rh(NBD)_2]SbF_6$	MeOH	100	87
4	$[Rh(NBD)Cl]_2$	MeOH	100	89
5	$[Ir(COD)Cl]_2$	MeOH	100	88
6[d]	$[Rh(NBD)Cl]_2$	CF_3CH_2OH	100	95
7[e]	$[Rh(NBD)Cl]_2$	CF_3CH_2OH	97	95

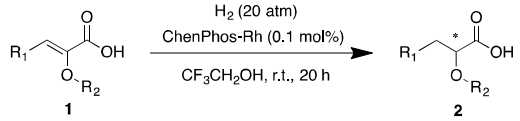
[a]Reaction conditions: 0.2 mmol scale, [substrate] = 0.1 mol/L, solvent = 2 mL, 1.0 mol% of catalyst. [b]Determined by ^1H NMR analysis. [c]Determined by chiral HPLC analysis on a chiral stationary phase. [d]S/C=1000. [e]S/C=5000.

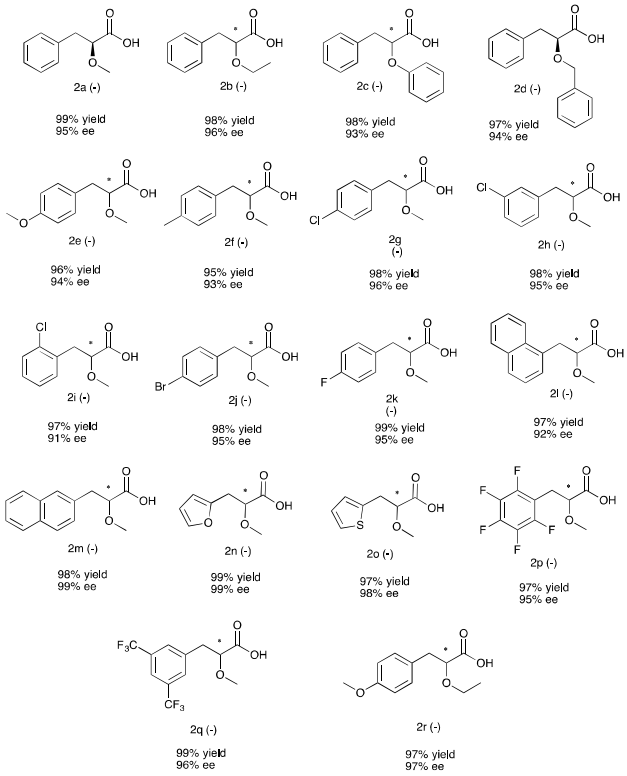
solvent, up to 95% ee was realized. Interestingly, the ee drops dramatically with the increase of the bulkiness and the PKa value of the alcohols. It seems that the alcohol is possibly involved in the ionic interaction. Using an alcohol with proper steric, electronic factors and PKa value, this secondary interaction could be stabilized to dictate the high efficiency of the catalyst; otherwise, unsatisfactory results were obtained. Other solvents, such as nonpolar solvent and polar aprotic solvent tested all gave low catalytic efficiencies and poor ee values (see ESI†). With CF_3CH_2OH as the solvent, complete conversion and up to 95% ee were obtained with 0.1 mol% of $[Rh(Chenphos)Cl]_2$ catalyst. In further test, up to 5000 turnovers were achieved while enantioselectivities remained (entries 6 and 7).

Under an optimal condition with 20 atm of H_2 in CF_3CH_2OH with 0.1 mol% of ChenPhos-Rh complex, hydrogenation of a series of α-oxy functionalized α, β-unsaturated acids were examined at r.t. for 20 h. As shown in Table 2, all the α-aryloxy and α-alkoxy cinnamic acid derivatives were hydrogenated with full conversions. In all these cases, high to excellent enantioselectivities were achieved. The hydrogenation appears to be insensitive to the position and the steric properties of the substituent on the aromatic ring, and both the α-aryloxy and α-alkyloxy α, β-unsaturated acids tested were all successfully hydrogenated to afford the corresponding products with high ees (Table 2, **2a**-**2d**). Especially, using a 2-naphthaldehyde derived unsaturated acid as the substrate, up to 99% ee was realized (**2m**). Importantly, the heteroaromatic ring substituted substrates also gave excellent ees (**2n**, **2o**). Moreover, the obtained chiral products **2d** and **2r** could serve

View Article Online
DOI: 10.1039/C5CC09089J

Table 2. Asymmetric hydrogenation of α-substituted α, β-Unsaturated acid by ChenPhos-Rh complex[a,b]

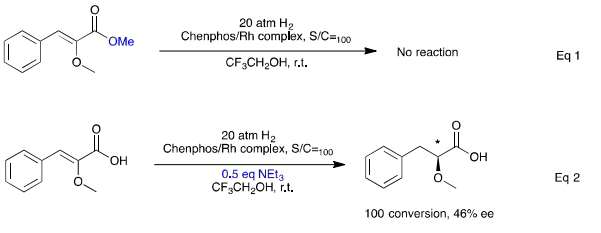




[a]Reaction conditions: 0.2 mmol scale, [substrate] = 0.1 mol/L, solvent = 2 mL, 0.1 mol% of catalyst. Full conversions were obtained in all cases. [b]Determined by chiral HPLC analysis on a chiral stationary phase, the configuration was determined with comparison with literature data.

as the key intermediate in preparation of Ertiprotafib[12] and Ragaglitazar[13] respectively, which are novel PPARa & PPARc agonists proposed for type Ⅱ diabetes. All these results have clearly illustrated the potential value of the developed Chenphos/Rh complex in organic synthesis.

To learn more details about the hydrogenation of unsaturated acids, we carried out two control experiments to verify whether the high enantioselectivities were resulted from the anticipated ionic interaction between the dimethylamino group of the ligand and the carboxylate unit of the substrate. On one hand, using the corresponding unsaturated ester as the substrate, no reaction was detected and all the substrate was recovered under the optimized hydrogenation conditions (Scheme 3, Eq 1); On the other hand, when 50 mol% of NEt_3 was added as additive, while all the substrate was consumed, the enantioselectivity was decreased dramatically to only 46% ee (Eq 2). These results have elucidated our original proposal about the critical role of ionic interaction in this catalyst system to achieve high enantioselectivities.



Scheme 3. Control Experiment Results

The application of the highly enantioselective hydrogenation was demonstrated in the synthesis of the core structure of neprilysin inhibitor Sacubitril (AHU 377), which is one of the compositions in a new FDA approved drug LCZ 696 (see ESI†).

In summary, this work demonstrates that the Chenphos/Rh complex could serve as a highly efficient catalyst system for the asymmetric hydrogenation of α-oxy functionalized α, β-unsaturated acids. Control experiment indicated the ionic interaction between the ligand and substrate plays a vital role for achieving high enantioselectivities in a proper solvent. The potential application of this catalyst system was demonstrated in the model reaction to prepare the core motif of a new drug LCZ 696. Further study of the Chenphos-Rh catalysts for other substrates is under investigation and will be reported in a due course.

We appreciate the National Science Foundation (NSF CHE 0956784), the China Scholarship Council and the National Natural Science Foundation of China (No. 21172262, 21272271) for finantial support.

Notes and references

1 (a) L. Haskelberg, *J. Org. Chem.*, 1947, **12**, 426; (b) K.-C. Joshi and S.-C. Bahel, *J. Ind. Chem. Soc.*, 1960, **37**, 365; (c) G.-W. Mueller-Warrant, *Weed Technol.*, 1991, **5**, 826; (d) A. Kikuo and Y. Kiyotaka, Patent JP 4202168, 1992; (e) N. Mathew, S. Subramanian and M. Kalyanasundaram, *Indian J. Chem.*, 1996, **35**, 40.

2 (a) D.-R.Feller, V.-S.Kamanna, H.-A. Newman, K.-J.Romstedt, D.-T.Witiak, G. Bettoni, S.-H. Bryant, D. Conte-Camerino, F. Loiodice and V. Tortorella, *J. Med. Chem.*, 1987, **30**, 1265; (b) F. Gualtieri, C. Bottalico, A. Calandrella, S. Dei, M.-P. Giovannoni, S. Maelli, M.-N. R omanelli, S. Scapecchi, E. Teodori, N. Galeotti, C. Ghelardini, A. Giotti and A. Bartolini, *J. Med. Chem.*, 1994, **37**, 1712; (c) R. Amoroso, G. Bettoni, M.-L. Tricca, F. Loiodice and *S. Ferorelli, Il Farmaco*, 1998, **53**, 73.

3 (a) T.-M.Willson, P.-J.Brown, D.-D.Sternbach and B.-R.Henke, *J. Med. Chem.*, 2000, **43**, 527; (b) K. Liu, J.-S. Smith, A.-H. Ayscue, B.-R.Henke, M.-H. Lambert, L.-M. Leesnitzer, K.-D. Plunket, T.-M.Willson and D.-D. Sternbach, *Bioorg. Med. Chem. Lett.*, 2001,**11**, 2385; (c) B.-R. Henke, *J. Med. Chem.*, 2004, **47,** 4118; (d) J. Aubert, L. Clary, P. Mauvais, M. Rivier, E. Thoreau and J.-G. Boiteau, Patent WO108352, 2005; (e) S. Shrestha, B.-R. Bhattarai, H. Cho, J. -K. Choi and H. Cho, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 2728.

4 For representative reviews see: (a) W.-J.Tang and X.-M. Zhang, *Chem. Rev.*, 2003, **103,** 3029; (b) J.-H. Xie and Q.-L. Zhou, *Acta Chim. Sinica*, 2012, **70**, 1427; (c) S. Khumsubdee, K. Burgess, *ACS Catal.*, 2013, **3**, 237; (d) J. verendel, O. -P. Oscar, M. -M. Dieeguez and P. - J. Anderson, *Chem. Rev.*, 2014, **114**, 2130. For representative examples, see: (e) T. Ohta, H. Takaya, M. Kitamura, K. Nagai and R. Noyori, *J. Org. Chem.*, 1987, **52**, 3174; (f) T. Uemura, X. Zhang, K.

View Article Online
DOI: 10.1039/C5CC09089J

Journal Name

COMMUNICATION

Matsumura, N. Sayo, H. Kumobayashi, T. Ohta, K. Nozaki and H.T akaya, *J. Org. Chem.*, 1996, **61**, 5510; (g) I. Yamada, M. Yamaguchi and T. Yamagishi, *Tetrahedron: Asymmetry,* 1996, **7**, 3339. (h) T. Benincori, E. Cesarotti, O. Piccolo and F. Sannicolo, *J. Org. Chem.*, 2000, **65**, 2043; (i) C.-C.Pai, C.-W. Lin, C.-C. Lin, C.-C. Chen, A.-S.-C. Chan and W.-T. Wong, *J. Am. Chem. Soc*., 2000, **122**, 11513; (j) T. Sturm, W. Weissen-Steiner and F. Spindler, *Adv. Synth. Catal*., 2003, **345**, 160; (k) X. Cheng, Q. Zhang, J.-H. Xie, L.-X. Wang and Q.-L. Zhou, *Angew. Chem., Int. Ed.*, 2005, **44**, 1118; (l) T.-T.Co, S.-C. Shim, C.-S. Cho, T.-J. Kim, S.-O. Kang, W.-S. Han, J. Ko and C.-K. Kim, *Organometallic*s, 2005, **24**, 4824; (m) R. Hoen, J.-A.-F. Boogers, H. Bernsmann, A.-J. Minnaard, A. Meetsma, T.-D.-A..Tiemersma-Wegman, H.-M. de Vries, J.-G. de Vries and B.-L. Feringa, *Angew. Chem., Int. Ed.*, 2005, **44**, 4209; (n) A. Scrivanti, S. Bovo, A. Ciappa and U. Matteoli, *Tetrahedron Lett.*, 2006, **47**, 9261; (o) L. Qiu, Y.- M. Li, F.-Y. Kwong, W.-Y. Yu, Q.-H. Fan, and A.-S.-C. Chan, *Adv. Synth. Catal.*, 2007, **349**, 517; (p) W.-P Chen, P.-J. McCormack, K. Mohammed, W. Mbafor, S.-M. Roberts and J. Whittall, *Angew. Chem. Int. Ed.*, 2007, **46**, 4141; (q) W.-P.Chen, F. Spindler, B. Pugin and U. Nettekoven, *Angew. Chem. Int. Ed.*, 2013, **52**, 8652.

5 P.-E. Maligres, S.-W. Krska and G.-R. Humphrey, *Org. Lett.*, 2004, **6**, 3147.

6 X. Cheng, J.-H. Xie, S. Li and Q.-L. Zhou, *Ad. Synth. Catal.*, 2006, **348**, 1271.

7 K. Puentener, M. Scalone, U.S. Patent 070714, 2005.

8 I.-N. Houpis, L.-E Patterson, C.-A. Alt, J.-R. Rizzo, T.-Y. Zhang and M. Haurez, *Org. Lett.*, 2005, **7**, 1947.

9 S. Li, S.-F. Zhu, J.-H. Xie, S. Song, C.-M. Zhang and Q.-L. Zhou, *J. Am. Chem. Soc.*, 2010, **132**, 1172.

10 Q.-J. Wang, X.-Y.Liu, X. Liu, B. Li, H.-F. Nie, S.-Y. Zhang and W.-P. Chen, *Chem. Commun*, 2014, **50**, 978.

11 C.-J. Cobley and P.-H. Moran, in *The Handbook of Homogeneous Hydrogenation*. de Vries J. G.; Elsevier, C. J. Ed. Wiley, Weinheim, 2007, 773.

12 (a) Wyeth, U.S. Patent 0187980, 2002; (b) R.-H. Huijsduijnen, W.-H.-B. Sauer, A. Bombrun and D. Swinnen, *J. Med. Chem.*, 2004, **47**, 4142; (c) D.-V. Erbe, S.-Y. Wang, Y.-L. Zhang, K. Harding, L. Kung, M. Tam, L. Stolz, Y.-Z. Xing, S. Furey, A. Qadri, L. Klaman and J.-F. Tobin, *Molecular Pharmacology*, 2005, **67**, 69; (d) L. Bialy and H. Waldmann, *Angew. Chem., Int. Ed.*, 2005, **44**, 3814; (e) S. Shresthaa, B.-R. Bhattaraia, H. Chob, J.-K. Choib and H. Cho, *Bioorg. Med. Chem. Lett*., 2007, 17, 2728; (f) K. Otake, S. Azukizawa, M. Fukui, M. Shibabayashi, H. Kamemoto, T. Miike, M. Kasai and H. Shirahase, *Chemical and Pharmaceutical Bulletin*, 2011, **59**, 1233; (g) S. Thareja, S. Aggarwal and M. Kumar, *Medicinal Research Reviews*, 2012, **32**, 459.

13 (a) S. Ebdrup, I. Pettersson, H.-B. Rasmussen, H.-J. Deussen, A.-F. Jensen, S.-B. Mortensen, J. Fleckner, L. Pridal, L. Nygaard and P. Sauerberg, *J. Med. Chem.*, 2003, **46**, 1306; (b) Z.-F. Cai, J. Feng, Y.-S. Guo, P.-P. Li, Z.-F. Shen, F.-M. Chu and Z.-R. Guo, *Bioorg. Med. Chem.*, 2006, **14**, 866; (c) S. Samuelsson, S. Johansson, S. Halldorsdottir, H. Stenhoff and K.-P. Oehman, *J. Clin. Pharmacol,* 2006, **46**, 1017; (d) D. Chaturvedi, S. Ray, A.-K. Srivastava and R. Chander, *Bioorg. Med. Chem.*, 2008, **16**, 2489; (e) M.-V.-S. Varma, R.-S. Obach, C. Rotter, H.-R. Miller, G. Chang, S.-J. Steyn and M.-D. Troutman, *J. Med. Chem.,* 2010*,* **53***,* 1098; (f) D.-K. Nevin, M.-B. Peters, G. Carta, D. Fayne and D.-G. Lloyd, *J. Med. Chem.,* 2012*,* **55***,* 4978.