ChemPubSoc Europe

DOI: 10.1002/chem.201503229

CHEMISTRY
A European Journal
Communication

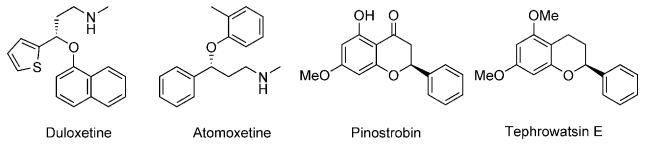
Asymmetric Catalysis

Minimizing Aryloxy Elimination in Rh^{I}-Catalyzed Asymmetric Hydrogenation of β-Aryloxyacrylic Acids using a Mixed-Ligand Strategy

Yang Li,[a] Zheng Wang,[a] and Kuiling Ding*[a, b]

Abstract: The first example of efficient asymmetric hydrogenation of challenging β-aryloxyacrylic acids was realized using a Rh^{I}-complex based on the heterocombination of a readily available chiral monodentate secondary phosphine oxide (SPO) and an achiral monodentate phosphine ligand as the catalyst. Excellent enantioselectivities (92–>99% *ee*) were achieved for a wide variety of chiral β-aryloxypropionic acids with minor aryloxy elimination in most cases. The resultant products were readily transformed into biologically active compounds through simple synthetic manipulations.

Asymmetric hydrogenation (AH) of β-aryloxy acrylic acids to directly afford optically active β-aryloxypropionic acids, one type of key structural element in a broad range of pharmaceuticals, bioactive compounds, and natural products (Scheme 1),[1–5] remains largely unexplored probably due to the difficulty associated with easy aryloxy elimination in the hydrogenation to give undesired achiral 3-aryl propionic acid derivatives,[6] despite the fact that a number of chiral catalysts have been successfully developed for AH of various substituted acrylic acids[7] including β-alkoxyacrylic amide or esters.[6,8] Herein, we communicate our results on the first example of highly efficient AH of β-aryloxyacrylic acids, using a Rh^{I} catalyst based on the heterocombination of a readily available chiral monodentate secondary phosphine oxide (SPO) and an achiral monodentate phosphine ligand. Excellent enantioselectivities (92–>99% *ee*) were attained for a variety of chiral β-aryloxypropionic acids with minor aryloxy elimination in most cases, some of which were transformed into biologically active compounds through simple synthetic manipulations.



Scheme 1. Representative pharmaceuticals, bioactive molecules, and natural products derived from β-aryloxypropionic acids.

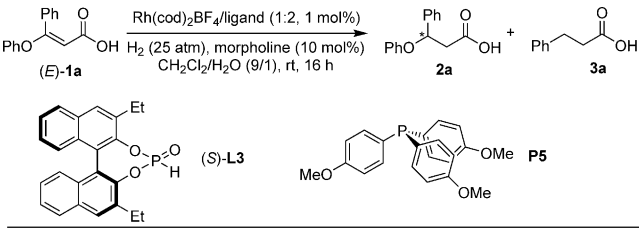
Secondary phosphine oxide (SPO) has been widely used as a preligand in a number of transition metal-catalyzed reactions,[9] and recently our group reported the successful applications of chiral SPO preligands in Rh^{I}-catalyzed AH of unsaturated phosphonic acids and carboxylic acids.[10] These results inspired us to explore the feasibility of using a Rh^{I}/SPO system for AH of β-aryloxyacrylic acids. The initial tests for AH of (*E*)-3-phenoxycinnamic acid [(*E*)-**1a**] using the catalysts generated in situ from $[Rh(cod)_2]BF_4$ (1.0 mol%) and a variety of chiral SPO ligands (2.0 mol%) only resulted in poor substrate conversions and low to moderate enantioselectivities for hydrogenation product **2a**, along with a significant amount of byproduct **3a** generated by phenoxy elimination (Table S1 in the Supporting Information), indicating the challenging nature of this type of substrates. A breakthrough in catalyst screening was eventually realized by using chiral/achiral mixed ligands (Tables S2–S4 vs. S1 in the Supporting Information). We thus decided to test the mixed-ligand strategy[10b,c,11,12] for AH of (*E*)-**1a** using Rh^{I}/SPO/PPh_3 (1.0 mol% Rh) as the catalyst. A comprehensive screening of chiral SPO ligands **L1**–**L6** and achiral triarylphosphine ligands (**P1**–**P7**), metal/ligand ratios, H_2 pressure, base additives, and solvents (Tables S2 and S3 in the Supporting Information) disclosed the importance of fine-tuning stereoelectronic properties of the component ligands and the reaction conditions for chemo and enantioselectivities of the catalysis. Ultimately, the 1:1 combination of SPO ligand (*S*)-**L3** with $(4\text{-}MeOC_6H_4)_3P$ (**P5**) turned out to be the best partners, affording **2a** in high chemoselectivity (**2a**/**3a** = 90/10) with >99% *ee* (Scheme 2).

Under the optimized reaction conditions, AH of an array of (*E*)- or (*Z*)-β-aryloxyacrylic acids **1a**–**v** and (*Z*)-β-methoxyacrylic acid **1w** were investigated with $[Rh(cod)_2]BF_4$/(*S*)-**L3**/**P5** (1:1:1, 1.0 mol% Rh^{I}) as catalyst, and the results are summarized in Table 1. The AH reaction proceeded smoothly to afford the corresponding β-aryloxy- or methoxy-propionic acids **2a**–**w** with generally good to high chemoselectivities (entries 1–26). It is remarkable that the catalyst system tolerates both electronic and steric modifications of the substituents on the β,β-posi-

[a] Dr. Y. Li, Dr. Z. Wang, Prof. Dr. K. Ding
State Key Laboratory of Organometallic Chemistry
Shanghai Institute of Organic Chemistry
Chinese Academy of Sciences
345 Lingling Road, Shanghai 200032 (P. R. China)
Fax: (+21) 6416-6128
E-mail: kding@mail.sioc.ac.cn

[b] Prof. Dr. K. Ding
Collaborative Innovation Center of Chemical Science and Engineering
(Tianjin), Tianjin 300071 (P. R. China)

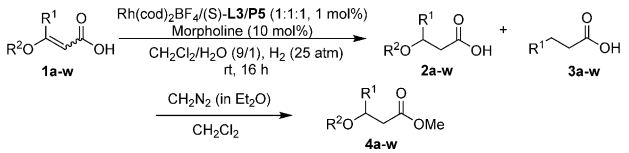
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201503229.



	conv of (*E*)-**1a**	**2a**/**3a**	*ee* of **2a**
(*S*)-**L3** (2 mol%)	trace	--	--
P5 (2 mol%)	68%	100/0	--
(*S*)-**L3**/**P5** (1/1, 2 mol%)	>99%	90/10	99%

Scheme 2. A heterocombination of chiral SPO with achiral (p-$MeOC_6H_4)_3P$ (**P5**) makes a difference in Rh^I-catalyzed AH of of β-phenoxy-β-phenyl acrylic acid (*E*-**1a**).

Table 1. Rh^I/(*S*)-**L3**/**P5**-catalyzed AH of β-aryloxyacrylic acids **1a**–**w**.[a]

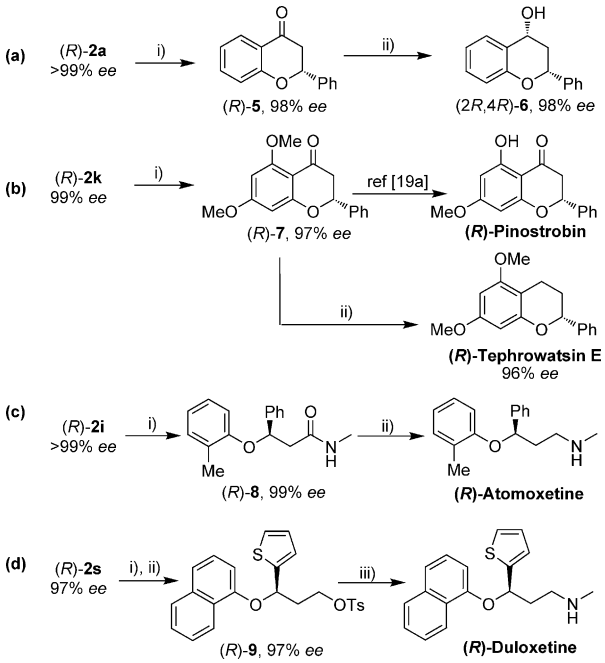


Entry	Substrate	R^1	R^2	**2**/**3**	Yield [%]	*ee* [%]
1	(*E*)-**1a**	Ph	Ph	90/10	87	>99(*R*)
2	(*Z*)-**1a**	Ph	Ph	88/12	85	96(*S*)
3	(*E*)-**1b**	Ph	4-MeC_6H_4	92/8	88	>99(+)
4	(*E*)-**1c**	Ph	4-$MeOC_6H_4$	90/10	87	>99(+)
5	(*E*)-**1d**	Ph	4-FC_6H_4	83/17	80	99(+)
6	(*E*)-**1e**	Ph	4-ClC_6H_4	77/23	75	98(+)
7	(*E*)-**1f**	Ph	4-BrC_6H_4	77/23	74	99(+)
8	(*E*)-**1g**	Ph	4-$CF_3C_6H_4$	70/30	68	98(*R*)
9	(*E*)-**1h**	Ph	3-IC_6H_4	81/19	78	98(−)
10[b]	(*E*)-**1i**	Ph	2-MeC_6H_4	94/6	90	>99(*R*)
11[b]	(*Z*)-**1i**	Ph	2-MeC_6H_4	92/8	86	98(*S*)
12[b]	(*E*)-**1j**	Ph	2-$MeOC_6H_4$	90/10	89	>99(+)
13	(*E*)-**1k**	Ph	3,5-di-$MeOC_6H_3$	90/10	86	99(*R*)
14	(*E*)-**1l**	Ph	1-naphthyl	88/12	85	99(−)
15[b]	(*E*)-**1m**	2-MeC_6H_4	Ph	96/4	94	>99(−)
16[b]	(*Z*)-**1m**	2-MeC_6H_4	Ph	79/21	77	98(+)
17	(*E*)-**1n**	3-MeC_6H_4	Ph	92/8	89	>99(−)
18	(*E*)-**1o**	4-MeC_6H_4	Ph	88/12	85	>99(+)
19	(*E*)-**1p**	4-$MeOC_6H_4$	Ph	83/17	81	95(+)
20	(*E*)-**1q**	4-FC_6H_4	Ph	86/14	82	98(−)
21[b]	(*E*)-**1r**	3,4-di-$MeOC_6H_3$	2-$MeOC_6H_4$	81/19	77	98(+)
22[b,c]	(*E*)-**1s**	2-thienyl	1-naphthyl	70/30	67	97(*R*)
23[d]	(*E*)-**1t**	Me	Ph	97/3	92	97(*S*)
24[d]	(*E*)-**1u**	Me	4-$MeOC_6H_4$	97/3	94	96(+)
25[d]	(*E*)-**1v**	Me	1-naphthyl	98/2	94	98(+)
26	(*Z*)-**1w**	Ph	Me	98/2	93	92(*S*)
27[e]	(*E*)-**1a**	Ph	Ph	89/11	87	98(*R*)

[a] Reaction conditions: [**1**] = 0.125 M. All conversions (>99%) and molar ratios of **2**/**3** were determined by ^1H NMR analysis of the crude reaction mixtures. The *ee* values of **2a**–**w** were determined by chiral HPLC analysis of their corresponding methyl esters **4a**–**w**, and the yields were based on the isolated **4a**–**w**. [b] 20 mol% morpholine. [c] CH_2Cl_2/THF/H_2O (7:2:1) was used as the solvent. [d] The free acids (*S*)-**2t**–**v** were isolated. [e] (*E*)-**1a** (0.6 g), 0.1 mol% catalyst loading, H_2 (50 atm), 24 h.

tions, affording the corresponding β-aryloxy- or methoxypropionates **4a**–**w** in consistently excellent enantioselectivities (92–>99% *ee*), albeit with varied isolated yields (67–94%), dependent on the extent of aryloxy elimination. It is noteworthy that under otherwise identical conditions, AH of the (*E*)- and (*Z*)-isomers of **1a**, **1i**, and **1m** gave their corresponding products **2a**, **2i**, and **2m**, respectively, with high *ee* values (>96%) but in the opposite sense of chiral induction (entries 1 vs. 2, 10 vs. 11, and 15 vs. 16). Substrate (*E*)-**1s** with a heteroaryl 2-thienyl group at β-position was also hydrogenated smoothly in CH_2Cl_2/THF/H_2O (7:2:1) as a mixed solvent, affording the corresponding β-thien-2-yl substituted propanoic acid **2s** with 97% *ee* (entry 22). Furthermore, the AH of substrates with an alkyl [methyl, (*E*)-**1t**–**v**] or alkoxy [methoxy, (*E*)-**1w**] at β-position have also been successful, affording the corresponding products **2t**–**v** and **2w**, respectively, with excellent *ee* values (entries 23–25 and 26). Finally, the catalyst loading could be lowered to 0.1 mol% for AH of (*E*)-**1a** under a higher H_2 pressure (50 atm), affording (*R*)-**2a** in high yield with 98% *ee* (entry 27).

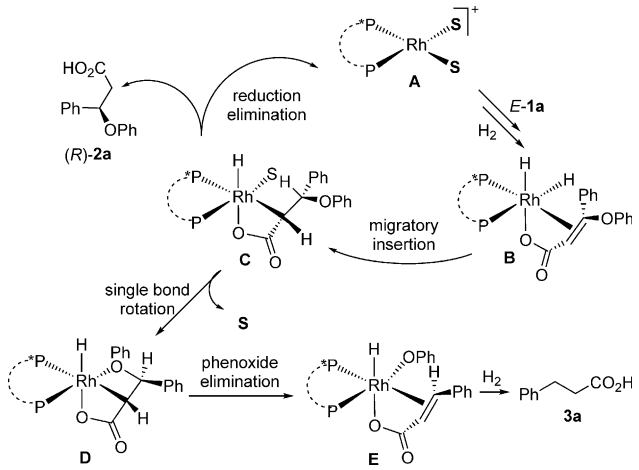
To highlight the synthetic utility of the methodology, the efforts were made using the hydrogenation products for the asymmetric synthesis of some useful chiral molecules, including several pharmaceuticals and bioactive flavanoids. Treatment of product (*R*)-**2a** with trifluoroacetic acid and trifluoroacetic acid anhydride afforded flavanone (*R*)-**5** through Friedel-Crafts acylation in 84% yield with 98% *ee*, which upon reduction with $NaBH_4$ gave the flavanol (2*R*,4*R*)-**6** in 87% yield and 95:5 d.r. without loss of optical purity (Scheme 3a).[1c] Intramolecular Friedel–Crafts acylation of (*R*)-**2k** under similar conditions furnished 5,7-dimethoxyflavanone (*R*)-**7** (97% *ee*), which, on selective demethylation using a literature procedure, would



Scheme 3. Transformation of the AH products to flavanone (*R*)-**5** and flavanol (2*R*,4*R*)-**6** (a), (*R*)-Pinostrobin and (*R*)-Tephrowatsin E (b), (*R*)-Atomoxetine (c), and (*R*)-Duloxetine (d). Conditions: a) i) TFA/TFAA, CH_2Cl_2, rt, 0.5 h, 84%; ii) $NaBH_4$, THF, rt, 12 h, 87%. b) i) TFA/TFAA, CH_2Cl_2, rt, 0.5 h, 70%; ii) Pd/C (10%), H_2, MeOH, 10 h, 85%. c) i) $MeNH_2$, HOBt, EDCI, NMM, CH_2Cl_2, rt,10 h, 84%; ii) BH_3, THF, reflux, 5 h, 69%. d) i) $NaBH_4/I_2$, THF, rt, 2 h; ii) *p*-TsCl/NEt_3, CH_2Cl_2, rt, 24 h, 61% for two steps; iii) $MeNH_2$, THF, reflux, 24 h, 60%.

give (*R*)-Pinostrobin (Scheme 3b).[14] Hydrogenolytic removal of ketone oxygen in (*R*)-**7** with Pd/C catalysis under 10 atm H_2 afforded (*R*)-Tephrowatsin E in 85% yield with 96% *ee* (Scheme 3b). An efficient route to (*R*)-Atomoxetin[15] has also been developed through amidation of (*R*)-**2i** with $MeNH_2$ followed by reduction with borane (Scheme 3c). Finally, (*R*)-**2s** was readily transformed into (*R*)-Duloxetine[16] through a three-step sequence without loss of optical purity (Scheme 3d).

It has been disclosed that switch of substrate configuration from *E*- to *Z*- or vice versa allows the access of both enantiomers of the products with the same catalyst (entries 1 vs 2, 10 vs 11, and 15 vs 16 in Table 1). This fact implies that the substrate most likely binds to the Rh center in a chelating mode through its vinyl and carboxylate moieties, so that the catalyst can effectively differentiate the enantiotopic faces of the alkene on the basis of the orientation of the carboxylic group.[10b,13,17] As shown in Scheme 4, a Rh species (complex **A**)



Scheme 4. Plausible mechanistic pathways for the asymmetric hydrogenation and phenoxy elimination. The relative positions of P* and P in the catalytic intermediates are uncertain and might be reversed.

generated under the catalytic conditions consisting of a heterocombination of a chiral SPO (P*) and an achiral phosphine (P) is most likely an intermediate step to the chiral hydrogenation product. In fact, ESI-MS analyses of the reaction systems prior to hydrogenation have unambiguously established the formation of hetero-ligand Rh complexes in the solution (Figures S2–S6 in the Supporting Information). The formation of substrate-bound Rh dihydride **B**, the transformation of **B** to an Rh alkyl intermediate **C**, and reductive elimination of **C** to afford the normal product (*R*)-**2a** and regenerate catalyst **A** follow the general pathway of Rh-catalyzed hydrogenation of olefins. However, on the other hand, the ligand substitution of a solvent molecule (S) in **C** by phenoxy group would give intermediate **D**, which undergoes β-phenoxy elimination and hydrogenation, leading to the formation of the byproduct **3a**. The control experiments (Scheme S1 in the Supporting Information) indicate that phenoxy elimination should have occurred through an intermediate inside the catalytic cycle rather than through an alternative secondary hydrogenation of (*R*)-**2a**, providing the circumstantial evidence for the assumed pathway above. This mechanistic proposal suggests that the electron density on the Rh atom would have a significant effect on the bifurcated reactivity of **C**, and an electron-rich Rh center in intermediate **C** should disfavor the formation of **D**, and thus may partially depress the phenoxy elimination pathway. This implication was verified by a comparison of the results using a heterocombination of a relatively electron-rich triarylphosphine and an electron-poor SPO ligand (Table S4 in the Supporting Information) and those using electron-poor SPO ligand alone (Table S1 in the Supporting Information), with the former often giving less phenoxy elimination products than the latter. In addition, comparative reaction profile studies also established that use of the Rh hetero-ligand complex resulted in a substantial rate enhancement compared to the reactions using Rh homo-ligand complexes (Figures S7 and S8 in the Supporting Information), indicating the synergistic effect of component ligands with push-pull electronic properties.

In conclusion, a range of challenging β-aryloxyacrylic acids has been hydrogenated with high chemo- and enantioselectivities using a catalyst generated in situ from $[Rh(cod)_2]BF_4$, an electron-poor chiral SPO ligand (*S*)-**L3**, and an electron-rich achiral triarylphospine ligand $[(4\text{-}MeOC_6H_4)_3P]$, affording various β-aryloxypropionic acids with minor aryloxy elimination in most cases. This methodology has also been successfully applied to the concise synthesis of several bioactive molecules, including (*R*)-Duloxetine, (*R*)-Atomoxetin, (*R*)-Pinostrobin, and (*R*)-Tephrowatsin E. The mechanistic understanding of the aryloxy elimination pathway in combination with the impacts of component ligands on the phenoxy elimination and catalytic efficiency of the process disclosed in the present work might stimulate future efforts to address the issue of aryloxy elimination in the related catalytic systems.

Experimental Section

Typical procedure for $[Rh(cod)_2]BF_4$/(*S*)-**L3**/$(4\text{-}MeOC_6H_4)_3P$ catalyzed asymmetric hydrogenation of (*E*)-3-phenoxy-3-phenylacrylic acid (*E*)-**1a**: To a vial containing a suspension of substrate (*E*)-**1a** (0.5 mmol, 1 equiv) in dichloromethane/H_2O (2.6/0.4 mL) was added morpholine (4.4 μL, 0.05 mmol, 0.1 equiv), and the resulting mixture was stirred at rt for 10 min to form the substrate solution. Into a Schlenk tube were added chiral monodentate secondary phosphine oxide preligand (*S*)-**L3** (2.0 mg, 0.005 mmol, 0.01 equiv), $[Rh(cod)_2]BF_4$ (2.0 mg, 0.005 mmol, 0.01 equiv), tris(4-methoxyphenyl)phosphine (**P5**, 0.005 mmol, 0.01 equiv), and dichloromethane (1.0 mL) under argon atmosphere. The resulting mixture was stirred for 10 min at rt to give the precatalyst solution, which was transferred into the vial containing the substrate solution. The vial was transferred into a Parr steel autoclave in a glove box. The autoclave was sealed and purged three times with hydrogen, before finally being pressurized to the specified pressure of hydrogen (25 atm). The reaction mixture was stirred at rt for the specified period of time (16 h). The hydrogen gas was released in a hood, and the conversion of (*E*)-**1a** and the relative amount of the hydrogenation and phenoxide elimination products (**2a**/**3a** molar ratio) were determined by ^1H NMR analysis of an aliquot of the mixture. The product mixture was esterified with CH_2N_2 to give the corresponding methyl esters, which were isolated by silica gel chroma-

tography (EA/petroleum ether = 1/30) to give **4a**. The *ee* of the product (*R*)-**2a** was determined by chiral HPLC analysis of (*R*)-**4a**: colorless oil, 87% yield, >99% ee; $[\alpha]_D^{25} = -3.5$ (c 1.0, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): $\delta = 7.39–7.37$ (m, 2H), 7.32–7.24 (m, 3H), 7.15 (t, $J = 8.0$ Hz, 2H), 6.87–6.84 (m, 3H), 5.63 (dd, $J = 9.2$, 4.4 Hz, 1H), 3.65 (s, 3H), 3.04 (dd, $J = 15.6$, 9.2 Hz, 1H), 2.76 (dd, $J = 15.6$, 4.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 170.7$, 157.6, 140.3, 129.2, 128.6, 127.9, 125.9, 121.1, 116.1, 76.6, 51.7, 43.5 ppm; FTIR (neat) $\nu = 3087$, 3063, 3030, 2951, 2845, 1736, 1596, 1587, 1490, 1226, 1165, 1025, 751, 690 cm^{-1}; HRMS (ESI) *m/z*: calcd. for $C_{16}H_{20}NO_3^+$: 274.1438; found: 274.1442 $[M + NH_4]^+$.

Procedure for asymmetric hydrogenation of (*E*)-**1a** under a catalyst loading of 0.1 mol%: the procedure was generally similar to that described above with a slight modification in conditions: (*E*)-**1a** = 0.60 g (2.5 mmol), total dichloromethane/H_2O (9:1) volume = 8.0 mL, morpholine (0.5 mmol), with hydrogen pressure of 50 atm and reaction time of 24 h. (*R*)-**4a** was isolated in 87% yield with 98% *ee*.

Acknowledgements

Funding for this project was provided by NSFC (grant nos.: 21121062, 21232009, 91127041), the Chinese Academy of Sciences, and the Science and Technology Commission of Shanghai Municipality.

Keywords: asymmetric catalysis · hydrogenation · rhodium · secondary phosphine oxide · β-aryloxyacrylic acids

[1] For examples, see: a) A. Lévai, J. Ott, G. Snatzke, *Monatsh. Chem.* **1992**, *123*, 919; b) W. H. Miles, E. S. Fialcowitz, H. S. Halstead, *Tetrahedron* **2001**, *57*, 9925; c) M. Kawasaki, H. Kakuda, M. Goto, S. Kawabataa, T. Kometani, *Tetrahedron: Asymmetry* **2003**, *14*, 1529; d) A. Kamal, G. B. R. Khanna, R. Ramu, T. Krishnaji, *Tetrahedron Lett.* **2003**, *44*, 4783; e) R. K. Rej, T. Das, S. Hazra, S. Nanda, *Tetrahedron: Asymmetry* **2013**, *24*, 913; f) C. A. Lipinski, C. E. Aldinger, T. A. Beyer, J. Bordner, D. F. Burdi, D. L. Bussolotti, P. B. Inskeep, T. W. Siegel, *J. Med. Chem.* **1992**, *35*, 2169; g) S. Wang, R. Beck, T. Blench, A. Burd, S. Buxton, M. Malic, T. Ayele, S. Shaikh, S. Chahwala, C. Chander, R. Holland, S. Merette, L. Zhao, M. Blackney, A. Watts, *J. Med. Chem.* **2010**, *53*, 1465; h) S. Singh, *Chem. Rev.* **2000**, *100*, 925; i) J. Zhao, H.-X. Ding, D.-G. Zhao, C.-M. Wang, K. Gao, *J. Pharm. Pharmacol.* **2012**, *64*, 1785; j) A. K. Ghosh, X. Cheng, B. Zhou, *Org. Lett.* **2012**, *14*, 5046.

[2] a) F. P. Bymaster, E. E. Beedle, J. Findlay, P. T. Gallagher, J. H. Krushinski, S. Mitchell, D. W. Robertson, D. C. Thompson, L. Wallace, D. T. Wong, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 4477; b) J. R. Cashman, S. Ghirmai, *Bioorg. Med. Chem.* **2009**, *17*, 6890.

[3] a) A. K. Christman, J. D. Fermo, J. S. Markowitz, *Pharmacotherapy* **2004**, *24*, 1020; b) S. Chumpradit, M.-P. Kung, C. Panyachotipun, V. Prapansiri, C. Foulon, B. P. Brooks, S. A. Szabo, S. Tejani-Butt, A. Frazer, H. F. Kung, *J. Med. Chem.* **1992**, *35*, 4492.

[4] For reviews, see: a) A. E. Nibbs, K. A. Scheidt, *Eur. J. Org. Chem.* **2012**, 449; b) J. K. Lin, S. H. Tsai, S. Y. Lin-Shiau, *Drugs Future* **2001**, *26*, 145.

[5] a) H. D. Smolarz, E. Mendyk, A. Bogucka-Kocka, J. Kocki, *Z. Naturforsch., C: J. Biosci.* **2006**, *61*, 64; b) K. J. Hodgetts, *Tetrahedron Lett.* **2000**, *41*, 8655.

[6] a) G. W. Stewart, M. Shevlin, A. D. G. Yamagata, A. W. Gibson, S. P. Keen, J. P. Scott, *Org. Lett.* **2012**, *14*, 5440; b) J.-H. Xie, Q.-L. Zhou, *Acta Chim. Sinica* **2012**, *70*, 1427.

[7] For an elegant review, see: S. Khumsubdee, K, Burgess, *ACS Catal.* **2013**, *3*, 237.

[8] Y. Zhu, K. Burgess, *Adv. Synth. Catal.* **2008**, *350*, 979.

[9] For reviews, see: a) L. Ackermann, *Synthesis* **2006**, 1557; b) T. M. Shaikh, C. M. Weng, F. E. Hong, *Coord. Chem. Rev.* **2012**, *256*, 771; for a highlight, see: c) N. V. Dubrovina, A. Börner, *Angew. Chem. Int. Ed.* **2004**, *43*, 5883; *Angew. Chem.* **2004**, *116*, 6007; for selected examples of transition metal catalysis with secondary phosphine oxide as the preligands, see: d) M. T. Reetz, T. Sell, R. Goddard, *Chimia* **2003**, *57*, 290; e) J. Bigeault, L. Giordano, G. Buono, *Angew. Chem. Int. Ed.* **2005**, *44*, 4753; *Angew. Chem.* **2005**, *117*, 4831; f) H. Landert, F. Spindler, A. Wyss, H.-U. Blaser, B. Pugin, Y. Ribourduoille, B. Gschwend, B. Ramalingam, A. Pfaltz, *Angew. Chem. Int. Ed.* **2010**, *49*, 6873; *Angew. Chem.* **2010**, *122*, 7025.

[10] a) K. Dong, Z. Wang, K. Ding, *J. Am. Chem. Soc.* **2012**, *134*, 12474; b) L. Yang, K. Dong, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2013**, *52*, 6748; *Angew. Chem.* **2013**, *125*, 6880; c) K. Dong, L. Yang, Z. Wang, K. Ding, *Angew. Chem. Int. Ed.* **2013**, *52*, 14191; *Angew. Chem.* **2013**, *125*, 14441; d) K. Dong, Y. Li, Z. Wang, K. Ding, *Org. Chem. Front.* **2014**, *1*, 155; e) X. Liu, Z. Han, Z. Wang, K. Ding, *Acta Chim. Sinica* **2014**, *72*, 849.

[11] For an elegant review, see: M. T. Reetz, *Angew. Chem. Int. Ed.* **2008**, *47*, 2556; *Angew. Chem.* **2008**, *120*, 2592.

[12] For examples, see: a) M. T. Reetz, G. Mehler, *Tetrahedron Lett.* **2003**, *44*, 4593; b) M. T. Reetz, O. Bondarev, *Angew. Chem. Int. Ed.* **2007**, *46*, 4523; *Angew. Chem.* **2007**, *119*, 4607; c) D. Peña, A. J. Minnaard, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, B. L. Feringa, *Org. Biomol. Chem.* **2003**, *1*, 1087; d) R. Hoen, J. A. F. Booger, H. Bernsmann, A. J. Minnaard, A. Meetsma, T. D. Tiemersma-Wegman, A. H. M. De Vries, J. G. de Vries, B. L. Feringa, *Angew. Chem. Int. Ed.* **2005**, *44*, 4209; *Angew. Chem.* **2005**, *117*, 4281; e) C. Monti, C. Gennari, U. Piarulli, *Tetrahedron Lett.* **2004**, *45*, 6859; f) L. Pignataro, B. Lynikaite, R. Colombo, S. Carboni, M. Krupicka, U. Piarulli, C. Gennari, *Chem. Commun.* **2009**, 3539; g) M. Weis, C. Waloch, W. Seiche, B. Breit, *J. Am. Chem. Soc.* **2006**, *128*, 4188; h) J. Wieland, B. Breit, *Nat. Chem.* **2010**, *2*, 832; i) M. Kuil, P. E. Goudriaan, P. W. N. M. van Leeuwen, J. N. H. Reek, *Chem. Commun.* **2006**, 4679; j) P.-A. R. Breuil, F. W. Patureau, J. N. H. Reek, *Angew. Chem. Int. Ed.* **2009**, *48*, 2162; *Angew. Chem.* **2009**, *121*, 2196; k) D. J. Frank, A. Franzke, A. Pfaltz, *Chem. Eur. J.* **2013**, *19*, 2405.

[13] For an example, see: S. Song, S.-F. Zhu, Y.-B. Yu, Q.-L. Zhou, *Angew. Chem. Int. Ed.* **2013**, *52*, 1556; *Angew. Chem.* **2013**, *125*, 1596.

[14] a) K. J. Hodgetts, *Tetrahedron* **2005**, *61*, 6860; b) C. Valla, A. Baeza, F. Menges, A. Pfaltz, *Synlett* **2008**, 3167; c) T. Korenaga, K. Hayashi, Y. Akaki, R. Maenishi, T. Sakai, *Org. Lett.* **2011**, *13*, 2022.

[15] For examples of Atomoxetine synthesis, see: a) M. Srebnik, P. V. Ramachandran, H. C. Brown, *J. Org. Chem.* **1988**, *53*, 2916; b) C. Xu, C. Yuan, *Tetrahedron* **2005**, *61*, 2169.

[16] Y. Suzuki, M. Iwata, R. Yazaki, N. Kumagai, M. Shibasaki, *J. Org. Chem.* **2012**, *77*, 4496; and the references therein.

[17] For a related study of phenoxy elimination, see: M. Á. Chávez, S. Vargas, A. Suárez, E. Álvarez, A. Pizzano, *Adv. Synth. Catal.* **2011**, *353*, 2775.

Received: August 15, 2015
Published online on October 1, 2015