Highly Enantioselective Hydrogenation of Styrenes Directed by 2′-Hydroxyl Groups
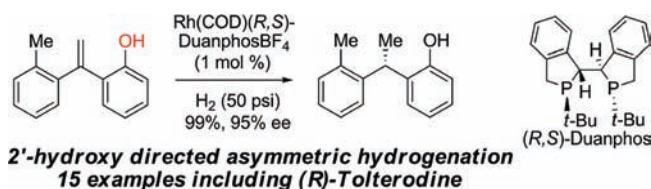
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ABSTRACT

2′-hydroxy directed asymmetric hydrogenation
15 examples including (R)-Tolterodine

A new synthetic strategy that turns styrene-type olefins into excellent substrates for Rh-catalyzed asymmetric hydrogenation by installing a 2′-hydroxyl substituent is described. This methodology accommodates trisubstituted olefinic substrates in various *E/Z* mixtures, leading to valuable benzylic chiral compounds including (*R*)-tolterodine. It is also demonstrated that the 2′-hydroxyl groups could be readily removed in high yield without loss of ee from the products. Thus, this technology represents an attractive alternative to the Ir(P−N) catalyst system for the asymmetric hydrogenation of unfunctionalized olefins.

Many pharmaceutically important molecules, including a number of commercial drugs, contain one or more tertiary benzylic chiral centers (Figure 1).[1] Asymmetric hydrogenation of the corresponding styrene-type olefins represents one of the most atom-economic approaches to these molecules.[2] However, the success of such transformations has been largely limited to olefins directly attached to one or more polar functional groups (carbonyl, ester, amide, etc.) or heteroatoms, which are often not present in the target molecules.[3] As a result, significant efforts have been directed toward asymmetric hydrogenation of unfunctionalized olefins.[4] Recently, Pfaltz has pioneered the development of the Ir/P−N ligand systems that wer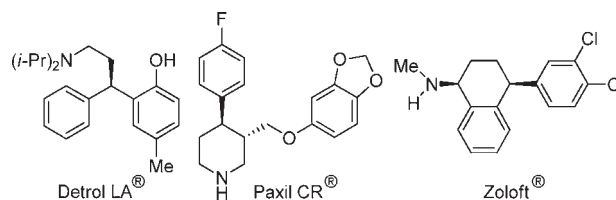e excellent catalysts for asymmetric hydrogenation of unfunctionalized olefins.[5] Despite this significant breakthrough, for high enantioselectivity the Ir/P−N systems require substrates isolated as a single olefinic *E/Z* isomer,[2a] which is often difficult to achieve. Additionally, an expensive counterion (BAr$_F$) is required and the preformed catalysts are incompatible with high throughput ligand screening. Herein we report an alternative strategy to this problem by installing a removable directing group on styrene-type olefins, which enables highly enantioselective hydrogenation of unfunctionalized olefins in *E/Z* mixtures, catalyzed by readily available in situ or preformed Rh complexes.[6]

Figure 1. Tertiary benzylic chiral centers in pharmaceuticals.

Through our screening efforts in an internal project, we came to realize that installing a 2′-hydroxyl group on styrenes might direct olefins to selectively bind to chiral transition

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(2) (a) Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T. L.; Leung, A. W. M.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855–8860. (b) RajanBabu, T. V. *Chem. Rev.* **2003**, *103*, 2845–2860.

(3) (a) Noyori, R. *Asymmetric Catalysis in Organic Synthesis*; Wiley: New York, 1994. (b) Brown, J. In *Comprehensive Asymmetric Catalysis*; Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds; Springer-Verlag: Berlin, Germany, 1999; Vol. 1 (c) Nugent, W. A.; Rajanbabu, T. V.; Burk, M. J. *Science* **1993**, *259*, 479–483.

(4) (a) Cui, X.; Burgess, K. *Chem. Rev.* **2005**, *105*, 3272–3296. (b) Roseblade, S. J.; Pfaltz, A. *Acc. Chem. Res.* **2007**, *40*, 1402–1411.

Table 1. Condition Screening for Hydrogenation of **1**

entry	R	H$_2$ (psi)	solvent	conv (%)	ee (%)
1	H(**1**)	200	DCM	76	95.5
2	H	200	THF	100	38.5
3	H	200	Me OH	100	98.8
4	H	200	toluene	100	99.1
5	H	100	toluene	100	99.2
6	H	50	toluene	100	99.2
7	Me (**1a**)	50	toluene	50	<20

metal complexes, transforming otherwise unreactive olefins into excellent substrates for asymmetric hydrogenation under very mild conditions. For example, 2-(1-phenylvinyl)-phenol (**1**), a styrene-type olefin with a 2′-hydroxyl substituent, underwent hydrogenation catalyzed by Rh(COD)-BF$_4$ (1 mol %) and (*R,S*)-DuanPhos (1.2 mol %) at 200 psi in CH$_2$Cl$_2$ to give hydrogenation product (*S*)-**2** in 76% conversion and 95.5% ee (Table 1, entry 1).[7,8] Switching the solvent from CH$_2$Cl$_2$ to toluene and lowering the pressure to 50 psi further increased the ee and conversion (Table 1, entry 6).[9] The presence of the hydroxyl group was essential to the success of highly enantioselective hydrogenation, and when the hydroxyl in **1** was replaced by a methoxy group, both the conversion (∼50%) and ee (<20%) suffered significantly (entry 7).[10]

We then expanded this strategy to other styrenes bearing 2′-hydroxyl groups and found that they were excellent substrates for the Rh-catalyzed enantioselective hydrogenation (Table 2). Catalyst loading as low as 0.1%

Table 2. Scope of Phenol-Directed Asymmetric Hydrogenation[a,b]

entry	substrate	product	yield[b]	ee%[c]
1	**1**	**2**	95	99
2[d]			97	99
3	R = Me (**3**)	**16**	99	99
4	F (**4**)	**17**	99	>99
5	OCH$_3$ (**5**)	**18**	95	99
6	CO$_2$Me (**6**)	**19**	98	99
7	**7**	**20**	93	99
8	**8**	**21**	96	98
9	**9**	**22**	99	95
10	**10**	**23**	91	>99
11[e]	R = Me (**11**, 2.6:1 E/Z)	**24**	95	95
12[e]	Et (**12**, 1.5:1 E/Z)	**25**	92	95
13[e]	i-Pr (**13**, 6.5:1 E/Z)	**26**	94	92
14[e]	Bn (**14**, 2.0:1 E/Z)	**27**	87	90
15[f]	**15**	**28**	93	95

[a] Conditions: H$_2$ (50 psi), Rh(COD)[(*R,S*)-DuanPhos]BF$_4$ (1 mol %), NEt$_3$ (5 mol %), toluene, rt, 1−12 h. [b] Isolated yield of >95% purity judged by GC analysis. [c] From crude reaction mixture measured by HPLC. [d] 0.1 mol % catalyst loading. [e] 1 mol % Rh(COD)[(*S,S*)-Me-BPEphos]BF$_4$. [f] 1 mol % Rh(COD)$_2$BF$_4$ and 1.2 mol % Josiphos SL-J210-1, see the Supporting Information for details.

was well tolerated, provided 5 mol % of NEt$_3$ was added in the reaction mixture (entry 2). Substrates with various electron-withdrawing and -donating groups such as methyl, fluoro, methoxy, and methyl ester at the 4-position of phenol all gave excellent ee (99%) and very high yield (>95%) (entries 3−6). A methyl substituent at the ortho-position of the phenol did not adversely affect the efficiency of the reaction (entry 7, 99% ee). The catalyst system was also compatible with substrates containing aryl bromide functional groups (98% ee, entry 8) and with heteroaryls

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(6) A process based on this chemistry was recently scaled up to 100 g scale with 0.1% catalyst loading.

(7) For catalytic reactions employing DuanPhos, see: (a) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029–3069. (b) Zhang, W.; Chi, Y.; Zhang, X. *Acc. Chem. Res.* **2007**, *40*, 1278–1290. (c) Zigterman, J. L.; Woo, J. C. S.; Walker, S. D.; Tedrow, J. S. T.; Borths, C. J.; Bunel, E. E.; Faul, M. M. *J. Org. Chem.* **2007**, *72*, 8870. (d) Phan, D. H. T.; Kim, B.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 15608.

(8) Preformed catalyst Rh(DuanPhos)BF$_4$ performed similarly to the catalyst formed in situ, and was used later on for convenience. The absolute stereochemistry was established by comparing optical rotation with literature references.

(9) For an example of Rh-catalyzed hydrogenation in the pharmaceutical industry, see: (a) Gridnev, I. D.; Imamoto, T.; Hoge, G.; Kouchi, M.; Takahashi, H. *J. Am. Chem. Soc.* **2008**, *130*, 2560–2572. (b) Hoge, G.; Wu, H.-P.; Kissel, W. S.; Pflum, D. A.; Greene, D. J.; Bao, J. *J. Am. Chem. Soc.* **2004**, *126*, 5966–5967.

(10) For an example of *N*-containing heteroarenes as directing groups in asymmetric reduction see: Rupnicki, L.; Saxena, A.; Lam, H. W. *J. Am. Chem. Soc.* **2009**, *131*, 10386–10387.

(11) For use of Me-BPEphos in catalysis see: (a) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142–5143. (b) Burk, M. J. *Acc. Chem. Res.* **2000**, *33*, 363–372.

(12) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879–933.

(13) For recent asymmetric syntheses of (*R*)-tolterodine see: (a) Gallagher, B. D.; Taft, B. R.; Lipshutz, B. H. *Org. Lett.* **2009**, *11*, 5374–5377. (b) Ulgheri, F.; Marchetti, M.; Piccolo, O. *J. Org. Chem.* **2007**, *72*, 6056–6059. (c) Paras, N. A.; Simmons, B.; MacMillan, D. W. C. *Tetrahedron* **2009**, *65*, 3232–3238.

(14) A stoichiometric amount of LiO*t*-Bu was needed for the success of the hydrogenation, presumably because a strong base is needed to free the phenol from the internal hydrogen bonding in **31**.

(>99% ee, entry 10). Importantly, trisubstituted olefins in various E/Z isomeric ratios were also well tolerated, as methyl, ethyl, isopropyl, benzyl, and phenyl substituents on the terminal olefin all yielded >90% ee, when Rh (COD)[(S, S)-Me-BPEphos]BF$_4$ was used as the catalyst (entries 11−14).[11] It is worth noting that biaryl systems were not required for high enantioselectivity, as evidenced by a cyclopentenyl substrate **15** that underwent efficient hydrogenation to give the corresponding product in 93% yield, 95% ee (entry 15).

Scheme 1
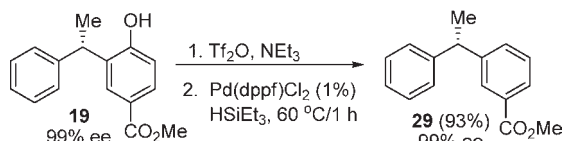
Styrene-type olefins bearing a 2′-hydroxyl substituent could be readily synthesized via phenol-directed ortho-lithiation followed by ketone addition/elimination sequences from the corresponding phenols.[12] Also importantly, the hydroxyl group in the hydrogenation product could be removed in a two-step sequence in high yield without loss of ee. Specifically, triflate protection of the phenol **19** followed by a palladium-catalyzed deoxygenation with HSiEt$_3$ afforded the des-hydroxyl product in 93% yield (two-step) with full retention of stereochemistry (Scheme 1). Thus, the 2′-hydroxyl group could serve as a traceless directing group, while facilitating both the synthesis of the olefinic substrates and the asymmetric hydrogenation.

Finally, we successfully applied the strategy of phenol-directed asymmetric hydrogenation to the synthesis of (R)-tolterodine, the active ingredient of Detrol LA (Scheme 2).[13] Alkene **31** was derived in 69% overall yield in 4 steps from commercially available ketone **30**, existing mostly in the Z isomer (>50:1 Z:E ratio) due to internal hydrogen bonding. With LiOt-Bu as the base,[14] **31** underwent efficient hydro-

Scheme 2
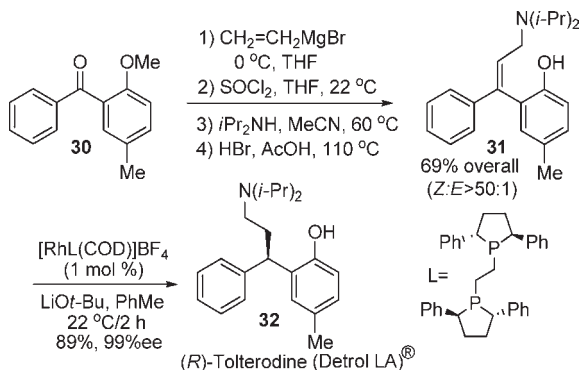
genation catalyzed by 1 mol % Rh[(COD)(S,S)-Ph-BPE-phos]BF$_4$ at room temperature to give (R)-tolterodine in 89% isolated yield, 99% ee.

The ability of this hydrogenation system to employ E/Z mixtures in trisubstituted substrates represents a major improvement from the Ir/P−N system, which requires the substrate isolated as a single E/Z isomer. This tolerance of substrates as E/Z mixtures, as well as the beneficial role of a base, implies that the enantioselectivity of the hydrogenation stems from the coordinating effect of the deprotonated phenol with rhodium, as proposed in Scheme 3.[15,16]

Scheme 3
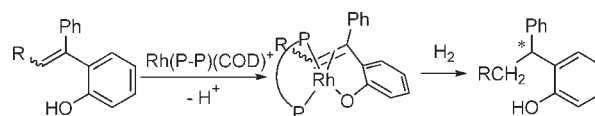
This hypothesis would explain why methoxy-capped substrate **1a**, despite its structural similarity to **1**, fails to undergo efficient hydrogenation under the same conditions (Table 1, entry 7). This argument is also corroborated with the observation that substrate **9** gave 95% ee via Rh-catalyzed hydrogenation, despite little steric bias between the two olefinic pro-chiral faces (Table 2, entry 9).

In summary, we have demonstrated that styrene-type olefins bearing a 2′-hydroxyl substituent undergo highly enantioselective Rh-catalyzed hydrogenations leading to valuable benzylic chiral compounds including (R)-tolterodine. As an improvement to the Ir(P−N) catalyst system, this methodology accommodates trisubstituted olefins in various E/Z mixtures. As 2′-hydroxyl groups could be readily removed without any loss of ee from the products, this technology represents an attractive alternative for the asymmetric hydrogenation of unfunctionalized olefins.

Supporting Information Available. Experimental procedures, full spectroscopic data for new compounds, and HPLC chromatograms. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) Homoallylic hydroxyl groups are known directing groups for diastereoselective hydrogenations, see: (a) Zhu, Y.; Burgess, K. J. Am. Chem. Soc. **2008**, 130, 8894–8895. (b) Evans, D. A.; Morrissey, M. M.; Dow, R. L. Tetrahedron Lett. **1985**, 26, 6005–6008.

(16) Enamide directed enantioselective hydrogenation is known to tolerate E/Z mixtures, see: Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. J. Am. Chem. Soc. **1993**, 115, 10125–10138.