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Asymmetric Hydrogenation of *o*-Alkoxy-Substituted Arylenamides

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A series of (2-alkoxyaryl)glycinols have been prepared in up to 97.8% ee by asymmetric hydrogenation with cationic rhodium Me-BPE or Me-DuPhos complexes. Others have shown that the presence of ortho substituents on related α-arylenamides causes a decrease in enantioselectivity. However, in this study it was found that *o*-alkoxy α-arylenamides were reduced with high enantioselectivity irrespective of substituent size.

The value of *β*-amino alcohols as chiral ligands in asymmetric catalysis,[1] as resolving agents in asymmetric synthesis,[2] and as building blocks of many important biologically active compounds[3] is well-documented. As a consequence, the development of efficient synthetic methods for the preparation of these compounds in optically pure form is of considerable interest. Recently, we required a scaleable and efficient route to a family of optically active (2-hydroxyphenyl)glycinols and (2-alkoxyphenyl)glycinols. Such amino alcohols can in principle be obtained by several methods, including asymmetric aminohydroxylation of styrenes[4] or reduction of the corresponding α-amino acids or esters.[5] The development of synthetic strategies for accessing arylglycines has been spurred in part by interest in vancomycin antibiotics, and noteworthy approaches include cuprate or Friedel−Crafts coupling to bromoglycinates,[6] amination (or the equivalent) of α-aryl enolates,[7] and $TiCl_4$-promoted Friedel−Crafts reaction of phenols with chiral *N*,*O*-hemiacetals.[8] Given the commercial unavailability of starting materials or the need for chiral auxiliaries by these methods, we sought to access the desired amino alcohols by asymmetric hydrogenation.

Recently, Zhang and co-workers reported a practical and highly enantioselective synthesis of *β*-amino alcohols by rhodium-catalyzed asymmetric hydrogenation of α-arylenamides with a MOM-protected *β*-hydroxy group.[9] Despite the ostensible utility of that published procedure, we are unaware of its application to the asymmetric hydrogenation of arylenamides bearing *o*-hydroxy or *o*-alkoxy substituents. Herein, we wish to report a highly enantioselective asymmetric hydrogenation of new aryl *o*-alkoxy-substituted enamides catalyzed by a cationic rhodium Me-DuPhos or Me-BPE catalyst system (Scheme 1).[10,11]

Arylenamides bearing *o*-hydroxy substituents can be prepared in gram quantities from readily available of *o*-hydroxyacetophenone derivatives by adoption of the protocols described independently by the groups of Zhang[9a] and Burk[12] (Scheme 2). Protection of the phenol **1a**−**k** (K_2CO_3, acetone, alkyl halide) and α-ketone oxidation

(1) (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833−856. (b) Butsugan, Y.; Ariki, S.; Watanabe, M. *Ferrocenes*; VCH: Weinheim, Germany, 1995; pp 143−169. (c) Takehara, J.; Hashiguichi, S.; Fujii, A.; Inoue, S.-i.; Ikariya, T.; Noyori, R. *Chem. Commun.* **1996**, 233−234. (d) Peper, V.; Martens, J. *Chem Ber.* **1996**, *129*, 691−695.

(2) (a) Sawayama, T.; Tsukamoto, M.; Sasagawa, T.; Naruto, S.; Matsumoto, J.; Uno, H. *Chem. Pharm. Bull.* **1989**, *37*, 1382−1383. (b) Kawai, M.; Omori, Y.; Yamamura, H.; Butsugan, Y. *Tetrahedron: Asymmetry* **1992**, *3*, 1019−1020.

(3) (a) Roemer, D.; Buescher, H. H.; Hill, R. C.; Pless, J.; Bauer, W.; Cardinaux, F.; Closse, A.; Hauser, D.; Huguenin, R. *Nature* **1977**, *268*, 547−549. (b) TenBrink, R. E. *J. Org. Chem.* **1987**, *52*, 418−422. (c) Fincham, C. I.; Higginbottom, M.; Hill, D. R.; Horwell, D. C.; O'Toole, J. C.; Ratcliffe, G. S.; Rees, D. C.; Robert, E. *J. Med. Chem.* **1992**, *35*, 1472−1474. (d) Wu, S. Y.; Takeya, R.; Eto, M.; Tomizawa, C. *J. Pestic. Sci.* **1987**, *12*, 221−227.

(4) (a) O'Brien, P.; Osborne, S. A.; Parker, D. D. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2519−2526. (b) Li, G.; Chang, H.-T.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 451−454. (c) Rudolph, J.; Sennhenn, P. C.; Vlaar, C. P.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 2810−2813. (d) Rubin, A. E.; Sharpless, K. B. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2637−2640.

(5) (a) Gage, J. R.; Evans, D. A. *Org. Synth.* **1990**, *68*, 77−82. (b) Abiko, A.; Masamune, S. *Tetrahedron Lett.* **1992**, *33*, 5517−5518. (c) McKennon, M. J.; Meyers, A. I.; Drauz, K.; Schwarm, M. *J. Org. Chem.* **1993**, *58*, 3568−3571. (d) Nicolás, E.; Rusell, K. C.; Hruby, V. J. *J. Org. Chem.* **1993**, *58*, 766−770.

(6) Williams, R. M.; Hendrix, J. A. *J. Org. Chem.* **1990**, *55*, 3723−3728.

(7) (a) Evans, D. A.; Evrard, D. A.; Rychnovsky, S. D.; Früh, T.; Whittingham, W. G.; DeVries, K. M. *Tetrahedron Lett.* **1992**, *33*, 1189−1192. (b) Evans, D. A.; Nelson, S. G. *J. Am. Chem. Soc.* **1997**, *119*, 6452−6453. (c) Vicario, J. L.; Badía, D.; Dominguez, E.; Crespo, A.; Carrillo, L.; Anakabe, E. *Tetrahedron Lett.* **1999**, *40*, 7123−7126.

(8) Ge, C.-S.; Chen, Y.-J.; Wang, D. *Synlett* **2002**, 37−42.

(9) (a) Zhu, G.; Casalnuovo, A. L.; Zhang, X. *J. Org. Chem.* **1998**, *63*, 8100−8101. (b) Tang, W.; Zhang, X. *Chem. Rev.* **2003**, *103*, 3029−3069.

(10) Abbreviations: BICP, 2,2-bis(diphenylphosphino)-1,1-dicyclopentane; BPE, 1,2-bis(2,5-dimethylphospholano)ethane; TangPhos, 1,1′-di-*tert*-butyl-[2,2′]-diphospholanyl; DuPhos, 1,2-bis(2,5-dialkylphospholane)benzene; Butiphane, 2,3-bis(2,5-diethylphospholan-1-yl)benzo-[*b*]thiophene; DIOP, 2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane; Walphos, 1-[2-(2′-diphenylphosphinophenyl)ferrocenyl]ethyldi(bis-3,5-trifluoromethylphenyl)phosphine; Josiphos, 1-[(2-dicyclohexylphosphino)ferrocenyl]ethyldicyclohexylphosphine; Taniaphos, 1-diphenylphosphino-2-[α-(*N*,*N*-dimethylamino)-*o*-(diphenylphosphinohenyl)methyl]ferrocene; Mandyphos, 2,2′-bis(α-*N*,*N*-dimethylaminophenylmethyl)-1,1′-bis(dicyclohexylphosphino)ferrocene.

(11) For the syntheses of these complexes see: Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc.* **1993**, *115*, 10125−10138.

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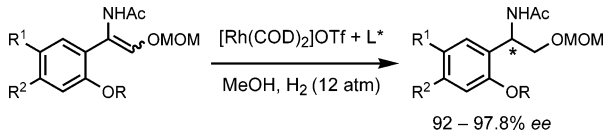
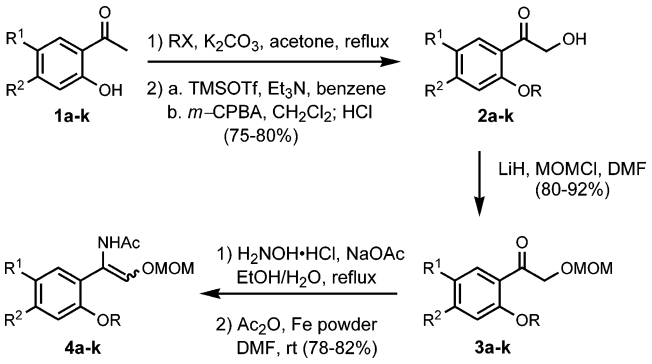
SCHEME 1



SCHEME 2



(TMSOTf, Et_3N; *m*-CPBA) gave **2a**−**k** in 75−80% yield for the three steps. MOM protection followed by reduction of the ketone oximes with iron powder in acetic anhydride and DMF gave an inseparable mixture of *Z*/*E* enamide isomers **4a**−**k**.

For the initial catalyst screening, we selected a substrate with the phenol protected as its methyl ether, **4a** (Table 1). The reductions were generally carried out at room temperature with 1 mol % of rhodium catalyst in dry, degassed methanol under 170 psi of hydrogen for 24−36 h.

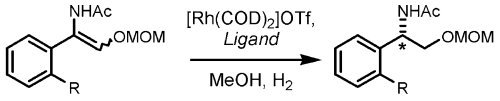
Four different ferrocenyl ligands and *p*-TolBINAP were examined, but the enantioselectivities observed with these were disappointing (entries 1−5). Switching to DIOP (entry 6) gave a promising 74% ee. Hydrogenation with Me-DuPhos gave a useful 94.2% ee, but two DuPhos analogues, Et-Butiphane (entry 7) and Rhophos (entry 8), were slightly less effective (80 and 89% ee, respectively). TangPhos (entry 10) gave an impressive 94.7% ee, but the best results were attained with Me-BPE (entry 11, 97.8% ee). Note that in the absence of ortho substitution, DIOP and Rhophos gave noticeably higher ee values (entries 6 and 8).

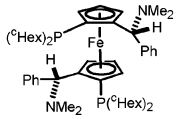
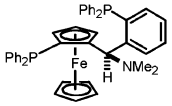
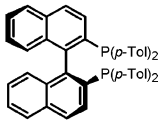
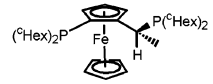
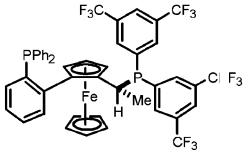
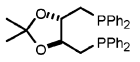
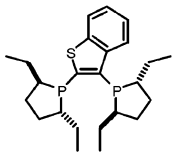
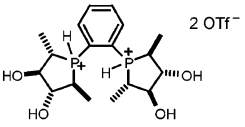
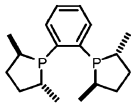
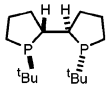
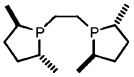
We found that preparing the Me-BPE catalyst in situ (by mixing 1.1 equiv of (*S*,*S*)-Me-BPE and 1.0 equiv of $[(COD)_2Rh]^+OTf^-$ prior to introduction of enamide) gave slightly lower enantiomeric excess than when the discrete, isolated rhodium−ligand complex was employed (94% ee vs 98% ee). Varying the hydrogen pressure from 30 to 210 psi did not substantially affect any of the observed ee values with the ortho-substituted enamides (except for entry 10). Complete conversion was observed in all cases.

Also included in Table 1 are the ee values measured for hydrogenation of the parent unsubstituted enamide, and similar enantioselectivity was obtained with this series of ligands.[9] The high enantiomeric excess observed from hydrogenation of the ortho-substituted enamides is significant because it has been reported that in reduction of enamides lacking the 2-*O*-MOM group that replacing

(12) Burk, M. J.; Casy, G.; Johnson, N. B. *J. Org. Chem.* **1998**, *63*, 6084−6085.

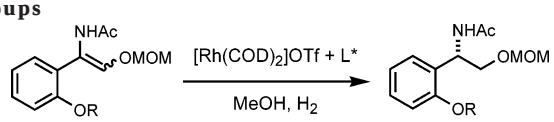
TABLE 1. Asymmetric Hydrogenation of *o*-Methoxylphenyl Enamide and Comparison with Nonsubstituted Enamide



entry	ligand		% ee[g] R = OMe	% ee[g] R = H
1[a]	(*R*,*S*)–NMe_2-PPh_2 (Mandyphos)		3	3
2[a]	(*R*,*S*)–$Ph_2P(C_6H_4)CHNMe_2$-T-PPh_2 (Taniaphos)		7	5
3[a,c]	(*S*)-*p*-TolBINAP		28	32
4[a,c]	(*R*,*S*)–Cy_2PF-PCy_2 (Josiphos)		32	35
5[a]	(*R*,*R*)–Walphos		39	25
6[a]	(+)–DIOP		74	84
7[b,c,d]	(*R*,*R*)–Et-Butiphane		80	80
8[a,c,e]	(*S*,*S*,*S*,*S*)–Rophos-Bis(OTf) salt		89	93.5
9[b]	(*R*,*R*)–Me-DuPhos		94.2	94.6
10[a,f]	(1*S*,1*S*′,2*R*,2*R*′)–TangPhos		94.7	95.4
11[b]	(*R*,*R*)–Me-BPE		97.8	96.2

[a] Reactions were carried out with in situ generated Rh catalysts. [b] Reactions were carried out with 1 mol % isolated Rh catalysts. [c] Opposite enantiomer predominated. [d] Hydrogenation was done in methanol at ca. 40 °C under 200 psi of H_2. [e] Sodium carbonate is used as a base and hydrogenation was done in methanol at room temperature under 14 psi of H_2. [f] Hydrogenation was done in THF at room temperature under 20 psi of H_2. [g] The ee values were determined by chiral HPLC (Whelk-O1) with *i*-PrOH and hexanes. Complete conversion was observed in all cases (97−98% yield).

TABLE 2. Asymmetric Hydrogenation of Phenylenamides with Different Phenolic Protective Groups



4a-d 5a-d

		% ee[b] (**5**) for two ligands	
entry[a]	R	(*R*,*R*)-Me-BPE	(*R*,*R*)-Me-DuPhos
1	Me (**a**)	97.8	94.2
2	CH_2CH_2Cl (**b**)	96.9	93.8
3	Bn (**c**)	97.2	95.4
4	PMB (**d**)	93.9	92.8

[a] Reactions were carried out in methanol at room temperature with 1 mol % of Rh isolated catalysts and 170 psi of H_2. [b] The ee values were determined by chiral HPLC (Whelk-O1) with *i*-PrOH and hexanes.

an *o*-hydrogen with a bromo or methyl group acutely reduced the observed enantioselectivities (89% and 75% ee, respectively, vs 98% ee).[13]

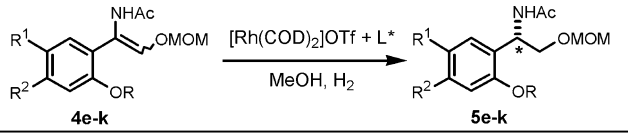
With future synthetic applications for these (2-hydroxyphenyl)glycinols in mind, we explored the hydrogenation of enamides with different phenolic protective groups (Table 2). Surprisingly, the ee values attained with either Me-DuPhos-Rh or Me-BPE-Rh catalysts proved to be remarkably consistent regardless of the size of the protective group. Methyl, 2-chloroethyl, and benzyl ethers all gave nearly identical ee values. The more rigid Me-DuPhos ligand was generally slightly less effective than the related Me-BPE. From the hydrogenation of arylenamides bearing benzyl and *p*-methoxybenzyl (PMB) protecting groups an insignificant amount of debenzylation products were formed (~3%) when in situ generated Rh catalysts were employed.

The influence of substituents at the meta and para positions was also examined (Table 3). Gratifyingly, the enantioselectivity proved to be unaffected by additional aryl substituents or protective group size. Compatible substrate modifications include the addition of a 5-methyl (entry 1, 95% ee), a 5-chloro (entry 2, 94% ee), or a 5-*tert*-butyl group (entry 4, 94% ee). A 2-naphthyl enamide and a 4-methoxy were each reduced in 93% ee. No substantial electronic effects were observed in these reductions, although the electronic variation within the series of substrates tested was only moderate (e.g., 5-chloro vs 4-methoxy, Table 3, entries 2 and 7). The substrate in entry 1 was reduced in the greatest ee by Me-DuPhos, whereas in all other cases Me-BPE was the most effective.

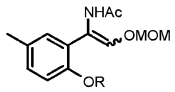
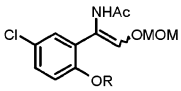
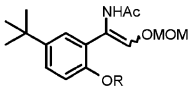
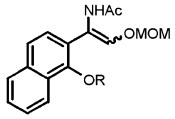
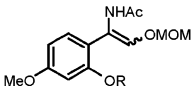
In summary, a new series of chiral orthogonally *N*,*O*-diprotected ortho-substituted arylglycinols has been prepared in high enantiomeric excess by asymmetric hydrogenation of arylenamides with commercially available cationic (*R*,*R*)-Me-BPE-Rh and (*R*,*R*)-Me-DuPhos-Rh complexes. With these substrates the size of a substituent at the ortho position was found to have little effect on the asymmetric induction. The use of these arylglycinols for the preparation of novel chiral scaffolds with applications in asymmetric catalysis will be reported elsewhere.

(13) Burk, M. J.; Wang, Y. M.; Lee, J. R. *J. Am. Chem. Soc.* **1996**, *118*, 5142−5143.

TABLE 3. Asymmetric Hydrogenation of Aromatic Enamides



4e-k 5e-k

					(1*S*,1*S*', 2*R*,2*R*')–TangPhos
			(*R*,*R*)–Me-BPE	(*R*,*R*)–Me-DuPhos	
entry[a]	Substrate (**4**)	R	ligands and % *ee*[b] (**5**)		
1		Me (**e**)	94.7	95.3	93.0
2		Me (**f**)	94.6	91.7	–
3		Bn (**g**)	95.5	93.0	–
4		CH_2CH_2Cl (**h**)	95.6	92.4	–
5		PMB (**i**)	94.3	92.3	–
6		Me (**j**)	93.1	92.6	–
7		PMB (**k**)	93.7	93.1	91.4

[a] Reactions were carried out in methanol at room temperature with 1 mol % of Rh isolated catalysts and 170 psi of H_2. [b] The ee values were determined by chiral HPLC (Whelk-O1) with *i*-PrOH and hexanes.

Experimental Section

General Procedure for Hydrogenation: With in Situ Generated Catalyst. $[Rh(COD)_2]OTf$ (4.7 mg, 0.01 mmol) and ligand (0.011 mmol) were added to a test tube in a drybox, the tube was sealed with a rubber septum, and degassed MeOH (3 mL) was introduced. After the mixture was stirred for 10 min, a solution of substrate **4a**−**k** (1 mmol) in MeOH (3 mL) was added. The flask was placed in an argon-filled high-pressure stainless steel bomb, the rubber septum was removed, and the bomb was sealed and charged with H_2 [three cycles of vacuum (20 psi) and hydrogen (20 psig)]. The final fill of H_2 was raised to the indicated pressure. After 12−48 h at room temperature the hydrogen was released, and the reaction mixture was filtered through a short silica gel plug to remove the catalyst. Solvent was removed with a rotary evaporator under vacuum, and the yellow solid was purified by flash chromatography on silica gel with 20% hexanes/EtOAc to give the desired product as a white powder (97−98% yield). Enantiomeric excesses were measured by chiral HPLC ((*S*,*S*)-Poly Whelk-01 column; particle size: 5.0 μm; column dimensions: 25 cm × 0.46 cm).

With Isolated Catalyst. The rhodium−ligand complex was added to a test tube in a drybox, and subsequently treated as described above.

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Supporting Information Available: General experimental protocols and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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