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Enantioselective Hydrogenation of α-Aryloxy α,β-Unsaturated Acids. Asymmetric Synthesis of α-Aryloxycarboxylic Acids

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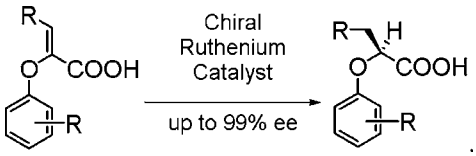
ABSTRACT



A facile preparation of chiral α-aryloxy carboxylic acids via asymmetric hydrogenation of the corresponding unsaturated acids has been discovered. A number of catalysts have been identified that give high product enantioselectivity, and the scope of the reaction has been examined with respect to substitution on the aromatic ring and olefin.

The α-aryloxy acids and their derivatives have important applications in the agrochemical field as herbicides,[1] plant hormone and growth regulators,[2] pesticides,[3] and fungicides.[4] In addition, they exhibit important pharmacological properties, making them useful as nootropic and analgesic agents,[5] hypocholesterolemic and hyperlipidemic agents,[6] and imaging agents.[7] Furthermore, these compounds, especially when optically active, are useful synthetic intermediates.[8]

Until now, there have been few reported methods for synthesis of optically active α-aryloxy acids. Although a number of methods exist for the enantioselective preparation of structurally related 2-hydroxyacids, among them enzymatic,[9] microbial,[10] chiral auxiliary,[11] chiral reagent,[12] and asymmetric hydrogenation,[13] further elaboration of these intermediates to the corresponding α-aryloxy acids without racemization is expected to be a nontrivial process.[14] The direct preparation of α-aryloxy acids can be accomplished,

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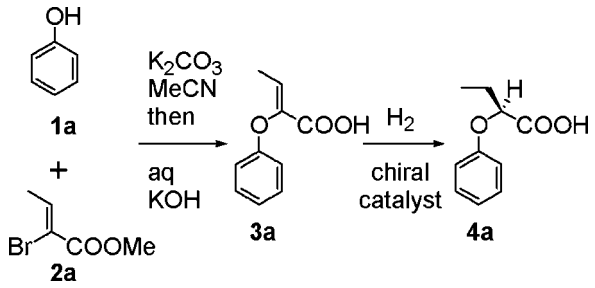
albeit in 50% maximum theoretical yield, by microbial or enzymatic resolution of the racemic acids or esters[15] or the well-known resolution of carboxylic acid salts via crystallization with optically active amines. The microbial deracemization of the racemic α-aryloxy acids with the potential of a quantitative yield is known.[16] Unfortunately, this microbial deracemization is sensitive to the nature of the aryloxy substituent where steric bulk would not allow the reaction to proceed, and ortho or meta substituents resulted in unselective reactions.

As part of an ongoing effort to synthesize key intermediates for a clinical program, we required rapid access to chiral α-aryloxy acid derivatives. Homogeneous enantioselective hydrogenation of prochiral olefins is a powerful technique for synthesizing a variety of chiral compounds with excellent enantioselectivity.[17] Given the general utility of asymmetric hydrogenation of unsaturated acids,[17] we envisioned the α-aryloxy α,β-unsaturated acids could potentially provide directly a broad variety of α-aryloxy acids in high optical purity. Despite isolated reports on the enantioselective hydrogenation of benzofuran,[18] furan,[19] and benzopyran[20] carboxylic acids, to the best of our knowledge α-aryloxy α,β-unsaturated acids represent a new substrate class for asymmetric hydrogenation.[21] Herein we report that asymmetric hydrogenation of α-aryloxy α,β-unsaturated acids provides saturated α-aryloxy acids in high optical purity.

Our initial studies focused on α-phenoxybutenoic acid (Z)-**3a**,[22] which was prepared from the reaction of 2-bromobutenoate **2a**[23] with phenol **1a** followed by hydrolysis of the methyl ester (Scheme 1). The enantioselective hydrogenation of **3a** to **4a**[2,5,8a] was examined using a library of

Scheme 1



(bisphosphine)ruthenium precatalysts prepared in situ from [(*p*-cymene)$RuCl_2$]$_2$ and the commercially available bisphosphine ligands.[24] The hydrogenation was conducted in the presence of triethylamine in MeOH. The results of the catalyst screen are shown in Table 1. We were pleased to find high conversions and >90% ee for a number of ligands. In most cases, the chemical selectivity was high with the only by-product being low levels of phenol. It is noteworthy that the sense of enantioinduction observed in the hydrogenation of **3a** ((*S*)-**4a**[25] with (*S*)-BINAP) was the same as that observed with simple 2-alkyl and 2-arylacrylates.[17]

Among all the ligands tested, the atropisomeric bisphosphines, BINAP, Synphos, P-Phos, Cl-MeO-BIPHEP, and TMBTP, provided the highest enantioselectivities, consistent with literature precedent.[17] Of this series BINAP is by far

Table 1. Catalyst Screen for Hydrogenation[a] of **3a** to **4a**

ligand[b]	% conversion	% ee[c]	area % phenol
(*S*)-Synphos	100.0	97(*S*)	0.4
(*S*)-P-Phos	95.4	91(*S*)	2.6
(+)-TMBTP	100.0	99(*R*)	0.0
(*R*)-Cl-MeO-BIPHEP	100.0	92(*R*)	2.1
(*S*)-BINAP[d]	100.0	93(*S*)	0.0
(*S*)-BINAM	92.1	55(*S*)	4.4
(*R,S*)-PPF−P*t*Bu	98.6	48(*R*)	1.8
(*S,S,S,S*)-Me-f-KetalPhos	100.0	1(*S*)	0.0
(*S*)-Binapine	100.0	78(*R*)	0.7
(*R,R*)-*i*Pr-DUPHOS	100.0	89(*S*)	0.9
(*R*)-PHANEPHOS	100.0	21(*S*)	0.0
(*R,R*)-Et-FerroTANE	100.0	86(*R*)	0.0
(*S*)-Me-*BoPhoz*	100.0	0	0.0

[a] Solution containing 4 mg/mL of **3a**, 1.05 equiv of Et_3N, 11.5 mol % ligand, and 5.75 mol % [(*p*-cymene)$RuCl_2$]$_2$ in a mixture of 80:13:7 by volume MeOH/EtOH/CH_2Cl_2 was hydrogenated at 20−25 °C under 90 psig hydrogen for 20 h. The reaction mixtures were directly assayed by HPLC for % conversion and % ee. [b] See Supporting Information for ligand structures. [c] Absolute configuration[25] in parentheses. [d] Performed with 20 mol % [(*S*)-BINAP]$RuCl_2$.

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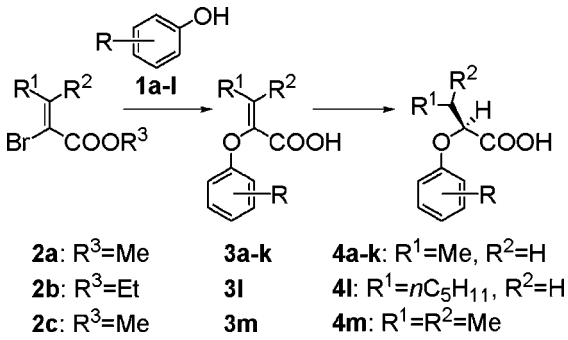
the least expensive and most widely available and was therefore chosen for further studies to examine the scope of the hydrogenation reaction with respect to substrate. To

Scheme 2



explore the scope of the asymmetric hydrogenation, α-aryloxy unsaturated acids **3b**−**k** were prepared in excellent yields as the (*Z*)-isomers[22] by reaction of phenols **1b**−**k** with bromobutenoate **2a** in a manner like that used for **3a** (Table 2). The unsaturated acids were readily isolated in high yields

Table 2. Preparation of α-Aryloxy Unsaturated Acids

R	ArOH	bromoenoate	unsaturated acid	% assay yield[a]	% yield[b]
H	**1a**	**2a**	**3a**	99	94
2-Me	**1b**	**2a**	**3b**	99	92
4-Me	**1c**	**2a**	**3c**	99	93
2-OMe	**1d**	**2a**	**3d**	99	94
2-F	**1e**	**2a**	**3e**	96	92
4-F	**1f**	**2a**	**3f**	94	93
2-Cl	**1g**	**2a**	**3g**	99	95
3-Br	**1h**	**2a**	**3h**	98	98
2-I	**1i**	**2a**	**3i**	99	94
3-I	**1j**	**2a**	**3j**	95	94
4-NO_2	**1k**	**2a**	**3k**	99	98
H	**1a**	**2b**	**3l**	98	97[c]
4-OMe	**1l**	**2c**	**3m**	97	95

[a] Assay yield determined by quantitative HPLC at the end of the reaction. [b] Isolated yield of crystallized product **3**. [c] Isolated by extraction of the acidified reaction mixture with *t*-BuOMe followed by crystallization as the dicyclohexylamine salt.

as crystalline solids by simple acidification of the aqueous reaction mixture after basic hydrolysis. The unsaturated acids **3l** and **3m** were prepared from **2b**[26] and **2c**,[27] respectively, to observe the effects of further substitution on the olefin.

Substrates **3a**−**m** were screened using 20 mol % [(*S*)-BINAP]$RuCl_2$ as precatalyst giving α-aryloxy acids **4a**−**m** with >99% conversion and moderate to high yields (Table 3). Substrates **3a**−**l** with a trisubstituted olefin gave the

Table 3. Asymmetric Hydrogenation of α-Aryloxy Unsaturated Acids[a]

unsaturated acid	mol % catalyst	α-aryloxy acid (% yield)[b]	phenol (area %)[c]	% ee[d]
3a	20, 1	**4a** (99, 93)	**1a** (<1, <1)	93, 94
3b	20	**4b** (79)	**1b** (3.8)	93
3c	20, 1	**4c** (96, 98)	**1c** (<1, 0.9)	92, 95
3d	20, 1	**4d** (79, 89)	**1d** (<1, <1)	94, 93
3e	20	**4e** (74)	**1e** (1.5)	88
3f	20, 1	**4f** (94, 94)	**1f** (<1, <1)	95, 95
3g	20	**4g** (84)	**1g** (2.8)	77
3h	20, 1	**4h** (84, 97)	**1h** (2.5, 1.6)	92, 95
3i	20	**4i** (80)	**1i** (6.4)	86
3j	20, 2	**4j** (90, 91)	**1j** (2.0, 2.0)	91, 93
3k	20	**4k** (79)	**1k** (9.7)	61
3l	20	**4l** (65)	**1a** (<1)	90
3m	20	**4m** (90)	**1l** (<1)	32

[a] Unsaturated acids **3a**−**m** (0.5 mmol) were hydrogenated in the presence of [(*S*)-BINAP]$RuCl_2$ and Et_3N (0.54 mmol) in MeOH (1 mL) at 25 °C under 90 psig hydrogen for 20 h. [b] Assay yield determined by quantitative HPLC; all reactions reached >99% conversion. [c] Area % phenol byproduct by HPLC. [d] Optical purity determined by chiral HPLC. Optical rotation in all cases was negative.

corresponding saturated products **4a**−**l** in moderate to high optical purities, while tetrasubstituted olefin **3m** exhibited markedly lower enantioselectivity in the hydrogenation. The enantioselective hydrogenation accepted a variety of substitution on the aryl group, including ortho and meta substituents, which were not tolerated in the microbial deracemization protocol mentioned previously.[16] Furthermore, the reaction was demonstrated to proceed using only 1 mol % catalyst for a number of substrates (**3a**,**c**,**d**,**f**,**g** in Table 3) without appreciable effect on the yield or optical purity.[28] Interestingly, it appears that the levels of the phenol impurity are increased in the presence of greater steric bulk in the ortho-substituted cases and in the more electron-deficient aryl ethers. It is also noteworthy that functionalities sensitive to reduction (cf. **3i**, **3j**, and **3k**) are unaffected by the enantioselective hydrogenation.

In summary, we have shown that asymmetric hydrogenation of α-aryloxy unsaturated acids provides an efficient means to synthesize optically active α-aryloxy acids. This method tolerates a variety of substitution patterns on the aromatic ring as well as limited variation in substitution on the olefin.

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(28) Hydrogenation of **3a** was demonstrated to proceed to complete conversion in 72 h using only 0.24 mol % [(*S*)-BINAP]$RuCl_2$.

Supporting Information Available: General experimental methods for preparation of **3a**−**m**, racemic acids **4a**−**m** and for the enantioselective hydrogenations with isolated yields; characterization data for **2b**, **3b**−**m**, and **4h**; HPLC data and methods for all compounds; HPLC traces of racemates and isolated products **4a**−**m** from the hydrogenations; X-ray crystal data for **3e** and (*S*)-**4h**; literature references for **4b**−**g** and **4i**−**m**; and structures and sources of ligands in Table 1. This material is available free of charge via the Internet at http://pubs.acs.org.

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