

# Enantioselective Synthesis of $\beta$ -Aryloxycarboxylic Esters via Asymmetric Hydrogenation of $\beta$ -Aryloxy- $\alpha,\beta$ -Unsaturated Esters

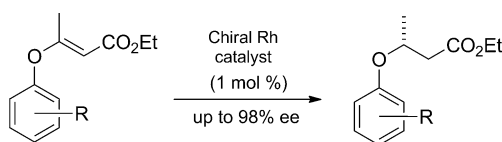
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## ABSTRACT



A novel synthesis of  $\beta$ -aryloxycarboxylic esters via asymmetric hydrogenation of the corresponding  $\beta$ -aryloxy- $\alpha,\beta$ -unsaturated esters has been demonstrated. Bis(norbornadiene)rhodium(I) tetrafluoroborate (1 mol %) and Walphos W008-1 were used to generate the saturated products with high enantioselectivity and in high yield. The tolerability of the reaction to a diverse range of substituents on the aromatic ring was also explored.

Enantioenriched  $\beta$ -aryloxycarboxylic acid derivatives are pharmacologically active molecules with a wide range of physiological activity, such as antithrombotic,<sup>1</sup> anticancer,<sup>2</sup> vasodilatory,<sup>3</sup> and antimitogenic<sup>4</sup> effects. In addition, this

structural motif is present in natural products,<sup>5</sup> agricultural chemicals,<sup>6</sup> and synthetic intermediates.<sup>7</sup>

Enantioenriched  $\beta$ -aryloxycarboxylic acid derivatives have been prepared by enzymatic resolution (with a maximum yield of 50%)<sup>8</sup> while cyclic  $\beta$ -aryloxycarboxylic acid derivatives have been synthesized using the asymmetric Stetter reaction,<sup>9</sup> asymmetric conjugate additions,<sup>10</sup> and enantioselective C–H insertions.<sup>11</sup>

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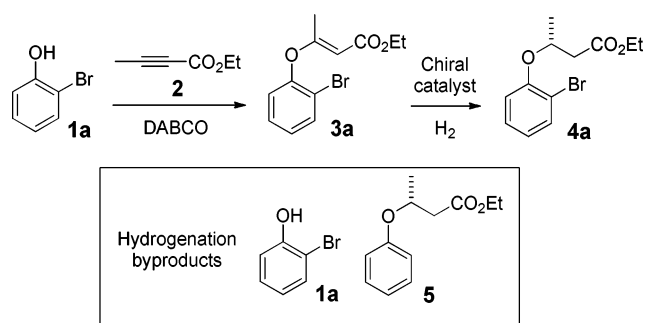
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The asymmetric hydrogenation of  $\alpha$ -aryloxy- $\alpha,\beta$ -unsaturated acids has been reported.<sup>12</sup> To the best of our knowledge, however, there have been no reports of asymmetric hydrogenations of  $\beta$ -aryloxy- $\alpha,\beta$ -unsaturated carboxylic acid derivatives. The enantioselective reduction of structurally similar  $\beta$ -alkoxy- $\alpha,\beta$ -unsaturated esters has been reported; however, these reactions require high pressures and employ a catalyst that is not commercially available.<sup>13</sup>

In the course of our research to synthesize key intermediates for a clinical program, we required rapid access to enantioenriched  $\beta$ -aryloxybutanoic acid esters. Given that asymmetric hydrogenation of prochiral olefins is a powerful method for synthesizing compounds with high optical purity,<sup>14</sup> and enantioselective reduction of  $\alpha,\beta$ -unsaturated esters can generate a wide variety of chiral esters,<sup>14</sup> we envisioned that asymmetric hydrogenation of  $\beta$ -aryloxy- $\alpha,\beta$ -unsaturated esters could provide access to chiral  $\beta$ -aryloxyesters in high optical purity. Encouraged by a report of racemic hydrogenation of  $\beta$ -aryloxy- $\alpha,\beta$ -unsaturated esters by homogeneous rhodium catalysis,<sup>15</sup> we began our search for an enantioselective reaction.

Scheme 1



We began by focusing on the reduction of substrate **3a** which was prepared by conjugate addition of phenol **1a** to alkyne **2** (Scheme 1).<sup>16</sup> The (*E*)-olefin was separated from a 97:3 mixture of *E/Z* isomers (<sup>1</sup>H NMR ratio) using chromatography. 2-Bromophenol **1a** was selected to assess the tolerance of an Ar–Br bond to hydrogenation

conditions for further manipulation at this position. The enantioselective hydrogenation of **3a** was examined with a wide range of rhodium and ruthenium catalysts prepared *in situ* from chiral ligands (Figure 1) and bis(norbornadiene)rhodium(I) tetrafluoroborate<sup>17</sup> or (cyclooctadiene)bis(methallyl)ruthenium(II) and tetrafluoroboric acid.<sup>18</sup>

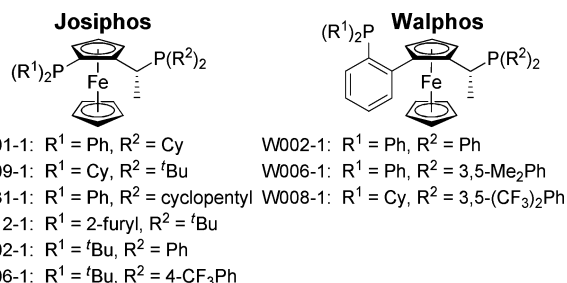


Figure 1. Ligands used in screening.

We were encouraged to find that the Ru/J212-1 catalyst system, previously reported for the asymmetric hydrogenation of a  $\beta$ -aryl- $\alpha,\beta$ -unsaturated ester,<sup>19</sup> gave good conversion to the desired product with good enantioselectivity (Table 1, entry 1). Further screening revealed that higher enantioselectivity could be obtained with Josiphos ligands<sup>20</sup> containing a bis(*tert*-butyl)phosphino substituent on the ferrocene ring (entries 2 and 3). However, the highly respectable enantiomeric excesses achieved (91.2 and 96.6%) still fell short of the requirements of our clinical program. We next turned our attention to rhodium catalysts. While Rh/J212-1 and Rh/J506-1 provided excellent reactivity, they suffered from poor enantioselectivity (entries 4 and 5). Josiphos ligands J009-1, J001-1, and J031-1 provided increasing levels of enantioselectivity, but they also caused significant cleavage of the sensitive aryl enol ether moiety to form phenol **1a** (entries 6–8). Switching to the structurally related Walphos ligands<sup>21</sup> also gave good reactivity and selectivity (entries 9–11). In particular, the Rh/W008-1 catalyst system gave high conversion and very good selectivity for this reaction (entry 11). In all cases, formation of byproduct **5** via reduction of the aryl halide was minimal.

Having identified the optimal catalyst, we turned our efforts toward optimizing the reaction parameters. Given that the solvent can have a marked influence on the

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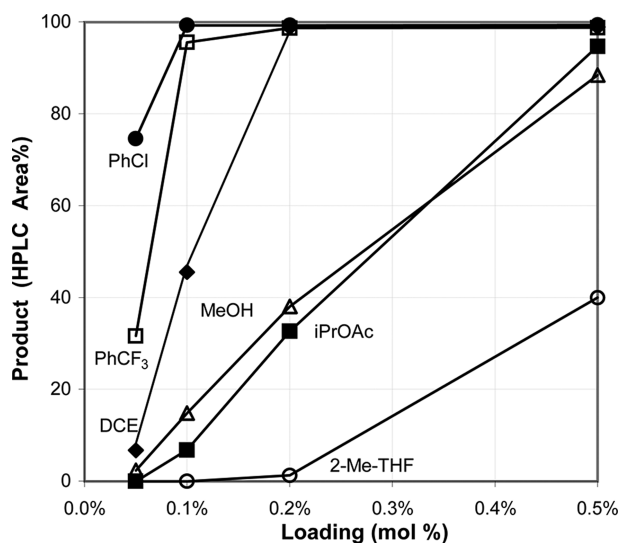
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**Table 1.** Catalyst Screening<sup>a</sup>

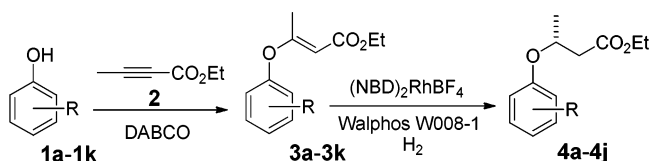
entry	M	ligand <sup>b</sup>	4a <sup>c</sup>	% ee <sup>d</sup>	5 <sup>c</sup>	1a <sup>c</sup>
1	Ru	J212-1	93.5	90.2 ( <i>R</i> )	3.4	3.1
2	Ru	J502-1	71.1	91.2 ( <i>R</i> )	1.1	1.7
3	Ru	J506-1	95.6	96.6 ( <i>R</i> )	3.3	0.3
4	Rh	J212-1	98.1	41.5 ( <i>R</i> )	0.7	1.2
5	Rh	J506-1	98.0	7.8 ( <i>S</i> )	0	2.0
6	Rh	J009-1	97.7	76.1 ( <i>S</i> )	0.9	1.4
7	Rh	J001-1	78.8	89.7 ( <i>R</i> )	2.6	18.5
8	Rh	J031-1	65.4	92.2 ( <i>R</i> )	0	34.6
9	Rh	W006-1	81.3	87.9 ( <i>R</i> )	0.7	18.1
10	Rh	W002-1	86.5	92.5 ( <i>R</i> )	0	13.5
11	Rh	W008-1	94.0	98.0 ( <i>R</i> )	0.7	5.3

<sup>a</sup> Reaction conditions: 25 mol % (COD)Ru(Methallyl)<sub>2</sub>/HBF<sub>4</sub>·OEt<sub>2</sub> in 2-Me-THF or 25 mol % (NBD)<sub>2</sub>RhBF<sub>4</sub> in EtOH, 500 psi H<sub>2</sub>, 0.016 M substrate, 50 °C, 18 h. <sup>b</sup> See Figure 1 for ligand structures. <sup>c</sup> HPLC Area Percentage. <sup>d</sup> Optical purity determined by chiral HPLC analysis.

reactivity of asymmetric hydrogenations,<sup>22</sup> we conducted catalyst loading studies in a number of different solvents.<sup>23</sup> Common solvents for hydrogenation such as MeOH, iPrOAc, and 2-MeTHF gave lower reactivity and slightly diminished enantioselectivity (94–97%), but 1,2-dichloroethane (DCE) gave complete conversion and 98.2% ee even at 0.2% catalyst loading (Figure 2). Still better performance was observed in halogenated aromatics, with good conversion using as little as 0.1 mol % catalyst and high enantioselectivities in PhCF<sub>3</sub> and chlorobenzene (97.6 and 98.2% ee, respectively). We postulate that the halogenated solvents offer superior performance (over MeOH, iPrOAc, and 2-MeTHF) due to their relatively weak coordination with the catalyst. We chose chlorobenzene as the solvent for further studies, as it facilitated higher reactivity in the hydrogenations and is commercially available on a large scale.

**Figure 2.** Catalyst loading studies in various solvents.

With optimized conditions in hand,<sup>24</sup> we turned our attention to investigating the scope and limitations of this chemistry. Unsaturated esters **3a–3k** were prepared predominantly as the (*E*)-olefin isomers<sup>25</sup> in good yield by conjugate addition of phenols **1a–1k** to alkyne **2** in the presence of DABCO in acetonitrile (Scheme 2, Table 2). These conditions were established through screening and were optimized to minimize formation of the minor (*Z*)-isomer (removed by chromatography) which was demonstrated to favor the undesired enantiomer of the saturated ester in the subsequent asymmetric hydrogenation (*vide infra*). Variables screened included type of base, concentration, and temperature, but the choice of acetonitrile as solvent and the stoichiometry of DABCO were found to be particularly important factors.

**Scheme 2****Table 2.** Preparation of  $\beta$ -Aryloxybuten-2,3-oates<sup>a</sup>

entry	phenol	R	unsat. ester <sup>b</sup>	yield <sup>c</sup>
1	<b>1a</b>	2-Br	<b>3a</b>	77
2	<b>1b</b>	H	<b>3b</b>	74
3	<b>1c</b>	2-Me	<b>3c</b>	81
4	<b>1d</b>	4-Me	<b>3d</b>	79
5	<b>1e</b>	2-OMe	<b>3e</b>	69
6	<b>1f</b>	2-F	<b>3f</b>	81
7	<b>1g</b>	4-F	<b>3g</b>	83
8	<b>1h</b>	2-Cl	<b>3h</b>	78
9	<b>1i</b>	3-Br	<b>3i</b>	74
10	<b>1j</b>	2-I	<b>3j</b>	81
11	<b>1k</b>	4-NO <sub>2</sub>	<b>3k</b>	56

<sup>a</sup> Reaction conditions: 1.2 equiv of **1**, 0.98 equiv of DABCO, MeCN, 70 °C, 2 h. <sup>b</sup> Ratio of *E/Z* formed was at least 96:4 in each case by <sup>1</sup>H NMR. <sup>c</sup> Isolated yield obtained by chromatographic purification of stereoisomerically pure (*E*)-isomer.

(23) Catalyst loading studies were performed at 120 psi H<sub>2</sub>, 0.3 M substrate, 50 °C, 18 h. See Supporting Information for tabular results.

(24) We also examined the effect of other parameters on the outcome of the reaction. Decreasing the pressure of H<sub>2</sub> led to reduced reactivity (with no observable impact on enantioselectivity), but a lower pressure was used due to autoclave constraints. To compensate, increasing the temperature increased reactivity (with a slight decrease in enantioselectivity) and increasing the concentration also led to increased reactivity (with minimal impact on enantioselectivity). See Supporting Information for details.

(25) Olefin geometry determined by NMR (see Supporting Information).

(26) The absolute configuration of **4a** was established by chemical correlation with a sample independently synthesized from commercially available (*S*)-4-penten-2-ol (see Supporting Information). The absolute configuration of **4b–4j** were assigned by analogy.

**Table 3.** Asymmetric Hydrogenation of  $\beta$ -Aryloxy Ene-Esters<sup>a</sup>

entry	unsat. ester	product	yield <sup>b</sup>	%ee <sup>c</sup>
1	<b>3a</b>	<b>4a</b>	83	97.7 ( <i>R</i> )
2	<b>3b</b>	<b>4b</b>	88	95.7 ( <i>R</i> )
3	<b>3c</b>	<b>4c</b>	88	96.0 ( <i>R</i> )
4	<b>3d</b>	<b>4d</b>	83	95.7 ( <i>R</i> )
5	<b>3e</b>	<b>4e</b>	95	91.3 ( <i>R</i> )
6	<b>3f</b>	<b>4f</b>	85	94.5 ( <i>R</i> )
7	<b>3g</b>	<b>4g</b>	87	96.7 ( <i>R</i> )
8	<b>3h</b>	<b>4h</b>	90	95.1 ( <i>R</i> )
9	<b>3i</b>	<b>4i</b>	81	96.8 ( <i>R</i> )
10	<b>3j</b>	<b>4j</b>	77 <sup>d</sup>	71.9 ( <i>R</i> )
11	<b>3k</b>	<b>4k</b>	— <sup>e</sup>	—
12	( <i>Z</i> )- <b>3a</b>	( <i>S</i> )- <b>4a</b>	81	96.0 ( <i>S</i> )
13	( <i>Z</i> )- <b>3b</b>	( <i>S</i> )- <b>4b</b>	93	93.9 ( <i>S</i> )
14	( <i>Z</i> )- <b>3f</b>	( <i>S</i> )- <b>4f</b>	93	94.5 ( <i>S</i> )

<sup>a</sup> Reaction conditions: 1% (NBD)<sub>2</sub>RhBF<sub>4</sub>, 1.05% SL-W008-1, PhCl, 80 °C, 125 psi H<sub>2</sub>, 20 h. <sup>b</sup> Isolated yield. <sup>c</sup> Optical purity determined by chiral HPLC analysis. <sup>d</sup> 3 mol % catalyst used. <sup>e</sup> Nitro functional group reduced to aniline.

Unsaturated substrates **3a–3i** were reduced to the analogous saturated products **4a–4i** in good yield and high optical purity (Table 3, entries 1–9).<sup>26</sup> Hydrogenation of *ortho*-iodo substrate **3j** proceeded in lower yield and selectivity (entry 10), presumably due to steric effects. The nitro functionality in substrate **3k** was not tolerated and was reduced to the corresponding aniline (entry 11). We also examined several of the (*Z*)-olefin isomers using

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the same catalyst/ligand combination and found that they gave good yields of the product with high but opposite absolute stereochemistry (entries 12–14). We believe this is an unusual instance where a given enantiomer of a hydrogenation catalyst can enantioselectively hydrogenate either the (*E*)- and (*Z*)-isomers of a prochiral substrate with opposite but equally high selectivity. This observation highlights the importance of controlling *E/Z* selectivity in the conjugate addition step.<sup>27</sup>

In summary, we have demonstrated an efficient method of preparing highly enantioenriched  $\beta$ -aryloxy-carboxylic esters via a two-step conjugate addition/asymmetric hydrogenation sequence, starting from commercially available materials. Specifically, a highly (*E*)-selective conjugate addition of substituted phenols to ethyl but-2-ynoate was developed. The resulting (*E*)-olefins were then asymmetrically hydrogenated in the presence of just 1 mol % bis(norbornadiene)rhodium(I) tetrafluoroborate and Walphos W008-1 to afford the saturated products in high enantiopurity and yield. The compatibility of the reaction with a range of aromatic substituents was also demonstrated.

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**Supporting Information Available.** General experimental methods for the preparation of **3a–3k** and **4a–4j** with isolated yields; characterization data for **3a–3k**, (*Z*)-**3a**, (*Z*)-**3b**, (*Z*)-**3f**, and **4a–4j**; chiral HPLC methods and traces for racemates and saturated products **4a–4j**, (*S*)-**4a**, (*S*)-**4b**, and (*S*)-**4f**; NMR evidence for (*E*)-olefin geometry; details of independent synthesis of **4a** from (*S*)-4-penten-2-ol to establish absolute configuration. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.