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Asymmetric Hydrogenation of α-Substituted Acrylic Acids Catalyzed by a Ruthenocenyl Phosphino-oxazoline−Ruthenium Complex

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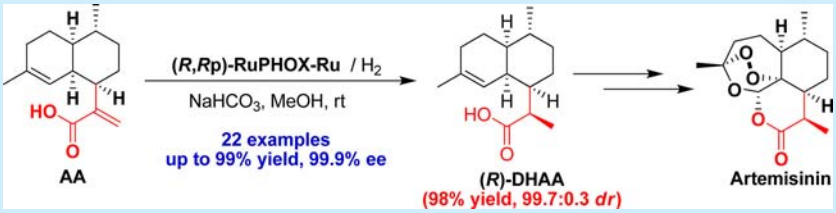
Supporting Information



ABSTRACT: Asymmetric hydrogenation of various α-substituted acrylic acids was carried out using RuPHOX−Ru as a chiral catalyst under 5 bar H_2, affording the corresponding chiral α-substituted propanic acids in up to 99% yield and 99.9% ee. The reaction could be performed on a gram-scale with a relatively low catalyst loading (up to 5000 S/C), and the resulting product (97%, 99.3% ee) can be used as a key intermediate to construct bioactive chiral molecules. The asymmetric protocol was successfully applied to an asymmetric synthesis of dihydroartemisinic acid, a key intermediate required for the industrial synthesis of the antimalarial drug artemisinin.

Optically pure α-substituted propanoic acids and their derivatives represent a large range of biologically active compounds, chiral drugs, and key intermediates.[1] Some examples are shown in Figure 1. A number of these compounds

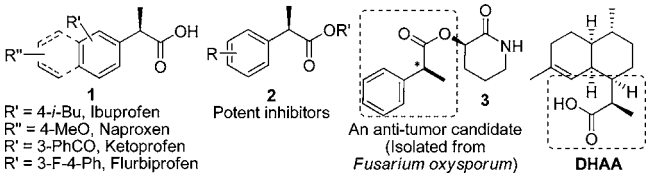


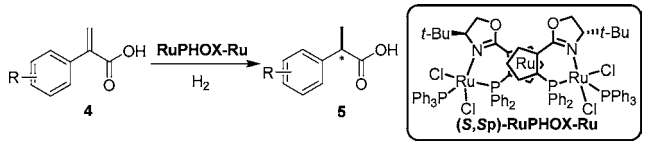
Figure 1. α-Substituted propanic acids and their derivatives.

(**1**) were used directly as nonsteroidal anti-inflammatory drugs, such as ibuprofen, naproxen, ketoprofen, and flurbiproxen.[2] Esterification products **2** are potent inhibitors against the inflammatory phenotype of cystic fibrosis.[3] The bioactive natural product **3**, isolated from the *Fusarium oxysporum*, shows cytotoxicity against three human cancer cell lines, PC-3, PANC-1, and A549.[4] Dihydroartemisinic acid (DHAA) is a key intermediate for the synthesis of artemisinin, currently the only recommended antimalarial drug.[5]

Transition-metal-catalyzed asymmetric hydrogenation of α-substituted acrylic acids is one of the most powerful strategies for the synthesis of chiral propanic acids, due to its atom efficiency and minimal environmental impact.[6] In 1977, James and McMillan reported a Ru-catalyzed asymmetric hydrogenation of 2-phenylacrylic acid by means of chelating bis-sulfoxide ligands.[7] Although in these initial studies the corresponding product was obtained with only 17% conversion and 4% ee, the past 30 years have seen obvious growth in this area of research.[8] However, the reported methodologies suffer from limited substrate scope (mainly focusing on the synthesis of ibuprofen and naproxen) and require high hydrogen pressures (approximately 100 atm) using chiral P,P-Ru complexes as catalysts. Since 1980, several chiral Rh complexes were developed and applied to the above reaction; however, these have given poor results compared to the hydrogenation of other prochiral olefins.[9] Due to recent progress on the successful asymmetric hydrogenation of α-substituted acrylic acids using chiral P,N-Ir complexes,[10] we sought to determine whether or not an inexpensive and efficient P,N-Ru complex would be suitable for such reactions.

We previously developed a ruthenocenyl phosphino-oxazoline−ruthenium complex with dual catalytic centers (RuPHOX−Ru, Scheme 1), which has shown promising catalytic activity in several asymmetric reactions.[11,12] Recently, this P,N-Ru complex was used as a chiral catalyst for the asymmetric hydrogenations of simple ketones and β-amino ketones, providing the correspond-

Scheme 1. Asymmetric Hydrogenation Catalyzed by RuPHOX−Ru



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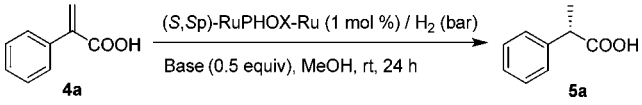
ing products in quantitative conversions and with up to 99.9% ee.[12] Encouraged by these promising results, we envisaged that the efficient and mild Ru-catalyzed asymmetric hydrogenation of α-substituted acrylic acids could be achieved using RuPHOX–Ru as a chiral catalyst. Herein, we disclose the preparation of α-substituted propanic acids using this methodology (Scheme 1).

Based on the screening of planar chiral phosphino-oxazoline ligands and solvents,[13] the RuPHOX–Ru-catalyzed asymmetric hydrogenation of 2-phenylacrylic acid (**4a**) was carried out under various hydrogen pressures in the presence of different bases in MeOH at room temperature (Table 1). Both organic and

Table 1. Base and Hydrogen Pressure Screening[a]



4a **5a**

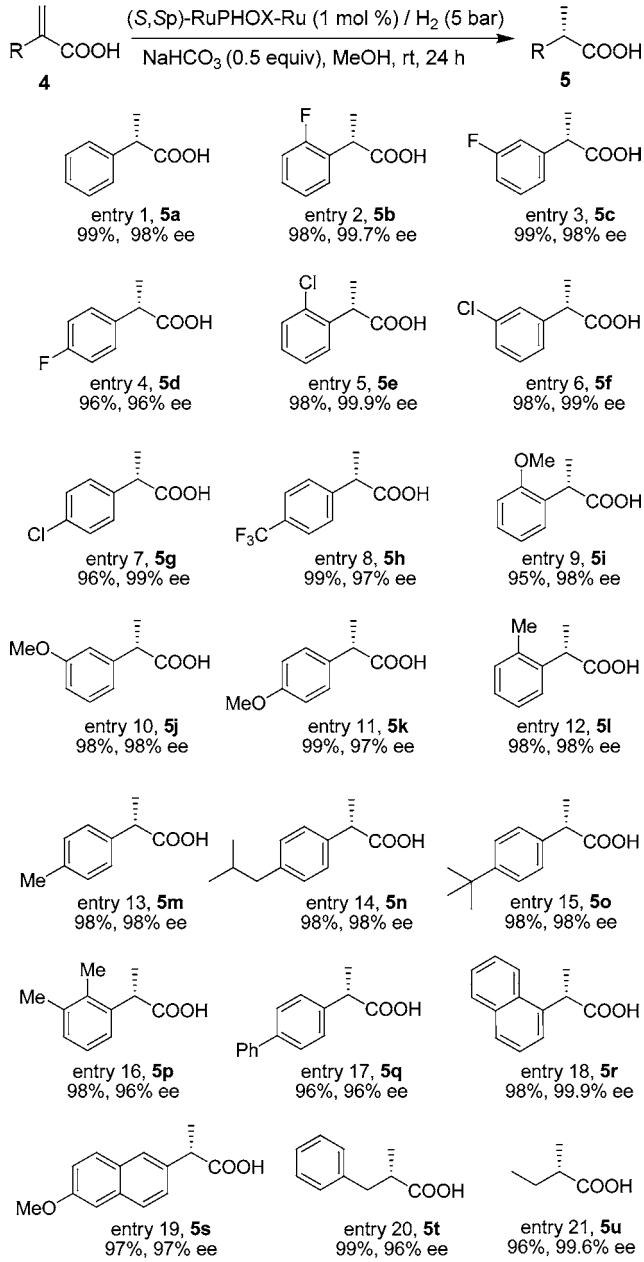
entry	additive	H_2 (bar)	conv (%)[b]	ee (%)[c]
1	Et_3N	50	>99	97.1
2	DIPEA	50	>99	96.0
3	DABCO	50	>99	96.3
4	DIPA	50	>99	97.7
5	Li_2CO_3	50	>99	89.9
6	Na_2CO_3	50	>99	97.6
7	K_2CO_3	50	>99	94.6
8	Cs_2CO_3	50	>99	95.9
9	NaOH	50	>99	97.1
10	$NaHCO_3$	50	>99	97.9
11	$NaHCO_3$	20	>99	98.0
12	$NaHCO_3$	10	>99	98.5
13	$NaHCO_3$	5	>99	98.3
14	$NaHCO_3$	2	>99	93.5
15	$NaHCO_3$	ambient	>99	88.0

[a]Conditions: **4a** (0.30 mmol), (*S*,*Sp*)-RuPHOX–Ru (1 mol %), base (0.5 equiv), and MeOH (3 mL) under a certain hydrogen pressure at rt for 24 h. [b]Determined by ^{1}H NMR. [c]Determined by chiral HPLC analysis of the corresponding methyl ester using an OJ-H column. Absolute configuration of **5a** was determined as *S*-configuration by comparing the sign of the optical rotation with reported data.[10]

inorganic bases were examined in the above reaction. Tertiary amines, such as Et_3N, DIPEA, and DABCO, afforded full conversion and excellent enantioselectivities (entries 1–3). Secondary amine DIPA also provided excellent catalytic behavior (entry 4). We then focused our attention on the effect that inorganic bases had on the reaction for the purpose of environmental and cost concerns. Carbonates with different cations were first examined with Na_2CO_3 giving the best result (entries 5–8). Subsequently, NaOH and $NaHCO_3$, with alkalinity stronger and weaker than that of Na_2CO_3, respectively, were used, and both provided excellent enantioselectivities (entries 9 and 10). $NaHCO_3$ was used to examine the effect of different hydrogen pressures on the reaction. Similar enantioselectivities were obtained even when the hydrogen pressure was decreased from 50 to 5 bar (entries 10–13). Further reductions of hydrogen pressure resulted in lower enantioselectivities, albeit with complete conversions (entries 14 and 15). Therefore, the optimal reaction conditions were found to be the following: using $NaHCO_3$ as a base in MeOH under 5 bar H_2 at room temperature.

Substrates bearing different 2-position substituents were then investigated (Scheme 2). When substrates possessing electron-withdrawing groups on the phenyl rings were used, excellent

Scheme 2. Substrate Scope[a]



[a]Conditions: **4** (0.30 mmol), (*S*,*Sp*)-RuPHOX–Ru (1 mol %), $NaHCO_3$ (0.5 equiv), MeOH (3 mL) under 5 bar H_2 at rt for 24 h. Isolated yields and ee values were determined by chiral HPLC analysis of the corresponding methyl ester using AD-H and OJ-H columns. Absolute configuration of **5** was determined as *S*-figuration by comparing the sign of the optical rotation with **5a**.

yields and enantioselectivities were obtained (entries 1–8). Substrates bearing an *ortho*-substituent on the phenyl ring provided the best enantioselectivity (entries 2 and 5). Replacing the electron-withdrawing substituent with an electron-donating group such as MeO or Me had no adverse effect on the reaction, with up to 98% ee being obtained in many cases (entries 9–13). Substrates with an *i*-Bu or *t*-Bu group at the *para*-position of the phenyl ring were examined, and both high yields and excellent enantioselectivities were obtained (entries 14 and 15). Multi-substituted **4p** bearing 2,3-disubstituted Me groups also provided excellent results (entry 16). A substrate bearing a Ph substituent

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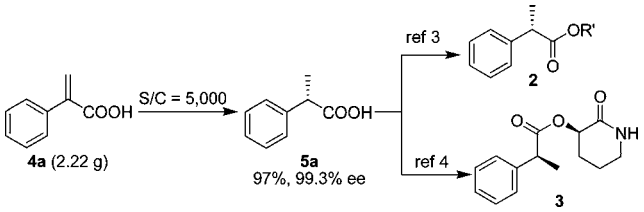
was examined, with the hydrogenated product being obtained in 96% yield and 96% ee value (entry 17). When the phenyl ring was replaced by naphthalene, high yields and excellent enantioselectivities were also obtained (entries 18 and 19). The phenyl ring could also be replaced by a Bn or Et group, with the desired products being prepared in quantitative yield and up to 99.6% ee (entries 20 and 21).

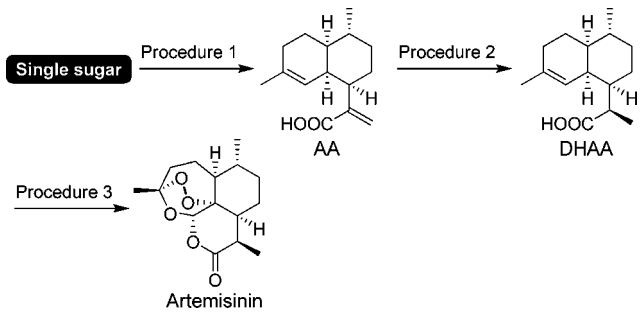
To examine the efficiency of the catalyst system, a gram-scale hydrogenation of **4a** (2.22 g) was carried out with a low catalyst loading of 0.02 mol % (S/C = 5000) with modified reaction conditions under 50 bar H_2 at 10 °C for 48 h.[13] Desired product **5a** was obtained in 97% yield and 99.3% ee (Scheme 3). **5a** can be used as a key intermediate for the construction of bioactive chiral molecules, such as **2** and **3**, via a simple procedure following previously reported methods.[3,4]

Scheme 3. Gram-Scale Synthesis of 5a and Its Transformation



Artemisinin and its derivatives (dihydroartemisinin, artemether, artesunate, etc.) are the most effective drugs for the treatment of malaria, thus efficient synthetic routes toward their preparation are required. We recently developed a simple and mild synthetic approach for the synthesis of artemisinin from DHAA that does not require any photochemical steps, with the product being obtained in 68% yield (Scheme 4, procedure 3).[14]

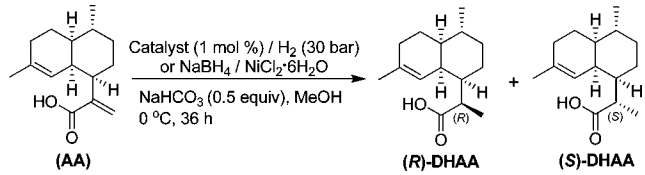
Scheme 4. Artificial Approach to Artemisinin



The technology was licensed to Shanghai Fosun Pharmaceutical (Group) Co. Ltd., and a kilogram-scale pilot synthesis of artemisinin was successfully completed. In 2006, scientists from Amyris Inc. and the University of California, Berkeley, developed a synthetic biology process with engineered yeast for the production of large quantities of artemisinic acid (AA) (procedure 1).[5a] The only challenge we encountered for the industrial synthesis of artemisinin was the efficient synthesis of DHAA from AA (procedure 2).

Desired product (*R*)-DHAA can be obtained with 85:15 dr by taking advantage of the adjacent chiral center using $NaBH_4$ as a nonchiral reductant (Scheme 5, entry 1). Based on the excellent performance of RuPHOX−Ru in the above reaction, we carried out the asymmetric hydrogenation of AA using the above (*S*,Sp)-RuPHOX−Ru as a chiral catalyst. Following optimization of the reaction conditions, we obtained (*S*)-DHAA in 98% yield and

Scheme 5. Asymmetric Synthesis of DHAA from AA



entry	catalyst and/or reductant	yield (%)	R / S
1	$NaBH_4$, $NiCl_2·6H_2O$	75%	85:15
2	(*S*,Sp)-RuPHOX-Ru, H_2	98%	0.1:99.9
3	(*R*,Rp)-RuPHOX-Ru, H_2	98%	99.7:0.3

0.1:99.9 dr (entry 2). Therefore, (*R*,Rp)-RuPHOX−Ru, the enantiomer of (*S*,Sp)-RuPHOX−Ru, was also applied to the above reaction. Desired product (*R*)-DHAA was obtained in excellent yield and 99.7:0.3 dr (entry 3). These results show that the industrial synthesis of artemisinin is possible using a combination of synthetic biology and chemistry processes.[15]

In summary, an asymmetric hydrogenation of α-substituted acrylic acids was achieved using RuPHOX−Ru as a chiral catalyst under a low hydrogen pressure, affording the corresponding chiral α-substituted propanic acids in up to 99% yield and 99.9% ee. The asymmetric protocol could be performed on a gram-scale with a relatively low catalyst loading (up to 5000 S/C), and the resulting product can be transformed to various biologically active compounds. The asymmetric hydrogenation of artemisinic acid was also achieved with DHAA being obtained in almost quantitative yield and 99.7:0.3 dr using the above catalytic system.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b00748.

Experimental procedures, compound characterization, NMR spectra, and HPLC data (PDF)

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Notes

The authors declare no competing financial interest.

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■ DEDICATION

In celebration of the Nobel Prize winner Professor Youyou Tu for the discovery of artemisinin.

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