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Highly Chemo- and Enantioselective Hydrogenation of 2-Substituted-4-oxo-2-alkenoic Acids

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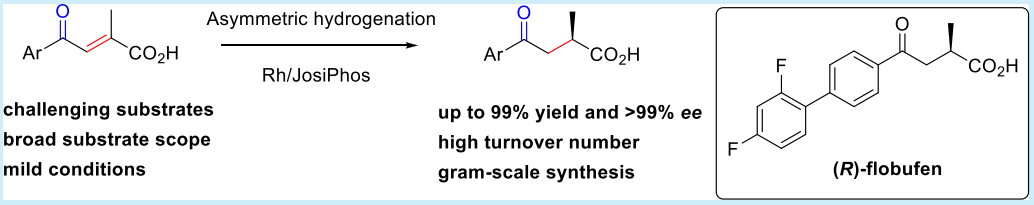

ABSTRACT: The highly chemo- and enantioselective hydrogenation of (*E*)-2-substituted-4-oxo-2-alkenoic acids was established for the first time using the Rh/JosiPhos complex, affording a series of chiral α-substituted-γ-keto acids with excellent results (up to 99% yield and >99% *ee*) and high efficiency (up to 3000 TON). In addition, the importance of this methodology was further demonstrated by a concise and gram-scale synthesis of the anti-inflammatory drug (*R*)-flobufen.

Chiral α-substituted-γ-keto acids are common motifs found in many chiral drugs and natural products. Important examples of this family molecules include (*R*)-(+)-flobufen,[1a] (*R*)-tanomastat,[1b] (*R*)-esonarimod,[1c] ganoderic acids,[1d] bisdehydrostemoninine A,[1e] (+)-applanatumol S,[1f] and fornicin C (Figure 1).[1g] This motif could also play an important role as a chiral backbone for the synthesis of bioactive compounds such as human neutrophile elastase inhibitors[2a] and angiotensin-converting enzyme inhibitors[2b] and the total synthesis of natural products.[2c]

Intrigued by the great importance, significant efforts have been made to develop synthetic approaches toward the enantioselective construction of chiral α-substituted-γ-keto acids. There have been several representative methods for the synthesis of chiral α-substituted-γ-keto acids, including the alkylation reaction or the coupling reaction using chiral

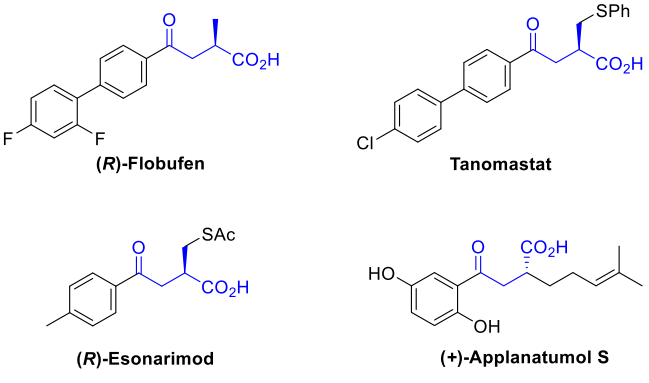

Figure 1. Representative chiral drugs and natural products with an α-substituted-γ-keto acid motif.

Scheme 1. Representative Approaches to Chiral α-Substituted-γ-Keto Acids

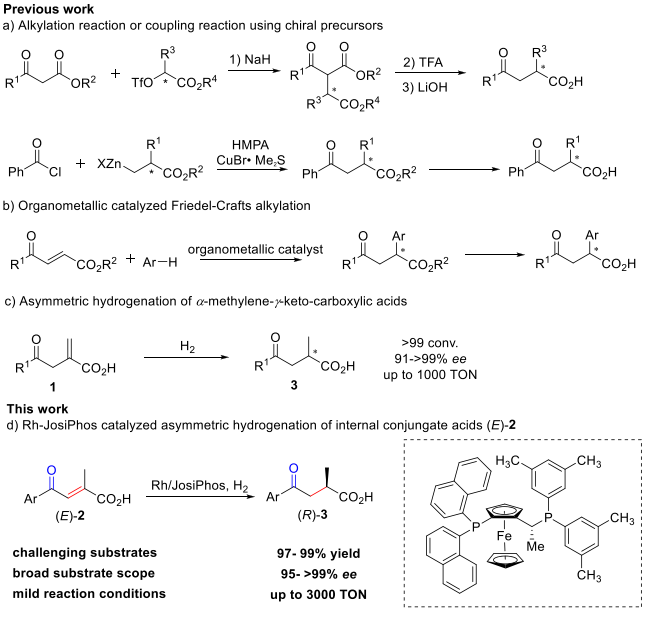

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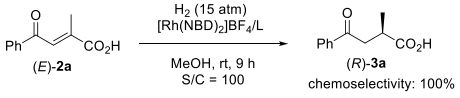
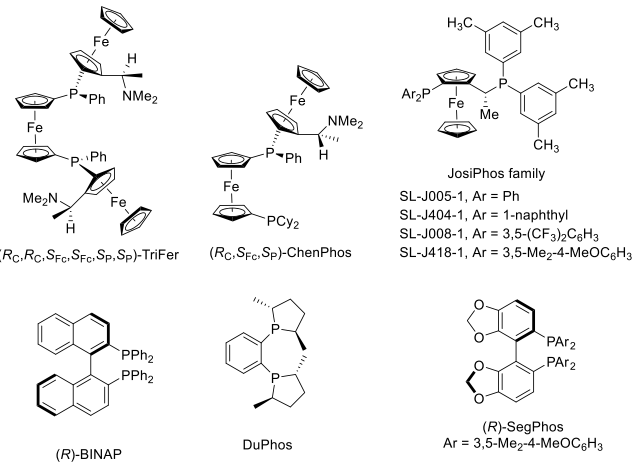
Table 1. Screening Ligands for the Asymmetric Hydrogenation of (*E*)-2-Methyl-3-benzoylpropenoic Acid 2a[a]





entry	ligand	conv. (%)[b]	*ee* (%)[c]
1	Trifer	>99	89
2	ChenPhos	>99	76
3	SL-J005-1	>99	96
4	SL-J404-1	>99	97
5	SL-J008-1	>99	90
6	SL-J418-1	>99	96
7	(*R*)-BINAP	80	−63
8	DuPhos	>99	87
9	(*R*)-SegPhos	>99	−76

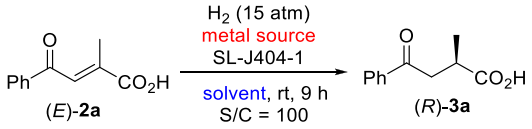
[a]Reaction conditions: 0.2 mmol scale, [substrate] = 0.2 mol·L^{-1}, solvent = 1.0 mL, 1.0 mol % of catalyst [Rh(NBD)$_2$]BF$_4$/ligand 1:1.1, 9 h. [b]Conversions were determined by ^{1}H NMR analysis. [c]Enantiomeric excesses were determined by chiral HPLC analysis using a chiral column after the products were converted to the corresponding amides.

precursors (Scheme 1a),[3] the organometallic-catalyzed enantioselective Friedel−Crafts alkylation (Scheme 1b),[4] and the asymmetric hydrogenation of α-methylene-γ-keto-carboxylic acids (Scheme 1c).[5]

It is well known that catalytic asymmetric hydrogenation[6] is one of the most efficient, environmentally friendly, and cost-effective approaches to various chiral compounds. Among these reported methods, the chemo- and enantioselective hydrogenation of α-methylene-γ-keto-carboxylic acid **1** has been one of the most efficient and straightforward approaches to chiral α-substituted-γ-keto acids. However, the terminal C=C bond undergoes rapid isomerization, shifting to the thermodynamically more stable internal conjugate acid (*E*)-**2**.[7] Therefore, it might be more practical to synthesize chiral α-substituted-γ-keto acids by the chemo- and enantioselective hydrogenation of this internal conjugate acid (*E*)-**2**.

α-Methylene-γ-keto-carboxylic acid **1**, which bears a coordinating carbonyl group at the β-position of the C=C double bond, enables efficient enantioinduction in hydrogenation due to the secondary coordination.[8] Unlike terminal olefin **1**, the conjugate groups make internal olefin in (*E*)-**2** more challenging for asymmetric hydrogenation. In addition,

Table 2. Optimization of the Reaction Conditions for the Asymmetric Hydrogenation of (*E*)-2a[a]



entry	solvent	metal precursor	conv. (%)[b]	*ee* (%)[c]
1	MeOH	[Rh(NBD)$_2$]BF$_4$	>99	97
2	EtOH	[Rh(NBD)$_2$]BF$_4$	>99	97
3	*i*-PrOH	[Rh(NBD)$_2$]BF$_4$	>99	98
4	CF$_3$CH$_2$OH	[Rh(NBD)$_2$]BF$_4$	>99	97
5	EtOAc	[Rh(NBD)$_2$]BF$_4$	>99	90
6	DCM	[Rh(NBD)$_2$]BF$_4$	96	79
7	THF	[Rh(NBD)$_2$]BF$_4$	95	95
8	MTBE	[Rh(NBD)$_2$]BF$_4$	>99	78
9	MeOH	[Ir(COD)Cl]$_2$	36	NA
10	MeOH	[Rh(COD)Cl]$_2$	53	NA
11	MeOH	[Rh(NBD)Cl]$_2$	>99	95

[a]Reaction conditions: 0.2 mmol scale, [substrate] = 0.2 mol·L^{-1}, solvent = 1.0 mL, 1.0 mol % of catalyst (metal/SL-J404-1 1:1.1). [b]Conversions were determined by ^{1}H NMR analysis. [c]Enantiomeric excesses were determined by chiral HPLC analysis using a chiral column after the products were converted to the corresponding amides.

because of the lack of a coordinating group at the β-position of the double bond, the enantiocontrol in the asymmetric hydrogenation of (*E*)-**2** might also be a problem. Therefore, we are focused on the highly chemo- and enantioselective hydrogenation of internal conjugate acid (*E*)-**2** (Scheme 1d).

Our investigation was initiated by using (*E*)-2-methyl-3-benzoylpropenoic acid **2a** as the model substrate. When TriFer and ChenPhos were used as ligands,[9] the Rh-catalyzed hydrogenation gave excellent chemoselectivities (100%) but moderate enantioselectivities (89 and 76% *ee*, respectively) (Table 1, entries 1 and 2). Then, the ferrocene-based bisphosphine ligand JosiPhos family was screened. To our delight, better results were obtained (entries 3−6), and the ligand SL-J404-1 afforded the best results (>99% conversion and 97% *ee*) (entry 4). Other well-known diphosphine ligands, such as (*R*)-BINAP, Duphos, and (*R*)-SegPhos, showed less attractive catalytic results (entries 7−9). The absolute configuration of **3a** was assigned by a comparison of its optical rotation with the reported value.[5d]

Next, the solvent and metal precursors for the hydrogenation were investigated with the ligand SL-J404-1 (Table 2). Among polar solvents, the enantioselectivities enhanced with the increase in the bulkiness of the alcohols, whereas the conversions remained excellent (entries 1−4, Table 2). *i*-PrOH was highly beneficial in terms of enantioselectivity and catalytic activity (>99% conversion, 98% *ee*) (entry 3, Table 2). Polar aprotic solvents such as EtOAc, MTBE, THF, and DCM gave less attractive results. Cationic [Rh(NBD)$_2$]BF$_4$ was superior to the neutral precursor [Rh(NBD)Cl]$_2$ with respect to enantioselectivity (97 vs 95% *ee*) (entry 1 vs 11, Table 2). Other metal precursors [Rh(COD)Cl]$_2$ and [Ir(COD)Cl]$_2$ showed poor catalytic activity under the reaction conditions (entries 9 and 10, Table 2).

With the optimized conditions in hand ([Rh(NBD)$_2$]BF$_4$/SL-J404-1 in *i*-PrOH under 15 atm hydrogen pressure at room temperature), we turned our attention to explore the substrate scope. A variety of 2-methyl-4-oxo-2-alkenoic acids (*E*)-**2** were

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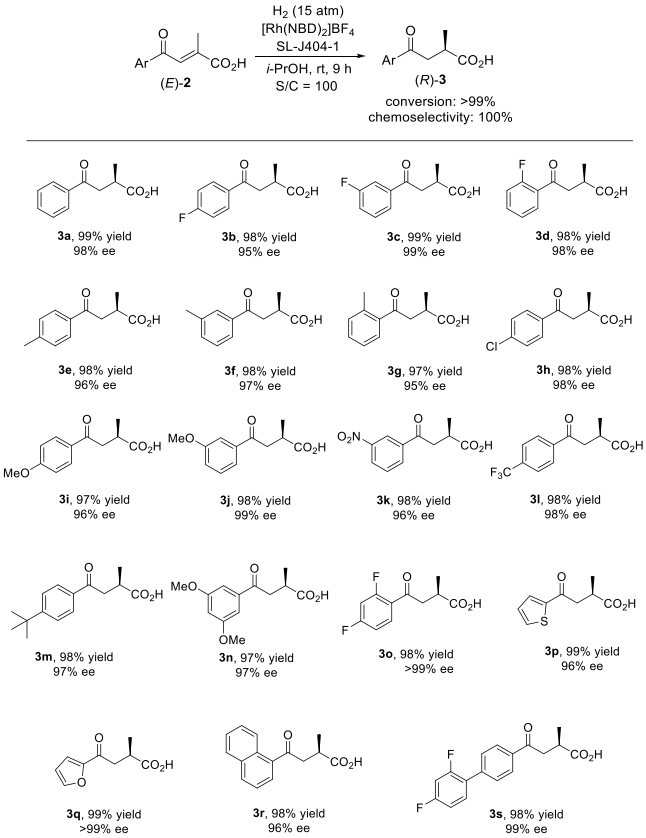
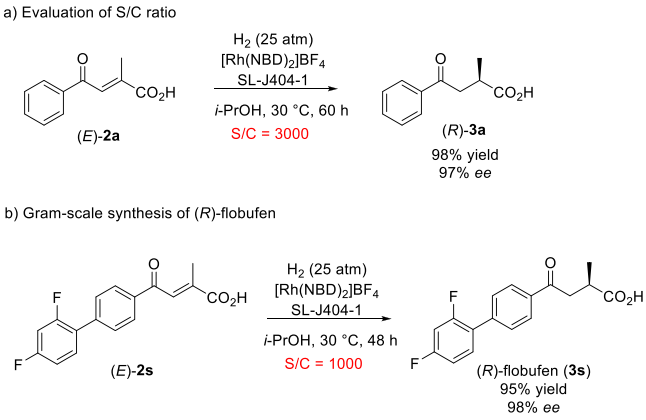
Table 3. Scope of Substrates for the Asymmetric Hydrogenation of (*E*)-2-Methyl-4-oxo-2-alkenoic Acids 2[a]



[a]Reaction conditions: 0.2 mmol scale, [substrate] = 0.2 mol·L^{-1}, solvent = 1.0 mL, 1.0 mol % of catalyst $[Rh(NBD)_2]BF_4$/SL-J404-1 1:1.1. Yield of product was obtained after isolation from flash column chromatography. Enantiomeric excesses were determined by chiral HPLC analysis using a chiral column after the products were converted to the corresponding amides.

Scheme 2. S/C Evaluation and Gram-Scale Synthesis of (*R*)-Flobufen



synthesized and hydrogenated under the optimized reaction conditions (Table 3). The reaction proceeded well in all cases, affording the corresponding α-substituted-γ-keto acids in excellent yields with excellent enantioselectivities (97−99% yield, 95 →> 99% *ee*). The substrates (**3a**−**o**) were hydrogenated well to give the desired products with excellent results, which indicated that the electronic and steric properties as well as the locations of substituents on the fused benzene ring had little influence on this asymmetric hydrogenation. Impressive results were also obtained with heteroaromatic substrates (**3p**−**q**), affording the hydrogenated products with excellent results (99% yield, 96 → 99% *ee*). Moreover, it is noteworthy that the nonsteroidal anti-inflammatory drug (*R*)-flobufen **3s**[10] was obtained in 98% yield with 99% *ee*.

To our delight, substrate (*E*)-**2a** could be hydrogenated well with an S/C ratio of 3000 for an extended time with the retention of high enantioselectivity, which highlighted the high efficiency of this catalytic system (Scheme 2a). The practicality of our methodology was further demonstrated by the gram-scale synthesis of (*R*)-flobufen **3s** (Scheme 2b). Applying the rhodium/bisphosphine catalytic system, (*R*)-flobufen was obtained in 95% yield with 98% *ee*.

In conclusion, a novel and straightforward synthetic method for the valuable chiral α-methyl-γ-keto acid scaffold through the asymmetric hydrogenation of the challenging (*E*)-2-methyl-4-oxo-2-alkenoic acid substrates utilizing the rhodium/bisphosphine catalytic system has been successfully established. A series of chiral α-methyl-γ-keto acids were obtained in almost perfect yields and with almost perfect chemo- and enantioselectivities (up to 99% yield, 100% chemoselectivity, and up to >99% *ee*). This synthetic system has been demonstrated to be highly efficient, with a TON of 3000. Moreover, the synthetic utility of this method was also highlighted in the gram-scale preparation of (*R*)-flobufen with 98% *ee*.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.0c01618.

General information, preparation of 2-substituted-4-oxo-2-alkenoic acids (*E*)-**2**, asymmetric hydrogenation of 2-substituted-4-oxo-2-alkenoic acids (*E*)-**2**, procedures for evaluation of S/C ratio, procedures for the gram-scale synthesis of (*R*)-flobufen, references, NMR spectra, and HPLC spectra (PDF)

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Notes

The authors declare no competing financial interest.

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