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Letter

Asymmetric Hydrogenation of β-Aryl Alkylidene Malonate Esters: Installing an Ester Group Significantly Increases the Efficiency

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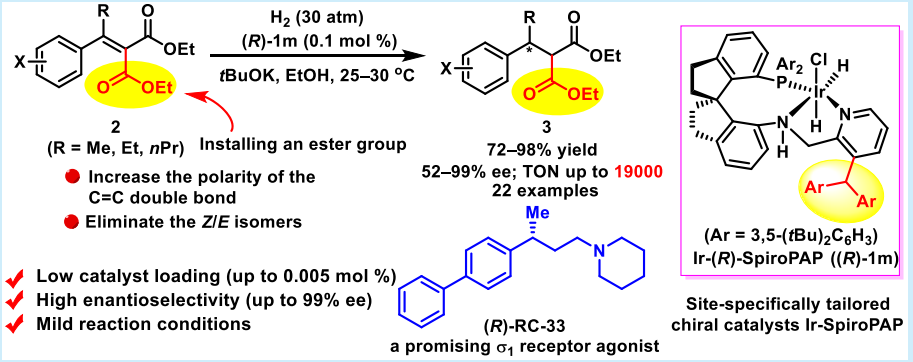

ABSTRACT: Herein, we report a practical method for efficient asymmetric hydrogenation of β-aryl alkylidene malonates. With a site-specifically tailored chiral spiro iridium catalyst, a series of β-aryl alkylidene malonate esters were hydrogenated to afford chiral malonate esters with good to excellent enantioselectivities (up to 99% ee) and high turnover numbers (up to 19000). The results showed that installing an ester group in α,β-unsaturated carboxylic esters significantly increased the efficiency of their asymmetric hydrogenation reactions.

Transition-metal-catalyzed asymmetric hydrogenation is one of the most efficient, reliable, and sustainable methods for the synthesis of chiral compounds.[1] Over the past several decades, considerable effort has been devoted to the development of highly enantioselective hydrogenation methods for obtaining optically active chiral products, and some of these methods have been successfully used for the industrial production of chiral pharmaceuticals, fragrances, and agrochemicals.[1a] One such method is the catalytic asymmetric hydrogenation of β-aryl α,β-unsaturated carboxylic acids and esters, a reaction that has been attracting the interest of synthetic chemists ever since 1971, when Morrison et al.[2] first reported the use of a chiral Rh-NMDPP catalyst for the asymmetric hydrogenation of (*E*)-β-methylcinnamic acid to 3-phenylbutanoic acid with 61% ee. This reaction provides a straightforward approach to optically active chiral carboxylic acids and esters bearing a β-tertiary benzylic stereocenter, which are important building blocks in the synthesis of pharmaceuticals and other bioactive molecules (Figure 1). A wide range of chiral catalysts, including Rh,[3] Ru,[4] Ir,[5] Ni,[6] and Co complexes[7] with various chiral ligands, have been developed, and the substrate scope has also been substantially broadened. Importantly, this reaction has been utilized in syntheses of chiral drugs such as tipranavir,[8] JNJ-26076713,[9] and (*R*)-RC-33[10] and the natural product (−)-juvabione.[11] However, a high catalyst loading and harsh reaction conditions

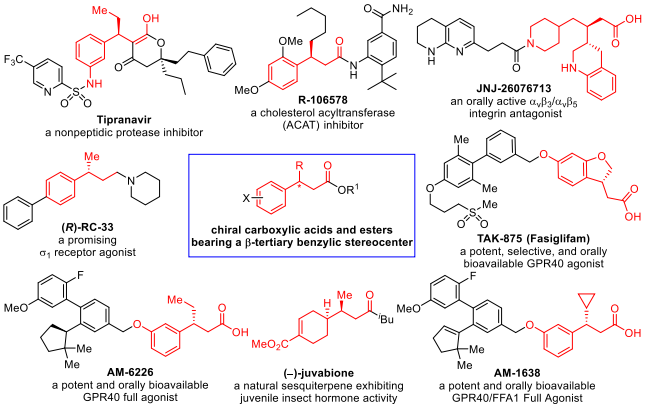

Figure 1. Selected pharmaceuticals and bioactive molecules containing a tertiary benzylic stereocenter.

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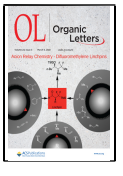
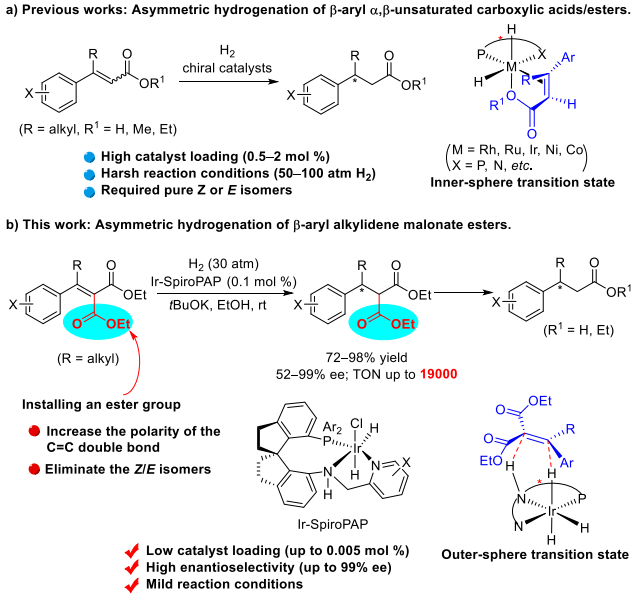


are generally required for good results (Scheme 1a). A more intractable problem is that the reaction requires that substrate

Scheme 1. Asymmetric Hydrogenation Synthesis of Chiral Carboxylic Acids/Esters with β-Tertiary Benzylic Stereocenters

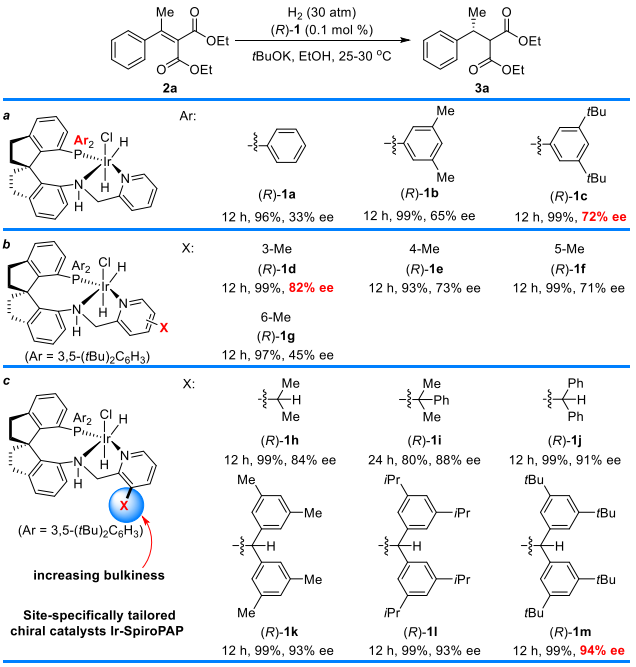


be a pure *Z* or *E* isomer; because such isomers are difficult to separate, this reaction has limited utility despite its high atom economy.

We have found that the chiral iridium complexes of spiro pyridine-aminophosphine ligands, Ir-SpiroPAP, are extremely efficient catalysts for the asymmetric hydrogenation of ketones with turnover numbers (TONs) exceeding 10^6.[12] The high efficiency of this type of metal-NH bifunctional catalyst is attributed to the hydrogenation proceeding via an outer-sphere six-membered-ring transition state.[13] In this reaction model, the substrate receives a hydride from the metal center and a proton from the amino group of the ligand but does not coordinate with the metal center of the catalyst, so the activity of the catalyst is maintained.[14] However, the reported metal-NH bifunctional catalysts, including Noyori's Ru-BINAP-diamine catalyst,[15] are effective only for the hydrogenation of highly polar double bonds such as the C═O and C═N bonds of ketones and imines.[13] With this fact in mind, we speculated that introduction of an ester group at the *α*-position of *α*,*β*-unsaturated carboxylic esters would increase the polarity of the C═C double bond, making the resulting alkylidene malonates suitable substrates for chiral metal-NH bifunctional catalysts (Scheme 1b). More importantly, the use of such substrates would eliminate the need to prepare *α*,*β*-unsaturated carboxylic esters in pure *Z* or *E* form. In this paper, we report a protocol for highly enantioselective hydrogenation of alkylidene malonates catalyzed by Ir-SpiroPAP catalysts.[12] By carefully tailoring the catalyst, we achieved high yields and good to excellent enantioselectivities (up to 99% ee) in the synthesis of *β*-aryl alkyl malonates (Scheme 1b), which could be decarboxylated to afford chiral carboxylic acids and esters bearing a *β*-tertiary benzylic stereocenter.

To evaluate various Ir-SpiroPAP catalysts **1**, we carried out the hydrogenation of diethyl 2-(1-phenylethylidene)malonate (**2a**) with 0.1 mol % catalyst in EtOH under 30 atm of H_2 at room temperature (25−30 °C). Under these conditions, the reaction was catalyzed by (*R*)-**1a**, which has *P*-phenyl groups, and gave a 96% yield of desired product **3a**, but the ee was only 33%. In contrast, (*R*)-**1b**, which has 3,5-dimethyl substitution on each of the *P*-phenyl rings, gave a 65% ee. The enantioselectivity could be increased to 72% ee by using catalyst (*R*)-**1c**, which has bulky 3,5-di-*tert*-butyl substitution on the *P*-phenyl rings (Scheme 2a). These results clearly

Scheme 2. Evaluation of Spiro Iridium Catalysts (*R*)-1 for Asymmetric Hydrogenation of 2a[a,b]



[a]Reaction conditions: 1.0 mmol scale, (*R*)-**1**/*t*BuOK/**2a** = 1:400:1000, EtOH (2.0 mL), room temperature (25−30 °C), 30 atm H_2, 12−24 h. [b]80−99% NMR yield (80−100% conversion).

showed that catalyst bulk was beneficial for enantioselectivity. Next, we evaluated catalysts bearing various groups on the pyridine ring (Scheme 2b). Comparison of catalysts with a methyl group at each of the four open positions on the pyridine ring showed that the catalyst with a methyl group at the 3-position, (*R*)-**1d**, gave the highest enantioselectivity (82% ee). Then we increased the steric bulk of the substituent at the 3-position (Scheme 2c) and found that (*R*)-**1m**, which has a 3-di(3,5-di-*tert*-butylphenyl)methyl-2-pyridine moiety, was the most enantioselective, giving a 99% yield of **3a** with an ee of 94%. Using this highly efficient catalyst, we optimized the reaction conditions for the asymmetric hydrogenation of **2a**.

Evaluation of various solvents showed that other alcohols were suitable, although EtOH gave the highest yield and enantioselectivity (Table 1, entries 1−4). In addition to *t*BuOK, other bases (*t*BuONa and K_2CO_3) could also be used, but the yield and enantioselectivity were slightly lower (compare entries 1, 5, and 6). Lowering the *t*BuOK/**2a** ratio to 1:5 decreased the yield but had a negligible effect on the enantioselectivity (entry 8). A decrease in enantioselectivity was observed when the reaction temperature was increased to 50 °C (entry 9). When the H_2 pressure was increased to 50 atm, the reaction time could be shortened to 10 h (entry 10), and we were delighted to find that the catalyst loading could be

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Table 1. Optimizing the Reaction Conditions of Hydrogenation of 2a with Catalyst (*R*)-1m[a]

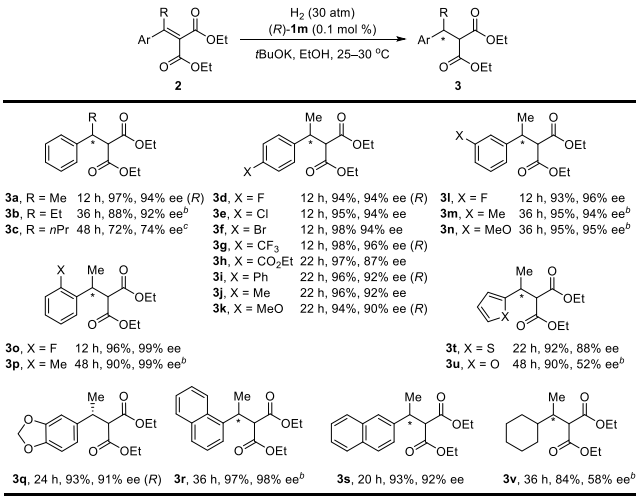
entry	solvent	base	time (h)	conv[b] (%)	yield[c] (%)	ee[d] (%)
1	EtOH	*t*BuOK	12	>99	99	94
2[e]	MeOH	*t*BuOK	12	80	80	88
3[e]	*n*PrOH	*t*BuOK	12	>99	99	93
4[e]	*i*PrOH	*t*BuOK	12	95	93	93
5	EtOH	*t*BuONa	12	>99	99	93
6	EtOH	K_2CO_3	24	85	83	90
7[f]	EtOH	*t*BuOK	12	98	97	94
8[g]	EtOH	*t*BuOK	12	87	87	93
9[h]	EtOH	*t*BuOK	8	>99	98	88
10[i]	EtOH	*t*BuOK	10	>99	99	94
11[j]	EtOH	*t*BuOK	24	>99	99	92
12[k]	EtOH	*t*BuOK	30	99	98	94
13[l]	EtOH	*t*BuOK	66	98	96	93
14[m]	EtOH	*t*BuOK	6 d	95	94	94

[a]Reaction conditions: 1.0 mmol scale, (*R*)-**1m**/*t*BuOK/**2a** = 1:400:1000, EtOH (2.0 mL), 30 atm H_2, room temperature (25–30 °C). [b]Determined by ^{1}H NMR. [c]NMR yield. [d]Determined by HPLC using chiral column. [e]Transesterification product was obtained. [f]*t*BuOK/**2a** = 1:1. [g]*t*BuOK/**2a** = 1:5. [h]At 50 °C. [i]50 atm H_2. [j]10 atm H_2. [k]5 mmol scale, 0.02 mol % (*R*)-**1m**. [l]10 mmol scale, 0.01 mol % (*R*)-**1m**, 80 atm H_2 (initial). [m]20 mmol scale, 0.005 mol % (*R*)-**1m**, 80 atm H_2 (initial).

decreased to 0.005 mol % (S/C = 20000) if the H_2 pressure was increased to 80 atm. Under these conditions, (*R*)-**3a** was obtained in 94% yield with a 94% ee (TON = 19000, entry 14).

Under the optimal reaction conditions, a series of *β*-aryl alkylidene malonate esters were hydrogenated with catalysis by (*R*)-**1m**, and chiral saturated malonates **3** were obtained in high yields with good to excellent enantioselectivities (52–99% ee) (Scheme 3). The *β*-alkyl group of the substrates had a marked effect on both the yield and the enantioselectivity of

Scheme 3. Asymmetric Hydrogenation of 2 with Catalyst (*R*)-1m[a–c]



[a]Reaction conditions: 1.0 mmol scale, (*R*)-**1m**/*t*BuOK/**2** = 1:400:1000, EtOH (2.0 mL), room temperature (25–30 °C), 30 atm H_2; isolated yield and the ee values were determined by Chiral HPLC. [b]0.2 mol % (*R*)-**1m**. [c]0.2 mol % (*R*)-**1m**, 50 atm H_2.

the reaction. Specifically, substrates with a small alkyl group such as methyl (**2a**, 94% ee) or ethyl (**2b**, 92% ee) gave good yields and high enantioselectivities, whereas the reaction of a substrate with an *n*Pr group showed lower enantioselectivity (**2c**, 74% ee). The electronic nature of the substituent at the 4-position of the phenyl ring of the substrate had little effect on either the yield or the enantioselectivity of reaction, although the presence of an electron-withdrawing substituent improved the reaction rate (**2d–2g**). The presence of an *ortho* substituent on the phenyl ring, whether it was electron withdrawing or electron donating, increased the enantioselectivity of reaction to 99% ee (**2o** and **2p**). Substrates bearing a heterocyclic moiety, such as 2-thiophenyl (**2t**) or 2-furanyl (**2u**), or a *β*-alkyl group, such as cyclohexyl (**2v**), also underwent the hydrogenation to afford the corresponding chiral malonate esters in high yields, albeit with only moderate to good enantioselectivity (52–88% ee).

DFT calculations were performed to study the stereochemistry-determining step, hydride/proton transfer, based on an outer-sphere mechanism[13] to understand the origins of the stereochemistry of reaction. Accordingly, models of the interaction between the substrate **2a** and catalyst (*R*)-**1m** based on the crystal structure of Ir-SpiroPAP[12a] were proposed (Figure 2). The hydride from Ir (Ir–H) and the proton from

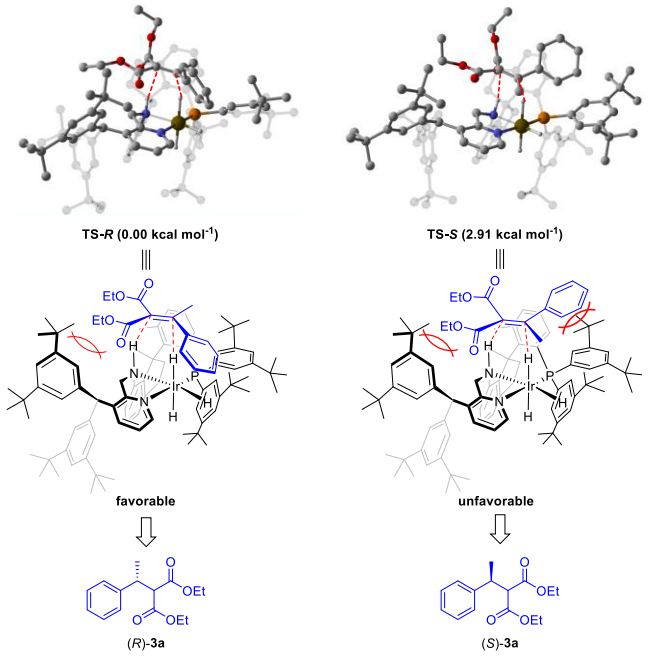


Figure 2. Models of stereochemistry control for asymmetric hydrogenations of **2a**.

nitrogen (N–H) of catalyst (*R*)-**1m** were transferred to the C=C double bond of the substrates **2a** via a six-membered-ring transition state. In this process, the bulky group at the 3-position of pyridine ring and the rigid spiro backbone of catalyst directed the approach of the substrate to the catalyst. To minimize the steric repulsion, **TS-*R*** were favorable for **2a**, leading to the formation of (*R*)-**3a**. These calculation results (98% ee) are in good agreement with the experimental results ((*R*)-**3a**, 94% ee).

To demonstrate the utility of the method, we converted (*R*)-**3a** to ester (*R*)-**4**, acid (*R*)-**5**, and malonate monoester (*R*)-**6** (Scheme 4a). Specifically, refluxing (*R*)-**3a** in DMSO in the

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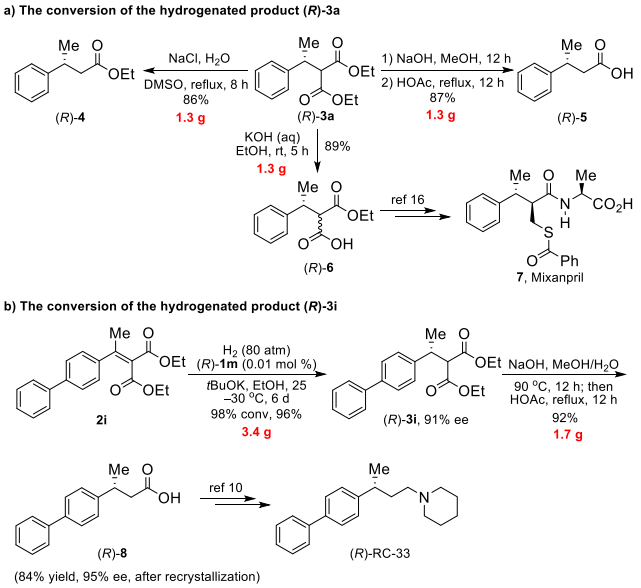
Scheme 4. Conversion of Hydrogenation Products



presence of NaCl and H_2O for 8 h produced ester (*R*)-**4** in 86% yield. Hydrolysis of (*R*)-**3a** with NaOH in MeOH, followed by refluxing in HOAc delivered acid (*R*)-**5** in 87% yield. Direct hydrolysis of (*R*)-**3a** with KOH in EtOH provided malonate monoester (*R*)-**6** as a mixture of *cis* and *trans* isomers. Compound (*R*)-**6** is a chiral intermediate in the synthesis of mixanpril (**7**),[16] an orally acting dual inhibitor of neutral endopeptidase and angiotensin-converting enzyme.[17] In addition, our hydrogenation method also provided an efficient route to (*R*)-RC-33,[10] a promising σ-receptor agonist (Scheme 4b). Specifically, unsaturated malonate ester **2i** was hydrogenated with catalysis by (*R*)-**1m** (0.01 mol %) on a gram scale (3.4 g, 10 mmol) to yield (*R*)-**3i** in 96% yield with 91% ee. Hydrolysis of (*R*)-**3i** with NaOH in MeOH and subsequent decarboxylation in refluxing HOAc afforded (*R*)-**8** in 92% yield (84% yield, 95% ee, after recrystallization).

In conclusion, we have developed an efficient and practical method for the synthesis of chiral carboxylic acids and esters bearing a β-tertiary benzylic stereocenter. Using site-specifically tailored chiral spiro iridium catalyst (*R*)-**1m**, we hydrogenated a series of β-aryl alkylidene malonate esters to obtain chiral malonate esters with good to excellent enantioselectivities (up to 99% ee) and high TONs (up to 19000). Installation of the ester group markedly enhanced the efficiency of the asymmetric hydrogenation and eliminated the need to start with a pure *Z* or *E* isomer of the substrate, which is a requirement of previously reported methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00093.

Synthetic procedures, characterization, and additional data (PDF)

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Notes

The authors declare no competing financial interest.

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