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Diastereo- and Enantioselective Synthesis of Structurally Diverse Succinate, Butyrolactone, and Trifluoromethyl Derivatives by Iridium-Catalyzed Hydrogenation of Tetrasubstituted Olefins

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S Supporting Information

ABSTRACT: A highly efficient iridium N,P-ligand-catalyzed asymmetric hydrogenation of functionalized tetrasubstituted olefins lacking a directing group has been developed. Various structural diverse chiral succinate derivatives were obtained in high yields and excellent enantio- and diastereoselectivities (up to 99% ee) using 0.5–1.0 mol % catalyst loadings. This stereoselective reaction is applicable for the synthesis of chiral acyclic molecules (up to >99% ee) having two contiguous stereogenic centers and is compatible with various aromatic, aliphatic, and heterocyclic systems, a variety of functional groups of different electronic nature. Furthermore, this asymmetric protocol allows a short enantioselective route to the butyrolactone building block, an intermediate in the synthesis of anticancer agent BMS-871 and pharmaceuticals (2S)-(-)-Verapamil and (2S)-(-)-Gallopamil.

KEYWORDS: tetrasubstituted olefin, asymmetric hydrogenation, iridium catalysis, enantioselective, diastereoselective

INTRODUCTION

Succinic acid derivatives are important building blocks in both organic and medicinal chemistry. For instance, these derivatives are employed as inhibitors of renin¹ and matrix metalloproteinases.² Moreover, succinates are used mainly as nonphthalate plasticizers³ in the cosmetic industry⁴ and agricultural chemistry, and in material science as monomers for polymers and dendrimers.⁵ Substituted butyrolactones are also common structural motifs in a wide range of complex natural products (Figure 1A) and serve as chiral building blocks in the synthesis of biologically active compounds (Figure 1B).⁶ Consequently, numerous methods and strategies have been developed for the synthesis of succinate derivatives.^{7,8} However, efficient catalytic and enantioselective synthesis⁸ of these important building blocks containing two contiguous stereocenters is unexplored, and the general catalytic asymmetric synthesis of these derivatives still presents a major challenge.^{8f}

Asymmetric hydrogenation of tetrasubstituted olefins (AHTOs) possesses tremendous potential in stereoselective synthesis because it enables the introduction of two vicinal stereocenters in one single step. Despite this, progress in this area has grown at a relaxed pace,⁹ partly because of the difficulties in differentiation of the prochiral faces of a fully substituted olefin, and partly the steric hindrance of the four

different substituents, which results in a slow rate of hydrogenation of these substrates in comparison to the di- and trisubstituted olefins. Highly enantioselective hydrogenation of olefins lacking a coordinative group is even more difficult as the coordinating group assists in the transfer of the chiral information from the catalyst to the product.¹⁰ The limited number of reports in the literature on the AHTOs without a coordinating group as compared to the AHTOs with a coordinating group further proves these difficulties.^{9a} To date, the catalytic system that has been reported was successful for only a few special types of substrates. Also, each class of olefins requires a special catalytic system.¹¹ Examples of AHTOs lacking a coordinating group are still limited¹² for cyclic olefins^{12a–e,g,h} and for acyclic olefins are very rare (Scheme 1).^{12c,f–h} The reported methods require either high catalyst loadings,^{12a–e} a mixture of catalysts,^{12e} or sophisticated reaction conditions.^{12e} Furthermore, there are only a few methods available for the hydrogenation of tetrasubstituted nonchelating olefins having functional groups that are able to create useful building blocks for further synthesis.^{12e} Thus, the development of a catalyst having a wide substrate scope for

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Figure 1. (A) Natural products containing butyrolactone motif. (B) Bioactive molecules derived from butyrolactone or chiral succinate compounds.

Scheme 1. Asymmetric Hydrogenation of Tetrasubstituted Olefins without Coordinating Group

70 AHTOs to access versatile building blocks is still a very
71 challenging task in asymmetric hydrogenation. Here, we report

our work to develop a general, simple, and efficient atom-
economical protocol for the highly enantioselective synthesis
of different chiral building blocks containing two stereogenic
centers.

RESULTS AND DISCUSSION

Initially, (*Z*)-diethyl 2-methyl-3-phenylmaleate **1a** was chosen
as a test substrate for asymmetric hydrogenation by using
an iridium-N,P complex as the catalyst. Normally, acyclic tetra-
substituted olefins containing nonchelating groups,^{12a} espe-
cially two ester groups,^{12f} are notoriously difficult substrates
because these olefins are both electron deficient and lack
chelating groups that would facilitate binding to the catalyst as
well as discrimination between the two enantiotopic faces.

It was found that olefin **1a** could be hydrogenated in good
yield using imidazole N,P-Ir complex **A** but with poor
enantioselectivity (Table 1). Subsequently, several chiral

Table 1. Evaluation of N,P-Iridium Catalysts in the Asymmetric Hydrogenation of **1a**^a

^aReaction conditions: 0.05 mmol of substrate, 0.5 mol % catalyst, 0.5 mL of CH₂Cl₂. Conversions were determined by ¹H NMR spectroscopy. Enantiomeric excess determined by HPLC and SFC-HPLC analysis using a chiral stationary phase.

Table 2. Optimization of Reaction Conditions for the Hydrogenation of Tetrasubstituted Maleate Olefins^a

^a0.5 mol % catalyst **H**, 0.5 mL of CH_2Cl_2 . Conversion determined by ^1H NMR spectroscopy. Enantiomeric excess determined by HPLC and SFC-HPLC analysis using a chiral stationary phase.

Table 3. Asymmetric Hydrogenation of Tetrasubstituted Maleate Olefins^a

^aReaction conditions: 0.1 mmol of substrate, 0.5 mol % catalyst **H**, 0.5 mL of CH_2Cl_2 . ^bReaction conditions: 0.2 mmol of substrate, 1.0 mol % catalyst **D**, 2.0 mL of benzene. ^c2.0 mol % catalyst **H**. ^d130 bar H_2 . Enantiomeric excess was determined by SFC-HPLC analysis using a chiral stationary phase. All yields are isolated yield. Conversions were determined by ^1H NMR spectroscopy.

88 iridium Crabtree-type catalysts having thiazole and oxazoline
 89 N,P-ligands were evaluated using 0.5 mol % of catalyst loading.
 90 The catalyst containing a thiazole ligand **B** resulted in poor
 91 conversion and enantioselectivity. Catalyst **C**, containing a
 92 bicyclic thiazole, led to an improved enantioselectivity (72%).
 93 Interestingly, the bulkier iridium N,P-catalyst **D** having a
 94 diphenyl-substituted oxazoline led to a much higher enantio-

95 meric excess, 96% ee. The promising result obtained for
 96 catalyst **D** prompted us to further modify the catalyst structure
 97 by varying the substituents on the phosphine and phenyl of the
 98 oxazoline ring. Changing the *ortho*-methyl group to an *ortho*-
 99 ethyl substituent on phosphine for catalyst **E** did not improve
 100 the efficiency nor the selectivity of the hydrogenation reaction.
 101 Catalyst **F** with the more electron-rich di(2,4-dimethylphenyl)-

Table 4. Asymmetric Hydrogenation of Monofunctionalized Tetrasubstituted Olefins^a

^aReaction conditions: 0.05 mmol of substrate, 1.0 mol % catalyst, 0.5 mL of CH₂Cl₂. The conversions were determined by ¹H NMR spectroscopy. (a) Catalyst I, (b) catalyst D, (c) catalyst J, and (d) catalyst D in benzene. Enantiomeric excess determined by SFC-HPLC analysis using a chiral stationary phase and GC analysis using a chiral stationary phase.

hydrogenation process, we also evaluated a number of tetrasubstituted trifluoromethyl olefins that results in synthetically useful chiral trifluoromethyl molecules with two contiguous stereogenic centers (Table 5). Optimization using (*E*)-ethyl trifluoromethyl-3-phenylbut-2-enoate **5a** as the standard substrate proved that catalyst **B** is most suitable (see the Supporting Information for optimization details). Both *E*- and *Z*-isomers of trifluoromethyl containing α,β -unsaturated ethyl ester could be hydrogenated in good to excellent enantioselectivity. *E*-Isomer **5a** provides 98% yield and 97% ee, whereas the opposite *Z*-isomer **5b** resulted in product **6b** with 84% ee albeit in only 13% conversion. The established catalytic system proved effective for a large variety of different esters (**5c–5f**) and produced the desired products in good to excellent yield (48–99%) and high enantioselectivities (91% → 99% ee). Weak electron-donating (Me) substituent on the aromatic ring **5g** was well tolerated, and the best result of 68% yield and 97% ee was obtained by using catalyst **D**. Another significant advantage of the reaction is that substrates (**5h** and **5i**) having aliphatic substituents can be hydrogenated in high yields (99%) and good levels of stereoselectivity (88% ee and 82% ee, respectively). The fruitful examples of this reported reaction conditions to synthesize chiral trifluoromethyl molecules with two contiguous stereogenic centers in mostly good to excellent yield, with exceptional diastereoselectivities (>99%) and enantioselectivities (up to >99%), again underline that this catalytic system is very general for tetrasubstituted trifluoromethyl-olefins.

The practicality of this Ir-catalyzed hydrogenation reaction was confirmed for the large-scale production of chiral succinate derivative. A gram-scale setup using, for 1.0 g of starting material **1b**, 0.5 mol % of catalyst **H** produced the desired compound **2b** in excellent 96% yield and >99% ee. Hydrogenolysis using Pd–C in EtOH under 1 bar hydrogen pressure resulted in the desired 4-ethoxy-3-methyl-4-oxo-2-

Table 5. Asymmetric Hydrogenation of CF₃ Containing Tetrasubstituted Olefins^a

^aReaction conditions: 0.05 mmol of substrate, 1.0 mol % catalyst, 0.5 mL of CH₂Cl₂. (a) 1.0 mol % catalyst B. (b) Corresponding ^tBu ester was used as starting material for compound 6c and used for absolute configuration determination (CCDC 1907708). (c) 1.0 mol % catalyst D. (d) 1.0 mol % catalyst C. The conversion was determined by ¹H NMR spectroscopy. Enantiomeric excess determined by SFC-HPLC analysis using a chiral stationary phase and GC analysis using a chiral stationary phase.

Scheme 2. Gram-Scale Production of Chiral Succinate Derivative

Scheme 3. Derivatization of Enantiomeric Compounds from Hydrogenation Reaction via Chemoselective Reduction

reaction proceeds with excellent preservation of stereochemistry.

To demonstrate the synthetic utility of the developed methodology, the reaction was successfully applied for the formal synthesis of anticancer agent BMS-871 and calcium channel-blockers Verapamil and Gallopamil (Scheme 4). Hydrogenated product 2f was efficiently converted to the butyrolactone 10a in 87% yield and 91% ee using the two-step strategy of hydrogenolysis and selective reduction of the carboxylic acid, followed by cyclization as discussed in the reaction sequence of Scheme 3. Similarly, succinate derivatives 2n and 2o were converted to the corresponding butyrolactones 10b or 10c in good yields and excellent ee. Butyrolactones 10a, 10b, and 10c are precursors for the formal synthesis of aforesaid bioactive molecules.^{6d}

CONCLUSION

A variety of tetrasubstituted, acyclic olefins have been successfully evaluated in asymmetric hydrogenation using catalytic amounts of new N,P-iridium catalysts (0.5–1 mol %). Two adjacent stereogenic centers were introduced during the asymmetric hydrogenation with complete diastereoselectivity and excellent enantiomeric excess (up to >99%). The enantiomerically enriched succinate derivatives were converted to chiral building block butyrolactones by simple and easy reaction conditions via hydrogenolysis followed by chemoselective reduction and lactonization, respectively. The feasibility and the utility of this protocol were finally confirmed by the gram-scale synthesis of useful building blocks and by the

Lactone 8 was prepared via selective reduction of the ethyl ester group of 7 using LiBH₄ to generate 4-hydroxy-3-methyl-2-phenylbutanoic acid. Under acidic conditions, this intermediate cyclized to produce lactone 8 in 61% isolated yield in 98% ee. The regio-isomeric *cis*-lactone 9 was prepared in 78% isolated yield with excellent 99% ee via a divergent route using a one-pot, chemo-selective reduction of the carboxyl acid group using BH₃·SMe₂ followed by cyclization in the presence of PTSA. Both the selective reduction and the cyclization

Scheme 4. Enantioselective Formal Syntheses of BMS-871, (2S)-(-)-Verapamil, and (2S)-(-)-Gallopamil^a

^aReaction conditions: (a) H₂ (1 bar), Pd/C (10 mol %), EtOH, rt, o.n. (b) BH₃·SMe₂ (3 equiv), THF, rt, o.n.; PTSA (1.0 equiv), THF, rt, 24 h. (c) LiBH₄ 2 M in THF (10 equiv), THF, reflux, 7 h.

243 formal stereoselective synthesis of anticancer agent BMS-871
 244 and pharmaceuticals (2S)-(-)-Verapamil and (2S)-(-)-Gallopamil.

246 ■ ASSOCIATED CONTENT

247 ⓘ Supporting Information

248 The Supporting Information is available free of charge on the
 249 ACS Publications website at DOI: 10.1021/acscatal.9b01508.

250 Experimental procedures, crystallography reports, and
 251 analytical data (PDF)

252 Crystallographic data for 6c (CIF)

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260 Notes

261 The authors declare no competing financial interest.

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