ORGANIC LETTERS

2013
Vol. 15, No. 7
1740–1743

Catalytic Enantioselective Desymmetrization of *Meso* Cyclic Anhydrides via Iridium-Catalyzed Hydrogenation

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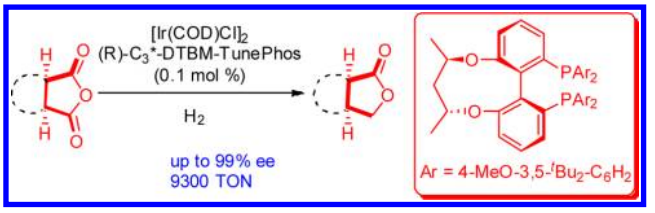
Received February 26, 2013

ABSTRACT



A novel method to desymmetrize *meso*-anhydrides into lactones via asymmetric hydrogenation catalyzed by the Ir−C_3*-TunePhos complex has been developed. Various chiral lactones were synthesized with full conversion and excellent enantioselectivity under high reaction temperature.

The asymmetric desymmetrization (ADS) of prochiral molecules in symmetrical bifunctional compounds has proven to be a straightforward and powerful strategy in asymmetric syntheses.[1] In particular, ADS of *meso* compounds is a remarkably valuable transformation in organic synthesis because it breaks the symmetry of the molecule without incorporating new stereogenic centers.[2] Stereoselective catalytic desymmetrization of *meso*-anhydrides has been developed as an advantageous methodology in the synthesis of many biologically active compounds, such as lactones and their derivatives.[3]

Among many important chiral lactones, water-soluble B-vitamin (+)-biotin (**1**) plays a crucial role in biochemical processes and overall physiological metabolism in human beings. Furthermore, it not only acts as a coenzyme in carboxylation reaction but also an essential growth factor in living cells,[4] Several efficient methods for preparation of (+)-biotin (**1**)[5] are shown in Scheme 1(A). Enantiomerically enriched lactones **3** and **3′** serve as the key intermediates for the practical synthesis of (+)-biotin (**1**). After asymmetric alcoholysis of *meso*-anhydride **2** with cinnamyl alcohol via the cinchona alkaloid-mediated nucleophilic ring-opening, chemoselective reduction of the ester with $NaBH_4$ followed by acid-catalyzed lactonization gave enantiomerically enriched lactone **3**.[6] Another route involved asymmetric hydrogenation of lactones **3′** catalyzed by Rh(I)-Josiphos catalyst system.[7] In Scheme 1(B),

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(1) For reviews on desymmetrization of *meso*-anhydrides, see: (a) Spivey, A. C.; Andrews, B. I. *Angew. Chem., Int. Ed.* **2001**, *40*, 3131. (b) Willis, M. C. *J. Chem. Soc., Perkins Trans. 1* **1999**, 1765. (c) Johnson, J. B.; Rovis, T. *Acc. Chem. Res.* **2008**, *41*, 327. (d) Atodiresei, I.; Schiffers, I.; Bolm, C. *Chem. Rev.* **2007**, *107*, 5683.

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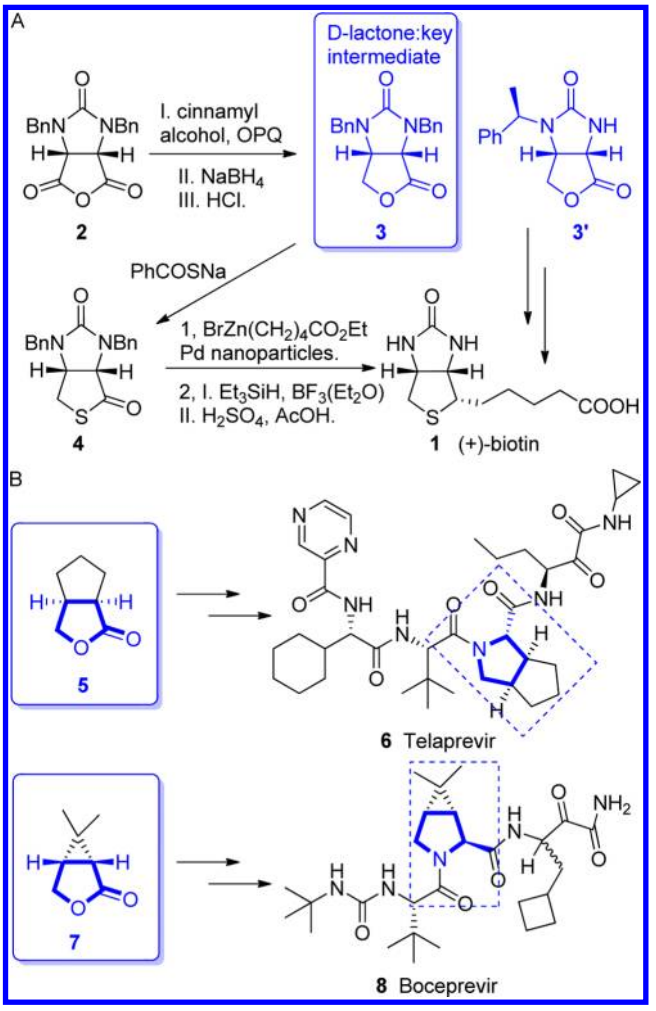
10.1021/ol400533g
Published on Web 03/13/2013

enantiomerically pure lactones **5** and **7** can be used to synthesize key drug intermediates of telaprevir (**6**)[8] and boceprevir (**8**),[9] respectively.

Scheme 1. Synthesis of (+)-Biotin and Other Synthetic Intermediates: (A) Synthesis of (+)-Biotin from Anhydride **2**; (B) Lactones as the Key Synthetic Intermediates of Drugs



In spite of the above-mentioned protocols developed to synthesize chiral lactones, the practical synthesis of enantiomerically enriched lactones from anhydrides remains a challenge.[10] Nevertheless, due to the lower reactivity of anhydrides, quite limited progress has been made in the area of asymmetric hydrogenation.[11,5a] Therefore, the development of catalytic asymmetric method for the straightforward synthesis of γ-lactones from anhydrides is in high demand. We envisioned that the rigid biaryl diphosphine ligand with steric hindered group such as C_3*-TunePhos, should provide satisfied performance in this ADS reaction under elevated temperature. Herein, we discovered an elegant procedure, the asymmetric hydrogenation of *meso*-cyclic anhydrides using Ir/C_3*-TunePhos catalyst system (Figure 1), taking advantage of the rigid

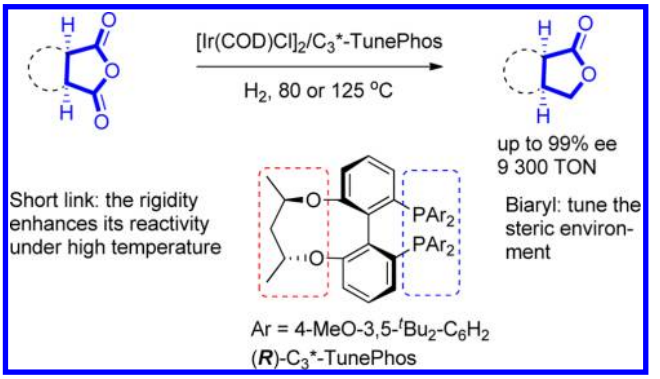


Figure 1. Asymmetric hydrogenation of *meso*-anhydrides.

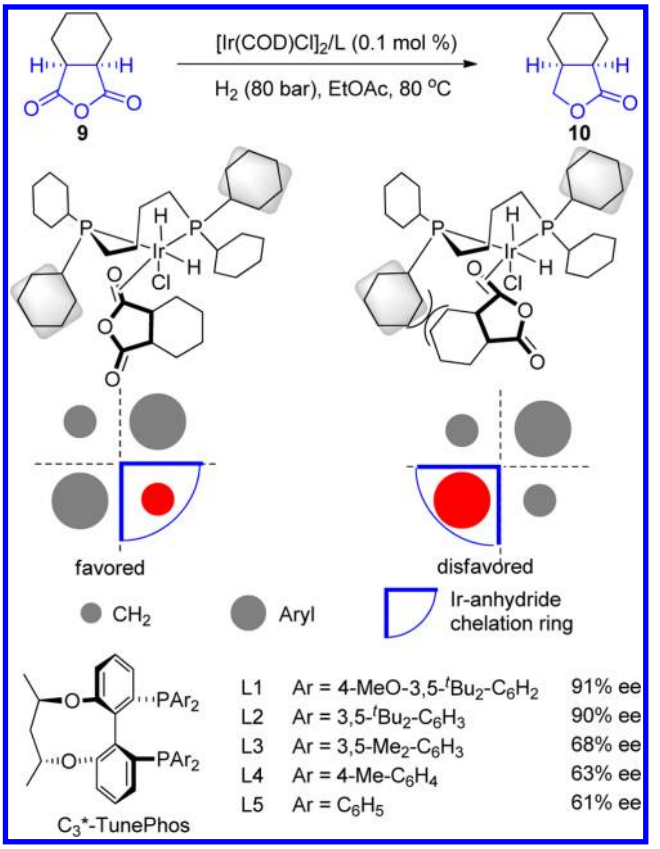


Figure 2. Model and origin for asymmetric hydrogenation of *meso*-anhydride.

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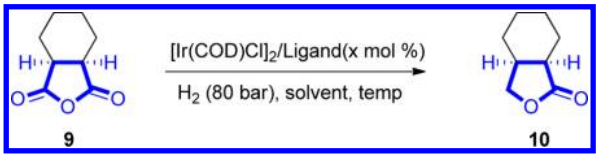
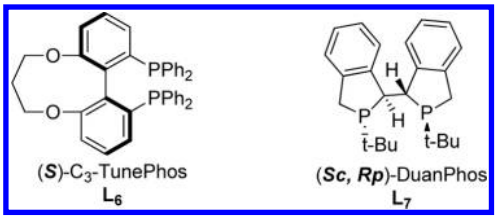
and tunable nature of biaryl bisphosphine ligand C_3*-TunePhos developed in our laboratory.[12] The catalyst can sustain high temperature to produce the corresponding chiral γ-lactones in high yields and with high ee values. Investigation of this transformation will result in highly efficient ADS, producing valuable enantiomerically enriched lactones.

Table 1. Optimization of the Hydrogenation of *meso*-Anhydride **9**[a]



entry	L	x (S/C)	solvent	temp[b] (°C)	conv[c] (%)	TON	ee[d] (%)
1	L_6	0.1 (1000)	EtOAc	80	45	450	72
2	L_7	0.1 (1000)	EtOAc	80	60	600	85
3	L_1	0.1 (1000)	EtOAc	80	>99	1000	91
4	L_1	0.1 (1000)	THF	80	75	750	90
5	L_1	0.1 (1000)	$PhCH_3$	80	20	200	90
6	L_1	0.1 (1000)	DCE	80	30	300	87
7	L_1	0.05 (2000)	EtOAc	80	>99	2500	91
8	L_1	0.02 (5000)	EtOAc	80	>99	5000	91
9	L_1	0.01 (10000)	EtOAc	80	93	9300	91

[a] Reaction conditions: **9** (0.1 mmol), [Ir(COD)Cl]2/L = 1:2.2, solvent (1 mL). [b] The temperature of oil bath. [c] Determined by NMR. [d] Enantioselectivity was determined by chiral GC analysis.



We attempted to prepare chiral lactone **10** via catalytic enantioselective hydrogenation of *meso*-anhydride **9** by using $[Ir(COD)Cl]_2/C_3$*-TunePhos complex (COD = 1,5-cyclooctadiene) as the catalyst. Initially, asymmetric hydrogenation of *meso*-anhydride **9** was investigated with 0.05 mol % of the $[Ir(COD)Cl]_2$ and 0.11 mol % of C_3*-DTBM-TunePhos (**L1**) in EtOAc at 80 °C under 80 bar of H_2. To our delight, full conversion was achieved with 91% ee. It was quite encouraging that we achieved such a high ee value at the enhanced temperature, in most cases, which was attributed to the rigidity and bulky biaryl bisphosphine in chiral ligands. After hydrogenation of (3a*R*,7a*S*)-**9** catalyzed by the complex of iridium and various chiral bisphosphine ligands developed by our group, we selected $[Ir(COD)Cl]_2/C_3$*-DTBM-TunePhos (**L1**) as the promising catalyst (Figure 2).

While optimizing the conditions of this reaction, further investigation indicated that solvent played an important role in this ADS. After screening of various solvents, ethyl

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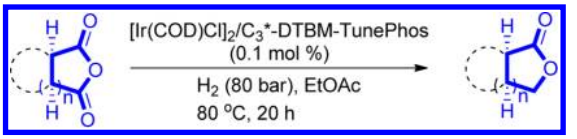
Table 2. Desymmetrization of Various *meso*-Anhydrides[a]

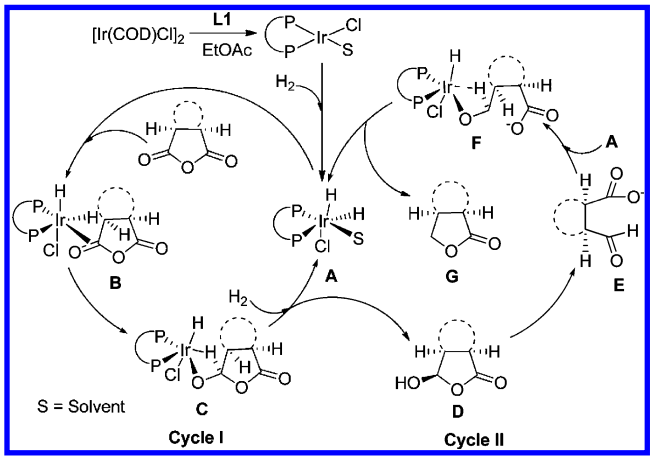


entry	anhydrides	lactones	conv[b] (yield)[c] (%)	TON	ee(%)[d]
1	9	10	>99 (94)	1000	91
2			>99 (92)	2000	91
3			>99 (93)	5000	91
4			93 (89)	9300	91
5	11	10	>99 (94)	1000	90
6	12	13	>99 (93)	1000	94
7	14	15	>99 (97)	1000	80
8	16	17	>99 (92)	1000	87
9	18	19	>99 (96)	1000	99
10	20	19	>99 (98)	1000	99
11[e]	2	3	>99 (96)	1000	96
12[e]			>99 (94)	2000	95
13[e]			>99 (93)	5000	88

[a] Reaction conditions: anhydrides (0.1 mmol), $[Ir(COD)Cl]_2$/L = 1:2.2, EtOAc (1 mL). [b] Determined by NMR. [c] The value in parentheses was the isolated yield. [d] Enantioselectivity was determined by chiral HPLC or GC analysis. [e] 125 °C was required.

acetate gave best reactivity and enantioselectivity (Table 1, entries 3 vs 4−6). It was noteworthy that the *meso*-anhydrides were alcoholised to hemiester when MeOH was used as the solvent (not shown in table 1). The highly catalytic capability of the catalyst $[Ir(COD)Cl]_2$/**L1** was further explored at lower catalyst loading (0.05 mol %), the standard lactone (3a*R*, 7a*S*)-**9** was smoothly hydrogenated without any erosion of ee value in 20 h (91% ee, entry 7). Furthermore, when the substrate/catalyst ratio was further increased to 5000, full conversion could still be achieved (entry 8). To test its maximum catalytic reactivity, in an

Scheme 2. Proposed Mechanism



extreme example of low catalyst loading (S/C = 10000), this reaction reached 93% conversion without any drop in enantioselectivity (91% ee) (entry 9).

After successfully optimizing the reaction conditions, we attempted to expand the substrate range to demonstrate the synthetic utilities of this strategy, as is listed in Table 2. By using 0.1 mol % of the catalyst under 80 bar of H_2, a series of bi- and tricyclic *meso*-anhydrides were readily desymmetrized to the corresponding lactones in excellent yields and with good to excellent enantioselectivities (80−99% ee). Notably, for the anhydrides bearing a C=C bond, saturated double reduction products were detected (Table 2, entries 5, 6, 8, and 9). In further attempts, the desymmetrization of cyclic anhydrides with the six-membered rings gave better results than that of the five-membered rings (Table 2, entries 1 vs 7 and 9, 10 vs 8).

The *meso*-anhydride (4*aS*,5*aR*)-**2** was also subjected to this ADS reaction under these reaction conditions, and full conversion and high enantioselectivity were obtained under 125 °C (Table 2, entry 11). Under these conditions, the catalyst loading could be decreased to 0.02% (S/C = 5000) without any loss of conversion or ee values.

According to our experimental results, we propose a possible mechanism for this desymmetrization reaction (Scheme 2). The reaction might be initiated by the formation of the Ir(H_2)/**L1** complex **A** under H_2. After coordination and hydride insertion steps, one of the two C=O bonds of the anhydride was reduced to a semiacetal, completing the catalytic cycle **I**. The following hydrolysis of **D**[13] provided intermediate **E**. Hydrogenation of **E** by the same catalyst species **A** enabled the formation of transition state **F**, which was then transferred to the readily esterification product lactone **G**.

In conclusion, we have developed a novel and practical method to desymmetrize *meso*-anhydrides into lactones via Ir/C_3*-DTBM-TunePhos (**L1**), which contains bulky biaryl bisphosphine, catalyzed asymmetric hydrogenation under high temperature. In the presence of a catalytic amount of the catalyst, asymmetric hydrogenation of various *meso*-anhydrides proceeded smoothly and afforded the corresponding enantiomerically enriched lactones in high yields and with good to excellent enantioselectivities. Study of the desymmetrization of other *meso*-carbonyl compounds as well as further modification of steric environment in C_3*-TunePhos ligand family is in progress and will be reported in due course.

Acknowledgment. We are grateful for financial support from the National Institutes of Health (GM58832), the Fundamental Research Funds for the Central Universities, and an academic award for excellent Ph.D. candidates funded by the Ministry of Education of China (5052011203011). The first author is supported by the fellowship provided by the China Scholarship Council for the studies at Wuhan University.

Supporting Information Available. Experimental procedures and compound characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.