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Asymmetric Hydrogenation of Maleic Anhydrides Catalyzed by Rh/Bisphosphine-Thiourea: Efficient Construction of Chiral Succinic Anhydrides

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Asymmetric hydrogenation of various 3-substituted maleic anhydrides catalyzed by Rh/bisphosphine-thiourea (ZhaoPhos) under mild conditions was successfully developed. A wide range of 3-alkyl and 3-aryl maleic anhydrides was hydrogenated well to provide the desired products 3-substituted succinic anhydrides in one hour with excellent results (full conversions, up to 99% yield, 99% ee, 3 000 TON). Importantly, we developed a creative and efficient synthetic route to construct the key intermediate of hypoglycemic drug mitiglinide through our catalytic system.

Chiral succinic anhydrides are useful synthetic intermediates and owned wide applications in the field of organic chemistry,[1] which can be readily ring opened to prepare chiral diacids,[2] diesters[3] and other succinate derivatives[4]. In addition, chiral succinic anhydrides and their derivatives are important structural skeletons in many biologically active natural products,[5] pharmaceuticals[6] and metalloprotease inhibitors,[7a] such as caspase 1 inhibitor, mupircocin H and mitiglinide (Figure 1).

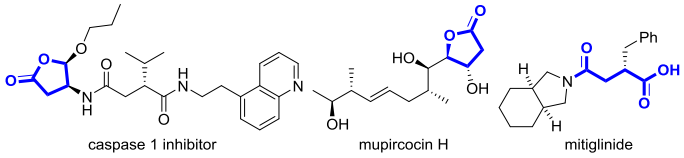
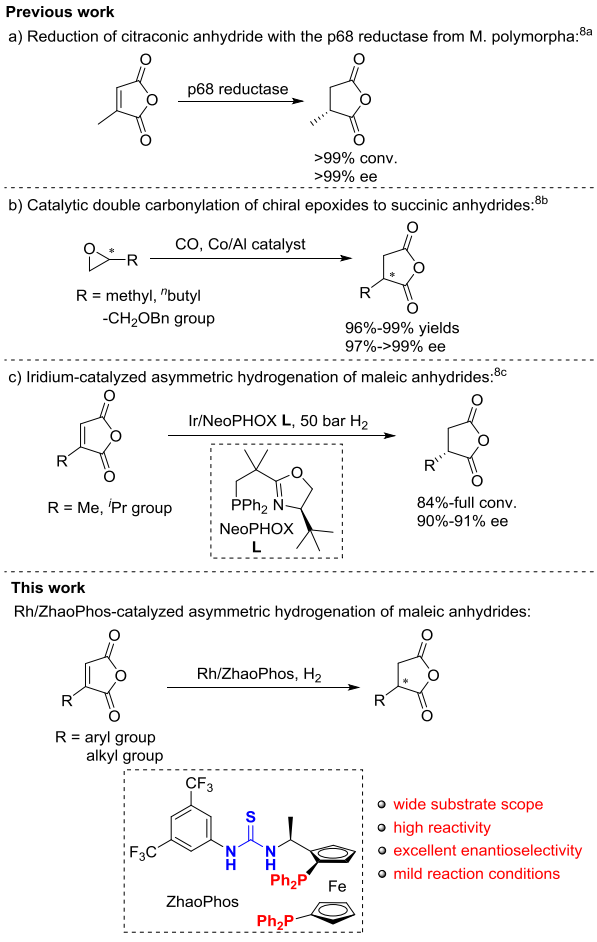


Figure 1. Examples of drugs and natural products containing chiral succinic anhydrides and derivatives.

Owing to the great importance, much effort has been devoted to develop efficient catalytic methodologies to approach chiral succinic anhydrides and derivatives in the last few decades.[7] In 2004, Shimoda and co-workers made use of the p68 reductase enzyme isolating from M. polymorpha to reduce citraconic anhydride, and (*R*)-methyl succinic anhydride product was obtained (scheme 1a).[8a] In 2007, Coates and co-workers reported catalytic double carbonylation of several chiral alkyl-substituted epoxides to construct chiral succinic anhydrides, which involved chiral substrate induction and toxic CO in high pressure (scheme 1b).[8b] In 2014, Pfaltz and co-workers developed asymmetric hydrogenation of 3-methyl, 3-isopropyl maleic anhydrides catalyzed by Ir/NeoPHOX with good conversions and enantioselectivities, but other maleic anhydrides weren't employed



Scheme 1. Representative methods for the preparation of chiral succinic anhydrides.

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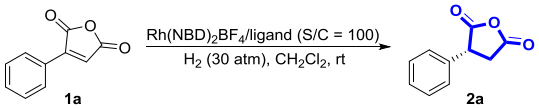
as substrates because of their poor solubility in this catalytic system (scheme 2c).[8c] Therefore, it remains an important goal to develop highly efficient catalytic system to prepare chiral succinic anhydrides with great tolerance of wide range of substrates and excellent enantioselectivity. It was well known that catalytic asymmetric hydrogenation of functionalized olefins was regarded as a powerful methodology for the construction of chiral compounds.[9] Recently, our group developed chiral bifunctional bisphosphine-thiourea ligands (ZhaoPhos) based on the synergistic activations strategy *via* combing catalytic modes of transition metal-catalysis and organo-catalysis, which has been successfully applied in some asymmetric hydrogenations.[10] Thiourea motif serving as a hydrogen-bond donor can activate the carbonyl group of substrates through hydrogen-bonding interaction.[10e-g] Herein, we successfully developed asymmetric hydrogenation of 3-substituted maleic anhydrides catalyzed by Rh/Zhaophos to afford chiral succinic anhydrides in one hour with excellent results (full conversions, 90%-99% ee, TON up to 3 000). The hydrogen bonds between the thiourea motif of ZhaoPhos and the carbonyl group of maleic anhydrides were greatly contributed to high reactivity and excellent enantioselectivity of this transformation.

We began our study by evaluating several chiral diphosphine ligands (Figure 2) for the asymmetric hydrogenation of 3-phenyl maleic anhydride (**1a**)[11] as the model substrate at room temperature with the catalyst generated *in situ* by mixing $Rh(NBD)_2BF_4$ and ligands (S/C = 100). As shown in Table 1, (*S*)-Segphos, JosiPhos, (*S*)-BINAP, Binapine, (R_C, S_P)-DuanPhos, Walphos and (*S*, *S*)-Me-DuPhos exhibited poor reacticities and enantioselectivities (Table 1, entries 1-7). The reaction system catalyzed by Rh/Walphos was in mess, and there was no desired product (Table 1, entry 6). To our delight, ZhaoPhos afforded >99% conversion and 92% ee (Table 1, entry 8). When the reaction time was reduced from 12 h to 1 h, the same result was still obtained (>99% conversion, 92% ee, Table 1, entry 9).

Table 1. Screening diphosphine ligands for the asymmetric hydrogenation of 3-phenyl maleic anhydride (**1a**). [a]



Entry	Ligand	Time (h)	Conv. (%)[b]	Ee (%)[c]
1	(*S*)-Segphos	12	<5	7
2	JosiPhos	12	7	49
3	(*S*)-BINAP	12	6.5	4
4	Binapine	12	13	10
5	(*Rc*, *Sp*)-Duanphos	12	<5	23
6	Walphos	12	40	NA
7	(*S,S*)-Me-DuPhos	12	NR	NA
8	ZhaoPhos	12	>99	92
9	ZhaoPhos	1	>99	92

[a] Unless otherwise noted, all reactions were carried out with a $[Rh(NBD)_2BF_4]$/ligand/**1a** (0.1 mmol) ration of 1:1.1:100 in 1.0 mL CH_2Cl_2. [b] Determined by ^1H NMR analysis. [c] Determined by HPLC analysis using a chiral stationary phase. Configuration of **2a** was determined by comparing the optical rotation data with those reported by the literature.[8c] NR = No Reation, NA = Not Available.

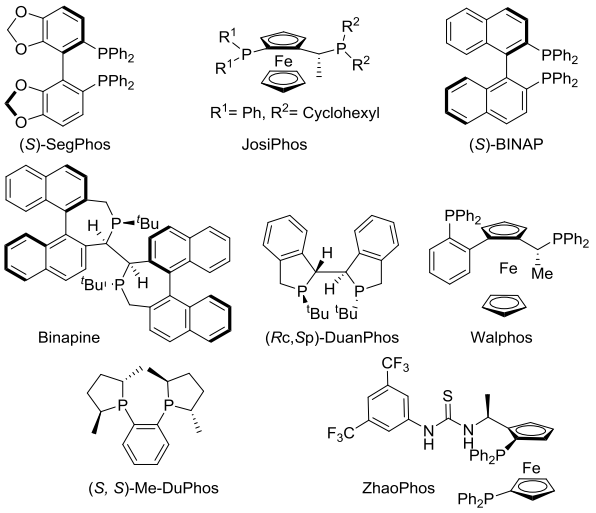
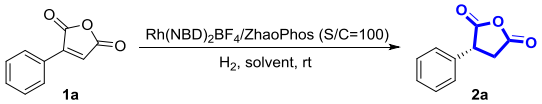


Figure 2. Chiral diphosphine ligands for the asymmetric hydrogenation of 3-phenyl maleic anhydride (**1a**).

Subsequently, this asymmetric hydrogenation was explored in various solvents catalyzed by $Rh(NBD)_2BF_4$/ZhaoPhos. These results were summarized in Table 2. The reaction proceeded well in CH_2Cl_2, 1,4-dioxane, $ClCH_2CH_2Cl$, $CHCl_3$ and ethyl acetate (EA) with high conversions and excellent enantioselectivities (98%->99% conversions, 92%-96% ee, Table 2, entries 1-3, 5-6). Moderate results were observed in THF (91% conversion, 81% ee, Table 2, entry 4). The ethyl acetate was chosen as the best solvent by considering both reactivity and enantioselectivity (>99% conversion, 96% ee, Table 2, entry 6). When the hydrogen pressure was reduced from 30 atm to 1 atm, we can obtain the same result (>99% conversion, 96% ee, Table 2, entry 7). We found that this asymmetric hydrogenation can be finished in 0.5 h with full conversion and 97% ee (Table 2, entry 8).

Table 2. Screening solvents, hydrogen pressure and reaction time for the asymmetric hydrogenation of 3-phenyl maleic anhydride (**1a**). [a]



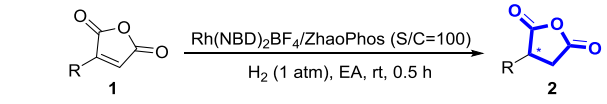
Entry	Solvent	H_2 (atm)	Time (h)	Conv. (%)[b]	Ee (%)[c]
1	CH_2Cl_2	30	1	>99	92
2	1,4-dioxane	30	1	>99	93
3	$ClCH_2CH_2Cl$	30	1	>99	95
4	THF	30	1	91	81
5	$CHCl_3$	30	1	98	96
6	EA	30	1	>99	96
7	EA	1	1	>99	96

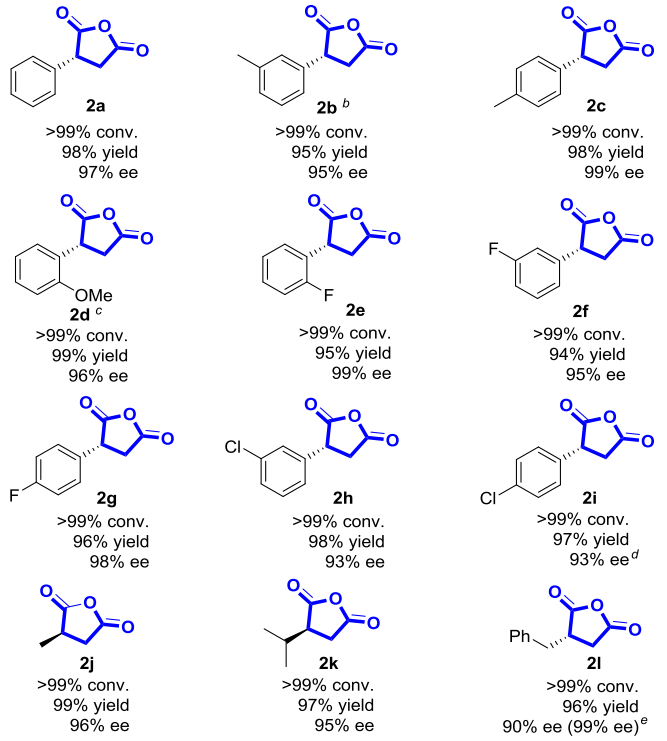
8	EA	1	0.5	>99	97

[a] Unless otherwise noted, all reactions were carried out with a [Rh(NBD)$_2$BF$_4$]/ZhaoPhos/**1a** (0.1 mmol) ration of 1:1.1:100 in 1.0 mL solvent. [b] Determined by ^{1}H NMR analysis. [c] Determined by HPLC analysis using a chiral stationary phase. Configuration of **2a** was determined by comparing the optical rotation data with those reported by the literature.[8c] EA is ethyl acetate.

With the optimized reaction conditions in hand, we explored the scope of the asymmetric hydrogenation of 3-substituted maleic anhydrides (Table 3). A series of 3-substituted maleic anhydrides were hydrogenated smoothly, and the desired hydrogenation products chiral succinic anhydrides were provided with full conversions, high yields and excellent enantioselectivities (94%-99% yields, 90%-99% ee). The substrates (**1a-1i**) containing different substitution patterns (*ortho*-, *meta*-, *para*-) on the phenyl ring were proceeded efficiently, regardless of their properties (electron-neutral, electron-rich, electron-deficient). In addition, the alkyl substrates 3-methyl (**1j**), 3-isopropyl (**1k**) and 3-benzyl (**1l**) maleic anhydrides also performed well with excellent results (full conversions, 96%-99% yields, 90%-96% ee). To our delight, the 3-benzyl succinic anhydride (**2l**) is solid, and the enantioenriched prodcut (99% ee) can be easily obtained by simple recrystallization in hexane/ethyl acetate.

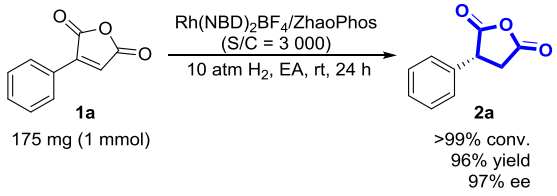
Table 3. Asymmetric hydrogenation of various 3-substituted maleic anhydrides with Rh/ZhaoPhos.[a]





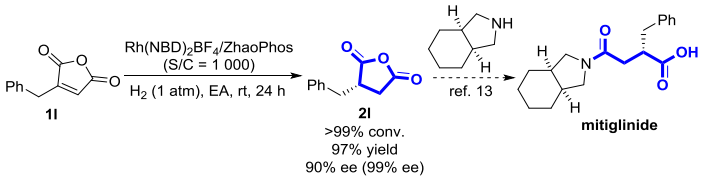
[a] Unless otherwise noted, all reactions were carried out with a [Rh(NBD)$_2$BF$_4$]/ZhaoPhos/**1** (0.1 mmol) ration of 1:1.1:100 in 1.0 mL ethyl acetate. Conversion was determined by ^{1}H NMR analysis. Ee was determined by HPLC or GC analysis (see the Supporting Information). [b] The reaction time is 50 min. [c] The reaction time is 60 min. [d] The ee was determined by the corresponding dimethyl ester.[8c,12] [e] 99% ee was achieved after simple recrystallization in ethyl acetate and hexane.

Moreover, our Rh-ZhaoPhos catalytic system is very efficient in this asymmetric hydrogenation of 3-phenyl maleic anhydride (**1a**). When the catalyst loading was reduced to 0.0333 mol% (S/C = 3 000), this transformation was hydrogenated smoothly in 24 h with excellent result (Scheme 2, >99% conversion, 96% yield, 97% ee).



Scheme 2. Asymmetric hydrogenation of 3-phenyl maleic anhydride (**1a**) with high TON.

Our highly enantioenriched hydrogenation products can be transformed to prepare other optically active drug molecules. As shown in Scheme 3, the 3-benzyl succinic anhydride (**2l**) can be easily obtained through our asymmetric catalytic hydrogenation system (0.2 mmol, 0.1 mol% catalyst, S/C = 1 000), which is the key intermediate for the construction of hypoglycemic drug mitiglinide.[13] Compared with previous methods through racemic resolution,[13] our asymmetric catalytic hydrogenation is highly efficient with low cost.



Scheme 3. Synthesis of mitiglinide.

In summary, we successfully reported a highly efficient asymmetric hydrogenation of 3-substituted maleic anhydrides catalyzed by Rh/bisphosphine-thiourea (ZhaoPhos) under mild reaction conditions, the desired products 3-substituted succinic anhydrides were obtained in one hour with excellent results (full conversions, up to 99% yield, 99% ee and 3 000 TON). Moreover, we made use of this catalytic system to develop a creative and efficient route for the synthesis of the key intermediate of hypoglycemic drug mitiglinide. Further investigations on the extension of our catalytic system are currently underway in the laboratory.

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