Synthetic Methods

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Iridium-Catalyzed Asymmetric Hydrogenation of α-Alkylidene Succinimides**

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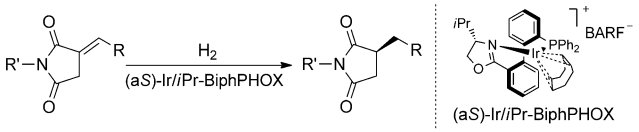
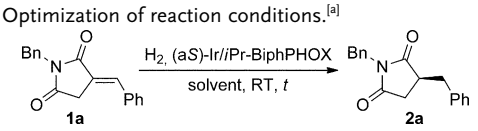
Enantiopure succinimide derivatives are key structures in biologically active natural products, pharmaceuticals, and important intermediates in organic synthesis.[1,2] Compounds containing a chiral pyrrolidine motif, which display activity in many biological systems, can be obtained from succinimide derivatives by simple transformations.[3] However, few methodologies exist concerning the synthesis of chiral succinimide derivatives through catalytic asymmetric reactions.[4–6] The most well-studied method involves enantioselective cycloaddition reactions using maleimides as the substrates.[5] Asymmetric catalytic addition of nucleophilic reagents to maleimides has also been reported.[6]

Enantioselective hydrogenation reactions are of great interest to the chemistry community because of their atom efficiency and minimal environmental impact.[7] In particular, iridium complexes consisting of phosphine nitrogen ligands have attracted much attention because of their ready availability, high reactivity, and high enantioselectivity in asymmetric hydrogenation reactions.[8,9] We have previously reported a class of axially flexible chiral phosphine-oxazoline ligands (BiphPHOX),[10] which were successful in iridium-catalyzed enantioselective hydrogenations.[11] Herein we report the first asymmetric hydrogenation of α-alkylidene succinimides catalyzed by (a*S*)-Ir/*i*Pr-BiphPHOX for enantioselective synthesis of succinimide derivatives (Scheme 1).



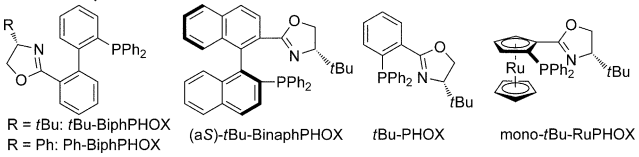
Scheme 1. Asymmetric hydrogenation of α-alkylidene succinimides catalyzed by (a*S*)-Ir/*i*Pr-BiphPHOX. BARF = tetrakis[3,5-bis(trifluoromethyl)phenyl]borate.

Table 1: Optimization of reaction conditions.[a]



Entry	Sol.	H_2 (bar)	*t*	S/C	Conv. [%][b]	*ee* [%][c]
1	CH_2Cl_2	20	10 min	100	>99	99
2[d]	CH_2Cl_2	20	10 min	100	>99	82
3[e]	CH_2Cl_2	20	10 min	100	>99	94
4[f]	CH_2Cl_2	20	10 min	100	40	88
5[g]	CH_2Cl_2	20	10 min	100	12	46
6[h]	CH_2Cl_2	20	10 min	100	<5	–
7	DCE	20	24 h	100	>99	98
8	$CHCl_3$	20	24 h	100	62	98
9	CH_2Cl_2	5	10 min	100	>99	98
10	CH_2Cl_2	1	12 h	100	98	96
11	CH_2Cl_2	50	10 min	100	>99	98
12	CH_2Cl_2	20	1 h	500	>99	98
13	CH_2Cl_2	20	1.5 h	1000	>99	98
14	CH_2Cl_2	20	24 h	2000	>99	98

[a] Reaction was conducted on a 0.25 mmol scale in 2 mL of the solvent under hydrogen at room temperature. [b] The conversion was determined by ^{1}H NMR spectroscopy. [c] Enantioselectivity was determined by HPLC using a chiral Daicel column. [d] Ph-BiphPHOX was used as the chiral ligand. [e] Used *t*Bu-BiphPHOX. [f] Used (a*S*)-*t*Bu-BinaphPHOX.[12a,b] [g] Used *t*Bu-PHOX. [h] Used mono-*t*Bu-RuPHOX.[12c] Bn = benzyl, DCE = 1,2-dichloroethane.



Hydrogenation reaction conditions were investigated as listed in Table 1. The reactions for screening different P,N-ligands were carried out in CH_2Cl_2 at room temperature under 20 bar of hydrogen for 10 minutes (entries 1–6). The catalytic activity of a series of (a*S*)-Ir/BiphPHOX catalysts was very high, and full conversion was observed within 10 minutes (entries 1–3). The substituents on the oxazoline ring had a strong influence on the enantioselectivity. With an *i*Pr substituent, the hydrogenation proceeded in quantitative yield with excellent enantioselectivity (99% *ee*; entry 1). A moderate enantioselectivity (88% *ee*) was obtained with 40% conversion using axial chiral (a*S*)-*t*Bu-BinaphPHOX as the ligand (entry 4). The hydrogenation of α-alkylidene succinimide **1a** with *t*Bu-PHOX as a chiral ligand, gave only a 12% conversion with 46% *ee* (entry 5). A trace of hydrogenated product was detected with the planar-chiral mono-*t*Bu-RuPHOX as the ligand (entry 6). Different solvents were also

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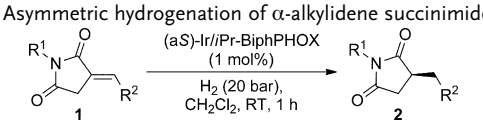
screened using (a*S*)-Ir/*i*Pr-BiphPHOX and catalysis in CH_2Cl_2 provided the most promising result (entries 6–8). In addition to CH_2Cl_2, other haloalkane solvents such as DCE and $CHCl_3$ are compatible solvents for catalysis, thus giving the desired product with excellent enantioselectivity (> 98 % *ee*; entries 7 and 8). Furthermore, optimization of the hydrogen pressure and catalyst loading were investigated using CH_2Cl_2 as the solvent (entries 9–14). To our delight the hydrogenation was also successful at lower pressures (entries 9 and 10). The hydrogenation proceeded rapidly, with full conversion of substrate in under 10 minutes at 5 bar of hydrogen (entry 9). Even with a pressure of 1 bar of hydrogen, the reaction gave a near-quantitative yield of the hydrogenated product in 96 % *ee* with a prolonged reaction time (entry 10). A slight decline in reaction enantioselectivity was observed when decreasing or increasing the hydrogen pressure (entries 9–11). In addition, reducing the catalyst loading to 0.05 mol % still provided quantitative yield of product in 98 % *ee* (entries 12–14).

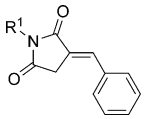
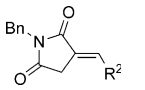
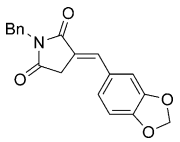
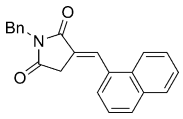
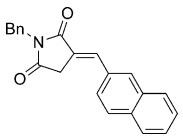
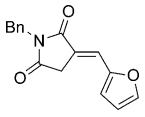
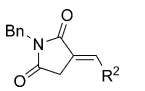
The substrate scope of the catalytic system was explored using the optimized reaction conditions (Table 2). The catalysis of substituted α-alkylidene succinimides was conducted at room temperature using (a*S*)-Ir/*i*Pr-BiphPHOX (1 mol %) in CH_2Cl_2 under 20 bar of hydrogen for 1 hour. Substrates were converted in excellent yields and high enantioselectivities (up to quantitative conversion and 99 % *ee*). The N-protecting group, R^1, has little effect on the reaction yield and enantioselectivity of the substrates (entries 1–4). Electron-donating and electron-withdrawing substituents on the phenyl ring of the substrate also had little influence on the enantioselectivity (entries 5–8, 10–12, and 14–16). However, reduction in enantioselectivity was noticed when steric bulk of the substituents increased (entries 9, 13, 17, 22, and 23). Substrates with fused-ring aryl substituents gave excellent yields of products and good to excellent enantioselectivities (entries 17 and 18). Heteroaryl or alkyl substituents could also be hydrogenated to give the desired products with high yields and enantioselectivities (entries 19–23). The α-alkylidene succinimides must be *E* configured for the hydrogenation to be successful (see the Supporting Information).

We next synthesized the biologically active compound **3** (Scheme 2). It can be used for synthesizing **4**, a class of useful compounds for modifying enzymes or proteins,[13] and **5**, derivatives for inhibition of human leukocyte elastase.[14] The asymmetric hydrogenation of **1x** was performed under a hydrogen atmosphere at 20 bar in the presence of 1 mol % of (a*S*)-Ir/*i*Pr-BiphPHOX for 1 hour, thus giving the corresponding succinimide derivative **2x** in quantitative yield. Deprotection using Pd/C under a hydrogen balloon gave **3** in 99 % yield (over 2 steps) and 96 % *ee*. This methodology provides additional opportunities for preparing a series of important intermediates with excellent yield and enantioselectivity.

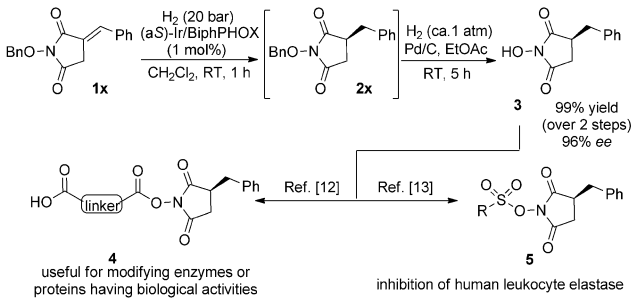
As a synthetic application of the present methodology, hydrogenation of **1a**, was carried out in the presence of 0.05 mol % (S/C = 2000) of (a*S*)-Ir/*i*Pr-BiphPHOX on a gram scale, thus giving the corresponding succinimide derivative **2a** as a single enantiomer (98 % *ee*; Scheme 3). The product was readily converted into 3-benzyl pyrrolidine by reduction and deprotection, and was isolated and characterized as the N-benzoyl derivative **6** (in 73 % yield over three steps). A series of 3-benzyl pyrrolidines can therefore be obtained in high yields and enantioselectivies through our methodology. The pyrrolidine motif is important for activity in many biological systems. Furthermore, 3-benzyl pyrrolidines, a particularly interesting class of pyrrolidine pharmacophores, exhibit portent activity as antagonists for the NK-3 receptor and[3h] dopamine receptor,[3f] and also as protein kinase C inhibitor-

Table 2: Asymmetric hydrogenation of α-alkylidene succinimides.[a]

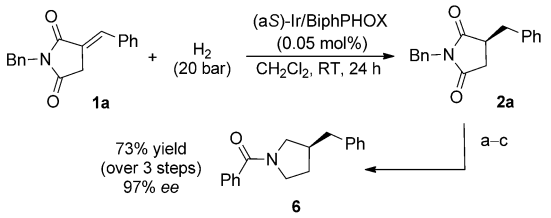


Entry		1	Conv. [%][b]	*ee* [%][c]
1		**1a**: R^1 = Bn	> 99	99
2		**1b**: R^1 = Ph	> 99	96
3		**1c**: R^1 = *n*Bu	> 99	98
4		**1d**: $R^1 = CH_2CH_2Ph$	> 99	95
5		**1e**: R^2 = 4-MeC_6H_4	> 99	99
6		**1f**: R^2 = 3-MeC_6H_4	> 99	98
7		**1g**: R^2 = 4-$MeOC_6H_4$	> 99	99
8		**1h**: R^2 = 3-$MeOC_6H_4$	> 99	97
9		**1i**: R^2 = 2-$MeOC_6H_4$	> 99	84
10		**1k**: R^2 = 4-FC_6H_4	> 99	99
11		**1l**: R^2 = 4-ClC_6H_4	> 99	98
12		**1m**: R^2 = 3-ClC_6H_4	> 99	98
13		**1n**: R^2 = 2-ClC_6H_4	> 99	82
14		**1o**: R^2 = 4-BrC_6H_4	> 99	95
15		**1p**: R^2 = 4-$NO_2C_6H_4$	> 99	95
16		**1j**	> 99	99
17		**1q**	> 99	79
18		**1r**	> 99	97
19		**1s**	85	97
20		**1t**: R^2 = Et	> 99	97
21		**1u**: R^2 = *n*Pr	> 99	95
22		**1v**: R^2 = *i*Pr	> 99	88
23		**1w**: R^2 = Cy	> 99	88

[a] Reactions were conducted on a 0.25 mmol scale in 2 mL of CH_2Cl_2 at room temperature using 1 mol % (a*S*)-Ir/*i*Pr-BiphPHOX under 20 bar of hydrogen for 1 h. [b] The conversion was determined by ^{1}H NMR spectroscopy. [c] Enantioselectivity was determined by HPLC using a chiral Daicel column. Cy = cyclohexyl.



Scheme 2. Asymmetric hydrogenation of α-alkylidene succinimide catalyzed by (a*S*)-Ir/*i*Pr-BiphPHOX.



Scheme 3. Iridium(I)-catalyzed asymmetric hydrogenation on a gram scale and synthesis of 3-benzyl pyrrolidine. For the hydrogenation: 0.05 mol% loading of (a*S*)-Ir/*i*Pr-BiphPHOX on a gram scale. For the transformation of **2a**: a) $LiAlH_4$ (6 equiv), RT; b) Pd/C (45%), H_2 (≈1 atm), 50°C; c) PhCOCl (2 equiv), NEt_3 (3 equiv), RT, 73% (over 3 steps), 97% *ee*.

s.[3i,j] In addition, the absolute configuration of the hydrogenation product **2a** was determined to be *S* by comparison of the optical rotation of **6** with the literature value (see the Supporting Information).

According to the X-ray crystal structure of (a*S*)-Ir/*i*Pr-BiphPHOX (Figure 1),[11b,15] the chiral induction and stereochemistry in the asymmetric hydrogenation of α-alkylidene succinimide **1** can be explained. The space in the front of iridium center at the oxazoline side can be modeled into four quadrants (Figure 1A).[16] The sterically hindered group, *i*Pr, which is attached to the chiral oxazoline ring, occupies quadrant 4, and can be accessed by the least sterically demanding part of the substrate. Quadrant 1 is occupied by a less sterically hindered group, that is, the backbone of the chiral ligand. Quadrants 2 and 3 are open, and thus may be accessed by the largest part of the substrate. The scenario depicted in Figure 1B is the most favored reaction pathway, thus leading to the major enantiomer (*S*)-**2a**. For the scenario depicted in Figure 1C, the steric interaction is stronger than for that in Figure 1B.

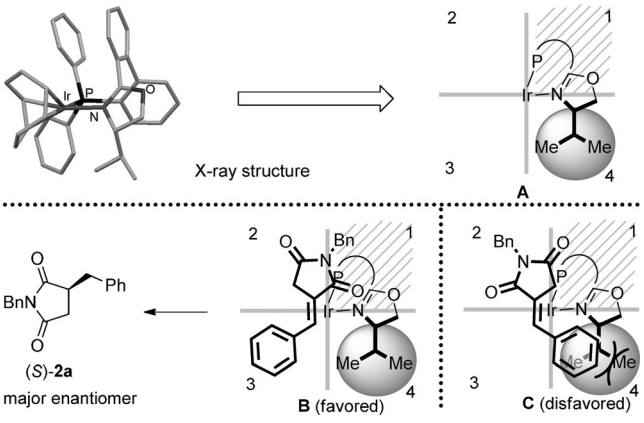


Figure 1. Hydrogenation model for **1a**.

In summary, an efficient asymmetric hydrogenation of α-alkylidene succinimides was developed using an Ir^I/*i*Pr-BiphPHOX complex to give the hydrogenated products in excellent yields (>99%) and enantioselectivities (up to 99% *ee*). The reaction was also successful at a reduced catalyst loading of 0.05 mol% and using just 1 bar of hydrogen. Novel approaches to the synthesis enantiopure motifs such as 3-benzyl-pyrrolidines and 1-hydroxypyrrolidine-2,5-dione were developed.

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[16] Previous studies showed that the C=C bond coordinated with iridium at the oxazoline side. Please see Refs. [8g–k].

