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Enantioselective Synthesis of Chiral 3-Substituted-3-silylpropionic Esters *via* Rhodium/Bisphosphine-Thiourea-Catalyzed Asymmetric Hydrogenation

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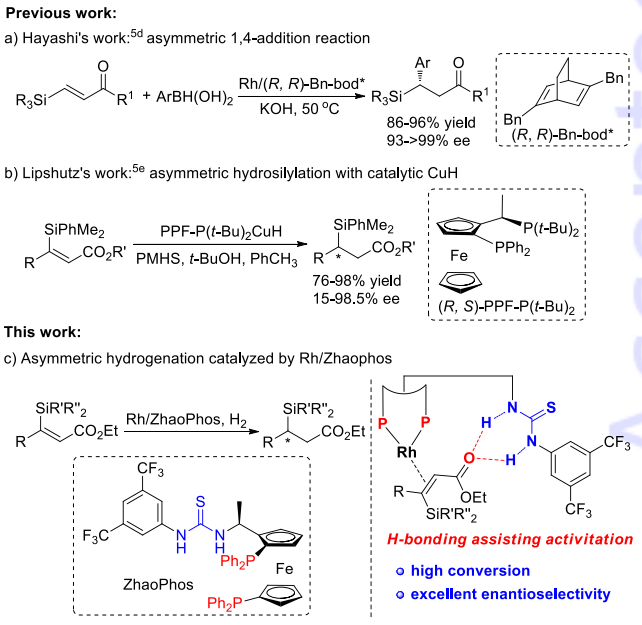
Abstract. We successfully developed asymmetric hydrogenation of β-silyl-α,β-unsaturated esters to prepare chiral 3-substituted-3-silylpropionic ester products catalyzed by rhodium/bisphosphine-thiourea (ZhaoPhos) with excellent results (up to 97% yield, >99% ee, 1 500 TON). Moreover, our hydrogenation product can be efficiently converted to other important organic molecules, such as chiral ethyl (*R*)-3-hydroxy-3-phenylpropanoate, (*R*)-3-(dimethyl(phenyl)silyl)-3-phenylpropanoic acid.

Keywords: Asymmetric hydrogenation; Bisphosphine-thiourea ligand; β-Silyl-α,β-unsaturated esters; Enantioselectivity; Chiral silicon compounds

Chiral organic silicon compounds are important intermediates due to their wide application in the field of organic synthesis.[1] Silyl groups are well established protective groups, which not only worked as hydroxyl surrogates *via* Tamao[2] or Fleming[3] oxidation but also took part in the asymmetric carbon-carbon bond formations.[4] Asymmetric catalysis represented several synthetic approaches for the preparation of chiral organic silicon compounds. [5] In 2005, Hayashi and coworkers reported Rh-catalyzed asymmetric 1,4-addition of arylboronic acids to β-silylated-α,β-carbonyl compounds using chiral diene (*R*, *R*)-Bn-bod* ligand with excellent results (Scheme 1a).[5d] In 2006, Lipshutz and coworkers reported CuH-catalyzed asymmetric conjugate reduction of α-silyl-α,β-unsaturated esters with polymethylhydrosiloxane (PMHS) as a stoichiometric source of hydride and *in situ* generated CuH ligated by (*R*, *S*)-PPF-P(*t*-Bu)$_2$ (Scheme 1b).[5e] Owing to the great importance of chiral organic silicon compounds, it is still significant to develop efficient and attractive catalytic methodologies to construct them. Catalytic asymmetric hydrogenation of functionalized olefins is recognized as a powerful synthetic strategy to access chiral molecules.[6] Herein, we successfully developed asymmetric hydrogenation of β-silyl-α,β-unsaturated esters for the synthesis of various chiral 3-substituted-3-silylpropionic esters catalyzed by Rh/bisphosphine-thiourea (ZhaoPhos) with high yields and excellent ee (Scheme 1c). Thiourea motif of ZhaoPhos worked as hydrogen bond donors, which successfully activated some substrates, such as nitroolefins, [7] unprotected imines,[8] (iso)quinolines,[9] and carbonyl compounds[10] through forming hydrogen-bonding interaction in the asymmetric hydrogenations. And the successful asymmetric hydrogenation of β-silyl-α,β-unsaturated esters is another excellent example of our powerful catalytic system.



Scheme 1. Synthesis of chiral 3-substituted-3-silylpropionic ester.

We began our initial study by investigating the effect of several chiral biphosphine ligands for the asymmetric hydrogenation of ethyl (*Z*)-3-phenyl-3-(trimethylsilyl)acrylate (**1a**)[11] as the model substrate

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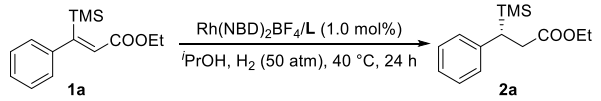
at 40 °C with the catalyst generated *in situ* by mixing $Rh(NBD)_2BF_4$ with ligands (S/C = 100). As shown in Table 1, (*S*)-BINAP, (*S*)-Segphos, (*S*)-DTBM-Segphos and (*R*c, *S*p)-DuanPhos exhibited poor reactivities and enantioselectivities in this asymmetric hydrogenation (10%-30% conversions, 5%-56% ee, Table 1, entries 1-4). We obtained moderate result when Binapine was applied to this transformation (83% conversion, 71% ee, Table 1, entry 5). To our delight, ZhaoPhos with a thiourea motif can provide excellent enantioselectivity (97% ee, Table 1, entry 6), which is mainly due to the activation between the ester group of substrate **1a** and the thiourea motif through forming hydrogen bonds.

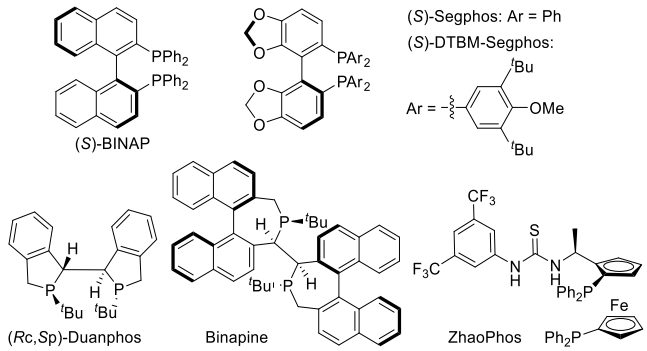
Table 1. Screening ligands for Rh-catalyzed asymmetric hydrogenation of ethyl (*Z*)-3-phenyl-3-(trimethylsilyl)acrylate (**1a**).[a]



1a 2a

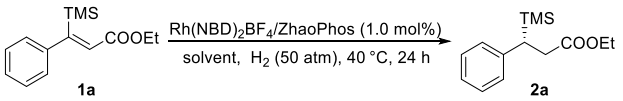
Entry	Ligand	Conv.(%)[b]	Ee (%)[c]
1	(*S*)-BINAP	23	56
2	(*S*)-Segphos	10	5
3	(*S*)-DTBM-Segphos	22	7
4	(*R*c, *S*p)-Duanphos	30	23
5	Binapine	83	71
6	ZhaoPhos	80	97

[a] All reactions were carried out with a $[Rh(NBD)_2BF_4]$/ligand/**1a** (0.1 mmol) ratio of 1:1.1:100 in 1.0 mL ^{i}PrOH under 50 atm H_2 at 40 °C for 24 h.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by HPLC analysis. TMS = trimethylsilyl group. The configuration of **2a** was determined as (*R*) by comparing the optical rotation data by the literature.[5d]



The solvents had a great effect in this asymmetric transformation, and we screened various solvents (Table 2). Moderate to good conversions were provided in ^{i}PrOH and EtOH, albeit with excellent enantioselectivities (61%-80% conversions, 97% ee, Table 2, entries 1, 3). No reaction was observed in CH_2Cl_2 (Table 2, entry 2). The asymmetric hydrogenation proceeded well in CF_3CH_2OH, toluene, THF with high conversions and excellent enantioselectivities (91%->99% conversions, 96%-97% ee, Table 1, entries 4-6). The CF_3CH_2OH was identified as the best solvent in terms of both high reactivity and excellent enantioselectivity (>99% conversion, 97% ee, Table 2, entry 4).

Table 2. Screening solvents for Rh-catalyzed asymmetric hydrogenation of ethyl (*Z*)-3-phenyl-3-(trimethylsilyl)acrylate (**1a**).[a]



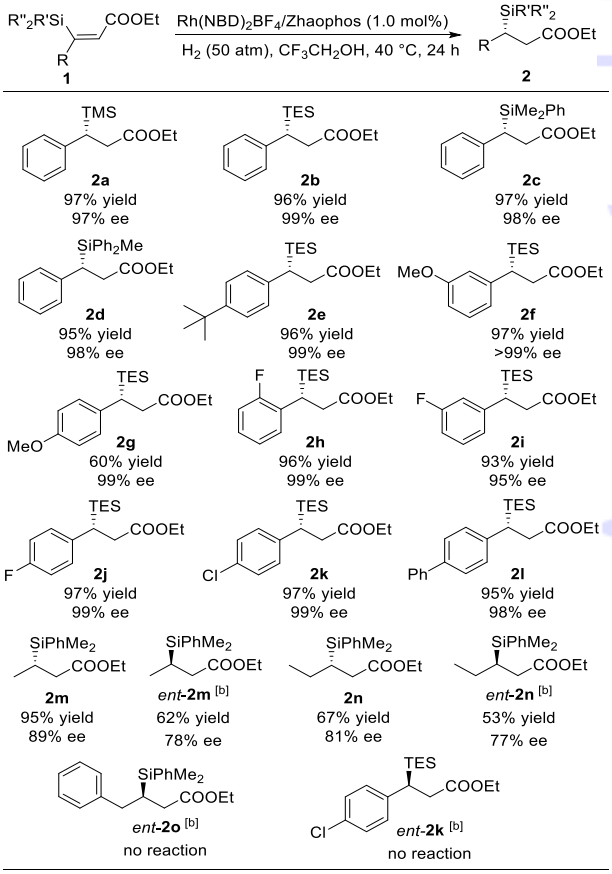
1a 2a

Entry	Solvent	Conv.(%) [b]	Ee (%)[c]
1	^{i}PrOH	80	97
2	CH_2Cl_2	NR	NA
3	CH_3CH_2OH	61	97
4	CF_3CH_2OH	>99	97
5	Toluene	94	96
6	THF	91	96

[a]All reactions were carried out with a $[Rh(NBD)_2BF_4]$/ligand/**1a** (0.1 mmol) ratio of 1:1.1:100 in 1.0 mL solvent under 50 atm H_2 at 40 °C for 24 h.
[b] Determined by ^{1}H NMR analysis.
[c] Determined by HPLC analysis. TMS = trimethylsilyl group. The configuration of **2a** was determined as (*R*) by comparing the optical rotation data by the literature. [5d] NR is no reaction. NA is not available.

After we optimized the reaction conditions, we focused on the investigation of the generality of the asymmetric hydrogenation of β-silyl-α,β-unsaturated esters. These results were summarized in Table 3. The Si-protecting group of the substrates (**1a-1d**) has little impact on the reactivities and enantioselectivities. When the Si-protecting group

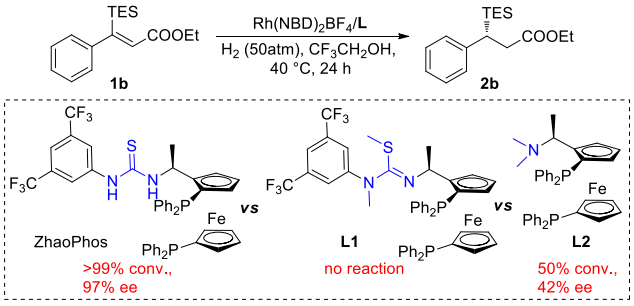
Table 3. Scope study of Rh-catalyzed asymmetric hydrogenation of β-silyl-α,β-unsaturated esters. [a]



[a] The yield was isolated yield. Ee was determined by HPLC analysis. TMS = trimethylsilyl group. TES = triethylsilyl group. The configuration of products **2** were determined as (*R*) by comparing the optical rotation data by the literature. [5d]
[b] Asymmetric hydrogenation of (*E*)-substrate.

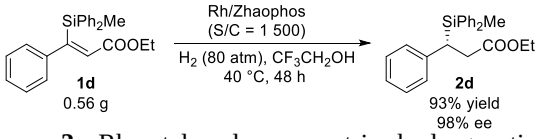
was changed from trimethylsilyl (**1a**) to triethylsilyl (**1b**), dimethylphenylsilyl (**1c**) and diphenylmethylsilyl (**1d**) group, the corresponding hydrogenation products (**2a**-**2d**) were obtained with high yields (95%-97% yields) and excellent enantioselectivities (97%-99% ee). The substrates β-silyl-α,β-unsaturated esters bearing electron-rich (**1e**-**1g**), electron-deficient (**1h**-**1k**) groups on the phenyl ring were hydrogenated efficiently to afford the hydrogenation products (**2e**-**2k**) with excellent results (60%-97% yields, 95->99% ee). The position of the substituents on the phenyl ring (**1e**-**1l**) have little effect on the reactivities and enantioselectivities. To our delight, the alkyl substrates, such as ethyl (*Z*)-3-(dimethyl(phenyl)silyl)but-2-enoate (*Z*)-**1m** and (*Z*)-ethyl 3-(dimethyl(phenyl)silyl)pent-2-enoate (*Z*)-**1n** also proceeded well with moderate results (67%-95% yields, 81%-89% ee). In addition, we also investigated the (*E*)-substrates in this asymmetric hydrogenation. The ethyl (*E*)-3-(dimethyl(phenyl)silyl)but-2-enoate (*E*)-**1m** and (*E*)-ethyl 3-(dimethyl(phenyl)silyl)pent-2-enoate (*E*)-**1n** can work and afford the corresponding hydrogenation products *ent*-**2m** and *ent*-**2n** with opposite configuration (53%-62% yields, 77%-78% ee). However, (*E*)-ethyl 3-(dimethyl(phenyl)silyl)-4-phenylbut-2-enoate (*E*)-**1o** and (*E*)-ethyl 3-(4-chlorophenyl)-3-(triethylsilyl)acrylate (*E*)-**1k** with relatively hindered groups showed very poor reactivity, and no reactions were observed.

In order to investigate the important role of thiourea motif of ZhaoPhos, control experiments were conducted. We applied ligands **L1** and **L2** without thiourea motif into the asymmetric hydrogenation of β-triethylsilyl-α,β-unsaturated ethyl ester **1b** under the optimized reaction conditions. As shown in Scheme 2, no reaction was observed when ligand **L1** was used in this reaction, and ligand **L2** provided poor conversion and enantioselectivity (50% conversion, 42% ee). These results displayed that the thiourea motif can activate our substrate and contribute to afford excellent enantioselectivity through forming hydrogen bonding between substrate and ligand.



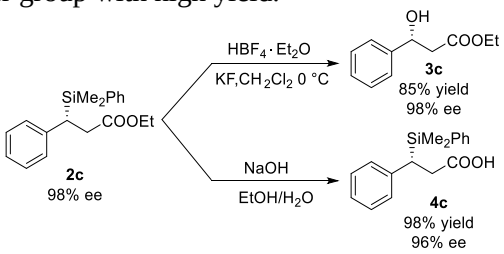
Scheme 2. Control experiments.

In addition, our Rh-ZhaoPhos catalytic system is very efficient in the asymmetric hydrogenation of ethyl (*Z*)-3-(methyldiphenylsilyl)-3-phenylacrylate **1d**. When the catalyst loading was reduced to 0.067 mol% (S/C = 1 500), the asymmetric hydrogenation of substrate **1d** with 0.56 g scale proceeded smoothly with 93% yield and 98% ee (Scheme 3).



Scheme 3. Rh-catalyzed asymmetric hydrogenation of ethyl (*Z*)-3-(methyldiphenylsilyl)-3-phenylacrylate **1d** with high TON.

In order to explore the synthetic utility of our catalytic methodology, further applications were carried out for the construction of other important organic molecules (Scheme 4). The hydrogenation product **2c** can be converted to ethyl (*R*)-3-hydroxy-3-phenylpropanoate **3c** without loss of ee value *via* Tamao oxidation.[5d] On the other hand, compound **2c** also can be transformed efficiently to the corresponding chiral (*R*)-3-(dimethyl(phenyl)silyl)-3-phenylpropanoic acid **4c** through the hydrolysis of ester group with high yield.[5e]



Scheme 4. Synthetic transformations of the hydrogenation product **2c**.

In summary, we have successfully developed Rh/ZhaoPhos catalyzed asymmetric hydrogenation of various β-silyl-α,β-unsaturated esters to access enantio-enriched 3-substituted-3-silylpropionic esters with excellent results (up to 97% yield, >99% ee). Our catalytic system is very efficient, and the TON is up to 1 500. In addition, the hydrogenation product **2c** can be efficiently converted to other important organic molecules through Tamao oxidation and the hydrolysis of ester group, providing chiral ethyl (*R*)-3-hydroxy-3-phenylpropanoate **3c**, (*R*)-3-(dimethyl(phenyl)silyl)-3-phenylpropanoic acid **4c**. Further investigations of this efficient catalytic system are ongoing in our laboratory.

Experimental Section

General procedure for the asymmetric hydrogenation of various β-silyl-α,β-unsaturated esters: A stock solution was made by mixing $[Rh(NBD)_2]BF_4$ with Zhaophos in a 1:1.1 molar ratio in trifluoroethanol at room temperature for 30 min in a nitrogen-filled glovebox. An aliquot of the catalyst solution (0.1 mL, 0.001 mmol) was transferred by syringe into the vials charged with different substrates (0.1 mmol for each) in anhydrous trifluoroethanol (1.0 mL). The vials were subsequently transferred into an autoclave into which hydrogen gas was

charged. The reaction was then stirred under H_2 (50 atm) at 40 °C for 24 h. The hydrogen gas was released slowly and carefully. The solution was concentrated and passed through a short column of silica gel (eluant: ethyl acetate) to get hydrogenation products. The ee values of all products **2** were determined by HPLC analysis on a chiral stationary phase.

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