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Chiral Frustrated Lewis Pairs Catalyzed Highly Enantioselective Hydrosilylations of 1,2-Dicarbonyl Compounds

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Supporting Information

ABSTRACT: A highly enantioselective hydrosilylation of 1,2-dicarbonyl compounds was successfully realized for the first time utilizing the combination of tricyclohexylphosphine and chiral alkenylborane derived *in situ* from diyne as a frustrated Lewis pair catalyst. A variety of optically active α-hydroxy ketones and esters were obtained in 52−98% yields with 86−99% ee's.

Optically active α-hydroxy carbonyl compounds are very important structural motifs in numerous biologically interesting compounds and are also utilized as versatile chiral building blocks for asymmetric synthesis.[1] Accordingly, various methods have been well established for the synthesis of these compounds. Among them, the asymmetric reduction of vicinal dicarbonyl compounds is a particularly powerful and straightforward approach. α-Keto esters are the most often studied substrates for the enantioselective reduction, and great progress has been achieved.[1c,2] But, in sharp contrast, the reduction of 1,2-diketone to α-hydroxy ketones has been less developed. In 1985, Ohta and co-workers reported a highly enantioselective reduction of benzils to benzoins catalyzed by the enzyme system of a microorganism.[3] Later on, several other biocatalysis systems were also employed for this reaction.[4] Besides the enzyme catalysis, only very few examples on the transition-metal catalyzed asymmetric hydrogenation were reported by Ohgo and co-workers using a chiral cobalt complex as catalyst to give up to 78% ee.[5] Despite these advances, the catalytic highly enantioselective reduction of 1,2-diketones still remains an unsolved problem.[6]

Catalytic hydrosilylation of unsaturated compounds is a very useful reaction in organic chemistry.[7] In 1996, Piers and co-workers disclosed an interesting $B(C_6F_5)_3$-catalyzed hydrosilylation of carbonyl compounds.[8] The borane Lewis acid activated the Si−H bond instead of the carbonyl group to form silylium and hydridoborate ions, which is very similar to the H−H bond activation mechanism in the chemistry of frustrated Lewis pairs (FLPs).[9] This type of activation attracts both synthetic and mechanistic interest for chemists, and this area has witnessed very rapid growth.[10,11] However, the asymmetric version of Piers type hydrosilylation is still in the start-up stage.[12] In 2008, Oestreich and co-workers reported a $B(C_6F_5)_3$-catalyzed hydrosilylation of acetophenone using a chiral silane to afford the chiral alcohol with 38% ee.[13] But the combination of $B(C_6F_5)_3$ with chiral silanes for the reduction of imines gave racemic products.[14] With the use of a binaphthyl-based chiral borane, up to 62% ee was obtained for imine substrates by the same group.[15] Recently, Klankermayer and co-workers utilized camphor derived chiral borane and tri-*tert*-butylphosphine as an FLP catalyst for the same reaction to give up to 87% ee.[16] Mechanistic studies suggest that the heterolytic cleavage of the Si−H bond by the FLP catalyst results in the formation of a silylium and hydridoborate ionic complex.[16] To the best of our knowledge, this is the highest enantioselectivity for this type hydrosilylation until now. Particularly, it is noteworthy that there is still a lack of highly enantioselective catalysts for the Piers type hydrosilylation of ketones and other unsaturated compounds, and FLP catalysts might be a good choice to solve this problem.

In our previous work, we developed an *in situ* catalyst generation strategy via a hydroboration of alkenes with Piers' borane $HB(C_6F_5)_2$, which has been successfully applied to the FLP-catalyzed hydrogenation.[17−19] Significantly, a chiral borane catalyst derived from chiral diene was found to be effective for the hydrosilylation of imines to give up to 82% ee.[20] Very recently, we developed chiral alkenylboranes derived from chiral diynes for the metal-free asymmetric hydrogenation of silyl enol ethers.[21] With these diverse and efficient chiral boranes in hand, we further devote our efforts to the challenging hydrosilylation of 1,2-diketones and α-keto esters. Herein, we wish to report our preliminary results on this subject.

Attempts were started by using chiral alkenylborane generated from chiral diyne **2a** and Piers' borane for the hydrosilylation of benzil (**1a**) with 1.1 equiv of $PhMe_2SiH$ (Scheme 1). The desired product benzoin (**4a**) can be obtained in 25% conversion and 22% ee (Table 1, entry 1). When tri-*tert*-butylphosphine (**3a**) was used as an additional Lewis base, 77% ee was obtained (Table 1, entry 2). The obvious improvement on the enantioselectivity using an additional phosphine Lewis base is also observed in the asymmetric hydrosilyalion of imines reported by Klankermayer and co-workers.[16] This promising result encouraged us to test commercially available phosphines **3b−d** for this reaction (Table 1, entries 3−5). To our pleasure, up to 76% conversion and 98% ee were obtained when tricyclohexylphosphine (**3d**) was used as a Lewis base (Table 1, entry 5). Under this condition, a variety of chiral diynes **2b−l** were next examined. Terminal diynes **2b−j** afforded low to moderate reactivities and good to excellent enantioselectivities (Table 1, entries 6−14).

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Scheme 1. Chiral FLP-Catalyzed Asymmetric Hydrosilylation of Benzil 1a

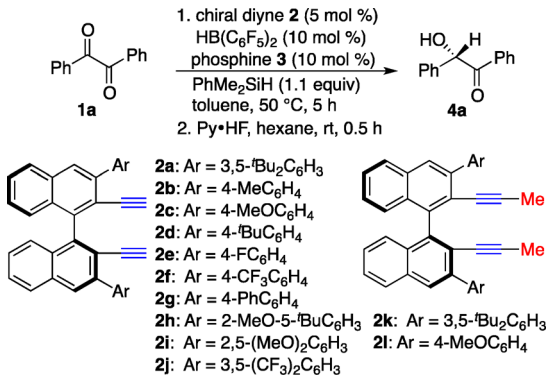


Table 1. Evaluation of Phosphines and Diynes[a]

entry	diyne 2	phosphine 3	conv. (%)[b]	ee (%)[c]
1	**2a**	–	25	22
2	**2a**	$^tBu_3P$ (**3a**)	12	77
3	**2a**	Mes_3P (**3b**)	27	74
4	**2a**	$Ph_2(C_6F_5)P$ (**3c**)	39	83
5	**2a**	Cy_3P (**3d**)	76	98
6	**2b**	**3d**	21	78
7	**2c**	**3d**	15	69
8	**2d**	**3d**	28	89
9	**2e**	**3d**	19	71
10	**2f**	**3d**	21	80
11	**2g**	**3d**	16	71
12	**2h**	**3d**	42	92
13	**2i**	**3d**	15	71
14	**2j**	**3d**	39	88
15	**2k**	**3d**	7	9
16	**2l**	**3d**	26	0

[a]All reactions were carried out with benzil (**1a**) (0.20 mmol), chiral diyne (0.01 mmol), $HB(C_6F_5)_2$ (0.02 mmol), phosphine (0.02 mmol), and $PhMe_2SiH$ (0.22 mmol) in toluene (0.4 mL) at 50 °C for 5 h. [b]Determined by crude ^1H NMR. [c]The ee was determined by chiral HPLC.

But, internal diynes **2k,l** gave extremely low conversions and ee's (Table1, entries 15 and 16). Overall, the combination of chiral diyne **2a** and tricyclohexylphosphine (**3d**) gave the optimal results.

The reaction conditions were optimized to further improve the reactivity. It was found that a higher temperature gave a slightly higher conversion without loss of enantioselectivity (Table 2, entries 1−4). Solvents were found to influence the hydrosilylation largely on reactivities and ee's (Table 2, entries 5−9). Increasing the amount of $PhMe_2SiH$ afforded a satisfactory 94% conversion with 99% ee (Table 2, entries 3, 10−12). A comparison of chiral diyne and diene for the hydrosilylation of benzil (**1a**) was subsequently conducted under the optimal reaction conditions. As shown in Figure 1, chiral diyne **2a** exhibited an obvious advantage over chiral diene **5** on both reactivity and enantioselectivity, which is likely attributed to the electronic and/or steric difference of alkenylborane and alkylborane. Obtaining a clear reason still awaits further efforts.

A variety of 1,2-diketones **1a−l** were then subjected to the hydrosilylation. As shown in Table 3, both electron-withdrawing or -donating substituents were well tolerated to give optically active α-hydroxy ketones **4a−l** in 52−98% yields with 86−99% ee's (entries 1−12). It is noteworthy that the diol

Table 2. Optimization of Reaction Conditions[a]

entry	$PhMe_2SiH$ (equiv)	solvent	temp (°C)	conv. (%)[b]	ee (%)[c]
1	1.1	toluene	50	76	98
2	1.1	toluene	30	74	98
3	1.1	toluene	60	82	98
4	1.1	toluene	80	80	98
5	1.1	CH_2Cl_2	60	30	83
6	1.1	Et_2O	60	20	80
7	1.1	dioxane	60	55	94
8	1.1	hexane	60	62	96
9	1.1	mesitylene	60	81	97
10	2.0	toluene	60	85	97
11	3.0	toluene	60	94	99
12	4.0	toluene	60	78	97

[a]All reactions were carried out with benzil (**1a**) (0.20 mmol), chiral diyne **2a** (0.01 mmol), $HB(C_6F_5)_2$ (0.02 mmol), and phosphine **3d** (0.02 mmol) in solvent (0.4 mL) for 5 h. [b]Determined by crude ^1H NMR. [c]The ee was determined by chiral HPLC.

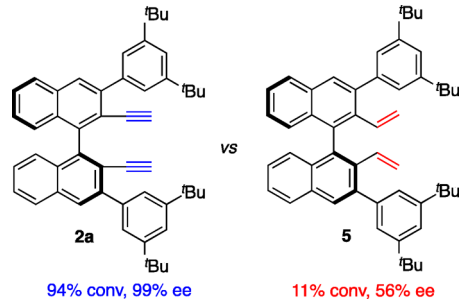
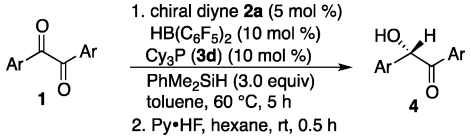


Figure 1. Comparison of chiral diyne **2a** with chiral diene **5**.

Table 3. Asymmetric Hydrosilylation of 1,2-Diketones[a]



entry	product (**4**)	yield (%)[b]	ee (%)[c]
1	**4a**: Ar = Ph	91	>99
2	**4b**: Ar = 2-FC_6H_4	89	99
3	**4c**: Ar = 3-MeC_6H_4	86	96
4	**4d**: Ar = 3-$MeOC_6H_4$	98	99
5	**4e**: Ar = 3-$^iPrOC_6H_4$	77	96
6[d]	**4f**: Ar = 3-ClC_6H_4	98	86
7	**4g**: Ar = 4-MeC_6H_4	94	96
8	**4h**: Ar = 4-EtC_6H_4	90	94
9	**4i**: Ar = 4-$^tBuC_6H_4$	96	96
10	**4j**: Ar = 4-CyC_6H_4	94	89
11[e]	**4k**: Ar = 4-FC_6H_4	70	88
12[d]	**4l**: Ar = 3,5-$Me_2C_6H_3$	52	94

[a]All reactions were carried out with 1,2-diketones **1** (0.40 mmol), $HB(C_6F_5)_2$ (0.04 mmol), chiral diyne **2a** (0.02 mmol), Cy_3P (0.04 mmol), and $PhMe_2SiH$ (1.2 mmol) in toluene (0.8 mL) at 60 °C for 5 h unless other noted. [b]Isolated yield. [c]The ee was determined by chiral HPLC. [d]$HB(C_6F_5)_2$ (0.06 mmol), chiral diyne **2a** (0.03 mmol), and Cy_3P (0.06 mmol) were used. [e]$HB(C_6F_5)_2$ (0.08 mmol), chiral diyne **2a** (0.04 mmol), and Cy_3P (0.08 mmol) were used.

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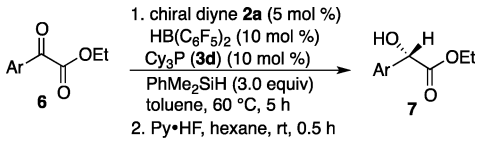
byproducts were not obtained in all cases although 3 equiv of $PhMe_2SiH$ were used. Moreover, this current catalytic hydrosilylation system was also effective for the reaction of α-keto esters without any further optimization. As shown in Table 4,

Table 4. Asymmetric Hydrosilylation of α-Keto Esters[a]



entry	product (7)	yield (%)[b]	ee (%)[c]
1	**7a**: Ar = Ph	96	98
2	**7b**: Ar = 2-MeC_6H_4	82	96
3	**7c**: Ar = 3-MeC_6H_4	86	99
4	**7d**: Ar = 3-$MeOC_6H_4$	93	99
5	**7e**: Ar = 3-ClC_6H_4	90	98
6	**7f**: Ar = 4-MeC_6H_4	82	>99
7	**7g**: Ar = 3,5-$Me_2C_6H_3$	83	99
8	**7h**: Ar = 2-thienyl	87	97

[a]All reactions were carried out with α-keto esters **6** (0.40 mmol), $HB(C_6F_5)_2$ (0.04 mmol), chiral diyne **2a** (0.02 mmol), Cy_3P (0.04 mmol), and $PhMe_2SiH$ (1.2 mmol) in toluene (0.8 mL) at 60 °C for 5 h. [b]Isolated yield. [c]The ee was determined by chiral HPLC.

the asymmetric hydrosilylation of α-keto esters **6a−h** proceeded cleanly to furnish the desired optically active α-hydroxy esters **7a−h** in high levels of reactivities and enantioselectivities (entries 1−8). Acetophenone was also an effective substrate for the asymmetric hydrosilylation; under the current reaction conditions, 1-phenylethanol was obtained in 95% yield with 42% ee.

In summary, a highly enantioselective hydrosilylation of 1,2-dikeones was successfully realized for the first time using the combination of Cy_3P and chiral alkenylborane derived *in situ* from chiral diyne as an FLP catalyst. A variety of optically active α-hydroxy ketones were afforded in 52−98% yields with 86−99% ee's. Notably, no diol byproducts were observed although 3 equiv of $PhMe_2SiH$ were used. Significantly, chiral diyne exhibited an obvious advantage over chiral diene in the hydrosilylation. Moreover, this catalytic hydrosilylation system can be further extended to α-keto esters without any further optimization and furnish the desired α-hydroxy esters in excellent yields and ee's. Further efforts on expanding the substrate scope of Piers type hydrosilylation and exploring chiral alkenylboranes in the asymmetric hydrogenation are underway in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b13104.

Procedure for the metal-free catalytic asymmetric hydrosilylation of 1,2-dicarbonyl compounds, characterization of products, and data for the determination of enantiomeric excesses along with the NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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