

Chiral Phosphine-Catalyzed Enantioselective Construction of γ -Butenolides Through Substitution of Morita–Baylis–Hillman Acetates with 2-Trimethylsilyloxy Furan

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The efficient synthesis of highly functionalized γ -butenolides remains an important challenge in organic chemistry.¹ Recently, an important finding by Krische's group indicates that, upon exposure of Morita–Baylis–Hillman (MBH) acetates to substoichiometric amounts of triphenylphosphane (20 mol %) in the presence of 2-trimethylsilyloxy furan, regioselective allylic substitution occurs to provide the γ -butenolides in good to excellent yields, high regioselectivities, and diastereoselectivities along with a chiral auxiliary approach.² Inspired by this elegant work, we report herein the first catalytic asymmetric version of this reaction with chiral multifunctional phosphines, (*R*)-*N*-(2'-diphenylphosphanyl-[1,1']binaphthalenyl-2-yl)methanesulfonamide **L2** and (*R*)-*N*-(2'-diphenylphosphanyl-[1,1']binaphthalenyl-2-yl)acetamide **L3**,³ as catalysts.⁴

Initial examination was carried out by using Morita–Baylis–Hillman acetate **1a** (1.0 equiv) and 2-trimethylsilyloxy furan **2** (2.0 equiv) as the substrates in the presence of chiral phosphines **L1**–**L5** (20 mol %) in THF (Figure 1). The results are summarized in Table 1. We found that the corresponding *syn*- γ -butenolide **3a** was produced in good chemical yields (81 and 74%) and enantioselectivities (70 and 61% ee) after the reaction was conducted for 57 and 48 h by using multifunctional phosphines **L2** and **L3**. Under the above conditions, the multifunctional chiral phosphine **L1** was proven to not be an efficient catalyst (Table 1, entries 1–3). Also, the use of chiral phosphines **L4** and **L5** afforded *syn*- γ -butenolide **3a** in poor yields and ee's (Table 1, entries 4 and 5). These observations suggest that an active amide proton of the catalyst is crucial for this asymmetric reaction (Table 1, entries 2 and 3). The examination of solvent effects using catalyst **L2** revealed that the protic solvent, methanol, can significantly facilitate the reaction to produce the corresponding adduct **3a** in 55% yield and 90% ee within a reaction period of 48 h (Table 1, entries 6–10). However, the bulky protic solvent, *tert*-butanol, did not perform well for this reaction (Table 1, entry 11). We then envisaged that addition of water would further improve this asymmetric reaction. We thus carried out the **L2**-catalyzed reaction in toluene together with various amounts of water under the standard conditions.^{5,6} As can be seen in Table 2, the addition of 1.0 and 3.0 equiv of water to the reaction system resulted in the corresponding *syn*- γ -butenolide **3a** in much better outcomes: 94% yield and 81% ee for 1.0 equiv, 94% yield and 88% ee for 3.0 equiv, respectively (Table 2, entries 1–3). Increasing the amounts of water to 6.0 equiv afforded **3a** in 94% ee but in a lower yield of 46% (Table 2, entry 4). Using 2.5 equiv of **2** along with 6.0 equiv of water provided **3a** in 94% yield and 94% ee (Table 2, entry 5). Further increase of water to 10 equiv did not improve the results (Table 2, entry 6).

Under these optimal conditions, we continued screening chiral phosphines **L1** and **L3**–**L5** for this reaction, and the results are given in the entries 7–11 of Table 2. We found that using phosphine

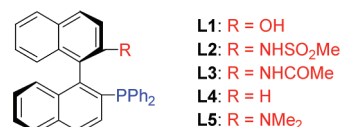


Figure 1. Chiral phosphines for asymmetric allylic substitutions.

Table 1. Chiral Phosphines Catalyzed Allylic Substitution of MBH Acetate **1a** with 2-Trimethylsilyloxy Furan **2** in Different Solvents

entry	catalyst	solvent	time (h)	yield (%) ^a	ee (%) ^b
1	L1	THF	57	50	33
2	L2	THF	57	81	70
3	L3	THF	48	74	61
4	L4	THF	48	40	1
5	L5	THF	72	37	–6
6	L2	CH ₂ Cl ₂	48	70	75
7	L2	DMF	48	69	0
8	L2	MeCN	48	60	19
9	L2	MeOH	48	55	90
10	L2	PhMe	48	85	55
11	L2	Me ₃ COH	48	93	48

^a Isolated yields. ^b Determined by chiral HPLC.

L3 (20 mol %) as a catalyst afforded **3a** in 98% yield and 94% ee within shorter reaction time (36 h), and similar results were obtained in the presence of **L3** (10 mol %) under identical conditions (Table 2, entries 8 and 9). Other chiral phosphines **L1**, **L4**, and **L5** are not as effective as **L2** and **L3**, suggesting that the combination of an active amide proton of the catalyst and an extra proton source (H₂O) is necessary for the present success (Table 2, entries 7, 10, and 11). In fact, it was also found that, when PPh₃ was used as a catalyst, water did not show an obvious effect on chemical yield.

We next examined the generality of this reaction using a variety of MBH acetates **1** derived from Michael acceptors such as methyl vinyl ketone (MVK), ethyl vinyl ketone (EVK), and methyl acrylate. The results are indicated in Table 3. The corresponding γ -butenolides **3** were obtained in high yields and ee's whether they have electron-donating or electron-withdrawing substituents on their benzene rings (Table 3, entries 1–7, 9, and 10). As for the aliphatic MBH acetate, the corresponding product **3i** was obtained in 60% yield and 71% ee in the presence of 25 mol % of **L3** (Table 3, entry 8). Using an acrylate-derived MBH acetate as the substrate afforded the corresponding product **3l** in 45% yield and 84% ee under the standard conditions (Table 3, entry 11).

Table 2. Screening of Water Loading on the Allylic Substitution of MBH Acetate **1a** with **2** To Form γ -Butenolide **3a** in the Presence of **L**

$\text{1a} + \text{2} \xrightarrow[\text{(1.0 equiv) (x equiv) PhMe, H}_2\text{O, 48 h, rt (dr>95:5)}]{\text{L (20 mol \%)} } \text{3a}$						
entry	catalyst	H ₂ O (equiv)	2 (equiv)	time (h)	yield (%) ^a	ee (%) ^b
1	L2	0.1	2.0	48	91	65
2	L2	1	2.0	48	94	81
3	L2	3	2.0	48	94	88
4	L2	6	2.0	48	46	94
5	L2	6	2.5	48	94	94
6	L2	10	2.5	48	60	94
7	L1	6	2.5	48	50	25
8	L3	6	2.5	36	98	94
9 ^c	L3	6	2.5	36	94	94
10	L4	6	2.5	48	57	29
11	L5	6	2.5	72	25	–55

^a Isolated yields. ^b Determined by chiral HPLC. ^c 10 mol% of catalyst was added.

Table 3. Chiral Phosphine **L3**-Catalyzed Allylic Substitution of Various MBH Acetates **1** with **2**

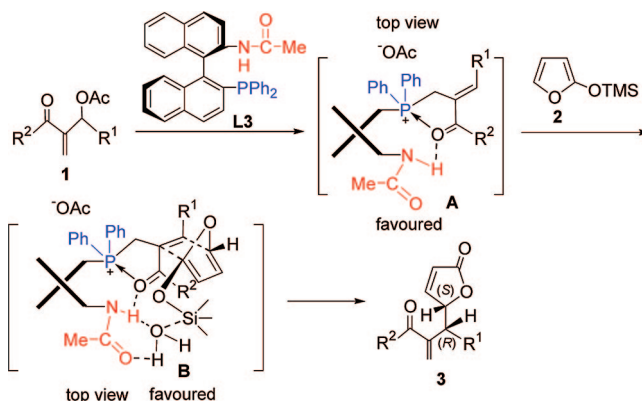
$\text{1 (1.0 equiv)} + \text{2 (2.5 equiv)} \xrightarrow[\text{PhMe, H}_2\text{O (6 equiv), rt}]{\text{L3 (10 mol\%)}} \text{3}$						
entry	R ¹	R ²	time (h)	yield (%) ^a	ee (%) ^b	absolute configuration
1	<i>p</i> -MeC ₆ H ₄	Me	36	3b : 94	96	<i>S, R</i>
2	<i>m</i> -MeC ₆ H ₄	Me	36	3c : 81	95	<i>S, R</i>
3	<i>p</i> -BrC ₆ H ₄	Me	24	3d : 85	95	<i>S, R</i>
4	<i>p</i> -ClC ₆ H ₄	Me	24	3e : 89	95	<i>S, R</i>
5	<i>m</i> -ClC ₆ H ₄	Me	24	3f : 95	94	<i>S, R</i>
6	<i>o</i> -ClC ₆ H ₄	Me	24	3g : 89	94	<i>S, R</i>
7	<i>p</i> -NO ₂ C ₆ H ₄	Me	24	3h : 98	91	<i>S, R</i>
8 ^c	C ₃ H ₇	Me	96	3i : 60	71	<i>S, R</i>
9	C ₆ H ₅	Et	72	3j : 98	91	<i>S, R</i>
10	<i>p</i> -NO ₂ C ₆ H ₄	Et	72	3k : 85	91	<i>S, R</i>
11	C ₆ H ₅	OMe	72	3l : 45	84	–

^a Isolated yields. ^b Determined by chiral HPLC. ^c In the presence of **L3** (25 mol %).

Their structures were determined by ¹H and ¹³C NMR spectroscopy and HRMS or microanalyses, and ee's were analyzed by chiral HPLC (see Supporting Information). The absolute configuration of **3** was determined as *S,R*-configuration by X-ray diffraction of **3d** containing a bromine atom on the benzene ring.⁷ The CIF data of **3d** are presented in the Supporting Information.⁸

A plausible mechanism for this asymmetric reaction is outlined in Scheme 1. As proposed by Krische,² the treatment of MBH acetate **1** with **L3** produces an electrophile–nucleophile ion pair, the enone intermediate **A**; this intermediate is stabilized by an intramolecular H-bonding.⁹ The *endo*-selective Diels–Alder cycloaddition of the siloxy furan ate complex with enone **A** affords intermediate **B** followed by subsequent Grob-type fragmentation to give γ -butenolide **3** (Scheme 1). This Diels–Alder mechanism has been originally proposed by Krische and co-worker.² Although water effect cannot be completely clarified at the present stage, it is possible for water to assist the Grob-type fragmentation through H-bonding and the formation of a pentacoordinated silicon intermediate **B**.¹⁰

In conclusion, we have established an efficient multifunctional chiral phosphine **L2** or **L3**-catalyzed allylic substitutions of MBH acetates **1** with 2-trimethylsilyloxy furan **2** to provide an easy access

Scheme 1. A Plausible Reaction Mechanism

to optically active γ -butenolides **3** under mild conditions. Good to excellent yields and ee's have been achieved by using water as a coadditive. Further efforts are in progress regarding the scope and mechanistic details.

Acknowledgment. We thank the Shanghai Municipal Committee of Science and Technology (04JC14083, 06XD14005), Chinese Academy of Sciences, and the National Natural Science Foundation of China for financial support (20472096, 20672127, and 20732008).

Supporting Information Available: ¹³C and ¹H NMR spectroscopic and analytic data for **3** and X-ray crystal data of **3d** as well as chiral HPLC traces. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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JA802422D