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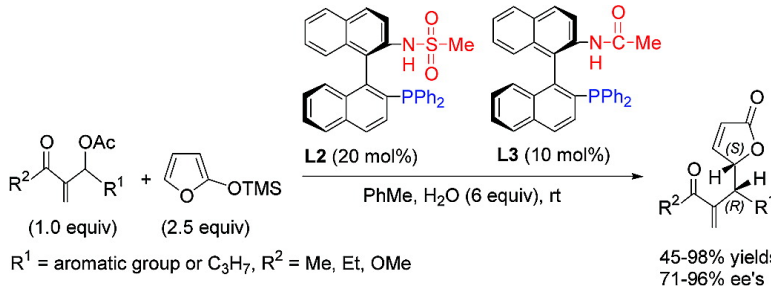

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Chiral Phosphine-Catalyzed Enantioselective Construction of γ-Butenolides Through Substitution of Morita−Baylis−Hillman Acetates with 2-Trimethylsilyloxy Furan

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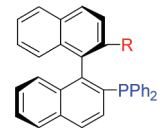
The efficient synthesis of highly functionalized γ-butenolides remains an important challenge in organic chemistry.[1] Recently, an important finding by Krische's group indicates that, upon exposure of Morita−Baylis−Hillman (MBH) acetates to substoichiometric amounts of triphenylphosphane (20 mol %) in the presence of 2-trimethylsilyloxy furan, regiospecific 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).

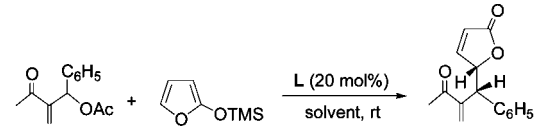
Under these optimal conditions, we continued screening chiral phosphines **L1** and **L3**−**L5** for this reaction, and the results are given in the entries 7−11 of Table 2. We found that using phosphine



L1: R = OH
L2: R = $NHSO_2Me$
L3: R = NHCOMe
L4: R = H
L5: R = NMe_2

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



1a (1.0 equiv) **2** (2.0 equiv) **3a** (dr > 95:5)

entry	catalyst	solvent	time (h)	yield (%)[a]	ee (%)[b]
1	**L1**	THF	57	50	33
2	**L2**		57	81	70
3	**L3**		48	74	61
4	**L4**		48	40	1
5	**L5**		72	37	−6
6	**L2**	CH_2Cl_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_3COH	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 phopshines **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 (H_2O) is necessary for the present success (Table 2, entries 7, 10, and 11). In fact, it was also found that, when PPh_3 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).

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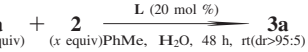
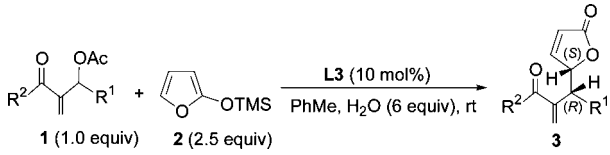
Table 2. Screening of Water Loading on the Allylic Substitution of MBH Acetate **1a** with **2** To Form γ-Butenolide **3a** in the Presence of **L**



entry	catalyst	H_2O (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**



entry	R^1	R^2	time (h)	yield (%)[a]	ee (%)[b]	absolute configuration
1	*p*-MeC_6H_4	Me	36	**3b**: 94	96	*S*, *R*
2	*m*-MeC_6H_4	Me	36	**3c**: 81	95	*S*, *R*
3	*p*-BrC_6H_4	Me	24	**3d**: 85	95	*S*, *R*
4	*p*-ClC_6H_4	Me	24	**3e**: 89	95	*S*, *R*
5	*m*-ClC_6H_4	Me	24	**3f**: 95	94	*S*, *R*
6	*o*-ClC_6H_4	Me	24	**3g**: 89	94	*S*, *R*
7	*p*-$NO_2C_6H_4$	Me	24	**3h**: 98	91	*S*, *R*
8[c]	C_3H_7	Me	96	**3i**: 60	71	*S*, *R*
9	C_6H_5	Et	72	**3j**: 98	91	*S*, *R*
10	*p*-$NO_2C_6H_4$	Et	72	**3k**: 85	91	*S*, *R*
11	C_6H_5	OMe	72	**3l**: 45	84	−

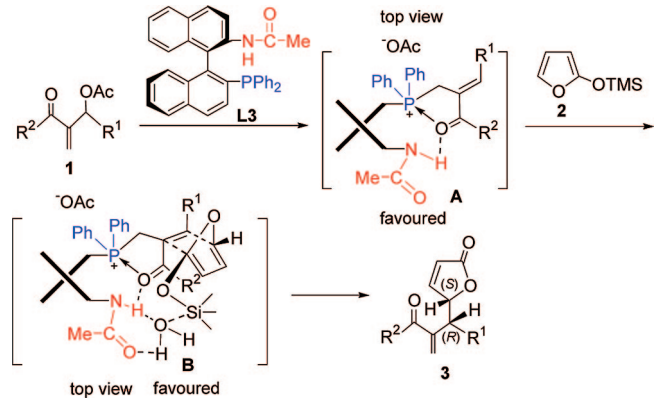
[a] Isolated yields. [b] Determined by chiral HPLC. [c] In the presence of **L3** (25 mol %).

Their structures were determined by ^1H and ^{13}C 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.

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Supporting Information Available: ^{13}C 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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