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Diastereo- and Enantioselective Construction of γ-Butenolides through Chiral Phosphane-Catalyzed Allylic Alkylation of Morita–Baylis–Hillman Acetates

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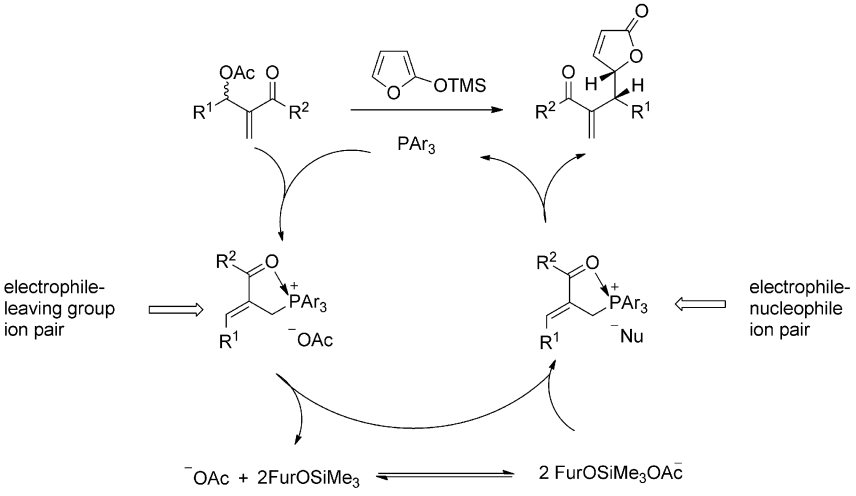
A series of multifunctional, chiral amide–phosphane organocatalysts have been designed and synthesized for the allylic substitution of Morita–Baylis–Hillman (MBH) acetate with 2-trimethylsilyloxyfuran for butenolide synthesis. This reaction was achieved in good to excellent yield (42–98 %) and high *ee* (85–99 %) with respect to a wide range of substrates in absolute MeOH or CH_3CN, using chiral amide–phosphane organocatalysts with an amide moiety including an active proton. NMR tracing experiments identified the critical phosphonium intermediates involved in the catalytic cycles. Computational studies disclosed the origins of diastereo- and enantioselectivity, in particular, revealing that the active proton of the amide moiety is the critical factor for the catalyst to have high enantiofacial control.

Introduction

Efficient methods for the construction of γ-butenolide ring systems have received considerable attention as these ubiquitous structural motifs have been found in numerous natural products and the γ-butenolide synthon has become a valuable architectural platform for the development of new asymmetric methodologies.[1] In this context, using 2-silyloxyfuran as a nucleophilic partner in the Mukaiyama aldol reaction,[2] Mukaiyama–Michael reaction,[3,4] and Mukaiyama–Mannich-type addition (vinylogous Mannich reaction)[5] has emerged as the effective strategy for butenolide synthesis.[6] Recently, nucleophilic phosphane organocatalysis has proved to be a powerful strategy to deliver multi-



Scheme 1. Postulated catalytic mechanism for γ-butenolide synthesis through tandem S_N2'/S_N2' substitution.

functional compounds.[7,8] Krische first reported the phosphane-catalyzed allylic alkylation of MBH acetates with 2-silyloxyfuran.[9,10] Upon exposure of MBH acetates to a substoichiometric amount of triphenylphosphane (20 mol-%) in the presence of 2-trimethylsilyloxyfuran (TMSOF), regiospecific allylic substitution occurs to provide γ-butenolides in good to excellent yields, with high region- and diastereoselectivities. Krische suggested that the phosphane-

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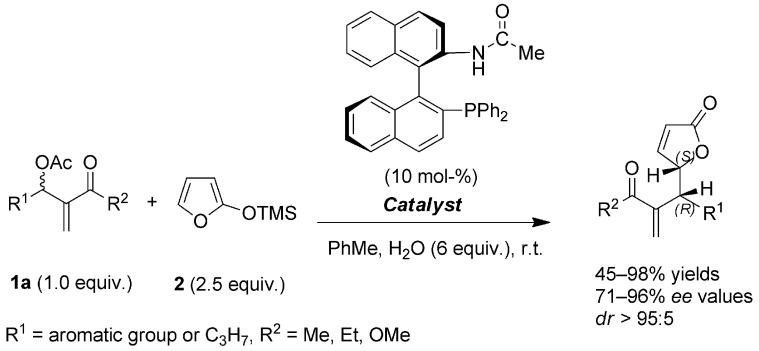


Scheme 2. Chiral phosphanes catalyzed allylic substitution of MBH acetates with TMSOF.

catalyzed allylic substitution of MBH acetates exhibited an exceptionally high level of regiospecificity through a tandem S_N2'/S_N2' mechanism (Scheme 1).[9,11] The generation of an electrophile–nucleophile ion pair, which suppresses direct addition of the nucleophile to the less substituted enone moiety of the starting MBH acetate, is proposed as a key step in this catalytic transformation. We first developed the asymmetric version of allylic substitution of MBH acetates with TMSOF to furnish γ-butenolides using an efficient multifunctional chiral phosphane organocatalyst under mild conditions (Scheme 2).[12] Our previous investigations on asymmetric versions of the allylic substitution of MBH acetates revealed that the amide moiety of the catalyst was the efficient functional group for achieving high enantioselectivity. Further studies demonstrated that employing water as an additive substantially increased the enantioselectivity for this asymmetric reaction. However, the substrate scope was limited to MBH acetates derived from activated α,β-unsaturated ketones and aromatic aldehydes. The substrates derived from aliphatic aldehydes or acrylates showed low reactivities and enantioselectivities. Chen has developed the direct asymmetric γ-allylic alkylation of butenolides with MBH carbonates promoted by modified cinchona alkaloids, which provided an alternative method to access γ-butenolides.[13]

In this article, we demonstrate that highly diastereo- and enantioselective allylic alkylation of a wide range of MBH acetates with TMSOF can be achieved using a series of multifunctional, chiral phosphane organocatalysts affording γ-butenolides in good to excellent yields with high *ee*. Moreover, mechanistic investigations were undertaken to reveal the stereochemical control on this allylic substitution.

Results and Discussion

Catalyst Screening

To seek more efficient catalysts and further evidence for the mechanism of stereochemical control of the phosphane-

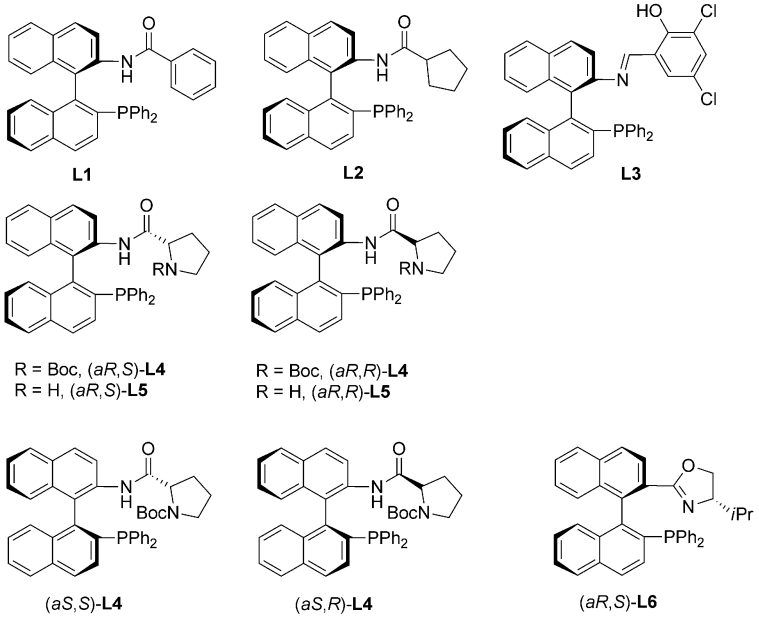


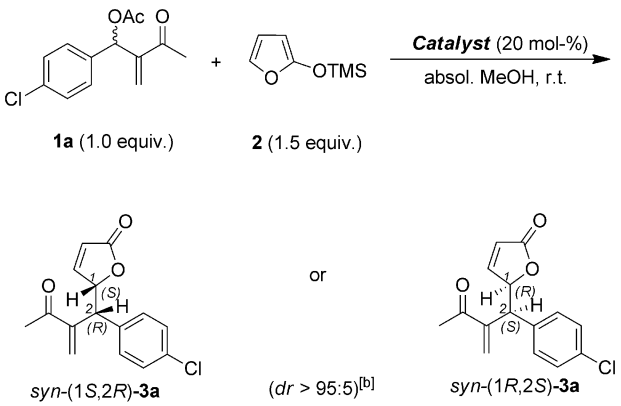
Figure 1. Chiral phosphane catalysts **L1**–**6**.

catalyzed allylic substitution, we modified the amide moiety and synthesized a series of catalysts (Figure 1). **L1** and **L2** were synthesized from the corresponding benzoyl chloride and cyclopentanecarbonyl chloride. The phosphane–Schiff base **L3** was synthesized from 3,5-dichloro-2-hydroxybenzaldehyde and (*R*)-(–)-2-(diphenylphosphanyl)-1,1′-binaphthyl-2′-amine. Proline (pro) and its derivatives are proven catalysts in a wide range of enantioselective reactions,[14] which inspired us to involve the pro moiety in the structures of **L4** and **L5**. The chirality of the pro–amide moiety and the chiral phosphane backbone may simultaneously affect the stereochemical preference and enantioselectivity of the catalyst. In order to find out whether there was a significant effect of match/mismatch between the chirality of the pro moiety and the chirality of the phosphane backbone, we synthesized the matches of these *N*-Boc-pro-amide-phosphane catalysts **L4** and **L5** without the Boc protecting group. Additionally, the axially chiral phosphane-oxazoline **L6**,[15] previously reported as a ligand in a phosphane/silver(I)-catalyzed asymmetric vinylogous Mannich reaction, was also included for evaluation.

Our previous studies revealed that protic methanol can significantly facilitate the reaction in the absence of water with high enantioselectivity.[12] Thus, we initially examined the performance of **L1**–**6** in absolute MeOH. The MBH acetate **1a** (1.0 equiv.) and TMSOF (**2**, 1.5 equiv.) were employed as the starting materials for the asymmetric allylic alkylation in absolute MeOH. The simplified amide–phosphane bifunctional **L1** and **L2** were found to be efficient and highly enantioselective for this reaction, producing γ-butenolide *syn*-(1*S*,2*R*)-**3a** in good yields (**L1** 91%, and **L2** 94%) with excellent enantioselectivities (**L1** 89% *ee*, and **L2** 96% *ee*, Table 1, entries 1 and 2). It should be mentioned that the *syn*-diastereomer was generated predominantly (*dr* >95:5 indicating that the minor isomer could not be detected by ^{1}H NMR spectroscopy). However, the phosphane–Schiff base **L3** could not catalyze this reaction efficiently, furnishing the racemic product *syn*-**3a** in low yield (36% yield, 0% *ee*, Table 1, entry 3). This result indicated that the amide proton in the catalyst plays a critical role in enantioselectivity. The catalysts (*aR*,*S*)-**L4** and (*aR*,*S*)-**L5** with pro moieties both facilitated this reaction. In particular, (*aR*,*S*)-**L4**, which includes a Boc-protected group, gave the best result with the shortest reaction time (5 h), affording *syn*-(1*S*,2*R*)-**3a** in 94% yield with the highest *ee* of 98% at room temperature (Table 1, entry 4). Catalyst (*aR*,*S*)-**L6**, without an active amino proton, yielded a product with the opposite configuration, *syn*-(1*R*,2*S*)-**3a**, in 33% yield with 28% *ee* (Table 1, entry 6), which again demonstrates that the amide proton in the catalyst significantly affects the enantioselectivity.

In order to ignore the effect of the protic solvent on the enantioselectivity, we optimized the catalysts in the presence of an aprotic solvent. Thus, we conducted the reactions using **L1**–**6** (20 mol-%) in acetonitrile. The results are summarized in Table 2. The performance of **L1**–**6** in acetonitrile was similar to that in absolute methanol. The simplified amide–phosphane bifunctional catalysts **L1** and **L2** are efficient and highly enantioselective for this reaction, producing γ-butenolide *syn*-(1*S*,2*R*)-**3a** in good yields (**L1** 65%, **L2** 72%) with excellent enantioselectivities (**L1** 93% *ee*, **L2** 97% *ee*, Table 2, entries 1, 2). The phosphane–Schiff base **L3** could not catalyze this reaction efficiently, furnishing *syn*-(1*R*,2*S*)-**3a** in low yield and enantioselectivity (36% yield, 12% *ee*, Table 2, entry 3). (*aR*,*S*)-**L4** and (*aR*,*S*)-**L5** with pro moieties still gave good results. (*aR*,*S*)-**L4** gave the best result, affording *syn*-(1*S*,2*R*)-**3a** in 76% yield with the highest *ee* of 99% at room temperature (Table 2, entry 4). (*aR*,*S*)-**L6**, without an active amino proton, cannot mediate this transformation, only yielding trace amounts of product after 3 d (Table 2, entry 10). We wondered whether the configuration of the stereocenter in the catalyst had an effect on the enantioselectivity, thus, we also conducted reactions using the *N*-Boc-pro-amide-phosphane catalysts **L4** with different stereochemical preference (Table 2, entries 4–7). All four catalysts facilitate this substitution reaction smoothly, giving γ-butenolide **3a** over the *syn*-diastereomer. (*aR*,*S*)-**L4** and (*aR*,*R*)-**L4**, which have the same axial chirality but the opposite stereochemical configuration of the pro stereocenter, have the same stereochemical preference, leading to *syn*-(1*S*,2*R*)-**3a** in 76% yield with 99% *ee* and 54% yield with 96% *ee*, respectively (Table 2, entries 4 and 5). It

Table 1. Screening of **L1**–**6** in the allylic substitution of MBH acetate **3a** in MeOH.[a]

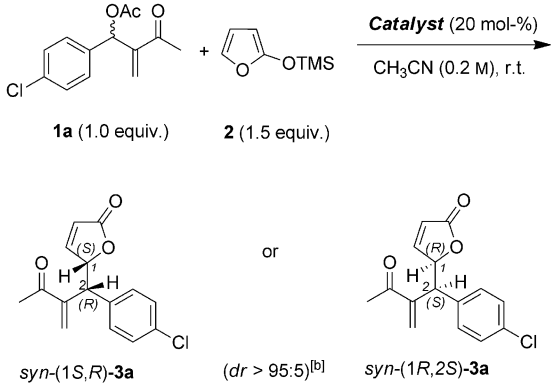


Entry	Catalyst	Time [h]	Yield [%][c]	*ee* [%][d]	Absolute config.[e]
1	**L1**	36	91	89	(1*S*,2*R*)
2	**L2**	36	94	96	(1*S*,2*R*)
3	**L3**	48	36	0	–
4	(*aR*,*S*)-**L4**	5	94	98	(1*S*,2*R*)
5	(*aR*,*S*)-**L5**	12	76	92	(1*S*,2*R*)
6	**L6**	36	33	28	(1*R*,2*S*)

[a] Reaction conditions: MBH acetate **1a** (0.1 mmol, 25.3 mg), TMSOF (**2**, 0.15 mmol, 25 μL), catalyst (0.02 mmol, 20 mol-%), absolute MeOH (0.5 mL, 0.2 M), room temperature for the time indicated. [b] *dr* > 95:5 means that the minor isomer could not be detected by ^{1}H NMR spectroscopy. [c] Isolated yields. [d] *ee* values were determined by HPLC using a Chiralcel AD-H column. [e] The absolute configurations were determined by comparing the optical rotation $[\alpha]_D$ with known data or HPLC analysis.

was found that replacing the L-pro moiety with D-pro somehow diminished the catalytic reactivity. On the other hand, (*aR*,*S*)-**L4** and (*aS*,*S*)-**L4**, which have the same chirality at the pro moiety but opposite axial chirality, led to products with opposite configuration with similar *ee* values: (*aR*,*S*)-**L4** 99% *ee* (1*S*,2*R*) vs. (*aS*,*S*)-**L4** 98% *ee* (1*R*,2*S*), (Table 2, entry 4 vs. 6); (*aR*,*R*)-**L4** 96% *ee* (1*S*,2*R*) vs. (*aS*,*R*)-**L4** 98% *ee* (1*R*,2*S*), (Table 2, entry 5 vs. 7). These results reveal that the axial chirality of the chiral phosphane backbone determines the stereochemical preference of products. Removing the *N*-Boc protecting group from (*aR*,*S*)-**L4** and (*aR*,*R*)-**L4** resulted in (*aR*,*S*)-**L5** and (*aR*,*R*)-**L5**, which have already been used by our group as very efficient catalysts in an allylic amination process,[16] gave the desired γ-butenolides in moderate to good yields (45–70%), with slightly diminished *ee* values (93–95%). It should be noted that the active amino proton of the pro moiety did not influence the asymmetric induction. (*aR*,*S*)-**L4** has been identified as the most efficient catalyst and was used for the further optimization of reaction conditions and the investigation of the scope of the reaction.

Table 2. Screening **L1**–**6** in the allylic substitution of MBH acetate **3a** in the presence of CH_3CN.[a]



syn-(1*S*,*R*)-**3a** (*dr* > 95:5)[b] *syn*-(1*R*,2*S*)-**3a**

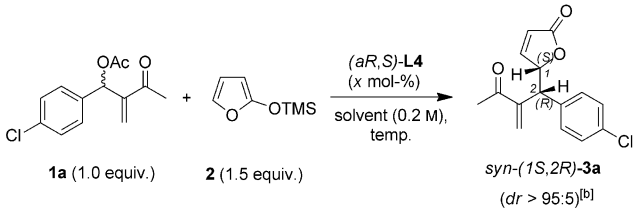
Entry	Catalyst	Time [h]	Yield [%][c]	*ee* [%][d]	Absolute config.[e]
1	**L1**	48	65	93	(1*S*,2*R*)
2	**L2**	48	72	97	(1*S*,2*R*)
3	**L3**	72	36	12	(1*R*,2*S*)
4	(*aR*,*S*)-**L4**	*24*	*76*	*99*	(1*S*,2*R*)
5	(*aR*,*R*)-**L4**	72	54	96	(1*S*,2*R*)
6	(*aS*,*S*)-**L4**	72	47	98	(1*R*,2*S*)
7	(*aS*,*R*)-**L4**	48	83	98	(1*R*,2*S*)
8	(*aR*,*S*)-**L5**	*48*	*70*	*95*	(1*S*,2*R*)
9	(*aR*,*R*)-**L5**	72	45	93	(1*S*,2*R*)
10	(*aR*,*S*)-**L6**	72	trace	n.d.[f]	n.d.

[a] Reaction conditions: MBH acetate **1a** (0.1 mmol, 25.3 mg), **2** (0.15 mmol, 25 μL), catalyst (0.02 mmol, 20 mol-%), CH_3CN (0.5 mL, 0.2 M) at room temperature for the indicated time. [b] *dr* > 95:5 means that the minor isomer could not be detected by ^1H NMR spectroscopy. [c] Isolated yields. [d] The *ee* values were determined by HPLC using a Chiralcel AD-H column. [e] The absolute configurations were determined by comparing the optical rotation $[\alpha]_D$ with known data or HPLC analysis. [f] n.d.: not determined.

Optimization of Reaction Conditions and Scope

Using (*aR*,*S*)-**L4**, the reaction conditions were optimized in terms of the solvent, catalyst loading, and temperature, and the results are summarized in Table 3. Initially, using the reaction conditions considered optimal in our previous study[12] (20 mol-% catalyst loading, toluene as the solvent, 6.0 equiv. H_2O as the additive, at room temperature), the reaction proceeded smoothly and **3a** was isolated in 90% yield with 96% *ee* (Table 3, entry 1). However, as mentioned above, with absolute methanol as the solvent, the reaction was complete within 5 h at room temperature, giving the desired γ-butenolide **3a** in 94% yield with 98% *ee* (Table 1, entry 4). Presumably, a protic additive or solvent donates protons, which can be involved in the formation of hydrogen bonding in the key transition state (TS), leading to high enantioselectivity. Decreasing the reaction temperature to 10 °C did not significantly affect the yield or enantioselectivity but increased the reaction time (Table 3, entry 2). Decreasing the catalyst loading to 10 mol-% and 5 mol-% diminished the yield without affecting the enantioselectivity (Table 3, entries 3 and 4). We showed above that the reaction catalyzed by (*aR*,*S*)-**L4** proceeded smoothly in the presence of CH_3CN (Table 2, entry 4). We therefore investigated the temperature effect again in the presence of CH_3CN. Increasing the temperature to 50 °C or decreasing the temperature to –20 °C led to a decrease in yield and enantioselectivity (Table 3, entries 5 and 6). Subsequently,

Table 3. Optimization of reaction conditions for the allylic substitution of the MBH acetate **3a**.[a]



syn-(1*S*,2*R*)-**3a** (*dr* > 95:5)[b]

Entry	*x* [mol-%]	Solvent	Temp. [°C]	Time [h]	Yield[c] [%]	*ee*[d] [%]
1	20	toluene/ 6.0 equiv. H_2O	r.t.	24	90	96
2	20	MeOH (absolute)	10	10	93	98
3	10	MeOH (absolute)	r.t.	48	65	98
4	5	MeOH (absolute)	r.t.	48	54	97
5	20	CH_3CN	50	24	40	85
6	20	CH_3CN	–20	96	50	98
7	20	THF	r.t.	12	85	92
8	20	THF/4 Å MS	r.t.	20	65	73
9	20	CH_2Cl_2	r.t.	12	80	95
10	20	Et_2O	r.t.	24	83	92
11	20	DCE	r.t.	12	63	96
12	20	DMF	r.t.	48	59	99

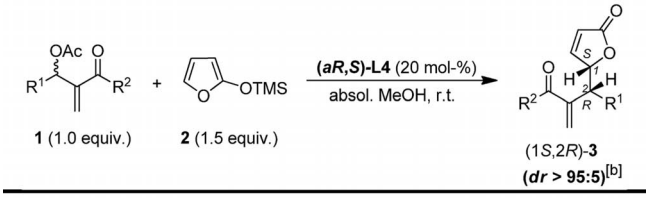
[a] Reaction conditions: MBH acetate **1a** (0.1 mmol, 25.3 mg), **2** (0.15 mmol, 25 μL), catalyst (*x* mol-%), solvent (0.5 mL, 0.2 M) for the indicated time. [b] *dr* > 95:5 means that the minor isomer could not be detected by ^1H NMR spectroscopy. [c] Isolated yields. [d] The *ee* values were determined by HPLC using a Chiralcel AD-H column.

we focused on the investigation of polar aprotic solvent effects on the enantioselectivities as protic species (e.g., H_2O or MeOH) may be involved in the formation of hydrogen bonds with the substrate and catalyst, which makes it difficult to identify whether there are hydrogen bonds formed directly between the substrate and catalyst. Other polar aprotic solvents, such as CH_2Cl_2, DCE, Et_2O, THF, and DMF (dried by standard methods), were also suitable for this reaction, affording γ-butenolide **3a** in good to excellent enantioselectivities (73–99% *ee*, Table 3, entries 7–12). In general, the allylic substitution of MBH acetates with TMSOF catalyzed by (*aR*,*S*)-**L4** (20 mol-%) can proceed either in the presence of a protic solvent (MeOH) or aprotic solvent (CH_3CN) at room temperature, affording the product in high yield with excellent enantioselectivity.

With these optimized conditions in hand, our next aim was to examine the substrate scope and limitations of the reaction. Thus, a series of MBH acetates derived from methyl vinyl ketone (MVK, **1b**–**p**), ethyl vinyl ketone (EVK, **1q** and **1r**), and methyl acrylate (**1s**) was prepared and its reactivity explored in absolute MeOH (Table 4). Aromatic aldehyde-derived MBH adducts **1b**–**l** with various substitution patterns on the benzene ring underwent the reactions smoothly, affording the corresponding allylic alkylation products **3b**–**l** in good to excellent yields (75–97%) along with excellent diastereoselectivities (*dr* > 95:5) and enantioselectivities (94–98% *ee*) (Table 4, entries 1–11). The substrates prepared from aliphatic aldehydes, **1m** and **1n**, led to the corresponding γ-butenolides **3m** and **3n** in 60% yield with 85% *ee* and in 42% yield with 88% *ee*, respectively (Table 4, entries 12 and 13). Similarly, the heteroatom-containing substrates, **1o** and **1p**, provided the corresponding γ-butenolides in good yields and excellent enantioselectivities (**3o**: 74% yield, 97% *ee*; **3p**: 73% yield, 96% *ee*, Table 4, entries 14 and 15). As for the EVK-derived MBH acetates **1q** and **1r**, the alkylation products **3q** and **3r** were obtained in 92% yield with 97% *ee* and in 61% yield with 94% *ee*, respectively (Table 4, entries 16 and 17). However, the acrylate-derived substrate **1s**, which was less electrophilic, showed less reactivity, affording the corresponding product **3s** in low yield (50%) but with high enantioselectivity (91% *ee*) (Table 4, entry 18).

Subsequently, we investigated the reactions **1b**–**s** in CH_3CN (Table 5). Aromatic aldehyde-derived MBH adducts **1b**–**j** with electron withdrawing substituents or no substituent on the benzene ring also underwent the reac-

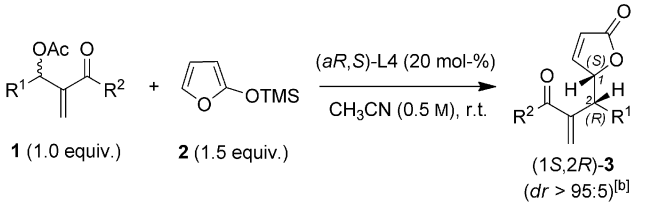
Table 4. (*aR*,*S*)-**L4** catalyzes the allylic substitution of various MBH acetates **1b**–**s** with TMSOF in absolute MeOH.[a]



Entry	Substrate	R^1	R^2	Time (h)	Yield (%)[c]	*ee* (%)[d]
1	**1b**	4-BrC_6H_4	Me	8	**3b**: 84	98
2	**1c**	4-FC_6H_4	Me	12	**3c**: 86	94
3	**1d**	3-ClC_6H_4	Me	5	**3d**: 95	97
4	**1e**	2-ClC_6H_4	Me	8	**3e**: 90	97
5	**1f**	4-CNC_6H_4	Me	12	**3f**: 93	98
6	**1g**	4-$CF_3C_6H_4$	Me	8	**3g**: 97	98
7	**1h**	4-$NO_2C_6H_4$	Me	5	**3h**: 92	97
8	**1i**	3-$NO_2C_6H_4$	Me	5	**3i**: 84	96
9	**1j**	C_6H_5	Me	24	**3j**: 65	97
10	**1k**	4-$CH_3C_6H_4$	Me	60	**3k**: 75	98
11	**1l**	3-$CH_3C_6H_4$	Me	60	**3l**: 78	96
12	**1m**	$C_6H_4CH_2CH_2$	Me	96	**3m**: 60	85
13	**1n**	$CH_3(CH_2)_6$	Me	96	**3n**: 42	88
14	**1o**		Me	72	**3o**: 74	97
15	**1p**		Me	72	**3p**: 73	96
16	**1q**	4-$NO_2C_6H_4$	Et	24	**3q**: 92	97
17	**1r**	C_6H_5	Et	24	**3r**: 61	94
18	**1s**	4-$NO_2C_6H_4$	OMe	24	**3s**: 50	91

[a] Reaction conditions: MBH acetate (**1**, 0.1 mmol), **2** (0.15 mmol, 25 μL), (*aR*,*S*)-**L4** (0.02 mmol, 20 mol-%, 13.0 mg), CH_3CN (0.5 mL, 0.2 M) at room temperature for the indicated time. [b] *dr* > 95:5 means that the minor isomer could not be detected by ^1H NMR spectroscopy. [c] Isolated yields. [d] The *ee* values were determined by HPLC using a Chiralcel AD-H or OD-H column.

Table 5. (*aR*,*S*)-**L4** catalyzes the allylic substitution of various MBH acetates **1b**–**s** with TMSOF in CH_3CN.[a]



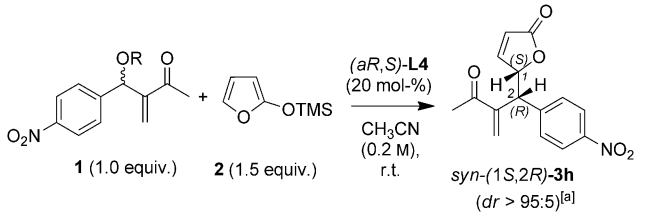
Entry	Substrate	R^1	R^2	Time [h]	Yield [%][c]	*ee* [%][d]
1	**1b**	4-BrC_6H_4	Me	12	**3b**: 88	99
2	**1c**	4-FC_6H_4	Me	12	**3c**: 70	96
3	**1d**	3-ClC_6H_4	Me	24	**3d**: 87	97
4	**1e**	2-ClC_6H_4	Me	24	**3e**: 94	99
5	**1f**	4-CNC_6H_4	Me	20	**3f**: 98	97
6	**1g**	4-$CF_3C_6H_4$	Me	12	**3g**: 98	98
7	**1h**	4-$NO_2C_6H_4$	Me	24	**3h**: 95	98
8	**1i**	3-$NO_2C_6H_4$	Me	36	**3i**: 95	98
9	**1j**	C_6H_5	Me	72	**3j**: 75	97
10	**1q**	4-$NO_2C_6H_4$	Et	36	**3q**: 83	95
11	**1r**	C_6H_5	Et	48	**3r**: 66	92
12	**1s**	4-$NO_2C_6H_4$	OMe	96	**3s**: 50	93

[a] Reaction conditions: MBH acetate (**1**, 0.1 mmol), **2** (0.15 mmol, 25 μL), (***aR*,*S*)-L4** (0.02 mmol, 20 mol-%, 13.0 mg), CH_3CN (0.5 mL, 0.2 M) at room temp. for the indicated time. [b] *dr* > 95:5 means that the minor isomer could not be detected by ^1H NMR spectroscopy. [c] Isolated yields. [d] The *ee* values were determined by HPLC using a Chiralcel AD-H or OD-H column.

tions smoothly, affording the corresponding products **3b**–**3j** in high yields with excellent *ee* (Table 5, entries 1–9). These results are similar to their performance in the presence of absolute MeOH. However, we observed that the reactions in the presence of CH_3CN need longer reaction times than in the presence of absolute MeOH. The reactions of aromatic aldehyde-derived MBH adducts with electron donating substituents on the benzene ring (**1k**, **1l**), aliphatic aldehyde-derived MBH adducts (**1m**, **1n**), and heteroatom-containing substrates (**1o**, **1p**) were extremely sluggish and could not achieve significant yields in a week. Thus we stopped these reactions and did not analyze the outcomes. As for the EVK-derived MBH acetates **1q** and **1r**, the corresponding alkylation products **3q** and **3r** were obtained in 83% yield with 95% *ee* and in 66% yield with 92% *ee*, respectively (Table 5, entries 10 and 11). However, the acrylate-derived substrate **1s** also showed less reactivity in CH_3CN, affording **3s** in low yield (50%), but with high enantioselectivity (93% *ee*) (Table 5, entry 12).

As shown in Scheme 1, the catalytic mechanism for γ-butenolide synthesis was proposed to be a tandem S_N2'/S_N2' substitution. The reaction is initiated by conjugate addition of the catalyst (phosphane) and MBH adducts to furnish an electrophilic leaving group ion pair, which reacts with the pronucleophile (TMSOF) to form hypervalent anions or "ate" complexes, and the requisite electrophile–nucleophile ion pair intermediates are generated. In order to examine the leaving group effect for the phosphane-catalyzed allylic alkylation of MBH adducts, a series of acyl derivatives based on MBH adducts were prepared and exposed to 20 mol-% (*aR*,*S*)-**L4** at room temperature in the presence of CH_3CN. Under the typical reaction conditions, the allylic substitution proceeded smoothly for all the MBH adducts bearing different leaving groups, producing γ-butenolide **3h** in moderate to good yields (95% R = Ac, 85% R = Boc, 60% R = Bz, 36% R = *p*-NO_2-Bz) with high enantioselectivities (94–98% *ee*) (Table 6, entries 1–4).

Table 6. Further investigation on the leaving group effect of the MBH acetate **1**.[a]



Entry	R	Time [h]	Yield [%][c]	*ee* [%][d]
1	Ac	24	95	98
2	Boc	24	85	98
3	Bz	48	60	94
4	*p*-NO_2-Bz	48	36	97

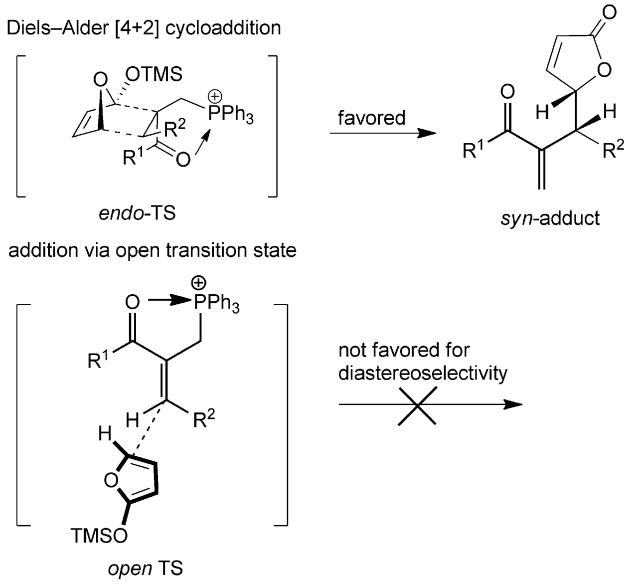
[a] Reaction conditions: MBH acetate (**1**, 0.1 mmol, 32.1 mg), **2** (0.15 mmol, 25 μL), (*aR*,*S*)-**L4** (0.02 mmol, 20 mol-%), CH_3CN (0.5 mL, 0.2 M) at room temperature for the indicated time. [b] *dr* > 95:5 means that the minor isomer could not be detected by ^1H NMR spectroscopy. [c] Isolated yields. [d] The *ee* values were determined by HPLC using a Chiralcel AD-H column.

NMR Tracing Experiments

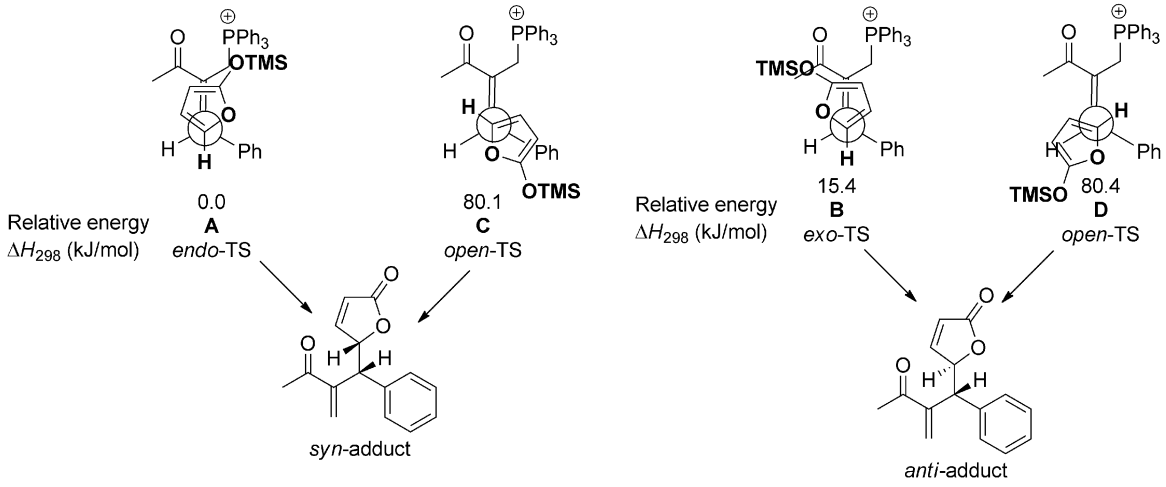
Having established a series of new efficient multifunctional amide–phosphane organocatalysts for allylic substitutions of MBH acetates with TMSOF and the reaction scope and limitations, we investigated the mechanistic details by NMR tracing experiments (see Supporting Information for details). We identified critical phosphonium intermediates involved in the catalytic cycles.

Theoretical Investigation on the Origins of Diastereo- and Enantioselectivity

Krische has proposed that the high diastereoselectivity attained in these substitutions arises as a consequence of a mechanism involving *endo*-selective Diels–Alder cycloaddition of the siloxyfuranate complex with the enone obtained by the addition of the phosphane followed by subsequent Grob-type fragmentation (Scheme 3).[9] On the basis of the TSs proposed by Krische and TS geometries proposed for various nucleophilic additions to carbonyl groups in vinylogous Mannich reactions,[17] a set of four limiting TSs are depicted in Scheme 4 and their structures optimized at the HF/3-21G* level are shown in Figure 2. The energies of these TSs were calculated at the MP2/6-31G(d)//HF/3-21G* level of theory and their relative energies are shown in Scheme 4. In terms of energy, Diels–Alder-like TS **A** and **B** are much more stable than open TS **C** and **D** by 80 kJ/mol and 64.5 kJ/mol or so, respectively, presumably due to the π–π stacking interaction between the furan ring and C=C double bond in TS **A** and **B**. The repulsion between the carbonyl group and OTMS group in *exo* TS **B** may lead to an increase in energy. Thus, the energy of *endo* TS **A** is lower than that of *exo* TS **B** by 15.4 kJ/mol, leading to the *syn*-diastereomer as the major product, consistent with ex-



Scheme 3. Krische's proposed transition states for diastereoselectivity.



Scheme 4. The transition states corresponding to the study of the origin of diastereoselectivity.

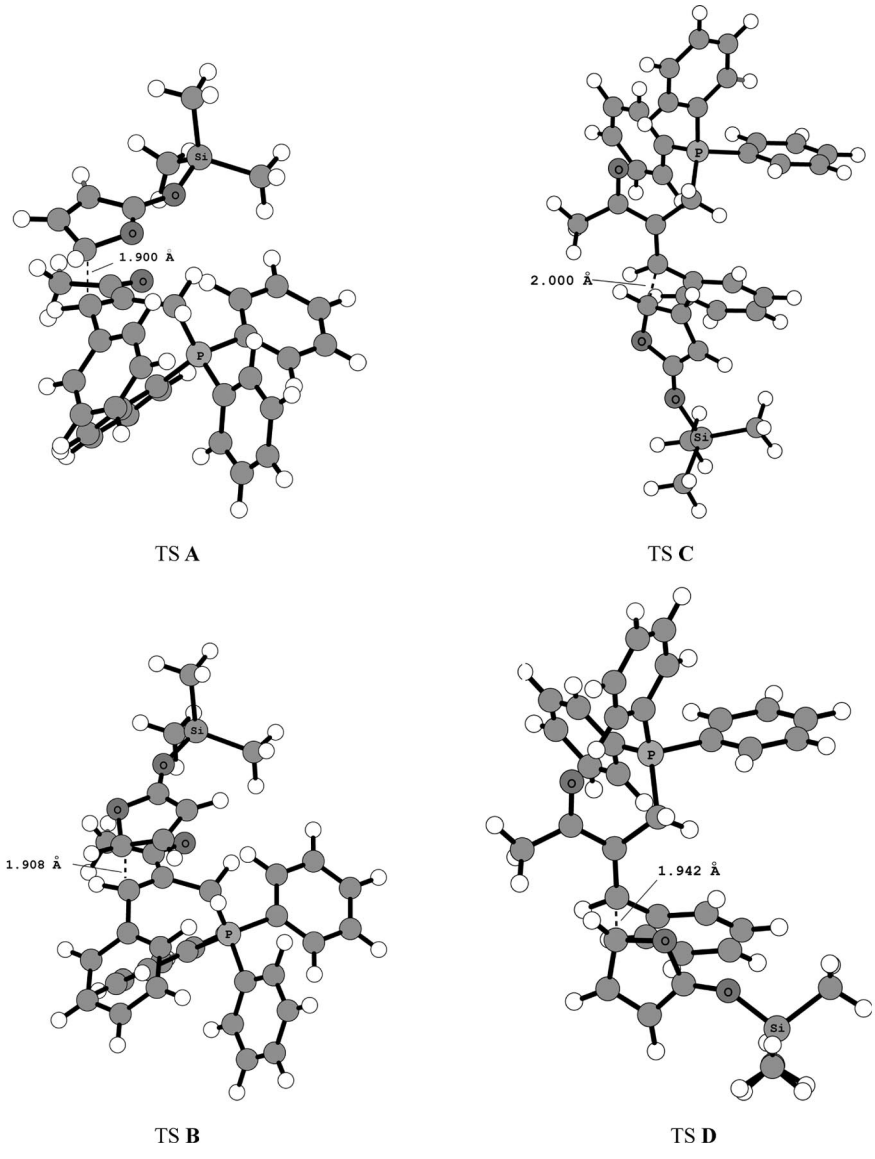
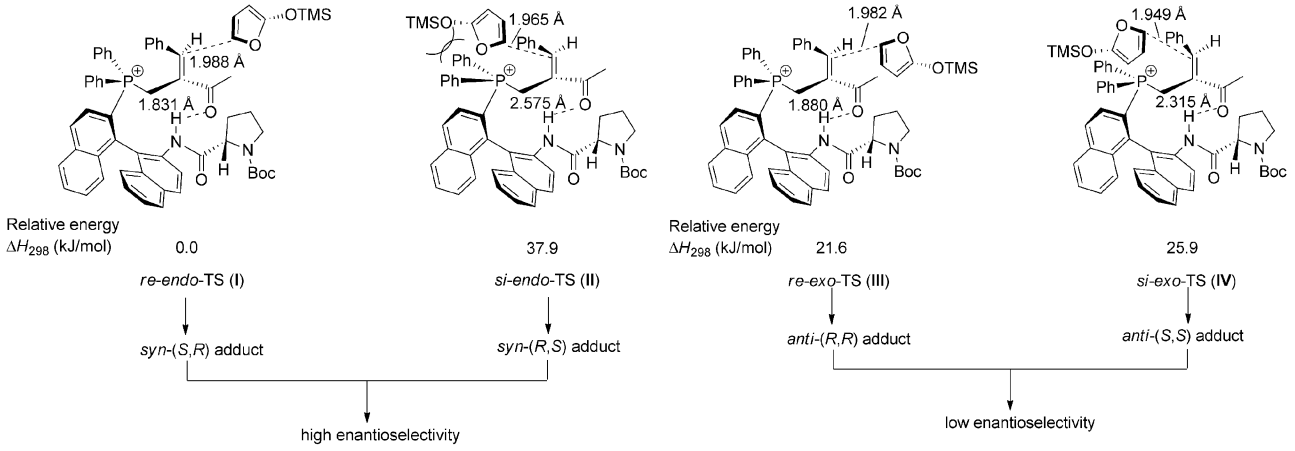


Figure 2. The optimized structures of TS **A**–**D** at the HF/3-21G* level.

perimental observations. On the other hand, the energy difference of open TS **C** and **D** is small (only 0.3 kJ/mol), hence it cannot account for high the diastereoselectivity observed experimentally.

Having rationalized the origin of diastereoselectivity, we further investigated the origin of enantioselectivity and the absolute stereochemistry of the substitution adducts in the catalysis of chiral phosphanes. Enantiofacial control is presumably governed by the energy differentiation between two modes of attack of TMSOF towards the enone, namely, *re* face or *si* face attack. We investigated the relative energies of four key TSs involving (*aR*,*S*)-**L4** shown in Scheme 5, and their optimized structures are depicted in Figure 3, which may account for the stereochemistry observed experimentally. Similar to the achiral phosphane, the energy of *endo* TS **I** involving (*aR*,*S*)-**L4** is lower than that of *exo* TS **III** by 21.6 kJ/mol, leading to high diastereoselectivity. If TMSOF approached the enone at the *re* face, a strong hydrogen bond could form between the amide N–H and the substrate carbonyl group, resulting in the more stable TS **I**



Scheme 5. The transition states of (*aR*,*S*)-**L4** corresponding to the study of origin of enantioselectivity.

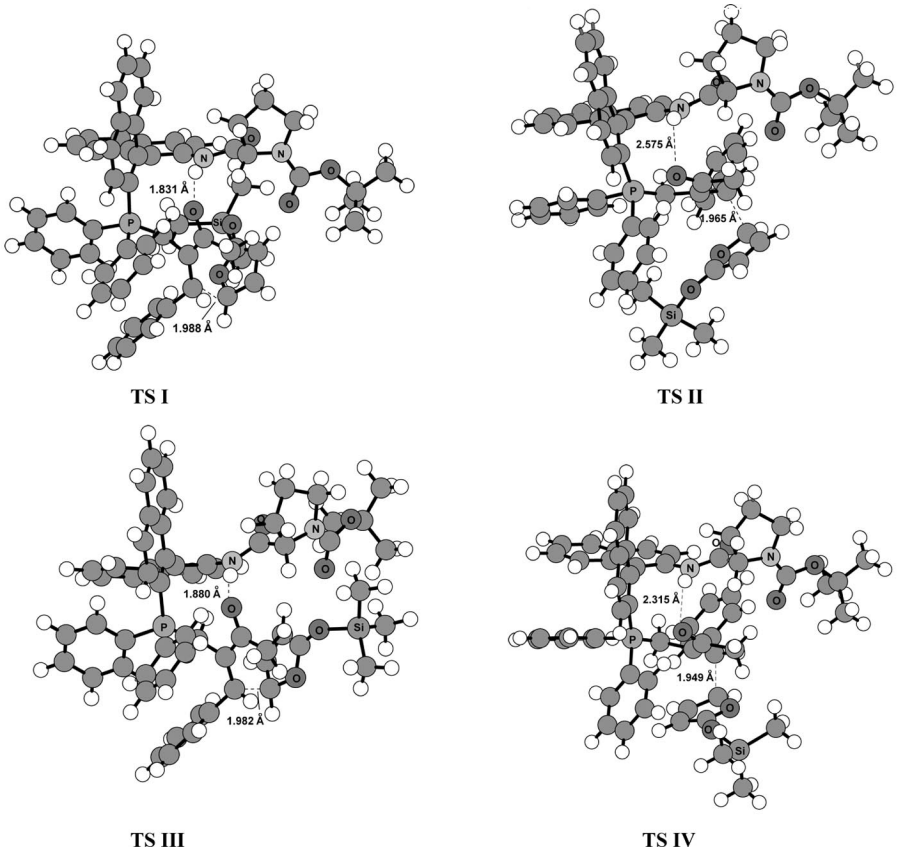


Figure 3. The optimized structures of TS **I**–**IV** at the HF/3-21G* level.

(NH···O=C 1.831 Å) and TS **III** (NH···O=C 1.880 Å). However, the amide N–H and the substrate carbonyl group are orientated parallel to each other in TS **II** and TS **IV**, which cannot lead to a hydrogen-bonding interaction. In addition, a strong hydrogen bond could not be formed in TS **II**, and the repulsion between the phosphane and OTMS moieties may be another reason for the relatively high energy of TS **II**. Thus, the large energy difference between TS **I** and TS **II** may account for the high enantioselectivity observed experimentally. The amide active proton stabilizes one of the TS diastereoisomers, leading to high enantioselectivity. Therefore, **L3** and **L6** without an amide active proton lose enantiofacial control. In a similar manner, we further investigated four TSs **V**–**VIII** for chiral (*aR*,*S*)-**L5** without the Boc group and obtained similar results (see Supporting Information for details).

We have previously reported that the addition of H_2O improved enantioselectivity.[12] We investigated the key TSs using the catalyst shown in Scheme 2 with one molecule of H_2O to explore its effect on the enantioselectivity. Preliminary results revealed that a hydrogen-bonding interaction between the C=O group in the amide terminus of the catalyst and water could be formed in the *endo* TSs. In the *re* face approaching mode, the oxygen atom in water has an interaction with the Si atom in the OTMS group, which directs the OTMS group to leave. However, this kind of interaction cannot be formed in the *si* face approaching mode (see Supporting Information for details). This may explain why the addition of water can increase the enantioselectivity.

Conclusions

We have synthesized a series of multifunctional chiral amide–phosphane organocatalysts **L1**–**6** and demonstrated that a highly enantioselective allylic substitution of MBH acetate with TMSOF could be achieved by multifunctional phosphane organocatalysts **L1**–**5** with an active proton on the amide moiety. The enantioselective allylic substitution reaction was achieved for butenolide synthesis in good yields with high *ee* with respect to a wide range of MBH acetates. NMR tracing experiments provided some evidence for the existence of phosphonium intermediates involved in the catalytic cycle, which supported the proposed mechanism. The computational studies disclosed that Diels–Alder-like transition states could account for the high diastereoselectivity attained in these phosphane-catalyzed allylic substitution reactions. Theoretical investigations also revealed that the active proton of the amide moiety is the critical factor for the catalyst to have high enantiofacial control. Studies directed towards more efficient chiral catalysts for enantioselective allylic substitution reactions and their variants are underway.

Experimental Section

General Remarks: All reactions and manipulations were performed using standard Schlenk techniques. Melting points were measured with a Yanagimoto micro melting apparatus and uncorrected. NMR spectra were recorded with a Bruker spectrometer 400 MHz or 300 MHz (^{1}H NMR), 75 MHz or 100 MHz (^{13}C NMR) in $CDCl_3$, respectively. Chemical shifts were reported in ppm downfield from internal TMS. ^{31}P NMR spectra were recorded at 162 MHz or 121 MHz in $CDCl_3$ with 85% H_3PO_4 as the external reference. *J* values are in Hertz. Optical rotations were determined at 589 nm (sodium D line) using a Perkin–Elmer 341 MC Polarimeter and $[a]_D$ values are given with units of 10 $cm^2 deg^{-1} g^{-1}$. Mass spectra were recorded with a HP-5989 instrument using EI/ESI methods. IR spectra were recorded with a Perkin–Elmer PE-983 spectrometer with absorption in cm^{-1}. Chiral HPLC was performed using a SHIMADZU SPD-10A *vp* series instrument with chiral columns (Chiralpak AD-H, OD-H columns, ϕ 4.6 × 250 mm, Daicel Chemical Co. Ltd.). Organic solvents were dried by standard methods where necessary. Commercially available reagents were used without further purification. All reactions were monitored by TLC with Huanghai GF254 silica gel coated plates. Flash column chromatography was carried out using 300–400 mesh silica gel at increased pressure. MBH acetates were prepared according to a literature method.[18]

General Procedure for the Asymmetric Allylic Alkylation of MBH Acetates: To a flame-dried Schlenk tube charged with MBH acetate (0.1 mmol, 25.3 mg), (*aR*,*S*)-**L4** or (*aR*,*S*)-**L5** (0.02 mmol), and anhydrous CH_2Cl_2 or CH_3CN (0.5 mL) was added **2** (0.15 mmol, 25 μL) under argon. The reaction was allowed to stir at 25 °C under argon. The reaction was monitored by TLC analysis. After the starting substrates were consumed, the solvent was removed under reduced pressure, and the residue was purified by silica gel column chromatography (eluent: EtOAc/petroleum ether = 1:6 to 1:4) to give the corresponding alkylation adducts **3**.

(*S*)-5-[(*R*)-1-(4-Chlorophenyl)-2-methylene-3-oxobutyl]furan-2(5*H*)-one (3a): Yield: 99%; this is a known compound. $[a]_D^{25}$ = –46.0 (*c* = 0.74, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$, TMS): δ = 7.31–7.27 (m, 5 H), 6.36 (s, 1 H), 6.08 (dd, *J* = 2.0, 5.6 Hz, 1 H), 6.03 (s, 1 H), 5.52 (ddd, *J* = 1.6, 3.2, 6.4 Hz, 1 H), 4.41 (d, *J* = 6.4 Hz, 1 H), 2.31 (s, 3 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$, TMS): δ = 198.4, 172.5, 155.6, 145.5, 137.6, 133.4, 129.8, 129.6, 129.0, 121.9, 83.0, 46.5, 25.7 ppm. HPLC condition: Chiralcel AD-H column, λ = 230 nm, eluent: hexane/2-propanol = 90:10, flow rate: 0.8 mL/min, t_{Rmajor} = 24.03 min, t_{Rminor} = 22.12 min; *ee* = 98%.

Supporting Information (see footnote on the first page of this article): Spectroscopic and analytical data for all catalysts, **3**, and NMR tracing experiments; detailed descriptions of experimental procedures and computational details are also available.

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