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Olefination of ketenes for the enantioselective synthesis of allenes via an ylide route

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Abstract—Pseudo-C_2-symmetric chiral phosphorus ylide is designed and synthesized for the enantioselective preparation of allenic esters, amides, ketone, and nitrile. Up to 92% ee is achieved.

1. Introduction

In recent years, optically active allenes have been used as versatile chiral building blocks in organic synthesis due to their high reactivity and the unique ability that they can transfer the axial chirality to final products efficiently.[1] In addition, allenes are important subunits in a variety of natural products and biologically active compounds.[2] Thus, the development of synthetic methodology for enantiomerically enriched allenes is of great interest and several strategies have been developed. One of the most commonly used approaches is substitution or isomerization of chiral propargylic derivatives.[3] Asymmetric catalysis[4] and kinetic resolution[5] also provide accesses to optically active allenes. Phosphorus ylides are good reagents for the synthesis of allenes by olefination of ketenes,[6] but only a few examples were reported for its asymmetric version.[7] The first example was described by Bestmann in 1964,[7a] in which a stabilized phosphorus ylide containing a chiral alcohol was documented to react with acyl chloride to afford optically active allenes. Later on, they reported a reaction of racemic phosphorus ylides with enantiomerically enriched acyl chloride and found that the resulting chiral allenes were obtained with up to 31% ee.[7b] Pure ketenes were first used as substrates by Musierowicz and his co-workers in the enantioselective synthesis of allenes. They found that the reaction between chiral phosphinate ester and ketenes afforded allenes with 23% ee.[7c] Tanaka et al. described that optically active 4,4-disubstituted allenic esters could be prepared with binol-derived HWE reagents in 21–71% yields with 23–89% ee's.[7d] Melo and his co-workers documented that a phosphorus ylide bearing 10-phenylsulfonylisoborneol reacted with methylketene to give penta-2,3-dienoic ester with excellent diastereoselectivity.[7e]

In a previous study on ylide chemistry in organic synthesis,[8] we were interested in developing asymmetric ylide-mediated synthesis of optically active allenes and communicated that newly designed chiral phosphorus ylides could react with ketenes to afford enantiomerically enriched allenic esters.[9] Recently, we modified the chiral ylides and found that the enantioselectivities were further improved in some cases. We also extended this method to the synthesis of chiral allenic ketones, amides, nitrile, and 4-monosubstituted allenic esters. In this paper, we wish to report the synthesis and the modification of the phosphorus ylides, the scope, and limitation in detail.

2. Results and discussion

2.1. Design and synthesis of phosphorus salts

In a previous study, we demonstrated that chiral telluronium salts **1** could react smoothly with α,β-unsaturated ketones, esters, and imines to afford optically active vinylcyclopropane derivatives with high diastereoselectivities and enantioselectivities.[8c,f] It is envisioned that phosphonium salt **2** with a similar structure is a potential reagent for the enantioselective synthesis of allenes (Fig. 1). One attractive advantage of salt **2** is its high flexibility since substituents R^1, R^2, and R^3 are readily variable. Another advantage is that the chiral phosphine oxide produced in the reaction is possible to be recovered and reused.

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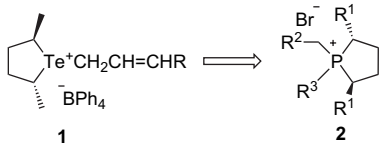
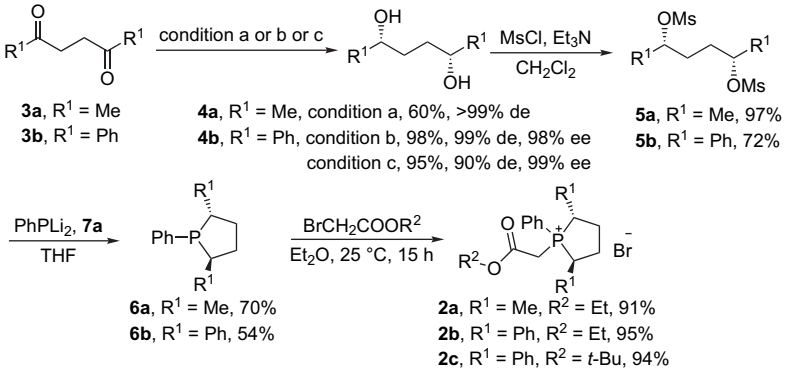


Figure 1. Design of phosphorus salt.

Phosphorus salts **2a**–**2c** are readily prepared from the corresponding diketones. As shown in Scheme 1, hexane-2,5-dione **3a** was reduced by baker's yeast to the corresponding diol **4a** in 60% yield with excellent de and ee.[10a] And 1,4-diphenylbutane-1,4-dione could be easily reduced by proline-derived chiral borane[10b] or by asymmetric hydrogenation[10c] in gram scale to give the desired diol **4b** in high yield with excellent selectivity. Diols **4a** and **4b** reacted with methanesulfonyl chloride, followed by reaction with dilithium phenylphosphate **7a** to afford **6a** and **6b**, respectively. Phosphines **6a** and **6b** reacted with the corresponding bromides to give the desired phosphonium salts **2a**, **2b**, and **2c**, respectively.

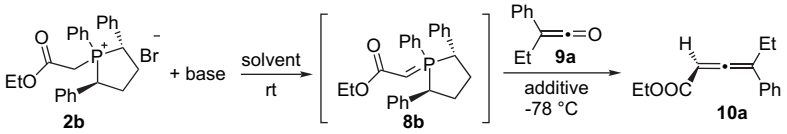
2.2. Effects of reaction conditions on the asymmetric olefination

Initially, the reaction of phosphonium salt **2b** with phenyl ethyl ketene **9a** was chosen as a model reaction to optimize the reaction conditions. As shown in Table 1, the cation of the base influenced both the yield and the selectivity strongly. The base bearing K^+ furnished the desired products in moderate yields with moderate ee's (entries 4 and 6). Although *n*-BuLi, LiHMDS, and LiTMP gave the allenes with good enantioselectivities (entries 1, 2, and 5), the yields were



Scheme 1. Synthesis of phosphonium salts **2a**–**2c**. Condition a: baker's yeast. Condition b: (2*S*)-2-(Diphenylhydroxymethyl) pyrrolidine, $B(OMe)_3$, $BH_3 \cdot SMe_2$, THF. Condition c: $RuCl_2(R_3P)_2[(S,S)\text{-DPEN}]$, *i*-PrOH, *t*-BuOK, H_2.

Table 1. Effects of reaction conditions on the asymmetric olefination of ketenes



Entry	Base	Additive	Solvent (v/v)	Yield[a] (%)	ee[b] (%)
1	*n*-BuLi	None	THF	60	80
2	LiHMDS	None	THF	67	80
3	NaHMDS	None	THF	80	81
4	KHMDS	None	THF	47	70
5	LiTMP	None	THF	63	79
6	*t*-BuOK	None	THF	42	59
7	NaH	None	THF	73	80
8	NaH	NaBr (0 equiv)	THF	69	64
9	NaH	NaBr (1 equiv)	THF	73	80
10	NaH	NaBr (2 equiv)	THF	56	80
11	NaH	LiBr (1 equiv)	THF	67	80
12	NaH	LiBr (2 equiv)	THF	42	81
13	NaH	$Et_3N \cdot HCl$ (2 equiv)	THF	14	70
14	NaH	None	DME/THF (5/1)	56	64
15	NaH	None	Ether	26	70
16	NaH	None	*n*-Butyl ether	46	39
17	NaH	None	CH_2Cl_2	67	56
18	NaH	None	$ClCH_2CH_2Cl/CH_2Cl_2$ (10/7)	67	52
19	NaH	None	Toluene	65	50
20	NaH	None	Hexane	37	60

[a] Isolated yield.
[b] Determined by chiral HPLC.

only moderate. In our screened conditions, NaHMDS was the optimal (entry 3).

'Salt effects' were observed in this reaction. $Et_3N \cdot HCl$ deteriorated both the yield and the selectivity greatly (entry 13). Addition of NaBr improved the enantioselectivities (entries 8–10). LiBr could also increase the ee but decreased the yield (entries 11 and 12). Solvent effect was also examined. It was found that the reaction proceeded well in toluene and dichloromethane (entries 17 and 19). The best result was achieved in THF (entry 7).

2.3. Effects of phosphonium salts

Having established the optimal reaction conditions, the effects of various phosphonium salts were examined. As shown in Table 2, **2a** gave the desired allene in moderate yields and ee's (entries 1 and 4). Replacement of methyl group in **2a** with phenyl group improved both the yield and enantioselectivity (entry 1 vs 2 and entry 4 vs 5). When ethyl ester was replaced by *tert*-butyl ester, 92% ee could be achieved but the yield decreased to 51% (entry 3).

2.4. Scope and limitation

Under the optimal conditions, the generality of the reaction was studied by investigating the reaction of various ketenes with **2b**. As shown in Table 3, 2-aryl-1-buten-1-one gave 4-aryl-2,3-hexadienoic esters in high yields with high enantioselectivities (entries 1, 11, and 12) and up to 91% ee was obtained. However, replacement of ethyl groups on ketene **9a** with other alkyl groups such as isopropyl, benzyl, and allyl groups decreased the enantiomeric excesses greatly (entries 5, 7–9). Ketene **9j**, with an *o*-methoxylbenzyl group, afforded the corresponding allene in low yield with poor selectivity probably due to the steric effects (entry 10).

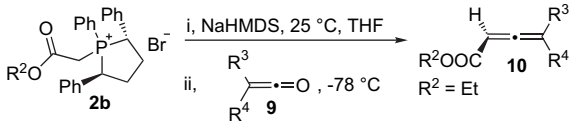
Since dialkyl ketene and monosubstituted ketene are not so stable and could not be purified as ketene **9a** is, we developed a one-pot protocol. It was found that, in the presence of triethylamine, the reactions of acyl chlorides with phosphonium salt **2b** proceeded well to give the desired allenic esters in moderate yields with moderate enantioselectivities. As shown in Table 4, compared with the use of ketene generated in situ, one-pot procedure gave lower ee (entry 1 in Table 4 vs entry 9 in Table 3). 2-Ethylhexanoyl chloride gave the corresponding allene in 51% yield with good ee (entry 2). By this protocol, monosubstituted allenic esters could be obtained in good yields with moderate enantioselectivities (entries 3 and 4). 2-Bromopropanoyl chloride was also a good substrate to give bromoallene **10q** in 61% yield with 30% ee (entry 5).

Further studies showed that allenic ketone, nitrile, and amides could also be synthesized by this method in good yields with moderate to good enantioselectivities. As shown in Table 5, phosphane **6b** reacted with bromides **12a–12d** in THF, followed by deprotonation with NaHMDS and then treated with ketene **9a** to afford the desired allenes.

2.5. Further modification of the olefination

For the Wittig reaction, traditionally, oxaphosphetane is recognized as a key intermediate and the selectivity could

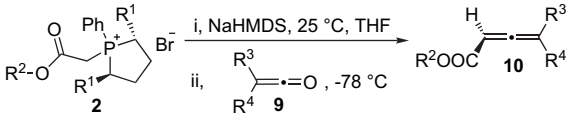
Table 3. Asymmetric synthesis of allenes **10** from phosphonium salt **2b**[a]



Entry	Ketene **9** (R^3/R^4)	Allene **10**	Yield[b] (%)	ee[c] (%)
1	**9a** (Et/Ph)	**10a**	80	81
2	**9b** (Me/Ph)	**10b**	61	45
3	**9c** (*n*-Pr/Ph)	**10c**	78	80
4	**9d** (*n*-Bu/Ph)	**10d**	70	64
5	**9e** (*i*-Pr/Ph)	**10e**	76	71
6	**9f** (*i*-Bu/Ph)	**10f**	71	85
7[d]	**9g** (Allyl/Ph)	**10g**	46	61
8[d]	**9h** (3-Butenyl/Ph)	**10h**	59	65
9[d]	**9i** (Bn/Ph)	**10i**	51	52
10	**9j** (Et/*o*-Me–C_6H_4)	**10j**	53	25
11	**9k** (Et/*p*-MeO–C_6H_4)	**10k**	78	91
12	**9l** (Et/*p*-Cl–C_6H_4)	**10l**	75	85

[a] Reactions were carried out in THF at −78 °C under N_2 with 0.2 mmol of salt **2b** (0.2 M in THF, 1.0 mL), 0.2 mmol of NaHMDS, and 0.2 mmol of ketene **9**.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Ketene was prepared in situ from 0.4 mmol of the corresponding acyl chloride and 0.6 mmol Et_3N.

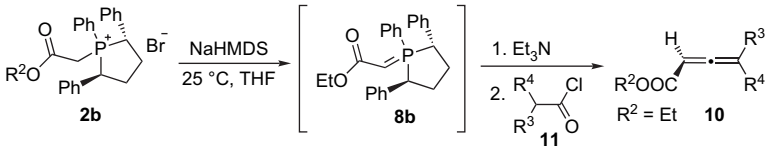
Table 2. Effects of phosphonium salts[a]



Entry	R^1/R^2 (salts **2**)	R^3/R^4 (ketene **9**)	Product	Yield[b] (%)	ee[c] (%)
1	Me/Et (**2a**)	Et/Ph (**9a**)	**10a**	56	43
2	Ph/Et (**2b**)	Et/Ph (**9a**)	**10a**	80	81
3	Ph/*t*-Bu (**2c**)	Et/Ph (**9a**)	**10m**	51	92
4[d]	Me/Et (**2a**)	*n*-$C_{10}H_{21}$/H (**9o**)	**10o**	20	19
5[d]	Ph/Et (**2b**)	*n*-$C_{10}H_{21}$/H (**9o**)	**10o**	53	55

[a] Reactions were carried out in THF at −78 °C under N_2 with 0.2 mmol of salt **2** (0.2 M in 1.0 mL of THF), 0.2 mmol of NaHMDS, and 0.2 mmol of ketene **9**.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] Ketene is prepared in situ, and the reaction was carried out at −20 °C.

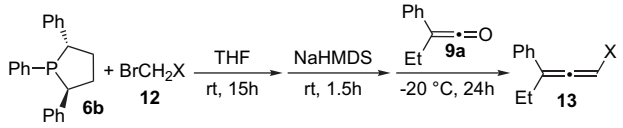
Table 4. One-pot enantioselective synthesis of allenes **10**[a]



Entry	Acyl chloride **11** (R^3/R^4)	Allene **10**	T (°C)	Yield[b] (%)	ee[c] (%)
1	**11a** (Bn/Ph)	**10i**	0	57	45
2	**11b** (*n*-Bu/Et)	**10n**	−20	51	63
3	**11c** (*n*-$C_{10}H_{21}$/H)	**10o**	0	53	55
4	**11d** (*t*-Bu/H)	**10p**	0	57	17
5	**11e** (Br/Me)	**10q**	0	61	30

[a] Reactions were carried out in THF under N_2 with 0.2 mmol of salt **2b** (0.2 M in THF, 1 mL), 0.2 mmol of NaHMDS, 0.3 mmol of Et_3N, and 0.24 mmol of acyl chloride.
[b] Isolated yield.
[c] Determined by chiral HPLC.

Table 5. Asymmetric synthesis of allenic amides, nitrile, and ketone[a]

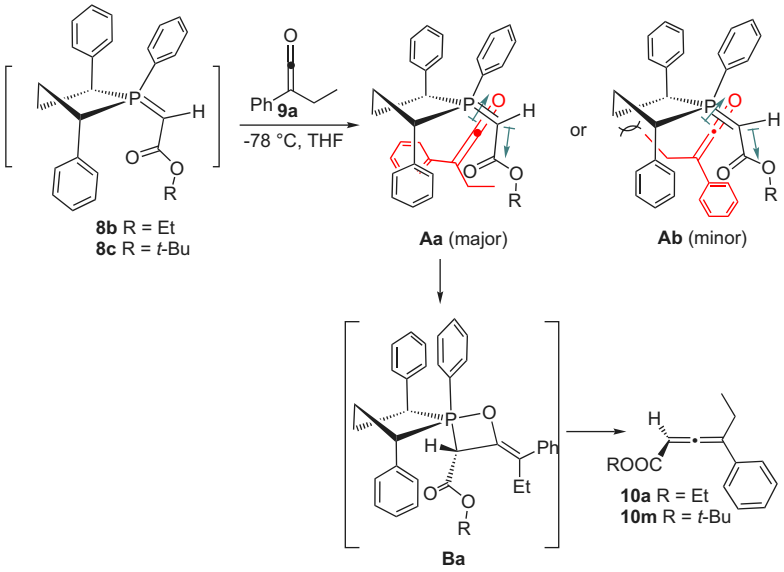


Entry	X ($BrCH_2X$ **12**)	Allene **13**	Yield[b] (%)	ee[c] (%)
1	$CON(CH_2)_4$ (**12a**)	**13a**	69	32
2[d]	$CONEt_2$ (**12b**)	**13b**	76	60
3	CN (**12c**)	**13c**	65	20
4	COPh (**12d**)	**13d**	65	40

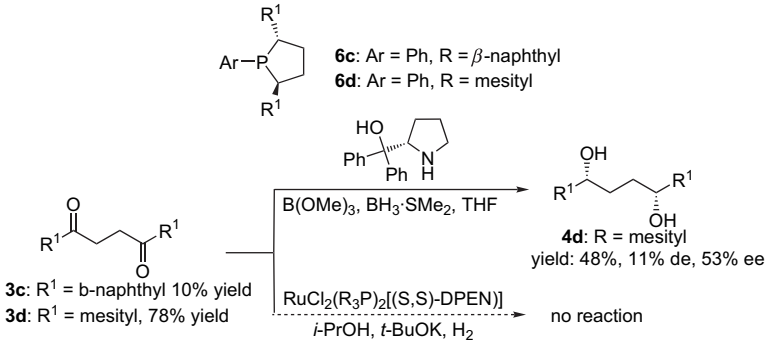
[a] Reactions were carried out in THF at −20 °C under N_2 with 0.2 mmol of chiral phosphine **6** (0.2 M in THF, 1.0 mL), 0.2 mmol of $BrCH_2X$ **12**, 0.2 mmol of NaHMDS, and 0.2 mmol of ketene.
[b] Isolated yield.
[c] Determined by chiral HPLC.
[d] 0.3 mmol of phosphine **6** and 0.3 mmol of $BrCH_2X$ **12** were used.

be explained by 1,2- and 1,3-steric interactions in the four-center transition state.[11] Recently, Aggarwal and his co-workers developed an elegant dipole–dipole interaction model to account for the selectivity in the reaction of stabilized phosphorus ylide with aldehyde.[12] Based on their mechanistic insights, we developed a stereochemical model in the previous communication[9] to explain the configuration of the allenic esters formed (Scheme 2).

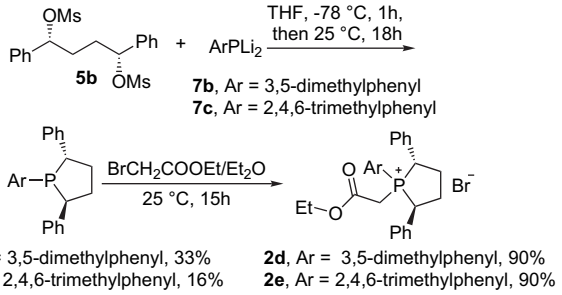
Based on the stereochemical model developed, it is envisioned that replacement of the phenyl of salt **2b** by a more bulky substituent should be beneficial to the enantioselectivity. And thus, we designed phosphanes **6c–6f**. However, several attempts to synthesize **6c** and **6d** failed due to the low yield for the synthesis of diketone **3c** and the poor selectivity for the reduction of **3d** (Scheme 3). Fortunately, the reactions of **5b** with dilithium arylphosphate **7b** and **7c** proceeded well to afford the desired phosphines **6e** and **6f**, respectively. The reactions of **6e** and **6f** with ethyl bromoacetate gave the corresponding phosphonium salts **2d** and **2e**, respectively, in excellent yields as shown in Scheme 4. Compared with **2b**, the newly designed phosphonium salts **2d** and **2e** gave allenes in similar yields under the optimal conditions.



Scheme 2. A proposed stereochemical model.

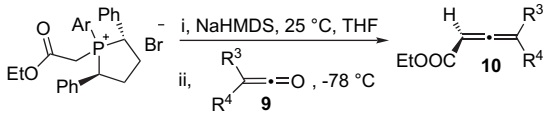


Scheme 3. Attempt for the synthesis of **6c** and **6d**.



Scheme 4. Synthesis of phosphonium salts **2d** and **2e**.

Table 6. Asymmetric olefination with phosphonium salts **2d** and **2e**[a]



2d: Ar = 3,5-dimethylphenyl; **2e**: Ar = 2,4,6-trimethylphenyl

Entry	Salt **2**	Ketene **9** (R^3/R^4)	Allene **10**	Yield[b] (%)	ee[c] (%)
1	**2d**	**9b** (Me/Ph)	**10b**	54 (61)	65 (45)
2	**2d**	**9k** (Et/*p*-$CH_3OC_6H_4$)	**10k**	80 (78)	92 (91)
3	**2d**	**9f** (*i*-Bu/Ph)	**10f**	77 (71)	91 (85)
4	**2d**	**9j** (Et/*o*-Me–C_6H_4)	**10j**	49 (53)	58 (25)
5	**2d**	**9l** (Et/*p*-Cl–C_6H_4)	**10l**	64 (75)	90 (85)
6[d]	**2d**	**9p** (*t*-Bu/H)	**10p**	51 (57)	25 (17)
7	**2e**	**9j** (Et/*o*-Me–C_6H_4)	**10j**	47 (53)	45 (25)
8[d]	**2e**	**9p** (*t*-Bu/H)	**10p**	56 (57)	25 (17)

[a] Reactions were carried out in THF at −78 °C under N_2 with 0.2 mmol of salt **2d** or **2e** (0.2 M in THF, 1.0 mL), 0.2 mmol of NaHMDS, and 0.2 mmol of ketene **9**.
[b] Isolated yield, number in bracket is the isolated yield when salt **2b** was used.
[c] Determined by chiral HPLC. Number in bracket is the ee when salt **2b** was used.
[d] Ketene was prepared in situ and the reaction was carried out at −20 °C.

As expected, the enantioselectivities were improved for most substrates although they are not good enough (Table 6). Compared with **2e**, **2d** gave the allene with higher ee (entry 4 vs entry 7). These results further supported the stereochemical model proposed above.

3. Conclusion

In summary, we have developed an efficient method for the preparation of optically active allenes. Using salt **2b**, **2d** or **2e**, 4-alkyl-4-aryl-2,3-allenic esters could be prepared with moderate to high enantioselectivities in moderate to good yields. By employing one-pot strategy, 4-monosubstituted, 4-dialkylsubstituted allenic esters, and bromoallene could be readily synthesized. Besides allenic esters, utilizing the corresponding salts prepared in situ, optically allenic amides, ketone, and nitrile could also be obtained. The easily available phosphonium salts, in particular the recovery and the reuse[9] of chiral phosphines make the present method potentially useful.

4. Experimental

4.1. General

All reactions were carried out under N_2 unless otherwise noted. All solvents were purified according to standard methods prior to use. ^{1}H NMR, ^{13}C NMR, and ^{31}P NMR spectra were recorded in chloroform-d_3 on a VARIAN Mercury 300.

4.1.1. Representative procedure for the preparation of phosphonium salts. Preparation of (2*S*,5*S*)-1-ethoxycarbonylmethyl-1-(3,5-dimethylphenyl)-2,5-diphenyl phospholanium bromide (2d).

(1*R*,4*R*)-1,4-Bis(methanesulfonyloxy)-1,4-diphenylbutane (**5b**) was prepared according to a literature procedure.[14]

*Preparation of (2S,5S)-2,5-diphenyl-1-(3,5-dimethylphenyl) phospholane **6e**.* To a slurry of Li_2PAr **7b** (17 mmol) in THF (110 mL) was added dropwise (1*R*,4*R*)-1,4-bis(methanesulfonyloxy)-1,4-diphenylbutane **5b** (7.3 g, 18.3 mmol) in THF (60 mL) at −78 °C. The mixture was allowed to stir at −78 °C for 1 h and then for further 18 h at 25 °C. After filtration through a short silica gel column under N_2, the filtrate was concentrated and the residue was extracted with *n*-hexane (100 mL). The hexane layer was collected, followed by concentration in vacuo yielding the crude product as pale yellow oil, which was used directly for the following reaction without further purification. Yield: 33%. ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 2.14 (s, 6H), 2.04–2.36 (m, 3H), 2.67–2.78 (m, 1H), 3.73–3.84 (m, 1H), 3.99–4.08 (m, 1H), 6.66–7.10 (m, 7H), 7.19–7.41 (m, 6H); ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 21.5.

To a vigorously stirred solution of **6e** (10 mmol) in petroleum ether (20 mL) at −15 °C was added dropwise 10% H_2O_2 (20 mmol) within 1 h. After 4 h at −15 °C, the

reaction mixture was diluted with $CHCl_3$ (40 mL). The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (3×30 mL). The combined organic extracts were washed with H_2O, dried (Na_2SO_4), and concentrated in vacuo. The residual oil was purified by flash column chromatography (CH_2Cl_2/CH_3OH=100/1) to afford (2*S*,5*S*)-(−)-1-r-oxo-2,5-diphenyl-1-(3,5-dimethylphenyl) phospholane **14b**. Yield: 50%. $[\alpha]_D^{20}$ −64.2 (*c* 0.4, $CHCl_3$). IR (KBr) ν/cm^{-1} 2943 (m), 1602 (vs), 1496 (vs), 1451 (vs), 758 (s), 697 (vs); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 2.17 (s, 6H), 2.22–2.37 (m, 1H), 2.50–2.74 (m, 3H), 3.45–3.56 (m, 1H), 3.79–3.94 (m, 1H), 6.92–7.30 (m, 13H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.28, 137.12, 135.87, 135.82, 135.59, 135.52, 132.95, 132.91, 130.37, 129.19, 128.60, 128.53, 128.49, 128.22, 127.82, 126.90, 126.84, 126.58, 126.06, 51.18, 50.36, 46.88, 46.07, 31.20, 31.10, 27.68, 27.57, 20.79; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 54.2; MS (EI, *m*/*z*, rel intensity) 360 (11.0), 107 (21.0), 91 (20.6), 84 (100.0), 77 (13.3), 47 (30.3); HRMS (MALDI/DHB) M+Na$^+$ calcd for $C_{24}H_{25}OPNa^+$: 383.1537. Found: 383.1535.

Pure **6e** was obtained by reduction of the corresponding oxide **14b** according to a literature procedure.[13,14]

*Preparation of phosphonium salts **2d***. A mixture of phosphine **6e** (2.5 mmol) and $BrCH_2COOEt$ (2.7 mmol) in Et_2O (5 mL) was stirred at 25 °C for 15 h. The resulting solid was collected, washed with ether, and dried in vacuo to give phosphonium salt **2d**. Yield: 90%. $[\alpha]_D^{20}$ −95.7 (*c* 0.83, $CHCl_3$). IR (KBr) ν/cm^{-1} 3031 (w), 1735 (vs), 1601 (m), 1496 (m), 761 (m), 701 (m); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 0.88 (t, *J*=6.9 Hz, 3H), 2.25 (s, 6H), 2.47–3.00 (m, 3H), 3.13–3.24 (m, 1H), 3.61–3.78 (m, 2H), 4.17–4.27 (m, 1H), 4.37–4.46 (m, 1H), 5.21–5.32 (m, 1H), 5.74–5.86 (m, 1H), 7.10–7.40 (m, 11H), 7.74 (d, *J*=7.2 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.81, 163.75, 139.52, 139.41, 135.96, 135.91, 132.18, 132.11, 132.03, 129.95, 129.84, 129.31, 129.25, 129.18, 128.95, 128.89, 128.44, 128.40, 128.25, 128.21, 127.93, 127.88, 116.07, 115.08, 62.17, 44.88, 44.31, 42.62, 42.03, 31.79, 31.69, 31.36, 31.24, 28.81, 28.15, 20.98, 13.39; ^{31}P NMR (121.5 MHz, $CDCl_3$) δ 41.6; MS (ESI, positive mode, *m*/*z*) 431.1 (M−Br$^-$); HRMS (MALDI/DHB) M−Br$^-$ calcd for $C_{28}H_{32}O_2P^+$: 431.2129. Found: 431.2134.

4.1.2. Representative procedure using ketenes (Table 3). Preparation of *S*-4-phenyl-hexa-2,3-dienoic acid ethyl ester (10a). To a solution of phosphonium salt **2b** (0.2 mmol) in THF (1.0 mL) was added NaHMDS (1 M in THF, 0.2 mL). After stirring for 1 h at room temperature, the reaction mixture was cooled to −78 °C and stirred for further 2 h. To the mixture was added ketene **9a** (0.2 mmol), and the resulting mixture was allowed to stir for further 48 h at −78 °C. After quenching with water, the reaction mixture was diluted with petroleum ether and filtered. The filtrate was concentrated and the residue was purified by flash chromatography to give **10a** as pale yellow oil. Yield: 80%. $[\alpha]_D^{20}$ +124.2 (*c* 0.74, $CHCl_3$). 81% ee. ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 1.18 (t, *J*=7.2 Hz, 3H), 1.28 (t, *J*=6.9 Hz, 3H), 2.51–2.59 (m, 2H), 4.17–4.26 (m, 2H), 5.96 (t, *J*=3.6 Hz, 1H), 7.25–7.41 (m, 5H).[9]

The filter cake was submitted to column chromatography to recover phosphine oxide **14a**.

4.1.3. Representative procedure using ketenes prepared in situ (Table 3). Preparation of 4-phenyl-hepta-2,3,6-trienoic acid ethyl ester 10g. To a solution of phosphonium salt **2b** (0.2 mmol) in THF (1.0 mL) was added NaHMDS (1 M in THF, 0.2 mL). After stirring for 1 h at room temperature, the reaction mixture was cooled to −78 °C and stirred for further 2 h to give the ylide solution.

A mixture of trifluoromethyl-benzene (BTF, 1.0 mL), Et_3N (61 mg, 0.6 mmol), and 2-phenyl-pent-4-enoyl chloride (0.4 mmol) was stirred for 2 h at room temperature, and then was filtered under N_2. The filtrate was concentrated in vacuo to give a light yellow oil, which was dissolved in THF (0.5 mL) and then added into the ylide solution prepared above. The resulting mixture was allowed to stir for further 48 h at −78 °C. After quenching with water, the reaction mixture was diluted with petroleum ether and filtered. The filtrate was concentrated and the residue was purified by flash chromatography to give **10g** as pale yellow oil. Yield: 46%. 61% ee. ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 1.28 (t, *J*=6.9 Hz, 3H), 3.29–3.33 (m, 2H), 4.17–4.26 (m, 2H), 5.13 (dd, *J*=1.5, 10.5 Hz, 1H), 5.23 (dd, *J*=1.5, 17.1 Hz, 1H), 5.88–6.00 (m, 2H), 7.26–7.42 (m, 5H).[9]

4.1.4. Representative one-pot protocol (Table 4). Preparation of 4-ethyl-octa-2,3-dienoic acid ethyl ester 10n. To a solution of phosphonium salt **2b** (0.2 mmol) in THF (1.0 mL) was added NaHMDS (1 M in THF, 0.2 mL) at room temperature. The reaction mixture was stirred for 1 h and then Et_3N (31 mg, 0.3 mmol) and acid chloride **11b** (0.24 mmol) were added in turn, at −20 °C. The resulting mixture was stirred at −20 °C for 24 h. After quenching with water, the reaction mixture was diluted with petroleum ether and then filtered. The filtrate was concentrated and the resulting oil was purified by flash chromatography to give **10n** as pale yellow oil. Yield: 51%. 63% ee. ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 0.89 (t, *J*=7.2 Hz, 3H), 1.03 (t, *J*=7.2 Hz, 3H), 1.27 (t, *J*=7.2 Hz, 3H), 1.31–1.48 (m, 4H), 1.99–2.18 (m, 4H), 4.17 (q, *J*=7.2 Hz, 2H), 5.57 (t, *J*=3.0 Hz, 1H).[9]

4.1.5. Representative procedure for the synthesis of allenic ketone, nitrile, and amide (Table 5). Preparation of 4-phenyl-1-pyrrolidin-1-yl-hexa-2,3-dien-1-one (13a). To a solution of chiral phosphine **6b** (0.2 mmol) in THF (1.0 mL) was added $BrCH_2CON(CH_2)_4$ **12a** (0.2 mmol), and the reaction mixture was stirred at room temperature for 15 h. To the reaction system, NaHMDS (1 M in THF, 0.2 mL) was added and the resulting mixture was stirred for 1.5 h. After the reaction mixture was stirred at −20 °C for 0.5 h, ketene **9a** (0.2 mmol) was added, and the mixture was stirred for further 24 h at −20 °C. The reaction mixture was quenched with water, diluted with petroleum ether, and then filtered. The filtrate was concentrated and the residue was purified by flash chromatography to give chiral allene **13a** as pale yellow oil. Yield: 69%. $[\alpha]_D^{20}$ +73.0 (*c* 0.78, $CHCl_3$). 32% ee. IR (KBr) ν/cm^{-1} 2970 (m), 2874 (m), 1942 (m), 1634 (vs), 1624 (vs), 1494 (w); ^{1}H NMR (300 MHz, $CDCl_3$/TMS) δ 1.19 (t, *J*=7.2 Hz, 3H), 1.80–1.97 (m, 4H), 2.50–2.60 (m, 2H), 3.48–3.57 (m, 4H), 6.22 (t, *J*=3.3 Hz, 1H), 7.22–7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 210.3, 163.3, 134.6, 128.4, 127.4, 126.2, 111.2, 93.1, 47.1, 46.4, 26.2, 24.1, 22.8, 12.3; MS (EI, *m*/*z*, rel intensity) 241 (9.4), 226 (21.0), 128 (18.2), 98

(56.9), 55 (100.0). Anal. Calcd for $C_{16}H_{19}NO$: C, 79.63; H, 7.94; N, 5.80. Found: C, 79.69; H, 7.79; N, 5.36.

4.1.5.1. 4-Phenyl-hexa-2,3-dienoic acid diethylamide 13b. Pale yellow oil. Yield: 76%. $[\alpha]_D^{20}$ 132.5 (*c* 0.52, $CHCl_3$). 60% ee. IR (KBr) ν/cm^{-1} 2971 (s), 2933 (m), 1945 (m), 1635 (vs), 1494 (m), 1456 (s); ^1H NMR (300 MHz, $CDCl_3$/TMS) δ 1.13–1.21 (m, 9H), 2.45–2.63 (m, 2H), 3.38–3.49 (m, 4H), 6.26 (t, *J*=3.3 Hz, 1H), 7.21–7.43 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 209.9, 164.1, 134.8, 128.3, 127.2, 126.1, 111.2, 91.4, 42.6, 40.6, 22.8, 14.4, 12.8, 12.2; MS (EI, *m*/*z*, rel intensity) 243 (3.5), 215 (20.8), 100 (68.9), 72 (100.0). Anal. Calcd for $C_{16}H_{21}NO$: C, 78.97; H, 8.70; N, 5.76. Found: C, 78.47; H, 8.83; N, 5.37.

4.1.5.2. 4-Phenyl-hexa-2,3-dienenitrile 13c. Pale yellow oil. Yield: 65%. $[\alpha]_D^{20}$ +61.6 (*c* 0.68, $CHCl_3$). 20% ee. IR (KBr) ν/cm^{-1} 2972 (vs), 2213 (vs), 1947 (w), 1617 (m), 1599 (m), 1494 (s), 1446 (s); ^1H NMR (300 MHz, $CDCl_3$/TMS) δ 1.19 (t, *J*=7.2 Hz, 3H), 2.53–2.62 (m, 2H), 5.61 (t, *J*=3.3 Hz, 1H), 7.26–7.44 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 216.5, 132.4, 128.7, 128.5, 126.5, 114.1, 113.4, 70.6, 22.8, 11.9; MS (EI, *m*/*z*, rel intensity) 169 (32.7), 154 (100.0), 129 (43.7), 113 (30.2), 51 (43.4); HRMS (EI) calcd for $C_{12}H_{11}N$: 169.0891. Found: 169.0888.

4.1.5.3. 1,4-Diphenyl-hexa-2,3-dien-1-one 13d. Pale yellow oil. Yield: 65%. $[\alpha]_D^{20}$ +45.5 (*c* 0.40, $CHCl_3$). 40% ee. IR (KBr) ν/cm^{-1} 2970 (w), 1933 (m), 1654 (vs), 1597 (m), 693 (m); ^1H NMR (300 MHz, $CDCl_3$/TMS) δ 1.15 (t, *J*=7.2 Hz, 3H), 2.53–2.62 (m, 2H), 6.71 (t, *J*=3.3 Hz, 1H), 7.20–7.33 (m, 1H), 7.33–7.41 (m, 6H), 7.41–7.60 (m, 1H), 7.87 (d, *J*=7.5 Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 215.0, 191.5, 137.6, 133.9, 132.5, 128.6, 128.5, 128.2, 127.7, 126.3, 111.6, 97.3, 23.0, 12.2; MS (EI, *m*/*z*, rel intensity) 248 (1.8), 105 (100.0), 77 (41.8), 51 (11.3). Anal. Calcd for $C_{18}H_{16}O$: C, 87.06; H, 6.49. Found: C, 86.81; H, 6.44.

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Supplementary data

Characterization data for new compounds, HPLC spectra of chiral allenes, and synthetic procedures (PDF) for key compounds are available. This material is available free of charge via the Internet at http://pubs.acs.org. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.05.053.

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