Enantioselective synthesis of allenic esters via an ylide route†

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Pseudo- C_2 -symmetric chiral phosphorus ylides have been designed and synthesized for the enantioselective preparation of allenic esters, and up to 92% ee has been achieved.

Chiral ylides have developed into excellent reagents for the synthesis of optically active epoxides,¹ cyclopropanes,² aziridines³ and olefins.⁴ Although the Wittig or Horner-Wadsworth-Emmons (HWE) reaction is good for the preparation of allenes,⁵ which are versatile building blocks⁶, as well as the basic units of numerous natural products and biologically-active compounds,⁷ only a few examples involve its asymmetric version.^{5c-g} Recently, Tanaka et al. described that optically-active 4,4-disubstituted allenecarboxylates could be prepared with binol-derived HWE reagents in 21-71% yields with 23-89% ee values.5e-5f Pinho e Melo and his co-workers^{5g} documented that a phosphorus ylide bearing a 10-phenylsulfonyll-iso-borneol reacted with methylketene to give a penta-2.3-dienoic ester with excellent diastereoselectivity. In our studies of ylides in organic synthesis,⁸ we are interested in developing the chiral ylide-mediated syntheses of optically active allenes9 and have found that newly-designed chiral phosphorus ylides 7a and 7b could react with ketene very well to afford allenes with ee values up to 92%. In this communication, we wish to report the preliminary results.

Phosphonium salts **4a** and **4b** were readily available from the corresponding diketone on a gram scale (Scheme 1). The diketone **1** was reduced with a proline-derived chiral borane to give diol **2** in 98% yield with 98% ee.¹⁰ The diol was treated with methanesulfonyl chloride,¹⁰ followed by reaction with dilithium phenylphosphate to afford chiral phosphine **3**, which reacted with bromoacetate to give the desired phosphonium salts **4a** and **4b**. Gratifyingly, after deprotonation by NaHMDS, salt **4a** reacted



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smoothly with ethyl phenyl ketene at -78 °C to afford chiral allene 6a with 81% ee in 80% yield. Further studies showed that the enantioselectivity could be improved to 92% ee when ethyl ester was replaced by tert-butyl ester (Scheme 2). This result encouraged us to study the generality of the reaction by investigating a variety of ketenes with different structures. As shown in Table 1, the substituents on the ketene proved to strongly influence both the vields and the enantioselectivities. For example, 2-aryl-1-buten-1one gave 4-aryl-2,3-hexadienoic esters in high yields with high enantioselectivities (Table 1, entries 1 and 6-7), and up to 91% ee was obtained. Replacement of the ethyl group on ketene 5a with other alkyl groups, such as iso-propyl, benzyl and allyl, decreased the enantiomeric excess greatly (Table 1, entries 2 and 4-5). As dialkyl ketene 5h and monosubstituted ketene 5i are not stable and could not be purified, as could ketenes 5a-5c, we developed a onepot strategy,¹¹ finding that in the presence of triethylamine, the reaction of acid chloride with phosphonium salt 4a worked well, giving the desired allenic esters in good yields with moderate enantioselectivities (Table 1, entries 8-9).

The absolute configurations of **6a** and **6e** were assigned as *S* by chemical transformations.¹¹ Very recently, Aggarwal and his coworkers developed an elegant dipole–dipole interaction model to account for the selectivity of the reaction of stabilized phosphorus ylides with aldehydes.¹² Based on their mechanistic insights, as well as the current experimental results, a stereochemical model, shown in Scheme 3, has been developed to explain the configuration of the allenic esters formed. This reaction was proposed to proceed *via* a $_{\pi}2_{s} + _{\pi}2_{a}$ cycloaddition, affording the oxaphosphetane, which then decomposed into the corresponding phosphine oxide and chiral allene. The ketene approached the *re* face of ylide **7a** preferentially due to the steric hindrance between the substituents of the ketene and the ylide. Thus allenes with *S*-configurations were obtained, consistent with the experimental results.¹¹

One of the advantages of the current reaction is that the chiral phosphine oxide could be recycled and reused. For example, **8** was recovered in 81% yield and was readily reduced by LiAlH₄ into phosphine **3** in 90% yield (Scheme 4).¹¹

In summary, we have developed an efficient method for the preparation of optically-active 4,4-disubstituted and 4-monosubstituted allenic esters in good yields. The easily available phosphonium salts, good to high enantioselectivity and, in particular, the recovery and the reuse of the phosphine oxide





4 ¹¹					
R-	$\begin{array}{c} \begin{array}{c} Ph \\ Ph $	i, M	NaHMDS, 25°C, THF $R^1 \rightarrow = 0$, -78°C $R^2 5$	H F ROOC 6	R^1 R^2
Entry	Ketene	4	6	Yield (%) ^a	ee (%) ^b
1	O=∙= 5a Ph	4 a	H Et EtO ₂ C co Ph	80	81
2	oa O=∙⊖ Pr ⁱ	4 a		76	71
3		4 a		71	85
4 ^{<i>c</i>}	5c Ph	4a		46	61
5 ^c	5d ^P ⊓ O=• → Bn	4 a		51	52
6	5e "" O=•=	4a	H Et EtO ₂ C 6f	78	91
7	O=• Et	4 a		75	85
8 ^{<i>d</i>}	$O = \bullet = \underbrace{Et}_{\text{5b}} Bu^{n}$	4 a		51	63
9 ^d	$O = \bullet = \bigvee_{c_1 \circ H_{21}^n}^{H}$	4a	$H \xrightarrow{H} C_{10}H_{21}$	52	55
10	$0=\bullet = \underbrace{\overset{\text{Et}}{\overbrace{5a}}}_{\text{Ph}}$	4b	$\overset{H}{\underset{But^{U}O_2C}{\overset{H}{\underset{\mathbf{6j}}{\overset{H}{\overset{H}{\underset{F}{\overset{H}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\overset{H}{\underset{G}{\underset{G}{\overset{H}{\underset{G}{\underset{G}{\overset{H}{\underset{G}{\underset{G}{\overset{H}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\atopG}{\underset{G}{\underset{G}{\underset{G}{\atopG}{\underset{G}{\underset{G}{\underset{G}{\underset{G}{\atopG}{\underset{G}{\underset{G}{\underset{G}{\atopG}{\underset{G}{\atopG}{\underset{G}{\atopG}{\atopG}{\atopG}{\atopG}{\atopG}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}{{G}}{{G}{{G}}{{G}{{G}{{G}{{G}{{G}}{{G}{{G}{{G}{{G}{{G}}{{G}{{G}}{{G}}{{G}{{G}}{{G}{{G}{{G}{{G}}{{G}}{{G}}{{G}{{G}}{{G}{{G}}{{G}{{G}}{{G}}{{G}}{{G}}{{{G}}{{G}{{G}}{{{G}}}{{{G}}{{{G}}}{{{G}}}{{{G}}}{{{G}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}{{{G}}}}{{{G}}}{{{G}}}{{{G}}}}}}$	51	92

Table 1Asymmetric synthesis of allenes 6 from phosphonium salts 4^{11}







Scheme 4

make the present method potentially useful. Studies on further improving the enantioselectivity and understanding the mechanism are in progress in our laboratory.

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