Enantioselective synthesis of allenic esters *via* an ylide route†

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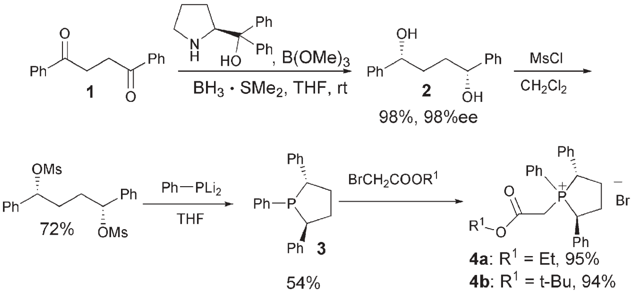
Pseudo-C_2-symmetric chiral phosphorus ylides have been designed and synthesized for the enantioselective preparation of allenic esters, and up to 92% ee has been achieved.

Chiral ylides have developed into excellent reagents for the synthesis of optically active epoxides,[1] cyclopropanes,[2] aziridines[3] and olefins.[4] Although the Wittig or Horner–Wadsworth–Emmons (HWE) reaction is good for the preparation of allenes,[5] which are versatile building blocks[6], 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 allenes[9] 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 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 yields and the enantioselectivities. For example, 2-aryl-1-buten-1-one 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 one-pot 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).

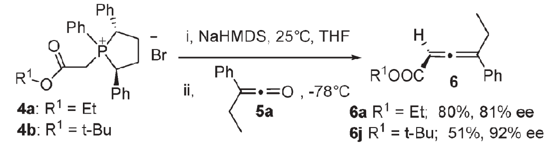


Scheme 1

The absolute configurations of **6a** and **6e** were assigned as *S* by chemical transformations.[11] Very recently, Aggarwal and his co-workers 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 $LiAlH_4$ 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-mono-substituted 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



Scheme 2

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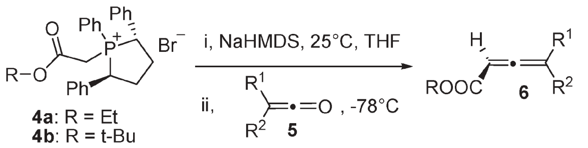
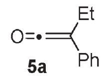
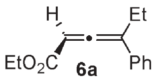
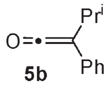
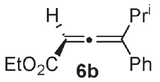
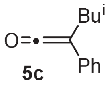
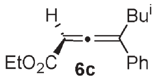
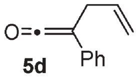
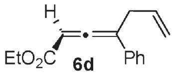
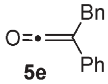
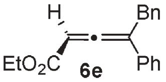
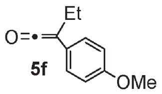
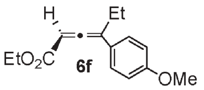
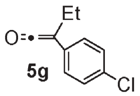
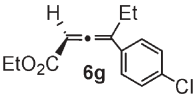
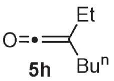
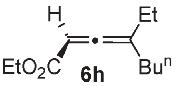
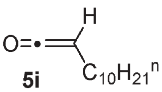
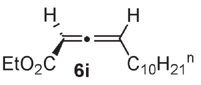
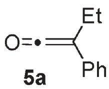
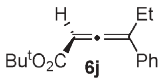
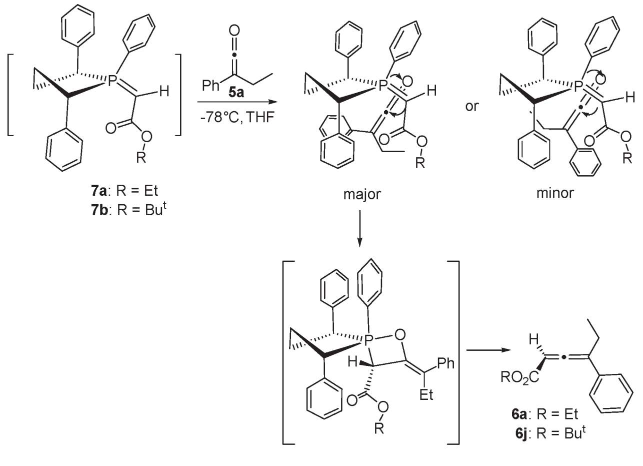
† Electronic Supplementary Information (ESI) available: Experimental details. See DOI: 10.1039/b603659g

Table 1 Asymmetric synthesis of allenes **6** from phosphonium salts **4**[11]

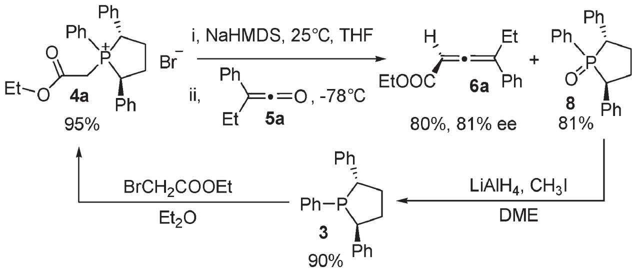


Entry	Ketene	4	6	Yield (%)[a]	ee (%)[b]
1	 5a	4a	 6a	80	81
2	 5b	4a	 6b	76	71
3	 5c	4a	 6c	71	85
4[c]	 5d	4a	 6d	46	61
5[c]	 5e	4a	 6e	51	52
6	 5f	4a	 6f	78	91
7	 5g	4a	 6g	75	85
8[d]	 5h	4a	 6h	51	63
9[d]	 5i	4a	 6i	52	55
10	 5a	4b	 6j	51	92

[a] Isolated yield. [b] Determined by chiral HPLC. [c] Ketene prepared *in situ*. [d] One-pot reaction.



Scheme 3



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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