Pergamon

Tetrahedron Letters, Vol. 37, No. 21, pp. 3735-3738, 1996

0040-4039/96 $15.00 + 0.00

PII: S0040-4039(96)00672-7

Enantioselective Preparation of Allenecarboxylates by Asymmetric Horner-Wadsworth-Emmons Reaction

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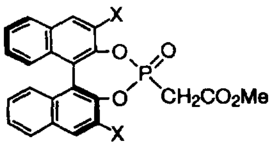
Abstract: Optically active 4,4-disubstituted conjugated allenecarboxylates were enantioselectively prepared *via* C=C bond formation through an asymmetric Horner-Wadsworth-Emmons reaction with an optically active phosphonoacetate reagent. Copyright © 1996 Elsevier Science Ltd

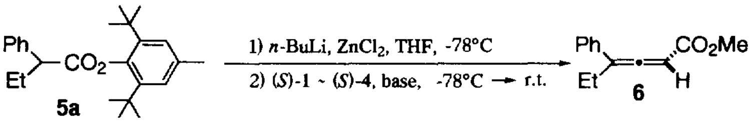
Conjugated allenecarboxylates (alka-2,3-dienoates) are interesting building blocks showing a versatile reactivity, and hence have been widely used in a variety of synthetic transformations.[1] More interesting is that the selective transfer of the axial chilarity of the optically active allenic molecules to the central chirality by appropriate chemical or biological transformation might result in an efficient method for construction of optically active compounds.[2] Among various methods for the synthesis of allenecarboxylic acid derivatives,[3] a relatively limited number of approaches to optically active 4,4-disubstituted alka-2,3-dienoates are known. The latter involves optical resolution of the allenic acids,[4] displacement from optically active propargylic compounds,[3a,5] enantioselective elimination of chiral selenoxides[6] or asymmetric Horner-Wadsworth-Emmons (HWE) reaction of unsymmetrical ketenes or their equivalents.[7] However, these transformations often suffered from tedious and multistage operational steps[5,6] as well as low chemical and optical yields.[7] We recently reported a convenient one-pot procedure for the preparation of allenecarboxyltes based on an HWE reaction of *in situ* generated ketenes[8] from enolates of 2,6-di-*tert*-butyl-4-methylphenyl (BHT) esters.[9] We wish to report herein an enantioselective version of the above reaction.



(*S*)-**1** : X = H
(*S*)-**2** : X = Me
(*S*)-**3** : X = SiMe$_3$
(*S*)-**4** : X = Ph

Beside (*S*)-**1**,[10] analogous reagents, (*S*)-**2**, -**3** and -**4**, possessing substituents at 3,3' positions in the binaphthyl auxiliary moiety,[11,12] were newly prepared and the reaction of ethyl phenyl ketene derived from the BHT ester of 2-phenylbutyric acid **5a** with these reagents was examined (Table 1). Our previous experiments[9] suggested that an additive ZnCl$_2$ or SnCl$_2$ is essential for high chemical yield in production of allenic esters. Therefore, a solution of ZnCl$_2$ (2 eq) in ether[14] was added after 1 h to a solution of the ketene generated from 2-phenylbutyrate (2 eq) and *n*-BuLi (2 eq) at -78 °C, and then the solution of the anion of the HWE reagent (1 eq) was added. Subsequently, the whole reaction mixture was allowed to room temperature with stirring for the indicated hours in Table 1. (*Ra*)-Allenecarboxylate **6** was obtained in all cases. The chemical yield of methyl allenecarboxylate **6** was generally high in the presence of an additive ZnCl$_2$ as expected; however, optical yields with (*S*)-**1** were disappointing (entries 1 - 3). Using LDA as a base, a better result was obtained with (*S*)-**2** (entry 5) and it turned out that the prolonged reaction time caused no significant racemization (entry 6). Use of Cp_2ZrCl_2, $SnCl_2$, $ClTi(O^iPr)_3$ or *n*-Bu_3SnF in place of $ZnCl_2$ as an additive under the reaction conditions of entry 5 gave no improvement. Among the bases employed, KHMDS provided more satisfactory results than LDA (entries 4-6, 9 and 11) and the optimum ee up to 67% was observed with the methyl substituted reagent (*S*)-**2** (entry 7). Compared with the reported value of 22.8% ee observed in a similar approach by asymmetric HWE reactions,[7] this value is remarkable. The usage of the increased amount of $ZnCl_2$ did not affect the optical yield but the chemical yield (entry 8). Neither DME nor Et_2O-toluene as solvent improved the results.

Table 1. Enantioselective Preparation of Allenecarboxylates **6**.[a]



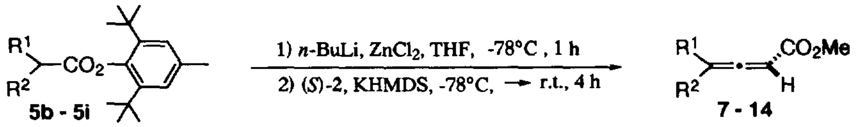
entry	phosphonoacetate	$ZnCl_2$ (eq)	base	time (h)	yield (%)[b]	% ee[c]
1	(*S*)-**1**	none	LDA	15	22	0
2	(*S*)-**1**	2	LDA	15	88	17
3	(*S*)-**1**	3	KHMDS	3	80	22
4	(*S*)-**2**	2	LDA	15	78	5
5	(*S*)-**2**	3	LDA	3	65	47
6	(*S*)-**2**	3	LDA	15	51	45
7	(*S*)-**2**	3	KHMDS	4	87	67
8	(*S*)-**2**	6	KHMDS	4	14	64
9	(*S*)-**3**	3	LDA	15	77	10
10	(*S*)-**3**	3	KHMDS	4	83	50
11	(*S*)-**4**	3	LDA	5	71	17
12	(*S*)-**4**	3	KHMDS	4	78	62

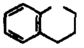
[a] **5a** (2.0 eq) and each 1.0 eq of base and the indicated amount of $ZnCl_2$ were employed toward 1.0 eq. of (*S*)-**1** - **4**. [b] Isolated yield based on (*S*)-**1** - **4**. [c] Determined by HPLC analysis (Chiralpak AS).

Using the optically active reagent (*S*)-**2** and the established conditions discussed above, i.e., in THF in the presence of $ZnCl_2$ (3 eq) with KHMDS as a base for 4 h, the asymmetric HWE reactions were examined with a variety of *in situ* generated ketenes from the BHT esters of 2,2-disubstituted acetic acid derivatives. The results are summarized in Table 2.[15] Generally, the reaction proceeded smoothly to give the corresponding allenecarboxylates in satisfactory chemical yields of 71-94% as well as enantioselectivities of 61-84% ee except for a few cases (entries 7 and 8). The absolute configuration of **6**,**7** and **10** was referred to the reported specific rotation[7] of these compounds and the CD analysis[16] allowed us to propose absolute configuration for the other optically active allenic carboxylates. These assignments are in full agreement with configurations predicted by the Lowe rule.[17] Of particular interest is that the considerably high optical yields were obtained even when the difference in bulkiness between two substituents on the ketene moiety is not so significant (entries 2, 3 and 4).

The observed enantioselectivity with (*S*)-**2** is best understood by considering the favorable transition state rather than the stability of the phosphoxetane intermediate. Thus, the addition of $ZnCl_2$ causes the rigidly

Table 2. Preparation of Optically Active Allenecarboxylates 7 - 14 with the Anion *(S)*-2.



	BHT esters			allenecarboxylate			
entry	5	R^1	R^2		yield(%)[a]	% ee[b] (*config.*)[c]	$[\alpha]^{20}_D$ (solv, conc)
1	**5b**	Ph	Me	**7**	94	62 (***Ra***)[d]	-168.1 (CCl_4, 0.5)
2	**5c**	*i*-Pr	Ph	**8**	71	81 (***Sa***)	+150.2 ($CHCl_3$, 0.25)
3	**5d**	cyclo-Hex	Ph	**9**	81	79 (***Sa***)	+106.0 ($CHCl_3$, 0.5)
4	**5e**			**10**[e]	74	84 (***Ra***)[d]	-9.5 (CCl_4, 0.25)
5	**5f**	2-Naphthyl	Et	**11**	91	72 (***Ra***)	-213.5 ($CHCl_3$, 0.25)
6	**5g**	Ph_2CH	Me	**12**	85	61 (***Ra***)	-4.5 ($CHCl_3$, 0.18)
7	**5h**	1-Naphthyl	Me	**13**	83	4 (***Ra***)	-5.6 ($CHCl_3$, 0.5)
8	**5i**	2,4,6-trimethyl-phenyl	Me	**14**	60	10 (***Ra***)	-23.1 ($CHCl_3$, 0.2)

[a]Isolated yield based on (*S*)-2. [b]Determind by HPLC analysis on chiral column. [c]Deduced from CD spectra (entries 1- 6)[16] and assumed on the basis of the Lowe rule[17] (entries 7 and 8). [d]Ref 7. [e]The product **10** had a tendency to decompose during isolation and purification procedures.

chelated phosphate anion bound by Zn^{2+} as depicted in Figure 1, where the axially dissymmetric binaphthyl group dictates the orientation of the approach to the electrophile from the less hindered *si* face of the reagent (route a). Assuming R^1 > R^2 in bulkiness, it is likely that the nucleophile approaches the LUMO of the ketene carbonyl from the face, including the less bulky R^2, to avoid the severer steric repulsive interaction with R^1. Consequently, the methyl group at 3-position on the naphthalene molecule exerts its efficiency as the bulkiness of R^2 group increases. No reasonable explanation for the low optical yields obtained with (*S*)-3, -4 as well as in reactions starting from the BHT esters of an aryl substituent bearing the substituent at the ortho position (entries 7 and 8 in Table 2), is available at the moment.

In conclusion, the present study demonstrates a simple one-flask preparation of 4,4-disubstituted allenecarboxylates with a high degree of optical purity. The increasing synthetic availability of optically active allenes must enhance their attractiveness as versatile chiral building blocks. Since both the starting BHT esters and the allenic products are rather stable compounds, this transformation might provide an alternative and practical methodology for construction of useful optically active compounds such as natural products.

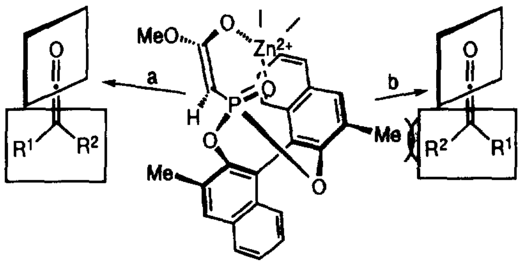


Figure 1. Possible Mechanistic Explanation for the Observed Enantioselectivity in Asymmetric HWE Reaction with (*S*)-2.

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12) (*S*)-**2** (100 %ee, $[\alpha]^{20}_D$ +414 ($CHCl_3$, c 1.0)) was prepared from (*S*)-3,3'dimethyl-1,1'-bi-2-naphthol (1.0 eq) with $Cl_2POCH_2CO_2Me$ (1.2 eq) in the presence of Et_3N (2.3 eq) in CH_2Cl_2 at 0 °C to r. temp. for 3 h in 72 % yield.[13] (*S*)-**3** (98 %ee, 73 % yield, $[\alpha]^{18}_D$ +418 ($CHCl_3$, c 1.0)) and (*S*)-**4** (100 %ee, 84 % yield, $[\alpha]^{18}_D$ +381 ($CHCl_3$, c 1.0)) were prepared from the corresponding binaphthol (1.0 eq) with $Cl_2POCH_2CO_2Me$ (1.1 eq) in the presence of *n*-BuLi (2.1 eq) in THF at -78 °C to r. temp. for 15 h.

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15) All new compounds in this paper provided satisfactory spectroscopic and analytical data.

16) CD (in MeOH) spectral data of allenecarboxylates **7** - **14** of the optical purity indicated in Table 2: **7**; λext 238nm (Δε-5.83), **8**; λext 232nm (Δε+7.07), **9**; λext 232nm (Δε+7.65), **10**; λext 249nm (Δε-6.48), **11**; λext 253nm (Δε-10.5), **12**; λext 228nm (Δε-2.60).

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(*Received in Japan* 7 *March* 1996; *revised* 3 *April* 1996; *accepted* 8 *April* 1996)