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Regio- and stereoselective preparation of dienylcarboxylic acids and dienylphosphonic esters using a (*Z*)-alkenyl sulfone–titanocene(II) system

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Abstract

Titanocene(II)-promoted alkenylation of functionalized alkynes with (*Z*)-alkenyl sulfones proceeded with high regio- and stereoselectivity to produce functionalized dienes. Conjugated dienylcarboxylic acids and dienylphosphonic esters were obtained using acetylenic lithium carboxylates and dialkyl phosphonates as starting materials.

Keywords: Alkenyl sulfones; Titanocene(II); Alkynes; Dienoic acids; Dienylphosphonic esters

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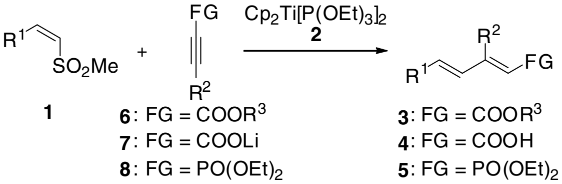
Functionalized conjugated dienes are useful synthetic intermediates for the synthesis of various natural products.[1] A variety of methods for their preparation have been developed; they often require a multistep procedure.

Recently, we have reported that the alkenylation of carbonyl compounds and alkynes proceeded with complete *E* stereoselectivity by the treatment with (*Z*)-alkenyl methyl sulfones **1** in the presence of the titanocene(II) reagent $Cp_2Ti[P(OEt)_3]_2$ **2**.[2] This alkenylation was successfully applied to the stereoselective preparation of titanium vinylvinylidene complexes from alkynyl phenyl sulfones, which involved regioselective coupling of alkynyl and alkenyl sulfones.[3] These results prompted us to further investigate the stereoselective preparation of functionalized dienes **3**, **4** and **5** by the titanocene(II)-promoted reactions of functionalized alkynes **6**, **7** and **8** with (*Z*)-alkenyl methyl sulfones **1** (Scheme 1).

First, we examined the titanocene(II) **2**-promoted reaction of α,β-acetylenic esters **6** with **1**. The treatment of ethyl 5-phenyl-2-pentynoate (**6a**) and methyl (*Z*)-4-phenyl-1-butenyl sulfone (**1a**) with the titanocene(II) reagent **2** followed by the aqueous workup gave the corresponding 2,4-dienoic ester **3a** along with a trace amount of its regioisomer (Scheme 2). Although the unsaturated ester **3a** thus obtained was a 1:1 mixture of the (2*E*,4*E*)- and (2*Z*,4*E*)-isomers, the former isomer was produced as a major product when the reaction was quenched by the addition of benzoic acid (3 equiv) before the aqueous workup. The similar reaction of the *tert*-butyl ester **6b** with sulfone **1b** also gave the (2*E*,4*E*)-dienoate **3b** preferentially (74%, 2*E*,4*E*:2*Z*,4*E* = 85:15).

Various methods for the preparations of 2,4-dienoic esters have been reported so far. For example, the Wittig olefination of α,β-unsaturated aldehydes with (triphenylphosphoranylidene)acetic esters,[4] the Heck reaction of



Scheme 1.

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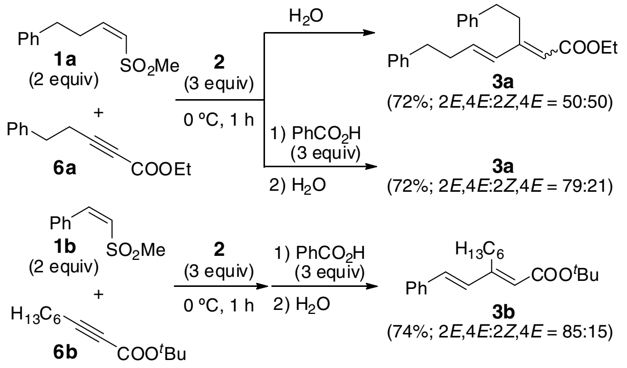


Scheme 2.

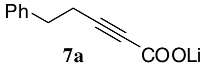
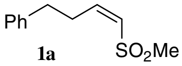
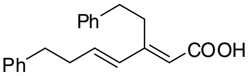
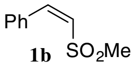
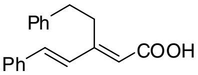
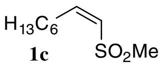
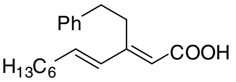
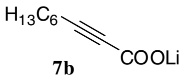
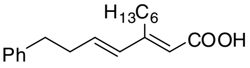
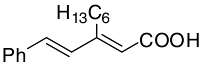
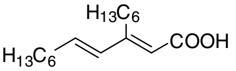
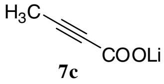
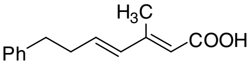
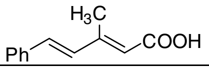
α,β-unsaturated esters,[5] the Suzuki coupling between alkenyl boranes and β-halo-α,β-unsaturated esters,[6] the Stille coupling between alkenystannanes and β-halo-α,β-unsaturated esters,[7] the ruthenium-catalyzed coupling between alkynes and acrylates[8] and the cross-metathesis between terminal olefins and electron-deficient 1,3-dienes.[9] Although the low-valent titanium reagent-mediated alkenylation of a certain acetylenic ester with terminal alkynes has been studied,[10] the alkenylation of acetylenic acids has not been investigated yet. Then we examined the alkenylation of lithium salts of α,β-acetylenic acids **7** utilizing a titanocene(II) **2**-(*Z*)-alkenyl sulfone **1** system. The lithium salts **7** were treated with sulfones **1** and **2** to produce the dienoic acids **4** after acidic aqueous workup (Table 1).[11]

It is of interest that the reaction of the acetylenic lithium carboxylates **7** is much more regio- and stereoselective than that of the corresponding esters **6**; the (2*E*,4*E*)-dienoic acids **4** were obtained with >91% stereoselectivity without the formation of their regioisomers.

The *E*-selective alkenylation is explained by the formation of the five-membered titanacycle **9** with retention of configuration of **1** and subsequent *syn*-elimination similarly to the alkenylation of unfunctionalized alkynes.[2] Protonation of the dienyltitanium species **10** affords the functionalized dienes **3** and **4** (Scheme 3). The formation of the (2*Z*,4*E*)-isomers in the reaction of acetylenic esters **6** would be attributable to the protonation via titanium allenolates **11** produced by the C to O-titanium migration of **10**. The formation of minor stereoisomers of dienoic acids **4** is also explained by a similar isomerization of the initially formed dienyltitanium species **10** to **11**.

This alkenylation system was found to be versatile for the preparation of functionalized conjugated dienes; the simple treatment of diethyl phenylethynylphosphonate (**8a**)[12] with **1a** (1.5 equiv) and **2** (3 equiv) at 0 °C for 1 h followed by the aqueous workup gave diethyl (1*Z*,3*E*)-2,6-diphenyl-1,3-hexadienylphosphonate (**5a**) in 59% yield as

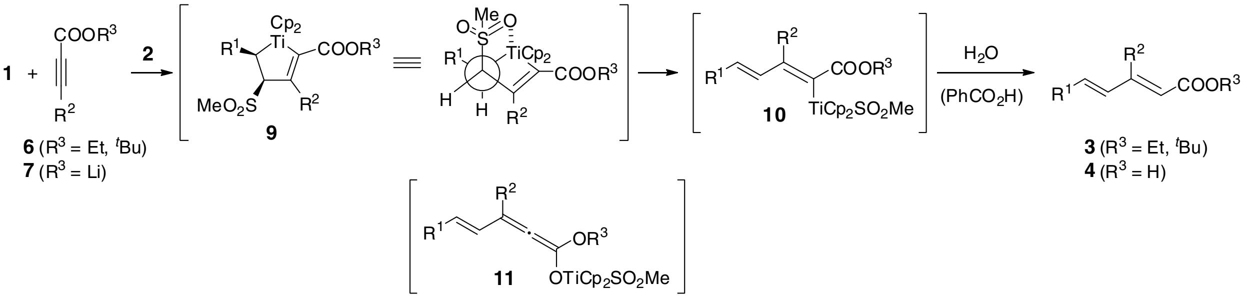
Table 1
Preparation of dienoic acids **4**[a]

Entry	Acetylenic lithium carboxylate **7**	(*Z*)-Alkenyl sulfone **1**	Dienoic acid **4** (Yield /%; 2*E*,4*E*:2*Z*,4*E*)[b]
1	 **7a**	 **1a**	 **4a** (78, >99:1)
2	**7a**	 **1b**	 **4b** (72, >99:1)
3	**7a**	 **1c**	 **4c** (85, 95:5)
4	 **7b**	**1a**	 **4d** (66, 93:7)[c]
5	**7b**	**1b**	 **4e** (86, 96:4)
6	**7b**	**1c**	 **4f** (69, 91:9)[c]
7	 **7c**	**1a**	 **4g** (68, 92:8)
8	**7c**	**1b**	 **4h** (72, 93:7)

[a] All the reactions were performed with a similar procedure as described in the text.

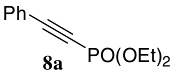
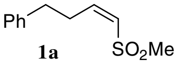
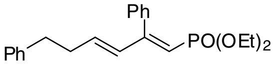
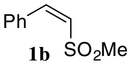
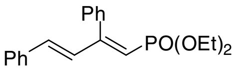
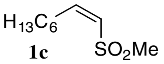
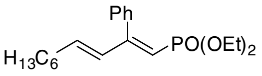
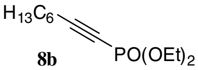
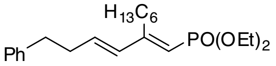
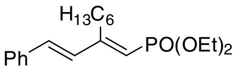
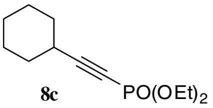
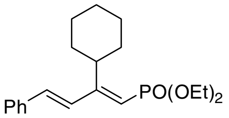
[b] Isolated yield based on the carboxylate **7** used.

[c] Contaminated with a small amount of (*Z*)-2-nonenoic acid. The yield is corrected for the contaminant.



Scheme 3.

Table 2
Preparation of dienylphosphonic esters **5**[a]

Entry	Acetylenic phosphonic ester **8**	(*Z*)-Alkenyl sulfone **1**	Dienylphosphonic ester **5** (Yield /%)[b]
1	 **8a**	 **1a**	 **5b** (59)
2	**8a**	 **1b**	 **5b** (60)[c]
3	**8a**	 **1c**	 **5c** (62)
4	 **8b**	**1a**	 **5d** (67)
5	**8b**	**1b**	 **5e** (59)[d]
6	 **8c**	**1b**	 **5f** (63)

[a] All the reactions were performed with a similar procedure for the preparation of dienoic acids **4**.

[b] Isolated yield based on the phosphonic ester **8** used.

[c] Contaminated with a small amount of triethyl phosphate. The yield is corrected for the contaminant.

[d] A mixture of stereoisomers (1*E*,3*E*:1*Z*,3*E* = 93:7).

a sole product. Similarly, various dienylphosphonic esters **5b–f** were obtained by the titanocene(II) **2**-promoted coupling of the alkenyl sulfones **1** with acetylenic phosphonic esters **8** with excellent regio- and stereoselectivity; no formation of regio- and stereoisomers was observed in all the reactions examined except for **5e** (Table 2). Although the preparation of dienylphosphonic esters by the zirconocene(II)-promoted coupling between terminal alkynes and acetylenic phosphonic esters was reported, the conjugated dienes obtained were mixtures of regioisomers.[13] As for the preparation of 1,3-butadienylene-1,4-diphosphonic esters, the Ti(O^{i}Pr)$_4$/^{i}PrMgBr-promoted dimerization of diethyl 1-hexynylphosphonate was reported.[14] The regioselective preparation of dienylphosphonic esters by the palladium-catalyzed Heck-type reaction of diethyl vinylphosphonate with cyclic triflates was also reported.[15] The results listed in Table 2 show that our new procedure is useful for the straightforward and regioselective preparation of acyclic dienylphosphonic esters.

In conclusion, we have developed regio- and stereoselective alkenylation of functionalized alkynes utilizing the titanocene(II) reagent and (*Z*)-alkenyl sulfones. These methods are useful for the preparation of various α,β,γ,δ-dienoic acids and dienylphosphonic esters with excellent stereoselectivity.

Acknowledgements

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11. *Typical procedure*: Finely powdered molecular sieves 4 Å (60 mg), magnesium turnings (16 mg, 0.66 mmol), and Cp$_2$TiCl$_2$ (149 mg, 0.6 mmol) were placed in a flask and dried by heating with a heat gun in vacuo (2–3 mmHg). After cooling, THF (1.5 mL) and P(OEt)$_3$ (0.21 mL, 1.2 mmol) were added successively with stirring at 25 °C. After 3 h, the reaction mixture was cooled to 0 °C. A THF (1 mL) solution of **1a** (63 mg, 0.3 mmol) was added dropwise over 5 min to the mixture and then the mixture was stirred for 30 min. After powdered **7a** (36 mg, 0.2 mmol) was added, stirring was continued at 0 °C for 1 h. The reaction was quenched by the addition of 1 M HCl, and the insoluble materials were filtered off through Celite and washed with ether. The layers were separated, and the aqueous layer was extracted with ether. After the combined organic extracts were dried (Na$_2$SO$_4$), the solvent was evaporated. Purification of the residue by silica gel column chromatography (hexane/AcOEt, 3:1) gave **4a** (48 mg, 78%; 2*E*,4*E*:2*Z*,4*E* = >99:1): ^{1}H NMR δ 2.53 (dt, $J = 13.5$, 7.2 Hz, 2H), 2.68–2.80 (m, 4H), 2.97–3.08 (m, 2H), 5.74 (s, 1H), 6.09 (d, $J = 15.8$ Hz, 1H), 6.24 (dt, $J = 15.6$, 6.8 Hz, 1H), 7.13–7.35 (m, 10H), 11.1 (bs, 1H); ^{13}C NMR δ 30.3, 34.8, 35.4, 35.9, 117.0, 126.0, 126.1, 128.3, 128.4, 128.5, 132.7, 137.2, 141.1, 141.8, 158.9, 172.2; IR (KBr) 3100–2300, 2925, 1671, 1634, 1591, 1417, 1285, 1265, 1248, 1198, 747, 700 cm^{-1}. Anal. Calcd for $C_{21}H_{22}O_2$: C, 82.32; H, 7.24. Found: C, 82.28; H, 7.19.
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