

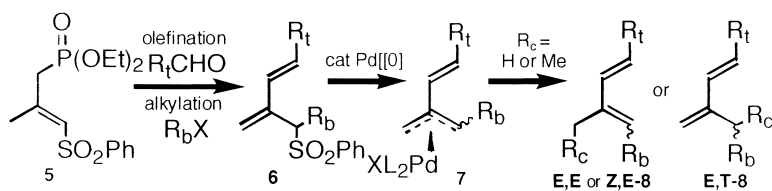
Communication

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γ -Allyl Phosphinoyl Phenyl Sulfone (GAPPS): A Conjunctive Reagent for the Synthesis of EE, EZ, and ET 1,3-Dienes[†]

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Callystatin A **1**,¹ scytophyacin C **2**,² apoptolidin **3**,³ and amphinolid E **4**⁴ all bear 1,3-diene segments which can be viewed as conjunctive⁵ connectors. We report that all three dienes are now available in high yield via a common strategy. Stereospecific synthesis of ET-diene **6** begins with Wadsworth–Emmons reaction of phosphonate reagent **5** followed by α -alkylation at the sulfone moiety. Palladium catalyzed ionization of **6** to π -allyl intermediate **7**, and nucleophilic reduction or alkylation then specifies the geometry of diene **8** via ligand-directed stereocontrol (Scheme 1).

Bromination of methallyl sulfone **9**⁵ to **10**, followed by direct treatment with collidine, smoothly provided a ~20:1 mixture of γ -bromovinyl sulfones **11E**/**11Z** in near-quantitative yield (Scheme 2). Arbuzov reaction in benzene at reflux for 48 h completed the synthesis of the GAPPS reagent **5/12**. This protocol delivered a 19.7/1/0.4/0.3 mixture of **5E**/**5Z**/**12E**/**12Z** in 91% overall yield on a 25 mmol scale.

Addition of catalytic base or using extended times gave various ratios of the GAPPS reagent isomers. While these materials were purified and separately characterized, this is not necessary, because crude mixtures of all four isomers of the reagent **5/12** undergo identically stereospecific Wadsworth–Emmons reactions (Table 1).

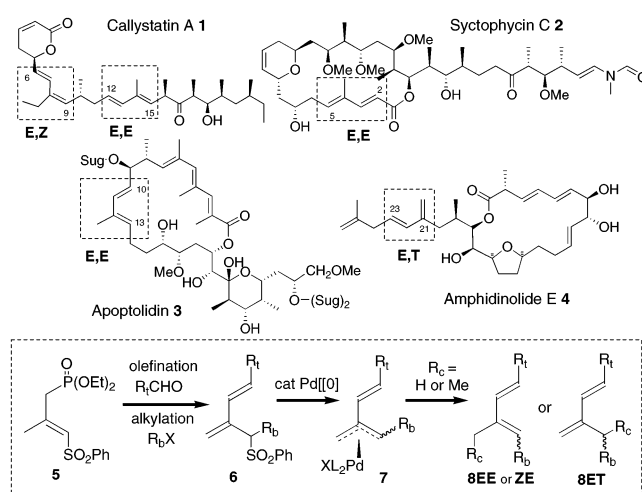
Alkylation of dienyl sulfones **15–17EE/EZ** is completely α -selective. Surprisingly, the alkylation reveals that the optimal conditions require the size-mismatched combination of NaHMDS with the crown ether **18-c-6**. This effect is absolutely reproducible, and this is apparently the first time it is observed (Table 2).

In reactions of α -sulfonyl carbanions, additives such as HMPA or crown ethers favor more reactive monomeric contact ion pairs rather than dimers.⁶ This result may arise from the atypical structure of the sulfone anion. Lithiated sulfones have been shown by Gais to have the cation located between the sulfonyl oxygens roughly in a plane consisting of the cation, the two oxygens, and the sulfur atom.⁶ Our current working hypothesis envisages coordination of the sodium ion with one of the sulfone oxygens and the six crown oxygens (CN = 7), giving improved access to the nucleophilic carbanion.

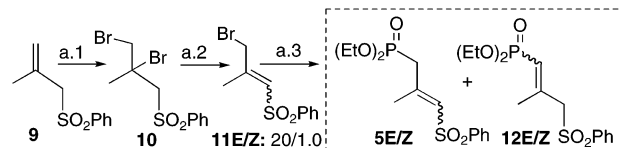
The final operation requires stereodivergent and regioselective functionalization of the allylic sulfones via reduction with hydride or substitution with methyl nucleophiles. Dissolving-metal cleavage⁵ and Kotake's Pd-mediated desulfonylation⁷ of sulfone **21ET α** randomly gave mixtures of **8EZ**/**EE**/**ET**. Tsuji's Pd-catalyzed hydrogenolysis protocol was applied, but none of the desired dienes were formed.⁸

Originally, we had expected that diastereomeric sulfones **21ET α** and **21ET β** would each form a π -allyl "matched" complex with an enantiopure Pd–P catalyst that would suffer stereospecific Super H reduction to **8EE** or **8EZ**, but this is clearly not the case (Table 3, entries 1–4). Interestingly, using Trost's enantiopure bidentate ligands, each diastereomer of **21ET** preferentially favors formation

Scheme 1



Scheme 2^a



^a (a.1) 1.0 equiv of Br₂, CCl₄, 25 °C, 4 h; (a.2) add 2 equiv of collidine, CCl₄, 25 °C, 2 d; (a.3) (EtO)₃P benzene, reflux, 2 d, 91% from **9** (25 mmol).

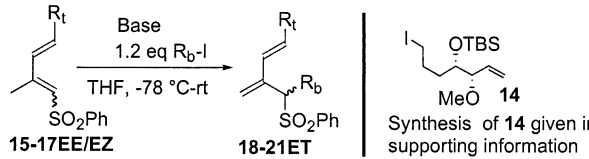
Table 1. Olefination Reaction of Reagents **5/12**

R ₁ CHO	base	product ratio	yield (%)
PhCHO	1.0 equiv of <i>n</i> -BuLi	15EE/EZ : 1/–	99
HO ₂ CCHO	2.2 equiv of <i>n</i> -BuLi	16EE/EZ : 1.9/1	75
13	1.1 equiv of <i>n</i> -BuLi	17EE/EZ : 2.2/1	89

of **8EZ** diene (entries 5–7). The regio/stereoselectivity might be attributed to the uniqueness of the Trost ligand, which has a large bite angle with a sterically demanding structure and σ -donation arising from its amido moiety.

Entries 8 and 9 dramatically demonstrate that the regio/stereoselectivity is strongly controlled by ligand properties other than absolute stereochemistry. Specifically, desulfonylation of **21ET α** correlates to the ligands' cone angles and σ -donating property. Tris-1-pyrrolidinyl phosphine, which possesses a moderate cone angle and moderate σ -donating property, strongly favors formation of **8EE** in 90% yield (entry 8). Alternatively, tris-*tert*-butyl phosphine, which bears both a large cone angle and a very

[†] Synthesis via vinyl sulfones **88**; for **87**, see: *Angew. Chem., Int. Ed.* **2003**, *37*, 3124–3131.

Table 2. Alkylation of the Allyl Sulfones 15–17


substrate	R _b I	conditions	yield (%) ^c
15EE	EtI	1.1 equiv of K or NaHMDS, 10% HMPA, 3 h	18ET , 88, 95
16EE	EtI ^b	2.5 equiv of K or NaHMDS, 20% HMPA, 4 h	19ET , 24, 70
16EE	EtI	2.5 equiv of KHMDS, 2.55 equiv of 18-c-6 , 4 h	19ET , 50
16EE	EtI	2.5 equiv of NaHMDS, 2.55 equiv of 15-c-5 , 4 h	19ET , 20
16EE^a	EtI	2.5 equiv of NaHMDS, 2.55 equiv of 18-c-6 , 4 h	19ET , 99
17EE/EZ	14	1.5 equiv of NaHMDS, 15% HMPA, 14 , 3 h	21ETαβ , 71
17EE/EZ	14	1.2 equiv of KHMDS, 1.3 equiv of 18-c-6 , 3 h	21ETαβ , 30
17EE/EZ	14	1.2 equiv of NaHMDS, 1.25 equiv of 15-c-5 , 3 h	21ETαβ , <5
17EE/EZ	14	1.5 equiv of NaHMDS, 1.55 equiv of 18-c-6 , 2 h	21ETαβ , 85

^a Repeating this reaction with *i*-butyl iodide, *i*-propyl iodide, and iodide **14** provided the analogous ET-alkylation products in 82, 73, and 64% yield, respectively. ^b 1.1 equiv of EtI was used. ^c 1:1 mixture of diastereomers.

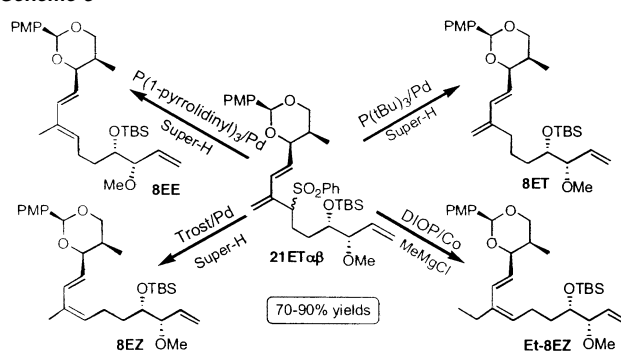
Table 3. Conversion of Allylic Sulfones to 1,3-Dienes^a

entry	21ET	conditions	ratio, yield (%)
		R _c = H	8EE/EZ/ET
1	α	2.5% Pd, 7.5% (<i>R,R</i>)DIOP, ^b 5 h	4.6/1/–, 72
2	β	2.5% Pd, 7.5% (<i>R,R</i>)DIOP, ^b 5 h	2.5/1/–, 52
3	α	2.5% Pd, 7.5% (<i>S,S</i>)DIOP, ^b 5 h	4.2/1/–, 60
4	β	2.5% Pd, 7.5% (<i>S,S</i>)DIOP, ^b 5 h	3.7/1/–, 85
5	α	PdCl ₂ [(<i>S,S</i>)-Trosl], ^{b,c} 10 h	1/7.7/–, 84
6	β	PdCl ₂ [(<i>R,R</i>)-Trosl], ^{b,c} 10 h	1/6.4/–, 89
7	αβ	PdCl ₂ [(<i>D,L</i>)-Trosl], ^{b,c} 10 h	6.5/15.0/1, 87
8	αβ	2.5% Pd, 15% (1-pyrrolidinyl) ₃ P, 20 min	13.2/–/1, 90
9	αβ	5% Pd[(<i>t</i> -Bu) ₃ P] ₂ , 4 h, 45 °C	–/–/1, 90
		R _c = Me	Et-8EZ/EE
10	αβ	5% CoCl ₂ [(<i>R,R</i>)-DIOP], 3 × 1.5 equiv of MeMgCl, ^d 4 h	9.3/1, 87

^a Unless specified, the reaction was done in THF at 0 °C, and super hydride (S–H) was used as the hydride source. ^b 5% LiCl was added. ^c Preformed catalyst was used. ^d MeMgCl was added portionwise in 2 h and stirred for 2 h. See Supporting Information for expanded tables.

strong σ -donating character, exclusively delivers the terminal diene **8ET** in 90% yield (entry 9). The ligand screening study also illustrates that ligands with a strong σ -donating character provide high yields and rapid reactions.

Preliminary studies with methylation reagents show that the diastereomeric mixture **21ETαβ** is also an appropriate precursor

Scheme 3

for 2-ethylated 1,3-dienes. The studies indicate that the reaction with catalyst CoCl₂[(*R,R*)DIOP] and MeMgCl selectively gives the 3-ethyl 1,3-EZ-diene with a 9.3/1 ratio of **Et-8EZ/EE** in 87% yield (Table 3, entry 10).

Therefore, the desulfonylation of **21ET** gives the four different dienes with good to excellent selectivity (Scheme 3, Table 3). Mechanistic definition and further optimization of the ligand-mediated process require further study, but the synthetic potential of this process is highly apparent.

In conclusion, a new three-operation conjunctive strategy is available for the synthesis of EE, EZ, and ET dienes (Scheme 1). This protocol employs a sequential Wadsworth–Emmons reaction using GAPPs reagent **5/12** followed by alkylation of an allylic sulfone anion, and finally ligand-mediated, palladium-catalyzed reductive or alkylative desulfonylation.

Acknowledgment. We are highly grateful to Professor Gais for his insights and extensive discussion of the mismatched crown ether effect in the alkylations of the α -sulfonyl carbanions.

Supporting Information Available: Additional experiments, discussion, experimental procedures, and ¹H, ¹³C spectra (PDF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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