

New Organic Chemistry of Sulfur Dioxide

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ABSTRACT

Simple 1,3-dienes undergo highly stereoselective hetero-Diels–Alder additions with SO₂ at low temperature giving sultines. These reactions that are faster than the more exothermic cheletropic additions of SO₂-producing sulfolenes. This has led to the invention of a new C–C bond-forming reaction combining electron-rich dienes and alkenes with SO₂. The reaction cascade has been exploited to develop combinatorial, one-pot, four-component syntheses of polyfunctional sulfones, sulfonamides, and sulfonic esters. It also allows us to generate, in one-pot operations, enantiomerically enriched polypropionate fragments containing up to three contiguous stereogenic centers and a (*E*)-alkene unit. These fragments can be used directly in further C–C bond-forming reactions, such as cross-aldol condensations, thus permitting the expeditious construction of complicated natural products of biological interest (e.g., Baconipyrones, Rifamycin S, Apoptolidinone) and analogues. New ene reactions of SO₂ have also been discovered; they open new avenues to organic synthesis.

1. Introduction

After wood burning, man discovered that sulfur burning in jars or other containers would help preserve food and beverages. Today, the U.S. demand for SO₂ amounts to ca. 300 × 10³ tons per year at ca. \$230/ton. It is used mostly as a beverage and food preservative (E220, ca. 25%), for bleaching paper and cloths (15%), gypsum manufacture (20%), corn processing (15%), water and waste treatment (10%), ore refining (6%), oil recovery (4%), and sulfonylation of oils and aromatic compounds (5%). Organic chemistry of SO₂ has been limited to the Friedel–Crafts sulfinylation, copolymerization of SO₂ with alkenes and alkynes, the synthesis of sulfinates and sulfones from polar organometallic species, the ring opening of epoxides and oxetanes leading to polysulfites, the isomerization of alkenes, and the formation of sulfolenes by cheletropic

Pierre Vogel was born in 1944, received his Ph.D. degree from the University of Lausanne with Professor Horst Prinzbach, was a postdoc with Martin Saunders (Yale University, New Haven, CT) and Pierre Crabbé (Syntex, Mexico City, Mexico), and is currently a Professor at the Swiss Institute of Technology in Lausanne (EPFL). His research interests are the asymmetric total synthesis of natural products of biological interest, glycochemistry and glycobiology, physical organic chemistry, and the discovery of new synthetic methodologies, including the development of new organic chemistry based on the pericyclic reactions of sulfur dioxide. He has co-authored more than 450 scientific publications and 3 textbooks.

additions with 1,3-dienes (for examples of classical organic reactions of sulfur dioxide reviews, see ref 1 and refs 1–13 cited therein; see also refs 2 and 3), a reaction reported first in 1914.⁴ Other cycloadditions of SO₂ have been described for the reaction of ketenes and ketimines,^{5–8} cyclic polyenes,^{9,10} and quadricyclane.¹¹ Homocheletropic additions of SO₂ to 1,4-dienes have been reported.^{12–14} The first examples of hetero-Diels–Alder additions of SO₂ involved highly reactive dienes **1**¹⁵ and **3**.¹⁶ In 1992, we reported that simple 1,3-dienes undergo hetero-Diels–Alder addition below –60 °C in the presence of a large excess of SO₂ and a protic or Lewis acid promoter (Scheme 1). We showed that (*E,E*)-5-deuteropiperylene (**6**) equilibrates with sultine **7** at –80 °C. At –60 °C, **7** is converted into the more stable isomeric sultine **8**, thus demonstrating the suprafaciability of the acid-catalyzed cycloaddition that obeys the Alder (*endo*) rule.¹⁷

This led us to investigate the factors affecting the competition between the hetero-Diels–Alder and the cheletropic addition of SO₂.^{18–20} Our studies have been reviewed.^{18–21} Apart from sultines resulting from reactions of SO₂ with 1-fluoro-1,3-dienes,²² sultines are less stable than their sulfolene isomers. They decompose into the corresponding 1,3-dienes and SO₂ above –50 °C.^{23–25} With 1-alkoxy- and 1-silyloxy-1,3-dienes **9**, the sultines **10** are not seen at –100 °C because these dienes generate the corresponding sulfolenes **11** at this temperature.²⁶ Nevertheless, sultines **10** are believed to be formed before the sulfolenes. In the presence of an acid catalyst, they equilibrate with zwitterionic intermediates **12** that can be reacted with electro-rich alkenes **13**, thus realizing a new C–C bond-forming reaction (Scheme 2), forming silyl sulfinates **14**.

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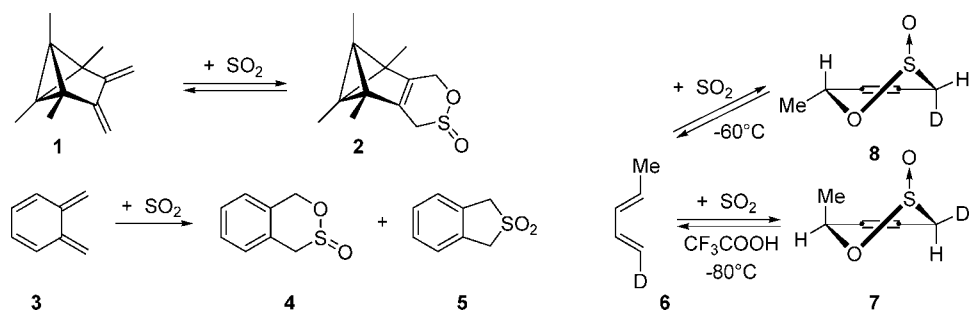
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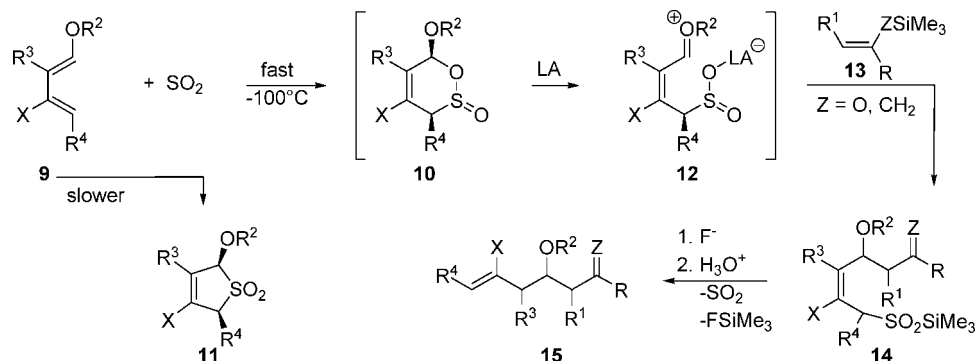
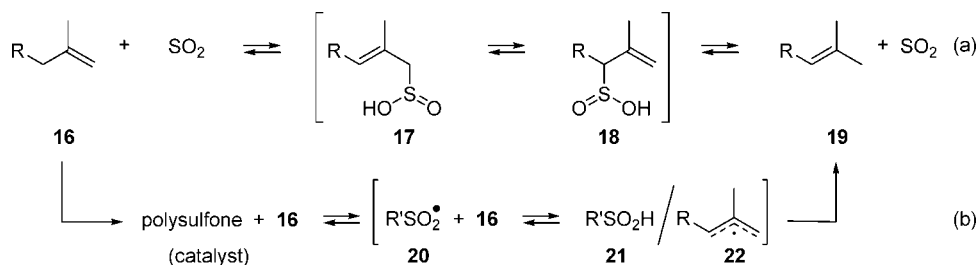
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Scheme 1. Early Examples of Hetero-Diels–Alder Additions of SO₂

Scheme 2. New C–C Bond-Forming Reaction between Electron-Rich Dienes and Alkenes, via Umpolung with Sulfur Dioxide

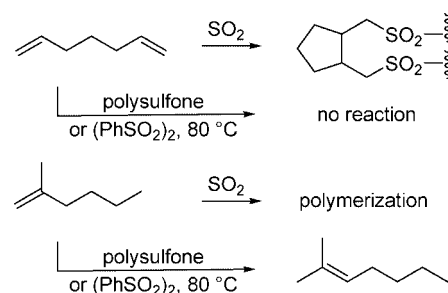
Scheme 3. SO₂-Induced Alkene Isomerization: (a) the Ene Mechanism and (b) the Sulfonyl Radical-Catalyzed Process

In situ desilylation and desulfonylation via retro-ene elimination of SO₂ generates in one-pot operations compounds **15** containing up to three contiguous stereogenic centers and one (*E*)-alkene unit.^{27,28} We review the characteristics of this reaction cascade and some applications to the asymmetric synthesis of polypropionate antibiotics and other compounds of biological interest. Because step **14** → **15** implies a retro-ene elimination of SO₂, we have explored the ene reactions of SO₂. These studies have also led us to discover new organic chemistry of SO₂ that is reviewed here.

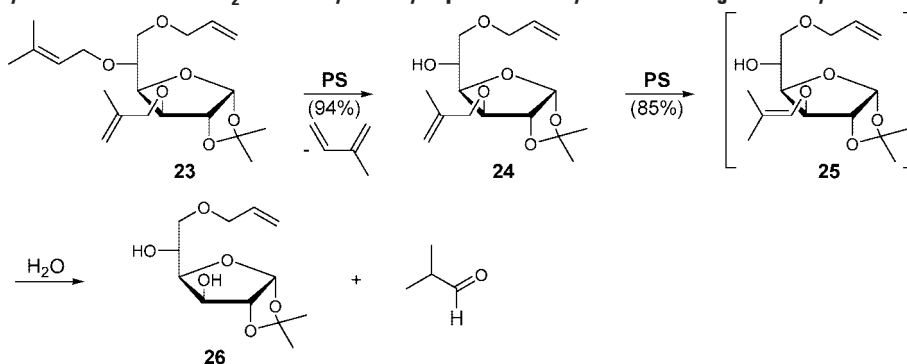
2. A Revisited Mechanism for the Sulfur-Dioxide-Induced Alkene Isomerization

Double-bond migration in alkenes **16** can be induced by SO₂ (Scheme 3). The process is explained by an ene reaction **16** + SO₂ → **17** followed by a [1,3]-sigmatropic shift **17** → **18** and subsequent retro-ene reaction that gives SO₂ and the isomeric alkenes **19**.^{29–34}

In the case of methylenecyclopentane and related alkyl substituted alkenes, we have found that their isomerizations are inhibited by radical-scavenging agents, such as 2,2,6,6-tetramethyl-1-piperidinyloxy free radical (TEMPO) and Bu₃SnH. Kinetic measurements showed induction periods

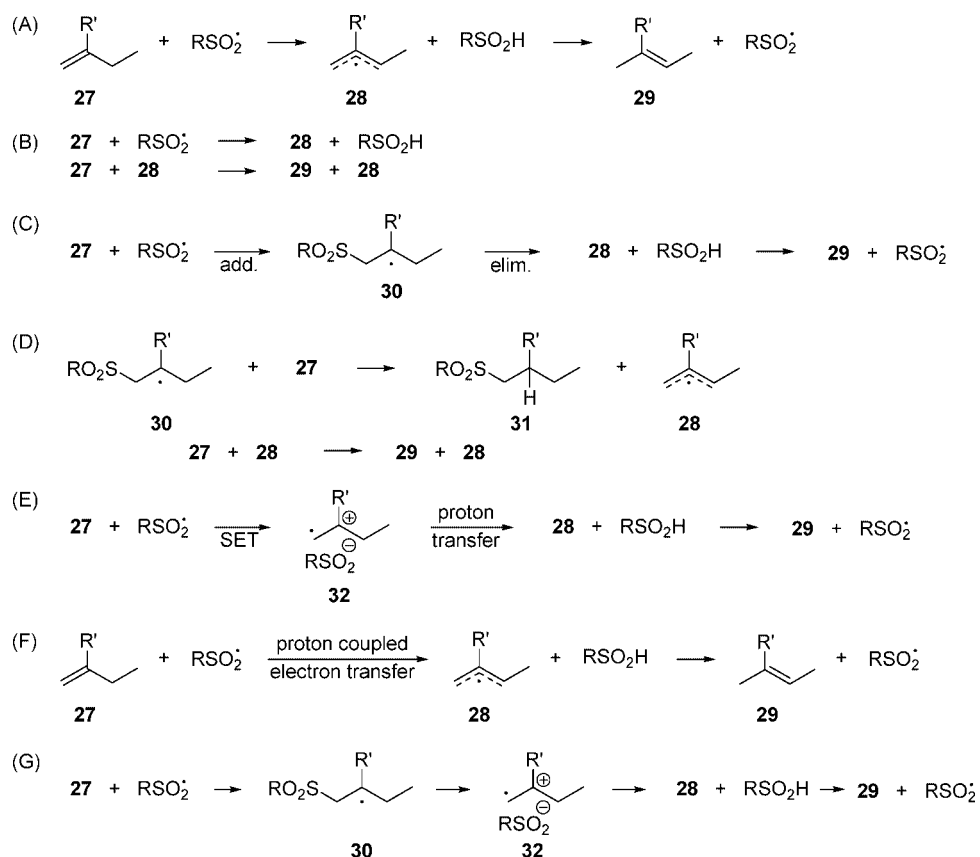
Scheme 4. Selectivity of SO₂ and Polysulfone-Catalyzed Alkene Isomerization

followed by zeroth-order reactions. During the induction period, a white precipitate of a 1:1 copolymer of the alkene and SO₂, a polysulfone,^{35,36} forms. In the absence of SO₂, the latter catalyzes the alkene isomerizations.³⁷ The electron spin resonance (ESR) spectrum of the polysulfones showed typical signals for carbon-centered and sulfonyl radicals (e.g., **20**).^{38–40} Alkene isomerization **16** → **19** is also induced upon heating (80–120 °C) or UV irradiation of **16** in the presence of a catalytic amount of diphenyldisulfone.^{41–43} Both the polysulfone- and diphenyldisulfone-catalyzed alkene isomerizations follow zeroth-order rate laws and are inhibited by radical scavenging agents. Importantly, these reactions are

Scheme 5. Polysulfone PS Made of SO₂ and Methylidenecyclopentane Catalyzes the Cleavage of Methyl-Substituted Allyl Ethers

^aThe reaction is faster for prenyl than methallyl ethers and does not occur for allyl ethers.

Scheme 6. Plausible Mechanisms for the Isomerization of Alkenes in the Presence of Sulfonyl Radicals (See the Text)

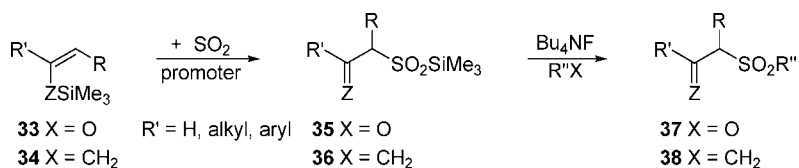
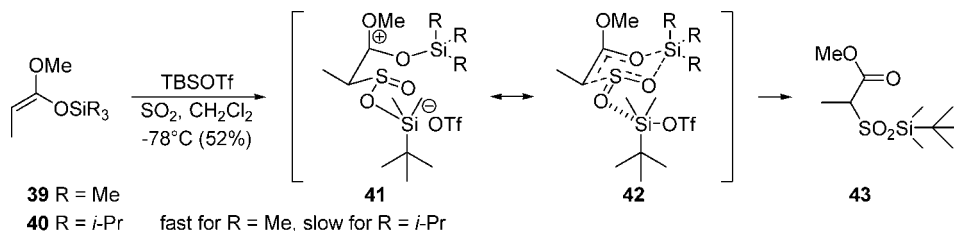


much better yielded than the SO₂-induced isomerizations, with the latter being accompanied by polymer formation.³⁷ Furthermore, the polysulfone- and diphenyldisulfone-catalyzed alkene isomerizations are highly chemoselective in the sense that linear, terminal alkenes (1-alkyl-substituted ethenes) and 1,2-dialkylethenes are not isomerized at all, whereas 2-alkyl-substituted alk-1-enes are isomerized (Scheme 4).

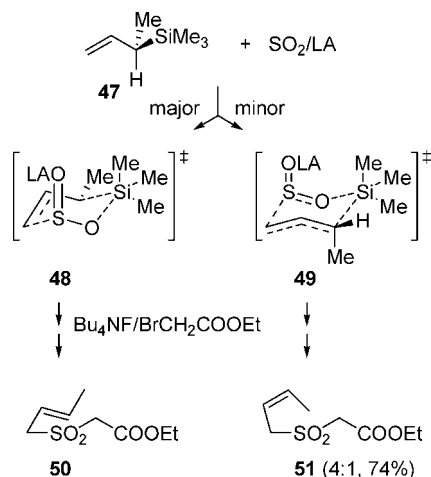
This discovery led us to invent new strategies for the protection and deprotection of alcohols and the semiprotection of polyols. Methallyl, prenyl, and methylprenyl ethers undergo selective cleavages catalyzed either by (PhSO₂)₂⁴⁴ or by the solid polysulfone PS (generated from the copolymerization of SO₂ with methylidenecyclopentane) under neutral conditions, without the use of transition-metal catalysts (Scheme 5).⁴⁵

A number of different routes to rationalize the isomerization of alkenes $27 \rightarrow 29$ in the presence of sulfonyl radicals have been considered (Scheme 6). In mechanism A, one-step hydrogen abstraction gives RSO₂H and radical **28**. The latter diffuses away from the solvent cage and is reduced by a sulfinic acid moiety. Another channel is the direct hydrogen transfer RSO₂H + **28** → **29** in the initial solvent cage (B). In mechanism C, **28** is formed through a two-step mechanism: first, the addition of the sulfonyl radical onto the alkene **27** produces the alkyl radical **30**, and then, elimination of RSO₂H forms the allyl radical **28**. As a variant (D), the intermediate tertiary alkyl radical **30** abstracts a hydrogen atom from **27** and generates the corresponding allyl radical **28**. This starts a chain process as that described for mechanism B. As found for polar radicals, the hydrogen atom transfer can proceed through

Scheme 7. One-Pot, Three-Component Synthesis of Polyfunctional Sulfones

Scheme 8. Possible Mechanism of the Sila-ene Reaction of SO_2 with Enoxysilanes

Scheme 9. Stereoselectivity of the Sila-ene Reactions of Sulfur Dioxide Promoted by TBSOTf = LA



a two-step process starting by an electron transfer to generate a radical cation **32**, followed by proton transfer to the sulfinate anion (E). This latter mechanism might also proceed through a single-step proton-coupled electron-transfer process (F). Finally, the sulfonyl radical addition to the alkene might be followed by heterolytic fragmentation, giving radical cation **32** and sulfinate anion (G), thus connecting with mechanism E. Calculations [CCSD(T)/6-311++6(d,p)/B3LYP/6-311++6(d,p)] suggested that a mechanism involving the reaction between allyl radical and the alkene (B and D) requires energy barriers 5–6 kcal/mol higher than those for mechanism A, in which the hydrogen atom is transferred via the sulfinic acid. On the other hand, the addition of the sulfonyl radical to the alkene (C) involves energy barriers notably lower than for the hydrogen abstraction (A). However, as for the case of the abstraction of an allylic hydrogen in the chlorine atom reactions with alkene,⁴⁶ *ab initio* calculations failed to locate any transition structure for the elimination channel.

Ionic mechanisms, such as E or G, imply solvent effects on the rates or reactions. *Ab initio* calculations, including one and two solvent molecules explicitly, showed only a slight increase in charge separation between the alkene and sulfonyl radical. Thus, quantum calculations⁴⁷ strongly suggest that the isomerization of alkenes in the presence of sulfonyl radicals proceeds through one-step hydrogen abstraction (mechanism A). The chemoselectivity is not governed by an exothermicity difference but by a difference in ionization energies of the alkenes. Calculations for $\text{MeSO}_2\cdot$ plus propene and $\text{MeSO}_2\cdot$ plus 2-methylpropene show a charge transfer of 0.34 and 0.38 electron, respectively, from the alkene to the sulfonyl radical in the transition state of these hydrogen transfers.⁴⁷

3. New Ene Reactions of Sulfur Dioxide

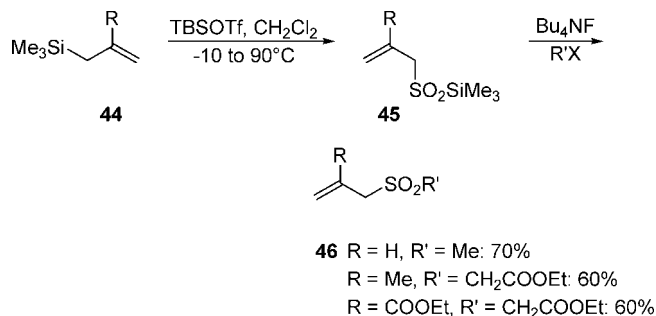
Before our work, metallo-ene reactions with SO_2 had been reported for allyltrialkyltin compounds,⁴⁸ enoxysilanes derived from esters,⁴⁹ and allyl germanes.⁵⁰ We have found that enoxysilanes **33**, derived from ketones and aldehydes, as well as allylsilanes **34** react with SO_2 to give silyl sulfonates **35** and **36**, respectively, that can be reacted in the same pot with a variety of electrophiles generating the corresponding

polyfunctional sulfones **37** and **38**, respectively (Scheme 7).⁵¹

The reactions are promoted by Lewis acids in agreement with a mechanism involving either zwitterionic intermediates of type **41** or a one-step process in which **41** is only a limiting structure of the transition state **42** (Scheme 8).

The reactions of allylsilanes **44** with $\text{SO}_2/\text{CH}_2\text{Cl}_2/\text{TBSOTf}$ provide the corresponding trimethylsilyl alkene-sulfonates **45** that can be reacted with Bu_4NF and electrophiles $\text{R}''\text{X}$ (e.g., MeI and $\text{BrCH}_2\text{COOEt}$) to generate the corresponding sulfones **46**. The ene reaction is the slowest for **44**, with R = COOEt , and the fastest for **44**, with R = Me. With silane **47**, a 4:1 mixture of (*E*- and (*Z*)-alkene **50** and **51** is obtained after workup with Bu_4NF and $\text{BrCH}_2\text{COOEt}$. This can be interpreted in terms of transition states **48** and **49** that adopt chair-like structures, the most stable one (**48**) with a pseudo-equatorial methyl substituent (Scheme 9). One key question is whether the S=O bonds in these transition states adopt pseudo-axial positions (conformational anomeric effect as in sultines **18**) or prefer pseudo-equatorial positions.

A spin-off of our studies has been the invention of a new method for the chemoselective silylation of alcohols, polyols, phenols, and carboxylic acids under nonbasic conditions and with the formation of volatile coproducts (SO_2 isobutylene).⁵²



The trimethylsilyl (**52**), triethylsilyl (**53**), and (*tert*-butyl)dimethylsilyl 2-methylprop-2-enesulfonates (**54**) (prepared as shown in Scheme 10) react with alcohols, phenols, and carboxylic acids to give the corresponding silyl ethers and esters in high yields. Reaction rates follow the order **52** \gg **53** \gg **54** and the order primary > secondary > tertiary alcohols and then allow chemoselective silylation as illustrated with **55** \rightarrow **56** + SO₂ + isobutylene.

Our silylation reaction is inhibited by Et₃N but accelerated by a small amount of SO₂. As the kinetic deuterium isotope effect $k_{\text{H}}/k_{\text{D}} = 1.00 \pm 0.05$ for the reactions *t*-BuOH(D) + **54** \rightarrow *t*-BuO-Si(*t*-Bu)Me₃ + SO₂ + isobutylene, we proposed the mechanism shown in Scheme 10. The alcohols add to SO₂, forming hydrogenosulfites **57** that react with the silyl sulfonates, forming intermediates **58**. Entropy-driven fragmentation occurs, which does not seem to be assisted by proton transfer. Because acids or bases are not required in these silylation techniques, they can be applied to fragile structures. Furthermore, sterically hindered alcohols can be silylated, including (*tert*-butyl)dimethylsilyl ethers.⁵²

Prop-2-ene-1-boronate (**60**) adds SO₂, giving mixed anhydride **61**, which reacts with Grignard reagents, producing allylsulfoxide **62**. It is noteworthy that the Grignard reagents prefer the sulfur electrophilic center rather than the boron center, in most cases. Using enantiomerically pure alk-2-ene-1-boronic esters, enantiomerically or diastereomerically enriched sulfoxides can be obtained as shown in Scheme 11.⁵³

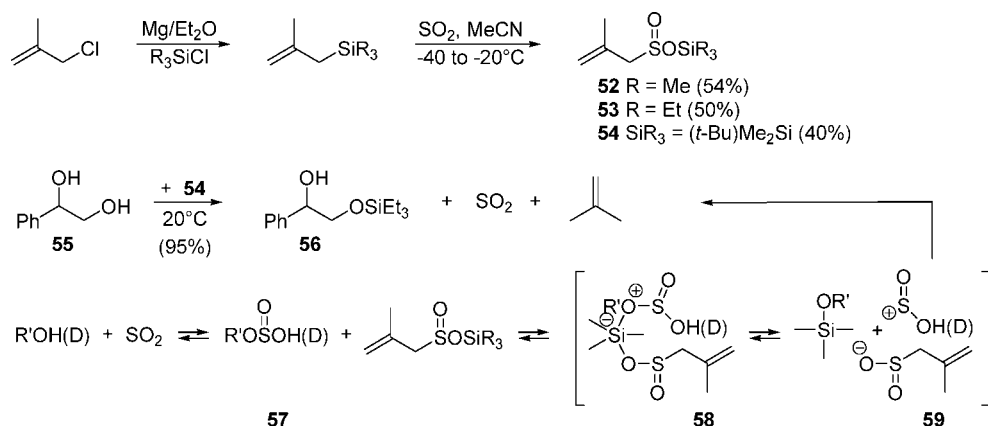
4. A New C–C Bond-Forming Reaction: Umpolung with Sulfur Dioxide

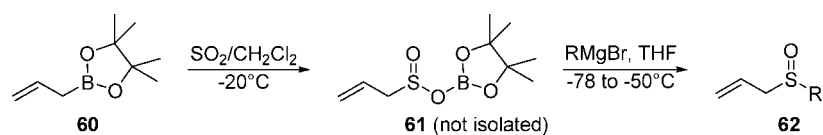
When (*E*)-1-methoxybutadiene (**68**) is reacted with a large excess of SO₂, in the absence or presence of a Lewis acid catalyst (e.g., TBSOTf), only sulfolene **69** is formed between –100 and –60 °C. At 0–20 °C, quick polymerization occurs. However, when a mixture of **68** and enoxysilane **72** is reacted with SO₂ + TBSOTf at –100 °C, silyl sulfinate **73** forms. After solvent evaporation (recovery of SO₂) and treatment with Bu₄NF and MeI, a 81:19 mixture of methyl sulfones **74** and **75** is obtained [100% (*Z*) stereoselectivity].^{27,28}

The formation of **73** is explained by invoking the fast hetero-Diels–Alder **68** + SO₂, giving sultine **70** that is immediately heterolyzed into zwitterion **71**. In the absence of enoxysilane, it equilibrates back to **68**, which finally undergoes the cheletropic addition with SO₂. In the presence of **72**, oxyallylation occurs, producing **73** and then **74** + **75** (Scheme 12). In the reaction of enantiomerically enriched diene (+)-**76** (Greene's chiral auxiliary;⁵⁴ ee >99%) and enoxysilane **77** in SO₂ and Yb(OTf)₃ as the catalyst, the same one-pot sequence of the reaction generates (–)-**78** in 79% yield and 25:1 diastereoselectivity. Similarly, diene (–)-**79** and enoxysilane **80** [with (CF₃SO₂)₂NH as the catalyst] give a 93% yield of a 14.1:1 mixture of (–)-**81** and **82** (Scheme 13).^{55–57}

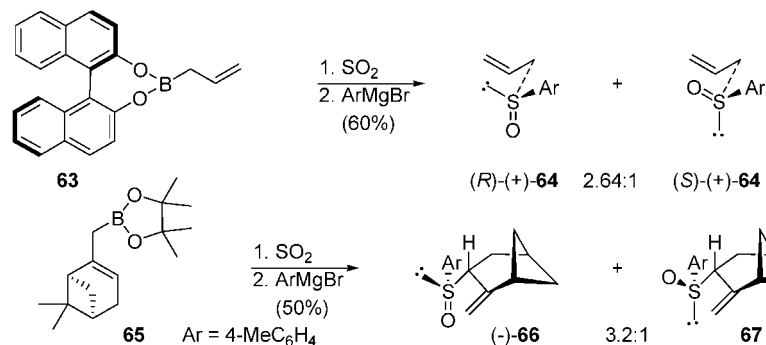
The results are interpreted (Scheme 14) in terms of the formation of sultines **83** that are ionized into zwitterions **84**. The least sterically hindered face of the diene undergoes suprafacial cycloaddition, leading to an *unlike* relative configuration between the β-alkoxy and ε-methyl groups in (–)-**81** and **82**. The face of the zwitterionic intermediate *anti* with respect to the sulfonyl moiety (which is not allowed to rotate freely because of Colombyic interactions between it and the oxycarbenium moiety of **84**) adds to the enoxysilane preferentially on the face, realizing a minimal steric interaction with **84**. In these C–C bond-formation reactions that condense two electron-rich unsaturated systems, sulfur dioxide realizes an Umpolung by converting the 1-oxy-1,3-dienes into 1-oxyallylic cationic intermediates that react with high regio- and face selectivity onto their C1

Scheme 10. Preparation of New Silylating Agents and Possible Mechanism for the SO₂-Catalyzed Silylation of Alcohols by Silyl 2-Methylprop-2-ene-sulfonates

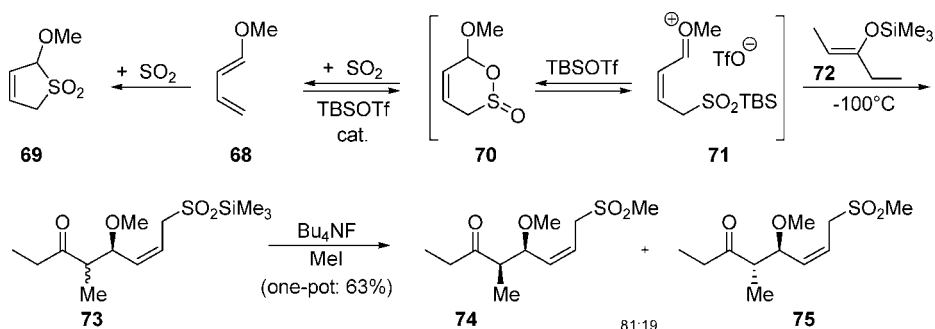
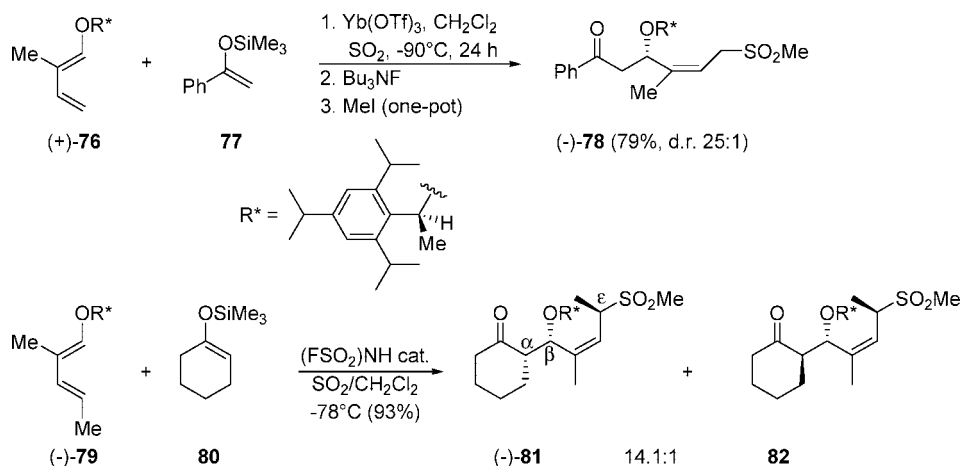


Scheme 11. Bora-ene Reactions of SO₂: New Route to Sulfoxides

R = Ph (62%), 4-MeC₆H₄ (61%), 3-MeC₆H₄ (60%), 1-naphthyl (50%), 2,4,6-(*i*-Pr)₃C₆H₂ (36%), Bn (48%), etc.



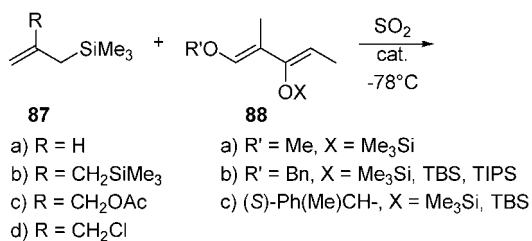
Scheme 12. Oxyallylation of Enoxysilanes

Scheme 13. Examples of One-Pot, Asymmetric and Diastereoselective Four-Component Synthesis of Polyfunctional (*Z*)-Alkenyl Methyl Sulfones Containing up to Three Stereogenic Centers

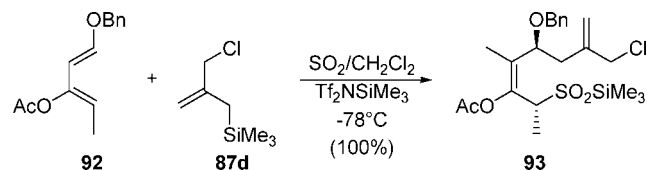
centers with nucleophilic alkenes. No direct experimental proof has been provided yet for the mechanism proposed in Scheme 14.

When diene (–)-79 and allylsilanes 87 are reacted with an excess of SO₂ in the presence of a Lewis acid [e.g., Yb(OTf)₃, (*t*-Bu)Me₂SiOTf, and (CF₃SO₂)₂NSiMe₃] or protic acid (e.g., (CF₃SO₂)₂NH), no product of condensation is observed. Not unexpectedly (see above), the allylsilane reacts rapidly with SO₂ in ene reactions, giving the corresponding silyl sulfonates (see e.g., 34 + SO₂ → 36),

thus allowing no chance for the allylsilanes to react with intermediate zwitterions 84. When (–)-79 is substituted for the more electron-rich (*E,E*)-1-alkoxy-3-trialkylsilyloxy-penta-1,3-dienes (88), their reactions with 87 and SO₂ do not produce the desired products of C–C coupling between the dienes and allylsilanes. Apart from the ene reaction of SO₂ with allylsilanes 87, giving 89, dienes 88 react with SO₂, giving mixtures of sulfolenes 90 and silyl β-oxosulfonates 91, with the latter resulting from ene reactions of 88 with their enoxysilane moieties.



To suppress the latter ene reactions, the reactivity of 1-alkoxy-3-acyloxy-1,3-dienes toward **87** in SO₂ was explored. They were found to give products of C–C coupling. For instance, diene **92** reacts with **87d** in an excess of SO₂ and in the presence of the (CF₃SO₂)₂-NSiMe₃ catalyst, giving silyl sulfinate **93** as a unique product.⁵⁸



5. One-Pot, Four-Component Synthesis of Sulfones, Sulfonamides, and Sulfonic Esters

Organosulfones and sulfonamides are important compounds because of their chemical and biological properties.⁵⁹ Other electrophiles, EX, than MeI (e.g., allyl, methallyl, and arylmethyl bromides, BrCH₂COOEt,⁶⁰ alkyl iodides, and 2,4-dinitrofluorobenzene) combine with a large variety of 1-alkoxy- or 1-trialkylsilyloxy-1,3-diene **94**, SO₂, and enoxysilanes or allylsilanes **95**, thus realizing a combinatorial, one-pot, four-component synthesis of polyfunctional sulfones **97**. If the crude silyl sulfonates **96** are oxidized with Cl₂ or *N*-chlorosuccinimide (NCS), the corresponding sulfonyl chlorides **98** are formed that can be reacted *in situ* with primary or secondary amines to generate polyfunctional sulfonamides **99** or with alcohols to give the corresponding sulfonic esters **100** (Scheme 15).

We have shown that enoxysilanes and allylsilanes undergo ene reactions with SO₂. The silyl sulfonates thus obtained can be converted also into sulfones, sulfonamides, and sulfonic esters, thus realizing one-pot, three-component syntheses of these compounds.⁶¹

For the first time, new medium-size heterocyclic systems, such as (+)-**103**, have been prepared (Scheme 16). The reaction of **87c** with diene (–)-**101** [97% enantiomeric excess (ee)] in SO₂/toluene premixed with 0.3 equiv of Tf₂NSiMe₃ at –78 °C gives a single silyl sulfinate **102**. Starting with (+)-**101** and **87c** and by treatment of the intermediate silyl sulfinate (*ent*-**102**) with Pd(Ph₃P), the

2*H*-thiocene derivative (+)-**103** is obtained in 41% overall yield (Scheme 16).⁶²

6. Stereoselective Synthesis of (*E,Z*)- and (*E,E*)-2,4-Diene-1-ones. Synthesis of the C1–C11 Polyene Fragment of Apoptolidine

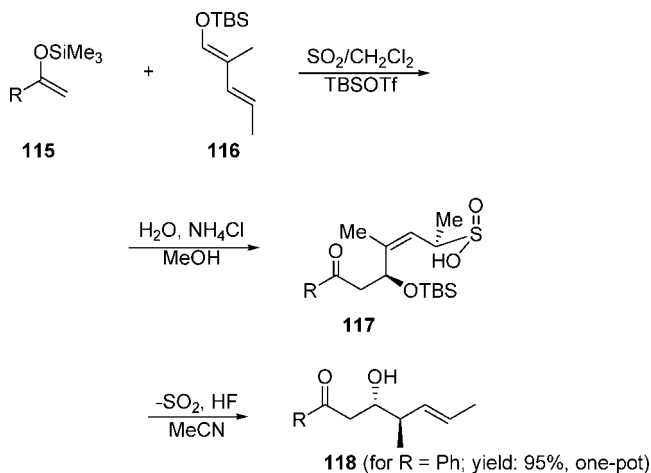
The oxo-sulfones of type **97** (Z = O; R* = R₃Si, Bn; X = H) eliminate R*OH readily under acidic conditions, giving (*E,Z*)-dienones (Scheme 17).

When the acid promoter HNTf₂ is used in a higher concentration (ca. 50% equiv) or when using TfOH (3%), the *s-trans* conformer of the 1-oxodiene **106** reacts with the activated SO₂ (SO₂H⁺), generating the zwitterionic intermediate **110** with an (*E*)-alkene moiety. The latter is then quenched by the enoxysilane **107**, leading to (*E,E*)-dienone **109** after desilylation, arylation with 1-fluoro-2,4-dinitrobenzene, and treatment with triflic acid (Scheme 18).⁶³

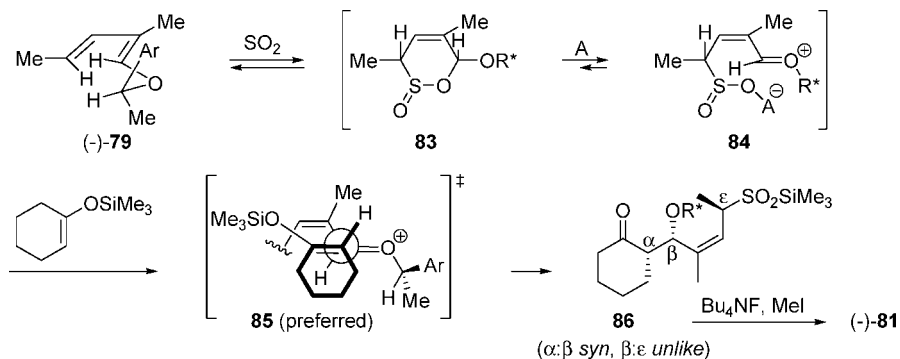
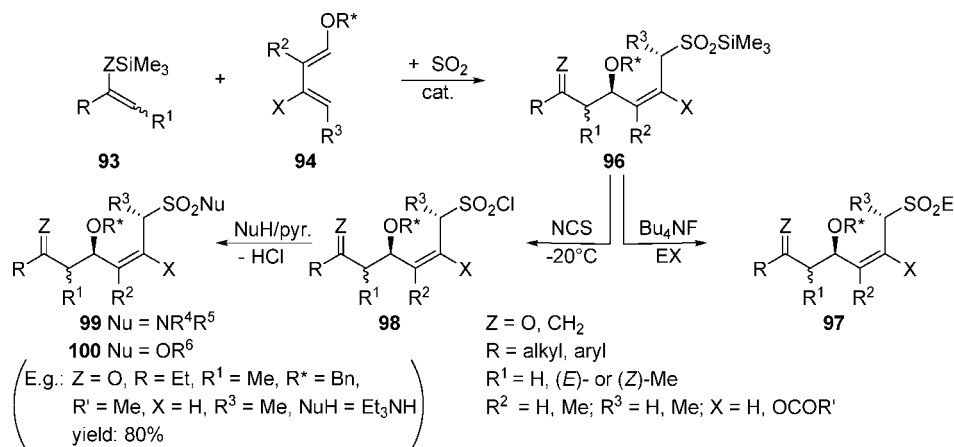
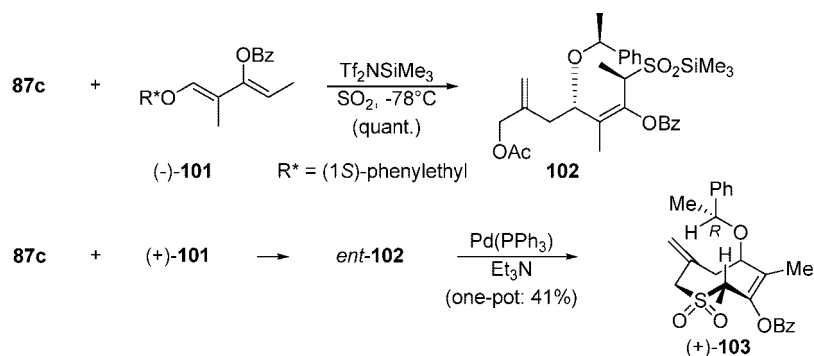
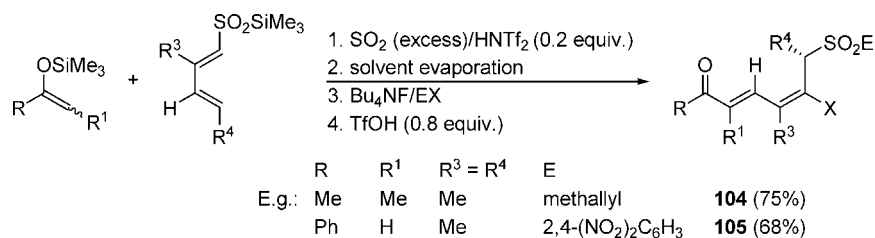
The usefulness of our one-pot synthesis of (*E,E*)-dienones is illustrated in Scheme 19 by a short synthesis⁶⁴ (requiring the isolation of only three synthetic intermediates) of Nicolaou's C₁–C₁₁ fragment of Apoptolidin,⁶⁵ a promising antitumor agent.⁶⁶

7. One-Pot Synthesis of Polypropionate Stereotriads: Total Asymmetric Syntheses of Natural Polyketide Antibiotics

The thermal desulfonylation of α-substituted β,γ-unsaturated sulfonic acids is stereoselective.^{67,68} This is also observed with **117** → **118** + SO₂.

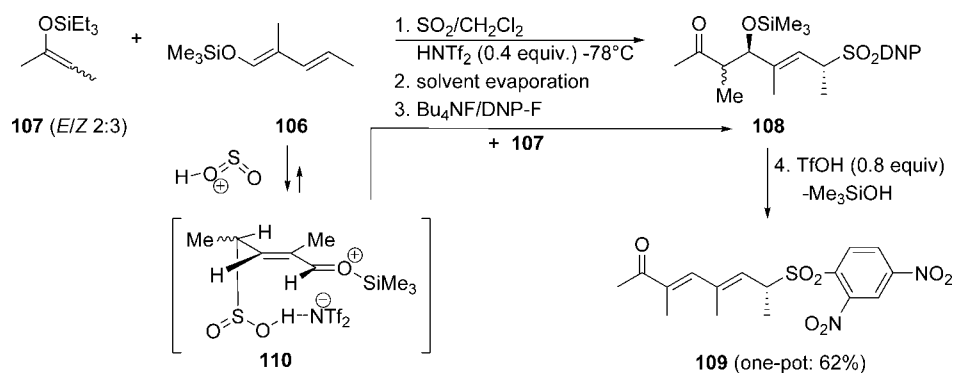
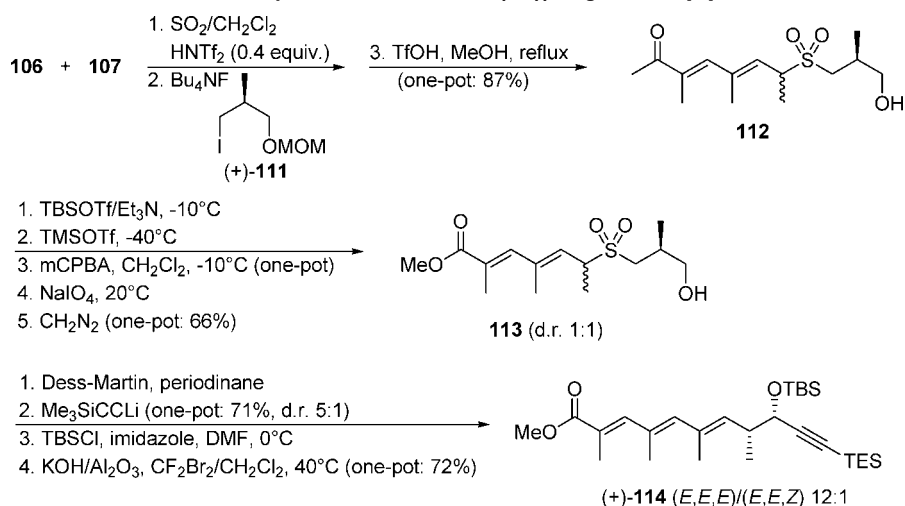


Because the desulfonylation of β,γ-unsaturated sulfonic acids requires acidic conditions (to form the sulfonic acids), it is often accompanied by elimination and/or retro-aldol reactions. Furthermore, sulfonic acids undergo disproportionation.⁶⁷ We have found that the silyl sulfinate intermediates of type **96** (Scheme 15) can be desilylated by the 1:1 Pd(OAc)₂/PPh₃ catalyst, liberating the corresponding β,γ-unsaturated sulfonic acids that undergo a palladium-catalyzed desulfonylation in the

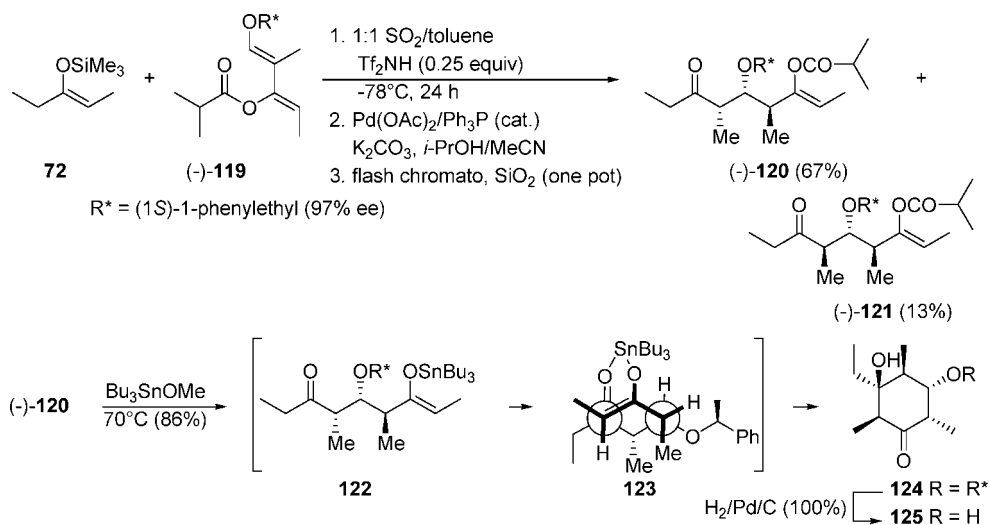
Scheme 14. Possible Interpretation of the Diastereoselectivity of the Reaction Cascade Hetero-Diels–Alder Addition, Zwitterion Formation, and Its Quenching by Enoxysilanes**Scheme 15. Combinatorial, One-Pot, Four-Component Syntheses of Sulfones, Sulfonamides, and Sulfonic Esters****Scheme 16. Syntheses of a Tetrahydro-2H-thiocene Derivative****Scheme 17. One-Pot Synthesis of (E,Z)-Dienones**

presence of K₂CO₃ and isopropanol with high yield and stereoselectivity.⁶⁹ The mechanism of the latter reaction is under investigation.

The usefulness of our one-pot polypropionate synthesis is demonstrated in the expeditious assemblies of the cyclohexanone unit **125** of baconipyrone A and B

Scheme 18. One-Pot Synthesis of (*E,E*)-DienonesScheme 19. Synthesis of Nicolaou's $\text{C}_1\text{--C}_{11}$ Fragment of Apoptolidin

Scheme 20. Three-Step Synthesis of the Cyclohexanone Subunit of Baconipyrones A and B

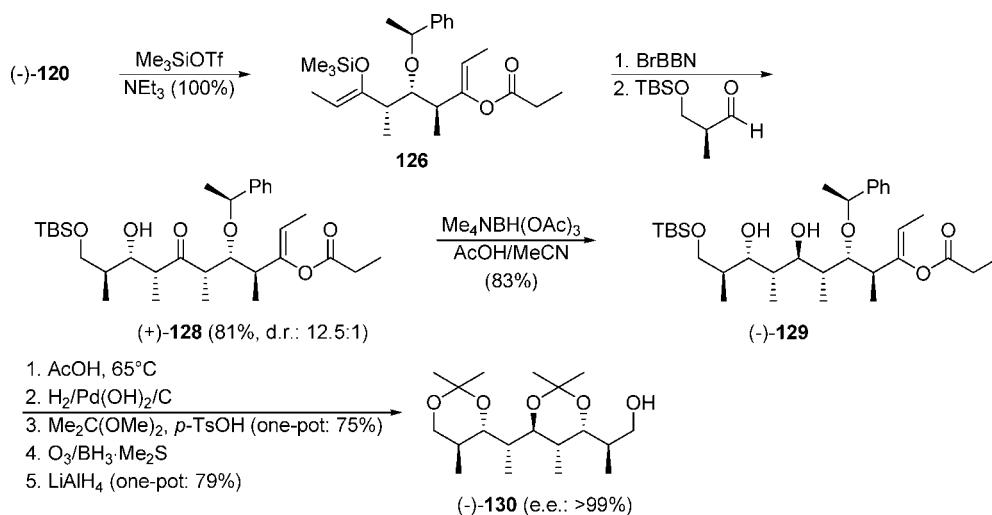


(Scheme 20)⁷⁰ and of a stereoheptad (-)-130 corresponding to the $\text{C}_{19}\text{--C}_{27}$ -ansa chain of Rifamycins (Scheme 21).⁷¹

Reaction of 72 and (-)-119 (97% ee) with SO_2 in toluene and Tf_2NH provides a silyl sulfinate. The residue is treated with the $\text{Pd}(\text{OAc})_2/\text{Ph}_3\text{P}$ catalyst in the presence of K_2CO_3 , isopropanol, and acetonitrile, providing pure stereotriads (-)-120 (67% yield) and (-)-121 (13%).

Treatment of (-)-120 with Bu_3SnOMe at 70°C promotes a highly stereoselective intramolecular aldol reaction, giving 124. Hydrogenolysis of 124 affords 125. In this case, inexpensive (1*S*)-1-phenylethanol is used as a chiral auxiliary to generate the starting diene (-)-119.

The silyl (*Z*)-enol ether 126 derived from (-)-120 reacts with 9-bromo-9-borabicyclo[3.3.1]nonane (Br-BBN) in CH_2Cl_2 (silyl/boron exchange) and then with

Scheme 21. Expedient Asymmetric Synthesis of C₁₉–C₂₇-ansa Chain of Rifamycins: Formal Total Synthesis of Rifamycin S

aldehyde (+)-127 to produce a 12.5:1 mixture of aldols (+)-128 and 9-epimer in 81% yield. Pure (+)-128 is reduced under Evans' conditions to give diol (-)-129 (83%), a stereoheptad equivalent to Kishi's intermediate (-)-130 of the asymmetric synthesis of Rifamycin S. The latter was derived from (-)-129 (does not have to be purified for the next step) as shown in Scheme 21. Thus, Kishi's advanced intermediate is obtained in 25% overall yield in eight steps starting from inexpensive diene (-)-119. The synthesis requires the isolation of only four synthetic intermediates.⁷¹ Application of our reaction cascade to the asymmetric synthesis of the polypropionate fragment of Apoptolidine is underway.⁷²

8. Conclusion

After 10 000 years of use as a food and beverage preservative and about 100 years in industrial applications, sulfur dioxide is just starting to show its potential in fine organic chemistry as a solvent, reagent, and catalyst. With the help of quantum calculations, little known reactions, such as the hetero-Diels–Alder of SO₂ and sulfonyl radical-induced alkene isomerization, have delivered some of their characteristics and opened new avenues to organic synthesis. Particularly interesting is the use of SO₂ as an Umpolung device, permitting the formation of C–C bonds between electron-rich dienes and alkenes. Before our studies, chemists looked down on SO₂ because it was just useful to induce polymerization of unsaturated hydrocarbons or produce polymers. Apart from its use as a sulfonylation agent of benzene derivatives and polar organometallic reagents, SO₂ had little applications in organic chemistry. A new reaction cascade combining enantiomerically enriched 1-(1-phenylethyl)oxy-1,3-dienes, enoxysilanes, or allylsilanes and SO₂ allows for the one-pot synthesis of enantiomerically pure polyfunctional sulfones, sulfonamides, and sulfonic esters, as well as polypropionate stereotriads that can be used without activation or transformation, in further C–C bond-forming reactions, thus realizing expeditious constructions of complicated natural products of biological interest and analogues. Our studies

have produced spin-offs, such as new chemoselective silylation agents that do not require basic media or acidic activation and new polysulfones that are solid catalysts for the chemoselective cleavage of methyl-substituted allyl ethers (new methods for the protection of alcohols and semiprotection of polyols).

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