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Palladium-Catalyzed Conversion of β,γ-Unsaturated Silyl Sulfinates into (*E*)-Alkenes: Asymmetric Synthesis of Polypropionate Fragments

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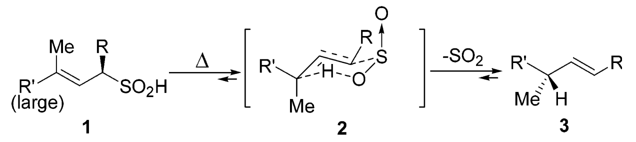
Received December 2, 2003

Abstract: At low temperature, 1-alkoxy-1,3-dienes add to sulfur dioxide activated by a Lewis or protic acid generating zwitterionic intermediates that can be quenched by enoxysilanes. The resulting β,γ-unsaturated silyl sulfinates can be desilylated by 1:1 $Pd(OAc)_2/PPh_3$ catalyst, liberating the corresponding β,γ-unsaturated sulfinic acids that undergo smooth and highly stereoselective retro-ene eliminations of sulfur dioxide. The method has been applied to generate enantiomerically pure polypropionate fragments.

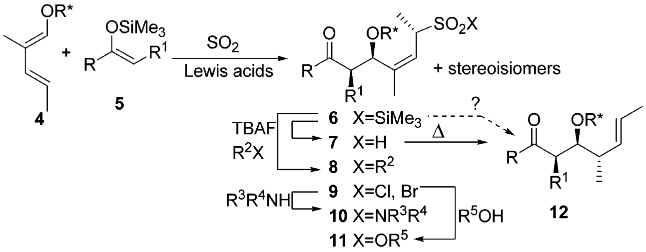
The thermal desulfitation of β,γ-unsaturated sulfinic acids is a useful reaction for the regio- and stereoselective synthesis of alkenes (Scheme 1)[1]. Starting with α-substituted sulfinic acids **1**, a concerted retro-ene reaction that leads to the elimination of SO_2 is assumed to be responsible for the chirality transfer of the α-carbon center to the γ-carbon center with formation of alkenes **3**. The stereoselectivity of the reaction is explained in terms of a chairlike transition state **2**[2] that places an optimal number of substituents in pseudoequatorial positions.[3]

In 1997, our group uncovered a new C−C bond-forming reaction that condenses butadien-1-yl ethers **4**, enoxysilanes **5,** and SO_2 to generate β,γ-unsaturated silyl sulfinates **6**. The mechanism of this process involves probably suprafacial hetero-Diels−Alder additions of SO_2 to dienes **4**, followed by acid-promoted ionizations into zwitterionic intermediates that react with the enoxysilanes **5** giving, after Me_3Si group transfer, the corresponding silyl sulfinates **6**.[4,5] The latter can be reacted with TBAF (Bu_4NF) and an electrophile to generate polyfunctional sulfones **8**[6] or be oxidized with Cl_2 (or *N*-chlorosuccinimide: NCS) or Br_2 (or *N*-bromosuccinimide: NBS) to generate intermediate sulfonyl halides **9** that react with nucleophiles such as amines and alcohols to provide libraries of sulfonamides **10** and sulfonic esters **11**, respectively, in one-pot operations.[7] Alternatively, acidic or basic hydrolysis of the silyl sulfinates **6** into the corresponding sulfinic acids **7** followed by thermal desulfitation allows the formation of the corresponding (*E*)-alkenes **12** (Scheme 2).[8] Unfortunately, the latter reaction sequence **6** → **7** → **12** is quite often low yielding and is accompanied by decomposition (e.g., alcohol elimination, retro-aldol, and polymerization). As our tandem oxyallylation ($\mathbf{4} + \mathbf{5} + SO_2 \rightarrow \mathbf{6}$), hydrolysis (**6** → **7**), and retro-ene elimination of SO_2 ($\mathbf{7} \rightarrow \mathbf{12} + SO_2$) realizes a one-pot synthesis of valuable polypropionate fragments constructing up to three contiguous stereogenic centers,[8] and since the latter can be obtained enantiomerically pure when starting with enantiomerically pure ethers **5**,[5] we have searched for better and reproducible conditions to convert our β,γ-unsaturated silyl sulfinates **6** into alkenes **12**.

SCHEME 1



SCHEME 2



We report here that such conditions are now available and rely on the palladium-catalyzed conversion of silyl sulfinates into the corresponding sulfinic acids.[9] The latter can then be desulfitated under mild conditions in acetonitrile/2-propanol as solvent without side reactions.

In one typical reaction, a 1:1.5 mixture of diene **13** and enoxysilane **14** in CH_2Cl_2 solution was added to a 1:1 (volume ratio) SO_2/CH_2Cl_2 solution of (t-Bu)Me_2SiOTf (0.2 equiv) cooled to −78 °C. After the solution was stirred for 12 h at this temperature, SO_2 and CH_2Cl_2 were evaporated under vacuum. The residue was taken by anhydrous acetonitrile/anhydrous 2-propanol (4:1). After

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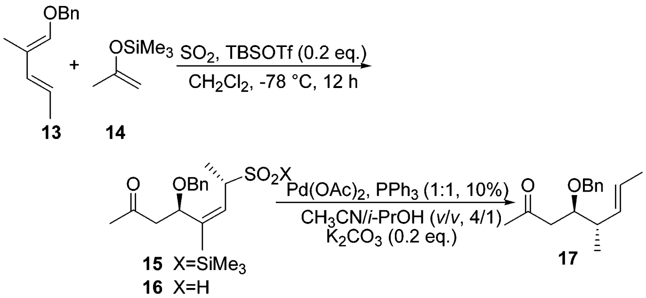
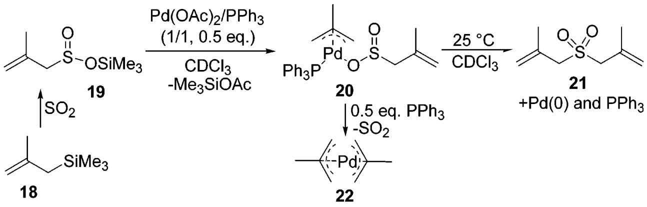
10.1021/jo0357622 CCC: $27.50

SCHEME 3



SCHEME 4

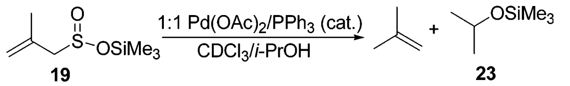


the addition of 1:1 $Pd(OAc)_2/PPh_3$ (0.1 equiv) and K_2CO_3 (0.2 equiv), the mixture was heated to 80 °C for 30 min. This converted silyl sulfinate **15** into alkene **17** in 72% yield (Scheme 3).

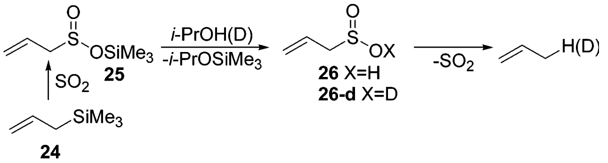
Further experiments showed that the reaction could not be realized by $Pd(OAc)_2$ alone or in CH_3CN alone. When a larger proportion of PPh_3 (2 equiv) vs $Pd(OAc)_2$ was used, the yield in **17** decreased dramatically to less than 10%. Thus, the 1:1 $Pd(OAc)_2/PPh_3$ ratio and *i*-PrOH are crucial for success. With the hope of understanding the role played by the 1:1 mixture of $Pd(OAc)_2/PPh_3$ and *i*-PrOH, we investigated the conversion of simpler β,γ-unsaturated silyl sulfinates under various conditions.

In the beginning, we used silyl sulfinate **19** obtained by ene reaction of SO_2 with trimethyl-2-methyl-prop-2-en-1-ylsilane **18**.[10] When 0.1−1 equiv of $Pd(OAc)_2$ was added to a solution of **19** in pure $CDCl_3$ or containing EtOH, no reaction occurred at 25 °C. Heating to 60 °C led to silicon/palladium transmetalation with formation of $AcOSiMe_3$. In contrast, adding a 1:1 mixture of $Pd(OAc)_2/PPh_3$ to the above solution induced a rapid reaction at 25 °C with formation of the palladium complex **21**. Its structure was proved by its ^1H NMR spectrum and by comparison with data from related η^3-allylpalladium complexes.[11] Using 0.5 equiv of $Pd(OAc)_2$ and PPh_3, **19** was completely converted into **20** in a few seconds. On standing at 25 °C, **20** was then converted in a few hours into sulfone **21**.[12] In another experiment, when using 1 equiv of $Pd(OAc)_2$ and 1 equiv of PPh_3, complex **20** was converted into bis(η^3-allyl)palladium complex **22** (1−2 h at 25 °C)[13](Scheme 4). Surprisingly, when using a 1:2 mixture of $Pd(OAc)_2/PPh_3$, no transmetalation occurred because of the formation of stable $Pd(PPh_3)_2(OAc)_2$ complex.

SCHEME 5



SCHEME 6



These experiments demonstrated that 1:1 $Pd(OAc)_2/PPh_3$ is able to cleave the Si−O bond of silyl sulfinates. In the presence of 2-propanol, a catalytic amount of 1:1 $Pd(OAc)_2/PPh_3$ (1−10% equiv) catalyzed the conversion of **19** into isobutylene and isopropyloxytrimethylsilane (**23**). The reaction was over in a few seconds at 25 °C (Scheme 5).

For kinetic studies, we synthesized sulfinate **25**, derived from the ene reaction of allyltrimethylsilane (**24**) with SO_2 (Scheme 6).[10] It was reported that the deuterium kinetic isotopic effect for the desulfitation of prop-2-enesulfinic acid (**26**) (k_H) and its O-deuterated analogue **26**-*d* (k_D) in $CDCl_3$ amounts to $k_H/k_D = 2.5 \pm 0.1$ at 25 °C, which confirms the hypothesis of a concerted retro-ene elimination mechanism with a cyclic transition state in which hydrogen is transferred from the sulfinic group to the carbon center C(3) (See **2**, Scheme 1).[2] If the palladium complex used in the reaction **25** → propene + SO_2 + *i*-$PrOSiMe_3$ does not intervene in the desulfitation of the sulfinic acid intermediate **26**, a similar kinetic deuterium isotopic effect k_H/k_D should be found. On the contrary, if the palladium complex should intervene by changing the mechanism of the desulfitation, different values of k_H/k_D should be observed. The kinetics for the reaction **25** → propene + SO_2 + *i*-$PrOSiMe_3$ in the presence of 1:1 $Pd(OAc)_2/PPh_3$ (0.1 equiv) were followed by ^1H NMR and showed $k_H/k_D = 2.2 \pm 0.2$ at 25 °C in $CDCl_3$. Thus, the palladium complex promotes the clean reaction **25** → propene + SO_2 + *i*-$PrOSiMe_3$ by catalyzing the Si−O bond cleavage, not by changing the mechanism of desulfitation. When CD_3CN was used as solvent, the kinetic isotope effect (k_H/k_D) for the desulfitation of **25** increased to 6.9 ± 0.2 at 25 °C.[14] This effect was not affected by addition of 1:1 $Pd(OAc)_2/PPh_3$ (0.1 equiv), which proved again that the palladium species does not

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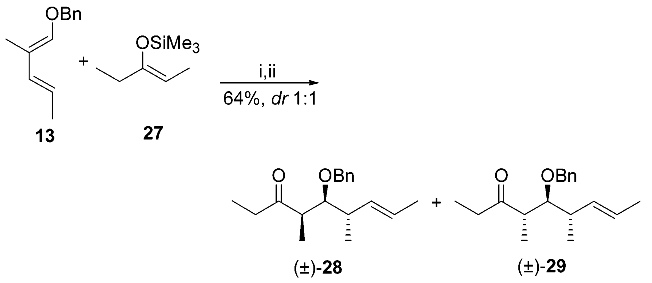
SCHEME 7



(i) $SO_2/CH_2Cl_2/(CF_3SO_2)_2NH$, -78 °C, 15 h;
(ii) evaporation from -78 °C to room temp., CH_3CN, $Pd(OAc)_2/PPh_3$(1:1) (10%), K_2CO_3/*i*-PrOH, 80°C, 30 min.

get involved into the retro-ene elimination of SO_2. It was also found that the desilylation and desulfitation of **25** in 1:5 *i*-PrOH/CD_3CN was twice as fast as in 1:5 *i*-PrOH/$CDCl_3$ at 25 °C.

We then turned to reaction **13** + **14** → **17** (Scheme 3) and confirmed that the role of $Pd(OAc)_2/PPh_3$ is to accelerate the desilylation of the intermediate silyl sulfinate **15** to give the sulfinic acid **16** without decomposition at low temperature. The reaction was over in a few seconds at −40 °C in CD_3CN containing a large excess of *i*-PrOH. However the sulfinic acid **16** was rather stable even at room temperature. Heating to 40 °C was required for desulfitation. The kinetics was followed by ^1H NMR at 40 °C, and it was found that the reaction in the presence of palladium species was 1.3 times faster than without catalyst.

The potential of our palladium-catalyzed reaction was evaluated first with the reaction shown in Scheme 7. Starting from achiral diene **13** and enoxysilane **27**, the oxyallylation/desilylation/retro-ene reaction sequence afforded a ∼1:1 diastereomeric mixture of (±)-**28** and (±)-**29** in 64% yield. When acidic conditions were applied to hydrolyze the silyl sulfinates intermediates,[8] no trace of polypropionates **28** and **29** could be detected and only products of decomposition were seen.[15]

We then turned to an asymmetric version of our oxyallylation/desilylation/retro-ene cascade. Under the same reaction conditions, two enantiomerically enriched dienes (−)-**30** (ee 97%) and (+)-**38** (ee 99%) were coupled with several enoxysilanes (Scheme 8). The results are shown in Table 1.

TABLE 1. Diastereoselectivities, Yields, and Enantiomeric Excesses of the Major Diastereomers Resulting from Oxyallylation/Desilylation/Retro-Ene Cascades

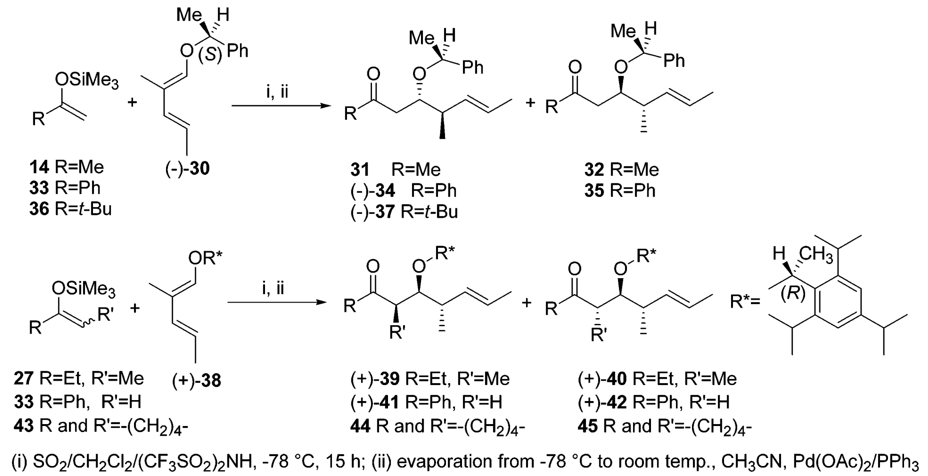
entry	diene	enoxysilane	products	dr[c]	yield (%)	ee (%) of the major diastereomer[e]
1	(−)-**30**[a]	14	**31**/**32**	5:1	66	nd
2	(−)-**30**	33	**34**/**35**	5:1	70 (0)[d]	94
3	(−)-**30**	36	**37**	20:1	71	92
4	(+)-**38**[b]	27	**39**/**40**	5:1	85	91
5	(+)-**38**	33	**41**/**42**	3:1	77 (30)[d]	99
6	(+)-**38**	43	**44**/**45**	7:1	66 (13)[d]	95

[a] ee = 97%. [b] ee = 99% by chiral HPLC. [c] The dr was established from ^1H NMR spectra of the crude product mixtures. [d] The yields given in parentheses were obtained[16] for desulfitations under acidic hydrolysis conditions.[8] [e] The enantiomeric excesses for the major diastereomers were determined by the Mosher's method applied to the corresponding alcohols obtained by treatment with CF_3COOH.

For the reaction of diene (+)-**38**[5b] bearing Green's (*R*)-chiral auxiliary[17] with enoxysilane **27** a 5:1 mixture of diastereomeric product (+)-**41** and (+)-**42** was obtained and was separated by flash chromatography in 70% and 15% yield, respectively. Under acidic hydrolysis conditions only products resulting from retro-aldol reactions were observed.[16] A significant increase of the yields was also found in the syntheses of diastereomeric mixtures of **41**/**42** and **44**/**45** (Table 1). Therefore, our method has a better compatibility with different kinds of dienes and enoxysilanes.

This work establishes that good diastereoselectivity and yields can be realized for the cascade hetero-Diels−Alder addition of SO_2 to penta-2,4-dien-1-yl ethers, ionization of the intermediate sultines into zwitterions,[5b] their electrophilic addition to enoxysilanes, desilylation of the intermediate silyl sulfinate, and retro-ene elimination of SO_2 when the silyl sulfinate desilylation is catalyzed by $Pd(OAc)_2/PPh_3$. This opens a new approach to the asymmetric synthesis of polyketide and polypropionate fragments using readily available readily available 1-oxydienes bearing inexpensive chiral auxiliaries ((*R*)- or (*S*)-1-phenylethanol, Greene's alcohols[17]).

SCHEME 8



(i) $SO_2/CH_2Cl_2/(CF_3SO_2)_2NH$, -78 °C, 15 h; (ii) evaporation from -78 °C to room temp., CH_3CN, $Pd(OAc)_2/PPh_3$ (1:1, 10%), K_2CO_3/*i*PrOH, 80 °C, 30 min.

Acknowledgment. We are grateful to the Swiss National Science Foundation and the Office Fédéral de l'Enseignement et de la Science (Bern, European COST D 13/0010/01 and COST D 28/004/02 actions) for financial support. We thank also Mr. Martial Rey, Francisco Sepulveda, and Srinivas Reddy Dubbaka for technical help.

Supporting Information Available: Detailed ^{1}H and ^{13}C NMR spectra and signal assignments, IR and MS spectra of all described compounds, kinetic studies, enantiomeric excess determination, and determination of relative configurations. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0357622