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Communications

Geminal Alkylation: Substitutions of Allyl Sulfones. Regiocontrol via Molybdenum Catalysis

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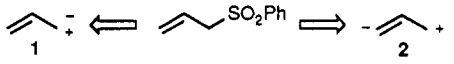
Summary: Base-catalyzed geminal alkylation of allyl sulfones combined with the ability of molybdenum to direct nucleophilic substitution of the sulfone converts allyl sulfones into 1,1- and 1,3-dipole synthons.

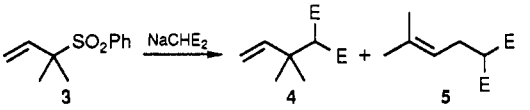
The ability of a sulfone group to stabilize an α-carbanion which can then react with electrophilic reagents has long been utilized in organic synthesis.[1] However, the use of sulfones as electrophilic partners to replace the C–S bond with a C–C bond in a direct intermolecular displacement with simple nucleophiles was virtually unknown until recently.[2] Such a displacement allows allyl sulfones to function as either 1,1-dipoles (1) or 1,3-dipoles (2).



1 2

While Lewis acids[3] are effective for the substitution, the desire to perform such reactions under neutral or basic conditions led us to explore transition-metal catalysis.[4] The ability of molybdenum catalysts to complement the regioselectivity exhibited by palladium catalysts suggested that geminal alkylation followed by molybdenum-catalyzed[5] substitution may be an effective approach to create quaternary carbon centers. Although the lower reactivity of molybdenum and its thiophilic properties[6,7] might endanger such a proposal, we report herein on the successful application of molybdenum catalysis in substitution reactions of allyl sulfones and selective formation of quaternary carbon centers.

Use of sulfone **3** as substrate allows us to test reaction feasibility and regioselectivity. Reaction of **3** with the sodium salt of dimethyl malonate and 20 mol % molybdenum hexacarbonyl catalyst in refluxing toluene provided alkylation products **4** and **5** (eq 1). In contrast to the poor selectivity of the palladium-catalyzed[4e] and nickel-catalyzed[4d] reactions, the molybdenum-catalyzed reaction was selective for alkylation at the more substituted allylic site, thereby creating a quaternary carbon center (9:1).



3 4 5 (1)

$Mo(CO)_6$–PhMe	90	:	10	61%
$Pd(PPh_3)_4$–THF	68	:	32	67%
$Ni(dppe)_2$–THF	39	:	61	92%

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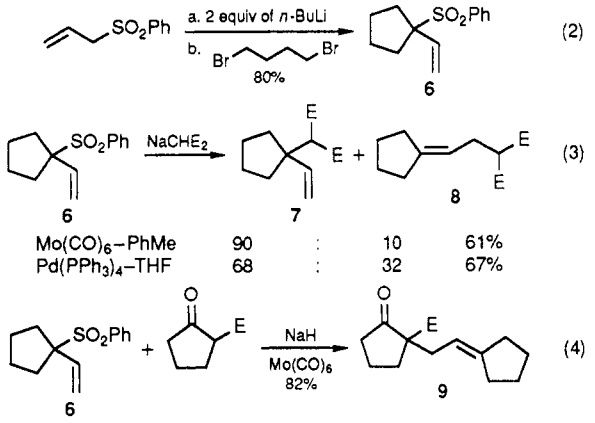
(6) *Aspects of Molybdenum and Related Chemistry*; Springer-Verlag: Berlin, 1978.

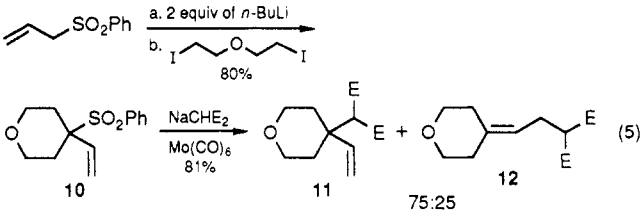
(7) During the course of our studies, the use of stoichiometric molybdenum hexacarbonyl for the alkylation of allyl sulfides was reported. Masuyama, Y.; Yamoda, K.; Kurusu, Y. *Tetrahedron Lett.* **1987**, *28*, 443.

0022-3263/90/1955-1127$02.50/0

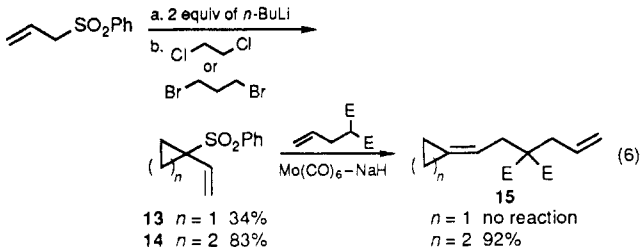
Cyclopentyl sulfone **6**,[8] readily available by cycloalkylation[9] of the 1,1-dianion[10] derived from allyl phenyl sulfone (eq 2), reacts under the same conditions to provide a mixture of products where the major isomer (9:1) results from alkylation at the most substituted carbon atom (eq 3). Again, the palladium-catalyzed reaction exhibits poorer regioselectivity but interestingly still favoring the more substituted terminus. Using the more sterically demanding nucleophile 2-carbomethoxycyclopentanone, the molybdenum-catalyzed reaction reverts to steric control of regioselectivity and keto ester **9** is the sole product (eq 4).



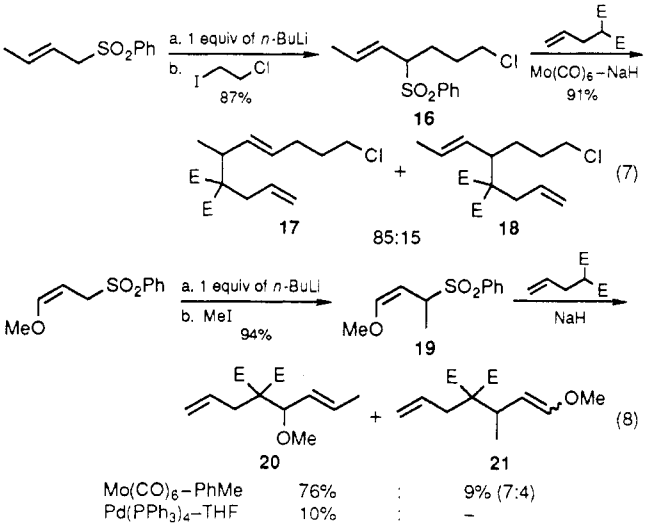
The subtle effect of a remote electronegative atom is seen in the alkylation of sulfone **10** (eq 5). Here the electronic bias for alkylation at the tertiary site due to stabilization of positive charge in an intermediate π-allylmolybdenum complex is reduced by the β-oxygen, thus increasing primary attack by the nucleophile.



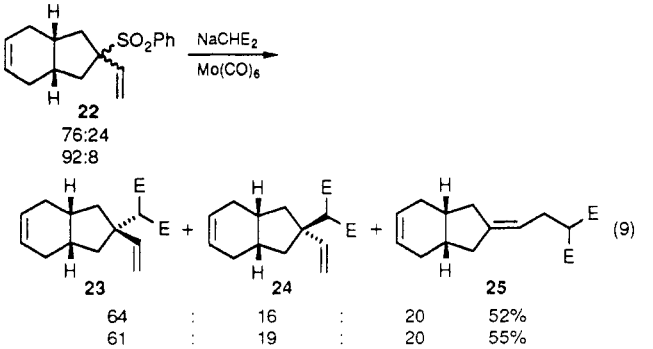
The cycloalkylation/sulfone displacement methodology can also be extended to cyclobutanes (eq 6), but the metal-catalyzed substitution in the cyclopropyl series fails. This is consistent with the reported inertness of cyclopropyl tosylates toward solvolysis.[11] Note that using a substituted malonate, the regioselectivity in eq 6 was 100% primary alkylation.



Sulfone substrates **16** and **19** were designed to test both the regioselectivity and chemoselectivity of the reaction (eqs 7 and 8). The question of regioselectivity was more subtle here, since in each case both possible alkylation sites are secondary. The regiochemistry exhibited in eq 8 is excellent, considering the small degree of steric differentiation between methyl and chloropropyl groups.[12] The chemoselectivity is also high; no competing alkylation of the alkyl chloride moiety was observed. The reaction in eq 8 also illustrates the selectivities obtainable in the molybdenum-catalyzed reaction. Although the steric sizes of the methyl and methoxy substituents on the allyl system (A values of 1.70 and 0.60, respectively) may influence the regioselectivity, the electronic stabilization imparted by a methoxy substituent on a center bearing positive charge is likely to be the controlling factor. The starting material and product demonstrate the compatibility of vinyl and allyl ethers to the reaction conditions. There was complete trans stereoselectivity in olefin geometry for the major regioisomer in both instances, which is in accord with the results of molybdenum-catalyzed reactions of allyl acetates.[5]



The stereochemistry of reaction was analyzed using bicyclic sulfone **22** (eq 9).[13] Alkylation was found to be independent of the isomeric composition of **22**, indicating a stereoselective, not stereospecific, reaction. Again, this is expected from our previous reports, but in this example there is an added bonus. Due to the templating ability of molybdenum, diastereomerization of the intermediate π-allyl complexes must be occurring, thus placing molybdenum on the least hindered exo face and directing nucleophilic attack to the endo face providing the contrasteric product **23**.



(8) All new compounds have been fully characterized spectroscopically. Elemental composition has been established by combustion analysis and/or high mass spectroscopy.

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(11) Roberts, J. D.; Chambers, V. C. *J. Am. Chem. Soc.* **1951**, *73*, 5034.

(12) Cf.: Keinan, E.; Sahai, M. *J. Chem. Soc., Chem. Commun.* **1984**, 648.

(13) Sulfone **22** was an epimeric mixture where the predominate isomer contained an endo sulfone moiety. See ref 10.

While these results demonstrate the potential of allyl sulfones as substrates in molybdenum-catalyzed allylic alkylations, it should be noted that they do have diminished reactivity compared to the corresponding allyl acetates. Agents which coordinate to molybdenum, such as acetonitrile or dioxane solvent and BSA[14] base, inhibit reaction. There is also a significant S_N1 component to the reaction. Tertiary sulfones react faster than the corresponding primary sulfones. Thus, the sulfone isomeric to **3**, prenyl phenyl sulfone, required 4 times as long to produce the same products. The regiochemistry exhibited here is best analyzed as a delicate balance between steric and electronic factors. Sterically demanding nucleophiles attack the intermediate π-allylmolybdenum complex at the least substituted position. Small nucleophiles such as dimethyl malonate, however, react under electronic control and attack at the site of greatest electron deficiency, which is the more substituted allylic terminus. Thus molybdenum catalysis can provide a unique entry into systems containing a quaternary carbon center.

(14) BSA = *O,N*-bis(trimethylsilyl)acetamide.

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Registry No. **3**, 72863-20-8; **4**, 74866-35-6; **5**, 43219-18-7; **6**, 97072-44-1; **7**, 124535-79-1; **8**, 124535-80-4; **9**, 124535-81-5; **10**, 124535-82-6; **11**, 124535-83-7; **12**, 124535-84-8; **13**, 97072-36-1; **14**, 97072-43-0; **15** (n = 2), 124535-85-9; **16**, 124535-86-0; **17**, 124535-87-1; **18**, 124535-88-2; **19**, 124535-89-3; **20**, 124535-90-6; **21**, 124535-91-7; **22** (isomer 1), 124561-56-4; **22**, 97072-38-3; **23**, 124535-92-8; **24**, 124535-93-9; **25**, 124535-94-0; $NaCH(CO_2Me)_2$, 18424-76-5; $Mo(CO)_6$, 13939-06-5; $H_2C{=}CHCH_2SO_2Ph$, 16212-05-8; $Br(CH_2)_4Br$, 110-52-1; $Pd(PPh_3)_4$, 14221-01-3; $I(CH_2)_2O(CH_2)_2I$, 34270-90-1; $Cl(CH_2)_2Cl$, 107-06-2; $Br(CH_2)_3Br$, 109-64-8; $H_2C{=}CHCH(CO_2Me)_2$, 40637-56-7; (*E*)-$CH_3CH{=}CHCH_2SO_2Ph$, 72863-24-2; (*Z*)-$MeOCH{=}CHCH_2SO_2Ph$, 124535-95-1; $I(CH_2)_3Cl$, 6940-76-7; 2-(carbomethoxy)cyclopentanone, 10472-24-9.

Supplementary Material Available: Characterization data for **6**, **7**, **9**–**14**, **16**, **17**, **20**, **23**–**25** and sample procedure for alkylation (3 pages). Ordering information is given on any current masthead page.

Synthesis of 16-Membered Macrolide Aglycons, Carbonolide A, Leuconolides, and Maridonolides, via Carbonolide B Type Compounds by Virtue of Completely Stereoselective Epoxidation and Reduction Based on the Conformational Control of Macrolide Rings with Protecting Groups[1]

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Summary: Carbonolide B type compounds were converted to seven typical 16-membered macrolide aglycons, carbonolide A, EOP aglycon, leuconolide A_1 and A_3, midecanolide A_1, and maridonolide II and I, by virtue of completely stereoselective epoxidation and/or reduction based on the conformational control of macrolide rings with protecting groups. NOE and NOESY measurements and MMP2-CONFLEX2 calculations were employed to predict the conformation of the carbonolide B type compounds.

The 16-membered aglycons of the largest group of macrolide antibiotics represented by carbomycins, leucomycins, and maridomycins are classified into four types, **1**, **2**, **3**, and **4**, according to their oxidation levels[2] and, except for **1**, most of these remain unsynthesized.[3] We recently reported the stereoselective total synthesis of typical macrolide aglycons[4] by virtue of the MPM (methoxyphenylmethyl) protection of hydroxy functions[5] and some stereocontrolled reactions in acyclic systems. This methodology, together with stereoselective epoxidation and reduction on 16-membered lactone rings,[6] is now extended to the first completely stereoselective synthesis of 16-membered macrolide aglycons: carbonolide A (**2b**),[8] leuconolide A_1 (**3a**)[9] and A_3 (josanolide) (**3b**),[10] midecanolide

[†] Faculty of Pharmaceutical Sciences.

[‡] Faculty of Sciences.

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