ORGANIC LETTERS

2006
Vol. 8, No. 25
5689−5692

A Highly Selective Synthesis of Dialkenyl Sulfones via Cross-Metathesis of Divinyl Sulfone

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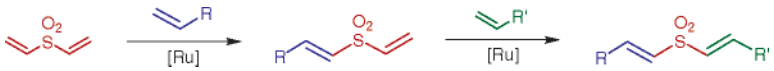
Received August 10, 2006

ABSTRACT



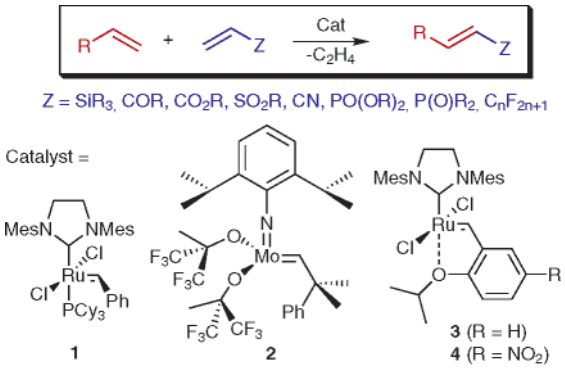
Catalytic cross-metathesis of commercial divinyl sulfone allowed direct access to novel (*E*)-alkenylvinyl sulfones and (*E*,*E*)-dialkenyl sulfones with excellent stereoselectivity. These compounds are useful building blocks, e.g., in the synthesis of substituted thiomorpholine 1,1-dioxide derivatives.

Functionalized olefins are important building blocks for organic synthesis. Catalytic olefin cross-metathesis (CM) is a convenient route to functionalized olefins from simple alkene precursors.[1]

One of the most appealing facets of this transformation is that a carbon−carbon double bond of one of the cross-metathesis partners can be substituted by a heteroatom-containing or electron-withdrawing group Z (Scheme 1).[1,2] With the advent of highly active catalysts **1**−**4**,[3,4] the range of electron-deficient olefins that participate in CM now include α,β-unsaturated carbonyl-containing olefins,[1,2] acrylonitrile,[5] vinylphosphonates,[6] vinyl phosphine oxides,[7,8] functionalized styrenes,[1d] vinylazulenes,[9] and perfluorinated alkane-containing olefins.[10] Therefore, CM complements other C−C coupling methods, such as Wittig, Horner−Wadsworth−Emmons, or Heck reactions.[1d]

Recently, we have found that phenyl vinyl sulfone gave good yields of cross-metathesis products with a variety of

Scheme 1. Catalytic Cross-Metathesis of Functionalized Olefins[a]



[a] Cy = cyclohexyl; Mes = 2,4,6-trimethylphenyl.

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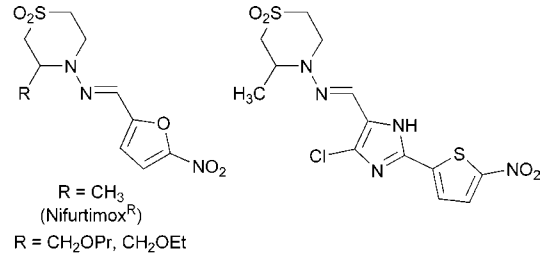
(4) Catalysts **1**−**3** are commercially available from Aldrich Chemical Co. and Strem Chemicals.

10.1021/ol061991+ CCC: $33.50
Published on Web 11/08/2006

terminal olefins in the presence of **1** and **4**.[11,12] This transformation was later successfully applied in stereoselective syntheses of natural products.[13]

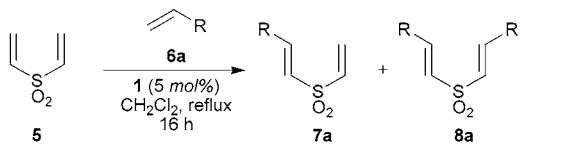
The commercially available divinyl sulfone **5** and its mono- and disubstituted derivatives are useful starting materials in the preparation of thiomorpholine 1,1-dioxides and other synthetically important macro- and heterocycles.[14] For example, introduction of a substituted thiomorpholine 1,1-dioxide fragment to the side chain of a pharmaceuticaly important compound is known to modify its physicochemical parameters affecting drug absorption, such as solubility or partition coefficient.[15] Two examples of thiomorpholine 1,1-dioxide-containing compounds of pharmaceutical interest are shown in Scheme 2.[16]

Scheme 2. Selected Examples of Biologically Active Thiomorpholine 1,1-Dioxide-Containing Compounds



On the basis of the results of our previous investigation,[11] we presumed that divinyl sulfone can be used as a substrate for a catalytic CM, producing hitherto unavailable unsymmetrically substituted products **7** (Scheme 3). Herein we present a detailed report on this transformation.

Scheme 3. Optimization of CM Reaction of Divinyl Sulfone **5** with Alkene **6a**



R = $(CH_2)_9CH_3$

entry	ratio **5 : 6a**	ratio **7a : 8a : 9a** [a]
1	1 : 1	74 : 20 : 6
2	1 : 3	41 : 22 : 37
3	3 : 1	82 : 7 : 11

[a] GC ratio.

After the exploration of a variety of reaction conditions to optimize the metathesis of sulfone **5** with 1-decene **6a**, we found that the best "monosubstituted" product selectivity was obtained using 1 equiv of the olefinic partner **6a** and 3 equiv of the diene **5** in DCM (0.02 M) under reflux in the presence of 5 mol % of catalyst **1** (Scheme 3, entry 3). Under these conditions, the formation of undesired disubstituted product **8a** and the "homodimer" **9a** was minimized. In line with the previous results with phenyl vinyl sulfone,[11] the CM of divinyl sulfone was highly stereoselective leading to (*E*)-**7a**,**b** as sole stereoisomers. The homo CM of divinyl sulfone **5** was not observed under these conditions, and this compound should therefore be classified as a pure type III substrate.[18]

In order to prove the general applicability of this reaction, we decided to extend this investigation to a more diverse set of olefinic partners **6**. All reactions were carried out in DCM under reflux in the presence of 5 mol % of **1**. Under these conditions, most of the olefins afforded the expected monosubstituted divinyl sulfones (*E*)-**7** in good isolated

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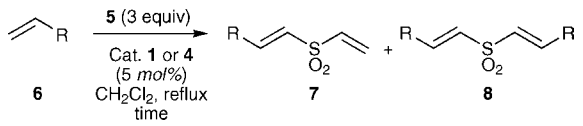
(18) For the definition of olefins types I−IV, see ref 2.

yields (51−84%; Table 1, entries 1, 3−8, and 10).[19] In some cases, we also observed the formation of smaller amounts of the undesired disubstituted products **8** (9−31%). In the case of **8b,e−g** and **8i** we were able to isolate and fully characterize them.

Table 1. Cross-Metathesis between Divinyl Sulfone **5** (3 equiv) and Alkenes **6b−i** (1 equiv)



entry	**6b−i**, R	cat.	time (h)	**7**[a] (%)	**8**[a] (%)
1	**6b**, $-CH_2Ph$	**1**	24	84	9
2	**6c**, $-(CH_2)_4CH_3$	**1**	20	42	
3	**6c**	**4**	20	51	
4	**6d**, $-(CH_2)_{16}CH_3$	**1**	21	59	
5	**6d**	**4**	17	70	
6	**6e**, $-(CH_2)_4OTBS$	**1**	16	69	13
7	**6f**, $-(CH_2)_9OH$	**1**	24	71	12
8	**6g**, $-(CH_2)_8Br$	**4**	22	72	19
9	**6h**, $-(CH_2)_4Br$	**4**	20	36	
10	**6i**, $-CH_2Si(CH_3)_3$	**1**	24	66	31

[a] Isolated yields of analytically pure products. Reaction conditions: catalyst **1**, **4** (5 mol %), dichloromethane, reflux.

It is well-established that Hoveyda−Grubbs catalyst **3** displays in some cases higher reactivity toward electron-deficient substrates.[1a,3a] Therefore, we decided to include the highly active carbene **4**, recently introduced by our group,[17] in this investigation. Catalyst **4** proved to be slightly more active in this transformation; however, the increase of activity over **1** was not as visible as in the case of methacrylonitrile[17a] or vinyl phosphine oxides.[7b] For example, the application of **4** instead of **1** in CM of **5** with 1-heptene **6c** allowed us to increase the yield from 42 to 51% and, for CM of **6d**, from 59 to 70% (Table 1, entries 2−5).

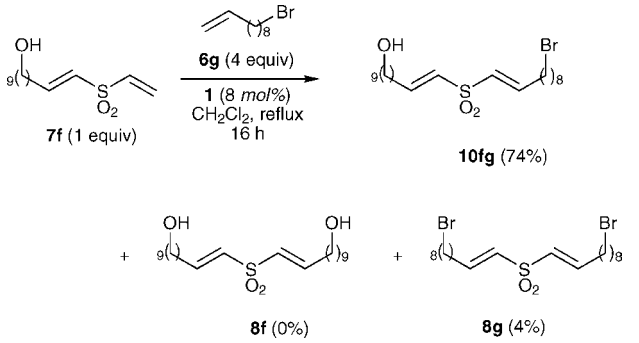
The CM of olefins **6a−i** and divinyl sulfone was in all cases fully stereoselective in favor of the (*E*)-isomer. Dimerization products **9a−i** of the terminal olefin **6** were also observed in minute amounts. These undesired byproducts can be easily separated by column chromatography, while the excess of **5** can be conveniently removed in vacuo and recycled, rendering this method useful from a practical point of view.

Next, we focused on the possibility of preparing the "unsymmetrically disubstituted" sulfones **10** by means of CM. Since the metathesis reaction is in general reversible, we considered that scrambling (the undesired rearrangement of substituents around the C−C double bonds of divinyl sulfone) can be a serious problem in this case.

(19) **Representative Procedure for CM between Divinyl Sulfone 5 and Alkene 6.** To a mixture of alkene (2.0 mmol) and divinyl sulfone (6.0 mmol) in CH_2Cl_2 (dry and distilled under Ar) (100 mL, $c = 0.02$ M) was added Ru catalyst **1** or **4** as a solid (5 mol %). The resulting mixture was stirred at reflux for 16−24 h under Ar. The solvent was removed under reduced pressure. The crude product was purified by flash chromatography using *c*-hexane/ethyl acetate as eluent (Merck silica gel 60, 230−400 mesh).

The crude mixture of the reaction between **7f** and 4 equiv of **6g** revealed the formation of two products identified as compounds **10fg** and **8g** in addition to homodimer **9g** and small amounts of unreacted **6g** and **7f** (Scheme 4). Interest-

Scheme 4. Scrambling during the CM Reaction of Divinyl Sulfone **7f** with Olefin **6g**[a]



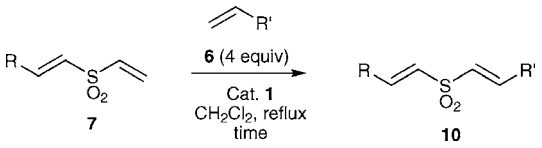
[a] Isolated yields. "Homometathesis" product **9g** not shown.

ingly, **8f** was not detected in the reaction mixture. All of these side products were separated from the desired desymmetrized **10fg** by silica gel chromatography. The formation of compound **8g** suggests that substitution one of the double bond with an alkyl chain was not sufficient to prevent its participation in CM. The presence of minor quantities of the scrambled product demonstrates that alkene group exchange is possible under these conditions, althought in a very limited extent.

As can be seen from the results compiled in Table 2, various *unsymmetrically disubstituted*[20] divinyl sulfones (*E*,*E*)-**10** can be obtained in good yield and excellent stereoselectivity (entries 1−4) under these conditions.

The presence of two double bonds in the products **7**, **8**, and **10** can be used for further functionalization.[21] In this paper, we present some representative results on the bis-

Table 2. Cross-Metathesis between Monosubstituted Divinyl Sulfones **7** (1 equiv) and Olefins **6** (4 equiv)



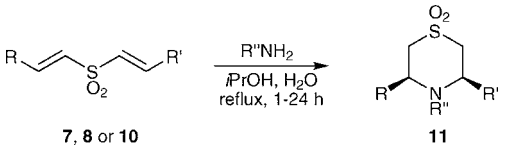
entry	**7**, R	**6**, R′	cat. (mol %), time (h)	**10** (yield)[a]
1	**7f**, $-(CH_2)_9OH$	**6g**, $-(CH_2)_8Br$	**1** (8), 44	**10fg** (74)
2	**7d**, $-(CH_2)_{16}CH_3$	**6b**, $-CH_2Ph$	**1** (20), 24	**10db** (54)
3	**7e**, $-(CH_2)_4OTBS$	**6c**, $-(CH_2)_4CH_3$	**1** (10), 23	**10ec** (85)
4	**7b**, $-CH_2Ph$	**6j**, $-CH_2C_6H_4Br$-*p*	**1** (8), 44	**10bj** (74)

[a] Isolated yields of analytically pure products. "Homodimerization" products **9** not shown.

heteronucleophilic Michael addition under the previously optimized conditions,[14] leading to new thiomorpholine 1,1-dioxide derivatives **11** (Table 3).

This study revealed that CM technology gives easy access to synthetically useful desymmetrized mono- or disubstituted divinyl sulfones with excellent (*E*)-selectivity under mild conditions. Given the synthetic potential of sulfones as both Michael acceptors and cycloaddition reaction substrates, these findings are of some value and interest in organic synthesis. The commercially available ruthenium complex (**1**) and the nitro-Hoveyda catalyst (**4**)[22] can be used in this transformation. In some cases, the latter complex revealed slightly better results with this class of compounds.

Table 3. Preparation of Substituted Thiomorpholine 1,1-Dioxide Derivatives **11**



7, **8** or **10** → **11**

entry	substrate	R	R′	R″	**11** (yield, %)[a]
1	**7c**	$-(CH_2)_{16}CH_3$	$-H$	$-CH_2Ph$	**11a** (80)
2	**7e**	$-(CH_2)_4OTBS$	$-H$	$-CH_2Ph$	**11b** (83)
3	**10ec**	$-(CH_2)_4OTBS$	$-(CH_2)_4CH_3$	$-CH_2Ph$	**11c** (71)
4	**7c**	$-(CH_2)_{16}CH_3$	$-H$	$-NH_2$	**11d** (66)
5	**8b**	$-CH_2Ph$	$-CH_2Ph$	$-NH_2$	**11e** (48)
6	**10fg**	$-(CH_2)_9OH$	$-(CH_2)_8Br$	$-NH_2$	**11f** (17)

[a] Isolated yields of analytically pure products.

Acknowledgment. A fellowship of the President of Polish Academy of Sciences to M.B. is gratefully acknowledged.

Supporting Information Available: Experimental procedures and characterization data for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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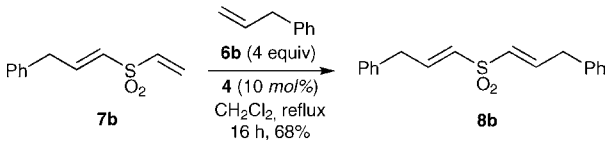
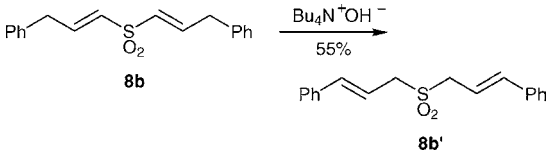
(20) This reaction can be also used as an indirect method for the preparation of *symmetrically* disubstituted sulfones, for example, (*E*,*E*)-**8b**:



7b **8b**

(21) Treatment of **8b** with strong bases leads to complete isomerization of C−C double bounds with formation of diallylic product **8b′**. See the Supporting Information for more details.



8b **8b'**

(22) Electron-withdrawing group activated Hoveyda-type catalysts are now available commercially from Strem Chemicals, Inc., and from Zannan Pharma.