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Selective C−S Bond Formation via Fe-Catalyzed Allylic Substitution

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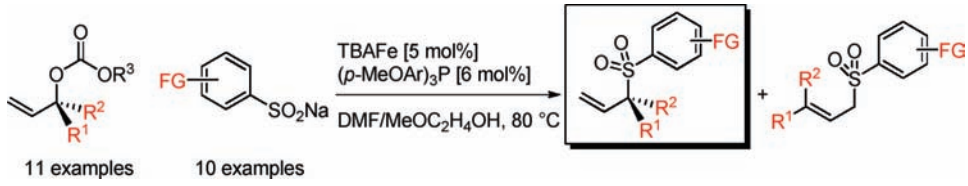
ABSTRACT



In contrast to the formation of C−O and C−N bonds it was only recently that the selective C−S bond formation by means of transition metal complexes moved more into the center of research. This is somewhat surprising given the fact that the sulfur atom in a functional group can possess different oxygenation levels which correspond to different chemical properties and reaction portfolios. Herein we wish to communicate a regioselective Fe-catalyzed allylic sulfonation that allows for the preparation of various chiral aryl allyl sulfones in good to excellent yields.

The selective formation of carbon heteroatom bonds remains one of the most important challenges within organic synthesis. Transition metal-catalyzed allylic substitutions serve as a textbook example and have found frequent use for these synthetic purposes.[1] However, whereas a variety of C−O and C−N bond forming processes have been developed within the past years, similar reactions in which a sulfur atom is introduced in a selective manner have found comparably less attention.[2,3] Among the various sulfur-containing organic compounds sulfones occupy an important space. These compounds allow for various follow-up reactions (e.g., Ramberg−Bäcklund reaction, Julia olefinations, etc.) and are hence of significant synthetic interest.[4,5] Palladium complexes have proven to be suitable catalysts for the formation of allylic sulfones starting from allylic acetates.[2] Whereas in most cases the dynamic character of the intermediate π-allyl

(1) Lu, Z.; Ma, S. *Angew. Chem., Int. Ed.* **2008**, *47*, 258.

(2) Pd-catalyzed allylic sulfonation: (a) review: Gais, H.-J. In *Asymmetric Synthesis with Chemical and Biological Methods*; Enders, D., Jäger, K.-E., Eds.; Wiley-VCH: Weinheim, Germany, 2007; p *215*. (b) Boldrini, G. P.; Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Organomet. Chem.* **1984**, *268*, 97. (c) Uozumi, Y.; Danjo, H.; Hayashi, T. *Tetrahedron Lett.* **1997**, *38*, 3557. (d) Liao, M.; Duan, X.; Liang, Y. *Tetrahedron Lett.* **2005**, *46*, 3469. (e) Gais, H.-J.; Eichelmann, H.; Spalthoff, N.; Gerhards, F.; Frank, M.; Raabe, G. *Tetrahedron: Asymmetry* **1998**, *9*, 235. (f) Seebach, D.; Devaquet, E.; Ernst, A.; Hayakawa, M.; Kühnle, F. N. M.; Schweizer, W. B.; Weber, B. *Helv. Chim. Acta* **1995**, *78*, 1636. (g) Inomata, K.; Yamamoto, T.; Kotake, H. *Chem. Lett.* **1981**, 1357. (h) Julia, M.; Lave, D.; Mulhauser, M.; Ramirez-Munoz, M.; Uguen, D. *Tetrahedron Lett.* **1983**, *24*, 1783. (i) Trost, B. M.; Schmuff, N. R. *J. Am. Chem. Soc.* **1985**, *107*, 396. (j) Trost, B. M.; Organ, M. G.; O'Doherty, G. A. *J. Am. Chem. Soc.* **1995**, *117*, 9662, and references cited therein. (k) Kang, S.-K.; Park, D.-C.; Jeon, J.-H.; Rho, H.-S.; Yu, C.-M. *Tetrahedron Lett.* **1994**, *35*, 2357. (l) Trost, B. M.; Crawley, M. L.; Lee, C. B. *Chem.—Eur. J.* **2006**, *12*, 2171. (m) Tsarev, V. N.; Konkin, S. I.; Shyryaev, A. A.; Davankov, V. A.; Gavrilov, K. N. *Tetrahedron: Asymmetry* **2005**, *16*, 1737. (n) Vasen, D.; Salzer, A.; Gerhards, F.; Gais, H.-J.; Bieler, N. H.; Togni, A. *Organometallics* **2000**, *19*, 539. (o) Hiroi, K.; Makino, K. *Chem. Pharm. Bull.* **1988**, *36*, 1744.

(3) Allylic sulfenylations: Pd-catalyzed: (a) Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1992**, *33*, 8099. (b) Goux, C.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1994**, *50*, 10321. (c) Moreno-Manas, M.; Pleixats, R.; Villarroya, M. *Tetrahedron* **1993**, *49*, 1457. (d) Frank, M.; Gais, H-J. *Tetrahedron: Asymmetry* **1998**, *9*, 3353. (e) Goux, C.; Sigismondi, S.; Sinou, D.; Pérez, M.; Moreno-Manas, M.; Pleixats, R.; Villarroya, M. *Tetrahedron* **1996**, *52*, 9521. (f) Trost, B. M.; Scanlan, T. S. *Tetrahedron Lett.* **1986**, *27*, 4141. Ru-catalyzed: (g) Kondo, T.; Morisaki, Y.; Uenoyama, S.; Wada, K.; Mitsudo, T. *J. Am. Chem. Soc.* **1999**, *121*, 8657. Rh-catalyzed: (h) Leong, P.; Lautens, M. *J. Org. Chem.* **2004**, *69*, 2194.

(4) For the use of sulfones possessing an acidic α-C−H bond see :(a) Fuchs, P. L.; Braish, T. F. *Chem. Rev.* **1986**, *86*, 903. (b) Grossert, J. S. In *The Chemistry of Sulphones and Sulphoxides*; Patai, S., Rapoport, Z., Stirling, C. J. M., Eds.; John Wiley and Sons Ltd.: Chichester, UK, 1988. (c) Simpkins, N. S. *Sulphones in Organic Synthesis*; Pergamon Press: Oxford, UK, 1993. (d) For an excellent review on Julia-olefinations see: Blakemore, P. R. *J. Chem. Soc., Perkin Trans. 1* **2002**, 2563. (e) For a recent review on the Ramberg−Backlund reaction see: Taylor, R. J. K.; Casy, G. *Org. React.* **2003**, *62*, 357.

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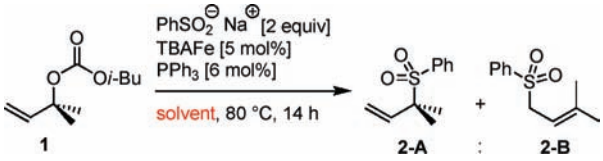
Table 1. Solvent Effects in Fe-Catalyzed Sulfonations[a]



entry	solvent	**2-A**:**2-B**[b]	yield (%)[b]
1	DMF	97:3	77
2	DMSO	90:10	15
3	CH_3CN	92:8	14
4	THF	99:1	12
5	2-methoxyethanol	93:7	85
6	*t*-BuOH	89:11	29
7	H_2O	24:76	23[d]
8	DMF/H_2O	29:71	27[c,d]
9	DMSO/H_2O	24:76	18[c,d]
10	CH_3CN/H_2O	25:75	29[c,d]
11	*t*-BuOH/H_2O	28:72	23[c,d]
12	DMF/*t*-BuOH	95:5	38[e]
13	DMF/2-methoxyethanol	97:3	92[c]
14	DMSO/*t*-BuOH	92:8	26[c]
15	CH_3CN/*t*-BuOH	89:11	40[c]
16	THF/*t*-BuOH	87:13	27[c]

[a] All reactions were performed on a 1.0-mmol scale in the presence of sodium benzenesulfinate (2.0 mmol), TBAFe (0.05 mmol), and PPh_3 (0.06 mmol) under a N_2 atmosphere in the given solvent (1 mL). [b] Determined by GC integration, using dodecane as external standard. [c] Both solvents were used in equal amounts (0.5 mL). [d] Hydrolysis of the carbonate detected. [e] Solvents were used in a mixture of DMF/2-methoxyethanol 3:1.

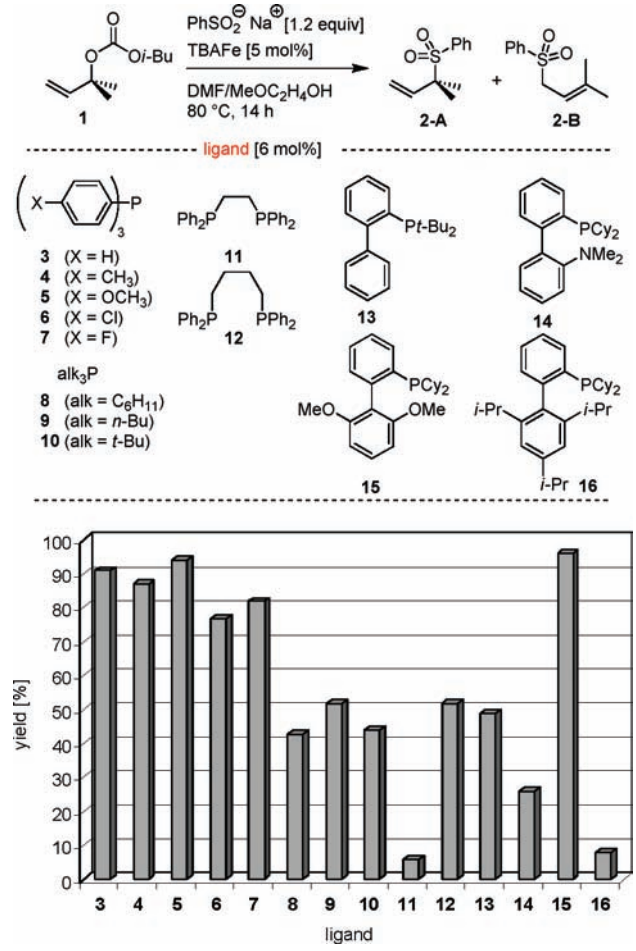
Pd complexes led to the formation of regioisomers, the presence of enantiopure ligands allowed for a control of the stereoselective course of this sulfonation. In light of these important contributions and with regard to the importance of sulfones in organic synthesis we envisioned an allylic *ipso*-sulfonation to complement the set of existing sulfone synthesis.

Recently we were able to show that low- valent iron(II) complexes are useful catalysts for the regio- and stereoselective allylation of C- or N-nucleophiles.[6] With regard to the importance of sulfones as intermediates in organic synthesis[4,5] we set out to develop the corresponding allylation of sulfinates by means of our Fe-catalyst. In particular the regioselective formation of the new C−S bond in this type of reaction seemed attractive from both a synthetic and a methodological point of view.

(5) A variety of transformations using sulfones lacking an acidic α-C−H bond have been reported, e.g., conjugate addition of Grignard reagents: (a) Julia, M.; Righini, A.; Verpeaux, J.-N. *Tetrahedron* **1979**, *26*, 2393. (b) Julia, M.; Righini-Tapie, A.; Verpeaux, J.-N. *Tetrahedron* **1983**, *39*, 3283. (c) Julia, M.; Verpeaux, J.-N. *Tetrahedron* **1983**, *39*, 3289. (d) Masaki, Y.; Sakuma, K.; Kaji, K. *J. Chem. Soc., Chem. Commun.* **1980**, 434. (e) Masaki, Y.; Sakuma, K.; Kaji, K. *J. Chem. Soc., Perkin Trans. 1* **1985**, 1171. (f) Trost, B. M.; Merlic, C. A. *J. Am. Chem. Soc.* **1988**, *110*, 5216. *ipso*-substitution of allyl sulfones: (g) Trost, B. M.; Ghadiri, M. R. *J. Am. Chem. Soc.* **1986**, *108*, 1098. Sulfones as leaving groups: (h) Trost, B. M.; Merlic, C. A. *J. Org. Chem.* **1990**, *55*, 1127. (i) Trost, B. M.; Merlic, C. A. *J. Am. Chem. Soc.* **1990**, *112*, 9590.

(6) (a) Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 1469. (b) Plietker, B. *Angew. Chem., Int. Ed.* **2006**, *45*, 6053. (c) Plietker, B.; Dieskau, A.; Möws, K.; Jatsch, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 198.

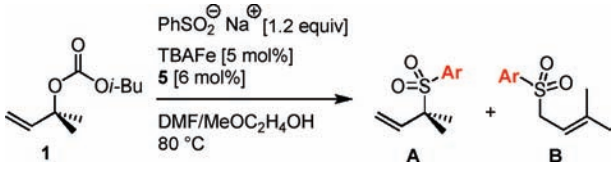
Scheme 1. Ligand Effect in Allylic Sulfonations

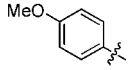
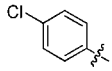
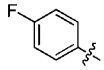
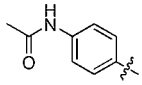
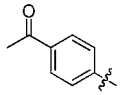
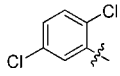


Initially we employed the ferrate catalyst $[Bu_4N][Fe(CO)_3(NO)]$ (TBAFe) under the reaction conditions that proved successful in the corresponding alkylation and aminations.[6a,b] However, although the yields were good the regioselectivity was not as good as in the case of C- or N-nucleophiles. Furthermore, the high nucleophile loading and low solubility of the sulfinic acid salt appeared problematic. Hence, the initial priority was set on an overall reduction of the amount of nucleophile in order to obtain a more homogeneous reaction mixture. Different solvents were tested (Table 1). We were pleased to find our catalyst to be active in the sulfonation under a variety of conditions. Even the presence of water did not result in a decomposition of the complex (entries 7−11, Table 1). At the outset of our solvent screening a binary solvent mixture of DMF/2-methoxyethanol (3:1) gave the most satisfying results (entry 13, Table 1). It has to be pointed out that the addition of a polar protic solvent improved the solubility of the starting material as well as that of the byproduct formed wihin the reaction, i.e., the carbonate leaving group. A further improvement of the yield was observed upon reducing the amount of sulfinate to 1.2 equiv.

At this point the influence of the phosphane ligand was reinvestigated (Scheme 1). As can be seen from Scheme 1

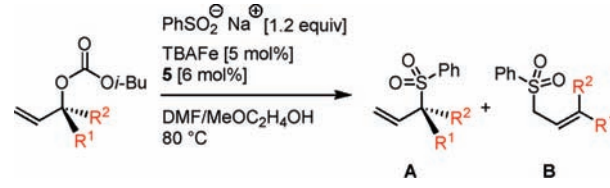
Table 2. Fe-Catalyzed Sulfonation: Nucleophile Scope[a]

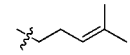
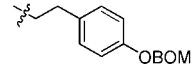
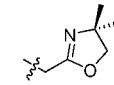
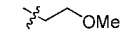
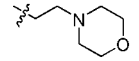
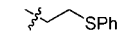
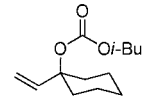
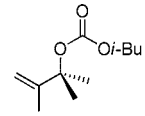
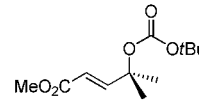


entry	Ar	product	**A**:**B**[b]	yield (%)[c]
1		**2**	97:3	83
2		**17**	96:4	70
3		**18**	98:2	78
4		**19**	97:3	86
5		**20**	97:3	84
6		**21**	96:4	75
7		**22**	96:4	86
8		**23**	96:4	73
9		**24**	55:45	46
10		**25**	75:25	54

[a] All reactions were performed on a 1.0-mmol scale in the presence of sodium arylsulfinate (1.2 mmol), TBAFe (0.05 mmol), and ligand **5** (0.06 mmol) under a N_2 atmosphere in DMF/2-methoxyethanol (2 mL). [b] Determined by GC integration. [c] Isolated yields.

Table 3. Fe-Catalyzed Sulfonation: Carbonate Scope[a]



entry	carbonate R^1	carbonate R^2	product	yield (%)[c] (**A**:**B**)[b]
1	Me	Me	**2**	83 (97:3)
2	Me	allyl	**26**	70 (94:6)
3	Me		**27**	83 (88:12)
4	Me		**28**	71 (88:12)[f]
5	Me		**29**	62 (97:3)[d,f]
6	Me		**30**	63 (86:14)
7	Me		**31**	-
8	Me		**32**	54 (87:13)[f]
9			**33**	31 (70:30)
10			**34**	78 (97:3)
11			**35**	77 (100:0)[d,e]

[a] All reactions were performed as indicated in Table 2. [b] Determined by GC integration. [c] Isolated yields. [d] Performed in *tert*-butanol with Boc-protected alcohol. [e] Performed on a 0.5-mmol scale. [f] Determined by HPLC.

most aryl-substituted phosphane ligands are suitable for the allylic sulfonation. However, a methoxy substituent within the ligand structure seems to accelerate the catalytic cycle to a significant extent (e.g., ligand **5** and **15**). Furthermore, the regioselective course of the reaction remained unaffected by the ligand structure and gave the products **2-A** and **2-B** in a ratio of 97:3 in favor of the *ipso*-substitution product.

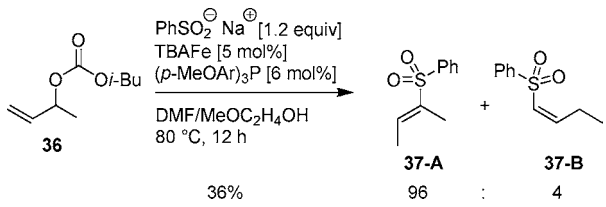
Having identified two potent ligands we finally set out to decrease the catalyst concentration. However, the rate of decrease in the catalyst loading corresponded well with the decrease in the turnover rate. Hence, in order to obtain the products in a reasonable time frame we subsequently explored scope and limiations using the reaction conditions shown in Scheme 1 and started with a screening of different aryl sulfinates (Table 2). A variety of sulfinates can be allylated in good to excellent yield with a high degree of regioselective preference for the *ipso*-substitution product. These results are in line with our previous reports on the TBAFe/PPh_3 system. Moreover, as for the allylic amination a strong influence of the ortho-substituent in the nucleophile was observed. Whereas both para- and meta-substitution led to the desired products in good overall yield and selectivities, an ortho-substituent inhibited the reaction or led to a nonregioselective product formation in low yields. However, apart from this limitation a variety of functional groups are tolerated: halides, amides, or enolizable ketones are stable under the reaction conditions.

With these encouraging results in hand we subsequently set out to explore the scope of allylic carbonates (Table 3). A variety of substituted allylic carbonates were transformed into their corresponding allylic aryl sulfones in good to excellent regioselectivities and isolated yields. The protocol tolerates functional groups like thioethers, alkoxyl groups, carboxylic acid esters, or oxazolines. Tertiary amines, however, proved to inhibit the reaction. Although the scope

of the reaction is broad with regard to the functional group tolerance the method is limited to tertiary allylic carbonates.

Secondary carbonates are reactive under the given conditions; however, a fast base assisted isomerization of the π-bond into the vinylic position was observed (Scheme 2).[7]

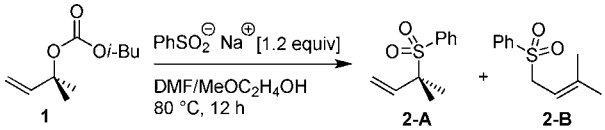
Scheme 2. Double Bond Migration in Allylic Sulfonations



Future work will focus on the elaboration of an improved protocol that allows for a similar effective transformation of secondary carbonates.

Although the regioselective course of most of the reaction presented in this study is in strong favor of the *ipso*-substitution product the decrease in some cases (e.g., entry 9, Table 3) attracted our attention. Different mechanistic scenarios might account for this observation. Apart from a metallotropic shift of the metal via a $\sigma-\pi-\sigma$-equilibrium in the intermediate allyl Fe-complex, a metal-by-metal displacement would result in a similar decrease in the regioselecitvity.[8] To shed light into the isomerization mechanism the dependency of the regioselective course of the catalyst concentration was investigated (Scheme 3). However, no significant influence was observed ruling out

Scheme 3. Regioselectivity−Catalyst Concentration Interplay

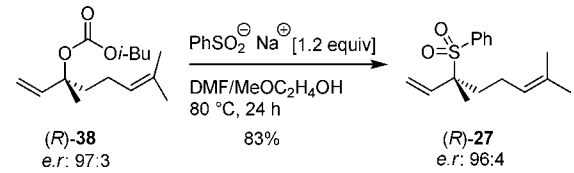


conditions	yield	regioselectivity	
TBAFe [5 mol%] (p-MeOAr)$_3$P [6 mol%]	83%	97 : 3	(1)
TBAFe [30 mol%] (p-MeOAr)$_3$P [36 mol%]	92%	97 : 3	(2)

the possibility of an isomerization via a metal-by-metal displacement.

With regard to the use of quarternary sulfones in organic synthesis[5] the stereochemical integrity of the final products is another important issue that needs to be addressed. Hence, the stereochemical course of the sulfonation was examined by using (*R*)-Linalool derived carbonate (*R*)-**38**. Subjecting the stereoisomerically enriched starting material (*R*)-**38** to the standard sulfonation conditions led to the corresponding sulfone (*R*)-**27** in identical enantiomeric ratio with overall retention of the configuration (Scheme 4).

Scheme 4. Stereochemical Course



With the results presented in this report we suggest the mechanistic model shown in Figure 1 as the working hypothesis for future development of this sulfonation reaction.

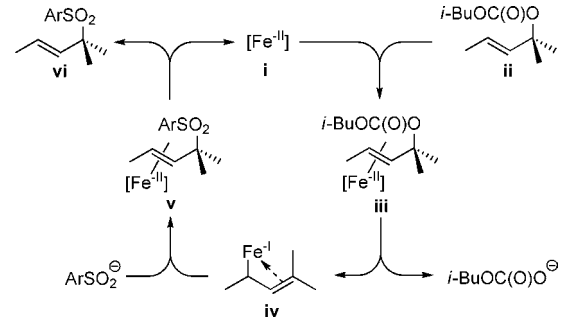


Figure 1. Mechanistic proposal for Fe-catalyzed allylic sulfonation.

In the present report we summarize our results in the Fe-catalyzed regioselective allylic sulfonation of allylic carbonates. Different aryl sulfinates can be converted into the corresponding allylic sulfones in good to excellent yields and regioselectivities with overall retention of the stereochemistry in favor of the *ipso*-substitution product. A variety of functionalized allylic carbonates can be employed in the reaction; however, at the moment the reaction is clearly limited to the use of tertiary carbonates. Future work will focus on an expansion of the reaction's scope and on the use of this methodology in natural product synthesis.

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Supporting Information Available: Characterization data for all new compounds and experimental procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Although not in the focus of the present study vinyl sulfones are imporant building blocks in medicinal chemistry, for a review see: Meadows, D. C.; Gervay-Hague, J. *Med. Res. Rev.* **2006**, *26*, 793. Investigations on the scope of the allylic sulfonation−isomerization are currently being carried out in our laboratories.

(8) A metal-by-metal displacement was observed in the related Rh-catalyzed allylic substitution: Wucher, B.; Moser, M.; Schumacher, S. A.; Rominger, F.; Kunz, D. *Angew. Chem., Int. Ed.* **2009**, *48*, 4417.