Stereoselective radical aryl migrations from sulfur to carbon

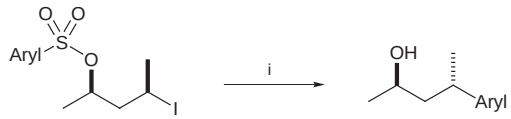
Armido Studer*† and Martin Bossart

Laboratorium für Organische Chemie, Eidgenössische Technische Hochschule, ETH-Zentrum, Universitätstrasse 16, CH-8092 Zürich, Switzerland

Stereoselective radical 1,5 aryl migrations from sulfur (in arenesulfonates) to carbon with diastereoselectivities of up to 14:1 are presented.

$C(sp^2)$–$C(sp^3)$ bonds occur in many natural products and new methods for their stereoselective formation are important. In the literature, there are only a very few methods for stereoselective $C(sp^3)$–aryl bond formation. The Heck[1] and Michael[2] reactions have to be mentioned at this point. Numerous examples of radical aryl transfers (C→C,[3] N→C,[4] O→C[5] and S→C[6]) have been published, however, we were surprised to find only three reports of stereoselective radical aryl migrations.[7] Herein we describe highly diastereoselective 1,5 aryl migrations from sulfur to carbon.

Motherwell, in his pioneering studies, has shown that intramolecular *ipso* substitution in arenesulfonates by aryl radicals is an efficient method for biaryl synthesis.[6] Based on our work on the stereoselective phenyl migration from Si to C[8] we decided to test arenesulfonates as possible 'arene sources' in the intramolecular stereoselective radical *ipso* substitution reaction. To this end, arenesulfonates **1–5** were prepared in moderate to good yields (50–90%) from (*like*)-4-iodopentan-2-ol and the corresponding commercially available sulfonyl chlorides in pyridine.[9] The racemic‡ iodo alcohol was easily prepared from (*meso*)-pentan-2,4-diol according to established procedures.[10] We were pleased to find that *ipso* substitution occurs smoothly (Scheme 1, Table 1). Slow addition of tin hydride to **1** in refluxing benzene under optimized conditions§ afforded the known[11] alcohol **6** in 76% yield with high selectivity (*u*:*l* = 13:1, entry 1). Both electron poor and electron rich arenes can be stereoselectively transferred. Thus, the *p*-fluorophenyl derivative **7** was obtained in 59% yield with a slightly lower selectivity (10:1, entry 2).¶ In the case of the electron rich anisyl and dansyl derivatives a lower yield was observed (**8**, 50%, 9:1; **10**, 52%, 11:1, entries 3 and 5). Even heteroarenes can be used in the *ipso* substitution as shown for the thienyl transfer (**9**, 74%, 9:1, entry 4). As a side product, the corresponding reduced (dehalogenated) sulfonate was always observed in these aryl migration reactions.



1–5 **6–10**

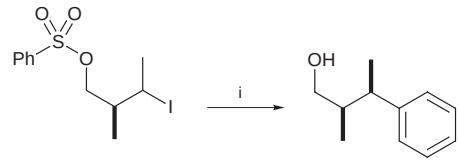
Scheme 1 *Reagents and conditions*: i, Bu_3SnH, AIBN, syringe pump, benzene (0.03 M)

Table 1 Stereoselective aryl transfer from sulfur to carbon

Entry	Sulfonate	Aryl	Product	Yield (%)	Ratio (*u*:*l*)[a]
1	**1**	Ph	**6**	76	13:1
2	**2**	4-FC_6H_4	**7**	59	10:1
3	**3**	4-$MeOC_6H_4$	**8**	50	9:1
4	**4**	thienyl	**9**	74	9:1
5	**5**	5-Me_2N-naphthyl	**10**	52	11:1[b]

[a] Determined by GC analysis. [b] Determined by ^1H NMR spectroscopy.

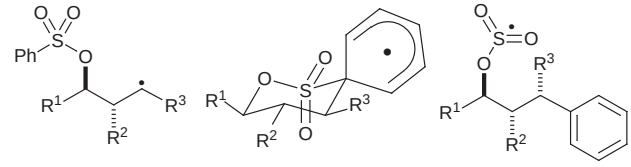
In order to study the 1,2-stereoinduction, sulfonate **11** was prepared as a 1:1 mixture of diastereoisomers. Aryl migration under analoguous conditions provided alcohol **12** in 49% yield (*l*:*u* = 7:1, Scheme 2). The relative configuration of the major isomer was assigned after oxidation (Swern) to the corresponding known[12] aldehyde.



11 **12** (49%, *l* : *u* = 7 : 1)

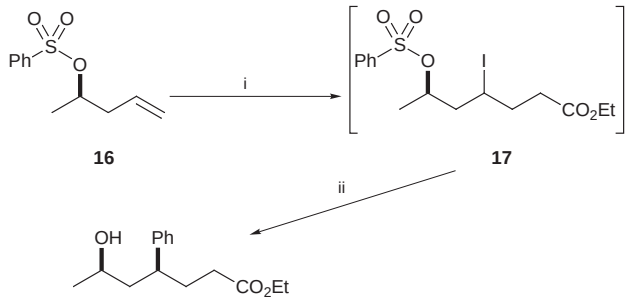
Scheme 2 *Reagents and conditions*: i, Bu_3SnH, AIBN, syringe pump, benzene (0.05 M)

From the stereochemical outcome of the reactions discussed above, we suggest the following model to explain the observed selectivities: radical **13** undergoes intramolecular *ipso* attack at the aryl group of the sulfonate to form cyclohexadienyl radical **14**. Products derived from 1,7 addition were not observed. We assume that the low energy transition state for the formation of **14** resembles a chair with the substituents in equatorial positions. Fragmentation (re-aromatization) then affords radical **15** which after SO_2 extrusion and reduction leads to the corresponding alcohol. It is not clear how fast the SO_2 extrusion process is by which the corresponding alkoxyl radical is formed. However, in the crude product mixture of the aryl migration reactions, we never observed sulfur-containing products derived from **15**; therefore, we assume that the SO_2 extrusion is faster than trapping of the intermediate radical **15** with Bu_3SnH.‖ According to this model, the observed 1,3- (→ *unlike* products) and 1,2-selectivity (→ *like* product) can be readily understood.



13 **14** **15**

As a first application of this method we studied a one pot reaction sequence where a radical addition reaction is followed by a stereoselective phenyl migration. Sulfonate **16** was prepared from the corresponding homoallylic alcohol and benzenesulfonyl chloride as described above (43%).[9] Radical acceptor **16** and ethyl iodoacetate (1.5 equiv.) were reacted under atom transfer conditions[13] in benzene [$Bu_3SnSnBu_3$ (10%), *hν*, 300 W sun lamp, 0.1 M] to afford iodide **17**, which after dilution (→ 0.05 M) was directly transformed upon slow addition of Bu_3SnH (1.8 equiv. over 7 h) and AIBN (0.25



18 (24%, *u* : *l* = 14 : 1)

Scheme 3 *Reagents and conditions*: i, $Bu_3SnSnBu_3$ (10%), *hν*, ICH_2CO_2Et, benzene (0.1 M); ii, Bu_3SnH, AIBN, syringe pump, benzene (0.05 M)

equiv.) to **18** (Scheme 3). Hydroxy ester **18** was isolated in 24% yield (unoptimized) as a 14:1 (*u*:*l*) mixture of diastereoisomers. The intermediate iodide **17** was formed with no selectivity, as shown in a separate experiment by ^{1}H NMR analysis of a sample taken after the iodine transfer reaction.

In summary, we have shown that the intramolecular *ipso* substitution is an efficient method for the stereoselective C(sp^2)–C(sp^3) bond formation. Since many sulfonyl chlorides are commercially available, a variety of aryl groups can be stereoselectively transferred to form products which are difficult to prepare by any other method.

We are grateful to Professor Dr D. Seebach for generous financial support and to Professor Dr D. P. Curran for helpful discussions.

Notes and References

† E-mail: studer@org.chem.ethz.ch

‡ All the compounds described herein were prepared as racemic mixtures. In the schemes only one enantiomer is shown.

§ *General procedure*: Bu_3SnH (1.5 equiv.) and AIBN (0.3 equiv.) in benzene (0.8–1.2 M) were added over 7 h (syringe pump) to a refluxing solution of the iodide in benzene (0.03 M). After complete addition the reaction mixture was stirred under reflux for additional 30 min. The mixture was then allowed to cool to room temperature and MeLi (5 equiv.) was slowly added. After stirring for 30 min the reaction mixture was hydrolyzed with saturated aq. NH_4Cl. Extraction with Et_2O and washing of the organic phase with brine afforded, after drying ($MgSO_4$) and purification by flash column chromatography (SiO_2, pentane–Et_2O), the corresponding alcohol. (MeLi treatment is not neccessary but advantageous since the tin halide formed is transformed to the corresponding methylated compound which is easily removed.)

¶ The relative configurations of the alcohols **7–10**, and **18** were assigned by analogy to **6** based on the characteristic chemical shift of the hydrogen atom (of the major isomer) at the newly formed stereogenic center.

‖ We believe that the products are formed under kinetic control; however, Motherwell has shown that SO_2 extrusion is rather slow in his systems and that in the biaryl synthesis the entire process is probably reversible [ref. 6(*c*)]. Experiments to elucidate the mechanism are planned.

1 M. Shibasaki, in *Advances in Metal-Organic Chemistry*, ed. L. S. Liebeskind, JAI, Greenwich, 1996, vol. 5, p. 119.
2 R. E. Gawley and J. Aubé, in *Principles of Asymmetric Synthesis*, ed. J. E. Baldwin FRS and P. D. Magnus FRS, Pergamon, 1996, p. 145; N. Krause, *Angew. Chem., Int. Ed.*, 1998, **37**, 283.
3 L. Giraud, E. Lacôte and P. Renaud, *Helv. Chim. Acta*, 1997, **80**, 2148 and references cited therein.
4 E. Lee, H. S. Whang and C. K. Chung, *Tetrahedron Lett.*, 1995, **36**, 913.
5 E. Lee, C. Lee, J. S. Tae, H. S. Wang and K. S. Li, *Tetrahedron Lett.*, 1993, **34**, 2343; D. Crich and J.-T. Hwang, *J. Org. Chem.*, 1998, **63**, 2765.
6 (*a*) S. Caddick, K. Aboutayab, K. Jenkins and R. I. West, *J. Chem. Soc., Perkin Trans. 1*, 1996, 675; F. Aldabbagh and W. R. Bowmann, *Tetrahedron Lett.*, 1997, **38**, 3793; (*b*) W. B. Motherwell and A. M. K. Pennell, *J. Chem. Soc., Chem. Commun.*, 1991, 877; M. L. E. N. da Mata, W. B. Motherwell and F. Ujjainwalla, *Tetrahedron Lett.*, 1997, **38**, 137; (*c*) M. L. E. N. da Mata, W. B. Motherwell and F. Ujjainwalla, *Tetrahedron Lett.*, 1997, **38**, 141; E. Bonfand, W. B. Motherwell, A. M. K. Pennell, M. K. Uddin and F. Ujjainwalla, *Heterocycles*, 1997, **46**, 523.
7 H. J. Köhler and W. N. Speckamp, *J. Chem. Soc., Chem. Commun.*, 1980, 142; D. L. Clive and T. L. B. Boivin, *J. Org. Chem.*, 1989, **54**, 1997; J. Aubé, X. Peng, Y. Wang and F. Takusagawa, *J. Am. Chem. Soc.*, 1992, **114**, 5466.
8 A. Studer, M. Bossart and H. Steen, submitted for publication.
9 R. S. Tipson, *J. Org. Chem.*, 1944, **9**, 235.
10 P. Place, M.-L. Roumestant and J. Goré, *Bull. Soc. Chim. Fr.*, 1976, 169.
11 J. M. Brown and R. G. Naik, *J. Chem. Soc., Chem. Commun.*, 1982, 348.
12 I. Fleming and J. J. Lewis, *J. Chem. Soc., Perkin Trans. 1*, 1992, 3257.
13 D. P. Curran, M-H. Chen and D. Kim, *J. Am. Chem. Soc.*, 1989, **111**, 6265.

Received in Cambridge, UK, 27th August 1998; 8/06718I