Pergamon

Tetrahedron Letters, Vol. 36, No. 21, pp. 3605-3608, 1995
Elsevier Science Ltd
Printed in Great Britain
0040-4039/95 $9.50+0.00

0040-4039(95)00604-4

Stereocontrolled Synthesis of Enantiomerically Pure 2-Dienyl Sulfoxides via Palladium-Catalyzed Coupling Reactions[1]

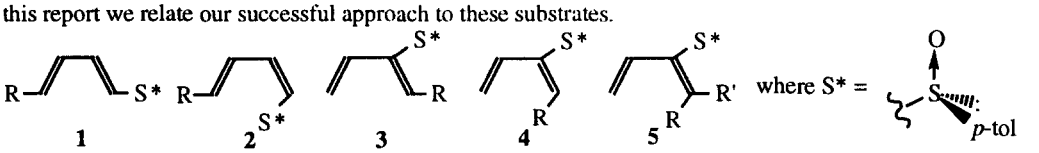
Robert S. Paley*[2], Heather L. Weers, Paloma Fernández

Swarthmore College, Department of Chemistry, Swarthmore, Pennsylvania 19081, USA

Roberto Fernández de la Pradilla*, Sonia Castro
Instituto de Química Orgánica, C.S.I.C., Juan de la Cierva 3, 28006 Madrid, Spain

Summary: Enantiopure 2-sulfinyl dienes can be prepared via regio- and stereoselective hydrostannylation of alkynylsulfoxides; after conversion to the corresponding vinyliodides these substrates may be coupled with vinylstannanes via Stille methodology in the presence of BHT.

The use of chiral sulfoxides as a element of enantio- and diastereocontrol has ample precedent in a variety of synthetic processes.[3] In the context of a project examining the diastereoselectivity of transition metal catalyzed cycloisomerizations of enantiopure dienyl sulfoxides tethered to alkene or diene units, we required a general method for the stereocontrolled preparation of acyclic sulfinyl dienes under mild conditions. Having developed a route to enantiopure 1-sulfinyl dienes **1** and **2** via a Stille coupling[4] of vinyl stannanes with (*E*)- or (*Z*)-2-halovinylsulfoxides,[5] we sought to extend this approach to prepare enantiopure 2-sulfinyl dienes **3-5**, and in this report we relate our successful approach to these substrates.



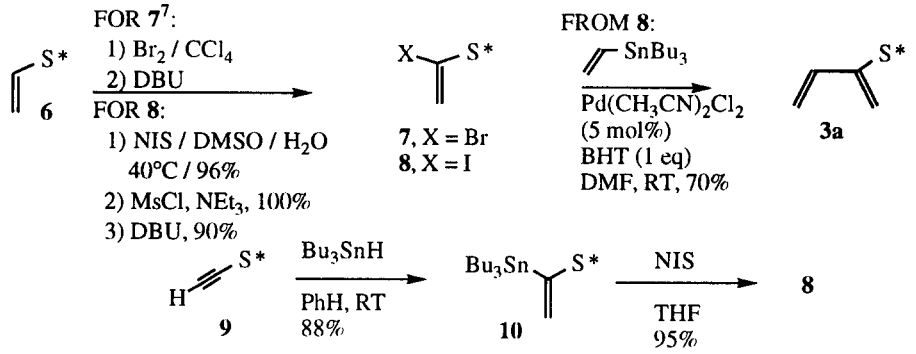
1 **2** **3** **4** **5**

Our first goal was the preparation of the simplest 2-sulfinyl diene, enantiopure 2-sulfinyl butadiene **3a** (R = H).[6] Since enantiopure 1-bromovinylsulfoxide[7] **7** was readily available from bromination of vinyl sulfoxide **6** and subsequent dehydrohalogenation, we reasoned that **3a** could be readily prepared by the Pd(0)-catalyzed coupling of **7** to vinyltri-*n*-butylstannane (as in the analogous preparations of **1** and **2**; R = H).[5] However, all efforts using a variety of catalysts, ligands, solvents, and temperatures failed to provide more than traces of **3a** (Scheme 1).

To enhance the reactivity of halovinyl sulfoxide coupling partner, we next turned towards the synthesis of the previously unknown enantiopure 1-iodovinylsulfoxide **8**; two efficient routes to **8** were ultimately developed (Scheme 1). First, vinylsulfoxide **6** was regiospecifically converted to its iodohydrin; mesylation and subsequent DBU-induced elimination afforded **8** in an excellent overall yield. Our second approach to **8** used a different strategy; alkynyl sulfoxide **9**[8] was treated with Bu_3SnH in a non-polar solvent (benzene) to regiospecifically afford stannylsulfoxide **10** which was then easily converted to iodovinylsulfoxide **8**. The outcome of this hydrostannylation implies that the reaction proceeds via conjugate addition of the hydride.[9]

With iodovinylsulfoxide **8** in hand, we were able to focus on efforts to obtain dienyl sulfoxide **3a**. As expected, **8** did prove to be a more reactive coupling partner with vinyltri-*n*-butylstannane, though the improvement in yield was only modest (25-35%). Again, a variety of conditions were tested: $Pd(CH_3CN)_2Cl_2$,

in DMF or NMP, RT to 100°C; $Pd_2(dba)_3$•$CHCl_3$ with PPh_3 or $AsPh_3$,[10] in THF (RT to Δ) or NMP (RT to 100°C). Fortunately **3a** was at last obtained in an acceptable yield (70%) with $Pd(CH_3CN)_2Cl_2$ (DMF, RT) *when the radical inhibitor BHT was included as an additive* (Scheme 1).[11]

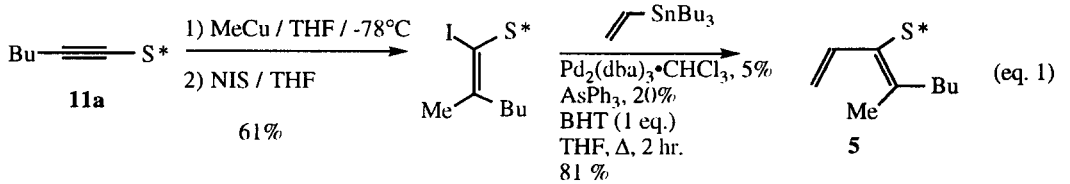


Scheme 1

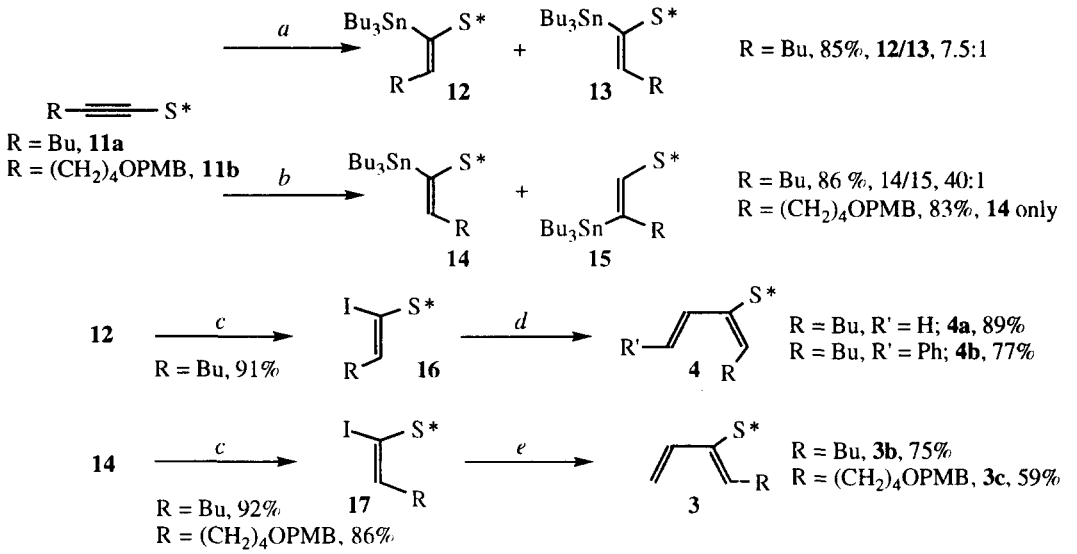
Having demonstrated that the synthesis of a 2-sulfinyl diene via Stille coupling was feasible, we next sought to extend this methodology to the more substituted analogs, **3-5** (R ≠ H); the success of this endeavor would ultimately depend on our ability to prepare the required iodovinylsulfoxide precursors with a high degree of regio- and stereoselectivity. These precursors were thus prepared by extending the hydrostannylation methodology depicted in Scheme 1 to non-terminal alkynylsulfoxides. Treatment of alkynylsulfoxide **11a**[8] with Bu_3SnH *in hexanes* (RT, 18 hr.) provided a 7.5:1 mixture of α-stannylsulfoxides **12** and **13** (total yield: 85%), where the product of *anti* hydrostannylation predominated. After easy separation of the stereoisomers by silica gel chromatography, the major α-stannylvinylsulfoxide **12** was readily converted to **16** which was elaborated into sulfinyl dienes **4a** and **4b** by using the BHT-modified Stille coupling conditions (Scheme 2).[12]

While the hydrostannylations described above proceeded in a predominantly *anti* manner, we were aware that the complementary *syn* hydrostannylation would likely occur under conditions employing a Pd(0) catalyst.[13] However, the regioselectivity of such a process was in doubt, as the only reported[14] example of a Pd(0)-catalyzed hydrostannylation (PhH, RT) of an alkynylsulfoxide gave a 2:1 regioisomeric mixture of α- and β-stannyl vinylsulfoxides. When alkynylsulfoxide **11a**[8] was hydrostannylated in this manner, a 6:1 α/β regioisomeric mixture was obtained. However, when the reaction was carried out low temperature (-78°C to RT over 3 hr., PhMe), a remarkable 40:1 selectivity[15] was obtained, with the α-stannylvinylsulfoxide **14** predominating. After chromatographic purification, **14** was converted to the corresponding iodide **17**, which in turn was coupled with vinyltri-*n*-butylstannane to afford sulfinyl diene **3b**. This sequence was also performed using functionalized alkynylsulfoxide **11b**,[16] which was readily converted into sulfinyl diene **3c** (Scheme 2).

Finally, the preparation of a more highly substituted 2-sulfinyl diene, exemplified by **5**,[17] was achieved via a regio- and stereospecific carbocupration-iodination sequence[18] beginning with sulfoxide **11a** (eq. 1).



(eq. 1)



Key: *a*) Bu_3SnH, hexanes, RT, 18 h; *b*) Bu_3SnH, $Pd(PPh_3)_4$ (2 mol %), PhMe, -78°C to RT, 3 h; *c*) NIS, THF, RT; *d*) (*E*)-R'-(CH=CH)-$SnBu_3$, $Pd_2(dba)_3$•$CHCl_3$ (5 mol%), $AsPh_3$ (20 mol%), BHT (1 eq.), THF, RT, 2 h; *e*) $(CH_2=CH)SnBu_3$, $Pd_2(dba)_3$•$CHCl_3$ (5 mol%), $AsPh_3$ (20 mol%), BHT (1 eq.), THF, Δ, 2 h.

Scheme 2

To conclude, we have described the stereocontrolled syntheses of a variety of enantiopure 2-sulfinyl dienes via complementary regio- and stereoselective hydrostannylations and subsequent Stille couplings, the latter process carried out in the presence of the radical inhibitor BHT. We are currently exploring the chemistry of these substrates (transition metal mediated cycloadditions, diastereoselective complexations to Fe(0)), and our results will be reported in due course.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society (Grant 26064-B1), and DGICYT (Grant PB93-0154) for support of this research.

REFERENCES:

1. Presented, in part, at the 6th Brazilian Meeting on Organic Synthesis, Sao Paulo, September 5-9, 1994, and is dedicated, with respect, to the late Prof. Francisco Fariña (I.Q.O., C.S.I.C.).
2. On leave, 1994-95. Current address: Massachusetts Institute of Technology, Department of Chemistry, Cambridge, MA 02139-4307.
3. For a recent application, see: Hiroi, K.; Arinaga, Y. *Tetrahedron Lett.* **1994**, *35*, 153-156. For reviews, see: (a) *The Chemistry of Sulphones and Sulphoxides*; Patai, S.; Rappoport, Z.; Stirling, C. J. M.; Eds.; John Wiley & Sons, 1988. (b) Posner, G. H. *Acc. Chem. Res.* **1987**, *20*, 72-87. (c) Solladié, G. *Synthesis* **1981**, 185-196. (d) Walker, A. J. *Tetrahedron: Asymmetry* **1992**, *3*, 961-968. For additional references, see ref. 5.
4. Reviews: a) Mitchell, T.N. *Synthesis*, **1992**, 803-815; b) Stille, J.K. *Angew. Chem. Int. Ed. Engl.*, **1986**, *25*, 508-524.
5. Paley, R.S.; de Dios, A.; Fernández de la Pradilla, R. *Tetrahedron Lett.* **1993**, *34*, 2429-2432.

6. Bonfand, E.; Gosselin, P.; Maignan, C. *Tetrahedron Lett.* **1992**, *33*, 2347-2348. For the preparation of more highly substituted 2-sulfinyl dienes, see: Bonfand, E.; Gosselin, P.; Maignan, C. *Tetrahedron: Asymmetry* **1993**, *4*, 1667-1676.
7. Cardellicchio, C.; Fiandanese, V.; Naso, F.; Scilimati, A. *Tetrahedron Lett.* **1992**, *33*, 5121-5124.
8. Kosugi, H.; Kitaoka, M.; Tagami, K.; Takahashi, A.; Uda, H. *J. Org. Chem.* **1987**, *52*, 1078-1082.
9. Leusink, A.J., Budding, H.A., Drenth, W. *J. Organometallic Chem.* **1967**, *9*, 295-306.
10. Farina, V., Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585-9595.
11. The optical rotation of **3a** was determined to be $[\alpha] = +168$ (c 1.79, EtOH), a value which is within experimental error of the literature value[6] ($[\alpha] = +174$; c 2.0, EtOH), and is independent of the route used to prepare precursor **8**. This establishes that the general approach to 2-sulfinyldienes reported here proceeds without loss of enantiopurity at sulfur. Additionally, we have found that **3a** is far less stable than orginally reported; purification by column chromatography must be carried out with deactivated silica gel, and storage of the purified material at -20°C is required to prevent decomposition. The other 2-sulfinyldienes reported here are stable at room temperature; all new compounds have been fully characterized (^1H and ^{13}C NMR, IR, MS, $[\alpha]$, combustion analysis).
12. Representative Procedure: To a solution of **11a** (88 mg, 0.40 mmol) in hexane (2 ml) was added a solution of Bu_3SnH (0.14 ml, 0.44 mmol) in hexane (2 ml) via syringe. After 18 h at room temperature, the solvent was removed *in vacuo*, and the residue was purified by column chromatography (silica, 5 to 15% EtOAc/hex) to give stannane **12** (153 mg, 75%) and stannane **13** (21 mg, 10%) as colorless oils. To a solution of **12** (139 mg, 0.27 mmol) in THF (3 ml) was added NIS (92 mg, 0.40 mmol). After stirring for 3 h at room temp., saturated aq. $Na_2S_2O_4$ (2 ml) was added; this mixture was then extracted with EtOAc (10 ml). The organic layer was washed with brine (2 ml), dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Two consecutive chromatographies (silica gel, 5 to 15% EtOAc/hex) gave iodide **16** (86 mg, 91%) as a colorless oil. To a solution of iodide **16** (86 mg, 0.25 mmol) in THF (5.4 ml) was added BHT (54 mg, 0.25 mmol), $AsPh_3$ (15 mg, 0.049 mmol) and vinyl tri-*n*-butylstannane (78 mg, 0.25 mmol). Argon was bubbled through the solution of 10 min, and then $Pd_2(dba)_3$•$CHCl_3$ (13 mg, 0.012 mmol) was added; the mixture was heated to reflux and stirred for 2 hr. Removal of the solvent *in vacuo* and two consecutive chromatographies on silica gel (5 to 15% EtOAc/hex) afforded diene **4a** (55 mg, 89%) as a pale yellow oil.
13. Zhang, H.X., Guibé, F., Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857-1867.
14. Magriotis, P.A., Brown, J.T., Scott, M.E. *Tetrahedron Lett.* **1991**, *32*, 5047-5050.
15. Product ratio based on weights of chromatographically purified products. It should be noted that all attempts to prepare 2-sulfinyldienes by coupling the α-stannylsulfinylsulfoxides with vinyl halides have been unsuccessful. However, couplings with aryl iodides have been modestly successful, producing 1-aryl-1-sulfinylalkenes in moderate yields.
16. Prepared by the method of Kosugi and Uda (ref. 8), in a 57% yield.
17. The stereochemistry of **5** has been verified by NOE measurements.
18. Truce, W.E.; Lusch, M.J. *J. Org. Chem.* **1978**, *43*, 2252-2258. To our knowledge, trapping of these sulfinyl vinyl copper intermediates with electrophiles other than proton has not been previously performed.

(*Received in USA* 17 *January* 1995; *revised* 22 *March* 1995; *accepted* 28 *March* 1995)