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COMPARISON OF VINYL ORGANOLITHIUM AND ORGANOPALLADIUM REAGENTS FOR INTRAMOLECULAR CONJUGATE ADDITION TO VINYL SULFONES.[1]

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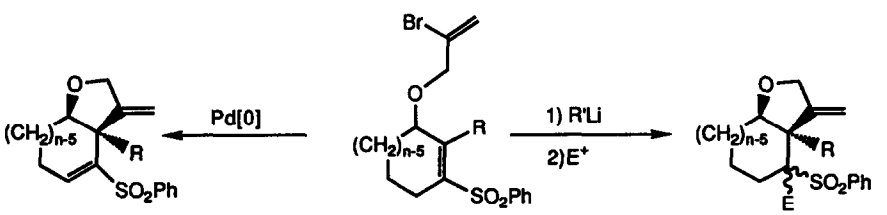
Abstract: Synthesis of cis-fused bicyclic ethers (**5-10**) by intramolecular conjugate addition of vinyl lithium and organopalladium reagents to cyclohexenyl/pentenyl moiety of vinyl sulfones is described.

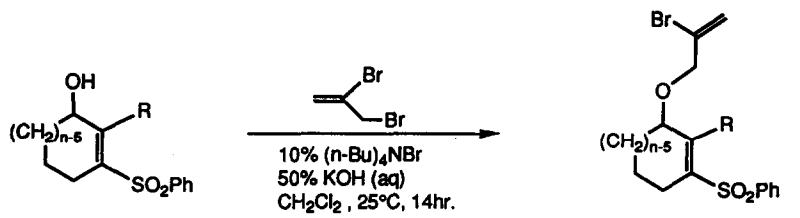
In the previous communication[2] we described a highly efficient and regiospecific palladium[0]-mediated method for the intramolecular addition of aryl halides to vinyl sulfones. The virtue of this strategy, which is well-known in the case of other polarized olefin acceptor species,[3] is that the olefin moiety is regenerated in the course of the reaction,[4] thus providing a locus for subsequent synthetic operations. In this communication we detail extension of this chemistry to the intramolecular addition of vinyl bromides and make comparisons with the complementary chemistry of vinyl lithium reagents prepared by transmetalation (Scheme 1).



Scheme 1

Preparation of the cyclohexenyl and cyclopentenyl sulfone substrates are shown in Scheme 2. Oxygen alkylation of γ-hydroxy vinyl sulfones (**1a,1b,2a**)[5] with 2,3-dibromopropene in aqueous potassium hydroxide and dichloromethane in the presence of a phase transfer catalyst[6] provided vinyl bromide ethers (**3a,3b,4a**) in 70-80% isolated yields (Scheme 2).

The results of cyclization experiments with vinyl lithium and vinyl palladium reagents derived from vinyl bromides **3a,3b,** and **4a** are summarized in Scheme 3.

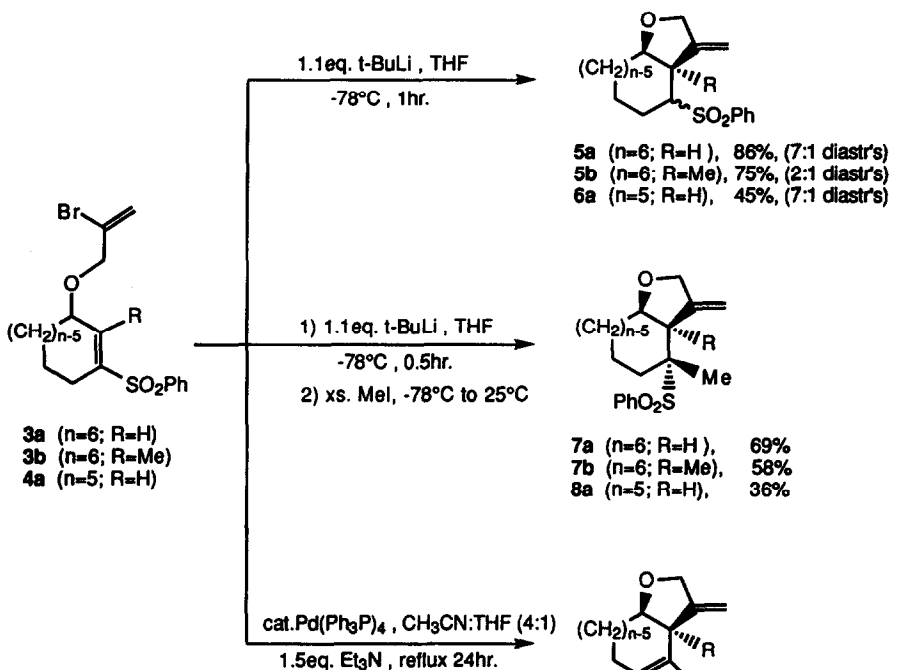


1a (n=6; R=H)
1b (n=6; R=Me)
2a (n=5; R=H)

3a (n=6; R=H), 72%
3b (n=6; R=Me), 70%
4a (n=5; R=H), 80%

Scheme 2

Treatment of vinyl bromide ethers (**3a,3b,4a**) in THF with 1.1eq. of t-butyllithium (1.7 M in pentane) at -78°C followed by quenching the reaction mixture with saturated ammonium chloride gave bicyclic ethers (**5a,5b,6a**)[7] as a mixture of (unassigned) diastereomers as determined by ^{1}H-NMR integration.



3a (n=6; R=H)
3b (n=6; R=Me)
4a (n=5; R=H)

5a (n=6; R=H), 86%, (7:1 diastr's)
5b (n=6; R=Me), 75%, (2:1 diastr's)
6a (n=5; R=H), 45%, (7:1 diastr's)

7a (n=6; R=H), 69%
7b (n=6; R=Me), 58%
8a (n=5; R=H), 36%

9a (n=6; R=H), 73%
9b (n=6; R=Me), 0% NR
10a (n=5; R=H), 58%

Scheme 3

In a parallel fashion, treatment of vinyl bromide ethers (**3a,3b,4a**) in THF with 1.1 eq. of t-butyllithium at -78°C afforded an α-sulfonyl anion which was quenched by addition of excess methyl iodide. A single diastereomer of methylated bicyclic ethers (**7a,7b,8a**) was produced in each instance. The relative stereochemistry of these compounds was assigned on the basis of ^{1}H-NMR and 2D nOe experiments.[8]

By comparison, vinyl bromides (**3a,3b,4a**) were reacted with 5 mole % of tetrakis(triphenylphosphine)palladium[0] and 1.5 eq. of triethylamine in acetonitrile/THF (4:1) at reflux for 24 hours. β-Unsubstituted vinyl bromide ethers **3a** and **4a** produced bicyclic ethers **9a** and **10a** in reasonable yield. No cyclization was observed in the case of β-methyl substituted vinyl bromide **3b** under identical reaction conditions, starting material being recovered in 75% yield. In an effort to promote the palladium[0]-mediated cyclization of vinyl bromide **3b**, 5.0 eq. of additional silver nitrate[9] was added to the reaction mixture, however no desired product was detected. Thus, palladium[0]-mediated cyclization of the β-substituted vinyl bromide vinyl sulfone failed, while the vinyl lithium intermediate underwent successful addition to the β-position.

In spite of the limitation in Pd[0]-mediated cyclization with β-substituted vinyl sulfones, the title cyclization of vinyl lithium or organopalladium reagents to vinyl sulfones has considerable potential for synthesis of fused bicyclic ethers. Application and extension of this strategy for natural product synthesis is under investigation.

Acknowledgments. We thank the National Institutes of Health (GM 32693) for support of this work. We are grateful to A. Rothwell for supplying mass spectra.

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[5](a) Lee,S. W.; Fuchs, P. L. Tetrahedron Lett., **1991**, 32, 2861. (b) **1b** may also be prepared in three steps in 48% overall yield from 2-methyl-cyclohexane-1,3-dione. The first step involves treatment of the dione with 1.5 equivalents of methanesulfonyl chloride in pyridine at room temperature for 2 h to form the β-mesyloxy enone (61%). This enone is reacted with 3.0 equivalents sodium benzenesulfinate in a mixture of NMP and benzene at reflux for 2 h to produce the β-phenylsulfonyl enone (84%). Reduction of this enone with 1.0 equivalent of sodium borohydride in the presence of 1.0 equivalent of cerium trichloride heptahydrate in a mixture of methanol and methylene chloride at -20°C for 30 min provided 93% of **1b**. (c) For a general procedure for syntheses of 3-hydroxy-2-substituted-1-(phenylsulfonyl) cyclohexenes from β-diketones, see J. E. Toth, Ph.D. Thesis, Purdue University ,1986.

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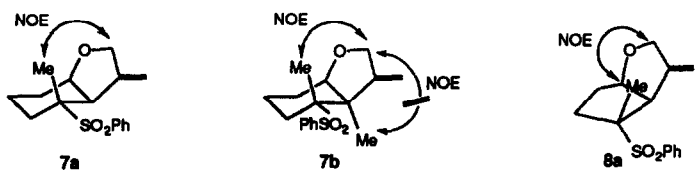
[7] **5a**(major); ^{1}H-NMR(200MHz, $CDCl_3$) δ 7.90-7.48(5H, m), 5.08(1H, m), 5.01(1H, m), 4.34(2H, m), 4.25(1H, m), 3.35(1H, m), 3.05(1H, m), 1.81-1.22(6H, m) ;^{13}C-NMR(50MHz, $CDCl_3$) δ 147.48(e), 138.21(e), 133.77(o), 129.26(o), 128.69(o), 107.31(e), 76.88(o), 68.89(e), 61.53(o), 41.31(o), 26.52(e), 22.95(e), 18.44(e); HRMS(CI) calculated for $(M+H)^+$ $C_{15}H_{18}O_3S_1$ 279.1055, found 279.1049.

7a; ^{1}H-NMR(200MHz, $CDCl_3$) δ 7.89-7.50(5H, m), 5.63(1H, m), 5.23(1H, m), 4.32(2H, m), 3.98(1H, m), 3.3(1H,d,J=4.6Hz), 1.42(3H, s), 2.15-1.21(6H, m) ;^{13}C-NMR(50MHz, $CDCl_3$) δ 147.67(e), 136.01(e), 133.68(o), 130.92(o), 128.82(o), 111.47(e), 78.54(o), 71.13(e), 64.68(e), 42.76(o), 32.47(e), 26.83(e), 16.84(o), 15.51(e); HRMS(CI) calculated for $(M+H)^+$ $C_{16}H_{20}O_3S_1$ 293.1211, found 293.1205.

9a; ^{1}H-NMR(200MHz, $CDCl_3$) δ 7.91-7.36(5H, m), 7.23(1H, m), 5.32(1H, m), 4.86(1H, m), 4.26(H, m), 4.08(2H, m), 3.60(1H, m), 2.60-1.48(4H, m) ;^{13}C-NMR(50MHz, $CDCl_3$) δ 145.39(e), 143.11(o), 141.75(e), 138.68(e), 133.33(o), 129.31(o), 127.99(o), 111.72(e), 77.22(o), 70.41(e), 43.42(o), 24.24(e), 22.03(e) ; HRMS(CI) calculated for $(M+H)^+$ $C_{15}H_{16}O_3S_1$ 277.0898, found 277.0893.

8



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