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REGIOSPECIFIC SILVER[I] PROMOTED, PALLADIUM[0]-CATALYZED INTRAMOLECULAR ADDITION OF ARYL IODIDES TO VINYL SULFONES.[1]

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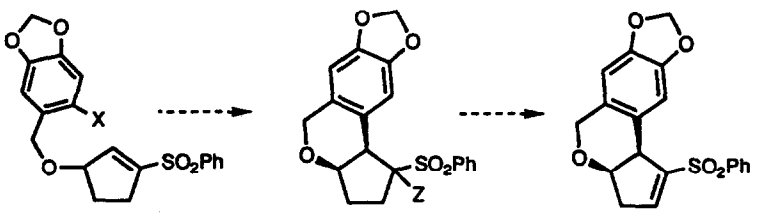
Abstract: Treatment of aryl iodides with 5% *tetrakis*(triphenylphosphine)palladium[0] in the presence of silver nitrate and triethylamine in acetonitrile at reflux effects intramolecular conjugate-addition/reductive elimination to generate an annulated vinyl sulfone. Omission of the silver nitrate produces mixtures of vinyl and allyl sulfones.



1-Br (X = Br)
1-I (X = I)
1-Li (X = Li)
1-H (X = H)

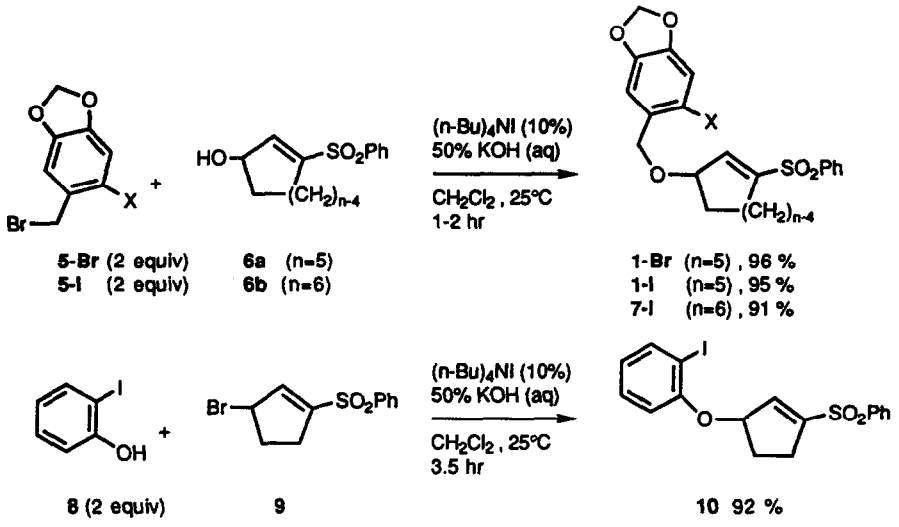
2a (Z = Li)
2b (Z = Leaving Group)
2c (Z = H)

3

In conjunction with a synthetic project in our laboratory we wished to effect the intramolecular conjugate addition of aryl lithium **1-Li** reagent to the cyclopentenyl vinyl sulfone moiety, thereby generating α-sulfonyl anion **2a** which was to have been directly functionalized to **2b** and ultimately eliminated to vinyl sulfone **3**. While our previous experiences with intramolecular conjugate-addition reactions of aryl anions to vinyl sulfones seemed to bode well for such a prospect,[2] such was not to be the case. Low temperature transmetalation of **1-Br** or **1-I** with n- or t-butyllithium in ether or THF followed by warming the presumed solution of **1-Li**, with or without a variety of additives, generated a plethora of products, including **1-H** (~ 20%), however NMR assay of the crude reaction mixture placed the maximal yield of **2c**[3] at less than 5%. Attempts to demonstrate the existence of **1-Li** by low-temperature silylation were uniform failures.

While the palladium[0]-mediated intramolecular addition of aryl and vinyl halides to polarized olefins is a well-known and useful synthetic protocol,[4] to the best of our knowledge this strategy has not been extended to include vinyl sulfones.[5] Preparation of the substrates for the palladium-mediated cyclization studies are shown in the scheme below. Oxygen alkylation of γ-hydroxy vinyl sulfones **6a,b**[6] with p-alkoxybenzylic halides **5-Br**[7] and **5-I**[7] proved to be quite difficult. The best method involved using two equivalents of the benzylic bromide with a phase-transfer protocol[8]

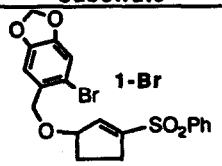
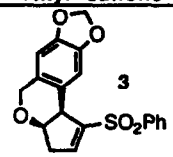
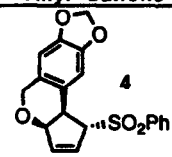
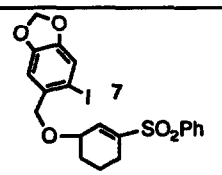
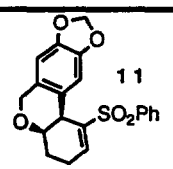
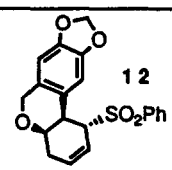
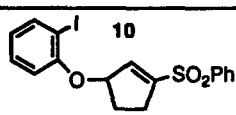
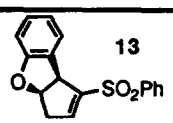
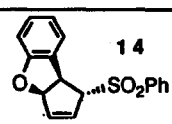
which provided the γ-benzyloxy vinyl sulfones in >90% isolated yields. Using only one equivalent of the alkylating agent decreased the yields to 63-69%. Synthesis of the o-iodophenoxy vinyl sulfone **10** was more straightforward, and involved simple oxygen alkylation of (two equiv) of phenol **8** with γ-bromocyclopentenyl phenyl sulfone **9**.[9]



Reaction of aryl bromide **1-Br** with 5% *tetrakis*(triphenylphosphine)palladium[0] and triethylamine (1.5 equiv) in acetonitrile at reflux for 1h provided, in addition to a major amount of starting material, a mixture of the desired vinyl sulfone **3**[13] (23.5%, Table entry 1) accompanied by a small amount of allyl sulfone **4**[13] (2.5%). Use of the more reactive aryl iodide **1-I** under the same conditions provided the same two products in the ratio of 3:1 (83% yield, Table entry 2).

Overman,[10] Larock,[11] and Hallberg[12] have documented the beneficial effect of added silver [I] salts at preventing formation of olefin regioisomers in palladium[0]-mediated reactions, presumably by irreversibly trapping the released hydrogen halide, thereby preventing re-establishment of organopalladium intermediates capable of generating the unwanted regioisomers. While utilization of this reagent combination to the reaction of aryl bromide **1-Br** was ineffectual (Table entry 3) treatment of aryl iodide **1-I** with palladium diacetate in the presence of silver nitrate provided superb remediation of the problem at hand (73% yield of **3** Table entry 4). Even better results were obtained using *tetrakis*(triphenylphosphine)palladium[0]; the reaction proceeding in shorter time affording a 97% yield of **3** unaccompanied by any trace of allyl sulfone isomer **4** (Table entry 5).

Application of this protocol to vinyl sulfones **7** and **10** was equally successful, providing the annulated vinyl sulfones **11**[13] and **13**[13] in near quantitative yield, again unaccompanied by the allylic isomers **12** and **14** which were produced in reactions run in the absence of added silver nitrate (Table entries 6-9).

Substrate	Conditions	Vinyl sulfone	Allyl Sulfone
 1-Br	$Pd(PPh_3)_4$ 5%, NEt_3 (1.5 equiv) CH_3CN, reflux, 1 h	 3 23 %[a]	 4 2.5 %[a]
1-I	$Pd(PPh_3)_4$ 5%, NEt_3 (1.5 equiv) CH_3CN, reflux, 1 h	3, 62%	4, 21%
1-Br	$Pd(PPh_3)_4$ 5%, $AgNO_3$ (5 equiv), NEt_3, CH_3CN, reflux, 12h	3, 0%[b]	4, 0%[b]
1-I	$Pd(OAc)_2$ 5%, PPh_3 20%, $AgNO_3$ (5 equiv), NEt_3, CH_3CN, reflux, 14h	3, 73%[c]	4, 0%[c]
1-I	$Pd(PPh_3)_4$ 5%, $AgNO_3$(5 equiv) NEt_3, CH_3CN, reflux, 3.5h	3, 97%	4, 0%
 7	$Pd(PPh_3)_4$ 5%, NEt_3 (1.5 equiv) CH_3CN, reflux, 1 h	 11 57 %	 12 29 %
7	$Pd(PPh_3)_4$ 5%, $AgNO_3$ (5 equiv), NEt_3, CH_3CN, reflux, 7h	11, 94%	12, 0%
 10	$Pd(PPh_3)_4$ 5%, NEt_3 (1.5 equiv) CH_3CN, reflux, 0.5h	 13 31 %[d]	 14 17 %[d]
10	$Pd(PPh_3)_4$ 5%, $AgNO_3$ (5 equiv) NEt_3, CH_3CN, reflux, 0.5h	13, 96%	14, 0%

[a]The reaction did not proceed to completion; 70% of 1-Br was recovered; [b]> 95% 1-Br was recovered; [c]13% 1-I was recovered; [d]No starting material was recovered in this reaction.

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References and notes

[1]Syntheses via vinyl sulfones 47. For paper 46, see Li, C.; Fuchs, P. L. *Tetrahedron Lett.* **1993**, *34*, 1855. Review: Braish, T.F.; Fuchs, P. L., *Chem Rev.* **1986**, *86*, 903.

[2]For leading references see: Toth, J. E.; Hamann, P. R.; Fuchs, P. L. *J. Org. Chem.* **1988**, *53*, 4694.

[3]An authentic sample of the alpha face sulfone diastereomer of **2c** was prepared in 92% yield by hydrogenation of 4(25°C, EtOAc, 18h, 5% Pd/C), attempts to secure the diastereomer were not successful.

[4](a) Nagasawa, K.; Zako, Y.; Ishihara, H.; Shimizu, I. *Tetrahedron Lett.* **1991**, *32*, 4937; (b) Negishi, E. -I.; Nguyen, T.; O'Connor, B.; Evans, J. M.; Silveira, Jr., A. *Heterocycles.* **1989**, *38*, 55; (c) O'Connor, B.; Zhang, Y.; Negishi, E. -I.; Luo, F. -T.; Cheng, J. -W. *Tetrahedron Lett.* **1988**, *29*, 3903; (d) Cacchi, S.; Arcadi, A. *J. Org. Chem.* **1983**, *48*, 4236; (e) Danishefsky, S.; Taniyama, E. *Tetrahedron Lett.* **1983**, *24*, 15.

[5]A related palladium [0] catalyzed process involves the intramolecular cycloaddition of trimethylenemethane to vinyl sulfones, see: (a) Trost, B. M.; Grese, T. A.; Chan, D. M. T. *J. Am. Chem. Soc.* **1991**, *113*, 7350; (b) Trost, B. M.; Grese, T. A. *J. Am. Chem. Soc.* **1991**, *113*, 7363.

[6](a) Conrad, P. C.; Fuchs, P. L. *J. Am. Chem. Soc.* **1978**, *100*, 346; (b) Saddler, J. C.; Conrad, P. C.; Fuchs, P. L. *Tetrahedron Lett.* **1978**, 5079.

[7](a) Semmelhack, M. F.; Chong, B. P.; Stauffer, R. D.; Rogerson, T. D.; Chong, A.; Jones, L. D. *J. Am. Chem. Soc.* **1975**, *97*, 2507; (b) Ponton, J.; Helquist, P.; Conrad, P. C.; Fuchs, P. L. *J. Org. Chem.* **1981**, *46*, 118.

[8]Kawamoto, K.; Nakai, T. *Chem. Lett.* **1985**, 1719.

[9]Allylic bromide **9** was prepared in 95% yield by the reaction of PBr_3 with **6a** for 1h in ether at reflux.

[10]Abelman, M. M.; Oh, T.; Overman, L. E. *J. Org. Chem.* **1987**, *52*, 4130-4133.

[11]Larock, R. C.; Gong, W. H.; Baker, B. E. *Tetrahedron Lett.* **1989**, *30*, 2603.

[12]Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1990**, *55*, 2464-2470. For a more complete compilation of the benefit of silver[I] in organopalladium reactions see reference 5 in Nilsson, K.; Hallberg, A. *J. Org. Chem.* **1992**, *57*, 4015-4017.

[13] **3**: ^{1}H NMR ($CDCl_3$) δ 7.56-7.22 (5H, m), 7.13-7.10 (1H, m), 7.02 (1H, s), 6.13 (1H, s), 5.84 (2H, s), 4.54-4.50 (1H, "t", J=4.9, 4.9Hz), 4.40 (1H, AB, J_{AB}=14.4Hz), 4.25 (1H, AB, J_{AB}=14.4Hz) 4.14 (1H, bs), 2.96-2.86 (1H, m), 2.76-2.69 (1H, m); ^{13}C NMR ($CDCl_3$) δ 147.11(e), 146.62(e), 145.34(o), 144.87(e), 140.54(e), 132.95(o), 129.34(e), 128.75(o), 127.67(o), 121.99(e), 111.94(o), 104.61(o), 101.24(e), 77.50(o), 65.93(e), 47.13(o), 39.50(e); HRMS (EI) calculated for M^+ $C_{19}H_{16}O_5S$ 356.0718, found 356.0711;

11: ^{1}H NMR ($CDCl_3$) δ 7.44-7.18 (6H, m), 6.99 (1H, s) 5.97 (1H, s), 5.84 (2H, s), 4.50 (1H, AB, J_{AB}=14.6Hz), 4.30 (1H,AB, J_{AB}=14.6Hz), 3.95-3.91 (1H, m), 3.70(1H, bs), 2.72-2.58 (1H, m), 2.51-2.38 (1H, m), 2.10-1.98 (1H, m), 1.84-1.70 (1H, m); ^{13}C NMR ($CDCl_3$) δ 147.27(e), 146.28(e), 143.43(o), 141.06(e), 138.91(e), 132.31(o), 128.63(e), 128.52(o), 126.93(o), 125.41(e), 112.79(o), 104.19(o), 101.29(e), 70.88(o), 67.16(e), 38.99(o), 26.50(e), 23.13(e); HRMS (EI) calculated for M^+ $C_{20}H_{18}O_5S$ 370.0875, Found 370.0868;

13: ^{1}H NMR ($CDCl_3$) δ 7.82-7.42 (5H, m), 7.37-7.34 (1H, m), 7.10-6.66 (4H, m), 5.50 (1H, m), 4.66 (1H, d, J=7.7Hz), 3.17-2.91 (2H, m); ^{13}C NMR ($CDCl_3$) δ 159.72(e), 144.94(e), 143.71(o), 140.76(e), 139.95(o), 129.62(o), 128.08(o), 127.22(o), 124.81(e), 121.05(o), 109.86(o), 87.20(o), 53.10(o), 40.53(e); HRMS (EI) calculated for M^+ $C_{17}H_{14}O_3S$ 298.0664, Found 298.0658.

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