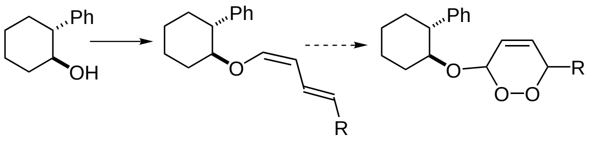
Application of the Sonogashira Coupling Reaction to the Stereoselective Synthesis of Chiral 1,3-Dienol Ethers

Patrick H. Dussault*, Darby G. Sloss, and David J. Symonsbergen
Department of Chemistry, University of Nebraska-Lincoln, Lincoln, Nebraska 68588-0304, USA
FAX (402) 472-9402 internet: dussault@unlinfo.unl.edu

Received 13 October 1998

Abstract: Sonogashira couplings of 2-iodo enol ethers or ynol ethers provide enynes which undergo semihydrogenation to afford 4-alkyl-1,3-dienol ethers. (1*Z*, 3*E*), (1*E*, 3*Z*) and (1*Z*, 3*Z*)-4-alkyl-1,3-dienol ethers are accessible using this strategy.

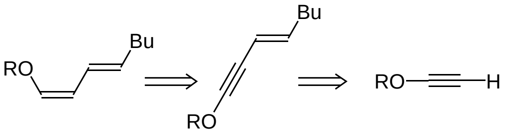
As part of a synthetic program targeting peroxide-containing natural products, we required a stereoselective preparation of chiral dienol ethers as substrates for stereoselective addition of singlet oxygen (eq. 1)



(1)

Equation 1

However, a review of the literature revealed surprisingly few general methods for synthesis of alkyl dienol ethers.[1-3] The Sonogashira (Stephens-Castro) coupling reaction is a convenient Pd(0)/Cu(I) mediated process which has been used for the formation of numerous enynes.[4] Herein we report the application of the Sonogashira coupling towards the stereoselective synthesis of (1Z, 3E), (1E, 3Z) and (1Z, 3Z)-4-alkyl-1,3-dienol ethers. As illustrated in eq. 2, our strategy relies upon a Sonogashira coupling followed by selective reduction of the alkyne for formation of the diene functionality.



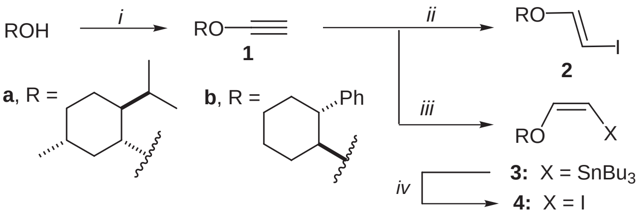
(2)

Equation 2

Alkynol ethers **1a** and **1b** were readily synthesized from *L*-menthol and (*R*,*S*)-*trans*-2-phenylcyclohexanol using the method of Greene[5] (Scheme 1). Alternatively, these alkynol ethers could be converted to (E)-2-iodo enol ethers **2** by hydrozirconation-iodination.[6] Hydrostannylation of the alkynyl ethers selectively produced (*Z*)-tributylstannyl enol ethers **3** which underwent iodination to produce the (*Z*)-2-iodo enol ethers **4** (Scheme 1).[7]

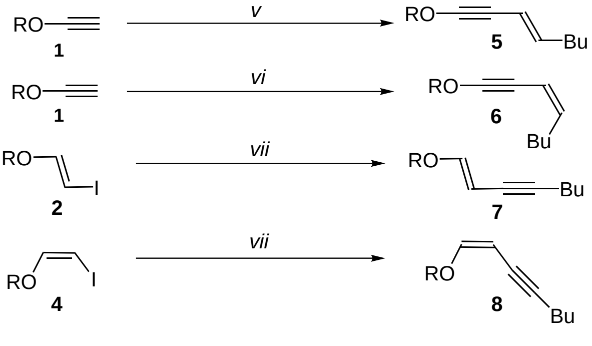
Coupling of **1** with (*Z*)- or (*E*)-1-iodohexene[8,9] furnished enynol ethers **5** and **6** in a stereospecific fashion (Table 1).[10] Coupling of the (*E*)- and (*Z*)-iodo enol ethers **2** and **4** with 1-hexyne furnished enynol ethers **7** and **8** (Scheme 2 and Table 1).

Semihydrogenation[11] of the enynes with P-2 Nickel selectively introduced a (Z)-alkene (Table 1). The dienol ethers were susceptible to overreduction to enol ethers under the semihydrogenation conditions, but overreduction could be minimized with careful monitoring of reaction progress. Attempted hydride reduction of the alkyne to the (E)-alkene[12] was unsuccessful, thus limiting the scope of this strategy to the preparation of dienol ethers containing at least one (Z)-olefin.



i. KH, THF, cat. imidazole, ROH, 0 °C; trichloroethene, -40 °C; *n*-BuLi, -78 °C; MeOH, -40 °C *ii.* ethynol ether, Cp_2ZrHCl, THF then I_2 *iii.* Et_3B, $HSnBu_3$; *iv.* THF, NIS

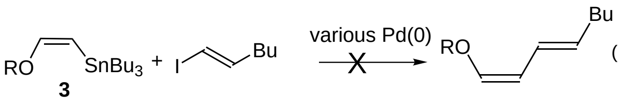
Scheme 1



v. *i*-$PrNH_2$, (*E*)-1-iodohexene, $Pd(Ph_3)_4$, CuI *vi.* *i*-$PrNH_2$, (*Z*)-1-iodohexene, $Pd(Ph_3)_4$, CuI *vii.* *i*-$PrNH_2$, hexyne, $Pd(Ph_3)_4$, CuI

Scheme 2

Yamanaka[13-15] and Suginome[16] have described the palladium catalyzed coupling of aryl and heteroaryl halides with (*Z*)-1-ethoxy-2-stannylethene or (*E*)-*tris*(2-ethoxyethenyl)borane; however, attempts to perform a direct synthesis of the dienol ether through Stille coupling between stannylenol ether **3** and iodohexene were unsuccessful under a variety of conditions (eq. 3), as were attempts to perform Suzuki couplings via the corresponding enol boronate.[17]



(3)

Equation 3

In summary, we have demonstrated that the use of the Sonagashira coupling permits rapid access to three of the four possible geometric isomers of dienol ethers. Application of this methodology for peroxide synthesis will be described in due course.

Acknowledgments: This work was supported by a grant from the NIH (GM 45571).

Notes and References

(1) Luengo, J. I.; Koreeda, M. *Tetrahedron Lett.* **1984**, *25*, 4881.

(2) McDougal, P. G.; Rico, J. G. *J. Org. Chem.* **1987**, *52*, 4817.

(3) Nicolaou, K. C.; Shi, G.-Q.; Gunzner, J. L.; Gärtner, P.; Zang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 5467.

(4) Sonogashira, K. In *Comprehensive Organic Synthesis*; B. M. Trost, Ed.; Pergamon Press: New York, 1991; Vol. 3; pp 521.

(5) Greene, A. E. *J. Org. Chem.* **1987**, 2919.

(6) Lipshutz, B. H.; Keil, R.; Ellsworth, E. L. *Tetrahedron Lett.* **1990**, *31*, 7257.

(7) Chen, S. M.; Schaub, R. E.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3450.

(8) Brown, H. C.; Blue, C. D.; Nelson, D. J.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6064.

(9) Polt, R.; Peterson, M. *Synth. Comm.* **1992**, *22*, 477.

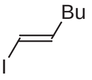
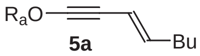
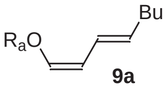
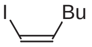
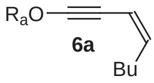
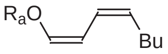
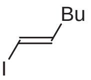
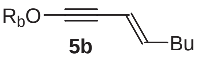
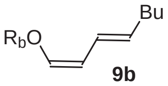
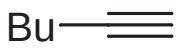
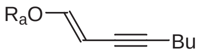
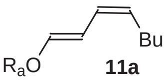
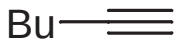
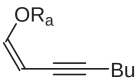
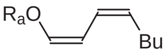
(10) To tetrakis(triphenylphosphine) palladium (100 mg, 0.086 mmol) dissolved in *i*-PrNH$_2$ (12 mL) was added (*E*)-1-iodo-1-hexene (362 mg, 1.73 mmol), (R,S)-*trans*-2-phenylcyclohexanol ethynyl ether **1b** (449 mg, 2.24 mmol), and copper (I) iodide (33 mg, 0.17 mmol) dissolved in *i*-PrNH$_2$ (5 mL). The resulting orange solution was stirred in the dark for 5 h. The reaction was diluted with hexane and thoroughly washed with NaHCO$_3$ (sat. aq.). The aqueous layers were combined and extracted with hexane. The combined organic layers were dried over Na$_2$SO$_4$, concentrated, and purified by chromatography (100% hexane, no Et$_3$N pretreatment of silica) to afford **5b** as an oil (375 mg, 77%): R$_f$ 0.66 (95% hexane-EtOAc); ^{1}H NMR (500 MHz, CDCl$_3$) δ 0.95 (t, *J*= 9 Hz, 3H), 1.33-1.51 (m, 6H), 1.58 (dq, *J*= 3, 13 Hz, 1H), 1.68 (dq, *J*= 4, 12.5 Hz, 1H), 1.79-1.82 (m, 1H), 1.97-2.00 (m, 2H), 2.10 (dq, *J*= 1, 7 Hz, 2H), 2.46-2.49 (m, 1H), 2.81 (app dt, *J*= 4, 11 Hz, 1H), 4.15 (dt, *J*= 4.5, 11 Hz, 1H), 5.44 (dt, *J*= 1.5, 15.5 Hz, 1H), 5.92 (dt, *J*= 7, 15.5 Hz, 1H), 7.35-7.38 (m, 2H), 7.26-7.31 (m, 3H); ^{13}C NMR (125 MHz, CDCl$_3$) δ 13.8, 22.0, 24.6, 25.5, 31.0, 31.1, 32.5, 33.8, 39.8, 49.0, 89.4, 95.6, 109.3, 126.5, 127.5, 128.3, 140.6, 142.5; FT-IR (neat) 698, 754, 940, 995, 1253, 1449, 2245, 2858, 2930, 3028 cm^{-1}; HRMS calcd for $C_{20}H_{26}O$ (M+) 282.1984, found 282.1973.

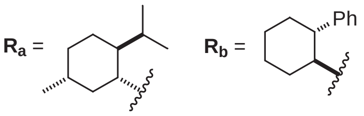
(11) To an oven dried 3-neck flask topped with a 3-way stopcock and a hydrogen balloon was added nickel (II) acetate (482 mg, 1.94 mmol) and 7 mL of absolute ethanol. Following two vacuum/ repressurization cycles (nitrogen), the flask was evacuated and charged with hydrogen. Sodium borohydride (73 mg, 1.9 mmol) dissolved in 5 mL of absolute ethanol was added. After stirring for 20 minutes, ethylenediamine (0.52 mL, 7.7 mmol) and a solution of the enynol ether (570 mg, 2.02 mmol, **5b**) in ethanol (3 mL) was added and the reaction was stirred at RT for 1 h. The hydrogen was released and the reaction mixutre was diluted with hexane and extracted with NaHCO$_3$ (10% aq.). The combined organics were dried over Na$_2$SO$_4$, evaporated and purified by flash chromatography (100% pentane, Et$_3$N pretreated) to afford a colorless oil (396 mg, 69%). When necessary, overreduced enol ether and dienol ether could be separated using HPLC (100% pentane): R$_f$ 0.87 (95% hexane-EtOAc); ^{1}H NMR (360 MHz, CDCl$_3$) δ 0.87 (t, *J*= 7 Hz, 3H), 1.60-1.24 (m, 8H), 1.74-1.79 (m, 1H), 1.85-2.01 (m, 3H), 2.13-2.19 (m, 1H), 2.66 (app dt, *J*= 4, 11 Hz, 1H), 3.63 (dt, *J*= 4, 10 Hz, 1H), 4.77 (dd, *J*= 6, 11 Hz, 1H), 5.37 (dt, *J*= 7, 15.5 Hz, 1H), 5.62 (d, *J*= 6 Hz, 1H), 6.08 (dd, *J*= 11, 15.5 Hz, 1H), 7.15-7.33 (m, 5H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 13.9, 22.2, 24.9, 25.8, 31.7, 32.5, 32.8, 33.4, 50.4, 84.5, 106.6, 123.1, 126.2, 127.7, 128.1, 130.2, 143.4, 143.6; FT-IR (neat) 698, 754, 970, 1075, 1108, 1448, 1615, 1656, 2856, 2927, 3029 cm-^{1}; HRMS calcd for $C_{20}H_{28}O$ (M+) 284.2140, found 284.2142.

(12) Denmark, S. E.; Thorarensen, A. *J. Am. Chem. Soc.* **1997**, *119*, 125.

(13) Sakamoto, T.; Kondo, Y.; Yasuhara, A.; Yamanaka, H. *Heterocycles* **1990**, *31*, 219.

Table 1

Entry	Alkyne	Iodide	Ene-yne	Yield^a (%)	Dienol Ether	Yield^a (%)
1	**1a**		 **5a**	94	 **9a**	82^b
2	**1a**		 **6a**	57	 **10a**	52
3	**1b**		 **5b**	77	 **9b**	69
4		**2a**	 **7a**	100	 **11a**	53
5		**4a**	 **8a**	63	 **10a**	99^c



a Isolated yields. All new compounds were characterized by ^{1}H and ^{13}C-NMR, and by HRMS or elemental analysis. *b* Contains 12% over-reduced enol ether that is separable by HPLC. *c* Without chromatographic purification.

(14) Sakamoto, T.; Kondo, Y.; Yasuhara, A.; Yamanaka, H. *Tetrahedron* **1991**, 1877.

(15) Sakamoto, T.; Satoh, C.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1993**, *41*, 81.

(16) Miyaura, N.; Maeda, K.; Suginome, H.; Suziki, A. *J. Org. Chem.* **1982**, 2117.

(17) Farina, V.; Krishnamurthy, V.; Scott, W. J. *Organic Reactions* **1997**, *50*, 1. $(MeCN)_2PdCl_2$, $(PPh_3)_2Pd(OAc)_2$, $(PPh_3)_2PdCl_2$, and $Pd_2dba_2/P(2\text{-furyl})_3$ catalysts in THF or DMF, with or without CuI cocatalyst, at 25-65°C for 2-117 h were utilized for the attempted Stille couplings. Attempted Suzuki couplings of the 9-BBN borane, catechol boronate, or boronic acid derives of the alkynol ether with (*E*)-1-iodohexne using $Pd(PPh_3)_4$ and K_3PO_4 at 65 °C in THF were unsuccessful.