Pergamon

Tetrahedron Vol. 50, No. 18, pp. 5489-5494, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0203-6

Palladium Catalysed Cross-Coupling of Vinyl Triflates with 9-Alkyl-9-borobicyclo[3,3,1]nonanes. Total Synthesis of (-)-Isoseiridine.

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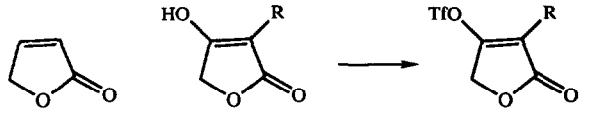
Abstract. *Pd(O) Catalysed cross-coupling of butenolide-3-triflates to 9-alkyl-9-borobicyclo[3.3.1]nonanes occurs in moderate to good yield and tolerates a range of functionality. Application of this methodology combined with addition of diethylzinc to a butenolide aldehyde in the presence of an ephedrine derivative leads to a 3-step synthesis of (-)-isoseiridine with 88%e.e. in good yield.*

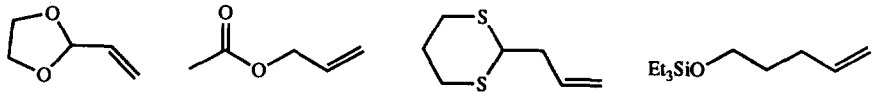
The Pd(0) catalysed cross-coupling of vinyl or aryl triflates with organometallic reagents is an important and versatile method for C-C bond formation. Thus the ease of accessibility of triflates[1] and their clean Pd(0) catalysed cross-coupling[2] with organo - Sn(IV)[3], - Al(III),[4] - Zn(II),[5] and - B(III)[6] derivatives has resulted in a continued high level of interest, with Suzuki's recent development of alkyl-alkyl coupling [alkyl halide + alkyl(BIII)] being particularly noteworthy.[7]

The butenolide moiety (1) occurs in a range of natural products and we were interested in developing a Pd(0) catalysed route to functionalisation of (1) at the 3-position.



(1) (2) a. R=H b. R=Me (3) a. R=H b. R=Me

The tetronic acids (2a,b) were readily converted to the corresponding triflates in 66 and 93% yield respectively by treatment with triflic anhydride in methylene chloride at -78°C in the presence of Hunig's base.



(4) (5) (6) (7)

A range of 9-alkyl-9-borobicyclo[3.3.1]nonanes (9-alkyl-9-BBN) (8-11) were prepared, and used *in situ*, from the corresponding alkenes (4-7) and 9-BBN. The Pd(0) catalysed cross-coupling was achieved using modified Suzuki conditions[6] with the catalyst being generated *in situ* from 10mol% $Pd(OAc)_2$ and 20mol% $PPh._3$

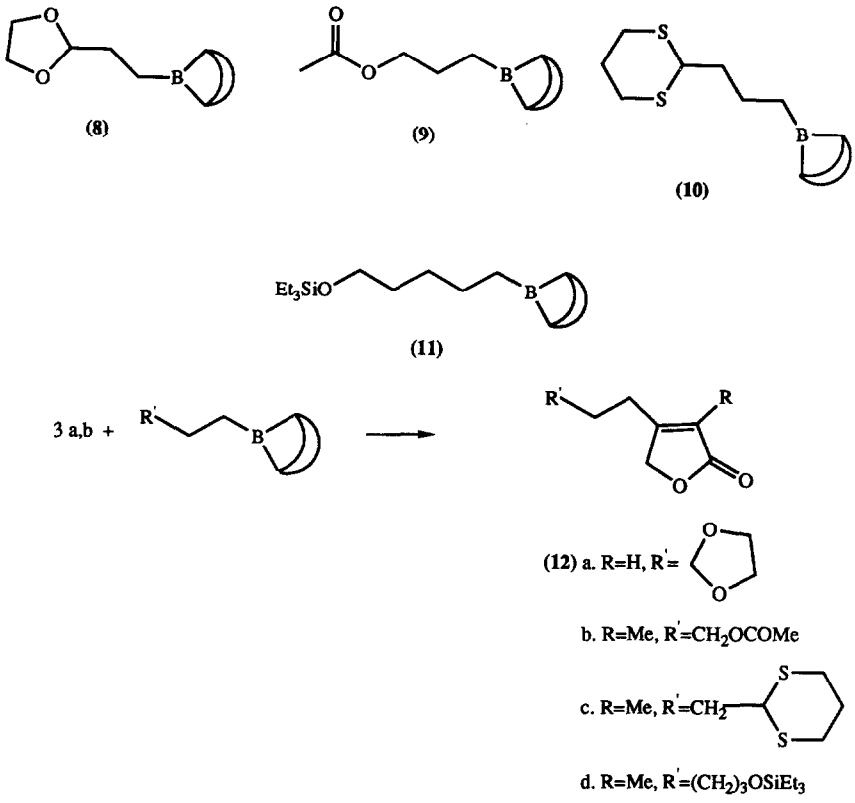


Table. Pd(0) catalysed cross-coupling of organoborane compounds with butenolide-3-triflates.[a]

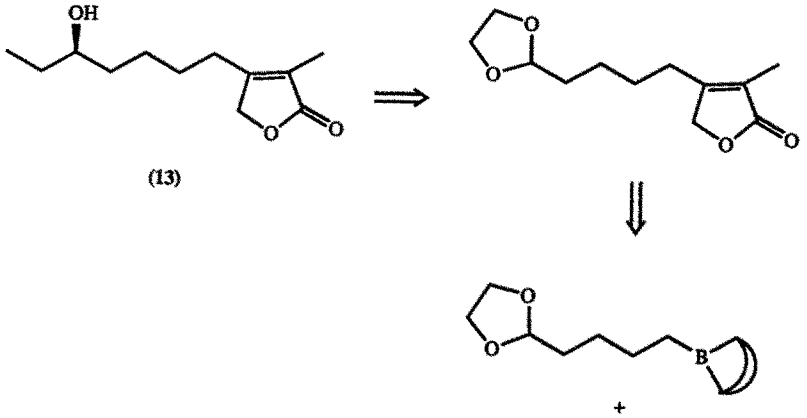
9-Alkyl-9-BBN	Triflate	Product	Yield(%)
8	3a	12a	51
9	3b	12b	40
10	3b	12c	75
11	3b	12d	67

a. All reactions were carried out in dioxan at 60°C in the presence of excess K_3PO_4.

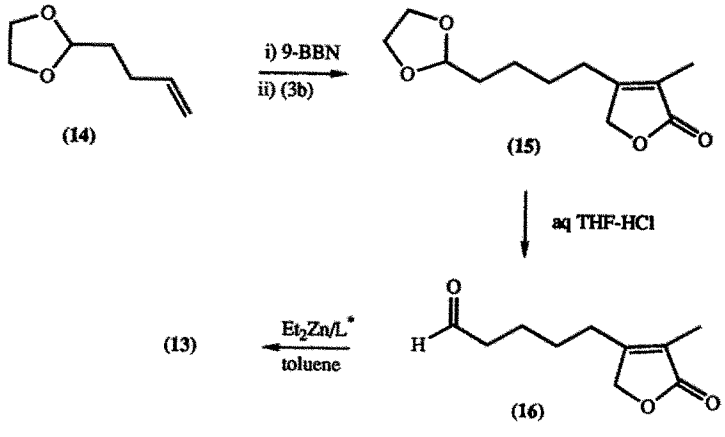
The results in the Table show the cross-coupling is tolerant of a range of functional groups in the 9-alkyl-9-BBN reactant and is not retarded by the adjacent methyl substituent in (3b). The potential of the reaction is further illustrated by its application to a short synthesis of (-)-isoseiridine (13).[8] Isoseiridine is a phytotoxin isolated from culture filtrates of *Seiridium cardinale*, the causal agent of cypress canker disease. It displayed significant antibacterial activity in preliminary experiments with *Pseudomonas Mig.* and *Bacillus Cohn.*

The retrosynthetic plan based on the Pd(0) butenolide triflate cross-coupling is summarised in Scheme 1. For the creation of the chiral centre it was planned to take advantage of the high asymmetric inductions observed in the addition of diethylzinc to aldehydes in the presence of chiral bidentate ligands.[9]

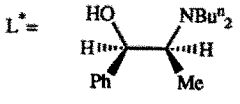
The protected aldehyde (14)[10] was cross-coupled with butenolide triflate as described previously. After column chromatography (15) was obtained in 57% yield. Deprotection of (15) in aqueous THF-HCl afforded the aldehyde (16)(82%) as a colourless oil. The aldehyde proton of (16) gives rise, surprisingly, to a singlet in the p.m.r. spectrum at δ9.79 ($CDCl_3$, 300MHz).



(13) Scheme 1 (3b)



(14) (15) (13) (16)



(17)

The final step, the addition of diethylzinc to the aldehyde (16), was performed in toluene at 0°C in the presence of the chiral ephedrine derivative (17).[11] (-)-Isoseiridine was isolated in 77% yield as a colourless oil. Chiral hplc (Chiralpak AD column, Daicel) eluting with 10% i-PrOH-hexane showed the product to be formed with 88% e.e. which accorded with its measured $[\alpha]_D$ of -5.2° (lit.[8] $[\alpha]_D$ -6.3°).

Experimental. General experimental details were as previously described.[12]

General Procedure for Preparation of Triflates. This method was adapted from that of Farina et al.[13] Ethyl diisopropylamine (4.4mmol) was added to a stirred solution of the butenolide (2a,b)(4.4mmol) in dry methylene chloride (30ml) at -78°C followed by triflic anhydride (4.4mmol). The mixture was stirred at -78°C for 45 min., diluted with methylene chloride (70ml), washed with water, dried ($MgSO_4$), and the solvent evaporated. Distillation of the residual oil afforded the product.

Triflate (3a). Obtained (66%) as a colourless oil, b.p. 60-62°C/0.08mmHg (Found: C, 25.9; H, 1.25; S, 14.0. $C_5H_3F_3O_5S$ requires C, 25.85; H, 1.3; S, 13.8%); δ 4.90(s, 2H, CH_2) and 6.03(s, 1H,= CH); m/z(%) 232(M^+,5), 139(54) and 69(100).

Triflate (3b). Obtained (93%) as a colourless oil, b.p. (Kuglrohr temp.) 110°C/0.3mmHg (Found: C, 29.05; H, 2.05; H, 1.95; S, 12.8. $C_6H_5F_3O_5S$ requires C, 29.25; H, 2.05; S, 13.0%); δ 1.95(s, 3H, Me), and 4.92(s, 2H, CH_2); m/z(%) 246(M^+,14), 153(89), 113(26), 83(40) and 69(100).

General Procedure for Cross-coupling Reactions.

(a) Hydroboration. The alkene (2mmol) was added under an argon atmosphere to a THF solution of 9-BBN (0.5M, 2mmol) stirred and cooled to 0°C. The reaction mixture was allowed to warm to room temperature and stirred for a further 3h.

(b) Cross-coupling. Dioxan (12ml), $Pd(OAc)_2$ (0.1mmol), PPh_3 (0.2mmol), K_3PO_4 (6mmol) and the appropriate triflate (2.2mmol) were added to the mixture from (a) above and the resulting mixture was stirred and heated at 60°C for 15h. The cooled reaction mixture was then filtered, the filtrate evaporated, and the residue flash chromatographed (SiO_2) to afford the product.

Butenolide (12a). Purified by flash chromatography eluting with 1:1v/v ethyl acetate-petroleum ether. the product (51%) crystallised as colourless needles from petroleum ether-methylene chloride, m.p. 41-41.5°C (Found: C, 58.5; H, 6.45. $C_9H_{12}O_4$ requires C, 58.7; H, 6.5%); δ 2.0(m, 2H, $CHC\underline{H}_2CH_2$), 2.56(t, 2H, J7.6Hz, $CH_2C\underline{H}_2C$=), 3.8-4.0(m, 4H, OCH_2CH_2O), 4.77(s, 2H, ring CH_2), 4.95(t, 1H, J4.1Hz, OCHO) and 5.87(s, 1H, =CH); m/z(%) 183(M^+-1,3), 149(6), 73(100), 55(9) and 45(38).

Butenolide (12b). Obtained (40%) as a pale yellow oil after purification by flash chromatography eluting with 1:1 v/v ethyl acetate-petroleum ether. (Found: C, 60.8; H, 7.25. $C_{10}H_{14}O_4$ requires C, 60.6; H, 7.05%); δ 1.84(s + m, 5H, MeC= and $CH_2C\underline{H}_2CH_2$), 2.06(s, 3H, MeCO), 2.48(t, 2H, J7.9Hz, $CH_2C\underline{H}_2C$=), 4.09(t, 2H, J6.4Hz, CH_2OCO), and 4.68(s, 2H, ring CH_2); m/z(%) 198(M^+,5), 138(54), 127(11), 109(58), 97(18), 81(39) and 43(100).

Butenolide (12c). Flash chromatography eluting with 2:3 v/v ethyl acetate-petroleum ether followed by

crystallisation from ether afforded the product (75%) as pale yellow needles, m.p. 58-59°C (Found: C, 55.9; H, 7.15; S, 24.7. $C_{12}H_{18}O_2S_2$ requires C, 55.8; H, 6.95; S, 24.8%); δ 1.62-2.17(m, 9H), 2.44 (t, 2H, J7.4Hz, $CH_2C\underline{H}_2C$=), 2.88(m, 4H), 4.07(t, 1H, J3.6Hz, SCHS) and 4.67(s, 2H, butenolide ring CH_2); m/z(%) 258(M^+,38), 185(9), 152(100), 119(94), 106(78), 74(40) and 41(69).

Butenolide (12d). Flash chromatography eluting with 3:7v/v ethyl acetate-petroleum ether afforded the product (67%) as a colourless oil. (Found: C, 64.55; H, 10.15. $C_{16}H_{30}O_3Si$ requires C, 64.45; H, 10.05%); δ 0.60(q, 6H, J7.9Hz, $MeC\underline{H}_2Si$), 0.95(t, 9H, $\underline{Me}CH_2Si$), 1.39-1.61 [m, 6H, $(CH_2)_3$], 1.82(s, 3H, MeC=), 2.42(t, 2H, J7.2Hz, $CH_2C\underline{H}_2C$=), 3.60(t, 2H, J6.3Hz, $C\underline{H}_2OSiEt_3$) and 4.66(s, 2H, ring CH_2); m/z(%), 269(M-29, 100), 241(26), 157(30), 103(52) and 75(35).

Butenolide (15). Flash chromatography eluting with 1:1 v/v ethyl acetate-petroleum ether afford the product (57%) as a colourless oil. (Found: C, 63.45; H, 8.05. $C_{12}H_{18}O_4$ requires C, 63.7; H, 7.95%); δ 1.43-1.73 [m, 6H, $(CH_2)_3$], 1.82(s, 3H Me), 2.43(t, 2H, J7.0Hz, $CH_2C\underline{H}_2C$=), 3.91(m, 4H, OCH_2O), 4.66(s, 2H, butenolide ring CH_2) and 4.85(t, 1H, J4.6Hz, OCHO); m/z(%) 225(M-1,3), 164(4), 125(4), 112(7), 95(3), 73(100) and 45(24).

Butenolide (16). A solution of the acetal (15) (460mg) in a mixture of THF (20ml) and 5% hydrochloric acid (4.1ml) was heated at 70°C for 3h. The solution was then neutralised with 10% aqueous sodium bicarbonate and the mixture extracted with methylene chloride. The combined chloride extracts were dried ($MgSO_4$) and evaporated and the residue chromatographed (SiO_2) eluting with ether to afford the product as a colourless oil (300mg, 82%). Found: C, 65.85; H, 7.8. $C_{10}H_{14}O_3$ requires C, 65.95; H, 7.7%); δ 1.6 [m, 4H, $(CH_2)_2$], 1.83(s, 3H, Me), 2.47(m, 4H, $C\underline{H}_2CHO$ and $CH_2C\underline{H}_2C$=), 4.67(s, 2H, ring CH_2) and 9.79(s, 1H, CHO); m/z(%) 183(M+1, 2), 164(22), 154(10), 125(48), 112(100), 97(29), 81(46), 73(48), 55(81) and 41(66).

(-)-Isoseiridine (13). Diethyl zinc (0.6ml, 1M hexane solution 0.6mmol) was added to a stirred solution of aldehyde (16)(50mg, 0.28mmol) and ephedrine ligand (17) (4mg, 0.0164mmol) in toluene (2ml) cooled to 0°C. The mixture was stirred at 0°C for 36h when 1M hydrochloric acid (1ml) was added and the mixture extracted with methylene chloride. The methylene chloride extract was dried ($MgSO_4$), the solvent evaporated and the residue purified by column chromatography (SiO_2) eluting with 2:3 v/v ethyl acetate-petroleum ether. The **product** (36mg, 77%), $\alpha]_D$-5.2°(c=0.25, CH_2Cl_2), (lit.[8] $\alpha]_D$-6.3°) was isolated as a colourless oil together with a small amount of aldehyde (16)(10mg). The enantiomeric excess was determined as 88% by hplc [Chiralpak AD column (Daicel)] eluting with 10% i-PrOH-'hexane with a flow rate of 0.6ml/min. The 'H n.m.r. spectrum of the **product** was consistent with that reported in the literature.[8] δ 0.95(t, 3H, $M\underline{e}CH_2$), 1.66-1.25(m, 8H), 1.83(s, 3H, MeC=), 2.43(br m, 2H, CH_2C=C), 3.53(br m, 1H, $C\underline{H}OH$) and 4.66(s, 2H, ring CH_2); m/z(%), 212($M,^+2$), 194(13), 183(61), 165(28), 149(23), 125(100), 112(93), 95(67), 59(82) and 41(72).

We thank Roussel and Leeds University for support.

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(*Received in UK* 20 *January* 1994; *revised* 24 *February* 1994; *accepted* 4 *March* 1994)