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Atom Economy A Simple Pd Catalyzed Addition of Pronucleophiles With Dienes

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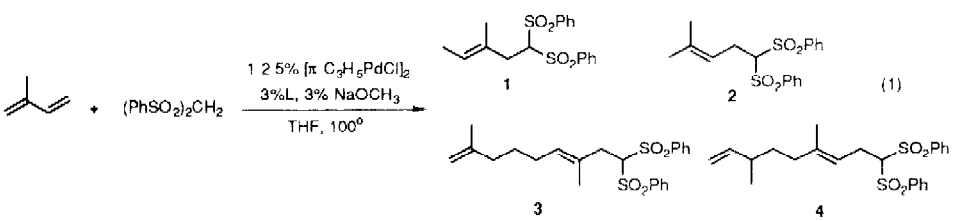
Summary. Replacing allylic alkylations involving allylic halides, carboxylates etc by the simple addition of pronucleophiles to dienes enhances efficiency of use of raw materials and reduces generation of stoichiometric by-products

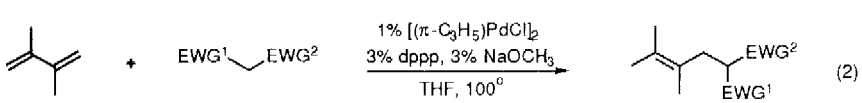
Considering the need to increase our repertoire of reactions that involve summing the reactants to create the desired products, i e. that maximize atom economy, we considered the formation of allylic alkylation products by transition metal catalyzed addition of pronucleophiles to dienes Such reactions normally have been complicated by the oligomerization of the diene competitive with the simple 1:1 addition [1-4] We report a simple practical catalyst system that permits efficient 1 1 addition and its applicability to the synthesis of a pseudoionone intermediate [3a]

Our initial studies evaluated the condensation of bis(phenylsulfonyl)methane with isoprene (eq 1) As a source of the active Pd(0) catalyst, π-allylpalladium chloride dimer is reduced *in situ* with sodium methoxide in the presence of the ligand With monodentate ligands like triphenylphosphine (TPP) and tris(2,6-dimethoxyphenyl)phosphine (TDMPP), only 2 1



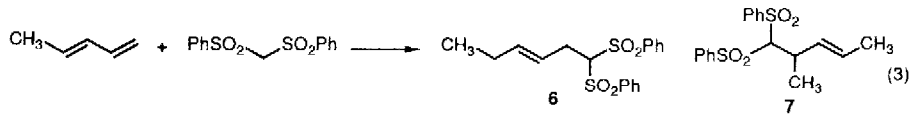
(diene pronucleophile) adducts form Interestingly, the choice of ligand dramatically affects the regioselectivity switching from 4 1 **3**:**4** with TPP (71% **3**, 18% **4**) to 1 6 **3**:**4** with the stronger donor ligand TDMPP (12% **3**, 70% **4**) [5] Bidentate ligands dppf, dppb and dppe give 1 1 (**1** and **2**) and 2 1 (**3** and **4**) adducts almost equally *Surprisingly, dppp gives a 73:27 ratio favoring the 1 1 adducts at 70° that increases to 95 5 ratio (56% **1**, 32% **2**) at 100°C!*

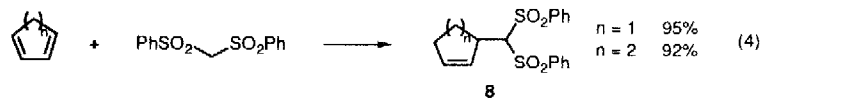
The condensation of 2,3-dimethylbutadiene explores the range of pronucleophiles using a standard set of conditions (eq 2) Esters, ketones and sulfones as the EWG in the pronucleophiles all lead to excellent yields[5] of 1 1 adducts **5** of a single regioisomer

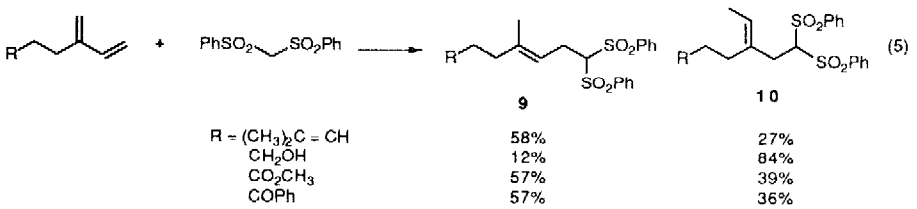


EWG^1	$PhSO_2$	$PhSO_2$	$PhSO_2$	CH_3CO
EWG^2	$PhSO_2$	CO_2CH_3	CH_3CO	CO_2CH_3
Yield	95%	92%	95%	99%

Variation of diene is explored using bis(phenylsulfonyl)methane as the pronucleophile because of the synthetic flexibility of sulfones (eqs 3-5). Excellent yields of 1 1 adducts (**6-10**) are obtained in all cases

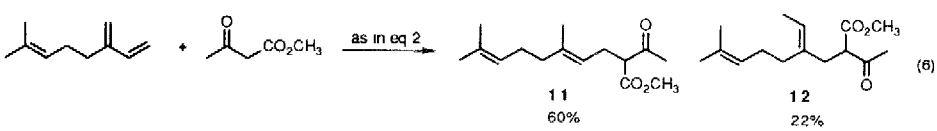






Olefin geometry is predominately (3.1) to exclusively **E** Regioselectivity depends upon diene substitution (eq 3) and the nature of the substituent (eq 5) The reaction is compatible with simple olefins, alcohols, ketones and esters in the diene fragment (eq 5) The speculative nature of any mechanistic considerations including interpretations of these effects precludes a detailed discussion at this time Suffice to say that π-allylpalladium complexes[6] are likely intermediates, since the new C-C bond always forms at the position allylic to the double bond of the product

The utility of 2-methoxycarbonyl-6,10-dimethyl-E,E-5,9-undecadien-2-one (**11**) as an intermediate for the synthesis of Vitamins A[7] and E[8] led us to also examine the condensation of technical grade myrcene with methyl acetoacetate (eq 6)[3] The major product is the pure E isomer **11**[9] in contrast to the olefin mixture formed in the aqueous rhodium catalyzed reaction [3a]



It appears that the simple addition of dienes to pronucleophiles whose pKa <20 to give allyl alkylation products is a selective process with wide applicability The special role of dppp to promote 1·1 adduct formation relative to other bidentate ligands and the inverse temperature effect on this selectivity are the keys The high atom economy makes such processes highly practical A general procedure follows. To a solution of 1 mmol of a pronucleophile, 1% of $[\pi\text{-}C_3H_5PdCl]_2$ and 3% of dppp in 4 mL of THF is added 4 mmol of diene After purging the solution with argon, a methanolic solution of sodium methoxide (3 mol% of methoxide) is added to reduce palladium The reaction is sealed under argon and heated at 100° for 3-5 h Removal of excess diene and solvent followed by chromatography gives the desired adducts [10]

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3 For a Rh catalyzed version, see a) Mercier C , Mignani, G , Aufrand, M , Allmang, G *Tetrahedron Lett* **1991**, *32*, 1433, b) Mignani, G , Morel, D ; Colleville, Y *Tetrahedron Lett* **1985**, *26*, 6337

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5 Yields are normally for isolated pure products with reactions going to 100% completion In two cases (eq 2 $EWG^1 = PhSO_2$ and $EWG^2 = CO_2CH_3$ and eq 4 n = 1) the yields are based upon recovered starting material

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10 The following characterization data for new compounds is recorded.

1 Mp 181-2°C IR($CDCl_3$) 1449,1332,1156, 1079 cm^{-1} ^1H NMR (300MHz, $CDCl_3$) δ 7 95 (d, J = 7 2Hz, 4H), 7 70 (t, J = 7.2Hz, 2H), 7 58 (t, J = 7.2Hz, 4H), 5 14 (q, J =6 7Hz, 1H), 4 59 (t, J =6 0Hz, 1H), 2 89 (d, J =6 0Hz, 2H), 1 43 (d, J = 6.7Hz, 3H), 1 38 (s, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 138 9, 135 1, 130 2, 129 6, 129 1, 124 9, 82 0, 35 4, 14 5, 13.7 Anal Calc'd for $C_{18}H_{20}O_4S_2$ C 59 32, H, 5 53; S, 17 59 Found C, 59 11, H, 5 60, S, 17 58

3 Mp 87-8°C. IR($CDCl_3$)· 1449, 1332, 1156, 1079 cm^{-1} ^1H NMR (300MHz, $CDCl_3$) δ 7 95 (d, J = 7 6Hz, 4H), 7 71 (t, J = 7 6Hz, 2H), 7.58 (t, J = 7.6Hz, 4H), 5 09 (t, J = 6 8Hz, 1H), 4 71 (s, 1H), 4 66 (s, 1H), 4 59 (t, J = 5 9Hz, 1H), 2 89 (d, J = 5 9Hz, 2H), 1 97 (t, J = 7 6Hz, 2H), 1.85 (td, J = 7 2, 6 8Hz, 2H), 1.70 (s, 3H), 1 43 (s, 3H), 1 40 (m, 2H) ^{13}C NMR (75MHz, $CDCl_3$) δ 146 3, 138 9, 135 1, 130 5, 130 2, 129 6, 128 8, 110 5, 82 2, 37 5, 35 4, 27 8, 27 3, 22 6, 15.1 Anal. Calc'd for $C_{23}H_{28}O_4S_2$· C, 63 86; H, 6.52, S, 14 82 Found submitted

4 Mp 67-8°C IR($CDCl_3$) 1448, 1331, 1312, 1155, 1079 cm^{-1} ^1H NMR (300MHz, $CDCl_3$) δ 7 97 (d, J = 7 3Hz, 4H), 7 70 (t, J = 7 3Hz, 2H), 7 58 (t, J = 7.3Hz, 4H), 5 65 (ddd, J = 17 5, 10.4, 7 7Hz, 1H), 5 05 (t, J = 6 3Hz, 1H), 4 94 (dd, J = 17 5, 1 0Hz, 1H), 4 93 (dd, J = 10 4, 1 0Hz, 1H), 4 42 (t, J = 6 3Hz, 1H), 2 87 (t, J = 6 3Hz, 2H), 2.05 (m, 1H), 1 86 (dd, J = 9 6, 6 2Hz, 2H), 1 45 (s, 3H), 1 26 (m, 2H), 0 97 (d, J = 6 8Hz, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 145 0, 140 5, 138.8, 135.1, 130 2, 129 6, 118 3, 113.4, 84 7, 37 7, 37 3, 34 7, 24 8, 20 3, 16 4 Anal Calc'd for $C_{23}H_{28}O_4S_2$ C, 63 86; H, 6 52, S, 14 82 Found. C, 63 90, H, 6 79, S, 14 65

5 ($EWG^1 = EWG^2 = PhSO_2$) Mp 179-180°C IR(neat) 1449, 1341, 1157, 1080 cm^{-1} ^1H NMR (300MHz, $CDCl_3$) δ 7 92 (d, J = 7 3Hz, 4H), 7 69 (t, J = 7 3Hz, 2H), 7 57 (t, J = 7 3Hz, 4H), 4 67 (t, J = 6 6Hz, 1H), 3 04 (d, J = 6 6Hz, 2H), 1 65 (s, 3H), 1 48 (s, 3H), 1 32 (s, 3H) ^{13}C NMR (75MHz, $CDCl_3$) δ 139 4, 135 0, 130 7, 129 9, 129 6, 120 5,

81.7, 30.7, 21.3, 21.0, 17.0. Anal. Calc'd for $C_{19}H_{22}O_4S_2$: C, 60.29; H, 5.86; S, 16.94. Found: C, 60.33; H, 5.91; S, 16.71.

6 and 7 Mp 109-110°C. ^{1}H NMR (300MHz, $CDCl_3$) **6** δ 8.00-7.78 (m, 4H), 7.73-7.51 (m, 6H), 5.72 (ddd, J = 15.1, 7.9, 1.6Hz, 1H), 5.35 (dq, J = 15.1, 7.5Hz, 1H), 4.55 (t, J = 1.7Hz, 1H), 3.32 (quint, J = 7.2Hz, 1H), 1.57 (dd, J = 7.5, 1.0Hz, 3H), 1.35 (d, J = 7.2Hz, 3H). **7** δ 8.00 - 7.78 (m, 4H), 7.73 - 7.53 (m, 6H), 5.50 - 5.30 (m, 2H), 4.44 (t, J = 5.8Hz, 1H), 2.88 (t, J = 5.8Hz, 2H), 1.92 (quint, J = 7.5Hz, 2H), 0.89 (t, J = 7.5Hz, 3H). Anal. Calc'd for $C_{18}H_{20}O_4S_2$: C, 59.32; H, 5.53; S, 17.59. Found: C, 59.54; H, 5.73; S, 17.66.

8 (n = 1) Mp 136-7°C. IR(neat) 1447, 1329, 1312, 1156, 1079 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ 8.02 - 7.80 (m, 4H), 7.72 - 7.50 (m, 6H), 5.82- 5.75 (m, 1H), 5.43 - 5.39 (m, 1H), 4.77 (d, J = 3.0Hz, 1H), 3.88 - 3.78 (m, 1H), 2.45 - 2.28 (m, 2H), 2.14 (q, J = 8.3Hz, 2H). ^{13}C NMR (75MHz, $CDCl_3$) δ 140.4, 139.3, 135.3, 135.1, 134.9, 134.6, 130.5, 130.2, 130.0, 129.7, 129.6, 129.5, 128.7, 86.8, 44.9, 32.3, 27.3. Anal. Calc'd for $C_{18}H_{18}O_4S_2$: C, 59.65; H, 5.01; S, 17.69. Found: C, 59.56; H, 5.23; S, 17.55.

9 [R = $(CH_3)_2C$ = CH] Mp 84-5°C. IR (neat): 1448, 1331, 1312, 1155, 1079 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.97 (d, J = 7.3Hz, 4H), 7.70 (t, J = 7.3Hz, 2H), 7.58 (t, J = 7.3Hz, 4H), 5.05 (t, J = 6.9Hz, 1H), 5.00 (t, J = 6.9Hz, 1H), 4.42 (t, J = 6.2Hz, 1H), 2.88 (dd, J = 6.9, 6.2Hz, 2H), 2.00 - 1.78 (m, 4H), 1.67 (s, 3H), 1.58 (s, 3H), 1.44 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 140.2, 138.8, 135.1, 132.4, 130.2, 129.7, 124.4, 118.6, 84.7, 39.7, 26.5, 25.9, 24.8, 17.9, 16.3. Anal. Calc'd for $C_{23}H_{28}O_4S_2$: C, 63.86; H, 6.52; S, 14.82. Found: C, 64.02; H, 6.68; S, 14.56.

10 [R = $(CH_3)_2$ C = CH] ^{1}H NMR (300MHz, $CDCl_3$) δ 7.95 (d, J = 7.3Hz, 4H), 7.70 (t, J = 7.3Hz, 2H), 7.58 (t, J = 7.3Hz, 4H), 5.16 (t, J = 6.8Hz, 1H), 5.05 (t, J = 6.9Hz, 1H), 4.59 (d, J = 6.0Hz, 1H), 2.89 (d, J = 6.0Hz, 2H), 2.00 - 1.78 (m, 4H), 1.67 (s, 3H), 1.58 (d, J = 6.8Hz, 3H), 1.47 (s, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 139.0, 135.1, 133.5, 133.0, 130.2, 129.6, 125.3, 123.9, 82.3, 32.8, 28.5, 26.5, 25.9, 17.8, 13.6. Anal. Calc'd for $C_{23}H_{28}O_4S_2$: C, 63.86; H, 6.52; S, 14.82. Found: C, 64.02; H, 6.68; S, 14.56.

9 (R = CH_2OH) IR(neat): 3545, 3410, 1448, 1331, 1156, 1079 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.94 (t, J = 7.5Hz, 4H), 7.69 (d, J = 7.5Hz, 2H), 7.57 (t, J = 7.5Hz, 4H), 5.34 (q, J = 6.9Hz, 1H), 4.80 (t, J = 6.3Hz, 1H), 3.55 (t, J = 6.2Hz, 2H), 3.01 (d, J = 6.3Hz, 2H), 1.92 (t, J = 7.6Hz, 2H), 1.73 (bs, 1H), 1.58 (d, J = 6.9Hz, 3H), 1.55 - 1.46 (m, 2H). ^{13}C NMR (75MHz, $CDCl_3$) δ 138.8, 135.1, 132.8, 130.0, 129.6, 124.6, 81.4, 62.4, 31.5, 30.8, 25.8, 13.9. Calc'd for $C_{13}H_{17}O_3S$ (M^+ - SO_2Ph) 267.1054. Found: 267.1051.

10 (R = CH_2OH) Mp 123-5°C. IR(neat) 3545, 3410, 1448, 1331, 1156, 1079 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) δ 7.94 (t, J = 7.5Hz, 4H), 7.69 (d, J = 7.5Hz, 2H), 7.57 (t, J = 7.5Hz, 4H), 5.16 (q, J = 6.9Hz, 1H), 4.68 (t, J = 5.8Hz, 1H), 3.55 (t, J = 6.2Hz, 2H), 2.92 (d, J = 5.8Hz, 2H), 1.92 (t, J = 7.6Hz, 2H), 1.73 (bs, 1H), 1.55 - 1.46 (m, 2H), 1.45 (d, J = 6.9Hz, 3H). ^{13}C NMR (75MHz, $CDCl_3$) δ 138.9, 135.1, 133.3, 130.2, 129.6, 125.6, 82.0, 62.5, 32.6, 30.7, 24.4, 13.6. Anal. Calc'd for $C_{20}H_{24}O_5S_2$: C, 58.80; H, 5.92; S, 15.70. Found: C, 58.80; H, 5.94; S, 15.65.

12 IR(neat): 1745, 1719, 1436, 1358 cm^{-1}. ^{1}H NMR (300MHz, $CDCl_3$) **E** (70%) δ 5.24 (q, J = 6.7Hz, 1H), 5.15 - 5.05 (m, 1H), 3.72 (s, 3H), 3.64 (t, J = 7.7Hz, 1H), 2.56 (d, J = 7.7Hz, 2H), 2.22 (s, 3H), 2.08 - 2.00 (m, 4H), 1.68 (s, 3H), 1.57 (s, 3H), 1.56 (d, J = 6.7Hz, 3H), **Z** (30%) δ 5.34 (q, J =6.7Hz, 1H), 5.15 - 5.05 (m, 1H), 3.73 (s, 3H), 3.61 (t, J = 7.6Hz, 1H), 2.63 (d, J = 7.6Hz, 2H), 2.23 (s, 3H), 2.08 - 2.00 (m, 4H), 1.68 (s, 6H), 1.60 (d, J = 6.7Hz, 3H). Anal. Calc'd for $C_{15}H_{24}O_3$: C, 71.39; H, 9.59. Found: C, 71.49; H, 9.40.

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