



Observations on Some Pd⁰ Catalysed Intermolecular Reaction of Electron Deficient Alkylidene Cyclopropanes with Olefins : A Novel Route to Highly Functionalised Skipped Diene Units.

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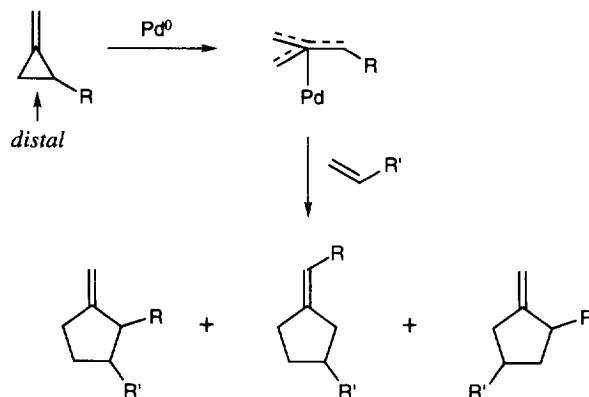
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Abstract : Methylene cyclopropanes **1** bearing an electron withdrawing group react under palladium (0) catalysis with electron poor olefins to give skipped dienes **2**. This reaction, which is believed to proceed via hydride transfer, highlights the fact that the reactivity of methylene cyclopropanes can be dramatically influenced by the nature of ring substituents.

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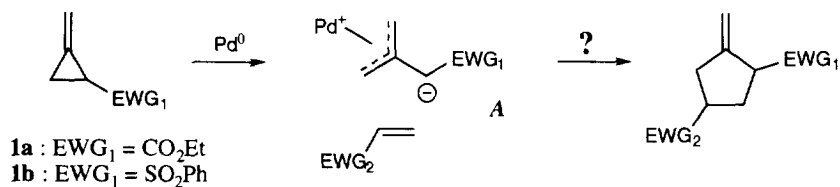
The pioneering and comprehensive studies of Binger¹ have established that the methylenecyclopropane unit is a particularly attractive trimethylenemethane synthon for transition mediated [3+2] cycloaddition reactions with olefinic and acetylenic acceptors; and that its inherent chemical reactivity complements the alternative related bifunctional conjunctive reagents introduced by Trost.²

However as shown in scheme 1, considerable problems of efficiency and regioselectivity can arise in the simplest intermolecular reactions despite the fact that palladium⁰ catalysis is known to proceed via exclusive distal bond cleavage of the cyclopropane ring, irrespective of the substitution pattern involved. A greatly improved level of regio- and stereocontrol is of course possible through the selection of the entropically favoured intramolecular variant of this reaction,³ which has proved to be increasingly popular in recent times.



Scheme 1

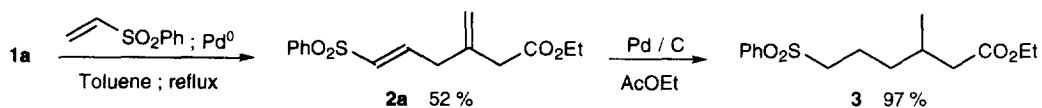
We were particularly intrigued by the possibility that the introduction of an electron withdrawing group on the cyclopropane ring, as in the case of the ester **1a** or the sulfone **1b** would predispose the resultant trimethylenemethane derivative to behave in a more electronically biased fashion as implied by structure **A**, with the possible consequent implications for a greater degree of asynchronous bond formation and regiocontrol shown in scheme 2.



Scheme 2

The known ester **1a** was accordingly prepared by Michael addition of 1-chloro-1-nitroethane to ethyl acrylate, followed by sodium hydride induced cyclisation and elimination,⁴ and sulfone **1b** was also available by a modified literature sequence⁵ involving formation of the dibromocyclopropane adduct from reaction of dibromocarbene with phenyl vinyl sulfide, followed by methylation with butyllithium and methyl iodide, subsequent dehydrohalogenation with potassium *tert*-butoxide, and finally oxidation with Oxone®.

Ester **1a** was then subjected to palladium catalysis under standard conditions⁶ in the presence of phenyl vinyl sulfone as an olefinic trap. To our initial surprise, no trace of a cyclopentanoid derivative was formed under these conditions, and the n.m.r. spectrum of the isolated product was consistent with the formation of the open chain skipped diene **2a** in which clean alkylation of the vinyl sulfone had occurred with total regiocontrol and with stereospecific formation of the (*E*) alkene (scheme 3). Subsequent hydrogenation of **2a** over a palladium on carbon catalyst afforded **3** thereby confirming the presence of an *exo*-methylene group in the initial adduct.



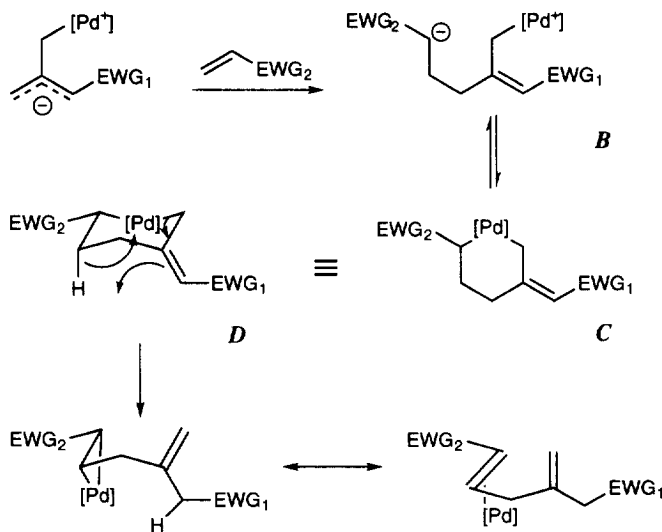
Scheme 3

The results of our preliminary study are shown in the Table and reveal that ester **1a** can also be induced to react with acrylate and fumarate acceptors, although in the later case, as is commonly observed⁷, the problem of alkene isomerisation when using a disubstituted olefinic acceptor led to a 70:30 mixture of geometric isomers in the case of **2c**. By way of contrast, the behavior of the sulfone congener **1b** indicates that while phenyl vinyl sulfone can be used as the alkene trap to give **2d**, all efforts to use acrylate acceptors (R=Me, Et, Bu) were uniformly unsuccessful, and only starting materials were recovered.

Table : Reaction of Alkylidenecyclopropanes **1a** et **1b** with Electron Deficient Acceptors.

Methylene cyclopropane	Olefin	Product	Yield	<i>E/Z</i> ratio
1a			45	100 / 0
1a			30	70 / 30 ⁶
1b			39	100 / 0
1b		no reaction	-	-

From a mechanistic standpoint, it is apparent that the formation of the crucial carbon-carbon bond does not occur as implied in scheme 2 but at the "γ terminus" of the allyl unit to afford an intermediate **B** which can also formally be represented as the metallacycle **C** in which the substituent preferentially adopts a pseudoequatorial position (scheme 4). At this stage it is clear that the subsequent β-hydride elimination step, which is responsible both for the stereospecific formation of the (*E*) alkene and leads to exclusive formation of an exomethylene terminus, is energetically preferred over reductive elimination to give the five membered ring. Although reactions involving the commonly accepted 4-electron-4-centre mechanism can be written, it is tempting to speculate that the presence of the β-γ unsaturated unit in the metallacycle also allows a cyclic 6-electron-6-centre transition state (arrows as in **D**) to be involved. This would formally generate a metallacyclopropane which is equivalent to the π-2 alkene complex and evidence for such mechanisms in π-allylpalladium chemistry have recently been presented.⁸

**Scheme 4**

From a more practical synthetic viewpoint, the present method provides a useful route to highly functionalised and chemically differentiated skipped dienes which have considerable potential for further classical transformations.

Acknowledgements

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References and Notes

- For reviews see Binger, P.; Büch, H.M. *Top. Curr. Chem.*, **1987**, *135*, 77. Ohta, T.; Takaya, H. in *Comprehensive Organic Synthesis*, Trost, B.M.; Ed. Pergamon Press: Oxford, **1991**, vol. 5, p 1185.
- Trost, B.M.; Chan, D.M.T. *J. Am. Chem. Soc.*, **1979**, *101*, 6429. For reviews see Trost, B.M. *Angew. Chem., Int. Ed. Engl.*, **1986**, *25*, 1. Trost, B.M. *Pure Appl. Chem.*, **1988**, *60*, 1615.
- Lewis, R.T. Motherwell, W.B.; Shipman, M. *J. Chem. Soc. Chem. Commun.*, **1988**, 948. Yamago, S.; Nakamura, E. *J. Chem. Soc. Chem. Commun.*, **1988**, 1112. Yamago, S.; Nakamura, E. *Tetrahedron* **1989**, *45*, 2887. Bapuji, S.A.; Motherwell, W.B.; Shipman, M. *Tetrahedron Lett.*, **1989**, *30*, 7107. Motherwell, W.B.; Shipman, M. *Tetrahedron Lett.*, **1991**, *32*, 1103. Lautens, M.; Ren, Y.; Delanghe, P.H.M. *J. Am. Chem. Soc.*, **1994**, *116*, 8821. Lewis, R.T.; Motherwell, W.B.; Schipman, M.; Slawin, A.M.Z.; Williams, D.J. *Tetrahedron* **1995**, *51*, 3289. Corlay, H.; Lewis, R.T. Motherwell, W.B.; Schipman, M. *Tetrahedron* **1995**, *51*, 3303. Corlay, H.; Motherwell, W.B.; Pennel, A.M.K.; Schipman, M.; Slawin, A.M.Z.; Williams, D.J.; Binger, P.; Stepp, M. *Tetrahedron* **1996**, *52*, 4883.
- Russel, G.A.; Makosza, M.; Hershberger, J. *J. Org. Chem.*, **1979**, *44*, 1195.
- Weber, A.; Sabbion, G.; Galli, R.; Stömpfi, U.; Neuenschwander, M. *Helv. Chim. Acta*, **1988**, *71*, 2031.
- In a 25 ml round-bottomed flask was added triisopropylphosphite (75 μ l, 4.0 eq/Pd) to a purple solution of Pd₂(dba)₃ (35.6 mg) in anhydrous toluene (1.5 ml) to give a green solution upon sonication for 10 minutes. A solution of phenyl vinyl sulfone (517 mg, 4.0 eq) and 1-phenylsulphonyl-2-methylenecyclopropane **1b** (150 mg) in anhydrous toluene (3.5 ml) was then added and the reaction was heated under argon at reflux for 30h. After cooling the reaction was filtered and removal of the solvents afforded an orange oil. Chromatography on silica gel column (dichloromethane:ether 80:20) gave the recovered sulfone (460 mg, 3.56 eq), **1b** (70 mg, 0.47 eq) and the skipped diene **2d** as a white solid (109 mg, 39 %). Spectral data for **2d** ¹H NMR (400 MHz in CDCl₃) δ (ppm) *J* (Hz) : 7.86-7.78 (4H, m), 7.65-7.49 (6H, m), 6.88 (1H, dt, *15.0*, *7.1*), 6.37 (1H, dt, *15.0*, *1.4*), 5.07 (1H, bs), 4.85 (1H, bs), 3.70 (2H, s), 3.14 (2H, d, *7.1*). ¹³C NMR (126 MHz in CDCl₃) δ (ppm) : 142.2, 140.1, 137.8, 133.9 (2C), 133.5 (2C), 133.1, 132.8, 129.3 (2C), 129.1 (2C), 128.3 (2C), 127.6, 123.0, 62.3, 37.1. IR (cm⁻¹) : 3061, 1629, 1585, 1447, 1308, 1148, 1085, 916, 804, 752, 729, 688 neat. m/z : 362 (M⁺), 221, 195, 141, 131, 125, 115, 105, 97, 91.
- Isomerisations are frequently reported when using disubstituted olefins either with Pd⁽⁰⁾ or Ni⁽⁰⁾ catalysts see Binger, P.; Wedemann, P. *Tetrahedron Lett.*, **1985**, *26*, 1045. Binger, P.; Schuchardt, U. *Chem. Ber.*, **1981**, *114*, 3313.
- Keinan, E.; Kumar, S.; Dangur, V.; Vaja, J. *J. Am. Chem. Soc.*, **1994**, *116*, 1151.