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Carbopalladation of functionalized allenes : Regioselectivity of the reaction of carbonucleophiles with the intermediate π-allyl palladium complexes.

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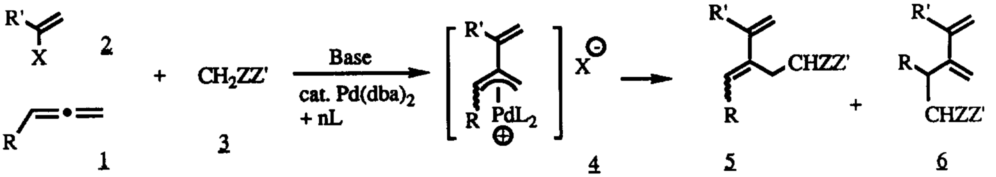
Abstract *. Carbopalladation of functionalized allenes leads to π-allyl palladium complexes, the regiochemistry of which towards carbonucleophiles has been studied : a methoxy group has been demonstrated to reverse the classical regioselectivity and to allow the formation of the more substituted product.*

Carbopalladation of allenic compounds 1 by vinylic or arylic palladium species, generated in situ from unsaturated halides or triflates 2 and a Pd(0)L_n catalyst allows 2-substituted π-allyl palladium complexes 4 to be formed. These intermediates react with high regio and stereoselectivity with carbonucleophiles 3 and lead to 1,3-dienic (or styryl) compounds 5 [1, 2]. This overall palladium-catalyzed three component reaction does provide straightforward access to several classes of functionalized dienic compounds 5 such as unsaturated α-amino acids [3] or dienylsilanes [4].



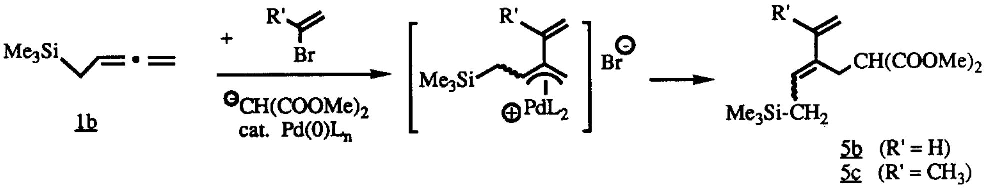
Using bis(dibenzylideneacetone)palladium associated with 1,2-bis(diphenylphosphino)ethane (dppe) or triphenylphosphine as the catalytic system, we isolated the diene 5 as the major compound. The regioisomer 6 , corresponding to the nucleophilic attack of the carbonucleophile on the less hindered terminus of the intermediate π-allyl complex 4 , was either undetectable or present in a very small amount (< 10-15 %) [1] , as usually observed for "classical" (unsubstituted by a conjugated group on the central carbon atom) monosubstituted π-allyl palladium complexes.

The regioselectivity of the nucleophilic substitution of a π-allyl palladium complex is known to depend on several parameters such as the nature (acceptor or donor ligand) of the phosphine [5] or of the nucleophile [6]. Another prominent factor is the substitution pattern of the two terminal carbons of this complex, the influence of which is dependent on steric [7] and electronic effects [8] of the substituents. In particular, 1,1-dialkyl substituted π-allyl complexes have been demonstrated to react preferentially at the more substituted position, presumably because of some stabilisation of the positive charge of the complex on this position [9].

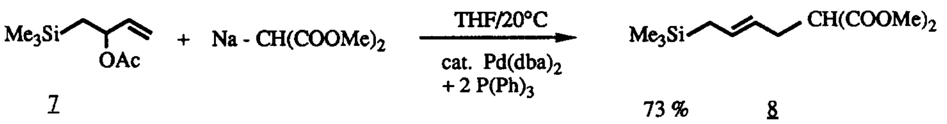
We report here our investigations on the changes observed in regioselectivity according to the nature of the R substituent of the allenic component 1 . We selected for our study four allenes 1a-d with R group [phenyl , (trimethylsilyl)methyl [10] and methoxy] which might be able to stabilise a positive charge on the secondary terminus of the catalytic π-allyl intermediate 4 . Furthermore these allenes 1a-d should lead to new functionalized (silylated or oxygenated) dienes 5 or 6 . Preliminary results of this study are listed in the table.

Following a standard reaction procedure [1,11] , phenylallene 1a gives the phenylbutadiene 5a as a major product (5a / 6a = 91/9) ; this regioselectivity is usually observed and seems to demonstrate that the phenyl group exhibits only a steric effect.

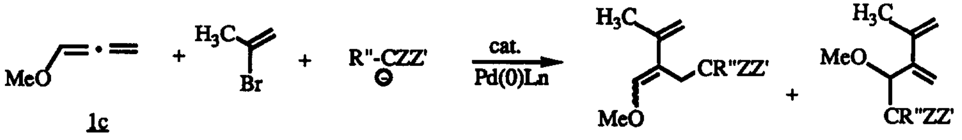
The same conclusion can be deduced for the effect of a (trimethylsilyl)methyl group, since the silylated allene 1b gives dienes 5b-c as the sole products.



Thus, the silicon β-effect does not seem to occur ; the dominating steric effect of the (trimethylsilyl)-methyl might be the consequence of a "neopentyl character" of this group, which has been also demonstrated with a more simple model 7 : this one leads regiospecifically to the malonate 8 .



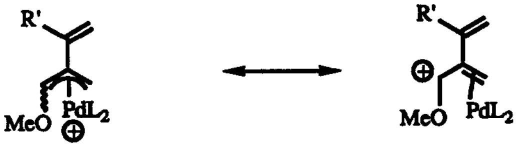
On the contrary, a methoxy group reverses totally the regioselectivity of the reaction : methoxyallene 1c associated with dimethyl malonate leads to diene 6d as the sole product, whereas its reaction with substituted acetylacetate or malonate yields again predominantly the regioisomers 6e and 6f .



			5		6
d	R" = H	Z = Z' = COOMe	0	/	100
e	R" = CH$_3$	Z = Z' = COOEt	8	/	92
f	R" = CH$_3$	Z = CO-Me Z' = COOEt	15	/	85

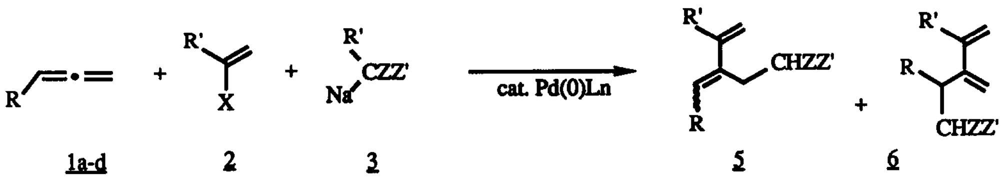
A mechanistic rationale for this large influence of a methoxy group on the regiochemistry is based upon the increased stabilisation of the positive charge of the intermediate complex on the more substituted secondary terminus. We can speculate that the electronic dissymetry of 4 (R = OMe) might be associated also with a dissymetric location of the palladium towards the primary carbon because of an electronic repulsion between the lone pairs of oxygen and the aromatic rings of the phosphine ligand . These two effects would direct the carbonucleophile with high regioselectivity onto the secondary carbon.

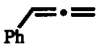
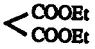
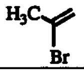
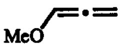
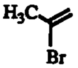
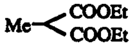
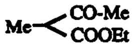
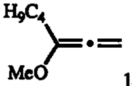
4 (R=OMe)



4' (R=OMe)

Table



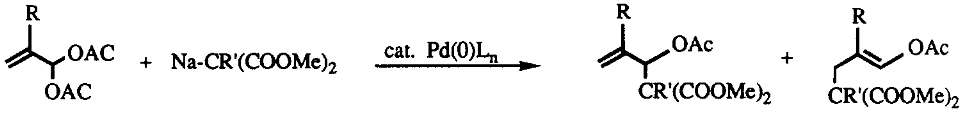
Allene 1	Vinyl derivative 2	Carbonucleophile 3		E/Z[b] 5	ratio 5 / 6	Yield[a] (5+6)
 1a			Pd(dba)2 + dppe 65°C/THF	35/65	91 / 9	69 %
 1b			Pd(dba)2 + dppe 65°C/THF	35/65	100 / 0	47 %
				100/0	100 / 0	21 %
 1c			Pd(dba)2 + dppe DMSO 40°C-20 h		0 / 100	94 %
"	"		Pd(dba)2 + dppe DMSO 40°C-20 h	67/33	8 / 92	62 %
"	"		Pd(dba)2 + dppe DMSO 40°C-20 h	23/77	15 / 85	60 %
 1d			Pd(dba)2 + dppe DMSO 55°C- 48 h		90 / 10	41 %

a) Yields are cumulative yields of 5(E+Z) and 6, isolated as pure materials through flash chromatography

b) The E/Z stereochemistry and ratio were assigned through proton NMR analysis.

The last result obtained with allene 1d demonstrates that the effect of the methoxy group is masked by the steric hindrance of another alkyl group on the same carbon : the nucleophilic attack on the less hindered pole is then restored.

To our knowledge this large influence of a methoxy group on the regioselectivity of the reaction of a π–allyl palladium complex had not been disclosed previously, although such methoxy substituted complexes had already been isolated [12]. However, two related studies have shown that some other oxygen-substituted π-allyl palladium complexes, generated from allylic geminal diacetates, react in some cases with a similar regioselectivity [13,14] :



$R = CH_3$, $R' = H$ 70 / 30
$R = H$, $R' = CH_3$ 0 / 100

Yet, from these and our present works, an acetoxy group seems to be less prone than a methoxy group to orient an attacking nucleophile to the allylic carbon bearing the oxygen atom.

Further mechanistic studies and synthetic applications involving the carbopalladation of alkoxyallenes are currently under investigation.

References and Notes

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10. For the stabilisation of a positive charge in β-position to a silicon atom see : Fleming, I. ; "Organic Silicon Chemistry", in *Comprehensive Organic Chemistry* (Barton, D.H.R. and Ollis, W. Eds) , Pergamon Press, Oxford, **1979** , vol 3 , p. 539.
11. Preparation of malonate 6d (R=OMe, R"=H) is given as a typical experiment : methoxyallene 1c (5.54 mmol) and isopropenyl bromide (3.47 mmol) were successively added to a solution at 20°C of $Pd(dba)_2$ (0.13 mmol, 3.7% molar), bis(diphenylphosphino)ethane dppe (0.14 mmol) and dimethylsodiomalonate (3.6 mmol ; obtained from the reaction of 6.9 mmol of malonate with 3.6 mmol of NaH) in DMSO (20 ml). The mixture was heated at 35°C for 20 h . Classical workup and flash-chromatography (Merck silica gel 60 ; petroleum ether/AcOEt : 70/30) gave 790 mg (94 %) of pure malonate 6d . ^1H NMR ($CDCl_3$, 300 MHz) , δ (ppm) : 1.91 (3H, s) ; 3.27 (3H, s) ; 3.65 and 3.75 [6H, 2 s, $CH(COOC\underline{H_3})(COOC\underline{H_3})$] ; 3.82 [1H, d, J=9.1 Hz, $C\underline{H}(COOCH_3)_2$] ; 4.61 (1H, d, J=9.1 Hz, $C\underline{H}$-OCH_3) ; 5.04 (1H,s) ; 5.29 (1H, s) ; 5.32 (1H,s) ; 5.35 (1H, s).
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