Palladium catalysed γ-addition of pronucleophiles to allenyl sulfides

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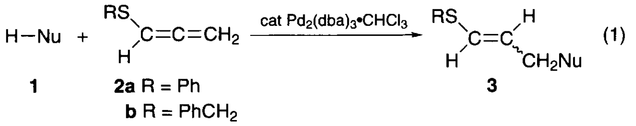
The palladium catalysed addition of pronucleophiles 1 to allenyl sulfides 2 gives the γ-addition products in good to high yields, whereas the addition to alkoxyallenes affords the α-addition products.

We previously reported that pronucleophiles **1** (H–Nu) add to the carbon–carbon double bond of allenes in the presence of a palladium catalyst to give the corresponding alkenes in good to high yields (hydrocarbonation reaction).[1] The regiochemistry of the addition depends upon the allene substituents; dialkyl-, monoalkyl- and aryl-allenes give terminal (γ) adducts,[1a] arylallenes bearing an electron withdrawing group at the *para*-position of the aromatic ring produce internal (β) adducts[1b] and alkoxy (or phenoxy) allenes afford α-adducts.[1c]

Here we report that the palladium catalysed addition of **1** to sulfur substituted allenes, allenyl sulfides **2**, gives the γ-addition products **3** in good to high yields [eqn. (1)]. This regioselectivity is in marked contrast to that obtained with oxygen substituted allenes. The results are summarized in Table 1.

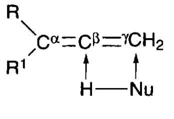


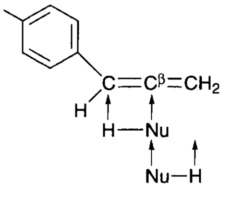
Ethyl cyanophenyl- and cyanomethyl-acetate and methylmalononitrile reacted smoothly with **2a** to give the corresponding γ-adducts in high yields with exclusive or predominant *E*-stereoselectivities (entries 1–3). The reaction of activated methylenes, such as malononitrile and ethyl cyanoacetate, afforded the double addition products in good to high yields (entries 4–5). The initial addition would give the ordinary mono-γ-adducts (activated methynes), which would be more reactive than the original activated methylenes. Further addition of the resulting methynes to **2a** would afford the double addition products. Even when 1 equiv. of allene and 1 equiv. of pronucleophile were utilized, the double addition product was obtained without being accompanied by formation of the mono-addition product. Not only the pronucleophiles bearing α-CN substituents but also Meldrum's acid derivatives (methylated and phenylated derivatives) reacted smoothly with **2a** and **2b** to give the corresponding γ-adducts in good to high yields (entries 6–7, 11–12). The reaction of Meldrum's acid itself afforded the corresponding double addition product, as was observed in entries 4–5 (entry 8). Not only allenyl phenyl sulfide but also allenyl benzyl sulfide reacted smoothly with the pronucleophiles to give the γ-adducts in good to high yields (entries 9–12).

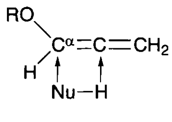
The general procedure is as follows. To the reaction flask charged with an allenyl sulfide (0.25 mmol), $Pd_2dba_3{\cdot}CHCl_3$ (5 mol%, 13 mg) and dppb (26 mol%, 28 mg) under an Ar atmosphere were added the pronucleophile (0.275 mmol) and THF (1.5 ml). The reaction mixture was heated under reflux for 12–16 h and monitored by TLC. When the starting allene was consumed, the reaction mixture was filtered through a silica gel column using hexane–ethyl acetate (20 : 1) as eluent. All yields were of pure products, and their HR mass and ^{1}H NMR data were satisfactory.

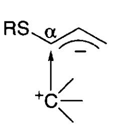
To help clarify the reason for the difference of the regioselectivity between the sulfanyl-**2**, alkoxy- and phenyl-substituted allenes, we measured their ^{13}C NMR spectra (Table 2). The α-carbon of phenoxyallene appeared at significantly lower field than those of phenyl- and phenylsulfanyl-allenes, indicating that the α-carbon is highly electrophilic. The α-regioselectivity of alkoxy (and aryloxy) allenes can be explained by the strong electrophilic character of the α-carbon. The γ-carbons of phenyl- and phenylsulfanyl-allenes exhibited similar δ values, suggesting the same regioselectivity would be obtained from these two allenes, which is actually the case. It is well accepted in heteroatom substituted allyl anion and allyl cation chemistry[2] that (i) an oxygen substituent stabilizes a neighbouring carbocation and destabilizes a neighbouring carbanion due to the electron donating effect of the oxygen atom, (ii) a sulfur substituent destabilizes a neighbouring carbocation and stabilizes a neighbouring carbanion due to the electron withdrawing effect of sulfur atom. A lower $\sigma^*_{\text{c-s}}$ level, compared to $\sigma^*_{\text{c-o}}$ level, may be the origin of the electron withdrawing effect of sulfur. Consequently, the classical and traditional heteroatom substituent effect of allylic carbocations and carbanions can be applied to understand the regioselectivity of a modern palladium catalysed addition reaction.

The present γ-addition reaction can be accounted for either by the hydro- or carbo-palladation mechanism as pointed out previously.[1,3] Irrespective of the precise mechanism, the remarkable difference of regioselectivities may be synthetically useful. For example, an easily available α-sulfur substituted allyl anion can afford an α-C–C bond forming product very









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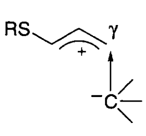

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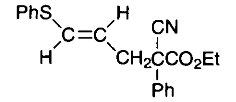
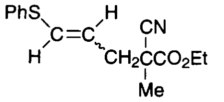
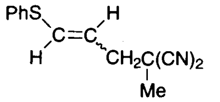
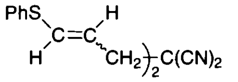
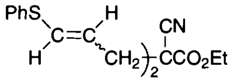
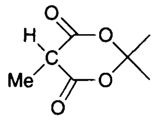
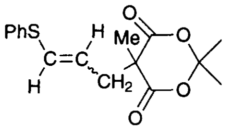
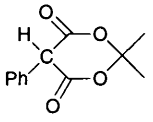
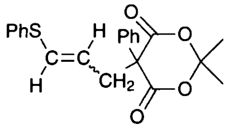
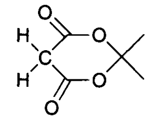
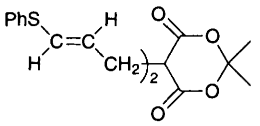
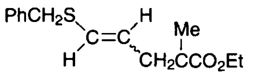
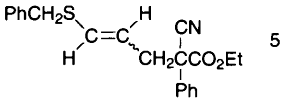
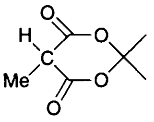
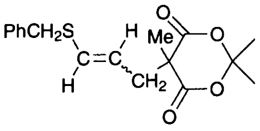
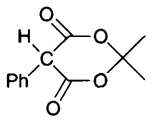
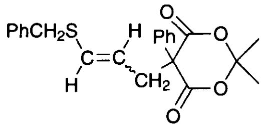
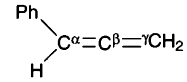
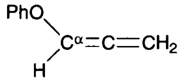
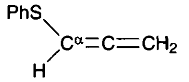
Table 1 Pd catalysed γ-addition of pronucleophiles **1** to allenyl sulfides **2**[a]

Entry	H–Nu **1**	Allene **2**	Product **3**	Isolated yield (%)	*E*/*Z*
1	$H{-}C(Ph)(CN)CO_2Et$	**a**		99	~100/0
2	$H{-}C(Me)(CN)CO_2Et$	**a**		89	77/23
3	$H{-}C(Me)(CN)_2$	**a**		81	70/30
4	$H{-}CH(CN)_2$[b]	**a**		74	~100/0
5	$H{-}CH(CN)CO_2Et$[b]	**a**		92	~100/0
6		**a**		67	91/9
7		**a**		87	79/21
8	 [b]	**a**		67	[c]
9	$H{-}C(Me)(CN)_2$	**b**		73	72/28
10	$H{-}C(Me)(CN)CO_2Et$	**b**		59	67/33
11		**b**		71	84/16
12		**b**		82	91/9

[a] A mixture of an allenyl sulfide (1 equiv.), pronucleophile (1.1 equiv.), $Pd_2dba_3{\cdot}CHCl_3$ (0.05 equiv.), and dppb (0.26 equiv.) in THF (1.5 ml) was heated under reflux, except where otherwise indicated. [b] 2 equiv. allene and 1 equiv. pronucleophile were used. [c] The exact ratio of *E*/*Z* was not determined, because a mixture of three stereoisomers (*EE*, *EZ*, *ZZ*) was produced.

readily (**4**), whereas formation of a γ-C–C bond forming product is not so easy available *via* allyl anion chemistry. The present Pd-catalysed system is a synthetic equivalent to the combination between a sulfur substituted allyl cation, not readily available, and a carbanion (**5**).

Table 2 ^{13}C NMR chemical shifts of substituted allenes

Allenes	δ[a]		
	α-C	β-C	γ-C
	93.788	209.580	78.497
	114.839	202.769	89.426
	85.940	209.200	78.670

[a] In $CDCl_3$. Me_4Si as internal standard.

References

1 (*a*) Y. Yamamoto, M. Al-Masum and N. Asao, *J. Am. Chem. Soc.*, 1994, **116**, 6019; (*b*) Y. Yamamoto, M. Al-Masum, N. Fujiwara and N. Asao, *Tetrahedorn Lett.*, 1995, **36**, 2811; (*c*) Y. Yamamoto and M. Al-Masum, *Synlett*, 1995, 969.

2 Y. Yamamoto, in *Comprehensive Organic Synthesis*, ed. B. M. Trost and I. Fleming, vol. 2, p. 55, Pergamon Press, 1991; W. C. Still and T. L. Macdonald, *J. Org. Chem.*, 1973, **95**, 2715.

3 B. M. Trost and V. J. Gerusz, *J. Am. Chem. Soc.*, 1995, **117**, 5156.

Received, 4th December 1995; Com. 5I07847D