Regioselectivity in Organo-transition-metal Chemistry. A Remarkable Steric Effect in π-Allyl Palladium Chemistry

Ehud Keinan* and Mahendra Sahai

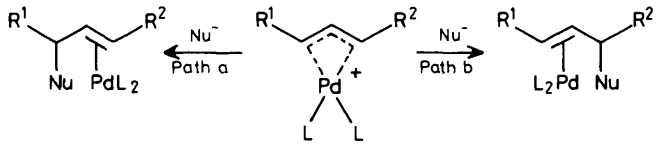
Department of Organic Chemistry, The Weizmann Institute of Science, Rehovot 76100, Israel

The regioselectivity of the palladium catalysed allylic substitution by several representative nucleophiles was found to be highly dependent on very small steric differences that exist at the two ends of the allylic system: attack by stabilized nucleophiles occurred at the less hindered position while PhZnCl led to substitution at the more hindered position.

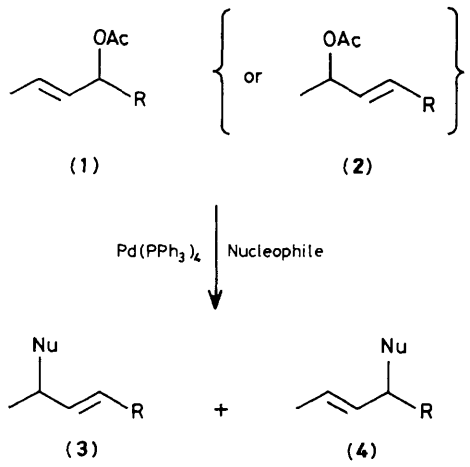
The usefulness of π-allyl palladium electrophiles in organic synthesis has been demonstrated by their deployment together with stabilized carbanions and amines for regioselective and stereospecific creation of new bonds.[1] The regioselectivity of attack by these nucleophiles on the allylic unit, possessing sterically non-equivalent allylic termini, has been postulated to be the net result of two competing driving forces[2] (Scheme 1): path a, preferential attack at the less-hindered terminus and path b, preferential formation of the less-hindered η^2 olefin–palladium complex. Consequently, regioselectivity could be controlled by modifying the steric bulk of either the nucleophile (Nu) and/or the ligand (L).

Evidence that 'harder' organometallic nucleophiles also react with π-allyl palladium intermediates is rapidly growing. Several useful examples involve organometallic reagents of tin,[3] zinc,[4] aluminium,[5] and zirconium.[5,6] While the stereospecificity observed in allylic alkylations with these non-stabilized nucleophiles could be explained by a transmetallation–reductive-elimination sequence,[7] regioselectivity in these reactions[6,7] has been scantily investigated and, therefore, remains much less understood.

In order to decipher this selectivity, we initiated a systematic study, trying to identify the factors governing it. We report here on a remarkable dependence of the regioselectivity of nucleophilic attack on the steric environment of the allylic system. Seven allylic acetates (**1**) or (**2**)† were allowed to react with five different nucleophiles in the presence of a catalytic amount (5—10%) of $Pd(PPh_3)_4$. All reactions were carried out in tetrahydrofuran (THF) at room temperature under N_2 atmosphere. The results given in Table 1 indicate a striking regioselectivity despite the small steric differences that exist at the two ends of the allylic unit. The following observations should be emphasized.



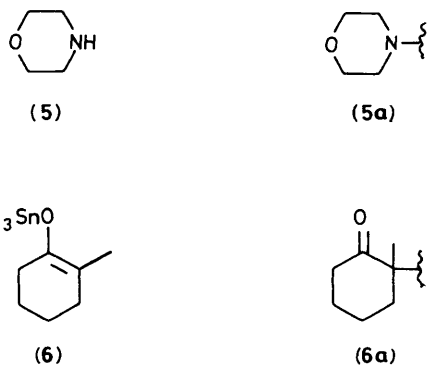
Scheme 1



The first four nucleophiles (**5**)—(**8**), on the one hand, and the fifth nucleophile phenyl zinc chloride, (**9**), on the other, represent two groups of nucleophiles which interact differently with the reactive allyl palladium intermediate.[7] The first group of four stabilized nuclephiles attack the allylic ligand at the less-hindered terminus with a high degree (80—100%) of selectivity, while the latter, a typical non-stabilized nucleophile also exhibits a very high degree (>99%) of selectivity, but in the opposite direction.[8]

The product distribution [ratio of (**3**) : (**4**)] is by no means a reflection of the relative thermodynamic stability of (**3**) and (**4**). This is evident from the palladium-catalysed equilibration of (**1**) and (**2**) which produces similar concentrations of both (last row, Table 1), as expected for simple disubstituted olefins.[9]

It has been previously observed that, in the case of stabilized nucleophiles,[10] the location of the leaving group in the starting material, (**1**) or (**2**), is irrelevant to the regioselectivity by which those nucleophiles attack the reactive intermediate. Table 1 suggests this feature to be true, not only for stabilized nucleophiles, but also for non-stabilized ones. The symmetric allylic intermediate derived from (**1**) R = CD_3, reacts nonregioselectively with all nucleophiles.

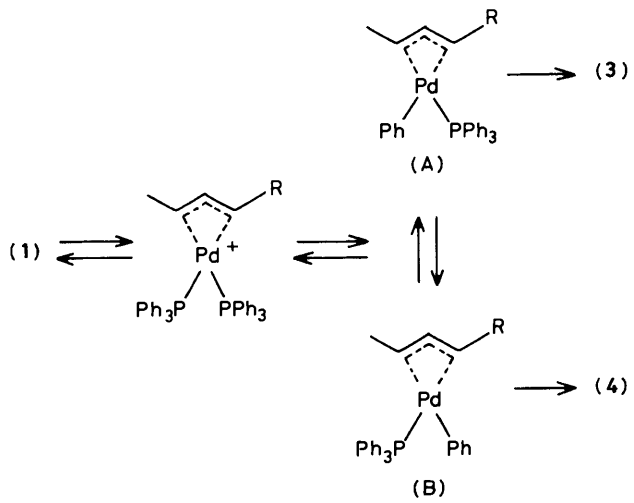


† All starting materials (**1**) [R = Pr^n, Bu^n, i-pentyl(Am^i), Bu^i, Pr^i, CD_3] were prepared by the addition of the corresponding Grignard reagent, RMgX to crotonaldehyde, followed by acetylation. Compound (**2**) (R = Pr^i) was prepared by $NaBH_4$ reduction of 5-methylhex-3-en-2-one (Aldrich), followed by acetylation.

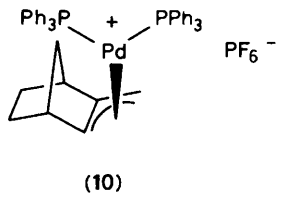
Table 1. Regioselectivity in Pd-catalysed allylic substitution.

Nucleophile	Nu	Ratio (3) : (4) (yield)[a] (1) R = Pr^n	(1) R = Bu^n	(1) R = Am^i	(1) R = Bu^i	(1) R = Pr^i	(2) R = Pr^i	(1) R = CD_3
(5)	(5a)	94 : 6 (75%)	91 : 9 (86%)	97 : 3 (76%)	>99 : 1 (71%)	>99 : 1 (68%)	>99 : 1 (64%)	50 : 50 (89%)
(6)	(6a)	91 : 9[c] (84%)	89 : 11[c] (90%)	93 : 7 (83%)	>99 : 1 (84%)	>99 : 1 [b]	>99 : 1 [b]	49 : 51[c] [b]
$NaCH(CO_2Me)_2$ (7)	$(MeO_2C)_2CH$	77 : 23 (88%)	78 : 22 (92%)	88 : 12 (86%)	93 : 7 (90%)	>99 : 1 (67%)	>99 : 1 (64%)	50 : 50 (84%)
Bu_3SnOPh (8)	PhO	81 : 19 (82%)	80 : 20 (80%)	77 : 23 (88%)	91 : 9 (85%)	92 : 8 (72%)	>99 : 1 (77%)	50 : 50 (85%)
PhZnCl (9)	Ph	1 : 99[c] (71%)	1 : 99[c] (67%)	1 : >99 (64%)	1 : >99[c] (58%)	[e]	[e]	50 : 50[c] (40%)
AcO[d]	AcO	59 : 41 (96%)	55 : 45 (95%)	54 : 46 (95%)	58 : 42 (92%)	67 : 33 [b]	65 : 35 [b]	48 : 52 [b]

[a] The isomeric ratio (3) : (4) was determined by ^{1}H n.m.r. (270 MHz). Yields are of isolated, distilled products. [b] Not determined. [c] Isomeric ratio was confirmed by g. c. mass spectrometry with less than 5% error. [d] The starting material was allowed to isomerize in the presence of 5% $Pd(PPh_3)_4$ in THF at room temperature for 72 h and in the absence of added nucleophile. [e] Only one coupling product, (3), was obtained in 0.7—1.6% yield (unisolated, determined by ^{1}H n.m.r. using an internal reference).



Scheme 2



(10)

Although both types of nucleophiles react with a high degree of regioselectivity, it seems that (9) is more sensitive to steric effects than the stabilized nucleophiles. It reacts with pronounced selectivity even with an allylic system which is substituted with two similar alkyl groups, (1) R = Pr^n.

While the regioselectivity associated with stabilized nucleophiles may be rationalized on the basis of previous work (Scheme 1)[2] the differentiation between methyl and propyl or butyl substituents is still remarkable. The behaviour of PhZnCl is even more intriguing. Based on stereochemical results,[4] substitution with this nucleophile involves initial attack at the palladium atom, with subsequent reductive elimination, a process which is outlined by Scheme 2.

The high regioselectivity in the reaction of PhZnCl with (1), favouring isomeric product (4) over (3), may suggest similar preferential formation of the square planar intermediate, which undergoes reductive elimination, namely (B) is favoured over (A). Such a preference, in square planar complexes is known to be influenced by electronic factors (where the phosphine donor ligand prefers to be located at a position *trans* to a stronger acceptor ligand)[11] and by steric factors, where the large phosphine ligand is positioned *cis* to the smaller group.[12] It seems unlikely that the two ends of the allylic system, being monosubstituted with alkyl groups are different from one another in terms of donor/acceptor properties.[13] Therefore, stability differences between (A) and (B) should be viewed on steric grounds. It was suggested by Schwartz[6] that strong steric effects in such square planar complexes may change the electronic properties of the two allylic termini, by virtue of uneven bonding to the metal. However, in our straight chain model compounds, which are less sterically demanding than steroidal substrates,[6] the π-allyl complexes seem to be symmetrical. Obviously this question is still open in the absence of appropriate crystallographic data. Nevertheless, we have recently found that even in the highly sterically congested system, (10),[14] the palladium atom is symmetrically located with respect to the two allylic termini.

In conclusion, we wish to emphasize that even before a full understanding of the regioselectivity phenomena in π-allyl palladium chemistry is achieved, the observed amplification of steric factors caused by the intervention of the transition-metal, especially when hard nucleophiles are employed, may be effectively utilized in highly controlled organic syntheses.

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