Stereoelectronic Control in Transition Metal-catalysed Substitution and Rearrangement of Allylic Esters and Alcohols

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In competitive experiments with *cis*- and *trans*-5-t-butyl-2-methylenecyclohexanols and their acetates, stereocontrol in the Pd- and Ni-catalysed alkylation of allylic derivatives and the Mo-catalysed isomerisation of allylic alcohols is observed.

Stereoelectronic effects in organic chemistry are now well understood and taken into account in synthesis.[1] Less attention has been paid to these effects in organometallic reactions.

Palladium-catalysed allylic substitution[2] by various 'soft' (delocalised carbanions,[3] lithium[4] or tri-n-butyltin[5] enolate, thiophosphide anions[6] *etc.*) or 'hard' (vinylaluminium,[7] vinylzirconium,[8] arylzinc[7] reagents) nucleophiles proved to be highly stereoselective, and allowed efficient transfer of asymmetry.[9] The elementary steps of the overall process should therefore be highly stereoselective and subject to stereoelectronic control.†

To establish the stereochemical requirements of the allylic substrates for reactivity in their Pd- and Ni-catalysed substitution reactions, we carried out competitive reactions with two conformationally semi-rigid allylic alcohols *trans*-(**1**) and *cis*-(**1**)[12] in which the C–O bonds are approximately (by examination of molecular models) parallel and orthogonal to the p atomic orbitals of the C=C bonds respectively.

The data obtained in the metal-catalysed competitive reaction between *cis*/*trans*-allylic substrates (**1**) or (**2**)‡ with various nucleophiles are collected in Table 1. It was found, in agreement with Normant's results on the copper-catalysed alkylation of allylic ethers by Grignard reagents,§ that the reaction of lithium di-n-butylcuprate with the 3:2 mixture of *cis*-(**2**)/*trans*-(**2**) left *cis*-(**2**) unreacted while *trans*-(**2**) yielded regioselectively (**3**) (R = Bu^n). The same trend was observed in the palladium-catalysed reaction of sodium dimethylmalonate; *cis*-(**2**) survived under the reaction conditions [tetrahydrofuran (THF), 5 mmol % $Pd(PPh_3)_4$, room temp.], while *trans*-(**2**) was entirely converted into (**3**) [R = $CH(CO_2Me)_2$]. An estimate for the relative rates of substitution was obtained from competition studies, indicating that *trans*-(**2**) (with an axial acetate) was substituted faster than *cis*-(**2**) (equatorial acetate) by a factor of over 250. The palladium-catalysed coupling of the diastereoisomeric mixture of (**2**) and hex-1-enyl di-isobutylaluminium afforded 29% of a mixture of the linear and branched dienes (**3**) and (**3'**) (R = $CH{=}CHC_4H_9$),

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† The Pd-catalysed substitution of allylic acetates proceeds in two steps, *i.e.* oxidative addition of the allylic substrate to the metal, followed by attack by the nucleophile on the (η^3-allyl)palladium complex thus formed (either at the ligand or at the metal, according to the nature of the nucleophile).[10] Stereoelectronic control has been shown in alkylation of (η^3-allyl)palladium complexes by stabilized enolates.[11]

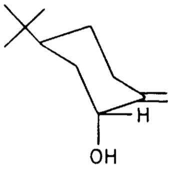
‡ A 3:2 mixture of *cis*-(**1**)/*trans*-(**1**) was readily obtained by base-catalysed $(LiNEt)_2$ ring-opening[13] of a diastereoisomeric mixture of the epoxides of t-butyl-4-methylcyclohex-1-ene.[14]

§ Normant established by comparative experiments that allylic isomers showed differences in reactivity according to their configuration. In the more reactive isomer, the leaving group is quasi orthogonal to the plane of the double bond.[15]

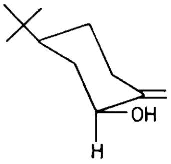
Table 1. Competitive experiments on a *cis*/*trans* mixture of (**1**) or (**2**).

Substrate[a]	RM	Solvent (temp.)	Catalyst	Product[c] (% yield)	Recovered starting material[c]	
					Yield (%)	*cis*/*trans*[d]
(**2**)	$Bu^n{}_2CuLi$	Et_2O (−20 °C)		(**3**), R = Bu^n (36)	54	100 : 1
(**2**)	$NaCH(CO_2Me)_2$	THF (room temp.)	5% $Pd(PPh_3)_4$	(**3**) R = $CH(CO_2Me)_2$ (40)	57	100 : 1
(**2**)	$Bu^i{}_2Al(CH{=}CHC_4H_9)$	THF (room temp.)	5% $Pd(PPh_3)_4$	(**3**) R = $CH{=}CHC_4H_9$ (29)	26	100 : 1
(**1**)	MeMgBr	C_6H_6[b]	5% $NiCl_2(PPh_3)_2$	(**3**) + (**3′**) R = Me (40)	33	100 : 1

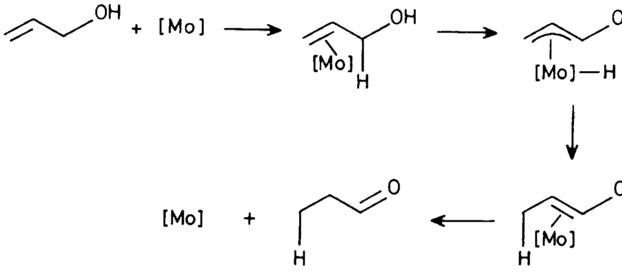
[a] *Cis*/*trans* = 3:2. [b] Reflux, 12 h. [c] Yields reported are for isolated products. [d] Determined by v.p.c.



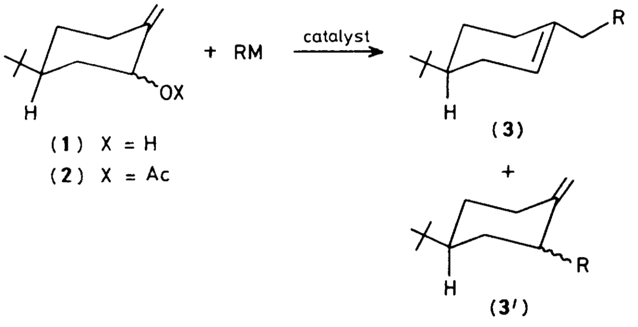
trans -(**1**)



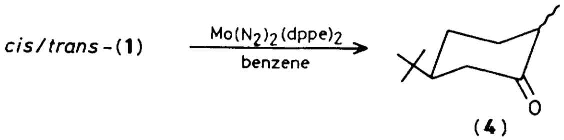
cis -(**1**)



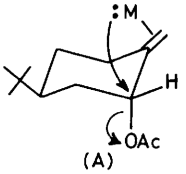
(1)



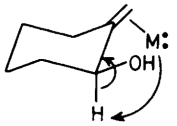
(**1**) X = H
(**2**) X = Ac
(**3**)
(**3′**)



(**4**)



(A)



(B)

while 26% *cis*-(**2**) was recovered. The above results reveal the kinetic effect of the geometrical disposition of the C–O bond to be cleaved and the π-orbital of the double bond.

To determine whether the diastereoselectivity arose from the η^3-allyl forming step, or from nucleophilic attack on the diastereoisomeric η^3-allylic cationic intermediate, the 3 : 2 mixture of *cis*/*trans*-(**2**) was treated with stoicheiometric amounts of $Pd(dba)_2$,[16] dppe, and PPh_3 [dba = dibenzylidene acetone, dppe = bis(diphenylphosphino)ethane] without any nucleophile present. *trans*-(**2**) was quantitatively consumed within 24 h (as determined by v.p.c.), while 36% starting material was recovered as *cis*-(**2**). This result suggests that the different rates of reaction of *cis*- and *trans*-(**2**) should be attributed to diastereoselectivity in the (η^3-allyl)palladium forming step.

Other examples of stereoelectronic control in the oxidative addition of allylic derivatives to low valent transition metal complexes are given in Table 1. The allylic alcohol *trans*-(**1**) was far more reactive than the corresponding *cis*-isomer in the nickel-catalysed alkylation[17] by methylmagnesium bromide. This result is consistent with the inversion of configuration reported[18] in this reaction for the formation of the (η^3-allyl)nickel complex: this step implied an antiperiplanar situation between the forming nickel–carbon bond and the breaking C–O bond.

Such stereoelectronic control was also observed in a reaction involving the metal-induced scission of an allylic C–H bond. The molybdenum-catalysed isomerisation of allylic alcohols into saturated ketones has been postulated to proceed through a suprafacial 1,3-hydride shift according to equation (1).[19] We found that the 3 : 2 mixture of diastereoisomeric alcohols *cis*-(**1**)/*trans*-(**1**) in the presence of 20 ml% $Mo(N_2)_2(dppe)_2$[20] in refluxing benzene for 1 h gave the rearranged ketone (**4**) in 51% yield; *trans*-(**1**) was recovered in 20% yield, while the *cis*-isomer was completely consumed. In the more reactive diastereoisomer *cis*-(**1**) the C–H bond broken by the metal is parallel to the p atomic orbitals of the double bond.

These competitive reactions on conformationally rigid substrates show the dependence between the stereochemical structure and the rate of the metal-catalysed reaction of allylic substrates. The experiments constitute strong evidence for stereoelectronic control in the η^3-allyl forming step after metal co-ordination to the double bond. The bond to be broken (C–O or C–H) and the metal–carbon bond should have an antiperiplanar arrangement in the allylic acetate and alcohol substitution (A) and a synperiplanar one for the alcohol isomerisation (B).

Diastereoisomeric alcohols (**1**) and derivatives are useful models for detecting stereoelectronic control in a metal-catalysed transformation involving oxidative addition of an allylic compound on a metal and should have wide application in organometallic chemistry.

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