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PALLADIUM-CATALYZED ASYMMETRIC COUPLING REACTIONS BETWEEN ALLYLIC ACETATES AND ORGANOZINC REAGENTS. MECHANISTIC IMPLICATIONS

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Summary

Asymmetric induction and deuterium distribution studies have provided information about the mechanism of the palladium-catalyzed coupling reaction between allylic acetates and phenylzinc chloride, namely the presence of a symmetric η^3-allylic ligand in the intermediate, probably along with a monodentate phosphine ligand.

Introduction

On the basis of stereochemical studies Schwartz [1] and Negishi [2] postulated that Pd-catalyzed coupling between allylic acetates and organometallic (zinc and zirconium) reagents takes place via an oxidative addition, transmetallation, reductive elimination sequence. This process differs from that in the Pd-catalyzed substitution of allylic acetates by stabilized enolates, which is generally regarded as involving attack (*anti* to the palladium) of the nucleophile on a cationic η^3-allylic intermediate [3]. Asymmetric syntheses have been achieved for this latter reaction with chiral phosphines [4,5], but no asymmetric induction studies have previously been reported for the former.

We thus decided to examine asymmetric induction in the Pd-catalyzed reaction of a cyclic (I) or acyclic (IV) allylic acetate with phenylzinc chloride in the presence of optically active phosphines, in order to gain insight into the mechanism of the reaction.

Experimental

All the reactions were carried out under nitrogen, and solutions were transferred by Schlenk tube techniques. THF (Aldrich) was distilled from benzophenone ketyl under nitrogen before use.

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Cyclohex-2-en-1-ol and pent-3-en-2-ol were purchased from Aldrich. The corresponding deuterated alcohols were prepared by $LiAlD_4$ reduction of the ketones in ether. Acetates were obtained by reaction of Ac_2O and triethylamine in dichloromethane, with DMAP (4-dimethylaminopyridine) as a catalyst [6]. (*S,S*)-chiraphos ≡ (2*S*,3*S*)-bis(diphenylphosphino)butane, $[\alpha]_D$ 211° (*c* 1.5, $CHCl_3$) and (+)-NMDPP (neomenthyldiphenylphosphine) [7] $[\alpha]_D$ 87° (*c* 1.6, CH_2Cl_2) were purchased from Strem Chemicals. (−)-DMPP ≡ (dimenthylphenylphosphine) [8] had $[\alpha]_D^{22}$ −176.8° (*c* 5.94, benzene) and (−)-DIOP ≡ (2,3-O-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphinobutane) [9] $[\alpha]_D^{22}$ −12.5° (*c* 8, $CHCl_3$). $Pd(dba)_2$ (where dba denotes dibenzylideneacetone) was prepared by a reported procedure [10].

Liquid products were usually purified by Kugelrohr distillation, with a Büchi oven, model GKR-50, the temperature of the oven being recorded. Flash chromatography was carried out on silica gel (Merck, Kieselgel 60, 230–400 mesh, Art. 9385).

Proton (^1H) NMR spectra were recorded in the indicated solvent on a Perkin–Elmer R 32 (at 90 MHz) instrument. Chemical shifts are relative to tetramethylsilane.

Microanalyses were carried out by the Service Central de Microanalyse, I.C.S.N., Gif-sur-Yvette.

General procedure

To a solution (5 ml) of PhZnCl (2 mmol), prepared from reaction of equimolecular amounts (2 mmol) of $ZnCl_2$ in THF and PhMgBr in ether, was added a mixture of the allylic acetate (3 mmol), 5 mol% $Pd(dba)_2$ (57.5 mg, 0.1 mmol), and 10 mol% monophosphine (0.2 mmol) or 5 mol% diphosphine (0.1 mmol) in THF (2 ml). After 24 h stirring (40°C) the mixture was cooled, diluted with ether (50 ml), washed with aqueous saturated NH_4Cl (2 × 10 ml), then water (10 ml), and dried ($MgSO_4$). The residue was purified by Kugelrohr distillation then flash chromatography.

3-Phenylcyclohex-1-ene (II)

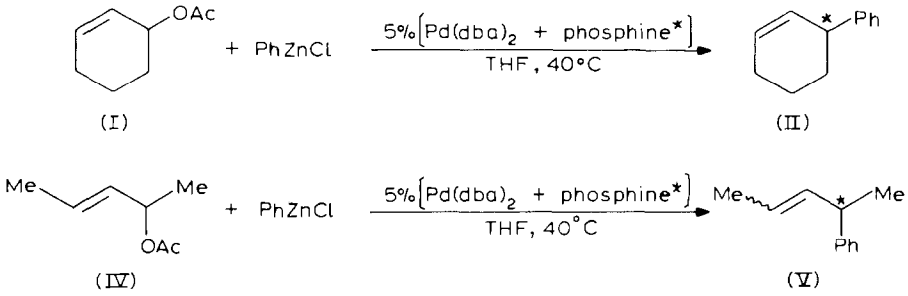
^1H NMR ($CDCl_3$): 1.4–1.8 (4H,CH_2), 1.9–2.15 (m, 2H, allylic), 3.3–3.5 (m, 1H, PhC*H*), 5.7–6 (2H, vinylic), 7.3 (s, 5H, aromatic). With NMDPP as the ligand in the catalyst, the product II had $[\alpha]_D^{20}$ −14° (*c* 14.7, cyclohexane), 9% e.e. based on the reported rotation of optically pure (II), +149.7° (*c* 0.53, benzene) [11]. Hydrogenation of the product (PtO_2, ethanol) gave a material $[\alpha]_D^{20}$ 0.0°, indicating the absence of optically active impurities in II.

4-Phenylpent-2-ene (V)

With DMPP as the ligand in the catalyst, V had $[\alpha]_D^{20}$ +15.86° (*c* 3.7, cyclohexane). ^1H NMR ($CDCl_3$) (18/42 *cis/trans* mixture); *trans*: 1.28 (d, 3H, CH_3CH, *J* 4.6); 1.4 (d, 3H, CH_3C=, *J* = 4); 3.8 (dq, 1H, CHC_6H_5, *J* = 5, *J* = 5); 5.41 (dq, 1H, *J* = 10.6, *J* = 4, CH_3CH=); 5.59 (dd, 1H, CHC*H*=, *J* = 10.6, *J* = 7.3); 7.2 (s, 5H, aromatics); *cis*: 3.73 (m, 1H, CHC_6H_5); 5.4 (m, 1H, CH_3CH=); 5.5 (dd, 1H, CHC*H*=). Anal. Found: C, 90.31; H, 9.66. $C_{11}H_{14}$ calcd. C, 90.35; H, 9.65%. Hydrogenation of V over PtO_2 afforded (*S*)-(+)-2-phenylpentane $[\alpha]_D^{20}$ 2.14° (*c* 5.6, hexane) 12% e.e., estimated from the reported value for the enantiomerically pure (*R*)-compound −17.8° (*c* 4.5, heptane) [12].

TABLE 1

YIELDS, ENANTIOMERIC EXCESSES (% e.e.) AND ABSOLUTE CONFIGURATIONS IN ASYMMETRIC COUPLING REACTIONS OF I AND IV WITH PhZnCl



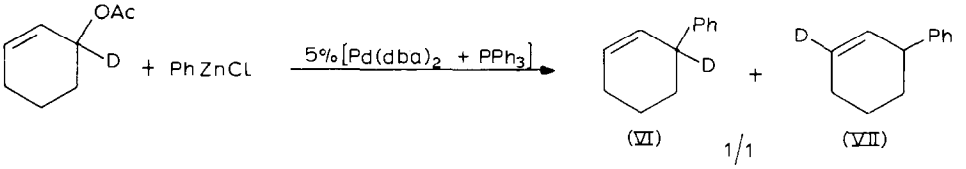
Phosphine	II			V		
	Yield [a] (%)	$[\alpha]_D$ [b] (°)	% e.e (conf.)	Yield [a,c] (%)	$[\alpha]_D$ [b,d] (°)	% e.e (conf.) [d]
(+)-NMDPP	87	−14	9.4 (*S*)	12	+1.96	11 (*S*)
(−)-DMPP	5	n.d.		60	+2.14	12 (*S*)
(−)-chiraphos	50	−1.5	1 (*S*)			
(−)-DIOP	< 5	n.d.		25	−0.36	2 (*R*)

[a] Yields are for isolated products. [b] In cyclohexane. [c] Obtained as a *cis/trans* diastereomeric mixture. [d] $[\alpha]_D$, e.e. and configuration of 2-phenylpentane obtained by hydrogenation of V over PtO_2 in methanol.

Results and discussion

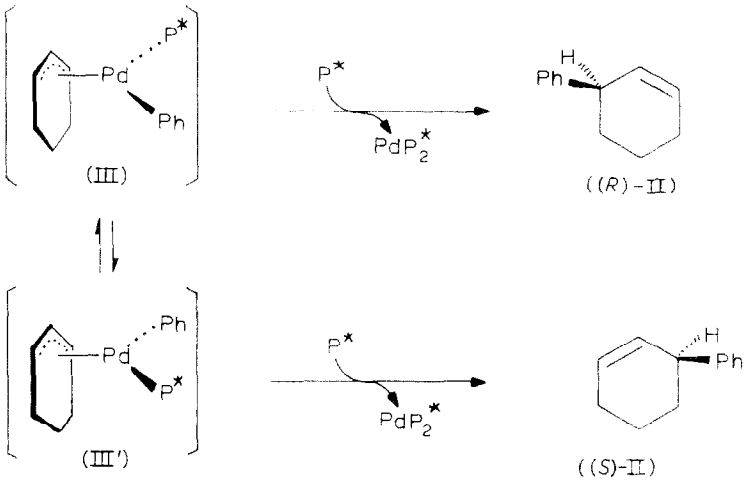
The data reported in Table 1 show the dependence of the chemical and optical yields upon the nature of the chiral ligand. Chiraphos, when acting as a bidentate ligand, usually gives high asymmetric inductions, e.g. in rhodium-catalyzed hydrogenation [13], palladium-catalyzed allylation [5] or nickel-catalyzed coupling reaction [14]. The low asymmetric inductions obtained with this ligand in the present study suggest that the chiraphos was probably involved in the asymmetric C–C bond forming step as an unidentate ligand. This is also the case for the DIOP ligand. The largest asymmetric inductions were in fact obtained with monophosphines (used as 2 equiv./Pd), namely NMDPP for conversion of I and DMPP for IV.

The ratio of the deuterated regioisomers VI and VII was measured by NMR, and found to be 1/1 for the reaction with an achiral phosphine (PPh_3). This suggests



that the reaction proceeds through a symmetric η^3-allyl ligand in the intermediate and displays no secondary deuterium isotopic effect. These results are in agreement with the involvement as intermediates of neutral square planar η^3-allylic palladium complexes of type III with a single coordinated phosphine.

In terms of the mechanism suggested above, the reaction of I with PhZnCl must proceed via coordination of the phenyl moiety to the metal to give either enanti-



SCHEME 1

omers III and III' (achiral phosphine), or diastereomers (chiral phosphine) which produce the (*R*)-II and (*S*)-II enantiomers by reductive elimination (Scheme 1).

Monitoring of the optical activity of the starting acetate I showed it to remain racemic. Provided I does not epimerize under the reaction conditions *. this would indicate that the asymmetric induction is not the result of a selection of the enantiomeric substrates by the chiral catalyst.

Production of optically active coupling products requires an equilibration at some stage of the reaction between species coming from (*R*)-I and (*S*)-I, e.g. between diastereomeric complexes III and III', via a η^3–η^1–η^3 process. The asymmetric induction could thus be thermodynamic in origin (involving differences in energy between the rapidly interconverting diastereomers III and III') or kinetic (involving differences in reductive elimination rates for III and III'), or both. The asymmetric induction process may be regarded as involving selection from rapidly interconverting diastereomers. Such a process had been invoked to account for the regioselectivity in coupling reaction between η^3-allylic palladium complexes and vinylzirconium compounds [15].

Comparable results were obtained for the Pd-catalyzed coupling of the acyclic allylic acetate IV with phenylzinc chloride. Optically active 4-phenylpent-2-ene was formed as a mixture of *cis*/*trans* (18/42) isomers, which could not be separated. The e.e. observed for the 2-phenylpentane obtained after catalytic hydrogenation of the diastereomeric mixture thus represents a measure of the combined e.e. values for the two olefins.

* 2-Methylcyclohex-2-enyl acetate has been shown to be optically stable under comparable reaction conditions (5 mol% dppe, THF, room temperature for 24 h); less than 10% loss of optical activity was observed [16].

Conclusion

Results in the asymmetric induction and deuterium distribution studies in the Pd-catalyzed coupling reaction between allylic acetates I and IV and phenylzinc chloride support Schwartz's [1] and Negishi's [2] postulated mechanism. It must involve at some stage a four-coordinated neutral allylic complex, containing a single phosphine ligand.

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