Kinetic Resolution of Racemic Allyl Acetates in Asymmetric Allylic Alkylation Catalysed by a Chiral Ferrocenylphosphine–Palladium Complex

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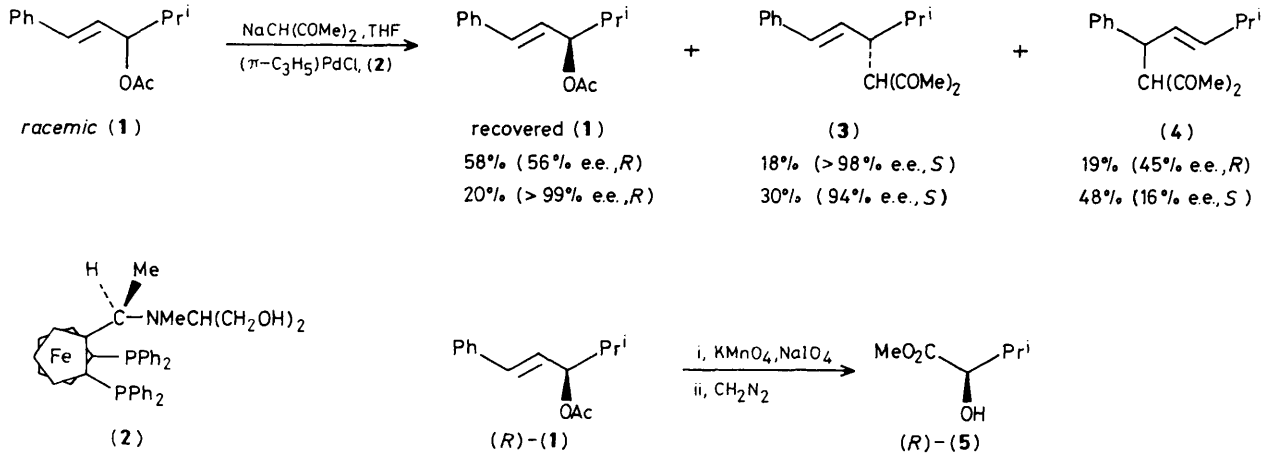
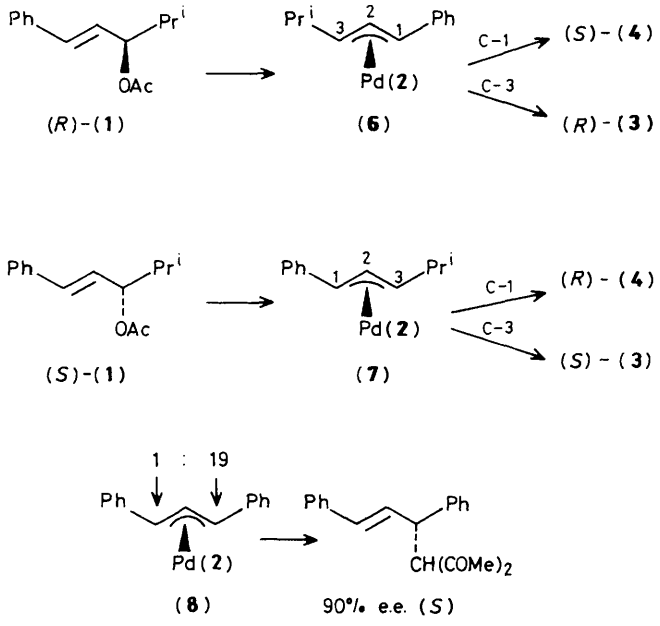
A chiral ferrocenylphosphine–palladium catalyst effects a highly selective kinetic resolution (k_S/k_R = 14) of racemic allyl acetates such as 1-[(*E*)-styryl]-2-methylpropyl acetate in asymmetric allylic alkylation.

Kinetic resolution of racemic compounds provides one important method for obtaining optically active compounds. Although there have been many examples of effective kinetic resolution with enzymes,[1,2] only a few reports have appeared which involve synthetic chiral catalysts of high selectivity.[3,4] Here we report that an effective kinetic resolution of racemic allyl acetates was attained by asymmetric allylic alkylation in the presence of a chiral ferrocenylphosphine–palladium catalyst.

Racemic 1-[(*E*)-styryl]-2-methylpropyl acetate (**1**) was allowed to react with 0.5 equiv. of sodioacetylacetonate in tetrahydrofuran (THF) at 40 °C for 3 days in the presence of 1 mol% of a palladium catalyst prepared *in situ* by mixing di-μ-chloro-di(π-allyl)dipalladium with (*R*)-*N*-methyl-*N*-bis-(hydroxymethyl)methyl-1-[(*S*)-1′,2-bis(diphenyl)phosphino)-ferrocenyl]ethylamine[5] (**2**) (P/Pd = 2.2/1). Aqueous work-up followed by preparative t.l.c. on silica gel (hexane–ethyl acetate, 5:1) gave 58% of the recovered acetate (**1**) {$[\alpha]_D^{20}$



Scheme 1



Scheme 2

+56.3° (*c* 1.4, CCl_4)} and 37% of allylic alkylation products consisting of 1-[(*E*)-styryl]-2-methylpropylacetylacetone (**3**) and its regioisomer (**4**) in a ratio of 48:52 (Scheme 1). The recovered (**1**) was determined to be an (*R*) isomer of 56% enantiomeric excess (e.e.) by ^{1}H n.m.r. spectroscopy in the presence of Eu(hfc)$_3$† and by converting it into the known (*R*)-(−)-methyl 2-hydroxy-3-methylbutanoate[6] (**5**) {$[\alpha]_D^{25}$ −9.6° (*c* 1.4, CCl_4)} (Scheme 1). The products (**3**) and (**4**), which were separated after deacetylation (MeONa–MeOH),‡ were found to be formed in >98% e.e. and 45% e.e., respectively. The configurations of (**3**) and (**4**) were deduced to be (*S*) and (*R*), respectively, from the configuration of the consumed acetate, since the catalytic allylic alkylation has been established to proceed with retention of stereochemistry.[7,8] The relative rate ratio of the enantiomer of the acetate (**1**) is calculated to be k_S/k_R = 14 using an established equation for kinetic resolution,[2,3]§ and it is expected that enantiomeric purity of the recovered substrate should exceed 99% for a conversion of 67%. Actually, the reaction carried to 80% conversion and gave the acetate (**1**) of effectively complete optical purity (>99% e.e.), accompanied by the formation of 30% of (*S*)-(**3**) (94% e.e.) and 48% of (*S*)-(**4**) (16% e.e.).

In addition to the high value of the ratio k_S/k_R, it is worth noting that the enantiomeric purity of one of the regioisomeric products is high regardless of the conversion. Scheme 2 illustrates a mechanism to explain the stereochemistry of the products. Thus, the π-allyl complex (**6**) which contains the chiral ligand (**2**) and the (1*R*,2*R*,3*S*)-1-phenyl-3-isopropyl-π-allyl group and its diastereoisomeric π-allyl complex (**7**) will be formed by stereospecific (inversion) oxidative addition[9] of (*R*)-(**1**) and (*S*)-(**1**), respectively, to a palladium(0) species, and the complexes (**6**) and (**7**) will undergo stereospecific (inversion) nucleophilic attack[8,10] on either C-1 or C-3 of the π-allyl carbon atoms to produce (*S*)-(**4**) or (*R*)-(**3**) and (*R*)-(**4**) or (*S*)-(**3**), respectively. The ratios of nucleophilic attack on the π-allyl carbon atoms are calculated, based on the results shown in Scheme 1, to be C-1:C-3 = >25:<1 for (**6**) and 1:1.3—1.4 for (**7**). It has been shown[5] that (**2**) is an effective ligand for the asymmetric allylic alkylation which proceeds *via* a π-allylpalladium intermediate containing a symmetrical π-allyl group and the selectivity of the nucleophilic attack was 19:1 for (1,3-diphenyl-π-allyl)palladium (**8**). It is likely that the selectivity is raised in (**6**) and lowered in (**7**) by the regioselectivity inherent in the 1-phenyl-3-isopropyl-π-allyl system, the preferential attack on the carbon substituted with phenyl to produce (**4**) [(**4**):(**3**) = 18:1] being observed in the reaction catalysed by a palladium complex with an achiral ligand, 1,1′-bis(diphenylphosphino)ferrocene.

Use of dimethyl sodiomalonate instead of acetylacetonate for the reaction of (**1**) resulted in a small decrease in the

† Eu(hfc)$_3$ = tris[3-(heptafluoropropylhydroxymethylene)-(+)-camphorato]europium(III).

‡ The specific rotations of the deacetylated products, 1-[(*E*)-styryl]-2-methylpropylacetone and its regioisomer were $[\alpha]_D^{20}$ −63° (*c* 0.7, CCl_4) and $[\alpha]_D^{20}$ ±0.0° (CCl_4), respectively. Their enantiomeric purities were determined by ^{1}H n.m.r. spectroscopy using Eu(hfc)$_3$.

§ k_S/k_R = [ln(1−*C*/100)(1−e.e./100)]/[ln(1−*C*/100)(1 + e.e./100)] (*C* = % conversion; e.e. = % e.e. of the recovered substrate).

enantiomeric ratio (k_S/k_R = 6.6). The ligand (**2**) was also effective for the kinetic resolution of racemic [(*E*)-styryl]cyclohexylmethyl acetate (**9a**) (k_S/k_R = 7.0) to give (*R*)-(**9a**) {$[\alpha]_D^{20}$ +33.4° (*c* 1.6, CCl_4)} of 61% e.e. at 51% conversion but was not effective for 1-[(*E*)-styryl]ethyl acetate (**9b**) (k_S/k_R = 1.2).

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