

## Enantio- and regiocontrol in palladium- and tungsten-catalyzed allylic substitutions

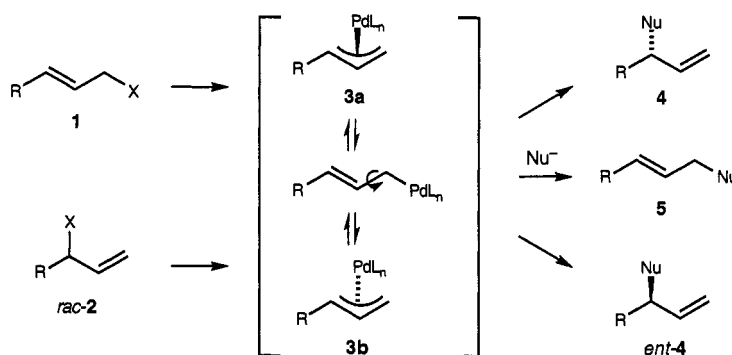
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**Abstract:** Tungsten catalysts with chiral phosphinoxazoline ligands react with 3-aryl-2-propenyl diethyl phosphates and the sodium salt of dimethyl malonate to give the corresponding chiral substitution products with regioselectivities of 3–24:1 and 88–96% ee. A new class of chiral P,N-ligands has been developed which allow efficient regio- and enantiocontrol in analogous Pd-catalyzed allylic substitutions of 1- and 3-aryl-2-propenyl acetates with dimethyl malonate.

### INTRODUCTION

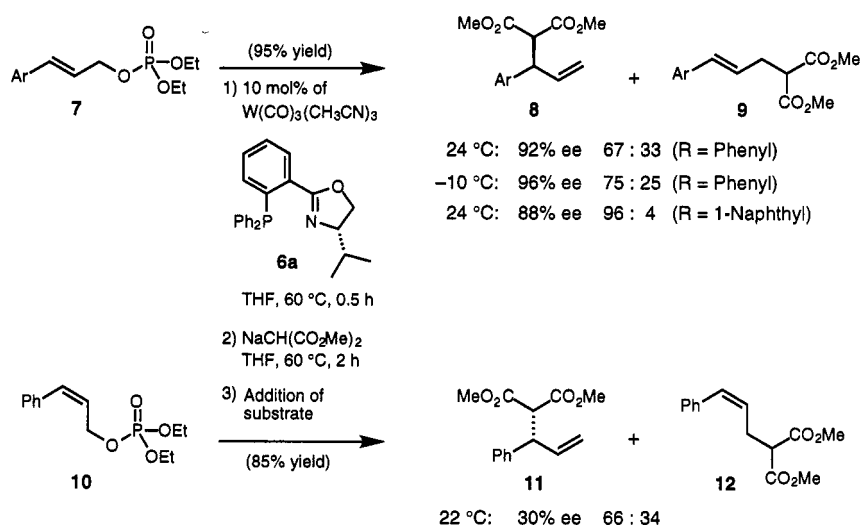
Palladium-catalyzed allylic substitutions are among the most efficient methods for enantioselective C-C or C-heteroatom bond formation. New chiral ligands have been developed which can induce impressive enantiomeric excesses in reactions of allylic acetates or related substrates with stabilized carbanions and various *N*-, *O*-, and *S*-nucleophiles (ref. 1). However, with unsymmetrically substituted allylic substrates the formation of the undesired regioisomer or insufficient regioselectivity is often a problem. For instance monosubstituted allyl systems in general react predominantly at the unsubstituted terminus (for exceptions, see ref. 2). So the achiral linear product **5** is formed rather than the chiral branched isomer **4** or its enantiomer which are the preferred products for applications in asymmetric synthesis (Scheme 1). Although predominant formation of the branched isomer has been observed with achiral catalysts derived from other metals - most notably tungsten (ref. 3) and iridium (ref. 4) - the development of enantioselective catalysts for this class of substrate remains a challenge.



Scheme 1

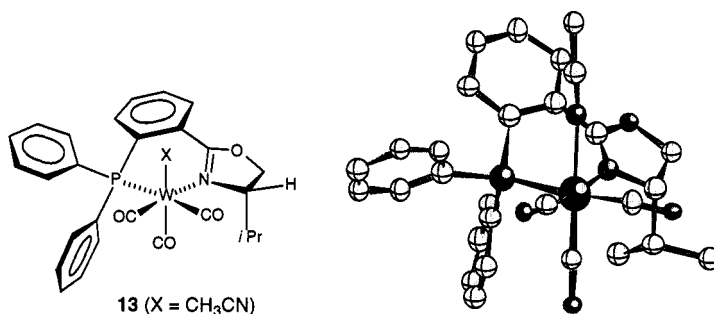
### CHIRAL PHOSPHINOXAZOLINE-TUNGSTEN COMPLEXES

Chiral phosphinoxazolines such as **6a** have proven to be effective ligands for palladium-catalyzed enantioselective substitutions (ref. 5-7). In reactions of 1,3-diphenyl- and 1,3-diisopropyl-2-propenyl acetate excellent ee's (96-99%) were obtained with stabilized carbanions and various *N*-nucleophiles. Monoaryl-substituted allylic acetates **1** (R = Ph, X = OAc), on the other hand, gave almost exclusively the achiral linear product **5** (**5:4** = 96:4; R = Ph, Nu = CH<sub>2</sub>(CO<sub>2</sub>Me)<sub>2</sub>). In view of these results, we decided to test phosphinoxazoline-tungsten complexes as catalysts for this reaction (ref. 8). The best results have been obtained with a catalyst derived from the isopropyl-oxazoline **6a** (Scheme 2).



Scheme 2

Since the tungsten complexes proved to be less reactive than the analogous palladium catalysts, substrates with a more reactive leaving group had to be used. The diethyl phosphate group proved to be the optimum choice. The catalyst was prepared in the following way:  $[W(CO)_3(CH_3CN)_3]$  or  $[W(CO)_3(\text{cycloheptatriene})]$  was reacted first with **6a** at 60 °C, then dimethyl sodiomalonate and finally with the allylic phosphate. Using this procedure, substrate **7** afforded (*R*)-**8** as the major regioisomer in good yield and with high ee. The order of addition and careful exclusion of oxygen were found to be crucial (treatment of  $[W(CO)_3(CH_3CN)_3]$  with **6a** and then with **7** in the absence of dimethyl sodiomalonate generated a stable but catalytically inactive tungsten-allyl complex). The importance of adding the nucleophile before the substrate has also been noted with tungsten-bipyridine catalysts (ref. 3). The isolated, crystallized complex **13** (Fig. 1) afforded an equally selective but more reactive catalyst than that generated in situ. Similarly high enantio- and regioselectivities were also observed with other aromatic substrates. (*E*)-2-Butenyl phosphate, on the other hand, reacted with reverse regioselectivity and only moderate enantioselectivity. The analogous molybdenum complex afforded mainly the linear regioisomer in low yields.

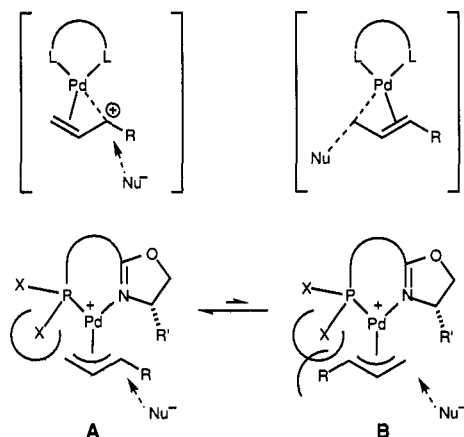
Fig. 1. Crystal structure of complex **13** (refs. 8b and 9).

The rapid *E-Z* equilibration and epimerization processes that are prevalent under palladium catalysis (cf. Scheme 1) were not observed in any of the tungsten-catalyzed reactions, consistent with previous observations by Trost *et al.* (ref. 3a). Hence compared to **7** (Ar = Phenyl), the *Z*-isomer **10** yields the opposite enantiomer **11** in 30% ee together with **12** but no detectable *E*-isomer **9**. Obviously, the mechanism must be different from that of analogous palladium-catalyzed allylic substitutions. However, attempts to identify the catalytically active species involved in the tungsten-catalyzed process have not been successful. Studies with different catalyst precursors **13** showed that one of the axial coordination sites in the octahedral complex must be occupied by a weakly bound ligand (X = acetonitrile or THF). An analogous tetracarbonyl complex (X = CO) did not exhibit any catalytic activity.

## CHIRAL PALLADIUM CATALYSTS

Although high enantioselectivities have been obtained with the tungsten complex **13**, the narrow range of possible substrates, which is restricted to linear (*E*)-propenyl phosphates **7**, limits the scope of this catalyst. If chiral palladium catalysts could be found that exhibit the desired regioselectivity, analogous (*Z*)-propenyl derivatives and racemic substrates **2** could be used as well due to the usually rapid *E-Z*-isomerization and epimerization of the intermediate allyl complexes (Scheme 1).

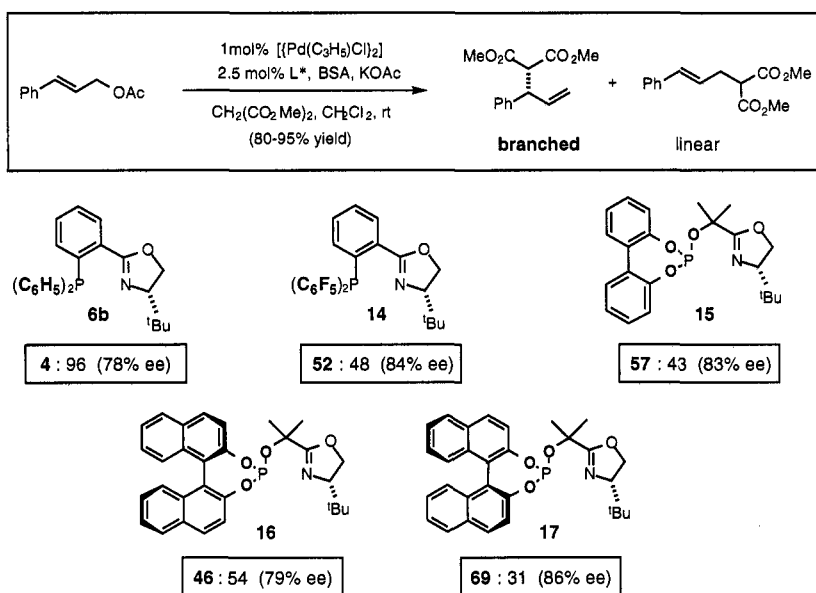
There are several factors influencing the regioselectivity of allylic substitutions (Scheme 3). Nucleophilic attack by an  $S_N2$ -type process should take place preferentially at the less substituted allyl terminus, whereas the opposite regioselectivity would be expected in an  $S_N1$ -like reaction via a cationic transition state. In order to enhance the  $S_N1$  character, we decided to introduce electronegative substituents at the P atom that



Scheme 3

render the Pd center more electrophilic. Steric factors affecting the equilibrium between the two allyl intermediates **A** and **B** also can play an important role. Bulky groups at the P atom are expected to destabilize isomer **B** as well as the transition states of the reaction pathways leading from **B** to the corresponding substitution products. Therefore, a pathway via **A** should be preferred and, assuming that nucleophilic attack at the allyl terminus trans to the Pd-P bond is electronically favored (Ref. 10), reaction at the substituted allyl end should be facilitated. Although other important factors such as the stability of the palladium-olefin  $\pi$ -complexes, that are formed as the primary products, are neglected, these simple concepts provided a useful guideline for the design of new ligands.

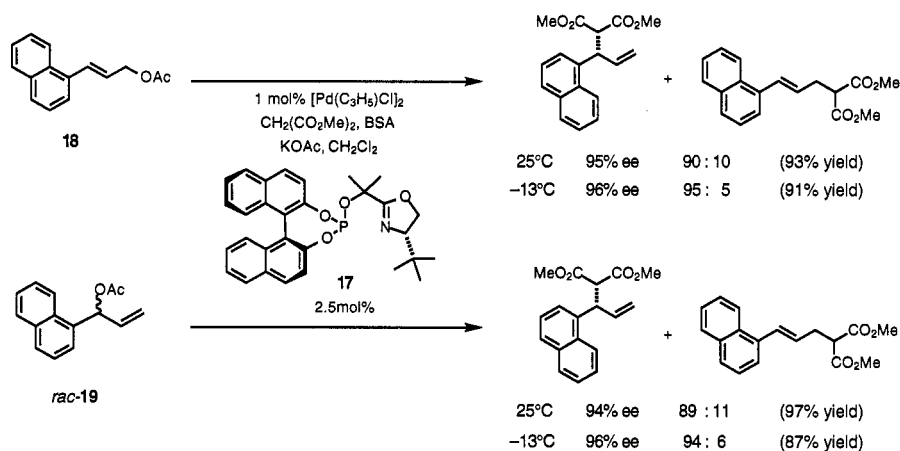
Replacement of the phenyl groups at the P atom by electron-withdrawing pentafluorophenyl groups shifted the regioselectivity in the desired direction from 4:96 to 22:48 (Scheme 4; ref. 11). A similar effect was observed using ligand **15** with a biphenyl phosphite group in place of the diphenylphosphino substituent. The regio- and enantioselectivity could be further improved by introduction of a second stereogenic unit



Scheme 4

derived from binaphthol. The best results were obtained with ligand (*S,S*)-**17** whereas the (*R,S*)-diastereomer **16**, derived from (*R*)-binaphthol, gave lower regio- and enantioselectivity. Apparently, the enantioselectivity is determined largely by the chiral oxazoline ring while chiral binaphthol unit has a minor, but still significant effect. Replacement of the *tert*-butyl group at the oxazoline ring by phenyl or other alkyl substituents resulted in lower regio- or enantioselectivity. Introduction of two ortho-methyl groups in the binaphthol system of **17** improved the ee to 92%, while the regioselectivity decreased to 55:45. The best results were achieved with ligand **17** in benzene at 23 °C (90% ee, b/l = 76:24) and in dichloromethane at low temperature (-35 °C: 88% ee, 79:21).

Even better regio- and enantioselectivities were obtained with 1-naphthyl-substituted allylic acetates. (Scheme 5). The achiral substrate **18** afforded essentially the same ratio of regioisomers and the same ee as the corresponding racemic isomer **19**. Apparently, the intermediate allyl complexes undergo rapid isomerization before they react with the nucleophile in the subsequent slower step which determines the regio- and enantioselectivity (cf. Scheme 1).



Scheme 5

The limitations of these catalysts become apparent with substrates bearing a methyl or alkenyl substituent instead of an aryl group. The reaction of (*E*)-2-butenyl acetate gave mainly the linear regioisomer (l/b = 70:30; 41% ee). (*E*)-5-Methyl-2-hexenyl acetate, on the other hand, afforded the branched isomer as the main product but with only moderate enantioselectivity (b/l = 75:25, 51% ee).

After completion of this work, Hayashi *et al.* (ref. 2c) reported a chiral monophosphine-Pd catalyst which affords mainly the branched isomer in the reaction of 3-aryl-2-propenyl acetates with dimethyl methylmalonate. Starting from 3-phenyl-2-propenyl acetate, they obtained the corresponding substitution product with 68–86% ee and a regioselectivity of 4:1. A direct comparison with our catalysts is not possible because only dimethyl methylmalonate was used as the nucleophile.

The structure of the allyl-palladium complex **20** illustrates the difference between the binaphthyl phosphite ligand **17** and the diphenylphosphino-oxazoline **6b** (Fig. 2). In complex **21**, there is sufficient space in the coordination sphere near the two *P*-phenyl groups to accommodate a substituent at the allyl terminus *cis* to the *P* atom. In complex **20**, on the other hand, the naphthyl ring system blocks this side of the allyl ligand. Therefore, a monosubstituted allyl ligand would be expected to coordinate with the substituted end located next to the oxazoline ring (see Scheme 3, complex **A**). The coordination geometry of the two complexes is very similar as shown by the superposition of the two structures.

A comparison of 3-phenyl-2-propenyl acetate with the corresponding *p*-methoxyphenyl- and *p*-cyano-phenyl-2-propenyl acetates confirms that the regioselectivity is strongly affected by electronic factors (Scheme 6). While the electron-donating *p*-methoxy substituent enhances the regioselectivity to 76:24 in favor of the chiral regioisomer, the cyano group has the opposite effect resulting in a reversed product ratio of 13:87 with the linear isomer as the main product.

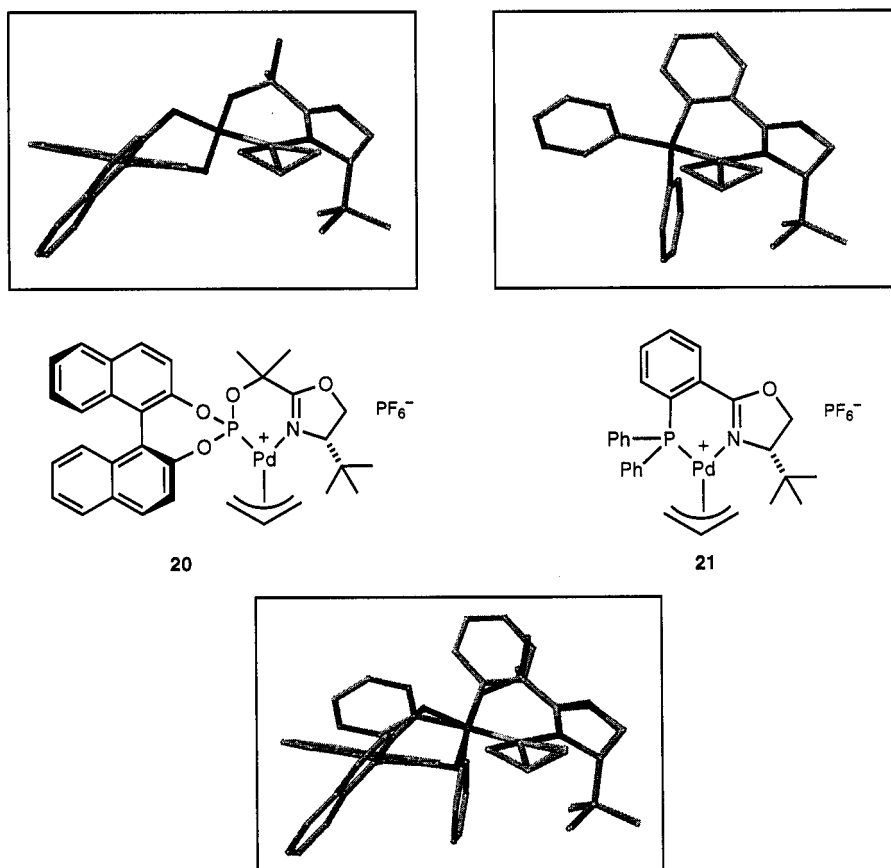
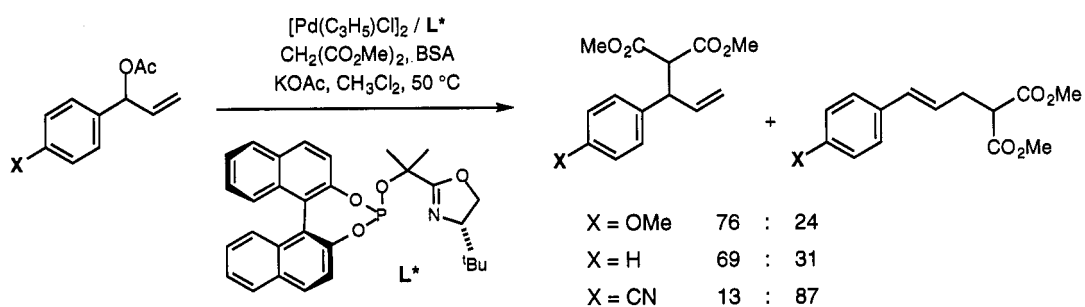
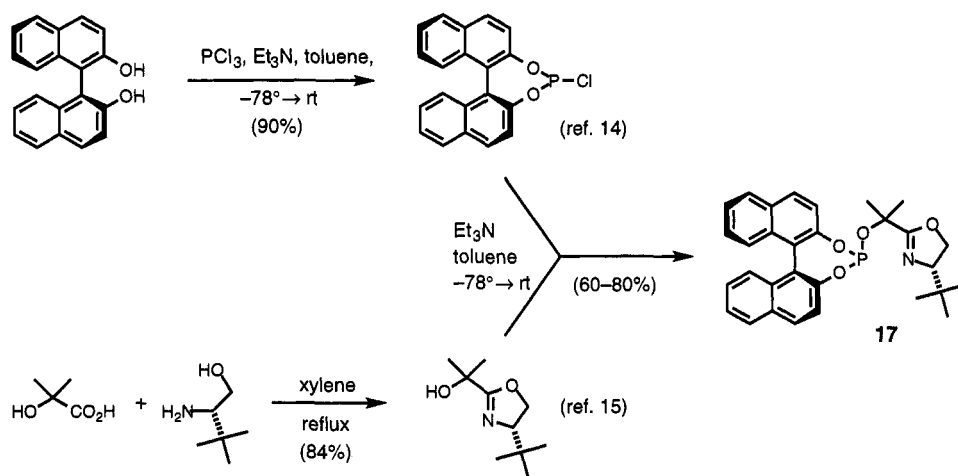


Fig. 2. Crystal structures of allyl-palladium complexes **20** (ref. 12) and **21** (ref. 13). The  $\text{PF}_6^-$  ion is not shown.



Scheme 6

The synthesis of ligand **17** is straightforward and modular (Scheme 7). Starting from different amino alcohols, hydroxy acids, and diols, a wide variety of analogues can be readily prepared in this way. Libraries of ligands that are accessible by this route could be used to further optimize the selectivities obtained so far.



Scheme 7

Our results demonstrate that the regioselectivity of allylic alkylations can be strongly influenced by the electronic and steric properties of the ligands attached to the palladium catalyst. Using a new type of chiral P,N-ligand, practically useful enantio- and regioselectivities have been obtained in the reaction with 1- and 3-aryl-2-propenyl acetates. Although at present the range of substrates that afford good selectivities is limited to aryl-substituted derivatives, the concepts which the ligand design was based on may serve as a guideline for the development of new catalysts for other classes of substrates. In addition, the same ligands could well prove useful for other applications in asymmetric catalysis.

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