Pd-Catalyzed Allylic Substitution with Enantiomerically Pure Catalysts and Chiral Non-Racemic Substrates: A New Approach to Catalyst-Based Regiocontrol

Preliminary Communication

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Dedicated to *Albert Eschenmoser* with best wishes on the occasion of his 75th birthday

Chiral, enantiomerically pure Pd-catalysts were used to control the regioselectivity of nucleophilic attack in allylic substitutions with optically active 1,3-disubstituted allyl acetates (*Schemes 4–6*). In contrast to reactions with achiral catalysts, where the regioselectivity is determined by the steric and electronic effects of the allylic substituents, chiral catalysts allow selective preparation of either one of the two regioisomeric products, depending on which enantiomer of the catalyst is employed. It is not necessary to start from an enantiomerically pure substrate, because the major and minor enantiomers are converted to different regioisomers (not to enantiomeric products; see *Scheme 3*), resulting in products of very high ee, even when the starting material is only of moderate enantiomer purity.

Introduction. – Palladium-catalyzed allylic substitutions belong to the standard repertoire of modern organic synthesis. Mild conditions, compatibility with many functional groups, and the option to control the reactivity and selectivity of the catalyst by complexing the Pd-atom with a specific ligand are attractive features, distinguishing these reactions from ordinary nucleophilic substitutions [1]. During the last few years, highly effective chiral ligands have been developed that can induce very high enantioselectivities in Pd-catalyzed allylic substitutions [2]. While high levels of enantiocontrol have been achieved in many cases, regiocontrol often remains a problem.

With substrates of type **1**, for example, the nucleophile can attack at either end of the allyl system and, with an achiral Pd-catalyst, the regioselectivity is determined by the steric and electronic effects of the allylic substituents R^1 and R^2 (*Scheme 1*). If the two substituents are similar, a *ca.* 1:1 mixture of regioisomers **2** and **3** is obtained, whereas if they are sterically or electronically distinct, moderate to high regioselectivities may be achieved. However, the regioisomer resulting from nucleophilic attack at the less reactive terminus is not accessible by this method and, therefore, it would be highly desirable to have at hand a catalyst that directs the nucleophile selectively to the desired allyl terminus, irrespective of the nature of the allylic substituents.

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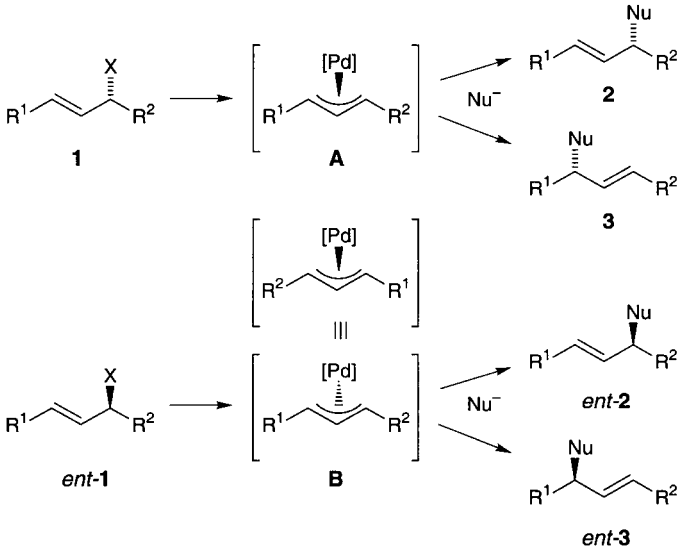
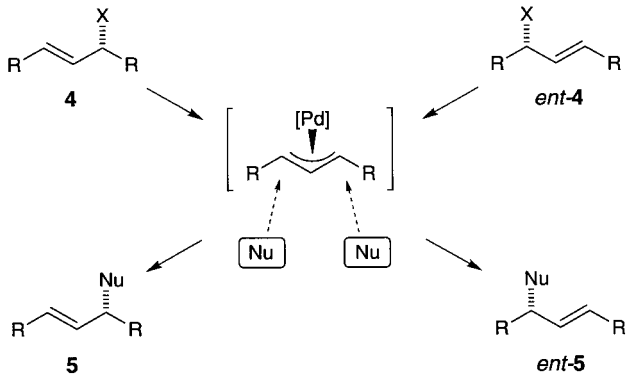
Scheme 1

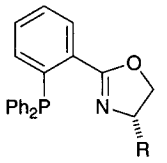


A number of chiral ligands that induce high enantioselectivities in reactions of symmetrically substituted allyl systems are known [2]. In this case (*cf. Scheme 2*), both enantiomers **4** and *ent*-**4** of a racemic substrate are converted to the same allyl intermediate and the enantioselectivity results from regioselective attack of the nucleophile at one of the two enantiotopic termini of the intermediate allylpalladium complex. The high enantiomer excess obtained with chiral ligands such as **6** (up to 99% ee) [3–5] implies that it is possible to discriminate the two enantiotopic termini of a symmetrical allyl system very effectively with a chiral catalyst.

The reaction scheme for substrates bearing different substituents at the two allylic termini is more complex (*cf. Scheme 1*). In this case, **1** and its enantiomer *ent*-**1** were converted to different allyl complexes, **A** and **B**, with opposite absolute configuration at

Scheme 2





(*S*)-**6a** R = Ph
b R = ^{t}Bu
c R = CH_2Ph

the allyl C-atoms. Nucleophilic addition with 'soft' nucleophiles proceeds stereoselectively with inversion, converting **A** to the regioisomers **2** and **3**, whereas **B** affords the corresponding enantiomeric products *ent*-**2** and *ent*-**3** [1][2]. Under the usual reaction conditions, complexes **A** and **B** do not interconvert and, therefore, it is not possible to transform a racemic mixture of **1**/*ent*-**1** selectively to one of the product enantiomers. The absolute configuration of the products is determined by the configuration of the substrate because the overall process proceeds with retention. Accordingly, the use of a chiral catalyst has no consequences regarding the stereoselectivity. However, a chiral catalyst, which is capable of enantiocontrol (*i.e.* regiocontrol) in symmetrically substituted allyl systems (*cf. Scheme 2*), will also influence the regioselectivity of nucleophilic addition to the two allyl intermediates **A** and **B** (*Scheme 1*). If the regioselectivity is completely controlled by the chiral catalyst while the influence of the substituents R^1 and R^2 is negligible, a racemic substrate is converted to a 1:1 mixture of enantiomerically pure regioisomers (**2** and *ent*-**3** or **3** and *ent*-**2**).

If the substituents play a role as well, as in the case of substrate **7**, then one of the allyl intermediates reacts with high regioselectivity, while the other displays significantly lower regioselectivity (*cf. Scheme 3*)[2]. From the enantiomer excesses and the ratio of the products **8** and **9**, one can calculate that one of the allyl intermediates reacts almost exclusively at the Ph-substituted C-atom (complex **C**; match between substituent effects and catalyst control), while the other exhibits a 9:1 preference for nucleophilic attack next to the ^{i}Pr group (**D**; mismatch between catalyst control, which dominates, and substrate control).

The regioselectivity obtained with the chiral catalyst (55:45) is distinctly different from the regioselectivity resulting from the achiral catalyst derived from PPh_3 (86:14), which reflects the higher reactivity of the Ph- compared to the ^{i}Pr-substituted terminus. For the discussion later on, it is important to note that the major pathways from intermediates **C** and **D** lead to different regioisomers (**C** to **8**, **D** to **9**).

An obvious conclusion can be drawn from this analysis: if an enantiomerically pure substrate is chosen, then the chiral catalyst can be used to control the regioselectivity of the reaction. This is illustrated in *Scheme 4* by the reaction of enantiomerically pure phenyl-*p*-tolyl-disubstituted allyl acetate (*R*)-**10** with dimethyl malonate [7]. Depending on the configuration of the chiral ligand, either one of the regioisomers, (*R*)-**11** or (*S*)-**12**, can be obtained with very high selectivity. There is no loss of enantiomer purity, implying that racemization of the starting material or inversion of configuration at the allyl C-atoms in the intermediate allylpalladium complex does not occur. Thus, the use of chiral catalysts in combination with optically active substrates should be a useful

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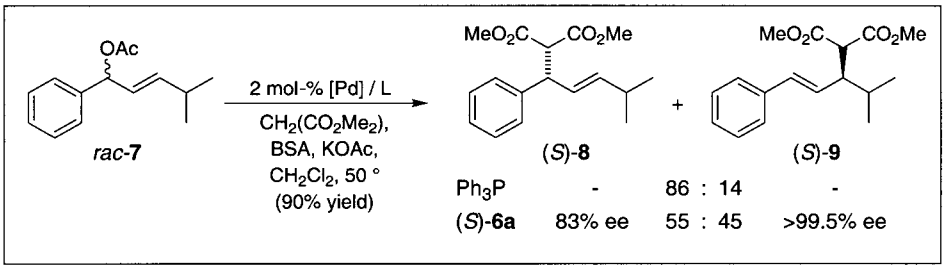
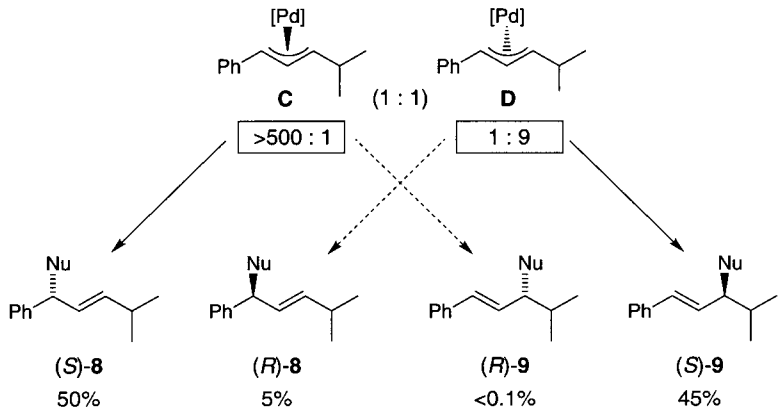
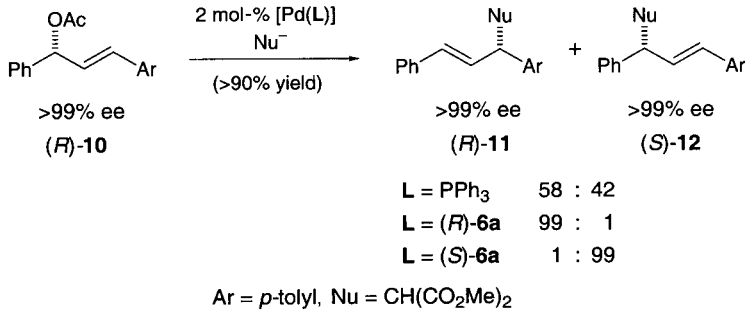
[2] For related examples and kinetic resolution of racemic substrates, see [6].

Scheme 3





Scheme 4



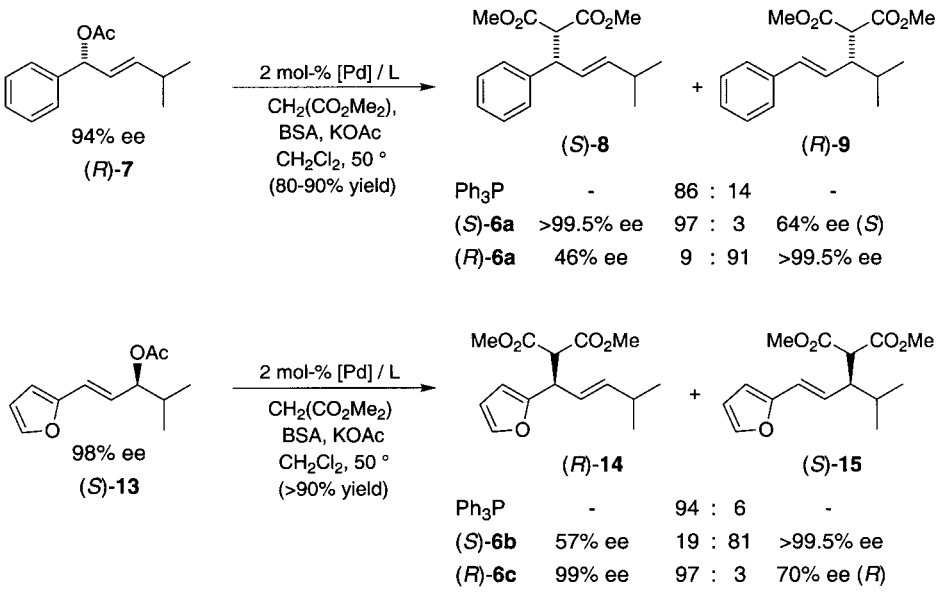
strategy for solving the difficult problem of regiocontrol in allylic substitutions of this type. To demonstrate the utility of this concept, we have prepared a number of optically active allyl acetates bearing two different substituents at C(1) and C(3) to study their reactions with dimethyl malonate and chiral catalysts.

Results and Discussion. – Allyl acetates **7** and **13** (*Scheme 5*) were prepared in optically active form by kinetic resolution of the corresponding alcohols by the *Sharpless* epoxidation method ((−)-diisopropyl tartrate, (^{i}PrO)$_4$Ti) [8][9]. The ee

values were determined by HPLC on chiral columns (see *Exper. Part*). The absolute configuration was assigned assuming the same stereochemical course as reported for analogous kinetic resolutions [8]. The assignment of the (*R*)-configuration to (−)-**7** was confirmed by oxidative degradation of the corresponding allyl alcohol, involving *O*-methylation with MeI and subsequent cleavage of the C=C bond with $KMnO_4$ on silica gel, as reported previously for compound **10** [7]. The resulting carboxylic acid was treated with diazo(trimethylsilyl)methane to give methyl (+)-2-methoxy-2-phenylacetate, which is known to have the (*S*)-configuration [7]. In the same way, (−)-**13** was converted to methyl (+)-(*S*)-2-hydroxy-3-methylbutanoate of known absolute configuration [10].

Allylic substitutions were carried out under standard conditions [7] with 2 mol-% of catalyst prepared *in situ* from $[\{Pd(\eta^3\text{-}C_3H_5)Cl\}_2]$ and 1.25 equiv. of chiral ligand, and *N*,*O*-bis(trimethylsilyl)acetamide (BSA) and KOAc [2]. The ratio of the two regioisomers was determined by ^{1}H-NMR spectroscopy, and the ee values were obtained by HPLC analysis (see *Exper.*). The absolute configuration of the products was assigned based on the well-established mechanism of Pd-catalyzed allylic substitutions with 'soft' nucleophiles, which involves overall retention [1][2]. For **8**, this assignment was confirmed by oxidative degradation: a sample of (+)-(*R*)-**8** was subjected to decarbomethoxylation in DMSO/NaCl at 180° [11][7], and the resulting mono-acid ester was then treated with $KMnO_4$ on silica gel followed by esterification with diazo(trimethylsilyl)methane to give dimethyl (−)-(*R*)-2-phenylsuccinate [12].

Scheme 5



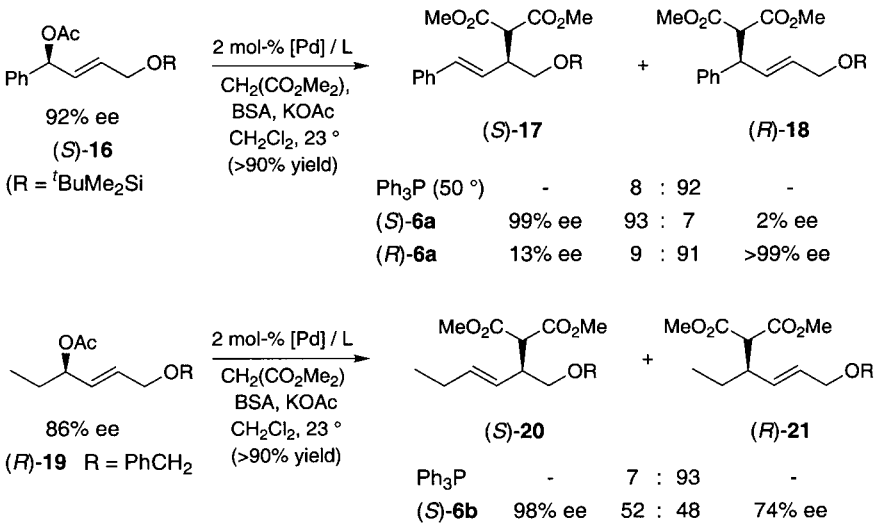
The reaction of (*R*)-**7** with dimethyl malonate and chiral catalysts (*Scheme 5*) takes a distinctly different course than the analogous reaction of the corresponding racemate (*cf. Scheme 3*). With the catalyst derived from ligand (*S*)-**6a**, the same regioisomer (*S*)-

8 predominates as with an achiral (triphenylphosphine)palladium complex. However, the regioselectivity induced by the chiral catalyst is higher (97:3 *vs.* 86:14). Obviously, the catalyst-induced regioselectivity and the substitution pattern in the allyl system both favor nucleophilic attack adjacent to the Ph group (matched case). With the enantiomeric catalyst derived from (*R*)-**6a**, the opposite regioisomer (*R*)-**9** is the major product, implying that catalyst control dominates over the influence of the allylic substituents. Although the enantiomer excess of the starting material is only 94%, with both of the two enantiomeric catalysts, the major regioisomer is formed with >99.5% ee. The reason for this remarkable enantiomer enrichment is that the minor enantiomer (*S*)-**7** is converted to the regioisomer and not to the enantiomer of the main product, as discussed above (*cf. Scheme 3*).

Similar results are obtained with the analogous furyl-substituted substrate (*S*)-**13** (*Scheme 5*). Although the furyl group strongly activates the adjacent allyl terminus, as seen from the 94:6 ratio of **14**/**15** obtained with the achiral Pd-catalyst derived from triphenylphosphine, it is possible to revert the regioselectivity to 19:81 in favor of (*S*)-**15** with ligand (*S*)-**6b**.

Additional examples are shown in *Scheme 6*. The required optically active substrate **16** was prepared from the corresponding racemic propargyl alcohol by oxidation with MnO_2 and enantioselective reduction of the ketone with (*R*)-*Alpine-Borane*® [13], followed by reduction of the triple bond with *Red-Al*® [14] and acetylation. The absolute configuration of (*S*)-**16** was assigned by oxidative degradation of the corresponding allyl alcohol to methyl (−)-(*R*)-2-methoxy-2-phenylacetate (see above). The dialkyl-substituted substrate **19** was prepared in an analogous manner, starting from racemic 6-{[(*tert*-butyl)dimethylsilyl]oxy}hex-4-yn-3-ol. The silyl ether was converted to (*R*)-**19** by treatment with Bu_4NF and subsequent benzylation with benzyl bromide/NaH/Bu_4NI in THF. The ee values of the substrates and the products were determined by HPLC on chiral columns (see *Exper. Part*).

Scheme 6



The reaction of (*S*)-**16** with dimethyl malonate could again be selectively directed to either (*S*)-**17** or the regioisomer (*R*)-**18**, depending on which enantiomer of the catalyst was used. As before, the main products were of much higher enantiomer purity than the starting allyl acetates. In the case of substrate (*R*)-**19**, the effect of the chiral catalyst was less pronounced, and the regioselectivity could only be shifted to 52:48 from the corresponding ratio of 7:93 observed with an achiral triphenylphosphine-derived catalyst. Nevertheless, ligand (*S*)-**6b** still made it possible to obtain significant amounts of the usually less-favored regioisomer (*S*)-**20** in high enantiomer purity from enantioenriched (*R*)-**19** which itself possessed only a modest enantiomer excess of 86%. When the corresponding (*tert*-butyl)dimethylsilyl ether was used instead of the benzyl ether (*R*)-**19**, the reaction showed an even stronger bias toward nucleophilic attack at the ethyl-substituted allyl terminus (97:3 with [Pd]/PPh_3). With the chiral ligand (*S*)-**6b**, the product corresponding to (*R*)-**21** still predominated with a regioselectivity of 67:33.

Conclusion and Outlook. – Our results demonstrate that the use of chiral enantiomerically pure catalysts in combination with chiral non-racemic substrates is a powerful strategy for controlling the regioselectivity in allylic substitutions. Depending on which enantiomer of the catalyst is employed, either one of the two regioisomeric products can be prepared selectively. An additional bonus is the removal of the minor enantiomer during the reaction, which results in products of very high ee, even when the starting material is only of moderate enantiomer purity.

So far, chiral catalysts have been used mainly to carry out enantioselective transformations of prochiral and racemic substrates, or diastereoselective reactions in which an additional stereogenic element is introduced into a chiral molecule under catalyst control. We have shown here that the specific interactions between a chiral catalyst and a chiral substrate can also be exploited for regiocontrol. The phenomenon of catalyst-induced regioselectivity has been observed previously in other types of reactions of racemic substrates with chiral catalysts, and in a general analysis of such transformations, *Kagan* has pointed out that the regioselectivity of a reaction starting from an enantiomerically pure substrate can in principle be controlled by the absolute configuration of the catalyst (or reagent)[3]). Moreover, a chiral catalyst can induce two completely different reactions of two enantiomeric substrates. A spectacular example is the decomposition of racemic cyclohex-2-en-1-yl diazoacetate catalyzed by a chiral rhodium catalyst, which converts one enantiomer to cyclohexenone by fragmentation while the other enantiomer undergoes intramolecular cyclopropanation [16]. Thus, a considerable potential of chiral catalysts for different types of reaction control can be envisioned, extending to areas of application beyond asymmetric catalysis.

Experimental Part

HPLC Analysis for Determining the ee of Compounds **7**–**9** *and* **13**–**21** (25°, flow 0.5 ml/min, *Daicel Chiralcel OD-H* and *OJ* columns (0.46 × 25 cm), detection at 220 nm). (–)-(*R*)-**7** (*OD-H*, heptane/^{i}PrOH 999:1): t_R 19.1 (*R*), 21.6 min (*S*). (–)-(*S*)-**8**: HPLC analysis (*OD-H*, hexane/^{i}PrOH 99:1) was carried out after decarbomethoxylation (DMSO/NaCl, 180° [11]) to methyl (*R*,*E*)-3-phenyl-6-methylhept-4-enoate; t_R 10.1 (*S*),

[3]) For a general discussion of reactions of chiral reagents or catalysts with racemic substrates, see [15].

24.7 min (*R*). (+)-(*R*)-**9** (*OD-H*, hexane/^{i}PrOH 99 :1): t_R 12.8 (*S*), 14.3 min (*R*). (−)-(*S*)-**13** (*OJ*, heptane/^{i}PrOH 9 :1): t_R 10.1 (*R*), 12.4 min (*S*). (*R*)-**14**: HPLC analysis (*OD-H*, hexane/^{i}PrOH 99 :1) was carried out after decarbomethoxylation (DMSO/NaCl, 180° [11]) to methyl (*S,E*)-3-(furan-2-yl)-6-methylhept-4-enoate; t_R 9.1 (*R*), 10.9 min (*S*). (*S*)-**15** (*OJ*, heptane/^{i}PrOH 90 :10): t_R 15.7 (*R*), 21.1 min (*S*). (−)-(*S*)-**16** (*OJ*, heptane/^{i}PrOH 995 :5): t_R 10.6 (*R*), 12.1 min (*S*). (−)-(*S*)-**17** (*OD-H*, heptane/^{i}PrOH 99 :1): t_R 11.4 (*R*), 13.4 min (*S*). (+)-(*R*)-**18** (*OD-H*, heptane/^{i}Pr-OH 99 :1): t_R 12.6 (*R*), 14.0 min (*S*). (+)-(*R*)-**19**: HPLC analysis (*OD-H*, heptane/^{i}PrOH 9 :1) was carried out on the cinnamic-ester derivative prepared from cinnamoyl chloride and (*R*)-6-{[(*tert*-butyl)dimethylsilyl]oxy}hex-4-yn-3-ol, the precursor used in the synthesis of (*R*)-**19**; t_R 8.4 (*S*), 13.6 min (*R*). (−)-(*S*)-**20** (*OD-H*, heptane/^{i}PrOH 99 :1): t_R 23.0 (*R*), 24.5 min (*S*). (+)-(*R*)-**21** (*OJ*, heptane/^{i}PrOH 99 :1): t_R 46.1 (*S*), 48.3 min (*R*).

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