

Review Article

Enantiocontrol in Some Palladium- and Copper-Catalyzed Reactions*

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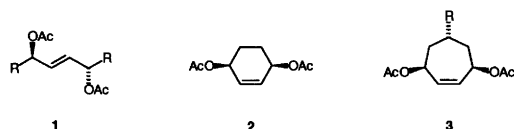
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This review discusses enantiocontrol in some palladium- and copper-catalyzed reactions and the general theme involves the use of products from palladium-catalyzed 1,4-oxidation of conjugated dienes. In the first part the use of 1,4-diacetoxy-2-alkenes in desymmetrization reactions is described. A combination of enzyme and palladium catalysis leads to a useful enantiocontrol. In the second part 4-amino-2-alkenol derivatives as key intermediates for the synthesis of 2,5-disubstituted pyrrolidines and pyrrolidine-containing alkaloids are discussed. These amino-alcohol derivatives are available from palladium-catalyzed 1,4-oxidation of conjugated dienes but an alternative procedure for their enantioselective preparation will be presented. Finally, in the third part some recent results in enantioselective copper-catalyzed allylic substitution are presented.

The palladium-catalyzed 1,4-oxidation of 1,3-dienes has been developed into a useful synthetic reaction.^{1,2} The chloroacetoxylation^{2a} and diacetoxylation^{2b} of cyclic and acyclic 1,3-dienes offer useful levels of stereocontrol and the products can be used for further functionalization. These reactions have been used by us and by others for stereo- and regio-selective natural product synthesis,^{3–5} and recently they were extended to intramolecular versions.^{1b} In some cases symmetrical *meso* compounds are obtained in palladium-catalyzed 1,4-additions to conjugated dienes, for example diacetates 1–3.

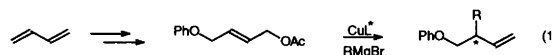
The use of these substrates in desymmetrizations will be discussed in the first part of this review.



The second part will deal with 4-amino-2-alkenol derivatives as key intermediates for the synthesis of 2,5-disubstituted pyrrolidines and pyrrolidine-containing alkaloids. These aminoalcohol derivatives are available from palladium-catalyzed 1,4-oxidation of conjugated dienes but an alternative procedure for their enantioselective preparation will be presented.

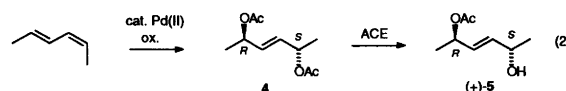
* Contribution presented at the Nobel Symposium on *Catalytic Asymmetric Synthesis*, September 3–7, 1995 at Tammsvik, Bro, Sweden.

Finally, in the third part, enantioselective copper-catalyzed allylic substitution will be presented, which is of interest in the functionalization of the 1,4-oxidation products obtained via palladium catalysis [eqn. (1)].



Combination of enzyme and palladium catalysis

We first investigated the enzymatic hydrolysis of the *meso* diacetate 4, which is readily prepared by Pd-catalyzed *syn*-diacetoxylation of (*E,Z*)-2,4-hexadiene.^{2b} Enzymatic hydrolysis of diacetate 4 employing acetylcholine esterase (ACE) in the presence of a phosphate buffer afforded the hydroxy acetate (+)-5 in 92% ee and 77% isolated yield [eqn. (2)].⁶ The best result was obtained if some over-hydrolysis to diol was allowed (ca. 5%). This phenomenon is well understood⁷ and rests upon the fact that the enzyme is selective towards hydrolysis of the acetate at the *S*-carbon.

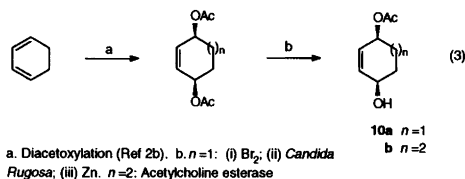


In the minor non-desired enantiomer of the hydroxyacetate the remaining acetate is bound to a carbon of *S*-configuration. Therefore, the minor enantiomer of the

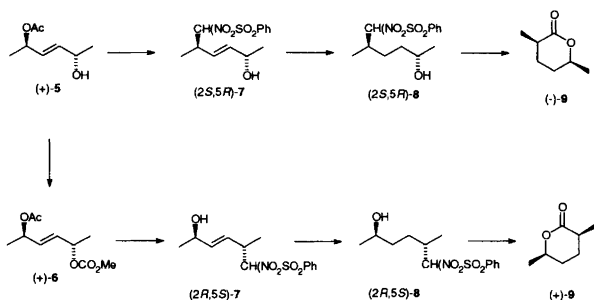
hydroxy acetate is hydrolyzed to diol faster than the major enantiomer of the hydroxyacetate.

The hydroxyacetate (+)-**5** was used for the enantiodivergent synthesis of the carpenter bee pheromone (**9**, Scheme 1).⁶ This transformation relies on the principle that either of the allylic leaving groups can be substituted with a nucleophile, which gives access to both enantiomers. The acetate can be directly substituted in a palladium-catalyzed nucleophilic substitution. Alternatively the alcohol can be transformed into a carbonate, a leaving group which reacts several hundred times faster than acetate in Pd(0)-catalyzed allylic substitution.⁸ In this way both enantiomers of the substituted compound can be obtained. In the synthesis shown in Scheme 1, a stabilized carbon nucleophile was employed which acts as a masked carboxy anion ($[\text{COOH}]^-$). In this way both enantiomers of the substitution products, (2*S*,5*R*)-**7** and (2*R*,5*S*)-**7**, were obtained. After reduction of the double bond in **7** the carboxy group was released and the hydroxy acid (hydroxy ester) spontaneously cyclized to the corresponding lactone [(–)-**9** or (+)-**9**].

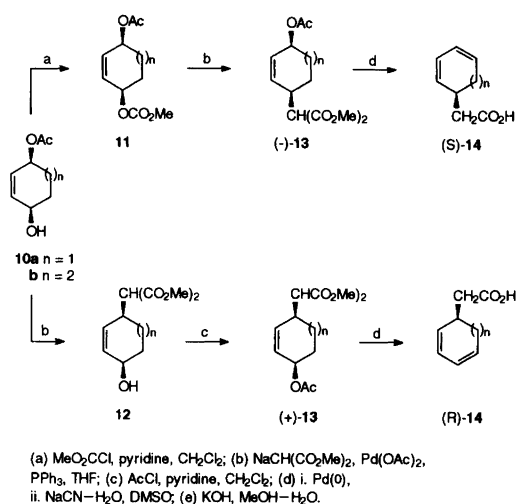
The same principle was applied to the cyclic diacetates **2** and **3** (R=H). The requisite *meso* diacetates were obtained from the corresponding 1,3-dienes in good yield and high stereoselectivity.^{2b} The diacetates were transformed into their monoacetates via enantioselective enzyme-catalyzed hydrolysis [eqn. (3)].⁹



In the case of the six-membered ring it was necessary to brominate the double bond prior to enzyme hydrolysis.¹⁰ The hydroxy acetates were selectively transformed into both enantiomers of the corresponding 2,4-cycloalkadienylacetic acid in an enantiocontrolled manner (Scheme 2).⁹ Again, palladium(0)-catalyzed substitution reactions at either of the chiral allylic centers were achieved via the use of carbonate **11** (*vide supra*). In this way the two enantiomers (–)-**13** and (+)-**13** were obtained and transformed into the enantiomeric diene acids (*S*)-**14** and (*R*)-**14**, respectively. The diene acids



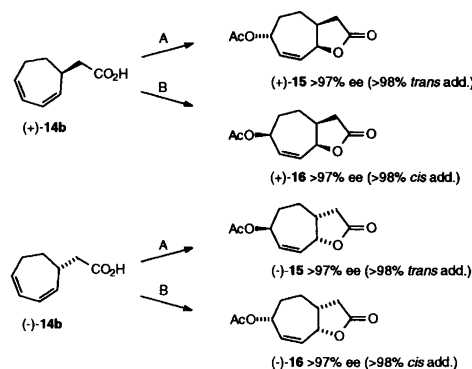
Scheme 1.



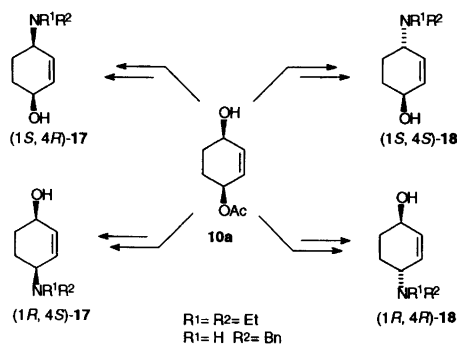
Scheme 2.

were allowed to undergo a stereocontrolled palladium-catalyzed acetoxylation. In this way the four stereoisomers of the lactones given in Scheme 3 were obtained from **14b** in >97% ee in each case.⁹

The hydroxy acetate **10a** was also used for the preparation of biologically active amino alcohols. Amino alcohols of this structure are of potential use in the treatment of bronchial diseases ('mucolyticum'). In a similar manner the monoacetate **10a** was transformed into all four isomers of several 4-amino-2-alkenols in an enantiocontrolled manner (Scheme 4).¹¹



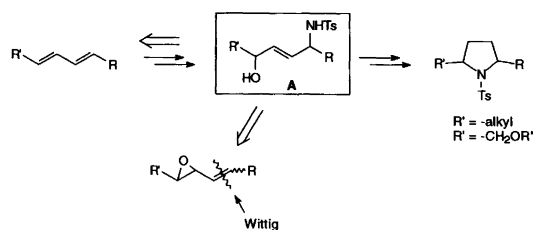
Scheme 3.



Scheme 4.

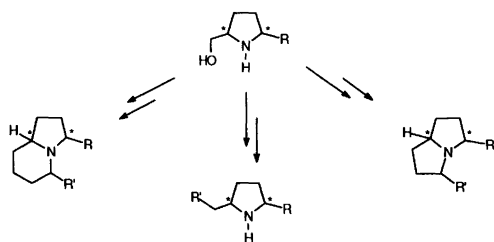
Homochiral 2-hydroxy-5-alkylpyrrolidines

Palladium-catalyzed 1,4-functionalization has also been used to prepare 2,5-disubstituted pyrrolidines.^{12–14} In this approach 4-amino-2-alken-1-ols (A) are key intermediates and are prepared from the corresponding conjugated dienes as either the *syn* or *anti* diastereoisomer via palladium-catalyzed 1,4-functionalization. One limitation with the 1,4-oxidation approach is that it is not yet enantioselective.* We therefore considered another route for the enantioselective preparation of the amino alcohol intermediates. One such approach would be via vinyloxyepoxides, which are accessible in enantiomerically pure forms.

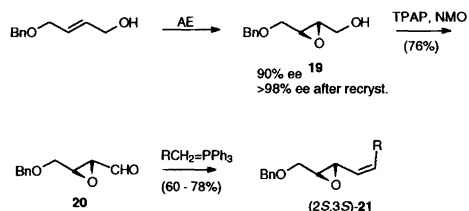


A number of 2,5-disubstituted pyrrolidines are structural elements of natural products and alkaloids. Furthermore, 2-hydroxymethyl-5-alkylpyrrolidines are versatile synthetic intermediates in the synthesis of indolizidine and pyrrolizidine alkaloids as well as simple 2,5-disubstituted pyrrolidines. With the vinyloxyepoxide approach in Scheme 5 an enantioselective route to *cis*- and *trans*-2-hydroxymethyl-5-alkylpyrrolidines was developed.¹⁵

Synthesis of the vinyloxyepoxide (2*S*,3*S*)-**21** is shown in Scheme 6. Asymmetric epoxidation (AE) using the



Scheme 5. 2-Hydroxymethyl-5-alkylpyrrolidines: useful synthetic intermediates.



Scheme 6.

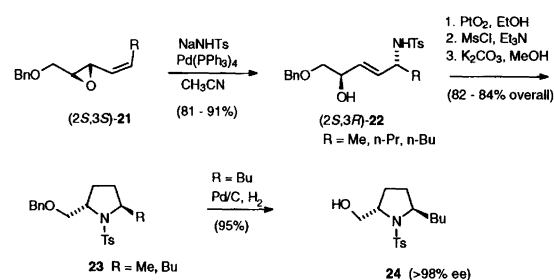
* Work is going on in our laboratory with the use of chiral ligands in the palladium-catalyzed 1,4-oxidations.

Sharpless procedure¹⁶ gave epoxide **19**. Oxidation of the alcohol with tetrapropylammonium perruthenate (TPAP)–NMO and subsequent Wittig reaction afforded the requisite vinyloxyepoxide (2*S*,3*S*)-**21**.

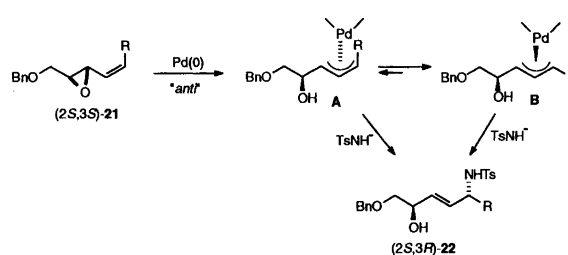
Subsequent transformation of the vinyloxyepoxide according to Scheme 7 afforded the target *trans* pyrrolidine in >98% ee.¹⁵ The chirality transfer in the palladium-catalyzed reaction proceeded with high selectivity.

The mechanism of the palladium-catalyzed reaction with vinyloxyepoxide (2*S*,3*S*)-**21** is shown in Scheme 8. Oxidative addition of Pd(0) to the vinyl epoxide occurs *anti* and initially gives the (π -allyl)palladium complex A. Now if this π -allyl complex reacts with the tosylamide anion via an external attack, the observed *anti* product is obtained. It is likely that the π -allyl complex A undergoes an isomerization to π -allyl complex B via the terminal σ -allyl complex. External attack on this complex will again give the observed product.

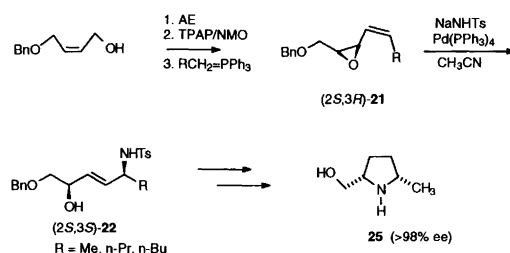
The corresponding *cis*-pyrrolidines are accessible in enantiomerically pure form according to the same methodology via the *cis*,*Z*-vinyloxyepoxide (Scheme 9). Also in this case the chirality transfer in the palladium-catalyzed ring-opening with tosylamide was stereospecific. The *cis*-pyrrolidine was obtained in >98% ee.¹⁵



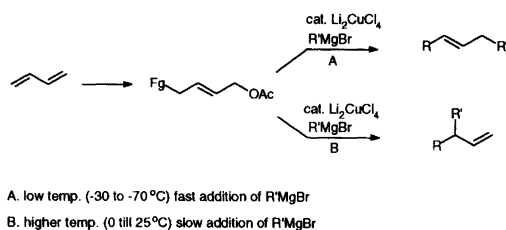
Scheme 7.



Scheme 8. Efficient chirality transfer in the Pd-catalyzed reaction.



Scheme 9.



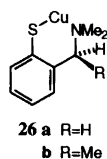
Scheme 10.

Enantioselective copper-catalyzed allylic substitution

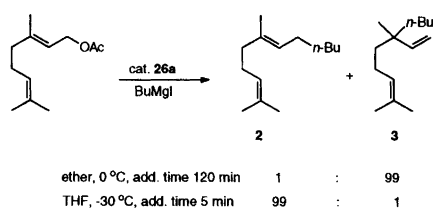
Several years ago we started a project on selective carbon-carbon bond formation of the allylic acetate products obtained from palladium-catalyzed functionalization of conjugated dienes. In this way a highly regiocontrolled copper-catalyzed reaction between primary allylic acetates and Grignard reagents was developed (Scheme 10).¹⁷ By a slight change of the reaction conditions it was possible to change the regioselectivity from complete α -selectivity to complete γ -selectivity.

The high γ -selectivity was extended to include copper-catalyzed reactions of aryl Grignard reagents with allylic substrates.¹⁸ The combination of palladium-catalyzed 1,4-oxidation and stereo- and regio-selective (γ) copper-catalyzed Grignard reactions has been used in natural product synthesis.^{19, 20} The high γ -selectivity is also of interest for enantioselective applications since a new chiral center is formed from a primary allylic acetate. Recent work on asymmetric induction in copper-based γ -selective reactions of primary allylic substrates has involved stoichiometric copper reagents with the use of chiral leaving groups.²¹

A more attractive approach is the use of a chiral ligand in a copper-catalyzed reaction of an allylic acetate with a Grignard reagent. One ligand of particular interest was the (thiophenolate)copper catalyst of type **26**, which had previously been used by van Koten in asymmetric copper-catalyzed Michael additions of Grignard reagents to α,β -unsaturated ketones.²²



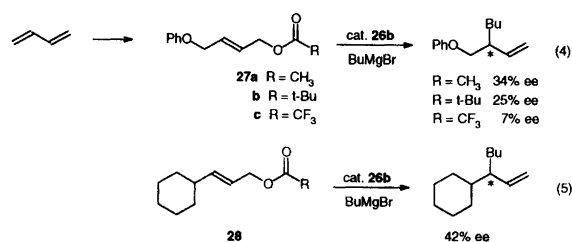
Studies on the use of catalyst **26** showed that it was possible to change from complete α -selectivity to complete γ -selectivity (Scheme 11).²³ An unusual reversal of



Scheme 11.

reactivity between leaving groups was also observed. Thus an allylic acetate was made more reactive than an allylic chloride. An explanation of this reversed reactivity of leaving groups is that the allylic acetate coordinates to magnesium in a chelate of the catalyst (*vide infra*).^{23b}

The copper-catalyzed reaction of primary allylic acetates and BuMgI employing **26b** as the catalyst led to some enantioselectivity.²⁴ The importance of the chelate formation was reflected by the use of different allylic carboxylates **27 a-c** [eqn. (4)]. Acetate **27a** gave much higher asymmetric induction than trifluoroacetate **27c**, which is in line with the formation of a chelate. With trifluoroacetate, coordination to magnesium in the chelate would be much better. Also, with the higher reactivity of the trifluoroacetate it is possible that it reacts before the chelate is formed. With the cyclohexyl derivative **28** a 42% *ee* was obtained [eqn. (5)].



The intermediate in which the diastereoselective interaction occurs is shown in Fig. 1. In this chelate the allylic acetate is bound to the copper-magnesium complex in a rigid structure. A six-membered ring is formed in which it is believed that the iodide and R group on the chiral ligand are *trans* to one another. As a consequence, magnesium becomes a chiral center. In Fig. 1 the favored *Si-Si* coordination is shown. With this interaction *R*-ligand will give *R*-product and *S*-ligand will give *S*-product. This is observed for the cyclohexyl derivative in eqn. (5).

Conclusions

In this review enantiocontrol in some palladium- and copper-catalyzed reactions of allylic substrates has been discussed: (i) the combination of enzyme and palladium catalysis was efficiently used in the enantiodivergent synthesis of lactones; (ii) an enantioselective synthesis of pyrrolidine compounds is described; and (iii) some pre-

Favored intermediate:

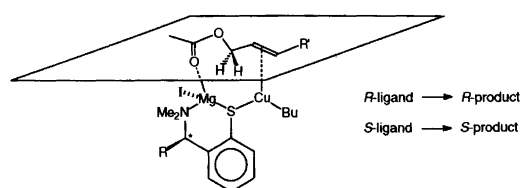


Fig. 1.

liminary results from enantioselective copper-catalyzed reactions of allylic acetates with Grignard reagents is presented.

Acknowledgments. I wish to express my sincere appreciation to my coworkers whose names appear in the reference list, for their efforts in exploring the chemistry outlined in this review. Financial support from the Swedish Natural Science Research Council and the Swedish Research Council for Engineering Science is gratefully acknowledged.

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