



Development of an Asymmetric Palladium-Catalysed Elimination

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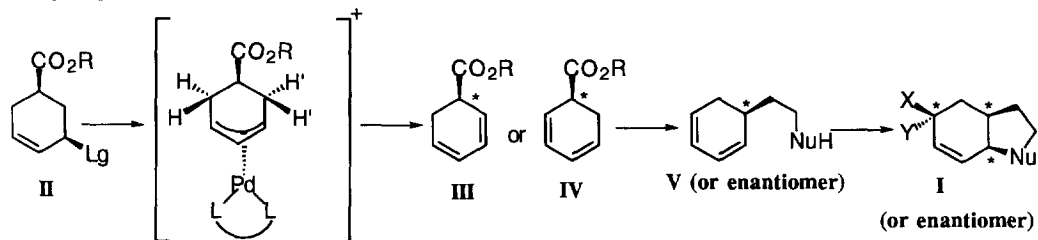
Abstract: We herein describe a novel example of a palladium-catalysed asymmetric allylic elimination leading to enantiomerically enriched dienes. The use of chiral ligands such as BINAP or DIOP allows the catalyst to discriminate between the enantiotopic hydrogens H and H' and leads to *e.e.* up to 37%. Higher degrees of asymmetric induction was possible by the introduction of a chiral auxiliary (R*) in the substrate (89 : 11 diastereomeric ratio).

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Introduction:

Regio- and stereo-defined heterocyclic compounds such as **I** have proven to be useful building blocks in organic synthesis.¹ These can in turn be easily prepared by a palladium(II)-catalysed cyclisation of chiral dienes **V** with a pendant nucleophile.² This transformation is enantiospecific in that the absolute configuration of the new stereogenic centers created in the product depend on that residing in the starting material and it is therefore highly desirable to develop an asymmetric synthesis of these dienes. We now report on our results concerning the synthesis of optically active conjugated dienes **III** and **IV** from racemic **II** via an asymmetric palladium-catalysed elimination (scheme 1).³

Scheme 1

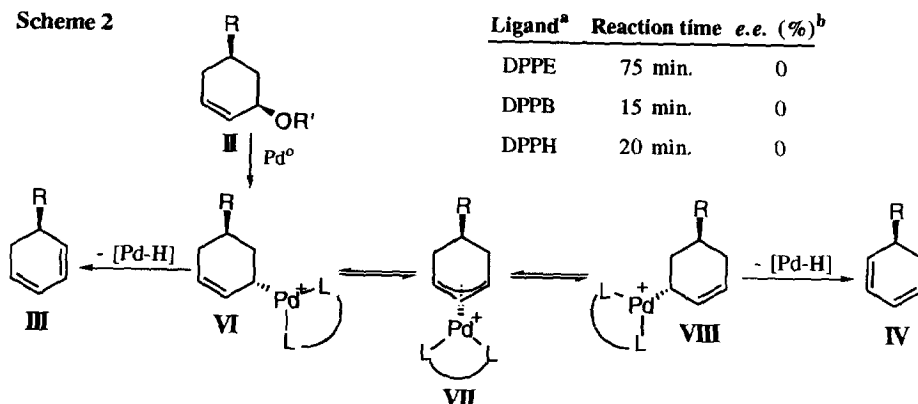


Lg = Leaving group, R = chiral or non chiral group, L = chiral or non chiral diphenylphosphine ligand, X = Cl, RCO₂ or RO, Y = RCO₂, Nu = CO₂, O or NR.

The postulated mechanism of palladium(0)-catalysed elimination is depicted in scheme 2. Coordination and subsequent oxidative addition of Pd(0) to the allylic moiety in **II** results in the formation of a σ -allyl Pd-complex. This σ -allyl complex is in fast equilibrium with the symmetric π -allyl palladium complex **VII** and the diastereomeric σ -allyl complex **VIII**. Elimination of [Pd-H] is assumed to occur on σ -complexes **VI** or **VIII**, which results in the formation of the enantiomeric dienes **III** or **IV** respectively.

The fast equilibrium between complexes **VI**, **VII** and **VIII**, which is a prerequisite for the enantioselective process, was confirmed in a control experiment. When enantiomerically pure *cis*-carveol methyl carbonate (**II**, R = 2-propenyl, R' = CO₂Me; scheme 2) was subjected to the palladium-catalysed elimination using an achiral bis-phosphino ligand, racemic diene was produced,⁵ indicating that the equilibrium

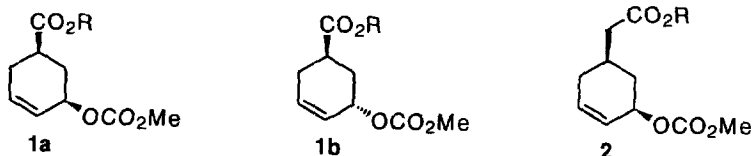
Scheme 2



a) DPPE; 1,2-Bis(diphenylphosphinoethane), DPPB; 1,4-Bis(diphenylphosphinobutane), DPPH; 1,6-Bis(diphenylphosphino hexane). b) Determined by measuring the optical rotation $[\alpha]_D^{25} = 0$ ($c = 1$, Et_2O).

VI→VII→VIII is much faster than the elimination of Pd-H (Scheme 2). The rate of the elimination was found to depend on the chelate size of the ligand-palladium complex, with the larger chelates being more reactive than the smaller. The effect of the leaving group on the elimination rate was also evaluated. The methyl carbonate showed the highest reactivity of those screened (Cl^- , AcO^- , MeOCO_2^- , EtOCO_2^-), and led to a rapid elimination using 3% $\text{Pd}(\text{dba})_2$ in refluxing benzene.

The asymmetric elimination was studied using three different substrates; *cis*- and *trans*-1 and the one carbon homologue 2.



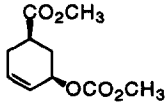
Enantioselective eliminations:

Several chiral bis-phosphines and bis-nitrogen compounds were examined as ligands in the asymmetric elimination. A large difference in reactivity between the phosphine and the nitrogen complexes was observed. The phosphine ligands, except Me-DuPHOS,⁶ gave rise to palladium complexes which efficiently catalyzed the elimination whereas the corresponding nitrogen complexes did not show any catalytic activity at all. The highest asymmetric induction was obtained using BINAP as ligand for palladium, which led to 37% *e.e.* for 1a, and 24% *e.e.* for 2. The results obtained are summarised in table 1.

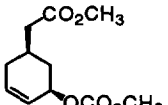
Diastereoselective eliminations:

In order to further improve the asymmetric induction in the elimination step, a chiral auxiliary was incorporated in the substrate. Several commercially available alcohols were examined,⁷ and the best results were obtained employing either (-)-2,10-camphorsultam⁸ 4 or (-)-8-phenylmenthol⁹ 5a, 5b as the chiral auxiliary (table 2). The chelate size of the palladium-phosphine complexes was found to have a large impact on the reactivity, as well as on the diastereoselectivity of the catalyst. For instance, when (-)-2,10-camphorsultam 4

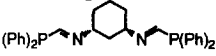
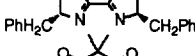
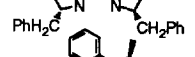
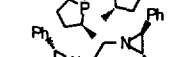
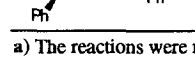
Table 1



1a

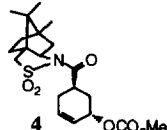


2

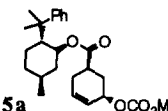
| Ligand | 1a | | | 2 | | |
|---|----------------------------|------------------------|------------------------------|----------------------------|------------------------|------------------------------|
| | Reaction time ^a | Yield (%) ^b | <i>e.e.</i> ^c (%) | Reaction time ^a | Yield (%) ^b | <i>e.e.</i> ^d (%) |
| (+) BINAP | 3 h. 15 min. | 98 | 37 | 1 h. 15 min. | 30 | 24 |
| (-) BINAP | 2 h. 45 min. | 98 | 35 | 1 h. 15 min. | 31 | 19 |
| (+) DIOP | 1 h. 15 min. | 99 | 21 | 15 min. | 80 | 6 |
| (-) Sparteine | no reaction | | | | | |
|  | 2 h. 15 min. | 100 | 0 | | | |
|  | no reaction ^e | | | | | |
|  | no reaction ^e | | | | | |
|  | no reaction ^e | | | | | |
|  | no reaction ^{e,f} | | | | | |

a) The reactions were monitored by tlc, and quenched when all starting material was consumed. b) Yields refer to isolated product. c) Determined by titration by $\text{Eu}(\text{tfc})_3$ in deuterated benzene. d) Determined from the specific rotation of the purified product (see ref. 4). e) No exchange between dba and the ligand could be observed; the starting material was recovered. f) Traces of UV active product could be detected on tlc.

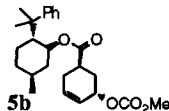
Table 2



4



5a



5b

| Ligand ^a | 4 | | | 5a | | | 5b | | |
|-------------------------|-----------------------------------|------------------------|------------------------------|-----------------------------------|------------------------|------------------------------|-----------------------------------|------------------------|------------------------------|
| | Reaction time ^b (min.) | Yield ^c (%) | <i>d.e.</i> ^d (%) | Reaction time ^b (min.) | Yield ^c (%) | <i>d.e.</i> ^d (%) | Reaction time ^b (min.) | Yield ^c (%) | <i>d.e.</i> ^d (%) |
| $\text{P}(\text{Ph})_3$ | | | | 30 | 93 | 23 | 45 | 41 | 19 |
| DPPE | 60 | 74 | 65 | 60 | 63 | 23 | 45 | 44 | 29 |
| DPPP | 30 | 98 | 37 | 20 | 49 | 29 | 45 | 62 | 24 |
| DPPB | 45 | 37 | 77 | 30 | 93 | 22 | 45 | 83 | 31 |
| DPPPent | 30 | 89 | 36 | 20 | 64 | 50 | 45 | 98 | 39 |
| DPPH | 45 | 74 | 64 | 20 | 74 | 6 | 45 | 93 | 26 |
| (+)-BINAP | 240 | 25 | 45 | 120 | 44 | 26 | 120 | 57 | 2 |
| (-)-BINAP | 240 | 10 | 27 | 90 | 64 | 60 | 120 | 52 | 30 |
| (+)-DIOP | 240 | 44 | 43 | 30 | 93 | 58 | 120 | 93 | 6 |

a) DPPP; 1,3-diphenylphosphinopropane, DPPent; 1,5-diphenylphosphinopentane. b) Completion of the reaction was determined by tlc. c) All yields that are given refer to compounds purified by flash chromatography. d) The diastereomeric excess was determined by ^1H NMR and did not change during isolation of the product.

was used, the diastereoisomeric ratio varied from 68 : 32 to 89 : 11 depending on the tether length in the bidentate phosphine ligand. Double asymmetric induction by the employment of a chiral ligand on palladium was also investigated. However, the results using (+)- and (-)-BINAP clearly show that the induction of the auxiliary overrides that of the ligand and in no case could the ligand change the diastereoselectivity.

Acknowledgements. Financial support from the Swedish Natural Science Research Council is gratefully acknowledged. We are grateful to Prof. J. E. Bäckvall for helpful discussions and to Johnson Matthey for a generous gift of palladium chloride.

References and footnotes:

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4. Prepared in two steps from (-)-carvone via reduction and alkylation with methyl chloroformiate. For the diastereoselective reduction of (-)-carvone see: Ireland, R. E.; Maienfisch, P. *J. Org. Chem.* **1988**, *53*, 640.
5. Enantiomerically pure diene was prepared following the procedure described by Cornforth and al., *J. Chem. Soc. Perkin Trans I*, **1987**, 851. $[\alpha]_D^{25} = -212.4$ (c = 1.06, Et₂O).
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7. (-)-Borneol, α -terpineol, (+)-isopinocampheol, (1S)-fenchyl alcohol, (S)-(-)- α -methyl-1-naphthalene methanol, (+)-isomenthol and (+)-menthol were also studied, but did not lead to any significant diastereoselectivity in the elimination.
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(Received in UK 17 June 1996)