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PALLADIUM-PROMOTED ASYMMETRIC OXYAMINATION OF ALKENES
APPLICATION TO THE SYNTHESIS OF OPTICALLY ACTIVE ARYLOXYPROPANOLAMINES

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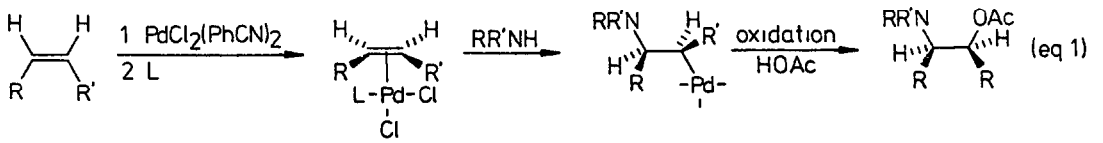
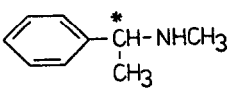
Summary: Palladium-promoted oxyamination of some alkenes using optically active N-methyl-α-phenylethylamine as amine nucleophile, or using optically active N,N-dimethyl-α-phenylethylamine as ligand, produces optically active aminoalcohol derivatives in an optical yield of 3-60%. Oxyamination of aryl allyl ethers gives optically active 1-amino-3-aryloxy-propan-2-ol derivatives, which are important β-blockers

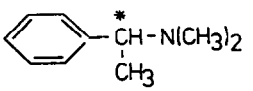
Although transition metals in an asymmetric environment (usually with a chiral ligand) have been extensively used in asymmetric synthesis,[1,2] there are only limited examples of the use of nucleophilic additions to coordinated olefins.[3] We recently developed a stereospecific oxyamination of olefins[4] involving a nucleophilic addition of amine[5] to a π-olefinpalladium complex (eq. 1). We have now found that by the use of chiral reagents, we can induce asymmetry in the amination step and in this way prepare optically active aminoalcohols.



We have used two different approaches for introducing asymmetry into the aminoalcohol derivative. In the first approach optically active N-methyl-α-phenylethylamine (1) has been utilized as nucleophile. In this case the amine itself may also serve as a ligand. In the second approach optically active N,N-dimethyl-α-phenylethylamine (2) has been used as a chiral ligand.



1



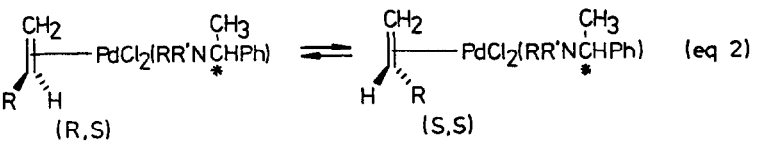
2

To the π-olefin complex, prepared by stirring the olefin with $PdCl_2(PhCN)_2$ in THF at 0°C,[4,5] was added one equivalent of chiral amine 1 or 2 at -30°C The mixture was stirred for 15 min at -30°, then cooled to -50°C and three equivalents of the appropriate amine were added. Oxidative cleavage of the palladium-carbon bond in the σ-complex as described previously[4] gave the amino-alcohol derivative. Results from some asymmetric oxyamination reactions are given in Table 1 The asymmetric induction varies with the amine and the olefin used and an optical yield of up to 60% is obtained in one case . The use of aryl allyl ethers as substrates produces optically active aryloxypropanolamines, which are important β-adrenergic blockers.[6,7] It is of particular interest to prepare only one of the optical isomers of aryloxypropanolamines, since the pharmacological activity of one enantiomer can be 50-500 times higher than the activity of the other [7]

In the case where the optically active amine is used as nucleophile the product is readily debenzylated by hydrogenation (Pd/C).[8]

The optical purity of the products were determined by ^1H NMR spectroscopy. In the case where a chiral amine is used as nucleophile this analysis is simple, since the products formed are pair of diastereoisomers.[9] Although three chiral centra are present in the products obtained from oxy-amination of internal olefins only two diastereoisomers are formed, since the addition is stereo-specific (*cis*-oxyamination) [4a] In the case where the product is a mixture of enantiomers the enantiomeric excess was determined by addition of MTPA ($PhC^*(OMe)(CF_3)COOH$) and subsequent ^1H NMR analysis of the diastereoisomeric salts formed.[10]

When the chiral ligand coordinates to the metal in the π-olefin complex, a pair of diastereo-isomeric complexes are formed, which may be in equilibrium with each other (eq 2). It is known that analogues resolved diastereomeric π-olefin complexes of platinum, which presumably react slower in olefin-for-olefin exchange than 3 and 4, epimerize at a moderate rate at room temperature.[11] The enantiomeric excess of the product from nucleophilic attack on 3, will now depend on the ratio of the diastereoisomers 3a and 3b



(eq 2)

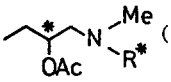
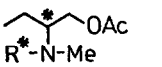
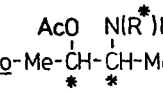
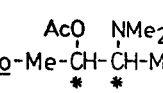
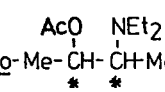
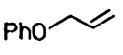
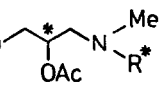
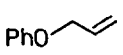
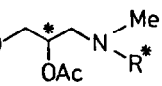
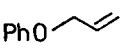
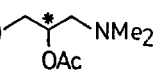
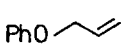
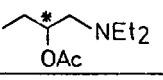
3a R=R'= CH_3 3b

4a R= CH_3, R'= H 4b

In the case where the secondary optically active amine 1 is used both as ligand and nucleophile, the asymmetric induction may be due to two effects Asymmetry can be induced because of the different distribution between isomers 4a and 4b (eq. 2), and it can be induced because of the different reactivity of the olefin in 4a and 4b towards amine 1 in a diastereomeric transition state.[12] In the latter case the optical yield will also depend on the rate of olefin for olefin exchange; if the exchange 4a ⇄ 4b is slow compared to nucleophilic attack, the optical yield will decrease with increasing chemical yield

In order to estimate the contribution of the two different effects ("ligand effect and

Table 1 Palladium-promoted asymmetric oxyamination[a]

Entry	Olefin	First amine added[b]	Amine added as nucleophile[b]	Product (% yield)[c]	Asymmetric induction (%)[d]
1		R^*NHMe	R^*NHMe	 (25)[e]	22
				 (25)[e]	22
2		R^*NHMe	R^*NHMe	 (20)[f]	60
3		R^*NMe_2	Me_2NH	 (81)[f]	3
4		R^*NMe_2	Et_2NH	 (38)[f]	7
5		Et_3N	R^*NHMe	 (20)[e]	28
6		R^*NHMe	R^*NHMe	 (39)[e]	20
7		R^*NMe_2	Me_2NH	 (45)[e]	11
8		R^*NMe_2	Et_2NH	 (50)[e]	12

a Lead tetraacetate was used as the oxidant, b. R^* denotes optically active $PhCH(CH_3)$- of S-configuration, c. Yield is based on the amount of palladium used, d. Enantiomeric or diastereomeric excess. In the case where diastereomeric products were formed, the asymmetric induction was determined both before and after purification (no significant difference of the diastereomeric excess could be observed), e. Isolated yield, f. Determined by gas chromatography using an internal standard.

"diastereoselectivity in the nucleophilic attack") we have performed the oxyamination of $PhOCH_2CH{=}CH_2$ using racemic amine 1. The diastereomeric excess determined from this experiment was 33% This should be compared with the experiments in entries 5 and 6, where optically pure amine S-1 was used as nucleophile The use of triethylamine as first amine followed by S-1 gives 28% optical yield, whereas the use of S-1 both as ligand and nucleophile gives 20% optical yield.

The lower diastereomeric excess obtained from optically pure 1 compared to racemic 1 may be explained in two ways. One explanation is that the amine S-1 as ligand induces a slight enrichment of S- or R-coordinated olefin and that the less enriched asymmetrically coordinated olefin

is the one reacting faster in the nucleophilic attack by S-1. Another explanation is that the equilibrium 4a ⇄ 4b is slow compared to nucleophilic addition. Further studies are needed to distinguish between these possibilities.

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