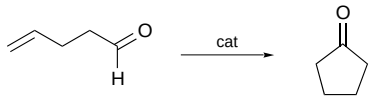
Asymmetric catalytic intramolecular hydroacylation of 4-substituted pent-4-enals to β-substituted cyclopentanones

Richard W. Barnhart, David A. McMorran and B. Bosnich

Department of Chemistry, The University of Chicago, 5735 South Ellis Avenue, Chicago, Illinois 60637, USA

The catalyst, [Rh(*S*,*S*-Me-duphos)(acetone)$_2$]$^+$, rapidly and efficiently converts 4-substituted pent-4-enals bearing primary and secondary substituents to the corresponding cyclopentanones and for a variety of substituents the ee was found to range from 93 to 96% at 25 °C.

Asymmetric catalytic intramolecular hydroacylation involving the conversion of pent-4-enals to cyclopentanones (eqn. 1) is



(1)

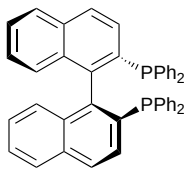
potentially an important transformation because it provides pivotal precursors for the generation of elaborate molecules. Generally, cationic rhodium(i) complexes bearing chelating diphosphines provide catalysts which have high turnover frequencies and numbers.[1,2] In contrast, analogous complexes bearing unidentate phosphines give poor turnover numbers[3] because decarbonylation of the substrate leads to the formation of stable monocarbonyl rhodium complexes which are catalytically inactive. In order to achieve efficient catalysis with chelating diphosphine rhodium(i) complexes, two vacant or virtually vacant coordination positions are required in order to allow ready access of the substrate to the metal.[1,2] This is usually achieved by hydrogenation of the dialkene (norbornadiene or cycloocta-1,4-diene) complex to produce the cationic disolvento catalyst. Weakly bound solvento complexes give the highest rates. Generally, high yields and rapid turnover frequencies are observed for substrates bearing substituents at the 3- and 4-positions whereas substituents at the 2- and 5-positions hinder the rate of hydroacylation.

We recently reported that the *S*-binap (**1**) catalyst, [Rh(*S*-binap)(solvent)$_2$]$^+$, where solvent is dichloromethane or acetone, is a very efficient and highly enantioselective catalyst for certain 4-substituted pent-4-enals **2**.[4] In particular, when R is a tertiary carbon or tertiary silicon group, cyclopentanone products are produced in > 99% ee and in quantitative chemical yield. Similarly, when R is an ester group, essentially enantiomerically pure products are also produced and when R is a ketone, very high ees are observed. Significantly, all of these high enantioselectivities occur at 25 °C and at low catalyst loadings and given the consistency of the results, it would appear that the binap catalyst will give essentially enantiomerically pure cyclopentanones for any tertiary or ester R group and will give high ees for ketonic substituents.

The binap catalyst, however, gives modest ees for substrates bearing a primary or secondary R group and we sought to find a catalyst which would serve to produce consistently high ees for these substituents. The rhodium(i) complex incorporating *S*,*S*-Me-duphos, **3**, proved to be effective for these substrates. The catalytic precursor, [Rh(*S*,*S*-Me-duphos)(NBD)]PF$_6$, where NBD is norbornadiene, was isolated as crystals and the catalyst, [Rh(*S*,*S*-Me-duphos)(acetone)$_2$]PF$_6$, was generated by hydrogenation of the NBD ligand in acetone solution. Addition of the 4-substituted pent-4-enals at 25 °C to these solutions causes rapid catalysis in nearly all cases and quantitive chemical yields are observed.

In Table 1, we list the results obtained for a variety of substrates, one class where primary alkyl groups are present α to the vinyl group (entries 1–6) and the other where a secondary carbon is bound to the vinyl group (entries 7–10). All reactions were carried out in acetone, with substrate concentrations of 0.15–0.2 mol dm^{-3}, and the time to completion data are listed for 5 mol% catalyst loadings. The times listed in Table 1 were obtained from ^{1}H NMR spectroscopy and no side products were detected. For large scale experiments, 2 mol% catalyst loadings were employed and the % ee was determined by ^{13}C NMR spectra of the Samp[5] derivatives **4**. The absolute configurations were determined by comparing the optical rotations with those reported. Where the absolute configuration was unknown, it was assumed that the ^{13}C NMR chemical shifts of the Samp diastereoisomers would be consistent throughout as they were found to be for those cyclopentanones of known configuration.[6]

Aside from entry 6 where the substrate carries a phenyl group, all of the reactions are essentially complete upon mixing at 25 °C. It will be noted that all of the products have the same absolute configuration, that all ees are consistently high and vary very little over a variety of substituents. It seems reasonable to conclude that the Me-duphos catalyst is likely to provide high enantioselectivity for any 4-substituted pent-4-enal bearing a primary or secondary carbon atom substituent. Using the Et-duphos catalyst gave similar ees for these substrates. Because the catalytic turnover frequency is so high for most of the substituents, we investigated the enantioselectivity at −10 °C for two substrates. The time of reaction and the ees are given in the square brackets (Table 1). At −10 °C, the ee is raised to 98% in both cases, suggesting that essentially optically pure products are accessible by manipulation of the catalytic conditions. Further, catalysis proceeds even at 0.5 mol% loading, although at 25 °C, 2 h were required for complete conversion of the butyl substrate (entry 3). No side products were observed. It is probable that the low turnover frequency for the phenylated substrate (entry 6) is due to the formation of the catalytically inactive π-aryl complex of the catalyst.[7]



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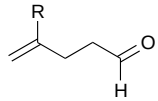

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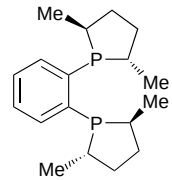

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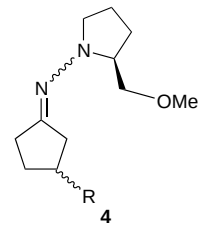

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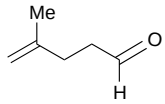
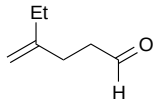
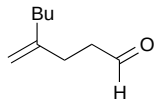
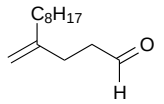
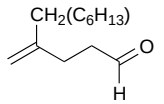
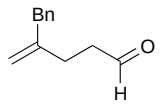
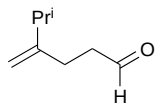
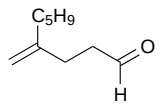
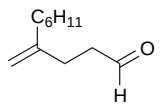
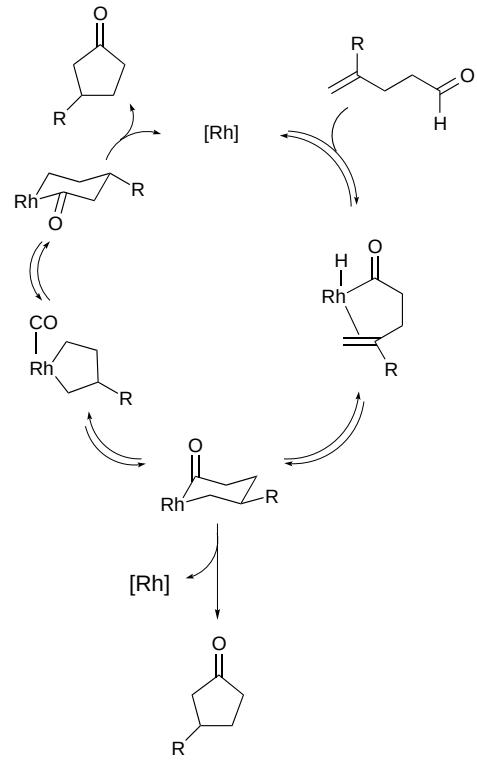
Table 1 Asymmetric catalytic intramolecular hydroacylation of 4-substituted pent-4-enals using 5 mol% of the [Rh(*S*,*S*-Meduphos) (acetone)$_2$]PF_6 catalyst in acetone solution

Entry	Substrate	*t*/min[a]	Ee (%) (abs. config.)
1		< 5	94 (*S*)
2		< 5	95 (*S*)
3		< 5 [60][b]	94 (*S*) [98][b]
4		< 5	93 (*S*)
5		< 5	93 (*S*)
6		180	94 (*S*)
7		< 5	96 (*S*)
8		< 5	96 (*S*)
9		< 5 [60][b]	94 (*S*) [98][b]

[a] For > 95% completion. [b] Results obtained at −10 °C, all other entries refer to 25 °C.

In the context of the consistency of the results listed in Table 1 and those reported for the binap catalyst, it is interesting that the Me-duphos catalyst gives modest ees at 25 °C for substrates bearing tertiary groups. Thus, when the R substituent in the substrate **2** is Bu^t, Me_3Si or $PhMe_2Si$, the Me-duphos catalyst gives the corresponding *S*-cyclopentanones with ees of 44, 64 and 61%, respectively. As for the case of the binap catalyst, the Me-duphos catalyst gave moderate ees for 4-aryl substituted pent-4-enals. It was found that for the substrates where R = phenyl, *p*-tolyl, *p*-methoxyphenyl and *o*-methoxyphenyl, the ees were 46 (*R*), 72 (*R*), 70 (*R*) and 54% (*S*), respectively, using the *S*,*S*-Me-duphos catalyst. The chiraphos catalyst remains the most effective for these aryl bearing substrates where the ees range from 65 to 78%.[4]

The probable mechanism for hydroacylation is outlined in Scheme 1.[8] Except for the final reductive elimination step to produce the product, all of the steps are reversible. As was shown previously,[8] however, these reversible steps are not at equilibrium but the enantioselectivity is to some extent controlled by these steps. Thus the enantioselectivity is controlled by a complex mix of rate constants and it is not possible to identify a particular intermediate which determines



Scheme 1

the ee, and, consequently, there is no guiding principle that can be postulated for the origins of the enantioselection.

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