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The Enantioselective Step in the Nickel-Catalyzed Hydrocyanation of 1,3-Cyclohexadiene

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The nickel-catalyzed asymmetric hydrocyanation is a useful CC bond formation reaction for the production of optically active compounds; yet, the contributions regarding this topic are scarce in the literature.[1] Only vinylarenes[2−6] and norborn(adi)enes[6−14] have been applied as prochiral substrates so far. The generally accepted mechanism for dienes as well as vinylarenes is depicted in Figure 1. The reductive elimination of the product is the rate-determining step, which causes the rate law to be zero order in the substrate.[15] In the case of vinylarenes as substrates, Casalnuovo and RajanBabu concluded that the enantioselective step has to be either the substrate insertion into the Ni−H bond and/or the reductive elimination of the product since all diastereoisomers of the metal−substrate intermediate (**II**) were observed spectroscopically and are formed in almost equal amounts.[2] They also showed that the insertion is reversible by using a deuterium-labeled substrate, and the relative rate of reductive elimination over β-hydride elimination increases when the electron density on phosphorus is reduced by electron-withdrawing groups on the ligand. For electron-poor ligands, the insertion is essentially irreversible. So far, little is known about preventing the deactivation of the catalyst by ligand design as well as the enantioselective step.

The enantioselective step in asymmetric catalytic reactions is intrinsically difficult to determine experimentally; nevertheless it has been studied in several reactions. Substrate coordination is commonly believed to be the enantioselective step in biocatalytic transformations. In asymmetric hydrogenation, the enantioselectivity is determined during the oxidative addition of H_2 and the consecutive insertion.[16,17] Moreover, there is a delicate balance for kinetic versus thermodynamic control.[18] In the allylic alkylation, the attack of the nucleophile on the allyl group is believed to be the enantioselective step.[19] In rhodium- and platinum/tin-catalyzed hydroformylation, the enantioselective step changes with temperature, from olefin insertion into the M−H bond at low temperature to the reductive elimination of the product at high temperature.[20,21] In this contribution, we discuss our efforts on the determination of the enantioselective step in the hydrocyanation of 1,3-cyclohexadiene.

Addition of HCN to 1,3-cyclohexadiene results in the formation of 2-cyclohexene-1-carbonitrile; both 1,2- and 1,4-addition lead to identical products, as at stage (**V**) a symmetrical allyl fragment is formed in which the positions 2 and 4 cannot be distinguished (Figure 1).

However, by using DCN instead of HCN, one can distinguish between the 1,2- and 1,4-addition products by NMR. Tolman demonstrated that insertion of cyclopentadiene into $DNiL_4^+$ results in a deuterated (π-allyl)nickel complex in which the nickel center and deuterium atom are located on the same side of the ring.[22] Bäckvall and Andell showed *cis* addition of DCN over the diene in 1,3-cyclohexadiene using $Ni(P(OPh)_3)_4$ as the catalyst system.[23]

Even though 1,2- and 1,4-addition results in opposite enantiomers, we achieved an enantiomeric excess of 86% with the chiral

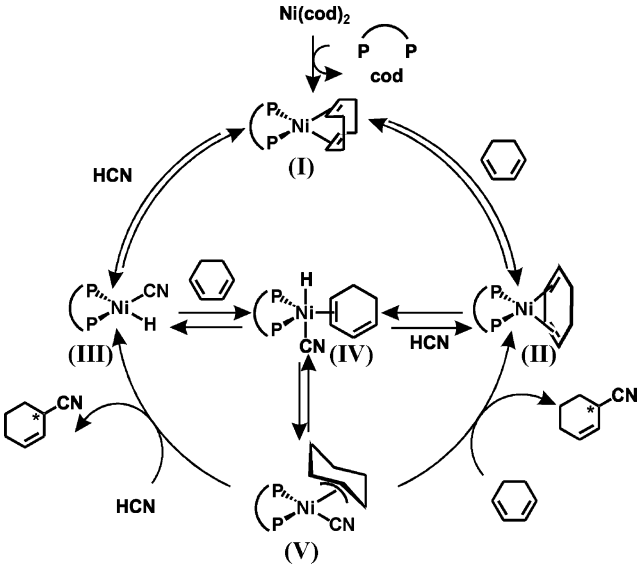

Figure 1. Catalytic cycle for Ni(0)-catalyzed hydrocyanation.

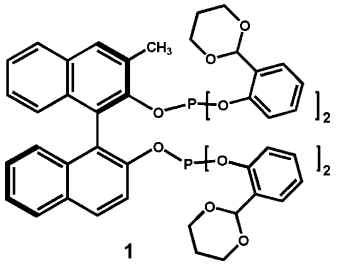

Figure 2. Asymmetric diphosphite ligand **1**.

diphosphite ligand **1** (Figure 2). This means that the CN addition takes place preferably at one terminus of the η^3-allyl fragment. Addition of CN on the *Re* side of the Ni−allyl fragment results in formation of the *R* enantiomer (eqs 1 and 2 in Scheme 1), while addition on the *Si* side of the Ni−allyl fragment leads to the formation of the *S* enantiomer. A series of β-hydrogen elimination without dissociation of 1,3-cyclohexadiene (**V** → **IV** in Figure 1) and subsequent insertion reactions could give the intramolecular interconversion of the two nickel−allyl intermediates (**K2**). If this would take place, the 1,3-product would also be formed. However, the 1,3-product was not detected by either ^{13}C or ^{2}H NMR spectroscopy. Intermolecular conversion is excluded since this would lead to *trans* addition.

These three rather unique features give the possibility to distinguish between insertion (**IV** → **V**) and reductive elimination (**V** → **II/III**) as the enantioselective step on the basis of product distribution. In the theoretical case of 100% ee (*R*), we can expect, depending on the enantioselective step, the following product distributions:

10.1021/ja064378u CCC: $33.50

Scheme 1

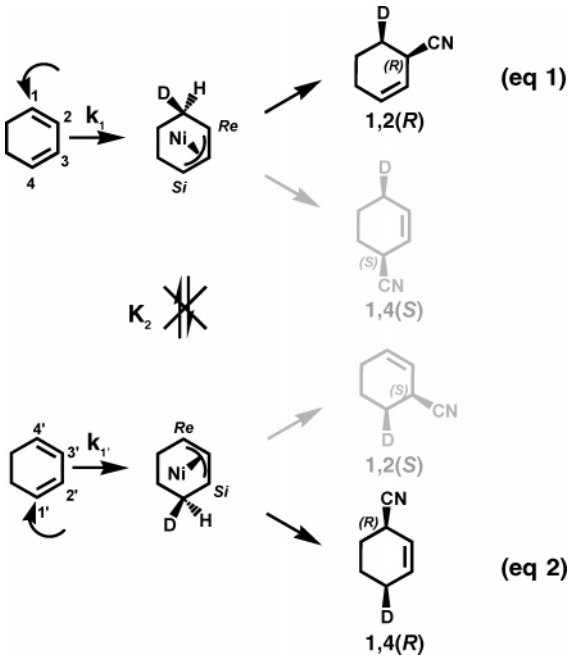

Table 1. Hydro- and Deuteriocyanation of 1,3-Cyclohexadiene

entry	H/D CN	*T* (°C)	yield (%)	ee (%)[a]	1,2/1,4[c]	subs/Ni
1	HCN	60	57	71		500
2	DCN	60	50	75[b]	52/48 (5)	100
3	HCN	0	45	86		500
4	DCN	0	10	85[b]	54/46 (10)	100

[a] Enantiomeric excess was determined with GC, lipodex E (130 °C, 50 kPa H_2). [b] Enantiomeric excess = $\{[1,2(R) + 1,4(R)] - [(1,2(S) + 1,4(S)]\}/\{[1,2(R) + 1,4(R)] + [(1,2(S) + 1,4(S)]\}$. [c] Ratio was determined by means of $^{13}C\{^1H\}$ NMR spectroscopy with an estimated error in parentheses. For reaction conditions, see Supporting Information.

Insertion: The reaction proceeds either via eq 1 ($k_1 \gg k_{1'}$) or via eq 2 ($k_1 \ll k_{1'}$) as 1,3-cyclohexadiene inserts in a specific way. Only one regioisomer will be formed (either **1,2(*R*)** or **1,4(*R*)**).

Reductive Elimination: Random insertion ($k_1 = k_{1'}$) of the substrate will form the regioisomers, **1,2(*R*)** and **1,4(*R*)**, in equal amounts.

Insertion and Reductive Elimination: That is, eq 1 is favored over eq 2 by a small factor ($k_1 > k_{1'}$ or $k_1 < k_{1'}$), and the **1,2(*R*)** and **1,4(*R*)** products will be formed in uneven amounts.

The results obtained for the asymmetric hydrocyanation of 1,3-cyclohexadiene with HCN and DCN at different temperatures are shown in Table 1. From GC−MS measurements, it is clear that the product has incorporated one deuterium atom and the substrate had no detectable deuterium incorporation (k_1 is irreversible). While chiral GC separates both enantiomers, the diastereoisomers **1,2(*R*)** and **1,4(*R*)** as well as **1,2(*S*)** and **1,4(*S*)** could not be separated. However, we were able to determine the product ratio by means of $^{13}C\{^1H\}$ NMR spectroscopy of the nitrile (entries 2 and 4) as well as ^1H and ^2H NMR of the corresponding amine (entry 2).

The reaction proceeds at 60 °C with an enantiomeric excess of 75%. This would result in a theoretical product distribution of 87.5/12.5 when the enantioselectivity is determined during the insertion step and of 50/50 when the reductive elimination is the enantioselective step. From Table 1, it is obvious that equal amounts of 1,2- and 1,4-product were formed when DCN was applied in the hydrocyanation reaction. Therefore, the enantioselective step has to be the reductive elimination. Although the activity is affected (the reported isotope effect is 3.6), we found no isotope effect on the enantiomeric excess, which is in agreement with the observations made by RajanBabu in the hydrocyanation of 6-methoxy-2-vinylnaphthalene.[2]

In summary, we established the reductive elimination of the product to be the enantioselective step in the nickel-catalyzed hydrocyanation of 1,3-cyclohexadiene, on the basis of deuterium labeling experiments and an equal 1,2-/1,4-product distribution. This could be achieved by successfully exploiting the rather unique features of this reaction: identical product formation for 1,2- and 1,4-addition, *cis* addition over the diene, and high enantiomeric excess.

Supporting Information Available: GC, GC−MS, and NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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