DOI: 10.1002/chem.200800090

Generation and Reactivity of Enantiomeric (BINOLato)Ni$^+$ Complexes with Chiral Secondary Alcohols in the Gas Phase

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Dedicated to Professor Emanuel Vogel on the occasion of his 80th birthday

Abstract: In the presence of secondary alcohols, electrospray ionization of dilute methanolic solutions of nickel(II) salts and 1,1′-bis-2-naphthol (BINOL) leads to complexes of the formal composition [(BINOLato)Ni(CH$_3$CH(OH)R)]$^+$ (BINOLato refers to a singly deprotonated (*R*)- or (*S*)-1,1′-bis-2-naphthol ligand; R = CH$_3$, C$_2$H$_5$, *n*-C$_3$H$_7$, *n*-C$_4$H$_9$, *n*-C$_5$H$_{11}$, *n*-C$_6$H$_{13}$, *c*-C$_6$H$_{11}$, and C$_6$H$_5$). Upon collision-induced dissociation, each mass-selected nickel complex either loses the entire secondary alcohol ligand or undergoes bond activation followed by elimination of the corresponding ketone, as revealed by deuterium labeling. When enantiomeric BINOLato ligands (*R* or *S*) are combined with chiral secondary alcohols (*R* or *S*), differences in the branching ratios between these channels for the two stereoisomers of the secondary alcohols provide insight into the chiral discrimination operative in the C–H- and O–H-bond activation processes. For saturated alkan-2-ols, the chiral discrimination is low, and if any preference is observed at all, ketone elimination from the homochiral complexes (*R*,*R* and *S*,*S*) is slightly favored. In contrast, the diastereomeric (BINOLato)Ni$^+$ complexes of 1-phenylethanol exhibit preferential ketone losses for the heterochiral systems (*S*,*R* and *R*,*S*).

Keywords: bond activation · chiral discrimination · mass spectrometry · nickel · transition-metal complexes

Introduction

Studying the molecular origin of enantioselectivity is an intriguing topic in its own right, not least due to its importance in asymmetric synthesis and because of the distinct role chirality plays in biological systems. Gas-phase studies may help understanding of the intrinsic properties underlying the mechanisms of chiral discrimination.[1–4] In this respect, many successful attempts have been made in the last years, and most of them can be assigned to three different approaches.

In the first of these, chiral selectivity is probed through the differences in abundance of diastereomeric proton-bound complexes generated in the gas phase[5] by means of chemical ionization (CI),[6,7] fast atom bombardment (FAB), electrospray ionization (ESI), or matrix-assisted laser desorption ionization (MALDI).[7,8]

Another technique is based on ion–molecule reactions. For example, proton-bound complexes, each consisting of an optically pure chiral host and one enantiomer of a chiral guest, are mass-selected and allowed to undergo exchange reactions with a neutral gas. The chiral effects can then be derived from the different rate constants measured for the exchange of each of the enantiomers of the guest, with the chirality of the host being kept constant.[9–11]

In the third approach, based on the application of "Cooks' Kinetic Method",[12–14] collision-induced dissociation (CID) of a proton- or a metal-bound complex formed between a chiral analyte and an optically pure reference leads to the loss either of the reference or of the analyte, and the branching ratio (BR) of the fragments can be used to determine the enantiomeric composition of the analyte.[15]

In none of the above cases, however, is chiral discrimination connected to a fundamental chemical process—making or breaking of covalent bonds, for example—within one of the complex's building blocks.

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Mass spectrometric studies have revealed the ability of transition-metal ions to activate a broad variety of substrates, including activation of C–H and C–O bonds.[16,17] However, examples of chiral effects in bond-activation processes are very rare,[18] and in many cases no significant enantioselectivities are observed. Here[19] we report a detailed mechanistic study on the enantioselective oxidation of chiral secondary alcohols—$CH_3CH(OH)R$ (with $R = CH_3$, C_2H_5, n-C_3H_7, n-C_4H_9, n-C_5H_{11}, n-C_6H_{13}, c-C_6H_{11}, and C_6H_5)—to the corresponding ketones. In analogy to well known asymmetric hydrogenation catalysts involving a transition metal (particularly Ru) bound to a ligand with a binaphthyl skeleton,[20] the chiral BINOLato ligand attached to a Ni^{II} center has been chosen, where BINOLato stands for singly deprotonated 1,1′-bis-2-naphthol (BINOL).[21] At low collision energies, CID of a complex consisting of (BINOLato)Ni^+ and a secondary alcohol leads to two different fragmentation channels: the loss of the entire secondary alcohol ligand [Eq. (1)] or the expulsion of the corresponding ketone [Eq. (2)]. Comparison of the branching ratios of the two competing channels for alcohol/BINOLato ligand complexes with different chiralities is used to deduce the stereoselective effect (SE) operative in the bond-activation processes.

$$[(\text{BINOLato})\text{Ni}(CH_3CH(OH)R)]^+ \rightarrow [(\text{BINOLato})\text{Ni}]^+ + CH_3CH(OH)R \quad (1)$$

$$[(\text{BINOLato})\text{Ni}(CH_3CH(OH)R)]^+ \rightarrow [(\text{BINOL})\text{Ni}(H)]^+ + CH_3COR \quad (2)$$

Conventional mass spectrometric experiments are inherently symmetrical with regard to ion mass or kinetic energy because they do not depend on the chirality of the compounds under investigation. For that very reason, in this investigation of chiral induction by gaseous (BINOLato)Ni^+ ions we make use of a second chiral substrate: that is, the secondary alcohols $CH_3CH(OH)R$. Enantioselective discrimination can thus be monitored by mass spectrometric means by investigation of diastereomeric complexes[22] formed from a chiral precursor—(*R*)- or (*S*)-BINOL—and a chiral substrate: (*R*)- or (*S*)-$CH_3CH(OH)R$.

Results and Discussion

Electrospray ionization of milimolar solutions of nickel(II) nitrate, 1,1′-bis-2-naphthol, and a secondary alcohol (ROH) in pure methanol leads to, among other ions, monocations with the formal composition $[(\text{BINOLato})\text{Ni}(\text{ROH})]^+$. Formally, formation of this species corresponds to heterolysis of $Ni(NO_3)_2$ in solution to afford solvated Ni^{2+}, followed by recombination with a BINOLate anion. The alternative alkoxo structure $[(\text{BINOL})\text{Ni}(\text{OR})]^+$ cannot strictly be ruled out on the basis of experiment.[23] However, as phenols such as BINOL are generally substantially more acidic than alcohols,[24] and because loss of the neutral alcohol ROH concomitant with formation of (BINOLato)Ni^+ is observed as a major process upon CID, we assign the generic structure $[(\text{BINOLato})\text{Ni}(\text{ROH})]^+$ to these ions below[25] and focus on the effects that variation of the substituent R exerts on the stereoselective bond activation of the secondary alcohols.[18]

As a representative example, Figure 1 shows the CID spectrum of $[\{(R)\text{-BINOLato}\}\text{Ni}\{(R)\text{-1-phenylethanol}\}]^+$ at a collision energy of $E_{lab} = 5$ eV. At such low collision energies (ca. 1.1 eV in the center-of-mass frame), only two different fragmentations are observed for all alcohols examined. One dissociation channel leads to a mass-to-charge (m/z) ratio of 343, which is assigned to the loss of the intact secondary alcohol ligand according to Equation (1). A second peak appears at m/z 345, pointing to the formation of a cation with the formal composition $[\{(R)\text{-BINOL}\}\text{Ni}(\text{H})]^+$; this is produced by dehydrogenation of the secondary alcohol concomitant with uptake of two hydrogen atoms by the $[\{(R)\text{-BINOLato}\}\text{Ni}]^+$ fragment, as in Equation (2).

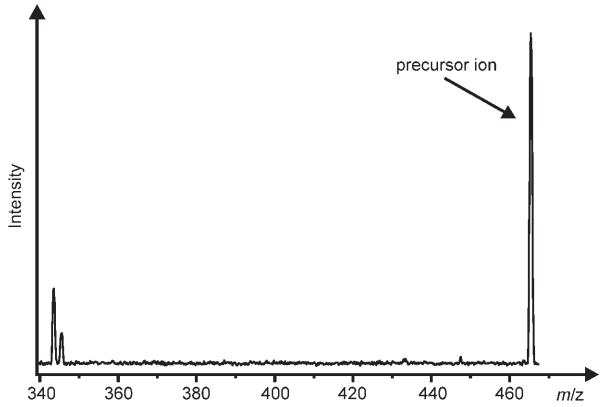
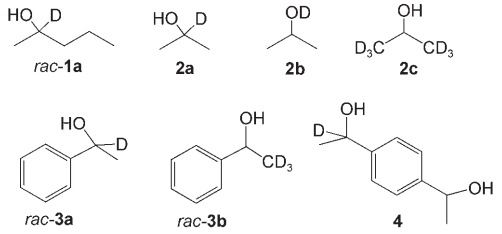


Figure 1. CID spectrum of mass-selected $[\{(R)\text{-BINOLato}\}\text{Ni}\{(R)\text{-1-phenylethanol}\}]^+$ at a collision energy of $E_{lab} = 5$ eV.

There are three obvious possibilities for how the dehydrogenation of the alcohol ligand can take place in the complexes under study. The first corresponds to the oxidation of the alcohol to the corresponding ketone. A second option may involve dehydrogenation of the alcohol to the corresponding enol. Finally, for higher alcohols, dehydrogenation may occur in positions of the alkyl chain remote from the functional group.[26,27]

In order to unravel the regioselectivity of the alcohol dehydrogenation, labeling experiments have been performed. Specifically, the (BINOLato)Ni^+ complexes of [2-D]-pentan-2-ol (**1a**), [2-D]-isopropanol (**2a**), [*O*-D]-isopropanol



(**2b**), and [1,1,1,3,3,3-D_6]-isopropanol (**2c**), as representative examples of aliphatic alcohols, as well as [1-D_1]-1-phenylethanol (**3a**) and [2,2,2-D_3]-1-phenylethanol (**3b**), as representative examples of aromatic alcohols, have been investigated to shed light on the products formed in the dehydrogenation of a secondary alcohol. 1-[4-(1-Hydroxyethyl)phenyl]-[1-D]-ethanol (**4**) has been used to study the kinetic isotope effect (KIE) associated with the hydrogen-transfer step.[28] Note that the labeled samples were prepared as racemic mixtures.

Inspection of the data summarized in Table 1 reveals that CID of the (BINOLato)Ni$^+$ complexes of **1a**, **2a**, and **3a** exclusively leads to signals at *m*/*z* 343 and 346, where the latter indicates incorporation of deuterium into the ionic product. Because of the easily exchangeable deuteration in **2b**, this compound was measured in CH_3OD solution. CID of the corresponding complex [([*O*-D]-BINOLato)Ni(**2b**)]$^+$ affords signals at *m*/*z* = 344 and 347, respectively. In contrast, CID of [(BINOLato)Ni(**2c**)]$^+$ and [(BINOLato)Ni(**3b**)]$^+$ affords signals at *m*/*z* 343 and 345: that is, the same values as for the unlabeled compounds. These findings have several implications. At first, the formation of the fragment with *m*/*z* 343, independent of the nature and the deuterium content of the alcohol, confirms the loss of the entire secondary alcohol and thus rules out a possible fragmentation of the BINOLato ligand. Next, formation of *m*/*z* 346 from the complexes of the [2-D] compounds **1a**, **2a**, and **3a** reveals the selective transfer of H(D) from the 2-position of the alcohol. Together with the generation of [([*O*-D]-BINOL)Ni(D)]$^+$ (*m*/*z* 347) from the complex of the [*O*-D]-labeled compound **2b** (here, the hydroxy group of the BINOLato ligand is also labeled by deuterium originating from the solvent CH_3OD), the oxidation of the alcohol to the corresponding ketone is implied. Finally, this conclusion is also supported by the exclusive production of [(BINOL)Ni(H)]$^+$ (*m*/*z* 345) from the corresponding complexes of **2c** and **3b**. We note in passing that consecutive fragmentations of the BINOLato ligand (e.g. decarbonylation) are only observed at elevated collision energies and are not pursued any further in this contribution.[25] As shown in Table 1, upon CID of the complex [(BINOLato)Ni(**4**)]$^+$ the amount of C–H bond activation exceeds that of C–D bond activation, resulting in a KIE of 1.6 ± 0.1. KIE values of similar size have been found previously for related metal-mediated C–H(D) bond activations of methoxy groups.[29] It can thus be concluded that the rate-determining step of the reaction involves the activation of the C–H bond.

Table 1. Mass-to-charge ratios (*m*/*z*) and abundances of the fragment ions obtained upon CID of mass-selected [(BINOLato)Ni(alcohol)]$^+$ ions.[a] All spectra have been recorded at a collision energy of E_{lab} = 5 eV.

Alcohol	*m*/*z* ligand loss		*m*/*z* bond activation		
	343	344	345	346	347
1a	56			44	
2a	70			30	
2b[b]		75			25
2c	68		32		
3a	69			31	
3b	68		32		
4	72		17	11	

[a] Data normalized to a sum of 100. [b] This complex was measured in CH_3OD.

Further mechanistic insight into the dehydrogenation channel is provided by inspection of the energy dependencies of the competing fragmentations according to Equations (1) and (2). Figure 2 shows the breakdown graphs for the CID fragments of mass-selected [{(*R*)-BINOLato}-Ni{(*R*)-$CH_3CH(OH)C_6H_5$}]$^+$. The loss of acetophenone—$CH_3COC_6H_5$—shows an apparent threshold at (1.0 ± 0.2) eV, reaches an intensity maximum at about 3.5 eV, and then declines at higher collision energies. In contrast, the elimination of the 1-phenylethanol ligand shows a continuous increase from the apparent threshold at about (1.2 ± 0.2) eV. Energy behavior of such a kind is mechanistically significant because it implies that the elimination of acetophenone is kinetically hindered, whereas the loss of the alcohol is a simple, continuously endothermic process.[30] In the competition between these two processes at variable collision energies, the ketone elimination occurs first—that is, at lower collision energy than the loss of the alcohol—but has to pass through a rate-determining transition structure associated with bond activation. In contrast, once a sufficient amount of energy for the direct loss of the alcohol ligand is available in CID, this barrier-free reaction can occur and predominates over the kinetically controlled ketone formation at larger collision energies. The physicochemical origin of the decrease in the ketone channel is thus the more rapid increase in the rate constant of the continuously endothermic, but barrier-free loss of the alcohol ligand above its thermochemical threshold in relation to the rate constant for the less energy-demanding, but entropically restricted rearrangement to the ketone complex. Accordingly, the activation barrier associated with the formation of the postulated intermediate ketone complex [{(*R*)-BINOL}-Ni(H)($CH_3COC_6H_5$)]$^+$ must be somewhat lower than the

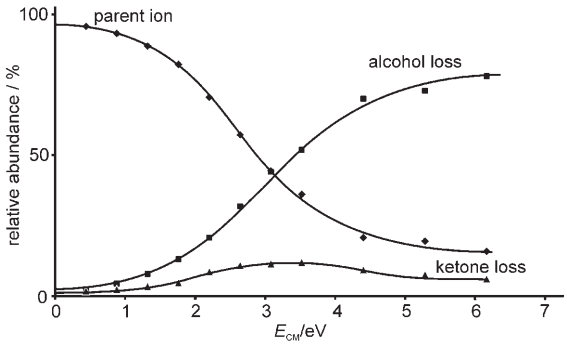


Figure 2. Breakdown graph of the CID fragments of [{(*R*)-BINOLato}-Ni{(*R*)-$CH_3CH(OH)C_6H_5$)}]$^+$ as a function of collision energy in the center-of-mass frame; the spectrum in Figure 1 corresponds to the entry at E_{CM} = 1.1 eV.

bond energy of 1-phenylethanol to the (BINOLato)Ni^+ fragment. In principle, the different onsets of ketone and alkanol loss could also be explained by the presence of the ketone intermediate that might be formed in the spray process or might already be present in the solution subjected to the ESI source. The energy dependence revealed in Figure 2, however, also excludes the presence of major amounts of the ketone, since a mixture of $[\{(R)\text{-BINOLato}\}Ni(R)\text{-}CH_3CH(OH)C_6H_5]^+$ and $[\{(R)\text{-BINOL}\}Ni(H)(CH_3COC_6H_5)]^+$ already in solution cannot account for the experimentally observed decrease in the ketone channel at elevated collision energies. In addition, ion–molecule reactions of the mass-selected $[(BINOLato)Ni(CD_3CH(OH)R)]^+$ complexes with the corresponding unlabeled alcohols $CH_3CH(OH)R$ lead exclusively to the exchange of the entire alcohol ligands and thus do not show any evidence for the presence of a significant fraction of the corresponding ketone intermediate. A qualitative potential energy surface (PES) of the system consistent with the observed energy behavior is accordingly depicted in Figure 3.

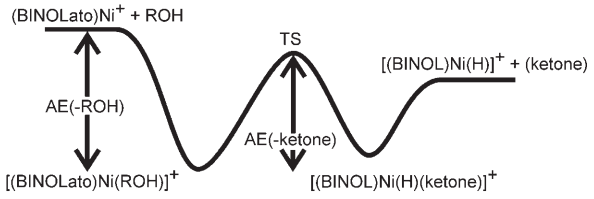


Figure 3. Schematic potential energy surface (PES) for the competing losses of an alcohol and a ketone from a $[(BINOLato)Ni(ROH)]^+$ complex with the assumption of kinetic control for the loss of the ketone.

The system under study can be regarded both as a gas-phase model for the oxidation of alcohols and also, by reference to the principle of microscopic reversibility, as a model for the transition-metal-catalyzed hydrogenation of ketones, including nickel-containing systems.[31–33] Consideration of Figure 3 from right to left implies that the metal hydride species forms an encounter complex with the ketone in a first step, followed by hydrogen transfer to produce the corresponding alcohol. After liberation of the alcohol, the catalytic cycle would be closed by hydrogenation of the catalyst. Whereas chemoselective reductions of ketones in the condensed phase have long been known,[34] a general strategy for enantioselective reduction of prochiral carbonyl compounds was developed only around ten years ago.[35] Many laboratory reduction catalysts that allow for enantioselective reduction of C=O double bonds are based upon chiral metal hydrides, which can transfer a hydrogen molecule to the carbonyl moiety.[35c] Hence, the key question on which we concentrate below is whether in our gas-phase model system a certain preference for dehydrogenation of one member of an enantiomeric pair of alcohols can be observed. In this respect, these complexes are well suited for systematic variation by changing the chirality either of the aryloxo ligand (i.e., (*R*)- and (*S*)-BINOL as precursor) or of the substrate (i.e., (*R*)- and (*S*)-alkan-2-ols). With regard to the latter, we take advantage of the fortunate situation that binding of alkan-2-ols to (BINOLato)Ni^+ is largely preferred over binding of methanol, which is used as the bulk solvent in the ESI measurements. As a result, the desired complexes are already obtained at low molar fractions of the alkan-2-ols in solution ($<1\,\%$), thereby avoiding changes in the bulk properties of the solution that might have altered the electrospray process. As a measure for a possible stereoselective effect (SE), we consider the branching ratio between the ligand-loss channel and the intensity of the activation channel for the different diastereomeric complexes investigated (Tables 2 and 3).

Inspection of the data reported in Tables 2 and 3 reveals competition between alcohol and ketone loss for all substituents R. As has already been concluded from the breakdown curves (Figure 2), the energy demand of the transition structure associated with the rearrangement to the corresponding ketone is thus of similar magnitude to the binding energy of the alkan-2-ols. The stereochemical effects (SEs) operating in the dehydrogenations of the secondary alcohols in the complexes $[(BINOLato)Ni(CH_3CH(OH)R)]^+$ are given in the last columns of Tables 2 and 3. For the smaller aliphatic alcohols up to heptan-2-ol, the data do not reveal any significant stereoselective effects at all (entries II to IX in Table 2). This finding is consistent with the reasoning that chiral discrimination in alkan-2-ols is associated with the differentiation between the alkyl substituents R and the terminal methyl group, and this difference is not pronounced enough for small alkyl substituents. With increasing size of the alkyl chain, modest but noticeable chiral effects are observed: 0.92 for octan-2-ol and 0.87 for 1-cyclohexylethanol at a collision energy of 3 eV, for example. These SEs (entries VIII to XIII in Tables 2 and 3) can be assigned either to a smaller activation barrier for dehydrogenation in the case of the homochiral complex or to a less facile expulsion of the alcohol ligand for the heterochiral complex.

A markedly different scenario is observed for 1-phenylethanol (entries XIV and XV in Table 3). Firstly, the ratio between direct ligand loss and ligand activation is slightly larger than with the other alcohols studied, thus indicating that the evaporation of the alcohol outweighs the activation. Secondly and more importantly, a more pronounced SE is observed. In this case, either the heterochiral complex is more easily activated at the chiral center than its homochiral counterpart or, alternatively, the alcohol ligand evaporates more easily in the homochiral complexes. Further, the reversed direction of the SEs relative to the aliphatic alcohols (entries II to XI in Table 2), and particularly 1-cyclohexylethanol (entries XII and XIII in Table 3), as the fully hydrogenated analogue of 1-phenylethanol, points to a different type of interaction between the (BINOLato)Ni^+ subunit and 1-phenylethanol in relation to the saturated alcohols. In the latter case, differentiation by mere steric effects may be assumed, whereas the opposite direction of the SE for 1-phenylethanol may point to the operation of an attractive

Table 2. Abundances of the fragments due to the loss of the alcohol ligand [Eq. (1)] and the elimination of the corresponding ketone [Eq. (2)] upon CID of mass-selected [(BINOLato)Ni($CH_3CH(OH)R$)]$^+$ ions of alicyclic alkan-2-ols at variable collision energies (E_{lab} in eV, collision gas: xenon) and the stereochemical effects (SEs) originating from them with error bars derived from repeated experiments.[a]

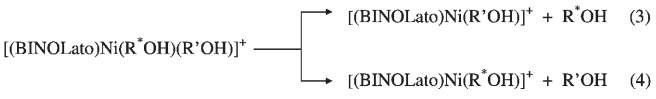
Alcohol			E_{lab}	−Alcohol	−Ketone	SE[b]
I	$CH_3CH(OH)CH_3$	(*R*)-BINOL	3	65	35	–
II	(*R*)-$CH_3CH(OH)C_2H_5$	(*R*)-BINOL	2	56	44	1.06 ± 0.05
			3	49	51	0.98 ± 0.05
			8	60	40	0.98 ± 0.05
III	(*S*)-$CH_3CH(OH)C_2H_5$	(*R*)-BINOL	2	55	45	
			3	50	50	
			8	60	40	
IV	(*S*)-$CH_3CH(OH)C_3H_7$	(*S*)-BINOL	2	48	52	0.96 ± 0.05
			3	50	50	1.03 ± 0.05
			5	55	45	1.11 ± 0.05
			8	73	27	1.02 ± 0.05
V	(*S*)-$CH_3CH(OH)C_3H_7$	(*R*)-BINOL	2	49	51	
			3	49	51	
			5	52	48	
			8	73	27	
VI	(*S*)-$CH_3CH(OH)C_4H_9$	(*S*)-BINOL	2	38	62	0.93 ± 0.05
			3	49	51	1.04 ± 0.05
			5	54	46	0.95 ± 0.05
			8	71	29	0.98 ± 0.05
VII	(*S*)-$CH_3CH(OH)C_4H_9$	(*R*)-BINOL	2	40	60	
			3	48	52	
			5	55	45	
			8	72	28	
VIII	(*R*)-$CH_3CH(OH)C_5H_{11}$	(*R*)-BINOL	2	33	67	0.94 ± 0.05
			3	51	49	0.97 ± 0.05
			5	58	42	0.96 ± 0.05
			8	70	30	1.02 ± 0.05
IX	(*S*)-$CH_3CH(OH)C_5H_{11}$	(*R*)-BINOL	2	35	65	
			3	52	48	
			5	59	41	
			8	69	31	
X	(*R*)-$CH_3CH(OH)C_6H_{13}$	(*R*)-BINOL	2	52	48	0.86 ± 0.06
			3	53	47	0.92 ± 0.05
			5	60	40	0.93 ± 0.05
			8	73	27	0.99 ± 0.05
XI	(*S*)-$CH_3CH(OH)C_6H_{13}$	(*R*)-BINOL	2	56	44	
			3	55	45	
			5	62	38	
			8	73	27	

[a] Branching ratios derived from repeated experiments and normalized to $\Sigma = 100$. [b] Stereochemical effects defined as $SE = [BR(1)/BR(2)]_{homo}/[BR(1)/BR(2)]_{hetero}$, where the indices "homo" and "hetero" indicate the homo- (*R*,*R* and *S*,*S*) and heterochiral (*R*,*S* and *R*,*S*) complexes, with the first indicator assigning the chirality of the BINOL and the second one the chirality of the secondary alcohol.

interaction between the arene substituent and the positively charged metal center.[36,37]

Table 4 summarizes the results of CID measurements for all four possible combinations of enantiomers in [(BINOLato)Ni(1-phenylethanol)]$^+$, performed in order to confirm the selectivity observed for the 1-phenylethanol system further. Comparison of the homo- and heterochiral complexes reveals a significant stereochemical effect of (1.46 ± 0.10), whereas no SE is found within the homo- and heterochiral pairs (0.99 ± 0.05). These results thus demonstrate the validity of this mass spectrometric approach for investigation of chiral reactions in the gas phase.[13,18]

One disturbing complication associated with this approach is that the loss of the secondary alcohol according to Equation (1), which is used as an internal reference channel, may also be subject to a stereochemical effect. Figure 4 shows the two limiting cases in which the SE can operate either only on the TS associated with the hydrogen transfer to convert the alcohol to the ketone (left) or on the evaporation of the alcohol from the diastereomeric complexes while the barrier heights relative to the reactant minima are the same (right). With the approach used so far it is impossible to deconvolute these two effects directly. However, the reference channel can be probed independently by application of the kinetic method.[13] To this end, trisligated complexes of the type [(BINOLato)Ni(R*OH)-(R′OH)]$^+$ are generated, where R*OH stands for a chiral secondary alcohol ligand and R′OH for an achiral reference alcohol. For the latter, heptan-4-ol was used as an achiral secondary alcohol of similar size, such that the binding properties would not be expected to differ too largely from those of the alkan-2-ols. Upon introduction of mixtures of BINOL, Ni-$(NO_3)_2$, heptan-4-ol, and the chiral alcohols $CH_3CH(OH)R$ (R = *n*-C_6H_{13} and *c*-C_6H_5) dissolved in MeOH to the ESI source, the desired trisligated complexes were generated under soft ionization conditions, mass-selected, and subjected to CID.



Given the fact that the alcohols are obviously more weakly bound then the covalently attached BINOLato ligand in [(BINOLato)Ni(R*OH)(R′OH)]$^+$, it can be expected that these complexes dissociate according to Equations (3) and (4), where the branching ratios reflect the relative binding energies of the two alcohols R*OH and R′OH to the (BINOLato)Ni$^+$ fragment. With regard to stereochemical effects, Equation (3) gives rise to a pair of separat-

Table 3. Abundances of the fragments due to the loss of the alcohol ligand [Eq. (1)] and the elimination of the corresponding ketone [Eq. (2)] upon CID of mass-selected [(BINOLato)Ni($CH_3CH(OH)R$)]$^+$ ions of cyclic alcohols at variable collision energies (E_{lab} in eV, collision gas: xenon) and the stereochemical effects (SEs) originating from them with error bars derived from repeated experiments.[a]

Alcohol			E_{lab}	−Alcohol[a]	−Ketone[a]	SE[b]
XII	(*S*)-$CH_3CH(OH)c$-C_6H_{11}	(*S*)-BINOL	2	52	48	0.94 ± 0.05
			3	52	48	0.87 ± 0.04
			5	64	36	0.93 ± 0.05
			8	69	31	1.10 ± 0.05
XIII	(*S*)-$CH_3CH(OH)c$-C_6H_{11}	(*R*)-BINOL	2	54	46	
			3	56	44	
			5	66	34	
			8	67	33	
XIV	(*R*)-$CH_3CH(OH)c$-C_6H_5	(*R*)-BINOL	2	61	39	1.43 ± 0.07
			3	64	36	1.52 ± 0.07
			5	67	33	1.15 ± 0.06
			8	68	32	1.06 ± 0.05
XV	(*S*)-$CH_3CH(OH)c$-C_6H_5	(*R*)-BINOL	2	52	48	
			3	54	46	
			5	64	36	
			8	67	33	

[a,b] See footnotes to Table 2.

Table 4. Abundances of the neutral fragments lost as shown in Eqs. (1) and (2) upon CID of mass-selected [(BINOLato)Ni($CH_3CH(OH)C_6H_5$)]$^+$ ions formed from precursors of different chirality.[a,b]

BINOL	1-Phenylethanol	Alcohol	Ketone	SE[c]
(*R*)	(*R*)	61	39	1.44 ± 0.07
	(*S*)	52	48	
(*S*)	(*R*)	52	48	1.48 ± 0.07
	(*S*)	62	38	

[a] Branching ratios of Eqs. (1) and (2) derived from repeated experiments and normalized to Σ = 100. [b] These CID experiments are performed at a collision energy of 2 eV in the laboratory frame; collision gas: xenon. [c] Stereochemical effects defined as $SE = [BR(1)/BR(2)]_{RR \text{ or } SS}/[BR(1)/BR(2)]_{RS \text{ or } SR}$, where the first indicator stands for the chirality of the BINOL and the second for the chirality of the alcohol.

ed enantiomers, which cannot be distinguished in the mass spectrometer. In contrast, Equation (4) yields a diastereomeric ion, and the energetics of its formation may thus be sensitive to the chirality of the components. As loss of the reference alcohol R′OH from the trisligated species [(BINOLato)Ni(R*OH)(R′OH)]$^+$ leads to the bisligated [(BINOLato)Ni(R*OH)]$^+$ ions, the branching ratio directly links Equation (4) with Equations (1) and (2) described above. Because this reasoning is not immediately straightforward, let us outline the strategy for the deconvolution of the SEs associated with the losses of the alcohol ligand and the ketone formed by dehydrogenation of the alcohol in some more detail.

According to the kinetic method, the ratio between Equations (3) and (4) is proportional to the differences between the free binding energies (ΔG) of the alcohol ligands to the (BINOLato)Ni$^+$ fragment at a given effective temperature T_{eff}: that is, $\Delta\Delta G(T_{eff}) = \Delta_r G(T_{eff}) = -RT_{eff}\ln(k_3/k_4)$, where the ratio of the rate constants k_3/k_4 is assumed to correspond to the abundance ratio of the corresponding ionic products. Accordingly, analysis of the branching ratios provides the relative binding energies of the alcohol ligands to the (BINOLato)Ni$^+$ fragment. With regard to the diastereomeric complexes of (BINOLato)Ni$^+$ with a chiral alkan-2-ol (R*OH) and an achiral reference alcohol (R′OH), the resulting energetic situation is depicted in Figure 5 (only the (*R*)-BINOLato ligand is shown). The trisligated species [{(*R*)-BINOLato}Ni{(*R*)-R*OH}R′OH]$^+$ and [{(*R*)-BINOLato}Ni{(*S*)-R*OH}R′OH]$^+$ are diastereomeric ions, the relative stabilities of which differ by the energy $\Delta E_{RS,dimer}$ (in Figure 5, the homochiral combination is deliberately assumed to be more stable). Loss of the chiral alcohols R*OH from both complexes leads to the chiral ionic fragment [{(*R*)-BINOLato}Ni(R′OH)]$^+$ and the chiral neutral molecule R*OH, but as these species are infinitely separated after dissociation, these channels are isoenergetic in a mass spectrometric set-up. These fragment channels are further

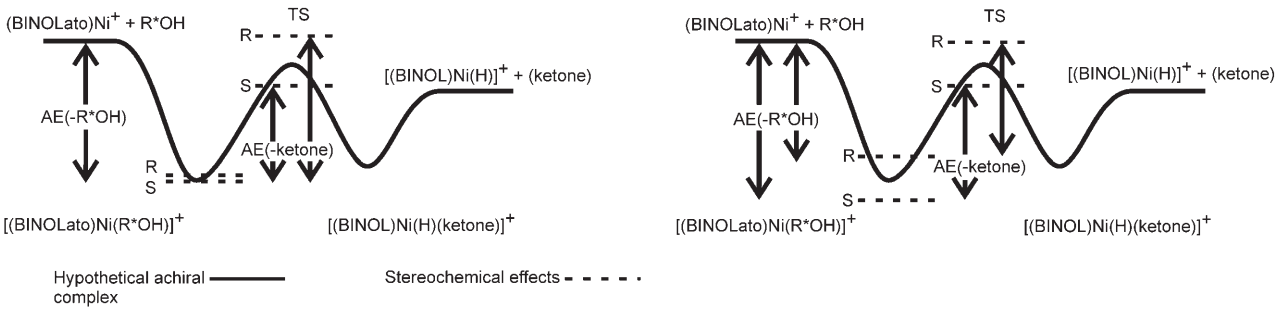


Figure 4. Schematic potential energy surfaces for the competing losses of a chiral alcohol and a ketone from [{(*R*)-BINOLato}Ni(R*OH)]$^+$ complexes. The solid line stands for a hypothetical achiral complex (SE = 1), whereas the dashed lines show the changes for the two different chiralities of the alcohol (*R* and *S* are chosen arbitrarily) due to stereochemical effects (SE ≠ 1), caused by the presence of the chiral ligand. For the loss of the ketone, kinetic control via the indicated TS is assumed.

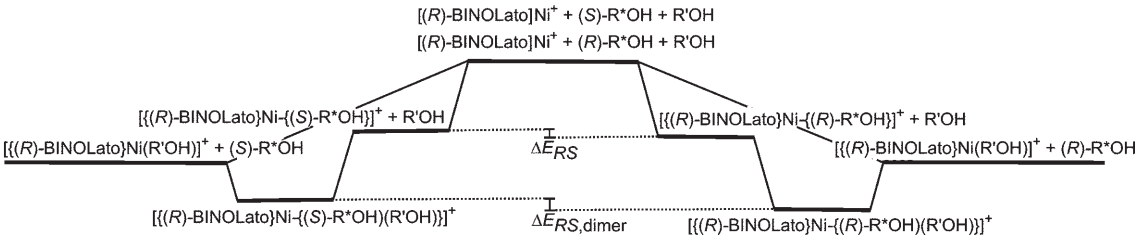


Figure 5. Schematic energy levels for the dissociation of [(*R*)-BINOLato]Ni$^+$ complexes with a chiral alkan-2-ols (R*OH) and an achiral alcohol (R′OH) serving as an internal reference.

connected by a loop to the completely separated species [(*R*)-BINOLato]Ni$^+$, R*OH, and R′OH, which is again isoenergetic for all combinations of enantiomers. The abundance ratio of products due to Equations (3) and (4) thus also provides a measure for the stability difference (ΔE_{RS}) of the bisligated complexes [{(*R*)-BINOLato}Ni(R*OH)]$^+$, which is the missing term to be evaluated in order to enable a deconvolution of the SEs operative in Equation (2). The only weakness of this line of reasoning concerns the effective temperatures, which cannot be assumed a priori to be identical for bis- and trisligated complexes (the latter would be expected to have lower T_{eff} values). Differences in T_{eff} might cause some error in this type of analysis if the energy differences ΔE_{RS} and $\Delta E_{RS,\text{dimer}}$ were large, which is not the case here, however (see below).

In the system with 1-phenylethanol, the heptan-4-ol reference ligand is lost with a large preference (Table 5), whereas in the complex with octan-2-ol, the latter is lost in higher amount. This finding lends further support to the assumed existence of an attractive interaction between the aromatic ring of the 1-phenylethanol and the positively charged metal center. Despite the opposite directions of the BRs, the SEs associated with the binding of octan-2-ol and 1-phenylethanol are both close to unity. With this additional information it can be concluded that the SEs reported in Tables 2 and 3 are indeed associated with the bond-activation step in the dehydrogenation of the alkan-2-ols to the corresponding ketones.

As a result of the relatively intense parent ion signal and high selectivity, for the 1-phenylethanol system it is possible to analyze the enantioselectivity as a function of the collision energy (Figure 6). First principle considerations would on the one hand suggest that the SEs are largest at low collision energies, which would therefore be considered most sensitive to stereochemical effects. On the other hand, CID is less efficient at low energies, such that the determination of the fragment ion abundances is associated with an increased error. Consistently with this line of reasoning, the selectivity is indeed largest for low collision energies. As the energy differences between the diastereomeric transition structures may be assumed to be small, the SE decreases with increasing internal energy and approaches an asymptote with SE = 1 at larger collision energy. This observation once more supports the conclusion that in case of the complex [(BINOLato)Ni(1-phenylethanol)]$^+$ the oxidation of the alcohol is kinetically controlled by the diastereomeric transition structures.

Table 5. Branching ratio of Eqs. (3) and (4) upon CID of mass-selected [{(*R*)-BINOLato}Ni(heptan-4-ol)(R*OH)]$^+$ ions with different chiralities of the secondary alcohol and the stereochemical effects originating from them.[a,b]

R*OH	−R*OH	−R′OH	SE[c]
(*R*)-1-phenylethanol	13	87	1.03 ± 0.05
(*S*)-1-phenylethanol	13	87	
(*R*)-octan-2-ol	67	33	1.01 ± 0.04
(*S*)-octan-2-ol	67	33	

[a] Branching ratios of Eqs. (1) and (2) derived from repeated experiments and normalized to $\Sigma = 100$. [b] The average value of different experiments performed at variable collision energies is reported (E_{lab} 2–8 eV). [c] Stereochemical effects defined as $\text{SE} = [\text{BR}(3)/\text{BR}(4)]_{RR \text{ or } SS}/[\text{BR}(3)/\text{BR}(4)]_{RS \text{ or } SR}$, where the first indicator stands for the chirality of the BINOL and the second for the chirality of the alcohol.

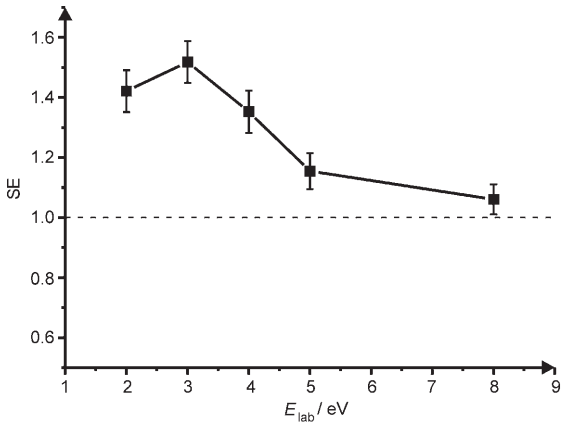


Figure 6. Stereochemical effects (SEs) obtained upon CID of mass-selected [{(*R*)-BINOLato}Ni(1-phenylethanol)]$^+$ complexes at different collision energies.

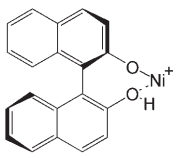
Conclusion

Mass spectrometric investigations of [(BINOLato)Ni(alkan-2-ols)]$^+$ complexes generated by electrospray ionization reveal the occurrence of a Ni^{II}-mediated dehydrogenation of the alkan-2-ol ligands to the corresponding ketones. The insights gained into the oxidation of chiral alcohols by reference to the concept of microscopic reversibility have some

bearing on the molecular mechanisms of the reverse process: that is, the synthetically important enantioselective hydrogenation of ketones by transition metal catalysts. In our approach, the demanding task of measuring stereoselective effects is achieved by using a fragmentation channel as an internal standard, which is insensitive with respect to the chirality of the diastereomeric complex. Whereas the [(BINOLato)Ni(alkan-2-ols)]$^+$ complexes of small secondary alcohols do not show significant stereoselective discrimination, interactions of the remote substituents in octan-2-ol and 1-cyclohexylethanol induce discrimination in the rate-determining step in that hydrogen transfer is slightly favored for the homochiral complexes. In the case of 1-phenylethanol, however, significant enantioselectivity in the opposite direction is found, which points to the existence of an interaction between the aromatic substituent of the alcohol and the (BINOLato)Ni$^+$ fragment.

Experimental Section

The mass spectrometric experiments were carried out with a commercial VG BIO-Q mass spectrometer, which has been described in detail elsewhere.[38] In brief, the VG BIO-Q consists of an ESI source combined with a tandem mass spectrometer of QHQ configuration (Q: quadrupole, H: hexapole). In the present experiments, mmolar solutions of nickel(II) nitrate, (*R*)- or (*S*)-1,1′-bisnaphthol, and the chiral secondary alcohol, (*R*)- or (*S*)-$CH_3CH(OH)R$, in pure methanol are introduced by syringe pump (flow rate 5 μL min^{-1}) into the fused silica capillary of the ESI source. Nitrogen is used as a drying and nebulizer gas at a source temperature of 80 °C. For the ions of interest, the instrument parameters are optimized for maximal ion abundances and are kept constant for each diastereomeric couple. The most crucial parameter of the ion optics is the cone voltage U_C, which determines the extent of collisional activation of the ions evolving from solution in the differential pumping stage of the ESI source.[39,40] Among others, cation signals are observed, which correspond to (BINOLato)Ni$^+$ (see below). Among others, cation signals corresponding to (BINOLato)Ni$^+$ are observed and adducts of the formal composition [(BINOLato)Ni-($CH_3CH(OH)R$)]$^+$; these species form the subject of this contribution.[25] The stoichiometric identities of all complexes were confirmed by comparison with the expected isotope patterns[41] in either the ion-source spectra or in appropriate neutral-loss scans.[42]



[(*R*)-BINOLato]Ni$^+$

For CID, the [(BINOLato)Ni($CH_3CH(OH)R$)]$^+$ cations were mass-selected by use of the first quadrupole Q1 and were then allowed to interact with xenon serving as a collision gas in the hexapole at various collision energies (E_{lab} = 0–20 eV) at a pressure of about 3.0×10^{-4} mbar; these approximately correspond to single-collision conditions.[38] Product ions were analyzed by Q2 scanning. The laboratory collision energies were converted to the center-of-mass frame: $E_{CM}=[m/(M+m)]\times E_{lab}$, in which m and M are the masses of the collision gas and the ionic species, respectively. Variation of the collision energy leads to breakdown diagrams that allow the determination of phenomenological appearance energies (AEs)[43] of the fragmentation channels by linear extrapolation of the signal onsets to the baseline. The errors of the *AE*s are estimated by applying different linear extrapolations that are still in reasonable agreement with the experimental data. As pointed out elsewhere,[38] the VG-BIO-Q is not equipped with differential pumping in the analyzer region, and consequently the collision gas may be present not only in the hexapole collision cell, but also in the focusing region between the mass analyzers. Therefore, the *AE*s reported below do not correspond to the true thermodynamic thresholds, but are only proportional to them.[44]

Acknowledgements

Ongoing financial support by the Academy of Sciences of the Czech Republic (Z40550506), the Deutsche Forschungsgemeinschaft, the Fonds der Chemischen Industrie, the Gesellschaft der Freunde der Technischen Universität, and the Grant Agency of the Czech Academy of Sciences (KJB400550704) is gratefully acknowledged. We thank Waltraud Zummack for the synthesis of various substances employed in this study.

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Received: January 16, 2008
Published online: May 21, 2008

