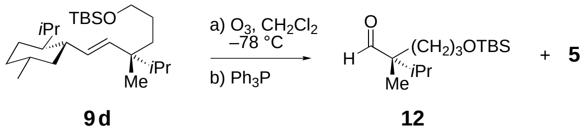
Table 2. S_N2' displacements of cuprates on the pivalates of alcohols **6**.

Entry	**11**	R^1	R^3	**9**	Yields [%]	*d.e.*[a] [%]
1	**a**	cyclohexyl	*i*Pr	**a**	95	> 98
2	**b**	$PhCH_2$	*i*Pr	**b**	92	> 98
3	**c**	Ph	*i*Pr	**c**	90	91
4	**d**	$-(CH_2)_3OTBS$	*i*Pr	**d**	95	> 98
5	**d**	$-(CH_2)_3OTBS$	Et	**e**	89	> 98[b]
6	**e**	*n*Bu	nC_7H_{15}	**f**	90	> 95[c]

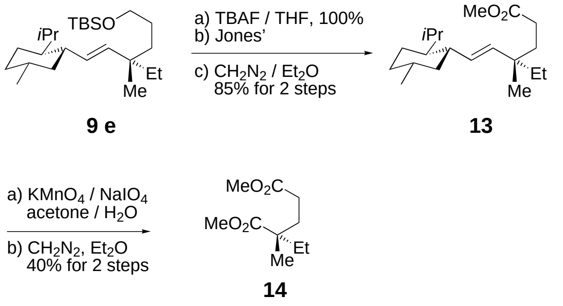
[a] Determined by comparison of the HPLC traces with authentic mixtures of **9** and **10**. [b] Inferred from the optical rotation in comparison with literature value. [c] *d.e.* value based on differences in ^{13}C NMR signals.

tert-Butyl, phenyl, and benzyl cyanocuprates were not reactive enough to take part in the reaction. The phenyl and benzyl groups could nonetheless be introduced starting from phenyl- or benzylacetylene. However, neopentyl alkynes could not be carboaluminated efficiently. Also, the stereoselectivity in the cuprate addition was slightly lower in the case of phenyl-substituted allyl pivalates **6c** and **7c**. This decrease was also observed in our first generation system with aryl-substituted allyl carbonates (Scheme 1, $R^1 = Ar$).[1b]

The disubstituted double bonds in adducts **9** were easily cleaved with ozone or with $KMnO_4/NaIO_4$ leading to good yields of aldehydes, carboxylic acids, or alcohols depending on the work-up performed. For example, **9d** was cleaved with O_3 in dichloromethane to yield 65% of the aldehyde **12** (Scheme 4). The chiral auxiliary was recovered in 80% yield after chromatography and could be re-used. The conversion of **9e** into **14** (Scheme 5) was confirmed by comparison of its optical rotation ($[\alpha]_D$) with that of its enantiomer reported in the literature ($[\alpha]_D = -9.7°$, $CHCl_3$, $c = 0.3$; literature $[\alpha]_D = +9.8°$, $c = 0.3$).[20] This observation indicated that the stereochemistry of **9e** results from an *anti*-selective cuprate addition on the configuration and conformation corresponding to **D** (Scheme 2).



Scheme 4. Oxidative cleavage of **9d**. TBS = *tert*-butyldimethylsilyl.



Scheme 5. Proof of the absolute configuration of **9e**. TBAF = tetrabutylammonium fluoride.

The present method should prove a valuable addition to the arsenal of asymmetric reactions available for the synthesis of natural or unnatural chiral compounds.

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Exceptional Deshielding of ^{59}Co Caused by Deuteration of the Hydrogen Bonds in Cobaloximes**

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Transition metal shieldings are useful probes of structure and reactivity for coordination compounds, since they allow even tiny variations at the coordination site to be detected.[1] The isotope ^{59}Co exhibits the largest known shielding range. Its NMR properties have been extensively studied for

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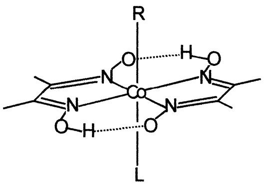
cobaloximes [RCo(Hdmg)$_2$L] (Hdmg = dimethylglyoximate)[2] and are excellent candidates for the investigation of structural changes. For example, in these molecules the ^{59}Co chemical shift increases with increasing steric bulk of R and with increasing Co–C bond length.[2] Here we discuss the effects of hydrogen-bond deuteration and temperature variation on the ^{59}Co chemical shift in cobaloximes.

Usually for compounds of transition metals with d^6 configuration, the chemical shift increases with increasing bond length. A temperature increase implies bond extensions consistent with the higher population of the excited rovibrational states. The dependence of chemical shift on temperature can be used either to study how the shielding changes with bond length[3] or, conversely, how the bonds lengthen with increasing temperature. For **1** (py = pyridine) and **2** the ^{59}Co chemical shift is an almost linear function of temperature, with slopes of 1.0 and 1.3 ppm K^{-1}, respectively. These sensitivities are rather low in comparison with those of other hexacoordinate cobalt complexes (1.38 ppm K^{-1} for [Co(CN)$_6$]$^{3-}$, 1.42–1.68 ppm K^{-1} for [Co(NH$_3$)$_6$]$^{3+}$ and 2.85–3.04 ppm K^{-1} for [Co(NO$_2$)$_6$]$^{3-}$).[4]



	R	L
1	Me	py
2	Me	PPh$_3$
3	*i*Pr	PPh$_3$

The mass dependence of the chemical shift, measured as the NMR isotope effect, is also related to the change in nuclear shielding with increasing bond length. Usually, the introduction of a heavier isotope into a ligand induces a decrease in bond lengths and a consequent decrease in chemical shift for the coordinated metal center. The magnitude of these effects increases with increasing chemical shift range of the observed nucleus, and for cobalt they are quite large: [Co(NH$_3$)$_6$]$^{3+}$ and [Co(en)$_3$]$^{3+}$ complexes (en = ethylenediamine) exhibit a shift variation of about $\Delta\delta = -5$ for each deuterium substituent.[5] For cobaloximes, H/D replacement at each hydrogen bond, three bonds remote from the metal, causes changes in ^{59}Co chemical shift that are remarkably large and of unexpected sign ($\Delta\delta = +25$ in **1** (Figure 1); $\Delta\delta = +27$ in **2** and **3**).[6] This reflects significant geometrical variations at the coordination site. Given the dependence of cobalt shielding on bond lengths for [Co(CN)$_6$]$^{3-}$,[3, 7] the isotope effect observed in cobaloximes may correspond to a lengthening by some tenths of a picometer of the Co–N bonds on the side of the deuterated hydrogen bond.

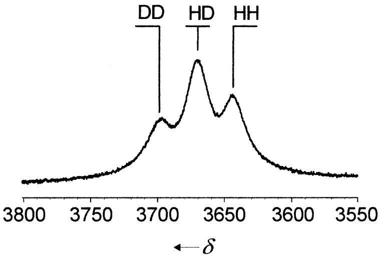


Figure 1. ^{59}Co spectrum of **1** in [D$_6$]acetone upon addition of D$_2$O. DD = [MeCo(Ddmg)$_2$py], HD = [MeCo(Hdmg)(Ddmg)py], HH = [MeCo(Hdmg)$_2$py].

The exceptional isotope effect can be explained by the peculiarities of the hydrogen bond in cobaloximes. In a O–H$\cdots$O bridge, the proton is shared by two O atoms, and the potential energy depends, to a first approximation, on the O–H, H$\cdots$O and O$\cdots$O distances and is a multidimensional double well. It reduces to a single well for very strong hydrogen bonds, in which for the vibrational ground state the highest probability density of the proton is at the midpoint.[8]

^{1}H and ^{2}H NMR spectroscopy has been used profitably for the investigation of hydrogen bonding. The ^{1}H chemical shift, which increases with increasing r(O–H) and concomitant shortening of the H$\cdots$O distance, is considered an index of the hydrogen-bond energy.[9] The values of $\delta = 18.65$ for **1**, $\delta = 18.41$ for **2**, and $\delta = 18.18$ for **3** at 300 K are typical of fairly strong interactions. The primary isotope effect, that is, $^{\mathrm{p}}\Delta = \delta(\mathrm{H}) - \delta(\mathrm{D})$, is the most important and reliable probe of the shape of the potential curve.[8, 10] The $^{\mathrm{p}}\Delta$ value is large and positive (about +380 ppb for **1** and +410 ppb for **2**), does not depend on temperature,[11] (Figure 2) and fits well to the correlation with ^{1}H chemical shift found for molecules having intramolecular hydrogen bonds.[10] A large positive $^{\mathrm{p}}\Delta$ is characteristic of a double-well potential with a low central barrier and high anharmonicity. Here, upon substitution of D for H, the hydron fundamental vibrational wavefunction is modified so that $\langle r(\text{O–hydron})\rangle$ is smaller and $\langle r(\mathrm{O}\cdots\mathrm{O})\rangle$ is larger (secondary geometric effect).[8] A double minimum is consistent with the r(O$\cdots$O) values found in cobaloximes, which cluster about 2.49 Å,[12] provided the O-H-O angle is less than 180°, as was previously proposed on the basis of IR data for [Ni(Hdmg)$_2$].[13] The magnitude of $^{\mathrm{p}}\Delta$ leads to an estimated secondary geometric effect of about 1–2 pm[14] (note that 3 pm is the maximum secondary geometric effect reported so far[15]). Hence, the increase in Co–N bond lengths upon H/D substitution, suggested by the cobalt chemical shift, can be explained by the increase of the O$\cdots$O distance inferred from $^{\mathrm{p}}\Delta$.

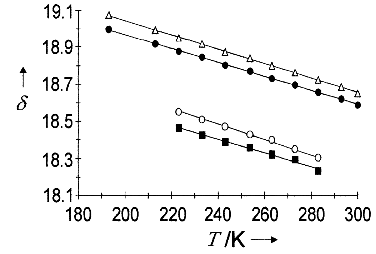


Figure 2. Temperature dependence of the hydrogen-bridge hydron chemical shift for the isotopomers of **1**. ^{1}H for HH (△), ^{1}H for HD (●), ^{2}H for HD (○), and ^{2}H for DD (■).

Further insight into the expansion of the coordination site is provided by the secondary isotope effect observed at the opposite hydrogen bond, six bonds away. The $^6\Delta$ value for the proton ($\delta(\mathrm{H})_{[\mathrm{RCo(Hdmg)(Ddmg)L}]} - \delta(\mathrm{H})_{[\mathrm{RCo(Hdmg)_2L}]}$), as well as that for the deuteron ($\delta(\mathrm{D})_{[\mathrm{RCo(Ddmg)_2L}]} - \delta(\mathrm{D})_{[\mathrm{RCo(Hdmg)(Ddmg)L}]}$) is about −70 ppb. The two hydrogen bonds are coupled[16] in a cooperative way: not only the hydrogen bond where deuteration occurs is weakened, but also the other. The deuteration of either one or two hydrogen bonds results in further long-range secondary isotope shifts $^n\Delta$ (n is the number of intervening bonds). The equatorial C=N carbon atoms of **1** are 64 ppb less shielded for [MeCo(Ddmg)$_2$py] than for the undeuterated complex. The same $^3\Delta$ value is observed on the side of the D bridge for [MeCo(Hdmg)(Ddmg)py], where the inequivalence of the C=N carbon atoms clearly evidences the symmetry decrease caused by deuteration of one bridge. A long-range effect with opposite sign ($^5\Delta = -4$ ppb) was observed for the equatorial methyl protons in **2**. The axial methyl protons show a $^5\Delta$ of about +14 ppb for each deuteration step in both **1** and **2**.

The dependence of the ^{1}H and ^{2}H chemical shift of the hydrogen bond on temperature is linear with a negative slope (−0.004 ppm K^{-1} for **1** (Figure 2) and **2**), as was already found for enolates,[17] which have the same kind of potential shape. It is noteworthy that such a negative dependence is also shared with the important class of hydrogen bonds whose lowest vibrational energy is higher than the potential barrier and which are characterized by negative $^p\Delta$ and negative secondary geometric effects.[18]

From the above results, it can be concluded that the hydrogen bonds of cobaloximes have double-well potentials with a low central barrier and high anharmonicity and are subject to a positive secondary geometric effect upon deuteration. The latter is accompanied by a lengthening and weakening of the Co–N bonds that is large enough to drastically increase the ^{59}Co chemical shift.

Experimental Section

All the compounds were prepared according to literature procedures.[19] NMR spectra were recorded on a 400 MHz JEOL EX-400 spectrometer on [D$_6$]acetone solutions. For ^{59}Co spectra, a pulse width of 45°, a relaxation delay of 0.1 s, a sweep width of 60240 Hz, 8192 points, 10000 scans, and a broadening factor of 30 were used, and the data were zero-filled once before Fourier transformation. The solvent signal was used as internal standard at $\delta = 2.00$ for ^{1}H and ^{2}H, and at $\delta = 30.30$ for ^{13}C. The ^{59}Co chemical shift data were referred to [K$_3$Co(CN)$_6$] at 300 K. The isotopic substitution was accomplished by adding a few microliters of D$_2$O to the 2×10^{-2} M solutions of the cobaloximes in [D$_6$]acetone.

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Enantiopure Simple Analogues of Annonaceous Acetogenins with Remarkable Selective Cytotoxicity towards Tumor Cell Lines**

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Annonaceous acetogenins, a relatively new class of natural products so far only found in Annonaceae, have been attracting worldwide attention in recent years because of their potent biological activities, especially as growth inhib-

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