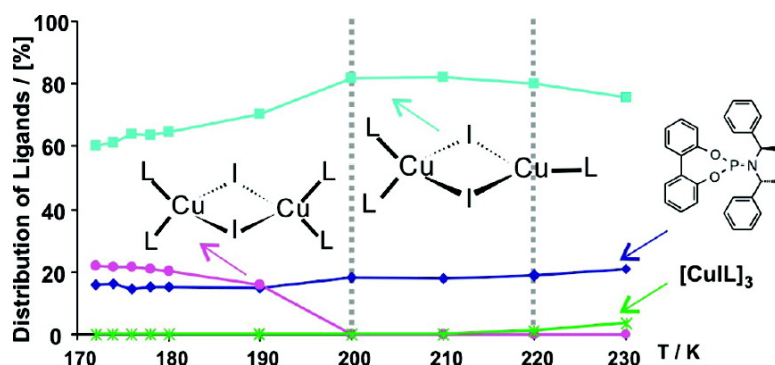


Temperature-Dependent Interconversion of Phosphoramidite#Cu Complexes Detected by Combined Diffusion Studies, P NMR, and Low-Temperature NMR Spectroscopy

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Temperature-Dependent Interconversion of Phosphoramidite–Cu Complexes Detected by Combined Diffusion Studies, ^{31}P NMR, and Low-Temperature NMR Spectroscopy

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Abstract: For copper-catalyzed enantioselective conjugate additions, knowledge about the precatalytic and catalytic complexes has not yet been sufficiently developed to understand the strong influence of different temperatures on these famous reactions. Therefore, NMR experiments with four Cu(I) salts and two phosphoramidite ligands have been performed to elucidate the temperature dependence and the low-temperature structures of these copper complexes. The existence of the precatalytic binuclear complex with a mixed trigonal/tetrahedral coordination on copper is for the first time proven with direct NMR spectroscopic methods. Below 200 K, intermolecular interactions between free ligands and $[\text{Cu}_2\text{X}_2\text{L}_3]$ complexes induce binuclear $[\text{Cu}_2\text{X}_2\text{L}_4]$ complexes similar to the crystal structures. By combining diffusion experiments and ^{31}P integrals at different temperatures, it is for the first time possible to follow the formation of stoichiometrically different complexes, even under experimental conditions in which the ^{31}P signals of the complexes are spectroscopically not resolved due to exchange processes. This allows a first correlation between the complex species observed and the synthetic conditions reported. Furthermore, different preferences to build homo- or heterochiral complexes are detected for binaphthol and biphenol phosphoramidite complexes.

1. Introduction

Enantioselective catalytic 1,4-conjugate addition reactions have been widely used as one of the most attractive strategies for carbon–carbon bond formation bearing a new stereogenic center.¹ Among the various catalytic systems reported so far, copper-catalyzed 1,4-additions of dialkylzinc in the presence of chiral monodentate phosphoramidite ligands have been reported to show excellent enantioselectivities, particularly with the advantage of cheap catalysts.^{2–5} Among a huge variety of different ligands, two of the most promising ones are presented in Figure 1. The ligands **1**³ and **2**^{6,7} represent the binaphthol-based and biphenol-based phosphoramidite ligands, which were originally introduced and practically rendered by the groups of Feringa and Alexakis.

The study of copper–phosphoramidite catalysts has become an active area also in fields like cyclization reactions,⁵ allylic

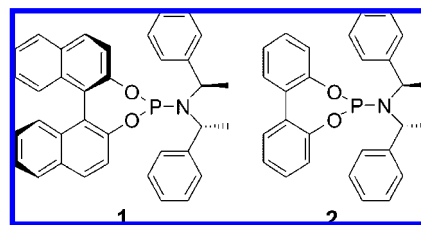


Figure 1. Representative binaphthol (**1**) and biphenol (**2**) phosphoramidite ligands used in this study.

alkylation,^{8–11} and conjugate addition of acyclic α,β -unsaturated imides.¹² But investigations of the underlying mechanism are still rare.^{2,13–16} The currently accepted mechanism suggests a

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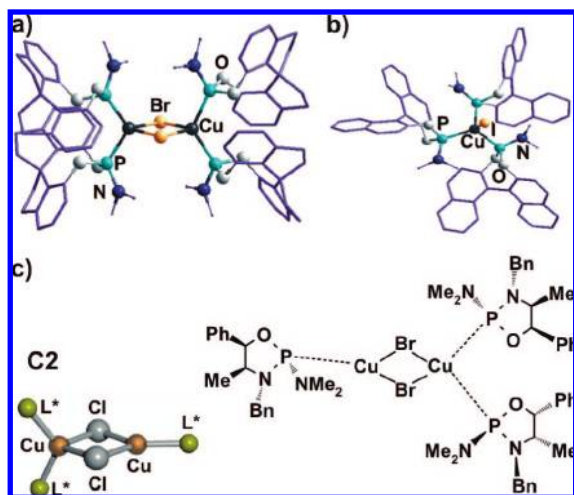


Figure 2. Known crystal structures or their schemes of (a) $[\text{CuBr}(\text{O},\text{O}'-(R)-(1,1'-\text{spirobiindane-7,7'-diyl})-N,N'-\text{dimethylphosphoramidite})_2]_2$,²⁰ (b) $\text{CuI}(\text{O},\text{O}'-(S)-(1,1'-\text{dinaphthyl-2,2'-diyl})-N,N'-\text{dimethylphosphoramidite})_3$,²⁰ and (c) tris(3-benzyl-*N,N,N*,4-trimethyl-5-phenyl-1,3,2-oxaphospholidin-2-amine)-di- μ -bromo-dicopper(I),²³ a phosphoramidite copper complex with a binuclear structure proposed also for the precatalytic complexes C2 ($[\text{Cu}_2\text{Cl}_2\text{I}_3]$) and $[\text{Cu}_2\text{Cl}_2\text{I}_3]$.²⁴ Reprinted with permission from ref. 22. Copyright 2007 Wiley-VCH.

transmetalation of an alkyl group from zinc to the chiral copper complex acting as enantioselective catalyst.^{4,17,18} However, the structure of the catalytically active chiral phosphoramidite–copper complex is not yet fully understood. Only a few crystal structures of Cu(I) complexes with less selective phosphoramidite ligands have been published so far (see Figure 2). In addition, it is unclear whether it is possible to infer the structures of copper complexes in solution from crystal structures, since the very few structural studies in solution report sometimes deviating structures.¹⁹ For example, the crystal structure shown in Figure 2a represents a dimer with two phosphoramidite ligands coordinated to each copper atom and dibromo halide bridging.²⁰ The copper atoms show tetrahedral coordination, which is very improbable for ligand-accelerated catalyses,³ because one of the ligands has to dissociate to allow for the coordination of a substrate. Interestingly, for copper bromide complexes with chiral diphosphine ligands, a similar dimeric structure has recently been found in a solvent-dependent equilibrium with a trigonal–planar mononuclear copper complex.¹³ Such a monomer–dimer equilibrium is one of the possibilities to create open coordination sites for catalytic reactions.

The second crystal structure, a copper complex with the Monophos ligands (*N,N'*-dimethylphosphoramidite), adopts a monomeric structure $[\text{CuIL}_3]$ in the solid state (see Figure 2b).²¹ Also, our recent NMR study in solution using four copper salts and the Monophos ligand showed for all complexes a preference for the 3:1 stoichiometry but higher aggregation levels

$[\text{CuIL}_3]_n$.²² This higher coordination number and aggregation level of complexes with Monophos compared to those with the highly stereoselective ligands **1** and **2** can most probably be attributed to the reduced steric hindrance of the relatively small methyl substituents on nitrogen in Monophos. Thus, from the crystal structures and NMR investigations reported so far, a strong influence of the steric hindrance of the nitrogen substituents on the coordination number, aggregation level, and dimerization tendency can be expected.

Recently, we reported a binuclear Cu(I) complex with mixed trigonal/tetrahedral stereochemistry as new structural motif for precatalytic copper complexes with phosphoramidite ligands in copper-catalyzed asymmetric 1,4-additions, which is hereafter denominated as C2 (see schematic drawing in Figure 2c).²⁴ This new structural motif was deduced indirectly from a combination of ³¹P NMR spectra, NMR spectroscopic diffusion experiments, elemental analyses, and mass spectrometric investigations. Interestingly, it provides an open coordination site on copper, supporting the ligand-accelerated catalysis. As a large number of external factors (such as the nature of copper salts, ligands, solvents, and temperature) are known to affect the catalytic activity and enantioselectivity,^{4,25–27} additional investigations of the influence of copper salt, ligand size, and solvent on the aggregation level of the precatalytic copper complexes at 220 K were performed. The results indicated that the binuclear complexes with three ligands are a basic structural motif.²²

In principle, phosphoramidite–Cu(I) complexes are capable of forming such binuclear structures with three ligands. This is confirmed by crystal structures, e.g., with a less selective phosphoramidite ligand²³ (see Figure 2c), simpler phosphoramidite^{28,29} or phosphane ligands,^{21,30,31} and ESI-MS investigations.³² However, up to now, there has been no classical spectroscopic proof that the proposed binuclear phosphoramidite complex definitely exists in solution. Over a large temperature range, ligand-exchange processes form a severe obstacle for classical NMR spectroscopic approaches, leading to averaged ³¹P signals of the two structurally inequivalent ligands. Under the experimental conditions applied in ESI-MS experiments, this precatalytic copper complex decomposes. Furthermore, the influence of different temperatures on the structure and amount of precatalytic complexes and their aggregation level in solution have not yet been investigated. Insight into the temperature-dependent interconversion of copper complexes with chiral ligands in solution would be of great importance to synthetic applications, because it is widely known that the reaction temperature plays an essential role in achieving high enantiomeric excess (ee) values and yields in copper-catalyzed reactions.^{2,25–27,33,34} For example, in copper-catalyzed conjugate additions of diphenylzinc to cyclohexenone using **1** as chiral

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ligand, an optimization of the reaction temperature resulted in excellent ee values at 210 K (94% ee).²⁷ In conjugate additions to cyclic enones, low enantioselectivity was achieved at room temperature using spirocyclic phosphoramidite ligands. In contrast, reducing the temperature below 240 K led to significantly enhanced ee values.³³ Furthermore, using chiral phosphine ligands, Hoveyda et al. showed impressively that sometimes subtle changes in the chiral ligand structure can lead to significant variations in the temperature dependence of the enantioselectivity in copper-catalyzed 1,4-additions to enones.³⁴ In addition, organocuprates and organocuprate intermediates, which are a generally accepted model system for mechanistic and structural studies of copper systems, show a pronounced temperature dependence of their supramolecular structures.^{35–37}

Therefore, it is highly probable that also in enantioselective copper-catalyzed reactions, the temperature-dependent formation of different complex species is responsible for the deviations in the ee values. Moreover, the ligand-dependent tendencies of phosphoramidite–copper complexes to form homo- or heterochiral complexes are unknown, although both positive and negative nonlinear effects have been reported for syntheses with these complexes.³

Therefore, in this study, we have investigated the low-temperature structures of phosphoramidite complexes, the temperature-dependent equilibrium of different complex species, and the ligand-dependent trend of these complexes to form homo- or heterochiral complexes.

2. Results and Discussion

2.1. Identification of Low-Temperature Complexes. To investigate the temperature dependence and the low-temperature structures of precatalytic phosphoramidite copper complexes, CuCl, CuBr, CuI, and CuTC (TC = thiophene-2-carboxylate) were chosen as copper salts and **1** and **2** as ligands. Unless otherwise noted, a 2:1 ratio of ligand to copper salt was selected as standard experimental conditions. CD₂Cl₂ was used as solvent because it allows low-temperature measurements down to approximately 180 K and the number of NMR-detectable copper complexes coexisting in solution is minimized in this solvent.²² With respect to the ratio between copper salt and ligand, this experimental setup follows the synthetic protocols.⁴ Furthermore, it allows a direct comparison with our previous study of the influence of copper salts, solvents, and ligands on the structures of precatalytic phosphoramidite–copper complexes.²² In this study, it became evident that copper complexes with Monophos ligands (*N,N'*-dimethylphosphoramidite), which are preferably used in X-ray investigations (see Figure 2), show additional complex species with three ligands coordinated to copper and higher aggregation values than complexes with **1** and **2**. Furthermore, in conjugate addition reactions to enones, the application of Monophos leads to ee values only up to 65%.^{3,21} Therefore, these low-temperature studies concentrate on the highly enantioselective ligands **1** and **2**.

The low-temperature ³¹P NMR spectra of complexes composed of **1** or **2** and CuCl, CuBr, CuI, or CuTC are presented in Figure 3. The eight spectra show signals of the remaining free ligands in several cases between 146 and 150 ppm. More

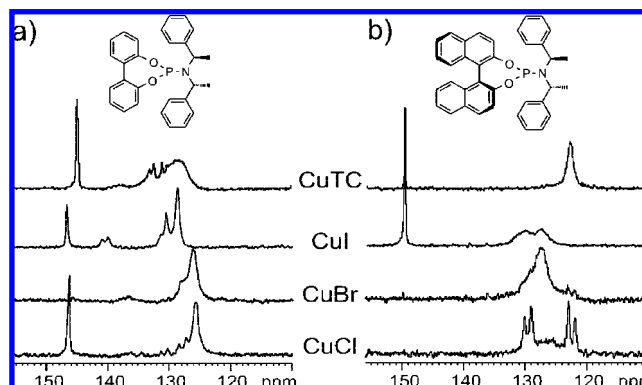


Figure 3. Low-temperature ³¹P NMR spectra of complexes composed of (a) **2** and (b) **1** and four different copper salts at 180 K in CD₂Cl₂ using 2:1 ratios of ligand to copper salt.

interestingly, a comparison of these spectra seems to demonstrate a variety of low-temperature complex species, revealed by the signals between 117 and 142 ppm. Most of these complex signals are broadened due to remaining ligand-exchange contributions, even at 180 K. Especially, the ³¹P signals of **1**/CuTC and **1**/CuI are severely affected by line broadening. Only for a few complexes do the existing internal exchange processes of the ligands become slow on the NMR time scale. Particularly, in the case of the combinations **2**/CuI and **1**/CuCl, two well-resolved low-temperature species can be identified (see Figure 3). With these two signal patterns at hand, it becomes evident that the signals in the remaining six spectra are most likely combinations of these two basic species at different ligand exchange rates. The **2**/CuI pattern (second row in Figure 3a) is partially and/or in differing resolution also observable for **2**/CuBr, **2**/CuCl, and **1**/CuBr. In turn, the **1**/CuCl pattern (fourth row in Figure 3b) can be identified in the spectra, e.g., for **2**/CuTC, **1**/CuBr, and **1**/CuI. This modulation of the structural preferences and the dynamic behavior of these precatalytic copper complexes may explain, to some extent, the strong influence of the counterion on the enantiomeric excess of the products in copper-catalyzed 1,4-additions. However, also specific interactions between dialkylzinc species and the copper salts can strongly influence the ee values, as recently proposed in an excellent contribution about copper-catalyzed 1,4-additions of Grignard reagents.¹³ Nevertheless, the spectra presented in Figure 3 show clearly that the combinations **1**/CuCl and **2**/CuI are the best model systems to elucidate the low-temperature structures of precatalytic phosphoramidite complexes.

In Figure 4, the ³¹P NMR spectra of the combinations **1**/CuCl and **2**/CuI in CD₂Cl₂ at temperatures between 230 and 180 K are presented. At 230 K, both spectra show averaged signals for the precatalytic copper complexes previously identified as C2 at 126 and 130 ppm.²² In addition, the signals of the free ligands appear at 150 and 146 ppm, respectively. For the combination **2**/CuI, an additional small signal at 123 ppm is detected representing the 1:1 complex [CuI]_n, hereafter denominated as C1. The detection of only one signal for the two chemically inequivalent phosphorus moieties in C2 indicates ligand-exchange processes being fast on the NMR time scale. At lower temperatures, the ³¹P signals of both complexes broaden, and at 180 K well-resolved signal patterns appear. For **1**/CuCl, the AA'BB' ³¹P pattern with a ²J_{P,P} of 260 Hz (see Figure 4a) indicates a CuL₂ moiety with two chemically inequivalent ligands. A ³¹P,³¹P COSY at 180 K confirms that scalar couplings between the two ligands are responsible for

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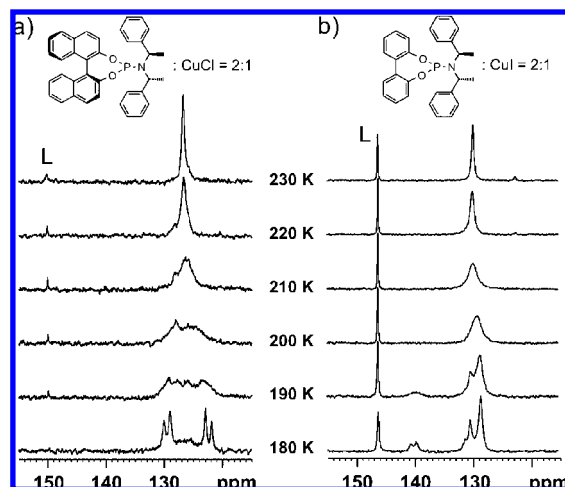


Figure 4. ^{31}P NMR spectra of complexes composed of (a) CuCl and **1** and (b) CuI and **2** at a 2:1 ratio in CD_2Cl_2 at varying temperatures.

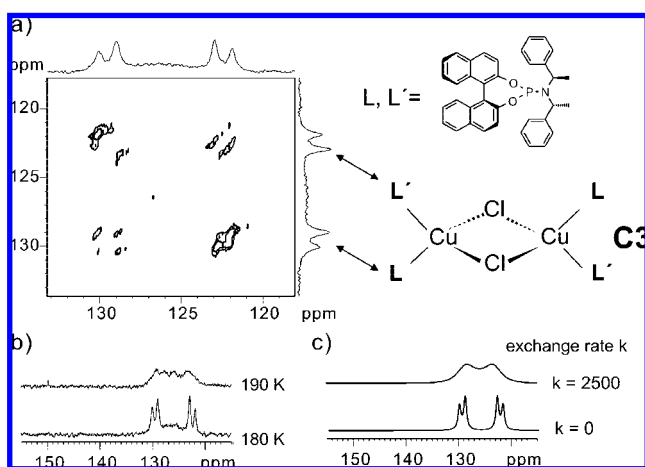


Figure 5. (a) $^{31}\text{P},^{31}\text{P}$ COSY spectrum at 180 K and scheme of the corresponding binuclear complex (C3) with tetrahedral coordination on Cu. (b) Experimental and (c) simulated ^{31}P spectra of a complex composed of **1** and CuCl at a 2:1 ratio in $[\text{D}_2]\text{CH}_2\text{Cl}_2$ at 180 and 190 K.

the observed signal pattern (Figure 5a). In addition, diffusion experiments indicate four ligands per complex at 180 K (see below). Both facts are in good agreement with the crystal structures reported previously for a binuclear phosphoramidite–copper complex with four ligands (shown in Figure 2a)²⁰ and a triphenylphosphine–copper complex.³⁸ Thus, the first identified low-temperature structure of phosphoramidite complexes in solution is a dimeric complex $[\text{Cu}_2\text{X}_2\text{L}_4]$ which shows two inequivalent ^{31}P signals for the CuL_2 subunits. This structural type is hereafter denominated as C3 (see schematic representation in Figure 5a).

In order to confirm this result, the low-temperature spectra of $\text{C3}_{1/\text{CuCl}}$ were simulated theoretically. Experimental and simulated ^{31}P spectra of $\text{C3}_{1/\text{CuCl}}$ at 180 and 190 K are presented in Figure 5b,c. Interestingly, the experimental spectra show additional broad signals in the center of the AA'BB' pattern compared to the simulated ones. This indicates the presence of further, spectroscopically unresolved complex species in solution.

A second low-temperature species can be identified in the ^{31}P spectrum of $2/\text{CuI}$ at 180 K (see Figures 4b and 6). In that

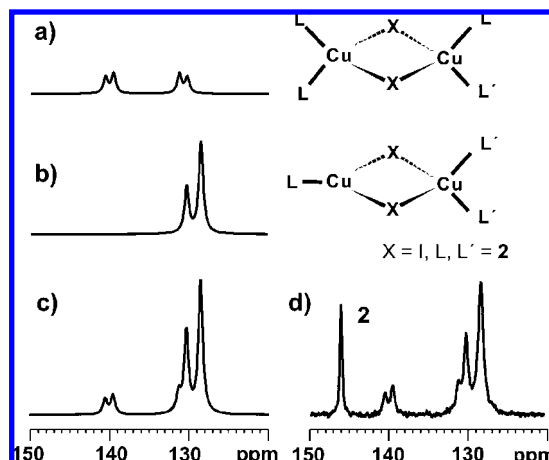


Figure 6. Simulations of the ^{31}P NMR spectra of the binuclear complex with (a) tetrahedral Cu coordination and (b) mixed trigonal/tetrahedral coordination. (c) Superposition of spectra a and b for comparison with (d) the experimental ^{31}P NMR spectrum of ligand **2** and CuI at 2:1 ratio in CD_2Cl_2 at 180 K.

spectrum, a large singlet at 128.5 ppm, a second smaller singlet with a pronounced shoulder at 130.3 ppm, and one-half of the already known AA'BB' pattern at 140 ppm are detected in addition to the signal for the free ligand at 146 ppm. The integral ratio of the two singlets at 128.5 and 130.3 ppm is close to 2:1. This strongly suggests that C2, the binuclear precatalytic complex with three ligands, is the second low-temperature species. To confirm this assumption, the ^{31}P spectra of C3 and C2 were simulated for the combination $2/\text{CuI}$ (see Figure 6). The subsequent intensity-adapted superposition shows an excellent agreement with the experimental ^{31}P spectrum. The presented spectra show clearly that, for the combination $2/\text{CuI}$, the binuclear complex with mixed trigonal/tetrahedral coordination (C2) is the main species, accompanied by a small amount of a binuclear complex with four ligands (C3) at 180 K. The presented spectra are the first classical and direct experimental proof of the new precatalytic Cu structure, which has previously been proposed only on the basis of diffusion experiments.²⁴ This classical NMR spectroscopic confirmation of the existence of C2 in solution shows the reliability of very carefully interpreted diffusion data.

2.2. Temperature-Dependent Interconversion of Copper Complexes. The identification of the low-temperature species with four ligands (C3) raises questions about the temperature range and origin of its formation. There are two principal possibilities. The first is that C3 also exists at higher temperatures together with smaller copper complexes, e.g., $[\text{CuXL}_2]$. In this case, dynamic processes would lead to averaged NMR signals of these complexes above 200 K, which would explain the observed diffusion coefficients fitting to three ligands per complex between 210 and 220 K.²² The second possibility is that aggregation of free ligands and C2 leads to partial formation of C3 at very low temperatures. In this case, chemical exchange processes at 180 K would lead to better-resolved ^{31}P signals of C3 compared to those of C2. This effect is caused by the larger chemical shift separation between the two signals of C3 compared to those of C2. As a result, the more severe line broadening of C2 leads to an overestimation of the amount of C3 in solution, as already shown by the comparison of the experimental and simulated spectra of C3 in Figure 5b,c.

2.2.1. Diffusion Experiments. In order to differentiate between these two possibilities, one straightforward experimental setup

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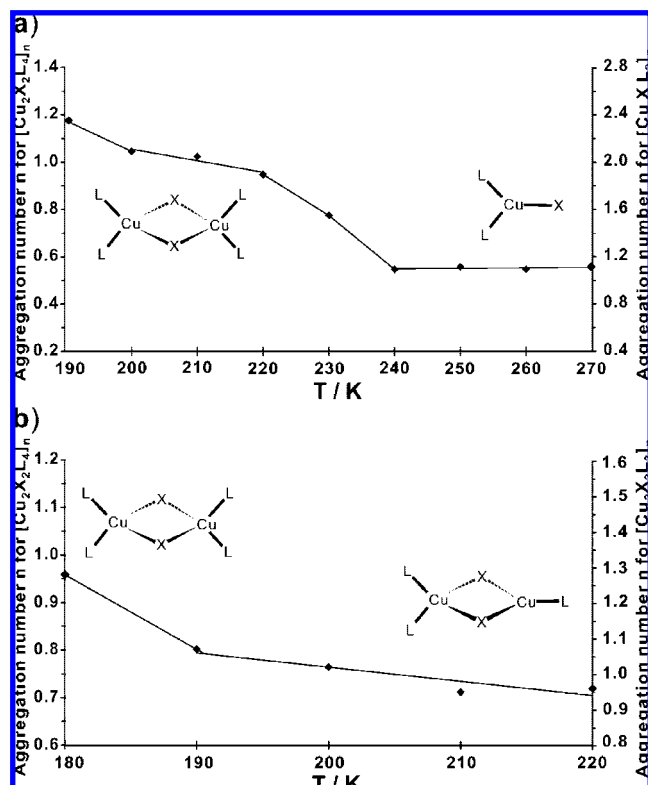


Figure 7. Temperature-dependent aggregation numbers of copper complexes composed of (a) **2** and CuBr and (b) **1** and CuI in CD_2Cl_2 based on ^1H DOSY data.

would be to measure the temperature dependence of the diffusion coefficients. However, for the precatalytic copper complexes with copper salt-to-ligand ratios of 2:1, the determination of diffusion values is very limited. Severe overlap of the proton chemical shifts in combination with exchange processes between the free ligand and the complex at temperatures above 220 K prevent reliable diffusion measurements at these temperatures. In a small window between 220 and 210 K, the deviating internal dynamics of the complexes and the free ligand allow the diffusion values to be determined as reported previously.^{22,24}

Exceptional cases are the complexes with CuBr and **1** and **2**. Despite the ligand-to-CuBr ratio of 2:1, no signals for the free ligands were detected in their ^{31}P spectra, as observed for the other 10 phosphoramidite–copper complexes investigated previously.²² The missing signal of free ligand indicates the preference of **1**/CuBr and **2**/CuBr for structures with a 2:1 stoichiometry, such as $[\text{CuXL}_2]$ and $[\text{Cu}_2\text{X}_2\text{L}_4]$. The similar catalytic reactivity of these complexes with CuBr in spite of the deviating precatalytic structures was discussed previously.²² Nevertheless, the exclusive formation of one single NMR-detectable species allows the direct measurement of the temperature-dependent aggregation behavior by diffusion experiments.

The resulting aggregation trend of **2**/CuBr is presented in Figure 7a, in which the aggregation numbers calculated from the experimental self-diffusion coefficients are correlated to the complexes $[\text{Cu}_2\text{X}_2\text{L}_4]$ and $[\text{CuXL}_2]$. Interestingly, the graph indicates one plateau area and two temperature ranges with significantly different slopes in aggregation. Between 270 and 240 K, a very stable aggregation level with two ligands is detected. Between 240 and 220 K, a steep increase in aggregation is observed, and between 220 and 190 K, four ligands per

complex are detected with a slightly increasing aggregation level toward lower temperatures. This temperature-dependent aggregation behavior and the missing signal of the free ligand at all temperatures suggest strongly that, in the case of **2**/CuBr, a mixture of two complexes with two and four ligands, respectively, exists in solution. The exclusive existence of $[\text{CuXL}_2]$ at 240 K and higher temperatures may be one possible explanation why, in copper-catalyzed enantioselective reactions, it is often reported that the ee values drop dramatically at higher temperatures.^{2,33}

Out of six ligand/copper salt combinations showing complex signals as well as free ligand signals in their ^{31}P spectra, **1**/CuI is the only system that provides sufficiently separated ^1H signals for copper complex and free ligand.^{22,24} This allows us to measure exemplary diffusion coefficients at temperatures between 220 and 180 K. At higher temperatures, exchange processes between ligand and complex falsify the obtained diffusion coefficients. The resulting aggregation trend of **1**/CuI with aggregation numbers correlated to the complexes $[\text{Cu}_2\text{X}_2\text{L}_3]$ and $[\text{Cu}_2\text{X}_2\text{L}_4]$ is presented in Figure 7b. In the temperature range between 220 and 190 K, the diffusion coefficients of the 2:1 mixture of **1** and CuI indicate three ligands per complex, with a slightly increasing aggregation level toward lower temperatures. At 180 K, the aggregation level increases to nearly four ligands per complex. Compared to the complex composed of CuBr and **2**, the slope of the aggregation is very similar, but the absolute amount of the ligands is reduced by one. Therefore, the temperature-dependent aggregation of **1**/CuI indicates the formation of C3 by intermolecular interactions of the free ligand and C2 at temperatures below 200 K.

Qualitatively, the temperature-dependent development of C2 for the combination **1**/CuI can be assumed to be representative for all investigated phosphoramidite–copper complexes C2. However, the relative amounts of C2 and C3 (and C1) seem to be variable and dependent on the actual combination of ligand and copper salt. For example, the ^{31}P spectra of **1**/CuI and **2**/CuI in Figure 4 and the comparison of experimental and theoretical spectra in Figures 5 and 6 indicate the presence of both complexes C2 and C3 at 180 K. For **1**/CuI the major species is C3, whereas for **2**/CuI a larger amount of C2 is detected.

2.2.2. Monitoring of Copper Complexes by ^{31}P NMR. If the formation of C3 is caused by intermolecular interactions between the free ligand and C2 according to the scheme in Figure 8a, a direct correlation between the appearance of C3 and the decrease of the free ligand signal should be observable by integration of their ^{31}P signals. As evident from Figure 3, only the combination **2**/CuI provides sufficiently resolved ^{31}P low-temperature spectra to allow for an integration of C2 and C3. Due to the partial overlap of their ^{31}P signals, the integration was done according to the simulation of the two species presented in Figure 6. The resulting temperature-dependent distribution of **2** in a 2:1 mixture of **2** and CuI is shown in Figure 8b. The relative ^{31}P integrals of **2** observed either as free ligand or as coordinated ligand in one of the complexes C1, C2, or C3 is monitored graphically. For the quantitative interpretation of the graphs, it is important to consider that the varying amounts of ligand in the different complexes lead to different slopes of the single curves. For example, the formation of one C3 complex by intermolecular interactions of C2 and free ligand causes different changes of their ^{31}P integrals. The ligand signal is reduced by a factor x , C2 is reduced by $3x$, and C3 increases by a factor of $4x$.

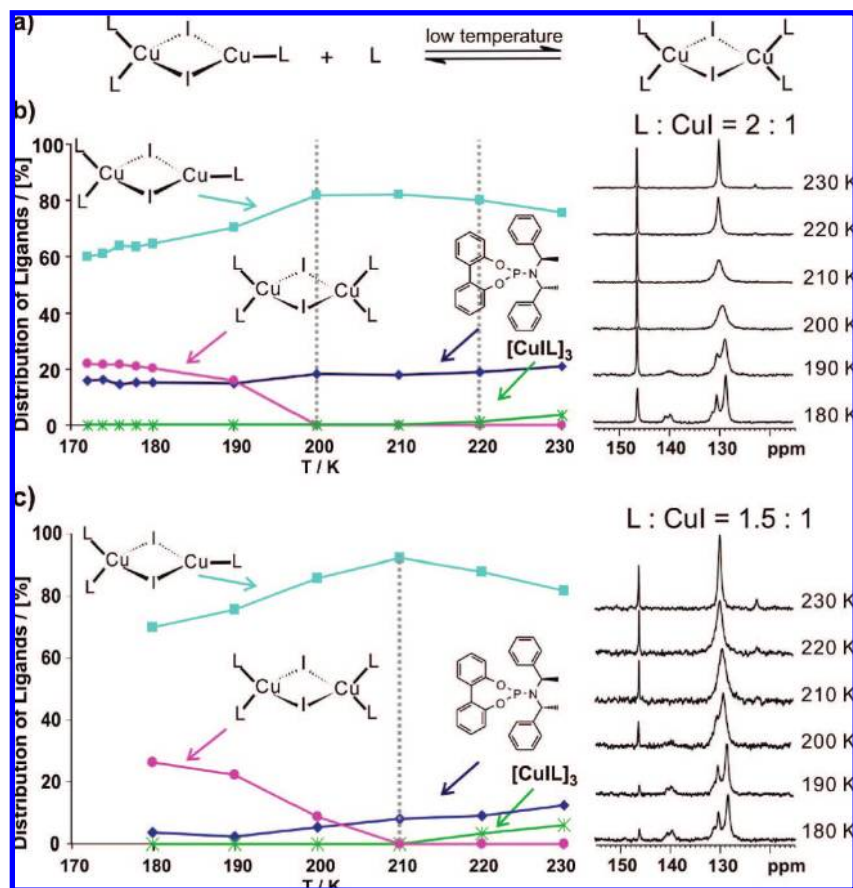


Figure 8. (a) Formation of C3 caused by intermolecular interactions between the free ligand and C2. Temperature-dependent formation of the complexes C1, C2, and C3 in the cases of a 2:1 ratio (b) and a 1.5:1 ratio (c) of ligand **2** and CuI in CD₂Cl₂, monitored by the distribution of the ligands as free ligands or as parts of the complexes C1, C2, or C3 in the corresponding ³¹P spectra. For details, see text.

With this method, it is possible to track the temperature-dependent formation of the different species in solution. At 230 K, a small amount of the 1:1 complex [CuIL]_n (C1) exists in solution, which is reduced at 210 K and below the detection limit at lower temperatures. A simultaneous slight increase of C2 and a decrease of **2** show that C2 is produced from C1 and **2**. Between 220 and 200 K, there is nearly a plateau situation in which only C2 and free ligand exist in solution. Below 200 K, the amounts of free ligand and C2 are reduced, and simultaneously the integral of C3 increases. Within the experimental error range, the relative distribution of the ligand follows exactly the scheme expected for the addition of a free ligand to C2 according to Figure 8a.

Considering the spectroscopically unresolved, exchange-broadened signal of the copper complexes between 220 and 200 K (see Figure 4b), it is at first glance not evident whether this signal comes solely from C2 or whether it represents an exchange averaged signal of C2 and C3. In other words, the formation of C3 from free ligand and C2 does not necessarily cause separate signals of C3. The formation of C3 can also be covered by ligand-exchange rates being fast on the NMR time scale, which would lead to an averaged signal of C2 and C3. These two possibilities can be differentiated using the kind of ³¹P monitoring shown in Figure 8. In the case that C3 contributed to the broad complex signal between 220 and 200 K, the amount of free ligand would be directly reduced by the amount of C3. As a result, the integral of the free ligand would decrease and that of C2 would increase without showing separate signals of C3. However, in Figure 8b, it can be clearly seen

that, at 210 and 200 K, the amount of ligand and C2 is stable and at 230 and 220 K, the amount of free ligand is directly correlated to the amount and disappearance of C1. Therefore, it can be concluded that, under the experimental conditions applied for Figure 8b, the formation of C3 starts at 190 K. In addition, it becomes evident that, for interconversions of stoichiometrically different complexes, the monitoring of the free ligand makes it possible to elucidate the contributions of different complex species even from spectroscopically unresolved complex signals.

With this method at hand, it is very interesting for synthetic applications to determine whether it is possible to optimize the ratio between ligand and copper salt in order to stabilize the precatalytic complex, reduce other complex species, or reduce cost by using smaller amounts of ligand. Considering the precatalytic structure consisting of two copper salts and three ligands, it is of special interest to investigate the effect of using a lower ligand-to-copper salt ratio of 1.5:1. The results of the corresponding measurements of a 1.5:1 ratio of **2** and CuI are shown in Figure 8c. Surprisingly, a destabilization of C2 is observed. Above 210 K, C2 is converted into C1 and **2**. At 210 K, exclusively C2 and **2** exist in solution, and below 210 K, again C3 is formed from C2 and **2**. The fact that the formation of C3 is not affected by the reduction of the amount of free ligand hints at a relatively high stability of that coordinatively saturated low-temperature species. Its formation seems to be induced by intermolecular interactions between **2** and the ligands in C2, since a series of diffusion experiments shows that also the

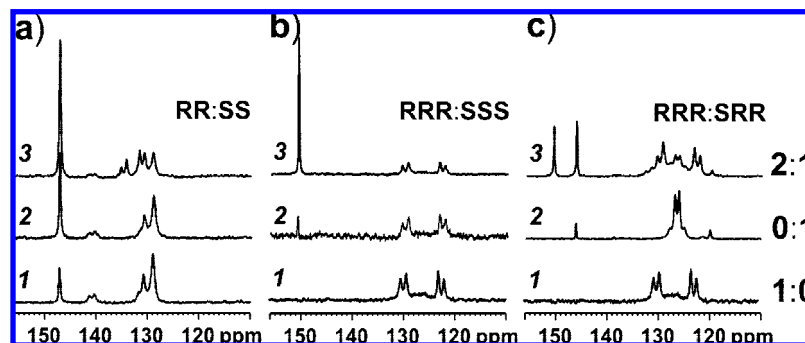


Figure 9. Formation of (a) heterochiral and (b,c) homochiral complexes shown on ^{31}P NMR spectra of 2:1 ratios of (a) **2** and CuI and (b,c) **1** and CuCl in CD_2Cl_2 at 180 K.

free ligands alone show self-aggregation below 210 K. These results show that the 2:1 ratio of ligand to copper salt deduced from synthetic optimization procedures stabilizes the precatalytic complex C2 over a broader temperature range by reducing the formation of C1 and C3. Interestingly, the experimental conditions (2:1 ratio, 210 K), which support the exclusive formation of the precatalytic complex $[\text{Cu}_2\text{X}_2\text{L}_3]$, are also reported to yield the best ee values in synthetic optimization procedures.^{4,27} This further supports the identification of C2 as the precatalytic complex in copper-catalyzed enantioselective reactions.

The presented ^{31}P NMR results for complexes with CuI show clearly that the structures of the copper complexes existing in solution are highly temperature dependent. The diffusion experiments (Figure 7) and the low-temperature ^{31}P spectra of the other complexes (Figure 3) support the suggestion that complexes with **1** and **2** show a general trend toward higher coordination at reduced temperatures up to tetracoordinated copper complexes. That means that the tetracoordinated species represent the thermodynamically most stable complexes. Therefore, it is not astonishing that most of the crystal structures of phosphoramidite–copper complexes show tetracoordinated copper atoms.²⁸ However, from the temperature dependence shown, it becomes evident that, in the case of structurally flexible chiral copper complexes, one has to act with great caution to infer the complex structures in solution from known X-ray structures. This problem is well known for lithium complexes, for which, e.g., Collum stated that “one cannot infer from crystal structures the dominance or even the existence of these forms in solution” and that “the solution aggregation numbers must be determined independently”.³⁹ These statements were based on structural studies in which species were characterized crystallographically that were not detectable in solution.^{40–42} In the case of flexible structures of copper complexes in solution, which show ligand-exchange rates that are fast on the NMR time scale, to our knowledge this is the first example of a spectroscopic approach to address such structural details.

With respect to the methodical approach, the presented study shows that combined ^{31}P spectra, diffusion experiments, and simulations allow identification of different copper complexes that coexist in solution and show sufficiently deviating ^{31}P signals. Beyond that, even at temperatures at which the signals of the different copper complexes may be averaged by exchange processes, the existence of different complex species can be investigated using the sharp ^{31}P signal of the free ligand. In the case of complexes with varying ligand-to-copper salt ratios, the amount of free ligand is directly correlated to the appearance of the different complex

species. Thus, by integration of the sharp ^{31}P ligand signal, it is possible to obtain reliable information about the different complexes, even in samples with spectroscopically unresolved ^{31}P NMR complex signals.

2.3. Formation of Homo- and Heterochiral Complexes. Feringa and co-workers reported small negative nonlinear effects for the enantioselective 1,4-addition of diethylzinc to cyclohexenone catalyzed by $\text{Cu}(\text{OTf})_2$ and varying ratios of (*S,R,R*)-**1** and (*R,S,S*)-**1** in toluene,³ indicating a small asymmetric depletion according to Kagan’s model.⁴³ For 1,4-addition reactions with **2** as chiral ligand, these nonlinear effects have not yet been reproduced (A. Alexakis, personal communication). The experimental conditions used in this study to detect homo- or heterochiral complexes in solution are not congruent with those reported for the observation of the nonlinear effects. Nonetheless, the detection of individual and assigned signal patterns for the different complex species at 180 K allows for the first time a direct spectroscopic investigation of the tendency of phosphoramidite–copper complexes to build homo- and/or heterochiral complexes.

For this purpose, a series of ^{31}P NMR spectra at 180 K was recorded with varying combinations of enantiomeric and diastereomeric ligands (see Figure 9). As test systems, again 2:1 ratios of **2**/CuI and (*R,R,R*)-**1**/CuCl were selected because these combinations show the best spectral resolution at 180 K (see Figure 3). Considering that nonlinear effects were observed for reactions with (*S,R,R*)-**1** but not for those with **2**, the experiments were repeated with the diastereomeric (*S,R,R*)-**1**. To exclude the possibility that the signals of the homochiral and heterochiral complexes are accidentally identical, the atropisomer (*S,R,R*)-**1** was chosen as second ligand. As it is known that the axial chirality of the ligand plays a crucial role in determining the chirality of the product formed, it is moreover highly interesting to choose this atropisomeric pair of (*R,R,R*)-**1** and (*S,R,R*)-**1**.

As expected, the enantiomeric complexes with (*R,R*)-**2** and (*S,S*)-**2** (see Figure 9a, spectra 1 and 2) or (*R,R,R*)-**1** and (*S,S,S*)-**1** (see Figure 9b, spectra 1 and 2) show identical NMR spectra,

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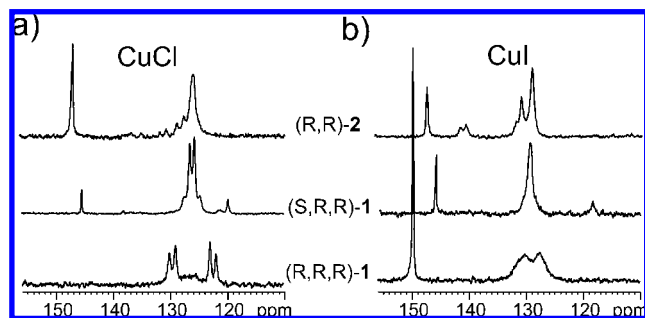


Figure 10. Influence of the type of ligand and the kind of salt, (a) CuCl or (b) CuI, on the complex formation at 180 K, shown on ^{31}P NMR spectra of C2 complexes with selected ligands.

and the complexes with *(S,R,R)*-**1** and *(R,R,R)*-**1** (see Figure 9c, spectra 1 and 2) produce different signals.

For a 2:1 mixture of *(R,R)*-**2** and *(S,S)*-**2** (see Figure 9a, spectrum 3), new signals appear at 132 and 135 ppm, in addition to the signals of the homochiral complexes. This indicates the formation of a heterochiral species for complexes with **2**. For the new signals of the heterochiral complex around 134 ppm, again parts of the scalar coupling pattern of an AA'BB' spin system are observed, which indicate CuL_2 units in these complexes. By contrast, the ^{31}P spectrum of a 2:1 mixture of *(R,R,R)*-**1** and *(S,S,S)*-**1** shows no detectable amount of any diastereomeric heterochiral complex (see Figure 9b, spectrum 3). Only the familiar signal pattern of the homochiral complex is observed. The ^{31}P spectrum of a 2:1 mixture of *(R,R,R)*-**1** and *(S,R,R)*-**1** shows also a clear superposition of the spectra with pure ligands (Figure 9c, spectrum 3) and again no evidence of heterochiral species. Hence, the binaphthol-based phosphoramidite **1** does not form any detectable heterochiral complexes at 180 K in CD_2Cl_2 . This is quite surprising, given the reported nonlinear effects for **1**.³ However, our previous studies about the influence of the solvent on the phosphoramidite–copper complexes showed that additional complex species are formed in toluene, which may be responsible for the small nonlinear effects reported.^{22,24,43} In the case of **2**, where heterochiral complexes are formed at 180 K, no nonlinear effects have been reported so far. One possible explanation would be the assumption that homo- and heterochiral complexes with **2** would show very similar reactivity, leading to nonobservable nonlinear effects.

To investigate whether the kind of ligand or the type of salt influences the signal pattern of the complexes more significantly, the low-temperature ^{31}P spectra of the complexes composed of *(R,R)*-**2**, *(R,R,R)*-**1**, or *(S,R,R)*-**1** and CuCl or CuI were measured (see Figure 10). A comparison of the six spectra shows that the signal patterns vary significantly upon changing the ligand. In contrast, the patterns of complexes with identical ligands and different types of salt are, in principle, very similar and show differences only in the linewidths. These spectra suggest that

the kind of ligand is decisive for the principal complex formation and the type of salt influences only the exchange dynamic of the ligands.

3. Conclusion

Using four different Cu(I) salts and two highly stereoselective phosphoramidite ligands, the low-temperature structures of precatalytic phosphoramidite–copper complexes are elucidated in CD_2Cl_2 . With the aid of experimental and simulated ^{31}P spectra, for the first time a direct experimental proof of the precatalytic binuclear structure with mixed trigonal/tetrahedral stereochemistry is presented. A second low-temperature species, a binuclear complex with tetrahedral coordination on both copper atoms, is identified that is similar to known crystal structures. Furthermore, for the first time, a temperature-dependent interconversion of chiral copper complexes is elucidated by combined diffusion experiments and ^{31}P NMR, which are moreover used in highly stereoselective catalytic transformations. For complexes with varying ligand-to-copper salt ratios, the ^{31}P signal of the free ligand allows us to obtain reliable information about the amount of different complexes, even in samples with spectroscopically unresolved ^{31}P NMR complex signals. To our knowledge, this method for monitoring spectroscopically unresolved species has not previously been applied. For the majority of copper salt–ligand combinations, the complexes $[\text{CuXL}]_3$, $[\text{Cu}_2\text{X}_2\text{L}_3]$, and $[\text{Cu}_2\text{X}_2\text{L}_4]$ were detected with a clear trend to higher coordination numbers at lower temperatures. In the temperature range used in synthetic applications, the major component is $[\text{Cu}_2\text{X}_2\text{L}_3]$. Interestingly, at a 2:1 ratio of ligand to copper salt, the presence of free ligand represses the formation of the complexes $[\text{CuXL}]_3$ and $[\text{Cu}_2\text{X}_2\text{L}_4]$ in a certain temperature range. Both results explain, for the first time on a structural level, the ee trends reported in synthetic optimization procedures. Furthermore, the presented temperature-dependent interconversion shows that one has to act with great caution when inferring the structures of copper complexes in solution from X-ray data. In addition, for the first time, the tendencies of phosphoramidite–copper complexes to build homo- and/or heterochiral complexes were investigated with a direct spectroscopic method, revealing significant differences for binaphthol- and biphenol-based phosphoramidite ligands.

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Supporting Information Available: Experimental section, diffusion values and experimental volumes for Figure 3, and calculation of the volumes from diffusion coefficients. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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