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Influence of Copper Salts, Solvents, and Ligands on the Structures of Precatalytic Phosphoramidite Copper Complexes for Conjugate Addition Reactions

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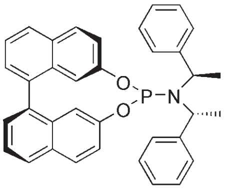
Abstract: For copper-catalyzed enantioselective conjugate addition reactions of organozinc reagents, the available knowledge about the mechanism and the structures involved is still insufficient to understand in detail the strong influences of solvent, salt, and ligand size, or to enable a rational control of this reaction. Screening with three phosphoramidite ligands and four copper(I) salts using NMR spectroscopy has revealed a binuclear copper complex with mixed trigonal/tetrahedral stereochemistry as the basic structural motif of the ground state of precatalysts with highly stereoselective ligands. Ligands with smaller amine moieties allow higher coordination numbers and higher aggregation levels, leading to reduced *ee* values. Since the ESI mass spectra of several precatalytic copper halide complexes show a striking correlation with the structures observed in solution, ESI-MS may be used as a fast tool to determine the maximum number of phosphoramidite ligands attached to copper.

Keywords: asymmetric catalysis · conjugate addition · copper · NMR spectroscopy · phosphoramidite ligands

Introduction

The reaction of organometallic reagents under conditions of copper catalysis is one of the most important methods for the asymmetric construction of carbon–carbon bonds.[1] The crucial breakthrough with regard to copper-catalyzed enantioselective conjugate addition reactions using organozinc reagents was achieved by the introduction of phosphoramidites as chiral ligands.[2] The introduction of a chiral amine moiety in 2,2′-binaphthol-based phosphoramidite ligands such as **1** results in a remarkable reactivity and selectivity of the copper complexes, and in this way catalytic 1,4-additions of R_2Zn reagents to cyclic enones with very high enantiocontrol ($>98\,\%$) were observed for the first time.[3] Soon after, Alexakis and co-workers designed a new type of ligand (**2**) by hypothesizing that the induced atropisomerism of the flexible biphenol unit will lead to adoption of the same configuration as that of the corresponding binaphthol-related ligand. With ligand **2**, results similar to or even better than those achieved with the parent ligand **1** have been obtained, with the advantage that **2** is much less expensive.[4] This reaction is now applicable to a broad range of substrates, including enones[5] and unsaturated malonates,[6] as well as for the ring-opening of oxabicyclic alkenes[7] or unsaturated lactams.[8]



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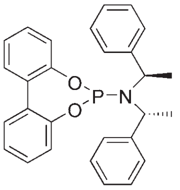

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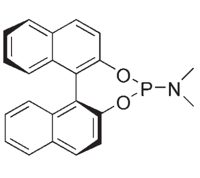

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Despite the synthetic importance of this promising catalytic process, as yet relatively few mechanistic studies have been reported on enantioselective copper-catalyzed cycloaddition reactions of dialkylzinc reagents.[9–11] No detailed mechanistic or structural study concerning the combination of phosphoramidite ligands with copper salts and dialkylzinc reagents has been published to date, but a mechanism based on the principles proposed for non-catalytic organocuprate addition[12–15] has been postulated.[4,5] The current mechanistic view is that as a first step a transmetalation between the organometallic compound and the copper species takes place, with experimental evidence from NMR chemical shifts in two cases.[16,17] The cycloaddition itself is postulated

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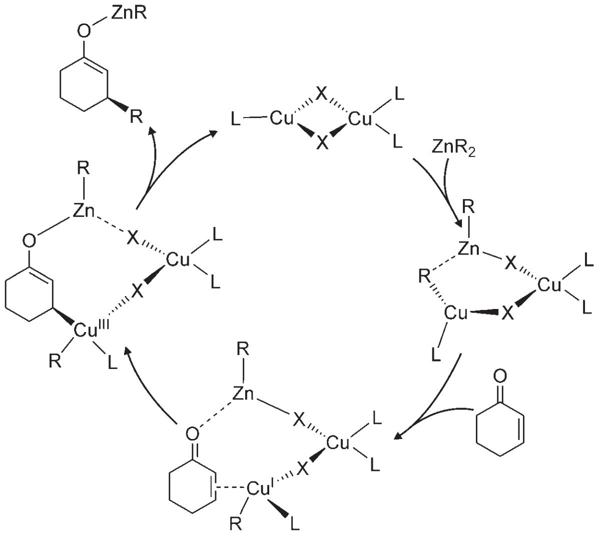
to proceed through reversible formation of a copper(I)–alkene complex, followed by an oxidative addition to give a copper(III) species and finally a reductive elimination to form the enolate (Scheme 1). The widely accepted opinion that two ligands at one copper center are present in the active catalyst is based on the facts that at an optimum ligand-to-copper ratio of 2:1, nearly identical selectivities with mono- and bidentate phosphoramidites are obtained (except with cyclopentenones)[18] and nonlinear effects are observed.[5] In contrast, Alexakis proposed a catalytic cycle with only one ligand attached to copper,[4] and synthetic optimization procedures showed that only ligand-to-copper ratios below 1.5:1, and not below 2:1, were detrimental to the catalysis.[1]



Scheme 1. Proposed catalytic cycle for the copper-catalyzed 1,4-addition of dialkyl zinc to 2-cyclohexenone.

At present, the available structural tools for analyzing possible precatalytic or catalytic copper complexes involved in enantioselective reactions with phosphoramidite ligands are still very limited. Only two crystal structures with less stereoselective phosphoramidite ligands are known (Figure 1a, b).[18,19] The copper complex with the binaphthol-based ligand **3**, applicable in conjugate addition reactions, adopts a monomeric structure, $CuIL_3$ (Figure 1b),[18] which produces only modest *ee* values.[5] The crystal structure of the second copper complex, used in substitution reactions, shows a C_2-symmetric dimer with two phosphoramidite ligands coordinated to each copper atom and dibromo halide bridging (Figure 1a).[19] A similar dimeric structure has recently been found for copper bromide complexes with chiral diphosphine ligands, in a solvent-dependent equilibrium with a trigonal-planar mononuclear copper complex.[16] Comparative studies concerning the structures in solution and in the solid state are very rare for copper complexes with chiral ligands. A notable exception relates to a tetranuclear Cu^I catalyst based on monodentate thiol analogues of TADDOL, which was examined both in the solid state and in solution (Figure 1c).[20]

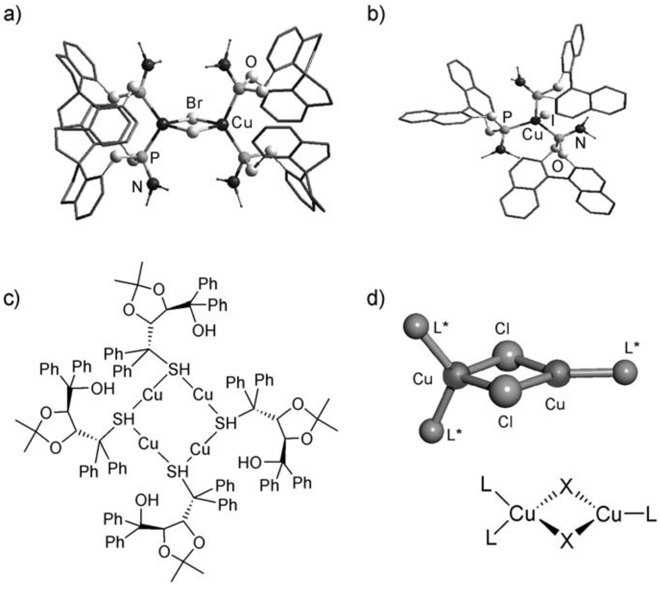


Figure 1. Known crystal structures or schematic representations of a) [CuBr(*O*,*O*′-(*R*)-(1,1′-spirobiindane-7,7′-diyl)-*N*,*N*′-dimethylphosphoramidite)$_2$]$_2$;[19] b) [CuI(*O*,*O*′-(*S*)-(1,1′-dinaphthyl-2,2′-diyl)-*N*,*N*′-dimethylphosphoramidite)$_3$];[18] c) a tetranuclear Cu complex with thiol-TADDOL ligands;[20] d) a phosphoramidite copper complex[21] with a binuclear structure, as also proposed for the precatalytic complexes [$\mathbf{1}_2$·Cu(μ-Cl)$_2$Cu·**1**] and [$\mathbf{2}_2$·Cu(μ-Cl)$_2$Cu·**2**][22].

Recently, we were able to gain a first insight into the ground-state structures of precatalytic copper complexes with phosphoramidite ligands in solution.[22] On the basis of ^{31}P NMR spectra, NMR spectroscopic diffusion experiments, elemental analyses, and mass spectrometric investigations, we identified a binuclear copper complex with mixed trigonal/tetrahedral stereochemistry for complexes of ligands **1** and **2** with CuCl in $CHCl_3$ (Figure 1d). That phosphoramidite Cu^I complexes are capable of forming such binuclear structures with three ligands attached is confirmed by a crystal structure of a less selective phosphoramidite ligand.[21] This new structural motif of the ground state of catalytically active copper complexes offers an explanation for the results of earlier synthetic optimization procedures, for example, the strong ligand acceleration and the minimum ligand-to-copper salt ratio of 1.5:1. However, the supramolecular structures of organocuprate complexes,[23–26] as well as the *ee* values and yields of copper-catalyzed conjugate addition reactions,[4] are both known to be highly salt- and solvent-dependent. Moreover, the size of the amine moiety of a phosphoramidite ligand seems to be decisive for its enantioselectivity. Therefore, in this study, we have investigated the influence of different copper salts, different ligands, and different solvents on the structures and aggregation levels of precatalytic copper complexes in solution. In addition, the applicability of electrospray mass spectrometry as a rapid and inexpensive analytical tool for phosphoramidite copper complexes is demonstrated.

Results and Discussion

Influence of the copper salt: ^{31}P NMR spectra: The enantiomeric excesses of the investigated copper-catalyzed conjugate addition reactions to enones are highly sensitive to the nature of the copper salt used.[4] In synthetic procedures, Cu^{I} and Cu^{II} salts have proved to be equally successful.[1] However, in order to avoid the severe NMR problems that stem from the paramagnetic character of Cu^{II} salts, we used exclusively Cu^{I} salts in our study of the salt dependence of the precatalytic copper complexes. Among the commercially available Cu^{I} salts, CuCl and CuTC (copper(I) thiophene-2-carboxylate) were selected in view of the excellent conversions and *ee* values that have been achieved by combining them with ligand **2** in various solvents.[4] To enable a comparison between the different halides, and to widen the structural investigations to a second highly enantioselective ligand, combinations of CuBr and CuI with ligand **1** were also studied. In synthetic protocols, two equivalents of monodentate phosphoramidite with respect to Cu are usually applied. Despite the fact that we identified a precatalytic complex with a ligand-to-copper salt ratio of 1.5:1 (vide supra), we chose the traditional ratio of 2:1 (ligand-to-copper salt) to obtain results that could be compared with those in the literature. In addition, we also examined the complexes at a ratio of 1:1. $CDCl_3$ and CD_2Cl_2 were selected as solvents, because single complex species were observed in both media at a 1:1 and a 2:1 ratio (spectra in CD_2Cl_2 not shown).[22]

The resulting ^{31}P NMR spectra of the complexes of CuCl, CuBr, CuI, and CuTC with ligand **2** in $CDCl_3$ are presented in Figure 2. With CuCl as the salt and a 2:1 ratio of ligand to CuCl, a signal attributable to the binuclear copper complex C2 with mixed trigonal/tetrahedral stereochemistry is observed at $\delta = 126.6$ ppm, together with a signal due to the free ligand at $\delta = 145.5$ ppm. At a 1:1 ratio, a signal due to a trinuclear complex $L_3Cu_3Cl_3$, designated as C1, is seen at $\delta = 121.7$ ppm, as recently reported elsewhere.[22] Compared to the CuCl system, the spectra obtained with CuBr and ligand in a 1:1 ratio and with CuI and ligand in a 2:1 ratio are very similar. However, with two equivalents of ligand **2** and CuBr, the ^{31}P NMR spectrum differs from that seen with the CuCl system. Again, a singlet at $\delta = 127.4$ ppm (due to the species denoted as $C2_{\mathbf{2}/CuBr}$) is observed; however, the signal of the free ligand is significantly diminished and a weak signal due to C1 is also observed. The absence of a significant amount of the free ligand indicates that the ligand-to-copper salt ratio within the C2 complexes is shifted from 1.5:1 for CuCl to 2:1 for CuBr. This is confirmed by the fact that the solubilities of the pure copper salts (CuCl, CuBr, CuI, and CuTC) in $CHCl_3$ or CH_2Cl_2 are all very low (about 1 mM at room temperature; for details, see the Supporting Information). For the combination of ligand **2** and CuI in a 1:1 ratio, two singlets are observed. In addition to the signal for the 1:1 complex $C1_{\mathbf{2}/CuI}$ at $\delta = 122.1$ ppm, the signal of $C2_{\mathbf{2}/CuI}$ at $\delta = 129.3$ ppm is also apparent and a white precipitate is observed in the NMR tube. An attempt to generate exclusively $C1_{\mathbf{2}/CuI}$ by reducing the ratio of ligand to copper salt to 0.5:1 failed and produced only an increased amount of the precipitate. Both observations point to a low solubility of the 1:1 complexes with CuI and the precipitation of excess CuI. A similar significantly reduced solubility of CuI complexes compared to CuCl or CuBr complexes has been noted for 1:1 Cu^{I} halide/phosphine complexes in CD_2Cl_2.[27]

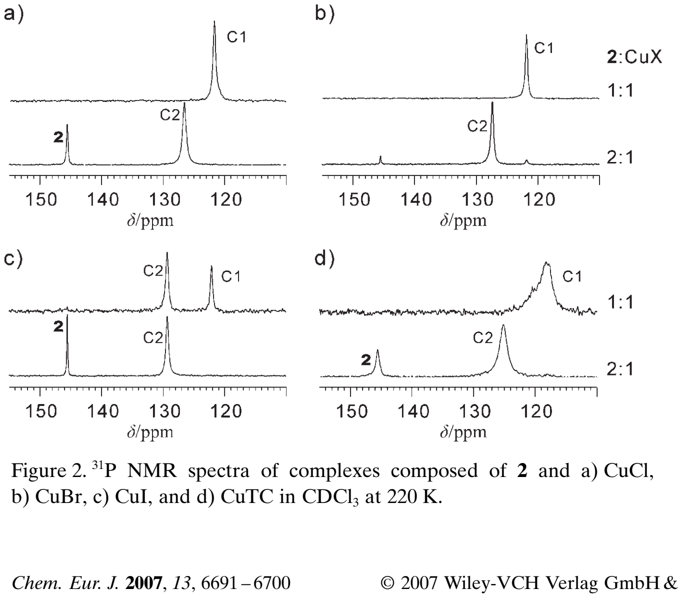


Figure 2. ^{31}P NMR spectra of complexes composed of **2** and a) CuCl, b) CuBr, c) CuI, and d) CuTC in $CDCl_3$ at 220 K.

Changing the anion of the copper salt from monodentate halides to the potentially bidentate thiophene-2-carboxylate (TC) leads to significantly broader linewidths of the signals in the ^{31}P NMR spectra in $CDCl_3$. For a 1:1 ratio of **2** to CuTC, a very broad signal ($\Delta\nu_{1/2} = 468$ Hz) with a noticeable shoulder is observed at $\delta = 118.2$ ppm, indicating the presence of two different complex species. Owing to the fact that neither a separation of these signals nor a differentiation between them was possible, the two complexes are considered together as one in the subsequent discussion ($C1_{\mathbf{2}/CuTC}$). Interestingly, at a 2:1 ratio, the signal pattern is very similar to those seen with chloride and iodide, with the signal of the complex ($C2_{\mathbf{2}/CuTC}$) at $\delta = 125.2$ ppm ($\Delta\nu_{1/2} = 285$ Hz) accompanied by a further signal attributable to the free ligand **2**.

To investigate whether the dependence of the structures of the phosphoramidite copper complexes on the nature of the salt is similar for similarly active and selective ligands, the combinations described above for ligand **2** were repeated with ligand **1**. The respective ^{31}P NMR spectra with **1** are shown in Figure 3. Comparison of the spectra obtained with ligand **2** (Figure 2) with those obtained with ligand **1** reveals a very similar signal pattern, except that the ^{31}P chemical shift differences between C1 and C2 are much smaller for **1** than for **2**. The only significant difference is observed in the case of CuI, with both the ^{31}P and ^{1}H NMR spectra of the complexes in a 1:1 and 2:1 ratio showing identical patterns, albeit with a reduced intensity of the signal of the free ligand at the 1:1 ratio. This, together with the precipitate observed in the NMR tube at a 1:1 ratio, strongly suggests that the solubility of the C1 complex with CuI is further reduced below the detection limit[27] such that only C2 and the free ligand are detected. A second difference compared to ligand

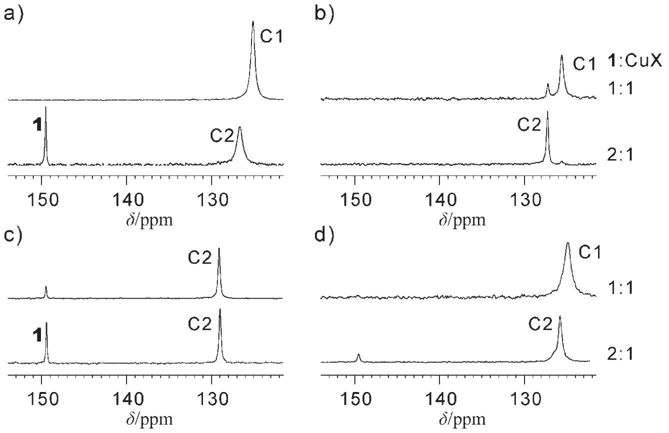


Figure 3. ^{31}P NMR spectra of complexes composed of **1** and a) CuCl, b) CuBr, c) CuI, and d) CuTC in $CDCl_3$ at 220 K.

2 is evident using CuTC, in which case significantly narrower linewidths are observed and at the 2:1 ratio the amount of free ligand is reduced (Figure 3d).

NMR diffusion measurements: To obtain additional information about the molecular sizes of the complexes C1 and C2 with different salts and ligands, ^1H NMR diffusion experiments were performed as recently described in detail elsewhere.[22] In this earlier study, severe ^1H NMR chemical shift overlap between the signals of the free ligand and C2 was resolved by exploiting the differential line broadening of the methine signal caused by a difference in internal dynamics. Possible exchange contributions were excluded on the basis of EXSY data. The viscosity-corrected diffusion coefficients of **1**, **2**, and the complexes C1 and C2 composed of different copper salts (CuCl, CuBr, CuI, and CuTC) and **1** or **2** in $CDCl_3$ at 220 K are listed in Table 1. An alternative method for simultaneously determining the diffusion coefficients of the free ligand **1** and C2 could be applied for the complex of **1** and CuI. In this case, two discrete sets of signals for the free ligand **1** and C2 were observed in the aromatic region for the first time (the ^1H,^{31}P HMBC spectrum at 220 K is shown in Figure S1 in the Supporting Information). The resulting diffusion coefficient of $2.26 \times 10^{-10}\,m^2s^{-1}$ for **1** is consistent with the value of $2.30 \times 10^{-10}\,m^2s^{-1}$ for a pure solution of **1** within the experimental error range of 2%. The diffusion coefficient of $1.57 \times 10^{-10}\,m^2s^{-1}$ for $C2_{\mathbf{1}/CuI}$ is similarly close to that of $C2_{\mathbf{1}/CuI}$ given in Table 1. This also confirms the previously stated result that exchange contributions between the complex and the free ligand do not affect the diffusion coefficients of the complexes C2 listed in Table 1.

In general, ligand **1** and its complexes show lower diffusion coefficients compared to those seen with **2**, as expected from the larger molecular size of **1**. Similarly to the results obtained for CuCl, the D values of C1 and C2 with the same ligand and the same copper salt differ by less than 5%, indicating similar hydrodynamic radii. Comparing the copper halides, the C2 diffusion values with CuCl and CuI are very similar, which is consistent with the strong similarity of their ^{31}P NMR spectra. With CuBr, the diffusion coefficients of the complexes are slightly reduced for both C1 and C2, indicating larger hydrodynamic radii compared to those with iodide or chloride. For the CuTC system, no general trend in the diffusion coefficients compared to those with the copper halides is observed. Complexes C1 and C2 with ligand **1** exhibit higher diffusion constants, but complex C2 with ligand **2** exhibits an average value.

Table 1. Diffusion coefficients D ($10^{-10}\,m^2s^{-1}$) of the free ligands and the complexes C1 and C2 composed of copper salts (CuCl, CuBr, CuI or CuTC) and ligands **1** or **2** (0.02 M) in $CDCl_3$ at 220 K.

	Free ligand	$C1_{CuCl}$	$C1_{CuBr}$	$C1_{CuI}$	$C1_{CuTC}$	$C2_{CuCl}$	$C2_{CuBr}$	$C2_{CuI}$	$C2_{CuTC}$
1	2.30	1.60	1.50	–	1.72	1.62	1.49	1.60	1.68
2	2.68	1.81	1.65	–[a]	–[b]	1.83	1.72	1.80	1.77

[a] Preparation as a single complex not possible. [b] Transversal relaxation too fast.

Volumes, molecular formulae, and related structures: Recently, we showed that the accuracy of the diffusion coefficients is sufficiently high to determine the number of ligands in a complex, but far too low to obtain the number of salt units attached.[22] The lacking information about the ratio between the ligand and the copper salt is obvious from Figure 2 and Figure 3 for all of the complexes, except those with CuI.[28] The very low solubilities of the pure copper salts in chloroform or dichloromethane, together with elemental analyses of the solutions, ensure that the ratios indicated in the figures truly reflect the actual ratios in solution. The experimentally determined volumes of C1 and C2, and the theoretically calculated volumes of all possible complex stoichiometries $[L_m(CuX)_n]$ with two to four ligands and ligand-to-copper salt ratios between 1:1 and 2:1, are given in Table 2. The theoretical values that fit the experimental re-

Table 2. Experimental volumes [Å^3] of C1 and C2, and calculated volumes [Å^3] according to the molecular formulae $L_m(CuX)_n$ composed of copper salts (Cu^IX; X = Cl, Br, I, TC) and ligands **1** or **2**. For each model complex, the ratio of ligand to copper salt is given in brackets; the theoretical values that fit the experimental results are highlighted in bold for C2 and in italics for C1.

Ligand/ CuX	C1	C2	$L_2Cu_2X_2$ (1:1)	L_2CuX (2:1)	$L_3Cu_3X_3$ (1:1)	$L_3Cu_2X_2$ (1.5:1)	L_3CuX (3:1)	$L_4Cu_2X_2$ (2:1)	$L_4Cu_4X_4$ (1:1)
1/CuCl	*2305*	**2228**	1595	1565	*2393*	**2363**	2333	3131	3190
1/CuBr	*2815*	**2810**	1605	1570	*2408*	**2373**	2338	**3141**	*3210*
1/CuI	–	**2436**	1620	1578	2430	**2388**	2346	3155	3240
1/CuTC	*1851*	**1974**	*1756*	**1646**	2634	**2524**	2414	3292	3512
2/CuCl	*1588*	**1525**	1018	989	*1528*	**1498**	1468	1977	2036
2/CuBr	*2018*	**1832**	1028	994	1543	1508	1473	**1987**	*2056*
2/CuI	–	**1610**	1043	1001	1564	**1522**	1481	2002	2086
2/CuTC	–	**1674**	1179	1069	1769	**1659**	1549	2138	3348

sults are highlighted for each ligand/copper salt combination (bold for C2, italics for C1), indicating the molecular formula for each complex in solution.

Typical structures corresponding to the molecular formulae in Table 2 are exemplified in the crystal structures and schematic drawings of the respective triphenylphosphine $\mathrm{Cu^I}$ halide complexes in Figure 4. The crystal structures of triphenylphosphine $\mathrm{Cu^I}$ halide complexes were chosen to be representative of a well-known and thoroughly investigated system composed of monodentate trivalent phosphorus ligands and $\mathrm{Cu^I}$ salts, thus representing a wealth of different structures that, in principle, are also possible for phosphoramidite copper complexes. The structures shown in Figure 4d,[29] e,[30] and g[31] are indeed very similar to the known crystal structures of the phosphoramidite copper complexes discussed in the introduction. For the 1:1 ligand-to-copper salt ratios, the situation is more complicated. It is well known that a combination of a copper(I) halide and a monodentate ligand can produce a wide array of oligomeric structure types through halide bridging.[31–36] Typical, well-known examples are square (rhomboid) dimeric,[32] cubane tetrameric,[32] and "stair step" oligomeric[33] structures, as shown in Figure 4a, b, and c. With potentially bidentate carboxylate derivatives as copper salts, monomeric copper(I) centers with a distorted tetrahedral geometry are often observed.[37]

For $\mathrm{C2}_{\mathbf{1}/\mathrm{CuCl}}$, $\mathrm{C2}_{\mathbf{2}/\mathrm{CuCl}}$, $\mathrm{C2}_{\mathbf{1}/\mathrm{CuI}}$, $\mathrm{C2}_{\mathbf{2}/\mathrm{CuI}}$, and $\mathrm{C2}_{\mathbf{2}/\mathrm{CuTC}}$, the experimental volumes conform very well to the molecular formula $\mathrm{L_3Cu_2X_2}$, indicating a dimeric complex with a mixed tetrahedral/trigonal-planar geometry (Figure 4d). For $\mathrm{C2}_{\mathbf{1}/\mathrm{CuBr}}$, the correlation between the experimental and theoretical volumes is at first glance ambiguous, falling between $\mathrm{L_4Cu_2X_2}$ and $\mathrm{L_3Cu_2X_2}$. However, temperature-dependent measurements show that at lower temperatures the experimental value fits the formula $\mathrm{L_4Cu_2X_2}$, whereas at higher temperatures it fits $\mathrm{L_3Cu_2X_2}$, indicating an average diffusion coefficient at 220 K. For $\mathrm{C2}_{\mathbf{2}/\mathrm{CuBr}}$, the trend towards higher volumes is even stronger, with the experimental value close to an $\mathrm{L_4Cu_2X_2}$ complex being consistent with the absence of a free ligand peak in its ^{31}P NMR spectrum. This shows that with bromide as the anion, a dimeric structure with two tetrahedrally coordinated $\mathrm{Cu^I}$ centers predominates in solution, as is also shown by the crystal structure.[16,19] However, the trend in the experimental volumes towards three ligands per complex indicates that one of the ligands is rather labile and, therefore, a free coordination site, which is necessary for ligand acceleration, is easily obtained. For $\mathrm{C2}_{\mathbf{1}/\mathrm{CuTC}}$, the aggregation trend is reversed, with the experimental value being between $\mathrm{L_3Cu_2X_2}$ and $\mathrm{L_2CuX}$ with a trend towards the latter. Here, the $\mathrm{TC^-}$ anion seems to be partially coordinated as a bidentate ligand, as shown in Figure 4f,[38] favoring a lower degree of aggregation. Interestingly, parallel aggregation trends with higher numbers of ligands attached are observed for the complexes C1 with the smaller ligand **2**. The experimental volumes of $\mathrm{C1}_{\mathbf{1}/\mathrm{CuCl}}$ and $\mathrm{C1}_{\mathbf{2}/\mathrm{CuCl}}$ conform to $\mathrm{L_3Cu_3X_3}$; $\mathrm{C1}_{\mathbf{1}/\mathrm{CuBr}}$ shows a value intermediate between $\mathrm{L_3Cu_3X_3}$ and $\mathrm{L_4Cu_4X_4}$; $\mathrm{C1}_{\mathbf{2}/\mathrm{CuBr}}$ exhibits a higher volume close to $\mathrm{L_4Cu_4X_4}$, and $\mathrm{C1}_{\mathbf{1}/\mathrm{CuTC}}$ shows an inverse aggregation trend with a volume close to $\mathrm{L_2Cu_2X_2}$. As several structures are known, it is not possible to assign specific structures to the molecular formulae $\mathrm{L_3Cu_3X_3}$ and $\mathrm{L_4Cu_4X_4}$. For $\mathrm{L_2Cu_2X_2}$ with $\mathrm{TC^-}$ as the anion, a dimeric structure with distorted tetrahedral $\mathrm{Cu^I}$ centers can be assumed on the basis of known monomeric crystal structures.[37–39]

Precatalytic structures and known reactivities/selectivities in conjugate addition: Alexakis and co-workers recently published a table detailing salt and solvent dependences in copper-catalyzed asymmetric conjugate addition reactions of diethylzinc to cyclohexen-2-one using ligand **2**.[4] In their study, yields and *ee* values higher than 90 % were found with CuTC in nearly all of the solvents tested. With CuCl, reduced *ee* values of about 14 % were obtained. Interestingly, with CuI, both the yields and the *ee* values fell to disap-

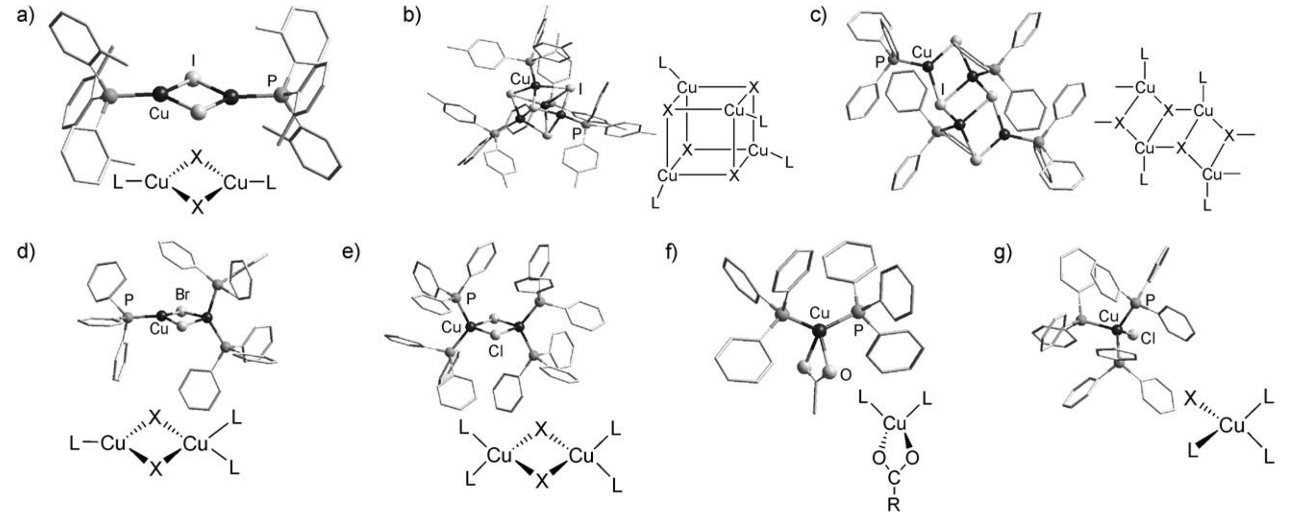


Figure 4. Typical crystal structures of several triphenylphosphine $\mathrm{Cu^I}$ halide complexes and one triphenylphosphine $\mathrm{Cu^I}$ carboxylate complex and corresponding schemes (L = ligand; X = halide).

pointingly low values. No results relating to CuBr in CH_2Cl_2 were reported, but the values in the other solvents used were quite similar to those for CuCl. To the best of our knowledge, no data for ligand **1** in CH_2Cl_2 or $CHCl_3$ have hitherto been published.

The precatalytic structures of ligand **2** with both CuTC and CuCl show the new structural motif of a dimeric complex with mixed trigonal/tetrahedral stereochemistry at the Cu^I centers, consistent with the excellent reactivity and selectivity values. With CuBr, a trend towards four ligands in the dimeric complex is observed. However, the detected lability of one of the ligands readily accounts for the fact that values comparable to those seen with CuCl are obtained. The low yield and low selectivity seen with CuI are somewhat surprising. The structure of its precatalytic complex is clearly identical to that seen with CuCl. From these results, it is evident that Cl^- and I^- produce different catalytic complexes incorporating Zn starting from identical precatalytic copper complexes. The importance of the interplay between zinc and copper in the coordination sphere of the ligand has been reported.[40] Interestingly, Feringa and co-workers found a very similar trend for CuI during their investigation of conjugate addition reactions of Grignard reagents.[16] In their study, the precatalytic copper(I) diphosphine complexes with iodide, bromide, and chloride exhibited almost identical electrochemistry, but after addition of the Grignard reagent significant structural differences were found, especially for the copper iodide complexes.

Influence of the ligand: In addition to the highly enantioselective ligands **1** and **2**, ligand **3** was also selected for study, which has a significantly smaller amine moiety (NMe_2) and produces only modest enantioselectivities and yields. The choice of ligand **3** offers two advantages; first, the decisive influence of the size of the amine moiety on the catalytic reaction can be investigated in terms of aggregation and structural differences and, second, a direct comparison of the structure in solution with that in the solid state is possible, because its crystal structure[18] ($\mathbf{3}_3$•CuI, see Figure 1b) is the only one hitherto reported for a copper salt and a ligand of the Feringa type.

The ^{31}P NMR spectra of ligand **3** with CuCl, CuBr, CuI, and CuTC in $CDCl_3$ are presented in Figure 5. In addition to the usual ratios of 1:1 and 2:1, spectra with a ratio of 3:1 were also measured to enable a direct comparison with the crystal structure. In none of the spectra is a signal of the free ligand detected, and single complex species ($C3_{3/CuX}$) are observed for all of the copper halides at a 3:1 ratio. These facts directly indicate that the smaller size of ligand **3** enables a higher coordination number for its copper complexes. Comparing the spectra of the halides at the 1:1 and 2:1 ratios, it is obvious that the trend towards a 1:1 ratio in the complexes decreases on going from CuCl to CuI, and that CuI shows the highest preference for a complex with a 3:1 ratio. Using CuTC in combination with ligand **3**, the ^{31}P NMR spectra differ significantly. Only one signal is observed at a 1:1 or a 2:1 ratio. Upon addition of more ligand up to three equivalents, a continuous broad signal appears, but $C2_{\mathbf{3}/CuTC}$ remains as the main species.

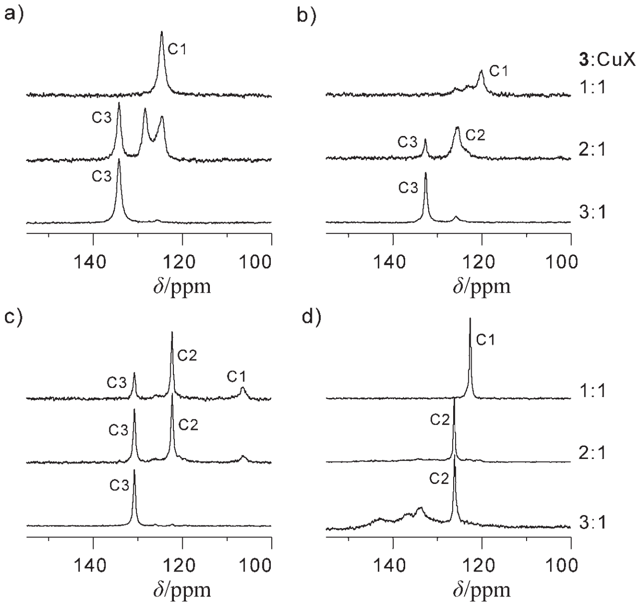


Figure 5. ^{31}P NMR spectra of complexes composed of **3** and a) CuCl, b) CuBr, c) CuI, and d) CuTC in $CDCl_3$ at 220 K.

Table 3. Diffusion coefficients D ($10^{-10}\,m^2s^{-1}$) and corresponding experimental volumes V_E [Å^3] of the complexes of **3** with CuCl, CuBr, CuI, and CuTC (0.02 M in $CDCl_3$ at 220 K). In addition, the molecular formulae derived from the ligand-to-copper salt ratio are given, where the subscripts denote the requisite number of multiples to fit the experimental volumes.

	$C1_{\mathbf{3}/CuCl}$	$C1_{\mathbf{3}/CuTc}$	$C2_{\mathbf{3}/CuTC}$	$C3_{\mathbf{3}/CuCl}$	$C3_{\mathbf{3}/CuBr}$	$C3_{\mathbf{3}/CuI}$
D	1.32	1.64	1.70	1.57	1.62	1.56
V_E	4041	2131	1889	2436	2180	2468
mol. formula	$(\mathbf{3}\cdot CuCl)_{10.4}$	$(\mathbf{3}\cdot CuTC)_{4.5}$	$(\mathbf{3}_2\cdot CuTC)_{2.3}$	$(\mathbf{3}_3\cdot CuCl)_{2.2}$	$(\mathbf{3}_3\cdot CuBr)_{2.0}$	$(\mathbf{3}_3\cdot CuI)_{2.2}$

In systems with more than one copper complex, chemical-exchange processes were observed in the EXSY spectra even at 220 K. Therefore, the measurement of individual diffusion coefficients was not possible for these copper complexes. Interpretable ^1H NMR diffusion experiments could only be obtained for systems with one complex signal. The respective viscosity-corrected diffusion coefficients, the corresponding experimental volumes, and the molecular formulae derived from the known ligand-to-CuX ratios for the complexes $C1_{\mathbf{3}/CuCl}$, $C3_{\mathbf{3}/CuCl}$, $C3_{\mathbf{3}/CuBr}$, $C3_{\mathbf{3}/CuI}$, $C1_{\mathbf{3}/CuTC}$, and $C2_{\mathbf{3}/CuTC}$ in $CDCl_3$ at 220 K are listed in Table 3.

The diffusion coefficient of the free ligand **3**, which amounts to $2.96\times10^{-10}\,m^2s^{-1}$ at 220 K in $CDCl_3$, is 29% larger than that of ligand **1**. In contrast, the diffusion coefficients of the complexes with **3** are similar to or even smaller than those of the complexes with **1** (see Table 3 and Table 1), indicating larger hydrodynamic radii for the complexes with the smaller ligand **3**. Analyzing the molecular formulae of the complexes $\mathrm{C1}_{\mathbf{3}/\mathrm{CuX}}$ and $\mathrm{C2}_{\mathbf{3}/\mathrm{CuTC}}$ with regard to their multiples to fit the experimental volumes, the complexes with lower coordination numbers show a tendency for higher aggregation. For $\mathrm{C1}_{\mathbf{3}/\mathrm{CuCl}}$, an average complex of $(\mathbf{3}\cdot\mathrm{CuCl})_{10.4}$ is found, indicating a degree of aggregation more than three times higher than for $\mathrm{C1}_{\mathbf{1}/\mathrm{CuCl}}$ or $\mathrm{C1}_{\mathbf{2}/\mathrm{CuCl}}$. Also, the degrees of aggregation of $\mathrm{C1}_{\mathbf{3}/\mathrm{CuTC}}$ and $\mathrm{C2}_{\mathbf{3}/\mathrm{CuTC}}$, amounting to $(\mathbf{3}\cdot\mathrm{CuTC})_{4.5}$ and $(\mathbf{3}_2\cdot\mathrm{CuTC})_{2.3}$, are more than two times higher than those of $\mathrm{C1}_{\mathbf{1}/\mathrm{CuTC}}$ and $\mathrm{C2}_{\mathbf{1}/\mathrm{CuTC}}$. Interestingly, the complexes with three ligands attached to each copper ($\mathrm{C3}_{\mathbf{3}/\mathrm{CuCl}}$, $\mathrm{C3}_{\mathbf{3}/\mathrm{CuBr}}$, and $\mathrm{C3}_{\mathbf{3}/\mathrm{CuI}}$), with molecular formulae of $(\mathbf{3}_3\cdot\mathrm{CuCl})_{2.0-2.2}$, also form dimeric complexes as opposed to monomeric ones, as might be expected from their crystal structures.

These experimental results from solution studies impressively show that too small an amine moiety on the chiral ligand allows higher coordination numbers and higher aggregation levels of the precatalytic copper complexes, which produce lower *ee* values in conjugate addition reactions with such ligands.[5] In contrast to previous results concerning tetranuclear Cu^{I} catalysts based on monodentate thiol analogues of TADDOL,[20] which showed similar structures in solution and in the solid state, a twofold higher aggregation level was observed in solution as compared to the known crystal structure for the copper complex with ligand **3**. A similar trend towards higher aggregation levels in solution compared to the situation in the solid state has also been found for organocuprates by our group in the past few years.[23–26]

Influence of the solvent: The choice of solvent plays a crucial role in the success of a catalytic reaction. A solvent study showed that several solvents, such as toluene, CH_2Cl_2, and THF, might be used in the investigated reaction.[4] Under the experimental conditions described for the synthetic procedures, we studied the precatalytic systems consisting of **1**, **2**, or **3** and CuCl (ligand-to-CuCl ratio 2:1) in $[D_8]$toluene, $[D_8]$THF, CD_2Cl_2, and $CDCl_3$ by means of ^{31}P probe resonance.

The resulting ^{31}P NMR spectra of the three ligands with CuCl in the different solvents are presented in Figure 6. With ligand **2** in CD_2Cl_2 and $CDCl_3$, a signal attributable to only one complex species (C2) is observed, beside the signal of the free ligand. However, in $[D_8]$toluene and $[D_8]$THF, in addition to the signal of C2, the ^{31}P NMR spectra show further signals indicating the coexistence of other copper complexes.[22] With ligand **1**, a meaningful interpretation of the spectra in terms of the relative amounts of the copper complexes is not possible due to the broad linewidths of the phosphorus signals together with the smaller chemical shift differences between the different complex species (see above). Only for the less active ligand **3** are three closely linked species observed in each of the solvents, but the amounts of the three species are seen to vary depending on the solvent.

Thus, the strong influence of the solvent on the types and relative amounts of copper complexes existing in solution can be monitored by their ^{31}P NMR spectra. To date, comparative reactivity and selectivity data in different solvents have only been reported for complexes with ligand **2**.[4] With CuCl, the reactivities in toluene, Et_2O, and CH_2Cl_2 are identical, and the *ee* values are quite similar, falling in the range 76–82 %. Considering these closely similar reactivity and selectivity values as opposed to the widely differing ^{31}P NMR spectra in Figure 6a (the ^{31}P NMR spectra of the complex of **2** and CuCl in $[D_8]$THF and $[D_{10}]Et_2O$ are identical; data not shown), it is most likely that the investigated copper complexes form a highly selective, ligand-accelerated catalyst with several other less reactive complexes coexisting in solution, as is typical for copper.[41]

ESI mass spectra: Electrospray ionization-mass spectrometry (ESI-MS) is a soft and direct method for transferring ions pre-existing in solutions into the gas phase.[42] The energy imparted to the ions is quite low compared to that in conventional spectrometric ionization techniques. However, under the anaerobic conditions in the capillary and with fewer stabilizing solvent molecules, this energy is often still high enough to induce the loss of a ligand or of a metal ion, or the fragmentation of the molecular ion.[42] Therefore, for every new system, the question arises as to whether the ions detected by the ESI-MS technique really reflect the complexes in solution. If a correlation is possible, ESI-MS is a very fast, sensitive, and inexpensive tool.

To investigate whether such a correlation is possible for phosphoramidite copper complexes, we chose four representative samples with different aggregation structures in solution: a 1:1 mixture of **2**/CuCl, a 2:1 mixture of **2**/CuCl, a 2:1 mixture of **2**/CuBr, and a 3:1 mixture of **3**/CuI.

The ESI mass spectra of the four mixtures in pure CH_2Cl_2 are shown in Figure 7. Under the applied experimental conditions, none of the spectra feature a detectable molecular ion peak of the whole aggregate existing in solution. How-

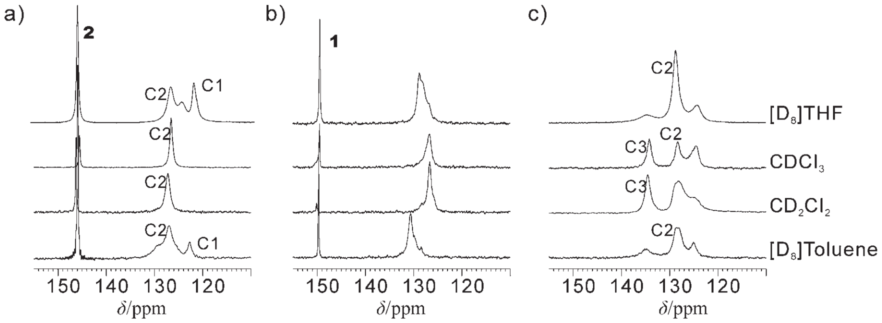


Figure 6. ^{31}P NMR spectra of the complexes composed of CuCl and ligands a) **2**, b) **1**, and c) **3** in a 1:2 ratio in different solvents at 220 K.

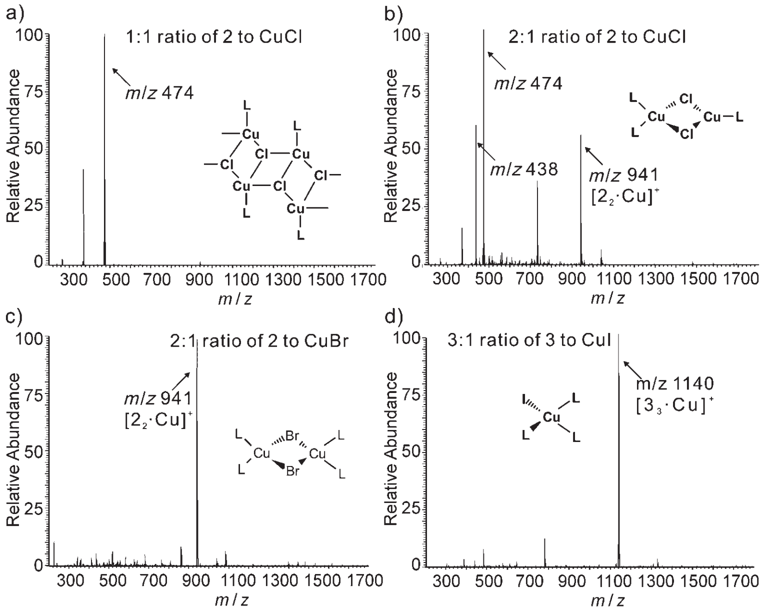


Figure 7. ESI mass spectra of a) 1:1 and b) 2:1 mixtures of **2** and CuCl; c) a 2:1 mixture of **2** and CuBr; d) a 3:1 mixture of **3** and CuI in CH_2Cl_2, recorded on a Thermo Quest Finnigan TSQ 7000 spectrometer. The corresponding complexes in solution are shown schematically.

ever, the composition of the base peaks correlates significantly with the situation in solution. For a 3:1 mixture of **3**/CuI in CH_2Cl_2 solution, existing as a $(\mathbf{3}_3\cdot CuI)_2$ complex, the mass spectrum shows one strong fragment ion peak at *m*/*z* 1140.5 ($[\mathbf{3}_3\cdot Cu]^+$) (Figure 7d), which accurately reflects the number of ligands attached to copper. A very similar result is obtained for the 2:1 mixture of **2**/CuBr, which exists as the $(\mathbf{2}_2\cdot CuBr)_2$ complex in solution. Only one intense fragment peak is detected at *m*/*z* 941, corresponding to $[\mathbf{2}_2\cdot Cu]^+$. The situation is slightly different for the 2:1 mixture of **2**/CuCl, representing the precatalytic complex $\mathbf{2}_2\cdot Cu(\mu\text{-}Cl)_2Cu\cdot\mathbf{2}$ plus free ligand **2** in solution. Peaks originating from the ligand (*m*/*z* 438 and *m*/*z* 474) and the fragment with two ligands attached $[\mathbf{2}_2\cdot Cu]^+$ (*m*/*z* 941) are observed, but no peak for $[\mathbf{2}\cdot Cu]^+$. This indicates a lower stability of $[\mathbf{2}\cdot Cu]^+$ as compared to $[\mathbf{2}_2\cdot Cu]^+$ under the applied experimental conditions. This interpretation is supported by the spectrum of the 1:1 mixture of **2**/CuCl, which reveals the formation of complexes of the composition $(\mathbf{2}\cdot CuCl)_n$ in solution. The expected fragment ion peak of $[\mathbf{2}\cdot Cu]^+$ is again absent and only the two peaks originating from the ligand (*m*/*z* 438 and *m*/*z* 474) appear in the spectrum (Figure 7a). Using acetonitrile as an additive, it is possible to effectively stabilize the **2**·Cu species and, as a result, the adduct of $[\mathbf{2}\cdot Cu\cdot MeCN]^+$ is detected as a strong fragment ion at *m*/*z* 543 for $(\mathbf{2}\cdot CuCl)_n$ (see Figure S2 in the Supporting Information). The addition of acetonitrile has such a strong stabilizing effect through the formation of the ion $[\mathbf{2}\cdot Cu\cdot MeCN]^+$ that the ESI mass spectra of $\mathbf{2}_2\cdot Cu(\mu\text{-}Cl)_2Cu\cdot\mathbf{2}$ and $(\mathbf{2}_2\cdot CuBr)_2$ look very similar. In both spectra, the two main peaks are attributable to $[\mathbf{2}\cdot Cu\cdot MeCN]^+$ and $[\mathbf{2}_2\cdot Cu]^+$. Only a slightly higher relative abundance of $[\mathbf{2}_2\cdot Cu]^+$ in the case of $(\mathbf{2}_2\cdot CuBr)_2$ correlates with the different structures in solution. For $(\mathbf{3}_3\cdot CuI)_2$, the mass spectrum measured in the presence of acetonitrile again seems to be unambiguous, showing the expected fragment ion $[\mathbf{3}_3\cdot Cu]^+$.

The discussed results indicate that with ESI-MS it is not possible to obtain molecular ion peaks of the phosphoramidite copper complexes existing in solution under the applied experimental conditions. However, for structural fragments with more than one ligand attached to copper, the ESI mass spectra obtained from solutions in pure CH_2Cl_2 exactly reproduce the number of ligands attached to copper as were proposed from the NMR investigation in solution. After the addition of small amounts of acetonitrile, a copper fragment with the maximum number of ligands identified in solution is detected in each of the spectra. This is even more surprising if one considers the different concentrations and temperatures applied for the two methods and the ability of acetonitrile to change the structures of copper complexes. The correlation between solution structure and ESI mass spectrum is valid for both ligands and all three halides investigated. Therefore, it is highly probable that ESI-MS may also be used as a fast analytical method to provide information about the maximum number of ligands attached to copper for other phosphoramidite copper complexes with slightly modified ligands as well.

Conclusion

The presented investigation of the ground-state structures of precatalytic copper complexes using four different Cu^I salts and two highly stereoselective phosphoramidite ligands in solution has shown that the proposed binuclear complex with mixed trigonal/tetrahedral copper stereochemistry is not an exception existing only for complexes with CuCl, but a basic structural motif for precatalysts with highly stereoselective ligands. Only with CuBr is a tendency observed for the formation of dimeric copper complexes with four ligands attached, as known from their crystal structures. However, diffusion measurements show a high lability of one of the ligands, which accounts for the fact that the reactivities and selectivities are similar to those seen with CuCl. Ligands with smaller amine moieties allow higher coordination numbers and higher aggregation levels of the precatalytic complexes, leading to lower *ee* values in conjugate addition reactions. Similarly to organocuprates and at variance with results relating to Cu^I catalysts based on thiol analogues of TADDOL, a higher degree of aggregation was measured for copper complexes with ligand **3** as compared with the known crystal structures. Studies concerning the influence of the solvent on the amounts and ratios of different precatalytic species composed of CuCl and ligand **2** show that the ligand acceleration of the active precatalytic species is strong enough to produce high *ee* values even with several other precatalytic species coexisting in solution. The ESI mass spectra of several precatalytic copper halide complexes show a striking correlation with the structures observed in solution. Thus, it is highly probable that ESI-MS represents a fast analytical method to provide information about the maximum number of ligands attached to copper for other phosphoramidite copper complexes with slightly modified ligands as well.

Experimental Section

Sample preparation: All manipulations were carried out under an argon atmosphere in heat-gun-dried Schlenk flasks, using freshly distilled solvents throughout. $[D_8]$Toluene and $[D_8]$THF were distilled from sodium/potassium alloy, CD_2Cl_2 and $CDCl_3$ from CaH_2. The ligands **1** and **2** were prepared according to reported protocols.[43] The samples were prepared by adding solvent to a mixture of free ligand and copper salt. The solution was stirred at ambient temperature for 1 h, and then the solvent was evaporated until a solid remained. This was redissolved in the corresponding deuterated solvent and the resulting solution was transferred into an NMR tube. The samples were kept at 195 K. Different stabilities of the copper complexes were observed. Under argon, copper halide complexes remained stable without change for more than three months, whereas CuTC complexes degraded within two days.

ESI-MS measurements: All samples for ESI-MS measurements were prepared in freshly distilled CH_2Cl_2 at a concentration of 10^{-3} M. PI-ESI mass spectra were recorded on a Thermo Quest TSQ 7000 using samples in pure CH_2Cl_2 and after the addition of acetonitrile (MeCN). To minimize interferences from the mass spectrometer, a low tube lens at 44.2 V was applied for all samples. All samples were freshly prepared for the ESI measurements and measured directly after each other under identical conditions to enable direct comparison. Each complex ion was characterized by its *m*/*z* value and the characteristic isotopic distribution pattern.

NMR data collection and processing: NMR spectra were recorded on a Bruker DRX 500 or DRX 600 spectrometer equipped with a 5 mm broadband triple-resonance Z-gradient probe (maximum gradient strength 53.5 Gauss cm^{-1}). All chemical shifts were referenced to TMS; for the ^{31}P chemical shifts the corresponding Ξ value was applied. The ^1H chemical shifts of $C2_{1/CuI}$ were identified with the aid of a $^1H,^{31}P$ HMBC spectrum, which was obtained with 4 K data points for F_2 and 128 data points for F_1 increments. The number of scans was 32, and a relaxation delay of 5 s was used. For 1D ^{31}P NMR experiments, relaxation delays of 3 s, acquisition times of 0.3 s, spectral widths of 95–155 ppm, TD = 1–4 K data points, and 32–256 scans were used. All diffusion measurements were performed with a convection-suppressing pulse sequence[44] in pseudo-2D mode and processed with the Bruker software package t1/t2. For each experiment, 16 dummy scans and an accumulation of 16–128 scans were used, with a relaxation delay of 5 s and a diffusion delay of 40–60 ms depending on the concentration and temperature. Sinusoidal shapes and pulse lengths in the range 3–3.5 ms were used for the gradients, and a linear gradient ramp with 16 increments between 5% and 95% was applied. The diffusion coefficients were calculated with the Bruker software package t1/t2. The diffusion experiments were repeated two or three times, sometimes with different samples, resulting in an error range of ±5% for the diffusion coefficients of all of the samples, except in the case of the CuTC system. Due to the broad signal of the CuTC system at 220 K, the largest number of scans of 128 was used, and the estimated error range extends to 10%. All of the various temperatures applied were checked with a Bruker standard methanol sample and temperature stability was controlled by a BVT 3000 unit.

Calculation of the reported volumes: In all of the diffusion measurements, a drop of TMS was added as an internal reference for viscosity corrections.[45] Comparing the diffusion coefficients of TMS measured in 1) TMS + $CDCl_3$ at 220 K (η_{220K}) and 2) TMS + complexes + solvent (η_{comp}) at the experiment temperature, viscosity correction factors η_{comp}/η_{220K} for the complexes were determined. The viscosity-corrected diffusion coefficients listed in this paper were calculated according to: $D = D_{obs}(\eta_{comp}/\eta_{220K})$. The absolute viscosity values of $CDCl_3$ and CD_2Cl_2 at 220 K were determined experimentally using samples of TMS + solvent at 220 K. The viscosities were determined by using the diffusion coefficient and volume of TMS, as calculated from hard-sphere increments.[46]

The hydrodynamic volumes of C1 and C2 given in Table 2 and Table 3 were calculated from the experimentally determined diffusion coefficients using the Stokes–Einstein equation without shape correction: $r_H = kT/(6\pi\eta D)$.

The volumes of the model complexes were calculated according to $V = V_{ligand}+V_{CuX}$. The hydrodynamic volumes of the three ligands were determined experimentally by diffusion experiments on the free ligands. These volumes were found to be independent of concentration and temperature down to 230 K. For the copper salts, hard-sphere volume increments were used,[46] because experimental values are not accessible.

The experimental error of the diffusion coefficient estimated from repeated measurements on the same sample was less than 1%; even a complete change of the university (new laboratory, new sample, and new spectrometer) led only to an experimental error of 2%. For a conservative estimate of the error, a systematic error of 3% was also included, referring to possible deviations arising from the calculations of the volumes using hard-sphere increments and neglecting form factors. The systems incorporating $C2_{1/CuTC}$, $C2_{2/CuTC}$, or $C1_{1/CuTC}$ were subject to a greater margin of error, up to 10%, because of the broad NMR signals observed at 220 K.

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