# Elusive Transmetalation Intermediate in Copper-Catalyzed Conjugate Additions: Direct NMR Detection of an Ethyl Group Attached to a Binuclear Phosphoramidite Copper Complex

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Ⓢ Supporting Information

ABSTRACT: Copper-catalyzed asymmetric conjugate addition reactions are a very powerful and widely applied method for enantioselective carbon−carbon bond formation. However, structural and mechanistic insight into these famous reactions has been very limited so far. In this article, the first direct experimental detection of transmetalation intermediates in copper-catalyzed reactions is presented. Special combinations of $^1H, ^{31}P$ HMBC spectra allow for the identification of complexes with chemical bonds between the alkyl groups and the copper complexes. For the structural characterization of these transmetalation intermediates, a special approach is applied, in which samples using enantiopure ligands are compared with samples using enantiomeric mixtures of ligands. It is experimentally proven, for the first time, that the dimeric copper complex structure is retained upon transmetalation, providing an intermediate with mixed trigonal/tetrahedral coordination on the copper atoms. In addition, monomeric intermediates with one ligand, but no intermediates with two ligands, are detected. These experimental results, in combination with the well-known optimal ligand-to-copper ratio of 2:1 in synthetic applications, allow us to propose that a binuclear transmetalation intermediate is the reactive species in copper-catalyzed asymmetric conjugate addition reactions. This first direct experimental insight into the structure of the transmetalation intermediate is expected to support the mechanistic and theoretical understanding of this important class of reactions and to enable their further synthetic development. In addition, the special NMR approach presented here for the identification and characterization of intermediates below the detection limit of ^1H NMR spectra can be applied also to other classes of catalyses.
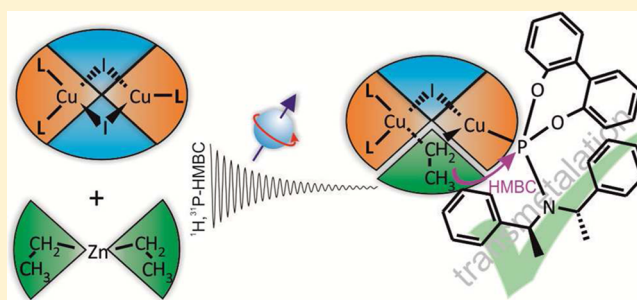
■ INTRODUCTION

The copper-catalyzed asymmetric conjugate addition (ACA) reaction is one of the most powerful methods for enantioselective carbon−carbon bond formation in organic synthesis (Scheme 1), which often combines excellent regio- and

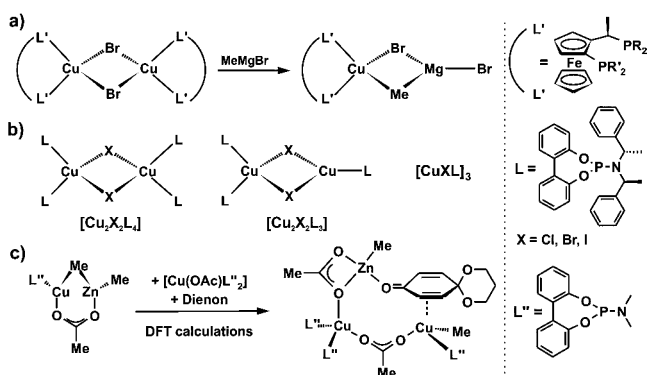**Scheme 1. General Reaction Scheme for ACA Reactions**
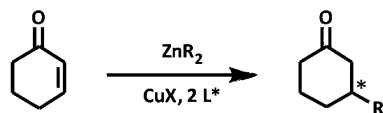
stereoselectivities, high compatibility with many functional groups, and low cost of the copper salts (for recent reviews, see refs 1−4). In this active research area, recent efforts considerably enlarged the scope of substrates and nucleophiles, allowing numerous syntheses of complex chiral organic compounds, including, e.g., biologically active and natural compounds.[1−7] However, despite the great synthetic success of the ACA reaction, structural and mechanistic studies focused on the copper complexes and their reaction intermediates are very rare. Therefore, more structural information about the

reaction intermediates and the enantiodiscriminating steps were claimed to be an essential prerequisite for the further development of this important class of reactions.[1,4,8]

To our knowledge, the only in-depth experimental study of transmetalation intermediates in copper-mediated ACA reactions so far was done by Feringa et al. using a combination of copper complexes with chiral bidentate ferrocenyl-based diphosphine ligands and Grignard reagents.[9] In that brilliant study, a binuclear, halide-bridged diphosphine copper complex was reported as a precatalyst e.g., on the basis of ^{31}P NMR spectroscopic, electrochemical, and kinetic investigations (Scheme 2a). After performing several sophisticated indirect experimental studies, Feringa reasoned that the dimeric copper precatalyst breaks up via transmetalation with the Grignard reagent and forms a bimetallic complex, which is mononuclear in copper (Scheme 2a).[9] This mixed metallic composition of the complex proposed by Feringa agrees perfectly with the core elements of the famous intermetallic Knochel cuprates, e.g., $FGRCu(CN)ZnI$.[10]

Scheme 2. Proposed Structures of Precatalysts and Transmetalation Intermediates[a]

[a](a) Monomerization and formation of a bimetallic transmetalation complex upon addition of MeMgBr.[9] (b) Interconversion/coexistence of phosphoramidite copper complexes $[Cu_2X_2L_4]$, $[Cu_2X_2L_3]$, and $[CuXL]_3$ with $[Cu_2X_2L_3]$ as the proposed precatalyst of the ACA reaction.[11] (c) Monomeric in Cu, but bimetallic transmetalation intermediate and a π-complex, which essentially agrees with $[Cu_2X_2L_3]$ calculated theoretically.[16]

In our NMR studies of copper complexes with monodentate phosphoramidite ligands, similar binuclear copper complexes were found to be the basic structural motif of the thermodynamic ground state of precatalysts with highly stereoselective ligands.[11−13] However, in solution, a binuclear copper complex with mixed trigonal/tetrahedral stereochemistry (see $[Cu_2X_2L_3]$ in Scheme 2b) was identified as the main species. At temperatures below 200 K, self-aggregation of the phosphoramidite ligands starts,[14] and intermolecular interactions between free ligand and $[Cu_2X_2L_3]$ induce the formation of the binuclear complex $[Cu_2X_2L_4]$, corroborating the known crystal structures.[9,15] Recently, a density functional theory (DFT) study of the reaction mechanism of ACA reactions with monodentate phosphoramidite ligands corroborated both studies.[16] Monomeric zinc cuprates were identified as the lowest energy transmetalation complexes accessible from simplified phosphoramidite ligands, Cu(OAc) and ZnMe$_2$ (Scheme 2c, left).[17] However, starting from this monomeric zinc cuprate, reasonable energetic pathways were accessible only for π-complexes derived from the binuclear structure with mixed trigonal/tetrahedral stereochemistry (Scheme 2c, right).[16]

Transmetalation of an organic moiety from ZnR$_2$, RMgX, or AlR$_3$ reagents is a commonly accepted step in the mechanistic schemes of ACA reactions.[1,3,4,8] However, to the best of our knowledge, direct experimental detection of a transmetalated intermediate has been elusive so far, and no information about the structure or even the stoichiometry of transmetalation complexes with ZnR$_2$ or AlR$_3$ is available.[1,4]

Therefore, we present in this paper an NMR spectroscopic investigation of the transmetalation reaction between phosphoramidite copper precatalyst $[Cu_2X_2L_3]$ and diethylzinc. For the first time, direct experimental evidence of a transmetalation intermediate in the ACA reaction is presented. In addition, for the first time, a transmetalation complex that is binuclear in copper is detected, which essentially retains the structure of the precatalytic complex $[Cu_2X_2L_3]$. Apart from this binuclear transmetalation complex, also several mononuclear copper transmetalation complexes were detected.

■ RESULTS AND DISCUSSION

For the NMR spectroscopic investigation of transmetalated phosphoramidite copper complexes, a 2:1 ratio of the highly enantioselective phosphoramidite ligand **L** to CuI in CD$_2$Cl$_2$ was chosen (see Scheme 3). Previous investigations[11] and low-

Scheme 3. Proposed Transmetalation Step of ZnEt$_2$ to $[Cu_2X_2L_3]$[a]
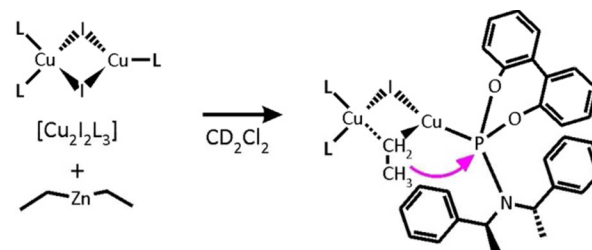
[a]In the case in which an ethyl group and a phosphoramidite ligand are both bound to one copper atom, a ^{1}H,^{31}P HMBC cross peak between those moieties (see purple arrow) should indicate a transmetalation intermediate.[26]

temperature studies[12] showed that this model system provides the best ^{31}P NMR chemical shift dispersion at 180 K and the broadest temperature range for the exclusive existence of $[Cu_2X_2L_3]$. Furthermore, in CD$_2$Cl$_2$, narrow line widths were observed for the complex species.[13] From a variety of organometallic reagents, ZnEt$_2$ as well as ZnMe$_2$ and ZnPh$_2$ were selected to cover a wide range of transmetalation reagents. ZnEt$_2$ is broadly used in synthetic applications, providing high yields and enantioselectivities.[1] The methyl groups in ZnMe$_2$ should stabilize the transmetalation intermediate, due to their lower reactivity,[18,19] and phenyl groups are assumed to be more readily transferred than alkyl groups.[18,20−23] However, for ZnMe$_2$ and ZnPh$_2$, only non-specific interactions with the copper complexes were detected (see the Supporting Information (SI)). Therefore, in the following, only investigations with ZnEt$_2$ are discussed.

In synthetic applications, a high excess of ZnEt$_2$ with regard to the copper complex is applied (60−70 equiv).[24] In order to increase the signal-to-noise ratio (S/N) and to enable the detection of upstream intermediates, here a reduced excess of ZnEt$_2$ is used (4−20 equiv compared to $[Cu_2X_2L_3]$). With commercially available solutions of ZnEt$_2$ in toluene, the spectral quality was too bad to detect any transmetalation intermediates. Therefore, neat ZnEt$_2$ in CD$_2$Cl$_2$ was used (for spectra and details, see the SI). Investigations in the temperature range of 170−250 K showed that both the highest signal intensities and the highest number of intermediate species were detected at 170 and 180 K. Therefore, in the following, the only low-temperature spectra (170−180 K) are discussed.

After addition of ZnEt$_2$ to the copper complex, neither in the ^{1}H nor in the ^{31}P NMR spectra could any signals for transmetalated species be detected. Therefore, ^{1}H,^{31}P heteronuclear multiple-bond correlation (HMBC) spectra were recorded, which allow for magnetization transfers via multibond scalar couplings, ^{n}J$_{H,P}$, and additionally act as a spectroscopic filter for free ZnEt$_2$.[25] By removing the huge signals of free ZnEt$_2$ (up to 20 equiv), the dynamic range of the NMR spectrometer can be increased, and so the sensitivity of the resulting ^{1}H,^{31}P HMBC spectra to transmetalation complexes is

much higher than in classical one-dimensional (1D) ^{1}H or ^{31}P NMR spectra. In case of the transmetalation intermediate expected here (see Scheme 3 for the example of [Cu$_2$X$_2$L$_3$]), a magnetization transfer of the protons of the ethyl group via copper to the phosphorus atom of a ligand should be possible. Similar to classical $^nJ_{H,P}$ scalar coupling transfers within a ligand, such a magnetization transfer across copper would then be visible as cross signal in a ^{1}H,^{31}P HMBC spectrum.

^{1}H,^{31}P HMBC spectroscopy was already successfully applied in investigations of palladium-catalyzed Negishi coupling reactions.[27] However, in contrast to the palladium complexes used in the previous study, the transfer of magnetization via copper is much more difficult.[28] The high quadrupole moment of $^{63/65}$Cu provides an efficient relaxation pathway for magnetization, leading to short relaxation times and broad line widths of the nuclei directly coordinated to the copper atom (see, e.g., the ^{31}P line width of [Cu$_2$I$_2$L$_3$] versus **L** in the SI, Figure SI1). Therefore, especially in complexes with relevant electric field gradients, i.e., with P-, N-, or S-ligands, and structures deviating from a highly symmetrical coordination, scalar couplings across copper are usually not detectable.[28] As a result, successful experimental magnetization transfers via copper have only been reported for a few examples, e.g., in ^{1}H,^{13}C HMBC spectra of ^{13}C-labeled organocuprates,[29] in ^{1}H,^{31}P HMBC spectra of Me$_3$Cu(PPh$_3$)$_2$Li,[30] and in ^{31}P,^{31}P COSY spectra of complexes [Cu$_2$X$_2$L$_2$] (X = Cl, Br; L = **L**).[8,11] In the present study, the ^{1}H,^{31}P HMBC pulse sequence should eliminate the signals of free ZnEt$_2$ (see above); thus, even extremely small amounts of intermediates could be detected. In addition, 1D versions of HMBC spectra are superior in sensitivity compared to two-dimensional (2D) versions. Therefore, first a 1D ^{1}H,^{31}P HMBC pulse sequence was applied (see Figure 1a, and for details see the SI). Indeed,
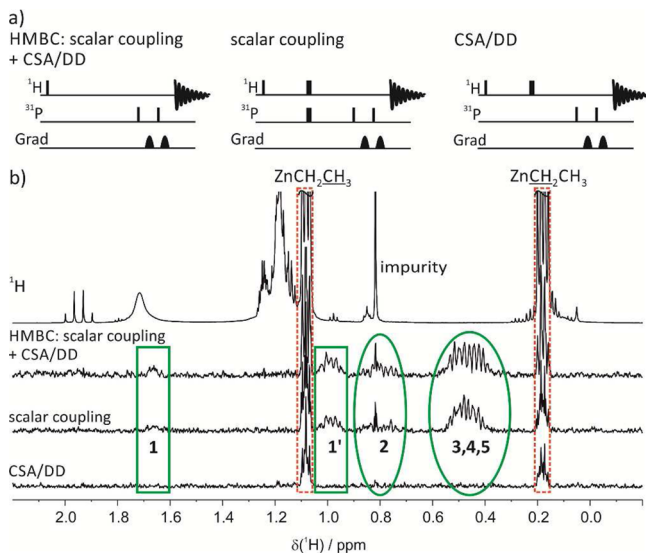
despite all the obstacles associated with copper complexes, we were able to detect very small cross signals between ethyl groups and ^{31}P species under transmetalation conditions (see Figure 1b, trace two; each signal in the 1D ^{1}H,^{31}P HMBC spectrum corresponds to a magnetization transfer between ^{1}H and ^{31}P). In these 1D ^{1}H,^{31}P HMBC spectra and later also in the 2D ^{1}H,^{31}P HMBC spectra (see Figure 2 and SI), two types of signals can be observed. First are signals (cross peaks) indicating the chemical shifts of free ZnEt$_2$ and free ligand or precatalytic complex (see red dashed boxes in Figure 1b). Such a retention of the chemical shift is implausible for real transmetalation intermediates[9] and is most probably caused by non-specific interactions in aggregates without specific structures. Second are new signals detectable neither in ^{1}H nor in ^{31}P NMR spectra, which correspond to new species (green boxes and ellipses in Figure 1b). Due to the similar signal intensities of both of these kinds of signals, it was necessary to find a spectroscopic method to differentiate between non-specific aggregates and structurally defined intermediates providing scalar coupling transfers. Within the two-spin approach, it is well known among NMR spectroscopists that not only scalar coupling but also relaxation interference (also called cross-correlated relaxation) between ^{1}H chemical shift anisotropy (CSA) and ^{1}H–^{31}P dipolar interactions (DD) can contribute to the polarization transfer in HMBC spectra.[31−37] The ^{1}H CSA/^{1}H–^{31}P DD relaxation interference can be manipulated by 180° pulses in a different way than scalar coupling, and as a result ^{1}H CSA/^{1}H–^{31}P DD relaxation interference can be separated from polarization transfer via scalar couplings.[35−39] This concept was already successfully applied in investigations of H-bond networks of acylguanidine complexes and flavoproteins,[35−37] but to our knowledge it has not been applied to organometallic compounds or transition metal complexes so far. Thus, two further 1D ^{1}H,^{31}P HMBC pulse sequences were measured with one or two additional 180° pulses on ^{31}P and ^{1}H (see Figure 1a and Figure SI11 for spectroscopic details). In the spectrum with one 180° pulse, the scalar coupling transfer is eliminated; in that with two 180° pulses, the ^{1}H CSA/^{1}H–^{31}P DD relaxation interference is canceled.[40]

Figure 1b compares the ^{1}H NMR spectrum and the three different 1D ^{1}H,^{31}P HMBC spectra. Significantly, all signals without chemical shift changes in the ^{1}H and ^{31}P dimensions show signals in all three types of HMBC spectra (see red dashed boxes in Figure 1b, and for further examples see the SI), indicating non-specific aggregates. In contrast, all signals with chemical shift changes show high contributions of scalar coupling transfers and small or no signals originating from ^{1}H CSA/^{1}H–^{31}P DD relaxation interference (see green boxes and ellipses in Figure 1b), which is typical for complexes or structures with well-defined chemical bonds allowing for scalar coupling transfers. This correlation of chemical shift changes and transfer pathways shows that, also for transition metal complexes and organometallic substances, extremely small signals originating from well-defined intermediates can be separated from those of non-specific aggregates present in the bulk phase with this method.

Next the intermediate signals originating from EtCuL and EtZnL structural arrangements were separated. For this purpose, mixtures of ZnEt$_2$ and free ligand without copper salt were investigated by HMBC spectroscopy. Several samples with concentration ratios of ZnEt$_2$ to **L** between 3:1 and 8:1 showed only signal 1′, with scalar coupling contributions,

Figure 1. (a) Pulse sequences of the 1D ^{1}H,^{31}P HMBC spectra, allowing for magnetization transfers via scalar coupling and ^{1}H CSA/^{1}H–^{31}P DD relaxation interference (CSA/DD) as well as modified versions canceling CSA/DD or scalar coupling (for description see text, and for experimental details see the SI). (b) Comparison of the ^{1}H NMR and 1D ^{1}H,^{31}P HMBC spectra of 2 equiv of **L**$^{(ss)}$, 1 equiv of CuI, and 7 equiv of ZnEt$_2$ at 230 K in CD$_2$Cl$_2$. Green ellipses and boxes indicate transfers via scalar couplings; red dashed boxes represent non-specific interactions.
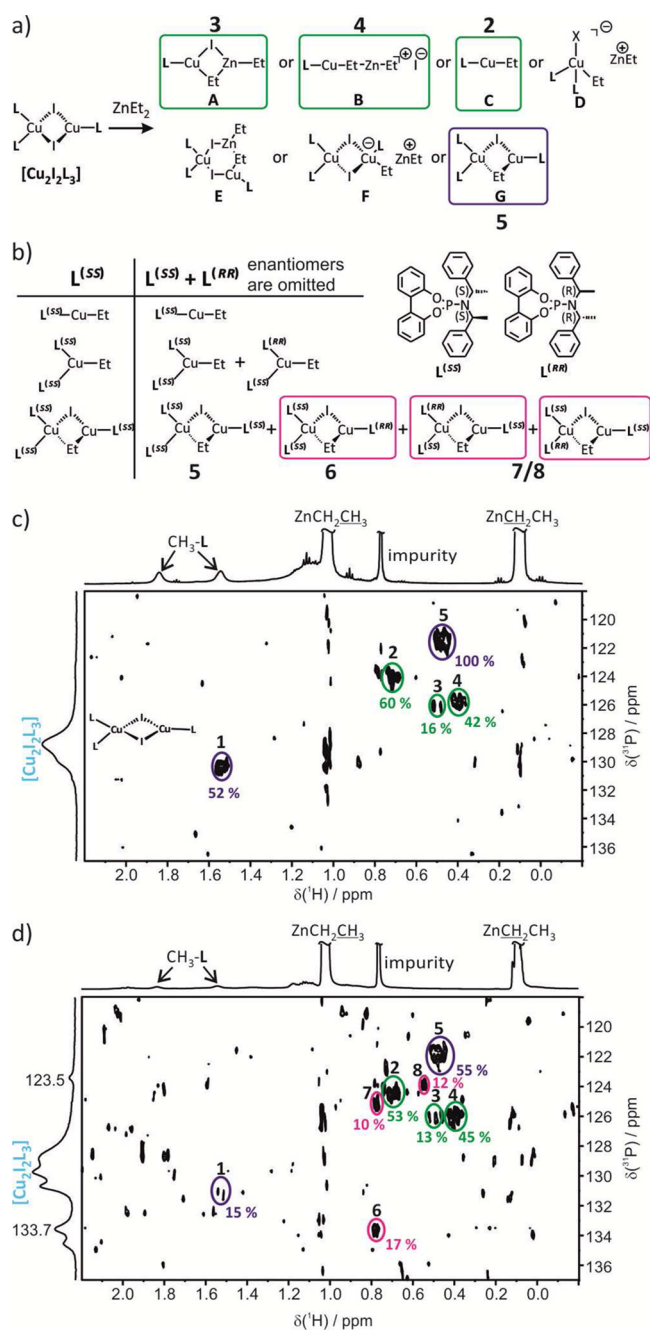
Figure 2. (a) Possible monomeric (**A**−**D**) and dimeric (**E**−**G**) transmetalation intermediates after the addition of $ZnEt_2$ to the precatalyst $[Cu_2I_2L_3]$. The numbers indicate the signals ultimately assigned to these structures. (b) Signal distribution of the transmetalation intermediates with enantiopure ligands ($L^{(SS)}$) and an enantiomeric mixture ($L^{(SS)}$ + $L^{(RR)}$), including signal assignment. (c) Section of the 2D $^1H,^{31}P$ HMBC spectrum with 2 equiv of $L^{(SS)}$, 1 equiv of CuI, and 14.7 equiv of $ZnEt_2$ at 170 K in CD_2Cl_2. (d) Corresponding section of the 2D $^1H,^{31}P$ HMBC spectra with 1 equiv of $L^{(SS)}$, 1 equiv of $L^{(RR)}$, 1 equiv of CuI, and 14.5 equiv of $ZnEt_2$ at 170 K in CD_2Cl_2. The signal integrals given are referenced to signal 5 of the enantiopure sample. The integrals of signals 2−4 (green) are nearly identical in both spectra, indicating monomeric complexes with one ligand. In contrast, signal 5 (blue) diminishes and signals 6−8 arise in the enantiomeric mixture (pink), indicating a complex with three ligands. For structure assignment see panels a and b and the text. (The reason for the reduction of signal 1 is explained in the SI, section 1.3.3.)

beside non-specific interactions (see Figure SI3a−d) in the 1D $^1H,^{31}P$ HMBC spectra. In none of the 2D $^1H,^{31}P$ HMBC spectra were cross signals of 1′ detected (see Figure SI 3e and Figure 2c,d); therefore, the structure of 1′ was not further investigated. Samples with free ligand and $ZnMe_2$ or $ZnPh_2$ without copper salt showed cross peaks of RZnL moieties in $^1H,^{31}P$ HMBC spectra that were not detectable after addition of copper salt (see Figure SI4a,b and ref 41). These experiments show that, in general, RCuL are preferentially formed relative to RZnL structural arrangements. In the case of $ZnEt_2$, only signal 1′ represents an EtZnL or EtL species, but the other signals (1−5) appear only in the presence of copper salt. Therefore, in the following, EtZnL structures are not further discussed. Signal 1 was assigned to a ligand with the ethyl group directly bound to the phosphorus atom, providing classical $^3J_{H,P}$ scalar couplings (for details see SI, section 1.3.3).

Signals 2−5 (green ellipses in Figure 1b) show the two characteristics expected for transmetalation intermediates: scalar coupling transfer between the ethyl group and the phosphorus of the ligand, and presence only under transmetalation conditions. However, due to the extremely low S/N of these signals, the further structural characterization of these intermediates can only rely on chemical shift analyses and on combinations of $^1H,^{31}P$ HMBC spectra.

The signals of the transmetalation intermediates, 2−5, could also be detected in the 2D $^1H,^{31}P$ HMBC spectra (see Figure 2c,d). Their ^1H chemical shift range of 0.80−0.30 ppm is in agreement with a CH_2 group transmetalated to a neutral Cu(I) complex. CH_2 of negatively charged cuprates shows upfield-shifted $\delta(^1H)$ signals (for $Et_2CuLi·LiI$ and $Et_2CuLi·LiCN$, −0.53 and −0.54 ppm, respectively[42]), whereas ethyl groups bound to Cu(III) show low-field-shifted signals (e.g., $Me_3EtCuLi$, 0.54 ppm;[43] $Me_2EtCuPMe_3$, 1.89 ppm; $Me_2EtCuP(OMe)_3$, 2.07 ppm; and $Me_2EtCu(PPh_3)$, 2.31 ppm[44]). In the ^{31}P dimension, all four signals of the transmetalation intermediates are upfield shifted compared to those of the precatalytic copper complex by 2.9−7.4 ppm. This is in agreement with the upfield shifts observed for transmetalation intermediates of Grignard reagents and ferrocenyl-based diphosphine copper complexes (1.8 and 3.1 ppm).[9] Thus, to our knowledge, the presented $^1H,^{31}P$ HMBC data provide the first direct experimental proof for transmetalation intermediates of copper complexes. The low-field shifts of the ^1H and the upfield shifts of the ^{31}P resonances of the transmetalation intermediates relative to free $ZnEt_2$ and the precatalytic copper complex corroborate previous results by Bertz and Feringa.[9,30]

Next the structure of these transmetalation intermediates was addressed. In principle, several structures of transmetalation intermediates are feasible that are either mono- or dimeric in copper and contain one, two, or three ligands (one ethyl group as well as varying amounts of $ZnEt_2$ or ZnEtI; see Figure 2a). Using DFT calculations, simplified phosphoramidite ligands, Cu(OAc), and $ZnMe_2$, Woodward and co-workers identified the monomeric zinc cuprate **A** as the lowest energy structure for transmetalation intermediates.[16] Furthermore, species **A** and **C** were proposed as monomeric transmetalation intermediates with Grignard reagents in the work described by Feringa and co-workers.[9] Monomeric transmetalation intermediates with two ligands, **D**, were proposed in several reaction mechanisms due to the typical ligand-to-copper ratio of 2:1.[4,7,24] For the

dimeric transmetalation intermediates with three ligands, the corresponding structures are **E**−**G**.

To address the structure under the prerequisite that exclusively ^{1}H,^{31}P HMBC spectra can be used, a special approach has to be applied. In principle, information about the number of ligands can be gained by comparing ^{1}H,^{31}P HMBC spectra of transmetalation intermediates with enantiopure phosphoramidite ligands (**L**) and such with the spectra of equal amounts of enantiomeric phosphoramidite ligands (50% **L**$^{(SS)}$, 50% **L**$^{(RR)}$). Intermediates with one ligand are not affected by the use of the enantiomeric mixture of the phosphoramidite ligands, because complexes with one ligand form only enantiomers, which are not distinguishable by NMR spectroscopy (for a graphical representation, see Figure 2b). As a result, all complexes with one ligand appear with the same integral in both samples. In contrast, species with two or three ligands are expected to appear with reduced signal integrals for the enantiopure intermediates, because **L** is known to form both homo and hetero complexes.[47,48] In addition, new signals should arise due to formation of diastereomers with mixed ligand arrangements. For monomeric transmetalation intermediates with two ligands, one reduced signal and one new signal are expected; for dimeric structures with three ligands, a pattern of one reduced signal and three new signals is expected (see Figure 2b).[45]

In Figure 2, the 2D ^{1}H,^{31}P HMBC spectra of the complexes with enantiopure ligands **L**$^{(SS)}$ (Figure 2c) and with the enantiomeric mixture of **L**$^{(SS)}$ and **L**$^{(RR)}$ (Figure 2d) are presented after addition of ZnEt$_2$. Indeed, three classes of signals are seen in the spectrum of the enantiomeric ligand mixture. Signals 2−4 (green) show similar integrals within the experimental error. This indicates monomeric species with one ligand for complexes 2−4. In contrast, signal 5 (blue) shows around half the integral. In addition, three new signals, 6−8 (pink), appear in the enantiomeric mixture. This pattern fits exactly to a dimeric structure with three ligands (see Figure 2b). Furthermore, the integrals of the signals for these four intermediates, 5−8, sum up to 94%, which is strong evidence that all four of these intermediates in the enantiomeric mixture indeed originate from intermediate 5 in the enantiopure sample (see the discussion above). The integral distribution of signals 5−8 shows that the diastereomers have energetically deviating interligand interactions, because the assumption of identical interligand interactions for **L**$^{(SS)}$**L**$^{(SS)}$ and **L**$^{(SS)}$**L**$^{(RR)}$ would lead to a statistical distribution of 25% for all four diastereomers (for details, see the SI). This is in agreement with previous and ongoing investigations of non-covalent interligand interactions in phosphoramidite palladium and copper complexes, which show distinct preferences for special ligand combinations[46−48] and quite pronounced interligand interactions.[14,46−48] Such significant interaction preferences directly lead to non-statistical distributions as observed here. Signal 5, appearing over-statistically at 55%, indicates a preference for interactions between enantiopure ligands (see Figure 2d). This is also visible on a lower level in the integrals of signals 6−8, at 17%, 12%, and 10%, showing lower values for mixed ligand arrangements at the copper fragment with two ligands (see Figure 2b).

To sum up, signals 2−4 are assigned to monomeric species with one ligand. The signal and integral pattern of signals 5−8 indicate a dimeric transmetalation intermediate with three ligands, i.e., experimental evidence for the retention of the binuclear complex structure upon transmetalation with mixed

trigonal/tetrahedral coordination on the copper atoms. Monomeric intermediates with two ligands are not detected.

Next the structures of the transmetalation intermediates 2−8 were refined to assign the signals 2−8 to the structures **A**−**C** and **E**−**G** (see Figure 2a,b). Since selective chelation of zinc versus copper is very difficult, the involvement of ZnI units was addressed by varying the amount of ZnI$_2$. For this purpose, 12 equiv of ZnI$_2$ was added to a sample of 2 equiv of **L**$^{(SS)}$, 1 equiv of CuI, and 7.7 equiv of ZnEt$_2$ (for spectra see the SI). The Schlenk equilibrium of ZnEt$_2$ and ZnI$_2$ is known to lie well to the side of ZnEtI.[49] Thus, only signals of the complexes with ZnI moieties should become stronger, whereas those of the complexes without ZnI moieties should decrease.[50] In the resulting ^{1}H,^{31}P HMBC spectrum, only signal 3 of a monomeric complex remained. Thus, signal 3 represents the only structure with a ZnI unit directly incorporated in the complex, and it was assigned to the monomeric species **A**. Signals 2 and 4 are also associated with monomeric species (see above) but without ZnI units. They show significant differences in their proton chemical shifts, as expected for species with a ZnEt unit (upfield shift of the CH$_2$ group) and without. Therefore, signal 4 is assigned to **B** and signal 2 to **C**. The addition of ZnI$_2$ also shows that no ZnI moiety is incorporated in the complex of signal 5, which excludes structure **E**. The involvement of a halogen bridge was proven by further investigations with CuCl as copper salt. For CuI and CuCl, no identical signals of transmetalation intermediates were observed in the 2D ^{1}H,^{31}P HMBC spectra (for details see the SI). This indicated the existence of a halogen bridge in the dimeric transmetalation complex. In addition, samples with CuCl and high amounts of ZnEt$_2$ showed cuprate-like structures with distinct upfield-shifted signals (for details see the SI). This pronounced chemical shift difference excludes two ethyl groups bound to one copper atom in the transmetalation intermediates discussed here. The remaining differentiation between structures **F** and **G** for signal 5 can be solved by the trends of the transmetalation intermediates dependent on the equivalents of ZnEt$_2$ added (see Figure 3). Analysis of the
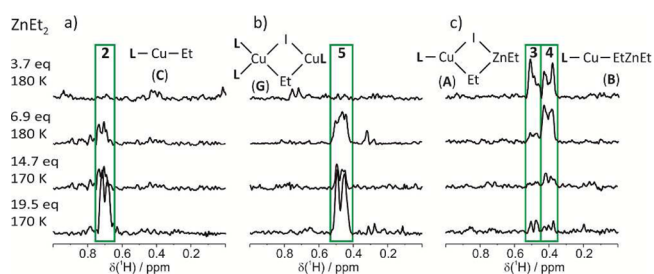

Figure 3. Formation trends of transmetalation intermediates with 2 equiv of L, 1 equiv of CuI, and an increasing excess of ZnEt$_2$ (typical synthetic conditions use about 60 equiv of ZnEt$_2$) at 170 and 180 K in CD$_2$Cl$_2$. The 1D rows are taken from the 2D ^{1}H,^{31}P HMBC spectra at the ^{31}P chemical shifts of the respective intermediates, revealing intermediates 3 and 4 as precursors, and 2 and 5 as final intermediates.

monomeric transmetalation intermediates with one ligand shows that **A** and **B**, containing ZnEt units, are preferentially formed at lower amounts of ZnEt$_2$, whereas the "final" transmetalation intermediate **C**, without a ZnEtI unit, accumulates at higher amounts of ZnEt$_2$. Due to the fact that in this investigation we used a significantly reduced excess of ZnEt$_2$ compared to that used in the synthetic application (see above), in synthesis the preference of **C** is expected to be even

more pronounced. Assuming similar trends for the formation of dimeric transmetalation intermediates, as indicated by similar intensity trends of signals 2 and 5, signal 5 can be assigned to the "final" transmetalation intermediate **G**, without a ZnEt unit. Considering the results described above, further structural characteristics of **G** one ethyl and one iodine bridge and retention of the mixed trigonal/tetrahedral coordination on the copper atoms. This structural assignment is corroborated by the number (three) of the newly appearing signals 6−8 in the enantiomeric mixture as well as by their integral pattern, representing the three possible diastereomers of **G** with mixed ligand arrangements and indicating a preference for homo-ligand interactions.

The existence of monomeric transmetalation intermediates with one ligand coordinated to copper is in agreement with the results of Feringa and co-workers, who found exclusively monomeric transmetalation intermediates with one ligand with Grignard reagents.[9] The structures proposed in their study are similar to **A** and **C** observed here. Monomeric intermediates with CuL_2 fragments, as often proposed in reaction mechanisms, were not detected in our study nor previously by Feringa. Furthermore, here for the first time, a trans-metalation intermediate with a binuclear structure with mixed trigonal/tetrahedral coordination on the copper atoms is experimentally detected, which provides both an open coordination place for the enone and plenty of ligand interactions for high stereoselectivities (see studies on palladium phosphoramidite complexes for interaction schemes of phosphoramidite ligands).[47,48] Now, the question remains whether the monomeric **C** or the binuclear **G** is the reactive transmetalation intermediate, since both are detected in similar amounts. So far, there is no direct experimental proof, but there are strong indirect arguments. The most substantial argument for the binuclear complex **G** as the reactive species is the well-known ligand-to-copper ratio of 2:1 in synthetic applications. At ligand-to-copper ratios of 2:1, stabilizing optimally the binuclear complex with the mixed trigonal/tetrahedral coordination on copper,[12] highly enantioselective reactions can be performed.[1,8,24] At ligand-to-copper ratios of 1:1, stabilizing optimally the monomeric complex **C** with only one ligand, considerably reduced enantioselectivities are obtained. Considering **G** as the reactive species, at first glance the high enantioselectivities in the presence of nearly equal amounts of **G** and **C** are puzzling. At this point, Woodward's DFT calculations give an explanation, because in that theoretical study, starting from monomeric transmetalation intermediates only, suitable energetic pathways were found for dimeric copper complexes with mixed trigonal/tetrahedral coordination.[16]

CONCLUSIONS

In summary, the first direct experimental detection of transmetalation intermediates in copper-catalyzed asymmetric addition reactions is presented, using phosphoramidite copper complexes $[Cu_2X_2L_3]$ and an excess of $ZnEt_2$. The trans-metalation intermediates, which are below the detection limit in one-dimensional ^1H and ^{31}P spectra, were identified by using a special set of 1D ^1H,^{31}P HMBC spectra separating complexes with ethyl groups chemically bound from those with non-specific interactions. For the structure characterization, again a special approach was applied using samples with enantiopure ligands and samples with mixtures of enantiomeric ligands. This and experiments with CuCl, ZnI_2, and varying amounts of $ZnEt_2$ revealed two main transmetalation intermediates: one

with one ethyl group and one ligand as well as, for the first time, a binuclear intermediate with three ligands, one ethyl group and a mixed trigonal/tetrahedral coordination on the copper atoms. Intermediates with two ligands were not observed. The well-known optimal ligand-to-copper ratio of 2:1, in combination with theoretical calculations proposing feasible reaction pathways only for binuclear complexes, and the experimental study presented here reveal retention of the binuclear copper complex with mixed trigonal/tetrahedral coordination in the reactive transmetalation intermediate. This first direct experimental insight into the structure of transmetalation intermediates is expected to aid the mechanistic understanding and the further synthetic development of the copper-catalyzed asymmetric conjugate addition reaction and related methods. In addition, the special NMR approach presented here to identify and characterize the structure of reaction intermediates below the detection limit of ^1H and ^{31}P spectra can be also applied to other catalytic system.

ASSOCIATED CONTENT

ⓢ Supporting Information

Experimental details and additional NMR data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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