On the Role of P^{III} Ligands in the Conjugate Addition of Diorganozinc Derivatives to Enones

Tatjana Pfretzschner,[a] Lutz Kleemann,[b] Birgit Janza,[a] Klaus Harms,[a] and Thomas Schrader*[a]

Abstract: A mechanistic study on the conjugate addition of diethylzinc to cyclohexenone catalyzed by various chiral P^{III} ligands, provides new insights into its mechanism. Complete in situ conversion of the catalytic amount of $Cu(OTf)_2$ into Cu^I species by excess $ZnEt_2$ is demonstrated by EPR spectroscopy. Experimental evidence is presented in favor of a critical ternary 1:1:1 complex between enone, Et_2Zn and catalyst, supporting a rate-limiting reductive elimination or carbocupration from a preformed mixed Cu/Zn cluster carrying one- or two-ligand molecules. A crystal structure has been obtained for a $CuI{\cdot}L_2$ complex, which shows catalytic turnover on addition of reagent and substrate. NMR spectroscopic analyses and VT experiments reveal that steric hindrance may prevent complexation of a second ligand molecule on the Cu^I cation, leading to extremely fast precatalysts based on $CuX{\cdot}L$ species.

Keywords: asymmetric catalysis · conjugate addition · dialkylzinc · kinetics

Introduction

The copper-catalyzed conjugate addition of diorganozinc compounds to enones has become a powerful synthetic tool for asymmetric catalytic Michael additions.[1] Catalytic routes to cycloalkanones as well as tandem and annulation procedures are now available offering almost quantitative chemical yields and excellent enantioselectivities.[2] Chiral induction in this valuable process has been achieved mainly by ligand acceleration with chiral phosphoramidites, phosphites and phosphonites.[3] Since the first report by Alexakis in 1993, many other P^{III} ligands have been tested in this reaction during the past decade.[4] These differ substantially both in their reactivity and their enantioselectivity. Systematic optimization of Feringa's original catalyst[5] has led to a ligand with a second chiral structural unit which usually gives enantiomeric excesses $>95\,\%$ with enones.[6] High optical yields are also achieved with Alexakis' conformationally tunable biphenyl-based phosphoramidites,[7] and with Pfaltz' phosphate–oxazolinones.[8]

However, in spite of the importance of this promising catalytic process, very few mechanistic studies have been undertaken to elucidate its mechanism. In the related area of the conjugate addition of Gilman cuprates[9] early kinetic studies by Krauss and Smith[10] and subsequent NMR studies by Ullenius and Smith[11] clearly pointed to a mechanism, where an intermediate formed in equilibrium with the starting material goes through an irreversible step to give the conjugate adduct. Further support came from mechanistic studies by Krause, who identified such an intermediate, followed by elegant investigations on kinetic isotope effects by Singleton.[12,13] It became clear, that the rate-limiting step is C–C bond formation by reductive elimination of a Cu^{III} intermediate.[14] Recently, Krause could determine the activation parameters for this process.[15] Finally, a much more detailed picture evolved from extensive density functional studies by Nakamura on conjugate additions of lithium organocuprates.[16] Based on these mechanistic insights and own observations, Feringa[17] and Alexakis[18] postulated a similar mechanism for the organozinc addition in the past years. Both assume an initial alkyl transfer from R_2Zn to the copper center followed by coordination of the hard Lewis acid RZnX to the enone carbonyl and formation of a π-complex between the soft Cu–alkyl species and the enone double bond. Oxidative addition of the organocopper(I) reagent to the enone is presumably followed by a reductive elimination with concomitant C–C-bond formation, the latter being the rate-determining step (Scheme 1). Product

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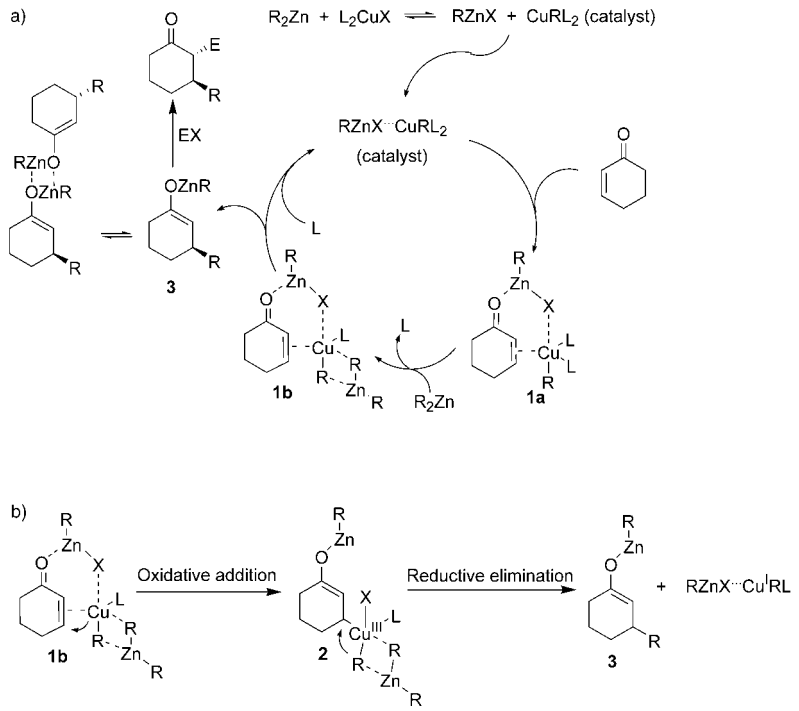
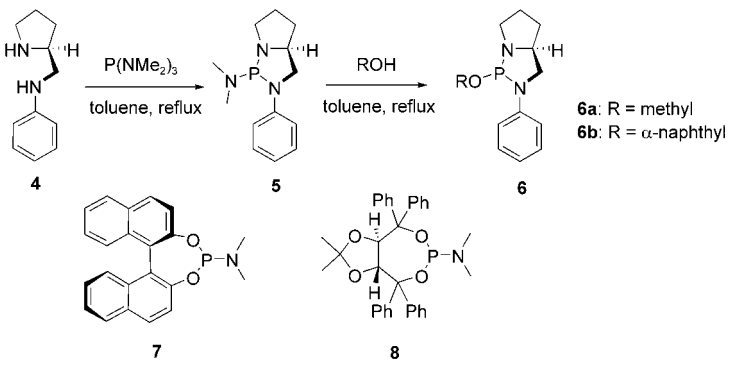


Scheme 1. Postulated catalytic cycle for the copper(I)-catalyzed conjugate addition of organozincs to cyclohexenone. b) In the key steps, oxidative addition of the organocopper(I)-species **1b** to the enone double bond is followed by the rate-determining reductive elimination of the catalytic copper(I)-complex **2** with simultaneous alkyl transfer to the γ-carbon of the enone. The resulting enolate anion **3** can be further processed by quenching with appropriate electrophiles.

inhibition is circumvented by liberation of the zinc enolate in its thermodynamically stable dimeric form. Both, Alexakis and Noyori assume that prior to this the CuR moiety captures another R_2Zn molecule to form a highly nucleophilic Cu/Zn cluster.[18] Noyori recently discovered that *N*-benzylbenzenesulfonamide itself catalyzes the 1,4-addition of dialkylzinc compounds to α,β-unsaturated ketones with a Cu:Zn ratio of up to 1:10000.[19] A catalytic cycle was proposed on the basis of a kinetic study and structural analysis of the zinc–enolate product. For this special case, kinetic isotope effects point to a concerted mechanism in the alkyl transfer step.[20] However, most mechanistic assumptions on the Cu-catalyzed conjugate organozinc addition with P^{III} ligands are only scarcely backed by experimental evidence.

We present in this paper a mechanistic study on the conjugate addition of diethylzinc to cyclohexenone catalyzed by various chiral P^{III} ligands. Experimental evidence is presented in favor of the above-outlined rationale, supporting a rate-limiting reductive elimination or a carbocupration from a preformed mixed Cu/Zn cluster carrying one or two ligand molecules. A crystal structure has been obtained for a $CuI{\cdot}L_2$ complex, which shows catalytic turnover on addition of reagent and substrate. NMR spectroscopic analyses and VT experiments reveal that steric hindrance may prevent complexation of a second ligand molecule on the Cu^{I} cation, leading to extremely fast precatalysts based on CuX·L species.

Kinetic studies: If the above-outlined assumption of a reductive elimination in the rate-limiting step is correct, one should observe a close correlation between the overall reaction rate and the structure of the respective P^{III} ligand, or more precisely, its electron density. With the most common standard reaction, that is, the conjugate addition of diethylzinc to cyclohexenone, we therefore carried out a systematic investigation on the degree of ligand acceleration exerted by various classes of P^{III} ligands.[21] Care was taken to alter the nucleophilicity of the phosphorus atom, by starting from N_3P systems and including more and more electron-withdrawing oxygen atoms as next neighbours to phosphorus. In addition, the steric demands of the ligands were varied from slim to bulky. To this end, we systematically synthesized a series of new phosphorous amides based on 2-aminomethylpyrrolidine **4**. The new ligands were derived from the parent compound **5** with a dimethylamino group, which was replaced by a slim alkoxy group (**6a**) and a sterically demanding aryloxy group (**6b**, Scheme 2).[22] We then carried out kinetic investigations with these ligands and a representative BINOL- (**7**) and TADDOL-phosphoramidite ligand[23] (**8**) used by Feringa and us before.



Scheme 2. Structures of all ligands examined in this comparative kinetic study.

The test reaction was carried out at −30 °C in toluene with 1 mol % of Cu^{II}–triflate and 2 mol % of ligand as catalyst system (Scheme 3). One might argue, that the oxidation state of $Cu(OTf)_2$ differs from that of the postulated copper(I) species. However, numerous earlier investigations have demonstrated that both Cu^{I} and Cu^{II} salts can be used with equal success.[2] It has been generally argued that the

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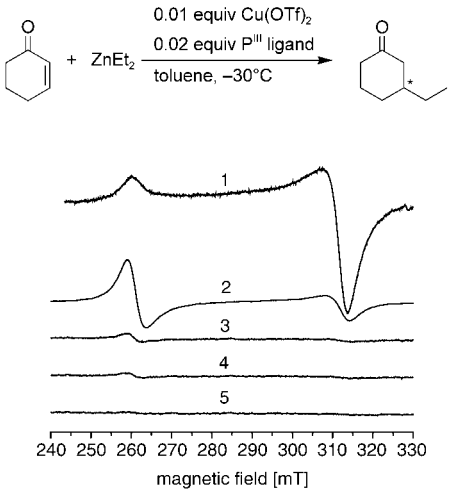
Cu^{II} salt is quantitatively reduced to the Cu^{I} form by the large excess of diethylzinc present in the reaction mixture.[24] In order to prove this assumption experimentally, we carried out EPR measurements on the reaction of $Cu(OTf)_2$ with a 25-fold excess of diethylzinc in toluene, which confirmed the complete conversion of paramagnetic Cu^{II} into diamagnetic Cu^{I} within 20 min (Scheme 3). This reduction is effected by the dialkylzinc reagent and not by the phosphorus ligand.[25]



Scheme 3. Top: Standard reaction protocol for the kinetic investigations. Bottom: EPR spectra of **1**, free $Cu(OTf)_2$ with $[Cu(OTf)_2] = 4.2$ mM in toluene; **2**, $Cu(OTf)_2$:ligand **8** (1:2); **3**, $Cu(OTf)_2$:ligand **8** (1:2) with a 24-fold excess of $ZnEt_2$ in toluene after 6 min; **4**, after 10 min; **5**, after 18 min (300 K).

In all cases, we observed a clean conversion of starting material to product (Figure 1), albeit at very different rates. The reaction was generally monitored as decreasing enone concentration, determined by calibrated GC analyses. Starting with 1 min, after $ZnEt_2$ addition was complete, 50 μL aliquots were drawn from the reaction mixture, quenched with water and extracted into Et_2O. The organic phases were directly examined by GC, with cyclohexanone as an internal standard.

The uncatalyzed background reaction was very slow (Figure 2), but not negligible, in our hands, leading to only

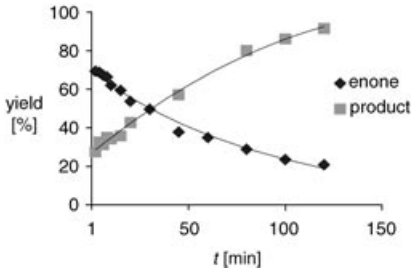


Figure 1. Kinetic curves for the continuous conversion of enone into 3-alkylketone catalyzed by phosphorous acid diamide monoester **6b** and $Cu(OTf)_2$. (GC analysis commenced after 1 min, when $ZnEt_2$ addition was complete. Cyclohexanone was used as the internal standard, added stoichiometrically to the reaction mixture simultaneously with the enone).

30% conversion after 3 h.[26] A very slow background reaction has also been reported independently by Alexakis[27] and Noyori,[19] with drastic accelerations by P^{III} ligands or benzenesulfonamides. Likewise, in our experiments only 1 mol% of catalyst greatly increased the reaction rate in all cases. Most interestingly, reactions with electron-rich P^{III} ligands containing two or three N atoms, proceeded much more slowly than those with only one N atom. This becomes especially impressive in our new ligand series based on 2-aminomethylpyrrolidine. The systematic variation of the linear substituent on phosphorus demonstrates two effects which seem to be of general relevance: heteroatom exchange of N against O leads to a marked increase in reaction rate ($NMe_2 \rightarrow OMe$), which is again decelerated by increasing steric bulk ($OMe \rightarrow$O-α-naphthyl). With NMe_2 substituents, the BINOL- (**7**) and especially the TADDOL-derived phosphoramidites (**8**) are the most efficient catalysts in this series, bringing the reaction to completion within less than 1 h at −30 °C; thus, in spite of their enormous steric bulkyness both phosphoramidites are much faster than the phosphorous triamide. Close inspection of early comparative studies directed by Alexakis, reveal that under identical conditions the simple achiral ligand $P(OEt)_3$ brings the Michael addition to completion much earlier than $P(NMe)_3$.[27] Since the reductive elimination step requires electron donation to the Cu^{III} centre, electron-rich P^{III} ligands should be counterproductive, while electron-withdrawing ligands should facilitate the process. This is exactly the case. The same argument is also valid for a potential carbocupration mechanism, which we cannot exclude a priori.[28] Sterically demanding ligands might further hinder the alkyl transfer step, which requires a close contact between $R^{\delta-}$ and C-$3^{\delta+}$ of the double bond in the π-complex. On the contrary, electron-donating ligands which increase the nucleophilicity of the attacking alkyl Cu species, should greatly accelerate the oxidative addition step.[29] In the light of Kitamura's recent $^{12}C/^{13}C$ isotope effect experiments on the CuOTf–sulfonamide system,[20] indicating a concerted mechanism, this seems contradictory, because for such a concerted alkylation step, electron-donating ligands should be most effective. However, it has to be kept in mind, that the catalytic effect originates in one case from a bridging sulfonamide anion on zinc, whereas in the other case a P^{III} ligand on copper accelerates the reaction; this may lead to entirely different situations in the key alkyl transfer step.

Kinetic order: With the final reductive elimination being the rate-limiting step, all reactions should follow first order kinetics, since in a preceding rapid equilibrium the substrate, catalyst and organozinc reagent are all assembled in one π-complex which goes directly to the products. First order kinetics in substrate, organozinc and (bridging) sulfonamide ligand were already observed by Noyori in a related Cu^{I}-sulfonamide system and pointed to a bissubstrate–uniproduct system with the alkyl-transfer step limiting the turnover rate.[19] In a logarithmic plot, this is also confirmed for all of the above-examined ligands: first order kinetics are observed, producing k values between $9 \times 10^{-5}\ s^{-1}$ and $2 \times 10^{-3}\ s^{-1}$ for the fast TADDOL-based ligand **8** (uncatalyzed

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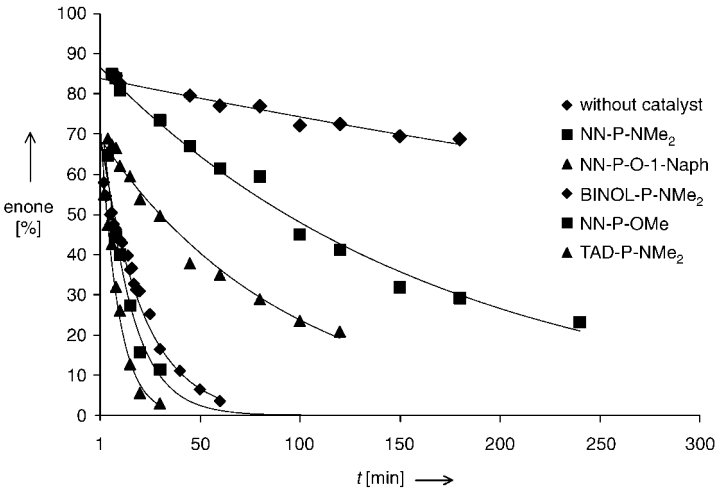

Figure 2. Kinetics of the conjugate ethylation of cyclohexenone by dialkylzinc catalyzed by Cu^{I} complexes of various P^{III} ligands, monitored as decreasing enone concentration (GC analysis, the first injection was only carried out after complete addition of diethylzinc and therefore does not start at 100%).

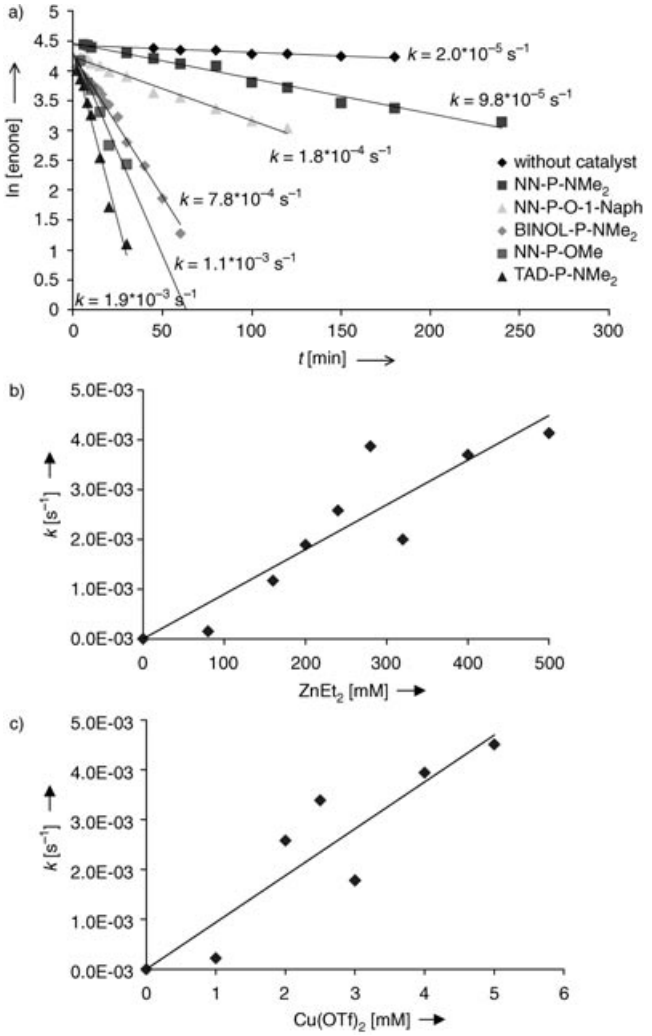

Figure 3. a) ln[enone] versus t plot with resulting k values demonstrating first order kinetics for all above-shown reactions (200 mM enone, 240 mM diethylzinc, 2 mM catalyst, −30 °C, toluene). b) Relation between reaction rate k and $[ZnEt_2]$ (200 mM enone, 2 mM catalyst, −30 °C, toluene/hexanes). First order kinetics in $[ZnEt_2]$ are observed.[30] c) Relation between reaction rate k and [catalyst = 1:2 mixture of $Cu(OTf)_2$ and ligand] (200 mM enone, 240 mM $ZnEt_2$, −30 °C, toluene/hexanes). First order kinetics in [catalyst] are observed.[30]

background reaction $2\times10^{-5}\,s^{-1}$). These reaction rates are comparable to Noyori's sulfonamide system. In agreement with the postulated mechanism, the reaction becomes faster, if more substrate and more catalyst are added, and also, if an excess of diethylzinc is used. First order kinetics were also established in experiments with varying $ZnEt_2$ or catalyst concentrations, while all other parameters were kept constant. The reaction rates were determined over the full time range and in a concentration range between 100 and 500 mM $ZnEt_2$ as well as 0.5 and 4 mol% catalyst (Figure 3b and c). We conclude that the catalyst forms a ternary 1:1:1 complex with one equivalent of diethylzinc and enone, in which alkyl transfer occurs. Product release regenerates the catalyst for the next cycle. As a consequence of this mechanism, the turnover rate must be limited by the alkylation step and not by the product release.

Recent variations in the copper salts indicate the importance of charge-alternating bridging anions for the mixed zinc cuprates.[2,18] Since especially aromatic Cu carboxylates produce highly efficient catalysts, the degree of lipophilicity seems to play some role, whereas the Lewis acidity is of minor relevance. This assumption is strongly supported by the above-mentioned mechanistic studies conducted by Noyori.[19] Likewise, exchange of the triflate anion for iodide greatly decelerated the conjugate addition in our system, pointing to the necessity of bridging the Cu and Zn center for efficient catalysis.

X-ray crystal structure:[31] Next we turned to the stoichiometry of the precatalyst formed between the Cu^{I} salt and the P^{III} ligand. Feringa and others observed that a 3:1 ratio of ligand and Cu salt produced a very stable, catalytically inactive complex, presumably because alkyl transfer to the Cu^{I} centre is hindered.[2] The only crystal structure known to date shows exactly this a 3:1 complex with Cu^{I}.[5,32] Recently Seebach et al. obtained a crystal structure of a Cu^{I}-TADDOL-thiolate, which catalyzes the somewhat related Grignard conjugate addition to enones. However, this complex is tetranuclear, and the thio-TADDOL acts as a monodentate ligand bridging two Cu atoms.[33] Optimal conditions were often found for a 2:1 ratio for monodentate, but a 1:1 ratio for bidentate phosphoramidite ligands; in connection with moderate nonlinear effects this led many authors to the conclusion, that in the stereodiscriminating step two ligand molecules are operating together.[34] Preliminary experiments with our new ligands confirmed that a 3:1 complex was catalytically inactive, as opposed to 2:1 mixtures which greatly accelerated the conjugate addition. Although we tried to crystallize a 3:1 complex from CuI and the N_3P ligand **5**, we obtained a crystal structure clearly showing a ligand/Cu ratio of 2:1, with a trigonal planar arrangement around Cu (Figure 4). Addition of a large excess of diethyl-

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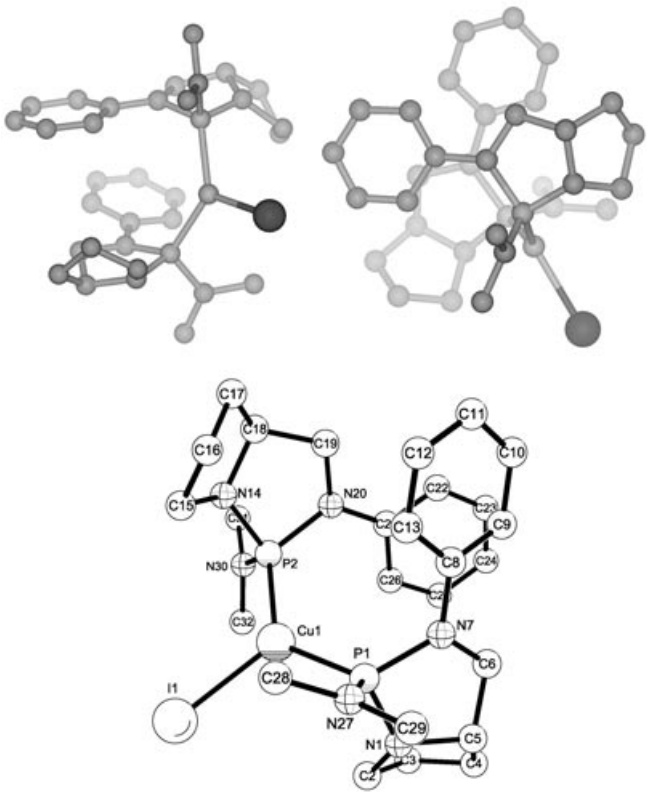

Figure 4. Crystal stucture of the 2:1 complex between the new N_3P phosphorous triamide ligand **5** and CuI (from toluene/CH_2Cl_2). Perspectives have been chosen comparable to those in Figure 5. Hydrogen atoms have been omitted for clarity.

zinc and cyclohexenone started the conjugate addition and proved the efficiency of this 2:1 precatalyst. Since we could also carry out an X-ray structural analysis on the free phosphorous triamide ligand (Figure 5), we were able to compare the bond lengths and angles around the critical P–N bonds: although no dramatic changes are observed, P–N bond lengths tend to be shortened on complexation (1.75 to 1.70 Å, 1.68 to 1.66 Å), whereas NPN angles are slightly widened by about three degrees (90 to 92°, 102 to 105°, 106 to 109°). With great caution, we take this as a first indication of electron density flowing from nitrogen via phosphorus to the Cu^I center. In the complex, both phosphorous triamide ligands form a quasi C_2-symmetric arrangement with respect to the Cu^I axis. The concave faces of the roof-like bicycles are oriented antiparallel to each other.[35] Similar to the free TADDOL-based ligand **8**,[5] one of the NMe_2 methyl groups stands coplanar to the lone pair on phosphorus. This creates steric hindrance for the copper complexation.

NMR spectroscopy: We finally carried out an NMR-spectroscopic comparative study of all complexes formed between CuI and the kinetically examined P^{III} ligands. Interestingly enough, in $CDCl_3$ a drastic upfield-shift of roughly 20 ppm is consistently produced in most 2:1-complexes. This result is counterintuitive, but may be explained by the direct Cu–P bond (in all cases, the $^nJ_{PH}$ couplings broke down).[36] We were again surprised by the TADDOL ligand **8**, which exclusively forms a 1:1 complex with CuI. A VT study revealed a coalescence temperature for the ligand exchange of $\sim+24\,^\circ C$, corresponding to a fast ligand exchange rate of $349\ s^{-1}$ with a low activation barrier of $\sim 11.1\ kcal\,mol^{-1}$ (Figure 6).[37] The high preference for 1:1 complexes may explain TADDOL's superior performance with respect to reaction rate and stereoselectivity, since in the catalytically active species, steric hindrance around the central copper atom is minimized.

Furthermore, the dioxolane CH and CH_3 groups turned magnetically equivalent, with a large downfield shift for the CH protons and a large upfield shift for the methyl group; this may indicate a conformational change in the ligand rotating certain groups in or out of the anisotropic shielding of TADDOL's benzene rings,[38] see Figure 6b.

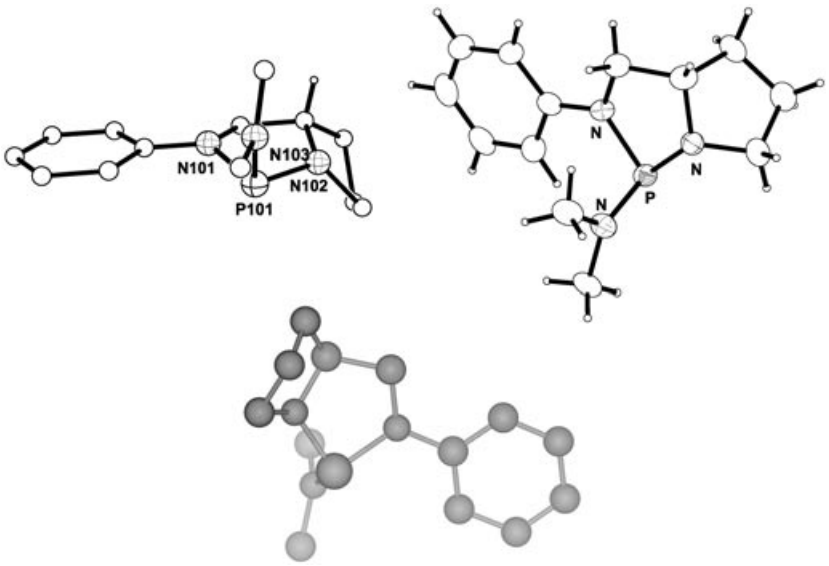

Figure 5. Crystal structure of phosphorous triamide ligand **5**.

Conclusion

Additional pieces of evidence have been collected in support of a reductive elimination or carbocupration as the rate-limiting step in the Cu^I-catalyzed conjugate addition of organozincs to enones. P^{III} ligands firmly bound to Cu^{III} seem to lower the activation energy barrier for this process, especially if they carry a high number of electron-withdrawing substituents, that is, P–O bonds.[39] 2:1 complexes between ligand and Cu^I are predominantly formed, with TADDOL being an exception, because it furnishes an extremely powerful 1:1 complex,

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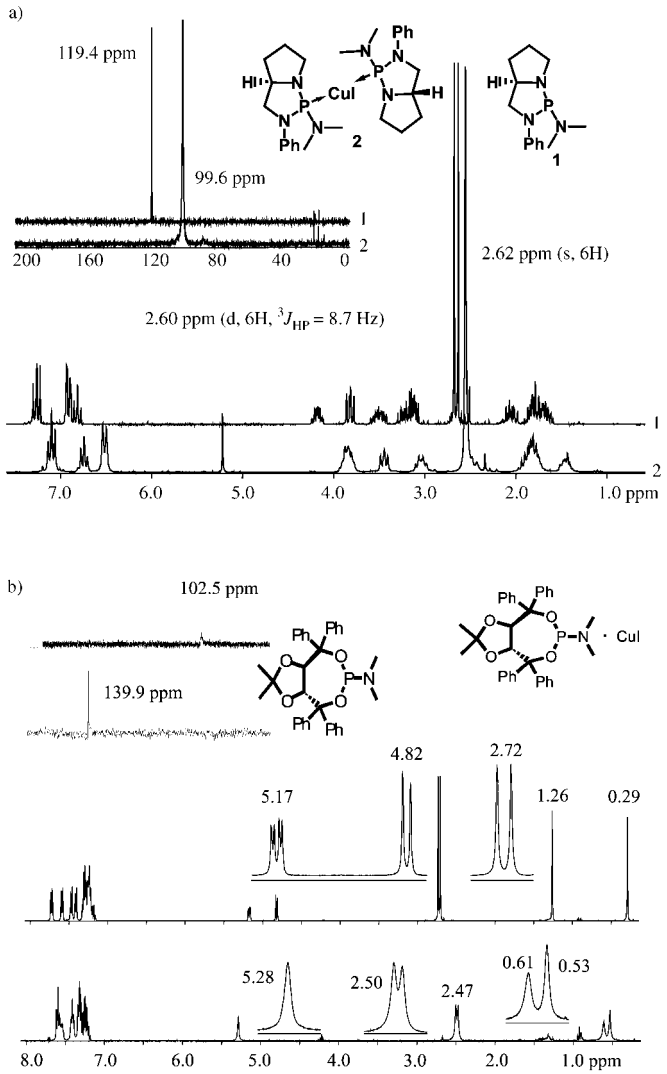


Figure 6. ^{1}H and ^{31}P NMR spectra for a) the free phosphorous triamide ligand **5** used for the above-discussed mechanistic investigations and its 2:1 complex with CuI, and b) the free phosphoramidite ligand **8** and its 1:1 complex with CuI, both in $CDCl_3$.

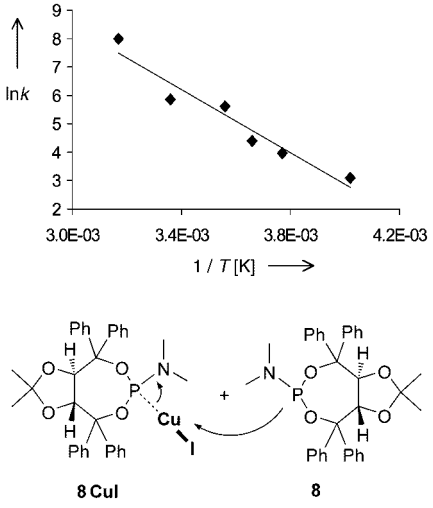


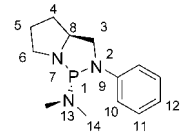
Figure 7. Linear dependence of ln$k$ for the TADDOL-based ligand **8** exchange on 1/T determined by lineshape analysis of the corresponding $PNMe_2$ ^{1}H NMR signals produced in VT experiments between 233 and 315 K.

exclusively. In the future, we will use our very slow N_3P ligand to characterize the reaction intermediates (e.g., the postulated π-complex) spectroscopically (^{1}H, ^{31}P, ^{13}C NMR).[40] In addition, kinetic isotope effects should further substantiate the postulated reductive alkyl transfer as the rate-limiting step as opposed to a potential carbocupration. In a cooperation, we also intend to calculate the whole process on a DFT level, following a similar approach as in Nakamura's seminal papers on Gilman cuprates.[16]

Experimental Section

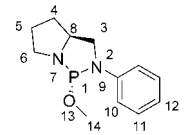
Ligands

(1*R*,8*S*)-1-(Dimethylamino)-2-phenyl-2,7-diaza-1-phosphabicyclo[3.3.0]octane (5): (*S*)-2-anilinomethylpyrrolidine (2.00 g, 11.5 mmol) was dissolved in anhydrous toluene (10 mL) under argon. After the addition of tris(dimethylamino)phosphine (1.88 g, 2.1 mL, 11.5 mmol) the



mixture was heated to reflux for 4 h. The reaction was monitored by ^{31}P NMR. After cooling to room temperature, the solvent and the excess of tris(dimethylamino)phosphine were distilled off. The remaining oil was subjected to fractional distillation in a Kugelrohr apparatus (2.8×10^{-1} mbar, 180 °C) to obtain the title compound as a colorless liquid (2.15 g, 86.2 mmol, 75.0 %). The compound crystallized after being stored at room temperature under argon for several months. M.p. 41 °C; ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.54–1.85 (m, 3H), 1.93–2.05 (m, 1H), 2.60 (d, $^3J_{H,P}$ = 8.7 Hz, 6H, C(14)-H), 3.02–3.24 (m, 2H, C(6)-H), 3.37–3.54 (m, 1H, C(8)-H), 3.77 (ddd, ^2J = 1.0, $^3J_{H,P}$ = 9.0, ^3J = 7.2 Hz, 1H, C(3)-H), 4.06–4.19 (m, 1H, C(3)-H), 6.76 (tt, ^3J = 7.2, ^4J = 1.0 Hz, 1H, C(12)-H), 6.84 (m, 2H, C(11)-H), 7.21 (m, 2H, C(10)-H); ^{31}P NMR (81 MHz, $CDCl_3$): δ = 119.3 (s); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 25.4, 32.3, 36.7, 37.1, 50.1, 62.3, 114.4, 114.6, 117.6, 128.9; MS (70 eV): *m*/*z* (%): 136 (49) [N-P-N-$C_6H_5^+$], 205 (100) [M^+-NMe_2], 249 (4) [M^+]; ESI-HRMS: *m*/*z*: calcd for $C_{13}H_{20}N_3P$: 249.1390, found 249.1390.

(1*R*,8*S*)-1-Methoxy-2-phenyl-2,7-diaza-1-phosphabicyclo[3.3.0]octane (6a): (*S*)-2-anilinomethylpyrrolidine (1.00 g, 5.71 mmol) was dissolved in anhydrous toluene (10 mL) under argon. After the addition of tris(dimethylamino)phosphine (0.99 g, 1.1 mL, 6.1 mmol, 1.1 equiv) the mixture



was heated to reflux for 4 h. The reaction was monitored by ^{31}P NMR. After cooling to room temperature, the solvent and the excess of tris(dimethylamino)phosphine were distilled off. The residue was diluted with anhydrous toluene (10 mL), treated with anhydrous methanol (0.20 g, 0.25 mL, 6.1 mmol, 1.1 equiv) and again heated to reflux. The solvent and the excess of methanol were distilled off in vacuo. The remaining oil was subjected to fractional distillation in a Kugelrohr apparatus (2.5×10^{-1} mbar, 190 °C) to obtain the title compound as a colorless liquid (0.80 g, 3.4 mmol, 60.0 %). ^{1}H NMR (200 MHz, $CDCl_3$): δ = 1.54–1.85 (m, 3H), 1.95–2.08 (m, 1H), 3.08–3.25 (m, 2H, C(6)-H), 3.33 (d, $^3J_{H,P}$ = 8.5 Hz, 3H, C(14)-H), 3.48–3.64 (m, 1H, C(8)-H), 3.75 (ddd, ^2J = 1.0, $^3J_{H,P}$ = 9.0, ^3J = 7.2 Hz, 1H, C(3)-H), 4.10–4.22 (m, 1H, C(3)-H), 6.83 (tt, ^3J = 7.2, ^4J = 1.0 Hz, 1H, C(12)-H), 6.99–7.04 (m, 2H, C(11)-H), 7.23 (m, 2H, C(10)-H); ^{31}P NMR (81 MHz, $CDCl_3$): δ = 123.5 (s); ^{13}C NMR (50 MHz, $CDCl_3$): δ = 26.1, 32.1, 48.3, 49.0, 54.1, 63.3, 114.5, 114.8, 118.8, 129.0; MS (70 eV): *m*/*z* (%): 167 (20) [NP(OMe)N-Ph], 205 (35)

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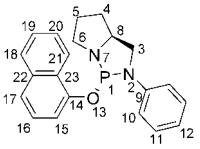
$[M^+-OMe]$, 236 (74) $[M^+]$; ESI-HRMS: m/z: calcd for $C_{12}H_{17}N_2OP$: 236.1072, found 236.1072.

(1*R*,8*S*)-1-(α-Naphthoxy)-2-phenyl-2,7-diaza-1-phosphabicyclo[3.3.0]octane (6b): (*S*)-2-anilinomethylpyrrolidine (1.00 g, 5.71 mmol) was dissolved in anhydrous toluene (10 mL) under argon. After the addition of

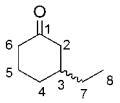


tris(dimethylamino)phosphine (0.99 g, 1.1 mL, 6.1 mmol, 1.1 equiv) the mixture was heated to reflux for 4 h. The reaction was monitored by ^{31}P NMR. After cooling to room temperature, the solvent and the excess of tris(dimethylamino)phosphine were distilled off. The residue was diluted with anhydrous toluene (10 mL), treated with α-naphthol (0.88 g, 6.1 mmol, 1.1 equiv) and again heated to reflux. The solvent was distilled off in vacuo. The remaining gum-like residue was subjected to fractional distillation in a Kugelrohr apparatus (1.9×10^{-1} mbar, 250 °C) to obtain the title compound as a yellow gum (0.85 g, 2.4 mmol, 42.0 %). ^1H and ^{31}P NMR spectra indicated a small impurity of (1*R*,8*S*)-1-(dimethylamino)-2-phenyl-2,7-diaza-1-phosphabicyclo[3.3.0]octane (**2**) as well as α-naphthol, which could not be completely eliminated. ^1H NMR (200 MHz, $CDCl_3$): $\delta=1.35$–1.47 (m, 1H), 1.61–1.83 (m, 3H), 3.00–3.20 (m, 2H), 3.41–3.76 (m, 3H), 6.86–6.95 (m, 2H), 7.11 (m, 2H), 7.20–7.46 (m, 7H), 7.71 (m, 1H); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=125.4$ (s); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=26.4$, 31.8, 47.3, 53.8, 62.7, 115.3, 115.6, 115.8, 119.6, 122.8, 123.1, 125.1, 125.8, 127.3, 128.4, 129.2, 145.2, 150.4.

(1*R*,7*R*)-4-*N*,*N*-Dimethylamino-9,9-dimethyl-2,2,6,6-tetraphenyl-3,5,8,10-tetraoxo-4-phosphabicyclo[5.3.0]decane (8): TADDOL (10.0 g, 21.4 mmol) was dissolved under argon in dry chloroform (50.0 mL) and HMPT (4.2 g, 4.7 mL, 25.7 mmol) was added dropwise with a syringe. The mixture was heated to reflux for 12–16 h. After 2 h the product begins to precipitate. At the end of the reaction the mixture is cooled to room temperature and the product is filtered off, washed with dry chloroform and dried in vacuo to furnish pure phosphoramidite (8.5 g, 73 %). A second crop (2.0 g, 18 %) of product was obtained after partial removal of the solvent. The product can be recrystallized from chloroform or dichloromethane. ^1H NMR (200 MHz, $CDCl_3$): $\delta=0.29$ (s, 3H), 1.26 (s, 3H), 2.72 (d, $^3J_{H,P}=10.5$ Hz, 6H), 4.82 (d, $J=8.5$ Hz, 1H), 5.18 (dd, $J=3.2$, $J=8.5$ Hz, 1H), 7.16–7.33 (m, 12H), 7.41 (d, $J=7.7$ Hz, 2H), 7.47 (d, $J=7.5$ Hz, 2H), 7.59 (d, $J=7.7$ Hz, 2H), 7.73 (d, $J=7.5$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=25.29$ (q), 27.51 (q), 35.18 (q), 35.44 (q), 81.17 (d, $J_{P,C}=7.3$ Hz), 81.81 (s), 82.35 (d, $J_{P,C}=23.2$ Hz), 82.45 (d), 111.71 (s), 127.09 (d), 127.25 (d), 127.44 (d), 127.65 (d), 128.07 (d), 128.67 (d), 128.74 (d), 128.95 (d), 141.77 (s), 142.09 (s), 146.43 (s), 146.85 (s); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=139.9$ (s).

General procedure for the conjugate addition of diethylzinc to α,β-unsaturated carbonyl compounds: copper(II)-bis(trifluoromethylsulfonate) (6.0 mg, 1.7 μmol, 1 mol %) were stirred with two equivalents of the respective ligand (3.4 μmol, 2 mol %) or its solution in toluene at room temperature for 2 h. The solution was cooled to −30 °C and treated with the respective enone (1.7 mmol) or its solution. After stirring for 30 min, a diethylzinc 15 % solution in hexanes (0.25 g, 2.2 mL, 2.2 mmol, 1.1 equiv) was added dropwise within 5 min, so that the reaction temperature did not rise above −30 °C. After 16 h the solution was warmed to 0 °C and treated with 1 N aqueous HCl. The resulting product was extracted with diethyl ether; then the combined organic phases were washed with satd aqueous $NaHCO_3$ and subsequently with aqueous NaCl and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo and the crude product was purified by chromatography.

3-Ethylcyclohexanone: The reaction was carried out with 2-cyclohexenone (0.16 mL, 0.16 g, 1.7 mmol). The reaction went to completion within 16 h with all ligands. The product was purified over silica gel eluting with *n*-hexane/ethyl acetate 4:1 ($R_f=0.40$) to yield the title compound (0.24 g,



1.6 mmol, 92 %). GC analyses ($t_R=14.5$ min) did not show any unwanted side products. ^1H NMR (200 MHz, $CDCl_3$): $\delta=0.91$ (t, $^3J=8.5$ Hz, 3H, C(8)-H), 1.31–1.42 (m, 3H), 1.58–1.72 (m, 2H) 1.89–1.96 (m, 1H, C(3)-H), 2.01–2.08 (m, 2H), 2.14–2.38 (m, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=11.0$ (C(8)), 25.2 (C(7)), 29.2, 30.8, 40.6 (C(3)), 41.4, 47.7, 211.9 (C(1)).

NMR spectroscopic characterization of 2:1 and 1:1 ligand complexes with CuI

Free ligand 5: ^1H NMR (200 MHz, $CDCl_3$): $\delta=1.54$–1.85 (m, 3H), 1.93–2.05 (m, 1H), 2.60 (d, $^3J_{H,P}=8.7$ Hz, 6H), 3.02–3.24 (m, 2H), 3.37–3.54 (m, 1H), 3.77 (ddd, $J=1.0$, $^3J_{H,P}=9.0$, $J=7.2$ Hz, 1H, C(3)-H), 4.06–4.19 (m, 1H), 6.76 (tt, $J=7.2$, $J=1.0$ Hz, 1H), 6.84 (m, 2H), 7.21 (m, 2H); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=119.3$ (s).

CuI-ligand 5 (2:1, dissolved crystals): ^1H NMR (200 MHz, $CDCl_3$): $\delta=$ 1.40–1.51 (m, 1H), 1.72–1.97 (m, 3H), 2.55 (s, 6H), 2.98–3.10 (m, 1H), 3.44 (t, $J=8.6$ Hz, 1H), 3.80–3.87 (m, 2H), 6.52 (d, $J=6$ Hz, 2H), 6.74 (t, $J=16$ Hz, 1H), 7.10 (t, $J=16$ Hz, 2H); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=$ 99.6 (br s); $\Delta\delta(^{31}P\ NMR)=20.3$ ppm.

Free ligand 6a: ^1H NMR (200 MHz, $CDCl_3$): $\delta=1.54$–1.85 (m, 3H), 1.95–2.08 (m, 1H), 3.08–3.25 (m, 2H), 3.33 (d, $^3J_{H,P}=8.5$ Hz, 3H), 3.48–3.64 (m, 1H), 3.75 (ddd, $J=1.0$, $^3J_{H,P}=9.0$, $J=7.2$ Hz, 1H), 4.10–4.22 (m, 1H), 6.83 (tt, $J=7.2$, $J=1.0$ Hz, 1H), 6.99–7.04 (m, 2H), 7.23 (m, 2H); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=123.5$ (s).

CuI-ligand 6a (4.79 mg, 0.025 mmol, 1 equiv CuI; 11.81 mg, 0.05 mmol, 2 equiv **6a**): ^1H NMR (200 MHz, $CDCl_3$): $\delta=1.52$–1.75 (m, 2H), 1.76–2.04 (m, 3H), 3.15 (t, $J=8.7$ Hz, 1H), 3.37–3.50 (br s, 3H), 3.62–3.86 (m, 2H), 3.87–3.99 (m, 1H), 6.84 (t, $J=14$ Hz, 1H), 7.02–7.27 (m, 4H); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=104$ (br s); $\Delta\delta(^{31}P\ NMR)=19.5$ ppm.

Free ligand 6b: ^1H NMR (200 MHz, $CDCl_3$): $\delta=1.35$–1.47 (m, 1H), 1.61–1.83 (m, 3H), 3.00–3.20 (m, 2H), 3.41–3.76 (m, 3H), 6.86–6.95 (m, 2H), 7.11 (m, 2H), 7.20–7.46 (m, 7H), 7.71 (m, 1H); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=125.4$ (s).

CuI-ligand 6b (3.81 mg, 0.02 mmol, 1 equiv CuI; 13.95 mg, 0.04 mmol, 2 equiv **6b**): ^1H NMR (200 MHz, $CDCl_3$): $\delta=1.18$–1.80 (m, 4H), 2.70–2.91 (m, 2H), 2.92–3.07 (dd, $J=7.8$ Hz, 1H), 3.27–3.39 (dd, $J=7.8$ Hz, 1H), 4.00–4.19 (br s, 1H), 6.74–6.88 (m, 2H), 7.01–7.61 (m, 9H), 7.71–7.78 (m, 1H), 8.22–8.33 (m, 1H) ; ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=96.5$ (br s); $\Delta\delta(^{31}P\ NMR)=29.1$ ppm.

Free ligand 7: ^1H NMR (200 MHz, $CDCl_3$): $\delta=2.54$ (d, $^3J_{H,P}=9$ Hz, 6H), 7.18–7.51 (m, 7H), 7.87–7.98 (m, 4H); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=$ 149 (s).

CuI-ligand 7 (3.05 mg, 0.016 mmol, 1 equiv CuI; 11.46 mg, 0.032 mmol, 2 equiv **7**): ^1H NMR (200 MHz, $CDCl_3$): $\delta=2.26$ (br s, 6H), 7.16–7.46 (m, 7H), 7.73–7.90 (m, 5H); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=128$ (br s); $\Delta\delta(^{31}P\ NMR)=21$ ppm.

Free ligand 8: ^1H NMR (200 MHz, $CDCl_3$): $\delta=0.29$ (s, 3H), 1.26 (s, 3H), 2.72 (d, $^3J_{H,P}=10.5$ Hz, 6H), 4.82 (d, $J=8.5$ Hz, 1H), 5.18 (dd, $J=3.2$, $J=$ 8.5 Hz, 1H), 7.16–7.33 (m, 12H), 7.41 (d, $J=7.7$ Hz, 2H), 7.47 (d, $J=$ 7.5 Hz, 2H), 7.59 (d, $J=7.7$ Hz, 2H), 7.73 (d, $J=7.5$ Hz, 2H); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=139.9$ (s).

CuI-ligand 8 (3.77 mg, 0.02 mmol, 1 equiv CuI; 10.95 mg, 0,02 mmol, 1 equiv **8**): ^1H NMR (200 MHz, $CDCl_3$): $\delta=0.45$–0.71 (br d, $J=32.0$ Hz, 6H), 2.49 (br d, $J=11.3$ Hz, 6H), 5.28 (br s, 2H), 7.17–7.36 (m, 11H), 7.37–7.46 (t, $J=7.5$ Hz, 4H), 7.50–7.66 (m, 6H); ^{31}P NMR (81 MHz, $CDCl_3$): $\delta=102.6$ (s); $\Delta\delta(^{31}P\ NMR)=37.3$ ppm.

Note: The oxygen and water sensitivity of the ligands required performance of their weighing procedure and subsequent transfer into NMR tubes inside a glove box.

Gas chromatography: Gaschromatographic analyses were carried out with a Hewlett-Packard gaschromatograph (HP 5890 Series II) equipped with FID and a Hewlett-Packard Integrator (HP 3396 Series II). The stationary phase was contained in a Supelco "γ-Dex 120" column (30 m × 0.25 mm × 0.25 μm). The same temperature program was used repeatedly (start $T=80$ °C (5 min), rate: 4 °C min^{-1}, final $T=140$ °C (5 min) (nitrogen carrier gas).

Kinetics of the 1,4-addition of diethylzinc to 2-cyclohexenone

a) Dependence on [enone]: 1 M reference solutions were prepared from 2-cyclohexenone and cyclohexanone as internal GC standard in dry tolu-

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ene. TADDOL-phosphoramidite **8** and BINOL-phosphoramidite **7** were used as solids, whereas 0.1 M solutions were prepared from the other ligands. Copper(II)-bis(trifluoromethylsulfonate) (7.2 mg, 0.02 mmol) was stirred with the ligand (0.04 mmol) or its solution in a total of 2.4 mL toluene for 16 h under argon at ambient temperature. Subsequent cooling to −30 °C was followed by addition of a 1 M solution of 2-cyclohexenone (2 mL, 0.19 g, 2 mmol) and a 1 M solution of cyclohexanone (2 mL, 0.20 g, 2 mmol). After 10 min, a 1 M solution of diethylzinc in hexanes (2.4 mL, 0.30 g, 2.4 mmol, 1.2 equiv), which was held at a constant temperature of 0 °C, was added within 1 min. As soon as the addition was complete, a 50 μL sample was taken from the reaction mixture and treated with water (1 mL) and diethyl ether (0.5 mL). Additional aliquots were taken after 2, 4, 6, 8, 10, 15, 20, 30, 45, 60, 80, 100, 120, 150 and 180 min and treated likewise. The ethereal phases were examined by GC. The reaction was carried on for another 13 h and finally quenched with 1 N aqueous HCl. Workup proceeded in the same manner as described above. The enantiomeric excess was determined by ^{13}C NMR spectroscopy after derivatization with (*R*,*R*)-1,2-Diamino-1,2-diphenyl-ethane.

b) Dependence on [$ZnEt_2$]: 1 M reference solutions were prepared from 2-cyclohexenone and cyclohexanone as internal GC standard in dry toluene. Copper(II)-bis(trifluoromethylsulfonate) (7.2 mg, 0.02 mmol) was stirred with ligand **5** (0.4 mL, 0.04 mmol in 0.1 M solution in toluene) in a total of 1.6 mL–2.4 mL dry toluene and 0.0 mL–2.4 mL dry *n*-hexane for 1 h under argon at ambient temperature. Subsequent cooling to −30 °C was followed by addition of a 1 M solution of 2-cyclohexenone (2 mL, 0.19 g, 2 mmol) and a 1 M solution of cyclohexanone (2 mL, 0.20 g, 2 mmol). After 30 min, 0.8 mL–5.0 mL of a 1 M solution of diethylzinc in hexanes (0.05 g, 2.4 mmol, 0.4 equiv to 0.625 g, 5.0 mmol, 2.5 equiv), which was held at a constant temperature of 0 °C, was added within 1 min (total capacity: 9.6 mL; total capacity for 2.5 equiv diethylzinc: 10.6 mL). As soon as the addition was completed, a 50 μL sample was taken from the reaction mixture and treated with 1 N aqueous HCl (1 mL) and diethyl ether (0.5 mL). Additional aliquots were taken after 1, 2, 3, 4, 5, 6, (7), 8, (9), 10, (11), 12, (13, 14), 15, 20, (25), 30, (40, 50), 60, 120 min and treated likewise. The ethereal phases were examined by GC.

c) Dependence on [catalyst]: 1 M reference solutions were prepared from 2-cyclohexenone und cyclohexanone as internal GC standard in dry toluene. 3.6 mg–18.0 mg copper(II)-bis(trifluoromethylsulfonate) (0.01 mmol–0.05 mmol) were stirred with 0.2 mL–1.0 mL (0.02 mmol–0.1 mmol in 0.1 M solution in toluene) of ligand **5** in a total of 2.4 mL dry toluene and 0.8 mL dry *n*-hexane for 1 h under argon at ambient temperature. Subsequent cooling to −30 °C was followed by addition of a 1 M solution of 2-cyclohexenone (2 mL, 0.19 g, 2 mmol) and a 1 M solution of cyclohexanone (2 mL, 0.20 g, 2 mmol). After 30 min, a 1 M solution of diethylzinc in hexanes (2.4 mL, 0.30 g, 2.4 mmol, 1.2 equiv), which was held at a constant temperature of 0 °C, was added within 1 min (total capacity: 9.6 mL). As soon as the addition was complete, a 50 μL sample was taken from the reaction mixture and treated with 1 N aqueous HCl (1 mL) and diethyl ether (0.5 mL). Additional aliquots were taken after 1, 2, 3, 4, 5, 6, (7), 8, (9), 10, (11), 12, (13, 14), 15, 20, (25), 30, (40, 50), 60, 120 min and treated likewise. The ethereal phases were examined by GC.

Note: With further increase of the ligand complex concentration the complex was not soluble any more in the available solvent quantity. Therefore a kinetic investigation was not possible beyond this point.

Lineshape analysis and calculation of T_C and $\Delta G^{\neq}$: A 2:1 mixture was prepared from the TADDOL-phosphoramidite **8** and CuI, and dissolved in dry $CDCl_3$, as described above. ^1H NMR spectra as well as ^{31}P NMR spectra were recorded in temperature intervals of 8 °C, starting from 233 K and ending at 315 K. While no change was observed within this temperature range in the ^{31}P NMR spectra, the ^1H NMR spectra showed dramatic changes corresponding to a dynamic exchange between the 1:1 complex **8**·CuI and the free ligand itself. At elevated temperatures, fast exchange leads to a simplified signal pattern with averaged shift values. At 297 K, coalescence is reached, demonstrated by extremely broad lines. Below 297 K, further cooling leads to the slow and very slow exchange regime, with the appearance of two sets of signals, one for the free ligand and the other one for the 1:1 complex. At 233 K, lines have become very sharp and correspond exactly to the superimposed NMR spectra of isolated 1:1 complex and free ligand.

Graphical representation as stacked plots: Stacked plots (aliphatic region) for the collected ^1H NMR data (400 MHz, dry $CDCl_3$) from the above-described VT experiment of a 2:1-mixture between TADDOL-$PNMe_2$ (**8**) and CuI (Figure 8). The black frame indicates the P-NMe_2 signal used for the line-shape analysis.

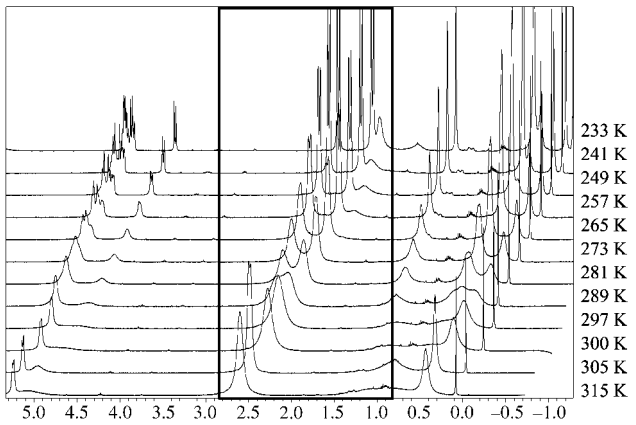

Figure 8. Lineshape analysis.

Evaluation: Since the equilibrium is degenerated, it can be described by Equation (1):

$$L + CuI \cdot L' \rightleftharpoons CuI \cdot L + L' \quad (1)$$

with L = L′. For the calculation of rate constants, the usual approximations were applied, depending on the time regime between fast and very slow exchange. A very well resolved signal is found in the methyl group of the P-NMe_2 moiety, which does not overlap with any other signal. Its linewidth was measured at half peak height at various temperatures and used for the calculation of *k* values from the respective approximation. Thus, the following values were obtained:

a) Fast exchange (> 10–15 °C above T_C) [Eq. (2)]:

$$k = \pi\Delta\nu_o^2/2(h_e - h_o) \quad (2)$$

with $\Delta\nu_o$ = peak separations [Hz] for spectra without exchange effects, and h_o = Full Width at Half-Height (FWHH, in Hz) for peaks showing *no* exchange effects, as well as h_e = FWHH for peaks widened from *exchange* effects.

At 315 K, $\Delta\nu_o$ = 157 Hz, h_e = 25, and h_o = 12 Hz. From this, $k = 2978\ s^{-1}$.

b) Coalescence temperature T_C [Eq. (3)]:

$$k = \pi\Delta\nu_o/2^{1/2} \quad (3)$$

with $\Delta\nu_o$ = peak separations [Hz] for spectra without exchange effects.

At 297 K, $\Delta\nu_o$ = 157 Hz. From this, $k = 349\ s^{-1}$.

c) Intermediate exchange (below T_C and > 20% peak overlap) [Eq. (4)]:

$$k = \pi(\Delta\nu_o^2 - \Delta\nu_e^2)^{1/2}/2^{1/2} \quad (4)$$

with $\Delta\nu_o$ and $\Delta\nu_e$ = peak separations [Hz] for spectra without and with exchange effects, respectively.

At 281 K, $\Delta\nu_o$ = 157 Hz, and $\Delta\nu_e$ = 96 Hz. From this, $k = 276\ s^{-1}$.

d) Slow exchange (well resolved peaks with less than ~20% overlap) [Eq. (5)]:

$$k = \pi\,(h_e - h_o) \quad (5)$$

At 273 K, h_e = 38 Hz, and h_o = 12 Hz. From this, $k = 82\ s^{-1}$.

At 265 K, h_e = 29 Hz, and h_o = 12 Hz. From this, $k = 53\ s^{-1}$.

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At 249 K, $h_e = 19$ Hz, and $h_o = 12$ Hz. From this, $k = 22\ s^{-1}$.
Since Equation (6):

$$\ln k = -E_a/RT + \ln A \quad (6)$$

a plot of ln$k$ vs $1/T$ (see Figures 7 and 9 and Table 1) yields $-E_a/R$ as its slope ($R = 8.314\ J\,mol^{-1}\,K^{-1}$). From this, E_a was calculated as 11.1 kcal mol^{-1}. Thus, the ligand exchange rate at T_C is $349\ s^{-1}$ and the activation energy barrier for this process amounts to $\Delta G^{\neq} = 46.4$ or 11.1 kcal mol^{-1}.

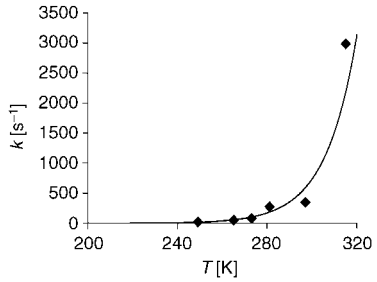

Figure 9. k versus T plot for the ligand exchange rate between Cu**I**·**8** and free **8**.

Table 1. Temperature dependence of rate constants for the exchange reaction between Cu**I**·**8** and free **8**.

T [K]	$1/T$	k [s^{-1}]	ln$k$
315	0.00317	2978	8.00
297	0.00336	349	5.85
281	0.00356	276	5.62
273	0.00366	82	4.40
265	0.00377	53	3.97
249	0.00402	22	3.09

EPR measurements: $Cu(OTf)_2$ (14.4 mg, 0.042 mmol) was weighed in a dry flask under argon (glovebox), treated with dry toluene (9.6 mL) and stirred vigorously for 2 h. An aliquot of 1.0 mL (corresponding to 0.0042 mmol $Cu(OTf)_2$, 1 equiv) of the resulting suspension was transferred into a 5 mm EPR tube and an EPR spectrum was taken at ambient temperature (ESP 300 E, Bruker, 9.2027 GHz, 300 K). In a second experiment, TADDOL-phosphoramidite **8** (43.2 mg, 0.08 mmol) was added under argon to $Cu(OTf)_2$ (14.4 mg, 0.04 mmol) (glovebox), and dissolved in dry toluene (9.6 mL) by intense stirring for 2 h. An EPR spectrum was taken from a 1.0 mL aliquot (corresponding to 0.0042 mmol $Cu(OTf)_2$, 1 equiv) of this (clouded) solution as well. Subsequent addition of $ZnEt_2$ (0.05 mL, 1.0 M in hexane, corresponding to 0.050 mmol, 25 equiv) to this aliquot in the EPR tube initiated the reduction of Cu^{II} to Cu^{I}. After 6, 10 and 18 min, EPR spectra were taken directly from this mixture under argon at 300 K (9.2332 GHz).

Results

The EPR spectrum of free suspended $Cu(OTf)_2$ (Scheme 3) shows the typical solid phase spectrum of a paramagnetic Cu^{II} species with $g_1 = 2.520$, $g_2 = 2.098$ and $g_3 = 2.098$. This spectrum markedly changes on addition of the phosphoramidite, indicating formation of the 2:1 Cu^{II}–phosphoramidite complex. After addition of excess diethylzinc immediate alkyl transfer concomitant with reduction of paramagnetic Cu^{II} to diamagnetic Cu^{I} takes place. Even without stirring, the EPR spectrum displays after 20 min only one straight baseline, indicating complete conversion of the starting material.

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