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Gas-Phase Study on the C–C Coupling of Naphthol Catalyzed by Cu^{II}·TMEDA: Evidence for the Key Role of Binuclear Clusters

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Abstract: The mechanism of oxidative coupling of two naphthol molecules to form binaphthol catalyzed by Cu(OH)Cl·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) was approached by means of a gas-phase model system. Concise evidence is provided that the coupling reaction proceeds in clusters with two Cu^{II} centers, whereby the intermediacy of free naphthoxy radicals in the coupling step is avoided. In the absence of TMEDA, the cluster is bound via a bridging counterion and the coupling reaction is followed by cluster cleavage. The coordination of one or two TMEDA molecules to the reactive complex results in more efficient coupling of naphthol molecules, and moreover, the binuclear cluster is also conserved after the reaction is completed. The effect of TMEDA is twofold: First, it supports clustering of copper and, second, as a ligand bound to a copper center in the reactive complex, it weakens the bond between copper and the naphtholato ligand such that the naphtholato unit is more prone to undergo C–C coupling. Furthermore, a pronounced counterion effect is found that correlates well with condensed-phase data: weakly bridging counterions (e.g., NO_3^-) yield less stable dicopper clusters and the coupling reaction hardly occurs, whereas better bridging counterions (e.g., Cl^- or Br^-) provide more stable clusters that make the coupling reaction more efficient.

Keywords: C–C coupling · copper · gas-phase reactions · mass spectrometry · reaction mechanisms

Introduction

Transition-metal-mediated oxidative coupling of aryl compounds is an important process in chemical synthesis.[1–3] In particular, oxidative C–C coupling is the major approach for preparation of 2,2′-disubstituted 1,1′-binaphthyls, which are important ligands in enantioselective synthesis.[4–7] The spectrum of transition metals that can be used for naphthol coupling ranges from the most frequently used copper[8] via iron[9] and manganese[10] as the classical reagents for phenol oxidation to more recent approaches using vanadium[11] and titanium.[12] Traditional preparations of substituted binaphthols (BINOLs) employ stoichiometric amounts of metal-based oxidants, but processes with catalytic amounts of metal-based oxidants have also been developed.[13] Another aspect is that binaphthyl compounds are usually prepared as racemic mixtures, which must be subsequently resolved into the enantiomers.[14,15] Modern strategies aim at direct synthesis of pure binaphthyl enantiomers.[16–22] For an efficient design of novel coupling catalysts,[23] a profound mechanistic understanding of the reaction sequence is of huge advantage. However, current knowledge is still far from complete and a comprehensive picture has not been emerged so far.

Scheme 1 summarizes mechanisms in which the transition metal acts merely as an electron acceptor.[4–7,23,24] Even in this seemingly simple case, however, four fundamentally different routes for the generation of the reactive species and the coupling reaction must be considered. Mechanism (i) involves recombination of two naphthoxy radicals and is often considered as the least important due to the low concentration of free radicals in solution. Mechanism (ii), a cation/anion recombination, does also not appear likely, because it involves an unstable α-carbonyl carbenium ion as intermediate. Mechanisms (iii) and (iv) involve coupling of naphthoxy radicals with either intact naphthol or its anion and are thus more probable scenarios; nevertheless, both routes require

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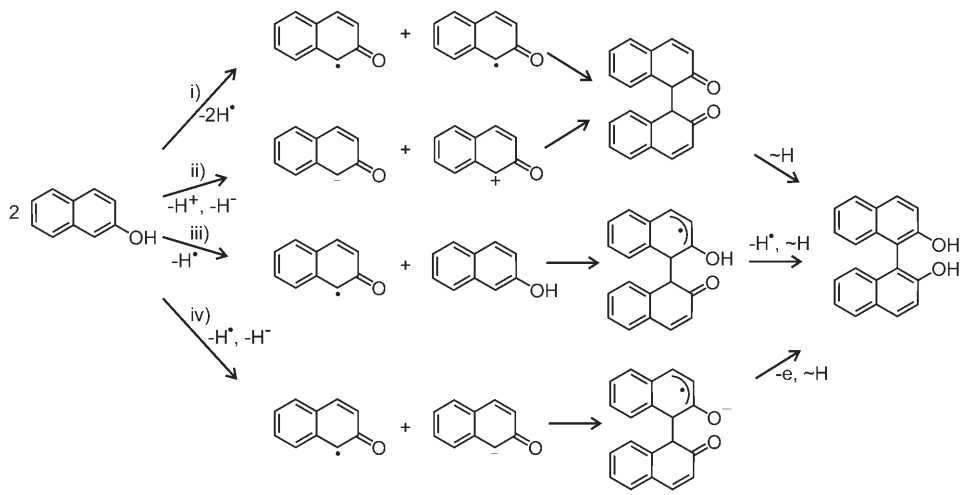
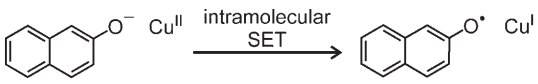


Scheme 1. Mechanistic manifold for C–C coupling of two 2-naphthol molecules.

formation of open-shell intermediates, which are expected to be not particularly favored.

The already quite complex situation shown in Scheme 1 becomes a mechanistic dilemma if active participation of the metal catalyst in the coupling process is assumed. How, for example, would the presence of a coordinating metal ion influence the generation of naphthoxy radicals, and would these be liberated as free radicals or be stabilized by coordination to the metal? If coordination of the metal is involved, it may play a role in one or both naphthol reactants which couple to form BINOL, and this leads to the obvious question whether mono- or polynuclear metal complexes are the catalytically active species. These questions are indeed relevant to some recent results on the metal-mediated coupling of naphthols. Thus, a number of chiral variants of the coupling reaction were developed in which chirality is induced by a ligand attached to a transition metal. The mere observation of an asymmetric induction implies that at least one metal ion is bound to the reactants or is at least present in the vicinity. Coordination of a metal to the reactants can influence their stability and reactivity, and this can have a major impact on the mechanistic considerations above. Moreover, in the presence of a redox-active metal compound, several of the mechanistic pathways proposed in Scheme 1 are connected to each other via single-electron transfer (SET) between the metal and the naphtholato ligand (e.g., Scheme 2).[25–27]

More recently, it has been shown that naphthol coupling proceeds efficiently with binuclear copper[23,28] and vanadium[21,22] catalysts, which results in yet another possible mechanistic manifold.[29] Thus, both reacting naphthol molecules can be bound to the metal centers of the binuclear cluster, which in part renders the distinction between the suggested



Scheme 2. SET between Cu^{II}/naphtholate and Cu^{I}/naphthoxy.

mechanisms in Scheme 1 redundant, because one or several SET processes in binuclear clusters can connect all pathways in Scheme 1.[30]

This kind of mechanistic dilemma in copper-mediated naphthol coupling is also reflected in the literature. In a systematic investigation of mixed cross-coupling reactions of naphthols, based on the selectivities Hovorka and Závada suggested mechanisms with free napthoxy radicals and mononuclear or binuclear copper clusters.[30] Smrčina et al. found that selectivities in naphthol cross-coupling reactions correlate with the stabilities of the respective naphthoxy radicals, but meanwhile they also excluded the involvement of free radicals.[24] Further evidence for direct participation of copper came from the observation of chiral induction in copper-mediated naphthol coupling. Smrčina et al. explained the observed enantioselectivities by using a mononuclear copper complex as a model system, in which the copper center is assumed to be coordinated in a square-planar fashion by a bidentate chiral diamine base and both naphthol molecules.[19] Kozlowski et al. reported that chiral induction in the course of the coupling reaction requires the naphthol molecule to bear an additional coordinating functionality in the 3-position. Accordingly, these authors proposed coupling between free naphthol and a mononuclear copper complex in which the metal has a tetrahedral coordination sphere with a bidentate, chiral diamine base and a bidentate naphthol molecule as a rationale for the observed enantioselectivities.[17,18,32] Similarly, Nakajima et al. proposed that a complex with a bidentate chiral diamine and a bidentate naphthol is formed; according to their scheme, however, the coupling reaction occurs between two of these complexes.[31] Finally, Gao et al. used polydentate Schiff base macrocycles as ligands and could thus fully support the coupling mechanism via binuclear, bridged copper clusters;[23] note, however, that the particular construction of the ligand also hardly offers alternatives to a dicopper complex.

In summary, the amount of experimental information is huge, but specific evidence for a particular mechanism is still limited, and systematic kinetic studies have not been performed so far. This is the point at which gas-phase studies may complement research in the condensed phase. Here we report a gas-phase model study on the mechanism of the coupling reaction between two naphthol molecules catalyzed by the complex Cu(OH)Cl·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine), which proceeds efficiently in a catalytic manner.[31] This reaction has also a chiral variant in which the TMEDA ligand is replaced by a chiral diamine.[18,32]

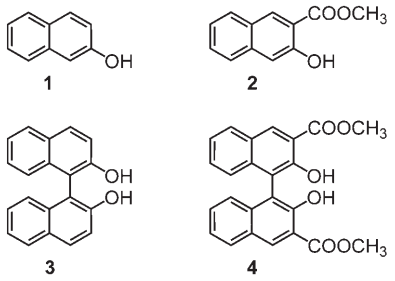
Experimental Section

The experiments were performed with a TSQ Classic mass spectrometer, which has been described elsewhere.[33,34] Briefly, the TSQ Classic consists of an electrospray ionization (ESI) source combined with a tandem mass spectrometer of QOQ configuration (Q stands for quadrupole, and O for octopole). The investigated ions were generated by ESI on solutions of the precursor naphthols or binaphthols in water, methanol, CH_2Cl_2, or mixtures thereof after addition of aqueous solutions of $CuCl_2$, $Cu(NO_3)_2$, Cu(OH)Cl·TMEDA, $Cu(NO_3)_2$/TMEDA, or $CuBr_2$/TMEDA. The first quadrupole was used as a mass filter to scan the ion spectrum or to select a certain ion of interest; the mass resolution of the quadrupole was sufficient to fully resolve the studied ions according to their m/z ratios. The mass-selected ions were then guided through the octopole serving as collision chamber followed by mass analysis of the ionic reaction products by means of the second quadrupole and subsequent detection. Reactant or collision gases were leaked into the octopole at typical pressures of the order of 10^{-4} mbar. The lower border of this range corresponds to approximate single-collision conditions, as verified by investigation of the pressure dependences. For collision-induced dissociation (CID), xenon was used at variable collision energies E_{lab} = 0–20 eV, whereas the reactivity studies with dimethyl disulfide were conducted with E_{lab} nominally set to zero. Natural isotope distributions and possible isobaric interferences were carefully considered in all experiments; the results reported below refer to the most abundant isotope ^{63}Cu.

Results and Discussion

As outlined in the introduction, concise mechanistic conclusions about copper-catalyzed oxidative coupling of naphthols to form BINOLs are anything but trivial. Moreover, consideration of macroscopic effects in catalytic reactions (e.g., reaction order) may be fairly remote from the elementary reaction steps. Our strategy for investigating the coupling mechanism therefore relies on the generation of possible reactive complexes by electrospray ionization (ESI) and then studying their unimolecular or bimolecular reactivity by means of mass spectrometry.[35,36] Our goal is thus to identify particularly reactive species which could be active with respect to the C–C coupling reaction, but we neither aim to study the origin of chiral effects in the presence of chiral ligands,[37] nor do we explicitly address the effects of solvation.

First, the complexes formed from an aqueous solution of naphthol (**1**) and $Cu(NO_3)_2$ are discussed. This combination is the simplest system and thus forms the basis for understanding the further studies. Electrospray ionization of this solution leads to the formation of $[(\mathbf{1}–H)Cu(H_2O)]^+$, $[(\mathbf{1}–H)Cu(\mathbf{1})]^+$, and $[(\mathbf{1})_2Cu]^+$ as the main ions which contain a naphthol unit and copper; here **1**–H stands for 2-naphtholate, and this notation is also used for the deprotonated forms of the other naphthols and BINOLs. Collision-induced dissociation (CID) spectra of the mass-selected ions support the indicated composition. The ion $[(\mathbf{1}–H)Cu(H_2O)]^+$ almost exclusively loses water (99.5%), with elimination of the naphthoxy unit as a minor channel (0.4%). Similarly, $[(\mathbf{1}–H)Cu(\mathbf{1})]^+$ predominantly loses the closed-shell naphthol ligand (87%), whereas loss of naphthoxy radical comprises only 13%, and $[(\mathbf{1})_2Cu]^+$ exclusively loses naphthol, as expected. Hence, water and naphthol are much more weakly bound to copper than the naphtholato ligand. Further, no evidence for the occurrence of C–C coupling was obtained for these mononuclear complexes, and polynuclear copper clusters with naphthol or naphtholato ligands were not formed under the conditions of the experiment.



Electrospray ionization of an aqueous solution of naphthol and Cu(OH)Cl·TMEDA gives an abundant signal for $[(\mathbf{1}–H)Cu(TMEDA)]^+$. The CID of this ion predominantly results in loss of a naphthoxy radical (98%), whereas the competitive loss of TMEDA amounts to only 1%. The stronger complexation of TMEDA to copper(II) compared to water or naphthol is clear: the nitrogen base TMEDA is a better ligand for copper than oxygen bases, and moreover a bidentate ligand.[38] With respect to the liberation of free naphthoxy radicals, it can be concluded that the interaction of TMEDA with copper destabilizes the bonding between copper and naphtholato ligand. Thus, at similar collision energies, loss of naphthoxy radical from the complexes $[(\mathbf{1}–H)Cu(H_2O)]^+$ and $[(\mathbf{1}–H)Cu(\mathbf{1})]^+$, respectively, accounts for less than 1% relative to the parent-ion intensity, whereas this channel is more than one order of magnitude more abundant (11%) upon CID of $[(\mathbf{1}–H)Cu(TMEDA)]^+$.

Investigation of the complexes formed from Cu^{II}/naphthol and Cu^{II}/naphthol/TMEDA shows that the TMEDA ligand has a dramatic effect on the bonding between copper and the naphtholato ligand. The weaker bonding in the presence of TMEDA can be interpreted in terms of stabilization of Cu^{I} by interaction with the base, and hence a significant change in the redox properties of the Cu^{I}/Cu^{II} couple. This in turn leads to a more pronounced radicaloid character of the naphtholato unit, which could explain why coordinating nitrogen bases make the coupling reactions more efficient. This scenario would be consistent with the previously proposed reaction mechanisms according to which interaction with copper leads to the generation of a naphthoxy radical, which subsequently reacts with a naphtholate anion or with neutral naphthol present in solution. The degree of localization of the radical center at the aromatic moiety was tested in the reaction of mass-selected $[(\mathbf{1}–H)Cu(TMEDA)]^+$ with dimethyl disulfide. Distonic ion radicals with carbon-centered radical sites are prone to abstract $CH_3S^{\bullet}$ from this reagent.[39] However, the reaction of $[(\mathbf{1}–H)Cu(TMEDA)]^+$ only affords the adduct $[(\mathbf{1}–H)Cu(TMEDA)(CH_3SSCH_3)]^+$ as well as the ligand-exchange product $[(CH_3SSCH_3)Cu(TMEDA)]^+$. This finding indicates that the naphtholato ligand does not readily react as a carbon-centered radical.[40]

With regard to the mechanism of the coupling reaction, no appreciable amounts of ions containing two naphthol or naphtholato ligands are produced from aqueous, methanolic, or CH_2Cl_2 solutions of **1** and Cu(OH)Cl·TMEDA. Due to the low solubility of naphthol in water, the aqueous solution yields primarily clusters of copper, TMEDA, and water without participation of naphthol. When the reactants are dissolved in methanol, naphthol dissolves readily, but the coupling reaction proceeds so fast that ESI yields mainly complexes with BINOL. Finally, ESI of a CH_2Cl_2 solution of naphthol and Cu(OH)Cl·TMEDA leads preferentially to clusters of copper and TMEDA without participation of naphtholato ligands. This unfavorable situation can be changed by appropriate variation of the substrate molecule. It is desired that the substrate has better complexation capability towards copper in competition with the solvent molecules water and methanol, and it should be less reactive with respect to the coupling reaction than pure naphthol. Both requirements are fulfilled by the methyl ester of 2-hydroxy-3-naphthoic acid (**2**), which contains a carboxymethyl group in the position *ortho* to the hydroxyl group, so that both groups can participate in binding to copper.[18] Moreover, the electron-withdrawing ester group should slow down the coupling reaction. Furthermore, this substrate has also been used in many studies on C–C coupling reactions in the condensed phase.[18,19,30–32]

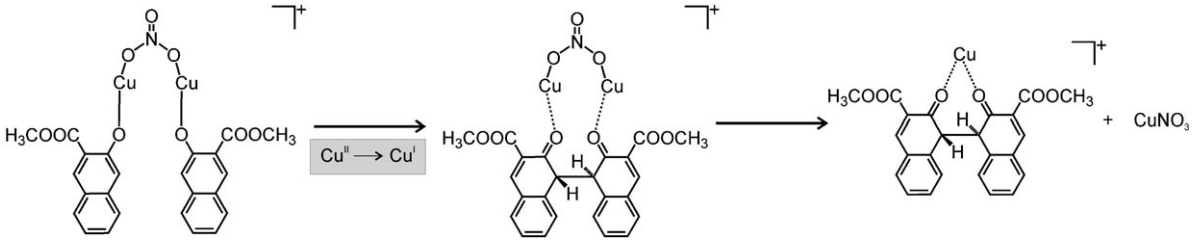
Electrospray ionization of **2** and $Cu(NO_3)_2$ dissolved in methanol/water yields the ions $[(\mathbf{2}-H)Cu(CH_3OH)]^+$, $[(\mathbf{2}-H)Cu(\mathbf{2})]^+$, $[(\mathbf{2}-H)_2Cu_2NO_3]^+$, and $[(\mathbf{2}-H)_3Cu_2]^+$ (spectra are shown in the Supporting Information). The CID of $[(\mathbf{2}-H)Cu(CH_3OH)]^+$ and $[(\mathbf{2}-H)Cu(\mathbf{2})]^+$ reveals that the binding of the naphtholato ligand is much stronger than that of either methanol or neutral **2**. In the dissociation of dicopper complex $[(\mathbf{2}-H)_2Cu_2NO_3]^+$, elimination of neutral $[(\mathbf{2}-H)CuNO_3]$ dominates (58%), which suggests that the cluster is composed of two $[(\mathbf{2}-H)Cu]^+$ units bound via an NO_3^- anion. Interestingly, loss of $CuNO_3$ (6%) and consecutive elimination of $CuNO_3$ and H_2O (5%) are also observed, which both correspond to Cu^{II}/Cu^{I} redox steps and thus possibly indicate the occurrence of C–C coupling with formation of the desired BINOL **4**.[41,42] Fragmentation of the dicopper cluster with three naphtholate ions $[(\mathbf{2}-H)_3Cu_2]^+$ leads to preferential losses of naphthol and naphthoxy radical (**2** and $(\mathbf{2}-H)^{\bullet}$, respectively). Minor dissociation channels include losses of methanol and neutral $[(\mathbf{2}-H)_2Cu]$.

The loss of $CuNO_3$, observed as a minor side reaction in the dissociation of $[(\mathbf{2}-H)_2Cu_2NO_3]^+$, is thus a first indication for the occurrence of coupling in a cluster with two copper ions, two naphtholato ligands, and one counterion. A possible scenario is suggested in Scheme 3: The coupling reaction is initiated by reduction of both copper ions from Cu^{II} to Cu^{I}, followed by C–C bond formation and subsequent cluster cleavage with elimination of neutral copper nitrate. Note that the product ion can also formally correspond to the complex of Cu^{III} with two separate naphtholato ligands (i.e., $[(\mathbf{2}-H)_2Cu]^+$); according to preliminary DFT calculations, however, the unpaired electrons in such a complex are localized at the aromatic rings of the naphtholato ligands, and therefore this arrangement is again likely to lead to the coupling reaction.

In the structure of $[(\mathbf{2}-H)_2Cu_2NO_3]^+$, obviously the carboxymethyl group also participates in bonding with copper, in particular with Cu^{II}, and the ester moiety may even act as bridging ligand.[18] Throughout this work, however, we present simplified structures in which these interactions are omitted. Other speculations about possible structural details of the reaction complexes are also not provided, and the formulas presented should be considered only as conceptual, mechanistically relevant models representing one of several plausible bonding possibilities. The mechanisms proposed are based solely on the observed experimental results and are not expected to be significantly influenced by the true most stable structure of the reported reaction complexes.

Electrospray ionization of a methanolic solution of **2** and Cu(OH)Cl·TMEDA yields $[(\mathbf{2}-H)Cu(TMEDA)]^+$ as the dominant ion (Figure 1a). In addition, significant amounts of dinuclear copper complexes such as $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)]^+$ and $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$ are formed. Similar to the analogous complex of naphthol, the TMEDA ligand facilitates elimination of a $(\mathbf{2}-H)^{\bullet}$ radical from $[(\mathbf{2}-H)Cu(TMEDA)]^+$ as the almost exclusive fragmentation path. Interestingly, although **2** is a better ligand than **1** due to its carboxymethyl group, which participates in binding to copper, it is still much more weakly bound to copper than the diamine ligand TMEDA.

The CID of $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)]^+$ revealed three significant dissociation channels (Scheme 4, Figure 1b). The major one leads to cluster degradation to afford neutral $[(\mathbf{2}-H)CuCl]$ and $[(\mathbf{2}-H)Cu(TMEDA)]^+$ as ionic fragment. The second channel leads to $[Cu_2Cl(TMEDA)]^+ + (\mathbf{2}-H)_2$, whereby the neutral product formally corresponds to the



Scheme 3. Proposed pathway for BINOL formation via dinuclear complex $[(\mathbf{2}-H)_2Cu_2NO_3]^+$.

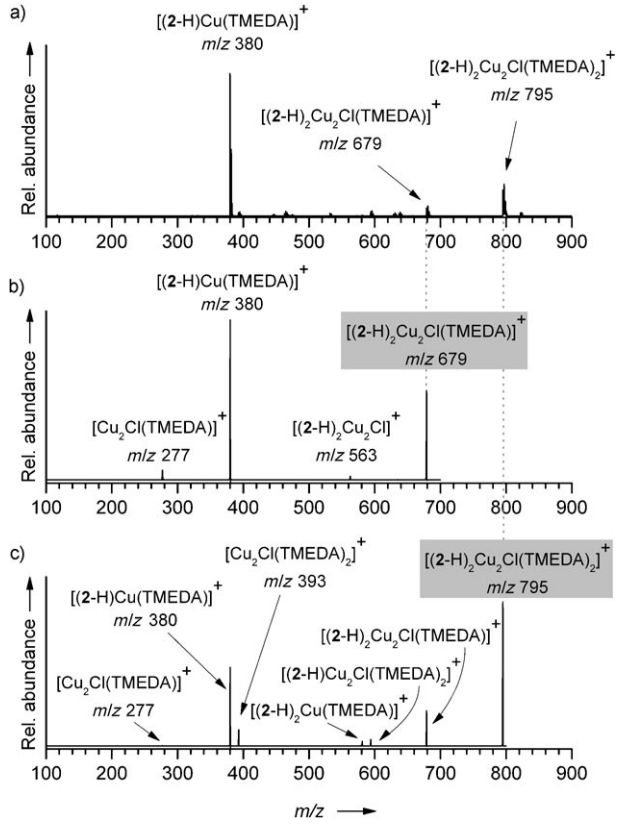
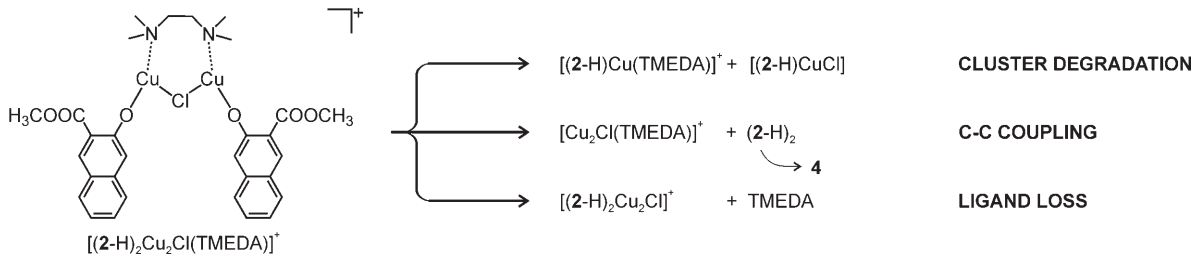


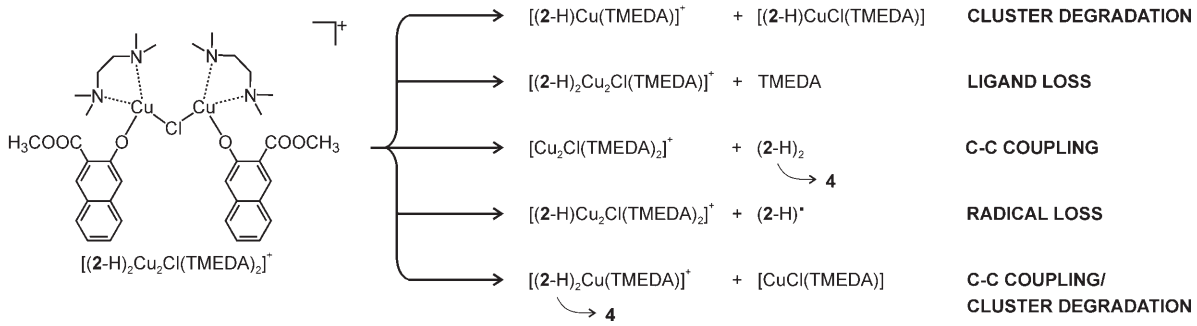
Figure 1. a) ESI mass spectrum of a methanolic solution of **2** and Cu(OH)Cl·TMEDA. b) CID spectrum of $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)]^+$ at $E_{coll}=1.6$ eV. c) CID spectrum of $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$ at $E_{coll}=1.4$ eV ($[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)]^+$ *m/z* 679, $[(\mathbf{2}-H)Cu_2Cl(TMEDA)_2]^+$ *m/z* 594, $[(\mathbf{2}-H)_2Cu(TMEDA)]^+$ *m/z* 581). Collision energies are given in the center-of-mass (CM) frame; collision gas: xenon.

coupling product **4**; the third channel is loss of TMEDA. The dominant fragmentation is consistent with a structure which contains the cations $[(\mathbf{2}-H)Cu(TMEDA)]^+$ and $[(\mathbf{2}-H)Cu]^+$, bound via a Cl^- counterion. Alternatively, TMEDA can also act as a bridging ligand, as suggested in Scheme 4. As shown above, fragmentation of the mononuclear species $[(\mathbf{2}-H)Cu(TMEDA)]^+$ leads preferentially to the loss of $(\mathbf{2}-H)^\bullet$. In marked contrast, no loss of $(\mathbf{2}-H)^\bullet$ is observed for $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)]^+$; instead, elimination of TMEDA takes place and is the third most populated fragmentation channel. It is thus suggested that the occurrence of the coupling reaction prevents the competition between the loss of the monomeric $(\mathbf{2}-H)^\bullet$ radical and TMEDA, and competition between two bidentate ligands, that is, newly formed BINOL and TMEDA, is observed instead. Given that the elimination of $(\mathbf{2}-H)^\bullet$ is not observed at all, the coupling reaction appears to proceed quite efficiently.

The major fragmentation channel of the cluster with two TMEDA ligands $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$ leads to separation into the subunits $[(\mathbf{2}-H)CuCl(TMEDA)]$ and $[(\mathbf{2}-H)Cu(TMEDA)]^+$ (Scheme 5, Figure 1c). Accordingly, a structure in which two $[(\mathbf{2}-H)Cu(TMEDA)]^+$ cations are bound via a chloride counterion is implied for the parent compound. Like above, besides the simple cluster cleavage, also the coupling reaction can occur. The leading mechanism is associated with the formation of $[Cu_2Cl(TMEDA)_2]^+$ concomitant with release of the coupled product **4** (Figure 1c). Another abundant fragmentation corresponds to elimination of TMEDA from the parent cluster. The thus-formed ion $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)]^+$ shows the same reactivity as suggested in Scheme 4. Interestingly, loss of the



Scheme 4. Fragmentation pathways of $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)]^+$.



Scheme 5. Fragmentation pathways of $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$

(**2**–H)$^{\bullet}$ radical is also observed to a small extent in Figure 1c, that is, the coupling reaction in $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$ does not entirely prevent the competition between loss of TMEDA and loss of (**2**–H)$^{\bullet}$, as is observed for the complex with only one TMEDA ligand. The last noteworthy process is elimination of CuCl·TMEDA (either at once or sequentially) leading to the formation of $[(\mathbf{2}-H)_2Cu(TMEDA)]^+$, in which $(\mathbf{2}-H)_2$ presumably is C–C coupling product **4**, because otherwise a formal Cu^{III} compound would be involved. This observation suggests that C–C coupling in $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$ can also proceed in analogy with the coupling sequence proposed for $[(\mathbf{2}-H)_2Cu_2NO_3]^+$ (Scheme 3), with the only difference that each copper center also carries a TMEDA ligand. This coupling mechanism ends with cluster degradation. However, the higher abundance of $[Cu_2Cl(TMEDA)_2]^+$ with respect to $[(\mathbf{2}-H)_2Cu(TMEDA)]^+$ indicates that the first mechanism for C–C coupling, which proceeds without cluster cleavage, is probably more efficient.

It could be proposed that the coupling reaction to form neutral product **4** does not occur, and instead fast sequential elimination of two (**2**–H)$^{\bullet}$ radicals takes place.[43] To disprove this scenario, the CID behavior of $[(\mathbf{2}-H)Cu_2Cl(TMEDA)_2]^+$ (m/z 594) was investigated ($E_{coll}=1.4$ eV, CM frame). This complex is the putative intermediate in the fragmentation of $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$ after loss of the first naphthoxy radical (Scheme 5, "radical loss"). If the scenario of rapid sequential losses of two (**2**–H)$^{\bullet}$ radicals from $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$ were true, complex $[(\mathbf{2}-H)Cu_2Cl(TMEDA)_2]^+$ should readily release a (**2**–H)$^{\bullet}$ radical. Instead, cluster degradation to yield neutral [CuCl(TMEDA)] and $[(\mathbf{2}-H)Cu(TMEDA)]^+$ (m/z 380) is observed almost exclusively, and elimination of (**2**–H)$^{\bullet}$ is about 300 times less abundant (see Figure 1S in the Supporting Information). Moreover, another minor fragmentation channel leading to the elimination of the TMEDA ligand, that is, formation of $[(\mathbf{2}-H)Cu_2Cl(TMEDA)]^+$ (m/z 478), is observed, which is not at all present in the spectrum shown in Figure 1c. Hence, the scenario of rapid sequential loss of two naphthoxy radicals can be safely excluded. Another indication for the elimination of $(\mathbf{2}-H)_2$ from $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$ being due to a coupling reaction was obtained by analysis of the CID of isovalent binuclear cluster $[(\mathbf{2}-H)Cu_2Cl_2(TMEDA)_2]^+$, in which one of the naphthoxo ligands is replaced by a chloride anion. Fragmentation of this cluster leads almost exclusively to cluster degradation (formation of $[(\mathbf{2}-H)CuCl(TMEDA)]^+$ and [CuCl(TMEDA)]), whereas elimination of the naphthoxy radical amount to only about 1% (see Figure 2S in the Supporting Information). In agreement with the finding that the TMEDA ligand is more strongly coordinated to copper than the naphtholato ligand, no TMEDA elimination is observed for $[(\mathbf{2}-H)Cu_2Cl_2(TMEDA)_2]^+$. In marked contrast, elimination of TMEDA constitutes the second most abundant fragmentation of the proposed reactive complex $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$ and greatly exceeds elimination of the bare naphthoxy radical. Accordingly, formation of a chelating ligand derived from BINOL **4** is proposed as the most convincing scenario to account for the various experimental observations.

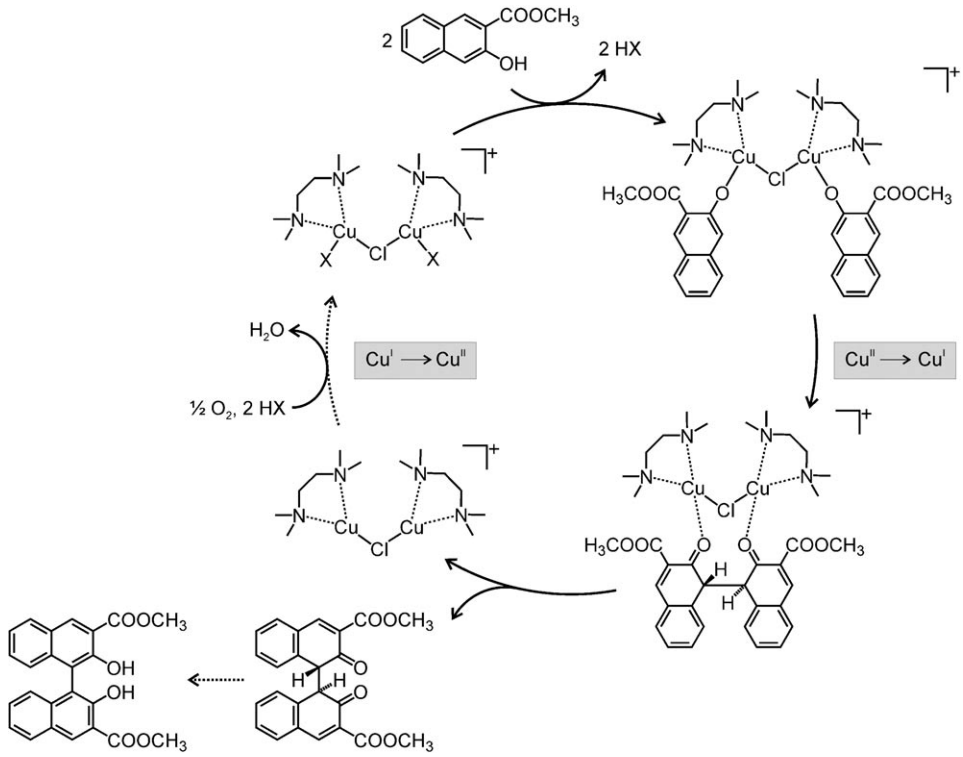
With regard to the structure of the $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$ complex, each TMEDA ligand can chelate one copper atom (Scheme 5), or the copper centers can be bridged by both TMEDA ligands. Note that structures suggested in Schemes 4–6 represent only one of several conceivable arrangements of the complexes. The most favorable structures for the given complexes will be the result of delicate equilibria between the bridging and chelating abilities of TMEDA, of the substrate **2**, and the resulting BINOL **4**, and also the steric demands of the given geometrical arrangements. However, the most favored structures of the studied complexes do not qualitatively influence the key features of the experimentally observed mechanism of the coupling reaction, and thus we restrict ourselves to showing only one of the possibilities for each complex discussed. Exact determination of the most stable structures of the reactive complexes will require rather extensive modeling and represents a challenge for future theoretical studies.

The effect of the counterion was investigated by comparing fragmentations of mass-selected $[(\mathbf{2}-H)_2Cu_2X(TMEDA)_2]^+$ (X = Cl, Br, or NO_3) upon collisional activation at $E_{coll}=1.4$ eV (CM frame). While the complex with $X=NO_3$ shows almost exclusive cluster degradation, that in which X = Br reveals enhanced reactivity towards C–C coupling compared to the system with X = Cl discussed so far. For the complex bound via chlorine, the branching between cluster degradation and C–C coupling amounts to 80:20, whereas for the complex bound via bromine this ratio is 60:40. This trend clearly demonstrates that poorly bridging ligands such as nitrate do not yield sufficiently stable dicopper complexes in the gas phase. As a consequence, only cluster degradation is observed and the coupling reaction hardly can occur. Better bridging anions such as chloride and even more so bromide provide stable dicopper complexes and thus allow the coupling reaction to take place. This rationale is in perfect agreement with experimental observations of Kozlowski et al. in the condensed phase, in which the effect of the counterions on the coupling of naphthol **2** catalyzed by CuX_2/diamine was investigated for X = Cl, Br, NO_3, and others.[18] For $X=NO_3$ the yield of isolated **4** was less than 10%, but it increased to 74% for X = Cl, and to even 93% in case of X = Br. The matching trends with regard to the counterion effect strongly support that the binuclear clusters play key role also in condensed media.

To further substantiate the proposed mechanism, the fragmentation of analogous complexes of the coupling product **4** were also studied. The ESI of a dilute solution of **4** and Cu(OH)Cl·TMEDA in CH_3OH/CH_2Cl_2 yields $[(\mathbf{4}-2H)Cu_2Cl(TMEDA)]^+$ and $[(\mathbf{4}-2H)Cu_2Cl(TMEDA)_2]^+$. These ions are not observed in the analogous spectrum of naphthol **2** (Figure 1a); hence, this is unambiguous proof that the C–C coupling does not proceed already in solution, but corresponds to a genuine gas-phase reaction.

Fragmentation of $[(\mathbf{4}-2H)Cu_2Cl(TMEDA)]^+$ reveals a competition between the elimination of (**4**–2H) and TMEDA (Figure 2a). Although **4**–2H is an oxidized form of BINOL, and hence different complexation abilities are expected, the fragmentation clearly shows that the coupled product can compete with the TMEDA ligand in bonding to copper, as suggested above. The fragmentation of the larger complex $[(\mathbf{4}-2H)Cu_2Cl(TMEDA)_2]^+$ leads to elimination of TMEDA and of the neutral complex CuCl·TMEDA, respectively (Figure 2b). The latter represents the redox reaction in $[(\mathbf{4}-2H)Cu_2Cl(TMEDA)_2]^+$.

The above findings provide a consistent picture for the reaction mechanism in the gas-phase model system (Scheme 6). Thus, the reaction sequence starts with the formation of $[Cu_2X_3(TMEDA)_2]^+$, where X are counterions from the employed Cu^{II} catalyst or anions formed on deprotonation of the solvent. In the next step, exchange of the counterions by naphtholate ions occurs, which, as an inherent side effect of clustering, brings the reactant molecules into proximity. In the further course of the sequence, formation of this complex then induces coupling of the two naphthol moieties concomitant with transfer of two electrons to the copper centers. The coupling product can be released either in the keto form, which can subsequently rearrange to the more stable enol, or rearrangement can occur already in the complex prior to dissociation.[44] On release of the coupled product, a cluster with two Cu^I ions, namely, $[Cu_2Cl(TMEDA)_2]^+$, is formed. In solution, this dicopper complex can be readily re-oxidized by molecular oxygen to regenerate the reactive species $[Cu_2X_3(TMEDA)_2]^+$.[45] Alternatively, the reaction sequence can begin with loss of the TMEDA ligand such that the coupling step occurs in the complex $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)]^+$ (Scheme 4; for the catalytic cycle see the Supporting Information).



Scheme 6. Catalytic cycle for BINOL formation via a Cu_2 complex with two TMEDA ligands.

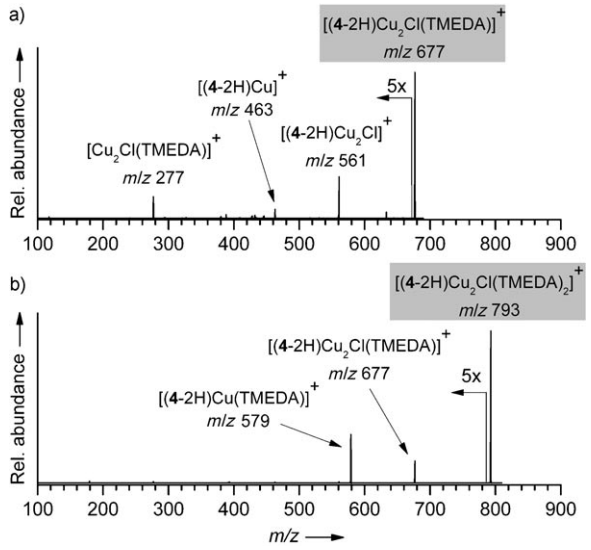


Figure 2. a) CID spectrum of $[(\mathbf{4}-2H)Cu_2Cl(TMEDA)]^+$ at $E_{coll}=1.6$ eV. b) CID spectrum of $[(\mathbf{4}-2H)Cu_2Cl(TMEDA)_2]^+$ at $E_{coll}=1.4$ eV. Collision energies given in the CM frame; collision gas: xenon.

Besides these two major pathways, the coupling reaction can also proceed in analogy to the reaction shown in Scheme 3. In this reaction sequence, the product is not released from the bicopper complex after the coupling step, but instead it binds to one copper atom only and the cluster dissociates. For coupling in the $[(\mathbf{2}-H)_2Cu_2Cl(TMEDA)_2]^+$ complex, this reaction mechanism is probably less efficient, but it becomes the major one when the coupling reaction is performed with copper(II) salts alone, that is, in the absence of TMEDA or other amine ligands which support clustering.[46]

While our gas-phase studies cannot directly be translated to solution chemistry, the present findings still suggest some objectives for the design of naphthol coupling catalysts in applied synthesis. First, our results demonstrate that, at least in the case of the Cu^I/Cu^{II} redox system, formation of binuclear complexes facilitates the coupling process. Second, ni-

trogen ligands promote cluster formation and thus also accelerate the coupling step. At the same time, coordination of a nitrogen base to the metal center weakens the bond between the metal and the naphtholato ligand, which again supports the coupling reaction. The key role of nitrogen ligands is emphasized when a chiral nitrogen base is used to obtain enantiomerically enriched or pure BINOLs. Reviewing the overall process also implies that efficient enantioselective coupling in the condensed phase requires an optimum ratio between copper and nitrogen base. Too low concentration of the base could lead to coupling on bare copper clusters, which would yield a racemic product. Too high concentration of the base could lead to poisoning of the catalyst, because nitrogen bases are much better ligands for copper than naphthol. Our model study further shows that the stability of copper clusters in the gas phase depends on particular counterions. Thus, poor bridging counterions do not provide sufficiently stable dicopper complexes, and therefore the coupling reaction is not observed. Better bridging counterions such as Cl or Br yield stable dicopper complexes and thereby promote the coupling reaction. As strong support for the proposed binuclear mechanism, the same trend was observed for various counterions in the condensed phase.[18] Finally, all the proposed aspects of the presented mechanism seem to be fulfilled for the recently reported catalyst of Gao et al.,[23] which contains two copper ions in the rigid framework of a macrocycle in which each copper atom is coordinated in a N_2O_2 compartment. Finally, several efficient vanadium catalysts with similar binuclear structures have been reported and, although containing a different metal, seem to work on an analogous basis.[22]

Conclusion

The experiments reported here demonstrate that binuclear Cu^{II} complexes are crucial for promoting oxidative C–C coupling of naphthols in the gas phase. The key role of the diamine ligand TMEDA consists of 1) supporting formation of dicopper complexes and 2) enhancing naphthol reactivity in the binuclear complex, which synergistically make the coupling reaction more efficient. Hence, a concise and experimentally supported mechanistic rationale for naphthol coupling is proposed. While the detailed structural analysis of the reactive complexes may remain a task for future theoretical calculations, the present gas-phase data provide solid evidence for the coupling mechanism and thus provide useful guidelines for condensed-phase synthesis which may help in the design of new catalysts for the oxidative coupling of naphthols.

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[40] For comparison, an analogous reaction of dimethyl disulfide with $[(PhO)Cu]^+$ (PhO^- = phenolate) leads to the abstraction of $CH_3S^\bullet$. The reaction of dimethyl disulfide with $[(PhO)Cu(TMEDA)]^+$ results preferentially in ligand exchange to form $[(CH_3SSCH_3)Cu(TMEDA)]^+$, but a minor channel leading to $CH_3S^\bullet$ abstraction is observed too.

[41] We note that the fragmentation of the mononuclear complex $[(\mathbf{4}-H)Cu(\mathbf{4})]^+$, which is formed on ESI of a methanolic solution of BINOL **4** and $Cu(NO_3)_2$ as the dominant ion, reveals subsequent losses of neutral BINOL **4** and OH radical. Thus, a complex of dehydrated BINOL **4** and Cu^I is formed as the final product, exactly as is observed in the reaction sequence $[(\mathbf{2}-H)_2Cu_2NO_3]^+ \rightarrow [(\mathbf{4})Cu]^+ \rightarrow [(\mathbf{4}-H_2O)Cu]^+$.

[42] Comparison of the reactivity of $[(\mathbf{2}-H)_2Cu_2NO_3]^+$ with that of the analogous $[(\mathbf{2}-H)_2Cu_2Cl]^+$ complex is impossible, because the latter is not formed in an amount sufficient to allow CID experiments with the mass-selected ion.

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