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Cross-Coupling

Reactions Catalysed by a Binuclear Copper Complex: Aerobic Cross Dehydrogenative Coupling of *N*-Aryl Tetrahydroisoquinolines

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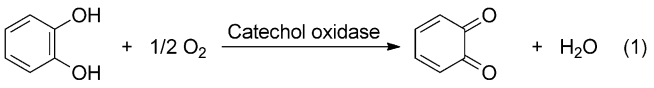
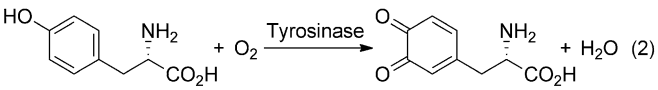
Abstract: Binuclear copper complex $[\{Cu(Sal)_2(NCMe)\}_2]$ (Sal = salicylate) was found to be an active catalyst for the aerobic oxidation of *N*-aryl tetrahydroisoquinolines to the corresponding iminium ions, which could be trapped by a wide range of nucleophiles to form coupled products. The reactions took place under 1 bar of O_2 at room temperature with 1 mol% of the copper catalyst being sufficient in most cases, and are considerably accelerated by catalytic chloride anions. Mechanistic studies show that the Cu^{II} dimer oxidizes the amine to the iminium ion, and this two-electron process requires O_2, whereby the resulting Cu^{I} is concomitantly re-oxidised back to Cu^{II}. Various lines of evidence suggest that the oxidative coupling reaction is turnover-limited by the step of iminium formation, and it is this step that is promoted by the chloride anion. Since it is more efficient than and mechanistically distinct from the well-studied simple copper salts such as CuBr and $CuCl_2$, the binuclear copper catalyst provides a new tool for oxidative coupling reactions.

Introduction

Catalytic oxidation with oxygen as oxidant is an ideal route for functionalization of organic molecules. In nature, enzymes activate oxygen, which then oxidizes the substrate, while oxygen is transformed into hydrogen peroxide/water (oxidases) or incorporated into the product (oxygenases).[1] The active site of many enzymes contains bimetallic centres.[2] For example, the R_2 protein of ribonucleotide reductase (RNR-R_2) and the hydroxylase component of soluble methane monooxygenase (sMMO) have carboxylate-bridged non-heme diiron centres.[2a–c] Dicopper proteins are particularly prominent and feature in a number of important biological reactions that involve oxygen.[2d,f,3] Well-known examples include haemocyanin,[4] tyrosinase[5] and catechol oxidase,[6] whereby hemocyanin acts as an oxygen transporter, and the other two enzymes catalyse the oxidation of phenolic compounds [Eqs. (1) and (2)]. Particulate methane monooxygenase (pMMO) is also believed to have a dicopper active site.[7] Inspired by nature, a great number of binuclear copper complexes bearing nitrogen ligands have been synthesized with the aim of mimicking the oxidation ability of these enzymes.[1e,2f,3b,6c]





Paddle-wheel Cu^{II} carboxylate dimers are another well-known class of binuclear copper complexes.[8] These complexes have been studied for their peculiar structures, magnetism and electrochemical properties.[8c,d,g–i] Of particular interest are complexes derived from salicylic acid and derivatives, for example, $[Cu_2(Aspirin-H)_2L_2]$ (Aspirin = 2-acetylsalicylic acid), which show potent anti-inflammatory, anticonvulsant and antitumour activities and have been extensively studied as superoxide dismutase mimetics, mainly owing to their ability to dismutate the reactive oxygen species O_2^{-}.[9] However, these binuclear paddle-wheel Cu^{II} carboxylates have rarely been studied as catalysts for synthetic chemistry.[8g,10] Herein, we report that a simple binuclear Cu^{II} salicylate complex catalyses highly efficient cross dehydrogenative coupling (CDC) of amines, which appears to operate by a novel mechanism.

The CDC reaction, or oxidative coupling, in which a new bond C–X is formed as a result of coupling of two molecular fragments RH and HX (X denotes a heteroatom) by oxidation, is a powerful tool for direct functionalization of C–H bonds [Eq. (3)].[11] In particular, the CDC reaction of amines, typified by *N*-phenyltetrahydroisoquinoline, with nucleophiles has been

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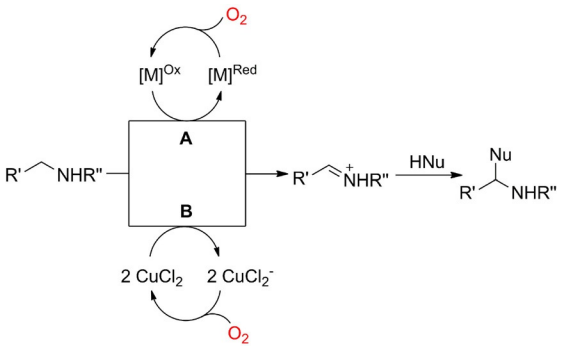
extensively investigated.[11a,d,f,12] Since the pioneering studies of Murahashi et al.[13] and Li et al.[14] on CDC reactions of *N*-phenyltetrahydroisoquinoline catalysed by $RuCl_3$ and CuBr, a variety of catalysts have been introduced, for example, $CuBr_2$,[14c] $CuCl_2$,[15] $Cu(OTf)_2$,[16] $FeCl_3$,[17] and $VO(acac)_2$ (acac = acetylacetonate),[18] which permit a wide range of CDC reactions. *tert*-Butyl hydroperoxide (TBHP) is the most often used oxidant in these reactions.[11a,12,14a] In comparison, the clean, economic O_2 has featured much less.[13b,15a,17a,19] In addition, for most of these catalysts, a shortfall is that they have only been explored for one or two types of substrates.

$$RH + XH \xrightarrow[[O]]{[M]} R\text{-}X \qquad (3)$$

The simple copper halides have been most extensively studied as catalysts for CDC reactions, and some have been shown to be particularly effective in the oxidative coupling of carbon nucleophiles with amines.[11a,e] One of the most notable examples is CuBr in conjunction with TBHP.[14a] Developed by Li and co-workers, this catalytic system enables *N*-aryl tetrahydroisoquinolines to couple with a wide variety of nucleophiles, such as alkynes, nitroalkanes, malonates, indoles, cyanides and naphthols.[11a] They also demonstrated that the coupling with nitroalkanes can be conducted with O_2[19a] or electrochemically.[20] Klussmann and co-workers recently revealed that $CuCl_2$ also catalyses the CDC reaction of *N*-aryl tetrahydroisoquinolines with a number of nucleophiles and, more interestingly, oxygen can be used as the terminal oxidant for this wide range of nucleophiles.[12b,15,21] We note that with these simple copper salts, the catalyst loading is usually high, typically 5–10 mol%.

It is generally believed, though rarely backed with evidence, that the aerobic oxidative coupling of an amine with a nucleophile (HNu) starts with catalyst-mediated electron transfer, which leads to an iminium cation, to which HNu is added to afford the coupled product.[10c,12b] The role of the terminal oxidant O_2 is to oxidize the catalyst back to its starting oxidation state (Scheme 1 A), with no bearing on the step of amine oxidation. In the last a few years, mechanistic studies by Klussmann et al.[15b,c,21] and Doyle et al.[17b] have shed new light on the CDC reactions of amines. In particular, the hypothetical iminium intermediate was isolated by Klussmann et al. in the aerobic CDC of *N*-phenyl tetrahydroisoquinolines catalysed by $CuCl_2 \cdot 2H_2O$,[15b,22] and a systematic study led to the refined mechanism shown in Scheme 1 B.[15b,21] The key feature of this mechanism is that the amine is oxidized by two molecules of the Cu^{II} catalyst in a two-electron oxidation process in which an iminium cation is formed and Cu^{II} is reduced to a Cu^{I} anion, namely, $CuCl_2^-$. The catalytic cycle is completed by O_2 oxidation of Cu^{I} back to Cu^{II}. A recent computational study by Wu and co-workers supports the mechanism.[23] This mechanism differs from the original proposal by Li et al. in that the iminium C=N bond does not coordinate to the copper centre.[11a,14c]

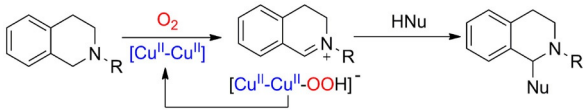


Scheme 1. Common mechanism and that proposed by Klussmann et al. for the CDC of amines.

Herein, we report that a dicopper tetrasalicylate complex catalyses efficient CDC of *N*-aryl tetrahydroisoquinolines with oxygen as oxidant (Scheme 2). The key features of the protocol are:

1) The catalyst is a well-defined binuclear copper complex and is much more active than the copper halide salts previously reported.
2) Chloride anion shows a remarkable accelerating effect on the CDC.
3) Oxygen is necessary for copper oxidation and iminium formation.

Mechanistically, the catalyst is thus different from the known CDC catalysts, but resembles, to a certain degree, some well-known copper enzymes, for example, dopamine β-monooxygenase (Scheme 2).[3b,24]



Scheme 2. Work reported herein and an outline of suggested reaction pathways.

Results and Discussion

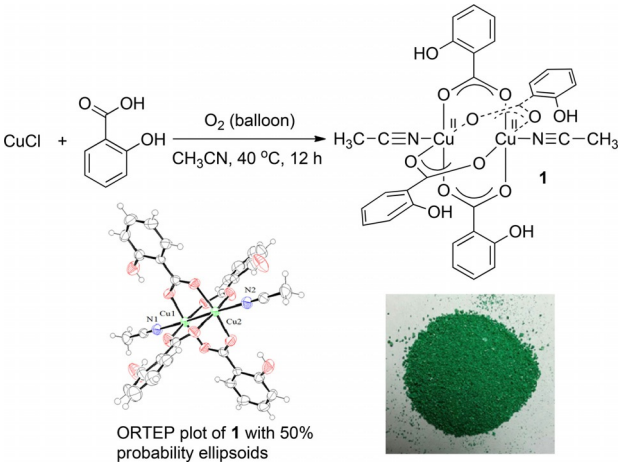
Oxidative coupling reactions

Bimetallic tetracarboxylate units are stable structures commonly found in metal complexes.[25] Many such dicopper carboxylate complexes have been synthesized, with hundreds crystallographically characterized.[8d–f] Surprisingly, their potential as catalysts for organic synthesis has rarely been explored thus far,[8g,10a,c] although these dicopper complexes have been extensively studied as superoxide dismutase mimetics in bioinorganic and medicinal chemistry.[8g,9c,e,f]

Synthesis of [{Cu(Sal)$_2$(NCMe)}$_2$]

Bimetallic tetracarboxylate Cu^{II} complexes can be readily accessed from a Cu^{II} salt in the presence of a carboxylic acid. However, reactions of the same Cu^{II} salt and a carboxylic acid may lead to copper complexes of differing structures depend-

ing on the synthetic conditions.[8d,9f,26] We found that the binuclear Cu^{II} salicylate complex [{$Cu(Sal)_2(NCMe)$}$_2$] (**1**) can be prepared easily and reproducibly by treating CuCl with salicylic acid under oxygen. Thus, on stirring CuCl and 2 equiv of salicylic acid in CH_3CN at 40 °C under a balloon pressure of oxygen for 12 h and leaving the resulting solution at −10 °C for 2–3 d, fine green crystals of complex **1** were isolated in 22% yield (Scheme 3). The structure of **1** was confirmed by



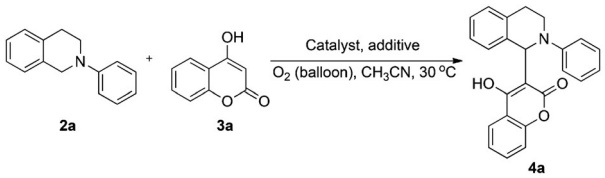
Scheme 3. Synthesis of binuclear copper complex [{$Cu(Sal)_2(NCMe)$}$_2$] (**1**).

single-crystal X-ray diffraction and is typical of paddle-wheel tetracarboxylate dicopper(II) complexes, with a Cu–Cu internuclear distance of 2.6643(6) Å.[8a,d,h,i,9b,d,e] X-ray photoelectron spectroscopy of the crystals showed that the oxidation state of the metal centres is Cu^{II} (Supporting Information, Scheme S1).[28] The complex is paramagnetic, probably due to population of its low-lying triplet state;[27] thus, its ^{1}H NMR spectrum shows no resonance in the aromatic region. However, a sharp singlet, corresponding to two free CH_3CN molecules, as judged by an internal standard, was observed in the spectrum in CD_3OD, that is, the coordinated CH_3CN dissociates from the complex upon dissolution in CD_3OD (Supporting Information, Scheme S1).

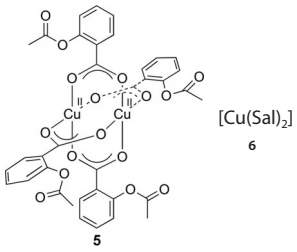
Effect of 1 and chloride on oxidative coupling

The catalytic activity of complex **1** was explored in the oxidative cross-coupling of *N*-phenyltetrahydroisoquinoline (**2a**) with hydroxycoumarin **3a** by using O_2 as the oxidant. In the absence of a catalyst, no reaction took place between **2a** and **3a** in CH_3CN under an oxygen atmosphere at 30 °C for 1 h (Table 1, entry 1). Upon addition of 1 mol% of **1** to the reaction, the cross-coupling product **4a** was obtained in 49% yield (Table 1, entry 2). However, the reaction became sluggish thereafter, and did not go to completion, even after a prolonged time of 24 h (Table 1 entry 3). Remarkably, upon introduction of 2 equiv (relative to **1**) of tetra-*n*-butylammonium chloride (TBAC), the reaction was dramatically accelerated, and 94% yield was obtained in 1 h (Table 1, entry 4). Under these

Table 1. Catalytic activity of selected copper complexes in the CDC of **2a** with **3a**.[a]



Entry	Catalyst	Catalyst loading [mol%]	Additive (mol%)	*t* [h]	Yield [%][b]
1	**1**	–	–	1	0
2	**1**	1	–	1	49
3	**1**	1	–	24	73
4	**1**	1	TBAC (2)	1	94
5	**1**	0.5	TBAC (1)	12	91
6	**1**	0.25	TBAC (0.5)	24	76
7[c]	**1**	1	TBAC (2)	1	42
8	**1**	1	TBAC (20)	1	<5
9	**1**	1	TBA Br (2)	1	70
10	**1**	1	TBA I (2)	1	0
11	**5**	1	TBAC (2)	1	42
12	**6**	1	TBAC (2)	1	29
13	CuCl	1	TBAC (2)	1	21
14	$CuCl_2$	1	TBAC (2)	1	36
15	CuCl	1	–	1	33
16	$CuCl_2$	1	–	1	40



[a] Reaction conditions: *N*-phenyltetrahydroisoquinoline (0.25 mmol), hydroxycoumarin (0.5 mmol), MeCN (1 mL), O_2 balloon, 30 °C. [b] Yield of isolated product. [c] The reaction was carried out under air.

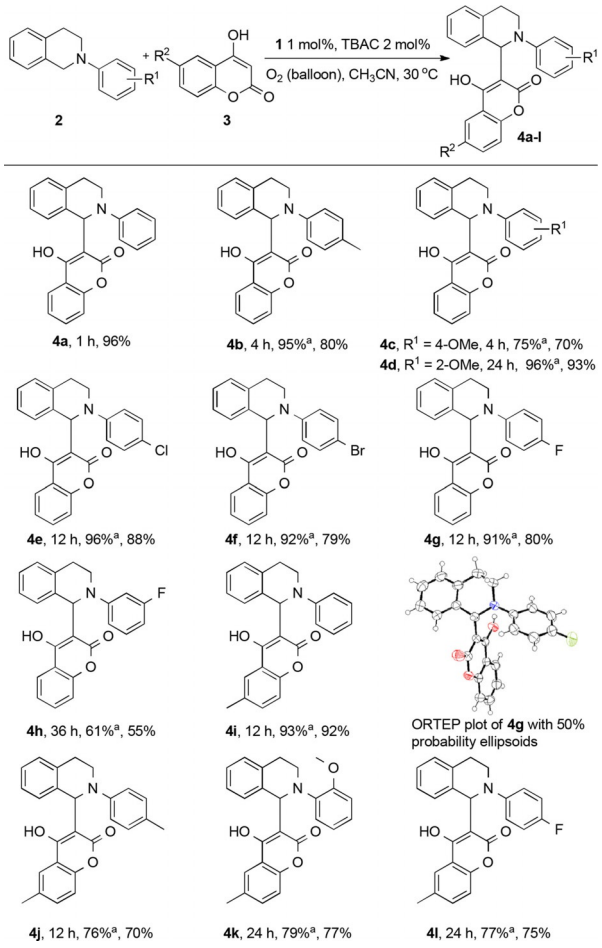
conditions the catalyst loading could be decreased to 0.5 and 0.25 mol%, with 91% yield in 12 h and 76% yield in 24 h, respectively (Table 1, entries 5 and 6). To the best of our knowledge, this is the highest substrate/catalyst ratio ever reported for copper-catalysed aerobic CDC reactions.[28] The reaction also took place under air, albeit with a lower yield (Table 1, entry 7). The addition of more TBAC was, however, detrimental to the coupling reaction (Table 1, entry 8). For more details of the chloride effect, see Supporting Information, Scheme S2. Tetrabutylammonium bromide also accelerated the reaction (Table 1, entry 9), albeit to a lesser degree. However, the reaction was totally inhibited by tetrabutylammonium iodide (Table 1, entries 10). These results show that it is the anion that affects the CDC rate, with chloride being the most promoting. The inhibiting effect of iodide may arise from its propensity to form stable iodide-bridged multicopper species.[29] Somewhat surprisingly, the aspirinate complex **5**,[30] in which the salicylic acid of **1** is protected by acetyl groups, is much less active, and so is the monomeric Cu^{II} salicylate complex [$Cu(sal)_2$] (**6**),[9e] in the presence of TBAC (Table 1, entries 11, 12). In its absence, neither **5** nor **6** afforded any coupling product under the con-

ditions used. The previously demonstrated simple copper salts, such as CuCl and $CuCl_2$,[11a,15a,c,21] could also catalyse the aerobic coupling, and showed similar activity in the absence or presence of TBAC (Table 1, entries 13–16). They are, however, much less effective than the combination of **1** and TABC, and afforded **4a** in $<60\%$ yield in a prolonged time of 12 h under the conditions given in Table 1.

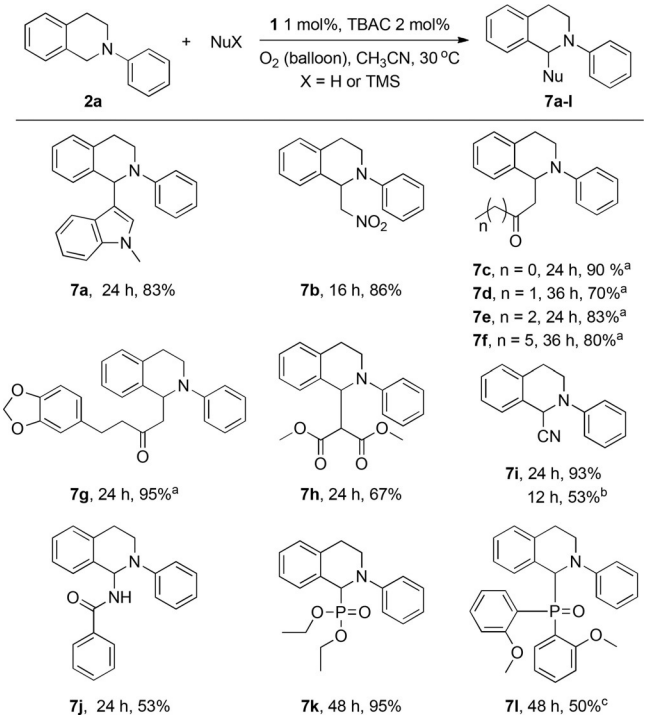
Scope of 1-catalysed cross-coupling

The combination of **1** (1 mol%) and TBAC (2 mol%) as catalyst (here after denoted **1**-Cl) was used to examine the substrate scope of **1**-Cl-catalysed CDC of *N*-aryl tetrahydroisoquinolines with hydroxycoumarins (Scheme 4). Apart from **2a**, *N*-aryl tetrahydroisoquinolines with substituents at the *N*-phenyl ring all reacted well with hydroxycoumarins, and afforded good to excellent yields (Scheme 4, **4a**–**4l**). It appears that electron-donating substituents generally bestow a higher activity than electron-withdrawing ones (**4b** versus **4e**–**4h**). However, the 2-OMe-substituted **2d** and **2k** required a considerably longer time to react with **3**, and this indicates inhibition by the substituent of possible coordination of **2** to the Cu^{II} catalyst (see below). Single crystals of product **4g** were obtained and its structure was confirmed by X-ray diffraction analysis (Scheme 4 and Supporting Information).

A range of other nucleophiles could also be coupled with *N*-phenyltetrahydroisoquinoline (Scheme 5, **7a**–**7l**). Good to excellent yields were obtained for carbon pre-nucleophiles, including indoles (**7a**), nitromethane (**7b**), ketones (**7c**–**7g**), dimethylmalonate (**7h**) and trimethylsilyl cyanide (**7i**). For the ketone substrates, 10 mol% of proline was required as cocatalyst for the coupling reaction to proceed. In its absence, no coupling products were observed. Proline has previously been found to promote similar coupling reactions, presumably via an enamine intermediate.[30] Although a racemic product was obtained for acetone here, a suitable chiral secondary amine catalyst might allow for enantioselective cross-coupling.[16b,31] Amide, dialkoxyl phosphonate and diaryl phosphonate are also viable pre-nucleophiles, which allow for the direct construction of C–N and C–P bonds from C–H bonds (**7j**–**7l**).



Scheme 4. Copper-catalysed coupling of *N*-aryl tetrahydroisoquinolines with hydroxycoumarins. See the Supporting Information for experimental details. Yields are given for isolated products. [a] Determined by ^1H NMR with 1,3,5-trimethoxybenzene as internal standard.



Scheme 5. Copper-catalysed coupling of *N*-aryl tetrahydroisoquinolines with various nucleophilic reagents. See the Supporting Information for experimental details. Isolated yield. [a] With 10 mol% proline as co-catalyst. [b] Malononitrile was used as the pre-nucleophile. [c] The reaction temperature was 60 °C.

Mechanistic studies

All of the previous studies on copper-catalysed CDC reactions have been based on mononuclear copper catalysts.[11a–e,h–j] The key steps of the CDC involve amine oxidation to an iminium cation by the Cu^{II} catalyst, and the resulting Cu^{I} species is oxidized by O_2, regenerating the Cu^{II}. Given the high activity and versatility of **1** and the striking difference between **1** and the mononuclear copper compounds in the CDC of **2** with **3a**

(Table 1), it was of interest to know whether the bimetallic copper complex **1** would operate by the same mechanism.

Binuclear versus mononuclear catalysis

Binuclear Cu^{II} carboxylates are known to exist as a mixture of dimers and monomers in polar coordinating solvents such as DMSO.[9e,32] To probe the mechanism of the **1**-catalysed CDC reaction, we first addressed whether or not the dimeric structure of **1** was maintained during the catalysis. Figure 1 compares the activity of dimeric **1**, monomeric **6** and $CuCl_2$ against

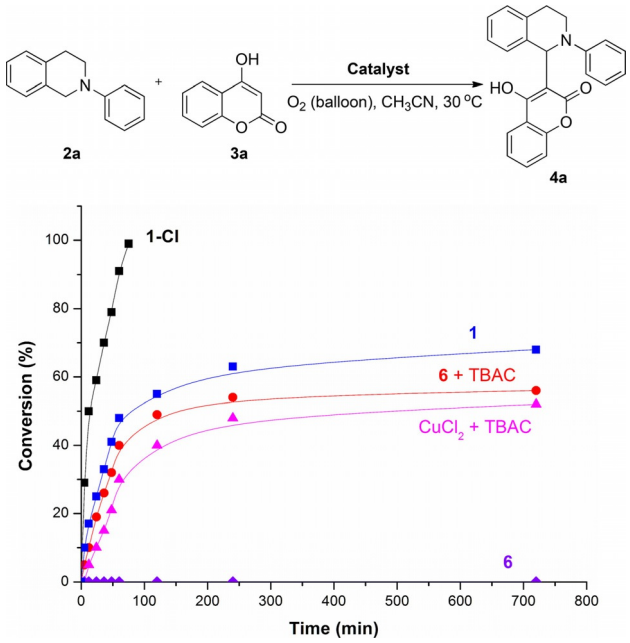


Figure 1. Performance of different catalysts in the CDC of **2a** with **3a**. 0.5 mol% **1** and 1 mol% TBAC (**1**-Cl); 1 mol% **1**, **6** and $CuCl_2$; 2 mol% of TBAC (if added). Conversions were determined by ^{1}H NMR spectroscopy with 1,3,5-trimethoxybenzene as internal standard.

time in the cross-coupling of **2a** with **3a** in CH_3CN. All three compounds showed catalytic activity in the presence of TBAC, but with distinct kinetic profiles. Whilst the reaction catalysed by **6** and $CuCl_2$ became sluggish at about 50% conversion in the presence of TBAC, that catalysed by **1**-Cl was significantly faster throughout, and was finished in 75 min. In addition, the kinetics exhibited by **1** and **6** in the absence of TBAC is also remarkably different: the former is active but is deactivated with time, whilst the latter is essentially inactive. Since breaking up of the dimeric structure of **1** may lead to species similar to **6**, the striking difference between **6** and **1** with or without TBAC indirectly supports the notion that **1**, or at least part of **1**, maintains its dimeric structure during the catalysis. Apparently, the chloride anion, which accelerates the reaction and presumably stabilizes the copper catalyst as well, plays a critical role in the CDC by **1**.

IR spectra provided more evidence. The solid-state IR spectrum of **1** shows $\nu_{sym}(COO^-)$ at 1595 cm^{-1} and $\nu_{asym}(COO^-)$ at 1391 cm^{-1}, characteristic of bridging carboxylate groups,[8b,10a]

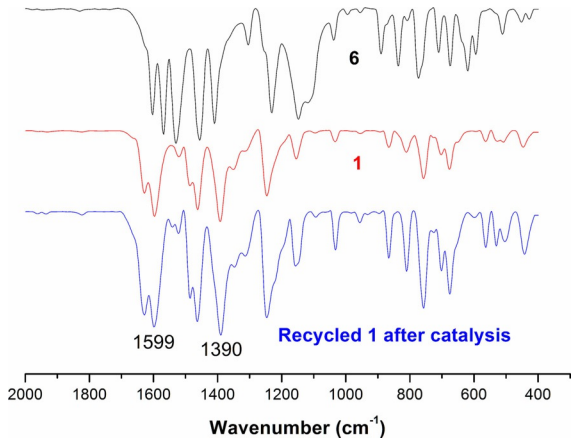


Figure 2. IR spectra of solid **6**, **1** and recycled **1** after catalysis. The sample of recycled **1** was prepared by removing CH_3CN from the reaction mixture of a catalytic reaction (20 mol% **1**, 1 h under the same conditions as a normal CDC) and washing with dichloromethane. IR spectra were measured with KBr pellets.

which are absent in that of **6** (Figure 2). In the IR spectrum of the mixture resulting from a completed oxidative coupling of **2a** with **3a** in the presence of a stoichiometric amount of **1**-Cl under 1 bar of O_2, these characteristic peaks remain clearly visible (Supporting Information, Scheme S3). Similarly, when **1**-Cl was used in a catalytic amount (20% of **1**) in the same reaction and the catalyst separated from the reaction mixture afterwards, the IR spectrum of the recovered catalyst again showed these characteristic absorptions (Figure 2), and this suggests that the reaction is catalysed by the dimeric complex.

Further evidence is provided by the UV/Vis spectrum in CH_3CN. Complex **1** shows a weak absorption at 401 nm, which is in the position of band II, usually considered to be due to a transition involving the binuclear Cu–Cu linkage (Figure 3).[8d] When **2a** was oxidized (to the iminium cation, see below) by a stoichiometric amount of **1**-Cl under an atmosphere of O_2, the UV/Vis spectrum of the resulting mixture showed a band II

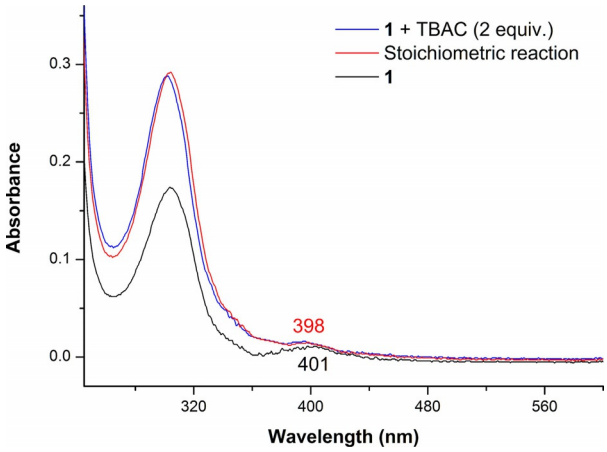
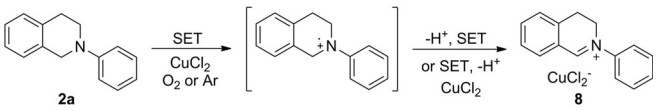


Figure 3. UV/Vis spectra of **1**, **1** + 2 equiv TBAC and the mixture following a stoichiometric oxidation of **2a** with **1**. The stoichiometric reaction was carried out with equimolar **1** and **2a** (2 equiv TBAC) in CH_3CN under 1 bar oxygen at 30 °C for 1 h. The concentration of **1** was 1×10^{-6} M in each case, with CH_3CN as solvent.

absorption at 398 nm, similar to that of **1**-Cl (Figure 3). Thus, both IR and UV/Vis spectroscopic studies on these low-turnover reactions appear to support that **1** maintains, at least partly, its binuclear structure in the studied CDC. Previous biomimetic studies have shown binuclear copper complexes to be generally more active than related mononuclear ones in catalysing catechol oxidation.[6c,8g]

Stoichiometric reactions

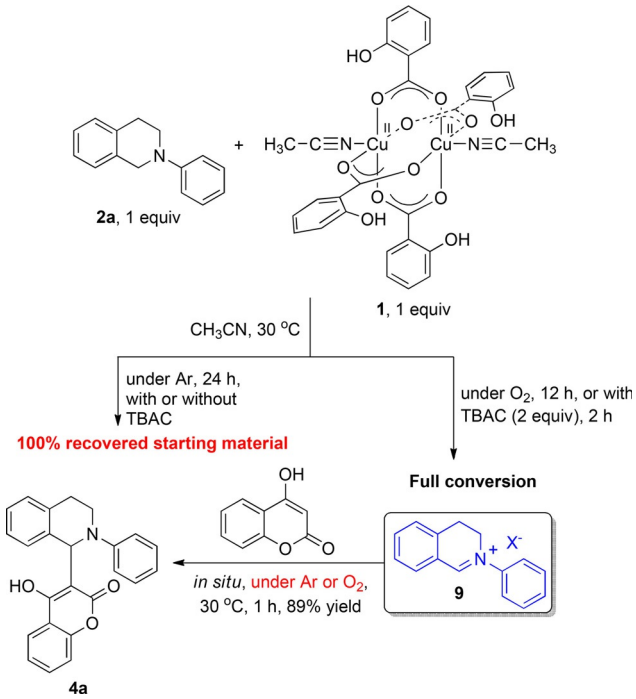
The oxidation of **2a** by Cu^{II} is thermodynamically a downhill process.[23] Indeed, Klussmann and co-workers reported that **2a** could readily react with $CuCl_2$ in MeOH to form iminium cuprate compound **8**, with or without O_2, probably via a nitrogen-centred cationic radial intermediate generated by single electron transfer (SET, Scheme 6).[15b,c,21] We repeated this reaction in MeOH under an argon atmosphere at ambient temperature. ^{1}H NMR analysis of the green precipitate indeed showed the formation of the iminium salt, supporting that "oxygen as the terminal oxidant is only involved in the reoxidation of copper".[15c]



Scheme 6. Formation of iminium cuprate with $CuCl_2$ under argon or oxygen at 25 °C.

In stark contrast, the dimeric complex **1** does not react with the amine in the absence of oxygen. Thus, no iminium salt was observed when equimolar **1** and **2a** were stirred under an argon atmosphere in CH_3CN at 30 °C for 24 h; **2a** was recovered quantitatively (Scheme 7). Switching the solvent to MeOH made no difference. In line with this, in the ^{1}H NMR spectrum of a 1:1 mixture of **1** and **2a** in CD_3CN at ambient temperature, the signals of the amine were visible and showed no observable change with time under Ar. However, when O_2 was introduced, a yellow-green solid precipitated from the mixture within 2 h, which was identified as the iminium salt **9**. The ^{1}H NMR spectrum of **9** is broad but shows resonances similar to those of **8**, and the presence of the cation is further supported by HRMS analysis of the precipitate, which revealed the molar mass of the iminium cation (m/z = 208.1113). The broadening of the NMR spectrum indicates that the anion in **9** forms an ion pair with the cation[15c] and, unlike that in **8**, it is paramagnetic. This is echoed by the X-ray photoelectron spectrum of the solid, which is identical to that of **1**, and shows the presence of a Cu^{II} species (Figure 4).[28] However, the structure of the anion remains unclear (for a suggested structure, see below), and efforts to grow single crystals of **9** have failed so far.

The observation of the inability of **1** to oxidize **2a**, the necessity for O_2 for this reaction and the preservation of the Cu^{II} oxidation state sends a strong signal that the mechanism of **1**-catalysed CDC differs from that catalysed by $CuCl_2$ or CuBr,



Scheme 7. Stoichiometric reaction of **1** with **2a** and subsequent transformations.

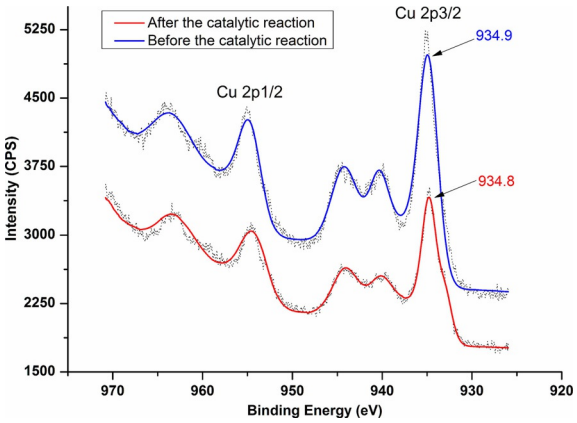


Figure 4. XP spectra of complex **1** and the reaction mixture resulting from the equimolar reaction of **1** and **2a** under O_2 (full conversion, as indicated by TLC analysis).

the most widely used CDC catalysts to date. A likely scenario is that a reversible SET from the amine to **1** occurs, and O_2 participates in the subsequent oxidation that gives rise to **9** (see below).

Further studies suggested that **9** is a key intermediate in the coupling reactions (Scheme 7). Thus, on reaction with 1 equiv of hydroxycoumarin **3a**, the **9** formed in situ afforded the coupling product **4a** in about 90% yield in 1 h under Ar or O_2.

The effect of chloride ion

The CDC reaction catalysed by binuclear **1** is promoted by the chloride anion. This raised the interesting question which step

was accelerated: iminium formation or nucleophilic addition (Scheme 7)? To address this question, we monitored the reaction of equimolar **2a** and **1** in CD_3CN without a nucleophile under air in an NMR tube by ^1H NMR spectroscopy (Figure 5). The reaction, which afforded **9**, was slower than with oxygen under the normal stirring conditions. With TBAC (2 equiv), the initial rate of the reaction was more than twice that without it. More strikingly, the reaction went to completion in 7 h in the presence of TBAC, but became extremely slow in its absence after about 6 h, reminiscent of the catalytic reaction (Figure 1) and indicative of catalyst deactivation. These results suggest that TBAC accelerates the iminium formation step in the CDC and stabilises the copper catalyst.

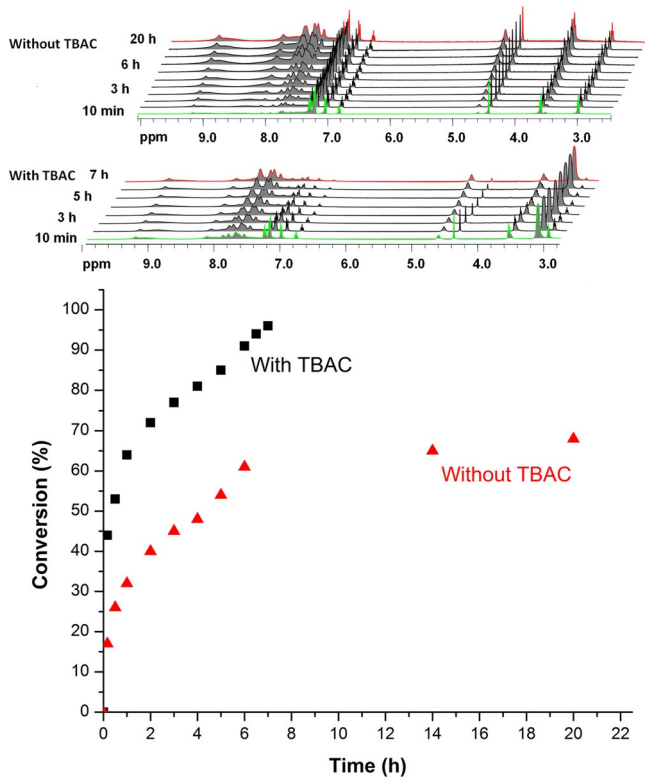


Figure 5. ^1H NMR monitoring of the iminium (**9**) formation process with or without TBAC (2 equiv). Reaction conditions: **1** (0.025 mmol), 2.0 equiv TBAC, 1.0 equivalent of **2a**, CD_3CN (0.5 mL), 25 °C, under air.

The effect of TBAC could stem from chloride coordination to **1** at the axial positions, given the easy coordination of ligands to similar Cu^{II} dimers.[8i,9b,d] This coordination is not expected to be strong, however, due to the well-known Jahn–Teller effect.[27,33] Indeed, in the presence of an excess of TBAC (2 equiv), the colour of **1** remained green in CH_3CN, and it was the CH_3CN-coordinated **1**, instead of the chloride analogue, that could be precipitated from the solution. However, both the IR and UV spectra indicated the formation of new species when **1** was mixed with TBAC in different ratios in CH_3CN. Thus, a shoulder peak at 1567 cm^{-1} grew in the IR spectrum when TBAC was added, while the characteristic peaks of **1** remained approximately the same (Figure 6). In the UV spectrum,

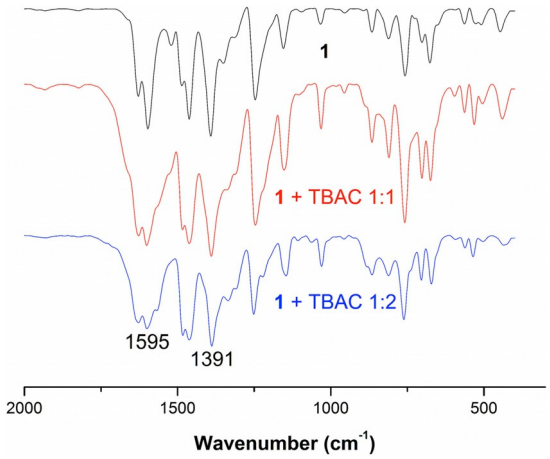


Figure 6. IR spectra of **1** and mixtures of **1** with TBAC with different molar ratios. The samples were obtained by evaporation of solvent from the solution prepared by stirring different ratio of **1** and TBAC in CH_3CN under Ar at room temperature for 1 h.

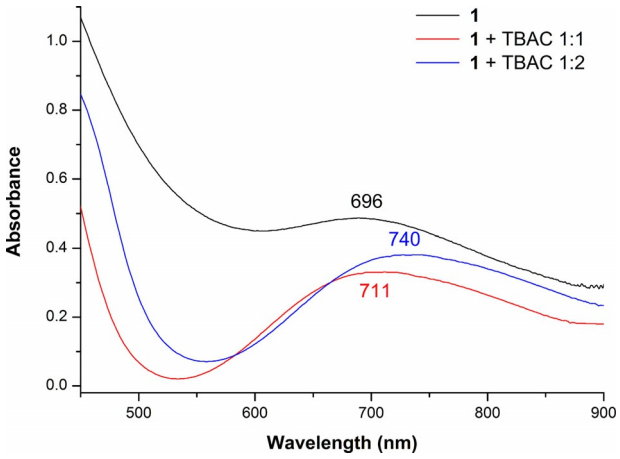
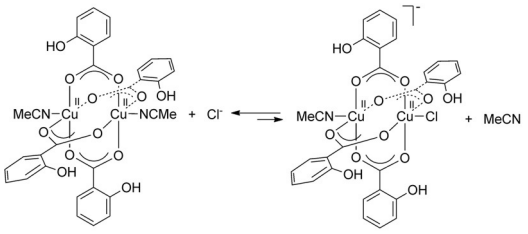


Figure 7. UV/Vis spectra of **1** and mixtures of **1** with TBAC with different molar ratios. The samples were obtained by evaporation of solvent from the solution prepared by stirring different ratio of **1** and TBAC in CH_3CN under Ar at room temperature for 1 h.

the absorption corresponding to the d–d transition[8d] of **1** was redshifted, and the degree of shift varied with the amount of TBAC added (Figure 7). These observations indicate that the chloride anion weakly binds to the copper dimer, with the equilibrium in favour of the chloride-free dimer [Eq. (4)].



(4)

We also examined the effect of TBAC on the electrochemical behaviour of **1**. The cyclic voltammogram of **1** revealed that

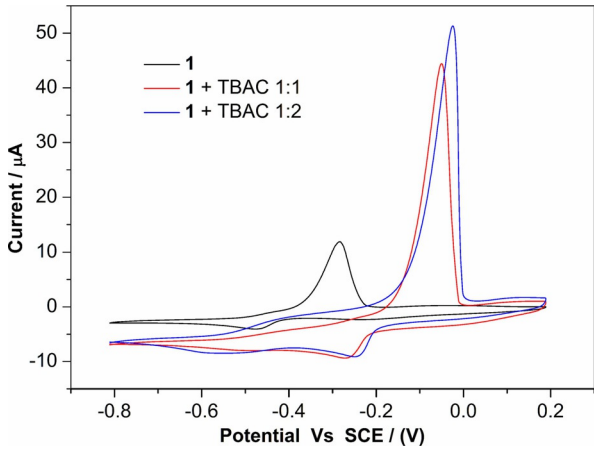


Figure 8. Cyclic voltammograms of **1** in the presence of different amounts of TBAC. Measurement conditions: platinum-button working electrode, 1×10^{-3} M **1**, 0.1 M tetrabutylammonium hexafluorophosphate buffer in acetonitrile, under an atmosphere of N_2, scan rate 20 mV s^{-1}, at 25 °C.

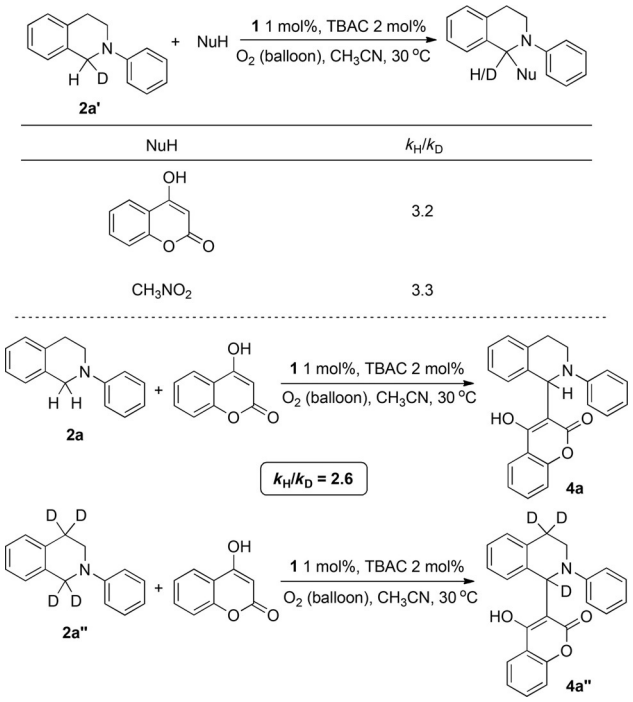
the redox potential of **1** became more positive in the presence of TBAC (Figure 8). This is in line with the observation made with copper salts such as $CuSO_4$ in aqueous solution, that is, the presence of chloride anion renders the formal redox potential for the Cu^{I}/Cu^{II} couple more positive, due to the preferential stabilisation of Cu^{I} by the chloride ion.[33–34]

Regardless, our results, taken together, indicate that the chloride anion coordinates to **1** reversibly, and the presence of the chloride promotes the reduction of Cu^{II}, presumably via its coordination to the resulting Cu^{I}. Thus, the accelerating effect of the chloride ion on iminium formation can be traced to **1**-Cl being more oxidizing than **1**. How **1** is stabilized by chloride remains to be further delineated, however (Figures 1 and 5).

Turnover-limiting step of the CDC

To gain further insight into the reaction mechanism, the kinetic isotope effect (KIE) in the oxidative coupling reaction was measured for substrate **2a′**, which was synthesized by iridacyle-catalysed transfer hydrogenation with DCOOD.[35] As shown in Scheme 8, the intramolecular CH/CD competition experiment revealed a significant KIE with hydroxycoumarin or nitromethane as the pre-nucleophile, which suggests that C–H bond cleavage is involved in the turnover-limiting step of the CDC reaction. The similarity of the KIEs with the two pre-nucleophiles also hints that the nucleophilic addition is less likely to be turnover-limiting. A recent computational study supports both propositions.[23]

However, it is possible that the observed KIE simply results from a product-determining step with a preceding rate-determining reaction.[36] To discern this possibility, two parallel, independent reactions were also carried out with **2a** and **2a′′**, which was prepared by the method published recently by Yan and co-workers.[37] The KIE of about 2.6, calculated on the basis of rates measured at low conversion, supports the conclusion drawn for the intramolecular reaction. This value is considerably larger than that of 1.3 found by Klussmman et al. for the



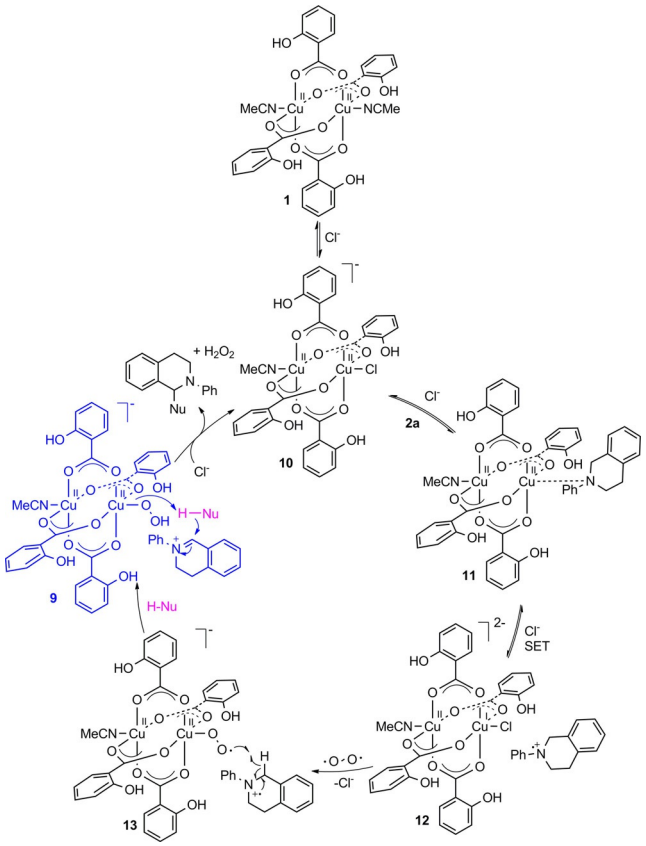
Scheme 8. Intra- and intermolecular KIEs observed in CDC. For details of how the KIEs were determined, see Supporting Information.

CDC of 1,1-dideuterated **2a** with a silyl enol ether catalysed by $CuCl_2$, and indicates a change in the turnover-limiting step or mechanism.[21] In the latter case, an SET event from the nitrogen atom of **2a** was suggested to be rate-determining.[21]

^{1}H NMR monitoring also supports that the iminium formation step is more difficult than the nucleophilic attack. Thus, whilst the reaction of equimolar **1** and **2a** in the presence of TBAC requires about 7 h to completely form **9** (Figure 5), the addition of 1 equiv of **3a** to the same NMR tube led to the immediate disappearance of **9** to form **4a**. Although only broad peaks were observed, the TLC analysis of the solution taken from the NMR tube supports formation of the coupling product **4a**.

Proposed mechanism

On the basis of the above mechanistic studies and the literature, a mechanism for the oxidative coupling reaction is suggested.[38] Scheme 9 depicts that proposed for the oxidative coupling of *N*-phenyltetrahydroisoquinoline with a nucleophile HNu. Complex **1** is likely to be in equilibrium with chloride-coordinated species such as **10** in MeCN. Coordination of the amine substrate **2a** is also likely. Indeed, the UV/Vis absorption of **1** at 696 nm was redshifted upon addition of **2a** to a MeCN solution of **1** (Supporting Information, Scheme S4), and coordination of amino compounds such as pyridine to similar Cu^{II} carboxylate dimers has been reported.[8i] The next step is an SET process, in which one electron is transferred from **2a** to form the $Cu^{II}Cu^{I}$ intermediate **12** and the radical cation of **2a**. The SET reaction is reversible, as indicated by **2a** remaining intact in the absence of O_2.



Scheme 9. Proposed mechanism for oxidative coupling of amines.[39]

The reversibility of SET in the metal-catalysed oxidation of *N*,*N*-dialkyl anilines by TBHP has been elegantly established by Doyle and Ratnikov.[18b] In the more closely related work by Wu et al. on the reaction of $CuBr_2$ with **2a** to form the radical cation, the SET is calculated to be thermodynamically feasible and kinetically facile (indeed, no barrier was revealed).[23] The presence of the chloride anion facilitates this process, presumably by shifting the equilibrium to favour **12**.

On reacting with O_2, **12** is converted to the $Cu^{II}Cu^{II}$ superoxo radical **13**, which abstracts a hydrogen atom from the amine radical cation to give **9**. The structure of **9** is less clear, however, as the negative charge on the copper complex could reside on the entire molecule or a partly dissociated carboxylate. NMR spectroscopy indicates that the anion of **9** forms a contact ion pair with the iminium cation (see above).

Cu^{I} compounds can be readily oxidized with O_2,[27] and the resulting Cu^{II} superoxo radicals and subsequent hydrogen-abstraction reactions to form Cu^{II} hydroperoxo species have been well documented in enzymatic and biomimetic catalysis,[1e,40] for example, oxidation of alcohols by O_2 with galactose oxidase[1e,40a] and of primary amines by O_2 with a biphenoxide-bridged copper dimer.[40b] A recent computational study on a Cu^{II}/bipy-catalysed CDC involving C–S bonds also showed that O_2 binds to the copper centre, forming a superoxo species, which then undergoes the rate-determining hydrogen-atom abstraction.[41] Alternatively, a proton-coupled electron transfer involving the coordinated carboxylate could take place.[17b,23]

The subsequent deprotonation of HNu by hydroperoxo complex **9** regenerates **10** and, followed by nucleophilic addition of the resulting Nu^- to the iminium ion, affords the coupling product and one molecule of H_2O_2. This reaction should be kinetically facile, as indicated by the calculations of Wu et al.[23] The production of H_2O_2 was supported by the observation that when PPh_3 was introduced into a MeCN solution of an oxidative coupling reaction of **2a** with **3a** in which the O_2 had been replaced with Ar, part of the phosphine (20%) was oxidized to $O{=}PPh_3$ (Supporting Information, section 5.5). The low yield of $O{=}PPh_3$ is probably due to in situ decomposition of H_2O_2 by the copper catalyst. Indeed, treating H_2O_2 with catalytic **1** in CH_3CN at ambient temperature results in its quick decomposition.

The overall CDC is limited in turnover by the hydrogen-abstraction step. This assertion finds support in the intra- as well as intermolecular CH/CD competition reactions (Scheme 8), and is also backed by the recent computational studies on CDC reactions.[23,41] An unanswered question is why complex **5**, in which the hydroxyl group of the salicylate ligand is acetylated, is much less active. One possible explanation may be that the hydroxyl group stabilizes the superoxo radical and/or participates in the transition state of the hydrogen-abstraction reaction through hydrogen bonding.[42] However, we cannot rule out the possibility of the hydroxyl group participating in the redox process leading to the formation of phenoxyl radicals.

Conclusion

Carboxylate-bridged binuclear Cu^{II} complexes have been known for several decades and extensively studied as superoxide dismutase mimetics. In fact, copper salicylate has been used as a potent anti-inflammatory.[9c] This study shows, for the first time, that Cu^{II} salicylate dimer **1** is a powerful catalyst for the aerobic oxidative coupling of amines with carbon-, nitrogen- and phosphorus-based nucleophiles. Mechanistically, the binuclear Cu^{II} salicylate is distinct from the widely used simple copper salts such as CuBr and $CuCl_2$ in the CDC.[15,21,43] Only in the presence of an oxidant can it oxidize the amine to the iminium intermediate, and this process is notably accelerated by the chloride ion. The oxidation of the SET-generated $Cu^{II}Cu^{I}$ species back to $Cu^{II}Cu^{II}$ by O_2 precedes, rather than follows, the formation of the iminium species, and O_2 is involved in each of these two steps, formation of the iminium cation and reoxidation of Cu^{I}. What remains unclear is why the binuclear copper complex **1** is more efficient than $CuCl_2$ and the analogous **5**, the role of the second copper atom and how chloride stabilizes the catalyst.

Experimental Section

General procedure for CDC of **2**: To a Schlenk tube equipped with a magnetic stir bar, **2** (0.25 mmol), nucleophilic reagent (0.5 mmol), **1** (0.0025 mmol, 3.0 mg) and TBAC (0.005 mmol, 2.8 mg) were added. MeCN (1.0 mL) was then introduced by a syringe, and the reaction tube was degassed (3 times), charged with dioxygen gas and kept under an oxygen atmosphere by using a balloon. After

stirring at 30 °C for the time indicated, the reaction mixture was diluted with water and then extracted with dichloromethane (3× 15 mL). The organic layers were combined, washed with brine and dried with Na_2SO_4. Finally, the solvent was removed by rotary evaporation and the crude product purified by column chromatography on silica gel with ethyl acetate/petroleum ether to afford the desired product.

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Keywords: copper · cross-coupling · homogeneous catalysis · oxidation · reaction mechanisms

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