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To be cited as: *ChemCatChem* 10.1002/cctc.202000212

Link to VoR: http://dx.doi.org/10.1002/cctc.202000212

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Chan-Evans-Lam C-N Coupling Promoted by a Dinuclear Positively Charged Cu(II) Complex. Catalytic Performance and Some Evidence for the Mechanism of CEL Reaction Obviating Cu(III)/Cu(I) Catalytic Cycle.

Nikolay Akatyev[a], Mikhail Il'in[a], Mikhail Il'in(Jr.)[a], Svetlana Peregudova[a], Alexander Peregudov[a], Anastasiya Buyanovskaya[a], Kirill Kudryavtsev[b], Alexander Dubovik[a,c], Valerij Grinberg[a], Victor Orlov[d], Alexander Pavlov[a], Valentin Novikov[a] , Ilya Volkov[a] and Yuri Belokon'[a]*

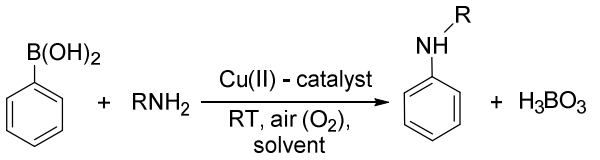
[a] A.N. Nesmeyanov Institute of Organoelement Compounds, Russian Academy of Sciences, Vavilov St. 28, 119991 Moscow, Russian Federation, yubel@ineos.ac.ru
[b] D. I. Mendeleyev University of Chemical Technology of Russia, Miusskaya sq. 19, 125047 Moscow, Russian Federation
[c] N.M. Emanuel Institute of Biochemical Physics, Russian Academy of Sciences, Kosygin St. 4, 119334 Moscow, Russian Federation
[d] M.V. Lomonosov Moscow State University, A.N. Belozersky Institute of Physico-Chemical Biology, Leninskie Gory, 1/40, 119991 Moscow, Russian Federation

Abstract: In the present study, we report the synthesis of a series of copper(II) complexes with a wide range of ligands and their testing in the copper catalysed Chan-Evans-Lam (CEL) coupling of aniline and phenylboronic acid. The efficiency of the coupling was directly connected with the ease of the reduction of Cu(II) to Cu(I) of the complexes. The most efficient catalyst was derived from 4-*t*-butyl-2,5-bis[(quinolinylimino)methyl]phenolate and two Cu(II) ions. Depending on the counter-anion nature and the concentration of the reaction mixture, the reaction can be directed to predominant C-N-bond formation. Forty-three derivatives of diphenylamine were prepared under the optimized conditions. The proposed mechanism of the catalysis was based on the reduction potential of a series of complexes, molecular weight measurements of the catalytic complex in MeOH and the kinetic studies of aniline and phenylboronic acid coupling. In addition, an ^{1}H NMR experiment in a sealed NMR tube, without external oxygen supply available, proved that no complete Cu(II) to Cu(I) conversion was observed under the condition, ruling out the usually accepted mechanism of the C-N coupling, which included the oxygenation of the intermediately formed Cu(I) complexes after the key step of C-N conversion had already been completed. Instead, a mechanism was proposed, involving an oxygen molecule coordinated to two copper ions in the key C-N bond formation without any detectable conversion of the Cu(II) complexes to Cu(I).

Introduction

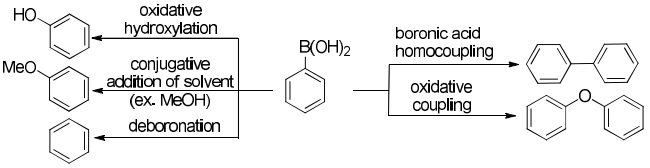
Copper-catalysed reactions are widely used in modern organic synthesis including natural product synthesis[1,2] and pharmaceuticals design.[3] As copper is an inexpensive, earth-abundant, relatively non-toxic metal,[4,5] its application in catalysis attracts ever-increasing attention of the chemical community for the construction of important organic molecules via formation of carbon–carbon and carbon–heteroatom bonds.[6] In particular, the discovery of an experimentally simple and convenient copper(II)-promoted C-N and C-O bond formation protocols by the oxidative Chan-Evans-Lam (CEL) coupling reaction (Scheme 1)[7–9] has, since 1998, opened new horizons in the field, especially important for the pharmaceutical industry.[10] Initially, the reaction represents a condensation of boronic acids and amino- or oxygen-based nucleophiles in the presence of oxidants and catalysts of oxidation, being predominantly copper salts. Air is routinely used for the reaction as an oxidant. The CEL coupling later was elaborated to allow C-N,[11–13] C-O,[14] C-S,[15] C-Se,[16] C-P[17] bond formation via copper(II)-catalyzed pathways of arylboronic acids with a wide range of nucleophiles, including sensitive substrates, which is critically important in numerous commercial chemical processes.[18] There are several reports for three-component,[19] tandem CEL-type reactions[20] and heterocycles synthesis.[21] Elegant CEL couplings catalysed by MOF's,[22] COF's,[23] copper-exchanged zeolites[24] and electrochemical means[25] were also reported.

Thus, the CEL reaction has greatly advanced the carbon–heteroatom cross-coupling chemistry and has become a powerful synthetic tool, made even more attractive by the mild conditions required, in comparison to the Ullmann-Goldberg or Buchwald Hartwig aminations catalysed by palladium or copper(II).



Scheme 1. The Chan-Evans-Lam (CEL)-reaction of C-N coupling

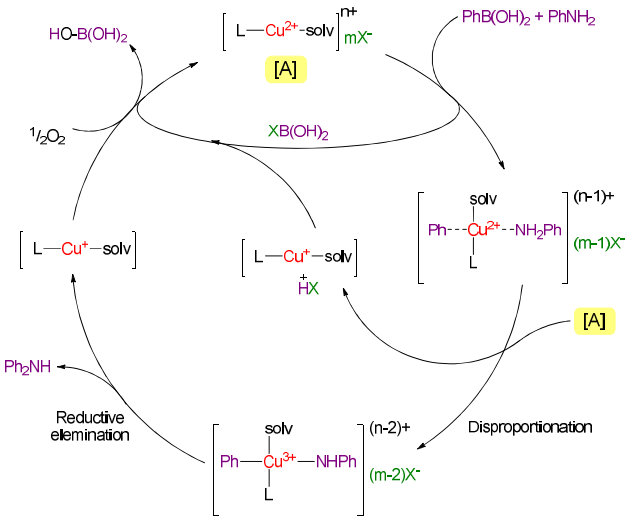
However, the main reaction is usually accompanied by certain undesirable side reactions, including: deboronation (to yield benzene derivatives); oxidative hydroxylation (to yield phenols); homocoupling of two boronic acid species (to yield diaryls); competitive addition of solvent (MeOH) (to yield anisole derivatives); and formation of diaryl ethers via oxidative couplings of two boronic acids (Scheme 2).



Scheme 2. Side reactions in CEL coupling

Although there is a series of papers dedicated to the elucidation of details of the reaction, a significant stumbling block for the development of the catalytic systems is poor understanding of the mechanism of CEL reactions. The generally held view of the catalytic cycle includes the redox Cu(III)/Cu(I) couple as the main driving force of the oxidative conversions. Scheme 3 illustrates this point, as was recently discussed by Stahl,[26] Schaper[27] and Watson.[28] According to the mechanism, one Cu(II) ion oxidizes another ion into the

Cu(III) version, at which both components of the coupling are coordinated. The reductive elimination yielded the product and another Cu(I) complex. Both Cu(I) complexes are then oxidized by air to yield the initial Cu(II) catalyst.



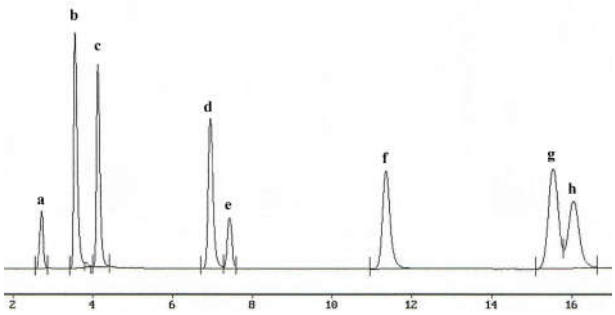
Scheme 3. Generally accepted concept of CEL coupling mechanism, as illustrated by the case of diphenylamine synthesis.

The postulated mechanism hinted at high importance of redox potentials of the complexes and the decisive role of the ligands in promoting CEL reactions.

In this work, we set ourselves the task of studying the CEL coupling of anilines and phenylboronic acids promoted by a series of closely related complexes, differing in their oxidative and reductive potentials. In addition, as the reaction involves two copper ions in the oxidative/reductive stages, we attempted to prepare ligands capable of encompassing two copper(II) ions and test the possible variations in CEL activity, coming from putting the two metal ions together in the same complex. The best precatalyst derived from 2,6-diformyl-4-*tert*-butylphenol and 2 equivalents of 8-aminoquinoline, and 2 equivalents of $Cu(OAc)_2$ was used to elaborate an efficient catalytic protocol for CEL generation of diphenylamines. Molecular weight measurements in MeOH and certain kinetic trials pointed towards the likely structure of the real catalytic particle. Additionally, some insights into the mechanism of the reaction were derived from ^{1}H NMR experiments on the reaction mixture devoid of air supply.

Results and discussion.

Analytic methods. First, we turned our attention to analytical methods allowing us to quantitatively assess the ratios of all formed products and the conversion of the initial reagents in the model reaction. The procedure should have facilitated the detection of easily volatile components of the reaction. HPLC was found to be the most suitable method for the point, permitting the quantitative assessment of anisole and benzene formation (Fig. 1). Such a combination facilitated good separation of all the components of the reaction mixture. Furthermore, we have successfully used this method to determine the product yields and employed the procedure for the kinetic studies.

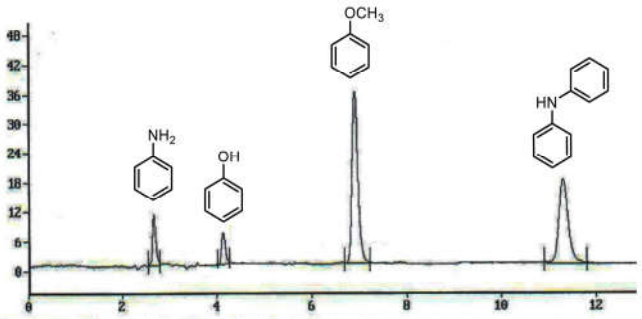


a - aniline (T_R = 2.803 min), **b** - phenylboronic acid (T_R = 3.583 min), **c** - phenol (T_R = 4.140 min), **d** - anisole (T_R = 6.912 min), **e** - benzene (T_R = 7.323 min), **f** - diphenylamine (T_R = 11.355 min), **g** - diphenyloxide (T_R = 15.433 min), **h** - biphenyl (T_R = 15.855 min).

Eluent: MeCN : (buffer pH=2,5 (Et_3N + H_3PO_4)) = 60 : 40 (*v/v*)
λ = 210,8 nm
Column Reprosil-PurC18-AQ 5 µm (250 x 4 mm)
Chromatograph: Agilent 1100 with diode matrix

Figure 1. HPLC chromatogram of a model mixture of reagents, and main and possible side products of the reaction of aniline and phenylboronic acid under the conditions of the Chan-Evans-Lam coupling.

Our literature review indicated the predominant use of copper(II) acetate (up to 1.5 eq. to substrate) for the CEL couplings in the earlier works.[9,29,30] To test the analytical procedure, a model reaction was performed using catalytic amounts of the $Cu(OAc)_2$ H_2O. Initially, MeOH was chosen as the solvent of choice, as it is easy to purify and remove and it is good for solving anilines and arylboronic acids. The HPLC chromatogram of the reaction mixture of aniline and phenylboronic acid in the presence of $Cu(OAc)_2$ H_2O (10 mol%) after the complete conversion of phenylboronic acid is depicted in Figure 2.



Reaction conditions: aniline 0.1 mmol, phenylboronic acid 1.5 eq., MeOH (1 ml), RT, air.

Figure 2. HPLC chromatogram of a real reaction mixture of aniline and phenylboronic acid (molar ratio 1/1.5) promoted by $Cu(OAc)_2$ H_2O (10 mol%) as the catalyst after the complete conversion of phenylboronic acid (144 h)

After complete conversion of the initial phenylboronic acid, the side product of the competitive addition of MeOH – anisole – was found to be the main product of the CEL reaction (52%) under the standard conditions. The yield of the desired product – diphenylamine – was only 42% (determined by ^{1}H NMR and the isolated yield was 40%, from 1 mmol scale experiment). Another side reaction was 7% of phenol formation. Furthermore, some unreacted aniline (56%) was also present. From this point forward, the rate of conversion of phenylboronic acid was taken as the CEL reaction rate, since in all cases, it was consumed first. The kinetics of the conversion of phenylboronic acid and the formation of the main and side products indicated that all these processes occurred in parallel (Fig. 3).

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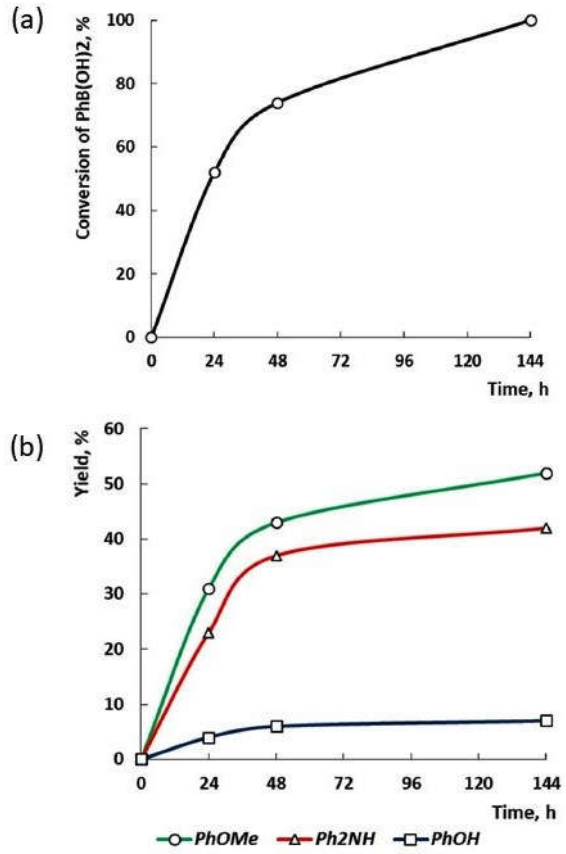


Figure 3. Kinetics of the conversion of phenylboronic acid (**a**) and the formation of the main and side products (**b**) in the reaction mixture of aniline and phenylboronic acid with $Cu(OAc)_2$ H_2O (10 mol%) as the catalyst.

The choice of catalysts. Among numerous possible structures of ligands, a simple variation of Schiff bases based on salicylaldehyde was chosen to approach the solution of the postulated problem. The ligands were easily prepared, and many of them already described in the literature earlier, the denticities of the ligands were easily controlled, and the overall charges of the resulting complexes were simply regulated. In addition, the ligands are strongly coordinated to the metal ions, ensuring the complexes are stable under the reaction conditions.

The set of tested complexes are presented in Figure 4. The chosen test reaction was the coupling of aniline and phenylboronic acid, run at an ambient temperature in air for 24 h. The results of the experiments are presented in Table 1. As can be seen from the data, another simple catalysts, $CuCl_2$ and $Cu(OTf)_2$, were much more reactive than $Cu(OAc)_2$. Even after 1 h, the initial boronic acid was completely consumed (Table 1, entries 2, 3). In both cases, the major product was PhOMe (45% and 47%, respectively), whereas the amount of Ph_2NH was diminished to 8% and 17% with the appearance of all other by-products with yields up to 26%.

All the complexes derived from ONNO, and ONO-type ligands (complexes **1-3**) displayed low catalytic reactivities (runs 4-6) with the phenylboronic acid conversion in the range of only 11-21%.

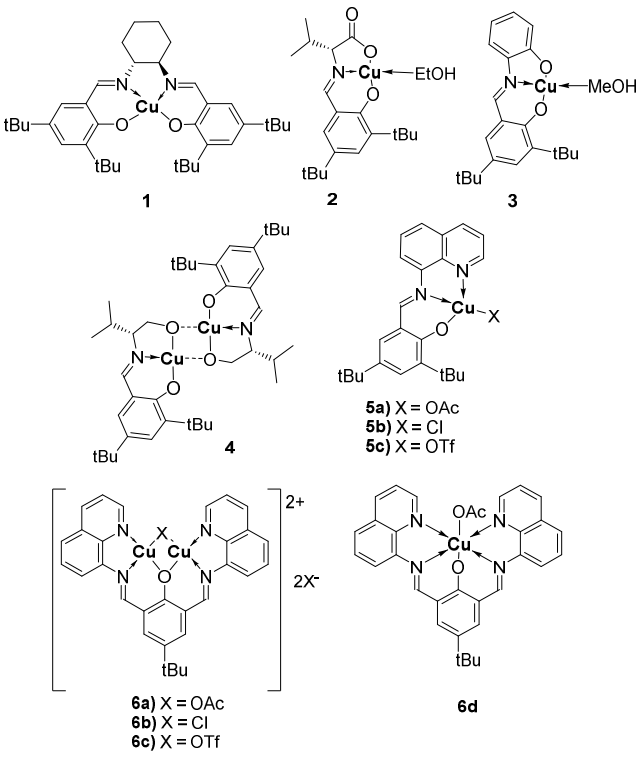


Figure 4. The set of catalysts employed in the work.

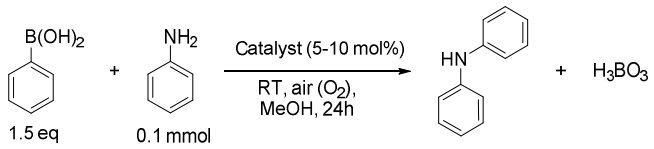
Unexpectedly, catalyst **4** – derived from a Schiff base of (*R*)-valinol and salicylaldehyde was an exception, as the conversion of the acid was already 95% complete after 12 h (run 7).

The first representatives of NNO ligand-derived catalysts were **5a-c**. The ligand was easily prepared by the condensation of substituted salicylaldehyde with 8-aminoquinoline. Complexes **5a-c** had very low catalytic reactivities (runs 8-10) and low selectivity.

Condensation of 2,6-diformyl-4-*tert*-butylphenol with 2 equivalents of 8-aminoquinoline led to pentadentate NNNNO ligand potentially capable of forming binuclear complexes with Cu(II) ions. The corresponding dinuclear complex derived from the analogues ligand and Ni(II) ions was well characterized by its X-ray analysis data.[31] By the reaction with the corresponding copper(II) salts, complexes **6a-c** were prepared. For the comparison reasons the mononuclear analogue **6d** (Fig. 4) was prepared by the reaction of the ligand with one equivalent of Cu(II) ion.

The complexes **6a-c** displayed much greater catalytic reactivity (runs 11-13) than the mononuclear analogue **6d** (run 14). The counter-anion affected the selectivity of the reaction, with **6b** promoting mainly the biphenyl formation (run 12), and **6a** predominantly leading to the target CEL C-N construction (run 11). Thus, the selectivity pattern of CuX_2 catalysis (runs 1 and 2) repeated itself in **6a** and **6b**. At the same time, complex **6c** has not demonstrated any selectivity (run 13).

Table 1. The CEL reaction catalysed by a series of Cu(II) complexes.



Run	Cat.	Cat. mol%	Reaction time, h	Conversion of $PhB(OH)_2$, %	Yield, %[a]						
					PhOH[b]	$PhOCH_3$[b]	PhH[b]	Ph_2NH[b]	Ph_2NH[c]	Ph_2O[b]	Ph-Ph[b]
1	$Cu(OAc)_2\ H_2O$	10	24	50	4	31	0	15	23	0	0
2	$CuCl_2\ 2H_2O$	10	1	96	12	45	6	5	8	2	26
3	$Cu(OTf)_2$	10	1	98	15	47	7	11	17	3	15
4	**1**	10	24	21	2	8	1	3	4	1	6
5	**2**	10	24	11	1	2	2	2	3	0	4
6	**3**	10	24	15	2	3	2	5	7	0	3
7	**4**	10	12	95	11	28	9	34	42	5	8
8	**5a**	10	24	7	3	2	0	1	4	0	1
9	**5b**	10	24	8	0	1	5	2	3	0	0
10	**5c**	10	24	12	2	2	0	3	4	0	5
11	**6a**	5	24	98	4	36	6	42	52	2	8
12	**6b**	5	24	85	8	34	0	3	4	0	40
13	**6c**	5	24	82	10	30	16	18	26	0	8
14	**6d**	10	24	9	2	4	3	traces	traces	traces	traces

Reaction conditions: aniline 0.1 mmol, phenylboronic acid 1.5 eq., MeOH (1 ml), RT, air. [a] - determined by HPLC, [b] – relative to $PhB(OH)_2$, [c] - relative to $PhNH_2$

The kinetics of product formation promoted by **6a** are shown in Figure 5.

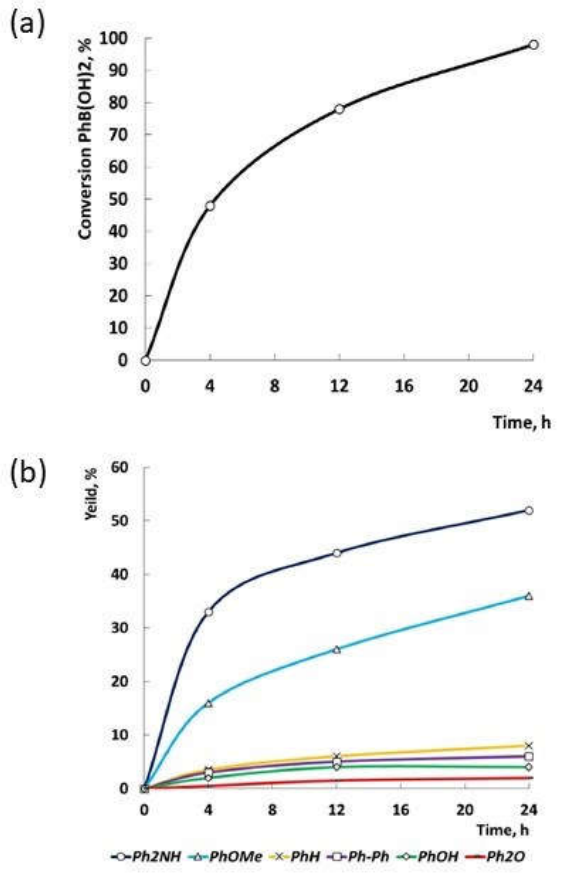


Figure 5. Kinetics of the conversion of phenylboronic acid (**a**) and the formation of the main and side products (**b**) in the CEL reaction catalysed by **6a** (5 mol%) at an ambient temperature for 24h.

As can be seen from the data summarized in Table 1 and Figures 3 and 5, the main side reaction observed in the process was the anisole formation. Evidently, the competition of MeOH and aniline in the catalytic cycle could be the main reason for the appearance of the side product.

The choice of solvents and the reaction conditions. The use of bulky alcohols or aprotic solvents seemed to be method by which to avoid the formation of the side products and increase the yield of the target diphenylamine. The results of the model reaction promoted by **6a** in different solvents are summarized in Table 2.

The coupling in *t*-BuOH was selective, with C-N-bond formation being the predominant reaction. Unfortunately, the conversion of the boronic acid was only 19% for 24 h (Table 2, run 1). The use of benzene and CH_2Cl_2 led to even less efficient system (runs 2 and 3). The catalysis in THF was more competent (48% conversion, run 4), but the selectivity of the reaction was significantly diminished, with the phenol formation increased. The use of MeCN inhibited the coupling almost completely (run 5), hinting at likely competitive coordination of the solvent to the active centre of the copper catalysts. Better results were achieved if DMF was employed (run 6). The selectivity of the reaction was significant with the C-N bond formation prevalent in the mixture. Bubbling of air (CO_2 removed) resulted in a sharp increase in the yield of the accompanying phenol, and the C-N bond formation was subjected to only limited influence (runs 6 and 7). The addition of Hünig's base (DIPEA) under the standard conditions led to the dominant formation of phenol (up to 48%, run 8). The addition of an inorganic base (K_2CO_3) suppressed the catalytic performance (run 9). Higher temperatures of the reaction led to complete loss of the reaction selectivity (run 10).

The performance of the coupling in MeOH was much better than in other solvents (run 11), but the addition of a base led to the predominant formation of biphenyl (run 12). Using a mixture of solvents (run 13) led to a loss of selectivity.

Water as a solvent almost completely inhibited the reaction (run 14).

Evidently, MeOH was the solvent of choice for the reaction. The straightforward way to eliminate the side reaction of PhOMe formation would be the relative increase in the concentration of aniline in the reaction mixture relative to that of MeOH.

Table 2. Solvent scope in the model CEL reaction catalysed by complex **6a** (5 mol%) for 24h.

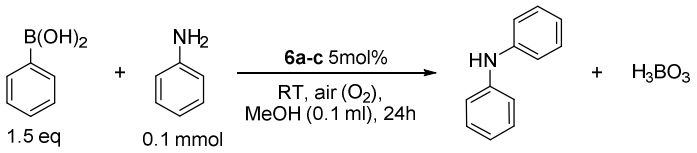
Run	Solvent	Conversion of $PhB(OH)_2$, %	Yield, %[a]						
			PhOH[b]	$PhOCH_3$[b]	PhH[b]	Ph_2NH[b]	Ph_2NH[c]	Ph_2O[b]	Ph-Ph[b]
1	*t*-BuOH	19	4	-	0	13	18	0	2
2	CH_2Cl_2	13	1	-	1	10	14	0	1
3	C_6H_6	16	7	-	-	9	12	0	0
4	THF	48	12	-	8	14	20	2	12
5	CH_3CN	5	1	-	0	3	5	0	1
6	DMF	28	2	-	7	19	26	0	traces
7[d]	DMF	41	14	-	5	21	30	1	traces
8[e]	DMF	68	48	-	4	15	22	1	traces
9[f]	DMF	11	6	-	2	3	4	0	traces
10[g]	DMF	55	18	-	5	13	18	0	19
11[h]	MeOH	98	4	36	6	42	52	2	8
12[f]	MeOH	80	8	17	9	5	7	1	40
13	DMF/MeOH = 1:1(*v/v*)	68	15	12	4	20	29	0	17
14	H_2O	10	7	-	2	1	2	0	0

Reaction conditions: aniline 0.1 mmol, phenylboronic acid 1.5 eq., solvent (1 ml), RT, air. [a] - Determined by HPLC, [b] – relative to $PhB(OH)_2$, [c] - relative to $PhNH_2$, [d] - air (CO_2 removed) bubbled through the reaction mixture. [e] - Hünig's base (DIPEA) was added (1 eq. related to the catalyst). [f] - K_2CO_3 0.075 mmol (0.5 eq to $PhB(OH)_2$) was added, [g] - 50°C, 6h, h Data from Table 1, run 11 were installed

To verify the assumption, the model reaction was conducted at much higher concentrations of the reagents, using one-tenth of the MeOH solvent volume, thereby reducing the amount of competing MeOH nucleophile and raising the concentration of the reaction components without changing of their molar ratios. Simultaneously, the counter-anion impact using **6a-c** as catalysts was assessed (Table 4, runs 1-4)). In addition, catalyst **4** was tested under the conditions (Table 3, run 6).

As shown in Table 3, the concept has been experimentally confirmed. The coupling promoted by **6a** gave the target product in 96% yield (Table 3, run 1).

Table 3. The CEL reaction catalysed by **6a-c** concentrated solution.



Run	Cat.	Conversion of $PhB(OH)_2$, %	Yield, %[a]						
			PhOH[b]	$PhOCH_3$[b]	PhH[b]	Ph_2NH[b]	Ph_2NH[c]	Ph_2O[b]	Ph-Ph[b]
1	**6a**	80	6	10	0	64	96 ± 4	0	0
2	**6b**	70	12	0	0	18	26	0	40
3	**6c**	88	8	20	21	34	51	0	5
4[d]	**6a**	55	4	6	0	45	59 ± 3	0	traces
5[e]	**6a**	51	<5	<5	0	40	48	0	0
6[e]	**4**	20	<5	<5	0	10	12	0	0

Reaction conditions: aniline 0.1 mmol, phenylboronic acid 1.5 eq., MeOH (0.1 ml), RT, air, cat. 5 mol%, stirring. [a] - determined by HPLC, [b] – relative to $PhB(OH)_2$ [c] – relative to $PhNH_2$, [d]- aniline 0.1 mmol, phenylboronic acid 0.1 mmol (1.0 eq.), MeOH (0.1 ml), RT, air, cat. 5mol%, [e] - The reaction was run for 1 h.

The effect of the counter-anion on the catalytic activities and selectivity of **6a-c** was also significant (Table 3, entries 1-3).The general tendencies were the same as in the dilute solution with chloride ion substitution of acetate, leading to greater percentage of biphenyl in the reaction mixture (Table 3, run 2). The introduction of triflate anion led to greater quantities of "parasitic" products (run 3).

If the reaction was carried out with a molar ratio of the reagents 1 : 1 instead of 1.5/1, the main product yield was reduced to 59% without selectivity loss (run 4).

In situ, synthesized **6a** give only 77% of C-N-coupling product. Complex **6a** showed excellent results only after its isolation and purification (see Fig. S8).

Changing the amount of catalyst under the conditions showed that 5 mol% of **6a** were the optimal amount to achieve the best yields of C-N coupling products (see Fig. S9).

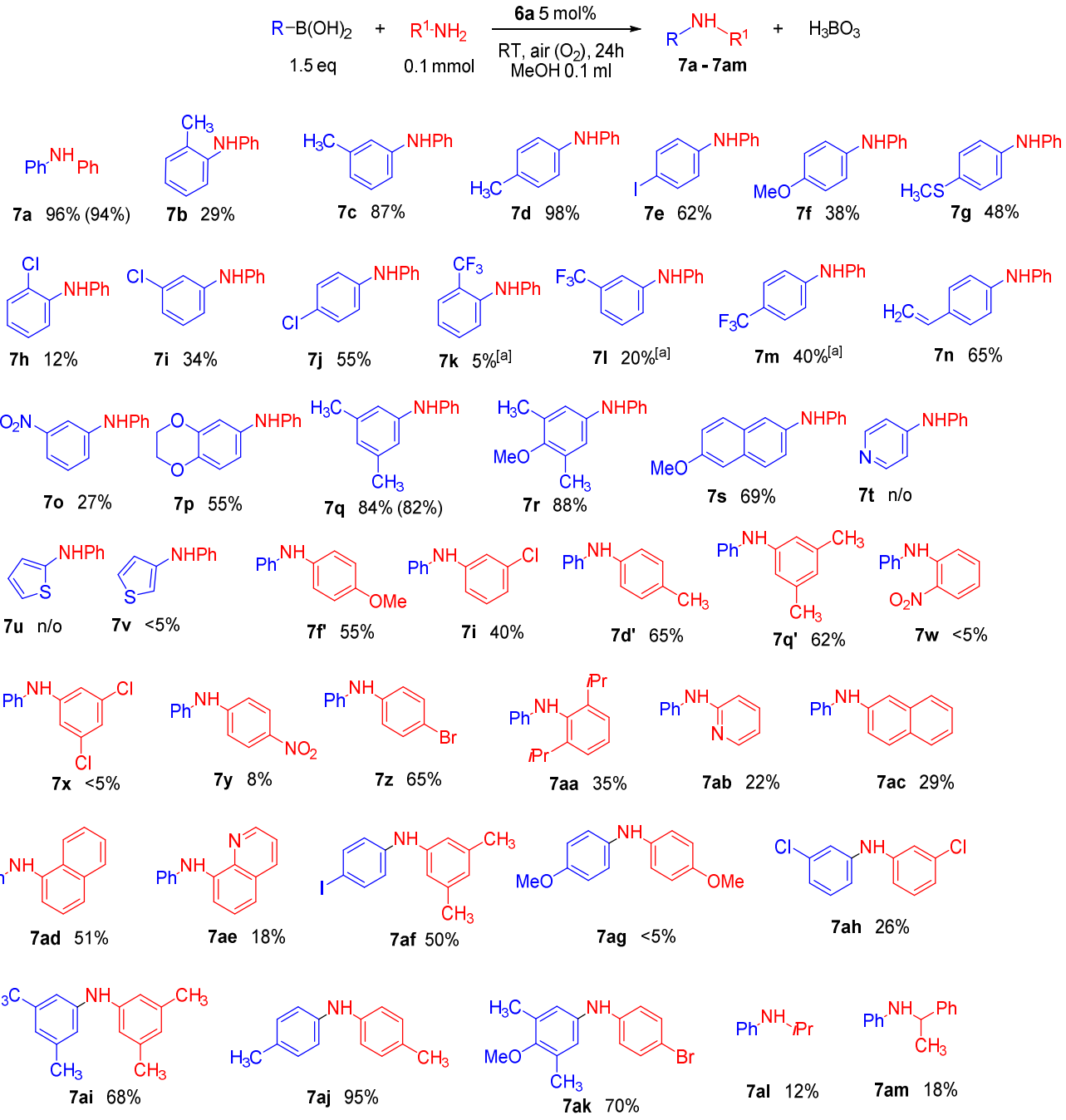
Another efficient catalyst **4** (Table 1, run 7) was also tested under the conditions. The comparision of the data of Table 3 (runs 5 and 6) testified that **6a** was much more active than **4** under the conditions.

The substrate scope. The substrate scope was explored under the conditions summarized in Table 3, run 1 (Scheme 4).

All product characteristics were in full accordance with the data supported in the extant literature (see S20).

Generally, the protocol featured moderate to good yields of the coupling products in the case of alkyl-substituted substrates, including both boronic acids and anilines (**7a**, **7c**, **7d**, **7n**, **7q**, **7al**, **7aj**). Even such sterically burdened amine as o,o'-diisopropylaniline gave an observable 35% yield of **7aa**. The introduction of the *–I* type of substituents to both anilines and phenylboronic acid led to a significant decrease of the yields (**7e**, **7f**, **7g**, **7i**, **7j**, **7k**, **7l**, **7m**, **7p**, **7x**, **7z**, **7w**, **7y**, **7ag**, **7af**, **7ah**). It looks as if the introduction of even *+I* substituents to the aniline substrate paired with unsubstituted phenylboronic acid diminished the product yields (compare **7d** and **7d'**, **7q** and **7q'**). However, if the boronic acid moiety was modified with a *+I* group also, the yield was greatly improved (**7aj**). Any heterocyclic derivatives proved to be incompetent substrates (**7t**, **7u**, **7v**, **7ab**, **7ae**). The rationalization of the substituent influence on the catalytic performance was additionally

sophisticated by the known ability of MeO- substituted boronic acids to form associates.[32–34] Aliphatic amines were bad substrates for the reaction, with only 17 - 18% chemical yields of **7al** and **7am**.



Reaction conditions: aniline (0.1 mmol), arylboronic acid 1.5 eq, RT, air, 24h, MeOH (0.1 ml) , **6a** 5 mol%. Products yields were determined by ^{1}H NMR using p-dinitrobenzene as the internal standard ($CDCl_3$, δ 8.45 s, 4H). Isolated yields are given in parenthesis. [a] - determined by ^{19}F NMR using perfluorobenzene (C_6F_6) as internal standard ($CDCl_3$, δ -161.75 s, 6F), n/o – no product observed.

Scheme 4. Substrate scope in CEL coupling catalysed by complex **6a**.

A large-scale (0.5-1 g) synthesis of **7a** and **7q** yielded 94% and 82% of the isolated products, respectively (see S30).

The reaction mechanism. Although increasing numbers of studies presume a Cu(I)/Cu(III) catalytic cycle in the CEL reactions (Scheme 1),[35] the limited stability of most Cu(III) complexes with the routine ligands makes their direct detection difficult. Whereas Cu(I) and Cu(II) complexes are the most common species in chemistry, the number of well-defined organometallic copper(III) complexes is very restricted. The Cu(III) species are stabilized by very strong ligands, such as porphyrins,[36] bearing C–Cu(III) bonds, azacalix*[1]*arene*[3]*pyridines, ionized amides,[37] substituted oxamates[38] or perfluorinated ligands.[39] An example of C-N bond formation involving aryl-Cu(III)-complexes was published by Stahl.[40] Moreover, aryl - Cu(III) species were proposed by Hartwig[41] in the reaction of α-arylation of enolates, in Hurtley-type coupling by Ribas[42] and invoked by Ma in his review as the most likely mechanistic scheme.[43] The formation of copper(III) - hydroxide unit through ligand structural variation was described by Tolman.[44] Recent advances in the field of

Cu(III)-species and their role in catalytic applications were reviewed by Sanford,[45] Lumb[46] and Ribas.[47]

However, the theme of the intermediate Cu(III) formation in copper ion catalyzed reactions invoked some scepticism. For example, recently, Gurjar *et al* suggested Cu(II)/Cu(I) instead of Cu(III)/Cu(I) catalytic cycle in the reaction of phenyl chloride with aniline leading to the C-N-bond formation. The conclusion was drawn on the basis of theoretical (density functional theory) calculations and supported by in situ ^{1}H NMR spectroscopy, UV vis spectroscopy, Fourier transform infrared spectroscopy, and cyclic voltammetry studies.[48]

Naturally, the performance of the series of our catalysts should be linked to the oxidation/reduction potentials of the Cu catalysts. Using the method of cyclic voltammetry (CVA), the electrochemical properties of the synthesized complexes and copper(II) salts were investigated. The experimental data is summarized in Table S1.

The data indicated that the value of the oxidation potential was not correlated with the catalytic performance of the complexes. Had the Cu(III) formation stage been present as the key step in the CEL reaction, **2-5** would become more active than **6**, which was not the case (Table 1).

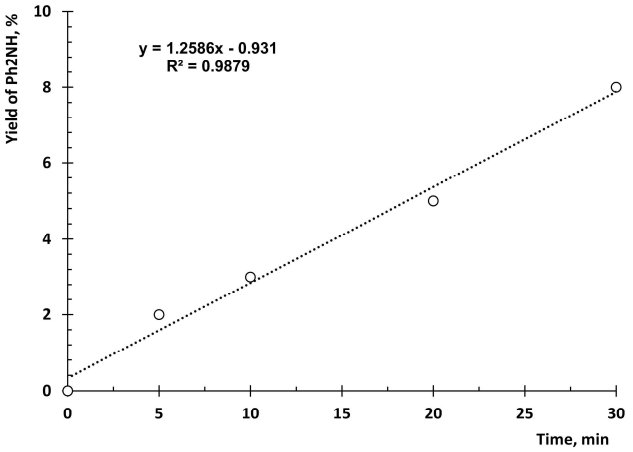
On the other hand, the ease of the complex reduction (Cu(II) to Cu(I)) roughly corresponded to the catalytic performance of the complexes. The most easily reduced complexes, $CuCl_2$, **6a** and **6b** (Table S1) were the most reactive (Table 1). Additionally, MeOH was the best solvent for the reaction (Table 2, run 11) may be because of its reductive properties.

Still the reduction and the oxidation potentials of the initial pure complexes have only indirect link with the catalytic reactivity of the complexes. Evidently, in the reaction mixture the pure initial complex (precatalyst) undergoes conversion into the real catalyst with the strongly donating groups coordinated with the metal ion (such as Ph – moieties alcoholate ions, amide ions and so forth) making the real reduction and oxidation potential of the complexes changed drastically. In addition, the protonation of the ligand strongly basic alcoholate group of 4 in MeOH could make its metal centre more susceptible to reduction which might explain the high reactivity of 4 (Table 1, run 7).

Additionally, the potentials of reduction had no correlation with the selectivity of the CEL reactions. The substitution of acetate ion for chloride in 6 (conversion of **6a** to **6b**) led to the switch of the selectivity of the reaction. The biphenyl formation was the predominant product (40%) in case of **6b** catalysis (Table 1, run 12). The yield of diphenylamine in this case decreased to 2%. The pattern was generally retained under the optimized conditions of Table 3 (runs 1 and 2). Since there are no other differences in reaction parameters, this unexpected change should be associated exclusively with the nature of the counter-anions. It is likely that the underlying reason for this behaviour lies in the relative coordination abilities of acetate and chloride ions. The ability may well be important, as the comparison of runs 2 and 3 indicates.

To estimate what kind of complex derived from **6a** was the initial material for the precatalyst formation, the determination of the apparent molecular weight of 6a was undertaken in a methanol solution using the sedimentation equilibrium method. The results showed that even in a diluted solution (0.14 mM), **6a** was predominantly present as a dimeric unit (78%) with the equilibrium constant equal to 1.6 x 10^5 M^{-1}. Hence, under the optimal reaction conditions (concentration of **6a** is 5.3×10 ^{2} M), the amount of the dimer constituted 99% of the total **6a** present in solution (see p.S31).

To ascertain if the dimer was the real precatalyst in the reaction, kinetic studies of the coupling had to be undertaken with the substrates taken in concentrations presented in Table 3.

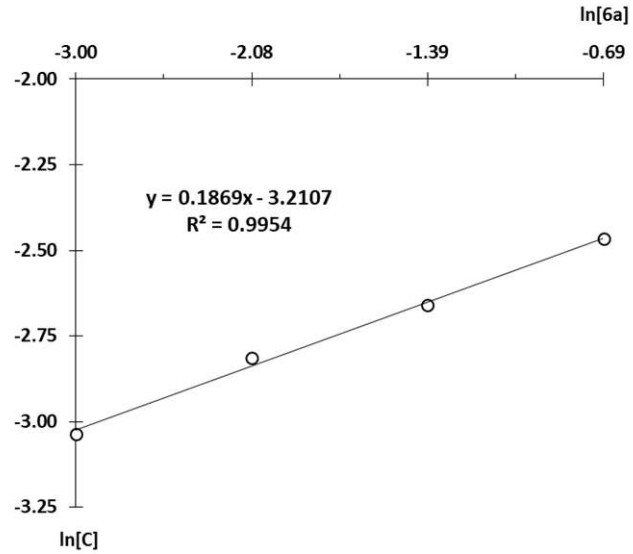


Reaction was carried out from 0.75 mmol (1.5 eq) of $PhB(OH)_2$, 0.5 mmol of $PhNH_2$, 5 mol% 6a in 0.5 ml of MeOH. After 5, 10, 20 and 30 minutes respectively 0.1 ml aliquots were taken, catalyst was removed by general procedure as given in experimental section. Product yields were determined by ^{1}H NMR.

Figure 6. Plot of **6a** (5% mol) promoted formation of diphenylamine (yield vs time). The conditions are those of Table 3.

In order for the kinetic experiments at the earlier stages of the reaction were valid, the absence of some induction periods had to be confirmed. Fig.6 shows that the reaction had no sizable induction period within 30 minutes interval.

The kinetic experiments with different amounts of **6a** were run as follows. After 30 minutes, the reaction was stopped, the catalyst removed and the yields of the diphenylamine were estimated by ^{1}H NMR with an internal standard (p-dinitrobenzene).



Reaction was carried out in four runs for 30 min by general procedure as given in experimental section with 1.0, 2.5, 5.0 and 10.0 mol% of **6a** respectively. Product yields were determined by 1H NMR.

Figure 7. Logarithmic approximation of the product yield [C] to amount of [**6a**].

The logarithmic dependences of the initial rates versus the amount of the catalyst are displayed in Fig.7. The slope was found to be 0.2 and clearly showed that the dimer had to dissociate before the reaction could take place. The monomer,

in its turn, had to undergo dissociation of acetate to generate a vacant site on the copper centers.

If the Cu(III)/Cu(I) couple were the real intermediate in the reaction sequence and the oxygenation of the generated Cu(I) intermediate occurred after the final stage of the C-N bond formation, then, without any oxidant present, all the Cu(II) had to convert to Cu(I). Consequently, the ^{1}H NMR spectra of the reaction mixture would display a narrowed line width of the substrates and the products as compared with the initial set of the broadened resonances due to the initial high concentration of paramagnetic Cu(II) ions. The event would have been inevitable had the paramagnetic Cu(II) ions been converted to Cu(I) ions in the absence of air or any other oxidants.

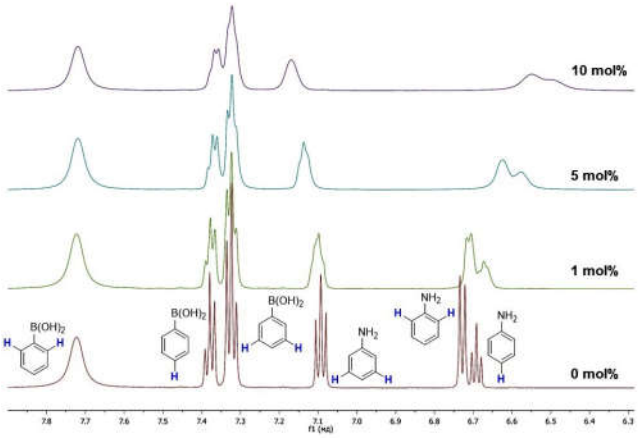


Figure 8. Variation of ^{1}H NMR spectra of the mixture of aniline (0.2M) and phenylboronic acid (1.5 eq, 0.3M) in CD_3OD with addition of different amounts of **6a**.

Fig. 8 displays the experimentally observed variations of the ^{1}H NMR spectra of the mixture of the initial substrates in CD_3OD, following the consecutive addition of 1-10% mol of paramagnetic **6a** (Fig. S1). The NMR tube was sealed, but the remaining air was not removed. Expectedly, the substrate resonances were broadened. In particular, the coordination of aniline to the copper ions led to broadening and shifting of m-H signals to weaker fields and o-/p-H signals to stronger fields. Coordination of phenylboronic acid to copper was weaker than that of aniline and takes place without any chemical shifts of the former. The results are depicted in Fig. 8. As the experiments were of particular importance for the understanding of the mechanistic details of CEL reaction it was conducted repeatedly 4 times and each time with different samples of **6a** prepared from different samples of the initial Schiff base. Every experiment had the same pattern of resonance changes.

Figure 9 illustrates the observed resonance shifts in the sealed tube after 2-24 hours staying at the ambient temperature. After 2 h, the chemical shifts of the broadened aniline resonances returned to their position, corresponding to 1% of **6a** added (Figs. 8 and 9). Still, there were only traces of the final product resonances detected in the spectra (Fig. 9). Most likely, the observation could be traced to a slow formation of another set of complexes originated from **6a** and the substrates as the UV/VIS spectra evolutions indicated (Fig. S7). The predominant formation of benzene was detected by ^{1}H NMR within the time interval (7.33 ppm, Fig. 9) and HPLC (yield of, at least, 50%, Fig. S11) after 24 hour interval.

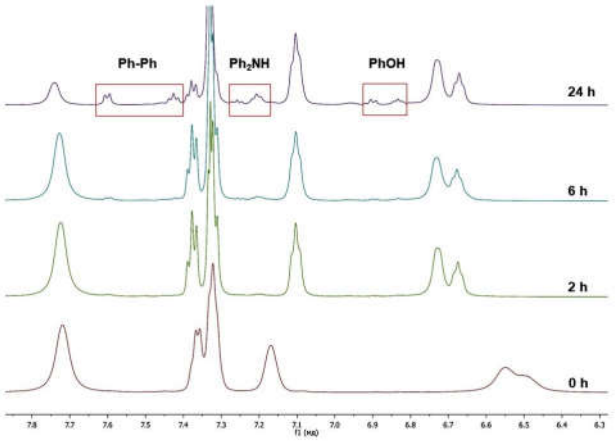


Figure 9. The variation in time of ^{1}H NMR spectra of a mixture of aniline (0.2M) and phenylboronic acid 1.5 eq., 0.3M (the conditions of run 11, Table 1) in CD_3OD with the addition of **6a** (10 mol%) devoid of air supply. The major product was benzene and the formation of Ph-Ph, Ph_2NH and PhOH observed as minor side products.

The accompanying variation of ^{11}B NMR spectra of the reaction mixture (Fig. S10) indicated that another single boron-containing compound was finally formed from the initial boronic acid. The process went parallel to the benzene formation (Fig. S11).

The data proved that under oxygen shortage conditions the target oxidative reaction of C-N bond formation was inhibited and instead protodeboronation side reaction predominated.

Although some amount of biphenyl and diphenylamine appeared in the spectra after 24 h, the broadening of the substrate proton resonances and their position remained the same (Fig. 9), hinting at the concentration of Cu(II) ions still being the same in solution, although, according to the accepted mechanism, the copper ions had to be in Cu(I) forms had the first catalytic cycles taken place and all the oxygen oxidant been consumed (Scheme 3).

In addition, the UV/Vis spectra of the reaction mixture without free supply of oxygen (Fig. 9) displayed undiminished absorption at 415-450 nm (*d-d* transition) as expected for Cu(II) complexes (Fig. S7). The absorption maximum shifted to shorter wave length as could be expected in case of coordinating stronger ligands such as MeO – anions (*vide infra*). Had the oxidation state of the copper ions been changed to +1, the absorption maximum in the region of d-d transition would have been changed and even disappear.

Additionally, the X-ray photoelectron spectra of **6a** testified that there were no Cu(I) admixtures in the sample (Fig S12). The paramagnetically shifted ^{1}H NMR signals of the initial complex (Fig. S1 and S2) were compared with those recorded in the reaction mixture (devoid of air supply) within the time intervals of Fig. 9. The spectra showed that the characteristic paramagnetically shifted signals of aromatic protons of **6a** at the range from 13 to 22 ppm remained constant during the catalytic 24 hours cycle (Fig. 10). There is the antiferromagnetic nature of the exchange electronic interaction between the two copper(II) ions in the dinuclear complex **6a** (Fig. S3). Had there been the conversion of even one Cu(II) ion to Cu(I) within the dinuclear catalyst, the antiferromagnetic interaction would have disappeared and the proton signals shifted and broadened. Consequently, the electronic structure of the complex **6a** (the oxidation state +2 of the copper ions) remained constant in the catalytic experiments under the short oxygen supply.

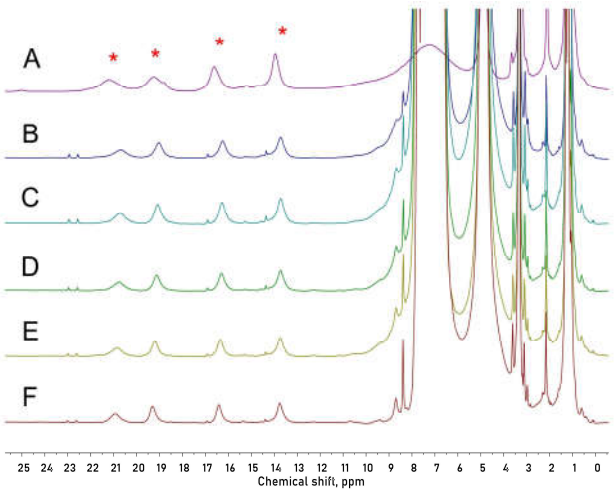
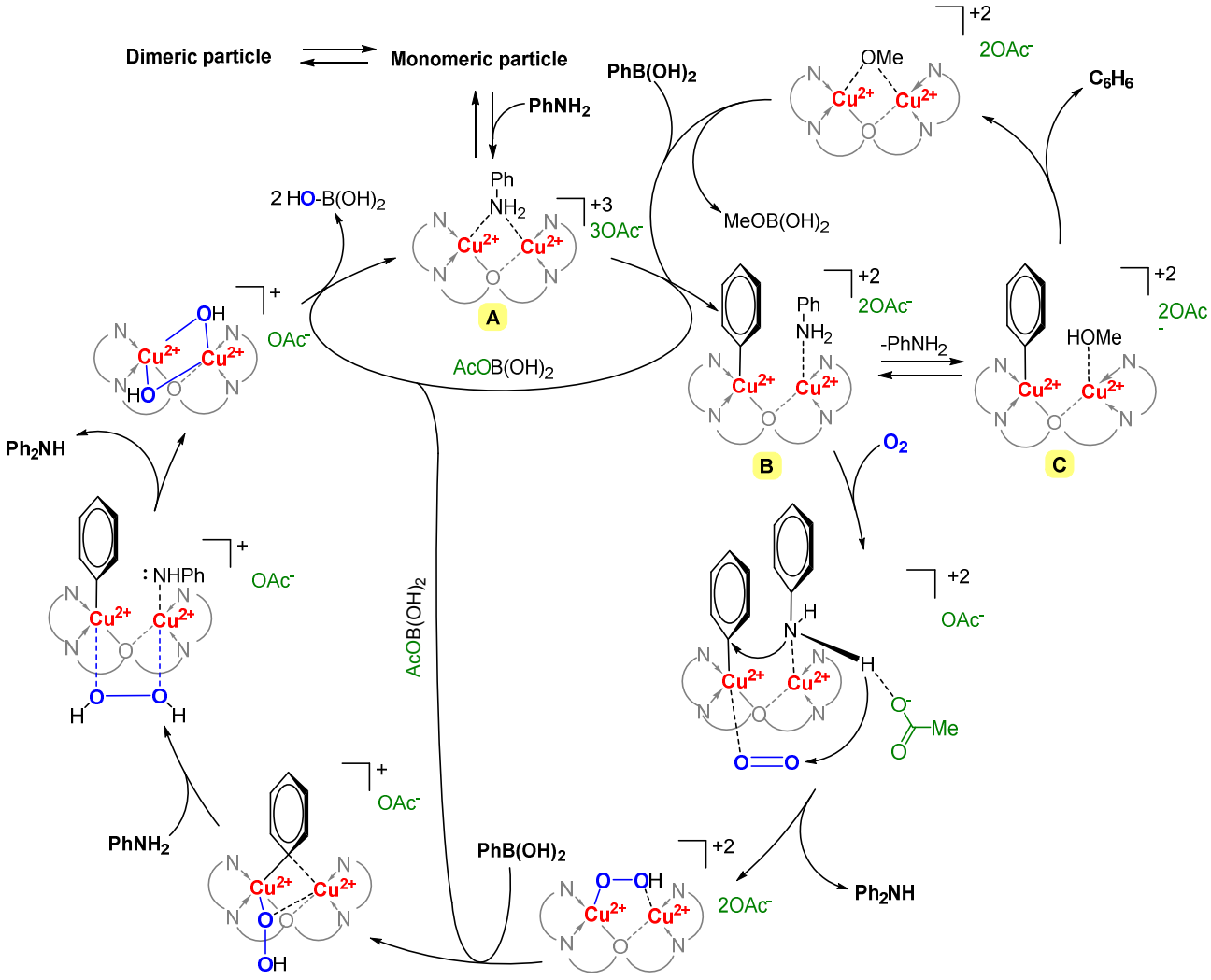


Figure 10. ^{1}H NMR spectra recorded at room temperature (paramagnetic range) in methanol-d_4 solutions of pure complex **6a** (A) and **6a** (B) with the substrates added. The experiment was the same as in Fig. 9. The variations of the spectra (runs C-F) were recorded at the same time intervals as those of Fig. 9. The characteristic paramagnetic signals of aromatic protons of **6a** are marked.

The results support our contention that no large quantities of copper(I) were formed under the reaction condition with air supply excluded.

Finally, we have conducted two stoichiometric experiment with 1/1/1.5 mol ratio of 6a/aniline/boronic acid. One was run under Ar and another under air and both conducted for two hours.The real ratio of Cu(II)/aniline was 2/1. Thus, the Cu(II) ions of **6a** at the beginning of the experiment were present in a large excess over the forming diphenylamine. Under the conditions the amount of the concomitant formation of Cu(I) would be small relative to the remaining Cu(II) ions and, consequently, the loss of the oxidative properties of the catalyst would be negligible. Thus no oxygen would be needed to restore the catalytic performance of 6a, as postulated by Cu(III)/Cu(I) cycle, at the early stage of the conversion. Had the accepted Cu(III)/Cu(I) mechanism been applicable in our case, the experiments under air and Ar would have given similar results. In fact, after two hours the “Ar” experiment produced 8-10% of diphenylamine whereas “air” experiment gave 25-30% yield. No other products were found in the reaction mixture. Even that small amount of diphenylamine in the “Ar” experiment might be formed because some oxygen was still present in the reaction vessel. Evidently, the presence of oxygen was needed to trigger the C-N bond formation and the oxidant seems to be present in the transition state of the reaction.

Based on the experimental and literature data, the hypothetical mechanism of the Chan-Evans-Lam reaction catalysed by the dinuclear copper(II) complex **6a** was proposed (Scheme 5).



Scheme 5. Proposed mechanism of CEL coupling catalysed by dinuclear copper(II) complex **6a.**

At the first stage of the reaction, an aniline molecule coordinates with a monomeric particle derived from the predominantly dimeric form of **6a** (Stage A, Scheme 5). Then a molecule of phenylboronic acid becomes decomposed by an acetate ion of **6a** with the formation of acetylboronic derivative $AcOB(OH)_2$ and the simultaneous coordination of the free phenyl anion to one of the two neighbouring copper(II) ions, or both ions (transmetallation step B). This type of coordination was recently shown to exist in similar dinuclear Cu(II)/Cu(I) complexes[49]. The stage may be responsible for the narrowing of the aniline proton signals in the ^{1}H NMR spectra after 2 hours (Fig. 9) as less Cu(II) sites become available for the aniline coordination. Among different types of equilibrated complexes the complex B with the two substrates situated in close proximity to each other could be formed. This type of conversions may be responsible for the observed changes in the UV/VIS spectra of the reaction mixture depicted in Fig.S7.

In presence of MeOH the aniline substrate may become substituted by a MeOH molecule (complex C) and then the intramolecular protonation of the neighbouring Ph moiety leads directly to C_6H_6 formation. Without oxygen present or with oxygen supply curtailed, the benzene formation becomes the predominant side reaction, as Fig 9 and Fig. S11 testify.

When the oxygen supply is restored, an oxygen molecule coordinates at the apical positions of the copper complexes. Further electron transfers coupled with a proton transfer from the aniline moiety to the coordinated oxygen molecule leads to the formation of the final diphenylamine and coordinated monoanion of hydroperoxide. The mechanistic scheme rationalizes the formation of anisole (PhOMe) in dilute solutions as forming from the intermediate C by the same mechanism. Expectedly, the formation of both biphenylamine and anisole is suppressed without oxygen presence (Fig. S11). Highly likely, that the side parasitic biphenyl formation occurs also at this stage. With limited oxygen supply the reaction is also suppressed (Fig.S11). The complex derived from **6a** with both coordinated sites occupied by the Ph moieties may be the initial starting intermediate. The formation of the intermediate is promoted by K_2CO_3 (Table 2, run 12) as should be expected with the transmetallation reaction promoted by bases.

Whatever the intimate mechanism of the C-N bond formation is operating in reality, its general outline can be presented as the nucleophilic substitution of the Cu(II)L(OOH)[50] leaving group at the phenyl moiety by the anilide ion. In other words, the oxygen molecule presence in the transition state of the C-N bond formation is prerequisite for its success.

The key role of the acetate ions in the target C-N coupling can be traced to its basic nature and bidentate properties realized in the aniline deprotonation step followed by the protonation of the coordinated oxygen with the formed acetic acid. Aniline cannot compete with the acetate as the base as the pK_a of the conjugated acid is 6.05 in MeOH whereas acetic acid has pK_a 9.52 in the solvent.[51] In addition, the local concentration of the acetate near the Cu(II) ions could be much greater than that of aniline. The reason for that is the negative charge of the acetate that makes its association with the positively charged complex much greater than that of aniline. Complex **6b** with monodentate Cl counter-anions, lacking basic properties of the acetate ion, made the target reaction of C-N formation slow. In addition, Cl – ion coordinates to Cu(II) ion weaker than the acetate ion by one - two orders of magnitude,[52,53] whereby favouring two phenyl moiety coordination at the neibouring Cu(II) ions of **6b**. It made the competing reaction of C-C formation predominant (Table 3, run 2). In case of weakly basic but bidentate triflate counter-anion the anisole formation was the main reaction with more acidic than aniline MeOH becoming much more competitive relative to aniline (Table 3, run 3). The failure of 6a to promote the reaction with strongly basic amines can be traced to the formation of inactive off-cycle complex with the two coordination sites of 6a occupied by the amine molecules. The inhibition of the CEL reaction by the nucleophilic anilines (compare the yields of **7a**, **7d'** and **7q'**, Scheme 3) could also be linked to the same cause. The analogous mechanism was earlier suggested by Shaper and supported by competition experiments in the paper on CEL reaction promoted by his sulfnato-diketimine copper(II) complexes.[11]

The next steps include the same type of oxidative and coordination steps, with the exception of peroxide being the oxidizing species instead of the initial oxygen molecule, producing diphenylamine. The resulting coordinated hydroxyl ions interact with $AcOB(OH)_2$, producing $B(OH)_3$, and the acetate ions effectively regenerating the initial catalyst.

Conclusion.

Monitoring the catalytic performance of differently ligated mono- and dinuclear copper(II) complexes in a model CEL reaction showed that neutral complexes bearing strong negatively charged ligands had no necessary catalytic activity. However, NNNNO-ligated dinuclear copper(II) complex, formed from a Schiff base of 2,6-diformyl-4-*tert*-butylphenol and 8-aminoquinoline as ligand and AcO^- as the counter-anions (**6a**), gave the highest yield in a model reaction of aniline and phenylboronic acid coupling. Methanol was found to be the solvent of choice, but at dilute solutions became a competitor in the coupling reaction. The importance of counter-anions was found, and switching from bidentate and the basic acetate ion to the chloride ion almost completely changed the reaction selectivity from predominant C-N to C-C coupling.

Special NMR experiments showed that in case of oxygen supply cancelled under standard **6a** promoted CEL coupling conditions, no detectable formation of Cu(I) complexes were observed. The oxidation state of copper was still +2 even after significant phenylboronic acid conversions had taken place. The result contradicted the generally accepted mechanism of the reaction, involving the Cu(III)/Cu(I) pair with the oxidant involved after the key C-N bond formation. The accepted mechanism predicted the full conversion of the Cu(II) to Cu(I) ion without an oxidant present after the first catalytic cycle. A mechanism including the Cu(II)/Cu(II) pair was suggested as an alternative for, at least, dimeric Cu(II) complexes.

The synthetic application of the new catalytic system was suggested with 43 examples of substituted boronic acids and aniline tested with the chemical yields ranging from 8% to 98%.

Keywords: Homogeneous catalysis • reaction mechanism • the Chan-Evans-Lam reaction • dinuclear copper(II) complexes • C-N-bond selectivity

ASSOCIATE CONTENT

Supporting Information

The Supporting Information is available free of charge**.** The material includes some figures, experimental procedures and spectra.

AUTHOR INFORMATION

Corresponding authors

Prof. Dr. Yuri Belokon yubel@ineos.ac.ru
Nikolay Akatyev niko_aikidzin@mail.ru
Dr. Mikhail Il'in mikhail-ilin@yandex.ru
Dr. Mikhail Il'in(Jr.) kotosok@yandex.ru
Dr. Svetlana Peregudova smp@ineos.ac.ru
Prof. Dr. Alexander Peregudov asp@ineos.ac.ru
Dr. Anastasiya Buyanovskaya analyst@ineos.ac.ru
Kirill Kudryavtsev gotros@yandex.ru
Dr. Alexander Dubovik adubovik@ineos.ac.ru
Prof. Dr. Valerij Grinberg grinberg@ineos.ac.ru
Dr. Victor Orlov orlovvn@mail.genebee.msu.ru
Dr. Alexander Pavlov alex90pavlov@mail.ru
Prof. Dr. Valentin Novikov novikov84@gmail.com
Dr. Ilya Volkov io_volkov@inbox.ru

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work is supported by grant 15-13-00039 of Russian Science Foundation

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10.1002/cctc.202000212

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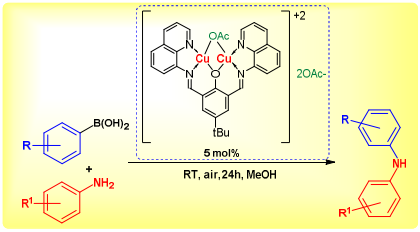

The dinuclear complex derived from 8-aminoquinoline and 2,6-diformyl-4-*tert*-butylphenol was an efficient catalyst of CEL-coupling reaction of phenylboronic acids and anilines. The counter-ion nature played an important role in determining the selectivity of the side reactions. Some evidence was presented in favor of oxygen molecule present in the stage of C-N-bond formation.