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Chan-Evans-Lam couplings with imino-arylsulfonate copper complexes: scope and mechanism

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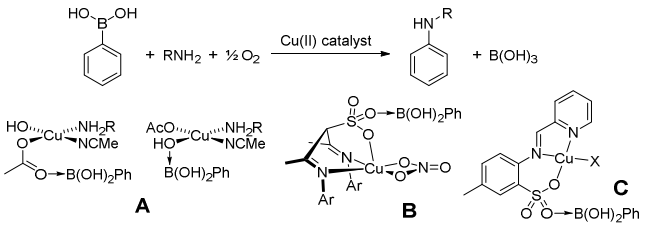
Supporting Information Placeholder

ABSTRACT: Pyridyliminoarylsulfonate Copper(II) complexes with chloride or triflate counteranions were employed in Chan-Evans-Lam (CEL) couplings of *N*-nucleophiles and arylboronic acids. The complexes avoided typical side reactions in CEL couplings and excess of boronic acid was not required. Water was tolerated and neither addition of base or other additives was necessary. Primary amines, acyclic and cyclic secondary amines, anilines, aminophenol, imidazole, pyrazole, and phenyl tetrazole can be quantitatively arylated at either 25 °C or 50 °C with 2.5 mol% catalyst. Reaction kinetics were investigated in detail. Kinetic and spectroscopic studies provide evidence for the formation of unproductive copper-substrate complexes. Formation of an aniline-phenylboronic acid adduct was responsible for zero-order dependence of reaction rates on phenylboronic acid concentration. Kinetic evidence indicate that the order of reaction steps is transmetallation, nucleophile coordination, followed by oxidation. Couplings performed poorly with electron-deficient arylboronic acids, due to a slower Cu(II)/Cu(III) oxidation in the catalytic cycle. Photoredox catalysis partially resolved this problem, but addition of copper acetate as a external oxidant proved to be more efficient.

Chan-Evans-Lam coupling, copper coordination complexes, homogenous catalysis, mechanism, C-N bond formation

INTRODUCTION

Over the last two decades, palladium-catalyzed coupling reactions have become a staple reaction of the pharmaceutical industry,[1] to an extend that processes to remove residual palladium from pharmaceutic products became an active area of research.[2] Partly due to their lower costs and higher availability, but mostly due to their significantly lower toxicity, there is thus an ongoing effort to replace catalysis with palladium-group metals by first-row transition metal alternatives for C-C, C-N, or C-O coupling reactions. Based on earlier work by Barton on couplings with aryl bismuth reagents,[3] Chan, Evans and Lam reported in 1998 the oxidative coupling of amines (and other nucleophiles) with arylboronic acids by copper salts (Scheme 1).[4-6] In the following years, Chan-Evans-Lam (CEL) couplings with catalytic amounts of copper were developed and the method proved to be applicable to a wide variety of nucleophiles.[7-15] Compared to the Ullmann-Goldberg reaction or Buchwald-Hartwig aminations catalyzed by palladium or copper, CEL couplings proceed under much milder conditions, often at room temperature, and are thus more attractive for complicated and sensitive substrates. While CEL couplings have now been successfully employed for a large variety of N-, O-, S-, and even C-nucleophiles, from the very beginning researchers remarked the "*somewhat capricious nature of this reaction*",[16] and its exceedingly high substrate-dependency. Early – and even current – work on CEL couplings thus report optimized reaction conditions which differ strongly even for closely related substrates such as amines,[17] anilines,[18] tetrazoles,[19, 20] aminopyridines,[21] and aminophenols.[22] In these optimized reaction protocols, water typically needs to be removed…[5, 23] when it is not beneficial,[24-26] the addition of base is essential…[27] or unnecessary,[17, 28-32] solvent dependence is strong, but completely empirical, and copper sources with acetate or triflate anions work best,[15, 33] with the exception of those cases where they don't.[20, 34, 35] Only lately, more general protocols for CEL couplings of *N*-nucleophiles emerged. Watson et al. reported a modified protocol with stoichiometric amounts of copper, addition of $B(OH)_3$ and an excess amine, which is generally applicable to a larger variety of amines and anilines.[36] Phukan reported CEL couplings with $[Cu(DMAP)_4I]I$ to proceed with high activities and to be likewise applicable to a larger variety of substrates under the same reaction conditions.[37]



Scheme 1. Chan-Evans-Lam coupling of *N*-nucleophiles and the dinuclear copper-boron intermediate proposed for CEL couplings with $Cu(OAc)_2$ (**A**), for previously investigated catalysts in our group (B) and for catalysts in this work (**C**).

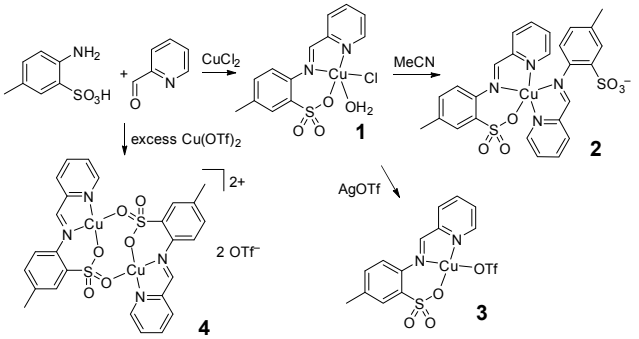
Typical catalysts in CEL couplings are simple copper salts, in most cases $Cu(OAc)_2$. Copper salts immobilized in resins, zeolites or other solid supports have also been employed.[32, 38-

[47] Coordination complexes have been used rarely, even though the first catalytic CEL coupling by Collman employed $[(tmeda)Cu(OH)]_2Cl_2$ for the arylation of imidazoles.[48, 49] A tetranuclear Copper(II) carbene complex was employed for arylations of benzimidazoles, but showed low activity with amines or anilines.[30] Copper salen complexes have been used to enable imidazole couplings in water,[50, 51] and likewise a cyclodextrin-based complex, which showed good activities for amines and anilines.[31] Recently, Phukan reported $[Cu(DMAP)_4I]I$ as a catalyst, which showed so far the highest and most general reactivity for *N*-nucleophiles.[37]

We hypothesized that the large variety of reaction conditions in CEL couplings and the strong dependence of reactivity on them is related to the use of simple copper salts as catalysts. Solvent and added base are required to solubilize and activate the copper salt, and base and counteranion play a role in the formation of dinuclear copper-boron complexes (Scheme 1, **A**), as a first step in the transmetallation.[36, 52] Incorporating these features into the ligand of a coordination complex could provide catalysts with a more general reaction protocol and – hopefully – increased reactivities. Given that Copper(II) tends to form square-planar or square-pyramidal complexes and that two coordination sites are required for interaction with the substrates, we targeted tridentate ligands. A sulfonate group was integrated in the ligand to enable a bridging coordination to boron and to facilitate transmetallation. We have previously reported sulfonatodiketimine complexes (Scheme 1, **B**), which showed indeed a more general reactivity towards amines and anilines, but proved to be unreactive even for slightly bulky substrates.[26] We then targeted sterically less crowded pyridylimino arylsulfonate complexes (Scheme 1, **C**), for which we reported a high reactivity towards amines, anilines, and *N*-heterocycles in a preliminary publication,[53] and which showed some of the highest activities in CEL couplings, in particular for challenging substrates. In the following, we investigate the mechanism of CEL couplings with complexes of type **C** and how to address remaining problems of reactivity.

RESULTS AND DISCUSSION

Catalyst synthesis and structures. The chloride-coordinated complex **1** can be prepared in a simple one-pot procedure, following previous protocols where ligand and complex are assembled in the same reaction from commercial starting materials (Scheme 2).[54] From undried methanol, **1** crystallized as the water-coordinated, mononuclear complex (Scheme 2).[53] Recrystallization of **1** in acetonitrile afforded the homoleptic complex **2** (Figure 1, Table 1).



Scheme 2. Preparation of **2-4**

The triflate complex **3** is obtained by anion exchange with silver triflate (Scheme 2) and crystallizes as a coordination polymer with triflate and sulfonate interactions between neighboring molecules.[53] **3** can also be prepared directly from the ligand precursors and $Cu(OTf)_2$, but required 2 equiv of the copper salt. Under these conditions **4**, a polymorph of **3** with a different constitution, was obtained, in which triflate dissociated from the coordination sphere and a dinuclear, dicationic complex is formed in the solid state (Figure 1, Table 1). **1** is soluble only in strongly polar solvents, such as water, DMSO or DMF and poorly soluble in methanol. The solubility of **3** is much higher and it is readily soluble in THF, CH_2Cl_2 or methanol.

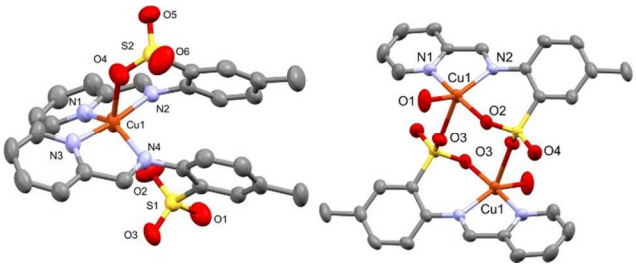


Figure 1. Crystal structures of **2** (left) and **4** (right). Thermal ellipsoids were drawn at the 50% probability level. Hydrogen atoms, cocrystallized water (**2**) and the anion (**4**) were omitted for clarity.

Table 1. Geometrical data of complexes 1-4.

	1 [a]	**3** [a]	**2**	**4**
Cu-N_{imine}	2.051(1)	2.026(1)	1.972(1), 1.986(1)	2.023(2)
Cu-$N_{pyridine}$	1.992(1)	1.967(1)	2.045(2), 2.073(1)	1.967(2)
Cu-$O_{sulfonate}$	1.969(1)	1.929(1)	2.200(1), 2.877(2)	1.934(1)
Cu-$O_{bridging}$		2.379(1)		2.235(1)
Cu-OH_2	2.307(1)			1.993(1)
Cu-$O_{triflate}$/Cl	2.243(1)	2.015(1)		
τ	0.1		0.5	0.5

[a] Data taken from ref. 53

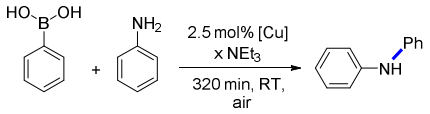
Despite τ-values[55] indicating a coordination geometry between square-pyramidal and trigonal-bipyramidal, coordination geometries around Cu are essentially square-pyramidal and contain one ligand in the apical position (water in **1**, sulfonate in **2** and **4**) with a 0.2-0.3 Å longer Cu-ligand distance. Complex **2** is essentially isostructural to its analogue lacking the *para*-methyl substituent.[56] Copper-ligand distances are otherwise in the range observed in complexes with very similar ligands (Cu-imino: 2.03(3) Å, Cu-pyridine: 2.00(2) Å, Cu-OSO_2: 1.98(6) Å based on 13 entries in the CSD).[53, 54, 56-60]

Chan-Evans-Lam couplings: general reaction conditions. Typical for CEL couplings is the requirement for a careful optimization of reaction conditions. Variables are the solvent (the choice of which depends strongly on the substrate and reaction conditions), the requirement to eliminate water (presence of molecular sieves), the presence of a (Lewis) base (typically NEt_3, pyridine or other *N*-bases), potential additives/ligands and the counteranion (most often acetate or triflate). We investigated if these factors would indeed be less important for couplings with **1**. Arylation of aniline with phenylboronic acid was chosen as the standard reaction. Reactions

were quenched after 5 h to provide an intermediate conversion which is sensitive to changes in conditions. Longer reaction times lead to full conversion (*vide infra*).

Solvent. Solvent dependence in CEL couplings is normally difficult to predict, since the solvent plays an activating role in solubilizing the copper catalyst and a deactivating role in saturating coordination sites required for substrate coordination. An empirical order of CH_2Cl_2 > 1,4-dioxane, THF, DMF > EtOAc, toluene > DMSO >> MeOH,[15] or 1,4-dioxane, CH_2Cl_2 >> DMF > EtOAc > THF > toluene > DMSO[10] has been claimed, but deviations from these are the rule. A more predictable dependence on solvent polarity was expected for **1**, since coordination complexes typically show less pronounced solvent interactions than simple copper salts. In fact, there is only a small dependence on the solvent in CEL couplings with **1** (Table 2, entries 1-5), with polar solvents working slightly better than less polar solvents. Only the use of acetonitrile was detrimental, most likely due to blocking of the copper coordination site. It is also possible that – as in recrystallizations in acetonitrile – **1** undergoes ligand exchange to the homoleptic complex **2**. The latter is not active in CEL couplings (Table S1, entry 1).

Table 2. Coupling of aniline and phenylboronic acid using **1** as a catalyst [a]



Entry	Solvent	Modification [a]	Yield
1	MeCN	-	0%
2	Toluene	-	36%
3	CH_2Cl_2	-	41%
4	THF	-	67%
5	MeOH	-	86%
6	MeOH	Molecular sieves, 4A	62%
7	MeOH	+ 20 equiv water	90%
8	MeOH	2.5 mol% NEt_3	12%
9	MeOH	1 equiv NEt_3	0% (12 h)
10	MeOH	2.5 mol% NaOH	0%
11	MeOH	2.5 mol% Na_2CO_3	52%
12	MeOH	1 equiv Na_2CO_3	23%
13	MeOH	**3** instead of **1**	99%
14	MeOH	N_2 atmosphere	0% (12 h) [b]
15	MeOH	N_2 atmosphere, 100 mol% **1**	45% (12 h)
16	MeOH	1 equiv $PhB(OH)_3$	98% (12 h)

[a] Conditions: room temperature, air, 320 min if not otherwise noted, 1.5 equiv. $PhB(OH)_2$, 1.0 M aniline, 2.5 mol% **1**. Equivalents refer to concentrations relative to amine. [b] 1% conversion would have been expected from the stoichiometric reaction, but was likely not detected.

Water. The influence of water in CEL couplings is complex, contradictory and undefined. Early reports of Evans indicated that the presence of water can be detrimental due to the formation of phenol and diphenyl ether byproducts from the oxidative coupling of phenylboronic acid with water.[5] Isotope labeling studies by Lam confirmed that water and not oxygen is the source of phenol byproducts.[61] Water is believed to originate from condensation of boronic acids to boroxines and yields increased in the presence of molecular sieves or when boroxines instead of boronic acids were used.[5, 23] Collman reported, however, that too high an excess of molecular sieves likewise reduces activities.[48] In other cases, the presence of water was tolerated[27] or even led – in the correct amounts – to improvements in reaction yields.[24-26] Last but not least, several CEL couplings were reported in water as a solvent.[31, 35, 41, 49-51] It is notable that in all cases where water was found to be beneficial or used as a solvent, coordination complexes or supported catalysts were employed rather than simple copper salts. In accordance with this, addition of molecular sieves slightly reduced yields in CEL couplings with **1**, while addition of 20 equiv of water (15 vol% of the solution) was well tolerated (Table 2, entries 6+7; Fig. S1).

Base. The requirement and role of an organic or inorganic base in CEL couplings is likewise unclear. While addition of base often increases yields, other couplings proceed better under base-free conditions. The base was speculated to be involved in the formation and activation of boroxine species, in the activation of the nucleophile by deprotonation, and in the formation of copper hydroxide or alkoxide species, which allow bridging to boron or acting as a ligand for the copper catalyst. Addition of base to arylations with **1** strongly suppressed the observed yields (Table 2, entries 8-12)). Investigation of time-dependent conversion showed that this was indeed due to a reduction of the apparent rate constant to one half and not due to decomposition or delayed activation (Fig. S2). In the case of NEt_3, reduced activity might be related to deactivating coordination of the base to copper, but the strongly suppressed activity upon addition of NaOH or Na_2CO_3 indicates that for **1** replacement of chloride by hydroxide or methoxide is also detrimental.

Counteranion. The most commonly employed catalyst in CEL couplings is $Cu(OAc)_2$, or more precisely $Cu_2(OAc)_4$.[15] $Cu(OTf)_2$ typically shows similar activities.[62, 63] $CuCl_2$, $Cu(NO_3)_2$, $Cu(ClO_4)_2$, or $CuSO_4$ are less active,[15, 20, 33, 62-64] although Stahl showed that $Cu(ClO_4)_2$ can be activated by addition of one equiv of acetate.[52] The anion dependence has be rationalized by formation of an acetate-bridged dinuclear copper-boron complex as an intermediate prior to transmetallation (**A**, Scheme 1).[49, 52] Despite these general findings, high activities have been observed for copper salts other than acetate. For example, Collman's tmeda/CuX catalyst showed identical activities for OTf^- and Cl^-,[49] and coupling of hindered imidazoles worked best with $Cu(NO_3)_2$.[34] Based on the rate increase upon addition of methoxide to $Cu(OAc)_2$-catalyzed reactions, Stahl proposed that a methoxide-bridged species is likewise a possible intermediate to transmetallation.[52] Watson later found HRMS-evidence for the formation of acetate-bridged and hydroxide-bridged dinuclear species, of which the hydroxide-bridged complex was calculated to be of lower energy.[36] The influence of the anion might thus be negated if a hydroxide-containing species is formed in the catalytic cycle, as it is the case for Collman's tmeda/CuX system.[48, 49]

For CEL couplings with **1** or **3**, we proposed that coordination of phenylboronic acid to the sulfonate group precedes transmetallation (Scheme 1, **C**). We would thus expect that the nature of the anion, which is crucial if the anion acts as a bridging ligand, has only a minor impact on reactivity. CEL couplings with the triflate complex **3** showed, however, notably higher conversions than with the chloride complex **1** (99% vs. 86%, Table 2, entry 13). A closer investigation of the reaction kinetics showed that the reduced activity of **1** was due to delayed catalyst activation, while the actual reactivities were

very similar with apparent first-order rate constants of k_{app} = 0.40(2) h^{-1} and 0.50(1) h^{-1}, respectively (Fig. 2).

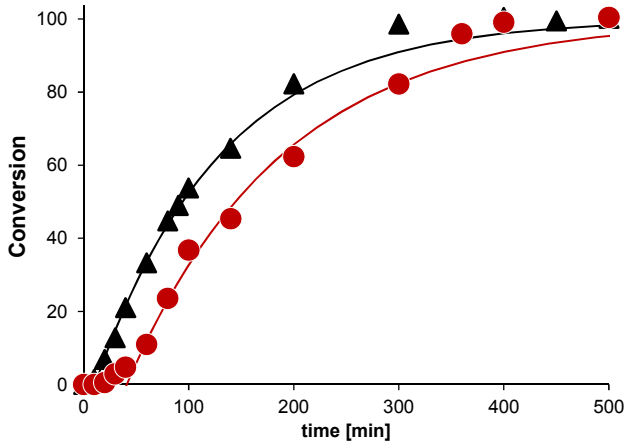


Figure 2. Conversion-time profiles for the arylation of aniline with $PhB(OH)_2$ in methanol ($[PhNH_2]$ = 1.0 M, $[PhB(OH)_2]$ = 1.5 M, [Cu] = 25 mM, RT, air). Black triangles: **3**, average of 4 experiments, k_{app} = 0.50(1) h^{-1}. Red circles: **1**, average of 4 experiments, k_{app} = 0.40(2) h^{-1}. For the deviations at high conversion, see discussion of reaction kinetics.

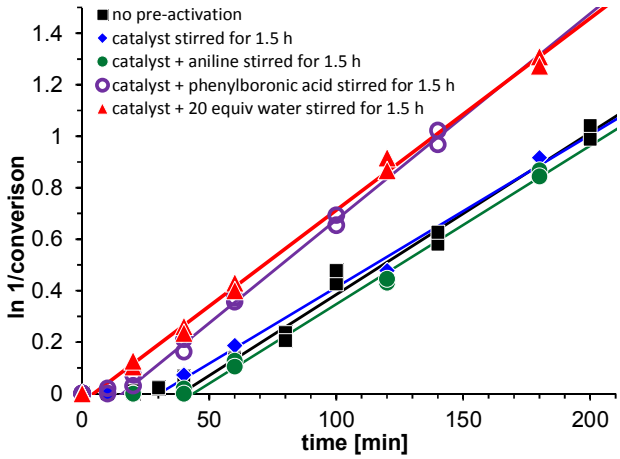


Figure 3. Semi-logarithmic conversion-time profiles for the arylation of aniline with $PhB(OH)_2$ under various pre-activation conditions ($[PhNH_2]$ = 1.0 M, $[PhB(OH)_2]$ = 1.5 M, [Cu] = 25 mM, RT, air). The two datapoints per time indicate conversions calculated from appearance of diphenylamine and disappearance of aniline, respectively.

The significantly longer induction period observed for **1** (40 min) in comparison to triflate-coordinated **3** (10 min) was puzzling, since anion-exchange reactions in Cu(II), d^9, complexes would be expected to be reasonably fast. Color changes during the reaction seem to point towards solubility problems as the main cause of the induction period: **3** is soluble in methanol to provide a green solution, while **1** is not, or only barely soluble. In CEL coupling reactions, the green color of the **1** or **3** in solution is never observed, however: the reaction mixture turns orange after the induction period and this color persists throughout the reaction. CEL couplings with **1** were thus investigated under a variety of pre-activation conditions to clarify the origin of the induction period. Preactivation of the catalyst for 1.5 h with or without added aniline substrate before addition of phenylboronic acid did not notably influence the induction period (Fig. 3). Preactivation with phenylboronic acid, on the other hand, reduced the induction period to one half. Finally, stirring in the presence of 20 equiv of water reduced it to <10 min, similar to that of the triflate complex **3**. It seems thus likely that water is required to solubilize the complex **1** in methanol. The analogous complex lacking the *para*-methyl group interconverts between a methanol-insoluble, dinuclear, chloride-bridged complex and a mononuclear, water-coordinated complex in the absence or presence of water.[60] In the absence of external water, the latter might be slowly taken up from atmosphere or – in the presence of phenylboronic acid - formed during the reaction or by boroxine formation (although we did not observe boroxines when reactions were followed by NMR). To avoid complications by the long induction time of **1**, further reactivity studies were – if not otherwise mentioned – conducted with **3** as the catalyst.

Oxidant. CEL couplings are oxidative couplings and the presence of an oxidant is required in the reaction. In most cases, either air or an oxygen atmosphere is sufficient, although other oxidants have been used originally.[65-67] For most CEL couplings, the accepted mechanism is the one proposed by Stahl, in which aryl Copper(II) is oxidized by another Copper(II) complex to aryl copper(III) prior to reductive elimination.[52, 68] The oxidant is required solely to re-oxidize the copper(I) complexes formed. Tromp reported successful CEL couplings of imidazoles in the absence of oxidants and found evidence for the formation of boranes under anaerobic conditions.[28, 69] To the best of our knowledge, this is the only report of successful catalytic CEL couplings in the absence of oxygen or external oxidant.

N-arylation of aniline with **1** under exclusion of oxygen did not lead to any observable formation of product. When the copper complex was added in stoichiometric amounts, 45% conversion to product was observed under exclusion of oxygen (Table 2, entries 14+15). CEL couplings with **1** thus require two equivalents of **1** to complete a catalytic cycle and oxygen for the regeneration of the catalyst, following the mechanism proposed by Stahl in this aspect.[52, 68]

Substrate reactivity. Since CEL couplings with **3** tolerate water, various solvents, do not require addition of base or additional ligand and since the sulfonate group rather than the anion participates in the transmetallation step, optimization of reaction conditions was essentially limited to choosing the reaction time and temperature. Satisfyingly, **3** was active in the arylation of a variety of *N*-nucleophiles, including anilines, amines and *N*-heterocycles. Reactions were conducted in undried methanol at room temperature or at 50 °C. In heated reactions, solvent vapor seemed to impede oxygen uptake from the atmosphere when condensers were used. Simple stirring of heated reactions open to air led to higher apparent conversions, but calibrated GC/MS-analysis showed in some cases a mass imbalance between the product formed at full conversion and the starting amine, most likely due to evaporation of the latter. Reactions at 50 °C were thus stirred in closed vessels under a supply of oxygen to ensure reproducible reaction conditions. Chart 1 reports the result of the reactivity study with various *N*-nucleophiles. To best characterize substrate reactivity, conversions were obtained from calibrated GC/MS-analysis of the quenched reaction mixtures. We have shown in a preliminary communication that pure compounds can be isolated after column chromatography in yields of >85%.[53]

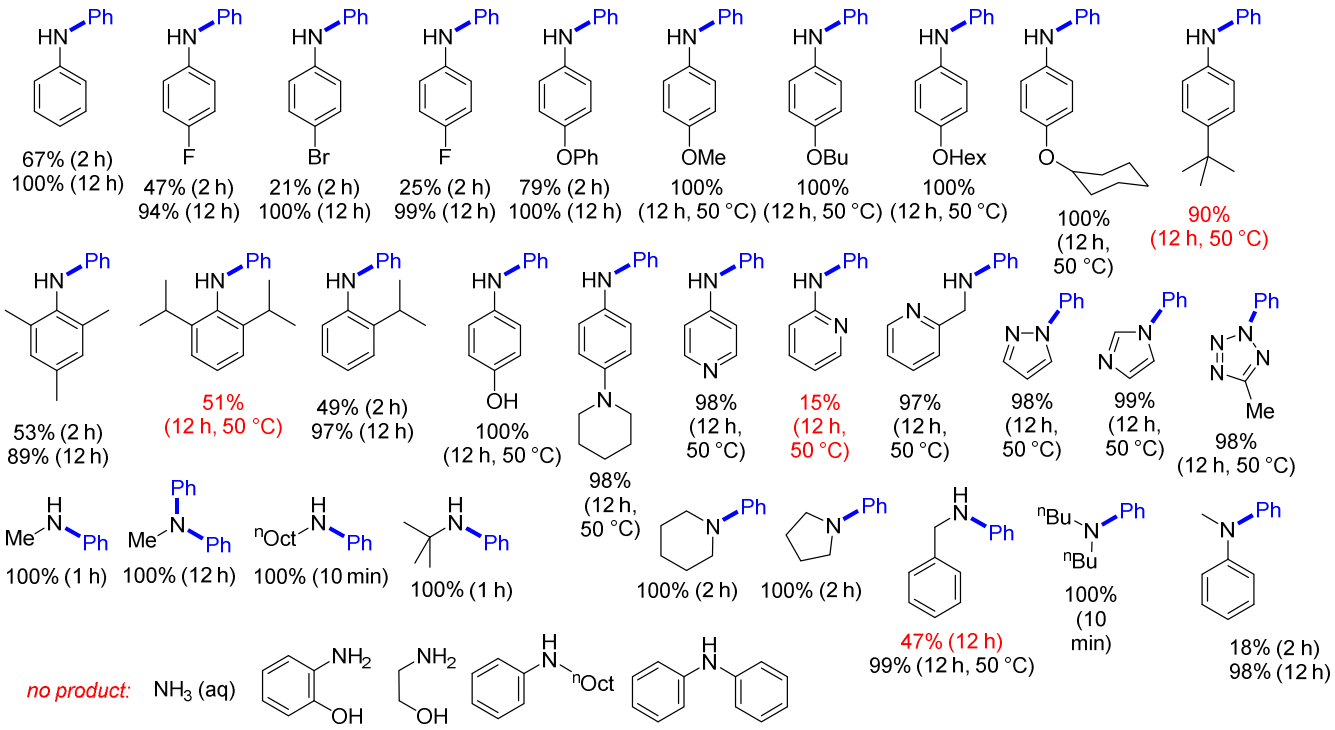
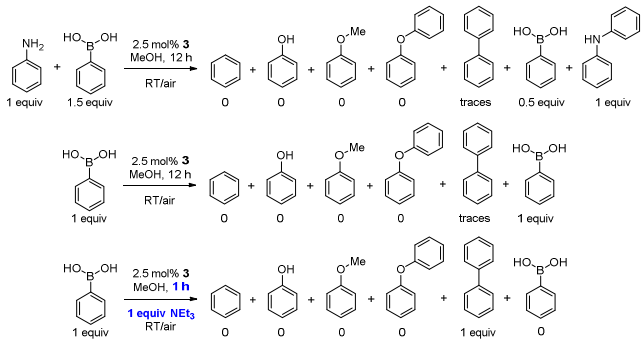


Chart 1. Products of CEL couplings of *N*-nucleophiles with phenylboronic acid catalyzed by **3**.

Notably, arylation proceeded well even for substrates typically reported to be difficult to arylate, such as aminopyridines, picolylamine and *tert*-butyl amine. Coupling of acyclic secondary amines, which are considered one of the biggest challenges in C-N bond formations via CEL coupling, proceeded not only well, but with very high activity. Water was tolerated well enough that methylamine could be added as an aqueous solution. Reduced reactivity was observed for some substrates, mainly due to secondary reactions which will be discussed in the next sections.

Substrate-independent side reactions. Typical side reactions in CEL couplings are deboration to yield benzene and oxidation or coupling with water to yield phenols or diphenyl ethers if the former undergo CEL coupling. Homocoupling of two arylboronic acids to provide the respective diaryl is another common side reaction. These parasitic reactions can be competitive with the coupling reaction and are the main reason why CEL couplings typically require excess arylboronic acid or do not reach completion. Neither of these products nor coupling to the methanol solvent have been observed in CEL couplings with **3**. Reactions in MeOD followed by NMR showed the excess amount of phenylboronic acid still present after 12 h of reaction. Neither NMR, nor GC/MS analysis provided any indication for the presence of other byproducts, although traces (<5%) of the diaryl were observed in some reactions (Scheme 3). Even in the absence of amine nucleophile, but under otherwise identical conditions (1.5 M $PhB(OH)_2$, 2.5 mol% **3**, methanol, RT/air), the only product formed was diphenyl and even this in less than 5% (Scheme 3). In presence of triethylamine, complete conversion of phenylboronic acid to diphenyl occurred in 1 h (Scheme 3), still without evidence of any other byproducts. Targeted homocoupling of arylboronic acids with copper catalysts has been reported previously with and without external base,[31, 70-77] the highest activity being full conversion in 15 min at room temperature.[77] Due to the complete absence of side reactions, CEL coupling with **3** is thus possible without using excess of phenylboronic acid. In the presence of a stoichiometric amount of $PhB(OH)_2$, 98% conversion of aniline to diphenylamine was observed after 12 h at RT (Table 2, entry 16). For the following mechanistic investigations, an excess of 1.5 equiv of boronic acid will continued to be used, however, to exclude any influence of side reactions on amine conversions and to ensure the reproducibility of these results.



Scheme 3. Possible parasitic reactions in CEL couplings.

Substrate poisoning. Typically, more electron-rich anilines react faster in CEL couplings.[18, 51, 64, 78] It was thus surprising that with **3** electron-poor anilines reacted with very comparable rate constants to aniline, while electron-rich anilines did not react at room temperature, but required heating (Table 3). We had previously observed catalyst poisoning by the substrate in CEL couplings with related sulfonate-diketimine complexes (Scheme 1, **B**),[26] and this provides a likely explanation for the observed reactivities. Competition experiments between aniline and bromoaniline with a limiting amount of phenylboronic acid confirmed the expected higher reactivity

of the more electron-rich aniline (Table 3). In the presence of methoxyaniline, on the other hand, arylation of *both* substrates was suppressed, indicating that electron-rich anilines, such as methoxyaniline, deactivate the catalyst by formation of an inactive aniline-copper complex.

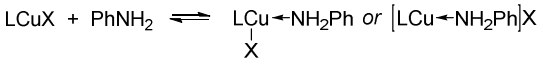
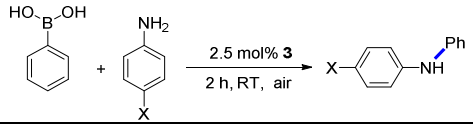


Table 3. Coupling of *para*-substituted anilines and phenylboronic acid with **3** [a]

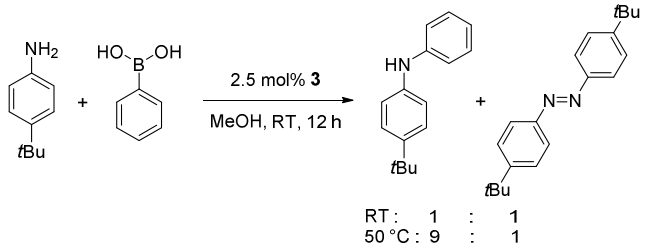


X	Conversion (12 h)	k_{app}
H	100%	0.55(1)
F	94%	0.49(7)
Br	100%	0.36(2)
OPh	100%	
OR [b]	0%	
H + OMe [c]	0%	
H + Br [c]	71% (X=H), 29% (X=Br)	

[a] Conditions: room temperature, air, 320 min if not otherwise noted, 1.5 equiv $PhB(OH)_2$, 1.0 M aniline, 2.5 mol% **3**. Equivalents refer to concentrations relative to amine. [b] R = Me, *n*Bu, *n*Hex, cyclohexyl. [c] 1.0 M aniline, 1.0 M *p*-X-aniline, 1.0 equiv $PhB(OH)_2$, 2.5 mol% **3**.

Formation of an aniline adduct **3**·NH_2Ph was confirmed by UV/vis spectroscopy. Upon addition of aniline to a green methanol solution of **3**, a color change to orange is observed. An isosbestic point persists up to an aniline concentration of 25 mM, indicating a simple aniline coordination to yield the putative **3**(NH_2Ph) complex. Upon further addition of aniline up to reaction concentrations of 1.0 M, new peaks appear which were assigned to a higher **3**(NH_2Ph)$_n$ complex. Simultaneous regression of the spectral changes at 347, 450, 540, 625, and 750 nm showed best agreement with the reaction of two additional aniline to form **3**(NH_2Ph)$_3$ with equilibrium constants of $K_1 \approx 50\ M^{-1}$ and $K_2 \approx 10\ M^{-2}$ (Fig. 4).

tert-Butyl aniline. A different reason was responsible for the reduced conversion with *tert*-butyl aniline. Reaction at room temperature led to complete conversion of *tert*-butyl aniline after 12 h, but the obtained product was a 1:1 mixture of the coupling product and 4,4'-di-*tert*-butylazobenzene (Scheme 4). The oxidative coupling of anilines by copper to azobenzenes is known since the '50s,[11, 79] but has, to the best of our knowledge, not been reported to interfere with CEL couplings. The mechanism of azobenzene formation most likely proceeds via an aniline radical, generated by oxidation of aniline either directly by Cu(II) or by a peroxocopper complex formed upon reaction of Cu(I) with oxygen.[80] Reactions under different conditions showed that oxygen as well as $PhB(OH)_2$ were required for azobenzene formation (Table 4) and a Cu(I)/O_2 reaction product is thus most likely responsible for generating the aniline radical. Consequently, azobenzene formation was strongly reduced to 8% if couplings were performed in the presence of tetramethylpiperidine to trap oxygen radicals (Table 4). However, the presence of a nitrogen base also suppressed CEL coupling and conversion to product was limited to 25%. At 50 °C formation of azobenzene could be mostly suppressed, even without tetramethylpiperidine, in favor of the CEL coupling product (Scheme 4).



Scheme 4. CEL coupling of *tert*-butylaniline with $PhB(OH)_2$

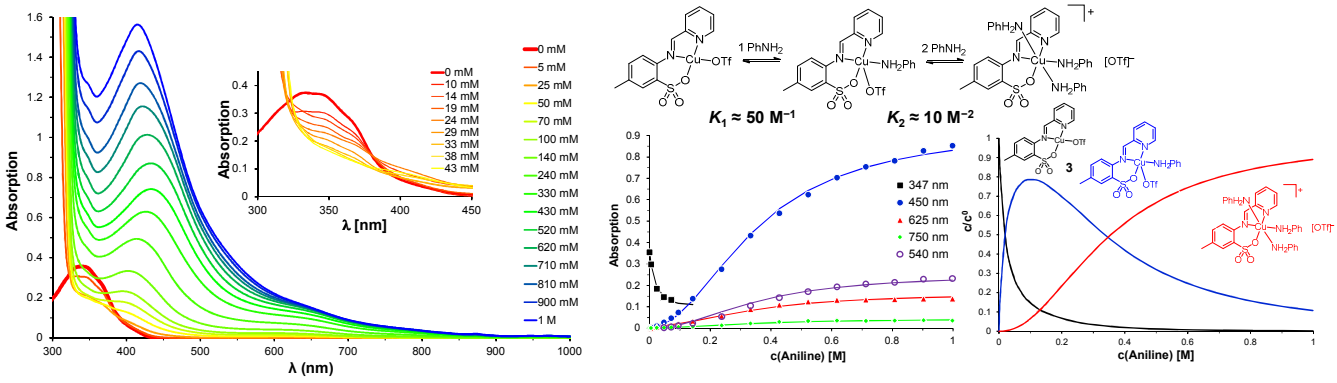


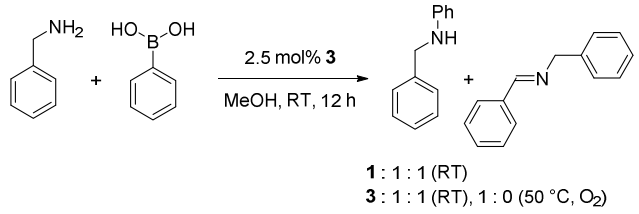
Figure 4. Left: UV/vis titration of **3** (58 µM) in MeOH with aniline. The inset shows the isosbestic point obtained until 25 mM aniline. Middle: Absorption at different wavelengths vs aniline concentration. The lines indicate the results of the simultaneous non-linear regression presuming reaction with 2 aniline in the second equilibrium. Right: Concentration of **3** and its aniline adducts at different aniline concentrations, calculated from $K_1 = 50\ M^{-1}$ and $K_2 = 10\ M^{-2}$.

Table 4. Oxidation of *tert*-butyl aniline catalyzed by **3** [a]

Temperature	$PhB(OH)_2$	Conditions	Yield azobenzene [b]
RT	1.5 equiv	Air	66%
RT	1.5 equiv	N_2	0%
RT	0 equiv	O_2	0%
50 °C	0 equiv.	O_2	0%
50 °C	1.5 equiv	O_2	10%
RT	1.5 equiv	Air [c]	8% [c]

[a] Conditions: MeOH, [tBuC$_6$H$_4$NH$_2$] = 1.0 M, 12 h, 2.5 mol% **3**. [b] Based on percentage of aniline which reacted to azobenzene. Molar ratios of coupling product to azobenzene were 1:1 at RT and 20:1 at 50 °C. [c] In the presence of 0.5 equiv tetramethylpiperidine.

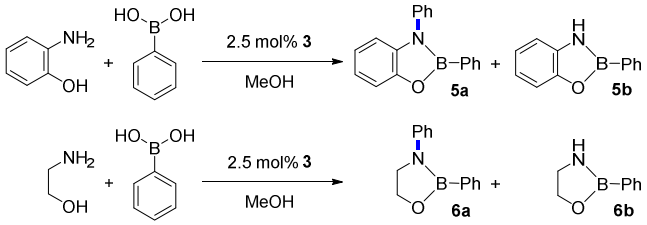
Benzylamine. Arylations of benzylamine likewise suffered from oxidative side reactions, in this case the formation of *N*-benzylidene benzylamine in an equimolar amount with the desired coupling product (Scheme 5). The side product is most likely the consequence of amine oxidation to the imine, followed by hydrolysis and condensation with benzylamine. The rate-determining step in aerobic copper-catalyzed amine oxidations is considered to be the abstraction of an α-H atom to form an amine radical.[11] The latter might explain while this side reaction was only observed for benzyl amine. Amine oxidation was avoided at 50 °C and only coupling product was observed.



Scheme 5. CEL coupling of benzylaniline with $PhB(OH)_2$

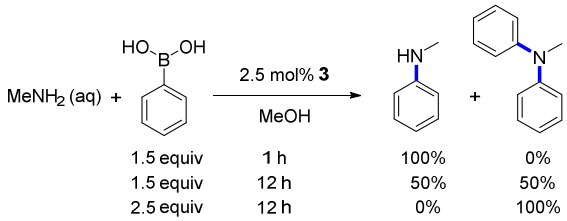
Ammonia. While an aqueous solution of methylamine reacted fast, aqueous solutions of ammonia were unreactive. From the unusual blue color of the reaction mixture and the fact that no diphenyl was produced, catalyst decomposition/deactivation is most likely responsible for this lack of reactivity.

Aminophenols and aminopyridines. CEL coupling of amines able of chelating coordination was reported to be difficult.[22] Using **3**, 4-pyridyl amine, 4-hydroxyaniline and 2-picolylamine were coupled readily at 50 °C, although picolylamine was the only alkyl amine substrate which required heating. 2-Pyridylamine reacted sluggishly and not to completion. 2-Hydroxyaniline and ethanolamine could no be coupled. In both of the latter cases, analysis of the reaction mixture showed the presence of arylated (**5a**, **6a**) and non-arylated boronic esters (**5b**, **6b**, Scheme 6). In the presence of 3 equiv of $PhB(OH)_3$, reactions with ethanolamine provided only the arylated boronic ester **6a** as the single observed product. Ester formation thus leads to deactivation of phenylboronic acid, rather than of the amine. Reactions with 2-hydroxyaniline, however, did not proceed to full arylation even under excess of phenylboronic acid.



Scheme 6. CEL coupling of β-hydroxyamines with $PhB(OH)_2$

Double arylation. Since **1** and **3** were active in CEL couplings of amines and anilines under the same reaction conditions, the question of chemoselectivity arises, i. e. if the reaction is complicated by double arylation. In fact, methylamine can be doubly arylated at prolonged reaction times and with 2.5 equiv $PhB(OH)_2$ present (Scheme 7). The same product was obtained by arylation of *N*-methylaniline (Chart 1). In the presence of 1.5 equiv $PhB(OH)_2$, selective and quantitative monoarylation was observed after one hour. If the reaction is continued over night, a 1:1 mixture of PhN(H)Me and Ph_2NMe was obtained. (Scheme 7). No double arylation was observed in any other reaction. Diphenylamine or *N*-octylaniline, when reacted independently, could not be further arylated (Chart 1). Reactions of aniline or octylamine with 2.5 equiv of $PhB(OH)_2$ consequently yielded selective conversion to the monoarylation products, even at 50 °C and upon addition of water to reproduce the reaction conditions with methylamine, where an aqueous solution of the amine was used (Table S1, entries 2-9). CEL couplings with **3** are thus highly selective for monoarylation.



Scheme 7. CEL coupling of methylamine with $PhB(OH)_2$

*Mechanism of CEL couplings with **1** and **3**.* The kinetics of CEL couplings with **3** were investigated for the *N*-arylation of aniline. Calibration of the GC-MS detector response and the use of internal standard allowed the determination of absolute quantities of unreacted aniline and the diphenylamine product. Both methods provided essentially identical conversion values, indicating that no aniline was lost in secondary reactions or due to evaporation (Fig. 5). After a short induction period of approx. 10 min, the reaction followed pseudo-first order kinetics. Conversions above approx. 80% were consistently higher than expected on the basis of a pseudo-first-order rate law (Fig. 5, solid line). Kinetics with **1** showed the same behavior (Fig. S3). A possible explanation for this deviation is formation of an inactive, aniline-coordinated complex as discussed above. In the concentration profiles calculated from the equilibrium constants determined in UV/vis-titrations of **3** with aniline, the concentration of the active LCuX species sharply increases at aniline concentrations below 0.2 M (Fig. 4), in good agreement with the observed increase in activity above 80% conversion (Fig. 5). If catalyst poisoning by substrate is taken into account, agreement with the observed con-

versions improved notably (Fig. 5, dashed line). It should be noted that the value for K_1 = 1 M^{-1} obtained in non-linear regression of the kinetic data was one magnitude lower than the value determined via UV/vis spectroscopy. If the coordination of two further aniline to yield [LCu(NH_2Ph)$_3$]X (K_2) is included in the fitting of the kinetic data, the value for K_2 refined to nearly zero. Inclusion of inhibition by substrate thus agrees with the kinetic data, but quantitative values differ significantly from those determined independently. This is not surprising, given that we neglected the presence of any other Lewis acids and bases in the reaction mixture.

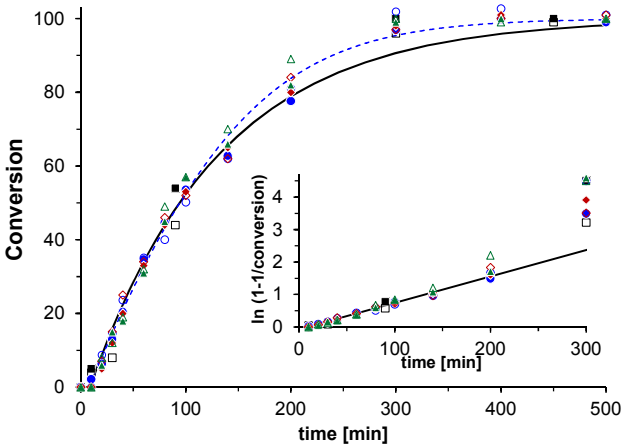


Figure 5. Conversion vs time profile for the *N*-arylation of aniline. Four independent reactions under identical conditions are shown (MeOH, RT, 1.0 M aniline, 1.5 equiv PhB(OH)$_2$, 2.5 mol% **3**). Filled symbols: conversion determined from remaining aniline. Hollow symbols: conversion determined from diphenyl amine product. The solid, black line is calculated from the pseudo-first-order rate constant k_{app} = 0.50(1) h^{-1}, determined from all datapoints in the range of 30-140 min. The blue, dashed line is the best-fit conversion trace with a pseudo-first-order rate constant k_{app} = 0.82 h^{-1} and an equilibrium constant of K_1 = 1 M^{-1} for the coordination of aniline to **3**. The inset shows the linearized ln (c^0/c) plot.

The pseudo-first-order rate constant was essentially independent from phenylboronic acid concentration. Tripling the phenylboronic acid concentration from 1.0 to 3.0 equiv led only to a small increase in the pseudo-first-order rate constant of approx. 40% (Fig. 6, Table 5). Stahl had observed for the arylation of methanol that the reaction displayed saturation kinetics in boronic acid concentration.[52] The small increase of k_{app} indicates a similar situation here, i. e. that transmetallation is not the rate-determining step.

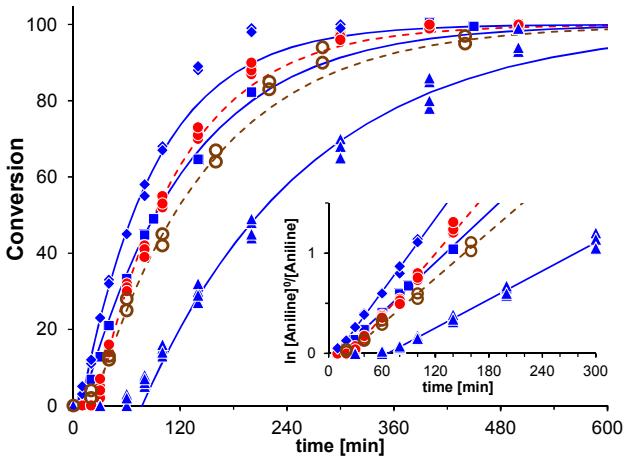


Figure 6. Conversion vs time profile for the *N*-arylation of aniline under different reactant concentrations (MeOH, RT, 1.0 M aniline) Squares, 1.5 M PhB(OH)$_2$, 2.5 mol% **3**, average of 4 experiments; red circles, 3.0 M PhB(OH)$_2$, 2.5 mol% **3**, 2 experiments; brown, hollow circles: 1.0 M PhB(OH)$_2$, 2.5 mol% **3**; diamonds, 1.5 M PhB(OH)$_2$, 5.0 mol% **3**; triangles, 1.5 M PhB(OH)$_2$, 1.0 mol% **3**, 2 experiments. The inset shows the linearized ln (c^0/c) plot.

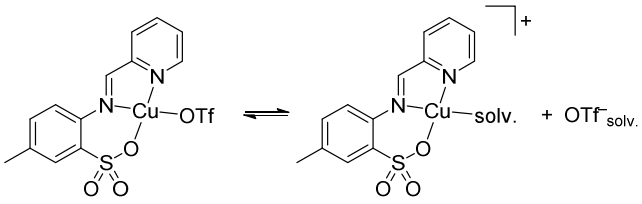
Table 5. Apparent First-Order Rate Constants for the *N*-Arylation of Aniline with **3**. [a]

Catalyst	[Catalyst]	[PhB(OH)$_2$]	k_{app}
3	0.025 M	1.0 M	0.46(2) h^{-1}
3	0.025 M	1.5 M	0.50(2) h^{-1} [b]
3	0.025 M	3.0 M	0.65(1) h^{-1} [c]
3	0.010 M	1.5 M	0.28(1) h^{-1} [c]
3	0.050 M	1.5 M	0.73(2) h^{-1}
1	0.025 M	1.5 M	0.40(2) h^{-1}
1/[NEt_4]Cl	0.025 M	1.5 M	0.15(1) h^{-1}

[a] Conditions: 1.0 M Aniline, 1.5 M PhB(OH)$_2$, 2.5 mol% catalyst, MeOH, RT, air. [b] Rate constant determined from datapoints of product appearance and aniline disappearance in 4 independent experiments. [c] Rate constant determined from datapoints of 2 independent experiments.

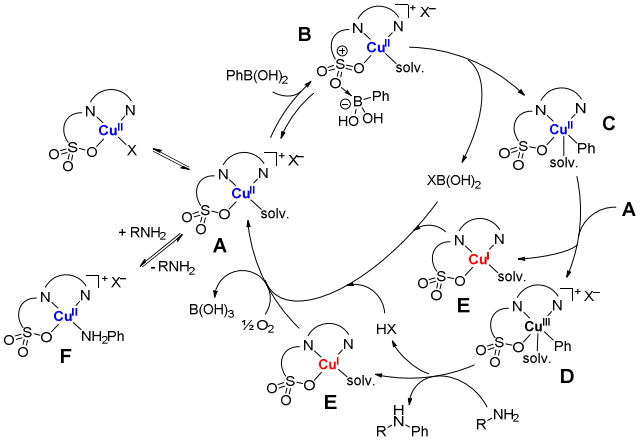
Arylation of aniline at 1.0 or 5.0 mol% of catalyst loading followed similar kinetics (Fig. 6, Table 5). The apparent rate constants and the initial rates of the reaction indicate a half-order dependence on catalyst concentration (Fig. S4). A half-order dependence is typically associated with association/dissociation equilibria and **3** shows indeed bridging sulfonate coordination in the solid state. However, in the presence of water **1** forms solvated, mononuclear complexes in the solid state and both complexes show very similar UV/vis spectra (Fig. S5 and S6).[53] It is thus unlikely that **3** would be present as a sulfonate-bridged dimer in undried methanol solution. An alternative explication for a half-order dependence on catalyst concentration would be formation of an active, cationic species by dissociation of the anion (Scheme 8). In the presence of such an equilibrium, the concentration of

the active, cationic species would be dependent on anion concentration. Indeed, addition of an equimolar amount of $[NEt_4]Cl$ to CEL couplings with **1** reduced the apparent rate constant to half its value (Table 5, Fig. S7). A similar anion dissociation equilibrium has been proposed by Stahl for the arylation of methanol with $Cu(OAc)_2$, where half-order dependence on catalyst concentration and deactivation by additional anion has likewise been observed.[52]



Scheme 8. Anion dissociation equilibrium for **3**

CEL couplings with copper iminosulfonates thus follow the mechanism proposed by Stahl (Scheme 9):[52] Formation of the active catalyst requires displacement of the anion, most likely by solvent. Transmetallation occurs from a dinuclear Cu-B-complex **B** to form the copper-aryl complex **C**. Oxidation by another complex **A** to the Cu(III) complex **D** is followed (or preceded) by coordination of the amine substrate, which then leads to product formation by reductive elimination. The catalytic cycle is closed by re-oxidation of the Cu(I) complexes **E** by oxygen. Modifications consists in our proposal that the sulfonate group and not hydroxide or the anion is bridging to boron in **B** (in agreement with the observations above) and the existence of the off-cycle, aniline-coordinated complex **F**, which was indicated by UV/vis and kinetic data. Substrate inhibition, i. e. **F** being off-cycle, also supports that transmetallation precedes interaction with the nucleophile in the catalytic cycle. If transmetallation would occur after aniline coordination, there is no reason why complex **F** should be unfavorable. (The alternative scenario, that aniline coordinates before transmetallation and that the off-cycle intermediate **F** contains more than one aniline cannot be excluded, but agrees less with the kinetic data.)



Scheme 9. First proposal of catalytic cycle for CEL couplings with **3**

The proposed mechanism is, however, inconsistent with the observed rate-law. The (near-) independence of the reaction rate from phenylboronic acid concentration and its first-order dependence on aniline concentration indicate that the catalyst resting state is located after transmetallation, but before reaction with the aniline. Neither **C** nor **D** are stable species, however. With the exception of Warren's isolation of a Cu(II)-perfluoroaryl complex[81] and Tilley's mixed-valence μ-aryl complex,[82] the few isolated organoCopper(II) aryl complexes stabilize the aryl group as part of a rigid macrocyclic ligand.[83-90] Accumulation of the catalyst in the Cu(II) aryl species **C** would lead to extensive aryl homocoupling. The unstabilized Cu(III) aryl species **D**, on the other hand, will undergo rapid reductive elimination.[91] In the absence of amine this would lead to arylation and thus destruction of the catalyst or to arylation of solvent, both of which is not observed. **D** is thus likewise an improbable catalyst resting state.

Alternatively, saturation of a pre-equilibrium would lead to zero-order-dependence on phenylboronic acid concentration. In this case, the catalyst resting state would be the dinuclear copper-boron complex **B** and transmetallation can remain the rate-determining transition state. Dinuclear copper-boron complexes have been proposed as intermediates in couplings with $Cu(OAc)_2$ by Collman and Stahl.[49, 52] Stahl found EPR-evidence for the formation of an adduct between phenylboronic acid and copper acetate, which he proposed as the catalyst resting state. Watson later found mass-spectroscopic evidence for the presence of bridged species in the catalytic cycle.[36] However, UV/vis titrations of solutions containing **3** with phenylboronic acid up to a concentration of 1.1 M, did not show notable changes of the absorption spectrum (Fig. 7). While this does not disprove the formation of a dinuclear **3**·boronic acid adduct (Scheme 9, **B**) in small equilibrium amounts, there is no indication that the latter can be the major catalyst species present in the reaction mixture.

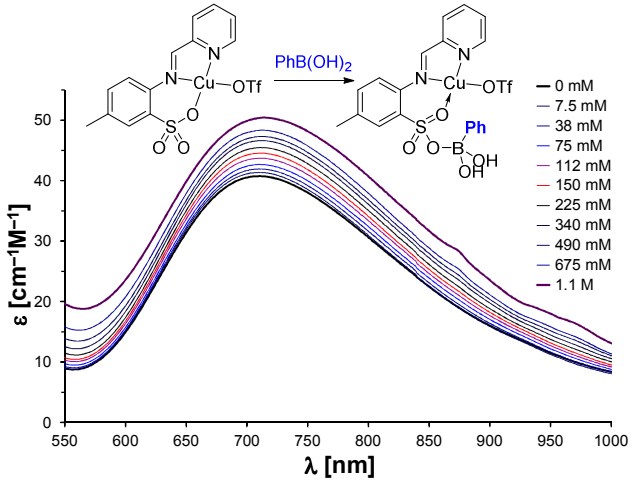


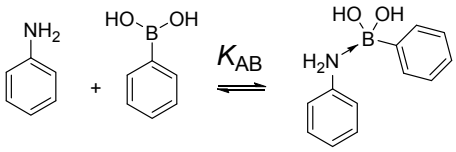
Figure 7. UV/vis spectra of **3** in methanol upon addition of phenylboronic acid. The slight increase in ε is due to phenylboronic acid.

In the absence of a plausible mechanism which would accommodate a fast transmetallation step, we considered possibilities which would provide an apparent zero-order dependence on the phenylboronic acid concentration despite slow transmetallation. Dependence on aniline concentration can be first-order, even if interaction with the aniline takes place after transmetallation as long as the latter is reversible. This is not unlikely, if transmetallation occurs in a dinuclear intermediate such as **B**. Should transmetallation remain the highest activation barrier, the rate law is expected to be:

$$v = k[\mathrm{PhB(OH)_2}][\mathrm{PhNH_2}][\mathrm{LCuX}]^{0.5}$$

(equation 1)

To explain the apparent independence of the rate law from phenylboronic acid concentration, we propose that aniline is involved in a Lewis acid-Lewis base adduct equilibrium with phenylboronic acid, similar to aniline coordination to **3**.



Incorporation of this equilibrium in rate law (1), provides,

$$v = \frac{k[\mathrm{PhNH_2}]^t[\mathrm{PhB(OH)_2}][\mathrm{LCuX}]^{0.5}}{1 + [\mathrm{PhB(OH)_2}]K_{AB}}$$

(equation 2)

where $[\mathrm{PhNH_2}]^t$ is the total concentration of unreacted aniline (see supp. information). For $[\mathrm{PhB(OH)_2}]K_{AB} \gg 1$, the rate law becomes independent from $[\mathrm{PhB(OH)_2}]$.

The existence of aniline-phenylboronic acid adducts was investigated by NMR spectroscopy in MeOD. An equimolar solution of phenylboronic acid and aniline showed signals displaced from the positions of the pure compounds, indicative of interaction of the two species in solution. A reliable determination of the equilibrium constant was not possible, however, since saturation of the equilibrium was barely occurring even at a 12 M concentration of one compound. At these high concentrations it is not possible to distinguish between the effect of the coordination equilibrium or changes due to the solvent composition. Nevertheless, from the concentration-dependent shifts between 1 M and 12 M concentration, a value of $K_{AB} \approx 1\ \mathrm{M^{-1}}$ was estimated (Fig. 8).

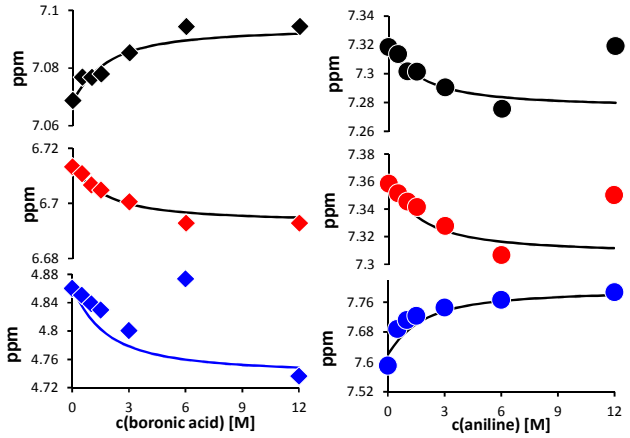


Figure 8. Displacement of chemical shifts in the NMR spectra of aniline upon addition of phenylboronic acid (left) or of phenylboronic acid upon addition of aniline (right). The solid line represents the theoretical displacement assuming an equilibrium constant of $K_{AB} \approx 1\ \mathrm{M^{-1}}$.

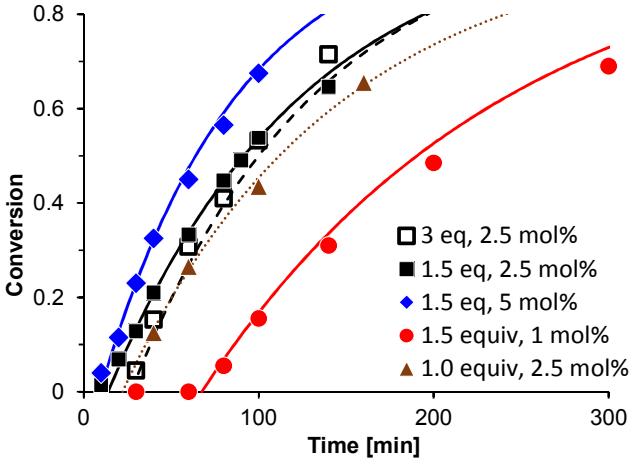


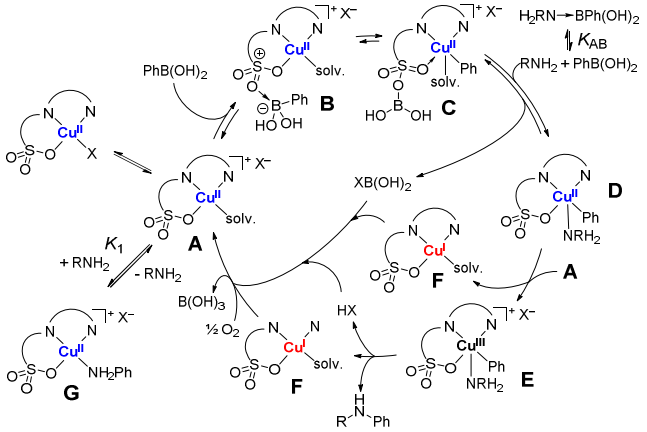
Figure 9. Conversion vs time profiles for the *N*-arylation of aniline under different reactant concentrations (MeOH, RT, 1.0 M aniline). Solid lines are the simulated conversions based on $v = k[\mathrm{PhB(OH)_2}][\mathrm{PhNH_2}][\mathrm{LCuX}]^{0.5}$ under consideration of aniline coordination to phenylboronic acid. K_{AB} and k refined to best-fit values of k = 0.4 $\mathrm{M^{-1.5}min^{-1}}$ and K_{AB} = 5 $\mathrm{M^{-1}}$ (see supp. information).

The observed reaction kinetics are well reproduced using rate law (1) and equilibrium K_{AB} (Fig. 9). Due to the overparametrization of the problem, aniline-coordination to **3** (equilibria K_1 and K_2) were ignored and only datapoints below 80% conversion were employed in the kinetic fit (c.f. Fig. 5). Free refinement of both parameters provided k = 0.4 $\mathrm{M^{-1.5}min^{-1}}$ and K_{AB} = 5 $\mathrm{M^{-1}}$, in reasonable agreement with the value of K_{AB} = 1 $\mathrm{M^{-1}}$ estimated from NMR investigations of the equilibrium (c. f. Fig. 8). Since the apparent rate law is nearly independent from phenylboronic acid concentration, K_{AB} and k are strongly correlated and nearly identical fits can be obtained in the range of K_{AB} = 1 – 10 $\mathrm{M^{-1}}$ (supp. information). Since the kinetic model also ignores the formation of $B(OH)_3$ and Ph_2NH (or assumes that their formation cancels each other out), values obtained from the kinetic fit should only be considered *apparent* equilibrium or kinetic values of a strongly simplified model. More important than quantitative values, the good agreement with the kinetic data in Fig. 9 shows that apparent saturation behavior in phenylboronic acid concentration is well explained by formation of an aniline-phenylboronic acid adduct and does not need to involve fast transmetallation or saturation of a pre-equilibrium.

Based on the above, we now propose the following adapted mechanism for CEL couplings with **3** (Scheme 10): the reversible transmetallation from the dinuclear complex **B** is rate-determining and yields the Cu(II)-aryl complex **C**. Warren recently reported a Cu(II)-perfluorophenyl complex, which undergoes oxidation to Cu(III) and reductive elimination when reacted with a nucleophile.[81] It seems thus more likely that coordination of the amine (**D**) occurs before oxidation. Amine coordination is in competition with the back-reaction of the transmetallation **C→B**. Product formation thus depends on both steps and is dependent on amine concentration, even if reaction with amine occurs after the rate-determining step. If phenylboronic acid is present in excess, any enhancement in the transmetallation reaction by increased boronic acid concentration is counterbalanced by a reduction in the concentration in free amine due to the Lewis acid-Lewis base complex formed. Due to its aryl substituent and the coordinated amine, complex **D** is significantly more electron-rich and can be

oxidized by the original Copper(II) species **A** to form the copper(III) complex **E**.

If transmetallation is slow, either Cu(II) complex **A**, amine-adduct **G**, or the Cu(I) complexes **F** might be catalyst resting states. We did not observe any accumulation of Cu(I) species when the reaction was followed by NMR, but they might be obscured by remaining paramagnetic Cu(II). The color of the reaction mixture, however argues in favor of species **G** as the resting state: a methanol solution of **3**, i. e. species **A**, is green. Under reaction conditions, the green catalyst powder dissolves to provide an orange solution, which is reminiscent of the color of the amine adduct observed in UV/vis titrations with aniline. For Cu(I) species, we would expect them to be re-oxidized at the end of the reaction, but the orange color remains stable for hours after the reaction reached completeness. While **G** is thus the most likely resting state (probably as an adduct with the product at the end of the reaction), we could not obtain any evidence for such as species in HRMS spectra of the reaction mixture.



Scheme 10. Final catalytic cycle for CEL couplings with **3**

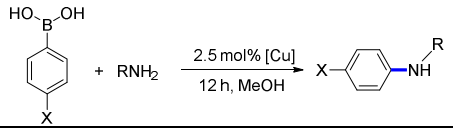
C-O and C-S couplings. The absence of coupling to methanol solvent and the tolerance of water already indicated that **1** and **3** are not highly reactive towards *O*-nucleophiles. Attempts of CEL couplings to phenol either in dichloromethane or methanol required the addition of base, either because this role is fulfilled by substrate in CEL couplings of amines and anilines, or because deprotonation is required to increase the nucleophilicity of phenol. However, even under these conditions reactions with phenols were sluggish at best and thiols did not react at all. This chemoselectivity of **3** was also indicated by the selective arylation of aminophenols (*vide supra*). While **3** outperforms near all catalyst systems in the coupling of *N*-nucleophiles, even simple copper salts show better reactivity towards weaker nucleophiles such as phenols. Hydroxy- and thiol substituents should thus be considered tolerated functional groups rather than potential reaction sites, and we did not further attempt to optimize reaction conditions for C-O or C-S couplings.

Electron-deficient boronic acid reagents. CEL couplings of aniline with *para*-ethoxyphenylboronic acid, catalyzed by **3**, proceeded smoothly with an activity 4 times higher than that observed with phenylboronic acid (Fig. S8). Electron-deficient boronic acids, on the other hand, are typically more difficult to couple.[52, 92] Indeed, couplings with *para*-iodophenylboronic acid did not yield any coupling product after 12 h at room temperature or at 50 °C. *Para*-fluorophenylboronic acid reacted likewise very sluggishly with less than 10% conversion (Table 6). For the first time, we noticed formation of the parent aryl from deboration side reactions. More important, however, was the notable amount of homocoupling. While homocoupling normally is only observed in trace amounts, the diaryl was the main product in these reactions.

The formation of diaryl species indicated that transmetallation is unlikely to be the problematic step. The lack of reactivity with electron-deficient boronic acid reagents probably stems from a slower oxidation to the Cu(III) species **E** (Scheme 10) Since the Copper(II) aryl species **C** or **D** would be more difficult to oxidize with more electron-deficient aryl substituents, C-C homocoupling from **C** now becomes competitive.[11] Oxidation to **E** would be facilitated by more nucleophilic amines. Reaction with *n*-octylamine indeed provided the coupling product in modest yields (Table 6). Similarly, we attempted to increase the nucleophilicity of aniline by addition of triethylamine, but without effect. This is consistent with the mechanistic proposal that deprotonation occurs after oxidation (Scheme 10). Addition of boric acid was proposed by Watson to be beneficial, in particular in the reoxidation of Cu(I) species.[36] Reaction conditions following Watson's protocol, i. e. 1 equiv $B(OH)_3$ and excess amine, which were beneficial for $Cu(OAc)_2$, strongly reduced conversions in couplings with catalytic amounts of **3** (Table S1, entries 10-13). Addition of substoichiometric amounts of boronic acid, however, increased the yield of couplings with *para*-fluorophenylboronic acid, but did not exceed 50% conversion (Table 6).

Photoredox catalysis. Light-induced electronic transitions, in particular charge-transfer transitions, can be considered intramolecular redox reactions and in recent years photocatalytic reactions have proved very useful in promoting otherwise difficult redox chemistry.[93, 94] We thus investigated if irradiation by light would facilitate the oxidation to Cu(III) species **E**. CEL couplings of aniline with *para*-fluorophenylboronic acid were conducted under irradiation with white, green (525 nm) or blue (452 nm) light (Table 7). While irradiation with white or green light was not effective, irradiation with blue light afforded the coupled product in moderate yields. Heating to 35 °C or 50 °C did not notably improve conversions.

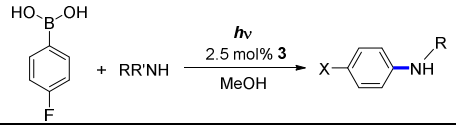
Table 6. CEL couplings of aniline with electron-deficient phenylboronic acids catalyzed by **3**. [a]



X	RNH_2	Conditions [a]	conversion
OEt	$PhNH_2$	RT, air	100%
NO_2	$PhNH_2$	RT, air	0%
I	$PhNH_2$	RT, air or O_2	0%
I	$PhNH_2$	50 °C, O_2	0%
I	nOctNH$_2$	RT, air	30%
F	$PhNH_2$	RT, O_2	4%
F	$PhNH_2$	50 °C, O_2	10%
I	$PhNH_2$	RT, air, 10 mol% NEt_3	0%
I	$PhNH_2$	RT, air, 10 mol% NEt_3	0%
F	$PhNH_2$	RT, air, 2.5 mol% $B(OH)_3$	33%
F	$PhNH_2$	RT, air, 10 mol% $B(OH)_3$	47%
F	$PhNH_2$	50 °C, O_2, 10 mol% $B(OH)_3$	50%

[a] 1.0 M RNH_2, 1.5 M $ArB(OH)_2$, 2.5 mol% **3**, MeOH, 12 h.

Table 7. Coupling of aniline or RR'NH and *para*-fluorophenylboronic acid with **3** under photoredox conditions



Light source	T, time	Conditions [a]	conversion
-	20 °C, 12 h		no reaction
white	20 °C, 12 h		no reaction
green	20 °C, 12 h		no reaction
blue	20 °C, 12 h		50%
blue	35 °C, 12 h		69%
blue	50 °C, 8 h		50%
blue	50 °C, 8 h	O_2	54%
-	35 °C, 12 h	1 mol% **PC1**	no reaction
blue	35 °C, 12 h	1 mol% **PC1**	59%
blue	35 °C, 12 h	1 mol% **PC1,** O_2	50%
blue	35 °C, 12 h	1 mol% **PC2**	50%
blue	50 °C, 12 h	1 mol% **PC1**	59%
blue	20 °C, 8 h	2.5 mol% $B(OH)_3$	54%
blue	20 °C, 8 h	10 mol% $B(OH)_3$	60%
blue	50 °C, 8 h	2.5 mol% $B(OH)_3$	50%
blue	50 °C, 12 h	2.5 mol% $B(OH)_3$, O_2	100%
blue	20 °C, 12 h	RR'NH = *n*HexNH$_2$	100%
blue	20 °C, 12 h	RR'NH = *n*OctNH$_2$	100%
blue	20 °C, 12 h	RR'NH = (*n*Bu)$_2$NH	no reaction
blue	20 °C, 8 h	RR'NH = Imidazole	no reaction
blue	50 °C, 12 h	RR'NH = Imidazole, 2.5 mol% $B(OH)_3$	no reaction
blue	50 °C, 12 h	$O_2NC_6H_4B(OH)_2$, 2.5 mol% $B(OH)_3$	no reaction

[a] 1.0 M aniline or RR'NH, 1.5 M $ArB(OH)_2$, 2.5 mol% **3**.

The UV/vis spectrum of **3** shows a charge-transfer transition centered at 337 nm and a *d-d* transition at 730 nm (Fig. S5 and S6). If the methyl group in the *para*-position of the arylsulfonate in **1** or **3** is replaced by hydrogen, the charge-transfer transition is displaced slightly (approx. 10 nm) hypsochromic. This would agree with an assignment as a ligand-to-metal charge-transfer transition. For photoredox catalysis, **3** seem to require irradiation of the LMCT band. Since an LMCT transition increases the electron density at the metal center in the excited state, it is unlikely that excitation directly enables reductive elimination from the excited state. Irradiation thus seems to facilitate the oxidation of **D** by **A**, but from the available data it is impossible to judge whether this occurs through oxidative quenching of an excited copper aryl species **D** or by reductive quenching of a photoexcited oxidant **A** (Scheme 10).

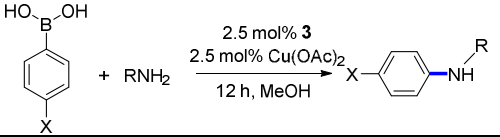
Kobayashi reported photoredox catalysis of CEL couplings using the typical $Cu(OAc)_2$ catalyst and an Iridium photocatalyst,[95] to the best of our knowledge the only other report of photocatalytic CEL coupling. We briefly investigated if electron transfer from dedicated photocatalysts is more efficient than direct excitation of **3**, but addition of 1 mol% of either $[Ir(ppy)_2(bipy)][PF_6]$, **PC1**, or $[Ru(bipy)_3][PF_6]_2$, **PC2** (see exp. section), did not show any remarkable improvement (Table 7). It has to be noted that the performance of Kobayashi's **PC1**/$Cu(OAc)_2$ system showed a strong solvent dependence, which we did not optimize. The results presented here should thus *not* be considered a limitation of the reported **PC1**/$Cu(OAc)_2$ system.

Addition of boric acid again improved reaction yields and at 50 °C and in the presence of 2.5 mol% $B(OH)_3$, we observed quantitative CEL coupling between aniline and fluorophenylboronic acid. The scope of the photocatalytic reaction was investigated briefly. Substrate reactivity is similar to catalysis without irradiation: hexylamine and octylamine showed complete conversion to the coupling product under photocatalytic conditions, while methoxyaniline and imidazole, which required heating in the reaction with phenylboronic acid, did not show any reactivity with *para*-fluorophenylboronic acid, even under heating and irradiation (Table 7). *Para*-nitrophenylboronic acid remained unreactive. While photoredox catalysis thus improved conversions and further supported that oxidation to Cu(III) became the reaction's bottleneck, it did not provide a generally applicable solution for electron-deficient phenylboronic acids.

Chemical oxidation. Addition of stoichiometric amounts of external oxidants, such as 4-phenylpyridine-oxide (PPO),[65-67] tBu_2O_2, or TEMPO,[65, 66] did not lead to product formation in the coupling of *para*-fluorophenylboronic acid with aniline. Curiously, in the presence of oxidants the main product was the deborated product instead of the diaryl. When the same oxidants were used in CEL couplings with phenylboronic acid, these reactions did not improve either (Table S1, entries 14-17). In the case of PPO, coupling was in fact suppressed. In agreement with Stahl's mechanistic proposal, an external oxidant thus does not participate directly in the Cu(II)/Cu(III) oxidation and is only required to re-oxidize the Cu(I) species formed.

We thus attempted to encourage the formation of the Cu(III) with a catalytic amount of a *copper-based* oxidant. Cyclic voltammograms of $Cu(OAc)_2$ and **3** are difficult to interpret due to the irreversibility of the Cu(II)/Cu(III) oxidation step and complications due to copper deposition on the cathode with $Cu(OAc)_2$, but they qualitatively provide that coordination of the imino-arylsulfonate ligand lowers the reduction potential for oxidation and reduction steps in **3** (Fig. S9). We thus conducted couplings with **3** in the presence of 2.5 mol% of $Cu(OAc)_2$ as oxidation aid. Under these conditions aniline as well as octylamine could be coupled quantitatively with *para*-fluorophenylboronic acid at room temperature. In fact, the reaction was complete in 3 h. Surprisingly, $Cu(OAc)_2$ itself is reactive under these conditions, but unlikely to be the active species in the **3**/$Cu(OAc)_2$ system: its activity in the coupling of aniline with *para*-fluorophenylboronic acid was only half of that of **3**/$Cu(OAc)_2$ (Table 8). In addition, couplings with $Cu(OAc)_2$ alone showed induction periods of 30 – 110 min (Fig. 10), while the **3**/$Cu(OAc)_2$ system showed the same 10 min induction period observed in couplings with **3** alone. These differences were even more pronounced in coupling of aniline with phenylboronic acid: while **3**/$Cu(OAc)_2$ coupled aniline and phenylboronic acid with a rate constant similar to that of **3** alone (Tables 5, 8) and with short induction periods, couplings with $Cu(OAc)_2$ were an order of magnitude slower, induction periods were above 1 h and the reaction was incomplete even after 12 h (Table 8, Fig. 10). Despite the surprisingly high activity of $Cu(OAc)_2$ in couplings with fluorophenylboronic acid, the active catalyst is thus **3**. Copper acetate acts as an oxidation aid in reactions with electron-deficient arylboronic acids, while it does barely increase rate constants for phenylboronic acid.

Table 8. CEL couplings of aniline with electron-deficient phenylboronic acids catalyzed by **3**/$Cu(OAc)_2$. [a]



X	RNH_2	Conditions [a]	k_{obs} [h^{-1}]	conversion
F	*n*OctNH$_2$	RT		100% (2 h)

I	*n*OctNH$_2$	RT		100% (2 h)
F	aniline	RT	1.10(8)	100%
I	aniline	RT		97%
H	aniline	RT	0.43(3)	100%
F	imidazole	50°C, O$_2$		0%
NO$_2$	*n*OctNH$_2$	RT		0%
F	aniline	Cu(OAc)$_2$ only	0.60(1), 0.64(1)	95%, 99% [b]
H	aniline	Cu(OAc)$_2$ only	0.06(1)	62%, 66% [b]

[a] 1.0 M RNH$_2$, 1.5 M ArB(OH)$_2$, 2.5 mol% **3**, MeOH, 12 h. [b] Two experiments.

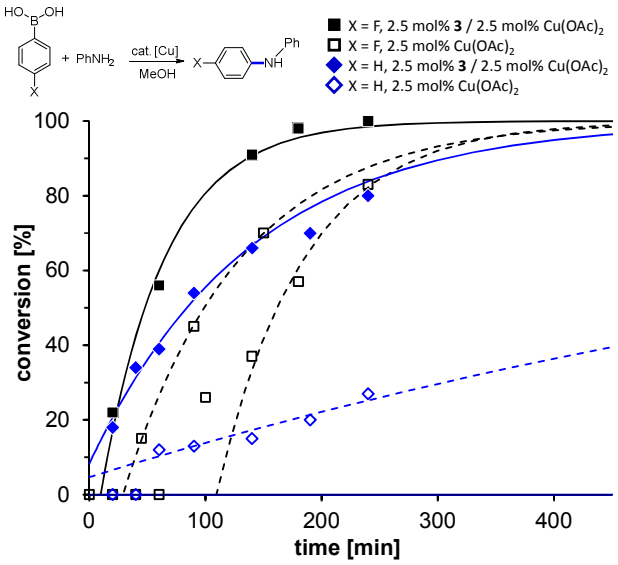


Figure 10. Conversion vs time profile for the *N*-arylation of aniline with **3**/Cu(OAc)$_2$ or Cu(OAc)$_2$ only. solid squares: **3**/Cu(OAc)$_2$, FC$_6$H$_4$B(OH)$_2$; hollow squares: Cu(OAc)$_2$, FC$_6$H$_4$B(OH)$_2$, two independent reactions with different induction periods shown; solid diamonds: **3**/Cu(OAc)$_2$, PhB(OH)$_2$; hollow diamonds: Cu(OAc)$_2$, PhB(OH)$_2$. (MeOH, RT, 1.0 M aniline, 1.5 equiv ArB(OH)$_2$). Solid lines are the simulated conversions calculated from the rate constants and induction periods determined by linear regression (Table 8, Fig. S10).

While addition of copper acetate gratifyingly solved the bottleneck of slow oxidation to Cu(III) for amines and anilines, the protocol was unfortunately not generally applicable. Imidazoles, which required heating for coupling with phenylboronic acid, did not couple to electron-poor phenylboronic acids even under heating. Likewise, *para*-nitrophenylboronic acid could not be coupled even with the reactive *n*-octylamine.

CONCLUSIONS

Use of **1** and **3** as catalysts in Chan-Evans-Lam couplings avoided common side reactions such as deboration or homocoupling. As a consequence, excess phenylboronic acid is not required and reactions typically run to quantitative conversion to product. Incorporation of the functionalities commonly achieved by choice of solvent, base and counter-anion into the ligand system avoided the need for an extensive optimization of reaction conditions and provided a general protocol for the arylation of amines, anilines and *N*-heterocycles, which includes sterically difficult substrates such as *tert*-butylamine and dibutylamine. The activity of **3** is among the highest reported for CEL couplings of these class of substrates. In fact, *n*-octylamine and *tert*-butylamine can be arylated in less than 1 h using 0.5 mol% of catalyst at room temperature.

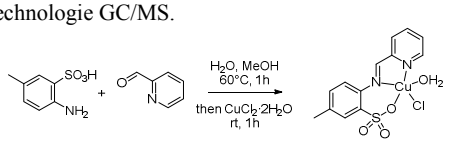
On the down side, the limited access to the metal center and its reduced Lewis acidity, which are the likely reason for the lack of typical side reactions, also limited reactivity towards weaker nucleophiles such as phenols or thiols.[96] While we believe that well-defined coordination complexes can also provide better performance for other substrate classes, these would require a different ligand framework than used in this work.

Mechanistic studies with **1** and **3** largely confirmed the general reaction mechanism established by Collman, Stahl and Watson for CEL couplings.[36, 48, 49, 52, 68] In addition to this, we propose that formation of nucleophile-boronic acid adducts might be responsible for saturation behavior in boronic acid concentrations. Dinuclear copper-boron species are likely present only in small concentrations, even if required as intermediates to transmetallation. Based on our observations herein, the series of steps in the catalytic cycle is likely to be transmetallation – nucleophile coordination – oxidation – reductive elimination for CEL couplings with **1** and **3**. Collman proposed nucleophile coordination prior to transmetallation for [(tmeda)Cu(OH)]$_2$Cl$_2$,[48, 49] and it is possible that the order of these two steps differ dependent on the Lewis acidity and the steric saturation of the copper complex employed. While deprotonation is required for product formation even with good nucleophiles such as amines (in no case we observed quaternisation of tertiary amines or pyridines), its actual position in the catalytic cycle remains unclear and might depend on the nucleophile employed.

CEL couplings have been praised for their reactivity under mild conditions, but criticized for their unpredictability. Placing the copper catalyst in a well-defined ligand environment can clearly overcome these limitations.

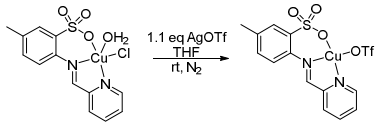
EXPERIMENTAL SECTION

General. Phenylboronic acid was purified by washing with dichloromethane until the filtrate stayed colorless. All other chemicals were purchased from common commercial suppliers and used without further purification. Elemental analyses were performed by the Laboratoire d'analyse élémentaire (Université de Montreal). UV/vis spectra were recorded on a Cary Series UV-Vis-NIR spectrophotometer from Agilent Technologie. GC-MS spectra were recorded on a Agilent Technologie GC/MS.



LCuCl(H$_2$O), 1. To a hot solution (60 °C) of 2-amino-5-methylbenzenesulfonic acid (187 mg, 1.0 mmol) in water (5 mL) and methanol (10 mL) was added 2-pyridinecarboxaldehye (95 µL, 1.0 mmol). The mixture was stirred for one hour, then copper chloride hydrate (205 mg, 1.1 mmol) was added, resulting in a green solution. Heating was stopped and the solution was stirred another hour. Slow evaporation of the solvent afforded green X-ray quality crystals (321 mg, 82%).

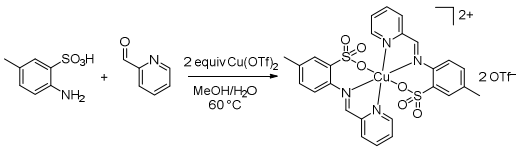
Anal. Calcd. for C$_{13}$H$_{13}$ClCuN$_2$O$_4$S : C, 39.80; H, 3.34; N, 7.14; S, 8.17. Found: C, 40.09; H, 3.37; N, 3.37; S, 8.47. UV-vis (DMSO, $1\cdot10^{-2}$ M or $1.49\cdot10^{-4}$ M) [λ_{max}, nm (ε, $M^{-1}\cdot cm^{-1}$)] : 338 (97 000), 800 (500).



{LCu(OTf)}$_n$, 3. Chloride complex **1** (390 mg, 1.0 mmol) was dissolved in dry THF (5 mL) under nitrogen atmosphere to give a green

solution. Silver triflate (328 mg, 1.1 mmol) was added. After one hour of reaction at ambient temperature, a precipitate appeared and the color of the solution intensified. Filtration through a syringe filter and slow evaporation of the green filtrate under N_2, afforded green X-ray quality crystals (236 mg, 54%).

Anal. Calcd. for $C_{14}H_{11}CuF_3N_2O_6S_2$: C, 34.46; H, 2.27; N, 5.74; S, 13.14. Found: C, 34.10; H, 2.59; N, 5.26; S, 12.61. UV-vis (DMSO, $1.2\cdot10^{-2}$ M or $3.35\cdot10^{-4}$ M) [λ_{max}, nm (ε, $M^{-1}\cdot cm^{-1}$)] : 338 (62 000), 730 (470).



[(LCu)$_2$](OTf)$_2$, 4. To a hot solution (60 °C) of water (5 mL) and methanol (10 mL) containing 2-amino-5-methylbenzenesulfonic acid (187 mg, 1.0 mmol) was added 2-pyridinecarboxaldehye (95 µL, 1.0 mmol). The mixture was stirred for one hour at 60 °C, then copper triflate (724 mg, 2.0 mmol) was added. Heating was stopped and the solution was stirred another hour. After filtration, slow evaporation of the solvent provided green X-ray quality crystals (195 mg, 40%).

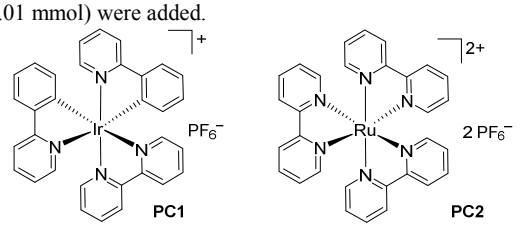
Anal. Calcd. for $C_{14}H_9CuF_3N_2O_5S_2$: C, 33.24; H, 2.59; N, 5.54; S, 12.67. Found: C, 33.24; H, 2.57; N, 5.10; S, 13.44. UV-vis (DMSO, $1.2\cdot10^{-2}$ M or $3.35\cdot10^{-4}$ M) [λ_{max}, nm (ε, $M^{-1}\cdot cm^{-1}$)] : 328 (19 000), 727 (430).

L$_2$Cu, 2. Recrystallization of complex **1** in a mixture of water and acetonitrile from 50 °C to RT provided to the homoleptic complex.

Anal. Calcd. for $C_{14}H_{11}CuF_3N_2O_6S_2$: C, 39.80; H, 3.34; N, 7.14; S, 8.17. Found: C, 40.09; H, 3.37; N, 7.37; S, 8.47. UV-vis (DMSO, $1.2\cdot10^{-2}$ M or $3.35\cdot10^{-4}$ M) [λ_{max}, nm (ε, $M^{-1}\cdot cm^{-1}$)] : 322 (23 000), 793 (810).

General procedure for Chan-Evans-Lam couplings. To a solution of amine or aniline (1.0 mmol) and phenylboronic acid (1.5 mmol) in methanol (1 mL) was added catalyst **1** or **2** (0.025 mmol). Trimethoxybenzene was added as internal standard. The reaction was stirred open to air at ambient temperature or at 50 °C under O_2 atmosphere. For kinetic experiments, 20 µL aliquots were taken, diluted in ethyl acetate and analyzed by GC-MS. After the desired reaction time, the reaction was quenched with 0.5 mL of a saturated aqueous solution of ammonium chloride. The organic layer was extracted and filtered through a short silica plug to remove remaining copper complex. Products and side-products were identified by the MS- and NMR-spectrum from comparison to literature. Conversion was typically analysed by GC-MS. Quantitative concentrations were determined by comparison to trimethoxybenzene standard. Calibration factors between starting materials, products, side-products and trimethoxybenzene were determined from simultaneous NMR and GC-MS analysis or by analysis of solutions prepared from isolated or commercially available products.

Photoredox catalysis. Following otherwise the general procedure, 20 mL headspace vials were used. For blue (λ = 452 nm, FWHM = 150 nm) and green light radiation (λ = 525 nm, FWHM = 170 nm), the vials were placed on a panel constituted of 90 x 1 W LED in a thermostatic bath with a Poly-Science controller set to 20 °C or 50 °C. For white light (λ = 445 and 552 nm, FWHM = 350 nm), a 10 W LED in a thermostatic bath with a A-Nova controller set to 20 °C or 50 °C was used. For reactions with additional photocatalyst, [Ir(ppy)$_2$(bipy)][PF$_6$] (8 mg, 0.01 mmol) or [Ru(bipy)$_3$][PF$_6$]$_2$ (9 mg, 0.01 mmol) were added.



Cyclic voltammetry. Electrochemical measurements were carried out in dry methanol at RT with a BioLogic-SP50 potentiostat-galvanostat interfaced to a PC on which was installed the EC-lab software. The working electrode was a glassy carbon electrode (3mm diameter) which was polished with 0.05 µm alumina paste before each sample. The counter electrode was a Pt wire and the pseudo-reference electrode was a silver wire (Ag/AgCl). The supporting electrolyte used for analysis was tetrabutylammonium perchlorate at 0.1 M in solution. The analyte concentration was about 1 mM and tetrabutylammonium hexafluorophosphate (TBAPF$_6$) was used as supporting electrolyte at 0.10 M. Cyclic voltammograms were obtained at scan rates of 100 mV/s.

X-ray diffraction studies. Crystal for X-ray diffraction were produced from synthesis as described above. Diffraction data were collected on a Bruker Venture METALJET diffractometer (Ga Kα radiation).[97] Data reduction was performed with SAINT,[98] absorption corrections with SADABS.[99] Structures were solved by dual-space refinement (SHELXT).[100] All non-hydrogen atoms were refined anisotropic using full-matrix least-squares on F^2 and hydrogen atoms refined with fixed isotropic U using a riding model (SHELXL97).[101] Further experimental details can be found in Table 9 and the supporting information (CIF).

Table 9. Experimental details of X-ray diffraction studies

		2	4
Formula		$C_{26}H_{24}CuN_4O_7S_2$	$C_{14}H_{13}CuF_3N_2O_7S_2$
M_w (g/mol); F(000)		632.5; 2600	505.92; 510
T (K); wavelength		100; 1.34190	150; 1.34190
Crystal System		Orthorhombic	Triclinic
Space Group		*P*bca	*P*-1
Unit Cell:	a (Å)	17.7588(4)	7.9814(3)
	b (Å)	13.9390(3)	11.0894(4)
	c (Å)	20.7682(4)	11.1020(4)
	α (°)	90	96.4610(10)
	β (°)	90	100.1760(10)
	γ (°)	90	110.0070(10)
V (Å^3)		5140.96(19)	892.77(6)
Z; $d_{calcd.}$ (g/cm^3)		8; 1.639	2; 1.882
μ (mm^{-1}); Abs. Corr.		5.89; multi-scan	8.50; multi-scan
Extinction coefficient		-	0.120(3)
θ (°); completeness		3.7-60.7; 0.997	7.2-121.3; 1.000
Collected reflections; R_σ		66841; 0.023	21646; 0.023
Unique reflections; R_{int}		5895; 0.051	4095; 0.037
Observ. reflections; $R1(F)$		5566; 0.033	4073; 0.036
w$R(F^2)$ (all data); GoF(F^2)		0.0894; 1.05	0.0933; 1.18
Residual electron density		0.64	0.45

ASSOCIATED CONTENT

Supporting Information

Additional tables and figures. Details of calculations. Details of crystallographic studies (CIF). The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

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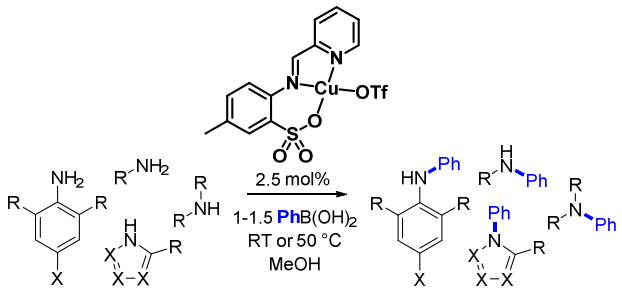
Table of contents graphics



general reaction protocol
quantitative conversion