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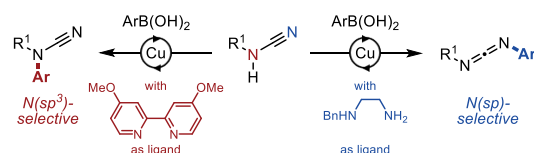
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Copper-Catalyzed, Ligand-Controlled N(sp³)- or N(sp)- Selective Arylation of Cyanamides

Jiaqi Fang,^{a,b} Oumaima Bekkouch,^a Guilhem Zeiser,^a Yurii Zubchuk,^b Vincent Bizet,^b Nicolas Blanchard,^{b,*}, Gwilherm Evano^{a,*}

^a Laboratoire de Chimie Organique, Service de Chimie et PhysicoChimie Organiques, Université libre de Bruxelles (ULB), Avenue F. D. Roosevelt 50, CP160/06, 1050 Brussels, Belgium.

^b Université de Haute-Alsace, Université de Strasbourg, CNRS, LIMA, UMR 7042, 68000 Mulhouse, France.



ABSTRACT: Cyanamides possess both nucleophilic and electrophilic centers and their arylation reactions are known to proceed at N(sp³) and C(sp)-sites, leading to *N*-aryl- cyanamides or amidines. N(sp)-Selectivity has also been reported only in the presence of amines, thus leading to guanidines. Herein, we report a general copper-catalyzed ligand-controlled Chan-Lam-Evans arylation of cyanamides proceeding regioselectively at the N(sp³) or N(sp) atoms and leading to either to *N*-aryl- cyanamides or dissymmetric carbodiimides. The nature of the ligand, either a bipyridine or a diamine, controls the product distribution and thus offers a divergent entry to useful building blocks from readily available cyanamides.

Cyanamides are versatile building blocks containing three reactive sites: a carbon atom (sp-hybridized) and two nitrogen atoms (sp- and sp³-hybridized).¹ This dense array of electrophilic and nucleophilic positions in cyanamides provides a unique reactivity and allows a myriad of ionic, radical, pericyclic and metal-catalyzed transformations.²⁻⁶ Moreover, it does also confer to cyanamides the ability to act as efficient ligands for various transition metals.⁷⁻⁹ In line with our interest in copper-catalyzed reactions^{10,11} and transition metal-catalyzed reactions of cyanamides,^{12,13} we became interested in their *N*-arylation and more particularly in the control over the chemoselectivity (sp- vs sp³-hybridized nitrogen atom) of the process.

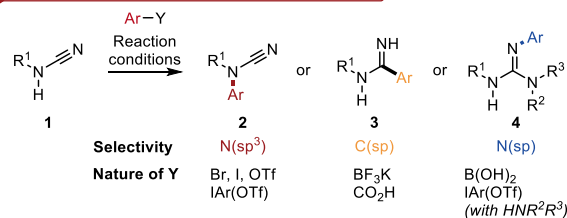
Indeed, it has been reported that arylation reactions of cyanamides **1** could proceed with N(sp³), C(sp) or N(sp) -selectivity depending on reaction conditions and aryl partners (Scheme 1A). The N(sp³)-arylated product **2** can be obtained selectively from (hetero)aromatic halides by aromatic nucleophilic substitution¹⁴⁻¹⁷ or from diaryliodonium triflates (not shown).^{18,19} Transition-metal catalyzed processes have also been disclosed and an efficient palladium-catalyzed (hetero)arylation using (hetero)aryl halides or triflates is shown on Scheme 1B.^{20,21} On one hand, the use of Pd₂dba₃ (2.5 mol%), tBuXphos (7.5 mol%) and cesium carbonate in t-amyl alcohol at 60-100 °C provides N(sp³)-arylated cyanamides **2** in moderate to excellent yields. On the other hand, amidines **3** resulting from a selective C(sp)-arylation can be obtained in a palladium trifluoroacetate-catalyzed reaction using 6-methyl-2,2'-bipyridine as a ligand (3 mol%) and trifluoroacetic acid in NMP at 120 °C (Scheme 1B).²² In this case, the nucleophilic species arise from the de-

carboxylation of benzoic acid derivatives **6** but the corresponding potassium trifluoroborate salts are also competent partners.²³ This C(sp)-selectivity has also been observed in a unique copper-catalyzed cross-coupling between **1** and tolylboronic acid leading to **3** in less than 20% yield.²⁴ Finally, the N(sp)-selective arylation of cyanamides **1** has only been reported in the presence of an external nucleophile, such as a primary or a secondary amine, thus leading to guanidines **4** (Scheme 1B).²⁵ This transformation can be metal-free with diaryliodonium triflates as arylation reagents,²⁶ or copper-catalyzed, as exemplified in Scheme 1B, using arylboronic acids.¹⁰ Indeed, in the presence of copper(II) chloride (10 mol%), bipyridine (10 mol%), potassium carbonate and oxygen in toluene at 100 °C, guanidines **4** were obtained in good to excellent yields. Depending on the nature of the substituents, further one-pot oxidative copper-catalyzed transformations of **4** can occur and deliver complex heterocycles such as benzimidazoles, quinazolines and their derivatives.^{27,28}

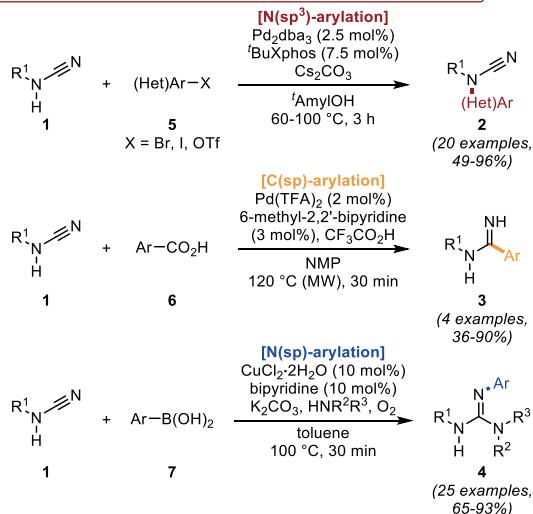
This brief literature overview demonstrates that copper-catalyzed N(sp³)-selective arylation of cyanamides **1** has yet to be discovered. In addition, the fine tuning of the coordination sphere of the active copper species might allow the modulation of the reactive site and redirect the arylation reaction from N(sp³) to N(sp), thereby delivering carbodiimides, central building blocks in organic synthesis.^{29,30} In this manuscript, we report our efforts in delineating a unique and divergent N(sp³)- or N(sp)- selective arylation reaction of cyanamides **1** in a ligand-controlled Chan-Lam-Evans³¹⁻³⁴ reaction (Scheme 1C).

Scheme 1. Arylation Reactions of Cyanamides and Control Over the N(sp³)-, C(sp)- or N(sp)-Selectivity

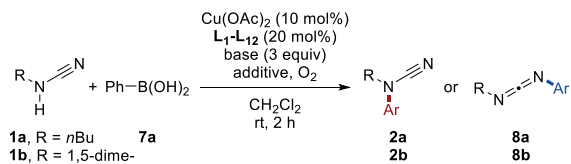
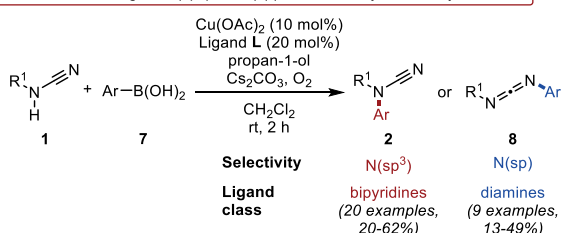
A. Selectivity trends in the arylation of cyanamides



B. Selected examples of N- or C- selective arylation of cyanamides

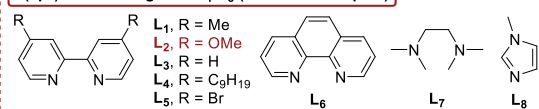


C. This work: divergent N(sp³)- or N(sp)- selective arylation of cyanamides

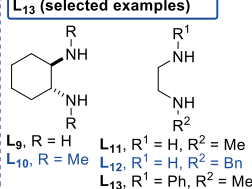


Entry	Cyanamide	Variation from reaction conditions	2 ^b	8 ^b
1	1a	Cu(OAc) ₂ (100 mol%), L ₁ (200 mol%), ^t BuOK, 4Å MS, ^c SiO ₂ , ^d 9 h	52%	<15%
2	1a	L ₁ , ^t BuOK, 4Å MS, ^c SiO ₂ , ^d 5 h	43%	<15%
3	1a	L ₂ , ^t BuOK, 4Å MS, ^c SiO ₂ , ^d 5 h	53%	<15%
4	1a	L ₃ -L ₈ , ^t BuOK, 4Å MS, ^c SiO ₂ , ^d 5 h	38±6%	<15%
5	1a	L ₂ , Cs ₂ CO ₃ , propan-1-ol ^e	71%	9%
6	1b	L ₉ , Cs ₂ CO ₃ , propan-1-ol ^e	9%	64%
7	1b	L ₁₀ , Cs ₂ CO ₃ , propan-1-ol ^e	17%	74%
8	1b	L ₁₁ , Cs ₂ CO ₃ , propan-1-ol ^e	10%	41%
9	1b	L ₁₂ , Cs ₂ CO ₃ , propan-1-ol ^e	10%	50%
10	1b	L ₁₃ , Cs ₂ CO ₃ , propan-1-ol ^e	5%	5%

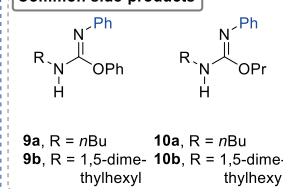
N(sp³)-selective ligands L₁-L₈ (selected examples)



N(sp)-selective ligands L₉-L₁₃ (selected examples)



Common side-products



Optimization of reaction conditions was performed with two distinct cyanamides differing by the nature of the alkyl side chain (butyl for **1a**, 1,5-dimethylhexyl for **1b**) and phenyl boronic acid **7a** (Table 1).³⁵ Indeed, it was rapidly observed that linear alkyl chains favor the N(sp³)-arylation to *N*-aryl-cyanamide **2** whereas a branched alkyl chain favors the N(sp)-arylation to the corresponding *N*-arylated dissymmetric carbodiimide **8**. It should be noted that the high electrophilicity of carbodiimides **8** leads in most cases to traces of isoureas **9** and **10** arising from the nucleophilic attack of phenol and propan-1-ol, respectively, onto the central carbon atom (see below).

Initial conditions for the arylation of cyanamide **1a** relied on copper(II) acetate (1 equivalent), 4,4'-dimethyl-bipyridine **L**₁ (2 equivalents), ^tBuOK (3 equivalents) and additives (4Å MS, silica gel^{36,37}) in dichloromethane under an oxygen atmosphere at room temperature for 9 h (Table 1, entry 1). Compound **2a** was obtained in 52% (NMR yield) together with approximately 15% of carbodiimide **8a**. Catalytic amount of copper acetate (10 mol%) led to a slightly diminished yield (43%, entry 2) which could be increased back to 53% using the more electron rich bipyridine ligand **L**₂ (53%, entry 3). Further structural variations of the ligand (**L**₃-**L**₈, entry 4) were not beneficial.

Table 1. Optimization^a

^aReactions performed using cyanamide **1** (0.3 mmol, 1 equiv), phenylboronic acid (1.5-2.5 equiv), copper acetate (10 mol%), ligand **L**_{*n*} (20 mol%), base (3 equiv), under an O₂ atmosphere (1 bar) in CH₂Cl₂ (0.1 M) at rt for 2 h. ^bDetermined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^c120 mg for 0.3 mmol of **1**. ^d50 mg for 0.3 mmol of **1**. ^e5 equiv.

Extensive screening of all parameters (including copper(II) sources and loading, bases, solvents, concentration, time)³⁶ identified cesium carbonate as the preferred base and propan-1-ol (5 equivalents) as an essential additive to increase both yields and reproducibility in a shorter reaction time (2 h). Using these N(sp³)-selective conditions, **2a** was obtained in 71% (NMR yield) together with only 9% of **8a** and traces (<5%) of isoureas **9a** and **10a** (entry 5). Formation of isourea **9a**, arising from the nucleophilic attack of **8a** by phenol (itself obtained by the copper catalyzed oxidation of **7a** under oxygen atmosphere³⁸) could be circumvented by operating under strictly anhydrous reaction conditions. Isourea **10a**, arising from the attack of propan-1-ol on **8a**, accounts for 5-15% of the reaction mixtures in all cases. It should be noted that these additions of alcohols to carbodiimides have recently been shown to be accelerated by oxygen in copper-catalyzed reactions.³⁹ Thus, a delicate balance must be found with the number of equivalents of propan-1-ol to limit the formation of isoureas **10** while maintaining a good reactivity in the arylation reaction.

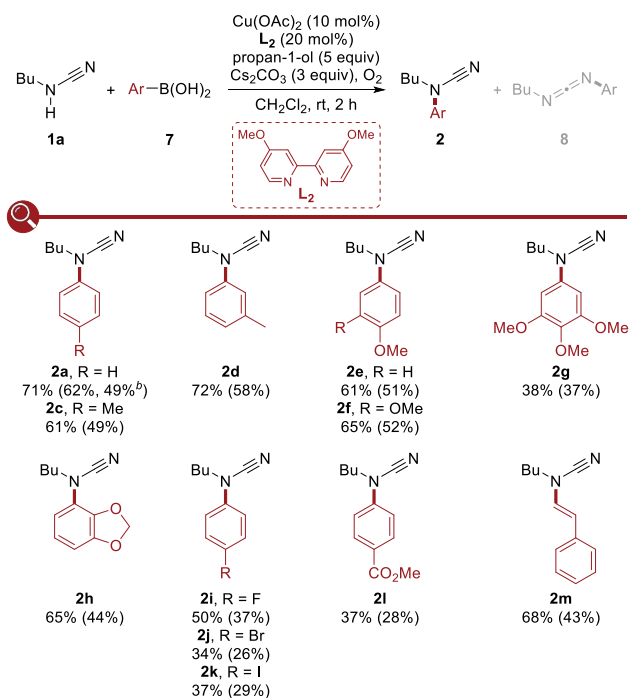
During the ligand screening phase, it was discovered that diamines such as **L**₉-**L**₁₂ led to increased amounts of carbodiimide **8b** when cyanamide **1b** was used as the starting material, all

other reaction parameters being identical (entries 6-9). In particular, **L**₁₀ and **L**₁₂ led to **8a** in 74% and 50% NMR yields, respectively, in a 4.4-5:1 ratio with **2b**. Although ligand **L**₁₀ led to better NMR and isolated yields than **L**₁₂ (74% vs 50% and 47% vs 28%, respectively), the latter performed better in subsequent studies of the scope of the reaction and was thus selected as the optimal ligand for this N(sp³)-selective copper-catalyzed arylation of cyanamides **1**. As ligand **L**₁₂ is also a competent nucleophile in the copper-catalyzed oxidative arylation reaction with phenylboronic acid, ligand **L**₁₃ was independently prepared⁴⁰ and its catalytic activity was evaluated (entry 10). Traces of **2b** and **8b** were obtained in the standard conditions, demonstrating the superiority of ligand **L**₁₂. This selectivity switch from N(sp³)- to N(sp²)- arylation of cyanamides is striking and has not yet been reported to the best of our knowledge and such a divergency holds great interest for the synthetic community by providing valuable nitrogen-containing small molecules that would be otherwise difficult to prepare using a single protocol.²⁹

With these optimized conditions in hands for both arylation reactions, we next examined the generality of these two procedures for the N(sp³)- and N(sp²)- selective arylation of a range of cyanamides **1** with a variety of arylboronic acids **7** (Schemes 2-4), starting with the N(sp³)-selective arylation of **1a** using ligand **L**₂ with a range of arylboronic acids **7** (Scheme 2). Conversions were found to be good to excellent (80-95%) in all cases and only minor amounts of carbodiimides **8a,c-m** were detected in the crude reaction mixtures. Electron-neutral arylboronic acids such as **7a,c,d** led to good NMR yields (**2a** 71%, **2c** 61% and **2d** 72%) although isolated yields were slightly lower. Scaling up the reaction leading to **2a** from 0.3 to 1 mmol scale gave a slightly diminished isolated yield (**2a**, from 62% to 49%). Electron-rich arylboronic acids **7e-h** led to similar results, the N(sp³)-arylated cyanamides **2e-h** being obtained in 38-65% (NMR yields), the use of a tris(methoxy)arylboronic acid leading to a lower efficiency. Conversion dropped with electron-deficient arylboronic acids substituted by halides (**7i-k**) or by an ester (**7l**) and compounds **2i-l** were obtained in lower isolated yields (**2i**, 37%, **2j** 26%, **2k** 29%, **2l** 28%). Besides arylboronic acids, it was found that *trans*-2-phenylvinylboronic acid **7m** was also a competent partner in this transformation, leading to **2m** in 43%. Limitations were found with *o*-cyanophenyl boronic acid and 2-thienyl boronic acid, for which no arylated cyanamides **2** could be detected (Scheme S1).³⁶

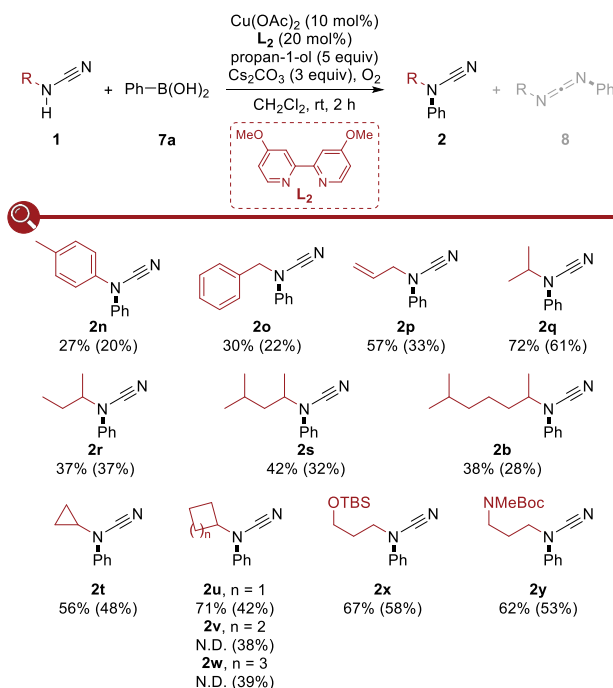
We then turned our attention to the structural variation of starting cyanamide **1**, under N(sp³)-selective arylation conditions with phenylboronic acid **7a** (Scheme 3). Compared to **1a** possessing a linear alkyl chain, branched alkyl or aromatic cyanamides **1b,n-y** led to diminished NMR and isolated yields, although conversions were generally good to excellent. Minor amounts of dissymmetric carbodiimides **8b,n-y** and of the corresponding isoureas could account for this experimental observation. Starting from *p*-tolyl-cyanamide **1n**, the copper-catalyzed phenylation led to **2n** in only 27% NMR yield, thus demonstrating the lack of reactivity of this class of cyanamides which is not surprising due to the conjugation of the cyanamide moiety with the tolyl ring. Yields slightly improved with *N*-benzyl- and *N*-allyl- cyanamides **1o** and **1p**, leading to **2o** and **2p** in 30% and 57% NMR yields, respectively. α -Branched alkyl chains improved yields, as in the case of **2q** (72%), although with longer alkyl chains, yields tend to decrease (**2r** 37%, **2s** 42%, **2b** 38%).

Scheme 2. N(sp³)-Selective Arylations of Cyanamides: Scope of Arylboronic Acids^a



^a Reactions performed on 0.3 mmol scale of **1a**. Yields and conversions determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields in parenthesis. ^b Reaction performed on 1 mmol of **1a**.

Scheme 3. N(sp³)-Selective Arylations of Cyanamides: Scope of Cyanamides^a



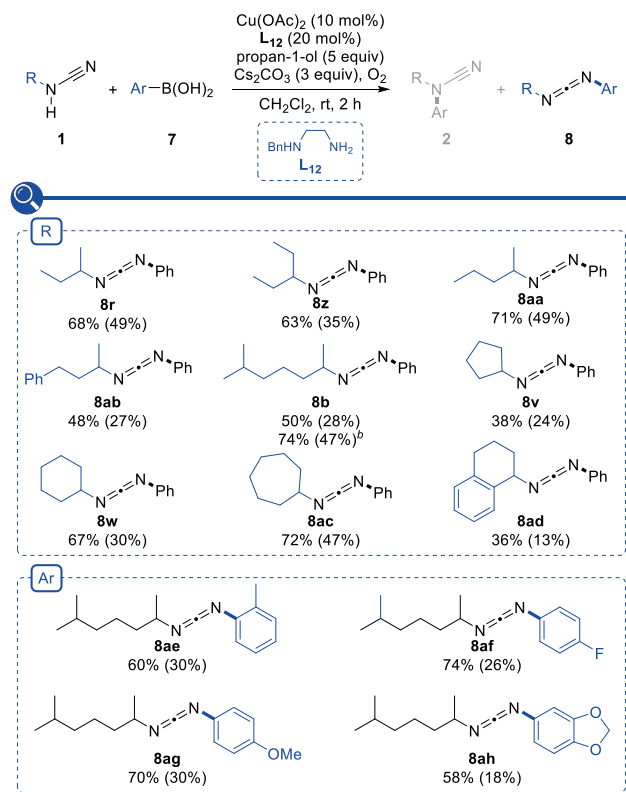
^a Reactions performed on 0.3 mmol scale of **1**. Yields and conversions determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields in parenthesis. N.D.: not determined.

Interestingly, cycloalkyl chains are also tolerated as in the cases of **1t-w** which led to the corresponding N(sp³)-phenylated cyanamides **2t-w** in moderate to good yields. Finally, linear cyanamides **1x** and **1y** possessing silyloxy- and ^tbutoxycarbamate

functionalities (respectively) were evaluated in the arylation reaction with **7a** and led to acceptable isolated yields of the corresponding *N*(sp³)-phenylated cyanamides **2x** (58%) and **2y** (52%).

Finally, the scope of the divergent *N*(sp)-selective arylation was examined with cyanamides **1** possessing α -branched alkyl chains, under conditions relying on ligand **L**₁₂ (Scheme 4). Dissymmetric aryl,alkyl-carbodiimides **8b,r,z-ah** were obtained with moderate to very good in 36-74% NMR yield (36-88%) as opposed to the isolated yields (13-49%). This could logically be traced back to the very high electrophilicity of diimides **8** towards any type of nucleophiles, thus complicating isolation by standard chromatography techniques. However, this single step protocol from cyanamides compares favorably to multi-step sequences required to access dissymmetric cyanamides.⁴¹ Cyanamides **1** possessing an acyclic α -branched alkyl chain led to the dissymmetric carbodiimides **8b,r,z-ab** in 48-74% NMR yield (**8r** 68%, **8z** 63%, **8aa** 71%, **8ab** 48% and **8b** 50%; 74% with **L**₁₀). Cycloalkyl side chains performed in a similar manner, delivering carbodiimides **8v-ad** in 36-72% NMR yields (**8v** 38%, **8w** 67%, **8ac** 72% and **8ad** 36%). Finally, we examined four different arylboronic acids while keeping constant cyanamide **1b** as starting material. Contrary to the *N*(sp³)-selective conditions, the electronic properties of the arylboronic acids didn't have a dramatic influence on the NMR yields as exemplified with the synthesis of **8ae** (60%), **8af** (74%), **8ag** (70%) and **8ah** (58%). The synthesis of carbodiimide **8r** is especially striking since it was obtained as a minor product with ligand **L**₂ (Scheme 3), thus highlighting the key role of the ligand in this arylation. Limitation was found with *o*-cyanophenyl boronic for which no *N*(sp)-arylated cyanamide **8** could be detected (Scheme S2).³⁶

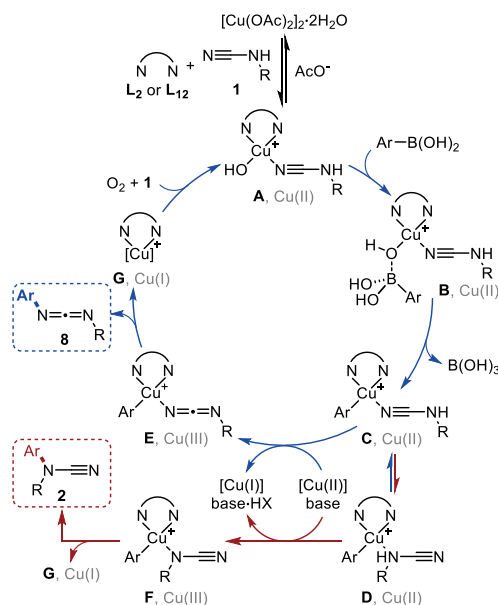
Scheme 4. *N*(sp)-Selective Arylations of Cyanamides^a



^aReactions performed on 0.3 mmol scale of **1**. Yields and conversions determined by ¹H NMR using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields in parenthesis. ^bWith **L**₁₀ instead of **L**₁₂, see Table 1.

A proposed mechanism accounting for the *N*(sp³)- or *N*(sp)-selective arylation of cyanamides is depicted on Scheme 5, based on previous investigations by Stahl^{42,43} and Watson.^{32,44} In a first step, dimeric copper acetate would undergo denucleation to a mononuclear copper(II) complex **A** by coordination with the starting cyanamide **1**, its more common coordination mode involving its sp-hybridized nitrogen atom.^{7,9} Transmetalation with the arylboronic acid would then lead to arylcopper(II) species **C** via intermediate **B**, a species that would be in metallo-tropic equilibrium with **D**. Disproportionation with a second equivalent of a copper(II) complex would lead to copper(III) species **E** and **F**, from which reductive eliminations would deliver the corresponding *N*(sp)-arylated dissymmetric carbodiimide **8** or the (sp³)*N*-arylated cyanamide **2**, respectively. Oxidation with molecular oxygen and coordination of the starting cyanamide **1** would finally close the catalytic cycle. As for the key role of the ligand, the more electron-rich diamine **L**₁₂ would facilitate the oxidation of copper(II) complexes **C** and **D** to the corresponding copper(III) species **E** and **F**, a reaction that would be slower with bipyridine ligand **L**₂. Oxidation of **C** to **E** would thus be faster than its equilibration to **D** when using **L**₁₂ as the ligand, the steric hindrance brought by this diamine ligand, which has in addition a bigger bite angle, moreover disfavoring this equilibration due to a steric clash between this ligand and the cyanamide R substituent in **D**.

Scheme 5. Proposed Mechanism of the Chan-Lam-Evans *N*(sp³)- or *N*(sp)- Selective Arylation of Cyanamides



In conclusion, we have developed a copper-catalyzed, ligand-controlled *N*(sp³)- or *N*(sp)-selective Chan-Lam-Evans arylation of cyanamides, a divergency which has no precedent in the literature. *N*(sp³)-selective arylation was predominant when cyanamides substituted by linear alkyl chains in combination with a bipyridine ligand were used. The use of cyanamides substituted by α -branched alkyl chains in combination with a diamine ligand switched the selectivity to the *N*(sp)-terminus of the cyanamides, thus allowing the synthesis of dissymmetric aryl,alkyl-carbodiimides. Mechanistic studies shedding light on the origin of this selectivity and their extension to other classes of ambident nucleophiles in Chan-Lam-Evans couplings are underway and will be reported in due course.

AUTHOR INFORMATION

Corresponding Authors

*Nicolas Blanchard - Université de Haute-Alsace, Université de Strasbourg, CNRS, LIMA, UMR 7042, 68000 Mulhouse, France ; orcid.org/ 0000-0002-3097-0548 ; Email: n.blanchard@unistra.fr

*Gwilherm Evano - Laboratoire de Chimie Organique, Service de Chimie et PhysicoChimie Organiques, Université libre de Bruxelles (ULB), Avenue F. D. Roosevelt 50, CP160/06, 1050 Brussels, Belgium ; orcid.org/0000-0002-2939-4766 ; Email: Gwilherm.Evano@ulb.be

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