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Copper-Promoted Tandem Three-Component Access to Quinazolin-4(*H*)-imines and Benzimidazo[1,2-*c*]quinazolines

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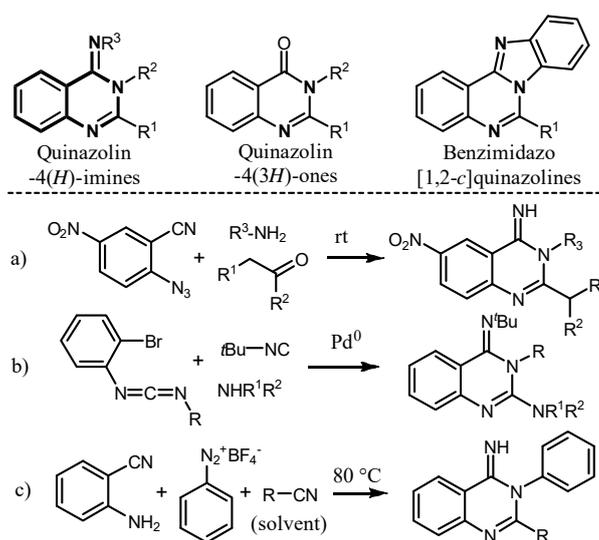
Abstract. A copper-catalyzed three-component assembly of cyanamides, 2-cyanoarylboronic acids and amines has been developed, providing functionalized quinazolin-4(*H*)-imines. Subsequent access to benzimidazo[1,2-*c*]quinazolines is achieved building again on copper-catalysis. One pot hydrolysis of quinazolin-4(*H*)-imines to quinazolin-4(3*H*)-ones is also described. Guanidine formation, cyclization and intramolecular C-H bond amination are key features of the process fully mediated by copper.

Keywords: Copper-catalysis; multicomponent reaction; C-H functionalization; Quinazolin-4(*H*)-imines; Benzimidazo[1,2-*c*]quinazolines

There is a continuous interest in the preparation of nitrogen containing heterocycles because of their wide occurrence in natural products, pharmaceuticals and materials with defined properties.^[1] Among these, quinazolin-4(*H*)-imines (scheme 1) are valuable targets as either bioactive compounds or organic photovoltaic devices.^[2] In addition, the value of the quinazolin-4(*H*)-imine scaffold relies on its proximity with quinazolin-4(3*H*)-ones,^[3] as well as on its presence in polycyclic heterocycles such as benzimidazo[1,2-*c*]quinazolines.^[4]

Among the reported processes to prepare quinazolinimines, many of them require multistep preparation of advanced building blocks (guanidines, carbodiimides, acetimidoyl or imidoyl chlorides or preformed heterocycles).^[5] Convergent versatile multicomponent processes^[6] have also been described (scheme 1). Erba reported a three-component synthesis of quinazolinimines involving 2-azidobenzonitriles, amines and aldehydes via a triazole formation/fragmentation pathway (scheme 1a).^[7] An alternative three-component process, based on a Pd-catalyzed isocyanide insertion onto a haloaryl carbodiimide in the presence of an amine, was also described to afford 2-amino quinazolin-alkylimines

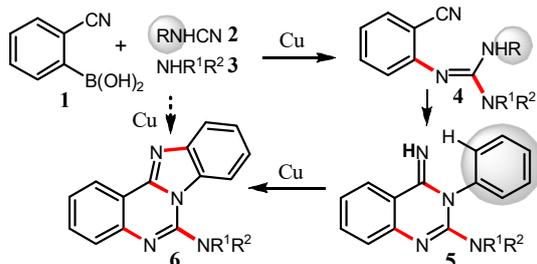
(scheme 1b).^[8] Recently, the metal free multicomponent reaction between anthranilonitriles, aryldiazonium salts and nitrilated solvents was reported to deliver quinazolinimines (scheme 1c).^[9] In addition to these truly three-component reactions, (2C+1C) component processes, involving two equivalents of one reagent, have also appeared.^[10] While these complementary methods allow building diverse quinazolinimines (2-carbonated, 2-aminated, NH or *N*-substituted imines), none of them is without limitations due for example to the use of costly metal, unfriendly or excess reagents (aryldiazonium salts and nitrile) and, in some cases, limited diversity (nitro-bearing aryl precursors).



Scheme 1. Quinazolin-4(*H*)-imines and scaffolds; Multicomponent approaches to quinazolin-4(*H*)-imines.

In this context, we decided to investigate a novel multicomponent strategy to access 2-amino quinazolin-*NH*-imines and probe a subsequent

cyclization of the newly formed NH-imine function to deliver benzimidazo[1,2-*c*]quinazolines (Scheme 2).^[11] Thus, we reasoned that 2-(2-cyanophenyl)guanidine (**4**) could be suitable precursors to quinazolin-*NH*-imines, the former being accessible via our recently described three-component copper-catalyzed synthesis of guanidines.^[12] In addition, based on known copper-catalyzed C-H amination^[13] and our experience,^[14] we anticipated that oxidative conditions involving copper(II) complexes could be operative for subsequent benzimidazoles formation, eventually allowing a one pot tandem process.



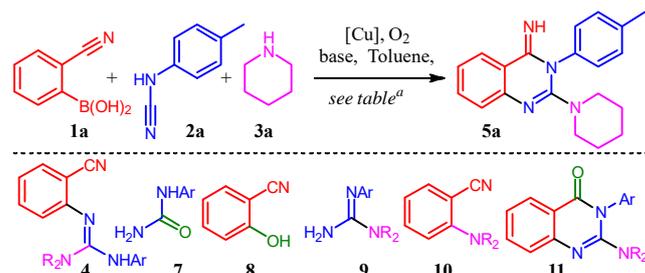
Scheme 2. Proposed strategy.

We initially evaluated the reaction between 2-cyanophenylboronic acid (**1a**), *p*-tolylcyanamide **2a** and piperidine (**3a**) under conditions previously optimized for guanidine formation (table 1, entry 1).^[12a] The corresponding guanidine **4** could not be identified from the reaction mixture but we were pleased to observe that quinazoline imine **5a** was directly formed, albeit in very low yields (10%). Several side products could be identified, resulting either from direct *N*-arylation without cyanamide incorporation (**10**), addition of the amine to the cyanamide (**9**), degradation of reactive partners **1** and **2a** (**7** and **8**), or hydrolysis of the targeted **5a** (**11**).

Extensive optimization was therefore undertaken from which selected results are reported below (table 1). Temperature was found to be important for such transformation and performing the reaction at 50 °C proved to be optimal (entry 5). Indeed, substantial degradation occurred at higher temperature (entries 1-4), while room temperature conditions required stoichiometric amount of copper salt to be kinetically viable (entry 15). Several Cu^I or Cu^{II} sources were able to catalyzed the reaction, and the best results was obtained with Cu(OAc)₂ (entry 11). Interestingly, while less efficient, NiCl₂ was also a competent catalyst for the transformation (entry 12). The base had a dramatically influence on the reaction. Whereas K₂CO₃ or Et₃N were detrimental (entries 3 and 8), Na₂CO₃ had a clear beneficial effect (entry 9) and omitting base led to fluctuating isolated yields (entry 5). Using a slight excess of boronic acid (1.3 equiv) and cyanamide (1.3 equiv.) compare to amine (1.0 equiv., limiting reagent) gave the best outcome, even if the nature of the limiting reactant had little influence (entries 11 vs 13-14). Interestingly, strict stoichiometry between the three partners worked

nearly as well (entry 17). Finally using air rather than pure O₂ as co-oxidant was beneficial (entry 16). It should be highlighted that over-arylation or possible Dimroth rearrangement^[15] were not an issue in the transformation. Moreover, despite the presence of the *ortho* electron-withdrawing group known to be problematic in copper-catalyzed coupling,^[16] use of only 1.3 equivalent of 2-cyanoarylboronic acid (**1a**) allows reaching up to 84% yield under optimized conditions.

Table 1. Optimization of Quinazolin-4(*H*)-imines formation.



Entry	[M] (equiv.)	Base (equiv.)	Temp (°C)	Time (h)	Yield (%) ^[b]
1 ^[c]	CuCl ₂ (0.2)	K ₂ CO ₃ (2.3)	100	0.5	10
2 ^[c]	CuCl ₂ (0.2)	K ₂ CO ₃ (2.3)	80	2	16
3	CuCl ₂ (0.2)	Et ₃ N (2.3)	80	2	10
4	CuCl ₂ (0.2)	(-)	80	2	40
5	CuCl ₂ (0.2)	(-)	50	3	30 to 60
6 ^[c]	CuTc (0.5) ^[h]	(-)	50	2	52
7 ^[c]	CuBr•DMS (0.5)	(-)	50	2	55
8	CuCl ₂ (0.2)	K ₂ CO ₃ (3)	50	3	21
9	CuCl ₂ (0.2)	Na ₂ CO ₃ (3)	50	2	70
10	CuCl ₂ (0.2)	NaHCO ₃ (3)	50	6	57
11	Cu(OAc) ₂ (0.2)	Na ₂ CO ₃ (3)	50	3	79
12	NiCl ₂ (0.2)	Na ₂ CO ₃ (3)	50	4	41
13 ^[d]	Cu(OAc) ₂ (0.2)	Na ₂ CO ₃ (3)	50	3	72
14 ^[e]	Cu(OAc) ₂ (0.2)	Na ₂ CO ₃ (3)	50	3	75
15 ^[f]	Cu(OAc) ₂ (1.0)	Na ₂ CO ₃ (3)	rt	10	82
16 ^[f]	Cu(OAc) ₂ (1.0)	Na ₂ CO ₃ (3)	50	4	84
17 ^[f,g]	Cu(OAc) ₂ (0.5)	Na ₂ CO ₃ (3)	50	3	79

^[a] Conditions: Metal source, base, **1a** (0.23 mmol), **2a** (0.23 mmol), **3a** (0.17 mmol), O₂ (1 atm), toluene (1.2 mL).

^[b] Isolated yield of compound **5a**.

^[c] Addition of 2,2'-bipyridine (0.2 equiv.).

^[d] **1a** (0.23 mmol), **2a** (0.17 mmol), **3a** (0.23 mmol)

^[e] **1a** (0.17 mmol), **2a** (0.23 mmol), **3a** (0.23 mmol).

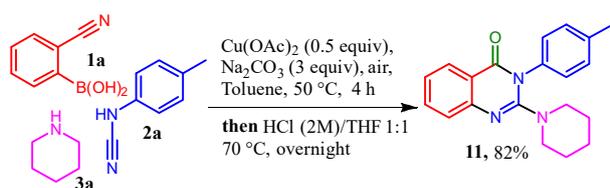
^[f] Air (1 atm) instead of O₂.

^[g] **1a** (0.17 mmol), **2a** (0.17 mmol), **3a** (0.17 mmol).

^[h] CuTc: Copper(I) thiophene-2-carboxylate

It is noteworthy that, in all these experiments, quinazolin-4(*3H*)-one **11** was systematically obtained in variable amount. We suspected that hydrolysis arose

from water generated during the reaction. Indeed, beside an adventitious presence or release from $\text{Cu}(\text{OAc})_2$ (used as hydrate), boroxine-boronic acid equilibrium^[17] or O_2 reduction could induce *in situ* water production. However, we found that hydrolysis did not occur during the reaction, but upon purification^[18] and performing the reaction in presence of water (3 equiv.) was even possible without substantial hydrolysis. Considering the value of quinazolin-4(3*H*)-ones a full hydrolysis was therefore targeted. Thus, use of stronger conditions, namely HCl (2*N*) in THF/ water (1:1) at 70 °C for 12 h, allows for achieving clean and complete hydrolysis.^[5a] Subsequently, a one pot synthesis of quinazolin-4(3*H*)-one was designed leading to the expected product **11** in 82 % yield (scheme 3).

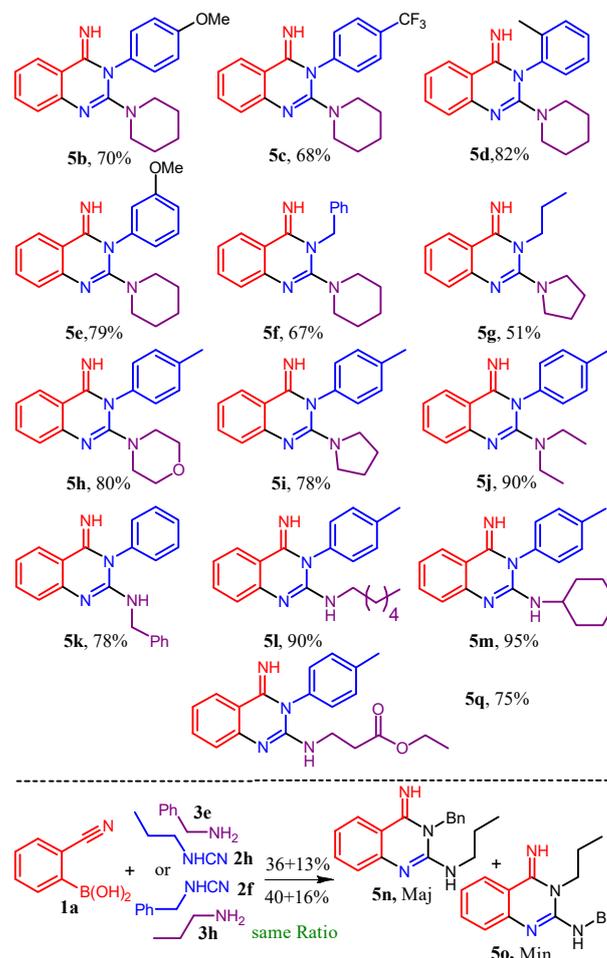


Scheme 3. One-pot synthesis of quinazolin-4(3*H*)-ones.

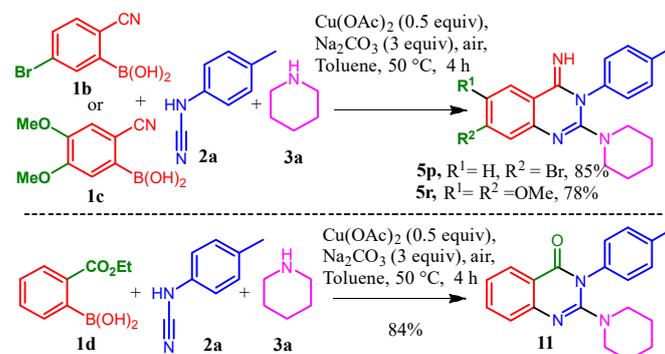
With suitable reaction and purification conditions in hand, the scope of quinazoline-imine synthesis was evaluated (scheme 4). Various arylcyanamides possessing electron withdrawing or donating groups were smoothly transformed to the quinazolinimines in yields ranging from 67 to 82% (**5a-5e**). *Ortho*, *meta* or *para* substitution was well tolerated. The process was not limited to arylcyanamides as benzyl and alkylcyanamides were competent partners (**5f**, 67% and **5g**, 51%). Both cyclic secondary amines such as piperidine, pyrrolidine or morpholine and acyclic amines could be used, delivering compounds **5a** and **5h-5j** in excellent yields. The reaction was compatible with the use of linear, branched and remotely functionalized (ester) primary alkyl amines as well as with benzylamine. For such cases, when opposed to arylcyanamide, a single compound was isolated in 78 to 95% yield (compound **5k-5m**, **5q**) with selective internalization of the aniline unit over benzyl- or alkylamines. Two separable isomers were however obtained when benzyl- or propyl-cyanamides (**2f** or **2h**) were engaged in the reaction with propyl- or benzylamine (**3e** or **3h**), respectively. In both cases, the ratio between the 2 regioisomers was the same, favouring 3-benzyl-4-imino-*N*-propyl-3,4-dihydroquinazolin-2-amine (**5n**).

Derivatives of 2-cyanophenylboronic acid such as potassium trifluoroborate, neopentyl boronic ester or boroxine proved to be less efficient than the parent boronic acid.^[20] The reaction was however not limited to commercially available 2-cyanophenylboronic acid (scheme 5). Indeed, use of 2-cyano-4-bromophenylboronic acid (**1b**),^[19a] or (2-cyano-4,5-dimethoxyphenyl)boronic acid (**1c**)^[19b] delivered chemoselectively the 7-bromo-analogue **5p** and 6,7-

dimethoxy-analogue **5r** in good yield, thereby demonstrating the tolerance to a bromine substituent under these metal catalyzed conditions. By contrast, other derivatives of 2-cyanophenylboronic acid such as potassium trifluoroborate, neopentyl boronic ester or boroxine proved to be less efficient.^[20] Interestingly, use of 2-(ethoxycarbonyl)phenylboronic acid (**1e**), bearing an ester group instead of the cyano, was also compatible, leading directly to the corresponding quinazolin-4(3*H*)-one **11** in good yield.

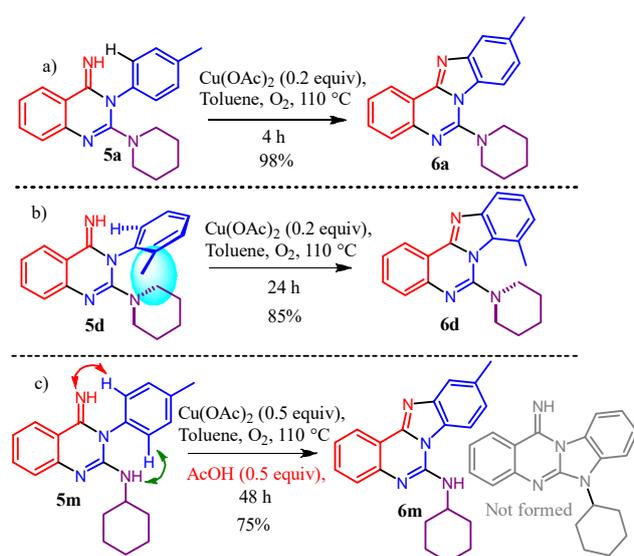


Scheme 4. Scope of quinazolin-4(3*H*)-imine synthesis. Condition A, see table 1, entry 17.



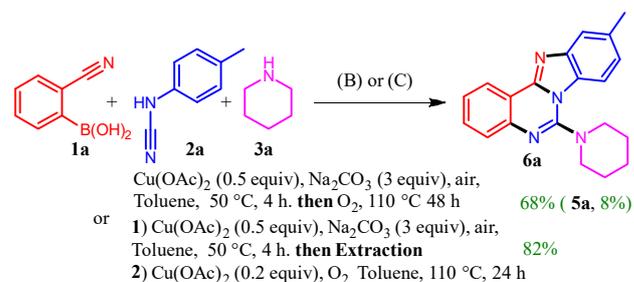
Scheme 5. Use of alternative aryl boronic acids.

We next turned our attention to the construction of benzimidazo[1,2-*c*]quinazolines **6** via C-H functionalization of pure quinazolin-4(3*H*)-imine **5a** under oxidative copper catalysis.^[21] To our delight, simply heating **5a** at 110 °C for 4 h in presence of 20 mol% of Cu(OAc)₂ under an atmosphere of O₂ delivered the expected polycyclic structure in nearly quantitative yield (scheme 6a). However, cyclisation of compound **5d** having an *ortho* substituent was more challenging. Indeed, it is well known that steric repulsion between the *ortho*-substituent of the aryl group and the C-2 methylene of the piperidine induces aryl rotation out of the plane of the quinazolin-4-imine, hence creating a chiral N-C axis.^[22] The difficulty to reach planarity necessary for C-H amination thus required time extension to 24 h to obtain full conversion (scheme 6b).



Scheme 6. Intramolecular CH amination.

We were also pleased to find that the intramolecular C-H amination can occur with high level of regiocontrol. Thus, out of the two possible cyclisation modes (amidine vs guanidine) for quinazolin-4(3*H*)-imine **5m** bearing an NH side chain, only the one involving amidine participation was observed, leading to **6m** (scheme 6c). The reaction stalled at about 50% conversion even by increasing the amount of Cu(OAc)₂ (0.2, 0.5 or 1 equiv.), but addition of 0.5 equivalent of acetic acid led to full conversion and good isolated yields.



Scheme 7. Synthesis of benzimidazo[1,2-*c*]quinazolines **6** via 3 component tandem sequence or via 3 component extractive 2 steps.

One pot preparation of benzimidazoles, from the three reactants, via a full domino process was next investigated (scheme 7). Stepwise heating and use of 0.5 equiv. of Cu(OAc)₂ lead to decent overall yield, but the second step of the process was seemingly slow (48 h) and did not go to completion with respect to the intermediate imine. This result was surprising given the relative ease of the C-H functionalization step from the isolated imine. A control experiment showed that this step was inhibited by B(OH)₃, which is a side product generated at the beginning of the sequence.^[20] A complementary 2 steps procedure, involving a simple extraction (NH₄OH_{aq}/AcOEt) after the initial three-component step, followed by reacting the crude imine with 0.2 equiv. of Cu(OAc)₂ was found to be more effective thereby allowing for isolating the expected compound **6a** with an excellent overall yield of 82%.

Various benzimidazo[1,2-*c*]quinazolines **6** were then prepared, either from isolated imines or applying a full sequence from the three starting reagents (Figure 1). Benzimidazole cyclization occurred smoothly from various aromatic bearing *ortho* or *para* electron withdrawing or donating groups (Me, OMe, CF₃, **6a-6d**). Two separable isomers (**6e** and **6e'**) were obtained in the case of *meta* substitution, favoring reaction at the least sterically hindered position (**6e**). The presence of a benzyl amine residue was not tolerated during the intramolecular C-H amination step leading to degradation. Secondary amines, whether cyclic (piperidine, **6a-e**), functionalized (morpholine, **6h**), or acyclic (diethylamine, **6j**) performed well as did primary amines (**6m-l**).

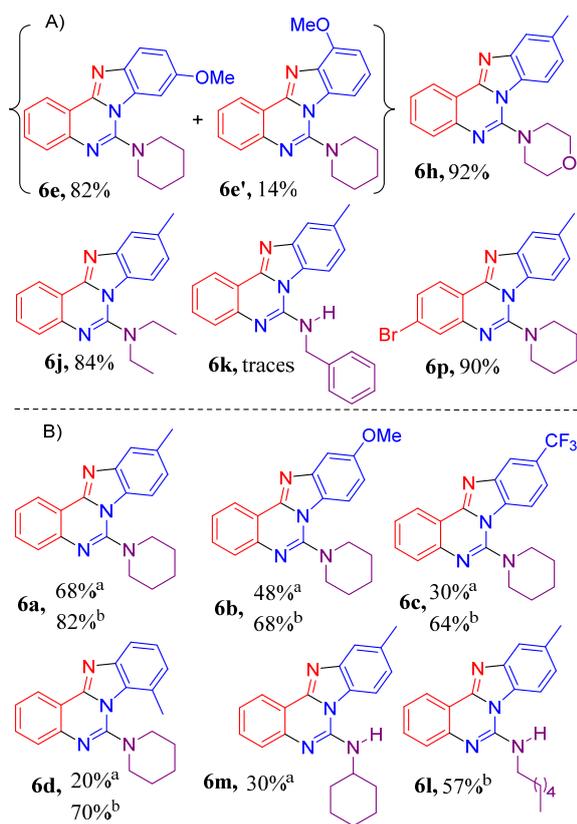
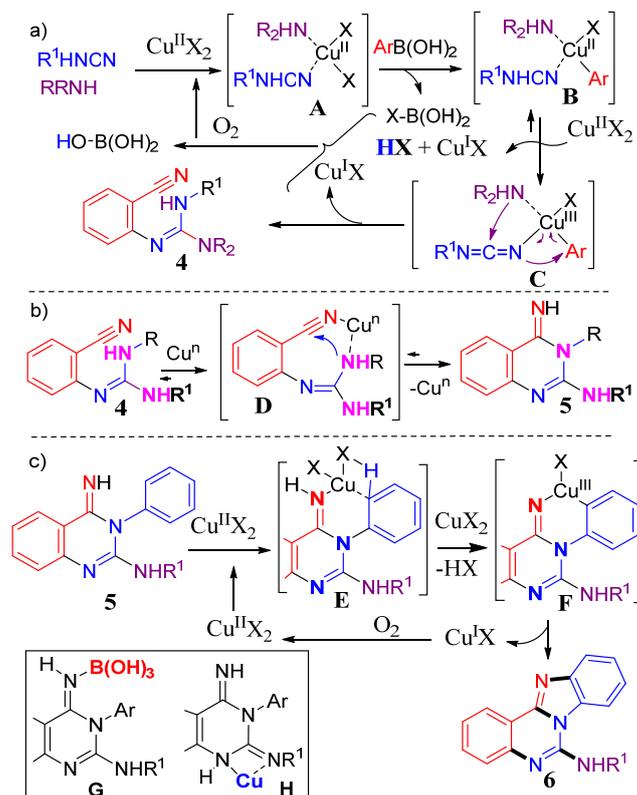


Figure 1. Scope for benzimidazo[1,2-*c*]quinazolines synthesis. A) From isolated quinazolin-4(3*H*)-imines; B) from 3-components sequence: ^[a] tandem sequence; ^[b] extractive 2 steps sequence.

Benzimidazoquinazolines could be synthesized directly from the three starting partners in modest to good yields. Whereas the full domino procedure is useful for simple cases (**6a**), the two steps extractive procedure is more general and clearly superior.

The overall benzimidazoquinazoline formation is believed to arise from three distinct copper-catalyzed steps: a) guanidine formation, b) nucleophilic cyclisation, c) C-H amination (Scheme 8).

Isolation of guanidines when using sterically encumbered cyanamides, without further quinazolin-4(3*H*)-imine formation, brings support to the first step (scheme 8a).^[20] The exact mechanism of this copper catalyzed three-component reaction remains unknown but can reasonably be assumed to follow a Chan-Evans-Lam type oxidative cycle.^[23] As such, nucleophiles coordination and transmetalation could lead to complex **B**; simultaneous deprotonation and co-copper oxidation would next lead to complex **C**. From there, addition of amine to the carbodiimide unit and reductive elimination, eventually concerted, would deliver the arylated guanidine **4**.^[24] Catalytic turnover would be ensured by O₂/acid mediated Cu^I re-oxidation. Base (Na₂CO₃) would not directly take part in this catalytic cycle, but, as recently advanced by Watson,^[25] would be important to maintain a delicate balance between Lewis basic *N*-containing species and acid, each involved in individual steps.



Scheme 8. Mechanistic insights.

The second step of the process would deliver quinazolin-4(3*H*)-imines **5** from the guanidine **4** (Scheme 8b). Facilitated by Lewis acidic copper species that would activate the nitrile,^[26] an intramolecular addition of the amidine moiety would deliver the imine **5**. Chemoselective internalization of a defined nitrogen (NAr >> NBn > NAlk) when primary amines are used, has precedent in related cyclization.^[27] Besides steric, the relative affinity (donor ability) of *N*-aromatic over *N*-alkyl guanidine residue toward copper, as reported by Herres-Pawlis' group,^[28] would explain the selectivity. Alternatively, in combination with reversibility, the selectivity might reflect the formation of the thermodynamic adduct. The final step consists in an intramolecular C-H amination leading to fused benzimidazoles (Scheme 8c). According to DFT studies reported for related system,^[29] copper would initially bind to the imine residue and undergo a Concerted-Metalation-Deprotonation. An aryl-imidate Cu^{III} complex **F**, obtained after oxidation and deprotonation, would then reductively eliminate to give the product. Disrupting the initial copper-imine interaction, either by the presence of competitive Lewis acids (for imine) or coordinating Lewis bases (for copper), would be detrimental to the C-H amination. Negative impact of boric acid,^[20] released during the initial three-component step, probably falls in the first category, explaining the poorer result achieved under Tandem domino conditions. Precursors containing a NH function probably fall in the second category. The guanidine moiety of the precursor/product, known to

be ligand for copper,^[30] could direct the metal at a non-productive site (intermediate **E**). Addition of acid (AcOH) would eventually protonate this position and/or favor reversible copper exchange.

In summary, we have developed a straightforward copper-catalyzed three-component process for quinazolin-4(*H*)-imines formation. The readily diversifiable process assembles cyanamides, 2-cyanoarylboronic acids and amines, by forming three distinct bonds under simple catalytic conditions (Cu, air). Quinazolin-4(*H*)-imines were subsequently used as linchpins to access quinazolin-4(3*H*)-ones under one pot hydrolytic conditions, or to build benzimidazo[1,2-*c*]quinazolines following a copper-catalyzed C-H amination. The key features of the process are the involvement of stable and available precursors used in a near stoichiometry under simple and cheap catalytic conditions (Cu salt, air).

Experimental Section

General procedure: To a round-bottom flask were added successively Na₂CO₃ (3.0 equiv.), Cu(OAc)₂ (0.5 equiv.), aryl boronic acid (1.3 equiv.), toluene (0.12 M) and cyanamide (1.3 equiv). Amine (1.0 equiv.) was added, and the reaction was heated to 50 °C and stirred for 4 h open to air. The reaction mixture was cooled to room temperature, quenched by addition of a saturated aqueous NH₃ solution and extracted with EtOAc. Combined organic layers were washed with H₂O, brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a residue.

1) Quinazolines-4-(3*H*)-imines: Purification of the residue by flash chromatography (basic alumina, eluent: PE/EtOAc=6/4) afforded pure quinazolines-4-(3*H*)-imine.

2) Benzimidazo[1,2-*c*]quinazoline: To purified imine or to the above crude mixture dissolved in toluene (0.12 M) was added Cu(OAc)₂ (0.2-0.5 equiv.) and AcOH (0 equiv. (**B** and **D**) or 0.5 equiv. (**B***)). The reaction was evacuated, and backfilled with oxygen (balloon), heated to 110 °C and stirred for 4 h or 24 h under an O₂ atmosphere. The reaction mixture was cooled to room temperature, quenched by addition of a saturated aqueous NH₃ solution and extracted with EtOAc. Combined organic layers were washed with H₂O, brine, dried over Na₂SO₄ and concentrated under reduced pressure to give a residue which was purified by flash chromatography (SiO₂, eluent: PE/EtOAc 80:20).

Acknowledgements

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