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# Exploration of the Copper-Catalyzed Sydnone and Sydnonimine-Alkyne Cycloaddition Reactions by High-Throughput Experimentation

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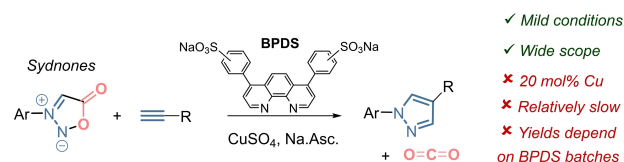
The reactivity of sydnones and sydnonimines toward terminal alkynes under copper catalysis has been explored using High-Throughput-Experimentation. A large panel of ligands and reaction conditions have been tested to optimize the copper-catalyzed sydnone click reaction discovered by our group ten years ago. This screening approach led to the identification of

new ligands, which boosted the catalytic properties of copper and allowed the discovery of a new copper-catalyzed click-and-release reaction involving sydnonimines. This reaction allowed chemoselective ligation of terminal alkynes with sydnonimines and, simultaneously, the release of an isocyanate fragment molecule that can be used for further transformations.

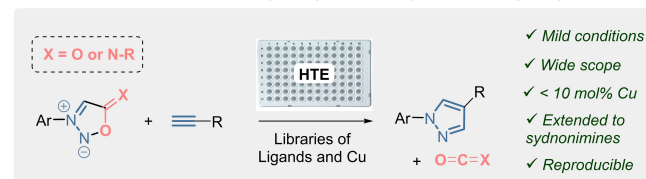
## Introduction

Among the mesoionics, sydnones are the most described in the literature and have been widely used as dipoles in non-catalyzed, thermal cycloaddition reactions.<sup>[1]</sup> In 2013 we reported the copper-catalyzed 1,3-dipolar cycloaddition of sydnones with terminal alkynes leading to 1,4-pyrazoles under mild conditions and with complete control of the regioselectivity.<sup>[2]</sup> This reaction, named CuSAC for Cu-catalyzed Sydnone-Alkyne Cycloaddition involves a copper-controlled [3 + 2] cycloaddition followed by a retro-Diels Alder (rDA) step leading to a pyrazole click product with the concomitant extrusion of CO<sub>2</sub> (Figure 1A). We later applied CuSAC to the straightforward preparation of pyrazoles<sup>[3]</sup> and successfully extended it to halogenated sydnones.<sup>[4]</sup> CuSAC has many advantageous properties respecting, at least partially, the criteria of click chemistry: mild conditions, high regio- and chemo-selectivities, good functional group tolerance as well as compatibility with biological fluids and functions.<sup>[2]</sup> However, it has some drawbacks: the reaction is rather slow and requires high amounts of copper. The catalytic system identified in 2013 is composed of 20 mol% of CuSO<sub>4</sub>, excess of sodium ascorbate and 40 mol% of bathophenanthroline disulfonate (BPDS), used as Cu ligand. This system is efficient in many cases, but

### A) CuSAC: Cu-catalyzed Sydnone-Alkyne Cycloaddition (Ref 2-4)



### B) This work: Improved Cu-catalyzed Sydnone and Sydnonimine-Alkyne Cycloadditions



**Figure 1.** Cu-catalyzed synthesis of pyrazoles from mesoionics. (A) From sydnones, CuSAC reaction; (B) HTE approach allowed the identification of optimized conditions for CuSAC and the discovery of a new reaction involving sydnonimines (X = NR).

sometimes requires gentle heating for recalcitrant substrates and always requires overnight reactions. Furthermore, we observed significant variations in the obtained yields depending on the quality of BPDS batches and suppliers (see Figure S2). Commercially available BPDS ligand is a mixture of isomers, due to the sulfonation of the phenyl rings of diphenylphenanthroline, inducing the formation of mixture of metal-complexes with different properties.<sup>[5]</sup> With no doubt, there is room for improvements of such catalytic system, which stimulated us to revisit the CuSAC reaction. In addition, we questioned whether the reaction could be extended to sydnonimines to develop a Cu-catalyzed click-and-release reaction. In this context, we decided to carry out a High-Throughput Experimentation (HTE)<sup>[6]</sup> program to screen libraries of ligands and reaction conditions to identify a more efficient and general protocol for CuSAC (Figure 1B).

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## Results and Discussion

Bridged biimidazoles (**bim**) and bibenzimidazoles (**bBim**) acting as *N,N*-chelates in metal complexes represent a unique class of ligands displaying higher angle between the two coordinative *N* atoms, as compared to phenanthrolines. Variation of the bridge length of **bim** and **bBim** ligands has indeed a profound impact on the *N–N* distances (Figure 2, upper panel, left). As a result of the smaller length of the ethylene bridge compared to the propylene group, the *N–N* distance increases by 0.35 angstroms. Aromatic bridge did not elongate much the *N–N* distance compared to the ethylene bridge (Figure S1). Large *N–N* distances of bidentate ligands should limit the formation of 2:1 ligand : Cu complexes, which should have a significant impact on the catalytic performances of the corresponding copper complexes. Surprisingly, although **bim** and **bBim** have been widely used for the preparation of metal complexes with optical properties,<sup>[7]</sup> their use as ligands for catalysis is largely underexplored. We previously described the beneficial use of **bim** ligands in CuSAC reaction with 4-bromo-sydnones<sup>[4a]</sup> and anticipated that such types of ligands may be able to improve the catalytic performances of Cu not only in reactions with sydnones but also with sydnimine substrates. To explore this hypothesis, we synthesized a library of **bim** and **bBim** ligands (Figure 2, lower panel). **Bim** and **bBim** ligands were synthesized from readily available precursors. **L1**, **L2** and **L11** were prepared according to a previously described protocol.<sup>[7b,8]</sup> **L4** and **L5** were prepared using similar conditions, the only difference being that sodium hydride was used instead of potassium carbonate, yielding to both ligands in 29% and 67% respectively. On the other hand, **L3** was obtained *via* a C–H activation reaction from **L2** in the presence of bromobenzene and a catalytic amount of Pd(OAc)<sub>2</sub> to give the product in 45% yield. The structure of **L3** was unambiguously confirmed by X-ray diffraction. **L6**, **L8**, **L9**, **L10** were prepared according to previous procedures developed by our team.<sup>[4a]</sup> Ligand **L7** was obtained in 98% yield from **L6** upon treatment with an excess of *N*-bromosuccinimide.

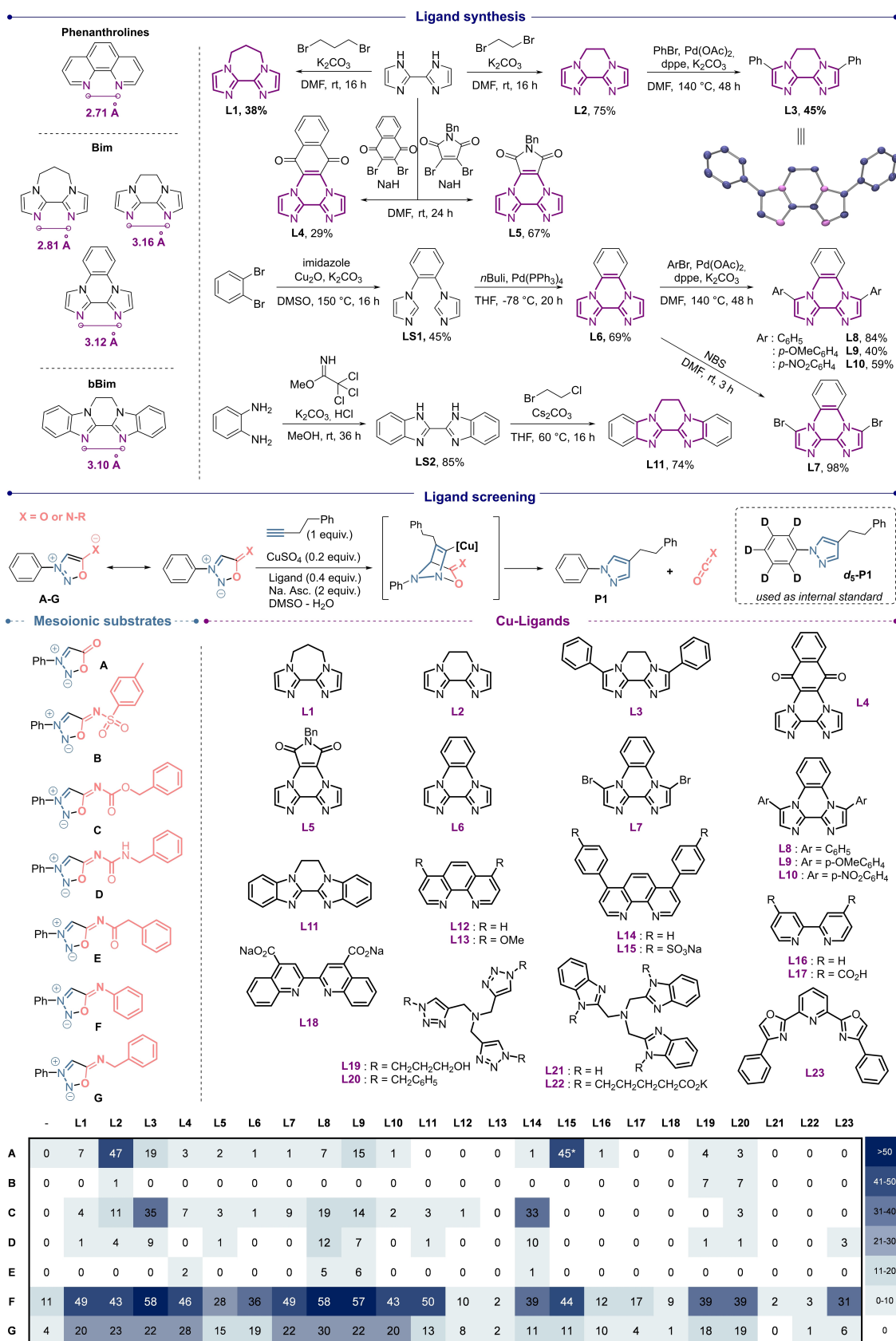
We began our investigations with a series of high-throughput experiments in which the effects of ligands and mesoionic substrates were evaluated (for details, see the Supporting Information). Phenylsydnone (**A**) and a series of 6 sydnimines (**B–G**) varying on the substituent attached on the exocyclic *N* atom, were chosen as model substrates for this campaign. As each reaction should form the same pyrazole product (**P1**), a quantitative LC-HRMS method was developed to allow rapid determination of crude yields. To that end, **P1** was synthesized as well as its deuterated analogue **d<sub>5</sub>-P1**, which was used as internal standard. Having this analytical tools in hands, we conducted a series of 168 reactions combining 7 mesoionics with 23 ligands in presence of CuSO<sub>4</sub> and excess of ascorbate. Each combination was performed in duplicate and their crude analyzed by HRMS. Key results are shown in Figure 2 (Lower panel). Only few ligands were found able to activate copper efficiently for the CuSAC reaction with phenylsydnone **A** but, interestingly, ligand **L2** was found to be as effective as the reference ligand bathophenanthroline **L15**. Importantly, reac-

tions conducted with **L2** were highly reproducible, whereas those carried out with **L15** were found to be dependent of the quality of the commercial source (compare Figure S2 with S21). Excitingly, formation of the desired product **P1** was observed in many of the experiments conducted with sydnimine **F**. This type of sydnimines were recently described by our group as highly reactive towards cyclooctynes generating phenyl isocyanates under physiological conditions.<sup>[9]</sup> The possibility to develop a Cu-catalyzed version of this reaction attracted our attention.

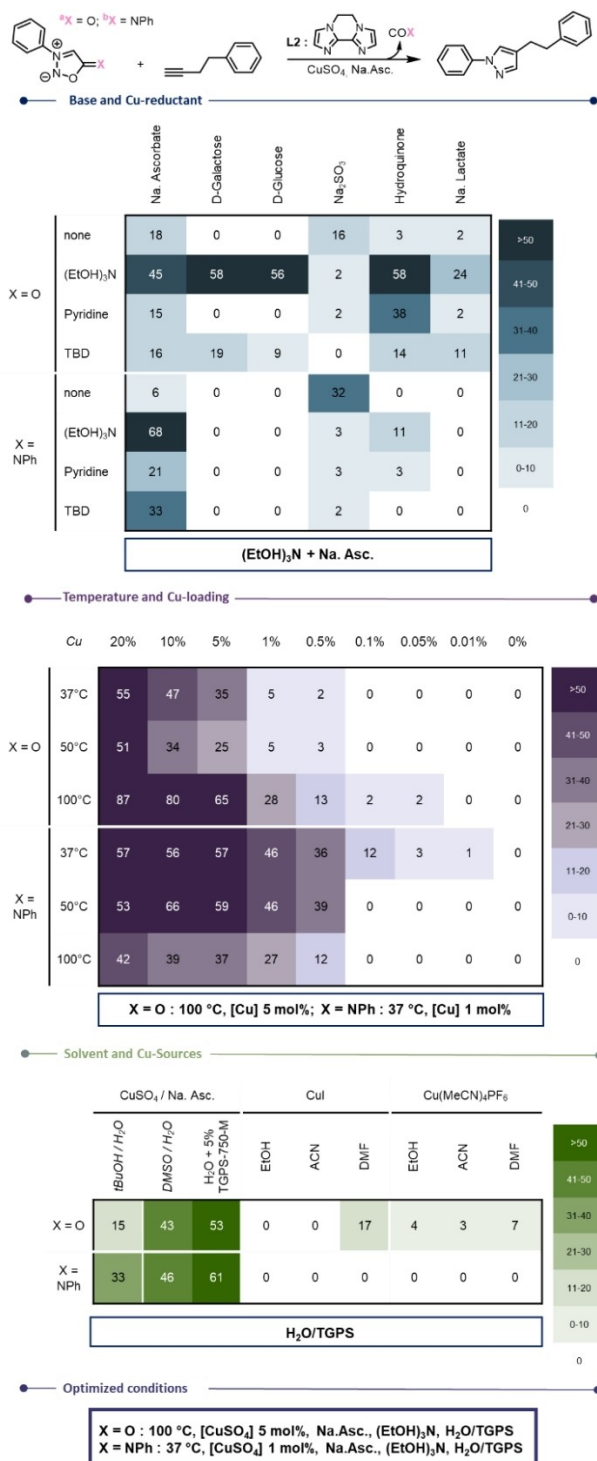
From these preliminary screening results, we thus focused our attention on Cu-catalyzed reactions with sydnone **A** and sydnimine **F** in presence of ligand **L2**. This ligand is structurally simple, easy to prepare in multigram scale and effective for both mesoionic substrates. We then performed a series of optimizations of the selected reactions using HTE (Figure 3).

First optimizations *via* HTE investigated the influence of Cu-reductant and base identity. The results clearly indicated triethanolamine as the most suitable base (Figure 3, upper panel). Several Cu-reductors can be used in the reaction with phenylsydnone **A**, but only sodium ascorbate was effective when sydnimine **F** was used. The use of glucose, galactose or hydroquinone as copper reductants was effective starting with sydnone **A** but increased the degradation of sydnimine **F**, Na ascorbate was therefore kept as reducing agent (Figure 3, upper panel). We then investigated the influence of temperature and catalyst loading. Interestingly, sydnimine **F** proved to be more reactive than sydnone **A** for CuSAC reactions, as product **P1** was observed with only 0.1% of Cu catalyst, but was also found to be more sensitive to temperature. Although control experiments showed good thermal stabilities of **F** even at 100 °C (Figure S16), degradation begins at 50 °C in presence of copper salts and bases. Conversely, sydnone **A** can be refluxed in a mixture of water and DMSO to improve yields if necessary (Figure 3, middle panel). Subsequent optimizations *via* HTE investigated the influence of solvent. The optimized catalytic systems identified for both model substrates were tested in series of aqueous and organo-aqueous media. Pure organic solvents in presence of Cu(I) salts were also evaluated but globally were ineffective (Figure 3, lower panel). Aqueous solvents were clearly better for the efficiency of the reactions. Addition of a surfactant such as TPGS-750-M<sup>[10]</sup> was found useful to improve the reaction with hydrophobic substrates and was therefore selected to provide a general procedure. Reactions can also be carried out efficiently in DMSO/water. The best HTE results were then verified in scale-up experiments and reproducibility tests (Figure S21). Reactions were reproduced in batches and repeated 3 times, affording the desired pyrazole **P1** in 91% ± 3.5% yields (n=3) starting from sydnone **A** and 82% ± 2% yields (n=3) starting from sydnimine **F**. Scale-up experiments also confirmed the robustness of the reaction affording 1.14 g (4.58 mmol) of **P1** in 75% yield starting from sydnone **A**.

Finally, we tested the robustness of the synthetic protocols by undertaking the synthesis of 144 compounds in parallel. In pursuit of this objective, the optimized conditions were applied



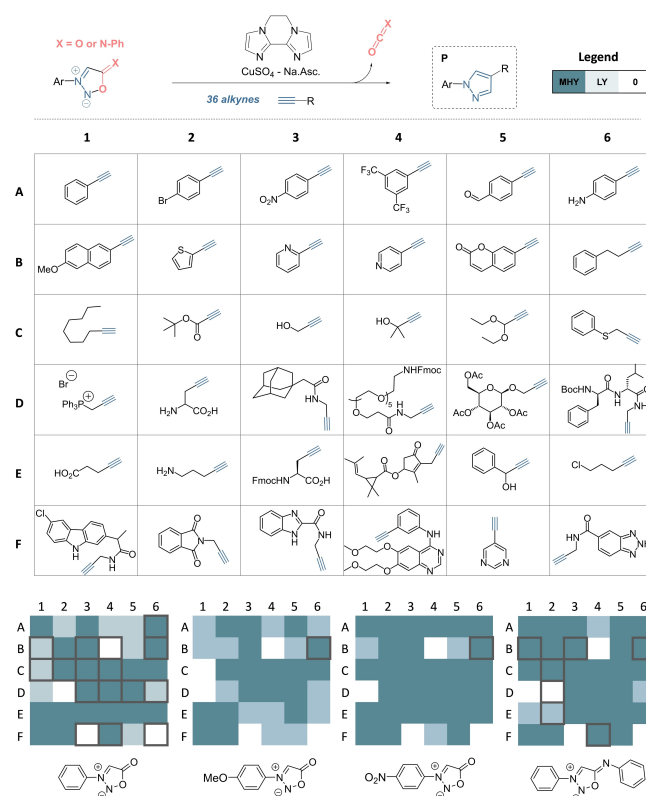
**Figure 2.** Ligand screening. Upper panel, left: General structure of ligands and distance between their *N* coordinating atoms. Upper panel, right: Synthesis of ligands L1-11. Lower panel, Ligand screening. Reaction conditions: [mesoionic] = [phenylbutyne] = [triethanolamine] = 25 mM, [CuSO<sub>4</sub>] = 5 mM (0.2 equiv.), [ligand] = 10 mM (0.4 equiv.), [Na. asc.] = 50 mM, solvent = H<sub>2</sub>O : DMSO (50:50), total volume = 100 μL, 37 °C - 16 h. Numbers are crude yields calculated by HRMS using d<sub>5</sub>-P1 as internal standard. A color code was used for clarity reasons. \*Result obtained with one particular batch of L15.



**Figure 3.** Selected HTE Optimizations. Numbers are crude yields calculated by HRMS using **d<sub>5</sub>-P1** as internal standard. A color code was used for clarity reasons. [mesoionic] = 25 mM, [phenylbutyne] = 25 mM, [L2] = 2[Cu]. Upper panel: Influence of Cu-reductant and base. Reactions conducted in water/DMSO (1:1) at 37 °C with [reductant] = 50 mM, [base] = 25 mM, <sup>a</sup>[CuSO<sub>4</sub>] = 1.25 mM, <sup>b</sup>[CuSO<sub>4</sub>] = 0.25 mM; Middle panel: Influence of Cu-loading and temperature. Reactions conducted in water/DMSO (1:1) with [Na.Asc.] = 50 mM, [(EtOH)<sub>3</sub>N] = 25 mM; Lower panel: Influence of solvents and Cu species. Reactions conducted at 37 °C with [Na.Asc.] = 50 mM, [(EtOH)<sub>3</sub>N] = 25 mM, <sup>a</sup>[CuSO<sub>4</sub>] = 1.25 mM, <sup>b</sup>[CuSO<sub>4</sub>] = 0.25 mM.

to 4 mesoionics and 36 alkynes at a scale of 2.5 μmol (Figure 4). The alkynes were chosen to feature examples with both aliphatic, aromatic and heteroaromatic substituents, including those with different substitution patterns and diverse functional groups, in order to assess the chemoselectivity of the reaction. Overall, the substrates incorporated a wide array of functional groups such as halogens, nitro, trifluoromethyl, carboxylic esters and amides, carbamate, thioether and acetal, in addition to fused/non-fused and saturated/unsaturated heteroaromatic rings. The 144 crude reactions were then analyzed by SFC-UV-MS to confirm product identity and estimate the reactions efficiencies. Pyrazoles UV absorbances were found close enough to allow an approximation of crude yields from product peak vs. internal standard UV-areas (see Supporting Information VII.C).

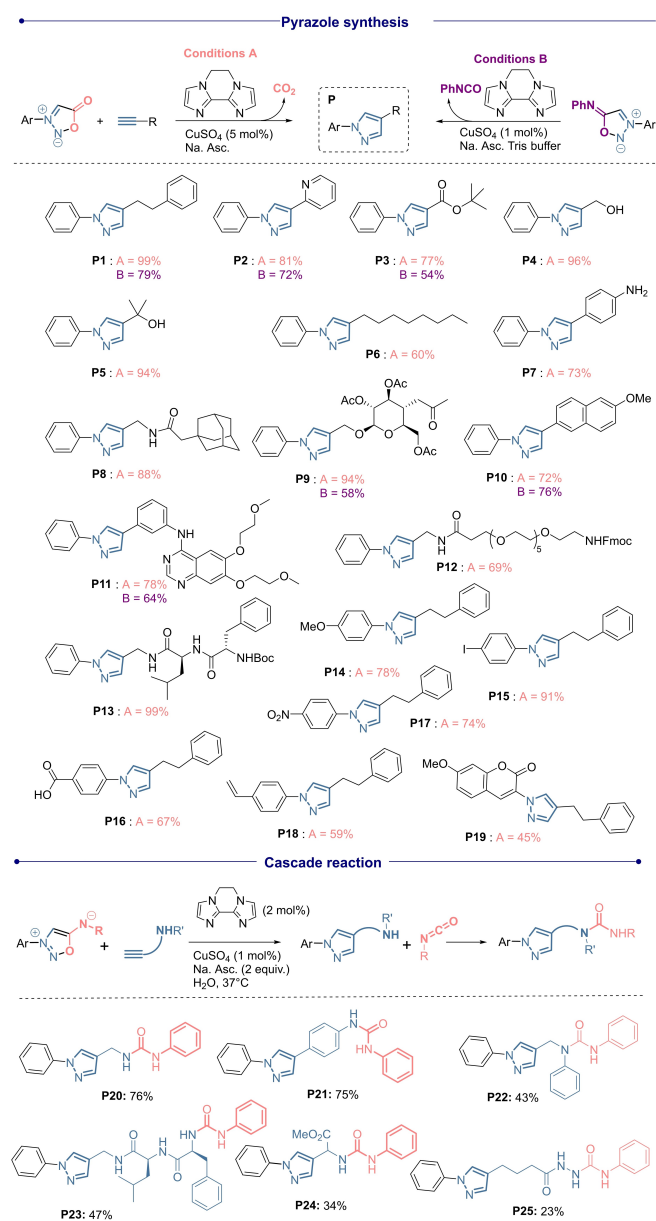
The results (Figure 4) showed that almost 90% of the 144 reactions gave the desired product. The reaction appears compatible with a series of functional groups: alcohols, carboxylic acids, acetals, thioethers, amines, carbamates and esters. Problematic substrates are phosphonium **1d** and heterocyclic alkynes **4b**, **3f** and **6f**, which were unreactive under CuSAC conditions. These results, which were confirmed in batch experiments, could be attributed to steric hindrance for **1d** and possible inhibition of the Cu-L2 complex in case of



**Figure 4.** HTE synthesis of pyrazoles from 3 sydnonime substrates and 36 alkynes. [mesoionic] = 25 mM, [Alkyne] = 25 mM, [Na.Asc.] = 50 mM, [(EtOH)<sub>3</sub>N] = 25 mM. For sydnonime (X = O): [CuSO<sub>4</sub>] = 1.25 mM, [L2] = 2.5 mM, 50 °C; for sydnonime (X = NPh): [CuSO<sub>4</sub>] = 0.25 mM, [L2] = 0.5 mM, 37 °C. Framed squares indicate the experiments reproduced in batches. Legend: 0 = no reaction, LY: Low yield < 20%, MHY: Medium to High Yield > 20%. Yields were estimated by SFC-UV-MS.

the chelating-alkynes **4b**, **3f** and **6f**. Selected examples (framed squares in Figure 4) were reproduced at 0.185 mmol scale to isolate the pyrazole products and compare HTE yields with isolated yields. Overall, the yields achieved in batch experiments were consistently at least 30% higher than those obtained under HTE conditions. In all instances, the yields exceeded 60% starting from sydnone **A** or sydnonimine **F** (products **P1-P14** in Figure 5).

Additional examples were carried out to investigate the influence of the sydnone structure. Good yields were obtained with either electron-rich or electron-poor sydnone substrates (**P14-19**, Figure 5, upper panel). All pyrazoles were obtained as a single 1,4-regioisomer confirming the regioselective control of the Cu-catalyzed cycloaddition.



**Figure 5.** Synthesis of pyrazoles from sydnones and sydnonimines. Numbers in % are isolated yields. Upper panel: Scopes of the reactions. **P1-14** from HTE reactions reproduced in 0.185 mmol scale for isolation. Lower panel: Cascade reaction in 0.171 mmol scale for isolation.

*N*-Aryl sydnonimines display interesting reactivity toward Cu-catalyzed cycloaddition with alkynes, even higher than sydnones. However, from a synthetic point of view, their use for pyrazoles synthesis is not atom economy friendly since preparation of sydnonimines substrates requires three steps<sup>[9]</sup> and, more importantly, isocyanates are generated from sydnonimines during the catalytic process. We thus decided to take profit of this isocyanate release to develop a two-steps cascade reaction starting from amine-containing alkynes. After CuSAC reaction, the formed pyrazole can then react with the released isocyanate leading to the corresponding urea. This cascade reaction was observed during the HTE scope study illustrated in Figure 4 with alkynes substrates **2d** and **2e** where pyrazoles bearing an urea function were detected. Encouraged by these results, we successfully carried out a series of CuSAC reactions with alkynes bearing primary and secondary aliphatic amines, as well as with aromatic amines and hydrazides (Figure 5, lower panel). In all cases, the expected pyrazole-urea products were successfully isolated together with minor amounts of pyrazole-amines. The reaction was surprisingly found not very effective with the hydrazide-alkyne substrate (**P25**) and globally more sensitive to steric hindrance than to the nucleophilicity of the amine function.

## Conclusions

In conclusion, we developed a practical CuSAC method for pyrazole synthesis utilizing a new bridged biimidazole Cu-ligand. The procedure allows effective CuSAC transformations with a variety of substrates and, importantly, in a more robust and reproducible manner than with BPDS ligand. The discovery, optimization and evaluation of this new procedure was carried out using HTE as a key tool to accelerate the work.<sup>[11]</sup> Notably, the HTE approach showed that this procedure is successful in around 90% of substrate cases, but also allowed to identify the limitations of the method. Finally, a new Cu-catalyzed click-and-release reaction was identified. Sydnonimines were found to react smoothly with terminal alkynes under Cu-catalysis, forming pyrazoles with the concomitant release of isocyanates. A synthetic application of this reaction was showed through the preparation of urea-containing pyrazoles in a two-steps cascade reaction. Biological applications of this Cu-catalyzed isocyanate release reaction are currently under investigation in our laboratory.

## Experimental Section

For details of synthetic procedures, chemical characterizations, HTE results, see the Supporting Information.

**General procedure** for the synthesis of pyrazoles from sydnones:

To a solution of aryl-sydnone (1 equiv.), Ligand L2 (0.1 equiv.), triethanolamine (1 equiv.),  $\text{CuSO}_4 \cdot 5 \text{H}_2\text{O}$  (0.05 equiv.) in  $\text{H}_2\text{O}$  containing 1%wt of TPGS-750-M surfactant (0.025 M) was added the alkyne (1 equiv.) followed by sodium ascorbate (2 equiv.). The mixture was stirred overnight at 50°C and evaporated. Then, the

crude mixture was purified by flash chromatography to give the desired product.

### X-ray Crystallography

Deposition Number 2284989 for L3 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service.

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### Abbreviations

Bim, benzimidazole; bBim, bibenzimidazole; Tris-Bim, tris-benzimidazole; Tris-Triaz, tristriazoles; BPDS, bathophenanthroline disulfonate; CuSAC, Cu-catalyzed Sydnone Alkyne Cycloaddition.

### Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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### Conflict of Interests

The authors declare no conflict of interest.

### Data Availability Statement

The data that support the findings of this study are available in the supplementary material of this article.

**Keywords:** Mesoionics · Screening · Sydnonones · Cycloaddition · Copper

- [1] a) D. L. Browne, J. P. A. Harrity, *Tetrahedron*. **2010**, *66*, 553–568; b) R. S. Foster, H. Jakobi, J. P. A. Harrity, *Tet. Letters* **2011**, *52*, 1506–1508; c) K. Harju, J. Vesterinen, J. Yli-Kauhala, *J. Org. Lett.* **2009**, *11*, 2219–2221; d) D. L. Browne, J. B. Taylor, A. Plant, J. P. A. Harrity, *J. Org. Chem.* **2010**, *75*, 984–987; e) R. S. Foster, H. Jakobi, J. P. A. Harrity, *Org. Lett.* **2012**, *14*, 4858–4861; f) R. S. Foster, J. Huang, J. F. Vivat, D. L. Browne, J. P. A. Harrity, *Org. Biomol. Chem.* **2009**, *7*, 4052–4056; g) D. L. Browne, J. F. Vivat, A. Plant, E. Gomez-Bengoia, J. P. A. Harrity, *J. Am. Chem.* **2009**, *131*, 7762–7769; h) D. L. Browne, M. D. Helm, A. Plant, J. P. A. Harrity, *Angew. Chem. Int. Ed.* **2007**, *46*, 8656–8658.
- [2] S. Kolodych, E. Rasolofonjatovo, M. Chaumontet, M.-C. Nevers, C. Créminon, F. Taran, *Angew. Chem. Int. Ed.* **2013**, *52*, 12056–12060.
- [3] S. Specklin, E. Decuypere, L. Plougastel, S. Aliani, F. Taran, *J. Org. Chem.* **2014**, *79*, 7772–7777.
- [4] a) E. Decuypere, S. Specklin, S. Gabillet, D. Audisio, H. Liu, L. Plougastel, S. Kolodych, F. Taran, *Org. Lett.* **2015**, *17*, 362–365; b) H. Liu, D. Audisio, L. Plougastel, E. Decuypere, D.-A. Buisson, O. Koniev, S. Kolodych, A. Wagner, M. Elhabiri, A. Krzyczmonik, S. Forsback, O. Solin, V. Gouverneur, F. Taran, *Angew. Chem. Int. Ed.* **2016**, *55*, 12073–12077.
- [5] G. P. McDermott, E. M. Zammit, E. K. Bowen, M. M. Cooke, J. L. Adcock, X. A. Conlan, F. M. Pfeffer, N. W. Barnett, G. A. Dyson, P. S. Francis, *Anal. Chim. Acta* **2009**, *634*, 222–227.
- [6] For recent review in the field of HTE see: a) S. M. Mennen, C. Alhambra, C. L. Allen, M. Barberis, S. Berritt, T. A. Brandt, A. D. Campbell, J. Castañón, A. H. Cherney, M. Christensen, D. B. Damon, J. Eugenio de Diego, S. García-Cerrada, P. García-Losada, R. Haro, J. Janey, D. C. Leitch, L. Li, F. Liu, P. C. Lobben, D. W. C. MacMillan, J. Magano, E. McInturff, S. Monfette, R. J. Post, D. Schultz, B. J. Sitter, J. M. Stevens, I. I. Strambeanu, J. Twilton, K. Wang, M. A. Zajac, *Org. Process Res. Dev.* **2019**, *23*, 1213–1242; b) M. Shevlin, *ACS Med. Chem. Lett.* **2017**, *8*, 601–607.
- [7] a) D. Walther, L. Böttcher, J. Blumhoff, S. Schebesta, H. Görls, K. Schmuck, S. Rau, M. Rudolph, *Eur. J. Inorg. Chem.* **2006**, *2006*, 2385–2392; b) B. Dietzek, W. Kiefer, J. Blumhoff, L. Böttcher, S. Rau, D. Walther, U. Uhlemann, M. Schmitt, J. Popp, *Chem. Eur. J.* **2006**, *12*, 5105–5115; c) C. Herrmann, J. Neugebauer, M. Presselt, U. Uhlemann, M. Schmitt, S. Rau, J. Popp, M. Reiher, *J. Phys. Chem. B* **2007**, *111*, 6078–6087; d) S. Kupfer, *Phys. Chem. Chem. Phys.* **2016**, *18*, 13357–13367; e) M. Brautigam, M. Wachtler, S. Rau, J. Popp, B. Dietzek, *J. Phys. Chem. C* **2012**, *116*, 1274–1281.
- [8] A. F. Henwood, D. Antón-García, M. Morin, D. Rota Martir, D. B. Cordes, C. Casey, A. M. Z. Slawin, T. Lebl, M. Bühl, E. Zysman-Colman, *Dalton Trans.* **2019**, *48*, 9639–9653.
- [9] M. Ribéraud, K. Porte, A. Chevalier, L. Madegard, A. Racht, A. Delaunay-Moisan, F. Vinchon, P. Thuéry, G. Chiappetta, P. A. Champagne, P. Pieters, D. Audisio, F. Taran, *J. Am. Chem. Soc.* **2023**, *145*, 2219–2229.
- [10] P. Klumphu, B. H. Lipshutz, *J. Org. Chem.* **2014**, *79*, 888–900.
- [11] For recent examples where HTE played a central role in the development of reactions, see: a) S. Felten, C. Q. He, M. Weisel, M. Shevlin, M. H. Emmert, *J. Am. Chem. Soc.* **2022**, *144*, 23115–23126; b) S.-E. Suh, L. E. Nkulu, S. Lin, S. W. Krska, S. S. Stahl, *Chem. Sci.* **2021**, *12*, 10380–10387.

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