Accepted Manuscript

Copper-mediated synthesis of *N*-vinyl ynamides from *N*-vinyl carbamates

Vincent Le Fouler, Guillaume Duret, Philippe Bisseret, Nicolas Blanchard

PII: S0040-4039(18)30934-1
DOI: https://doi.org/10.1016/j.tetlet.2018.07.053
Reference: TETL 50162

To appear in: *Tetrahedron Letters*

Received Date: 28 May 2018
Revised Date: 18 July 2018
Accepted Date: 23 July 2018

Please cite this article as: Fouler, V.L., Duret, G., Bisseret, P., Blanchard, N., Copper-mediated synthesis of *N*-vinyl ynamides from *N*-vinyl carbamates, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.07.053

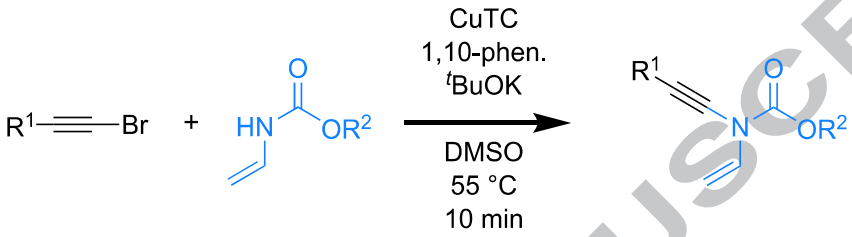
Graphical Abstract

To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

Copper-mediated synthesis of *N*-vinyl ynamides from *N*-vinyl carbamates

Leave this area blank for abstract info.

Vincent Le Fouler, Guillaume Duret, Philippe Bisseret and Nicolas Blanchard*



ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Copper-mediated synthesis of *N*-vinyl ynamides from *N*-vinyl carbamates

Vincent Le Fouler[a], Guillaume Duret[a], Philippe Bisseret[a] and Nicolas Blanchard[a,]*

[a]*Université de Haute-Alsace, Université de Strasbourg, CNRS, LIMA, UMR 7042, 68000 Mulhouse, France*

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Ynamide
Copper-mediated
Cross-coupling
Diels-Alder

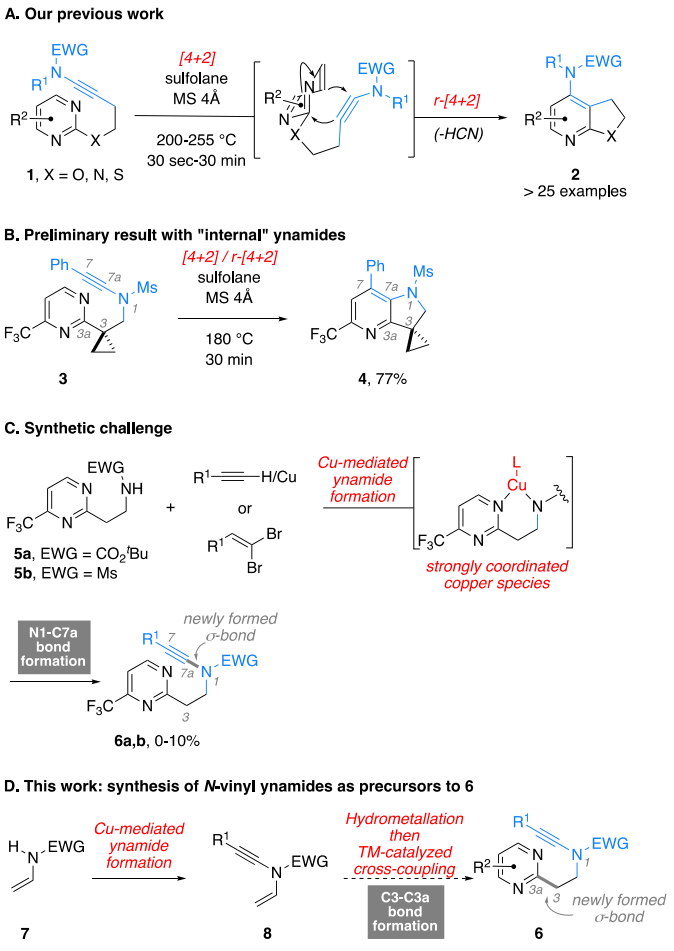
ABSTRACT

Ynamides are versatile 3-atoms building blocks for organic synthesis as they participate in a variety of ionic, radical and pericyclic processes. Converting ynamides into 5-atom building blocks, such as the yet unreported *N*-vinyl ynamides, would open new avenues in this fascinating chemistry. We describe herein our efforts towards such goal and demonstrate that the cross-coupling between *N*-vinyl carbamates and bromo-alkynes using copper(I) thiophene carboxylate, 1,10-phenanthroline and tBuOK in DMSO is a reactive system with an improved profile compared to the classical ynamides syntheses. The advantages and limitations of this copper-mediated reaction are discussed.

Ynamide π-systems can participate in a variety of pericyclic processes such as [4+2] and formal [4+2] cycloadditions, thus delivering structurally diverse nitrogen-containing heterocycles.[1-6] We have recently shown that ynamides could behave as competent electron-deficient dienophiles in intramolecular inverse electron demand Diels-Alder cycloadditions with pyrimidines, leading to complex 4-aminopyridines fused with a 5-membered ring after a spontaneous retro-[4+2] step (Scheme 1, A).[7-9]

Further investigations of this reaction, in particular of the connectivity within the cycloaddition precursor, demonstrated that 4-azaindolines such as **4** could be obtained in good yields when the nitrogen atom of the ynamide was placed *within* the tether between the azadiene and the dienophile ("internal" ynamides **3**, Scheme 1, B). The activation energy for this domino [4+2]/retro-[4+2] is not as high as for the "external" ynamides **1**, that required a temperature between 210 and 255 °C.[7,8] This promising result encouraged us to explore the scope of this transformation, as 4-azaindoles in general are relevant scaffolds for the chemical community and in particular for medicinal chemistry.[10,11]

The main challenge in the synthesis of 4-azaindolines using this strategy was rapidly identified as the synthesis of the cycloaddition precursors themselves (such as **3**). Indeed, a preliminary screening of copper-mediated and copper-catalyzed reactions for the elaboration of the N-C7a σ-bond of ynamide **6** from β-ethylamino pyrimidines **5** led to dramatically poor yields (Scheme 1, C).



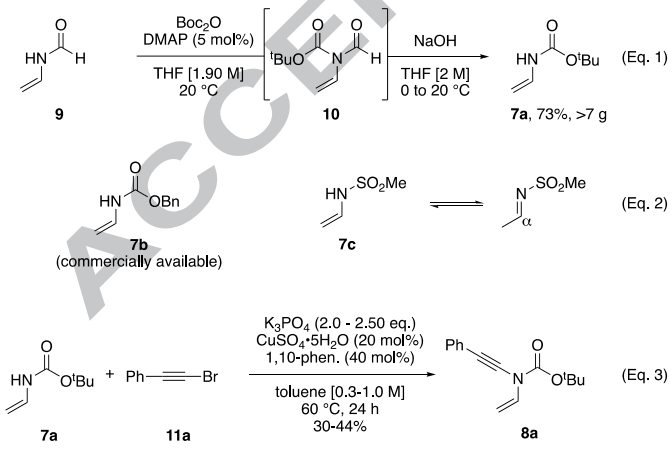
* Corresponding author. Tel.: +33-389336824; e-mail: n.blanchard@unistra.fr

Scheme 1. Ynamides in inverse electron demand Diels-Alder cycloadditions (A, B), synthetic challenge associated with the cycloaddition precursors (C) and working hypothesis (D).

Indeed, established methods[2-6] were extensively screened using *gem*-dibromoalkenes, bromoalkynes or copper acetylides and *tert*-butyl (2-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)carbamate **5a** or *N*-((1-(4-(trifluoromethyl)pyrimidin-2-yl)cyclopropyl)-methyl)methanesulfonamide **5b**, leading to 10% yield of the desired ynamides **6a,b** in the best cases. Glaser type homocoupling was usually the major product of these cross-coupling reactions. This outcome could be logically attributed to the strongly coordinating effect of pyrimidines,[12-14] which could lead to unproductive copper complexes (Scheme 1, C).

A second strategy for the synthesis of "internal" ynamides **6** would call for the construction of the C3-C3a σ-bond thanks to a transition metal-catalyzed cross-coupling reaction (Scheme 1, D). The reactive metallated intermediate would be obtained through a regio- and chemoselective hydrometallation reaction of *N*-vinyl ynamide **8**, itself prepared from the easily accessible (and commercially available in some cases) *N*-vinyl carbamate **7**. This strategy is reminiscent of previous research by Overman[15,16] who reported highly efficient hydroboration reaction/Suzuki cross-coupling of *N*-vinyl carbamates, although in the specific context of ynamide **8**, two π-systems would compete for the hydrometallation step.

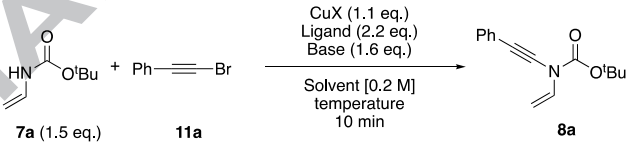
Although *N*-vinyl ynamides **8** are not reported to the best of our knowledge, this class of ynamides combining two different π-systems whose electronics and sterics could be finely tuned, would represent a fascinating playground for a diversity of ionic or pericyclic reactions. We report herein the development of a copper-mediated synthesis of *N*-vinyl ynamides **6** that, although not of a broad scope, allows the synthesis for the first time of these small and promising building blocks.



Scheme 2. Synthesis of *N*-vinyl carbamate **7a** (Eq. 1), availability of **7b** and unstability of **7c** (Eq. 2) and preliminary study of ynamide **8a** formation (Eq. 3).

Synthesis of ynamides **6** relies first on an easy access to nitrogen nucleophiles **7** possessing an alkoxycarbonyl or a sulfonamide group as the electron-withdrawing substituent, as these motifs are the most classical protecting groups for ynamides nitrogen atoms. The synthesis of *N*-alkenyl carbamates has been achieved using copper(I)-catalyzed *N*-vinylation of carbamates[17,18] or transition-metal catalyzed isomerization of *N*-allylcarbamates.[19,20] When considering the simpler *N*-vinyl motif, two methods were reported relying on the Curtius rearrangement of acryloyl azide (followed by trapping with an alcohol)[21-24] or protection/deformylation of *N*-vinyl formamide **9**.[25] For practical reasons, we selected the latter method that delivered *N*-vinyl carbamate **7a** in good yield (Scheme 2, Eq. 1). Note that the corresponding benzyloxycarbamate **7b** is a commercially available compound (Scheme 2, Eq. 2).[26] Also, it was observed that the synthesis of the corresponding *N*-vinyltosylamide **7c** proved impossible, which might be traced back to the high electrophilicity of the imine α-carbon, in equilibrium with the *N*-vinylsulfonamide.[24,27]

Having in hand the desired nitrogen nucleophiles **7a,b**, we turned our attention to their reactivity in ynamide formation using known methods such as the ones reported by Evano, Stahl or Danheiser.[2-6] Unfortunately, no traces of the desired ynamides **8** could be detected; diyne formation arising from the copper-mediated Glaser homocoupling of the alkyne partner was observed as the only side product. The use of Hsung's conditions[2] on the other hand delivered **8a** in moderate yields (37±7%) (Scheme 2, Eq. 3).

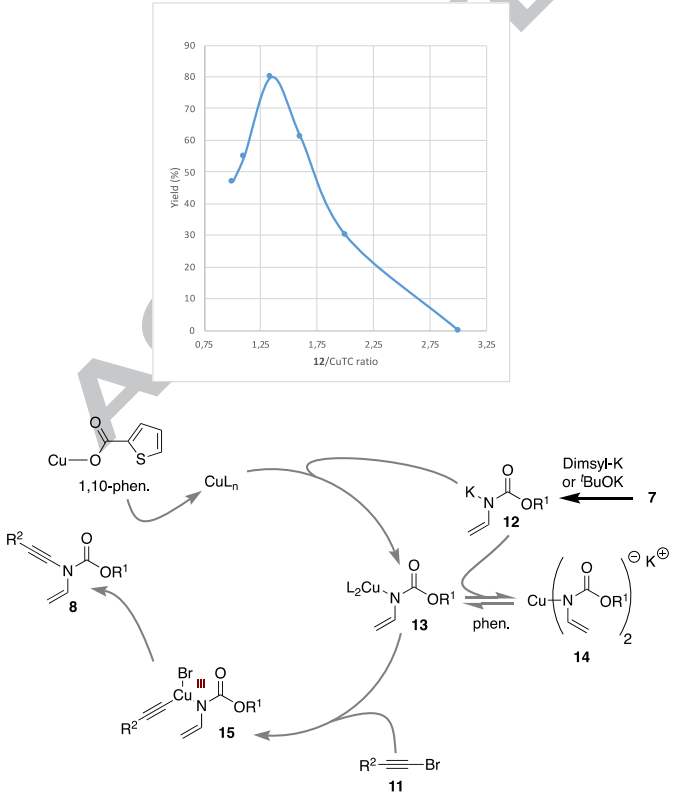


Entry	CuX	Ligand	Base	Solvent	Temp. (°C)	NMR yield (%)
1	CuTC	1,10-phen.	^{t}BuOK	THF	55	-
2	CuTC	1,10-phen.	^{t}BuOK	NMP	55	-
3	CuTC	1,10-phen.	^{t}BuOK	DMF	55	27
4	**CuTC**	**1,10-phen.**	**^{t}BuOK**	**DMSO**	**55**	**75**
5	CuTC	-	^{t}BuOK	DMSO	55	18
6	CuTC	*trans*-1,2-diaminocyclo-hexane	^{t}BuOK	DMSO	55	-
7	CuTC	DMEDA	^{t}BuOK	DMSO	55	-
8	CuTC	neocuproine	^{t}BuOK	DMSO	55	-
9	CuTC	1,10-phen.	^{t}BuOK	DMSO	40	74
10	CuTC	1,10-phen.	^{t}BuONa	DMSO	55	68
11	CuI	1,10-phen.	^{t}BuOK	DMSO	55	56
12	**CuTC[a]**	**1,10-phen.[b]**	**^{t}BuOK[c]**	**DMSO**	**55**	**80 (71)[d]**

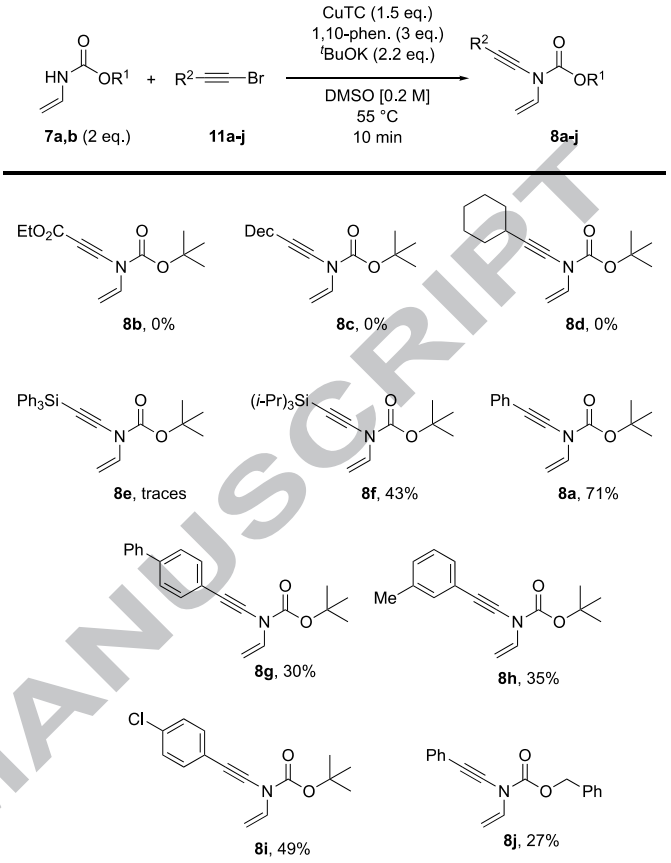
Table 1. Optimisation of the copper(I)-mediated C-N bond formation. [a] 1.5 equiv. [b] 3 equiv. [c] 2.2 equiv. [d] Isolated yield.

Unsatisfied by these moderate yields, we embarked on the screening of copper-mediated reaction conditions able to convert vinyl carbamates **7** to the corresponding *N*-vinyl ynamide **8** in good yields. Table 1 is a highlight of extensive research efforts that evaluated copper(I) salts, ligands, bases, solvents and temperatures, as well as the effect of syringe pump addition of the bromo-alkyne **11a** or *N*-vinyl carbamate **7**. Using copper thiophene carboxylate, 1,10-phenanthroline and tBuOK at 55 °C as the initial catalytic system,[28] various solvents (THF, NMP, DMF and DMSO, entries 1-4) were screened, leading to 75% of the desired *N*-vinyl ynamide **8a** in DMSO (entry 4). It should be noted that variations in the ligands (absence of ligand, trans-1,2-diaminocyclohexane, DMEDA and neocuproine, entries 5-8), the temperature (entry 9), the base (entry 10) and the copper(I) source (entry 11) were studied but led in all cases to the recovery of the starting materials or to lower yields.

Having identified the most promising combination of copper(I) salt, ligand, base and solvent, we next turned our attention to the efficiency of the cross-coupling reaction as a function of the ratio of the nucleophile **12** versus CuTC. Indeed, a reasonable mechanistic picture[2-6,18] (Scheme 3) of copper-catalyzed/mediated C-N bond forming reaction should take into account that multiple ligations of the *N*-nucleophile **12** to copper(I) can result in unproductive anionic copper complexes such as **14**.[28] The role of phenanthroline is key in the equilibrium between productive **13** and unproductive **14**. Indeed, variation of the **12**/CuTC ratio demonstrated that a maximum yield (80% NMR yield, 71% isolated yield) was reached for a **12**/CuTC ratio of 1.34. In line with previous studies related to Goldberg coupling, a rapid decrease in yield was observed at higher ratios.[29] Taken into account all these parameters, a final short optimization of the reaction conditions (not shown) identified that the best yield was obtained using 2 equivalents of the *N*-nucleophile **7**, CuTC (1.5 eq.), 1,10-phenanthroline (3 eq.) and tBuOK (2.2 eq.) (Table 1, entry 12).



Scheme 3. Yield of **8** as a function of the **12**/CuTC ratio (top) and proposed mechanism (bottom).



Scheme 4. Scope of the formation of *N*-vinyl ynamides **8**.

The scope of this copper(I)-mediated *N*-vinyl ynamide synthesis was then explored, using two types of *N*-vinylcarbamates (**7a,b**) and ten different bromo-alkynes[30] (**11a-j**) (Scheme 4). It was rapidly observed that the reaction possesses some limitations as bromoalkynes substituted by an ester (**11b**), an alkyl- or cycloalkyl (**11c,d**) or a triphenylsilyl (**11e**) led only to traces amount of the desired *N*-vinyl ynamides **8**. On the other hand, (bromoethynyl)triisopropylsilane **11f** led to **8f** in a moderate 43% yield. As already seen in Table 1, (bromoethynyl)benzene **11a** led to 71% of the desired **8a** but subtle structural variations in the alkynyl moiety, such as a para-substitution with a phenyl group (**8g**) or a meta-substitution with a methyl group (**8h**) led to a decrease in yield (30 and 35% respectively), the reason of which being not clear at the moment. para-Chloro substitution was tolerated and delivered the corresponding *N*-vinyl ynamide **8i** in 49%. Switching from a tert-butoxy carbamate to a benzyl carbamate proved detrimental to the yield, as **8j** was isolated in 27% yield only. In all cases and as previously observed (*vide supra*), diyne formation was observed as the only side product.

Although the scope of this new class of ynamide is not as wide as one can expect, their stability over time, even exposed to open air for more than 12 months at room temperature, makes them attractive small-building blocks for further transformation of their two different π-systems, whether in transition-metal catalyzed processes or in pericyclic reaction.

Preliminary hydrometallation and cross-coupling reactions with 2-halopyrimidines as presented in Scheme 1 (D) are underway and will be reported in due course.

Acknowledgments

We thank the CNRS, the Université de Strasbourg (doctoral contract for VLF), the Région Grand-Est (doctoral contract for GD) and the Université de Haute-Alsace. We also thank the referees for their suggestions.

References and notes

1. Duret, G.; Le Fouler, V.; Bisseret, P.; Bizet, V.; Blanchard, N. *Eur. J. Org. Chem.* **2017**, 6816.
2. DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, *110*, 5064.
3. Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed. Engl.* **2010**, *49*, 2840.
4. Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P. *Acc. Chem. Res.* **2014**, *47*, 560.
5. Cook, A. M.; Wolf, C. *Tetrahedron Lett.* **2015**, *56*, 2377.
6. Evano, G.; Blanchard, N.; Compain, G.; Coste, A.; Demmer, C. S.; Gati, W.; Guissart, C.; Heimburger, J.; Henry, N.; Jouvin, K.; Karthikeyan, G.; Laouiti, A.; Lecomte, M.; Martin-Mingot, A.; Métayer, B.; Michelet, B.; Nitelet, A.; Theunissen, C.; Thibaudeau, S.; Wang, J.; Zarca, M.; Zhang, C. *Chem. Lett.* **2016**, *45*, 574.
7. Duret, G.; Quinlan, R.; Martin, R. E.; Bisseret, P.; Neuburger, M.; Gandon, V.; Blanchard, N. *Org. Lett.* **2016**, *18*, 1610.
8. Duret, G.; Quinlan, R.; Yin, B.; Martin, R. E.; Bisseret, P.; Neuburger, M.; Gandon, V.; Blanchard, N. *J. Org. Chem.* **2017**, *82*, 1726.
9. Donnard, M.; Duret, G.; Bisseret, P.; Blanchard, N. *C. R. Chimie* **2017**, *20*, 643.
10. Shirude, P. S.; Shandil, R.; Sadler, C.; Naik, M.; Hosagrahara, V.; Hameed, S.; Shinde, V.; Bathula, C.; Humnabadkar, V.; Kumar, N.; Reddy, J.; Panduga, V.; Sharma, S.; Ambady, A.; Hegde, N.; Whiteaker, J.; McLaughlin, R. E.; Gardner, H.; Madhavapeddi, P.; Ramachandran, V.; Kaur, P.; Narayan, A.; Guptha, S.; Awasthy, D.; Narayan, C.; Mahadevaswamy, J.; Vishwas, K. G.; Ahuja, V.; Srivastava, A.; Prabhakar, K. R.; Bharath, S.; Kale, R.; Ramaiah, M.; Choudhury, N. R.; Sambandamurthy, V. K.; Solapure, S.; Iyer, P. S.; Narayanan, S.; Chatterji, M. *J. Med. Chem.* **2013**, *56*, 9701.
11. Zhang, J.; Yang, Q.; Cross, J. B.; Romero, J. A. C.; Poutsiaka, K. M.; Epie, F.; Bevan, D.; Wang, B.; Zhang, Y.; Chavan, A.; Zhang, X.; Moy, T.; Daniel, A.; Nguyen, K.; Chamberlain, B.; Carter, N.; Shotwell, J.; Silverman, J.; Metcalf, C. A.; Ryan, D.; Lippa, B.; Dolle, R. E. *J. Med. Chem.* **2015**, *58*, 8503.
12. Keller, S. W. *Angew. Chem. Int. Ed. Engl* **1997**, *36*, 247.
13. Navarro, J. A. R.; Barea, E.; Galindo, M. A.; Salas, J. M.; Romero, M. A.; Quirós, M.; Masciocchi, N.; Galli, S.; Sironi, A.; Lippert, B. *J. Solid State Chem.* **2005**, *178*, 2436.
14. Lippert, B.; Sanz Miguel, P. J. *Acc. Chem. Res.* **2016**, *49*, 1537.
15. Kamatani, A.; Overman, L. E. *J. Org. Chem.* **1999**, *64*, 8743.
16. Kamatani, A.; Overman, L. E. *Org. Lett.* **2001**, *3*, 1229.
17. Jiang, L.; Job, G. E.; Klapars, A.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 3667.
18. Evano, G.; Blanchard, N.; Toumi, M. *Chem. Rev.* **2008**, *108*, 3054.
19. Trost, B. M.; Cregg, J. J.; Quach, N. *J. Am. Chem. Soc.* **2017**, *139*, 5133.
20. Weber, F.; Steinlandt, P. S.; Ballmann, M.; Hilt, G. *Synthesis* **2017**, *49*, 440.
21. Hart, R. *Bull. Chem. Soc. Chim. Belg.* **1957**, *66*, 229.
22. Wolfrom, M.; McFadden, G.; Chaney, A. *J. Org. Chem.* **1961**, *26*, 2597.
23. Wieber, G. M.; Hegedus, L. S.; Akermark, B.; Michalson, E. T. *J. Org. Chem.* **1989**, *54*, 4649.
24. am Ende, D. J.; DeVries, K. M.; Clifford, P. J.; Brenek, S. J. *Org. Proc. Res. Dev.* **1998**, *2*, 382.
25. Tu, S.; Zhang, C. *Org. Proc. Res. Dev.* **2015**, *19*, 2045.
26. For these studies, **7b** was obtained from Advanced ChemBlocks Inc, USA.
27. For a related observation in the allenyl series, see: Blanchard, N.; Evano, G.; Guissart, C.; Dolbois, A.; Tresse, C.; Saint-Auret, S. *Synlett* **2016**, *27*, 2575.
28. This copper-mediated system represents one of the best combination of hundreds of runs. All reaction parameters have been systematically varied. For the sake of brevity, only a selection of variations is presented herein. It should be noted that the slow addition of **7** or **11** does not have any impact on the yields nor on the stoichiometry of CuTC and 1,10-phenanthroline.
29. Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78.
30. Bromo-alkynes **11a-d**, substituted by an aromatic motif, were selected first as representative alkynes, although substitution by alkyl and silyl motifs are also of interest.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.tetlet.

Highlights

- The first synthesis of *N*-vinyl ynamides has been demonstrated
- The method is a Cu(I)-mediated process between N-vinyl carbamates and bromoalkynes
- The screening optimization is discussed