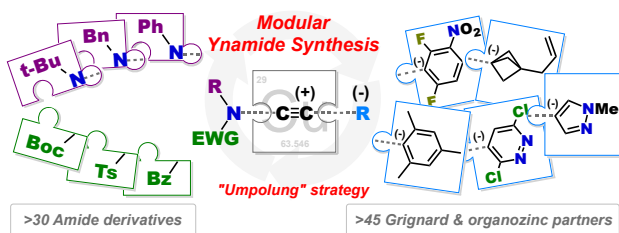


# A general copper-catalyzed synthesis of ynamides from 1,2-dichloroenamides

Steven J. Mansfield,<sup>a</sup> Russell C. Smith,<sup>b</sup> Jonathan R. J. Yong,<sup>a</sup> Olivia L. Garry<sup>a</sup> and Edward A. Anderson\*<sup>a</sup>

<sup>a</sup>Chemistry Research Laboratory, 12 Mansfield Road, Oxford, OX1 3TA, UK.

<sup>b</sup>Janssen PRD, 3210 Merryfield Row, San Diego, CA 92121, USA.



**ABSTRACT:** Ynamides are accessed via copper-catalyzed coupling of Grignard or organozinc nucleophiles with chloroynamides, formed in situ from 1,2-dichloroenamides. The reaction exhibits broad substrate scope, is readily scaled, and overcomes typical limitations in ynamide synthesis such as the use of ureas, carbamates, and bulky or aromatic amide derivatives. This modular approach contrasts with previous routes by installing both the *N*- and *C*-substituents of the ynamide as nucleophilic components.

Ynamides (**1**, Figure 1) are valuable building blocks in organic synthesis.<sup>1,2</sup> As precursors to an array of reactive intermediates,<sup>3</sup> they offer access to a wide variety of azacycles<sup>4</sup> and are also of interest in medicinal chemistry.<sup>5</sup> The prevailing strategy for ynamide synthesis involves copper-catalyzed C–N coupling of an amide nucleophile with an alkyne,<sup>6</sup> haloalkyne<sup>7</sup> or dibromoalkene<sup>8</sup> electrophile.<sup>9</sup> Despite the utility of these methods for substrates such as unhindered sulfonamides and oxazolidinones, other classes of ynamide are far less accessible. Acyclic amides, carbamates and ureas are challenging coupling partners<sup>10</sup> as are *N*-aryl and sterically-hindered amides, which generally require prolonged heating to achieve even modest conversions.<sup>7c, 11</sup> The use of alkynylidonium triflates as electrophilic coupling partners can overcome some of these restrictions,<sup>10a, 12</sup> but a general solution remains elusive for these substrates, preventing their wider exploitation in ynamide chemistry.

We targeted an alternative route to ynamides in which the disconnection point is shifted from C–N to C–C bond

formation. All previous examples of this tactic have employed nucleophilic ynamide components (for example, in reactions of metalated ynamides with *C*-centered electrophiles,<sup>13</sup> or cross-coupling of terminal ynamides,<sup>14</sup> which can be complicated by ynamide homodimerization). In contrast, the coupling of *C*-centered nucleophiles with ynamide electrophiles is without precedent, but is an appealing approach given the ready availability of carbon-based organometallics.

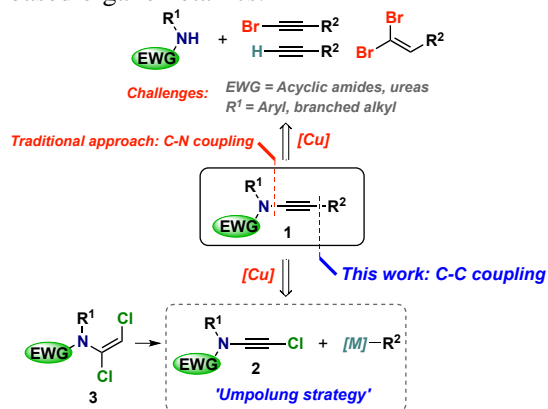


Figure 1. 'Traditional' and 'umpolung' copper-catalyzed ynamide formation.

In our previous work, chloroynamides **2** were identified as intermediates en route to lithiated ynamides from 1,2-dichloroenamides **3**.<sup>13f</sup> We questioned whether these substrates could instead serve as the electrophilic component in C–C coupling, albeit only a single report exists on chloroalkyne cross-coupling in general.<sup>15</sup> Here we describe the realization of this *C*-nucleophile coupling route to ynamides, a method that displays broad substrate scope and overcomes previous synthetic limitations such as

high steric hindrance on either the *N*- or *C*-component, and enables the synthesis of acyclic urea-, carbamate-, and amide-ynamides.

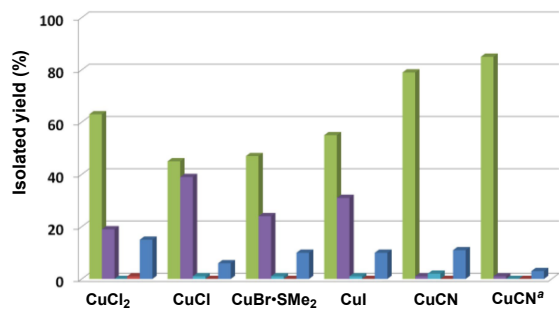
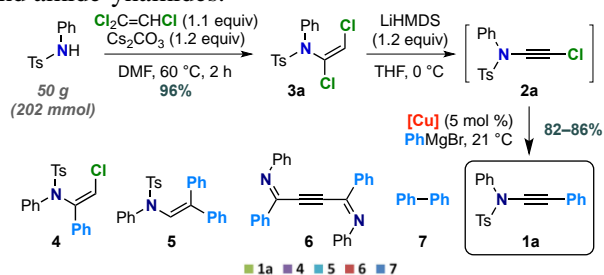


Figure 2. Optimization of the conversion of dichloroenamide **3a** to ynamide **1a**. <sup>a</sup> Optimized conditions: PhMgBr (1.03 equiv), [CuCN•2P(OMe)<sub>3</sub>] (1.25 mol %), TBME (0.34 M), 21 °C, 10 min, 82–86%.

To initiate studies, dichloroenamide **3a** (Figure 2) was prepared on 0.2 mol scale (66 g, 96%) from *N*-tosylaniline using our reported conditions.<sup>13f</sup> Reaction of **3a** with 1.2 equiv of LiHMDS in THF enabled smooth conversion to chloroynamide **2a**. This could be isolated in good yield,<sup>16</sup> however for the purposes of ynamide synthesis it proved equally convenient to perform the subsequent

coupling in situ. A number of copper salts (e.g. CuCl, CuBr•SMe<sub>2</sub>, CuI, CuCl<sub>2</sub>, CuCN) were screened as catalysts in the reaction with PhMgBr (1.2 equiv),<sup>15–16</sup> with all reactions reaching completion in 10–15 minutes at 21 °C. However, alongside the desired ynamide **1a**, most also afforded (*Z*)-chloroenamide **4** as a significant side product (19–39%), along with small amounts of **5–7**.<sup>17</sup> CuCN<sup>18</sup> alone delivered **1a** in high yield and selectivity (79%, **1a**:**4** >20:1). The inclusion of trimethyl phosphite (10 mol %) minimized the formation of biphenyl **7**,<sup>19</sup> while decreasing the amount of PhMgBr to 1.03 equiv suppressed the formation of **6**. TBME proved a superior reaction solvent, and finally the catalyst loading could be reduced to 1.25 mol % (2.5 mol % P(OMe)<sub>3</sub>) without detriment. Under these optimized conditions, ynamide **2a** was isolated in 82–86% yield over five runs.<sup>20</sup>

These conditions were broadly applicable to couplings with both Grignard and organozinc reagents (Figure 3a), with 38 organometallic coupling partners spanning a range of electron-rich and electron-poor aromatics, and 1°/2°/3° alkyl groups, being successfully converted to ynamides on reaction with **3a**. Amide, ester, nitrile and nitro functionalities were tolerated, (**1c**, **1p–1s**), as were potentially reactive halides (**1h**, **1n**), and hindered nucleophiles (**1f–1i**). A range of heterocyclic Grignards also underwent efficient couplings (**1t**, **1w–1ab**), while the formation of ynamide **1al** demonstrates an interesting entry to alkynyl bicyclo[1.1.1]pentanes.<sup>21</sup> Organozinc partners proved useful where Grignard reagents were unavailable or unstable, including several heteroaromatics (**1u**, **1v** and **1ac**), albeit these substrates required extended reaction times (12 h versus 10–30 min for Grignard coupling). For many of these examples, the avoidance of prolonged heating (as required for challenging ynamide C–N

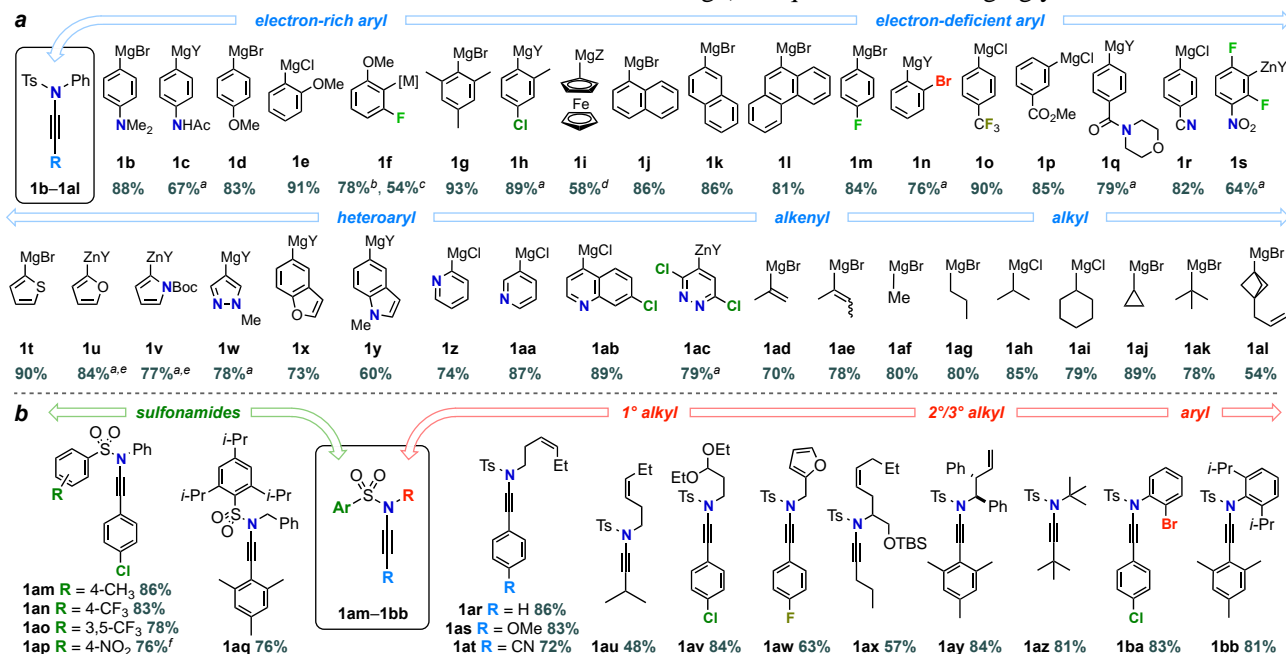


Figure 3. Synthesis of sulfonamide ynamides. **a.** Scope of organometallic coupling partners. **b.** Scope of sulfonamide. All reactions were conducted on 500 mg (1.46 mmol) scale using RMgX (1.03 equiv), [CuCN•2P(OMe)<sub>3</sub>] (1.25 mol %), TBME

(0.34 M), 21 °C, 10 min–1 h, unless otherwise stated. <sup>a</sup> Y = Cl·LiCl; <sup>b</sup> ArMgBr·LiBr was used; <sup>c</sup> ArZnCl·LiCl was used; <sup>d</sup> Z = TMP·LiCl; <sup>e</sup> TMEDA (1.3 equiv) was added; <sup>f</sup> Ar<sub>2</sub>Zn was used.

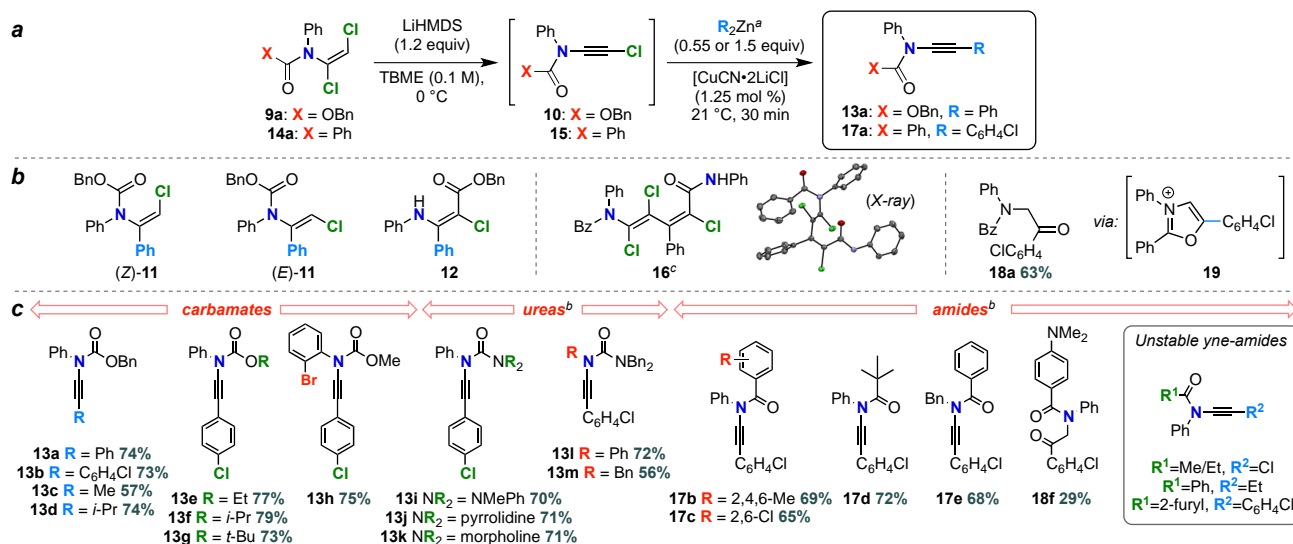
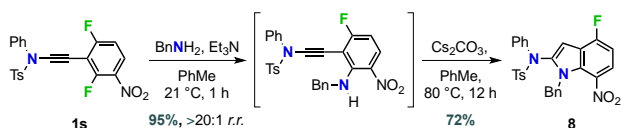


Figure 4. **a.** Synthesis of carbonyl ynamides. **b.** Reaction byproducts. **c.** Reaction scope. <sup>a</sup> Ar<sub>2</sub>Zn prepared using a 2:1 ratio of ArMgBr (in toluene or Et<sub>2</sub>O) and ZnCl<sub>2</sub>, Ar = Ph or 4-ClC<sub>6</sub>H<sub>4</sub>; <sup>b</sup> TMEDA (10 equiv) was added. The crystal molecular structure of **16** is displayed at 50% probability;<sup>15</sup> hydrogen atoms are omitted for clarity.

couplings) and the use of readily available Grignard / organozinc reagents (which obviates the need to pre-form haloalkene / alkyne coupling partners) enhances the range of functionality that can be introduced, and affords opportunities to develop novel ynamide reactivity. For instance, tolerance of nitro and fluoro substituents in the formation of ynamide **1s** enabled a concise synthesis of aminoindole **8** (Scheme 1) via S<sub>N</sub>Ar / cyclization.

### Scheme 1. Synthesis of an aminoindole from ynamide **1s**.



With the scope of the organometallic partner established, we next tested a selection of *N*-sulfonyl dichloroenamides to explore variation of the sulfonamide, and the steric / functional group tolerance of the nitrogen substituent (Figure 3b). Efficient reactions were observed irrespective of the nature of either the sulfonyl motif (**1am**–**1aq**) or the nitrogen atom substituent (**1ar**–**1bb**); particularly notable are ynamides **1aq**, **1ay**, **1az** and **1bb** featuring bulky substituents on both the nitrogen and alkyne (76–84%), and electron-deficient sulfonamides **1ao** and **1ap** (78% and 76%).

Having developed a general approach to sulfonyl ynamides, we decided to challenge the robustness of the transformation by targeting acyclic carbonyl ynamides, which have otherwise proven difficult to make. Carbamate dichloroamide **9a**, which was readily prepared on multigram scale (42 mmol / 12 g, 89%), was used as a test substrate (Figure 4a). Chloroynamide formation (**10**) was achieved in 80–85% yield, however its coupling with

PhMgBr led to significant amounts of chloroenamides (*Z*- and (*E*)-**11** and (*E*)-chloroester **12**, in addition to the desired ynamide **13a** (Figure 4b). These byproducts likely arise from competing addition of the Grignard to the intermediate chloroynamide,<sup>16</sup> but could be suppressed through the use of diarylzinc reagents (prepared by salt metathesis of the Grignard reagent with zinc(II) chloride). The addition of TMEDA was also found to be beneficial for the formation of urea-ynamides, and under these re-optimized conditions, a range of carbamate and urea dichloroenamides underwent smooth conversion to ynamides **13a–m** (Figure 4c). These couplings were complete within 30 minutes – a timescale that compares favorably with other carbonyl-ynamide synthesis routes – with both diaryl and dialkylzinc reagents proving effective.<sup>16</sup>

Acyclic amide substrates presented a significantly greater challenge, with both reaction intermediates and products displaying heightened reactivity compared to other derivatives. For example, the conversion of dichloroamide **14a** to chloroynamide **15** was accompanied by the unexpected formation of **16** (Figure 4b), which likely arises from reaction of **15** with the lithiated dichloroamide.<sup>13</sup> This side reaction, which was not observed with any other substrate class, could be minimized by conducting the elimination at room temperature, enabling rapid coupling of chloroynamides to give amide-ynamides **17b–e** in good yields (Figure 4c).

In certain cases, the amide-ynamide products were prone to hydration upon concentration, or during chromatography on neutralized silica gel, giving  $\delta$ -ketoamides (**18a/f**). This remarkable  $\beta$ -hydration of the ynamide may be explained by a 5-*endo-dig* cyclization<sup>22</sup> to oxazolium ion **19** and subsequent hydrolysis, and was particularly

apparent for *N*-phenylamide derivatives.<sup>23</sup> In contrast, *N*-benzyl benzoyl ynamide **17e** was comparatively stable (68%), as were amide-ynamides featuring bulky substituents (**17b–d**) where adoption of the conformation required for cyclization to the oxazolium ion may be disfavored. It is surprising that these amide-ynamides are somewhat fragile, given that equivalent carbamate- and urea-ynamides are not – for example, urea **131** withstood heating in ethanol during recrystallization. Although amide-ynamides have been prepared sporadically in the past,<sup>10</sup> it is clear that the nature of the electron-withdrawing group, and the second nitrogen substituent, are very important in modulating the stability and reactivity of these compounds.

In summary, we have established a new strategy to access ynamides from readily available dichloroenamides, in which intermediate chloroynamides act as electrophilic components in coupling with carbon-based nucleophiles. The reaction shows broad scope, accommodating a wide range of Grignard and organozinc reagents, and tolerating a diverse range of functionality, electronic character, and steric bulk on both coupling partners. This chemistry also offers a general route to acyclic carbonyl-based ynamides, and affords valuable insight into their stability and reactivity. In overcoming many previous limitations, this method provides a wealth of opportunities for the development of new ynamide chemistry.

## ASSOCIATED CONTENT

**Supporting Information.** Full optimization details, experimental procedures, copies of <sup>1</sup>H and <sup>13</sup>C NMR spectra and crystallographic data. This material is available free of charge via the Internet at <http://pubs.acs.org>.

## AUTHOR INFORMATION

### Corresponding Author

[edward.anderson@chem.ox.ac.uk](mailto:edward.anderson@chem.ox.ac.uk)

## ACKNOWLEDGMENT

S.J.M. is grateful for support from an Oxford R. E. Jones Scholarship, and the EPSRC Centre for Doctoral Training in Synthesis for Biology and Medicine (EP/L015838/1), generously supported by AstraZeneca, Diamond Light Source, Defence Science and Technology Laboratory, Evotec, GlaxoSmithKline, Janssen, Novartis, Pfizer, Syngenta, Takeda, UCB and Vertex. R.C.S. thanks the SBM CDT for the industrial partnership. E.A.A. thanks the EPSRC for additional support (EP/M019195/1).

## Notes

The authors declare no competing financial interest.

## REFERENCES

(1) (a) For selected recent examples, see: Prabagar, B.; Mallick, R. K.; Prasad, R.; Gandon, V.; Sahoo, A. K., Umpolung Reactivity of Ynamides: An Unconventional [1,3]-Sulfonyl and [1,5]-Sulfinyl Migration Cascade. *Angew. Chem. Int. Ed.* **2019**, *58*, 2365; (b) Dutta, S.; Mallick, R. K.; Prasad, R.; Gandon, V.; Sahoo, A. K., Alkyne

Versus Ynamide Reactivity: Regioselective Radical Cyclization of Yne-Ynamides. *Angew. Chem. Int. Ed.* **2019**, *58*, 2289; (c) Kaldre, D.; Klose, I.; Maulide, N., Stereodivergent synthesis of 1,4-dicarbonyls by traceless charge-accelerated sulfonium rearrangement. *Science* **2018**, *361*, 664; (d) Marien, N.; Reddy, B. N.; De Vleeschouwer, F.; Goderis, S.; Van Hecke, K.; Verniest, G., Metal-Free Cyclization of ortho-Nitroaryl Ynamides and Ynamines towards Spiropseudoindoxyls. *Angew. Chem. Int. Ed.* **2018**, *57*, 5660; (e) Gao, Y.; Wu, G.; Zhou, Q.; Wang, J., Palladium-Catalyzed Oxygenative Cross-Coupling of Ynamides and Benzyl Bromides by Carbene Migratory Insertion. *Angew. Chem.* **2018**, *130*, 2746; (f) Baldassari, L. L.; de la Torre, A.; Li, J.; Lüdtke, D. S.; Maulide, N., Ynamide Preactivation Allows a Regio- and Stereoselective Synthesis of  $\alpha,\beta$ -Disubstituted Enamides. *Angew. Chem. Int. Ed.* **2017**, *56*, 15723; (g) Siva Reddy, A.; Kumara Swamy, K. C., Ethanol as a Hydrogenating Agent: Palladium-Catalyzed Stereoselective Hydrogenation of Ynamides to Give Enamides. *Angew. Chem. Int. Ed.* **2017**, *56*, 6984; (h) Zhou, B.; Li, L.; Zhu, X.-Q.; Yan, J.-Z.; Guo, Y.-L.; Ye, L.-W., Yttrium-Catalyzed Intramolecular Hydroalkoxylation/Claisen Rearrangement Sequence: Efficient Synthesis of Medium-Sized Lactams. *Angew. Chem. Int. Ed.* **2017**, *56*, 4015; (i) Patil, D. V.; Kim, S. W.; Nguyen, Q. H.; Kim, H.; Wang, S.; Hoang, T.; Shin, S., Brønsted Acid Catalyzed Oxygenative Bimolecular Friedel–Crafts-type Coupling of Ynamides. *Angew. Chem. Int. Ed.* **2017**, *56*, 3670; (j) Shen, W.-B.; Xiao, X.-Y.; Sun, Q.; Zhou, B.; Zhu, X.-Q.; Yan, J.-Z.; Lu, X.; Ye, L.-W., Highly Site Selective Formal [5+2] and [4+2] Annulations of Isoxazoles with Heterosubstituted Alkynes by Platinum Catalysis: Rapid Access to Functionalized 1,3-Oxazepines and 2,5-Dihydropyridines. *Angew. Chem. Int. Ed.* **2017**, *56*, 605; (k) Nairoukh, Z.; Kumar, G. G. K. S. N.; Minko, Y.; Marek, I., Enantioselective allylic alkylation of stereodefined polysubstituted copper enolates as an entry to acyclic quaternary carbon stereocentres. *Chem. Sci.* **2017**, *8*, 627; (l) For reviews, see: Evano, G.; Blanchard, N.; Compain, G.; Coste, A.; Demmer, C. S.; Gati, W.; Guissart, C.; Heimbürger, 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., A Journey in the Chemistry of Ynamides: From Synthesis to Applications. *Chem. Lett.* **2016**, *45*, 574; (m) Zhang, Y.; DeKorver, K. A.; Li, H. Y.; Lohse, A. G.; Hayashi, R.; Lu, Z. J.; Hsung, R. P., Ynamides: A Modern Functional Group for the New Millennium. *Chem. Rev.* **2010**, *110*, 5064; (n) Evano, G.; Coste, A.; Jouvin, K., Ynamides: Versatile Tools in Organic Synthesis. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840.

(2) (a) For recent ynamide chemistry from our group, see: Mansfield, S. J.; Christensen, K. E.; Thompson, A. L.; Ma, K.; Jones, M. W.; Mekareeya, A.; Anderson, E. A., Copper-Catalyzed Synthesis and Applications of Yndiamides. *Angew. Chem. Int. Ed.* **2017**, *56*, 14428; (b) Mekareeya, A.; Walker, P. R.; Couce-Rios, A.; Campbell, C. D.; Steven, A.; Paton, R. S.; Anderson, E. A., Mechanistic Insight into Palladium-Catalyzed Cycloisomerization: A Combined Experimental and Theoretical Study. *J. Am. Chem. Soc.* **2017**, *139*, 10104; (c) Straker, R. N.; Peng, Q.; Mekareeya, A.; Paton, R. S.; Anderson, E. A., Computational ligand design in enantio- and diastereoselective ynamide [5+2] cycloisomerization. *Nat. Commun.* **2016**, *7*, 10109.

(3) (a) Keteniminium ions: Evano, G.; Lecomte, M.; Thilmany, P.; Theunissen, C., Keteniminium Ions: Unique and Versatile Reactive Intermediates for Chemical Synthesis. *Synthesis* **2017**, *49*, 3183; (b) Vinyl anion equivalents: Evano, G.; Michelet, B.; Zhang, C., The anionic chemistry of ynamides: A review. *Comptes Rendus Chimie* **2017**, *20*, 648; (c) Minko, Y.; Pasco, M.; Lercher, L.; Botoshansky, M.; Marek, I., Forming all-carbon quaternary stereogenic centres in acyclic systems from alkynes. *Nature* **2012**, *490*, 522; (d) Das, J. P.; Chechik, H.; Marek, I., A unique approach to aldol products for the creation of all-carbon quaternary stereocentres. *Nat. Chem.* **2009**, *1*, 128; (e) Carbene equivalents: Mukherjee, A.; Dateer, R. B.; Chaudhuri, R.; Bhunia, S.; Karad, S. N.; Liu, R.-S., Gold-Catalyzed 1,2-Difunctionalizations of Aminoalkynes Using Only N- and O-Containing Oxidants. *J. Am. Chem. Soc.* **2011**, *133*, 15372; (f) Liu, R.; Winston-McPherson, G. N.; Yang, Z.-Y.; Zhou, X.; Song, W.; Guzei, I. A.; Xu, X.; Tang, W., Generation of Rhodium(I) Carbenes from Ynamides and Their Reactions with Alkynes and Alkenes. *J. Am.*

- Chem. Soc.* **2013**, *135*, 8201; (g) Adcock, H. V.; Chatzopoulou, E.; Davies, P. W., Divergent C–H Insertion–Cyclization Cascades of N-Allyl Ynamides. *Angew. Chem. Int. Ed.* **2015**, *54*, 15525.
- (4) (a) Wang, X.-N.; Yeom, H.-S.; Fang, L.-C.; He, S.; Ma, Z.-X.; Kedrowski, B. L.; Hsung, R. P., Ynamides in ring forming transformations. *Acc. Chem. Res.* **2014**, *47*, 560; (b) Selected examples: Saito, N.; Ichimaru, T.; Sato, Y., Total Synthesis of (–)-Herbindoles A, B, and C via Transition-Metal-Catalyzed Intramolecular [2 + 2 + 2] Cyclization between Ynamide and Diynes. *Org. Lett.* **2012**, *14*, 1914; (c) Mak, X. Y.; Crombie, A. L.; Danheiser, R. L., Synthesis of Polycyclic Benzofused Nitrogen Heterocycles via a Tandem Ynamide Benzannulation/Ring-Closing Metathesis Strategy. Application in a Formal Total Synthesis of (+)-FR900482. *J. Org. Chem.* **2011**, *76*, 1852; (d) Alayrac, C.; Schollmeyer, D.; Witulski, B., First total synthesis of antiostatin A(1), a potent carbazole-based naturally occurring antioxidant. *Chem. Commun.* **2009**, 1464; (e) Campbell, C. D.; Greenaway, R. L.; Holton, O. T.; Chapman, H. A.; Anderson, E. A., Palladium-catalyzed cyclization of bromoenamides to tricyclic azacycles: synthesis of trikentrin-like frameworks. *Chem. Commun.* **2014**, *50*, 5187.
- (5) (a) Prochnow, T.; Maroneze, A.; Back, D. F.; Jardim, N. S.; Nogueira, C. W.; Zeni, G., Synthesis and anticholinesterase activity of 2-substituted-N-alkynylindoles. *Org. Biomol. Chem.* **2018**, *16*, 7926; (b) Laroche, C.; Li, J.; Kerwin, S. M., Cytotoxic 1,2-Dialkynylimidazole-Based Aza-Enediyne: Aza-Bergman Rearrangement Rates Do Not Predict Cytotoxicity. *J. Med. Chem.* **2011**, *54*, 5059; (c) Huang, W.-S.; Metcalf, C. A.; Sundaramoorthi, R.; Wang, Y.; Zou, D.; Thomas, R. M.; Zhu, X.; Cai, L.; Wen, D.; Liu, S.; Romero, J.; Qi, J.; Chen, I.; Banda, G.; Lentini, S. P.; Das, S.; Xu, Q.; Keats, J.; Wang, F.; Wardwell, S.; Ning, Y.; Snodgrass, J. T.; Broudy, M. I.; Russian, K.; Zhou, T.; Commadore, L.; Narasimhan, N. I.; Mohemmad, Q. K.; Iulucci, J.; Rivera, V. M.; Dalgarno, D. C.; Sawyer, T. K.; Clackson, T.; Shakespeare, W. C., Discovery of 3-[2-(Imidazo[1,2-b]pyridazin-3-yl)ethynyl]-4-methyl-N-{4-[(4-methylpiperazin-1-yl)methyl]-3-(trifluoromethyl)phenyl}benzamide (AP24534), a Potent, Orally Active Pan-Inhibitor of Breakpoint Cluster Region-Abelson (BCR-ABL) Kinase Including the T315I Gatekeeper Mutant. *J. Med. Chem.* **2010**, *53*, 4701.
- (6) (a) Hamada, T.; Ye, X.; Stahl, S. S., Copper-catalyzed aerobic oxidative amidation of terminal alkynes: Efficient synthesis of ynamides. *J. Am. Chem. Soc.* **2008**, *130*, 833; (b) Jouvin, K.; Heimbürger, J.; Evano, G., Click-alkynylation of N- and P-nucleophiles by oxidative cross-coupling with alkynylcopper reagents: a general synthesis of ynamides and alkynylphosphonates. *Chem. Sci.* **2012**, *3*, 756.
- (7) (a) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L. C.; Douglas, C. J., A copper-catalyzed C–N bond formation involving sp-hybridized carbons. A direct entry to chiral ynamides via N-alkynylation of amides. *J. Am. Chem. Soc.* **2003**, *125*, 2368; (b) Dunetz, J. R.; Danheiser, R. L., Copper-mediated N-alkynylation of carbamates, ureas, and sulfonamides. A general method for the synthesis of ynamides. *Org. Lett.* **2003**, *5*, 4011; (c) Zhang, X.; Zhang, Y.; Huang, J.; Hsung, R. P.; Kurtz, K. C. M.; Oppenheimer, J.; Petersen, M. E.; Sagamanova, I. K.; Shen, L.; Tracey, M. R., Copper(II)-catalyzed amidations of alkynyl bromides as a general synthesis of ynamides and Z-enamides. An intramolecular amidation for the synthesis of macrocyclic ynamides. *J. Org. Chem.* **2006**, *71*, 4170; (d) Yao, B.; Liang, Z.; Niu, T.; Zhang, Y., Iron-Catalyzed Amidation of Alkynyl Bromides: A Facile Route for the Preparation of Ynamides. *J. Org. Chem.* **2009**, *74*, 4630.
- (8) (a) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G., Copper-Mediated Coupling of 1,1-Dibromo-1-alkenes with Nitrogen Nucleophiles: A General Method for the Synthesis of Ynamides. *Angew. Chem. Int. Ed.* **2009**, *48*, 4381; (b) Yang, Y.; Zhang, X.; Liang, Y., Copper-catalyzed coupling of 1,2-dibromo-1-styrenes with sulfonamides for the preparation of ynamides. *Tetrahedron Lett.* **2012**, *53*, 6557.
- (9) (a) For other selected methods, see: Waldecker, B.; Kraft, F.; Golz, C.; Alcarazo, M., 5-(Alkynyl)dibenzothiophenium Triflates: Sulfur-Based Reagents for Electrophilic Alkynylation. *Angew. Chem. Int. Ed.* **2018**, *57*, 12538; (b) Tu, Y.; Zeng, X.; Wang, H.; Zhao, J., A Robust One-Step Approach to Ynamides. *Org. Lett.* **2018**, *20*, 280; (c) For a review and other methods prior to 2013, see: Evano, G.; Jouvin, K.; Coste, A., General Amination Reactions for the Synthesis of Ynamides. *Synthesis* **2013**, *45*, 17.
- (10) (a) Witulski, B.; Stengel, T., N-functionalized 1-alkynylamides: New building blocks for transition metal mediated inter- and intramolecular [2+2+1] cycloadditions. *Angew. Chem. Int. Ed.* **1998**, *37*, 489; (b) Marion, F.; Courillon, C.; Malacria, M., Radical Cyclization Cascade Involving Ynamides: An Original Access to Nitrogen-Containing Heterocycles. *Org. Lett.* **2003**, *5*, 5095; (c) Demmer, C. S.; Evano, G., A Simple Entry to Yne-amides from Yne-oxazolidinones. *Synlett* **2016**, *27*, 1873.
- (11) (a) Jouvin, K.; Coste, A.; Bayle, A.; Legrand, F.; Karthikeyan, G.; Tadiparthi, K.; Evano, G., Copper-Mediated Selective Cross-Coupling of 1,1-Dibromo-1-alkenes and Heteronucleophiles: Development of General Routes to Heterosubstituted Alkynes and Alkenes. *Organometallics* **2012**, *31*, 7933; (b) For a recent example, see: Alexander, J. R.; Cook, M. J., Formation of Ketanimines via the Palladium-Catalyzed Decarboxylative  $\pi$ -Allylic Rearrangement of N-Alloc Ynamides. *Org. Lett.* **2017**, *19*, 5822.
- (12) Witulski, B.; Stengel, T., Rhodium(I)-Catalyzed [2+2+2] Cycloadditions with N-Functionalized 1-Alkynylamides: A Conceptually New Strategy for the Regiospecific Synthesis of Substituted Indolines. *Angew. Chem. Int. Ed.* **1999**, *38*, 2426.
- (13) (a) Brückner, D., Synthesis of ynamides from formamides. *Tetrahedron* **2006**, *62*, 3809; (b) Rodríguez, D.; Martínez-Esperón, M. F.; Castedo, L.; Saá, C., Synthesis of Disubstituted Ynamides from  $\beta,\beta$ -Dichloroenamides and Electrophiles. *Synlett* **2007**, *2007*, 1963; (c) Wang, X.-N.; Hsung, R. P.; Qi, R.; Fox, S. K.; Lv, M.-C., A Highly Stereoselective Addition of Lithiated Ynamides to Ellman–Davis Chiral N-tert-Butanesulfinyl Imines. *Org. Lett.* **2013**, *15*, 2514; (d) Wang, X.-N.; Winston-McPherson, G. N.; Walton, M. C.; Zhang, Y.; Hsung, R. P.; DeKorver, K. A., Synthesis of Cyclopentenimines from N-Allyl Ynamides via a Tandem Aza-Claisen Rearrangement–Carbocyclization Sequence. *J. Org. Chem.* **2013**, *78*, 6233; (e) Zhang, P.; Cook, A. M.; Liu, Y.; Wolf, C., Copper(I)-Catalyzed Nucleophilic Addition of Ynamides to Acyl Chlorides and Activated N-Heterocycles. *J. Org. Chem.* **2014**, *79*, 4167; (f) Mansfield, S. J.; Campbell, C. D.; Jones, M. W.; Anderson, E. A., A robust and modular synthesis of ynamides. *Chem. Commun.* **2015**, *51*, 3316; (g) Gillie, A. D.; Jannapu Reddy, R.; Davies, P. W., Efficient and Flexible Synthesis of Highly Functionalised 4-Amino-oxazoles by a Gold-Catalysed Intermolecular Formal [3+2] Dipolar Cycloaddition. *Adv. Synth. Catal.* **2016**, *358*, 226; (h) Cook, A. M.; Wolf, C., Efficient Access to Multifunctional Trifluoromethyl Alcohols through Base-Free Catalytic Asymmetric C–C Bond Formation with Terminal Ynamides. *Angew. Chem. Int. Ed.* **2016**, *55*, 2929; (i) Moskowitz, M.; Wolf, C., Catalytic Enantioselective Ynamide Additions to Isatins: Concise Access to Oxindole Alkaloids. *Angew. Chem.* **2019**, *131*, 3440.
- (14) (a) Tracey, M. R.; Zhang, Y.; Frederick, M. O.; Mulder, J. A.; Hsung, R. P., Terminal ynamide Sonogashira coupling. *Org. Lett.* **2004**, *6*, 2209; (b) Martínez-Esperón, M. F.; Rodríguez, D.; Castedo, L.; Saá, C., Coupling and cycloaddition of ynamides: homo- and Negishi coupling of tosylynamides and intramolecular [4+2] cycloaddition of N-(o-ethynyl)phenyl ynamides and arylynamides. *Tetrahedron* **2006**, *62*, 3843; (c) Dooleweerd, K.; Ruhland, T.; Skrydstrup, T., Application of Ynamides in the Synthesis of 2-Amidoindoles. *Org. Lett.* **2009**, *11*, 221.
- (15) Cahiez, G.; Gager, O.; Buendia, J., Copper-Catalyzed Cross-Coupling of Alkyl and Aryl Grignard Reagents with Alkynyl Halides. *Angew. Chem. Int. Ed.* **2010**, *49*, 1278.
- (16) See the Supporting Information for details.
- (17) Single crystal X-ray diffraction data were collected for 15 compounds, see the Supplementary Information for details. CCDC 1895057–1895071 contain the crystallographic data for this paper.
- (18) Levin, A.; Basheer, A.; Marek, I., Regiodivergent Carbometalation Reactions of Ynol Ether Derivatives. *Synlett* **2010**, 329.
- (19) Dohle, W.; Lindsay, D. M.; Knochel, P., Copper-Mediated Cross-Coupling of Functionalized Arylmagnesium Reagents with Functionalized Alkyl and Benzylic Halides. *Org. Lett.* **2001**, *3*, 2871.

(20) These experiments used pre-dried solvents and freshly prepared LiHMDS under an inert atmosphere. The direct use of commercial reagents (anhydrous TBME, LiHMDS (1.0 M in TBME)), without additional precautions gave 79% of **1a**.

(21) (a) Kokhan, S. O.; Valter, Y. B.; Tymtsunik, A. V.; Komarov, I. V.; Grygorenko, O. O., Bicyclo[1.1.1]pentane-Derived Building Blocks for Click Chemistry. *Eur. J. Org. Chem.* **2017**, 6450; (b) Hazra, A.; Lee, M. T.; Chiu, J. F.; Lalic, G., Photoinduced Copper-Catalyzed Coupling of Terminal Alkynes and Alkyl Iodides. *Angew. Chem. Int. Ed.* **2018**, *57*, 5492.

(22) Ung, G.; Mendoza-Espinosa, D.; Bertrand, G., Ynamides: stable ligand equivalents of unstable oxazol-4-ylidenes (novel mesoionic carbenes). *Chem. Commun.* **2012**, *48*, 7088.

(23) Trace copper may be responsible for this degradation. See: Wilkerson-Hill, S. M.; Yu, D.; Painter, P. P.; Fisher, E. L.; Tantillo, D. J.; Sarpong, R.; Hein, J. E., Mechanism of a No-Metal-Added Heterocycloisomerization of Alkynylcyclopropylhydrazones: Synthesis of Cycloheptane-Fused Aminopyrroles Facilitated by Copper Salts at Trace Loadings. *J. Am. Chem. Soc.* **2017**, *139*, 10569.