

Discussion Addendum for:

Synthesis of Ynamides by Copper-Mediated Coupling of 1,1-Dibromo-1-alkenes with Nitrogen Nucleophiles. Preparation of 4-Methyl-*N*-(2-phenylethynyl)-*N*-(phenylmethyl)benzenesulfonamide

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Over the past decades, ynamides have clearly emerged as versatile and useful building blocks in chemical synthesis.² The electron-donating

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character of the nitrogen atom strongly polarizes the carbon – carbon triple bond, which can furnish remarkable levels of reactivity and chemo- and/or stereoselectivities. Although highly reactive, ynamides are also fairly stable thanks to the presence of an electron-withdrawing group on the nitrogen atom which provides increased stability compared to highly sensitive and easily hydrolyzable ynamines. The electron-withdrawing group can also act as a directing group, a chiral auxiliary and even participate in the reaction. As a consequence, tremendous developments have been reported recently and numerous elegant processes have been developed based on the unique chemistry of these nitrogen-substituted alkynes. Overall, ynamides provide with unique opportunities not only for the introduction of nitrogencontaining motifs into organic molecules but also for the generation of otherwise hardly accessible highly reactive intermediates.^{2c,3} All these developments have been made possible by major breakthroughs for their preparation reported since the beginning of the 21st century. Indeed, efficient and robust methods reported over the past twenty years paved the way for the use of ynamides in chemical synthesis: they will be briefly overviewed in the following paragraphs.

1. Synthesis of Ynamides: Copper as the General Solution

As already discussed in a previous review,⁴ the first routes for the synthesis of ynamides were mostly based on elimination reactions from haloenamides, on the isomerization of propargylamines or on the amination of hypervalent iodonium salts. While giving access to some ynamides, these methods were far too limited in terms of substrate scope and relied on rather harsh reaction conditions, which clearly hampered the synthesis and use of ynamides in organic synthesis. Since 2003, this problem has been tackled by the use of copper catalysis, which clearly had a deep impact on the synthesis of ynamides and contributed to unleashing their full potential as versatile buildings blocks in chemical synthesis.⁵

Indeed, various processes have been reported for the synthesis of a large variety of ynamides via copper-catalyzed cross couplings between a nitrogen nucleophile and an alkynylating agent, involving formation of the N–C \equiv C bond (Figure 1). Among all alkynylating agents used, one can cite alkynyl bromides^{6,7} and chlorides,⁸ 1,1-dibromo-1-alkenes^{6v,9} and other dihalo-alkenes,^{8,10} alkynyl(triaryl)bismuthonium salts,¹¹ as well as an alkynylboronate ester.¹² Additional routes have also been reported, based on

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oxidative copper-catalyzed cross couplings, which are quite efficient and usually take place under mild conditions. Alkynylating agents such as terminal alkynes,^{6t,13} alkynyltrifluoroborates,¹⁴ propiolic acids¹⁵ and copper acetylides have been used in such processes.¹⁶

In addition to copper-based processes featuring formation of the N-C=C bond, other strategies have also been reported over the past ten years and enable the synthesis of ynamides with variable levels of efficiency. These include elimination reactions,17 transition-metal-free reactions with hypervalent iodonium¹⁸ and (alkynyl)dibenzothiophenium¹⁹ salts or functionalization of terminal ynamides,²⁰ mostly through metalation²¹ and or Glaser²³ cross couplings. More recently, Sonogashira²² 1.2dichloroenamides, readily prepared from trichloroethylene, were shown to be convenient starting materials for the stepwise preparation of a wide variety of ynamides via a sequence involving a base-promoted elimination followed by reaction with an electrophile or an organometallic reagent in the presence of a copper catalyst.²⁴ Finally, some more specific processes have also been reported, including the opening of yne-oxazolidinones to form yneamides,²⁵ the addition of terminal alkynes to diazodicarboxylates to form yne-hydrazides²⁶ or the peculiar example of a base-promoted opening of an oxazolium salt to form the corresponding yne-amide.²⁷



Figure 1. Synthesis of ynamides via copper-catalyzed cross couplings

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Overall, ynamides are now readily available building blocks that can be easily and conveniently prepared on a multi-gram scale, some of them being even commercially available.²⁸ Among all methods described over the past 20 years for the preparation of ynamides, copper-based cross couplings have clearly proven to be the most efficient, general and straightforward ones. One can now prepare almost any desired ynamide with specific substitution patterns on a gram-scale using the right combination of alkynylating agent, nitrogen nucleophile, copper source and ligand. To this end, 1,1-dibromo-1alkenes appear to be excellent alkynylating agents as they are stable, cheap, readily available and easily prepared from the corresponding aldehydes using the classical Ramirez olefination²⁹ or Lautens' modification.³⁰ As a consequence, several processes have been reported by us and others since our original report on the use of 1,1-dibromo-1-alkenes for the synthesis of ynamides.^{9a,b} In this Organic Syntheses Discussion Addendum, we will first discuss several extensions that have been reported and which focused on extending the scope of the overall transformation. Secondly, representative examples of transformations based on ynamides obtained from the corresponding 1,1-dibromo-1-alkenes will be briefly presented to highlight the ever-growing interest of the synthetic community towards their use as building blocks in organic synthesis.

2. 1,1-Dibromo-1-alkenes as Practical Alkynylating Agents

In our original report, we described the synthesis of ynamides by a copper-catalyzed cross coupling between 1,1-dibromo-1-alkenes (1.5 equiv) and nitrogen nucleophiles (1 equiv) using copper(I) iodide (12 mol%) and *N*,*N*'-dimethylethylenediamine (DMEDA, 18 mol%) as a catalytic system with cesium carbonate (4 equiv) as the base. When using aryl-substituted 1,1-dibromo-1-alkenes, the reaction is usually performed in 1,4-dioxane (DMF being used in some cases to prevent solubility issues) at 60–70 °C for 24–48 h. More challenging alkyl-substituted 1,1-dibromo-1-alkenes require the use of DMF at 70–90 °C for 48 h. As for the nitrogen nucleophiles, sulfonamides, oxazolidinones, pyrrolidinones and a methyl carbamate were found to be reactive coupling partners; however, the use of simple secondary amides and ureas, which are reluctant reaction partners in copper-catalyzed cross-coupling reactions, proved unsuccessful (Figure 2).

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Interestingly, our group could also highlight the importance of the reaction conditions (*i.e.*, the base, solvent and stoichiometry), which have a dramatic effect on the outcome of the reaction. A fine tuning of these parameters indeed allows to promote a site-selective, double or alkynylative cross coupling between 1,1-dibromo-1-alkenes and nitrogen, oxygen and phosphorus nucleophiles.^{9d} This furnishes a divergent and straightforward access to diverse hetero-substituted alkynes and alkenes, important building blocks in chemical synthesis. As a note, the synthesis of a bis-ynamide has later been reported using the same catalytic system (CuI and DMEDA)^{9h} whereas a related system based on a stable adduct of CuI and Bu₄NI with a DMEDA·MsOH salt ligand was also reported for the cross coupling between (2,2-dibromoethenyl)benzene and 4-phenyloxazolidin-2-one.^{6v}

Subsequent studies reported by us and others aimed at extending the scope of the cross coupling to another class of nitrogen nucleophiles: N-heterocycles. Several copper-based catalytic systems have indeed been exploited to smoothly promote the direct alkynylation of N-heterocycles such as (benz)imidazoles, indazoles, pyrazoles and imidazoles;^{9c,d,e-g} those are illustrated in Figure 3.

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dibromo-1-alkenes

1,1-Dibromo-1-alkenes have also be successfully used for the direct alkynylation of sulfoximines using copper catalysis.^{9i,j} The cross coupling is based on the use of equimolar ratios of 1,1-dibromo-1-alkenes and sulfoximines, copper(I) iodide (10 mol%) and 1,10-phenanthroline (20 mol%) as the catalytic system with cesium carbonate as the base in THF at 80 °C for 3 days. In these conditions, the corresponding *N*-alkynylsulfoximines were obtained in fair to good yields (Figure 4).



Figure 4. Copper-catalyzed synthesis of *N*-alkynylsulfoximines with 1,1dibromo-1-alkenes

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More recently, Anderson described the synthesis of ynediamides from 1,1-dibromoenamides by using copper iodide (20 mol%) and 1,10-phenanthroline (40 mol%) as the catalytic system in the presence of cesium carbonate as the base in THF at 60 °C. Using these conditions, a series of ynediamides with various substitution patterns could be readily obtained in fair to good yields, even on a gram-scale, although the nature of both electron-withdrawing groups is mainly limited to sulfonamides (Figure 5). The authors also showed that these ynediamides were reactive substrates in various cyclization reactions.^{9k}



Figure 5. Synthesis of ynediamides

Additionally, Perumal reported two copper-catalyzed cross couplings between 1,1-dibromo-1-alkenes and nitrogen nucleophiles in which the corresponding ynamides are not isolated but rather directly converted into more complex polycyclic scaffolds by either a silver(I)-assisted intramolecular hydroarylation leading to pyrrolo-/indolo[1,2-*a*]quinolines and naphtho[2,1-*b*]thiophenes (Figure 6, Eq. 1)³¹ or a base-promoted intramolecular hydroamidation leading to 2-aminoindoles and indolo[1,2*a*]quinazolines (Figure 6, Eq. 2).³² A related approach was described by Verniest who reported the metal-free cyclization of *in situ* generated *ortho*nitroaryl ynamides from the corresponding 1,1-dibromo-1-alkenes and nitrogen nucleophiles, giving access to spiropseudoindoxyls.³³

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Figure 6. Synthesis of polycyclic scaffolds from 1,1-dibromo-1-alkenes and nitrogen nucleophiles via ynamide intermediates

As a final note, other dihalo-alkenes such as 1,2-dibromo-1-styrenes^{10a} and 2-bromo-1-iodoalkenes^{10b} have also been exploited for the synthesis of ynamides using copper catalysis while recent reports also describe the transition-metal-free preparation of ynamides starting from 1,1-dichloro-1-alkenes^{10c} and (*Z*)-1,2-dichloroalkenes.⁸ All these alkynylating agents however display a limited substrate scope compared to 1,1-dibromo-1-alkenes.

3. Chemistry of Ynamides: Versatile and Useful Building Blocks in Organic Synthesis

As previously mentioned, the development of efficient synthetic procedures for the preparation of ynamides, including those from 1,1dibromo-1-alkenes, paved the way for their use as building blocks in organic chemistry. Indeed, most classes of ynamides are now readily available and can be easily prepared on a multi-gram scale when using the appropriate method. As a consequence, numerous elegant and innovative synthetic transformations have been designed over the past decade to take advantage of the unique reactivity of ynamides. Representative examples of such transformations, for which ynamides have been prepared from the corresponding 1,1-dibromo-1-alkenes, will be briefly presented in the following paragraphs.

Ynamides are notably attractive building blocks as they allow the generation of otherwise hardly accessible highly reactive intermediates such as activated keteniminium ions, which can be easily generated upon

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activation of the starting ynamides under acidic conditions or with an electrophile.^{2c,34,35} For instance, we reported that ynamides could undergo a smooth hydrofluorination to provide the corresponding α -fluoroenamides in fair to good yields and with high levels of chemo- and stereoselectivities.³⁶ While our first approach was based on the use of anhydrous HF, we could then extend this procedure to the use of a more user-friendly hydrofluorination agent, HF·pyridine (Figure 7).



Figure 7. Hydrofluorination of ynamides

Due to their remarkable electrophilicity, keteniminium ions are also able to promote a [1,5]-hydrogen shift, which can be used to trigger cationic polycyclizations. Simple acids such as stoichiometric triflic acid or catalytic bistriflimide are indeed sufficient to promote novel cationic polycyclization of various ynamides, affording complex nitrogen heterocycles possessing up to three contiguous stereocenters and up to seven fused rings (Figure 8, Eq. 1).³⁷ We also demonstrated that activated keteniminium ions were suitable to initiate a [1,5]-hydride shift from unactivated C-H bonds which led to the development of a new route to highly functionalized tetrahydropyridines and piperidines (Figure 8, Eq. 2).³⁸



Figure 8. Cationic (poly)cyclization of ynamides through the generation of a keteniminium ion intermediate

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Besides the use of strong acids, electrophilic metal complexes have also proven successful to activate ynamides. In particular, gold complexes have been widely used and were shown to promote a variety of different transformations, most of them featuring cyclization of the starting ynamides to produce (poly)cyclic scaffolds. Representative examples of such transformations are the gold-catalyzed formal [3+2]-dipolar cycloaddition between pyridinium N-(heteroaryl)amidines and electron-rich alkynes to afford imidazopyrimidines reported by Davies (Figure 9, Eq. 1),³⁹ the generation of α -oxocarbenes from ynamides in the presence of pyridine Noxides as oxidants, followed by a subsequent cyclization, for the synthesis of fused γ -lactams reported by Davies (Figure 9, Eq. 2),⁴⁰ and other cyclization reactions from N-propargyl ynamides to form bicyclic and tricyclic pyrroles (Figure 9, Eq. 3)⁴¹ or from yne-ynamides to afford substituted inden-1-on-3carboxamides,⁴² both reported by Hashmi. As an additional note, Alcaide and Almendros reported the metal-free [2+2] cycloaddition of ynamides with Tf₂C=CH₂ to furnish aminocyclobutenes and aminocyclobutenols.⁴³



Figure 9. Gold-catalyzed transformations of ynamides for the synthesis of (poly)cyclic scaffolds

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The metal-catalyzed hydrofunctionalization of ynamides is also an attractive strategy that allows the synthesis of highly substituted enamides in a regio- and stereoselective fashion. Representative examples of this strategy are the palladium-catalyzed hydroalkynylation and hydroacyloxylation of ynamides reported by Reddy (Figure 10, Eq. 1)⁴⁴ and Lam (Figure 10, Eq. 2),⁴⁵ the nickel-catalyzed hydrophosphonylation of ynamides reported by Rabasso and our group (Figure 10, Eq. 3),⁴⁶ as well as the copper-catalyzed hydrosilylation of activated alkynes such as ynamides and propiolates reported by Riant and our group (Figure 10, Eq. 4).⁴⁷ In all four cases, highly substituted enamides are obtained in fair to good yields and with high levels of regio- and stereoselectivities.



Figure 10. Metal-catalyzed hydrofunctionalization of ynamides for the synthesis of highly substituted enamides

Lastly, ynamides can also act as good radical acceptors, although the number of transformations based on this reactivity is still limited. One elegant example has been reported recently by Perez-Luna and describes the

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radical germylzincation of ynamides which involves the regio- and stereoselective addition of germanium and zinc across the triple bond of diverse hetero-substituted alkynes, using R_3 GeH and $Et_2Zn.^{48}$ The intermediate vinylzinc species is then trapped by an electrophile to furnish the desired β -germylenamides *via* a radical-chain mechanism (Figure 11).



4. Conclusion

Since the first reports on the synthesis of ynamides using copper catalysis, including our original report on the use of 1,1-dibromo-1-alkenes as practical alkynylating agents, the chemistry of these nitrogen-substituted alkynes has experienced an impressive growth. Ynamides are now readily available building blocks that can be easily prepared on a multi-gram scale thanks to various efficient and reliable procedures. These developments had a dramatic impact on the use of ynamides in synthetic chemistry, as illustrated by the representative transformations discussed above. There is no doubt that ynamides will continue to be privileged building blocks as they are particularly attractive, versatile and powerful starting materials in organic synthesis.

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