A triazole-templated ring-closing metathesis for constructing novel fused and bridged triazoles†

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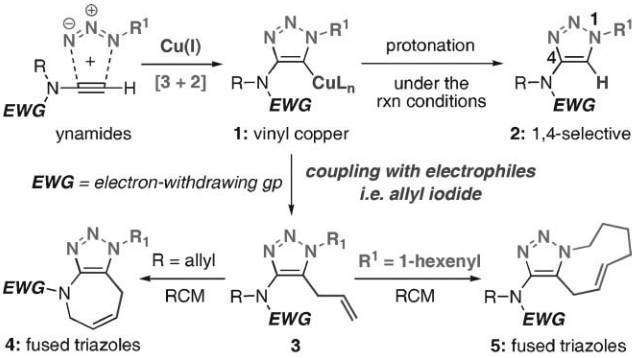
Received (in Bloomington, IN, USA) 23rd January 2007, Accepted 27th February 2007
First published as an Advance Article on the web 13th March 2007
DOI: 10.1039/b701040k

The feasibility of trapping the vinyl copper intermediate generated *in situ* from azide-[3 + 2] cycloadditions and viability of employing these triazoles as unique templates for ring-closing metathesis are described here; this work effectively combines the two powerful reactions for the first time to construct various *de novo* fused and bridged triazoles that are otherwise not trivial to synthesize.

Triazoles represent an important heterocyclic pharmacophore for developing anti-viral,[1] anti-cancer,[2] and antibiotic agents.[3] The 1,3-dipolar cycloaddition process[4,5] provides an excellent entry to these important N-heterocycles.[6] Given these implications, we have been developing [3 + 2] cycloadditions employing ynamides to construct novel heterocycles.[7–10] Specifically, we examined the classic Huisgen's azide-[3 + 2] cycloaddition[11–13] because of its current resurgence facilitated by Fokin–Finn–Sharpless' "click" chemistry.[14] During our efforts in establishing the feasibility of azide-[3 + 2] cycloadditions of ynamides,[15] we recognized that under Fokin and Sharpless'[16] catalytic copper(I) conditions, the cycloadditions terminates with a protonation step of the presumed vinyl copper intermediate **1**, leading to the formation of 1,4-disubstituted triazole **2** (Scheme 1).

We became intrigued and explored its reactivity *via* trapping with electrophiles such as allyl iodide *en route* to triazole **3** that can serve as a new template for ring-closing metathesis [RCM][17] to construct *de novo* fused (and bridged: not shown) triazoles **4** and **5** that are otherwise non-trivial to access. We report here our success in developing a sequence of Huisgen's azide-[3 + 2] cycloaddition and trapping of the vinyl copper intermediate en route to a triazole-templated RCM.

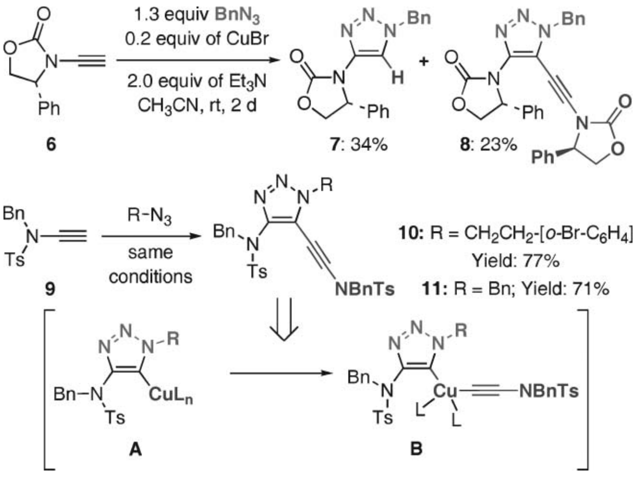


Scheme 1 A triazole templated RCM.

To develop conditions appropriate for azide-[3 + 2] cycloadditions of ynamides, we had to adopt a more anhydrous conditions to circumvent the problem of ynamide hydrolysis, which occurs under the $CuSO_4\cdot5H_2O$ condition run in aqueous/protic solvents.[15] However, as shown in Scheme 2, when ynamide **6** was reacted with BnN_3 in the presence of 0.2 equiv. of CuBr in CH_3CN,[18] in addition to triazole **7**, alkyne **8**[19] was isolated as a significant side product. When sulfonyl-substituted ynamide **9** was used, the respective alkynes **10** and **11** became the major products. These alkynes are most likely derived from reductive elimination of intermediate **B**, as suggested by Porco and co-workers in their related work,[20] thereby again implying the presence of vinyl copper **A**.

With this finding in hand, we chose to trap the vinyl copper intermediate in a synthetically useful manner. As shown in Scheme 3, allyl iodide was found to be an excellent electrophile suitable for the trapping to give triazole **12** in 68% yield,[21] although the reaction called for 1.0 equiv. of CuBr, as sub-stoichiometric amounts of copper led to slower reactions. The generality of this tandem process is illustrated in Table 1, and it features several different ynamides and azides. Given our interest in RCM, we focused on the utility of allyl and propargyl iodides.

Mechanistically, it is noteworthy that the related vinyl copper intermediate **C** (Fig. 1) appeared to fragment rapidly in a retro-[3 + 2] manner to give ynamide **D** or ketenimine **E** that were trapped by nucleophiles to construct acids and amides.[22] Our vinyl copper intermediate **F** was more robust and did not give di-ynamide **G** under these conditions but led to the desired product as



Scheme 2 Couplings of the vinyl copper intermediate.

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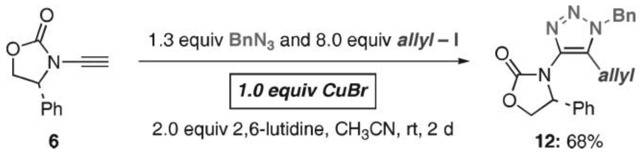
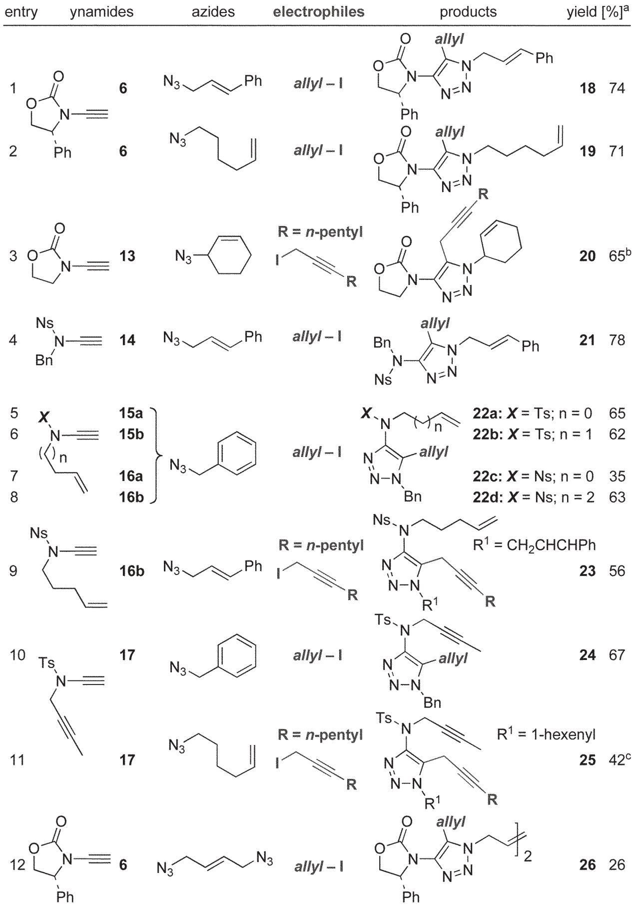
† Electronic supplementary information (ESI) available: Experimental procedures, characterizations, and NMR spectra for all new compounds. See DOI: 10.1039/b701040k



Scheme 3 Couplings of the vinyl copper intermediate.

Table 1 Tandem cycloaddition/vinyl-Cu trapping



entry	ynamides	azides	electrophiles	products	yield [%]^a
1	**6**		*allyl* – I	**18**	74
2	**6**		*allyl* – I	**19**	71
3	**13**		R = *n*-pentyl	**20**	65^b
4	**14**		*allyl* – I	**21**	78
5	**15a**		*allyl* – I	**22a**: *X* = Ts; n = 0	65
6	**15b**			**22b**: *X* = Ts; n = 1	62
7	**16a**			**22c**: *X* = Ns; n = 0	35
8	**16b**			**22d**: *X* = Ns; n = 2	63
9	**16b**		R = *n*-pentyl	**23** R^1 = CH$_2$CHCHPh	56
10	**17**		*allyl* – I	**24**	67
11	**17**		R = *n*-pentyl	**25** R^1 = 1-hexenyl	42^c
12	**6**		*allyl* – I	**26**	26

^{a}*Reaction conditions*: CuBr (1.0 equiv.), 2.6-lutidine (2.0 equiv.), iodide (8.0 equiv.) and BnN$_3$ (1.3 equiv.); solvent: CH$_3$CN (2.5 mL); temp = rt; time = 48 h. All yields are isolated yields. ^{b}A byproduct was isolated and identified as the [3 + 2] product without trapping. ^{c}A byproduct was assigned as the tandem [3 + 2]-coupling with the ynamide related to **10** or **11**.

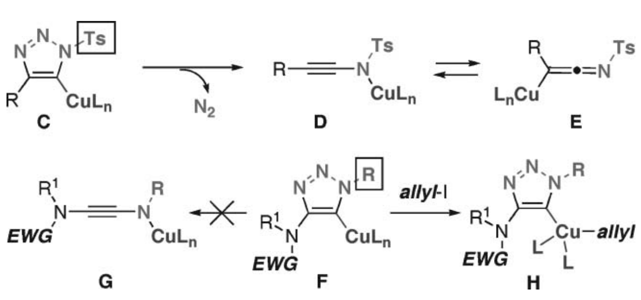
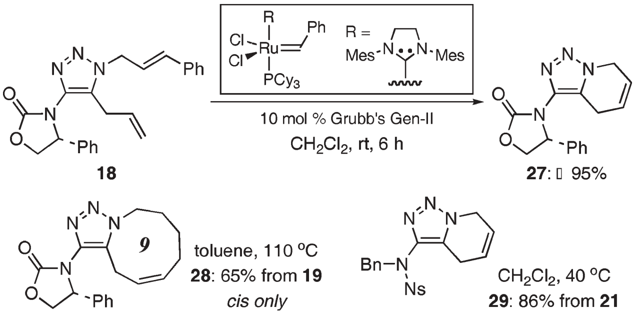


Fig. 1 A contrast with related systems.



Scheme 4 Triazole templated RCM: syntheses of fused triazoles.

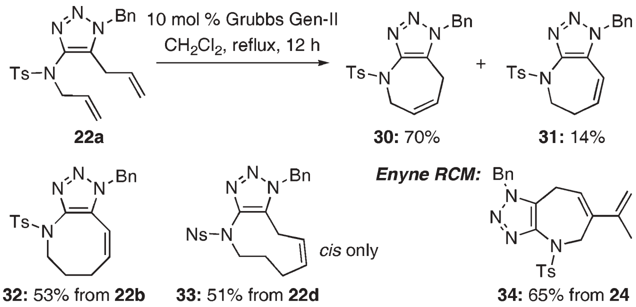
those shown in Table 1 either through a direct S$_N$2 reaction with allyl iodide or *via* reductive elimination of the copper intermediate **H**. The major difference is likely due to the ability of the electron withdrawing Ts group in **C** to promote the loss of N$_2$, leading to a more stabilized anion **D** relative to **G**.[23]

With triazoles prepared in Table 1 in hand, we were poised to examine ring-closing metathesis employing these triazoles as templates to construct fused triazoles. As shown in Scheme 4, the feasibility could be readily established employing triazole **18** with the fused triazole **27** being obtained in excellent yield using Grubb's Gen-II[17] as the catalyst at rt. In the same fashion, fused triazoles **28** and **29** could also be prepared from their respective triazole RCM-precursors in good yields. In particular, for the synthesis of **28**, refluxing in toluene was required, and it is noteworthy that the resulting nine-membered ring is exclusively *cis*.

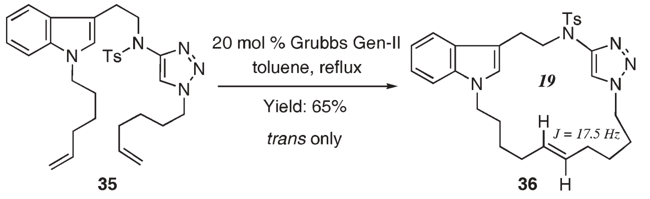
Another variation of fused triazoles could be accessed *via* RCM as shown in Scheme 5. RCM of triazole **22a** in which one of the two olefins is tethered through the ynamide nitrogen atom, led to triazole **30** in 70% yield accompanied with 14% of **31** where the olefin has migrated into conjugation with the triazole ring. Similarly, fused triazole **32** in which the olefin had completely moved into conjugation, and **33** (*cis* only) were captured from RCM of their respective triazole precursors.

In addition, the concept of enyne metathesis[24,25] could be established using triazole **24**, leading to the fused triazole **34** in 65% yield. It is noteworthy that in comparison with those fused triazoles prepared in Scheme 4, which in principle could be obtained through an intramolecular azide-[3 + 2] cycloaddition, it is not trivial to access the ones shown in Scheme 5 *via* a direct azide-[3 + 2] cycloaddition.

Finally, we examined the possibility of preparing interesting bridged triazoles but we encountered problems with competing dimerization and/or cross-metathesis when attempting to prepare systems containing ring sizes smaller than 13.[26] However, we were



Scheme 5 Fused triazoles through the ynamide nitrogen atom.



Scheme 6 A macrocyclic bridged triazole.

able to successfully synthesize bridged triazole **36** from triazole **35** in good yield (Scheme 6), and based on relevant proton coupling constant, we were able to unambiguously assign the olefin in **36** as exclusively *trans*.

We have described here the ability to trap the vinyl copper intermediate resulting from the azide-[3 + 2] cycloaddition in a tandem manner, and demonstrated the viability of using these triazoles as unique templates for ring-closing metathesis. This work effectively combines for the first time the two very powerful reactions to construct various fused and bridged triazoles that are otherwise non-trivial to access.

We thank NIH-NIGMS [GM066055] and UW-Madison for financial support.

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