Tandem azidination– and hydroazidination–Huisgen [3 + 2] cycloadditions of ynamides. Synthesis of chiral amide-substituted triazoles†

Xuejun Zhang, Richard P. Hsung* and Lingfeng You

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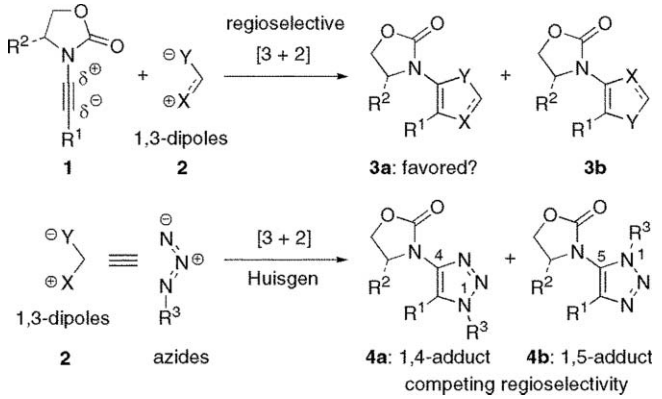
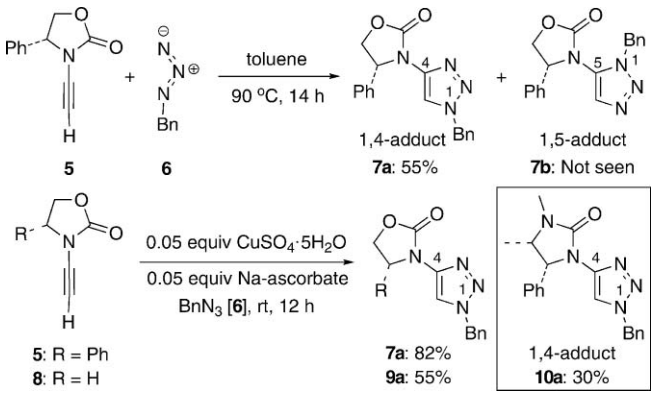
Tandem azidination– and hydroazidination–Huisgen [3 + 2] cycloadditions of ynamides are described here. These processes are regioselective and chemoselective, leading to the synthesis of chiral amide-substituted triazoles.

1,3-Dipolar cycloaddition[1,2] has captured strong interest from both synthetic and medicinal communities for the past four decades, given its power for constructing heterocyclic manifolds.[3] Our involvement with the chemistry of ynamides[4–7] has directed us to explore the potential of ynamides in 1,3-dipolar cycloadditions (**1** + **2** → **3a/b** in Scheme 1), which has not been revealed until very recently.[4,8] The inherent electronic bias imposed by the nitrogen atom in ynamides could play a role in the regioselectivity of these cycloadditions with a range of different 1,3-dipoles **2**. To establish such precedents, we elected to investigate Huisgen's organic azide-[3 + 2] cycloaddition[9–11] (**1** → **4a/b**) given the surging interest in this classic transformation.[12] We report here the regioselective tandem azidination– and hydroazidination–Huisgen [3 + 2] cycloadditions of chiral ynamides.



Scheme 1 Ynamides in 1,3-dipolar cycloadditions.

The feasibility was readily established as shown in Scheme 2. Huisgen's organic azide-[3 + 2] cycloaddition reactions of chiral ynamide **5** with BnN_3 proceeded well to give chiral amide-substituted triazole **7a**[13] in good yield as well as a single regioisomer under either the thermal or Fokin–Sharpless Cu(I) catalytic conditions.[14] While achiral ynamide **8** was also feasible to give



Scheme 2 Huisgen's azide-[3 + 2] cycloadditions of ynamides.

triazole **9a**, triazole **10a** (in the inset to Scheme 2) was attainable from a chiral urea-substituted ynamide (not shown), although in lower yield. The 1,4-regioselectivity found in triazole **7a** (in its relative stereochemsitry) was unambiguously assigned *via* its X-ray structure (Fig. 1).[13] In addition, the same 1,4-regioselectivity was also observed for cycloadditions of internal ynamides **11**–**13** that led to only cycloadducts **14a**–**16a**, respectively (Scheme 3).

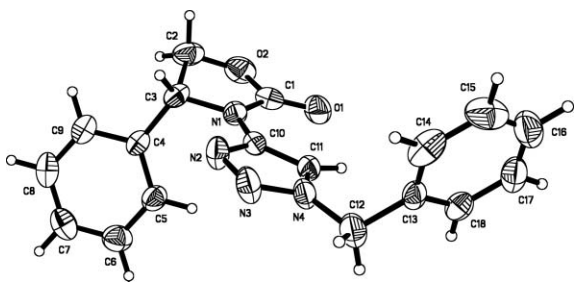
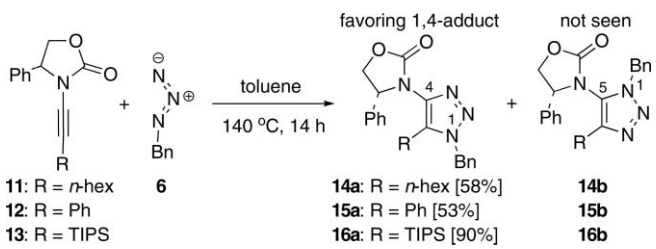


Fig. 1 X-Ray structure of triazole **7a** (ellipses at 50% probability).



Scheme 3 Azide-[3 + 2] cycloadditions of internal alkynes.

Division of Pharmaceutical Sciences and Department of Chemistry, Rennebohm Hall, 777 Highland Avenue, University of Wisconsin, Madison, WI 53705-2222, USA. E-mail: rhsung@wisc.edu

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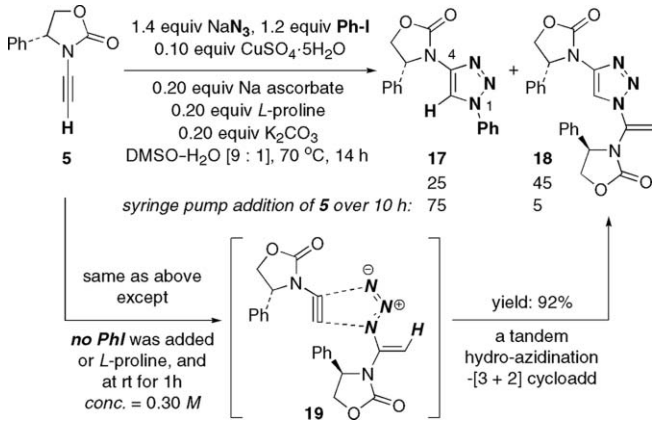
The obtained regioselectivities under both the thermal and Cu(I) catalytic conditions for either terminal or internal ynamides are of interest given that regioselectivity remains an important issue in azide-[3 + 2] cycloaddition[15] and in 1,3-dipolar cycloaddition in general.[1,2] Furthermore, it is also noteworthy that in Cintrat's seminal work,[8] urethane-substituted or urea-subsitituted ynamides were not successful in their respective cycloadditions with azides.

Mechanistically, 1,4-regioselectivity is mostly likely sterically driven with the assumption that the Evans chiral oxazolidinone moiety is consistently the larger of the two substituents on the alkyne (the other being substituent H for **5**, and *n*-hex, Ph, and TIPS for **11**–**13**, respectively). Although the aforementioned electronic bias of ynamides could still be a factor, it is somewhat counterintuitive based on arrow pushing.

Having established the basic concept, we examined the possibilities of a tandem azidination–Huisgen [3 + 2] cycloaddition.[16] As shown in Scheme 4, to our surprise, although the tandem azidination–Huisgen [3 + 2] cycloaddition was successful employing a hybrid of Ma's azidination[17] and Fokin–Sharpless 'click' conditions,[14] the major product was triazole **18**. While the former success represents a three-component coupling that gave triazole **17**, the latter is a result of an interesting tandem hydroazidination–Huisgen [3 + 2] cycloaddition. This hydroazidination of ynamide **5** is evidently highly regioselective,[6g] leading to vinyl azide **19** that would then undergo an ensuing cycloaddition with **5** either driven thermally and/or by Cu(I). The source of HN_3 is most likely the interaction of NaN_3 and H_2O. It is also possible to obtain **18** through a sequence of [3 + 2] cycloaddition followed by an addition of the resulting triazole to **5**. However, it is also more reasonable to assume that the addition of HN_3 across the ynamide triple bond is faster than any triazoles.

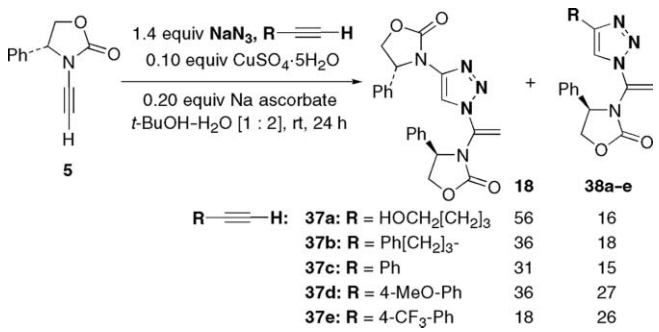


Scheme 4 Competing azidination and hydroazidination.

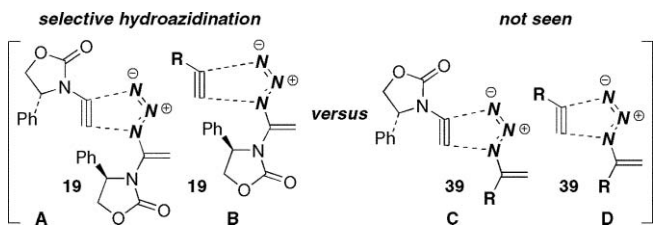
Synthetically, the access to either triazole **17** or **18** could be readily optimized. The use of syringe pump addition of ynamide **5** mostly eliminated the formation of **18** and gave **17** in 75% yield as a single regioisomer. This experiment suggests that **17** is likely not a result of a [3 + 2] cycloaddition followed by Cu(I)-catalyzed coupling of the resulting triazole to Ph-I, although it remains as a possibility. When the reaction was carried out in the absence of PhI, the tandem hydroazidination–Huisgen [3 + 2] cycloaddition proceeded smoothly to give **18** in 92% yield.[18]

The generality of the tandem-azidination [3 + 2] cycloaddition is prominently displayed in Table 1 for a range of different chiral ynamides, and both aryl halides and vinyl halides are feasible. Most reactions are regioselective and the key is the syringe pump addition of ynamides.

With the success in achieving the tandem azidination–[3 + 2] cycloaddition, we returned to the unexpected tandem hydroazidination–[3 + 2] cycloaddition and found an interesting competition when a second terminal alkyne was utilized. As shown in Scheme 5, in the presence of a second terminal alkyne (**37a**–**e**) the hydroazidination step was completely chemoselective in all cases and favored the more electron-rich ynamide **5** to give vinyl azide **19** (see Scheme 6). We did not observe any vinyl azide **39** (Scheme 6) or products that would imply its existence. This effectively rules out two (**C** and **D**) of the four possible tandem pathways (**A**–**D** in Scheme 6).



Scheme 5 Competing tandem hydroazidination–[3 + 2] cycloaddition.

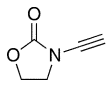
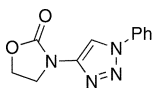
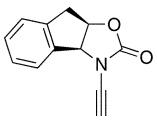
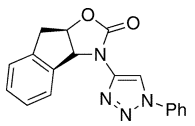
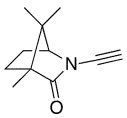
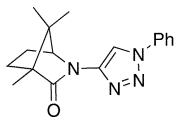
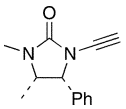
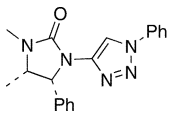
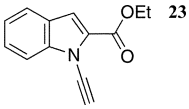
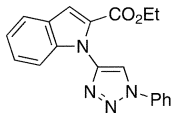
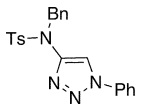
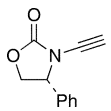
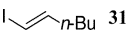
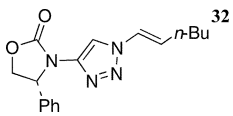
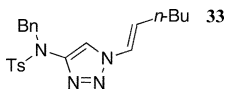
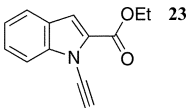
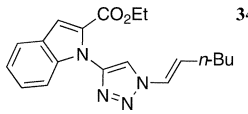
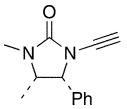
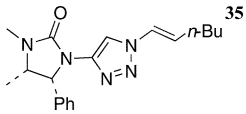
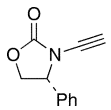
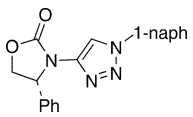


Scheme 6 Selectivities in the hydroazidination.

However, for the subsequent [3 + 2] cycloaddition, while triazole **18** is a distinct product, with the exception of aliphatic alkynes **37a** and **37b**, all aryl alkynes reacted with ynamide **5** to afford triazoles **38c**–**e** (Scheme 5). Triazoles **38c**–**e** represent other examples of three-component couplings. Equally intriguing, this result suggests that hydroazidination is much more of an electrophilic process than Huisgen [3 + 2] cycloadditions with organic azides.

We have described here tandem azidination– and hydroazidination–Huisgen [3 + 2] cycloadditions employing chiral ynamides for the synthesis of chiral amide-substituted triazoles. These tandem processes are highly regioselective and chemoselective in the case of the hydroazidination of ynamides, and both represent a multi-component coupling. Efforts in developing applications of this methodology are underway.

Table 1 Tandem azidination–[3 + 2] cycloadditions

Entry	Ynamide[a,b]	R–I (1.2 equiv.)	1,4-Cycloadduct	Yield (%)[c]
1	 **8**	Ph–I	 **25**	69
2	 **20**	Ph–I	 **26**	70
3	 **21**	Ph–I	 **27**	31
4	 **22**	Ph–I	 **28**	66
5	 **23**	Ph–I	 **29**	33
6	 **24**	Ph–I	 **30**	31[d]
7	 **5**	 **31**	 **32**	53[e,f]
8	**5**	**31**	**32**	67[b]
9	 **24**	**31**	 **33**	38[d]
10	 **23**	**31**	 **34**	69
11	 **22**	**31**	 **35**	71
12	 **5**	1-naph-I	 **36**	26[g]

[a] 1.4 equiv. NaN_3, 0.10 equiv. $CuSO_4 \cdot 5H_2O$, 0.20 equiv. sodium ascorbate, 0.20 equiv. L-proline, 0.20 equiv. K_2CO_3, DMSO–H_2O = 9 : 1, and at 70 °C for 14 h. [b] Syringe pump addition of the respective ynamide in all reactions. [c] Isolated yields only. [d] Hydrolysis of ynamides occurred extensively. [e] The reaction was run at 60 °C for 14 h. [f] Another side product believed to be the corresponding regioisomer was found in 9%, but **32** is the only product when not using the syringe pump. [g] Triazole **18** was found in 7% in addition to 14% of hydrolysis.

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Notes and references

1 For reviews, see: I. Coldham and R. Hufton, *Chem. Rev.*, 2005, **105**, 2765; K. Ruch-Braun, T. H. E. Freysoldt and F. Wierschem, *Chem. Soc. Rev.*, 2005, **34**, 507; A. I. Kotyatkina, V. N. Zhabinsky and V. A. Khripach, *Russ. Chem. Rev.*, 2001, **70**, 641; M. Harmata and P. Rashatasakhon, *Tetrahedron*, 2003, **59**, 2371; H. M. L. Davies, in *Advances in Cycloaddition*, ed. M. Harmata, JAI Press, Greenwich, CT, 1998, vol. 4, pp. 119–164; K. V. Gothelf and K. A. Jørgensen, *Chem. Rev.*, 1998, **98**, 863; F. G. West, in *Advances in Cycloaddition*, ed. M. Lautens, JAI Press, Greenwich, CT, 1997, vol. 4, p. 1; J. H. Rigby and F. C. Pigge, *Org. React.*, 1997, **51**, 351; A. Padwa, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, Pergamon Press, Oxford, 1991, vol. 4, pp. 1069–1109; W. Carruthers, *Cycloaddition Reactions in Organic Synthesis*, Pergamon Press, New York, 1990, pp. 270–331.

2 For recent general reviews on cycloadditions, see: J. A. Varela and C. Saá, *Chem. Rev.*, 2003, **103**, 3787; M. Rubin, A. W. Sromek and V. Gervorgyan, *Synlett*, 2003, 2265; C. Aubert, O. Buisine and M. Malacria, *Chem. Rev.*, 2002, **102**, 813; S. Saito and Y. Yamamoto, *Chem. Rev.*, 2000, **100**, 2901.

3 For reviews, see: W.-Q. Fan and A. R. Katritzky, in *Comprehensive Heterocyclic Chemistry*, ed. A. R. Katritzky, C. W. Rees and E. F. V. Scriven, Pergamon Press, Oxford, 1996, vol. 4, pp. 101–126.

4 For reviews on ynamides, see: C. A. Zificsak, J. A. Mulder, R. P. Hsung, C. Rameshkumar and L.-L. Wei, *Tetrahedron*, 2001, **57**, 7575; J. A. Mulder, K. C. M. Kurtz and R. P. Hsung, *Synlett*, 2003, 1379; A. R. Katritzky, R. Jiang and S. K. Singh, *Heterocycles*, 2004, **63**, 1455.

5 For recent reports on ynamides in the past three years, see: J. R. Dunetz and R. L. Danheiser, *J. Am. Chem. Soc.*, 2005, **127**, 5776; N. Riddell, K. Villeneuve and W. Tam, *Org. Lett.*, 2005, **7**, 3681; Y. Zhang, *Tetrahedron Lett.*, 2005, **46**, 6483; M. F. Martinez-Esperon, D. Rodriguez, L. Castedo and C. Saá, *Org. Lett.*, 2005, **7**, 2213; M. Bendikov, H. M. Duong, E. Bolanos and F. Wudl, *Org. Lett.*, 2005, **7**, 783; F. Marion, J. Coulomb, C. Courillon, L. Fensterbank and M. Malacria, *Org. Lett.*, 2004, **6**, 1509; M. Rosillo, G. Domínguez, L. Casarrubios, U. Amador and J. Pérez-Castells, *J. Org. Chem.*, 2004, **69**, 2084; S. Couty, B. Liégault, C. Meyer and J. Cossy, *Org. Lett.*, 2004, **6**, 2511; D. Rodríguez, L. Castedo and C. Saá, *Synlett*, 2004, 783; D. Rodríguez, L. Castedo and C. Saá, *Synlett*, 2004, 377; S. Hirano, R. Tanaka, H. Urabe and F. Sato, *Org. Lett.*, 2004, **6**, 727; M. Klein and B. König, *Tetrahedron*, 2004, **60**, 1087; F. Marion, C. Courillon and M. Malacria, *Org. Lett.*, 2003, **5**, 5095; B. Witulski, C. Alayrac and L. Tevzaadze-Saeftel, *Angew. Chem., Int. Ed.*, 2003, **42**, 4257; R. Tanaka, S. Hirano, H. Urabe and F. Sato, *Org. Lett.*, 2003, **5**, 67; B. Witulski, J. Lumtscher and U. Bergsträber, *Synlett*, 2003, 708; S. Naud and J.-C. Cintrat, *Synthesis*, 2003, 1391; F. Denonne, P. Paul Seiler and F. Diederich, *Helv. Chim. Acta*, 2003, **86**, 3096.

6 For our recent work on ynamides, see: (*a*) K. C. M. Kurtz, R. P. Hsung and Y. Zhang, *Org. Lett.*, 2006, **8**, 231; (*b*) K. C. M. Kurtz, M. O. Frederick, J. A. Mulder and R. P. Hsung, *Tetrahedron*, 2006, **62**, 3928; (*c*) Y. Zhang, R. P. Hsung, X. Zhang, J. Huang, B. W. Slafer and A. Davis, *Org. Lett.*, 2005, **7**, 1047; (*d*) M. R. Tracey, Y. Zhang, M. O. Frederick, J. A. Mulder and R. P. Hsung, *Org. Lett.*, 2004, **6**, 2209; (*e*) L. Shen and R. P. Hsung, *Tetrahedron Lett.*, 2003, **44**, 9353; (*f*) M. O. Frederick, R. P. Hsung, R. H. Lambeth, J. A. Mulder and M. R. Tracey, *Org. Lett.*, 2003, **5**, 2663; (*g*) J. A. Mulder, K. C. M. Kurtz, R. P. Hsung, H. A. Coverdale, M. O. Frederick, L. Shen and C. A. Zificsak, *Org. Lett.*, 2003, **5**, 1547.

7 For the synthesis of ynamides, see: M. O. Frederick, J. A. Mulder, M. R. Tracey, R. P. Hsung, J. Huang, K. C. M. Kurtz, L. Shen and C. J. Douglas, *J. Am. Chem. Soc.*, 2003, **125**, 2368; Y. Zhang, R. P. Hsung, M. R. Tracey, K. C. M. Kurtz and E. L. Vera, *Org. Lett.*, 2004, **6**, 1151. Also see: J. R. Dunetz and R. L. Danheiser, *Org. Lett.*, 2003, **5**, 4011; S. Couty, M. Barbazanges, C. Meyer and J. Cossy, *Synlett*, 2005, 906.

8 During our studies, Cintrat reported an elegant account describing reactions of azides with sulfonyl-substituted ynamides. See: M. IJsselstijin and J.-C. Cintrat, *Tetrahedron*, 2006, **62**, 3837.

9 R. Huisgen, *Angew. Chem.*, 1963, **75**, 604; R. Huisgen, G. Szeimies and L. Moebiu, *Chem. Ber.*, 1967, **100**, 2494; R. Huisgen, in *1,3-Dipolar Cycloaddition Chemistry*, ed. A. Padwa, Pergamon Press, Oxford, 1984, pp. 1–176.

10 For recent reviews on azide-alkyne cycloadditions, see: V. D. Bock, H. Hiemstra and J. H. Van Maarseveen, *Eur. J. Org. Chem.*, 2006, 51; A. R. Katritzky, Y. Zhang and S. K. Singh, *Heterocycles*, 2003, **60**, 1225; S. T. Abu-Orabi, *Molecules*, 2002, **7**, 302; H. C. Kolb, M. G. Finn and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2001, **40**, 2004.

11 For reviews on chemistry of organic azides, see: S. Bräse, C. Gil, K. Knepper and V. Zimmermann, *Angew. Chem., Int. Ed.*, 2005, **44**, 5188; C.-K. Sha and A. K. Mohanakrishnan, in *Chemistry of Heterocyclic Compounds*, ed. A. Padwa and W.H. Pearson, John Wiley & Sons, Inc., New York, 2002, vol. 59, ch. 9, pp. 623–679.

12 For some recent examples, see: V. D. Bock, R. Perciaccante, T. P. Jansen, H. Hiemstra and J. H. van Maarseveen, *Org. Lett.*, 2006, 919; F. Francesca Pagliai, T. Pirali, E. D. Grosso, R. D. Brisco, G. C. Tron, G. Sorba and A. A. Genazzani, *J. Med. Chem.*, 2006, **49**, 467; V. O. Rodionov, V. V. Fokin and M. G. Finn, *Angew. Chem., Int. Ed.*, 2005, **44**, 2210; L. Zhang, X. Chen, P. Xue, H. H. Y. Sun, I. D. Williams, K. B. Sharpless, V. V. Fokin and G. Jia, *J. Am. Chem. Soc.*, 2005, **127**, 15998; F. Himo, T. Lovell, R. Higraf, V. V. Rostovstsev, L. Noodleman, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2005, **127**, 210; J. F. Billing and U. Nilsson, *J. Org. Chem.*, 2005, **70**, 4847; V. Gracias, D. Darczak, A. F. Gasiecki and S. W. Djuric, *Tetrahedron Lett.*, 2005, **46**, 9053; H. Yanai and T. Taguchi, *Tetrahedron Lett.*, 2005, **46**, 8639; C. Chowdhury, S. B. Mandal and B. Achari, *Tetrahedron Lett.*, 2005, **46**, 8531; Y. Angell and K. Burgess, *J. Org. Chem.*, 2005, **70**, 9595.

13 Crystallographic data for **7a**: $C_{18}H_{16}N_4O_2$, $M = 320.35$, orthorhombic, $P2_12_12_1$, $a = 8.7353(7)$, $b = 9.8100(8)$, $c = 18.0556(15)$ Å, $\alpha = 90$, $\beta = 90$, $\gamma = 90°$, $V = 1547.2(2)$ Å^3, $T = 173(2)$ K, $Z = 4$, $\mu = 0.093$ mm^{-1}, 1823 ($R_{int} = 0.0299$), final R indices [$I > 2\sigma(I)$], $R_1 = 0.0332$, $wR_2 = 0.0768$, R indices (all data), $R_1 = 0.0423$, $wR_2 = 0.0837$. CCDC reference number 607119. For crystallographic data in CIF or other electronic format see DOI: 10.1039/b606680a.

14 V. Rostovtsev, L. G. Green, V. V. Fokin and K. B. Sharpless, *Angew. Chem., Int. Ed.*, 2002, **41**, 2596; P. Wu, A. K. Feldman, A. K. Nugent, C. J. Hawker, A. Scheel, B. Voit, J. Pyun, J. M. J. Frechet, K. B. Sharpless and V. V. Fokin, *Angew. Chem., Int. Ed.*, 2004, **43**, 3928; Q. Wang, T. R. Chan, R. Hilgraf, K. B. Sharpless and V. V. Fokin, *J. Am. Chem. Soc.*, 2003, **125**, 3192.

15 D. J. Hlasta and J. A. Ackerman, *J. Org. Chem.*, 1994, **59**, 6184; S. J. Howell, N. Spencer and D. Philp, *Tetrahedron*, 2001, **57**, 4945; J. Chen and J. Rebek, Jr., *Org. Lett.*, 2002, **4**, 327.

16 For a leading reference on a related tandem process employing simple terminal alkynes, see: A. K. Feldman, B. Colasson and V. V. Fokin, *Org. Lett.*, 2004, **6**, 3897.

17 W. Zhu and D. Ma, *Chem. Commun.*, 2004, 888.

18 The yield is based on the need of 2.0 equiv. of ynamide.

