HETEROCYCLES, Vol. 88, No. 1, 2014, pp. 179 - 186. © 2014 The Japan Institute of Heterocyclic Chemistry
Received, 11th June, 2013, Accepted, 4th July, 2013, Published online, 16th July, 2013
DOI: 10.3987/COM-13-S(S)30

N,N-BOND FORMATION IN INTRAMOLECULAR COBALT-CATALYZED [2 + 2 + 2] CYCLIZATIONS OF ALKYNYL-LINKED BISNITRILES, AND THE PREPARATION OF ANNULATED PYRIDAZINES

Cuifang Cai, Megan A. Audet, and John K. Snyder*

Department of Chemistry, and the Center for Chemical Methodology and Library Development (CMLD-BU), Boston University, 590 Commonwealth Ave., Boston, MA 02215, USA

Abstract – Cobalt(I) catalyzed intramolecular [2 + 2 + 2] cyclization of bisnitriles linked through a central alkyne has led to a facile route to annulated pyridazines. Ring closure through *N,N*-bond formation allows the construction of annulated pyridazine scaffolds that can be utilized in further small molecule library syntheses.

INTRODUCTION

Since the early pioneering work of Vollhardt and coworkers,[1] the transition metal catalyzed [2 + 2 + 2] cyclizations have become an important method for preparing highly substituted carbocyclic and heterocyclic aromatic systems.[2] Among the many reports of this general process, however, there are no examples of such a cyclization proceeding with the formation of an N-N bond, to the best of our knowledge. Heterocycles such as pyridazines, and its benzannulated analogues, the phthalazines and cinnolines which contain this N-N linkage within a heteroaromatic ring, are rarely found in Nature.[3] Probably the best known natural products which contain a pyridazine ring are the antifungal agent pyridazomycin,[4] and the highly unusual marine natural product azamerone.[5] At least three other reports have appeared of natural products possessing pyridazine rings, but two of these structures have been shown to be incorrect through synthesis. Thus, the marine cytotoxic agent zarsissine[6] was shown to be an imidazopyrazine,[7] while the correct structure of the fungal-derived schizocommunin[8] remains unknown after the proposed structure was determined to be incorrect.[9]

Despite their mere cameo appearance in Nature, pyridazines, cinnolines, and phthalazines, are important members of fragment-based screening libraries,[10] and are also found in several clinically employed compounds such as the anti-hypertensive hydralazine and the antidepressants minaprine and pipofezine

(Figure 1).[11-13] Pyridazine-containing heterocycles have recently been suggested to be the most "developable" scaffolds upon analysis of the GSK database.[14] Thus, these heterocycles are important synthetic targets for library development in drug screening efforts.

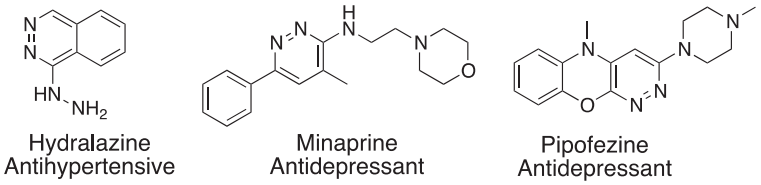
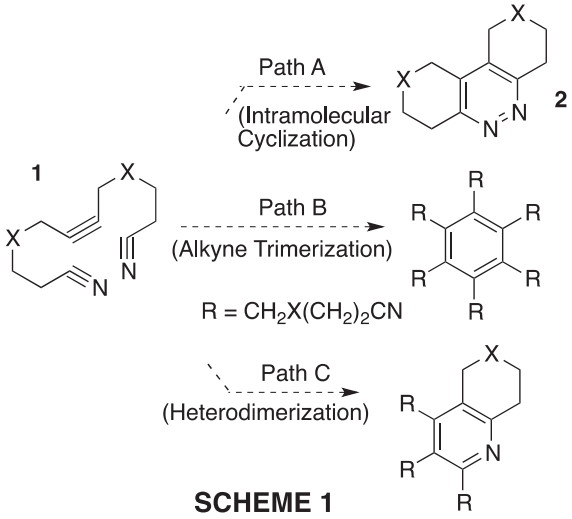


Figure 1. Drugs containing pyridazine subunits

Most routes to these 1,2-diazines incorporate the 1,2-dinitrogen subunit with the N-N bond already intact in a synthon such as a hydrazine, hydrazone or triazene, or in the case of cinnoline, through diazotization of an appropriately *o*-substituted aniline.[15-17] Cyclotrimerizations of nitriles, which proceed under conditions that don't require transition metal catalysis, are well known to give *s*-1,3,5-triazines,[18] though in 1984, Vollhardt had reported *N,N*-bond formation in the cyclizations of adiponitriles with mononitriles to form 1,2,4-triazines when strongly heated in the presence of iron carbonyl.[19] However, nitrile cyclizations resulting in pyridazine formation have not been reported.

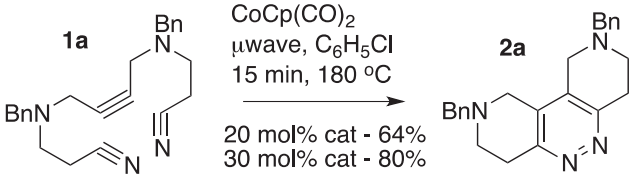


SCHEME 1

Given the success of the transition metal catalyzed [2 + 2 + 2] trimerizations of alkynes,[2,20] and the further application of this chemistry in pyridine syntheses incorporating a nitrile as 2π-partner,[21] we were interested in the possibility of creating 1,2-diazines (pyridazines) through a similar, intramolecular cyclization of bis-nitriles (Scheme 1). We were hoping that the intramolecular nature of the reaction would assist in the formation of the critical *N-N* bond (Path A), and enable diazine formation to compete with alkyne trimerization to a hexasubstituted benzene (Path B) and/or the dimerization to the pentasubstituted pyridine (Path C). We now report the success of this strategy, which we believe to be the first example of *N,N*-bond formation in a transition metal catalyzed [2 + 2 + 2] cyclization.

RESULTS AND DISCUSSION

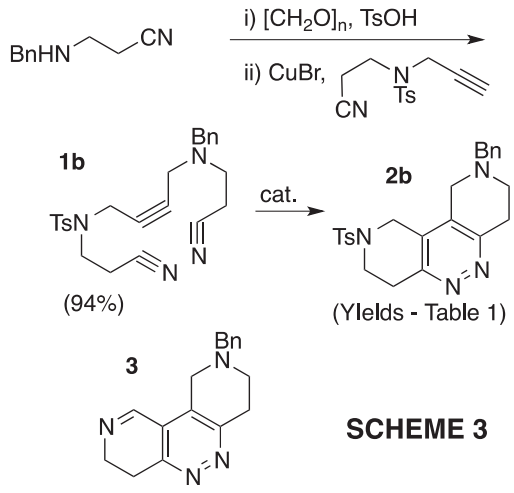
As a proof of principle experiment, the cyclization of bisnitrile **1a** with benzylamino linkage points on either end of a symmetric, internal alkyne was first examined since deprotection of the benzylated nitrogens would offer two sites for diversification in



SCHEME 2

subsequent library synthesis. The symmetric bisnitrile was chosen to simplify NMR analysis of the product. Employing the same cobalt catalyst, $CoCp(CO)_2$ (20 mol%) which we had successfully employed in the synthesis of naphthyridines[22] established that this approach to N,N-bond formation in a cyclization was possible (Scheme 2). Formation of the symmetric 1,2-diazine **2a** (64%) was readily apparent from the ^{1}H- and ^{13}C-NMR spectra, along with the HRMS, which confirmed the symmetry of the cyclized product with formation of the aromatic diazine ring. With 30 mol% catalyst, the yield could be increased to 80%.

Optimization studies of the cyclization were then undertaken with bisnitrile **1b** with the nitrogens orthogonally protected. Cyclization product **2b** would have the potential of being sequentially deprotected for two point diversification strategies in a library synthesis scheme. The preparation of **1b** was routine (Scheme 3) and centered on an alkynyl Mannich reaction[23] to form the bisnitrile **1b**. Cyclizations proceeded with the Co(I) catalyst $CoCp(CO)_2$ (20 mol%) under microwave conditions (5 min, 180 °C), producing annulated diazine **2b** (Table 1, entry 1). Increasingly longer reaction times with this particular substrate led to elimination of the tosyl group from the cyclized product with formation of by-product **3** in increasing amounts (Entries 2 – 4). Higher catalyst loading (30 mol%, entry 5) did not improve the yield, while lower loading (10 mol%, Entry 6) gave lower yields. The best yield was obtained at temperatures (70%, 160 °C, entry 7) which minimized production of **3**. The stable Co(I) catalyst reported by Malacria[24] yielded only small amounts of **2b** (9%, entry 9), while two Rh(I) catalysts failed to produce any cyclization products, returning only the non-cyclized precursor (Entries 10 – 11). Performing the reaction in refluxing chlorobenzene as opposed to microwave irradiation gave only a 20% yield of **2b**, with varying amounts of **3**.



SCHEME 3

With the preliminary success of the bisnitrile cyclization, three questions were then addressed. First, which nitrogen protecting groups would survive both the bisnitrile

Table 1. Optimization Studies for the Cyclization of **1b**.[a]

	Catalyst (eq)	Time (min)	Temp (°C)	Yield (%)[b]
1	$CoCp(CO)_2$ (0.2)	5	180	65
2	$CoCp(CO)_2$ (0.2)	10	180	59
3	$CoCp(CO)_2$ (0.2)	15	180	50
4	$CoCp(CO)_2$ (0.2)	30	180	24
5	$CoCp(CO)_2$ (0.3)	10	180	60
6	$CoCp(CO)_2$ (0.1)	10	180	50
7	$CoCp(CO)_2$ (0.2)	5	160	70
8	$CoCp(CO)_2$ (0.2)	10	160	54
9	$CoCp(CO)(MeO_2CC{=}CCO_2Me)$ (0.2)	15	180	9
10	$Rh(COD)_2BF_4$ (0.2)	10	180	0
11	$RhCl(PPh_3)_3$ (0.2)	15	180	0

a) All reactions were performed under microwave irradiation: 160 °C at 200 Watts, 180 °C at 300 Watts, 0.05 M in bisnitrile, 30-40 mg scale.

b) Isolated yields.

preparation and the cyclization with the Co(I) catalyst, and still allow for selective deprotection. Second, could five- and seven-membered rings also be formed in the cyclizations. Finally, how much substitution on the bisnitrile tethers would be tolerated as potential steric interactions increased. Screening of various *N*-protecting groups revealed that tosyl, Bn, PMB, and BOC could all be carried through the cyclization without difficulty (Chart 1), and that five-membered ring cyclization products (**4a** and **4b**, respectively) were also easily prepared. Seven-membered ring annulation products **5**, however, proved to be unstable and were prone to decomposition upon prolonged exposure to air. The survival of the BOC group during the acidic initial step of the alkynyl Mannich was a welcome surprise, since removal of the BOC group from the cyclization product **4a** (TMSI, 87%) with subsequent transformation to ureas **6a** (88%) and **6b** (93%) upon reaction with the corresponding isocyanate was straightforward (Scheme 4). In contrast, neither the FMOC- nor the corresponding Alloc-protected precursors participated in the cyclization, the latter protecting group proved to be unstable upon addition of the Co(I) catalyst, while former was covered unchanged.

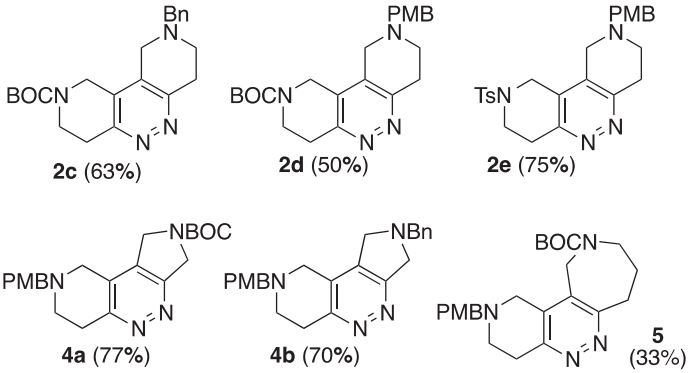
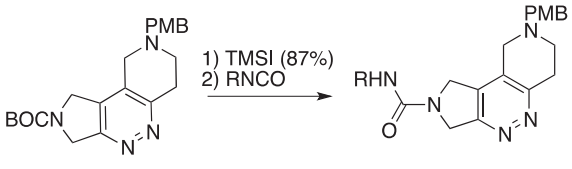
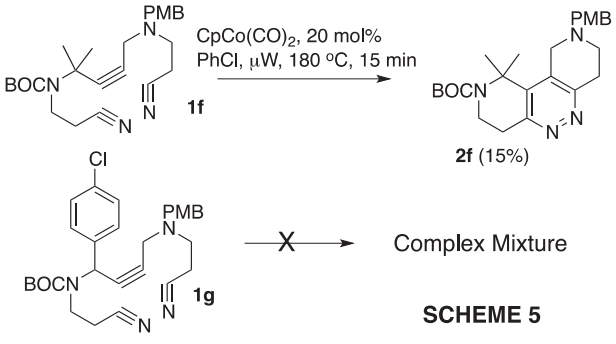


Chart 1. Additional annulated 1,2-diazines produced in the Co(I)-catalyzed [2 + 2 + 2] cyclizations

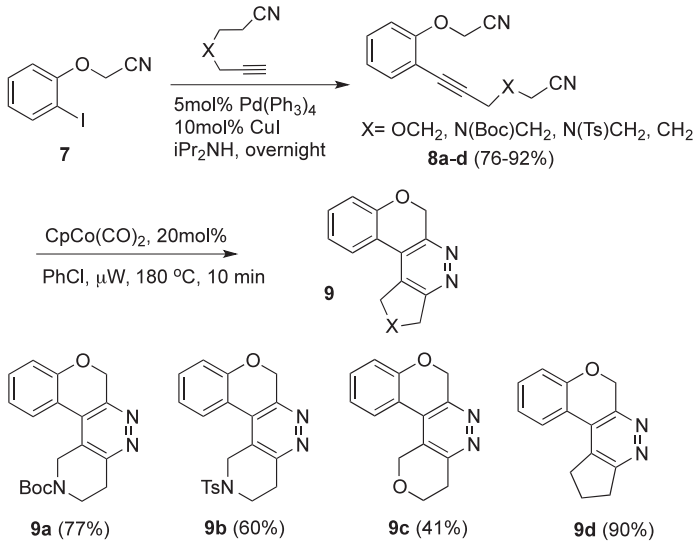


SCHEME 4

Substitution at the propargylic positions presented potential steric impediments to the cyclization. To test this impact, bisnitriles **1f** and **1g** were prepared and subjected to the optimized cyclization conditions (Scheme 5). As anticipated severe crowding hindered the cyclization of **1f** presumably due to the *endo*-positioning of the substituents in the cyclization process. In the case of **1g**, no cyclization product was detected, though no starting material was recovered either, only an intractable residue was produced.



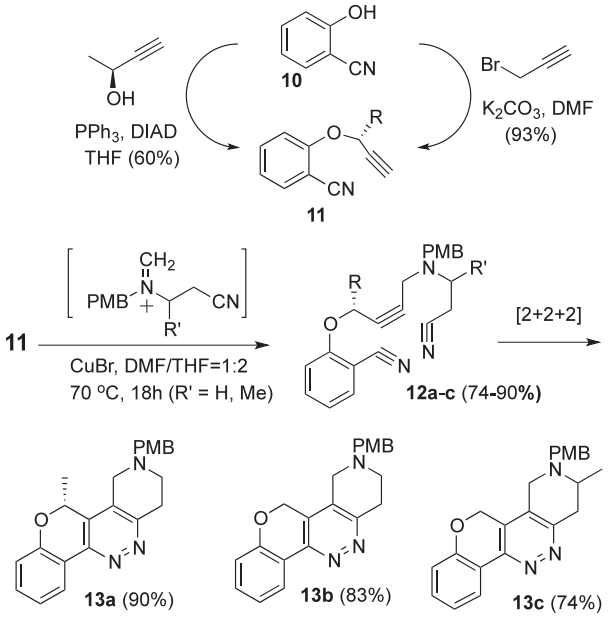
SCHEME 5



SCHEME 6

Tetracyclic systems with interior pyridazines rings could also be obtained from *o*-iodophenols (Scheme 6) and *o*-cyanophenols (Scheme 7), a strategy analogous to the benzofuran syntheses by Rh-mediated [2 + 2 + 2] cyclizations recently reported by Tanaka.[25] Alkylation of *o*-iodophenol with α-bromoacetonitrile gave **7** in 88% yield. Sonagashira coupling then produced cyclization precursors **8** in 76 – 92% yields. Finally, microwave promoted cyclization under the standard conditions yielded **9a** – **9d**.

The bisnitrile precursors for the tetracyclic core isomers **13a** – **13c** were formed by alkylation of *o*-cyanophenol (**10**) with the appropriate propargyl alcohol (Scheme 7). The Cu(I) controlled alkynyl Mannich reaction then gave the cyclization substrates **12**. Again, the Co(I) catalyzed cyclizations proceeded smoothly under microwave promotion to yield annulated pyridazines **13a** – **13c**.



SCHEME 7

SUMMARY

In summary, Co(I) catalyzed [2 + 2 + 2] cyclizations of bisnitriles linked through a central alkyne proceeded smoothly with N-N bond formation, leading to annulated pyridazines. Using this methodology, sixteen new annulated pyridazines were prepared. Use of tethering nitrogens in the preparation of the cyclization precursors incorporates points for further diversification in the preparation of small molecule libraries, the next step in development of this chemistry.

ACKNOWLEDGEMENTS

We thank the NIGMS CMLD initiative (P50 GM067041) for financial support, and the Boston University Undergraduate Research Opportunities Program (UROP) for a summer fellowship Megan Audet. We are

also grateful to the NSF for the purchase of the NMR (CHE 0619339) and HRMS spectrometers (CHE 0443618) used in this work. We also thank AstraZeneca for sabbatical support for JKS.

REFERENCES AND NOTES

1. K. P. C. Vollhardt, *Acc. Chem. Res.*, 1977, **10**, 1.
2. For recent reviews of [2+2+2] cyclization: S. Kotha, E. Brahmachary, and K. Lahiri, *Eur. J. Org. Chem.*, 2005, 4741; P. R. Chopade and J. Louie, *Adv. Synth. Catal.*, 2006, **348**, 2307; N. Agenet, O. Buisine, F. Slowinski, V. Gandon, C. Aubert, and M. Malacria, 'Organic Reactions, Vol. 68', ed. by T. V. RajanBabu, John Wiley & Sons, Hoboken, NJ, 2007, pp. 1 – 302; J. A. Varela and C. Saá, *Synlett*, 2008, 2571; T. Shibata and K. Tsuchikama, *Org. Biomol. Chem.*, 2008, **6**, 1317; Y. Shibata and K. Tanaka, *Synthesis*, 2012, **44**, 323; D. L. J. Broere and E. Ruijter, *Synthesis*, 2012, **44**, 2639.
3. C.-J. Chen, A.-J. Deng, C. Liu, R. Shi, H.-L. Qin, and A.-P. Wang, *Molecules*, 2011, **16**, 9049.
4. R. Grote, Y. Chen, A. Zeeck, Z. X. Chen, H. Zahner, P. Mischnick-Lubbecke, and W. A. Konig, *J. Antibiot.*, 1988, **41**, 595; H. Bockholt, J. M. Beale, and J. Rohr, *Angew. Chem., Int. Ed. Engl.*, 1994, **33**, 1648.
5. J. Y. Cho, H. C. Kwon, P. G. Williams, P. R. Jensen, and W. Fenical, *Org. Lett.*, 2006, **8**, 2471; J. M. Winter, A. L. Jansma, T. M. Handel, and B. S. Moore, *Angew. Chem. Int. Ed.*, 2009, **48**, 767.
6. N. Bouaicha, P. Amade, D. Puel, and C. Roussakis, *J. Nat. Prod.*, 1994, **57**, 1455.
7. Z.-K. Wan, G. H. C. Woo, and J. K. Snyder, *Tetrahedron*, 2001, **57**, 5497.
8. T. Hosoe, K. Nozawa, N. Kawahara, K. Fukushima, K. Nishimura, M. Miyaji, and K.-i. Kawai, *Mycopathologica*, 1999, **146**, 9.
9. A. Nishida, K. Uehata, and M. Nishida, 7th International Conference on Cutting-Edge Organic Chemistry in Asia, Singapore, Dec. 2012.
10. A. V. Velentza, M. S. Wainwright, M. Zasadzki, S. Mirzoeva, A. M. Schumacher, J. Haiech, P. J. Focia, M. Egli, and D. M. Watterson, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 3465; M. Krier, J. X. de Araujo-Junior, M. Schmitt, J. Duranton, H. Justiano-Basaran, C. Lugnier, J.-J. Bourguignon, and D. Rognan, *J. Med. Chem.,* 2005, **48**, 3816.
11. Pyridazines in drug discovery: C. G. Wermuth, *Med. Chem. Commun.*, 2011, **2**, 935.
12. Cinnolines in drug discovery: W. Lewgowd and A. Stanczak, *Arch. Pharm. Life Sci.*, 2007, **340**, 65.
13. Phthalazines in drug discovery: M. Asif, *Curr. Med. Chem.*, 2012, **19**, 2984.
14. T. J. Ritchie, S. J. F. Macdonald, S. Peace, S. D. Pickett, and C. N. Luscombe, *Med. Chem. Commun.*, 2012, **3**, 1062.
15. Reviews of pyridazine syntheses: R. N. Castle, 'Pyridazines' in The Chemistry of Heterocyclic Compounds (Monograph Series), Vol. 28, John Wiley, New York, 1973; D. J. Brown, "The

Pyridazines, Supplement I' in The Chemistry of Heterocyclic Compounds (Monograph Series), Vol. 57, John Wiley, New York, 2000.

16. Reviews of cinnoline syntheses: J. C. E. Simpson, 'Condensed Pyridazine and Pyrazine Rings (Cinnolines, Phthalazines and Quinoxazolines)' in The Chemistry of Heterocyclic Compounds (Monograph Series), Interscience, New York, 1953, pp. 3-65; G. M. Singerman, in 'Condensed Pyridazines Including Cinnolines and Phthalazines' in The Chemistry of Heterocyclic Compounds (Monograph Series), Vol. 27, ed. by R. N. Castle, John Wiley, New York, 1973, pp. 1-321; D. J. Brown, "Cinnolines and Phthalazines, Supplement II', in The Chemistry of Heterocyclic Compounds (Monograph Series), Vol. 64, John Wiley, New York, 2005; O. V. Vinogradova and I. A. Balova, *Chem. Heterocycl. Cmpds.,* 2008, **44**, 501. For a recent, general approach to cinnolines: K. Hasegawa, N. Kimura, S. Arai, and A. Nishida, *J. Org. Chem.*, 2008, **73**, 6363.
17. Reviews of phthalazine syntheses: J. C. E. Simpson, 'Condensed Pyridazine and Pyrazine Rings (Cinnolines, Phthalazines and Quinoxazolines)' in The Chemistry of Heterocyclic Compounds (Monograph Series), Interscience, New York, 1953, pp. 69-200; N. R. Patel, in 'Condensed Pyridazines Including Cinnolines and Phthalazines' in The Chemistry of Heterocyclic Compounds (Monograph Series), Vol. 27, ed. by R. N. Castle, John Wiley, New York, 1973, pp. 323-760.
18. E. M. Smolin and L. Rapoport, "*s*-Triazines and Derivatives" in The Chemistry of Heterocyclic Compounds (Monograph Series), Interscience, New York, 1959; J. H. Forsberg, V. T. Spaziano, T. M. Balasubramanian, G. K. Liu, S. A. Kinsley, C. A. Duckworth, J. J. Poteruca, P. S. Brown, and J. L. Miller, *J. Org. Chem.,* 1987, **52**, 1017; J. H. Forsberg, V. T. Spaziano, S. P. Klump, and K. M. Sanders, *J. Heterocycl. Chem.*, 1988, **25**, 767; F. Xu, J.-H. Sun, H.-B. Yan, and Q. Shen, *Synth. Commun.,* 2000, **30**, 1017; A. Herrera, R. Martinez-Alvarez, P. Ramiro, M. Chioua, and R. Chioua, *Synthesis*, 2004, 503.
19. E. R. F. Gesing, U. Groth, and K. P. C. Vollhardt, *Synthesis*, 1984, 351. An earlier paper had reported the cyclotrimerization of benzonitrile upon heating with iron carbonyl to give presumably the *s*-triphenyltriazine based on mp: S. F. A. Kettle and L. E. Orgel, *Proc. Chem. Soc.*, 1959, 307. For a recent report of nitrile trimerization to produce 1,2,4-triazines: F. Goettmann, A. Fischer, M. Antonietti, and A. Thomas, *New J. Chem.*, 2007, **31**, 1455.
20. Reviews: K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.,* 1984, **23**, 539; J. A. Varela and C. Saa, *Chem. Rev.*, 2003, **103**, 3787; V. Gandon, C. Aubert, and M. Malacria, *J. Chem. Soc., Chem. Commun.*, 2006, 2209.
21. Review: M. D. Hill, *Chem. Eur. J.*, 2010, **16**, 12052.
22. Y. Zhou, J. A. Porco, Jr, and J. K. Snyder, *Org. Lett.*, 2007, **9**, 393; Y. Zhou, A. B. Beeler, S. Cho, Y. Wang, S. G. Franzblau, and J. K. Snyder, *J. Comb. Chem.*, 2008, **10**, 534.

23. For a recent summary of Cu(I)-catalyzed alkynyl Mannich reaction: B. R. Buckley, A. N. Khan, and H. Heaney, *Chem. Eur. J.*, 2012, **18**, 3855. For the procedure used in this work: S. Su, J. R. Giguere, S. E. Schaus, and J. A. Porco, Jr., *Tetrahedron*, 2004, **60**, 8645.
24. A. Geny, N. Agenet, L. Iannazzo, M. Malacria, C. Aubert, and V. Gandon, *Angew. Chem. Int. Ed.*, 2009, **48**, 1810.
25. Y. Komine, A. Kamisawa, and K. Tanaka, *Org. Lett.,* 2009, **11**, 2361.