Pyridines *via* solid-supported [2 + 2 + 2] cyclotrimerization†

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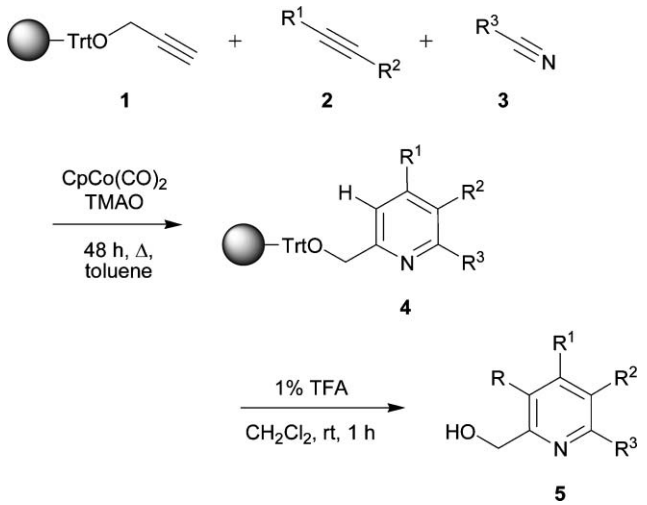
The formation of pyridines *via* a crossed [2 + 2 + 2] cycloaddition has been achieved on a solid-support for the first time.

We recently initiated a program in developing solid-supported multicomponent reactions (MCRs)[1–6] for the rapid construction of small molecule libraries. This approach combines the advantages of solid-supported chemistry (easy automatization, parallelization, and purification)[7–9] with the high convergence of MCRs. A classical MCR, the [2 + 2 + 2] cyclotrimerization towards highly substituted pyridine rings has surprisingly not received much attention in combinatorial chemistry.[10–13] The commercial availability of a wide range of alkynes and nitriles makes this reaction an ideal candidate for the rapid assembly of diverse heterocyclic libraries.[9,14] Pyridine rings are found in many biologically relevant structures including compounds with antiviral (HIV),[15] antimicrobial,[16,17] anticancer,[18] and protein kinase inhibition activity.[16,17] Catalyst systems applied in cyclotrimerizations towards pyridine synthesis are mainly based on cobalt, and recent developments have led to mild reaction conditions applicable to organic synthesis.[19,20,21–26] However, major problems are still associated with this reaction, including chemo- and regioselectivity issues.[13,27] The catalytic solution-phase cyclotrimerization of two alkynes and a nitrile results in the formation of mixtures of products including *crossed* pyridines (from the incorporation of two different alkynes) and *homo* pyridines (from the incorporation of two identical alkynes), as well as potential benzene byproducts. We resolved these problems by immobilizing one alkyne reaction partner on a polystyrene resin, thereby accomplishing the first catalytic crossed cyclotrimerization of this type. Specifically, propargyl alcohol was immobilized on a polystyrene resin (100–200 mesh)[28] using an acid labile trityl linker[29,30] under standard conditions (pyridine, THF, rt, 12 h). Resin **1** was obtained with a loading of 0.8 mmol g^{-1} as determined by GC-MS analysis of a sample cleaved with 1% TFA in CH_2Cl_2.

Scheme 1 illustrates the generalized reaction of **1** with an alkyne **2** and a nitrile **3** yielding the immobilized pyridine **4**. Only one regioisomer is displayed; however, regioselectivities observed in solution-phase reactions are typically low.[11–13] The resin **1** was swelled in degassed toluene in the presence of the alkyne **2**, the nitrile **3** (1 : 10 ratio to favor pyridine formation), and tetramethylammonium oxide (TMAO)[31] as a catalyst activating additive. The reaction mixture was heated to 80 °C and $CpCo(CO)_2$ (20 mol%) was added every 12 h for 48 h. Due to the pseudo-high dilution conditions on the resin surface, no pyridines resulting from the double incorporation of **1** were observed. Moreover, pyridines that result from the cyclotrimerization of two molecules of **2** and one molecule of **3** were removed in the workup step since they are not immobilized on the resin. The formation of benzenes through the reaction of **1** with two alkynes **2** was suppressed by using the catalyst $CpCo(CO)_2$ which favors pyridine formation in conjunction with an excess of nitrile **3**.[13] Therefore a highly chemoselective crossed [2 + 2 + 2] cycloaddition towards **4** was achieved. The pyridine was then cleaved under mild conditions using 1% TFA in DCM yielding clean TFA-salts of the products **5**. These salts were converted into the free bases by passing them through an ion exchange resin (Dowex 50WX8-100). The pyridines **5** were then analyzed by ^{1}H NMR, LC-MS, and GC-MS. They are observed in 43–85% yield (typical solution-phase yields are about 65%[13]) and excellent purity of generally >90%. By using a set of six different alkynes (**6–11**) and three different niriles (**12–14**) an array of 18 pyridines (**15–32**) was rapidly assembled. The reaction tolerates a variety of substituents, including alkyl groups (Me, Et, and Bu), aryl groups (Ph), hydroxy groups, alkoxy groups (CH_2OMe), and carbamates (BocNH). Free amines were not compatible with the reaction conditions; however, the Boc protecting group was conveniently removed from the corresponding carbamate in the cleavage step. Even alkynes which are less reactive due to sterical demand (**9**) or an internal triple bond (**11**) underwent cyclotrimerization. Crossed cyclotrimerizations lead to the formation of complex mixtures of



Scheme 1

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‡ These authors contributed equally to this work.

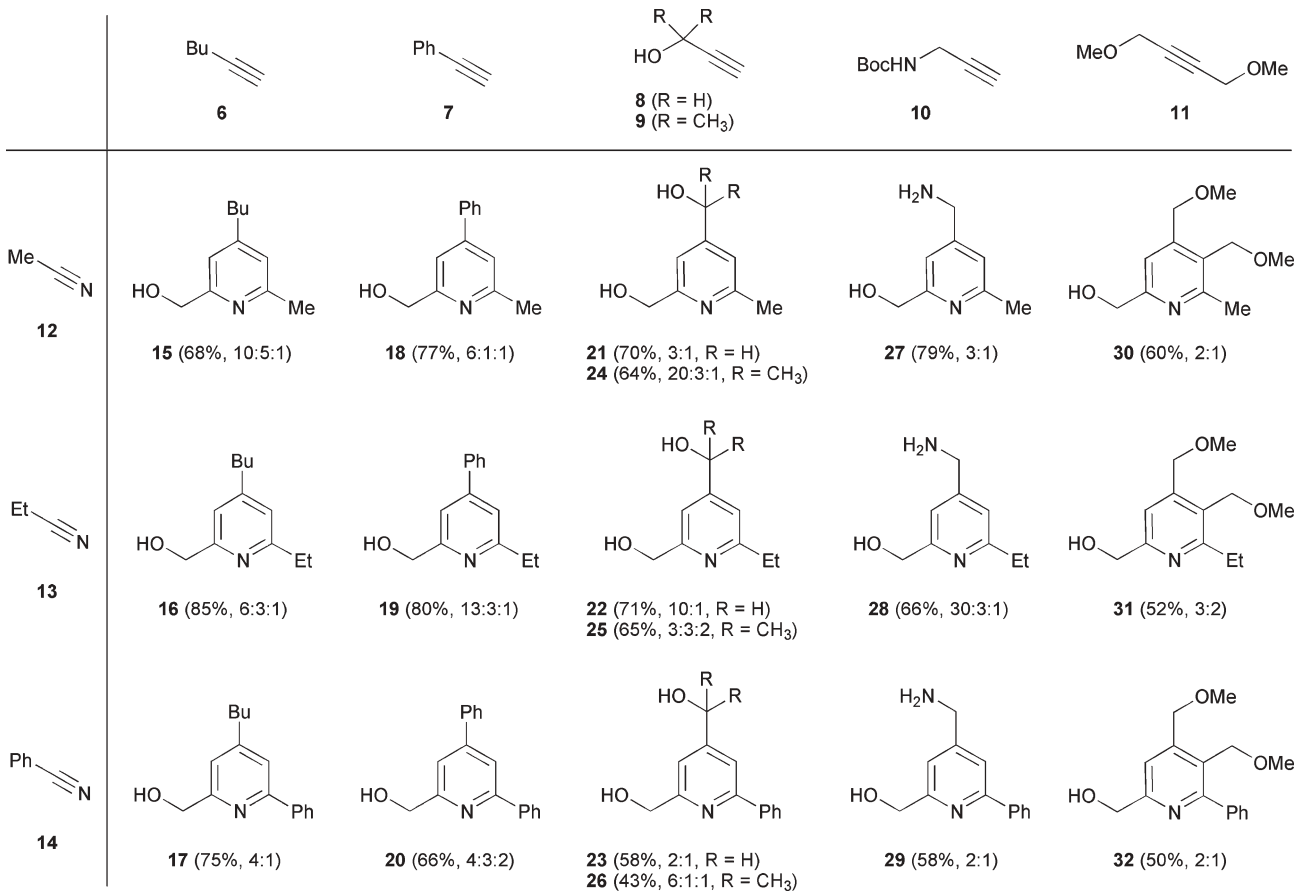
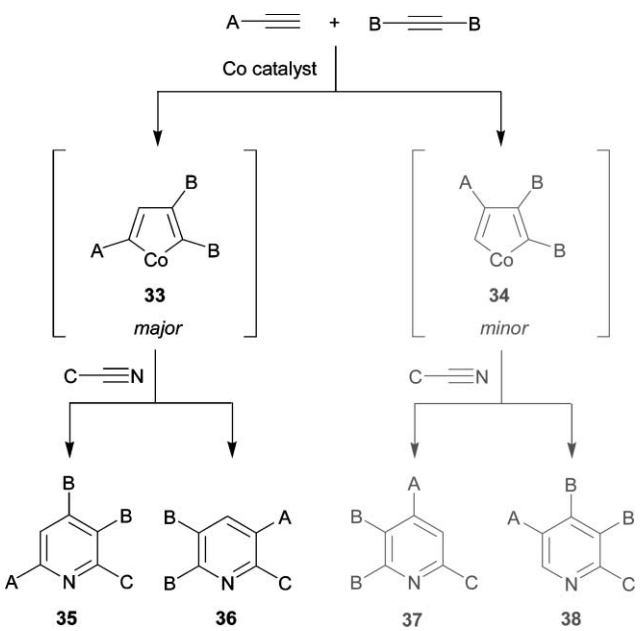


Fig. 1 Alkynes (**6–11**) and nitriles (**12–14**) employed in solid-supported [2 + 2 + 2] cyclotrimerizations with **1** yielding pyridines **15–32**. Yields and ratios of regioisomers are shown in parentheses. The regioisomeric ratios were determined by GC-MS (compounds **15–20**, **23–29**, and **32**) and ^{1}H NMR (**21–22** and **30–31**) analysis. The structure of only one (out of several possible) 2,4,6-regioisomer is shown. 2,4,6-Regioisomers generally represent the major substitution pattern as determined for **21–23** by ^{1}H NMR. Compound purities are generally >90% as determined by GC-MS and ^{1}H NMR.

regioisomers, which can be explained with a generally accepted reaction mechanism (see Supplementary Data†).[13] In these cases an assignment of regioisomers was not possible by spectroscopic means and a chromatographic separation was not feasible. However, the alkyne reaction partners **8** and **11** greatly simplify the formation of possible regioisomers and allow for an assignment of the major pyridine (the structure shown in Fig. 1). In the case of **8**, a regioselectively less challenging homocyclotrimerization was performed leading to the predominant formation (67–90%) of the 2,4,6-substituted homo-pyridines **21–23**. This is in agreement with literature observations in the solution phase.[13] The reaction proceeds through a 2,4-disubstituted cobaltacyclopentadiene as the major reactive species followed by regioselective insertion of the nitrile under carbon–carbon bond formation with the less sterically hindered C-atom attached to the metal (see Supplementary Data†). The 2,3,6-trisubstituted pyridine (not shown) is the minor regioisomer (10–33%).

In the case of a crossed [2 + 2 + 2] cyclotrimerization with the symmetrical alkyne **11**, only two regioisomeric pyridines were obtained with the shown 2,3,4,6-pyridines **30–32** (Fig. 1) being the major isomers and the 2,3,5,6-pyridines (not shown) being the minor isomers. This regioselectivity was established *via* extensive NMR experiments and can be explained by the mechanism depicted in Scheme 2.



Scheme 2

Using a symmetric and a terminal alkyne, two regioisomeric cobaltacyclopentadienes **33** and **34** can be potentially formed. However, the 2,3,4-cyclopentadiene **34** is the minor isomer due to steric interactions between the A and the B substituent. The major 2,3,5-isomer **33** reacts with the nitrile towards the regioisomeric 2,3,4,6- and 2,3,5,6-pyridines, **35** and **36** respectively. The regioisomers **37** and **38** were not observed in the cyclotrimerizations described in Fig. 1. The ratio of **35/36** was about 2 : 1 due to similar sterical demand of the two substituents. The slightly higher amount of **35** can potentially be attributed to the sterical demand of the trityloxy group. We are currently designing novel linker strategies in which the substituent A consists of sterical demanding groups thereby imposing a high regioselectivity on the reaction leading to the predominant formation of **35**. Ideally, these linker groups will be cleaved in a traceless fashion.

In summary, we demonstrated the first crossed [2 + 2 + 2] cyclotrimerization reaction leading to the formation of highly substituted pyridines. The reaction was conducted on a solid-support facilitating its application in the multi-component synthesis of combinatorial libraries with good yields and excellent purities. We are currently expanding its scope by using additional reaction partners (*e.g.* isocyanates) and are synthesizing a variety of small molecule arrays. The obtained heterocyclic structures will be subsequently screened for biological activity.

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Notes and references

1 R. W. Armstrong, A. P. Combs, P. A. Tempest, S. D. Brown and T. A. Keating, *Acc. Chem. Res.*, 1996, **29**, 123–131.
2 S. L. Dax, J. J. McNally and M. A. Youngman, *Curr. Med. Chem.*, 1999, **6**, 255–270.
3 A. Domling, *Comb. Chem. High Throughput Screening*, 1998, **1**, 1–22.
4 C. Hulme and T. Nixey, *Curr. Opin. Drug Discovery Dev.*, 2003, **6**, 921–929.
5 M. Pulici, G. Cervi, K. Martina and F. Quartieri, *Comb. Chem. High Throughput Screening*, 2003, **6**, 693–727.
6 L. Weber, *Curr. Med. Chem.*, 2002, **9**, 2085–2093.
7 S. Booth, P. H. H. Hermkens, H. C. J. Ottenheijm and D. C. Rees, *Tetrahedron*, 1998, **54**, 15385–15443.
8 P. J. Edwards and A. I. Morrell, *Curr. Opin. Drug Discovery Dev.*, 2002, **5**, 594–605.
9 B. Kundu, *Curr. Opin. Drug Discovery Dev.*, 2003, **6**, 815–826.
10 I. Nakamura and Y. Yamamoto, *Chem. Rev.*, 2004, **104**, 2127–2198.
11 J. A. Varela and C. Saa, *Chem. Rev.*, 2003, **103**, 3787–3801.
12 H. Bonnemann, *Angew. Chem., Int. Ed. Engl.*, 1985, **24**, 248–262.
13 N. E. Schore, in *Comprehensive Organic Synthesis*, ed. B. M. Trost, I. Fleming and L. A. Paquette, Pergamon Press, Oxford, 1991, vol. 5, pp. 1129–1162.
14 A. Nefzi, J. M. Ostresh and R. A. Houghten, *Chem. Rev.*, 1997, **97**, 449–472.
15 J. Balzarini, M. Stevens, E. De Clercq, D. Schols and C. Pannecouque, *J. Antimicrob. Chemother.*, 2005, **55**, 135–138.
16 A. R. Pinder, *Nat. Prod. Rep.*, 1992, **9**, 17–23.
17 A. O. Plunkett, *Nat. Prod. Rep.*, 1994, **11**, 581–590.
18 K. C. Nicolaou, R. Scarpelli, B. Bollbuck, B. Werschkun, M. M. Pereira, M. Wartmann, K. H. Altmann, D. Zaharevitz, R. Gussio and P. Giannakakou, *Chem. Biol.*, 2000, **7**, 593–599.
19 E. D. Sternberg and K. P. C. Vollhardt, *J. Org. Chem.*, 1982, **47**, 3447–3450.
20 K. P. C. Vollhardt, *Angew. Chem., Int. Ed. Engl.*, 1984, **23**, 539–556.
21 L. V. R. Bonaga, H. C. Zhang, A. F. Moretto, H. Ye, D. A. Gauthier, J. Li, G. C. Leo and B. E. Maryanoff, *J. Am. Chem. Soc.*, 2005, **127**, 3473–3485.
22 K. M. Brummond, H. F. Chen, P. Sill and L. F. You, *J. Am. Chem. Soc.*, 2002, **124**, 15186–15187.
23 P. A. Evans, J. R. Sawyer, K. W. Lai and J. C. Huffman, *Chem. Commun.*, 2005, 3971–3973.
24 S. R. Gilbertson and B. DeBoef, *J. Am. Chem. Soc.*, 2002, **124**, 8784–8785.
25 D. Suzuki, R. Tanaka, H. Urabe and F. Sato, *J. Am. Chem. Soc.*, 2002, **124**, 3518–3519.
26 T. Takahashi, F. Y. Tsai, Y. Z. Li, H. Wang, Y. Kondo, M. Yamanaka, K. Nakajima and M. Kotora, *J. Am. Chem. Soc.*, 2002, **124**, 5059–5067.
27 Y. Yamamoto, T. Arakawa, R. Ogawa and K. Itoh, *J. Am. Chem. Soc.*, 2003, **125**, 12143–12160.
28 Z. Yu and M. Bradley, *Curr. Opin. Chem. Biol.*, 2002, **6**, 347–352.
29 I. W. James, *Tetrahedron*, 1999, **55**, 4855–4946.
30 F. Guillier, D. Orain and M. Bradley, *Chem. Rev.*, 2000, **100**, 3859–3859.
31 C. Brandli and T. R. Ward, *J. Comb. Chem.*, 2000, **2**, 42–47.