Synthesis of Orthogonally Protected Angular Nitrogen Polyheterocycles via CpCo-Catalyzed Pyridine Formation

Yves Miclo,[a] Pierre Garcia,[a] Yannick Evanno,[b] Pascal George,[b] Mireille Sevrin,[b] Max Malacria,*[a] Vincent Gandon,*[a] Corinne Aubert*[a]

[a] UPMC Univ Paris 06, IPCM UMR 7201, FR2769, 4 Place Jussieu, 75252 Paris Cedex 05, France
Fax +33(1)44277360; E-mail: vincent.gandon@u-psud.fr; corinne.aubert@upmc.fr,

[b] Sanofi-Aventis R&D, CNS Research Department, 31 Avenue Paul Vaillant-Couturier, 92220 Bagneux, France

Received 1 July 2010

Abstract: Unprecedented nitrogen polyheterocycles have been prepared by means of intramolecular Co-catalyzed [2+2+2] cycloaddition of two alkynes to one nitrile. They exhibit two nitrogen-containing rings fused in an angular fashion to one pyridine unit. Several relative positions of the nitrogen atoms have been studied, giving rise to eight different new scaffolds. In order to allow selective functionalization of the two amino groups, orthogonal protecting groups (PG^1 and PG^2) were introduced prior to cyclization. Eleven combinations of seven different protecting groups (Bn, $COCF_3$, Cbz, Boc, Ts, SO_2-2-py, Ns) were tested, most of them being perfectly tolerated under the cyclization conditions.

Key words: alkyne, cobalt, cycloaddition, nitrile, pyridine

The development of synthetic methods aimed at the rapid construction of nitrogen heterocycles is of prime importance to sustain pharmaceutical innovation. Moreover, it is highly desirable that such methods grant an easy access to products that can be selectively functionalized at various sites to allow to set up large libraries of potential leads. Due to its compatibility with many protecting groups, the transition-metal-mediated [2+2+2]-cycloaddition reaction should address these two issues.[1] Pertaining to this idea is the recent work of Snyder who reported a [2+2+2]-cycloaddition approach to tricyclic pyridines fused to one nitrogen and one oxygen heterocycle.[2] The resulting 5,6,7,8-tetrahydro-1,6-naphthyridine scaffold could be used to build up a rich library of compounds after deprotection and functionalization of the nitrogen atom of the piperidine moiety.[3]

We have recently reported the first [2+2+2] cycloadditions involving an ynamide,[4] a nitrile, and an alkyne to give scaffolds of type **A**–**C** displaying two functionalizable nitrogen heterocycles (Figure 1).[5] We reasoned that the introduction of orthogonal protecting groups would dramatically increase the possibility of peptide couplings or other typical transformations used in combinatorial chemistry. We now report on our efforts to synthesize orthogonally protected polyheterocycles displaying one of the eight scaffolds **D**–**K**. To the best of our knowledge, these frameworks are all unprecedented to date, except **E** which was just reported by Pla–Quintana and Roglans.[6a]

Type **E** products were assembled by means of intramolecular rhodium-catalyzed [2+2+2] cycloadditions of two alkynes to one nitrile.[6]

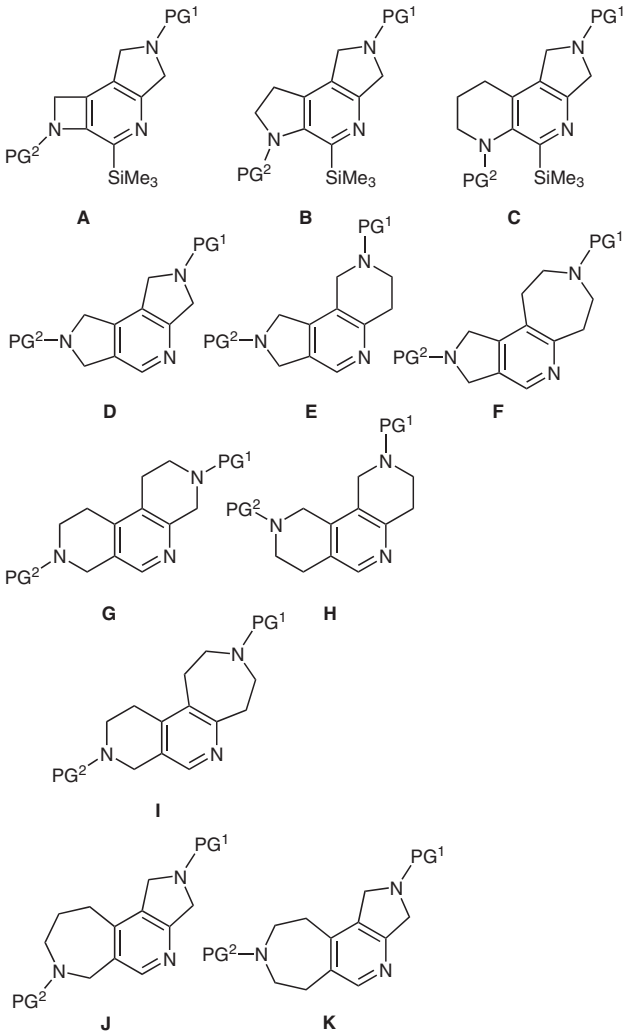
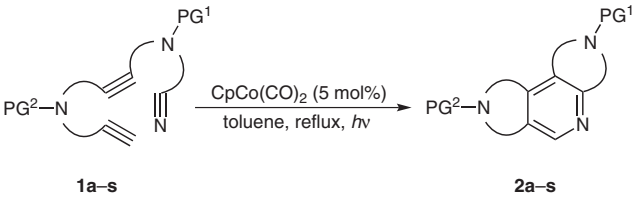


Figure 1

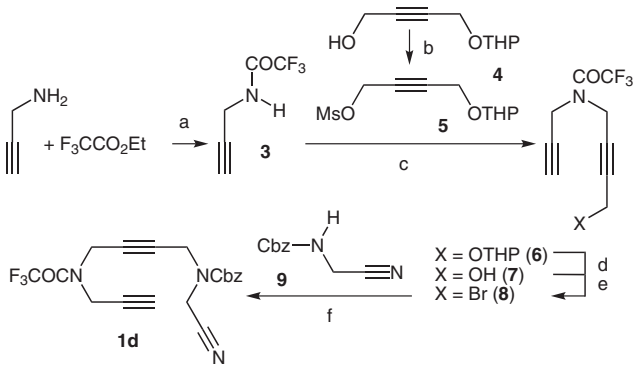
This paper prompted us to report our own results in that field. Our approach to these pyridines, twice fused to pyrrolidine, piperidine, or azepane rings in an angular fashion, relies on the cobalt-catalyzed [2+2+2] cycloaddition of diyne nitriles according to Scheme 1.

SYNLETT 2010, No. 15, pp 2314–2318
Advanced online publication: 12.08.2010
DOI: 10.1055/s-0030-1258041; Art ID: G19210ST



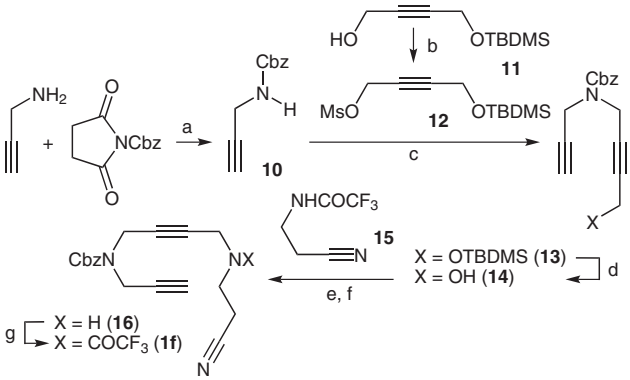
Scheme 1 Cobalt-catalyzed [2+2+2] cycloaddition of orthogonally protected diyne nitriles

The following protecting groups were incorporated in the substrates: benzyl (Bn), trifluoroacyl ($COCF_3$), benzyloxycarbonyl (Cbz), *tert*-butoxycarbonyl (Boc), *p*-toluenesulfonyl (Ts), 2-pyridylsulfonyl (SO_2-2-py), and 2-nitrobenzene-sulfonyl (Ns).[7,8] Representative examples of diyne nitriles synthesis exhibiting orthogonal combinations of protecting groups are shown in Schemes 2– 5. For instance, compound **1d**, potential precursor of a type **D** scaffold with $COCF_3$ (PG^2) and Cbz (PG^1) protecting groups, was obtained in six steps starting from propargyl amine, first protected as trifluoroamide **3** using ethyl trifluoroacetate (Scheme 2).[9] Butyne 1,4-diol monotetrahydropyranyl ether **4**[10] was converted into the corresponding mesylate **5**. The reaction of **3** with **5** under basic conditions led to diyne **6** in 90% yield. This compound was deprotected to give alcohol **7**, subsequently transformed into bromide **8**. Lastly, the bromide was coupled with carbamate **9**,[11] previously deprotonated using sodium hydride.



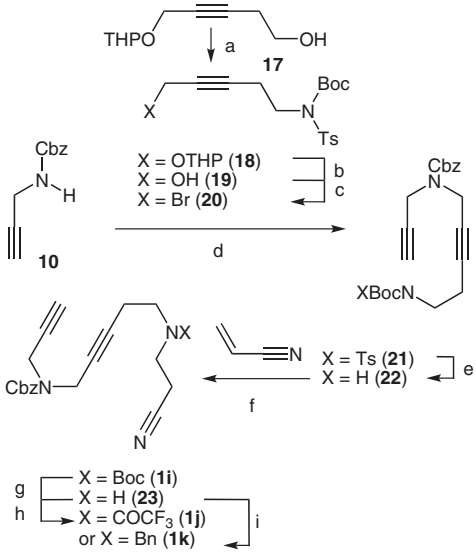
Scheme 2 Synthesis of diyne nitrile **1d**. *Reagents and conditions*: a) F_3CCO_2Et, MeOH, 0 °C to r.t., overnight, 92%; b) MsCl, Et_3N, CH_2Cl_2, 0 °C to r.t., 2 h, 100%; c) NaH (1 equiv), TBAI (10 mol%), THF, 0 °C to reflux, 2 h, 90%; d) PTSA·H_2O (1 mol%), MeOH, r.t., 1 h, 71%; e) CBr_4, Ph_3P, CH_2Cl_2, 0 °C to r.t., 2 h, 100%; f) NaH, DMF, –60 °C to r.t., 2 h, 63%.

The synthesis of **1f** (Scheme 3), potential precursor of a type **E** scaffold with $PG^1 = COCF_3$ and PG^2 = Cbz, was implemented the other way round, that is, by Cbz protection of propargyl amine first.[12] The resulting carbamate **10** was then coupled under basic conditions to mesylate **12**, previously prepared from alcohol **11**.[13] Diyne **13** was then desilylated into alcohol **14**, which was subject to Mitsunobu reaction conditions[14] with nitrile-amide **15**, prepared the same way as **3** (same conditions, same yield).[15] Unfortunately, it was not possible to separate the resulting diyne nitrile from byproducts and unreacted compound **15**. Removal of the $COCF_3$ group[16] allowed partial purification, and finally, reinstatement of the protecting group and flash chromatography furnished **1f** in analytically pure form.



Scheme 3 Synthesis of diyne nitrile **1f**. *Reagents and conditions*: a) CH_2Cl_2, 0 °C to r.t., overnight, 84%; b) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1 h, 93%; c) NaH (1 equiv), DMF, 0 °C to r.t., overnight, 74%; d) TBAF (1.5 equiv), THF, r.t., 12 h, 68%; e) Bu_3P (1.1 equiv), ADDP (1.0 equiv), **15** (2.0 equiv), toluene, 0 °C; f) K_2CO_3, 95% EtOH, r.t., overnight; g) $(F_3CCO)_2O$ (1.2 equiv), Et_3N, CH_2Cl_2, r.t., 30 min, 70% yield (3 steps).

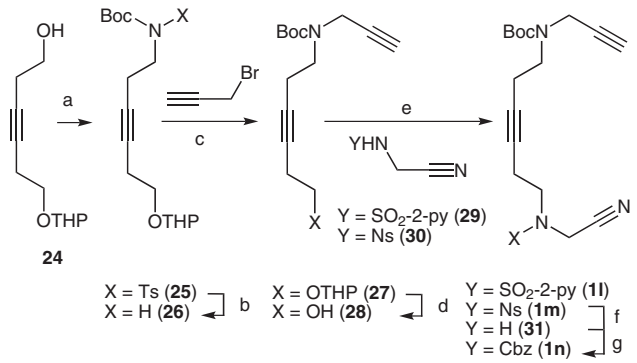
Potential precursors to scaffold **F** were prepared in a similar fashion from carbamate **10** and alcohol **17** (Scheme 4).[10] The latter was reacted under Mitsunobu reaction conditions with TsNHBoc[17] to yield **18** which was deprotected into **19** and then brominated to give **20**. Cou-



Scheme 4 Synthesis of diyne nitriles **1i–k**. *Reagents and conditions*: a) Ph_3P (1.0 equiv), DIAD (1.0 equiv), TsNHBoc (1.0 equiv), THF, r.t., 2 h, 73%; b) PTSA·H_2O (5 mol%), MeOH, r.t., 1 h, 80%; c) CBr_4, Ph_3P, THF, r.t., 3 h, 90%; d) KHMDS (1 equiv), TBAI (10 mol%), THF, r.t. to reflux, 1 h, 70%; e) Mg (5 equiv), MeOH, sonication, r.t., 30 min, 86%; f) KO*t*-Bu (0.3 equiv), *t*-BuOH–DMF (1:1), 0 °C, 10 min, then acrylonitrile (2 equiv), 0 °C, 1 h, 78%; g) TFA, CH_2Cl_2, r.t., 15 min, 73%; h) $(F_3CCO)_2O$ (1.2 equiv), Et_3N (1.5 equiv), CH_2Cl_2, 0 °C, 2 min, 78%; i) BnBr (8 equiv), Et_3N, reflux, 4 h, 42%.

pling of **10** and **20** was then followed by gentle tosyl deprotection using Mg/MeOH under sonication.[18] The resulting diyne was deprotonated by KO*t*-Bu prior to conjugate addition onto acrylonitrile to generate **1i**. The Boc group was removed using trifluoroacetic acid and replaced either by $COCF_3$ (**1j**) or Bn (**1k**).

Our synthetic approach to the larger diyne nitriles **1l–n**, potential precursors of scaffold **G**, is depicted in Scheme 5. Alcohol **24**[19] and TsNHBoc were reacted under standard Mitsunobu conditions to give **25**, from which the tosyl group was subsequently removed and replaced by a propargyl moiety. The tetrahydropyranyl residue was displaced under acidic conditions, and the resulting alcohol was submitted to a second Mitsunobu reaction with aminonitriles bearing SO_2-2-pyridyl (**29**)[20] or nosyl (**30**)[21] protecting group at the nitrogen atom, yielding diyne nitriles **1l** and **1m**, respectively. The latter was used to synthesize **1n** after straightforward deprotection of the nosyl group using thiophenol and potassium carbonate[8b] followed by introduction of the benzyloxycarbonyl group as for **10**.



Scheme 5 Synthesis of diyne nitriles **1l–n**. *Reagents and conditions*: a) Ph_3P (1.0 equiv), DIAD (1.0 equiv), TsNHBoc (1.0 equiv), THF, r.t., 1 h, 84%; b) Mg (5 equiv), MeOH, sonication, r.t., 30 min, 76%; c) KHMDS (1 equiv), THF, 0 °C, 10 min, then propargyl bromide, r.t., 2 h, 66%; d) PTSA·H_2O (5 mol%), MeOH, r.t., 1 h, 94%; e) Ph_3P (1.0 equiv), DIAD (1.0 equiv), **29** (1.0 equiv), THF, r.t., 1 h, 55%; or Ph_3P (1.5 equiv), DIAD (1.0 equiv), **30** (1.0 equiv), THF, r.t., 1 h, 48%; f) PhSH (1.3 equiv), K_2CO_3 (2 equiv), DMF, r.t., 30 min, 74%; g) *N*-(benzyloxycarbonyloxy)succinimide (1.3 equiv), CH_2Cl_2, r.t., overnight, 84%.

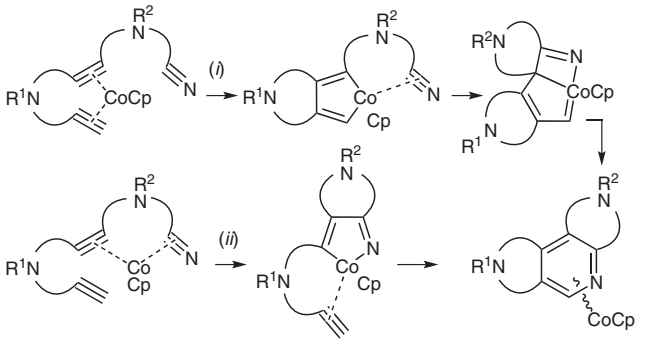
With the diyne nitriles in hand, we carried out cobalt-catalyzed [2+2+2] cycloadditions using 5 mol% of $CpCo(CO)_2$ under refluxing conditions and visible-light irradiation,[22] as shown in Scheme 1. Gratifyingly, these experimental conditions gave birth to scaffolds **D–J** in good yields (Table 1).[23] Any orthogonal combination of Cbz, Ts, $COCF_3$, Boc, and Bn groups were tolerated during the cyclization processes. For instance, in the **D** series, products **2d** and **2e**, displaying Cbz/$COCF_3$ and Cbz/Bn combinations at PG^1 and PG^2, were isolated in 76% and 85%, respectively. It is worthy of note that the synthesis of **2d** could be scaled up to 3 grams. The best results were observed in the **E** series, the naphthyridines **2f**, **2g**, and **2h** being isolated in 96%, 90%, and 91% yield, respectively. These compounds, as all those exhibiting a Cbz group at PG^2, exist as slow interconverting rotamers in $CDCl_3$ at room temperature, making their characterization quite difficult. At higher temperature, the peaks sharpen to give the expected number of signals. For instance, the coalescence of the pyridine proton of **2f**, which appears as two singlets around δ = 8 ppm at 22 °C, is observed at 30 °C, whereas the benzyl protons coalesce at 50 °C (Figure 2). In the **F** series, we were able to prepare three 5/6/7-tricyclic pyridines in 71% (**2i**), 89% (**2j**), and 78% (**2k**) yield. Three members of the **F** series could be obtained in good to high yields. The **G** series showed the compatibility of the 2-pyridylsulfonyl group, **2l** being obtained in 68% yield. On the other hand, in the presence of a Ns group, **2m** was obtained in 19% yield only, accompanied by degradation byproducts. Compound **2o**, corresponding to scaffold **H**, was obtained in 76% yield. For scaffold **I**, the 2-pyridylsulfonyl group was well tolerated at PG^1, the tricyclic pyridine being isolated in 74% yield. Lastly, representatives of the **J** and **K** families could be isolated, yet in decreasing yields.

Table 1 Results of the Cyclizations of Compounds **1a–s**

Scaffold	PG^1	PG^2	Product	Yield (%)[a]
A	Cbz	Ts	**2a**	55[b]
B	Cbz	Ts	**2b**	71[b]
C	Cbz	Ts	**2c**	91[b]
D	Cbz	$COCF_3$	**2d**	76[c]
D	Cbz	Bn	**2e**	85
E	$COCF_3$	Cbz	**2f**	96
E	Boc	Cbz	**2g**	90
E	Bn	Cbz	**2h**	91
F	Boc	Cbz	**2i**	71
F	$COCF_3$	Cbz	**2j**	89
F	Bn	Cbz	**2k**	78
G	SO_2-2-py	Boc	**2l**	68
G	Ns	Boc	**2m**	19
G	Cbz	Boc	**2n**	83
H	Boc	Cbz	**2o**	76
I	SO_2-2-py	Boc	**2p**	74
J	Cbz	Ts	**2q**	56
K	Boc	Cbz	**2r**	30
K	Boc	Ns	**2s**	15

[a] Isolated yields, 0.2–0.8 mmol scale unless stated otherwise.
[b] See ref. 5.
[c] 7.65 mmol scale (3 g).

A closer look at Table 1 suggests that low to moderate yields (<60%) may not only be attributed to the protecting groups (like in **2m**) but also to the size of the left ring (**2a**,**q**,**r**,**s**). Obviously the formation of 4- and 7- is more difficult than that of 5- and 6-membered cycles. This could be due to a slower coupling of the two alkyne units on the way to the key cobaltacyclopentadiene intermediate [Scheme 6, pathway (*i*)].[24]



Scheme 6 Mechanistic options for the synthesis of pyridines as proposed in ref. 25

This step, which precedes the insertion of the nitrile to give a cobalt(V) carbene and then its rearrangement into the pyridine nucleus, is supposed to be thermodynamically more favorable than the alkyne–nitrile coupling followed by alkyne cycloaddition [pathway (*ii*)].[25] Thus, if pathway (*i*) is the only viable option for the assembly of pyridines, the decrease of its rate may bring up competitive reactions such as intermolecular oligomerizations.[26]

In conclusion, we have been able to prepare new heterocyclic scaffolds by means of cobalt-catalyzed [2+2+2] cycloaddition of diyne nitriles. They are composed of a pyridine unit fused to two heterocycles of the pyrrolidine, piperidine, or azepane family. Our goal was not only to open an expedient route to these new polycyclic compounds, but also to facilitate potential functionalization by the orthogonal protection strategy. This was made possible by the extensive level of chemoselectivity of the [2+2+2]-cycloaddition process. Among the seven different protecting groups used, six proved perfectly compatible with the cyclization process. We now wish to create libraries from these compounds and evaluate their biological properties.

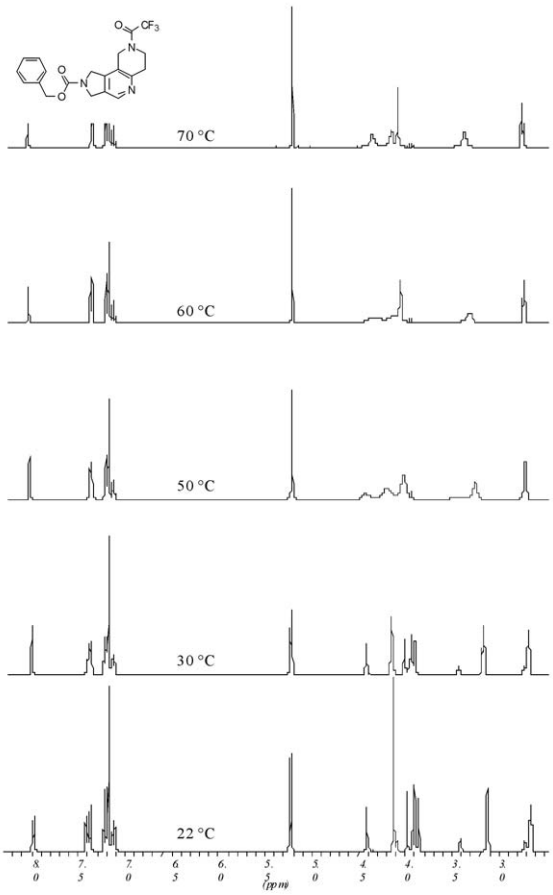


Figure 2 ^{1}H NMR spectra of **2f** ($CDCl_3$) at various temperatures

Acknowledgment

We thank the IUF, Ministère de la Recherche, and CNRS for financial support of this work. P.G. and Y.M. are thankful to Sanofi-Aventis and Sanofi-Synthelabo, respectively, for PhD grants.

References and Notes

(1) For reviews on [2+2+2] cycloaddition reactions, see: (a) Vollhardt, K. P. C. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 539. (b) Varela, J.; Saá, C. *Chem. Rev.* **2003**, *103*, 3787. (c) Yamamoto, Y. *Curr. Org. Chem.* **2005**, *9*, 503. (d) Gandon, V.; Aubert, C.; Malacria, M. *Curr. Org. Chem.* **2005**, *9*, 1699. (e) Kotha, S.; Brahmachary, E.; Lahiri, K. *Eur. J. Org. Chem.* **2005**, 4741. (f) Gandon, V.; Aubert, C.; Malacria, M. *Chem. Commun.* **2006**, 2209. (g) Chopade, P. R.; Louie, J. *Adv. Synth. Catal.* **2006**, *348*, 2307. (h) Agenet, N.; Gandon, V.; Buisine, O.; Slowinski, F.; Aubert, C.; Malacria, M. In *Organic Reactions*, Vol. 68; RajanBabu, T. V., Ed.; John Wiley and Sons: Hoboken, **2007**, 1–302. (i) Heller, B.; Hapke, M. *Chem. Soc. Rev.* **2007**, *36*, 1085. (j) Tanaka, K. *Synlett* **2007**, 1977. (k) Maryanoff, B. E.; Zhang, H.-C. *ARKIVOC* **2007**, *(xii)*, 7. (l) Varela, J.; Saá, C. *Synlett* **2008**, 2571. (m) Tanaka, K. *Chem. Asian J.* **2009**, *4*, 508. (n) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, 3537. (o) Shibata, T.; Tsuchikama, K. *Org. Biomol. Chem.* **2008**, 1317. (p) Scheuermann née Taylor, C. J.; Ward, B. D. *New J. Chem.* **2008**, *32*, 1850. (q) Lebuf, D.; Gandon, V.; Malacria, M. In *Handbook of Cyclization Reactions*, Vol. 1; Ma, S., Ed.; Wiley-VCH: Weinheim, **2009**, 367–406.

(2) Zhou, Y.; Porco, J. A.; Snyder, J. K. *Org. Lett.* **2007**, *9*, 393.

(3) Zhou, Y.; Beeler, A. B.; Cho, S.; Wang, Y.; Franzblau, S. G.; Snyder, J. K. *J. Comb. Chem.* **2008**, *10*, 534.

(4) For recent reviews on the chemistry of ynamides, see: (a) Evano, G.; Coste, A.; Jouvin, K. *Angew. Chem. Int. Ed.* **2010**, *49*, 2840. (b) DeKorver, K. A.; Li, H.; Lohse, A. G.; Hayashi, R.; Lu, Z.; Zhang, Y.; Hsung, R. P. *Chem. Rev.* **2010**, in press; DOI: 10.1021/cr100003s.

(5) Garcia, P.; Moulin, S.; Miclo, Y.; Leboeuf, D.; Gandon, V.; Aubert, C.; Malacria, M. *Chem. Eur. J.* **2009**, *15*, 2129.
(6) Examples of intramolecular [2+2+2] cycloaddition of two alkynes to one nitrile are rare, see ref. 2, 3, 5, and: (a) Garcia, L.; Pla-Quintana, A.; Roglans, A.; Parella, T. *Eur. J. Org. Chem.* **2010**, 3407. (b) Meißner, A.; Groth, U. *Synlett* **2010**, 1051. (c) Chang, H.-T.; Jeganmohan, M.; Cheng, C.-H. *Org. Lett.* **2007**, *9*, 505. (d) Yamomoto, Y.; Kinpara, K.; Ogawa, R.; Nishiyama, H.; Itoh, K. *Chem. Eur. J.* **2006**, *12*, 5618. (e) Groth, U.; Huhn, T.; Kesenheimer, C.; Kalogerakis, A. *Synlett* **2005**, 1758. (f) Nicolaus, N.; Strauss, S.; Neudörfl, J.-M.; Prokop, A.; Schmalz, H.-G. *Org. Lett.* **2009**, *11*, 341.
(7) (a) Green, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis*, 3rd ed.; John Wiley and Sons: New York, **1999**. (b) Kocieński, P. J. *Protecting Groups*, 3rd ed.; Thieme: Stuttgart, **2005**.
(8) The 2-pyridylsulfonyl group can be easily cleaved using for instance magnesium in methanol, see: (a) Pak, C. S.; Lim, D. S. *Synth. Commun.* **2001**, *31*, 2209. (b) On the other hand, the 2-nitrobenzenesulfonyl group can be removed using for instance thiophenol in the presence of potassium carbonate, see: Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373.
(9) Cruickshank, K. A.; Stockwell, D. L. *Tetrahedron Lett.* **1988**, *29*, 5221.
(10) Brillon, D.; Deslongchamps, P. *Can. J. Chem.* **1987**, *65*, 43.
(11) Summa, V.; Petrocchi, A.; Matassa, V. G.; Gardelli, C.; Muraglia, E.; Rowley, M.; Paz Gonzalez, O.; Laufer, R.; Monteagudo, E.; Pace, P. *J. Med. Chem.* **2006**, *49*, 6646.
(12) Masquelin, T.; Obrecht, D. *Synthesis* **1995**, 276.
(13) (a) McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D. *J. Org. Chem.* **1986**, *51*, 3388. (b) Guorong, C.; Wei, Z.; Dawei, M. *Tetrahedron* **2006**, *62*, 5697.
(14) Hughes, D. L. In *Organic Reactions*, Vol. 42; John Wiley and Sons: Hoboken, **1992**.
(15) The use of standard Mitsunobu conditions, Ph_3P/DEAD, proved less efficient than Bu_3P/ADDP: Tsunoda, T.; Yamamiya, Y.; Ito, S. *Tetrahedron Lett.* **1993**, *34*, 1639.
(16) Bergeson, R. J.; McManis, J. S. *J. Org. Chem.* **1988**, *53*, 3108.
(17) Neustadt, B. R. *Tetrahedron Lett.* **1994**, *35*, 379.
(18) Nyasse, B.; Grehn, L.; Regnarsson, U. *Chem. Commun.* **1997**, 1017.
(19) Efskind, J.; Römming, C.; Undheim, K. *J. Chem. Soc., Perkin Trans. 1* **2001**, 2697.
(20) Marquis, R. W.; Ru, Y.; LoCastro, S. M.; Zeng, J.; Yamashita, D. S.; Oh, H.-J.; Erhard, K. F.; Davis, L. D.; Tomaszek, T. A.; Tew, D.; Salyers, K.; Proksch, J.; Ward, K.; Smith, B.; Levy, M.; Cummings, M. D.; Haltiwanger, R. C.; Trescher, G.; Wang, B.; Hemling, M. E.; Quinn, C. J.; Cheng, H.-Y.; Lin, F.; Smith, W. W.; Janson, C. A.; Zhao, B.; McQueney, M. S.; D'Alessio, K.; Lee, C.-P.; Marzulli, A.; Dodds, R. A.; Blake, S.; James, I. E.; Gress, C. J.; Bradley, B. R.; Lark, M. W.; Gowen, M.; Veber, D. F. *J. Med. Chem.* **2001**, *44*, 1380.
(21) Excellent yields of Mitsunobu reactions in the presence of the 2-nitrobenzenesulfonyl group have been reported, see ref. 8b.
(22) (a) For technical details about the visible light irradiation, see: Agenet, N.; Mirebeau, J.-H.; Petit, M.; Thouvenot, R.; Gandon, V.; Malacria, M.; Aubert, C. *Organometallics* **2007**, *26*, 819. (b) **Procedure for [2+2+2] Cycloadditions** To a refluxing solution of the starting material in xylenes (*c* 0.1 M) under argon was added 5 mol% of cyclopentadienyledicarbonyl cobalt, and the mixture was irradiated (visible light) using a 300 W halogen lamp until completion of the reaction (TLC monitoring). After removal of the volatiles under reduced pressure, the crude mixture was purified by flash chromatography (gradient mixtures of PE and EtOAc), affording the corresponding tricyclic pyridines.
Compound **2f**: ^{1}H NMR (400 MHz, C_6D_6, 70 °C): δ = 2.84 (t, *J* = 6.0 Hz, 2 H), 3.46 (br s, 2 H), 4.18 (s, 2 H), 4.24 (br s,2 H), 4.44 (br s, 2 H), 5.30 (s, 2 H), 7.20–7.31 (m, 3 H), 7.45 (d, *J* = 7.6 Hz, 2 H), 8.14 (s, 1 H). ^{13}C NMR (100 MHz, C_6D_6): δ = 31.0–32.2 (CH_2), 41.2–42.1 (CH_2), 42.8–43.4 (CH_2), 49.5–49.9 (CH_2), 50.4–50.7 (CH_2), 67.3 (CH_2), 117.03 (q, *J* = 286 Hz, CF_3), 121.7–121.9 (C), 128.4 (CH), 128.5 (CH), 128.8 (CH), 131.3-131.7 (C), 137.4 (C), 142.3–142.9 (m, CH), 143.1–143.4 (C), 151.5–151.6 (C), 155.5 (q, *J* = 36 Hz, C). ^{19}F NMR (376 MHz, $CDCl_3$): δ = –69.7. IR (neat): 3089, 3064, 3033, 2949, 2864, 1689, 1138, 730 cm^{-1}. Mp 144.1 °C. HRMS: *m/z* calcd for $C_{20}H_{19}O_3N_3F_3$: 406.1370; found: 406.13727.
Compound **2i**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 2.78 (br s, 2 H), 3.17 (br s, 2 H), 3.59 (br s, 4 H), 4.69–4.72 (2 s, 2 H), 4.78 (br s, 2 H), 5.20 (s, 2 H), 7.28–7.41 (m, 5 H), 8.22–8.28 (2 s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 28.5 (CH_3), 28.7 (CH_2), 31.3–31.8 (m, CH_2), 40.1–45.9 (m, 2 CH_2), 50.7–51.2 (CH_2), 51.3–51.8 (CH_2), 67.3–67.4 (CH_2), 80.1 (C), 128.0 (CH), 128.3 (CH), 128.6 (CH), 130.5–131.4 (m, 2 C), 136.6 (C), 140.8–140.9 (CH), 145.6–145.9 (m, 2 C), 154.7–155.0 (C), 159.7 (C). IR (neat): 2974, 1692, 1414 cm^{-1}. Mp 154.1 °C. HRMS: *m/z* calcd for $C_{24}H_{30}O_4N_3$: 424.22308; found: 424.22297.
Compound **2k**: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.52–2.59 (m, 4 H), 2.68–2.73 (m, 2 H), 3.08–3.10 (m, 2 H), 3.55 (s, 2 H), 4.56 (s, 1 H), 4.61 (s, 1 H), 4.67 (s, 1 H), 4.69 (s, 1 H), 5.12 (s, 2 H), 7.15–7.30 (m, 11 H), 8.10–8.15 (2 s, 1 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 30.7–30.8 (CH_2), 39.3 (CH_2), 50.7–51.1–51.2–51.6 (mixture of slow interconverting rotamers) (2 CH_2), 53.7 (CH_2), 54.2 (CH_2), 63.5 (CH_2), 67.3 (CH_2), 127.2 (CH), 128.0 (CH), 128.2 (CH), 128.4 (CH), 128.6 (CH), 129.1 (CH), 130.1–131.1 (C), 131.4–131.6 (C), 136.7 (C), 138.5 (C), 140.5–140.8 (CH), 144.5–144.8 (C), 154.8 (C), 161.1–161.2 (C). IR (neat): 2942, 1703, 1412 cm^{-1}. HRMS: *m/z* calcd for $C_{23}H_{28}O_2N_3$: 414.21760; found 414.21754.
(23) It is worthy of note that attempts to cyclize monoprotected diyne nitriles such as **16**, **23**, or **31** failed.
(24) For theoretical calculations on the formation of cobaltacyclopentadienes and their reactivity, see: (a) Xu, R.; Winget, P.; Clark, T. *Eur. J. Inorg. Chem.* **2008**, 2874. (b) Agenet, N.; Gandon, V.; Vollhardt, K. P. C.; Malacria, M.; Aubert, M. C. *J. Am. Chem. Soc.* **2007**, *129*, 8860. (c) Aubert, C.; Gandon, V.; Geny, A.; Heckrodt, T. J.; Malacria, M.; Paredes, E.; Vollhardt, K. P. C. *Chem. Eur. J.* **2007**, *13*, 7466. (d) Gandon, V.; Agenet, N.; Vollhardt, K. P. C.; Malacria, M.; Aubert, C. *J. Am. Chem. Soc.* **2006**, *128*, 8509. (e) Dahy, A. A.; Koga, N. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 781. (f) Dahy, A. A.; Suresh, C. H.; Koga, N. *Bull. Chem. Soc. Jpn.* **2005**, *78*, 792. (g) Veiros, L. F.; Dazinger, G.; Kirchner, K.; Calhorda, M. J.; Schmid, R. *Chem. Eur. J.* **2004**, *10*, 5860.
(25) For a DFT study of the mechanism of pyridine formation via [2+2+2] cycloaddition, see: Dazinger, G.; Torres-Rodrigues, M.; Kirchner, K.; Calhorda, M. J.; Costa, P. J. *J. Organomet. Chem.* **2006**, *691*, 4434.
(26) Also we cannot exclude catalyst deactivation by the Ns group.