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Regioselective Cobalt-Catalyzed Formation of Bicyclic 3- and 4-Aminopyridines

Pierre Garcia,[†] Yannick Evanno,[§] Pascal George,[§] Mireille Sevrin,[§] Gino Ricci,[‡] Max Malacria,*[,†] Corinne Aubert,*[,†] and Vincent Gandon*[,†]

UPMC, Université Paris 06, IPCM 7201, 4 Place Jussieu, 75252 Paris Cedex 05, France, Sanofi-Aventis, 45 Chemin de Météline, 04200 Sisteron, France, and Sanofi-Aventis Recherche & Développement, 1 Avenue Pierre Brossolette, 91385 Chilly-Mazarin, France

max.malacria@upmc.fr; corinne.aubert@upmc.fr; vincent.gandon@u-psud.fr

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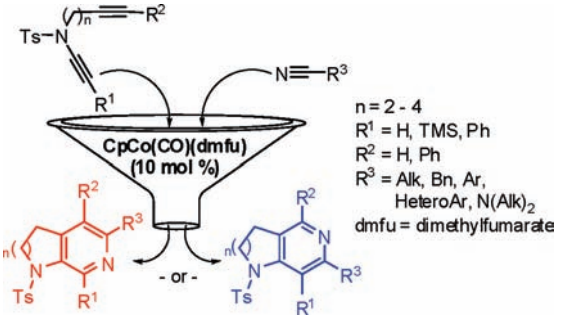
ABSTRACT



Bimolecular cobalt-catalyzed [2 + 2 + 2] cycloadditions between yne−ynamides and nitriles afford bicyclic 3- or 4-aminopyridines in up to 100% yield. The high regioselectivity observed depends on the substitution pattern at the starting ynamide. Aminopyridines bearing TMS and Ts groups are efficiently deprotected in an orthogonal fashion.

Nitrogen-substituted pyridines represent an important class of compounds displaying promising biological properties.[1] Thus, to sustain pharmaceutical innovation, synthetic methods allowing a rapid access to aminopyridine frameworks are highly desirable (Figure 1).[2] The known procedures usually rely on the functionalization of a preexisting pyridine ring (e.g., tandem ortho-metalation/alkylation,[2a,b] Chichibabine aromatic substitution,[2c] or Buchwald−Hartwig amination[3]).[4] On the other hand, we describe herein an approach based on the direct construction

[†] Université Paris.
[§] Sanofi-Aventis Recherche & Développement.
[‡] Sanofi-Aventis.

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of the pyridine nucleus by a cobalt-catalyzed [2 + 2 + 2] cycloaddition between two alkynes and one nitrile.[5]

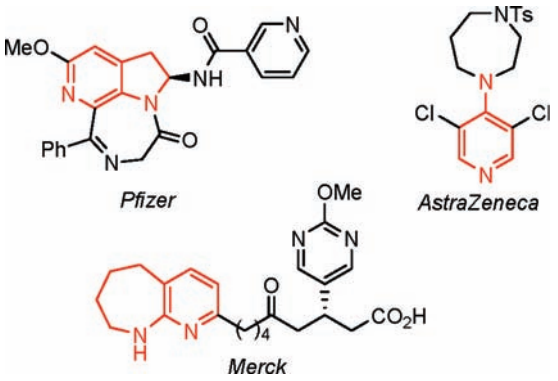


Figure 1. Aminopyridines from pharmaceutical companies.

To make this reaction applicable to the synthesis of 3-amino- as well as 4-aminopyridines, we decided to use ynamides[6] as alkyne partners (Figure 2). Although various [2 + 2 + 2] cycloadditions involving one ynamide and two alkynes to give N-substituted benzenes have been reported,[7] the formation of pyridines using such substrates has not received much attention and is still limited to intramolecular cyclizations (Figure 2, eq 1).[8]

Of course, only 3-aminopyridines can be formed in the intramolecular version, at least with relatively short tethers.[9] We were interested in the development of a more flexible method that could selectively provide the different regioisomers using yne-ynamides and readily available nitriles (Figure 2, eq 2).

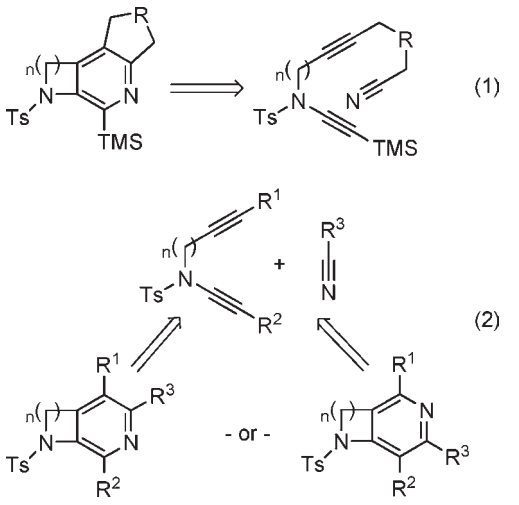
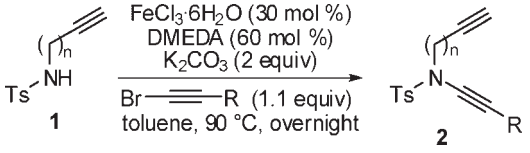


Figure 2. [2 + 2 + 2] approaches to polycyclic aminopyridines.

The starting ynamides **2a**−**d** could be prepared in quite large amounts from sulfonamides (up to 5 g), in moderate to good yields, using Zhang's conditions (Table 1).[10]

Table 1. Synthesis of the Ynamides



entry	product	*n*	R	yield (%)
1	**2a**	1	TMS	35
2	**2b**	2	TMS	79
3	**2c^{TMS}**	3	TMS	72
4	**2c^{Ph}**	3	Ph	65
5	**2d**	4	TMS	59

With these compounds in hand, we carried out [2 + 2 + 2] cycloadditions with several nitriles in the presence of 10 mol % of CpCo(CO)(dimethyl fumarate), an air-stable catalyst recently developed in our laboratory (Table 2).[11] Whatever the nitrile, total chemo- and regioselectivity toward 3-aminopyridines was observed. Neither the regioisomers nor oligomers could be detected in the ^{1}H NMR spectra of the crude materials.

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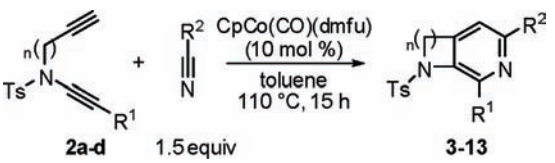
Table 2. Synthesis of Bicyclic 3-Aminopyridines[a]



entry	2a-d	product, yield [%]	entry	2a-d	product, yield [%]
1	**2a**	**0**	7	$\mathbf{2c^{TMS}}$	**8**, 50
2	**2b**	**3**, 90	8	$\mathbf{2c^{TMS}}$	**9**, 72[b]
3	$\mathbf{2c^{TMS}}$	**4**, 82	9	$\mathbf{2c^{TMS}}$	**10**, 36
4	**2d**	**5**, 91	10	$\mathbf{2c^{Ph}}$	**11**, 100
5	$\mathbf{2c^{TMS}}$	**6**, 90 (85)[c]	11	$\mathbf{2c^{TMS}}$	**12**, 83
6	$\mathbf{2c^{TMS}}$	**7**, 84	12	$\mathbf{2c^{TMS}}$	**13**, 85

[a] **2**: 0.3−0.6 mmol. [b] MeCN: 10 equiv. [c] $\mathbf{2c^{TMS}}$: 1 g scale (3 mmol). dmfu = dimethyl fumarate.

The formation of the 3-aminopyridine subunit was evidenced by the presence of diagnostic ^{1}H and ^{13}C pyridine signals. In addition, we were able to obtain single crystals of **6** suitable for an X-ray diffraction study, which unambiguously confirmed the proposed structure (Figure 3).[12] In the presence of benzonitrile, the propargylic ynamide **2a** did not furnish any cycloadduct (entry 1). In contrast, the two-, three-, and four-carbon tethered substrates **2b**, $\mathbf{2c^{TMS}}$, and **2d** led to the desired products in excellent yields (entries 2−4). The use of 4-(trifluoromethyl)benzonitrile did not alter the efficiency of the reaction (entry 5), **6** being isolated in 90% yield (85% on a 1 g scale). Nitriles bearing heteroaromatics were tested next. While $\mathbf{2c^{TMS}}$ reacted with furan-2-carbonitrile to afford **7** in 84% yield (entry 6), its reaction with picolinonitrile proved less efficient, with **8** being isolated in a moderate 50% yield (entry 7). This is presumably due to the chelating nature of the 2,2′-bipyridine scaffold which is able to trap cobalt.[13] We then turned our attention to alkyl-substituted nitriles. Acetonitrile, which was used in large excess to avoid excessive evaporation, gave rise to **9** in 72% yield when reacted with $\mathbf{2c^{TMS}}$ (entry 8). The sterically congested pivalonitrile furnished cycloadduct **10** in a modest 36% yield (entry 9). Gratifyingly, 2-(dimethylamino)acetonitrile allowed the formation of **11** from $\mathbf{2c^{Ph}}$ in quantitative yield (entry 10) and of **12** from $\mathbf{2c^{TMS}}$ in 83% yield (entry 11). In these two cases, the chelating ability of the products is greatly diminished compared to **8**, allowing higher yields. Bearing in mind the formation of 2-aminopyridines by Co-catalyzed [2 + 2 + 2] cycloadditions involving cyanamides,[14] we next engaged *N*-cyanomorpholine with $\mathbf{2c^{TMS}}$. By this means, the expected 2,5-diaminopyridine **13** was obtained in 85% yield (entry 12).

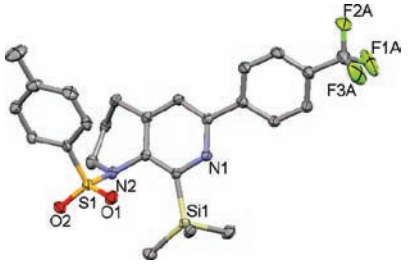


Figure 3. ORTEP view of compound **6**.

The mechanism of the Co-catalyzed [2 + 2 + 2] cycloaddition of two alkynes to one nitrile to give pyridines has been studied by means of DFT computations.[15] It was shown that (nitrile)Cp-cobalta-cyclopentadiene intermediates (Scheme 1) are preferably formed over (alkyne)Cp-azacobaltacyclopentadienes. They give rise to the pyridine nucleus either by insertion or by intramolecular [4 + 2] cycloaddition between the complexed nitrile and the diene framework of the metallacycle. Because all substrates used in Table 1 are monosubstituted at the alkyne terminus and give 3-aminopyridines exclusively, it transpires that the C−C bond formation occurs at the least sterically demanding carbon of the metallacycle (Figure 2, eq 1). Following this simple rationale, one can assume that a reversal of the steric demand on the substrate would favor the formation of 4-aminopyridines (Figure 2, eq 2) instead.

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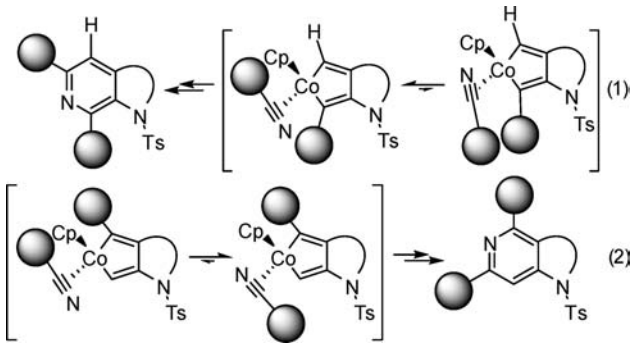
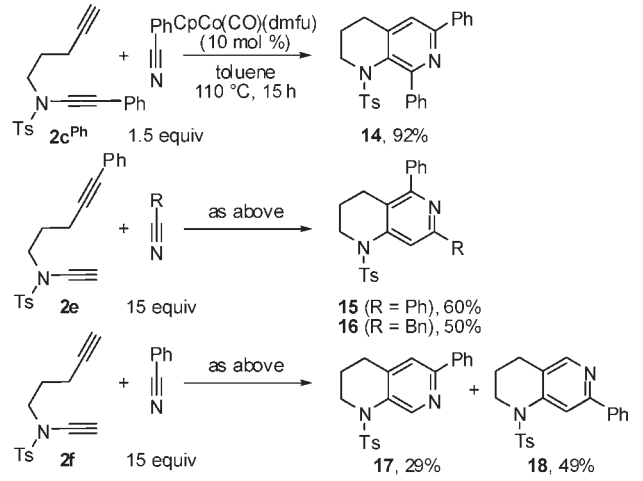
Scheme 1. Putative Intermediates on Route to Aminopyridines



To validate this hypothesis, we prepared compound **2e**, displaying a monosubstituted ynamide moiety and a Ph-substituted alkyne terminus (Scheme 2). Thus, in **2e**, the steric demand lies at the opposite site compared to $\mathbf{2c^{Ph}}$. The latter was reacted with benzonitrile and tranformed into the anticipated 3-aminopyridine **14** in 92% yield. In contrast, and in agreement with our rationale, no trace of 3-aminopyridine could be observed when using **2e**. Products that were attributed to oligomers of **2e** as well as the 4-aminopyridine **15** were isolated in mixture. To avoid autotrimerization of the ynamide, the reaction was carried out in the presence of a large excess of benzonitrile. This procedure eventually furnished **15** in 60% isolated yield.

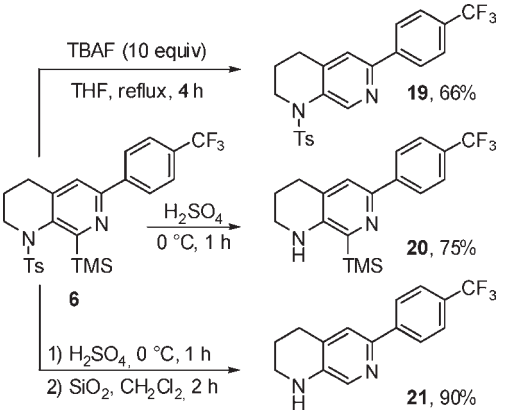
Phenylacetonitrile also allowed the formation of the 4-aminopyridine **16**, albeit in a lower 50% yield. Lastly, the unsubstituted yne−ynamide **2f** was tested and gave rise, as one could expect, to a mixture of the 3-amino- and 4-aminopyridines **17** and **18**.

Scheme 2. 3-Amino- vs 4-Aminopyridines[a]



[a] dmfu = dimethylfumarate.

Scheme 3. Selective Deprotections of **6**.[a]



[a] 0.2 mmol scale.

To find potential leads among aminopyridine derivatives, large libraries of compounds have to be set up by selective functionalization. Since most of the products shown above exhibit the two orthogonal protecting groups TMS and Ts,[16] we wanted to make sure that they could be easily and selectively cleaved. Starting from **6**, the TMS group was removed using TBAF in refluxing THF, affording **19** in 66% yield (Scheme 3). On the other hand, the Ts group was removed by dissolution of **6** in neat sulfuric acid, giving **20** in 75% yield. Interestingly, when **20** was absorbed on silica gel for 2 h, protodesilylation occurred.[17] Thus, the fully deprotected aminopyridine **21** could be obtained in two steps from **6** in 90% yield.

In conclusion, we have developed an expedient way to synthesize 3- and 4-aminopyridines selectively. Our strategy provides a rapid access to a wide variety of scaffolds such as dihydropyrrolopyridine, tetrahydronaphthyridine, tetrahydropyridoazepine, as well as 2,5-diaminopyridine. We are now employing this procedure to build a library of compounds which will be submitted to biological investigations.

Acknowledgment. We thank Sanofi-Aventis, the IUF, Ministère de la recherche, and CNRS for financial support.

Supporting Information Available. Experimental procedures, characterization of the new products, and NMR spectra.This material is available free of charge via the Internet at http://pubs.acs.org.

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