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Synthesis of Aminopyridines and Aminopyridones by Cobalt-Catalyzed [2+2+2] Cycloadditions Involving Yne-Ynamides: Scope, Limitations, and Mechanistic Insights

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Abstract: An in-depth study of the cobalt-catalyzed [2+2+2] cycloaddition between yne-ynamides and nitriles to afford aminopyridines has been carried out. About 30 nitriles exhibiting a broad range of steric demand and electronic properties have been evaluated, some of which open new perspectives in metal-catalyzed arene formation. In particular, the use of [CpCo(CO)(dmfu)] (dmfu = dimethyl fumarate) as a precatalyst made possible the incorporation of electron-deficient nitriles into the pyridine core. Modification of the substitution pattern at the yne-ynamide allows the regioselectivity to be switched toward 3- or 4-aminopyridines. Application of this synthetic methodology to the construction of the aminopyridone framework using a yne-ynamide and an isocyanate was also briefly examined. DFT computations suggest that 3-aminopyridines are formed by formal [4+2] cycloaddition between the nitrile and the intermediate cobaltacyclopentadiene, whereas 4-aminopyridines arise from an insertion pathway.

Keywords: alkynes · cobalt · cycloaddition · nitrogen heterocycles · reaction mechanisms · reactive intermediates

Introduction

Pyridine derivatives are important organic targets because they constitute a ubiquitous scaffold of bioactive and natural products. Pyridines are also present in many promising materials.[1] Of all the synthetic pathways leading to the pyridine core, the metal-catalyzed [2+2+2] cycloaddition reaction is probably one of the most elegant because it is 100% atom economical as far as the substrates are concerned.[2,3] Thus, in recent years, particular interest has been paid in our laboratory to the formation of pyridines using this strategy.[4] Specifically, we have shown that polycyclic 3- and 4-aminopyridines could be rapidly and regioselectively constructed by cobalt-catalyzed [2+2+2] cycloaddition between an ynamide,[5] an alkyne, and a nitrile.[4a,c,6] As a sequel, we report herein, a detailed investigation on the reactivity of yne-ynamides towards nitriles in the presence of the air-stable precatalyst [CpCo(CO)(dmfu)] (dmfu = dimethyl fumarate).[7] The nature of the nitriles as well as the substitution pattern at each alkyne terminus of the yne-ynamides have been scrutinized. Our results stimulated DFT computations aimed at getting a better overview of the mechanism of pyridine formation by cobalt-catalyzed [2+2+2] cycloadditions.

Results and Discussion

In a preliminary report, we showed that a few nitriles and yne-ynamides could be efficiently and regioselectively converted into bicyclic 3- and 4-aminopyridines under cobalt catalysis.[4c] To study the scope of this reaction, we decided to broaden the variety of substrates, starting with yne-ynamide **1a** and aliphatic nitriles (Table 1). This first set of experiments revealed the importance of steric factors in this process. Indeed, whereas the use of acetonitrile furnished 3-aminopyridine **2** in 72% yield, bulky pivalonitrile gave rise to **3** in only 36% yield (Table 1, entries 1 and 2). Among methylene-substituted derivatives, 2-phenylacetonitrile readily transformed into **4** and was isolated in 89% yield (Table 1, entry 3). On the other hand, haloacetonitriles were found to be inappropriate partners (Table 1, entry 4). Degradation of the catalyst was actually observed in this case,

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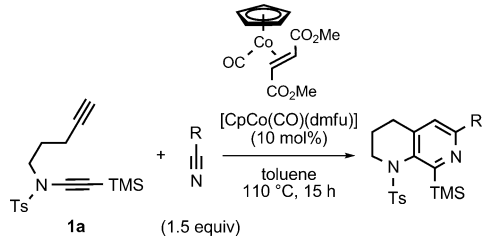
Table 1. Reaction of alkyl nitriles with yne-ynamide **1a**.



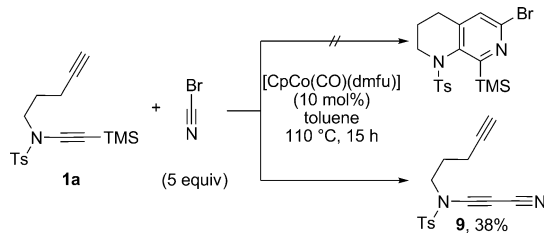
1a (1.5 equiv)

Entry	R	Product	Yield [%][a]
1[b]	Me	**2**	72
2	*t*Bu	**3**	36
3	Bn	**4**	89
4[c]	CH_2X	–	0
5	CH_2OMe	**5**	73
6	CH_2SMe	**6**	73
7	CH_2NMe_2	**7**	83
8	CH_2SO_2Ph	–	0
9	CH_2CO_2tBu	**8**	81
10	CH_2CO_2H	–	0

[a] Isolated product yield. [b] Nitrile: 10 equiv. [c] X = Cl, Br, or I.

both visually (the red color changing to green) and by ^{1}H NMR spectroscopic analysis.[8] Methoxy-, methylthio-, and dimethylaminoacetonitrile were converted into the expected 3-aminopyridines in high yields (73, 73, and 83%, respectively; Table 1, entries 5, 6 and 7). Whereas no reaction took place with phenylsulfonylacetonitrile (Table 1, entry 8), *tert*-butyl cyanoacetate proved perfectly compatible (81%, Table 1, entry 9). However, the use of the corresponding cyanoacetic acid resulted in catalyst degradation (Table 1, entry 10).

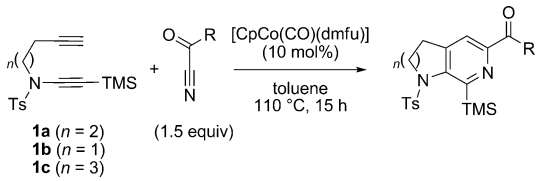
Inspired by our recent work on cobalt-catalyzed cycloadditions involving alkynyl halides,[9] we envisaged the use of cyanogen bromide as nitrile partner (Scheme 1). Although the expected bicyclic aminopyridine was not observed in this case, the unprecedented cyanoynamide **9** was isolated in 38% yield.[10,11]



Scheme 1. Unexpected reactivity of yne-ynamide **1a** with BrCN.

Because BrCN failed to deliver a pyridine that was amenable to functionalization at C6, we turned our attention to pyruvonitrile and cyanoformates (Table 2). With the former, only trace amounts of the expected product were observed in the ^{1}H NMR spectrum of the crude mixture (Table 2, entry 1). Gratifyingly, methyl and benzyl cyanoformates furnished the desired products in reasonable yields (Table 2, entries 2–5). With the latter, we could also use three- and four-carbon tethered yne-ynamides for the construction of dihydropyrrolopyridine **13** and tetrahydropyridoazepine **14**.

Table 2. Reaction of yne-ynamides **1a–c** with electron-deficient nitriles.



1a (*n* = 2)
1b (*n* = 1)
1c (*n* = 3)

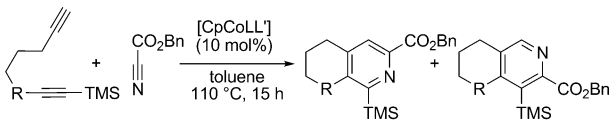
(1.5 equiv)

Entry	Ynamide	R	Product	Yield [%][a]
1	**1a**	Me	**10**	–[b]
2	**1a**	OMe	**11**	51
3	**1a**	OBn	**12**	59
4	**1b**	OBn	**13**	61
5	**1c**	OBn	**14**	52

[a] Isolated product yield. [b] Trace amounts.

The good results obtained with these electron-deficient nitriles are intriguing. Indeed, cyanoformates are known to react sluggishly with 1,7-octadiyne under cobalt catalysis.[12,13] Because a new catalyst was used during our work, we wanted to know whether the efficiency of the incorporation of cyanoformates in the [2+2+2] process was inherent to the complex or to the ynamide itself. To this end, a short comparative study was carried out (Table 3). With the classical air-sensitive complex $[CpCo(C_2H_4)_2]$,[14] both ynamide **1a** and diyne **1d** gave rise to pyridines in low yields (Table 3, entries 1 and 2). In sharp contrast, with [CpCo(CO)(dmfu)], the products were obtained in 59 and 60% yield in each case (Table 3, entries 3 and 4). With **1a**, only the 3-aminopyridine **12** was detected, whereas with **1d**, a 1.5:1 mixture of regioisomers **15** and **16** was obtained. Thus, beyond the great advantage of [CpCo(CO)(dmfu)] in terms of air-stability, it appears that this catalyst expands the field of applications of cobalt-catalyzed transformations by allowing the use of electron-poor nitriles. This effect cannot be attributed to the difference in electronic properties between yne-ynamides and diynes. However, the ynamide do actually play a role by controlling the regioselectivity of nitrile incorporation.

Table 3. Yne-ynamide **1a** versus diyne **1d** in the reaction with benzyl cyanoformate.



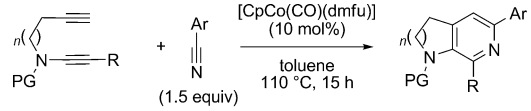
1a (R = NTs)
1d (R = CH_2)

12
15
16

Entry	Substrate	LL′	Product	Yield [%][a]
1	**1a**	$(C_2H_4)_2$	**12**	24
2	**1d**	$(C_2H_4)_2$	**15**	17
3	**1a**	(CO)(dmfu)	**12**	59
4	**1d**	(CO)(dmfu)	**15/16**	60 (1.5:1)

[a] Ratio determined by ^{1}H NMR spectroscopic analysis.

Table 4. Cycloadditions between yne-ynamides and aromatic nitriles.



1a (*n* = 2, PG = Ts, R = TMS)
1b (*n* = 1, PG = Ts, R = TMS)
1c (*n* = 3, PG = Ts, R = TMS)
1e (*n* = 2, PG = Ts, R = Ph)
1f (*n* = 2, PG = Ts, R = *n*Bu)
1g (*n* = 2, PG = *p*Ns, R = TMS)

Entry	Ynamide	Ar	Product	Yield [%][a]	Entry	Ynamide	Ar	Product	Yield [%][a]
1	**1a**	Ph	**17**	82	8	**1a**	2,4,6-F_3-C_6H_2	**24**	100
2	**1e**	Ph	**18**	92	9	**1a**	4-(MeO)-C_6H_4	**25**	40
3	**1f**	Ph	**19**	61	10	**1a**	4-pyridyl	**26**	92
4	**1b**	Ph	**20**	90	11	**1a**	3-pyridyl	**27**	90
5	**1c**	Ph	**21**	91	12	**1a**	2-pyridyl	**28**	50 (81)[b]
6	**1a**	4-(F_3C)-C_6H_4	**22**	90	13	**1a**	2-furyl	**29**	84
7	**1g**	4-(F_3C)-C_6H_4	**23**	79	14	**1a**	2-thienyl	**30**	90

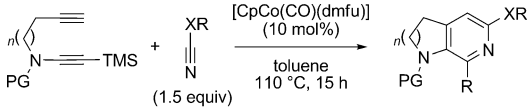
[a] Isolated product yield. [b] Reaction conducted on 1 g scale with 20 mol% catalyst.

The case of aromatic nitriles was studied next (Table 4). Benzonitrile allowed the formation of a range of cycloadducts in good to high yields (Table 4, entries 1–5), as well as electron-deficient 4-(trifluoromethyl)benzonitrile (Table 4, entries 6 and 7) and 2,4,6-trifluorobenzonitrile (Table 4, entry 8). The latter proved particularly well-tolerated because product **24** was isolated quantitatively. On the other hand, with the electron-rich 4-(methoxy)benzonitrile, the isolated yield was less than half of the previous yield (Table 4, entry 9). Use of regioisomeric cyanopyridines also permitted a highly efficient process to proceed (Table 4, entries 10–12), even for the formation of a 2,2′-bipyridine scaffold (Table 4, entry 12), although in this case an increase of catalyst loading to 20 mol% was required to reach 81% yield.[15] In spite of this limitation, it is worthy of note that the synthesis of **28** could be carried out on a 1 g scale. Finally, the reaction proved to be also compatible with oxygen- and sulfur-containing heteroaromatics 2-furonitrile and 2-thiophenecarbonitrile, with **29** and **30** being isolated in 84 and 90% yield, respectively (Table 4, entries 13 and 14).

Another approach to the synthesis of aminopyridines by metal-catalyzed [2+2+2] cycloaddition involves the use of cyanamides.[16] We have previously reported that yne-ynamide **1a** could be reacted with *N*-cyanomorpholine to give 2,5-diaminopyridine **31** in 85% yield (Table 5, entry 1).[4c] Regrettably, the other heterosubstituted nitriles that were evaluated next proved quite reluctant, affording yields of 20–51%. With *N*-cyanopyrrolidine, the expected pyridine was isolated in 32% yield (Table 5, entry 2). Nonetheless, it was possible to reach 75% yield with prolonged heating (48 h). Protodesilylation occurred on silica gel during purification of the crude mixture obtained after the reaction of **1g** (Table 5, entry 3).[4c,17] Five- and seven-membered rings could also be assembled by using ynamides **1b** (Table 5, entry 4) and **1c** (Table 5, entry 5). Interestingly, the use of ethyl thiocyanate allowed the formation of the original 2-ethylthio-5-aminopyridines **36** and **37** (Table 5, entries 6 and 7).

All the yne-ynamides discussed above display only one substituted alkyne terminus at the ynamide moiety, and transform into 3-aminopyridines. We have previously reported that the regioselectivity of the title reaction could be reversed to yield 4-aminopyridines when the alkyne terminus of the yne moiety was the only substituted region (Scheme 2).[4c] In the absence of substituents at both extremities, a mixture of regioisomers is formed.

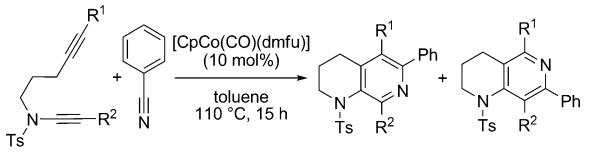
Table 5. Synthesis of heterosubstituted aminopyridines.



1a (*n* = 2, PG = Ts, R = TMS)
1b (*n* = 1, PG = Ts, R = TMS)
1c (*n* = 3, PG = Ts, R = TMS)
1g (*n* = 2, PG = *p*Ns, R = TMS)

Entry	Ynamide	X-R	Product	Yield [%][a]
1	**1a**	*N*-morpholyl	**31**	85
2	**1a**	*N*-pyrrolidyl	**32**	32 (75)[b]
3	**1g**	*N*-pyrrolidyl	**33**	49[c]
4	**1b**	*N*-pyrrolidyl	**34**	51
5	**1c**	*N*-pyrrolidyl	**35**	20
6	**1b**	SEt	**36**	37
7	**1a**	SEt	**37**	33

[a] Isolated product yield. [b] 48 h instead of 15 h. [c] Protodesilylation occurred: TMS/H 1:1.7.

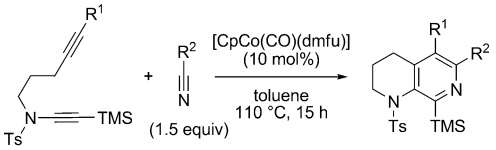


1e (R^1 = H, R^2 = Ph) — **18** (92%) — -
1h (R^1 = Ph, R^2 = H) — - — **38** (60%)
1i (R^1 = H, R^2 = H) — **39** (29%) — **40** (49%)

Scheme 2. Regioselectivity of nitrile incorporation.

In the context of this more detailed study, we wanted to test yne-ynamides that were substituted at both alkyne termini. For this purpose, while maintaining the TMS group at the ynamide fragment, we introduced methyl, ethyl, and phenyl groups at the yne moiety. These substrates were reacted with benzonitrile, phenylacetonitrile, and dimethylaminoacetonitrile (Table 6). This time, only 3-aminopyridines were formed. However, the steric demand of R^1 is

Table 6. Influence of the alkyne substitution.



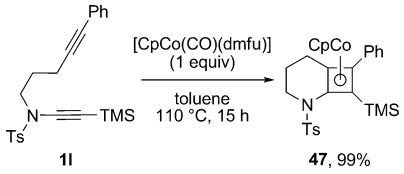
1j (R^1 = Me)
1k (R^1 = Et)
1l (R^1 = Ph)

Entry	Ynamide	R^2 = Ph	R^2 = Bn	R^2 = CH_2NMe_2
1	**1j**	**41** (76%)	**42** (68%)	**43** (83%)
2	**1k**	**44** (57%)	**45** (47%)	**46** (58%)
3	**1l**	_[a]	_[a]	_[a]

[a] No reaction.

a critical issue, as shown by the decrease in yields between R^1 = Me (Table 6, entry 1) and R^1 = Et (Table 6, entry 2). No cycloaddition took place with R^1 = Ph (Table 6, entry 3); in this case, the starting yne-ynamide was recovered in 90%, along with a small amount of a cobalt complex.

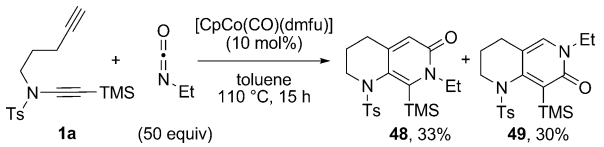
We reacted yne-ynamide **1l** with one equivalent of [CpCo(CO)(dmfu)] in the absence of nitrile and isolated the same complex in almost quantitative yield (Scheme 3).[18] The product results from a formal [2+2] cycloaddition and its formation inhibits completion of the three-component cycloaddition pathway because the metal is irreversibly trapped.[19]



1l **47**, 99%

Scheme 3. Formation of the η^4-cyclobutadiene complex **47**.

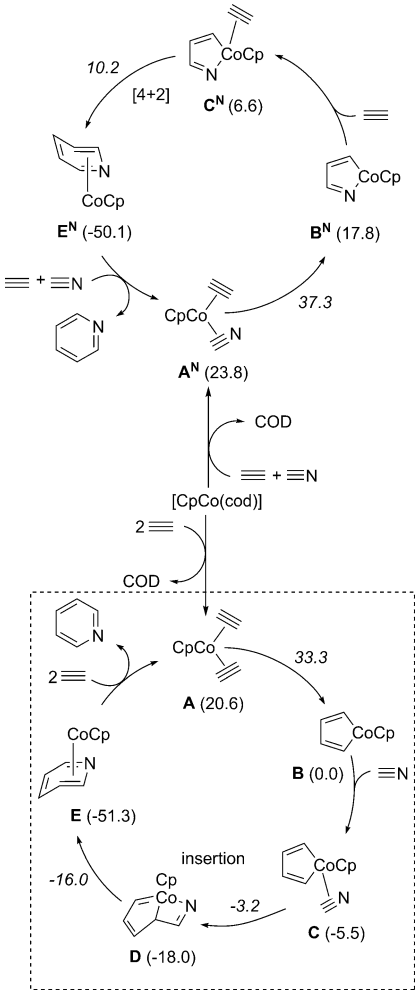
To conclude the experimental part of this work, we briefly turned our attention to the synthesis of the aminopyridones, by using yne-ynamides and isocyanates as unsaturated partners.[20] The preliminary result depicted in Scheme 4 demonstrates the feasibility of this process. However, two important limitations were revealed: 1) a large excess of isocyanate was required to reach good conversion, and 2) the two regioisomers were isolated in virtually a 1:1 ratio.



1a (50 equiv) **48**, 33% **49**, 30%

Scheme 4. First attempt of Co-catalyzed [2+2+2] aminopyridone synthesis between an yne-ynamide and an isocyanate.

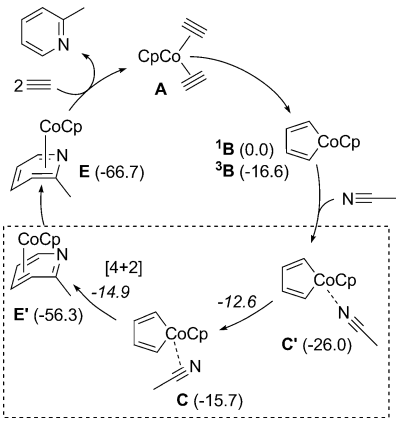
Mechanism: The mechanism of the cobalt-catalyzed [2+2+2] cycloaddition of alkynes to give benzene derivatives has long been a matter of debate. DFT computations have significantly contributed to this debate and have provided a pertinent overview of the mechanism, notably with respect to the reaction of the key metallacyclopentadiene intermediate with the third alkyne unit, which may proceed by insertion or formal [4+2] cycloaddition.[21] As far as pyridines are concerned, although several computational studies have also been reported, several issues are still not clearly understood. In 2006, Kirchner et al. described the two pathways, summarized in Scheme 5,[22] concerning the cycloaddition of two acetylene units with hydrogen cyanide. Initially, the 1,5-cyclooctadiene (COD) ligand is substituted by two acetylenes to give the bis-alkyne complex **A**. Oxidative cyclization follows to give metallacycle **B**. Hydrogen cyanide binds to cobalt in an η^2 fashion and inserts to give the Co(V) carbene **D**. Reductive elimination leads to the η^4-pyridine complex **E**. In the second pathway, the COD ligand is replaced by one acetylene and hydrogen cyanide to give $\mathbf{A^N}$ and then $\mathbf{B^N}$. Complexation of the second acetylene unit



Scheme 5. Insertion versus [4+2] pathways in the Co-catalyzed [2+2+2] cycloaddition of acetylene and hydrogen cyanide to give pyridine [B3LYP/SDD (Co)/6-31G(d,p) (N, H, C), ΔG in kcal mol^{-1}, the energies of the TS are given over the arrows].

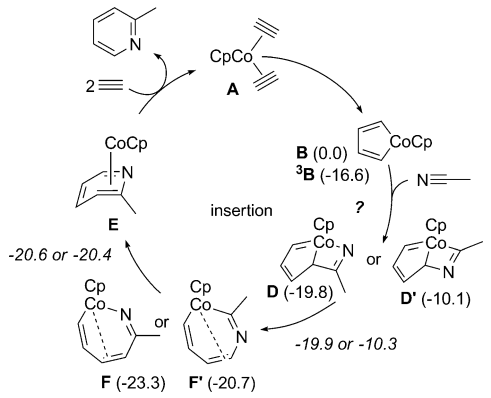
leads to $\mathbf{C^N}$ and then $\mathbf{E^N}$ by [4+2] cycloaddition with the heterodiene framework. Comparison of the energies shows that the insertion pathway is favored over [4+2] cycloaddition.

In 2009, Koga et al. studied the [2+2+2] cycloaddition of acetylene with acetonitrile by means of two-state DFT calculations involving a singlet 18-electron species and a triplet 16-electron species (Scheme 6).[23] The intermediate metallacycle **B** actually reacts in its triplet ground state ^{3}**B** with the nitrile to give the singlet η^1 complex **C′**, which subsequently rearranges into the η^2-nitrile complex **C**. The latter undergoes [4+2] cycloaddition to give **E′** and then **E**.



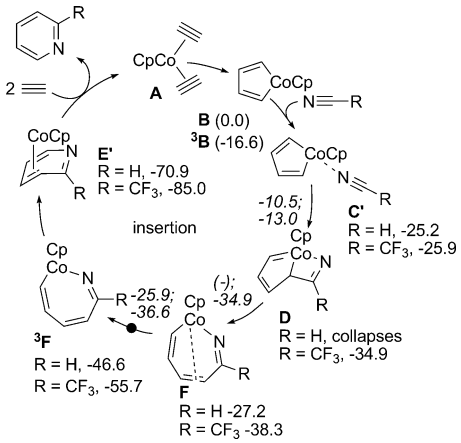
Scheme 6. [4+2] Pathway in the Co-catalyzed [2+2+2] cycloaddition of acetylene and acetonitrile to give 2-methylpyridine [B3LYP/6-31G(d,p) (all atoms) ΔE in kcal mol^{-1}, the energy of the TS are given over the arrows].

The insertion pathway was also computed (Scheme 7). In this case, the regioisomeric carbenes **D** and **D′** were located and their transformation into **E** was modeled in two steps; the first involving the formation of two azacobaltacycloheptadienes **F** and **F′**. Because it was not possible to connect **B** to **D** or **D′**, the insertion pathway was ruled out.



Scheme 7. Incomplete insertion pathways in the Co-catalyzed [2+2+2] cycloaddition of acetylene and acetonitrile to give 2-methylpyridine [B3LYP/6-31G(d,p) (all atoms) ΔE in kcal mol^{-1}, the energies of the TS are given over the arrows].

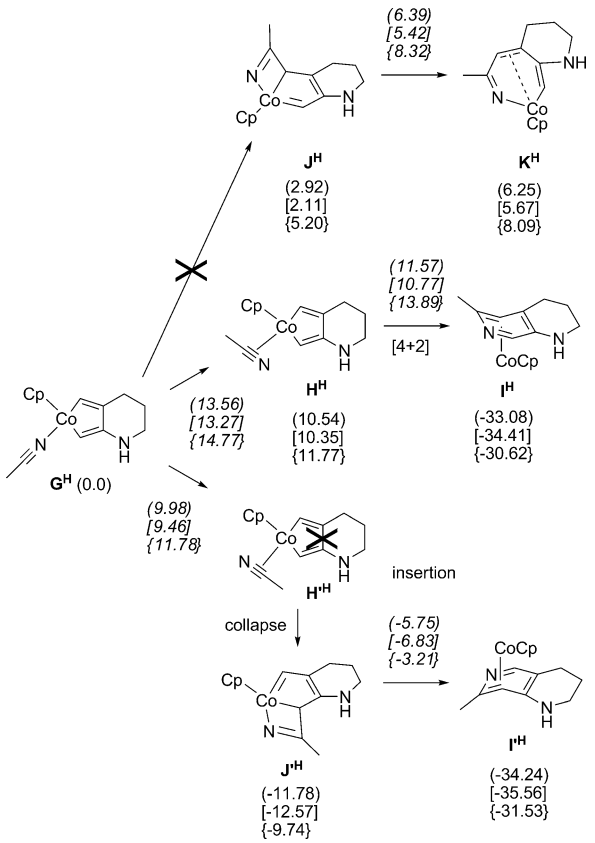
Koga et al. later showed that the insertion pathway becomes the best option with HCN or F_3CCN (Scheme 8).[24] Thus, by virtue of the energy of the frontier orbitals, it was concluded that electron-rich nitriles tend to follow the [4+2] mechanism, whereas electron-poor nitriles follow the insertion mechanism.



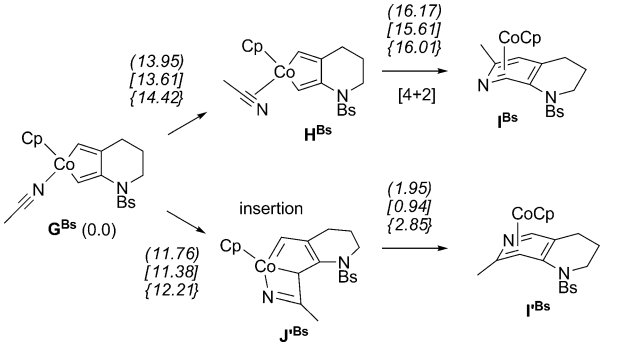
Scheme 8. Insertion pathway in the Co-catalyzed [2+2+2] cycloaddition of acetylene and hydrogen cyanide and trifluoroacetonitrile [B3LYP/6-31G(d,p) (all atoms) ΔE in kcal mol^{-1}, the energies of the TS or a minimum energy crossing point (·) are given over the arrows].

To shed more light on the insertion versus [4+2] cycloaddition issue, we decided to confront these theoretical studies with the case of ynamides. In our own computations, we first used acetonitrile and *N*-ethynylpent-4-ynamine as the model substrates. We chose to use the same level of theory as that employed by Koga et al. [B3LYP/6-31G(d,p) (all atoms)].[25,26] We focused on the regioselectivity of nitrile incorporation into the cobaltacyclopentadiene starting from the singlet species $\mathbf{G^H}$ (Scheme 9). In agreement with Koga's work in the acetonitrile series, we were unable to connect $\mathbf{G^H}$ with carbene $\mathbf{J^H}$, the precursor of the 3-aminopyridine framework. The formation of the 3-aminopyridine framework could be modeled by [4+2] cycloaddition through $\mathbf{H^H}$ and then $\mathbf{I^H}$. Surprisingly, attempts to locate the regioisomer $\mathbf{H'^H}$ on the potential energy surface were unsuccessful. It seems that the enamine moiety of the metallacycle readily reacts with the sp carbon of the nitrile to give carbene $\mathbf{J'^H}$ directly. Reductive elimination from the latter species provides the η^4-pyridine complex $\mathbf{I'^H}$, displaying a 4-aminopyridine framework. Experimentally, 4-aminopyridines are the major products when ynamides bear no substituent on the alkyne terminus (Scheme 2).[4c] The calculations corroborate this fact, with the transition states of the [4+2] pathway lying higher in energy than those of the insertion route.

Because the yne-ynamides used experimentally display an electron-withdrawing group at the nitrogen atom, the transition states were reoptimized in the benzenesulfonyl (Bs) series (Scheme 10). The deactivating effect of the Bs group on the nitrogen strongly increases the energies of both the



Scheme 9. Insertion versus [4+2] pathways in the Co-catalyzed [2+2+2] cycloaddition between *N*-ethynylpent-4-ynamine and acetonitrile [B3LYP/6-31G(d,p) (all atoms) (ΔE), [ΔH], {ΔG} in kcal mol^{-1}, the energies of the TS are given over the arrows).



Scheme 10. Insertion versus [4+2] pathways in the Co-catalyzed [2+2+2] cycloaddition between *N*-ethynyl-*N*-(pent-4-ynyl)benzenesulfonamide and acetonitrile [B3LYP/6-31G(d,p) (all atoms) (ΔE), [ΔH], {ΔG} in kcal mol^{-1}, the energies of the TS are given over the arrows).

[4+2] cycloaddition and insertion steps. However, formation of the 4-aminopyridine framework remains favored.

Thus, as a counterpart to the previous studies, which showed that the switch between the two pathways was critically dependent on the nature of the nitrile, we established that the electronic properties of the metallacycle itself are a critical feature. Indeed, although electron-rich acetonitrile is supposed to react with cobaltacyclopentadienes in a [4+2] manner, we have found that the substitution of the metallacycle by a nitrogen atom makes the insertion pathway more favorable. This subtle balance dictates the regioselective outcome of the formation of pyridines.

Conclusion

In summary, 28 nitriles were screened for the synthesis of aminopyridines through cobalt-catalyzed [2+2+2] cycloaddition with yne-ynamides. Although a few substrates such as haloacetonitriles were not tolerated, we found that most nitriles are suitable partners. In particular, it was possible to use cyanoformates to reach the expected cycloadducts. The success of this transformation is attributable to the use of [CpCo(CO)(dmfu)] as a precatalyst. The formation of 3- and 4-aminopyridines is regioselective, and depends on the substitution pattern of the reactive yne-ynamides. This feature allowed us to complete the overview of the mechanism of pyridine formation by cobalt-catalyzed [2+2+2] cycloaddition by means of DFT computations. Indeed, the calculations suggest that 3-aminopyridines are formed by formal [4+2] cycloaddition between the nitrile and the intermediate cobaltacyclopentadiene. On the other hand, 4-aminopyridines arise from an insertion pathway, which was not expected on the basis of previous computational studies. When both alkyne termini are substituted, the construction of aminopyridines is hampered by the formation of a stable η^4-cyclobutadiene cobalt complex. Extension of this reaction to the synthesis of aminopyridones is possible, although the regioselectivity issue remains to be solved. This aspect is being extensively investigated in our laboratory.

Experimental Section

Compound 14: Benzyl cyanoformate (70 mg, 0.43 mmol) and [CpCo(CO)(dmfu)] (9 mg, 0.03 mmol) were added to a solution of the starting ynamide (102 mg, 0.30 mmol) in toluene (6 mL) under an argon atmosphere. After heating to reflux for 15 h, the mixture was allowed to cool to RT, the mixture was purified by flash chromatography, eluting first with petroleum ether and then with petroleum ether/ethyl acetate (9:1) to give **14** as a brown solid (78 mg, 52%). M.p. 200 °C; ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.47$ (s, 9H), 1.11 (dd, $J = 24.9$, 13.0 Hz, 1H), 1.48 (td, $J = 13.6$, 2.0 Hz, 1H), 1.54–1.73 (m, 2H), 1.75–1.92 (m, 1H), 2.21 (dd, $J = 14.3$, 4.4 Hz, 1H), 2.41 (s, 3H), 3.04 (t, $J = 14.8$ Hz, 1H), 4.49 (dd, $J = 11.6$, 3.2 Hz, 1H), 5.43 (q, $J = 12.7$ Hz, 2H), 7.22 (d, $J = 7.9$ Hz, 2H), 7.33–7.42 (m, 3H), 7.45 (d, $J = 8.4$ Hz, 2H), 7.51 (d, $J = 7.3$ Hz, 2H), 7.65 ppm (s, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 0.1$ (CH_3), 21.7 (CH_3), 24.6 (CH_2), 27.4 (CH_2), 33.1 (CH_2), 50.7 (CH_2), 67.1 (CH_2), 125.1 (CH), 127.5 (CH), 128.1 (CH), 128.3 (CH), 128.7 (CH), 129.9 (CH), 136.0 (C), 138.8 (C), 143.4 (C), 143.7 (C), 147.3 (C), 150.0 (C), 165.3 (C), 172.0 ppm (C); IR (neat): $\tilde{\nu} = 2940$, 1741, 1719, 1156 cm^{-1}; HRMS: *m/z*: calcd for $[C_{27}H_{33}N_2O_4SSi]^+$: 509.19248; found: 509.19079.

Compound 36: Ethyl thiocyanate (39 mg, 0.45 mmol) and [CpCo(CO)(dmfu)] (9 mg, 0.03 mmol) were added to a solution of the starting ynamide (100 mg, 0.30 mmol) in toluene (6 mL) under an inert atmosphere. After heating to reflux for 15 h, the mixture was allowed to cool to RT and purified by flash chromatography, eluting first with petroleum ether and then with petroleum ether/ethyl acetate (9:1) to give **36** as a white solid (41 mg, 33%). M.p. 195 °C; ^{1}H NMR ($CDCl_3$, 400 MHz):

$\delta = 0.41$ (s, 9H), 1.04–1.14 (m, 1H), 1.38–1.44 (m, 4H), 1.71–1.86 (m, 1H), 2.08 (dt, $J = 15.6$, 4.8 Hz, 1H), 2.40 (s, 3H), 3.17 (dq, $J = 14.3$, 7.2 Hz, 1H), 3.32 (dq, $J = 14.5$, 7.2 Hz, 1H), 3.42–3.52 (m, 1H), 3.92–4.03 (m, 1H), 6.66 (s,1H), 7.19 (d, $J = 8.1$ Hz, 2H), 7.34 ppm (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta = 0.2$ (CH_3), 15.3 (CH_3), 21.7 (CH_3), 22.8 (CH_2), 24.3 (CH_2), 25.5 (CH_2), 45.5 (CH_2), 119.4 (CH), 127.7 (CH), 129.8 (CH), 135.5 (C), 136.3 (C), 143.8 (2 C), 155.6 (C), 167.6 ppm (C); IR (neat): $\tilde{\nu} = 2952$, 1162 cm^{-1}; HRMS: m/z: calcd for $[C_{20}H_{29}N_2O_2S_2Si]^+$: 421.14342; found: 421.14299.

Compound 47: [CpCo(CO)(dmfu)] (22 mg, 0.07 mmol) was added to a solution of the starting ynamide (30 mg, 0.07 mmol) in toluene (2 mL) under an inert atmosphere. After heating to reflux for 15 h the mixture was allowed to cool to RT and purified by flash chromatography, eluting with petroleum ether/ethyl acetate (4:1) to give **47** as a red oil (39 mg, 99%). ^{1}H NMR ($CDCl_3$, 400 MHz): $\delta = 0.39$ (s, 9H), 1.03 (br s, 1H), 1.66 (br s, 1H), 1.94 (ddd, $J = 16.5$, 6.6, 4.0 Hz, 1H), 2.38 (s, 3H), 2.43–2.48 (m, 1H), 3.59 (br s, 2H), 4.69 (s, 5H), 7.18 (d, $J = 7.7$ Hz, 2H), 7.23–7.29 (m, 5H), 7.68 ppm (d, $J = 8.1$ Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): $\delta =$ 2.1 (CH_3), 20.3 (CH_2), 20.9 (CH_2), 21.7 (CH_3), 46.8 (CH_2), 52.6 (C), 70.7 (C), 75.5 (C), 81.5 (CH), 95.1 (C), 125.6 (CH), 127.4 (CH), 127.9 (CH), 128.1 (CH), 129.9 (CH), 136.1 (C), 138.9 (C), 143.8 ppm (C). IR (neat): $\tilde{\nu} = 2952$, 1164 cm^{-1}; HRMS: m/z: calcd for $[C_{28}H_{32}N_2O_2CoSSi]^+$: 533.12495; found: 533.12395.

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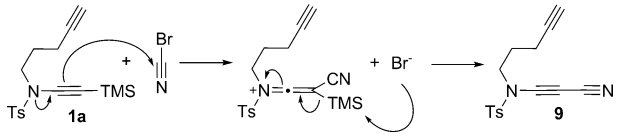

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