

Construction of Pyridine Rings by Metal-Mediated [2 + 2 + 2] Cycloaddition[†]

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Received March 20, 2003

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1. Introduction

Pyridines are increasingly being manufactured synthetically rather than isolated from coal tar.¹ It is desirable for syntheses to be simple, selective, flexible, and waste-free. Prominent among selective methods for the efficient formation of multiple bonds, rings, and stereocenters are cycloaddition reactions.² Although in principle thermal [2 + 2 + 2] cycloadditions are symmetry-allowed,³ purely thermal [2 + 2 + 2] cycloadditions are rare because they are disfavored by enthalpy barriers and, more significantly, by the decrease in entropy associated with bringing three reactants together.⁴ However, this entropy problem can be overcome by using a transition metal catalyst as the site of a stepwise addition process. This is currently one of the most convenient approaches to pyridines.

Although metal-mediated cycloadditions of two alkynes and a nitrile have been featured in several reviews of cycloaddition reactions in general,⁵ reviews devoted specifically to pyridine synthesis have only

mentioned cobalt-based catalysts.⁶ It is known that several other metals are also effective. In fact, most catalysts capable of alkyne cyclotrimerization⁷ are also capable of promoting the formation of pyridines, including both late transition metals such as cobalt and ruthenium and early transition metals such as titanium and zirconium. The purpose of this review is to survey transition-metal-mediated synthesis of pyridines and pyridones by [2 + 2 + 2] cycloaddition of alkynes to nitriles or isocyanates, respectively, concentrating in particular on the advances that have been made in the period 1994–2002.

2. [2 + 2 + 2] Cycloadditions of Alkynes to Nitriles: Synthesis of Pyridines

2.1. Cobalt

Most work on the mechanism of [2 + 2 + 2] cycloadditions, including isolation of intermediate complexes, has concerned CpCoL₂-catalyzed cyclotrimerization of three alkyne units to form benzene (L = CO, PR₃, olefin). Making the usual assumption that the results of this research are extrapolable to the synthesis of pyridine, we therefore begin by presenting the findings of this work on benzene. It is assumed that in the first steps of the cyclotrimerization reaction two alkyne molecules sequentially displace two molecules of L from the catalyst to form complexes **1** and **2** (Scheme 1). Oxidative coupling of the alkyne ligands in **2** would then generate the coordinatively unsaturated cobaltacyclopentadiene **3**, which would readily coordinate to a third acetylene to give an observed intermediate **4**, that is transformed into the η⁴-benzene complex **6**. In principle, this last step might involve either direct cycloaddition or insertion of the coordinated alkyne into one of the Co–C σ-bonds to form cobaltacycloheptatriene **5**, which would subsequently undergo reductive elimination to leave **6**. Finally, decomplexation of the arene and coordination of a pair of acetylene molecules would regenerate **2**, thus completing the catalytic cycle.

While there is experimental evidence of the existence of complexes of types **4** and **6**,⁸ evidence for **2** and **5** is lacking. To elucidate the path from **4** to **6**, a theoretical study has therefore been carried out:⁹ according to density functional theory (DFT) and other ab initio calculations, collapse of **4** to **6** is kinetically very easy (ΔH⁰ = 0.5 kcal/mol), in keeping with the extremely exothermic nature of this transformation (ΔH = –81.41 kcal/mol), whereas the

[†] Dedicated to Prof. K. P. C. Vollhardt with deep esteem and admiration.

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Jesús A. Varela was born in 1971 in Lugo, Spain, and studied chemistry at the Universidad de Santiago de Compostela, Spain. He completed his M.Sc. in 1994 and his Ph.D. thesis in 1999 (excellent award), both under the supervision of Prof. Dr. Carlos Saá for research on the synthesis of oligopyridines via cobalt chemistry. He spent a predoctoral research training period at Harvard University under the supervision of Prof. Dr. Matthew Shair, working on polyol synthesis by C–H insertion of metal carbenes. From 1999 to 2001, he spent a postdoctoral period as an Alexander Von Humboldt and Marie Curie Fellow with Prof. Dr. Paul Knochel at Ludwig Maximilians Universität in Munich, Germany, working on remote C–H activation via hydroboration. He is currently an assistant professor at the Universidad de Santiago de Compostela. His research interests are focused on metal-catalyzed cycloaddition reactions toward medium-sized carbo- and heterocycles.

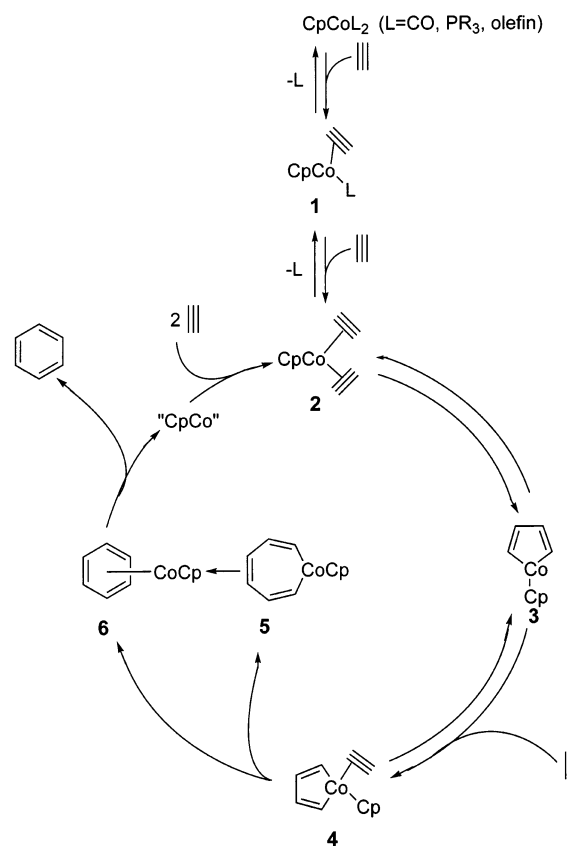


Carlos Saá, born in Lugo, Spain, studied chemistry at the Universidad de Santiago de Compostela, Spain, where he received his Ph.D. in 1985 under the supervision of Profs. L. Castedo, R. Suau, and J. M. Saá for research on synthesis of isoquinoline alkaloids. He spent two years (1987–1988) as a NATO postdoctoral research associate at the University of California, Berkeley, working with Prof. K. P. C. Vollhardt on Co(I)-catalyzed [2 + 2 + 2] cycloaddition of alkynes and nitriles: synthesis of ergot alkaloids. In 1990, he joined the faculty at the Universidad de Santiago de Compostela, Spain, as Profesor Titular. His research interest centers on the utilization of transition metals in organic synthesis and the chemistry of enediyne and polyenyne.

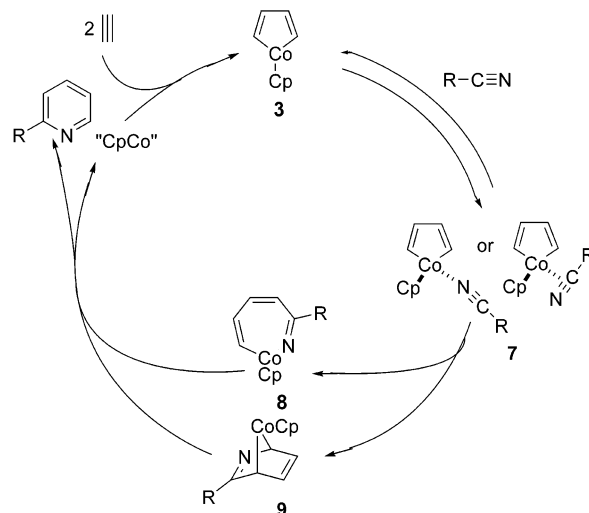
alternative path via **5** is energetically improbable due to the symmetry-forbidden nature of the reductive elimination converting **5** to **6**. Indeed, no stationary point corresponding to **5** could be located on the B3LYP potential energy surface. These calculations thus predict that the final carbon–carbon bond-forming step in the construction of the arene is an intramolecular metal-mediated [4+2] cycloaddition of the cobaltacycle to the coordinated alkyne.

Unlike alkyne cyclotrimerization, successful pyridine synthesis requires that alkyne and nitrile combine in 2:1 ratio. Fortunately, nitriles trimerize less

Scheme 1



Scheme 2



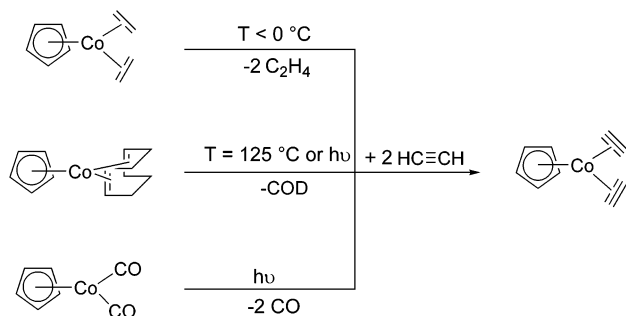
readily than alkynes in the presence of metals.¹⁰ CpCoL₂-catalyzed pyridine synthesis is thought to proceed as follows (Scheme 2).^{6,11}

Oxidative coupling of two coordinated alkynes to afford cobaltacycle **3**, as in Scheme 1, raises the oxidation number of the metal center by two, thus favoring subsequent coordination to a nitrile rather than an alkyne (unless the nitrile is electron-deficient, in which case the reaction fails to give satisfactory yields of pyridines). The resulting nitrile complex **7** then evolves either to metallacycloheptatriene **8**, in which the nitrile has been inserted into the metallacycle of **7** with its nitrogen bound to the metal, or to the cobaltacycle intermediate **9** via a

Diels–Alder-type reaction; in either case, reductive elimination then yields the pyridine and regenerates the CpCo core, which coordinates two new acetylene units to complete the catalytic cycle.

The most widely used metal-cored catalysts for $[2 + 2 + 2]$ cycloadditions between alkynes and nitriles are Co(I) complexes of general formula XCoL. According to the mechanism of Scheme 2, the organic group X remains attached to the metal throughout, while the neutral ligand L is exchanged for the alkynes in the first steps of the catalytic cycle. Prior to the reaction, L stabilizes the catalytic complex [XCoL], and its nature therefore decisively influences the “starting behavior” of the catalyst: if it stabilizes XCoL too effectively the “catalyst” is unreactive, while if it is too weakly stabilizing the catalyst tends to undergo decomposition reactions and be difficult to handle.⁶ Examples of widely used ligands L are ethylene, cyclooctadiene (COD), and carbonyl groups (Scheme 3).

Scheme 3

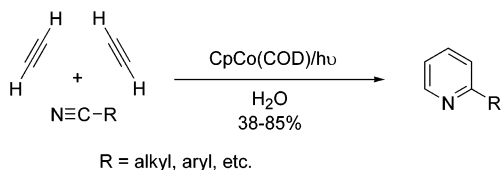


Ethylene, the most labile of the three, is replaced by alkynes even below 0 °C; COD can be displaced thermally or photochemically;¹² and CO requires photolysis, its thermal cleavage from Co being incomplete even at 150 °C.

The ligand X influences the ability of the catalyst to form pyridines by determining its chemoselectivity (i.e., whether three alkynes react to form benzenes, or two alkynes and a nitrile react to form pyridines) and its regioselectivity (when substituted reagents are used). When X = Cp, it has been observed that electron donor substituents on the Cp make the catalyst less able to promote the cocyclization of alkynes and nitriles, whereas electron-withdrawing substituents enhance catalytic activity but diminish regioselectivity.⁶

With CpCo(COD) as catalyst, acetylene and nitriles can be efficiently cocyclized under mild photochemical conditions in the most environmentally benign solvent, water (Scheme 4).¹³

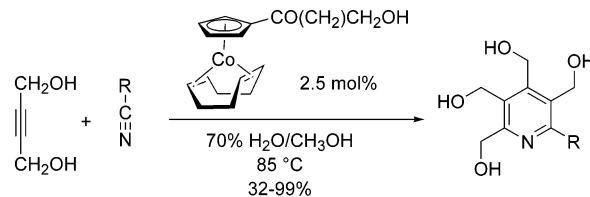
Scheme 4



Suitable substituents on the cyclopentadienyl ring facilitate the solubility of the catalyst in water, and

yields of up to 99%, with no benzene side products, have been recorded using only the stoichiometric amount of nitrile (Scheme 5).¹⁴

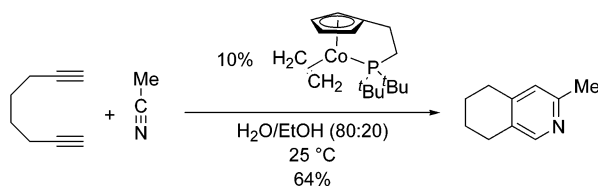
Scheme 5



R = alkyl, vinyl, aryl, etc.

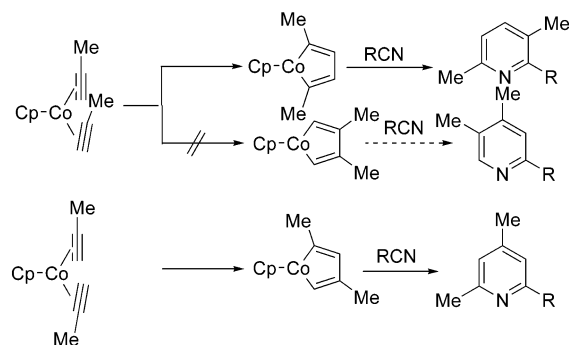
Pendant phosphane substituents on the cyclopentadienyl ring make the cobalt complex stable in water, thus allowing the preparation of pyridine derivatives at room temperature (Scheme 6).¹⁵

Scheme 6



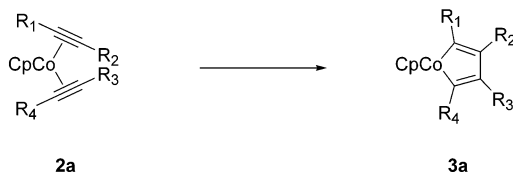
When symmetrically substituted alkynes are used, pentasubstituted pyridines are obtained in good yields (Scheme 5). However, terminally substituted alkynes usually afford roughly equal yields of 2,4,6- and 2,3,6- trisubstituted products and no 2,4,5- substituted isomer,¹⁶ showing that 2,4- and 2,5- dialkyl metallacycles **3** form much more readily than the 3,4-dialkyl metallacycle (Scheme 7).

Scheme 7



The observed regioselectivity can be explained in terms of steric and electronic factors. Sterically, it is predicted that the bulkiest substituents on the alkyne will be placed α to the Co in the intermediate cobaltacycle **3a** ($R_1 > R_2$; $R_4 > R_3$ in Scheme 8),¹⁷ while electronically the substituent with the largest coefficient in the π^* orbital (LUMO) of the alkyne will

Scheme 8



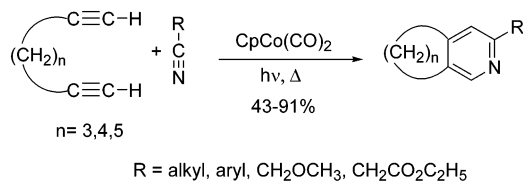
2a

3a

be placed β to the Co (e.g., $R_3 = \text{Me}$, $R_4 = \text{CO}_2\text{Me}$).¹⁸ The steric factor will generally override the electronic factor;¹⁷ groups such as TMS will be placed α to the Co. The reaction of the substituted cobaltacyclopentadienes with a nitrile is regioselective, retaining the substitution pattern of the metallacycle and placing the N α to the Co in the less hindered cobalt–carbon bond.^{5a,6a,11}

The regioselectivity described above can be circumvented by tethering two of the three components. For example, the use of short-chain α,ω -diynes with nitriles will afford cycloalka[*c*]pyridines (Scheme 9).¹⁹

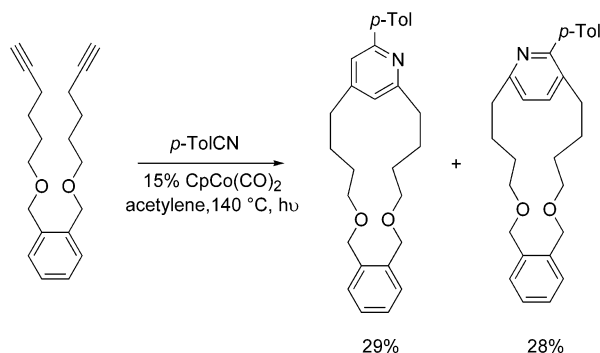
Scheme 9



Here the regioselectivity is controlled by the chelating nature of the alkyne component and by steric effects, whereas chemoselectivity is apparently controlled by electronic interactions.

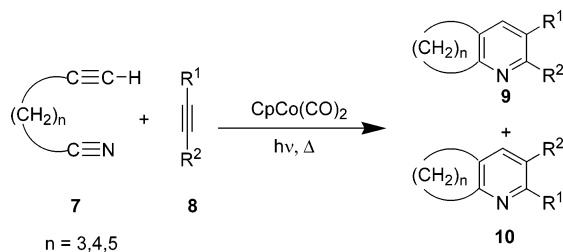
However, macrocyclization of long-chain α,ω -diynes with nitriles again gives 2,3,6- and 2,4,6-substituted pyridines (Scheme 10).²⁰

Scheme 10



A cyclization strategy complementary to that of Scheme 9, using α,ω -alkynenitriles and alkynes, allows the preparation of [*b*]annulated pyridines (Scheme 11 and Table 1).^{20–22} Although cyclobutapy-

Scheme 11



ridines are not accessible via this route, five-, six-, and seven-membered fused-ring systems are obtained in moderate to excellent yields. The fact that with asymmetric alkynes the bulky substituent is placed

Table 1

<i>n</i>	R ¹	R ²	yield (%) ^a	product ratio (9:10)
3	Me	Me ₃ Si	70	>95:1
4	COOMe	Me ₃ Si	82	1.1:1
4	COOMe	Et ₃ Si	78	1:1
4	COOMe	<i>i</i> -Pr ₃ Si	67	1.7:1
4	CONEt ₂	Me ₃ Si	87	1.4:1
4	OMe	Et ₃ Si	43	>95:1
4	H	Et ₃ Si	26	>95:1
4	Me	Me ₃ Si	70	>95:1
5	Me	Me ₃ Si	66	>95:1

^a Combined yield **9** + **10**.

next to the nitrogen implies the formation of the cobaltacyclopentadiene **4a** (Figure 1).

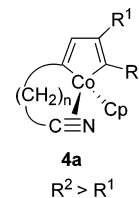
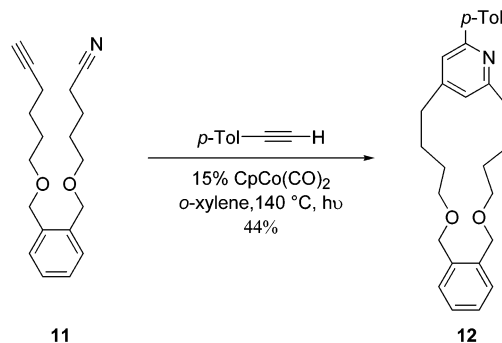


Figure 1.

Interestingly, when a long-chain α,ω -alkynenitrile such as **11** is reacted with a terminal alkyne under the usual conditions, the 2,4,6-substituted pyridine **12** is obtained exclusively in 44% yield (Scheme 12).

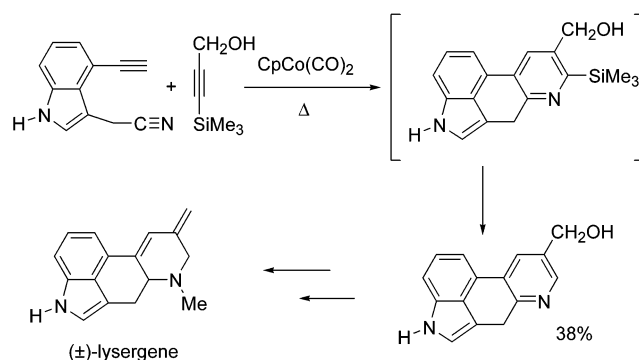
Scheme 12



Analysis of the intermediate metallacycles indicates that, in the transition state affording this product, steric interactions and conformational strain are much less than in those of competing reaction paths.²⁰

The above α,ω -alkynenitrile plus alkyne methodology has been successfully applied to the synthesis of ergot alkaloids such as lysergine and LSD (Scheme 13).²²

Scheme 13



Scheme 14

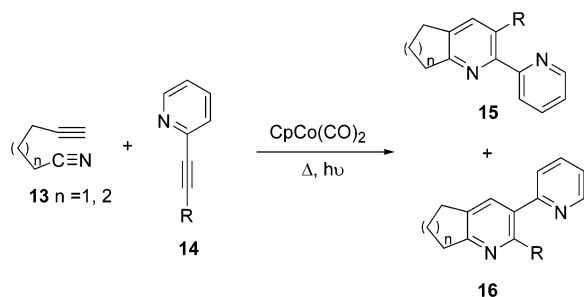


Table 2

n	R	yield (%) ^a	product ratio (15:16)
1	H	15	2.75:1
1	Me ₃ Si	61	1:1.2
1	CH ₂ OH	19	4:1
2	H	18	1:1
2	Me ₃ Si	76	1:1.5

^a Combined yield **15** + **16**.

This methodology has also been applied to the synthesis of annelated 3-substituted bipyridines by cocyclization of α,ω -alkynenitriles with 2-ethynylpyridines (Scheme 14 and Table 2).²³ In the case of 2-(trimethylsilylethynyl)pyridine (**14**, R = TMS), a 1:1.2 mixture of 2,2'-bipyridine **15** and 3,2'-bipyridine **16** is obtained, indicating an approximate balance between steric and electronic influences on the regiochemistry of the final cycloaddition. With R = CH₂-OH in the ethynylpyridine, the **15:16** ratio is 4:1.

3,3'-Substituted 2,2'-bipyridines are obtained in good yield by reaction of two α,ω -alkynenitrile molecules with a conjugated 1,3-diyne (Scheme 15 and Table 3).²⁴

Scheme 15

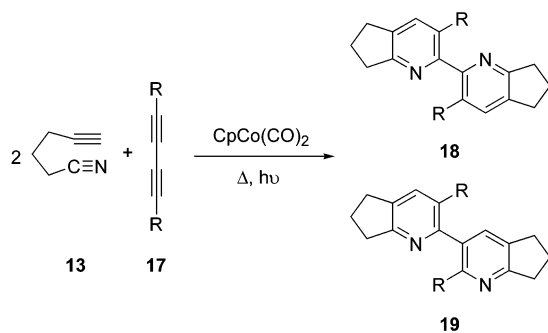


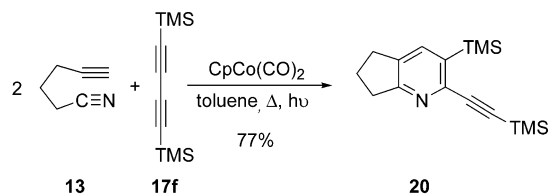
Table 3

1,3-diyne	R	yield (%) ^a	product ratio (18:19)
17a	Me	48	1.7:1
17b	CH ₂ OH	9	1:0
17c	CH ₂ OMe	63	2.7:1
17d	CH ₂ OSiEt ₃	45	4:1
17e	COOMe	18	1.4:1

^a Combined yield **18** + **19**.

However, when the diyne substituent is the bulky TMS, only one cycloaddition takes place, probably because of steric hindrance by the group at position 3 of the pyridine ring (Scheme 16). Pyridine **20** is obtained in good yield, but neither the 2,2'-bipyridine

Scheme 16



nor the 3,3'-bipyridine **21** (Figure 2), nor what would be its immediate precursor, pyridine **20a** (Figure 2), is observed.

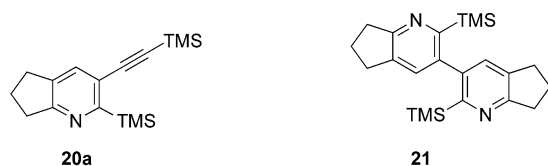
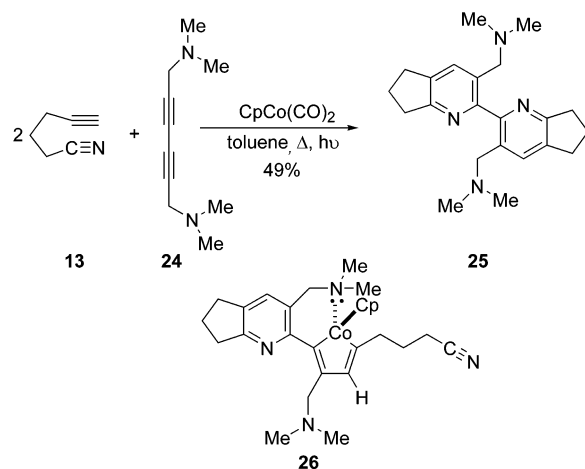


Figure 2.

The reaction shown in Scheme 17 highlights a common feature of all the above cycloadditions using

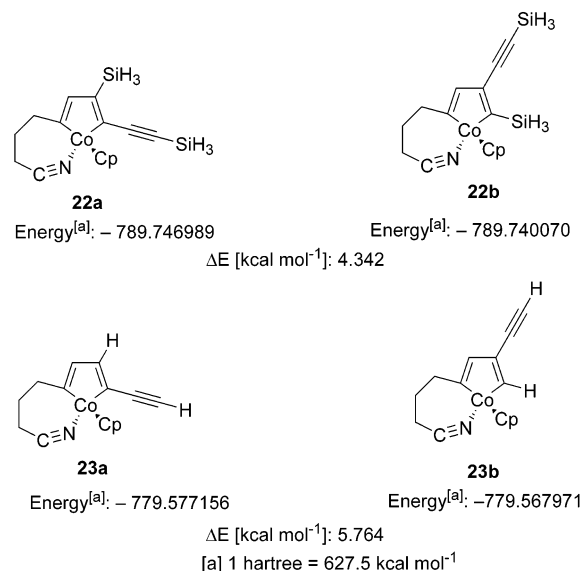
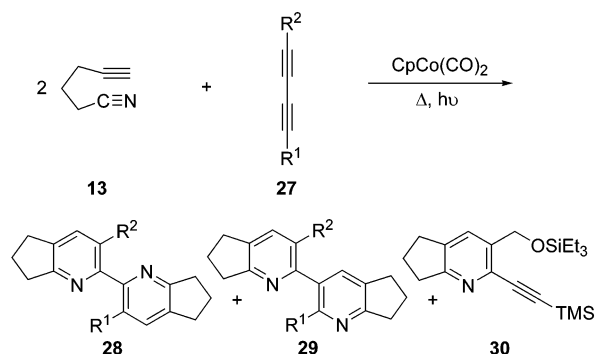
Scheme 17



1,3-diyne: their high regioselectivity in the initial cyclization. In keeping with this, *ab initio* calculations²⁴ on the intermediate metallacycles **22** and **23** show that in both cases it is energetically favorable for the triple bond to be α to the cobalt (Figure 3). Assuming that both electronic and steric factors are operative in **22** and only electronic factors in **23**, and that electronic and steric factors have opposite regioselective influences, it would appear that the electronic factor is responsible for the observed regioselectivity, in contradiction with the tendency noted above (Scheme 8 and discussion thereof).

Total regioselectivity can be achieved using a pair-donating diyne substituent to direct the second cycloaddition. When the amine derivative **24** was used, only the 2,2'-bipyridine **25** was obtained, and in reasonably good yield (49%). It is thought that coordination of the cobalt by the nitrogen (complex **26**) is responsible for the regioselectivity of the second cycloaddition (Scheme 17).²⁵

The chemoselectivity of the reaction with 1,3-diyne has been examined using the asymmetric 1,3-diyne **27** (Scheme 18 and Table 4).²⁵ In the case of

**Figure 3.****Scheme 18****Table 4**

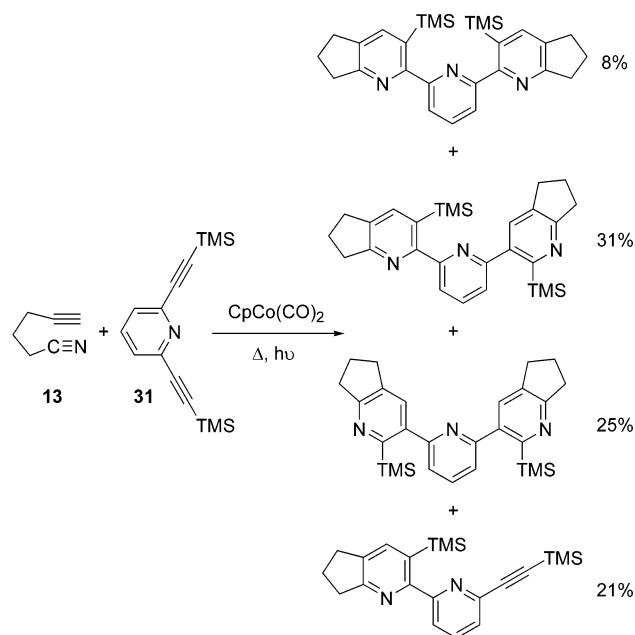
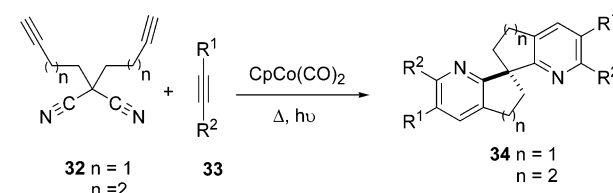
1,3-diyne	R ¹	R ²	products (yield, %) ^a	product ratio
27a	TMS	CH ₂ OSiEt ₃	28 + 29 + 30 (61%)	1.3:1:1.8 ^b
27b	≡-TMS	TMS	28 + 29 (31%)	1:2.1 ^c

^a Combined yield of the mixture. ^b **28:29:30**. ^c **28:29**.

27a, the first cycloaddition chemoselectively involves the CH₂OTES-substituted ethyne, placing the CH₂-OTES group β to the cobalt in the cobaltacyclopentadiene intermediate. In the case of **27b**, the initial cycloaddition is likely to have occurred at the central triple bond; further cycloadditions to the ethyne bonds ortho and meta to the pyridine nitrogen give **28** and **29**, respectively.

Terpyridines can be obtained by cobalt-catalyzed [2 + 2 + 2] cycloaddition between 5-hexynenitrile (**13**, *n* = 1) and the 1,6-diethynylpyridine **31** (Scheme 19). Although all three possible regioisomers of the terpyridine are produced, their combined yield is good (64%). Of the three, it is the 2,2':6',2''-terpyridine that has the lowest yield (8%); this is due to the lack of reactivity of its 2,2'-bipyridine precursor, which is also isolated (in 21% yield).²³

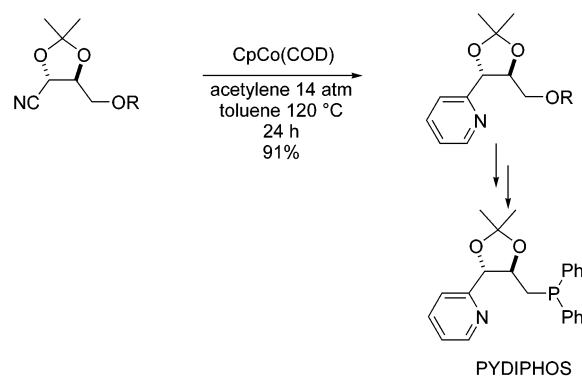
A remarkable Co-catalyzed double cocyclization between bis-α,ω-alkynenitriles and alkynes affords

Scheme 19**Scheme 20****Table 5**

<i>n</i>	R ¹	R ²	yield of 34 (%)
1	H	H	32
1	TMS	TMS	33
1	Ph	Ph	9
1	CO ₂ Me	CO ₂ Me	7
1	TMS	≡-TMS	8
2	TMS	TMS	32
2	TMS	≡-TMS	6

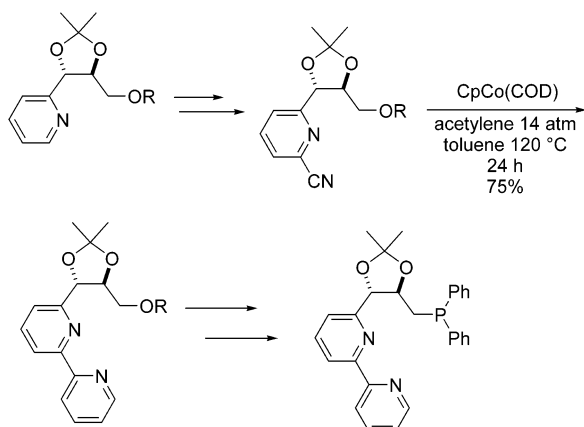
spiropyridines, a novel series of C₂-symmetric ligands (Scheme 20 and Table 5).²⁶ The relatively low yields of these cycloadditions may be due to the starting malononitriles being electron-poor.

Optically active pyridines can be obtained by cobalt(I)-catalyzed [2 + 2 + 2] cycloaddition of acetylene to optically active nitriles, as in the preparation of PYDIPHOS (Scheme 21).^{27,28}

Scheme 21

Optically active bipyridines can be synthesized by cycloaddition of acetylene to chiral cyanopyridines (Scheme 22).²⁸

Scheme 22



2.2. Rhodium

The [2 + 2 + 2] cycloaddition of alkynes and nitriles can also be carried out efficiently by half-sandwich rhodium(I) complexes of the type [RhCp'L_n]. Intriguingly, the dependence of efficiency and selectivity on the electronic properties of substituents on the cyclopentadienyl ring is the reverse of that observed with Co(I): increasing the electron-withdrawing power of the substituents on the Cp' ring reduces reactivity at low temperatures but somewhat increases chemoselectivity (favoring the formation of pyridines rather than benzenes) and regioselectivity (reducing the percentage of the 2,4,6-isomer) (Scheme 23 and Table 6).²⁹

Scheme 23

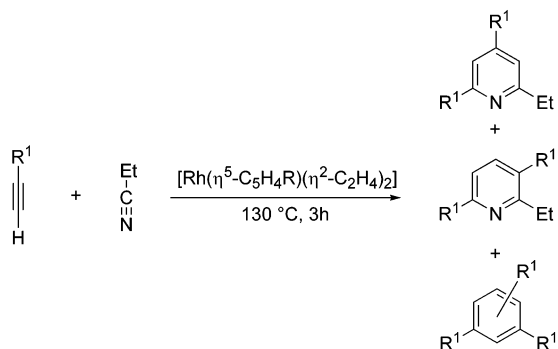


Table 6

R	R ¹ = Bu ^a	
	T = 100 °C	T = 130 °C
NMe ₂	26.3 (41.1)	21.3 (34.5)
^t Bu	28.3 (10.6)	67.8 (21.6)
Me	18.4 (7.6)	62.3 (19.6)
H	6.6 (3.3)	64.5 (18.7)
Cl	8.3 (7.3)	32.2 (20.0)
CF ₃	9.0 (9.2)	65.7 (15.5)
COOMe	18.8 (5.6)	67.7 (19.4)

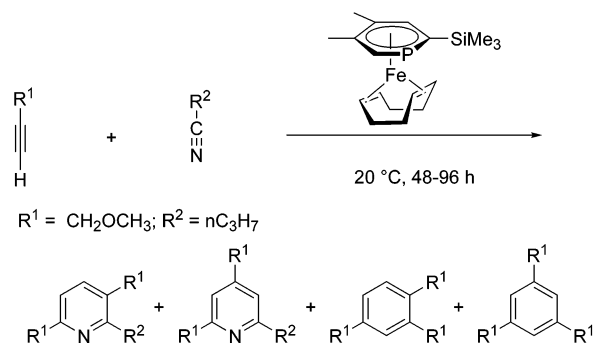
^a Combined yields of pyridine derivatives, with yields of benzene derivatives in parentheses.

2.3. Iron

The basic cyclotrimerization for obtention of pyridines was first observed in 1876 by Sir Willian

Ramsay, who led acetylene and hydrogen cyanide through a red-hot iron tube and obtained small amounts of pyridine.³⁰ From this pioneering work to much more recently, it is known that arene-iron complexes are isoelectronic to CpCo species and exhibit the same principal reaction pattern for the formation of substituted pyridine derivatives; however, the turnover numbers (TON) observed are smaller than those for the CpCo-based systems.³¹ In this case, like Cp, the arene ligands should remain π -complexed to the iron throughout the catalytic cycle; however, loss of the arene is much more likely than loss of Cp. In contrast, good stability is observed in the case of iron-coordinated P-heterocycles. Thus, when 3-methoxy-1-propyne was reacted with butyronitrile in a toluene solution of an iron-coordinated P-heterocycle, both pyridine and benzene compounds were formed (Scheme 24).³²

Scheme 24



It is observed that the symmetric 2,4,6-substituted pyridine derivative is preferred over the 2,3,6-derivative, but the symmetric 1,3,5-benzene derivative is produced in lower yield than the asymmetric 1,2,5-substituted benzene derivative. Several experiments were performed modifying the amounts of catalyst, alkyne, and nitrile, and the best values obtained in this series of experiments were the following: TON for pyridine formation, 160; alkyne consumption, 95%; and chemoselectivity, 0.69 (Table 7).

2.4. Ruthenium

Itoh et al. recently showed that a neutral complex of Ru(II), Cp^{*}Ru(COD)Cl, is able to catalyze the [2 + 2 + 2] cycloaddition of 1,6-diynes to alkenes,³³ to alkynes,³³ and to nitriles activated by an electron-withdrawing group,³⁴ although it fails to promote reaction with simple nitriles such as acetonitrile or benzonitrile (Scheme 25 and Table 8).

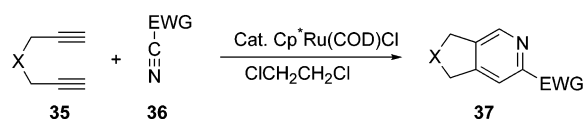
To establish the regiochemistry of this process, asymmetric 1,6-diynes were reacted with ethyl cyanoacetate, which afforded 2,3,4,6- and 2,3,4,5-substituted pyridines in proportions depending on the nature of the alkyne substituents (Scheme 26).³⁴ Substitution on the diyne also affected reactivity, which was less with alkyl and aryl substituents than with electron-withdrawing substituents.

The observed regiochemistry is probably due to the electron-withdrawing group on the nitrile reducing the antibonding orbital contribution to the C–N triple bond, which results in the catalytic cycle starting with the capture of nitrile by the catalyst

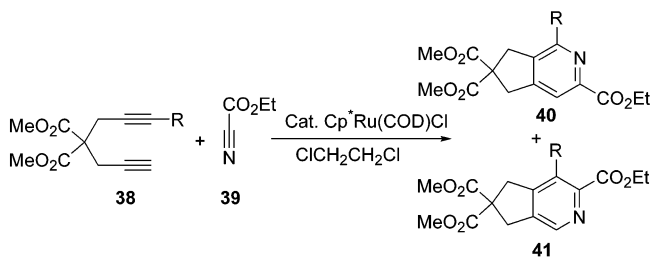
Table 7

amount of cat.	alkyne (mmol)	nitrile (mmol)	pyridines ^a	benzenes ^a	chemoselectivity ^b	alkyne consumption (%)
0.003	5.92	23.0	99	145	0.69	32
0.003	5.92	57.4	160	326	0.49	66
0.003	1.92	51.7	41	174	0.24	95

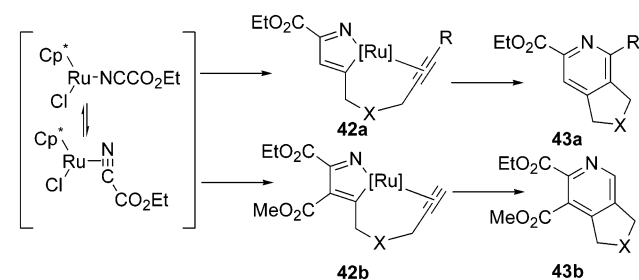
^a In moles of product per mole of catalyst = TON. ^b TON (pyridines):TON (benzenes).

Scheme 25**Table 8**

X	ewg	catalyst (mol %)	T (°C) ⁱ	t (h)	yield of 37 (%)
C(CO ₂ Me) ₂	CO ₂ Et	2	60	0.5	83
C(CO ₂ Me) ₂	COPh	2	60	0.5	84
C(CO ₂ Me) ₂	COMe	10	80	1	90
C(CO ₂ Me) ₂	Ts	10	80	24	31
C(CO ₂ Me) ₂	CCl ₃	10	60	24	44
C(CO ₂ Me) ₂	C ₆ F ₅	5	60	1	67
NTs	CO ₂ Et	2	60	0.5	75
O	CO ₂ Et	2	60	2	49

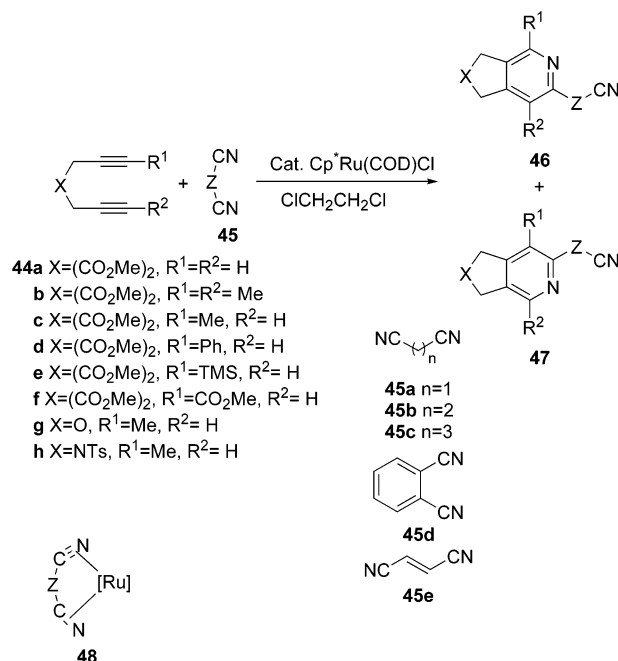
Scheme 26

R = Me: 5mol%, 60°C, 2h; 78% (**40a**:**41a** = 88:12)
 R = Ph: 20mol%, 60°C, 6h; 50% (**40b**:**41b** = 100:0)
 R = CO₂Me: 5%, r. t., 1h; 78% (**40c**:**41c** = 13:87)

Scheme 27

and its subsequent oxidative cyclization with one of the triple bonds of the diyne (Scheme 27).³⁴ In the case of alkyl- or aryl-substituted diynes, reaction with the sterically less hindered alkyne moiety will be favored in this cyclization, giving **42a**, whereas reaction with the terminally substituted alkyne moiety, giving **42b**, is favored if the electron-withdrawing nature of the substituent makes this triple bond electron-deficient and so capable of accommodating the Ru d electron. In both cases, subsequent intramolecular alkyne insertion and reductive elimination afford the corresponding pyridine, **43a** or **43b**, as the major isomer.

Cp*Ru(COD)Cl is also able to catalyze cycloaddition of 1,6-diynes to dicyanides under mild conditions (Scheme 28 and Table 9). It is noteworthy that unlike

Scheme 28**Table 9**

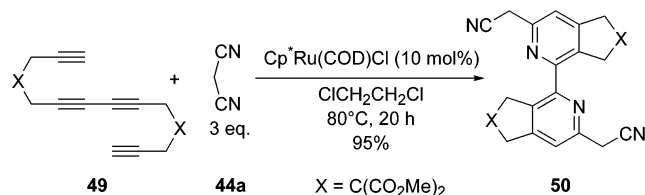
diyne/dicyanide	catalyst (mol %)/temp (°C) ^a /time (h)	yield (%)	product ratio (46 : 47)
44a/45a	2/rt/2.5	95	-
44b/45a	5/80/20	70	-
44c/45a	2/60/5	97	95:5
44d/45a	10/60/24	78	100:0
44e/45a	5/60/5.5	92	100:0
44f/45a	5/rt/24	80	100:0
44g/45a	2/60/16	97	95:5
44h/45a	2/60/0.5	95	100:0
44c/45b	2/60/1.5	73	100:0
44c/45c	5/rt/22	46	100:0
44c/45d	2/60/2.5	88	100:0
44c/45e	2/60/7	88	100:0

^a rt = room temperature.

Co(I) catalysts, which cocyclize dicyanides with alkynes to give dipyrindines,⁶ Ru(II) promotes reaction of only one of the two cyano groups in **45**, the other remaining intact after the complete conversion of the diyne (Scheme 28).³⁵ When only one of the diyne termini is substituted, the 2,3,4,6-substituted product **46** is obtained exclusively, or almost so.

Double cocyclization has worked very nicely on 1,6,8,13-tetrayne **49** (a bis-1,6-diyne), giving the bipyrindine **50** in excellent yield (Scheme 29).³⁵

Scheme 29



The origin of the significant chemoselectivity of the reaction with dicyanides has not yet been clarified, but a possible explanation is that η^4 -chelation of the Ru by the two cyano groups (**48** in Scheme 28) suppresses the cyclotrimerization of the diyne and facilitates the insertion of the C–N triple bond into the ruthenacyclopentadiene intermediate. It appears that an Ru(II) catalyst bearing Cp^* is necessary for this: the Ru(III) complex $[\text{Cp}^*\text{RuCl}_2]_2$, which is as efficient as $\text{Cp}^*\text{Ru}(\text{COD})\text{Cl}$ for cycloaddition of 1,6-diyne to alkynes or heterocycloalkynes, was found to be less effective for the synthesis of pyridines; the Ru(II) complex $\text{RuCl}_2(\text{COD})(\text{CH}_3\text{CN})_2$ gives no cycloadduct at all; and the Ru(0) complex $(\text{C}_6\text{Me}_6)\text{Ru}(\text{COD})$ is also unable to catalyze the reaction, despite having a planar hexamethylbenzene ligand.³⁵

2.5. Titanium

It has recently been found that pyridine-forming $[2 + 2 + 2]$ cycloaddition of alkynes to nitriles can be promoted not only by late transition metals such as cobalt and ruthenium, but also by early transition metals, notably Ti and Zr (the latter in combination with Ni or Cu). Although stoichiometric amounts of these metals are required (whereas the late transition metals usually act catalytically), these metals have the advantage of being able to assemble pyridines from a nitrile and two different asymmetric acetylenes. Following the formation of a dialkoxytitanacyclopentadiene from the acetylenes and the divalent titanium alkoxide (η^2 -propene) $\text{Ti}(\text{O}-i\text{-Pr})_2$ (generated in situ from $\text{Ti}(\text{O}-i\text{-Pr})_4$ and $i\text{-PrMgCl}$),³⁶ addition of a third alkyne gives a single aryltitanium compound,³⁷ and addition of a nitrile gives a single metalated pyridine such as **54**, which is easily demetalated by hydrolytic or deuteriolytic workup (in the latter case the production of a single highly deuterated pyridine confirms that the pyridyltitanium is formed before workup) (Scheme 30 and Table 10). Functionalization of the pyridine at position 6 is facilitated by iodination of the metalated pyridine **54**, which is easily achieved by treatment with I_2 .

Alkoxyacetone nitriles can be used as well as sulfonyl nitriles, the addition of α -methoxyacetone nitrile to the titanacyclopentadiene, followed by aqueous workup, giving pyridinecarbaldehyde **59** as a single isomer (Scheme 31 and Table 11).³⁸ In this case, however, deuteriolysis of the reaction mixture deuterates the aldehyde carbon, suggesting that the intermediate titanacycle **57** (the analogue of **52**) evolves to aldehyde **59** via the η^2 -carbonyltitanium complex **58**.

Scheme 30

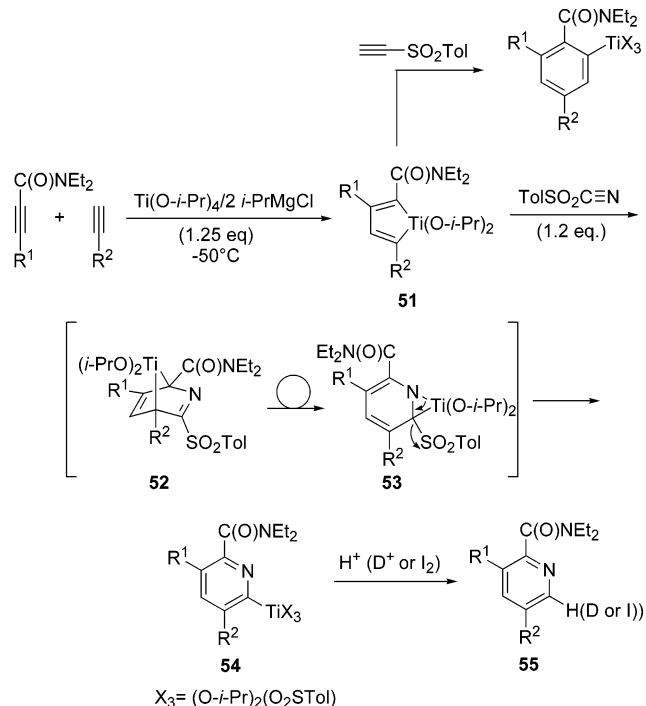


Table 10

R ¹	R ²	yield of 55 (%)	D (%) ^a
C ₆ H ₁₃	C ₆ H ₁₃	63	96
C ₆ H ₁₃	BnO(CH ₂) ₂	68	98
C ₆ H ₁₃	Ph	70	97
C ₆ H ₁₃	SiMe ₃	55	97
Ph	Ph	67	96

^a Percentage of **55** bearing deuterium.

Scheme 31

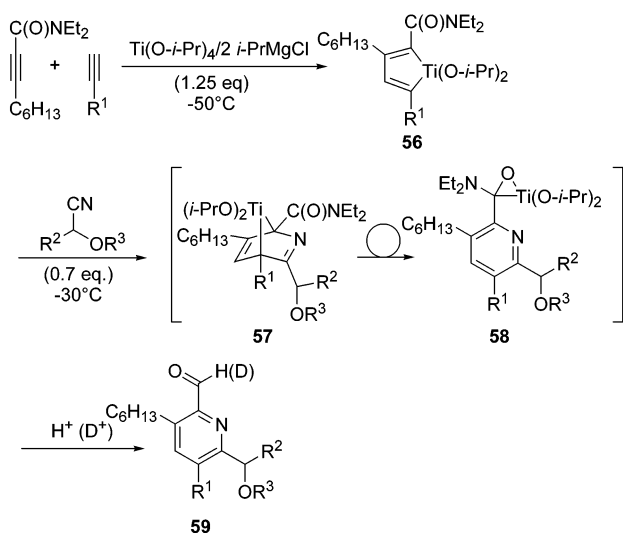


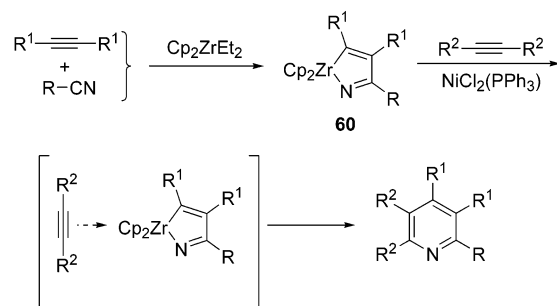
Table 11

R ¹	R ²	R ³	yield (%)
C ₆ H ₁₃	H	Me	84
Me ₃ Si	H	Me	65
Ph	H	Me	51
C ₆ H ₁₃	H	Bn	90
C ₆ H ₁₃	C ₈ H ₁₇	Me	71

2.6. Zirconium/Nickel and Zirconium/Copper

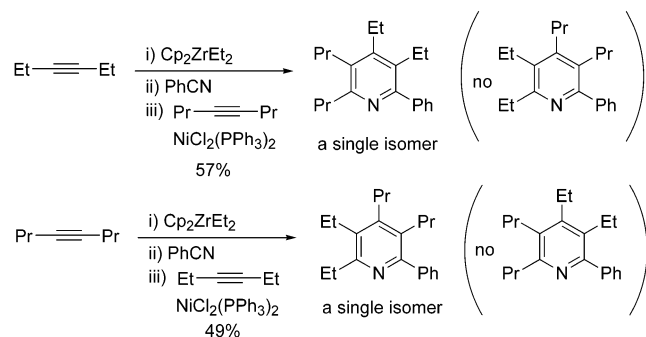
By contrast with the titanium-mediated reaction, the zirconium-mediated preparation of pyridine derivatives from two different alkynes and a nitrile involves first the coupling of one alkyne and a nitrile to give an azazirconacyclopentadiene, and then reaction with the second alkyne in the presence of $\text{NiCl}_2(\text{PPh}_3)_2$ or CuCl (Schemes 31–34).³⁹ The azazirconacyclopentadiene intermediates **60** can easily be isolated in good yield following preparation using the Negishi reagent,^{40,41} as in Scheme 32.

Scheme 32



Note that the first alkyne always couples to the carbon of the nitrile, and the second to its nitrogen (Scheme 33).^{39,42}

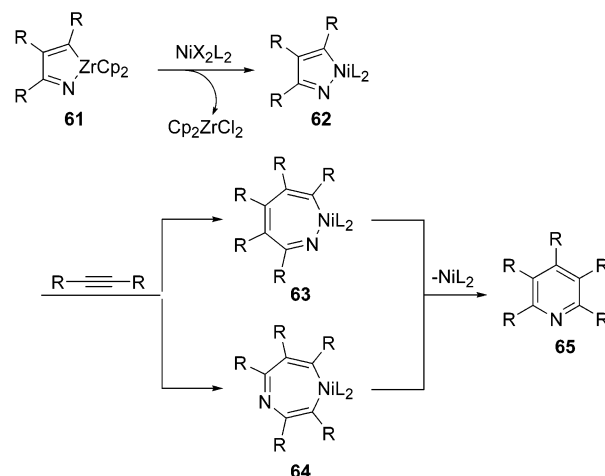
Scheme 33



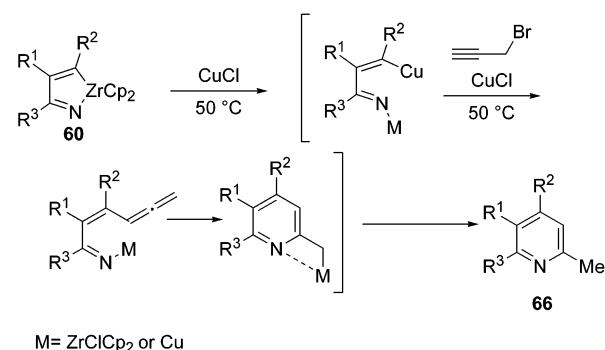
Although the mechanism of the second addition is not yet clear, it is plausible that when $\text{NiCl}_2(\text{PPh}_3)_2$ is used it reacts with azazirconacyclopentadienes **61** to form the azanickelacyclopentadienes **62** (Scheme 34); the latter have not yet been observed, but the formation of Cp_2ZrCl_2 has been detected.⁴³ The second alkyne might be inserted either into the Ni–C bond of **62**, affording **63**, or into the Ni–N bond, affording **64**. Reductive elimination of NiL_2 could then afford the substituted pyridine **65**.⁴²

If the second alkyne is asymmetric, its addition is regioselective. For example, reaction of propargyl bromide with azazirconacyclopentadienes in the presence of CuCl affords tetrasubstituted pyridines in which the methyl group is always adjacent to the nitrogen, regardless of whether the other substituents are alkyl or aryl in nature (Scheme 35).³⁹ In this case, the reaction mechanism probably involves selective transmetalation of the sp^2 C from Zr to Cu, followed by addition of the alkenylcopper species to the propargyl bromide and of the nitrogen to the resulting allene.

Scheme 34



Scheme 35

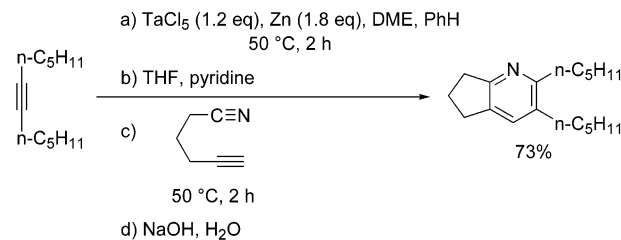


When both alkynes are asymmetric, addition of the first is regioselective if one of its substituents is a trialkylsilyl group, which takes up the α position in the azazirconacycles and hence position 4 of the final pyridine (entries 3–5 in Table 12).

2.7. Tantalum

Tantalum–alkyne complexes prepared from internal acetylenes and low-valency tantalum (TaCl_5/Zn) in DME and benzene react with terminal alkynenitriles in the presence of THF and pyridine to give tetrasubstituted pyridine derivatives in good to excellent yields (Scheme 36).⁴⁴

Scheme 36

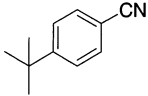
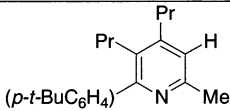

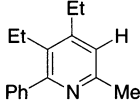

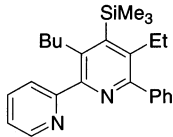



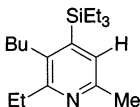


3. [2 + 2 + 2] Cycloadditions of Alkynes to Isocyanates: Synthesis of Pyridones

3.1. Cobalt

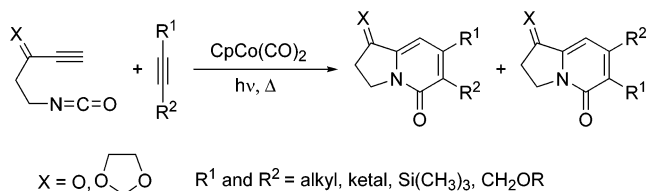
Just as Co(I)-catalyzed [2 + 2 + 2] cycloaddition of alkynes to nitriles affords pyridines, application of this approach to isocyanates is an efficient method

Table 12

Entry	1st Alkyne	Nitrile	Product	Yield (%)
1 ^a	Pr—≡—Pr			81
2 ^a	Et—≡—Et			77
3 ^b	Me ₃ Si—≡—Bu			62
4 ^a	Me ₃ Si—≡—Bu			46
5 ^a	Et ₃ Si—≡—Bu			81

^a Second alkyne: propargyl bromide. ^b Second alkyne: 1-phenyl-1-butyne.

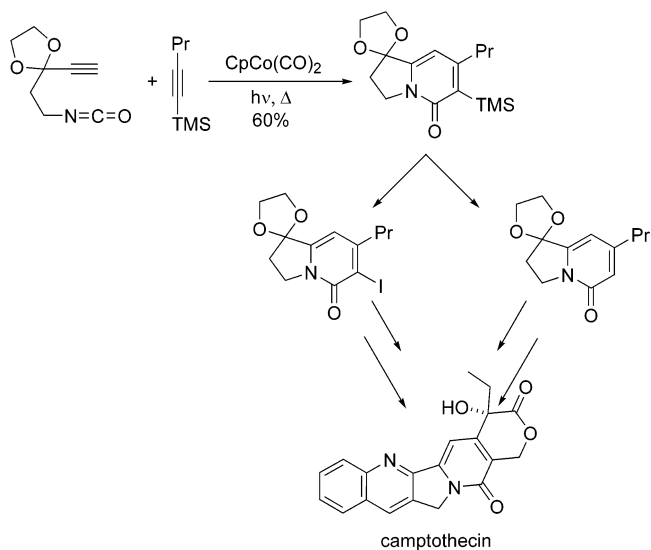
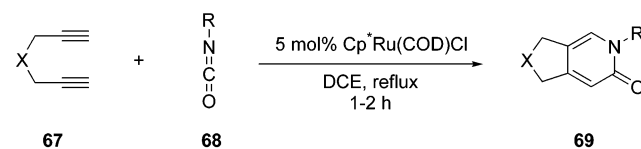
for the construction of substituted 2-pyridone rings. As in the case of pyridine synthesis, the reaction seems to proceed via cobaltacyclopentadienes **3** (Scheme 1), reaction of isolated cobaltacyclopentadienes and isocyanates affording the corresponding pyridones.⁴⁵ Problems of regioselectivity can be circumvented by tethering, in this case by the use of ω -alkynyl isocyanates (Scheme 37).^{5a,46}

Scheme 37

Good chemo- and regioselectivity are observed, the latter favoring placement of the bulky substituent (particularly trimethylsilyl) α to the carbonyl group (see section 2.1). The resulting pyridones can easily be further functionalized, and this strategy has been elegantly applied to the total synthesis of the anti-tumor agent camptothecin (Scheme 38).^{5a,46}

3.2. Ruthenium

The Ru(II) complex Cp^{*}Ru(COD)Cl effectively catalyzes the formation of bicyclic pyridones by [2 + 2 + 2] cycloaddition of 1,6-diyne to aryl or alkyl isocyanates (Scheme 39 and Table 13).⁴⁷

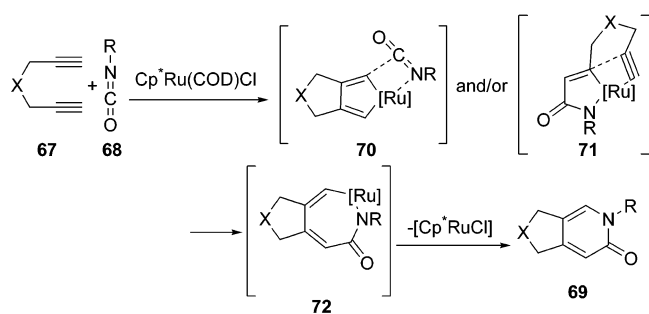
Scheme 38**Scheme 39**

The mechanism of these reactions may include either ruthenacyclopentadiene or azaruthenacyclopentenone intermediates (**70**⁴⁵ and **71**,⁴⁸ respectively). Both are assumed to evolve to the bicyclic pyridones **69** via intermediates **72** and reductive elimination of [Cp^{*}RuCl] (Scheme 40).

Table 13

67	68	69 (%)

Scheme 40

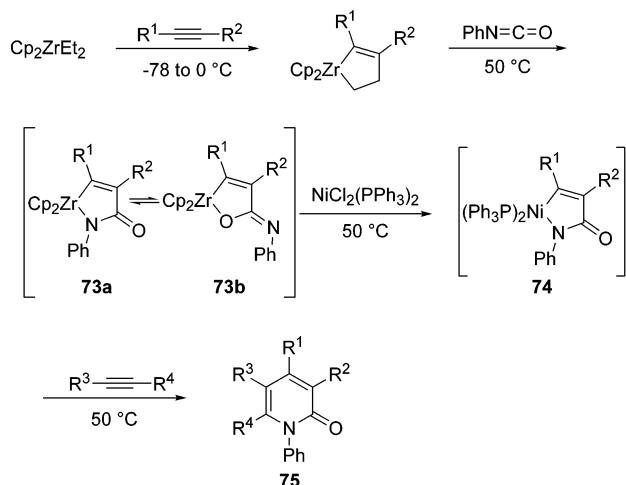


3.3. Zirconium/Nickel

Hoberg et al. have shown that the Ni(0) complex $\text{Ni}(\text{COD})_2$ effectively catalyzes the [2 + 2 + 2] cy-

cloaddition of alkynes to isocyanates via azanickelacyclopentadiene intermediates.⁴⁸ Takahashi et al. recently developed a method for the synthesis of pyridones from two alkynes and one isocyanate using a combination of Zr and Ni complexes. As in their similar synthesis of pyridines, the method starts with the formation of a zirconacyclopentadiene followed by incorporation of the N=C unit to give an azazirconacyclopentenone **73** (or possibly an equilibrium mixture of **73a** and oxaziriconacyclopentenone **73b**) (Scheme 41 and Table 14). Reaction of **73** with the second alkyne in the presence of $\text{NiCl}_2(\text{PPh}_3)_2$ then gives the corresponding pyridone, **75**, as a single isomer via the azanickelacyclopentenone intermediate **74**.^{39,48} It is noteworthy that when the first or second alkyne was asymmetrically

Scheme 41



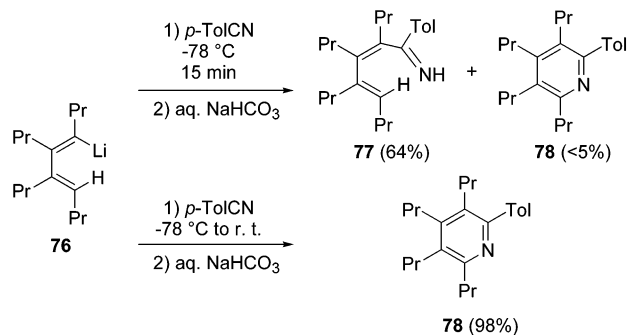
substituted, only one regioisomer was obtained. The reaction may also be carried out with electron-deficient alkynes such as DMAD, although the yield of the product is rather low.

4. Miscellaneous

Lithiation of 1-iodo-1,3-dienes or dilithiation of 1,4-diiodo-1,3-dienes, followed by treatment with a nitrile, affords pyridines in high yield. Although these methods are not formally $[2 + 2 + 2]$ cycloadditions, the fact that their starting materials may be obtained by iodolysis of metallacyclopentadiene intermediates has led us to include them in this review.

Lithiation of 1-iodo-1,3-dienes with 2 equiv of $t\text{-BuLi}$ affords monolithio compounds such as **76** in

Scheme 42



quantitative yield. Treatment of **76** with $p\text{-TolCN}$ at -78 °C for 15 min, followed by hydrolysis, gives the linear imine **77** in 64% isolated yield, along with <5% of the pyridine derivative **78**; but, if the reaction is allowed to reach room temperature before quenching, pyridine **78** is obtained as the only product in 98% yield (Scheme 42). Other pyridines prepared in this way are listed in Table 15.⁴⁹

Pyridine derivatives are also formed in high isolated yields when 1,4-dilithio-1,3-dienes such as **79**, generated in situ by lithiation of the corresponding 1,4-diiodo-1,3-dienes, are treated with nitriles in the presence of HMPA. When 2-cyanopyridine is used, 2,2'-bipyridines are obtained in good to excellent yields (Scheme 43 and Table 16).⁴⁹ Substituted 1,3,5-triazines,⁵⁰ the cyclotrimerization products of nitriles, were formed as byproducts in these reactions.

5. Conclusions

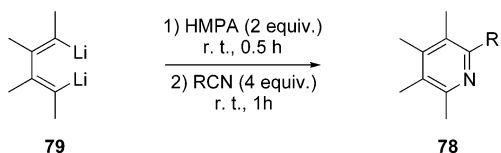
The use of transition metals to promote $[2 + 2 + 2]$ cycloadditions is a powerful method for pyridine

Table 14

1st Alkyne	2nd Alkyne	75	Yield (%)
$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{Ph}$	$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{Ph}$		67
$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{Ph}$	$\text{Pr}\text{---}\text{C}\equiv\text{C}\text{---}\text{Pr}$		72
$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{Ph}$	$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{Me}$		56
$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{Me}$	$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{Ph}$		65
$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{Ph}$	$\text{MeO}_2\text{C}\text{---}\text{C}\equiv\text{C}\text{---}\text{CO}_2\text{Me}$		20

Table 15

Monolithio compound	Nitrile	Product	Yield (%)
	<i>p</i> -TolCN		87
	C ₆ H ₅ CN		77
	C ₆ H ₅ CN		85
	C ₆ H ₅ CN		75

Scheme 43

synthesis that induces the occurrence of otherwise impossible reactions. The reactions described in this

review clearly demonstrate that highly regioselective pyridine synthesis can be efficiently performed using both late and early transition metals (by intramolecular reactions in the former case and intermolecular reactions in the latter). The broad scope and synthetic importance of this methodology has been demonstrated by its having allowed the unproblematic synthesis of natural products and of a wide variety of polysubstituted pyridine rings of great utility in basic and applied chemistry.

Table 16

Dilithio compound	Nitrile	Product	Yield (%)
	<i>p</i> -TolCN		63
	C ₆ H ₅ CN		62
			69
			83

6. Acknowledgments

We thank the Xunta de Galicia (Project PGIDT00PXI20908), the Ministerio de Ciencia y Tecnología (Spain), and the European Regional Development Fund (Project BQU2002-02135) for financial support.

7. Note Added after ASAP Posting

After this review was posted ASAP on 07/23/2003, the authors were directed to an addition and correction to ref 20, in which it was reported that the product of the reaction shown in Scheme 12 is actually a 1:1:1 mixture of three regioisomers. The erratum has been cited in ref 20, and the updated version was posted on 07/28/2003.

8. References

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CR030677F

