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Construction of fused heterocycles by metal-mediated [2+2+2] cyclotrimerization of alkynes and/or nitriles

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1. Introduction

Heterocycles constitute one of the most interesting divisions of organic chemistry. A majority of the compounds produced by nature as well as significant numbers of compounds synthesized in the industrial sector each year have heterocyclic rings as part of their structures. Heterocyclic systems are of immense importance biologically, industrially, and are essential to life in various ways. The majority of pharmaceuticals and biologically active agrochemicals is heterocyclic, as are countless additives and modifiers used in industries as varied as cosmetics, reprography, information storage, and plastics. Therefore, extensive efforts have been directed to develop new and efficient synthetic strategies for these compounds. Among a variety of these synthetic approaches, transition-metal-catalyzed cycloaddition reactions seem to be the most attractive methodologies. In particular, nowadays, metal-catalyzed [2+2+2] cyclotrimerization of alkynes and/or nitriles was reported in several reviews as a useful and established tool for the construction of highly functionalized carbo- and heterocycles.[1–10]

Since Reppe and Schweckendiek[11] discovered the transition-metal-catalyzed [2+2+2] cyclotrimerization of alkynes, this new synthetic method was applied to the synthesis of substituted benzenes (Fig. 1).

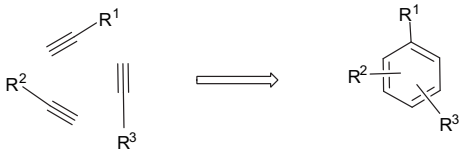
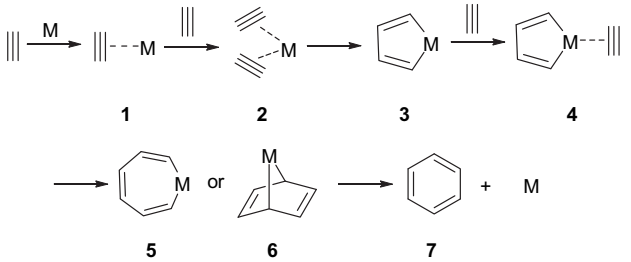


Fig. 1. [2+2+2] Cyclotrimerization of alkynes to substituted benzenes.

The mechanism of this reaction has been considered as described in Scheme 1. Thus, two alkyne moieties coordinate successively to the metal to give mono- and dialkyne complexes **1** and **2**, and then the coupling reaction proceeds to give the metallacyclopentadiene **3**. The latter underwent complexation with a third molecule of the alkyne to give **4**. Insertion or addition of an alkyne to the metallacycle **4** takes place to give a metallacycle, such as **5** or **6**. The benzene ring **7** is formed by the reductive elimination of the metal.[5]



Scheme 1. Mechanism of benzene ring formation by the [2+2+2] cyclotrimerization of alkynes.

In addition, metal-mediated cycloadditions of two alkynes and a nitrile led to the formation of pyridines (Fig. 2). Unlike alkyne cyclotrimerization, successful pyridine synthesis requires that alkyne and nitrile combine in a 2:1 ratio. Fortunately, nitriles trimerize less readily than alkynes in the presence of metals.[12,13]

Metal-catalyzed pyridine synthesis is thought to proceed as outlined in Scheme 2. Oxidative coupling of two coordinated

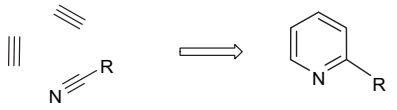
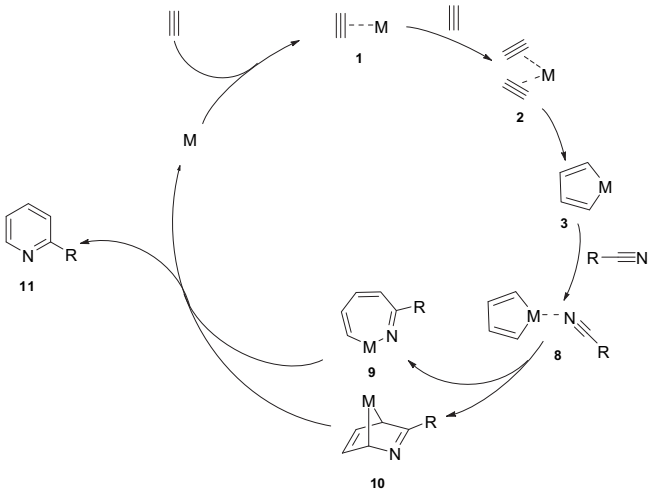


Fig. 2. Metal-catalyzed pyridine synthesis.

alkynes to afford metallacycle **3** 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 **8** then evolves either to metallacycloheptatriene **9**, in which the nitrile has been inserted into the metallacycle of **8** with its nitrogen bound to the metal, or to the metallacycle intermediate **10** via a Diels–Alder-type reaction; in either case, reductive elimination then yields the pyridine **11**.



Scheme 2. Mechanism of pyridine formation by metal-mediated cycloadditions of two alkynes and a nitrile.

In these reactions, C–C as well as C–N bonds of the aromatic or heterocyclic ring are formed in one step. However, chemo- and regioselectivity problems (if unsymmetrical alkynes were used) lead to complex mixtures of products, which severely limits the utility of this intermolecular reaction.

The regioselective synthesis of the cyclotrimerization products can be achieved especially when the reaction is carried out in a partially or totally intramolecular fashion (Fig. 3).[5,6]

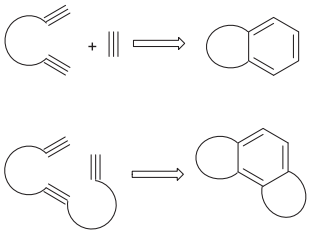


Fig. 3. Partial and total intramolecular synthesis of annulated benzene.

Although a number of different metal complexes derived from the whole range of transition metals[14–26] can be used for the catalysis of these reactions, cobalt is still the most effective.[27–45]

The present review casts light on the main strategies for the synthesis of fused heterocycles by metal-mediated [2+2+2] cyclotrimerization of alkynes and/or nitriles as well as their specific syntheses. A number of other reviews[1–6,8–10,12,13,46–56] that have appeared, concerning [2+2+2] cyclotrimerization of alkynes and/or nitriles to fused heterocycles, did not pay special attention to the synthesis of such systems in an organized manner with respect to the type of the heterocyclic systems.

2. General synthetic approaches for fused heterocycles by metal-mediated [2+2+2] cyclotrimerization of alkynes and/or nitriles

The catalytic construction of heterocyclic skeletons reported in this review is classified into five main processes (a–e) as outlined in Scheme 3.

(a) Two alkynes tethered in one molecule undergo partially intramolecular cycloaddition with an alkyne.
(b) Two alkynes tethered in one molecule undergo partially intramolecular cycloaddition with a nitrile.
(c) An Alkyne and a nitrile tethered in one molecule undergo partially intramolecular cycloaddition with an alkyne.
(d) Three alkynes connected in one molecule undergo totally intramolecular cycloaddition.
(e) Two alkynes and a nitrile connected in one molecule undergo totally intramolecular cycloaddition.

3. Specific synthesis of fused heterocycles by metal-mediated [2+2+2] cyclotrimerization of alkynes and/or nitriles

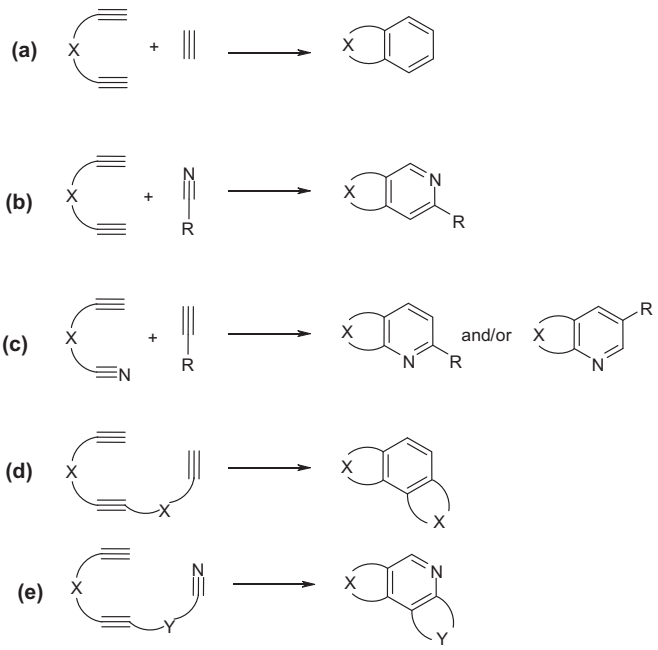
3.1. Fused bicyclic systems

3.1.1. Carbocyclic fused heterocycles.

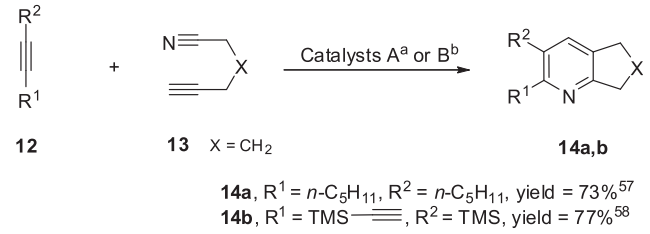
3.1.1.1. Carbocyclic fused with six-membered heterocyclic ring: one heteroatom.

3.1.1.1.1. Cycloalka[b]pyridine. Tantalum/alkyne complexes prepared from internal acetylene **12** (R^1=R^2=*n*-C_5H_{11}) and low-valency tantalum ($TaCl_5$/Zn) in DME and benzene reacted with terminal alkynenitrile **13** (X=CH_2) in the presence of THF and pyridine to give cyclopenta[*b*]pyridine derivative **14a** in 73% yield (Scheme 4).[57]

Cocyclization of **13** (X=CH_2) with 1,4-bis(trimethylsilyl)-1,3-diyne **12** (R^1=TMS—C≡C, R^2=TMS) in the presence of $CpCo(CO)_2$ afforded cyclopenta[*b*]pyridine derivative **14b** as a sole product in



Scheme 3. The main processes for catalytic construction of heterocyclic skeletons.



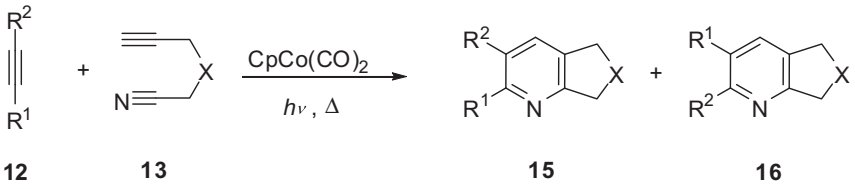
Scheme 4. Formation of cyclopenta[*b*]pyridines by cocyclization of 5-hexynenitrile with alkynes.

77% yield as shown in Scheme 4. The steric hindrance of the bulky TMS group allowed only one cycloaddition to take place, but neither of the expected bipyridines were observed.[58]

Saa et al., Vollhardt et al., and du Plessis et al. reported the cocyclization of α,ω-alkynylnitriles **13** with unsymmetrical alkynes **12** in the presence of $CpCo(CO)_2$. The reactions proceed to give a mixture of the expected cyclopenta[*b*]pyridine regioisomers **15** and **16** (Scheme 5, Table 1). High regioselectivity has been observed in some cases when a bulky trialkylsilyl group is introduced into the alkyne.[59–62]

Subjecting a solution of dihydro-2-(triethylsilyloxymethylethynyl)-3-(trimethylsilyl)-5*H*-cyclopenta[*b*]pyridine (**17**), 5-hexynenitrile **13** (X=CH_2), and $CpCo(CO)_2$ in toluene to 3 h of irradiation afforded a 17% yield of the annelated 2,2′-bipyridine **18** together with 40% recovery of **17** (Scheme 6).[58]

Saa et al.[58,61] and others[63–65] reported, as outlined in Scheme 7, that the cocyclization of **13** with 2,4-hexadiyn-1,6-diol **19** (R^1=R^2=CH_2OH) gave a complex mixture from which the annelated 2,2′-bipyridine **20a** could only be isolated in 9% yield. However, with the amine derivative **19** (R^1=R^2=CH_2NMe_2),[58,63] both [2+2+2] cycloadditions were completely regioselective, giving the



Scheme 5. Synthesis of cycloalka[*b*]pyridine regioisomers by cocyclization of alkynenitriles with unsymmetrical α,ω-alkynes.

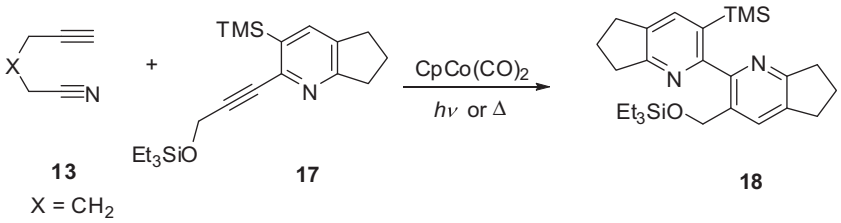
Table 1

Entry	**12**		**13**	**15/16**	Yield (%)	Ratio **15/16**	Ref.
	R^1	R^2	X	Product			
1	TMS	ME	CH_2	**15a/16a**	70	>95:1	59,60
2	2-Pyridyl	H	CH_2	**15b/16b**	15	2.75:1	61
3	2-Pyridyl	TMS	CH_2	**15c/16c**	61	1:1.1	61
4	2-Pyridyl	CH_2OH	CH_2	**15d/16d**	19	4:1	61
5	2-Pyridyl	H	$(CH_2)_2$	**15e/16e**	18	1:1	61
6	2-Pyridyl	TMS	$(CH_2)_2$	**15f/16f**	76	1:1.5	61
7	2-Pyridyl	TMS	$(CH_2)_2$	**15f/16f**	74	1.1:1	5,61
8	TMS	CO_2ME	$(CH_2)_2$	**15g/16g**	82	1.1:1	59,60,62
9	$SiEt_3$	CO_2ME	$(CH_2)_2$	**15h/16h**	78	1:1	59,60
10	$^iPr_3Si$	CO_2ME	$(CH_2)_2$	**15i/16i**	67	1.7:1	59,60
11	TMS	$CONEt_2$	$(CH_2)_2$	**15j/16j**	87	1.4:1	59,60
12	$SiEt_3$	OMe	$(CH_2)_2$	**15k/16k**	43	>95:1	59,60
13	$SiEt_3$	H	$(CH_2)_2$	**15l/16l**	26	>95:1	59,60
14	TMS	Me	$(CH_2)_2$	**15m/16m**	70	>95:1	59,60
15	TMS	Me	$(CH_2)_3$	**15n/16n**	66	>95:1	59,60

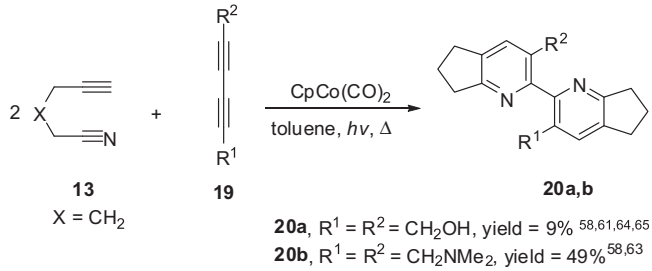
2,2′-bipyridine **20b** in 49% yield as a sole product. The total regioselectivity in this case is ensured by the cobalt coordinating to the aminomethyl rather than to the hexynenitrile nitrogen. This approach reverses the usual strategy for bipyridine synthesis, with the biaryl bond present prior to the construction of either of the two aryl rings.[58,61,64,65]

The same group reported a one-step synthesis of annelated substituted 2,2′-bipyridines **20c**–**h** as well as 2,3′-bipyridines **21a**–**f** by means of cobalt(I)-catalyzed [2+2+2] cycloadditions between 5-hexynenitrile **13** (X=CH_2) and the symmetrically sterically less demanding 1,3-diynes **19** (Scheme 8, Table 2).[58,66] In all cases, the 2,2′-bipyridines **20c**–**h** were obtained as the main reaction products.

The chemoselectivity of the reaction with 1,3-diynes has been examined using the unsymmetrical 1,3-diyne **19** (entry 5, Table 2).[58,66] Thus, cocyclization of **13** with **19** (R^1=TMS, R^2=CH_2OSiEt_3) afforded a mixture of the bipyridines **20g** and **21e** together with a 27% yield of the pyridine **23**. The formation of the latter as well as the absence of **22** and its corresponding regioisomer **17** from the



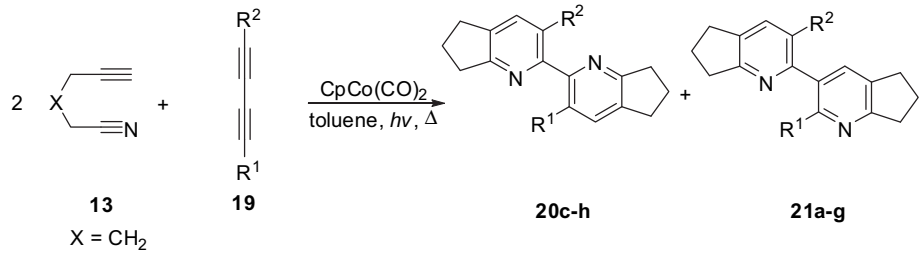
Scheme 6. Synthesis of annelated 2,2′-bipyridine by cocyclization of alkynenitrile with 2-alkynepyridine.



Scheme 7. Synthesis of 2,2′-bipyridines by cocyclization of 1,3-diynes with 5-hexynenitrile.

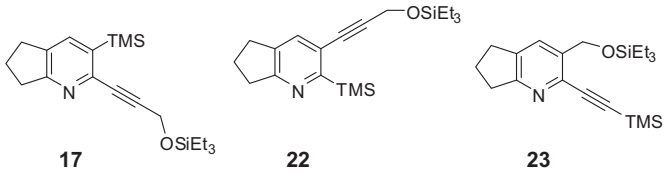
Table 2

Entry	**19**		**20/21**	Yield (%)	Ratio **20:21**	Ref.
	R^1	R^2	Product			
1	Me	Me	**20c/21a**	48	1.7:1	66
2	CH_2OMe	CH_2OMe	**20d/21b**	63	2.7:1	58,66
3	CH_2OSiEt_3	CH_2OSiEt_3	**20e/21c**	45	4:1	58,66
4	CO_2Me	CO_2Me	**20f/21d**	18	1.4:1	58,66
5	TMS	CH_2OSiEt_3	**20g/21e**	34	1.3:1	58,66
6	≡—TMS	TMS	**20h/21f**	31	1:2.1	58,66



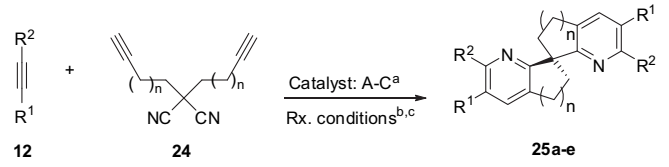
Scheme 8. Synthesis of 2,2′- and 2,3′-bipyridines by cocyclization of 1,3-diynes with 5-hexynenitrile.

reaction mixture clearly suggested that the initial cycloaddition was strongly chemoselective, and that it took place only at the CH_2O-$SiEt_3$-substituted ethyne moiety, since the TMS groups of these species would be likely to prevent a second cycloaddition.



Cocyclization of 1,3,5-hexatriyne **19** (R^1=TMS—C≡C, R^2=TMS) as an unsymmetrical 1,3-diyne, with **13** afforded two products that were identified as the 2,2′-bipyridine **20h** (10%) and the 2,3′-bipyridine **21f** (21%) (entry 6, Table 2).[58,66] The initial cycloaddition is likely to have occurred at the central triple bond followed by further cycloadditions on both the ethyne *ortho* to the pyridine nitrogen (giving **20h**) and the *meta* ethyne (giving **21f**). A third set of cycloadditions on the remaining ethyne is presumably prevented by steric hindrance.

Saa et al. reported a one-step synthesis of the novel C_2-symmetric spirocyclic 7,7′- and 8,8′-bicycloalka[*b*]pyridines **25a**–**e**, respectively, by Co(I)-catalyzed [2+2+2] cycloaddition between bis-alkynenitriles **24** and alkynes **12** (Scheme 9, Table 3). The bis-alkynenitriles **24** were easily prepared by dialkylation of malononitrile with tosylates of the corresponding alkyn-1-ols.[67]



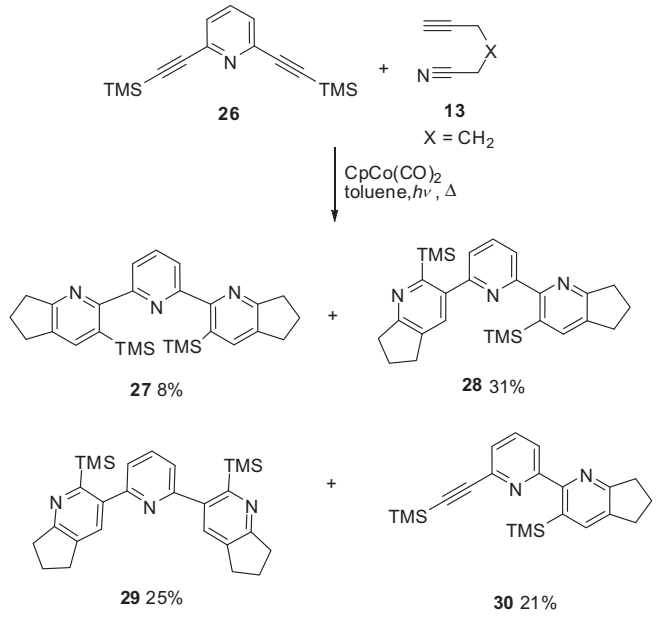
Scheme 9. Synthesis of spirocyclic 7,7′- and 8,8′-bicycloalka[*b*]pyridines by cycloaddition of bis-alkynenitriles to alkynes.

Table 3

Entry	12		24	Catalyst[a]	Product	Yield (%)
	R^1	R^2	*n*			
1	H	H	1	A[b]	**25a**	32
2	H	H	1	C[c]	**25a**	21
3	H	H	1	A[c]	**25a**	7
4	TMS	TMS	1	A[c]	**25b**	33
5	Ph	Ph	1	A[c]	**25c**	9
6	CO_2Me	CO_2Me	1	A[b]	**25d**	7
7	TMS	≡—TMS	1	A[b]	**25e**	8
8	TMS	TMS	2	A[b]	**25b**	32
9	TMS	≡—TMS	2	A[b]	**25e**	6

[a] Catalyst: A: $CpCo(CO)_2$, B: CpCo(Cod), C: $CpCo(C_2H_4)$.
[b] Reaction was carried out in toluene/*hν*, A.
[c] Reaction was carried out at rt.

Terpyridines can be obtained by cobalt-catalyzed [2+2+2] cycloaddition between 5-hexynenitrile **13** and 1,6-bis (trimethylsilylethynyl)pyridine **26** (Scheme 10). Although all three possible regioisomers **27**–**29** of the terpyridine are produced, their combined yield is good (64%). Of the three, it is the 2,2′:6′,2″-terpyridine **27** that has the lowest yield (8%); this is due to the lack of reactivity of its 2,2′-bipyridine precursor **30**, which is also isolated in 21% yield.[61]



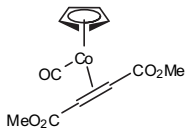
Scheme 10. Synthesis of terpyridines by cobalt-catalyzed cycloaddition of 5-hexynenitrile to 1,6-diethynylpyridine.

3.1.1.1.2. Cycloalka[c]pyridine. Cocyclization of symmetrical *α,ω*-diynes **32** with the appropriate nitrile **31** in the presence of $CpCo(CO)_2$, $Ni(cod)_2$, $Cp^*Ru(cod)Cl$ or $[Cp^*Ru(CH_3CN)_3]PF_6$ catalysts afforded the corresponding cyclopenta[*c*]pyridines **33a**–**t** (Table 4a), **33u**–**ag** (Table 4b), **33ah**–**bo** (Table 4c), and **33ai**, **33ar**, **33at**, **33au**, **33bp**–**bs** (Table 4d), respectively, in good to excellent yields (Scheme 11).[68–83] The reactions were carried out with various alkyl, aryl, and heteroaryl cyanides and poceeded under mild

Table 4a

Entry	31	32		Product	Yield[a] (%)	Ref.
	R	R^1=R^2	X			
1	Me	TMS	CH_2	**33a**	84[b]	69
2	^{n}Bu	H	CH_2	**33b**	67[b]	70
3	CH_2CO_2Et	H	CH_2	**33c**	37[b]	70
4	Ph	9-Bn-9*H*-purin-6-yl	CH_2	**33d**	31[c]	80
5	Ph	H	$(CH_2)_2$	**33e**	56[b], (65)[d]	70,81
6	Me	9-Bn-9*H*-purin-6-yl	$(CH_2)_2$	**33f**	33[c]	80
7	Ph	9-THP-9*H*-purin-6-yl	$(CH_2)_2$	**33g**	42[c]	80
8	4-$CF_3C_6H_4$	9-THP-9*H*-purin-6-yl	$(CH_2)_2$	**33h**	28[c]	80
9	Ph	H	$(CH_2)_2$	**33i**	70[b]	70
10	Me	H	$(CH_2)_2$	**33j**	81[b] (64)	70,73
11	CH_2COMe	H	$(CH_2)_2$	**33k**	62[b]	70
12	CO_2Et	H	$(CH_2)_2$	**331**	5.9[b]	70
13	CH_2CO_2Et	H	$(CH_2)_2$	**33m**	47[b]	70
14	^{t}Bu	H	$(CH_2)_2$	**33n**	47[b]	70
15	Et	H	$(CH_2)_2$	**33o**	70[d]	81
16	Me	H	$(CH_2)_3$	**33p**	81[b]	70
17	CH_2CO_2Et	H	$(CH_2)_3$	**33q**	22[b]	70
18	^{n}Bu	H	$(CH_2)_3$	**33r**	43[b]	70
19	Ph	H	$(CH_2)_3$	**33s**	54[b]	70
20	Ph	H	$C(CO_2Et)_2$	**33t**	89[e]	82

[a] Catalyst: A, $CpCo(CO)_2$, E,



[b] Reaction was carried out in refluxing xylene in the presence of 2–5 mol % cat.
[c] Reaction was carried out with cat. A 100 mol %/ MW (300 W)/200 °C/10 min.
[d] Reaction was carried out with cat. E 5 mol %/ toluene/h*ν*.
[e] Reaction was carried out under MW/300/xylene/140 °C.

Table 4b

Entry	31	32		Product	Yield[a,b] (%)	Ref.
	R	R^1=R^2	X			
21	Ph	Et	$(CH_2)_2$	**33u**	92	72
22	Me	Et	$(CH_2)_2$	**33v**	46	72
23	Me	Me	$(CH_2)_5$	**33w**	29	72
24	Ph	Me	$C(CO_2Me)_2$	**33x**	86	72,74–76
25	$MeOC_6H_4$-*p*	Me	$C(CO_2Me)_2$	**33y**	64	72
26	$CF_3C_6H_4$-*p*	Me	$C(CO_2Me)_2$	**33z**	94	72
27	MeC_6H_4-*p*	Me	$C(CO_2Me)_2$	**33aa**	81	72
28	MeC_6H_4-*o*	Me	$C(CO_2Me)_2$	**33ab**	69	72
29	Me	Me	$C(CO_2Me)_2$	**33ac**	69	72
30	^{i}Bu	Me	$C(CO_2Me)_2$	**33ad**	72	72
31	^{t}Bu	Me	$C(CO_2Me)_2$	**33ae**	56	72
32	1-Naphthyl	Me	$C(CO_2Me)_2$	**33af**	91	72
33	1-Methylpyrrol-2-yl	Me	$C(CO_2Me)_2$	**33ag**	97	72

[a] Catalyst: B, $Ni(cod)_2$.
[b] All reactions were carried out in toluene/rt.

Table 4c

Entry	31	32		Product	Yield[a] (%)	Ref.
	R	R^1=R^2	X			
34	CO_2Et	H	CH_2	**33ah**	89	68
35	$ClCH_2$	H	CH_2	**33ai**	65 (81)	71,83
36	$NCCH_2$	H	CH_2	**33aj**	77	83
37	CO_2Et	H	$C(CN)_2$	**33ak**	80	68
38	CO_2Et	H	$C(COMe)_2$	**33al**	90	68
39	CO_2Et	H	$C(CO_2Me)_2$	**33m**	83	68,77
40	COPh	H	$C(CO_2Me)_2$	**33n**	84	68,77
41	$NCCH_2$	H	$C(CO_2Me)_2$	**33ao**	91	79
42	$NCCH_2$	H	$C(CO_2Me)_2$	**33ao**	95l	79
43	$NCCH_2$	H	$C(CO_2Me)_2$	**33ao**	22l	79
44	$NCCH_2$	H	$C(CO_2Me)_2$	**33ao**	92	79,83
45	$NCCH_2$	H	$C(CO_2Me)_2$	**33ao**	64[b]	79,83
46	NCCH2	Me	$C(CO_2Me)_2$	**33ap**	70	79,83
47	$NC(CH_2)_2$	H	$C(CO_2Me)_2$	**33aq**	62	83
48	NCC_6H_4-*o*	H	$C(CO_2Me)_2$	**33ar**	61	83
49	NCC_6H_4-*m*	H	$C(CO_2Me)_2$	**33as**	50	83
50	NCC_6H_4-*p*	H	$C(CO_2Me)_2$	**33at**	43	83
51	NCH=CH	H	$C(CO_2Me)_2$	**33au**	88	83
52	CH_3CHCl	H	$C(CO_2Me)_2$	**33av**	87	78,83
53	$PhNHCH_2CHCl$	H	$C(CO_2Me)_2$	**33aw**	71	78,83
54	CH_2=CCl	H	$C(CO_2Me)_2$	**33ax**	84	78,83
55	$NC(CH_2)_4C(Cl)_2$	H	$C(CO_2Me)_2$	**33ay**	76	78,83
56	$CH{=}C(CH_2)_4C(Cl)_2$	H	$C(CO_2Me)_2$	**33az**	81	78,83
57	CH_2OMe	H	$C(CO_2Me)_2$	**33az**	23	83
58	CH_2OMe	H	$C(CO_2Me)_2$	**33az**	70[c]	83
59	CH_2OMe	H	$C(CO_2Me)_2$	**33ba**	45[b]	83
60	CH_2SMe	H	$C(CO_2Me)_2$	**33bb**	32	83
61	H_2C—≡—TMS	H	$C(CO_2Me)_2$	**33bc**	58	83
62	2-Furoyl	H	$C(CO_2Me)_2$	**33bd**	79	68
63	COMe	H	$C(CO_2Me)_2$	**33be**	90	68,77
64	Ts	H	$C(CO_2Me)_2$	**33bf**	31 (53)	68,77
65	CCl_3	H	$C(CO_2Me)_2$	**33bg**	44 (50)[b]	68,77
66	C_6F_5	H	$C(CO_2Me)_2$	**33bh**	67 (80)	68,77
67	$ClCH_2$	H	$C(CO_2Me)_2$	**33bi**	93	78,83
68	$ClCH_2$	H	$C(CO_2Me)_2$	**33bi**	78[b]	83
69	$ClCH_2$	H	$C(CO_2Me)_2$	**33bi**	68[d]	83
70	$ClCH_2$	H	$C(CO_2Me)_2$	**33bi**	74[d]	83
71	$ClCH_2$	H	$C(CO_2Me)_2$	**33bi**	69[d]	83
72	$ClCH_2$	Me	$C(CO_2Me)_2$	**33bj**	71	78,83
73	FCH_2	H	$C(CO_2Me)_2$	**33bk**	90	78,83
74	$BrCH_2$	H	$C(CO_2Me)_2$	**33bl**	42	78,83
75	Cl_2CH	Me	$C(CO_2Me)_2$	**33bm**	91	78,83
76	CO_2Et	H		**33bn**	88	68

(*continued*)

Table 4c (*continued*)

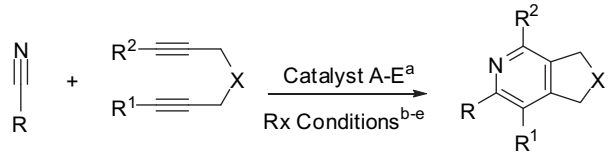
Entry	31	32		Product	Yield[a] (%)	Ref.
	R	R^1=R^2	X			
77	CO_2Et	H		**33bo**	86	68

[a] Catalyst: C, Cp*Ru(cod)Cl and reactions were carried out in DCE with 2–5 mol% cat./rt-80 °C unless otherwise mentioned.
[b] Reaction was carried out in the presence of $AgPF_6$ (10 mol% for entry 45), 10 mol% for entry 65 with cat. (10 mol%), and (4 mol% for entry 78).
[c] Cat. concentration was 10 mol%.
[d] Reaction was carried out in the presence of Et_4NCl (5 mol% for entry 69), (10 mol% for entry 70), and (20 mol% for entry 71).

Table 4d

Entry	31	32		Product	Yield[a,b] (%)
	R	R^1=R^2	X		
78	$ClCH_2$	H	CH2	**33ai**	56
79	CH_2=CH–	H	$(CH_2)_2$	**33bp**	14
80	$NCC(Me)_2$	H	$C(CO_2Me)_2$	**33bq**	95
81	SEt	H	$C(CO_2Me)_2$	**33br**	53
82	NCC_6H_4-*o*	H	$C(CO_2Me)_2$	**33ar**	56
83	NCC_6H_4-*p*	H	$C(CO_2Me)_2$	**33at**	61
84	6-Cyanopyridin-2-yl	H	$C(CO_2Me)_2$	**33bs**	72
85	NC–CH=CH–	H	$C(CO_2Me)_2$	**33au**	50

[a] Catalyst: D, $[Cp^*Ru(MeCN)_3]PF_6$.
[b] All reactions were carried out in DMF and in the presence of Et_4NCl (10%) at rt.



Scheme 11. Synthesis of cycloalka[*c*]pyridines by cocyclization of symmetrical as well as unsymmetrical α,ω-diynes with nitriles.

conditions. Some authors used a combination of $Ni(acac)_2$ and an imidazolium salt as a catalyst for performing these reactions. Some cyclotrimerizations were enhanced by carrying out the reactions under microwave irradiation.[80,82]

Cocyclization of the appropriate unsymmetrical α,ω-diynes **33** with the corresponding nitriles **31** proceeded in the presence of $CpCo(CO)_2$ or Cp*Ru(cod)Cl to give cyclopenta[*c*]pyridines **33bt**–**cj** (Table 5a) and **33ck**–**dg** (Table 5b), respectively, with exclusive regioselectivity (Scheme 11).[70,78–80,83] The regioselectivity is controlled by the chelating nature of the alkyne component and by steric effects, whereas the chemoselectivity is apparently controlled by electronic interactions. When Cp*Ru(cod)Cl was used to catalyze the cycloaddition of 1,6-diynes to dicyanides under mild conditions,[77–79,83] it is noteworthy that, unlike Co(I) catalysts,[80] which cocyclize dicyanides with alkynes to give bipyridines, Ru(II) promotes the reaction of only one of the two cyano groups while the other is remaining intact after the complete conversion of the diyne.

Some unsymmetrical 1,6-diynes **34** when subjected to cycloaddition with nitriles **31** (R=Bu, CH_2CN, COOEt) in the presence of a Ru(II) catalyst, led to the formation of 2,3,4,6-substituted pyridine isomers **35a**–**e** and 2,3,4,5-substituted isomers **36a**–**e** (Scheme 12, Table 6).[68,78,79] As summarized in Table 6, most of the reactions were carried out under mild conditions (rt or 60 °C) to furnish fused pyridines in good yields (78–97%) with excellent regioselectivity, depending on the nature of the alkyne substituents with preference

Table 5a

Entry	31	32			Product	Yield (%)	Ref.
	R	R^1	R^2	X			
1	Ph	9-Bn-9*H*-purin-6-yl	H	$(CH_2)_2$	**33bt**	(74)[a], (77)[b] (79)[c]	80
2	4-$MeO_2CC_6H_4$	9-Bn-9*H*-purin-6-yl	H	$(CH_2)_2$	**33bu**	(56)[a],(39)[b] (31)[c]	80
3	2-Furyl	9-Bn-9*H*-purin-6-yl	H	$(CH_2)_2$	**33bv**	(37)[a], (34)[b] (39)[c]	80
4	4-Pyridyl	9-Bn-9*H*-purin-6-yl	H	$(CH_2)_2$	**33bw**	(36)[a], (39)[b] (42)[c]	80
5	Me	9-Bn-9*H*-purin-6-yl	H	$(CH_2)_2$	**33bx**	(36)[b] (42)[c]	80
6	3-Pyridyl	9-Bn-9*H*-purin-6-yl	H	$(CH_2)_2$	**33by**	(71)[b] (75)[c]	80
7	Et	9-Bn-9 *H*-purin-6-yl	H	$(CH_2)_2$	**33bz**	(58)[a], (53)[b] (64)[c]	80
8	Ph	9-THP-9*H*-purin-6-yl	H	$(CH_2)_2$	**33ca**	(89)[b] (91)[c]	80
9	4-$MeOC_6H_4$	9-THP-9*H*-purin-6-yl	H	$(CH_2)_2$	**33cb**	(29)[b] (43)[c]	80
10	4-$MeO_2CC_6H_4$	9-THP-9*H*-purin-6-yl	H	$(CH_2)_2$	**33cc**	(30)[b](32)c	80
11	4-$F_3CC_6H_4$	9-THP-9 *H*-purin-6-yl	H	$(CH_2)_2$	**33cd**	(57)[b] (46)[c]	80
12	2-Furyl	9-THP-9*H*-purin-6-yl	H	$(CH_2)_2$	**33ce**	(40)[b] (42)[c]	80
13	4-Pyridyl	9-THP-9*H*-purin-6-yl	H	$(CH_2)_2$	**33cf**	(47)[b] (47)[c]	80
14	3-Pyridyl	9-THP-9*H*-purin-6-yl	H	$(CH_2)_2$	**33cg**	(50)[b] (61)[c]	80
15	Et	9-THP-9*H*-purin-6-yl	H	$(CH_2)_2$	**33ch**	(50)[b]	80
16	^{n}Bu	H	Et	$(CH_2)_4$	**33ci**	73[d]	70
17	^{n}Bu	Et	H	$(CH_2)_4$	**33cj**	4.1[d]	70

Catalyst: A: $CpCo(CO)_2$.

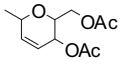
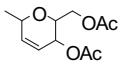
[a] Reaction was carried out with cat. (100 mol %), *hν*, 140 °C, in PhCN (for entries 1), in mesitylene (for entries 3, 4, and 7).

[b] Reaction was carried out with cat. (100 mol %), MW irradation (300 W)/200 °C in THF (for entries 2–5 and 9–13), PhCN (for entries 1 and 8), EtCN (for entry 7), MeCN (for entries 6 and 14).

[c] Reaction conditions are the same as in (b) but using 20 mol % cat.

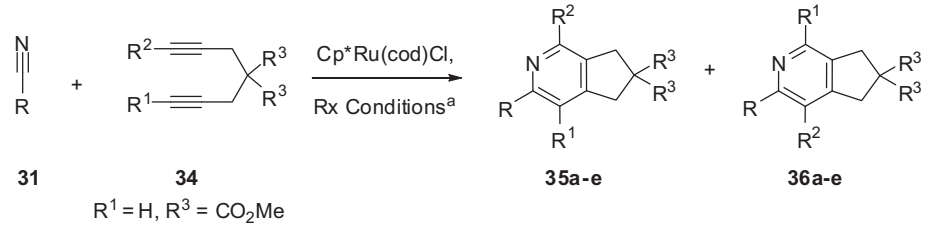
[d] Reaction was carried out in refluxing xylene (117 h) with cat. 0.5 mmol %.

Table 5b

Entry	31	32			Product	Yield	(%)[a,b] Ref.
	R	R^1	R^2	X			
1	$ClCH_2$	Me	H	$C(CO_2Me)_2$	**33ck**	88	78,83
2	$NCCH_2$	H	Ph	$C(CO_2Me)_2$	**33cl**	78	79
3	$NCCH_2$	H	$SiMe_3$	$C(CO_2Me)_2$	**33cm**	92	79
4	$NCCH_2$	H	CO_2Me	$C(CO_2Me)_2$	**33cn**	80	79
5	$NC(CH_2)_2$	H	Me	$C(CO_2Me)_2$	**33co**	73	79
6	$NC(CH_2)_3$	H	Me	$C(CO_2Me)_2$	**33cp**	46	79
7	NCPh(*o*)	H	Me	$C(CO_2Me)_2$	**33cq**	88	79
8	NCCH=CH	H	Me	$C(CO_2Me)_2$	**33cr**	88	79
9	CO_2Et	Ph	H	$C(CO_2Me)_2$	**33cs**	50	77
10	$ClCH_2$		H	$C(CO_2Me)_2$	**33ct**	77	83
11							
12							
13	Cl_2CH		H	$C(CO_2Me)_2$	**33cu**	75	83
14							
15	$NCCH_2$	Me	H	$C(CO_2Me)_2$	**33cv**	44	83
16	$NC(CH_2)_3$	Me	H	$C(CO_2Me)_2$	**33cw**	46	83
17	*o*-C_6H_4CN	Me	H	$C(CO_2Me)_2$	**33cx**	89	83
18	NCCH=CH	Me	H	$C(CO_2Me)_2$	**33cy**	89	83
19	$ClCH_2$	Me	H	$C(CO_2Me)_2$	**33cz**	88	83
20	$MeOCH_2$	Me	H	$C(CO_2Me)_2$	**33da**	79	83
21	$MeSCH_2$	Me	H	$C(CO_2Me)_2$	**33db**	81	83
22	H_2C—≡—TMS	Me	H	$C(CO_2Me)_2$	**33dc**	75	83
23	$NCCH_2$	Ph	H	$C(CO_2Me)_2$	**33dd**	78	83
24	$ClCH_2$	Ph	H	$C(CO_2Me)_2$	**33de**	80	78,83
25	$ClCH_2$	$SiMe_3$	H	$C(CO_2Me)_2$	**33df**	84	83
26	$SiMe_3$—≡—C_6H_4-*o*	Me	H	$C(CO_2Me)_2$	**33dg**	54	83

[a] Catalyst: C, Cp*Ru(cod)Cl.

[b] All reactions were carried out in DCE with cat. (2–10 mol %) at 25–60 °C for 1.5–24 h.



Scheme 12. Synthesis of cyclopenta[*c*]pyridine regioisomers by cocyclization of unsymmetrical 1,5-diynes with nitriles.

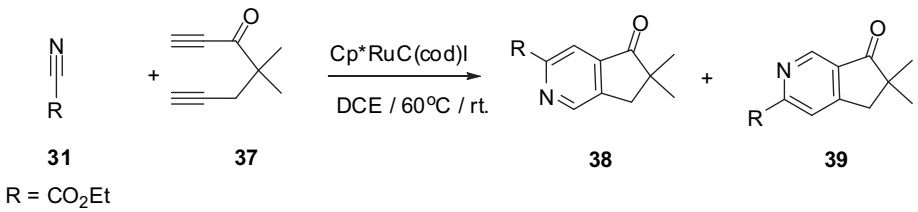
Table 6

Entry	**31**	**34**	**35/36**	Yield (%)[a]	Ratio **35**/**36**	Ref.
	R	R^2	Products			
1	$NCCH_2$	Me	**35a**/**36a**	97	95:5	79
2	CO_2Et	Me	**35b**/**36b**	78	88:12	77
3	CO_2Et	Me	**35c**/**36c**	87	88:2	68
4	CO_2Et	Ph	**35d**/**36d**	86	89:11	68
5	CO_2Et	CO_2Me	**35e**/**36e**	78	13:87	77

[a] Reactions were carried out in DCE at rt −60 °C (1−5 h) with 2 mol % cat.(entries 1 and 5), 5 mol % cat. (entries 2−4).

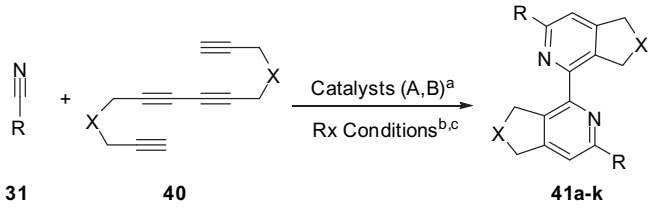
for the 2,3,4,6-substituted isomers over the 2,3,4,5-substituted isomers. In contrast, the reaction of an ester **34** (R^1=H, R^2=CO_2Me) and **31** (R^2=CO_2Et) proceeded at rt and, unexpectedly, a 2,3-dialkoxycarbonyl isomer **36e** was obtained as a major product along with a minor isomer **35e** in 78% total yield.[77] Therefore, the electron-withdrawing ester group in **34** reversed both the reactivity and the regioselectivity.

Yamamoto et al. reported the Cp*RuCl-catalyzed cycloaddition of **31** (R=CO_2Et) to the unsymmetrical diyne **37**, possessing an internal carbonyl group conjugated with one of the two alkyne moieties, as outlined in Scheme 13. The reaction gave rise to the pyridine-fused lactone regioisomers **38**/**39** in 64% combined yield with a ratio of 89:11.[68]



Scheme 13. Synthesis of cyclopenta[*c*]pyridinone regioisomers by cocyclization of unsymmetrical 1,5-diynes with ethyl cyanoformate.

1,6,8,13-Tetraynes **40** underwent cyclotrimerization with an excess of nitriles **31** in the presence of a catalytic amount of $CpCo(CO)_2$ under microwave irradiation to give regioselectively the corresponding bipyridines **41a**–**k** in reasonable isolated yields (Scheme 14, Table 7).[84]



Scheme 14. Synthesis of 2,2′-bipyridines by cocyclization of tetraynes with nitriles.

Moreover, a tetrayne **40** (X=$C(CO_2Me)_2$) was reacted with malononitrile **31** (R=CH_2CN) and chloroacetonitrile **31** (R=CH_2Cl) using 10 mol % of Cp*Ru(cod)Cl at 80 °C to afford the desired bipyridines **41j**,**k** as the sole products in 95 and 71% yield, respectively.[79,83]

3.1.1.2. Carbocyclic fused with six-membered heterocyclic ring: three heteroatom.

3.1.1.2.1. Tetrahydrobenzo[1,2-e]-1,2,4-triazine. Vollhardt et al. reported[85] a chemo- and regiospecific construction of 5,6,7,8-tetrahydrobenzo[1,2-*e*]-1,2,4-triazines **43a**–**f** by the cyclotrimerization of adiponitrile derivatives **42** with the appropriate

Table 7

Entry	**31**	**40**	Catalyst	Product	Yield[a] (%)	Ref.
	R	X				
1	Me	$(CH_2)_2$	A[b]	**41a**	36	84
2	Ph	$(CH_2)_2$	A[b]	**41b**	51	84
3	4-$CF_3C_6H_4$	$(CH_2)_2$	A[b]	**41c**	47	84
4	4-$MeOC_6H_4$	$(CH_2)_2$	A[b]	**41d**	50	84
5	3,4,5-$(MeO)_3C_6H_2$	$(CH_2)_2$	A[b]	**41e**	46	84
6	2-Tetrahydrofuryl	$(CH_2)_2$	A[b]	**41f**	48	84
7	Bn	$(CH_2)_2$	A[b]	**41g**	34	84
8	Cy	$(CH_2)_2$	A[b]	**41h**	21	84
9	c-Pr	$(CH_2)_2$	A[b]	**41 i**	9	84
10	CH_2CN	$C(CO_2Me)_2$	B[c]	**41j**	95	79,83
11	CH_2Cl	$C(CO_2Me)_2$	B[c]	**41k**	71	83

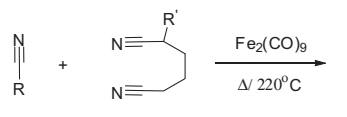
[a] Catalyst: A: $CpCo(CO)_2$; B: Cp*Ru(cod)Cl.
[b] Reaction was carried out in THF under MW (300 W), 200 °C, 30 min.
[c] Reaction was carried out in DCE with cat. (10 mol %) at 80 °C.

mononitrile **31** using iron carbonyl as a catalyst (Scheme 15, Table 8).

3.1.2. Benzo fused heterocycles.

3.1.2.1. Benzo fused with five-membered heterocyclic ring: one heteroatom.

3.1.2.1.1. Benzo[c]furan. Several benzo[*c*]furan derivatives **45a**–**v** have been prepared in moderate-to-good 88% yields by cyclo-



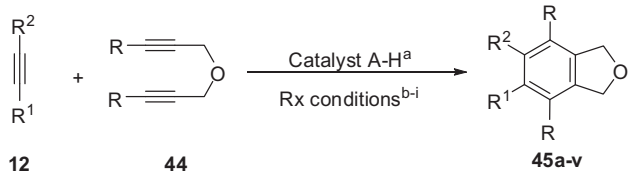
Scheme 15. Synthesis of tetrahydrotriazines by cocyclization of adiponitrile derivatives with nitriles.

Table 8

Entry	**31**	**42**	Product	Yield (%)
	R	R′		
1	^{n}Bu	H	**43a**	42
2	-$(CH_2)_4$-OCH_2Ph	H	**43b**	64
3	Bn	H	**43c**	58
4	Ph	H	**43d**	68
5	–$(CH_2)_4$–	H	**43e**	71
6	Bn	Bn	**43f**	62

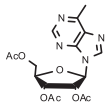
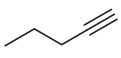
trimerization of symmetrical 1,6-diynes **44** with symmetrical as well as unsymmetrical alkynes (Scheme 16, Table 9).[86–93] The cyclotrimerization reactions were catalyzed by Ni, Ir, Pd, Ru, Co or Rh complexes.

Similarly, cyclotrimerization of unsymmetrical 1,6-diynes **46** with dimethylacetylene dicarboxylate **12** (R^1=R^2=COOMe) as a symmetrical alkyne in the presence of a Pd catalyst afforded benzo[*c*]furans **47a**,**b** in low-to-moderate yields (Scheme 17, Table 10).[86]



Scheme 16. Synthesis of benzo[*c*]furans by cocyclization of symmetrical 1,6-diynes with alkynes.

Table 9

Entry	12		44	Catalyst[a]	Product	Yield (%)	Ref.
	R^1	R^2	R				
1	COOMe	COOMe	COOMe	A[b]	**45a**	73	86
2	COOMe	COOMe	COOMe	A[c]	**45a**	67	86
3	COOMe	COOMe	COOEt	A[b]	**45b**	72	86
4	COOMe	COOMe	COOEt	A[c]	**45b**	66	86
5	COOEt	COOEt	COOMe	A[b]	**45c**	71	86
6	COOEt	COOEt	COOMe	A[c]	**45c**	61	86
7	Ph		H	B[e]	**45d**	5	87,88
8	Ph		H	C[e]	**45d**	87	87,88
9	Ph		H	D[e]	**45d**	88	87,88
10	CH_2OMe	CH_2OMe		E[d]	**45e**	84	89
11	Ph		H	B[e]	**45f**	47	87,88
12	H	^{n}Bu	H	F[f]	**45g**	68	90
13	H	^{n}Pr	H	G[g]	**45h**	58	91
14	H	C_6H_{13}	H	H[h]	**45i**	79	92
15	H	Ph	H	H[h]	**45j**	72	92
16	^{n}Pr	^{n}Pr	H	H[h]	**45k**	48	92
17	CH_2OAc	CH_2OAC	H	H[h]	**451**	52	92
18	H	Ph	H	H[i]	**45j**	82	93
19	H	^{n}Bu	H	H[i]	**45m**	77	93
20	H	CH_2OH	H	H[i]	**45n**	64	93
21	H	Cyclohexenyl	H	H[i]	**45o**	84	93
22	H	*p*-MeC_6H_4	H	H[i]	**45p**	84	93
23	Et	Ph	H	H[i]	**45q**	80	93
24	H	Bn	H	H[i]	**45r**	71	93
25	^{n}Bu	Ph	H	H[i]	**45s**	87	93
26	CH_2OH	Ph	H	H[i]	**45t**	74	93
27	CO_2Et	CO_2Et	H	H[i]	**45u**	34	93
28	H		H	H[i]	**45v**	67	93

[a] Catalyst: A: $Rd_2(dba)_3$, B: $NiBr_2(PPh_3)_2$/Zn, C: $NiBr_2(dppe)_2$/Zn, D: $CoBr(PPh_3)_2$, E: $[IrCl(cod)]_2$, F: Cp*RuCl(cod),G: $RhCl(PPh_3)_3$, H: $[Rh(cod)Cl]_2$.

[b] A solution of a diyne, acetylenic diester, catalyst, and PPh_3 in toluene was stirred at 110 °C for 1 h.

[c] The acetylenic diester was added to a solution of a diyne, catalyst, and PPh_3 in toluene and the reaction mixture was stirred at 110 °C for 1 h.

[d] Reaction was carried out in xylene at 100 °C.

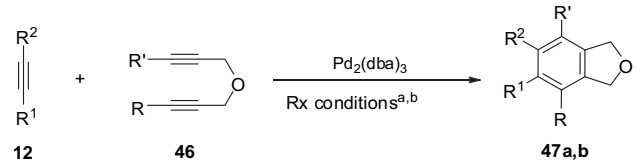
[e] Reaction was carried out in acetonitrile at 60 °C.

[f] Reaction was carried out in dichloroethane at rt.

[g] Reaction was carried out in EtOH at 0 °C/2 h.

[h] Reaction was carried out in H_2O/KOH at 60 °C/in air.

[i] Reaction was carried out in THF/H_2O at rt./1 h.



Scheme 17. Synthesis of benzo[*c*]furans by cocyclization of unsymmetrical diynes with dimethylacetylene dicarboxylate.

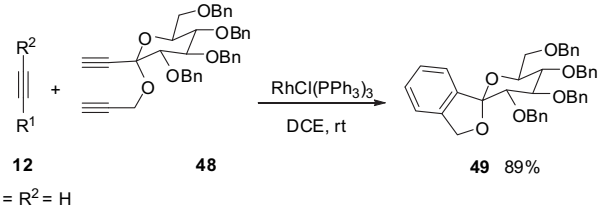
Table 10

Entry	12	46		Product	Yield (%)
	R^1=R^2	R	R′		
1	COOMe	Me	COOMe	**47a**	54[a]
2	COOMe	Me	COOMe	**47a**	43[b]
3	COOMe	COMe	COOMe	**47b**	17[a]
4	COOMe	COMe	COOMe	**47b**	13[b]

[a] A solution of a diyne, acetylenic diester, catalyst, and PPh_3 in toluene was stirred at 110 °C for 1 h.

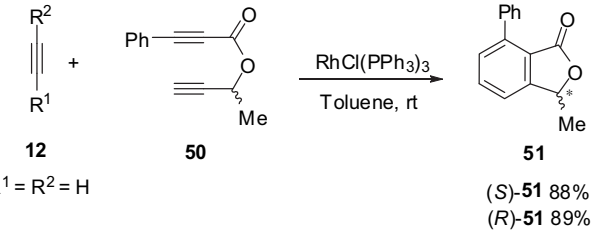
[b] The acetylenic diester was added to a stirred solution of a diyne, catalyst, and PPh_3 in toluene at 110 °C for1 h.

An interesting application of this reaction has been reported by McDonald et al., who succeeded in the synthesis of a *C*-acyl glycoside **49** by Rh-catalyzed [2+2+2] cyclotrimerization of carbohydrate derivative **48** with acetylene (Scheme 18).[94]



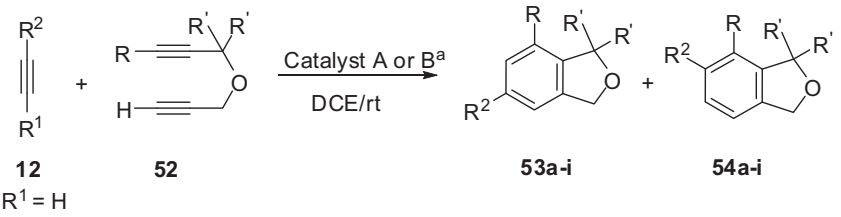
Scheme 18. Synthesis of benzo[*c*]furans with *C*-acyl glycoside derivative by cocyclization of diyne with acetylene.

Witulski and Zimmermann[95] synthesized chiral 3-substituted phthalides **51** in good yield (Scheme 19) by treatment of dialkyne **50** with acetylene in the presence of Wilkinson's catalyst. The best results were obtained when the reactions were carried out in toluene in the presence of acetylene gas and 5 mol % of the catalyst.



Scheme 19. Synthesis of chiral benzo[*c*]furans by cocyclization of diyne with acetylene.

In the presence of Cp*Ru(cod)Cl or $RhCl(PPh_3)_3$ the cycloaddition of various unsymmetrical 1,6-diynes **52** with unsymmetrical monoalkynes **12** proceeded at rt in 1,2-dichloroethane (DCE) to give benzo[*c*]furan regioisomers **53a**–**i** and **54**–**i** with notable *meta*-selectivity (Scheme 20, Table 11).[90,94,96,97] The regioselectivity of the reaction and the reactivity of the substrate are highly dependent on the steric size of the substituent attached to the substrates **52** and **12**.[94]



Scheme 20. Synthesis of benzo[*c*]furan regioisomers by cocyclization of unsymmetrical diynes with alkynes.

Table 11

Entry	12	52		Catalyst[a]	53/54	Yield (%)	Ratio[b] 53:54	Ref.
	R^2	R	R′		Products			
1	^{n}Bu	Me	H	A	**53a/54a**	75	95:5	90
2	^{n}Bu	Me	H	B	**53a/54a**	35	1.7:1	94
3	$C(Me)_2OH$	Me	H	B	**53b/54b**	54	**54b** only	94
4	CH_2OH	Me	H	B	**53c/54c**	53	1.8:1	94
5	^{n}Bu	$C(Me)_2OH$	H	B	**53d/54d**	36	**53d** only	94
6	$C(Me)_2OH$	$C(Me)_2OH$	H	B	**53e/54e**	60	**53d** only	94
7	^{n}Bu	OEt	Me	B	**53f/54f**	61	4:1	94
8	$C(Me)_2OH$	OEt	Me	B	**53g/54g**	53	**53d** only	94
9	^{n}Bu	H	Ph	B	**53h/54h**	82	54:46	96
10	2-Ferrocenyl	2-Ferrocenyl	H	A	**53i/54i**	82	**53i** only	97

[a] Catalyst: A: Cp*RuCl(cod), B: $RhCl(PPh_3)_3$.
[b] Determined by ^{1}H NMR.

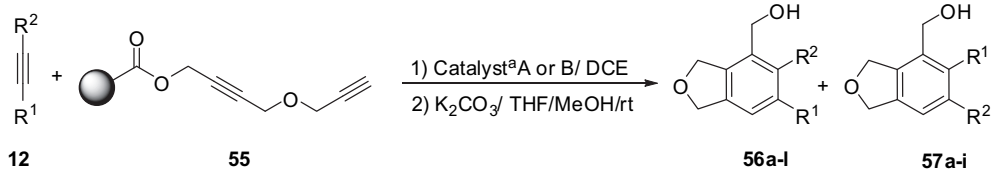
Interestingly, the reaction of **52** (R=H, R′=Ph) with **12** (R^2=^{n}Bu) exhibited almost no regioselectivity, although it has a bulky diphenylmethylene moiety adjacent to one of the two terminal alkynes.[96]

Cyclotrimerization of the carboxy resin **55** with symmetrical alkynes **12** in the presence of Wilkinson's catalyst in DCE at 60 °C or ruthenium catalysts in DCE at rt, followed by cleavage of the products from the resin upon treatment with K_2CO_3 in THF/MeOH, afforded the benzo[*c*]furans **56a**–**c** (entries 1–3) as single products in 57–95% yield (Scheme 21, Table 12).[98]

On the other hand, cycloadditions of **12** with the unsymmetrical diyne **55** led to the formation of the benzo[*c*]furans **56d**–**l** and **57a**–**i** (entries 4–11) as a mixture of regioisomers, as determined by ^{1}H NMR spectroscopic analysis. Low or no regioselectivity was obtained by using Wilkinson's catalyst. However, a slight substrate dependency was observed, which is in accordance with published reports.[19] In the case of performing the cyclotrimerization reactions in the presence of a ruthenium catalyst, a high degree of regioselectivity was observed, independent of the nature of the alkyne. The observed regioselectivity is in agreement with the previously reported observation in which the bulky Cp* ligand on the metal center directs the alkyne approach on the metallacycle intermediate to reduce steric interactions.[20] Surprisingly, while all alkyne substrates displayed a high regioselectivity, cyclotrimerizations with the electron-deficient alkyne **12** (R^1=H, R^2=CO_2Me) led to dramatically reduced regioselectivity (entry 12).

Yamamoto et al. reported the ruthenium-catalyzed cycloaddition of 1,6-diynes **58** having a carbonyl group at the 3 position with unsymmetrical monoalkynes **12** in order to study the effect of the electron-withdrawing group on the regiochemistry (Scheme 22).[96] The cycloaddition gave always regioisomers **59a**,**b**, in which the substituent R^2 is placed in the *para*-position to the carbonyl group, preferably over the other isomers **60a**,**b** (Table 13).

In order to evaluate the cooperative effect of the terminal substituents and the internal carbonyl group, variously substituted ester-diynes **58** were examined with respect to the cycloaddition



Scheme 21. Synthesis of benzo[*c*]furan regioisomers by cocyclization of carboxy diyne resin with alkynes.

Table 12

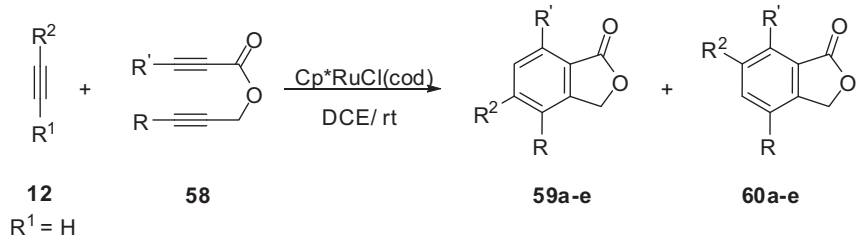
Entry	12		56/57	Yield[a,b] (%)	Ratio 56/57	Yield[a,c] (%)	Ratio 56/57
	R^1	R^2	Products				
1	H	H	**56a**	82	**56a** only	94	**56a** only
2	Et	Et	**56b**	57	**56b** only	68	**56b** only
3	CH_2OMe	CH_2OMe	**56c**	62	**56c** only	71	**56c** only
4	H	^{n}Bu	**56d/57a**	67	1:3	86	1:9
5	H	Ph	**56e/57b**	73	3:1	93	1:9
6	H	CH_2OH	**56f/57c**	64	1:1	79	1:9
7	H	CH_2OBn	**56g/57d**	74	1:1	78	1:9
8	H	CH_2NBoc	**56h/57e**	76	1:1	73	1:9
9	H	$(CH_2)_3CN$	**56i/57f**	71	1:3	90	1:9
10	H	$SiMe_3$	**56j/57g**	68	2:1	69	1:9
11	H	$(CH_2)_4Cl$	**56k/57h**	68	2:1	95	1:9
12	H	COOMe	**56l/57i**	75	1:1	73	1:3

[a] Catalysts: A: $[RhCl(PPh_3)_3]$, B: Cp*Ru(cod)Cl.
[b] Reaction was carried out at 80 °C using catalyst A.
[c] Reaction was carried out at rt using catalyst B.

with alkynes **12**. Thus, under the same reaction conditions, cocyclization of **12** with an ester **58** (R=Me, R′=H) possessing a methyl substituent at the electron-deficient alkyne terminal furnished the expected regioisomer **59c** in 88% yield as a major product (**59c**/**60c**=97:3).[96] These results suggest that the steric directing effect of the terminal methyl substituent effectively suppressed the formation of the minor regioisomer, resulting in the selective formation of **59**.

Moreover, the regioselectivity of the regioisomers **59d**/**60d** was decreased to 21:79, when an ester **58** (R=H, R′=Me) having a methyl substituent on the other alkyne moiety was used. In these cases, the electronic directing effect was almost offset by the conflicting steric influence of the terminal methyl substituent. As a consequence, both the reaction rate and regioselectivity were decreased to give rise to both regioisomers.[96]

Interestingly, an ester **58** (R=R′=Me) having methyl substituents on both alkyne termini gave rise to a 90:10 regioisomer mixture of **59e**/**60e**.[96]



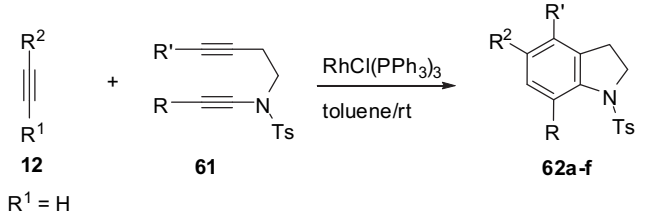
Scheme 22. Synthesis of benzo[*c*]furanone regioisomers by cocyclization of unsymmetrical diynes with alkynes.

Table 13

Entry	12	58		59/60	Yield (%)	Ratio[a] 59:60
	R^2	R	R′	Product		
1	^{n}Bu	H	H	**59a**/**60a**	93	70:30
2	Ph	H	H	**59b**/**60b**	87	75:25
3	^{n}Bu	Me	H	**59c**/**60c**	88	97:3
4	^{n}Bu	H	Me	**59d**/**60d**	78	21:79
5	^{n}Bu	Me	Me	**59e**/**60e**	94	90:10

[a] Determined by ^{1}H NMR.

3.1.2.1.2. Indoline. Cocyclization of aminodiynes **61** with acetylene and but-3-yn-1-ol **12** proceeded in the presence of Wilkinson's catalyst to give indolines **62a**–**f** in 68–93% yield (Scheme 23, Table 14).[99]



Scheme 23. Synthesis of indole derivatives by cocyclization of aminodiynes with monoalkynes.

Table 14

Entry	12	61		Product	Yield (%)
	R^2	R	R′		
1	H	H	H	**62a**	91
2	H	H	$(CH_2)_2OH$	**62b**	70
3	H	Ph	H	**62c**	85
4	H	Me_3Si	Ph	**62d**	93
5	H	Me_3Si	H	**62e**	68
6	$(CH_2)_2OH$	H	$(CH_2)_2OBn$	**62f**	88

Witulski et al.[100] reported the synthesis of 4,6- and 4,5-substituted indoline regioisomers **63a**–**e** and **64a**–**e** using either Grubbs' catalyst $[RuCl_2(NCHPh)(PCy_3)_2]$ or Wilkinson's catalyst $[RhCl(PPh_3)_3]$ by cocyclization of aminodiynes **61** (R′=Me and Ph) with unsymmetrical monoalkynes **12** (Scheme 24, Table 15).

Table 15

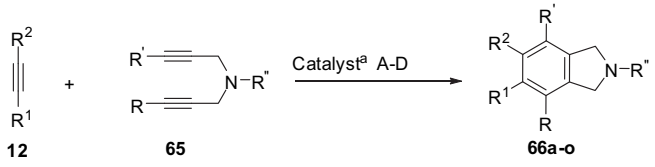
Entry	12	61	Catalyst[a] (mol %)	Products	Yield (%)	63:64[b]
	R^2	R′		*m*/*o*		
1	CH_2OH	Me	A (5)	**63a**/**64a**	70	9:1
2	CH_2OH	Me	B (5)	**63a**/**64a**	67	1:20
3	$(CH_2)_2OH$	Me	A 10)	**63b**/**64b**	51	9:1
4	$(CH_2)_2OH$	Me	B (5)	**63b**/**64b**	66	1:3
5	$(CH_2)_3OH$	Me	A (10)	**63c**/**64c**	57	9:1
6	CH_2OH	Ph	A (10)	**63d**/**64d**	60	9.5:1
7	CH_2OH	Ph	B (5)	**63d**/**64d**	70	1:1
8	Pr	Me	B (5)	**63e**/**64e**	54	1:10

[a] Catalyst A: $[RuCl_2(=CHPh)(PCy_3)_2]$ and B: $[RhCl(PPh_3)_3]$.
[b] Determined by ^{1}H NMR.

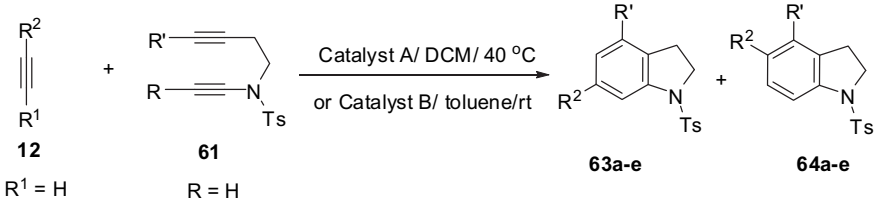
When Grubbs' catalyst was applied in CH_2Cl_2 at 40 °C the indolines **63a**–**d**/**64a**–**d** were obtained in 51–70% yield with excellent *meta*-selectivities of *meta*/*ortho*=9:1 and 9.5:1 for **63a**–**c**/**64a**–**c** (entries 1, 3, and 5) and **63d**/**64d** (entry 6), respectively (Table 15).[100]

On the other hand, when the 1,6-diynes **61** and the monoalkynes **12** (R^2=CH_2OH, $(CH_2)_2OH$, Pr) were treated with 5 mol % Wilkinson's catalyst in toluene at 20 °C, a switch in regioselectivity was observed, allowing the regioselective synthesis of 4,5-substituted indolines. Under these conditions, the products **63a**/**64a** (entry 2) and **63e**/**64e** (entry 8) were obtained in 67 and 54% yield with excellent selectivities of *meta*/*ortho*=1:20 and 1:10, respectively (Table 15). However, only a moderate preference for the *ortho*-isomer of **63b**/**64b** (entry 4) (*meta*/*ortho*=1:3) was found in the reaction of **61** (R′=Me) with but-3-yn-1-ol (**12**), and the reaction of **61** (R′=Ph) with **12** (R^2=CH_2OH) proceeded to give **63d**/**64d** (entry 7) without a significant selectivity.[100]

3.1.2.1.3. Isoindoline. The [2+2+2] cocyclization of symmetrical aminodiyne **65** (R=R′=H, R″=Ts) and gaseous acetylene **12** in the presence of 20 mol % nickel(0) complex, and THF at 23 °C gave the isoindoline derivative **66a** (entry 1) in 91% yield (Scheme 25, Table 16).[101]

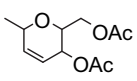
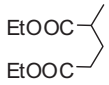
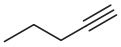


Scheme 25. Synthesis of isoindolines by cocyclization of aminodiynes with monoalkynes.



Scheme 24. Synthesis of indole regioisomers by cocyclization of aminodiynes with monoalkynes.

Table 16

Entry	12		65		Catalyst[a]	Solvent/°C	Time	Product	Yield (%)	Ref.
	R^1	R^2	R=R′	R″						
1	H	H	H	Ts	A	THF/23	12 h	**66a**	91	101
2		H	H		B	DCE/rt	5 h	**66b**	83	102
3	^{n}Bu	H	H	Ts	B	DCE/rt	10 min	**66c**	80	90
4	COOMe	COOMe	COOMe	Bn	C	Toluene/110	1 h	**66d**	40[b]	86
5	COOMe	COOMe	COOMe	Bn	C	Toluene/110	0.5 h	**66d**	53[c]	86
6	H	^{n}Bu	H	Ts	D	H_2O/60		**66e**	76[d]	92
7	H	C_6H_{13}	H	Ts	D	H_2O/60		**66f**	73[d]	92
8	H	Ph	H	Ts	D	H_2O/60		**66g**	68[d]	92
9	H	CH_2OH	H	Ts	D	H_2O/60		**66h**	54[d]	92
10	CH_2OAc	CH_2OAc	H	Ts	D	H_2O/60		**66i**	61[d]	92
11	H	Ph	H	Ts	D	THF/H_2O/rt		**66g**	97	93
12	H	^{n}Bu	H	Ts	D	THF/H_2O/rt		**66e**	92	93
13	H	Cyclohexenyl	H	Ts	D	THF/H_2O/rt		**66j**	90	93
14	H	*p*-MeC_6H_4	H	Ts	D	THF/H_2O/rt		**66k**	95	93
15	Me	Ph	H	Ts	D	THF/H_2O/rt		**66l**	76	93
16	H	Bn	H	Ts	D	THF/H_2O/rt		**66m**	92	93
17	^{n}Bu	Ph	H	Ts	D	THF/H_2O/rt		**66n**	64	93
18	H		H	Ts	D	THF/H_2O/rt		**66o**	94	93

[a] Catalyst: A: Ni(0)(PPh_3)2,B: Cp*RuCl(cod), C: $Pd_2(dba)_3$, D: $[Rh(cod)Cl]_2$.
[b] A solution of a diyne, acetylenic diester, catalyst, and PPh_3 in toluene was stirred at 110 °C over a period of 1 h.
[c] The acetylenic diester was added to a stirred solution of a diyne, catalyst, and PPh_3 in toluene at 110 °C over a period of 1 h.
[d] Reaction was carried out in the presence of KOH (20 mol %).

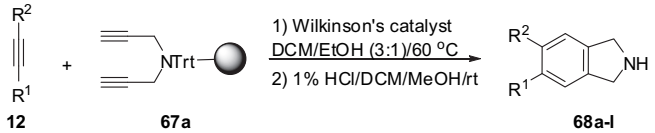
An Ru(II) complex possessing a bulky planar ligand, Cp*Ru(cod)Cl, catalyzed the cycloaddition of 1,6-diyne **65** with a terminal alkyne **12** at or below rt to give **66b** (entry 2) in 83% yield. Satisfactory chemoselectivity can be achieved using 2 equiv of a monoalkyne.[102] This example is interesting as a straightforward strategy to synthesize amino acid–sugar conjugate molecules, which are important structural motifs in glycopeptides. Using the same catalyst, isoindoline **66c** (entry 3) was obtained in 80% yield.[90]

When a dipropargylamine derivative **65** (R=R′=CO_2Me, R″=Bn) underwent cocyclization with **12** (R^1=R^2=CO_2Me) in the presence of 2.5 mol % of $[Pd_2(dba)_3]$, an isoindoline derivative **66d** (entries 4 and 5) was obtained only in 40 or 53% yield, respectively, depending on the addition sequence of the substrates.[86]

Some isoindoline derivatives **66e–o** (entries 6–18) were obtained in 54–97% yield by Rh-catalyzed cocyclization of the appropriate alkynes **12** with the corresponding aminodiynes **65** in H_2O or THF/H_2O.[92,93]

The cyclotrimerization of immobilized dipropargylamine **67** with symmetrical as well as unsymmetrical alkynes **12** (10 equiv) in the presence of 10 mol % Wilkinson's catalyst in 3:1 CH_2Cl_2/ethanol at 60 °C and subsequent cleavage of the products from the resin by treatment with 1% anhydrous hydrochloric acid afforded the isoindolines **68a–l** in 69–95% yield (Scheme 26, Table 17). The compounds were isolated as the HCl salts and the purities were determined to be >90% (^{1}H NMR spectroscopic analysis).[98]

Sato et al. reported the synthesis of isoindolines **70a–c** by a nickel(0)-catalyzed [2+2+2] cocyclization of unsymmetrical diynes **69** and gaseous acetylene in the presence of various chiral



12 **67a** **68a-l**

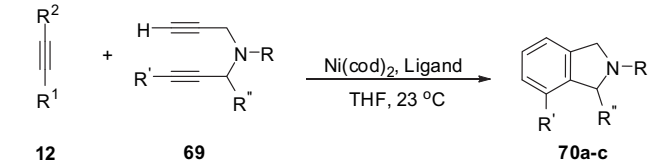
Scheme 26. Synthesis of isoindoles by cocyclization of immobilized dipropargylamine with monoalkynes.

Table 17

Entry	12		Product	Yield[a] (%)
	R^1	R^2		
1	H	H	**68a**	95
2	^{n}Bu	H	**68b**	90
3	Ph	H	**68c**	84
4	CH_2OH	H	**68d**	82
5	CH_2OBn	H	**68e**	93
6	CH_2NH_2	H	**68f**	69
7	$(CH_2)_3CN$	H	**68g**	81
8	$SiMe_3$	H	**68h**	75
9	$(CH_2)_4Cl$	H	**68i**	71
10	COOMe	H	**68j**	79
11	Et	Et	**68k**	70
12	CH_2OMe	CH_2OMe	**681**	87

[a] Isolated yields as HCl salt.

ligands (Scheme 27, Table 18). Although the level of asymmetric induction was modest, the possibility of further improvements is exciting.[101]



12 **69** **70a-c**

R^1 = R^2 = H

Scheme 27. Synthesis of isoindoles by cocyclization of unsymmetrical aminodiynes with acetylene.

Cycloaddition of unsymmetrical diynes **65** with unsymmetrical alkynes **12** mediated by Grubbs' catalyst $[RuCl_2(NCHPh)(PCy_3)_2]$ allows the efficient synthesis of substituted isoindoline

Table 18

Entry	69			Ligand	Product	Yield (%)	ee (%)
	R	R′	R″				
1	Bn	H	H	(*R*)-BINAP	**70a**	22	4
2	Bn	H	H	(−)-DIOP	**70a**	65	1
3	Bn	H	H	(*S*,*S*)-BPPM	**70a**	52	2
4	Bn	H	H	(*S*)-BINAPO	**70a**	34	7
5	Trt	H	H	dppb	**70b**	74	—
6	Trt	H	H	(*S*)-BINAPO	**70b**	66	12
7	Trt	H	H	(*S*,*S*)-BPPM	**70b**	82	45
8	Trt	TMS	TMS	dppb	**70c**	83	—
9	Trt	TMS	TMS	(*R*)-BINAP	**70c**	57	22
10	Trt	TMS	TMS	(*S*)-BINAPO	**70c**	52	18
11	Trt	TMS	TMS	(−)-DIOP	**70c**	87	0
12	Trt	TMS	TMS	(*S*,*S*)-BPPM	**70c**	92	60
13	Trt	TMS	TMS	(*R*,*S*)-BPPFA	**70c**	52	73

regioisomers **71a**–**d** and **72a**–**d** (entries 1, 3, 5, and 7) in 81–92% yield with high regioselectivity of the 4,6-substituted derivatives (Scheme 28, Table 19).[100]

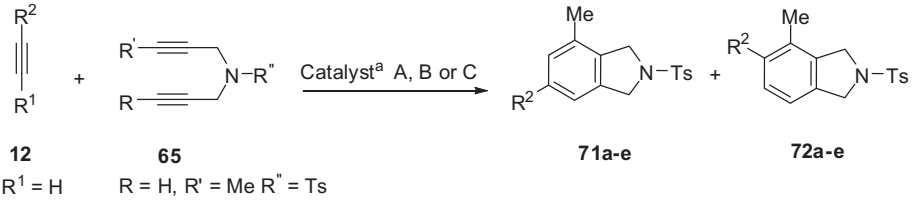
An isoindoline derivative **71e** (entry 9) was obtained in 82% yield and with a high *meta*-selectivity (**71e**/**72e**=93:7) when the alkyne cyclotrimerization was mediated by Cp*Ru(cod)Cl.[76] On the other hand, the alkyne cyclotrimerizations mediated by Wilkinson's catalyst [$RhCl(PPh_3)_3$] allowed the regioselective synthesis of the corresponding 4,5-substituted isomers **72a**–**d** (entries 2, 4, 6, and 8) in 52–90% yield.[100]

Yamamoto et al. studied the regioselective [2+2+2] cyclotrimerization of alkynes by taking advantage of an electronic influence of the internal substituent on the diyne substrate. Thus, ruthenium catalyzed the cycloaddition of 1,6-diynes **73**, having a carbonyl group at the 3 position, with alkynes **12** to give regioisomers **74a**–**e**, in which the substituent R^2 is placed in the *para*-position to the carbonyl group, preferably over the other isomers **75a**–**e** (entries 1–5) in which the substituent R^2 is placed in the *meta*-position to the carbonyl group (Scheme 29, Table 20).[96]

Table 20

Entry	**12**	**73**		**74**/**75**	Yield (%)[a]	Ratio[b] **74**:**75**
	R^2	R	R′	Products		
1	^{n}Bu	H	H	**74a**/**75a**	**74**/**75** (76)	63:37
2	^{t}Bu	H	H	**74b**/**75b**	**74**/**75** (40)	80:20
3	Ph	H	H	**74c**/**75c**	**74**/**75** (93)	80:20
4	CH_2OMe	H	H	**74d**/**75d**	**74**/**75** (90)	64:36
5	CH_2NMe_2	H	H	**74e**/**75e**	**74**/**75** (63)	64:36
6	^{n}Bu	H	Me	**74f**/**75f**	**74**/**75** (81)	100:0
7	^{n}Bu	Me	H	**74g**/**75g**	**74**/**75** (68)	18:82
8	^{n}Bu	Me	Me	**74h**/**75h**	**74**/**75** (93)	83:17

[a] Isolated yield.
[b] Determined by ^{1}H NMR.

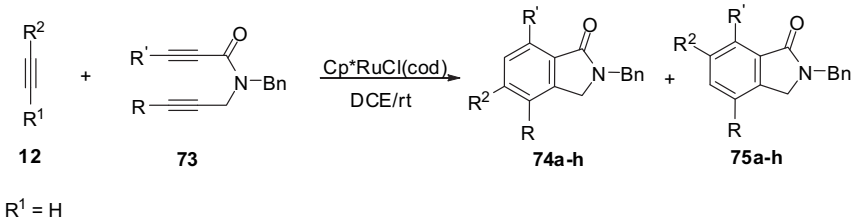


Scheme 28. Synthesis of isoindole regioisomers by cocyclization of unsymmetrical aminodiynes with unsymmetrical monoalkynes.

Table 19

Entry	**12**	Solvent/°C	Catalyst[a]	**71**/**72**	Yield (%)	Ratio[b] **71**:**72**	Ref.
	R^2			Products			
1	Ph	DCM/40	A	**71a**/**72a**	82	5:1	100
2	Ph	Toluene/rt	B	**71a**/**72a**	52	1:8	100
3	Pr	DCM/40	A	**71 b**/**72b**	92	6:1	100
4	Pr	Toluene/rt	B	**71b**/**72b**	61	1:4	100
5	CH_2OH	DCM/40	A	**71c**/**72c**	81	6:1	100
6	CH_2OH	Toluene/rt	B	**71c**/**72c**	90	1:10	100
7	$(CH_2)_2OH$	DCM/40	A	**71d**/**72d**	89	6:1	100
8	$(CH_2)_2OH$	Toluene/rt	B	**71d**/**72d**	79	1:1.5	100
9	^{n}Bu	DCE/rt	C	**71e**/**72e**	82	93:7	90

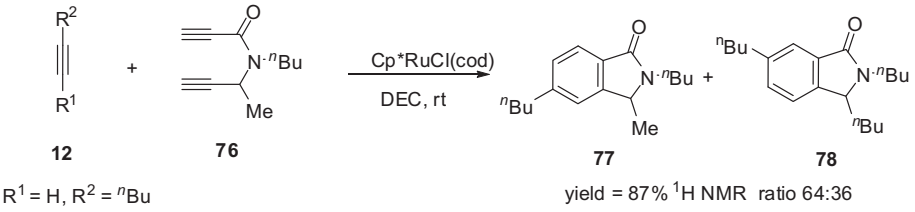
[a] Catalyst: A: $[RuCl_2(N{=}CHPh)(PCy_3)_2]$, B: $RhCl(PPh_3)_3$, C: Cp*RuCl(cod).
[b] Determined by ^{1}H NMR.



Scheme 29. Synthesis of isoindolinone regioisomers by cocyclization of unsymmetrical aminodiynes with unsymmetrical monoalkynes.

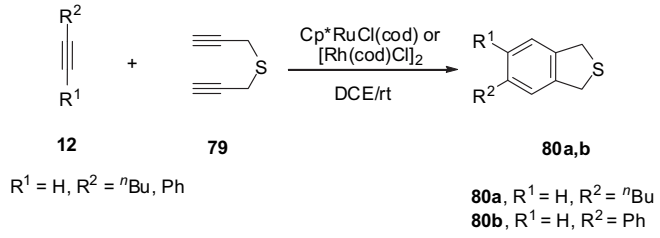
In order to evaluate the cooperative effect of the terminal substituents and the internal carbonyl group, Yamamoto et al. studied also the cycloaddition of alkyne **12** with various amides **73** under the same reaction conditions (Scheme 29, Table 20). Thus amide **73** (R′=Me, R=H) possessing a methyl substituent at the electron-deficient alkyne terminal furnished the expected regioisomer **74f** (entry 6) in 81% yield as the sole product while the regioisomer **75f** was not obtained even in traces. In striking contrast, the reaction of **73** (R=Me, R′=H) having a methyl substituent on the other alkyne moiety required an increased catalyst loading (5 mol %) as well as a longer reaction time for completion of the reaction. In addition, the isoindolinone **75g** was obtained in 56% yield as a major product together with 12% of the isoindolinone **74g** (entry 7). Interestingly, an amide-diyne **73** (R=R′=Me) reacted with **12** (R^2=^{n}Bu) to give rise to a mixture of isoindolinone regioisomers **74h** and **75h** (entry 8) with a ratio of 83:17, respectively.[96]

The steric influence of an internal methyl substituent on the regiochemistry was not observed for the reaction of **12** (R^1=H, R^2=^{n}Bu) with aminodiyne **76** (Scheme 30). Isoindolinones **77**/**78** were obtained with almost the same isomer ratio observed for the corresponding aminodiyne without an internal methyl substituent.[96]



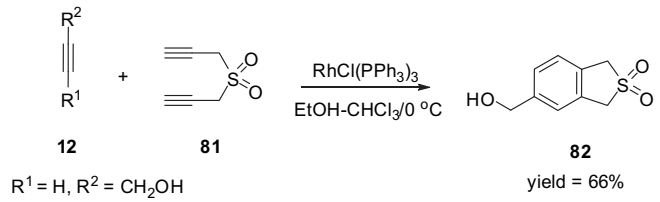
Scheme 30. Synthesis of isoindolinone regioisomers by cocyclization of unsymmetrical aminodiyne with 1-hexyne.

3.1.2.1.4. Dihydrobenzo[c]thiophene. Yamamoto et al. reported that a ruthenium catalyst effectively converts a dipropargyl sulfide **79** into a benzo[*c*]thiophene **80a** in 68% yield upon cocyclization with 1-hexyne (Scheme 31).[20] On the other hand, Wu et al. obtained only 10% of **80b** using $[Rh(cod)Cl]_2$ as a catalyst.[93]



Scheme 31. Synthesis of benzo[*c*]thiophene by cocyclization of dipropargyl sulfide with 1-hexyne.

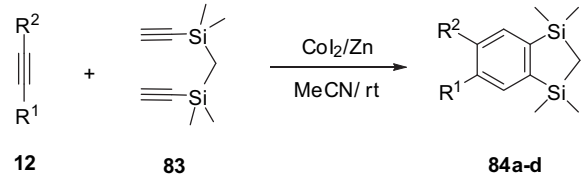
Wilkinson's catalyst has also been reported as an effective catalyst for the rapid intermolecular trimerization of dipropargyl sulfone **81** with propargyl alcohol **12** (R^1=H, R^2=CH_2OH) under mild conditions to give benzo[*c*]thiophene-1,1-dioxide **82** in 66% yield (Scheme 32).[91]



Scheme 32. Synthesis of benzo[*c*]thiophene-1,1-dioxide by cocyclization of dipropargyl sulfone with propargyl alcohol.

3.1.2.2. Benzofused with five-membered heterocyclic ring: two heteroatoms.

3.1.2.2.1. Benzo[b][1,3]disilole. Doszczak and Tacke reported the synthesis of benzo[*b*][1,3]disiloles **84a**–**d** in 50–64% yield by the Co–Zn catalyzed [2+2+2] cycloadditions of unprotected propargyl alcohols **12** to diyne **83** (Scheme 33, Table 21).[104]



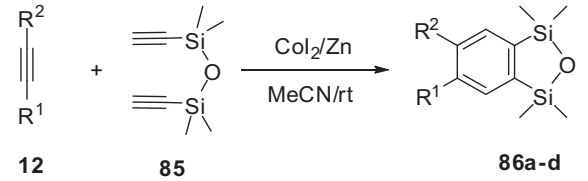
Scheme 33. Synthesis of benzo[*b*][1,3]disiloles by cycloadditions of unprotected propargyl alcohols to diyne.

Table 21

Entry	**12**		Product	Yield (%)
	R^1	R^2		
1	H	CH_2OH	**84a**	65
2	Me	CH_2OH	**84b**	50
3	Et	CH_2OH	**84c**	58
4	H	CH(Me)OH	**84d**	64

3.1.2.3. Benzo fused with five-membered heterocyclic ring: three heteroatoms.

3.1.2.3.1. Benzo[b][1,3]oxadisilole. A catalytic system consisting of commercially available cobalt(II) iodide and zinc powder can efficiently catalyze the [2+2+2] cycloadditions of unprotected propargyl alcohols **12** to diyne **85** to give benzo[*b*][1,3]oxadisiloles **86a**–**d** in 52–64% yield (Scheme 34, Table 22).[104]



Scheme 34. Synthesis of benzo[*b*][1,3]oxadisiloles by cycloadditions of unprotected propargyl alcohols to a diyne.

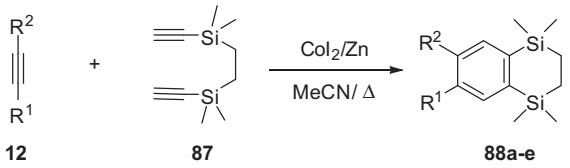
Table 22

Entry	**12**		Product	Yield (%)
	R^1	R^2		
1	H	CH_2OH	**86a**	64
2	Me	CH_2OH	**86b**	52
3	Et	CH_2OH	**86c**	62
4	H	CH(Me)OH	**86d**	59

3.1.2.4. Benzo fused with six-membered heterocyclic ring: two heteroatoms.

3.1.2.4.1. Tetrahydrobenzo[b][1,4]disiline. The [2+2+2] cycloadditions of monoalkynes **12** to a diyne **87** afforded tetrahydrobenzo[*b*][1,4]disilines **88a**–**e** in a very short time and in moderate yields

(Scheme 35, Table 23). The reactions have been performed under mild conditions and relatively low catalyst load [2.5% of CoI_2 and Zn powder].[104,105]



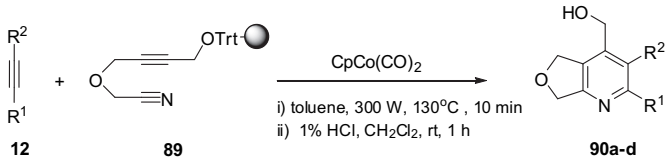
12 87 88a-e

Scheme 35. Synthesis of tetrahydrobenzo[*b*][1,4]disilines by cycloadditions of a diyne to unsymmetrical monoalkynes.

Table 23

Entry	12		Product	Yield (%)	Ref.
	R^1	R^2			
1	H	CH_2OH	**88a**	44	104
2	Me	CH_2OH	**88b**	51	104
3	Et	CH_2OH	**88c**	50	104
4	H	CH(Me)OH	**88d**	47	104
5	Me		**88e**	48	105

3.1.3. Two fused heterocycles. 3.1.3.1. Fused [5–6] systems: two heteroatoms [1:1]. 3.1.3.1.1. Dihydrofuro[3,4-b]pyridine. Fused pyridines **90** were obtained by cyclotrimerization of trityl-protected alkynylnitrile substrate **89** with the appropriate acetylene **12**. The cyclotrimerization was performed in toluene at 130 °C with 10 mol % [$CpCo(CO)_2$] under microwave irradiation (300 W) for 10 min. After removal of the protecting group with TFA, furopyridines **90a–d** were obtained in 78–91% yield (Scheme 36, Table 24).[106]



12 89 90a-d

Scheme 36. Synthesis of furo[3,4-*b*]pyridines by cocyclization of trityl-protected alkynylnitrile to unsymmetrical monoalkynes.

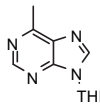
Table 24

Entry	12		Product	Yield %
	R^1	R^2		
1	^{n}Bu	H	**90a**	85
2	Ph	H	**90b**	91
3	^{t}Bu	H	**90c**	87
4	Ph	Ph	**90d**	78

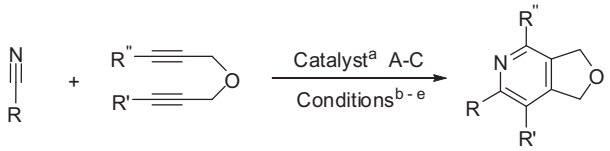
3.1.3.1.2. Dihydrofuro[3,4-c]pyridine. Louie et al. reported the synthesis of dihydrofuro[3,4-*c*]pyridines **92a,b** (entries 1 and 2, Table 25) by cocyclization of diyne **91** ($R'=R''=Me$) with the appropriate nitriles **31** (R=Me, Ph) in the presence of a nickel catalyst under very mild conditions (Scheme 37). The authors used a combination of $Ni(cod)_2$ and an imidazolium salt, from which the active catalyst was generated in situ by adding *n*-butyllithium as a base.[72]

Yamamoto et al. recently showed that Cp*Ru(cod)Cl is able to catalyze the [2+2+2] cycloaddition of 1,6-diyne **91** ($R'=R''=H$) with electron-deficient nitrile **31** ($R=CO_2Et$), which is an inefficient nitrile component under Co catalysis, to afford the desired

Table 25

Catalyst	31	91		Catalyst[a]	Product	Yield	Ref.
	R	R′	R″				
1	Me	Me	Me	A[b]	**92a**	37	72
2	Ph	Me	Me	A[b]	**92b**	93	72
3	CO_2Et	H	H	B[c]	**92c**	72 (49)	68,77
4	$ClCH_2$	H	H	B[c]	**92d**	71	78,83
5	$ClCH_2$	$SiMe_3$	H	B[c]	**92e**	76	78
6	$NCCH_2$	H	H	B[c]	**92f**	86	78,83
7	Me	$SiMe_3$	$SiMe_3$	C[d]	**92g**	—	69
8	Me	$SnMe_3$	$SnMe_3$	C[d]	**92h**	—	69
9	Ph		H	C[e]	**92i**	56	80
10	$ClCH_2$	H	Me	B[c]	**92j**	84	83

[a] Catalysts. A: $Ni(cod)_2$, B: Cp*RuCl(cod), C: $CoCp(CO)_2$.
[b] Reaction was carried out in toluene with 3 mol % cat./6% SIPr/rt.
[c] Reaction was carried out in DCE with 2 mol % cat./rt-60 °C/1.5–15 h.
[d] Reaction was carried out in *m*-xylene, 2 mol % cat./hν (250 W) 18–48 h.
[e] Reaction was carried out in PhCN with 100 mol % cat./MW/200 °C/10 min.



31 91 92a-g

Scheme 37. Synthesis of furo[3,4-*c*]pyridines by cocyclization of dipropargyl ether derivatives with nitriles.

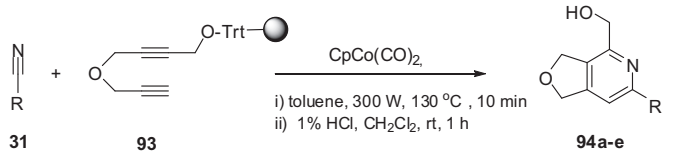
dihydrofuro[3,4-*c*]pyridine **92c** (entry 3, Table 25) in moderate-to-good yield (Scheme 37).[68,77]

Cocyclization of the appropriate dipropargyl ether **91** with chloroacetonitrile as well as malononitrile in the presence of Cp*Ru(cod)Cl afforded the corresponding furo[3,4-*c*]pyridines **92d–f** and **92j** (entries 4–6 and 10 Table 25) in 71–86% yield.[78,83]

Under similar conditions, the bis(trimethylsilyl)di(2-propynyl) ether **91** ($R'=R''=SiMe_3$) underwent cocyclization with acetonitrile in the presence of $CpCo(CO)_2$ to afford the bis-silylfuro[3,4-*c*]pyridine **92g** ($R'=R''=SiMe_3$) (entry 7, Table 25). The latter selectively protodesilylated at the 2-position to give a 68% yield of **92** ($R'=SiMe_3$, $R''=H$). Similarly, $CpCo(CO)_2$ catalyzed the cyclization of **91** ($R'=R''=SnMe_3$) with acetonitrile in *m*-xylene to give the corresponding bis(trimethylstannyl)furo[3,4-*c*]pyridine **92h** (entry 8, Table 25), which was rapidly monodestannylated upon chromatographic purification to afford **92** ($R'=SnMe_3$, $R''=H$) in 44% yield (Scheme 37).[69] The regioselective electrophilic substitution of the silyl or stannyl groups allows for a regiocontrolled construction of tetrasubstituted pyridines.

On the other hand, the cyclotrimerization of the unsymmetrical diyne **91** ($R'=$purinyl, $R''=H$) with benzonitrile **31** (R=Ph) was performed in the presence of $CpCo(CO)_2$ under microwave irradiation and led to the regioselective synthesis of the furopyridinyl-substituted purine **92i** (entry 9, Table 25) in 56% yield (Scheme 37).[80]

Employing microwave irradiation together with a solid support in the Co-catalyzed cyclotrimerization of protected dialkyne **93** with five different nitriles **31** afforded fused pyridines **94a–e** in excellent yield (87–94%) and high purities (>90%) after cleavage from the resin (Scheme 38, Table 26). Most importantly, complete regioselectivity was obtained under microwave irradiation conditions and the obtained furopyridine regioisomers are in agreement with the generally accepted cyclotrimerization mechanism for the [$CpCo(CO)_2$] catalyst.[106]



Scheme 38. Synthesis of furo[3,4-*c*]pyridines by cocyclization of protected diyne with nitriles.

Table 26

Entry	**31** R	Product	Yield %
1	Me	**94a**	87
2	Ph	**94b**	84
3	H_2C=CH–	**94c**	92
4	Et	**94d**	94
5	Anthracenyl	**94e**	91

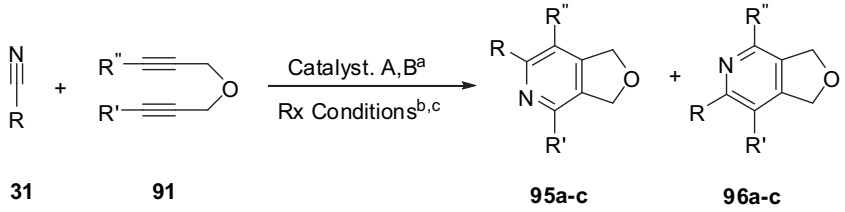
Cp*Ru(cod)Cl was able to catalyze the cycloaddition of unsymmetrical 1,6-diyne **91** (R′=H, R″=Me) to malononitrile **31** (R=CH_2CN) and ethyl cyanoformate **31** (R=CO_2Et) under mild conditions (Scheme 39, Table 27). It is noteworthy that; unlike Co(I) catalysts, which cocyclize dicyanides with alkynes to give dipyridines,[107] Ru(II) promotes the reaction of only one of the two cyano groups in malononitrile, the other remaining intact after the complete conversion of the diyne. The reaction was carried out under mild conditions (60 °C) to furnish fused pyridine regioisomers **95a**/**96a** in good yield (97%) with excellent regioselectivity, with preference for the 4,6-substituted isomers over the 4,5-substituted isomers (95:5) (Scheme 39, Table 27).[79]

Similarly, furopyridine regioisomers **95b**/**96b** were obtained in 87% combined yield in a ratio of 88:12, by cocyclization of **91** (R′=H, R″=Me) with ethyl cyanoformate.[68]

Moreover, a synthesis of 1,3-dihydrofuro[3,4-*c*]pyridines **95c**/**96c** in 84% combined yield in a ratio of 16:1 was performed by Co-catalyzed cycloaddition of MeCN with substituted di(2-propynyl) ether **91** (R′=CO_2Et, R″=$SiMe_3$) (Scheme 39, Table 27).[108]

Yamamoto et al. reported on the cycloadditions of diynes **58**, possessing an internal carbonyl group conjugated with one of the two alkyne moieties, to ethyl cyanoformate **31** (R=CO_2Et), catalyzed by Ru catalyst under mild conditions (Scheme 40, Table 28). Thus, the ester-diyne **58** (R′=H, R″=Me) gave rise to the furo[3,4-*c*]pyridinones **97a**/**98a** in 83% combined yield in a ratio of 82:18. Analogously, the ester-diyne **58** (R′=R″=H) gave rise to furo[3,4-*c*]pyridinones **97b**/**98b** in 84% combined yield in a ratio of 98:2.[68] In both reactions, the regioisomers in which the CO_2Et group is *para* to the carbonyl moiety are preferable over the corresponding *meta* isomers.

3.1.3.1.3. Dihydro-1H-pyrrolo[3,4-c]pyridine. Pyrrolo[3,4-*c*]pyridines **99a**–**d** were constructed using trityl-protected dipropargylamine **67** and the appropriate nitrile **31** as starting materials. The cyclotrimerization was performed in toluene at 110 °C with 10 mol % [$CpCo(CO)_2$] under microwave irradiation (300 W) (Scheme 41, Table 29). After removal of the protecting group with TFA, pyrrolopyridines **99a**–**d** (entries 3–6) were obtained in 87–95% yield.[106] When the same cyclotrimerization was conducted without microwave irradiation, only less than 5% of **99a** (entry 2) was observed, even after a prolonged reaction time. On the other hand, when the cyclotrimerization was conducted under microwave irradiation without a solid support, only 46% yield of the cyclized product **99a** (entry 1) was obtained.[89]



Scheme 39. Synthesis of furo[3,4-*c*]pyridine regioisomers by cocyclization of unsymmetrical diynes with nitriles.

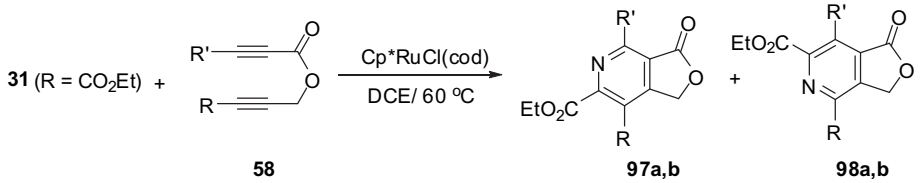
Table 27

Entry	**31** R	**91** R′	R″	Product	Catalyst[a]	Yield %	Ratio **95**:**96**	Ref.
1	CH_2CN	Me	H	**95a/96a**	A[b]	97	95:5	79,83
2	CO_2Et	Me	H	**95b/96b**	A[b]	83	88:12	68
3	Me	$SiMe_3$	CO_2Et	**95c/96c**	B[c]	84	16:1	108

[a] Catalyst, A: Cp*RuCl(cod), B: $CpCo(CO)_2$.
[b] Reaction was carried out in DCE/60 °C/2–16 h.
[c] Reaction was carried out in MeCN/140 °C.

Yamamoto's group investigated the [2+2+2] cycloaddition reaction of 1,6-diyne **65** (R=R′=H) with nitriles **31** (R=CO_2Et, $ClCH_2$, CH_2CN) in the presence of Cp*Ru(cod)Cl. The reactions were performed in 1,2-dichloroethane at 60–90 °C, to give pyrrolopyridines **99e**, **99f**, and **99h** (entries 7, 8, and 10) in 75, 80, and 85% yield, respectively.[68,77,78,83]

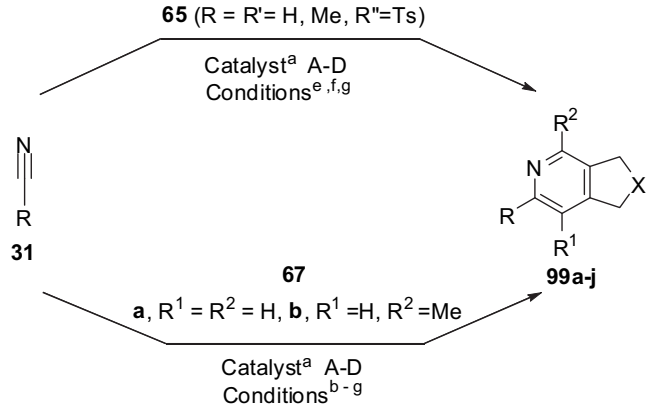
Louie et al. reported the synthesis of furo[*c*]pyridine **99g** (entry 9) in 78% yield by cocyclization of diyne **65** (R=R′=Me) with benzonitrile **31** (R=Ph) in the presence of a nickel catalyst under very mild conditions (Scheme 41, Table 29). The authors used a combination of a Ni(0) precursor and an imidazolylidene ligand, from which the active catalyst was generated.[72]



Scheme 40. Synthesis of furo[3,4-*c*]pyridinone regioisomers by cocyclization of unsymmetrical diynes with nitriles.

Table 28

Entry	**58**		Product	Yield (%)	Ratio **97**:**98**
	R	R′			
1	H	Me	**97a/98a**	83	82:18
2	H	H	**97b/98b**	84	98:2



Scheme 41. Synthesis of pyrrolo[3,4-*c*]pyridines by cocyclization of unsymmetrical diynes with nitriles.

Using similar precursors **65** and **31**, but in the presence of a [CpCo(CO)(fumarate)] complex, Aubert et al. reported the synthesis of pyrrolopyridines **99i** and **99j** (entries 11 and 12), in 63 and 66% yield, respectively.[81]

On the other hand, the cycloaddition reaction of the unsymmetrical 1,6-diyne **65** (R=H, R′=Me) with malononitrile as well as chloroacetonitrile **31** (R=CH_2CN, CH_2Cl) in the presence of Cp*Ru(cod)Cl as a catalyst furnished fused pyridines **100a** and **100c** in 95 and 86% yield, respectively, as the sole products.[79,83]

In both cases, the regioisomers **101a** and **101c** were not obtained even in traces.

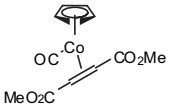
In the case of using ethyl cyanoformate, fused pyridines **100b** and **101b** were obtained in 86% combined yield with excellent regioselectivity with preference for the 4,6-substituted isomer over the 4,5-substituted isomer (Scheme 42, Table 30).[68]

The reaction of amide-diynes **101** with nitriles **31** (R=CO_2Et, $CHCl_2$) was carried out in the presence of Cp*Ru(cod)Cl at 60 °C to afford a mixture of eight substituted pyridine regioisomers **102a**/**103a**, **102b**/**103b**, **102c**/**103c**, and **102f**/**103f** (entries 1–3 and 6) in 77–89% combined yields and with 71:29, 96:17, 80:20, and 80:20 isomer ratios, respectively (Scheme 43, Table 31).[68,83] In these reactions, the regioisomers in which the CO_2Et and $CHCl_2$ moieties are *para* to the carbonyl are preferred over the corresponding *meta* isomers. On the other hand, cycloaddition of **101** with malononitrile as well as with chloroacetonitrile proceeded to give substituted pyridines **102d**/**103d** and **102e**/**103e** (entries 4 and 5) with no regioselectivity.[83]

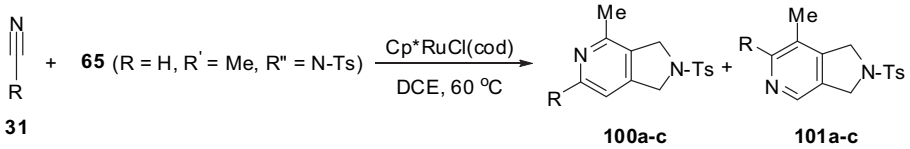
Table 29

Entry	**31**	**65**, **67**	Catalyst[a]	**99**		Yield (%)	Ref.
	R	R^1=R^2			X		
1	Ph	H	A[b]	**99a**	NH	46	106
2	Ph	H	A[c]	**99a**	NH	<5	106
3	Ph	H	A[d]	**99a**	NH	92	106
4	Me	H	A[d]	**99b**	NH	95	106
5	CH=CH_2	H	A[d]	**99c**	NH	95	106
6	CH_2Pip	H	A[d]	**99d**	NH	87	106
7	CO_2Et	H	B[e]	**99e**	NTs	75	68,77
8	$ClCH_2$	H	B[e]	**99f**	NTs	80	78,83
9	Ph	Me	C[f]	**99g**	NTs	78	72
10	CH_2CN	H	B[e]	**99h**	NTs	85	83
11	Et	H	D[g]	**99i**	NTs	63	81
12	Ph	H	D[g]	**99j**	NTs	66	81

[a] Catalyst, A: $CoCp(CO)_2$, B: Cp*RuCl(cod), C: $Ni(acac)_2$, D:



[b] Reaction was carried out in toluene using 10 mol % cat./MW (300 W)/no solid support/110 °C/24 h.
[c] Reaction was carried out in toluene using 10 mol % cat., no MW/115 °C/24 h.
[d] Reaction was carried out in toluene using 10 mol % cat./MW (300 W)/with solid support/110 °C/24 min.
[e] Reaction was carried out in DCE using 2 mol % cat./rt to 60 °C/0.5–4 h.
[f] Reaction was carried out in toluene, using 5 mol % cat./10 mol% NHC (*N*-heterocyclic carbene).
[g] Reaction was carried out in toluene/*hv*.

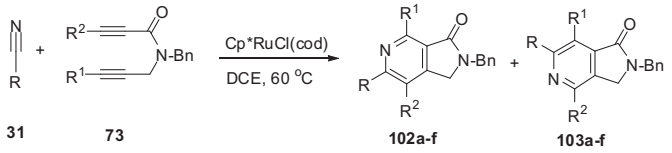


Scheme 42. Synthesis of pyrrolo[3,4-*c*]pyridines by cocyclization of unsymmetrical diynes with electron-deficient nitriles.

Table 30

Entry	31	Products	Yield (%)	Ratio 100/101	Ref.
	R				
1	$NCCH_2$	**100a/101a**	95	100:0	79,83
2	CO_2Et	**100b/101b**	86	89:11	68
3	$ClCH_2$	**100c/101c**	86[a]	100:0	83

[a] Reaction was carried out at rt.

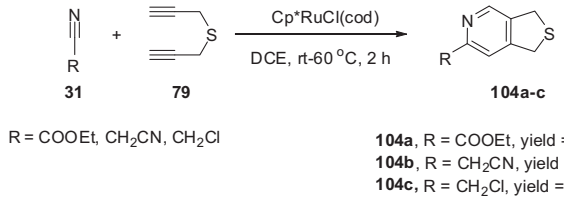


Scheme 43. Synthesis of pyrrolo[3,4-*c*]pyridinone regioisomers by cocyclization of unsymmetrical diynes with nitriles.

Table 31

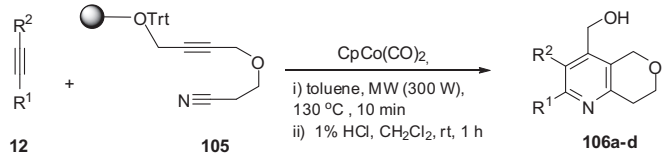
Entry	31	101		Rx. Time (h)	102/103	Yield (%)	Ratio 102/103	Ref.
	R	R^1	R^2		Products			
1	COOEt	H	H	18	**102a/103a**	77	71:29	68
2	COOEt	Me	H	0.5	**102b/103b**	89	96:4	68
3	COOEt	Me	Me	6	**102c/103c**	82	80:20	68
4	CH_2CN	H	H	1	**102d/103d**	90	50:50	83
5	CH_2Cl	H	H	3	**102e/103e**	84	50:50	83
6	$CHCl_2$	H	H	3	**102f/103f**	84	80:20	83

3.1.3.1.4. Dihydrothieno[3,4-c]pyridine. Yamamoto et al. reported that the cycloaddition of 1,6-diyne **79** to nitriles **31** catalyzed by Cp*RuCl(cod), afforded 61–64% yield of thieno[3,4-*c*]pyridines **104a–c** (Scheme 44).[68,83]



Scheme 44. Synthesis of thieno[3,4-*c*]pyridines by cocyclization of dipropargyl sulfide with nitriles.

3.1.3.2. Fused [6–6] systems: two heteroatoms [1:1]. 3.1.3.2.1. Dihydro-5H-pyrano[4,3-b]pyridine. Cyclotrimerization of the trityl-protected alkynylnitrile **105** with acetylene derivatives **12** using [$CpCo(CO)_2$] as a catalyst under microwave irradiation (300 W), followed by removal of the protecting group with TFA, afforded pyrano[4,3-*b*]pyridines **106a–d** in good yield (71–88%) (Scheme 45, Table 32).[106]

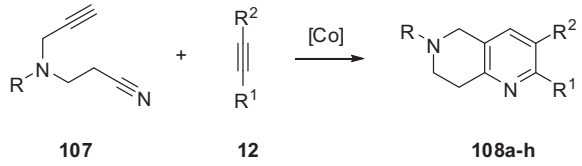


Scheme 45. Synthesis of pyrano[4,3-*b*]pyridines by cocyclization of protected alkynenitrile with monoalkynes.

3.1.3.2.2. Tetrahydro-1,6-naphthyridine. Snyder et al.[109] demonstrated a simple route to 5,6,7,8-tetrahydro-1,6-naphthyridines **108a–h** using Co-catalyzed [2+2+2] cyclizations of alkynitriles **107** with the appropriate alkynes **12** (Scheme 46, Table 33).[109] The reaction was probed with numerous catalysts under a variety of conditions and the best results were obtained with 20 mol % $CpCo(CO)_2$, CpCo(COD), or InCo(COD) under microwave promotion. The use of $CpCo(CO)_2$ was preferred, being more user friendly and stable to benchtop reaction conditions and storage, while CpCo(COD) and InCo(COD) required a drybox environment. Intermolecular cyclizations proceeded in moderate yields, notably those with a phenyl ring attached to the alkynes. Secondary and tertiary amines were tolerated (R^1=H, Me), although alkynes with carbonyl substituents and terminal alkynes did not react.

Table 32

Entry	12		Product	Yield (%)
	R^1	R^2		
1	^{n}Bu	H	**106a**	88
2	Ph	H	**106b**	79
3	^{t}Bu	H	**106c**	85
4	Ph	Ph	**106d**	71



Scheme 46. Synthesis of tetrahydro-1,6-naphthyridine by Co-catalyzed cyclizations of alkynitriles with alkynes.

Table 33

Entry	107	12		Catalyst[a]	108	Yield[b,c] (%)
	R	R^1	R^2		Products	
1	H	Ph	Ph	$CpCo(CO)_2$	**108a**	69
2	H	Ph	Ph	CpCo(COD)	**108a**	67
3	H	Ph	Ph	InCo(COD)	**108a**	67
4	H	Ph	Ph	$CpCo(CO)_2$[d]	**108a**[d]	60
5	H	Ph	Ph	$CpCo(CO)_2$[e]	**108a**[e]	33
6	Me	Ph	Ph	$CpCo(CO)_2$[e]	**108b**[e]	36
7	Me	Ph	Ph	$CpCo(CO)_2$[f]	**108b**[f]	22
8	Me	Ph	Ph	$CpCo(CO)_2$	**108b**	68
9	H	Et	Et	CpCo(COD)	**108c**	43
10	H	CH_2OH	CH_2OH	$CpCo(CO)_2$	**108d**	36
11	H	CO_2Me	CO_2Me	$CpCo(CO)_2$	No reaction	—
12	H	CO_2Me	CO_2Me	CpCo(COD)	No reaction	—
13	H	COMe	Ph	$CpCo(CO)_2$	No reaction	—
14	Me	TMS	H	$CpCo(CO)_2$	No reaction	—
15	H	TMS	H	$CpCo(CO)_2$	No reaction	—
16	H	Ph	H	$CpCo(CO)_2$	No reaction	—
17	H	TMS	Ph	$CpCo(CO)_2$	**108e**, **108f**[g]	32
18	H	TMS	Me	$CpCo(CO)_2$	**108g**[g]	21
19	H	Ph	Me	$CpCo(CO)_2$	**108h**	44

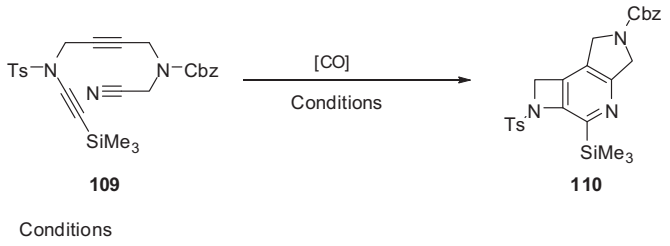
[a] Catalyst load 20 mol % unless otherwise noted.
[b] Isolated yields.
[c] All the reactions were run under microwave irradiation, 300 W, 15 min, 150 °C internal temperature, chlorobenzene as solvent unless otherwise noted.
[d] Catalyst load 10 mol %.
[e] Reaction was carried out in refluxing toluene, 12 h.
[f] Reaction was carried out in toluene with *hν* activation, 6 h.
[g] Minor regioisomers could be detected in trace amounts, and isolated only for **108f**.

3.2. Fused tricyclic systems

3.2.1. Fused [4–5–6] system: three heteroatom.

3.2.1.1. Tetrahydro-1H-azeto[3,2-d]pyrrolo[3,4-b]pyridine. Intramolecular [2+2+2] cycloaddition of diyne nitrile **109**

using 20 mol % of $CpCo(CO)_2$ in xylene under refluxing conditions and visible light irradiation or 10 mol % of $CpCo(C_2H_4)_2$ in THF at rt, respectively, afforded azeto[3,2-*d*]pyrrolo[3,4-*b*]pyridine **110** in 55 and 50% yield, respectively, as outlined in Scheme 47.[110,111]



109 **110**

Conditions

[a] $[CpCo(C_2H_4)_2]$/ THF, rt,1 h, 10 mol% catalyst, Yield 50%
[b] $[CpCo(CO)_2]$/ xylene, hv, 1 h, 20 mol% catalyst, Yield 55%

Scheme 47. Synthesis of azeto[3,2-*d*]pyrrolo[3,4-*b*]pyridine by Co-catalyzed intramolecular cyclotrimerization of cyanodiyne.

3.2.2. Fused [4–6–5] system: one bridgehead heteroatom. 3.2.2.1. Dihydroazeto[2,1-a]isoindole. Using phenylacetylene as a substrate, the feasibility of cyclotrimerization of the diynes **111a–c** has been examined by screening available Rh- and Ru-based catalysts. With the simple diyne **111a**, the reaction was facile with Wilkinson's catalyst (A). The two regioisomeric trinems **112a**/**112b** were formed in equal proportion. A marginal improvement in the product yields could be seen when the catalysts Cp*RuCl(cod) (B) and $[Rh(cod)_2]BF_4$/(*R*)-BINAP (C) were employed, albeit without any substantial improvement in the regioselectivity. The cyclotrimerization of the mono-substituted diynes **111b** and **111c** with phenylacetylene were not facile with Wilkinson catalyst. When the catalysts B and C were employed, the reactions proceeded smoothly at rt and gave the corresponding trinems **113** and **114**, respectively (Scheme 48, Table 34) in good yields.[112]

111a-c

112a, R = R' = H, R" = Ph
112b, R = R" = H, R' = Ph
113, R = *n*-C_6H_{13}, R' = H, R" = Ph
114, R = R" = Ph, R' = H

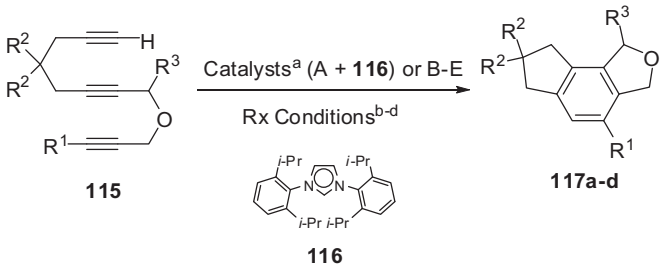
Scheme 48. Synthesis of azeto[2,1-*a*]isoindoles by cyclotrimerization of diynes with phenylacetylene using Rh or Ru catalyst.

Table 34

Entry	Temp/Time	Products	Ratio **a**/**b**	Yield (%)
1	80 °C/12 h	**112a**/**112b**	1:1	64[a]
2	rt/7 h	**112a**/**112b**	1:1	68[b]
3	rt/4 h	**112a**/**112b**	1:1	80[c]
4	80 °C/12 h	**113**	—	No reaction[a]
5	rt/7 h	**113**	—	78[b]
6	rt/4 h	**113**	—	—[c]
7	80 °C/12 h	**114**	—	No reaction[a]
8	rt/7 h	**114**	—	80[b]
9	rt/4 h	**114**	—	81[c]

[a] $RhCl(PPh_3)_3$ (5 mol %)/toluene-EtOH.
[b] $Rh(cod)_2BF_4$-(*R*)-BINAP, (5 mol %)/CH_2Cl_2.
[c] CpRuCl(cod), (5 mol %)/CH_2Cl_2.

3.2.3. Fused [5–6–5] system: one heteroatom. 3.2.3.1. Indeno[4,5-c]furan. An iron species derived from $FeCl_3$ by *in situ* reduction with zinc powder in the presence of imidazolium carbene **116** could effectively catalyze the intramolecular cyclotrimerization of triynes **115** to indeno[4,5-*c*]furans **117a–d**.[113,114] It has been reported that palladium[115] and ruthenium[20,116] catalysts were also very effective for performing this reaction (Scheme 49, Table 35).[81]



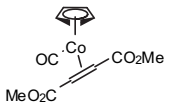
115 **116** **117a-d**

Scheme 49. Synthesis of indenofurans by intramolecular cyclotrimerization of triynes.

Table 35

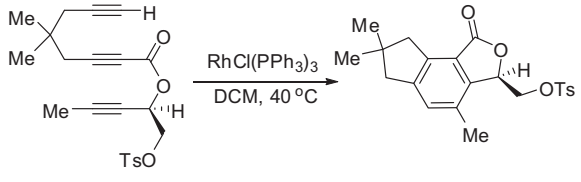
Entry	**115**			Product	Yield (%)	Catalyst[a]	Ref.
	R^1	R^2	R^3				
1	H	COOEt	Me	**117a**	98	A[b]	113,114
2	H	COOMe	H	**117b**	82, 48[d]	B,[b] E	20,81
3	Me	COOEt	H	**117c**	67	C[b]	115
4	H	H	H	**117d**	72	D[c]	116

[a] Catalysts: A: **116**+$FeCl_3$/Zn powder, B: Cp*RuCl(cod), C: $Pd(PPh_3)_4$, D: $Cl_2(PCy_3)_2Ru$=CH–Ph, E:



[b] Reaction was carried out in THF with catalysts A, B and in MeCN/AcOH with Catalyst C.
[c] Reaction was carried out in DCM/5 mol % of catalyst D.
[d] Reaction was carried out with cat. E 5 mol %/ DMF/MW/200 °C.

Recently, Witulski et al. reported that intramolecular cyclization of an enantiomerically pure trialkyne ester **118** catalyzed by Wilkinson's catalyst in CH_2Cl_2 at 40 °C afforded the enantiomerically pure indeno[4,5-*c*]furan **119** in 72% yield. The latter is a key step for the total synthesis of the sesquiterpenoid, alcyopterosin E (Scheme 50).[117]

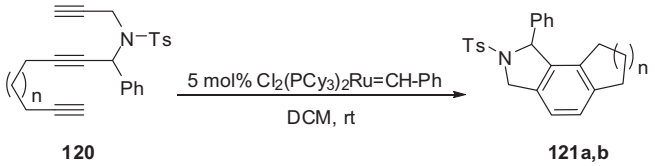


118 **119**

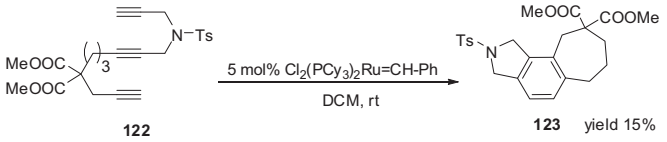
Scheme 50. Synthesis of chiral indenofuranone by intramolecular cyclotrimerization of chiral trialkyne ester.

3.2.3.2. Cyclopenta[e]isoindole and larger-membered ring analogues [5–6–6/7]. Indane derivative **121a** (*n*=1) was obtained in 74% yield by cyclotrimerization of the acyclic triyne **120** (*n*=1) with 5 mol % of a ruthenium catalyst [PhCH=$Ru(PCy_3)_2Cl_2$]. The reaction was complete after 12 h in CH_2Cl_2 at ambient temperature. The triynes **120** (*n*=2) and **122** cyclotrimerize under similar conditions to give a 35% yield of the hexahydrobenzo[*e*]isoindole **121b** (*n*=2) as well as the octahydrocyclohepta[*e*]isoindole **123** in 35 and 15% yield, respectively (Schemes 51 and 52). In the latter cases, the desired conversions proceeded slowly (2 days) and the competing

formation of obviously polymeric byproducts explains the diminished yields.[116]

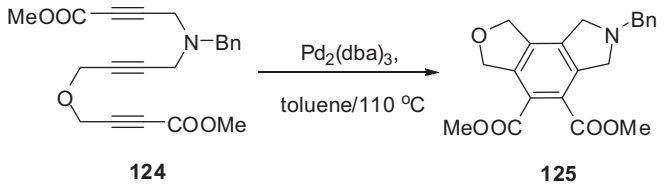


Scheme 51. Synthesis of cyclopenta[*e*]isoindole and hexahydrobenzo[*e*]isoindole by intramolecular cyclotrimerization of triynes.



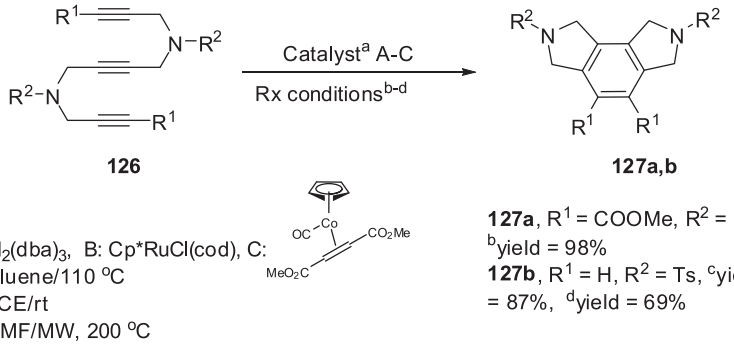
Scheme 52. Synthesis of octahydrocyclohepta[*e*]isoindole by intramolecular cyclotrimerization of triyne.

3.2.4. Fused [5–6–5] system: two heteroatoms [1:1]. 3.2.4.1. Tetrahydrofuro[3,4-e]isoindole. Intramolecular cyclotrimerization of triyne **124** in the presence of $Pd_2(dba)_3$ afforded furo[3,4-*e*]isoindole **125** in 91% yield (Scheme 53).[86]



Scheme 53. Synthesis of furo[3,4-*e*]isoindole by intramolecular cyclotrimerization of triyne.

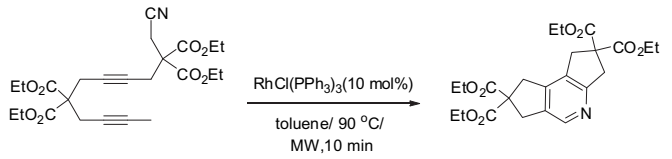
3.2.4.2. Pyrrolo[3,4-e]isoindole. Triyne derivatives **126** underwent cyclotrimerization in the presence of $Pd_2(dba)_3$[72] or Cp*Ru(cod)[20] to give pyrrolo[3,4-*e*]isoindoles **127a**,**b** in 98 and 87% yield, respectively (Scheme 54).[20,81]



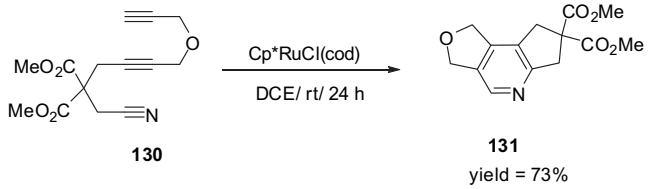
Scheme 54. Synthesis of pyrrolo[3,4-*e*]isoindole by intramolecular cyclotrimerization of triynes.

3.2.5. Fused [5–5–6] system: one heteroatom. 3.2.5.1. Hexahydrodicyclopenta[b,d]pyridine. The cycloaddition of dialkynenitrile **128** furnished an 89% yield of hexahydrodicyclopenta[*b*,*d*]pyridine **129** when treated with Wilkinson's catalyst (10 mol %) in toluene at 90 °C under microwave irradiation (Scheme 55).[103]

3.2.6. Fused [5–5–6] system: two heteroatoms [1:1]. 3.2.6.1. Tetrahydro-1H-cyclopenta[b]furo[3,4-d]pyridine. The cyanodiyne **130** bearing both a 1,6-diyne moiety and a pendent nitrile was converted successfully into tetrahydro-1*H*-cyclopenta[*b*]furo[3,4-*d*]pyridine **131** in 73% yield upon treatment with 5 mol % of Cp*RuCl(cod) in DCE at rt. The reaction proceeded by means of a slow-addition technique (syringe-pump addition of **130** over 3 h, then stirring for 24 h), as well as a high-dilution condition (0.01 M solution), to avoid bimolecular side reactions (Scheme 56).[83]

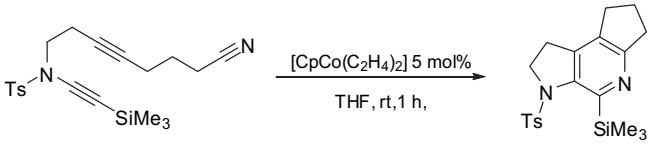


Scheme 55. Synthesis of dicyclopenta[*b*,*d*]pyridine by intramolecular cyclotrimerization of dialkynenitrile using Wilkinson's catalyst.



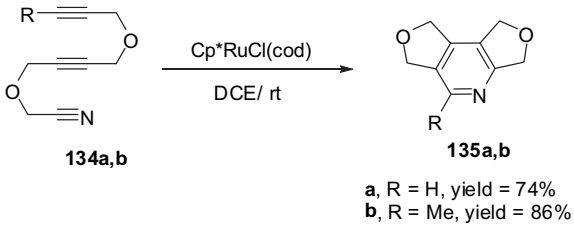
Scheme 56. Ruthenium-catalyzed cyclotrimerization of cyanodiyne to tetrahydro-1*H*-cyclopenta[*b*]furo[3,4-*d*]pyridine.

3.2.6.2. Hexahydrocyclopenta[b]pyrrolo[3,2-d]pyridine. The [2+2+2] cocyclization of the dialkynenitrile **132** using $[CpCo(C_2H_4)_2]$ as a catalyst afforded the hexahydrocyclopenta[*b*]pyrrolo[3,2-*d*]pyridine **133** in 90% yield (Scheme 57).[110]



Scheme 57. Synthesis of cyclopenta[*b*]pyrrolo[3,2-*d*]pyridine by [2+2+2] cocyclization of a dialkynenitrile using $[CpCo(C_2H_4)_2]$.

3.2.7. Fused [5–5–6] system: three heteroatoms [1:1:1]. 3.2.7.1. Tetrahydrodifuro[3,4-b:3′,4′-d]pyridines. Yamamoto et al. reported the synthesis of tetrahydrodifuro[3,4-*b*:3′,4′-*d*]pyridine **135a** in 74% yield by intramolecular cyclotrimerization of the cyanodiyne **134a** upon treatment with 5 mol % of [Cp*RuCl(cod)] in DCE at rt. The reaction proceeded by means of a slow-addition technique, as well as a high-dilution condition, to avoid bimolecular side reactions (Scheme 58).[83]

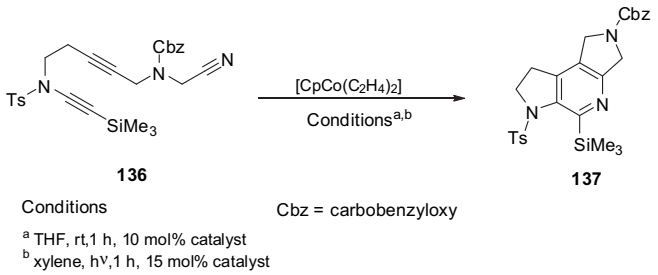


Scheme 58. Ruthenium-catalyzed cyclotrimerization of cyanodiynes to tetrahydrodifuro[3,4-*b*:3′,4′-*d*]pyridine.

On the other hand, with a catalyst loading of 5 mol % of [Cp*RuCl(cod)], **134b** was selectively converted into **135b** in 86% yield within 1 h at ambient temperature without the need for the slow-addition technique or the high-dilution condition.[83]

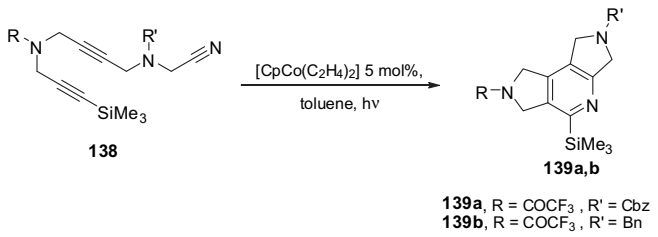
Roglans et al.[103] reported the synthesis of **135b** in 69% yield by intramolecular cyclotrimerization of **132b** with Wilkinson's catalyst (10 mol %) in toluene at 90 °C under microwave irradiation.

3.2.7.2. Hexahydrodipyrrolo[3,4-b:3′,2′-d]pyridine. Aubert et al. developed an expedient method for the synthesis of nitrogen polyheterocycles in which two nitrogen-containing rings are fused in an angular fashion to one pyridine unit.[110,111] These systems have been prepared by means of an intramolecular Co-catalyzed [2+2+2] cycloaddition of two alkynes to one nitrile. Under these conditions, dipyrrolo[3,4-*b*:3′,2′-*d*]pyridine **137** was obtained from dialkynenitrile **136** in 76% yield (Scheme 59).[110]



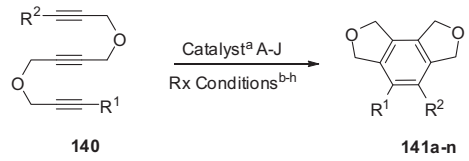
Scheme 59. Synthesis of dipyrrolo[3,4-*b*:3′,2′-*d*]pyridine via Co-catalyzed intramolecular [2+2+2] cycloaddition of two alkynes to one nitrile.

3.2.7.3. Hexahydrodipyrrolo[3,4-b:3′,4′-d]pyridine. Using 5 mol % of [CpCo(C_2H_4)$_2$] as a catalyst, the same group reported the synthesis of dipyrrolo[3,4-*b*:3′,4′-*d*]pyridines **139a**,**b** from dialkynenitriles **138a**,**b** in 85% yield (Schemes 60).[111]



Scheme 60. Synthesis of dipyrrolo[3,4-*b*:3′,4′-*d*]pyridine via Co-catalyzed intramolecular [2+2+2] cycloaddition of two alkynes to one nitrile.

3.2.8. Fused [6–5–5] system: two heteroatoms [1:1]. 3.2.8.1. Benzo[1,2-c:3,4-c]difuran. It was reported that transition-metal salts of Co, Pd, Rh, Ru, and Ni were used to catalyze the intramolecular cyclotrimerization of triynes **140** to isobenzofuro[5,4-*c*]furans **141a**–**p** (Scheme 61, Table 36). An iron species derived from $FeCl_3$ by *in situ* reduction with zinc powder in the presence of imidazolium carbene **116** or bidentate nitrogen ligand **142** could also effectively catalyze this reaction. The reaction of some disubstituted

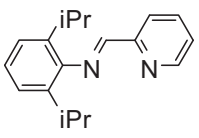


Scheme 61. Synthesis of benzodifurans by intramolecular cyclotrimerization of triynes.

Table 36

Entry	**140**		Products	Yield (%)	Catalyst[a]	Ref.
	R^1	R^2				
1	H	H	**141a**	82	C[b]	20
2	H	H	**141a**	79	J[d]	118
3	H	H	**141a**	91	F[e]	113,114
4	H	H	**141a**	98	G[e]	113,114
5	H	H	**141a**	95	H[e]	114
6	H	H	**141a**	75	D[h]	91
7	H	H	**141a**	80	I[b]	116
8	H	H	**141a**	80	E[c]	30
9	Me	Me	**141b**	60	C[b]	20
10	Me	Me	**141b**	35	A[c]	86
11	COOMe	COOMe	**141c**	95	A[c]	86,119
12	COOMe	COOMe	**141c**	85	A[c]	120
13	Ph	Ph	**141d**	90	F[e]	113,114
14	Ph	Ph	**141d**	5	G[e]	113,114
15	Ph	Ph	**141d**	82	H[e]	114
16	Ph	Ph	**141d**	86	E[c]	30
17	$SiMe_3$	$SiMe_3$	**141e**	31	F[e]	113,114
18	$SiMe_3$	$SiMe_3$	**141e**	20	G[e]	113,114
19	$SiMe_3$	$SiMe_3$	**141e**	24	H[e]	114
20	$SiMe_3$	$SiMe_3$	**141e**	86	E[c]	30
21	^{n}Bu	^{n}Bu	**141f**	69	F[e]	113,114
22	^{n}Bu	^{n}Bu	**141f**	57	G[e]	113,114
23	^{n}Bu	^{n}Bu	**141f**	64	H[e]	114
24	H	CH_2OH	**141g**	90	F[e]	113,114
25	H	CH_2OH	**141g**	97	H[e]	114
26	H	$SiMe_3$	**141h**	96	G[e]	113,114
27	H	$SiMe_3$	**141h**	98	F[e]	113,114
28	Me	COOMe	**141i**	61	A[c]	86
29	H	$CH_2OSiMe_2{}^tBu$	**141j**	85	F[e]	113,114
30	H	$CH_2OSiMe_2{}^tBu$	**141j**	90	G[e]	113,114
31	1-Naphthyl	1-Naphthyl	**141k**	82	B[f]	121
32	H	$CH_2OCH_2C{\equiv}CH$	**141l**	72	E[c]	30
33	H	$CH_2OCH_2C{\equiv}CH$	**141l**	68	I[g]	116
34	H	$CH_2OCH_2CH{=}CH_2$	**141m**	78	E[c]	30
35	H	Me	**141n**	84	C[b]	20
36	$CH_2OCH_2CH{=}CH_2$	$CH_2OCH_2CH{=}CH_2$	**141o**	73	H[e]	114
37	$CH_2OCH_2C{\equiv}CH$	$CH_2OCH_2C{\equiv}CH$	**141p**	77	H[e]	114

[a] Catalysts: A, $Pd_2(dba)_3$; B, $[IrCl(cod)]_2$; C, Cp*RuCl(cod); D, $RhCl(PPh_3)_3$; E, $(CO)_9Co_3(\mu^3\text{-}CH)$; F, 2 mol % **116**+2 mol % $FeCl_3$/Zn powder; G, **116**+$CoCl_2$; H, **142**+$FeCl_3{\cdot}6H_2O$ 6 mol %/Zn powder; I, $Cl_2(PCy_3)_2Ru{=}CH{-}Ph$; J, $[RhCl(cod)]_2$.
[b] Reaction was carried out in DCE at rt.
[c] Reaction was carried out in toluene at 110 °C.
[d] Reaction was carried out in Et_2O/H_2O at rt.
[e] Reaction was carried out in THF at 50 °C/ 48 h.
[f] Reaction was carried out in xylene at 60 °C.
[g] Reaction was carried out in DCM/ 2 days.
[h] Reaction was carried out in EtOH at rt.

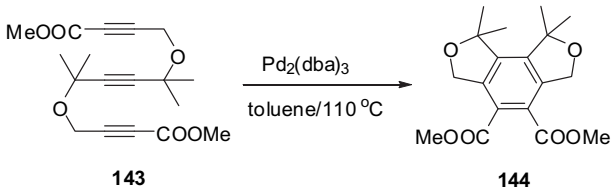


142

triynes at 50–60 °C resulted in a low yield of the products, probably due to steric hindrance, while an increase of temperature to reflux was found to improve the yields of the cyclized products.

Triyne **143** was cyclized in the presence of a Pd catalyst to give benzo[1,2-*c*:3,4-*c*]difuran **144** in 61% yield. The steric hindrance

around the central alkyne moiety slowed the rate of conversion from 4 to 5 days (Scheme 62).[86]

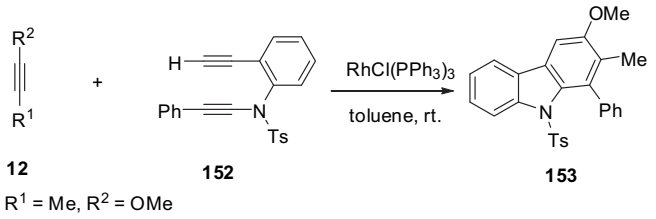


Scheme 62. Synthesis of benzodifurans by intramolecular cyclotrimerization of sterically hindered triyne.

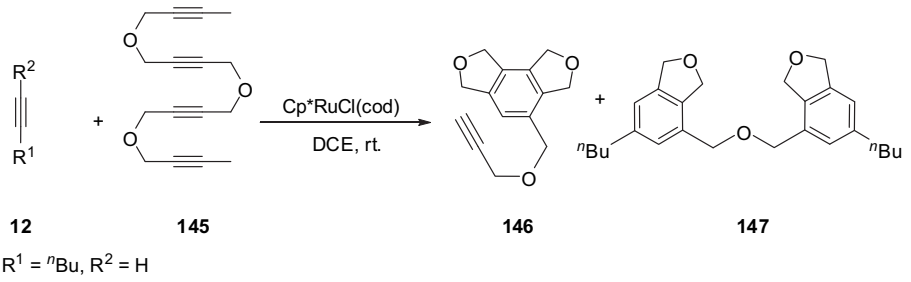
Yamamoto et al. investigated the cycloaddition of a 1,6,11,16-tetrayne **145** with 1-hexyne **12** (R^1=^{n}Bu, R^2=H) (Scheme 63). The desired tandem cycloaddition product **147**, in which two bicyclic benzenes are connected by an ether tether, was obtained in 39% yield. The intramolecular process leading to 28% yield of the cyclized product **146** competed with the tandem cycloaddition, even in the presence of 16 equiv of **12**. In the absence of 1-hexyne, **146** was solely isolated in 51% yield.[20]

The conversion proceeded slowly (2 days) in CH_2Cl_2 at ambient temperature and the competing formation of obviously polymeric byproducts explains the diminished yield.

3.2.9.2. 9H-Carbazole. In the presence of 10 mol % $RhCl(PPh_3)_3$, the diynamide **152** underwent cycloaddition with an electron-rich alkoxyalkyne **12** (R^1=Me, R^2=OMe) to give 9*H*-carbazole **153** in 89% yield with 30:1 regioselectivity (Scheme 66).[122]

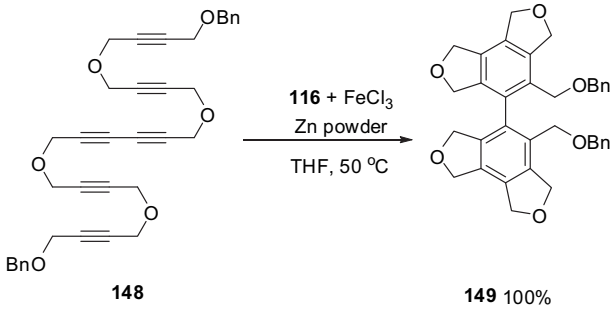


Scheme 66. Synthesis of 9*H*-carbazole by cocyclization of diynamide with monoalkyne.



Scheme 63. Synthesis of benzodifuran and bis-benzo[*c*]furan by cocyclization of tetraynes with 1-hexyne.

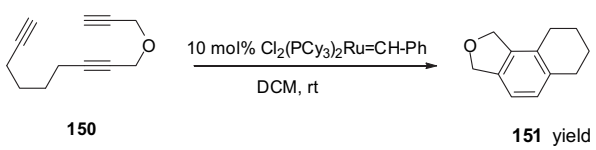
Hexayne **148** could effectively be transformed into the corresponding bi-benzo[1,2-*c*:3,4-*c*]difuran **149** upon treatment with a catalytic amount of zinc powder, $FeCl_3$, and an imidazolium carbene, at 50 °C (Scheme 64).[113]



Scheme 64. Synthesis of bi-benzo[1,2-*c*:3,4-*c*]difuran by intramolecular cyclotrimerization of hexayne.

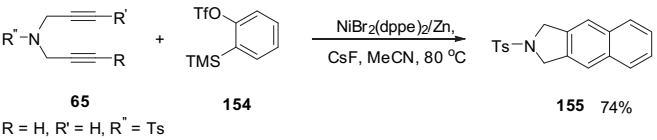
3.2.9. Fused [6–6–5] system: one heteroatom.

3.2.9.1. Hexahydronaphtho[2,1-c]furan. Peters and Blechert reported[116] the conversion of triyne **150** into hexahydronaphtho[2,1-*c*]furan **151** in a moderate yield (30%) upon treatment with 10 mol % of ruthenium catalyst [PhCH=Ru(PCy_3)$_2$$Cl_2$] (Scheme 65).



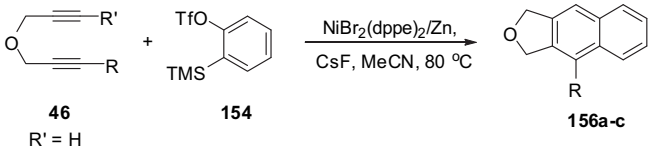
Scheme 65. Synthesis of hexahydronaphtho[2,1-*c*]furan by intramolecular cyclotrimerization of triyne.

3.2.9.3. Benzo[f]isoindole. Hsieh and Cheng reported the first example of nickel-catalyzed [2+2+2] cyclotrimerization of benzyne, which is formed *in situ* from **154**, with a diyne **65**, providing an efficient method for the synthesis of benzoisoindole **155** (Scheme 67).[123]



Scheme 67. Synthesis of benzo[*f*]isoindole by cocyclization of diynamide with benzyne.

3.2.9.4. Dihydronaphtho[2,3-c]furan. It was also reported that nickel promotes the [2+2+2] cocyclotrimerization of benzyne, which is formed *in situ* from **154**, with diynes **44**, to give naphthofurans **156a–c** in 47–71% yield (Scheme 68, Table 37).[123]



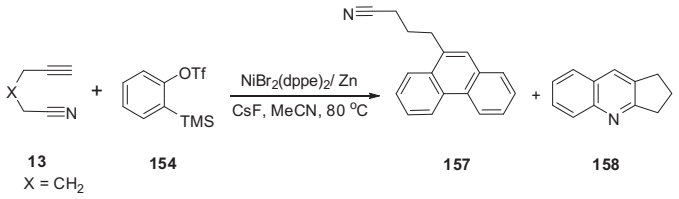
Scheme 68. Synthesis of naphthofurans by cocyclization of diynes with benzyne.

Table 37

Entry	**46** R′	Product	Yield (%)
1	H	**156a**	71
2	Me	**156b**	55
3	Ph	**156c**	47

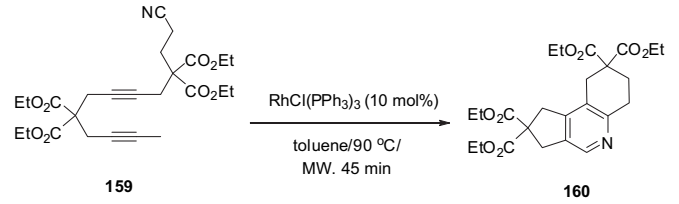
3.2.10. Fused [5–6–6] system: one heteroatom.

3.2.10.1. Cyclopenta[b]quinoline. The reaction of hex-5-ynenitrile (**13**) with benzyne (which is formed *in situ* from **154**) afforded a cyclopenta[*b*]quinoline derivative **158** in 11% yield together with a 56% yield of phenanthrene **157** (Scheme 69). The major product **157** was produced by the reaction of two benzynes with one hex-5-ynenitrile **13** during the cyclotrimerization. The minor product, a quinoline derivative **158** was formed from a [2+2+2] cocyclotrimerization of the carbon–carbon triple bond and the nitrile group in a hex-5-ynenitrile molecule and a benzyne moiety. The low reactivity of the nitrile moiety likely accounts for the low yield of **158**.[123]



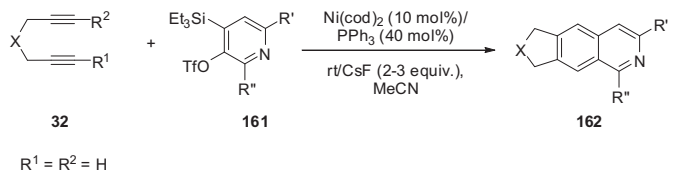
Scheme 69. Synthesis of cyclopenta[*b*]quinoline by cocyclization of benzyne with alkynenitrile.

3.2.10.2. Hexahydro-1H-cyclopenta[c]quinoline. The intramolecular cycloaddition of cyanodiyne **159** furnished a good yield of the pyridine derivative **160** when treated with Wilkinson's catalyst (10 mol %) in toluene at 90 °C under microwave irradiation (Scheme 70).[103]



Scheme 70. Synthesis of cyclopenta[*c*]quinoline by intramolecular cyclotrimerization of cyanodiyne using $RhCl(PPh_3)_3$.

3.2.10.3. 6H-Cyclopenta[g]isoquinoline. When a solution of diynes **32** was added to a mixture of the 3,4-pyridyne precursors **161**, nickel catalyst, and CsF in MeCN using a syringe pump over a period of 3 h, the isoquinoline derivatives **162** were obtained in 18–65% yield (Scheme 71, Table 38).[124]



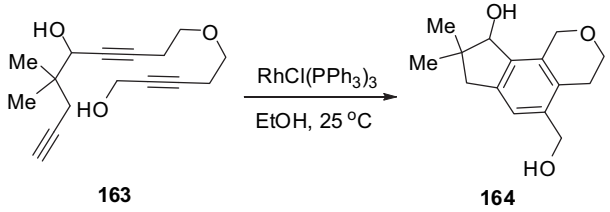
Scheme 71. Synthesis of cyclopenta[*g*]isoquinoline by intermolecular cycloaddition of pyridyne precursors to diynes using $Ni(cod)_2/PPh_3$ catalytic system.

Table 38

Entry	X	R′	R″	Yield of **162**[a]
1	CH_2	H	H	65
2	$C(CO_2Me)_2$	H	H	63
3	$C(CO_2Me)_2$	OMe	H	61
4	$C(CO_2Me)_2$	H	OMe	60
5	$C(CO_2Me)_2$	H	$CONEt_2$	18

[a] A solution of **32** was added over a period of 3 h to a mixture of **161,** Ni catalyst, and CsF and the reaction was quenched just after finishing addition of **32**.

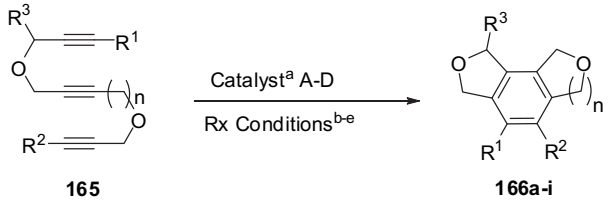
3.2.10.4. Cyclopenta[h]isochromene. Neesaon and Stevenson used Wilkinson's catalyst to perform the intramolecular cyclotrimerization of trialkyne **163** to give cyclopenta[*h*]isochromene **164** in 86% yield, and this was used as a key step for the total synthesis of the sesquiterpenoid, calomelanolactone (Scheme 72).[125]



Scheme 72. Synthesis of cyclopenta[*h*]isochromene by intramolecular cyclotrimerization of triyne.

3.2.11. Fused [5–6–6] system and larger-membered ring analogues [5–6–7/8/9/10]: two heteroatoms [1:1].

3.2.11.1. Furo[3,4-h]isochromene and larger-membered ring analogues. The intramolecular [2+2+2] cyclization of triynes **165** took place at ambient temperature under ruthenium catalysis to give furo[3,4-*h*]isochromene **166a** (entry 1) and isobenzofuro[4,5-*c*]oxepine **166b** (entry 4) in 89 and 53% yield, respectively (Scheme 73, Table 39).[20,118] In the presence of a Co catalyst (D), triyne **165** cyclotrimerizes under microwave irradiation to give a 54% yield of furo[3,4-*h*]isochromene **166a** (entry 3). Moreover, triynes **165** underwent cyclotrimerization in refluxing toluene in the presence of 2.5 mol % $[Pd_2(dba)_3]$ to afford the furo[3,4-*h*]isochromene **166f** (entry 9), isobenzofuro[4,5-*c*]oxepine **166g** (entry 10), and isobenzofuro[4,5-*c*]oxocine **166h** (entry 11) in 87, 77, and 16% yield, respectively.[72] Rhodium was also reported to catalyze the [2+2+2] cyclotrimerization of the appropriate triynes **165** in a water/organic biphasic system to give rise to 6- to 10-membered ring products **166a–e** (entries 2 and 5–8) and **166i** (entry 12) in 84–93% yield.[118]



Scheme 73. Synthesis of furoisochromones and larger-membered ring analogues by intramolecular cyclotrimerization of triynes.

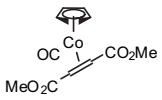
3.2.11.2. 2,3-Dihydro-1H-pyrrolo[3,4-g]isoquinoline. Iwayama and Sato[124] reported the synthesis of a pyrrolo[3,4-g]isoquinoline derivative **167** in 50% yield by the addition of a solution of a diyne **65** to a mixture of the 3,4-pyridyne precursor **161**, nickel catalyst, and CsF in MeCN using a syringe pump over a period of 3 h (Scheme 74).

3.2.11.3. 1,3-Dihydrofuro[3,4-g]isoquinoline. Dihydrofuro[3,4-*g*] isoquinoline **168** can be obtained in 38% yield by cycloaddition of a diyne **44** to a 3,4-pyridyne precursor **161** using a similar approach

Table 39

Entry	165				Product	Yield (%)	Catalyst[a]	Ref.
	n	R^1	R^2	R^3				
1	2	H	H	H	**166a**	89	B[b]	20
2	2	H	H	H	**166a**	93	C[c]	118
3	2	H	H	H	**166a**	54[e]	D[e]	81
4	3	H	H	H	**166b**	53	B[b]	20,118
5	3	H	H	H	**166b**	84	C[c]	118
6	4	H	H	H	**166c**	88	C[c]	118
7	5	H	H	H	**166d**	91	C[c]	118
8	6	H	H	H	**166e**	89	C[c]	118
9	2	COOMe	COOMe	H	**166f**	87	A[d]	86
10	3	COOMe	COOMe	H	**166g**	77	A[d]	86
11	4	COOMe	COOMe	H	**166h**	16	A[d]	86
12	3	H	H	Me	**166i**	85	C[c]	118

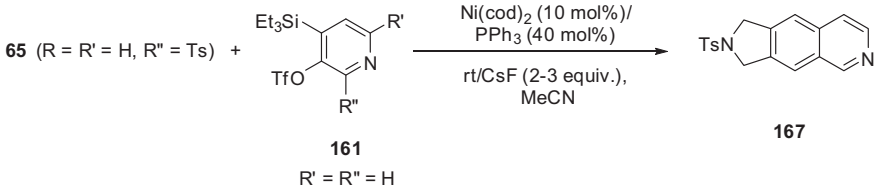
[a] Catalysts: A: $Pd_2(dba)_3$, B: Cp*RuCl(cod), C: $[RhCl(cod)]_2$, D:



[b] Reaction was carried out in DCE at rt.
[c] Reaction was carried out in H_2O/Et_2O at rt.
[d] Reaction was carried out in toluene at 110 °C.
[e] Reaction was carried out in DMF/MW/200 °C.

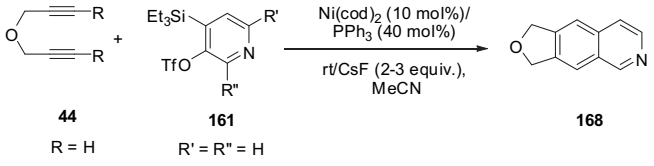
3.2.12. Fused [5–6–6] system: three heteroatoms [1:1:1].

3.2.12.1. Hexahydro-1H-pyrrolo[3,4-c][1,6]naphthyridine. The intramolecular [2+2+2] cycloaddition reactions of cyanodiynes **171** with $RhCl(PPh_3)_3$ (10 mol %) in toluene at 90 °C for 3–5 h gave 42–93% yields of pyrrolo[3,4-*c*][1,6]naphthyridines **172a–c** (entries 1–3). Substrates **171** were tested for a [2+2+2] cycloaddition process by using Wilkinson's catalyst under microwave heating. The use of toluene as a solvent led to decomposition products. On the other hand, when the solvent was changed to DMSO at 90 °C, the reaction, which was complete after 30 min, gave bipyridine **172e** (entry 5) in 92% yield. In a mixture of DMF/H_2O (1:1), the derivative **172d** (entry 4) was obtained in 89% yield.[103] Aubert et al. reported the synthesis of pyrrolo[3,4-*c*][1,6] naphthyridines **172f–h** (entries 6–8) in 90–96% yield by irradiation of a solution of the appropriate diyne nitrile **171** and 5 mol % of cyclopentadienyledicarbonylcobalt in toluene using a 300 W halogen lamp until completion of the reaction (Scheme 77, Table 40).[111] The bis dialkynenitrile **173** underwent complete cycloaddition using Wilkinson's catalyst in DMSO at 90 °C after a reaction time of just 10 min to afford bipyridine derivative **174** in 88% yield (Scheme 78).[103]



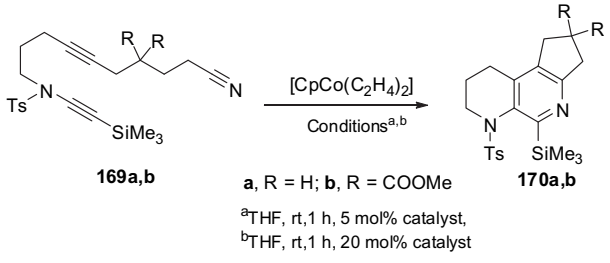
Scheme 74. Synthesis of pyrrolo[3,4-*g*]isoquinoline by intermolecular cycloaddition of pyridyne precursor to diyne using using $Ni(cod)_2/PPh_3$ catalytic system.

to that described for the synthesis of pyrroloisoquinoline derivative **167** (Scheme 75).[124]

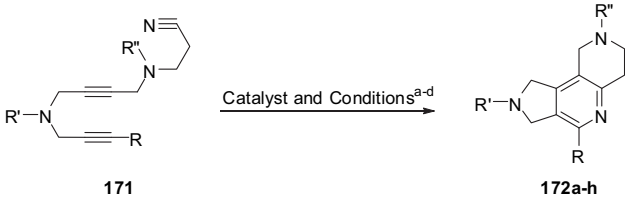


Scheme 75. Synthesis of furo[3,4-*g*]isoquinoline by intermolecular cycloaddition of pyridyne precursor to diyne using $Ni(cod)_2$.

3.2.11.4. Hexahydro-1H-cyclopenta[f][1,7]naphthyridine. The [2+2+2] cocyclizations between ynamides, nitriles, and alkynes of compounds **169a,b** using $[CpCo(C_2H_4)_2]$ as a catalyst led to the formation of cyclopentanaphthyridines **170a,b** in 100 and 76% yield, respectively (Scheme 76).[110]



Scheme 76. Synthesis of cyclopenta[*f*][1,7]naphthyridines by Co-catalyzed intramolecular cyclotrimerization of cyanodiynes.



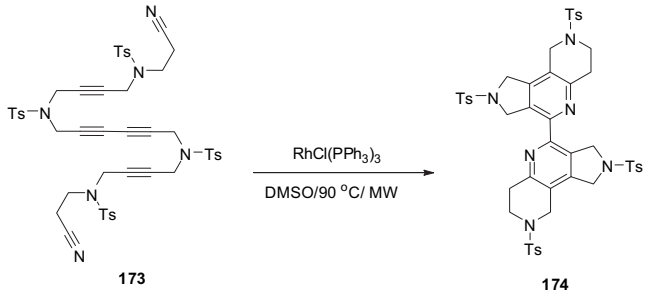
Scheme 77. Synthesis of pyrrolo[3,4-*c*][1,6]naphthyridines by Rh- or Co-catalyzed intramolecular cyclotrimerization of cyanodiynes.

Table 40

Entry	R	R′	R″	Product	Yield (%)	Ref.
1	Ts	$CH_2N(Boc)Ts$	Ts	**172a**	93[a]	103
2	Ts	$CH_2N(H)Ts$	Ts	**172b**	67[a]	103
3	Ts	Me	Ts	**172c**	42[a]	103
4	Ts	2-Pyridyl	Ts	**172d**	89[b]	103
5	Ts	3-Pyridyl	Ts	**172e**	92[c]	103
6	$SiMe_3$	Cbz	$COCF_3$	**172f**	96[d]	111
7	$SiMe_3$	Cbz	Boc	**172g**	90[d]	111
8	$SiMe_3$	Cbz	Bn	**172h**	91[d]	111

[a] $RhCl(PPh_3)_3$ (10 mol %) in toluene at 90 °C for 5–8 h.
[b] RhCl $(PPh_3)_3$ (10 mol %) in DMF/H_2O (1:1) at 90 °C.
[c] $RhCl(PPh_3)_3$ (10 mol %) in DMSO at 90 °C.
[d] $[CpCo(C_2H_4)_2]$ 5 mol %, toluene, *hν*.

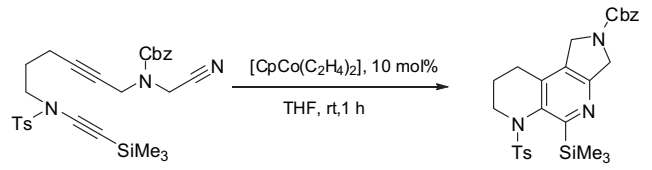
3.2.12.2. Hexahydro-1H-pyrrolo[3,4-f][1,7]naphthyridine. Hex ahydropyrrolo[3,4-*f*][1,7]naphthyridine **176** was obtained in 93% yield by intramolecular [2+2+2] cyclotrimerization of a diyne nitrile **175** using 10 mol % of $[CpCo(C_2H_4)_2]$ as a catalyst in THF at



173 174

Scheme 78. Synthesis of bis-pyrrolo[3,4-*c*][1,6]naphthyridine by Rh-catalyzed intramolecular cyclotrimerization of bisdialkynenitrile.

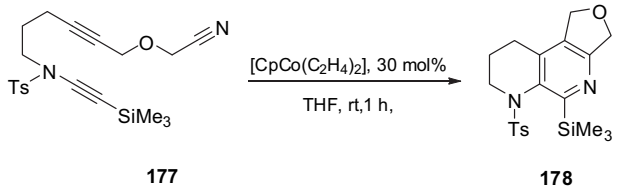
rt. The same compound was obtained in 91% yield using 15 mol % of the catalyst in refluxing xylene under visible light irradiation (Scheme 79).[110,111]



175 176

Scheme 79. Synthesis of pyrrolo[3,4-*f*][1,7]naphthyridine by Co-catalyzed intramolecular cyclotrimerization of cyanodiyne.

3.2.12.3. Hexahydrofuro[3,4-f][1,7]naphthyridine. Hexahydrofuro [3,4-*f*][1,7]naphthyridine **178** was obtained in 62% yield by intramolecular [2+2+2] cyclotrimerization of a diyne nitrile **177** using 30 mol % of $[CpCo(C_2H_4)_2]$ as a catalyst in THF at rt (Scheme 80).[110]



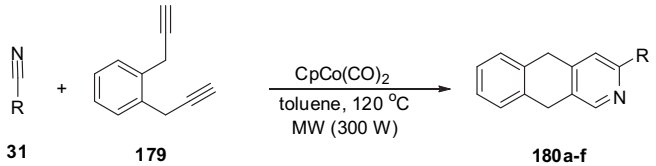
177 178

Scheme 80. Synthesis of furo[3,4-*f*][1,7]naphthyridine by Co-catalyzed intramolecular cyclotrimerization of cyanodiyne.

3.2.13. Fused [6–6–6] system: one heteroatom.

3.2.13.1. Dihydrobenzo[g]isoquinoline. Diyne **179** was reacted with nitriles **31** bearing a variety of functional groups including alkyl and alkene chains, hydroxy groups, benzene, and pyridine rings to give dihydrobenzo[*g*]isoquinolines **180a**–**f** in 80–94% yield (Scheme 81, Table 41).[126] The reactions were conducted under $CpCo(CO)_2$ catalysis in toluene using microwave irradiation (300 W).

3.2.13.2. Benzo[c]chromene. Subjecting a solution of diynes **181** and 1-hexyne **12** ($R^1={}^n$Bu, R^2=H) (10 equiv) in toluene to a Ru catalyst under microwave irradiation, afforded the cyclotrimerized



31 179 180a-f

Scheme 81. Synthesis of dihydrobenzo[*g*]isoquinoline by cocyclization of diyne with nitriles.

Table 41

Entry	31 R	Product	Yield (%)
1	Me	**180a**	94
2	Pr	**180b**	87
3	$(CH_2)_2OH$	**180c**	83
4	$CH{=}CH_2$	**180d**	90
5	Ph	**180e**	87
6	Py	**180f**	80

regioisomeric products of benzo[*c*]chromenes **182a**–**f**/**183a**–**f** (entries 1–6) in 61–97% yield (Scheme 82, Table 42).[127] It was noted that increased steric bulk leads to a more efficient cyclotrimerization with enhanced regioselectivity. When the cyclotrimerization was carried out in DCE, the regioisomers **182b**/**183b** (entry 7) were obtained in 41% combined yield, but with better regioselectivity (82:18).[96]

On the other hand, compound **184** underwent an efficient and regioselective Ru-catalyzed [2+2+2] cyclotrimerization reaction with propargyltrimethylsilane **12** ($R^1{=}CH_2{-}$TMS, R^2=H) under microwave irradiation to deliver the benzo[*c*]chromene **185** in 88% yield as a single regioisomer (Scheme 83).[127]

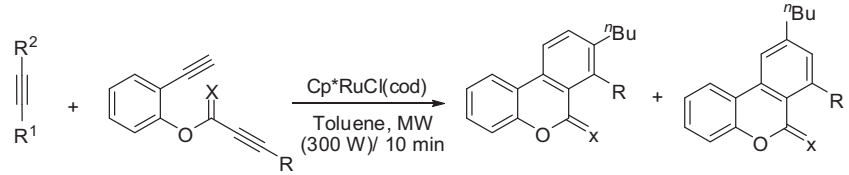
3.2.13.3. Phenanthridin-6(5H)-one. In the presence of 10 mol % of Cp*RuCl(cod), 1,7-diyne **186** underwent regioselective cycloaddition with 1-hexyne **12** ($R^1={}^n$Bu) in DCE to afford the phenanthridin-6(5*H*)-ones **187**/**188** in 70% combined yield with a regioisomeric ratio of 83:17 (Scheme 84).[96]

3.2.14. Fused [6–6–6] system: one bridgehead heteroatom.

3.2.14.1. Pyrido[1,2-b]isoquinoline. Cocyclization of excess ethyl cyanoacetate **31** ($R{=}CH_2CO_2Et$) with a diyne **189** in the presence of $CpCo(CO)_2$ afforded pyrido[1,2-*b*]isoquinoline **190** in 37% yield *via* initial formation of 3-(tetrahydroisoquinoline)acetate and subsequent *in situ* condensation with a second equivalent of nitrile **31** (Scheme 85).[76]

3.2.15. Fused [6–6–6] system: two heteroatoms [1:1].

3.2.15.1. Octahydrobenzo[f][1,7]naphthyridine. Using $[CpCo(C_2H_4)_2]$ as a catalyst, the intramolecular [2+2+2] cocyclization between ynamide, nitrile, and alkyne of compound **191** led to the formation of octahydrobenzo[*f*][1,7]naphthyridine **192** in 100% yield (Scheme 86).[110]



12 181 182a-f 183a-f

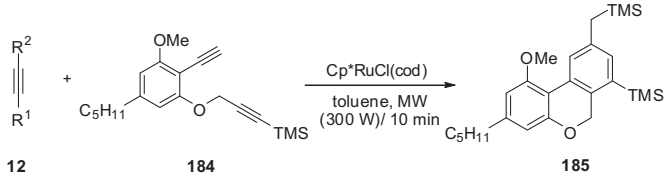
$R^1 = {}^n$Bu, R^2 = H

Scheme 82. Synthesis of benzo[*c*]chromene regioisomers by cocyclization of diynes with 1-hexyne.

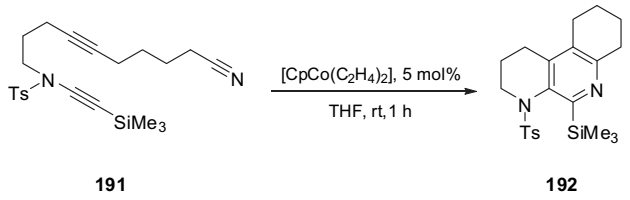
Table 42

Entry	X	181	182/183	Yield (%)	Ratio[a] 182/183	Ref.
		R	Product			
1	H_2	H	182a/183a	61	70:30	127
2	O	H	182b/183b	31	76:24	127
3	H_2	Me	182c/183c	96	95:5	127
4	O	Me	182d/183d	71	>95:5	127
5	H_2	TMS	182e/183e	97	>95:5	127
6	O	TMS	182f/183f	81	>95:5	127
7	O	H	182b/183b	41[b]	82:18	96

[a] Determined by GC–MS and ^{1}H NMR.
[b] All reactions were carried out in toluene under MW (300 W), except for entry 7, where the reaction was carried out in DCE, rt.



Scheme 83. Regioselective synthesis of benzo[*c*]chromene by cocyclization of diyne with propargyltrimethylsilane.

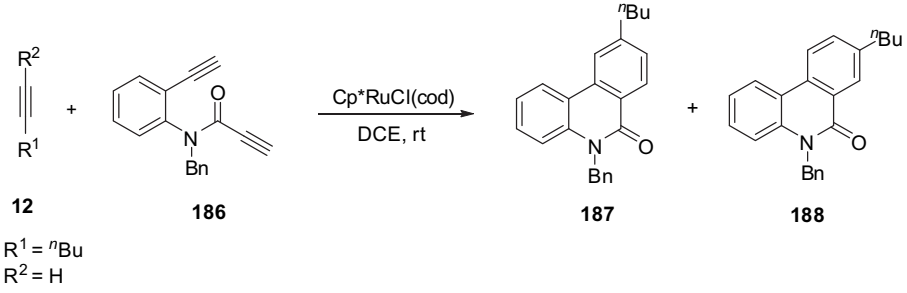


Scheme 86. Synthesis of benzo[*f*][1,7]naphthyridine by Co-catalyzed intramolecular cyclotrimerization of cyanodiyne.

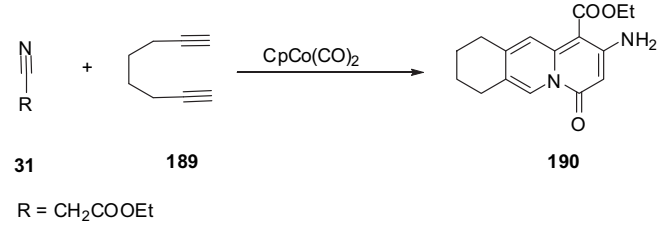
3.2.16. Fused [6–6–6] system: three heteroatoms [1:1:1]. 3.2.16.1. Hexahydro-1H-pyrano[4,3-c][1,6]naphthyridine. Snyder et al. reported on the microwave-promoted, cobalt-catalyzed intramolecular [2+2 + 2] cyclizations of dialkynylnitriles **193**. Cyclizations proceeded smoothly to give hexahydro-1*H*-pyrano[4,3-*c*][1,6]naphthyridines **194a–i** in excellent yields (Scheme 87, Table 43).[109]

3.2.16.2. Octahydropyrido[3,4-c][1,7]naphthyridine. With the diyne nitriles **195**, Aubert et al. carried out cobalt-catalyzed [2+2+2] cycloadditions using 5 mol % of $CpCo(CO)_2$ under refluxing conditions and visible light irradiation and successfully obtained octahydropyrido[3,4-*c*][1,7]naphthyridines **196a–c** in 19–83% yield (Scheme 88).[111]

3.2.16.3. Octahydropyrido[4,3-c][1,6]naphthyridine. The same group[111] used a similar approach to prepare octahydropyrido[4,3-*c*]



Scheme 84. Synthesis of phenanthridin-6(5*H*)-one regioisomers by cocyclization of diyne with 1-hexyne.

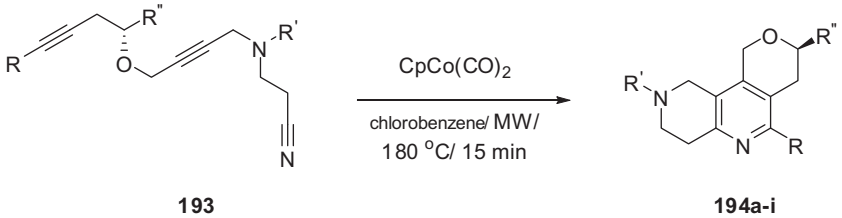


Scheme 85. Synthesis of pyrido[1,2-*b*]isoquinoline by cocyclization of diyne with ethyl cyanoacetate.

[1,6]naphthyridine **198** in 76% yield from a diyne nitrile **197** (Scheme 89).

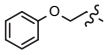
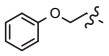
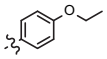
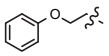
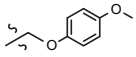
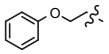
3.2.17. Fused [6–7–6] system: two heteroatoms [1:1].

3.2.17.1. Dihydrobenzo[c]oxepino[3,4-c]pyridine and 5,7-dihydrobenzo[c]oxepino[4,3-c]pyridine. Nicolaus and Schmalz developed a synthesis of dihydrobenzooxepinopyridines **200** exploiting a microwave-accelerated, cobalt-catalyzed [2+2+2] intermolecular cycloaddition of diynes **199** to nitriles **31**. The target compounds were regioselectively obtained in 20–52% yield. GC/MS analysis of the crude reaction mixtures indicated the formation of small amounts of isomeric products, which were assigned as the other regioisomer **201** (Scheme 90, Table 44).[128]

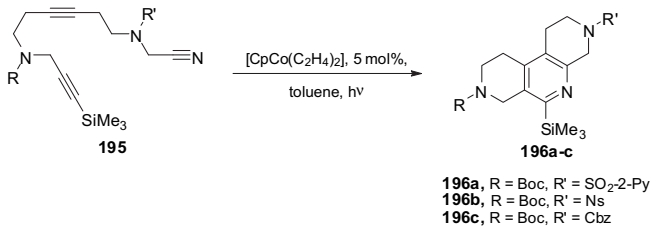


Scheme 87. Synthesis of pyrano[4,3-*c*][1,6]naphthyridines by Co-catalyzed intramolecular cyclotrimerization of cyanodiynes.

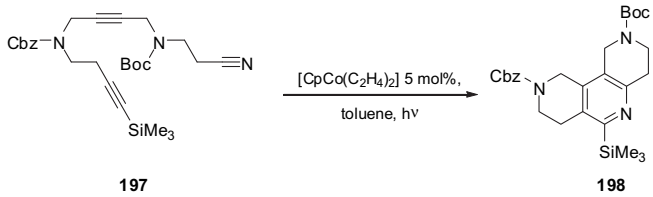
Table 43

Entry	R	R′	R″	Yield (%)[a]
1	Ph	Me		**194a**/83
2	Ph	Me		**194b**/93
3	Ph	Me		**194c**/86
4		Me		**194d**/89
5		Me		**194e**/87
6		Me		**194f**/88
7		Me		**194g**/99
8	Ph			**194h**/86
9		Me		**194i**/93

[a] All reactions were carried out in chlorobenzene under MW (300 W), 15 min, 180 °C.



Scheme 88. Synthesis of octahydropyrido[3,4-*c*][1,7]naphthyridines by Co-catalyzed intramolecular cyclotrimerization of cyanodiynes.



Scheme 89. Synthesis of pyrido[4,3-*c*][1,6]naphthyridine by Co-catalyzed intramolecular cyclotrimerization of cyanodiynes.

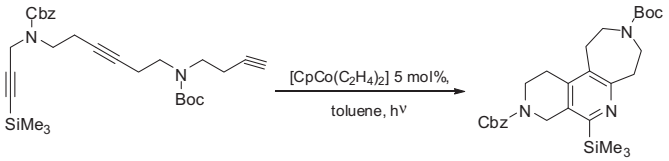
Table 44

Entry	**199**,**31**			Ratio **200**/**201**[a]	Yield[b] (%)
	R^1	R^2	R		
1	Me	H	Ph	n.d.	5
2	Me	Me	Ph	90:10	52
3	Me	Me	Me	n.d.	5
4	Me	Me	CH_2CN	n.d.	5
5	Me	Me	3,4,5-$(MeO)_3C_6H_2$	≥99:1	30
6	Me	Me	2-Furyl	75:25[c]	35
7	H	Me	Ph	≥99:1	35
8	H	Me	2-Pyridyl	≥99:1	20
9	Me	Me	1-Morpholinyl	98:2	35
10	H	Me	1-Morpholinyl	≥99:1	27

[a] Determined by GC–MS.
[b] Yield after chromatography.
[c] Determined by NMR.

3.2.18. *Fused [7–6–6] system: three heteroatoms [1:1:1].*

3.2.18.1. Octahydro-1H-azepino[4,5-c][2,7]naphthyridine. Intramolecular [2+2+2] cycloadditions of a diyne nitrile **202** using 5 mol % of $CpCo(CO)_2$ under refluxing conditions and visible light irradiation afforded octahydro-1*H*-azepino[4,5-*c*][2,7]naphthyridine **203** in 74% yield, as shown in Scheme 91.[111]



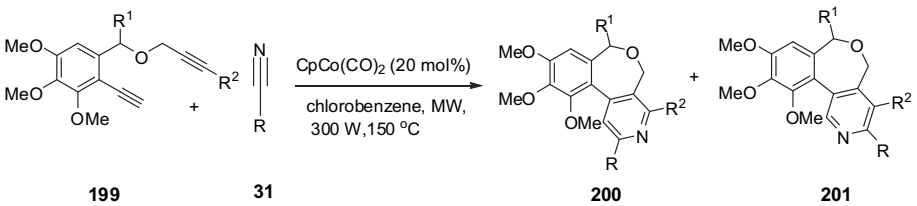
Scheme 91. Synthesis of azepino[4,5-*c*][2,7]naphthyridine by Co-catalyzed intramolecular cyclotrimerization of diyne nitrile.

3.2.19. *Fused [6–6–9] system: three heteroatoms (in one ring).*

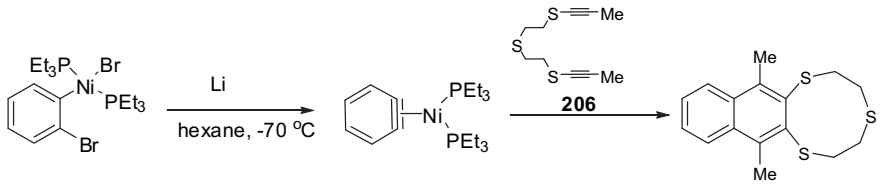
3.2.19.1. Tetrahydronaphtho[2,3-b][1,4,7]trithionine. Ni(0)/benzyne complex **205**, obtained from **204** by reduction with lithium at −70 °C, was allowed to react with a diyne possessing a trisulfur tether **206** to afford tetrahydronaphthotrithionine **207** in high NMR yield (>90%) (Scheme 92). Its instability, however, resulted in a diminished isolated yield (45%).[129]

3.2.20. *Fused heteromacrocycles.*

3.2.20.1. Dibenzocrown ethers. Cyclotrimerization of α,ω-diynes **208**–**210** with alkynes **12** in the presence of $Cp(Co)(CO)_2$ under an argon or CO atmosphere afforded the corresponding macrocycles **211**–**216** in 12–36% yield. Interestingly, a different regiochemistry was observed in this benzannulation, depending on whether an atmosphere of argon or carbon monoxide was used. The cycloaddition of diyne **209** and 4-octyne under argon provided *para* cyclophane **212** almost exclusively (entry 1), whereas the reaction under CO provided a mixture of *ortho* and *para* isomers **211** and **212** in a ratio of 1:2 (entry 2). Cyclization of the diyne **209** with dimethyl acetylenedicarboxylate (DMAD) under argon yielded benzannulene **213** (entry 3), while under carbon



Scheme 90. Synthesis of dihydrobenzo[*c*]oxepino[3,4-*c*]pyridines and 5,7-dihydrobenzo[*c*]oxepino[4,3-*c*]pyridines by intermolecular cycloaddition of diynes to nitriles using Co catalyst.



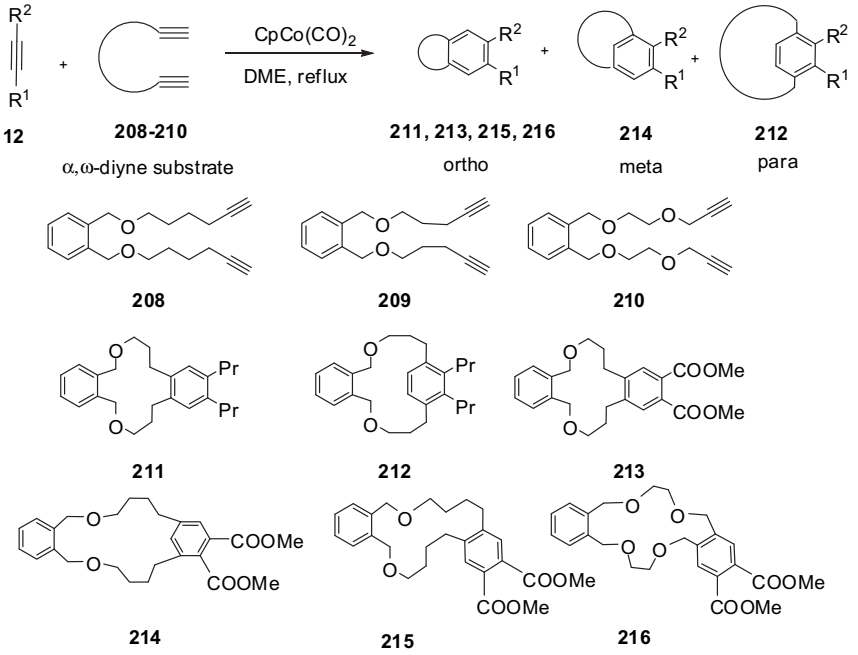
204 205 207

Scheme 92. Synthesis of tetrahydronaphthotrithionine by cocyclization of diyne with Ni(0)/benzyne complex.

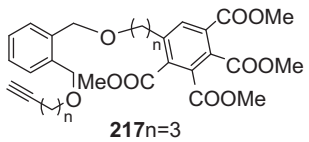
monoxide the reaction provided the *ortho* and *meta* isomers **213** and **214** in a ratio of 11:1 (entry 4). Similarly, macrocyclizations of DMAD with bis-alkynes **208** and **210** under argon furnished only the benzannulenes **215** and **216**, in 12 and 31% yield, respectively (entries 5 and 6). Macrocyclizations in DME and 1,4-dioxane gave similar yields and regiochemistry (entry 6). Undesired cycloadducts derived from the incorporation of two molecules of DMAD and only one of the alkyne moieties of the α,ω-diyne, such as **217** and **218**, were also isolated (Scheme 93, Table 45).[130]

Under similar conditions, macrocyclization of triyne **222** provided 12- and 13-membered ring systems **223** and **224** in 50 and 11% yield, respectively (Scheme 95).[118]

3.2.20.3. Pyridino-macrocycles. Long-chain α,ω-diynes **208**, **209**, and **225**–**230** underwent Co-mediated [2+2+2] cycloadditions with nitriles or cyanamides **31** to yield pyridine-containing macrocycles **231a**–**u** and **232a**–**u** in different regioisomeric ratio (*meta*/*para*) (Scheme 96, Table 46). The regioselectivity of these reactions was affected by the length and type of linker unit between the alkyne groups, as well as by certain stereoelectronic factors.[130]



Scheme 93. Synthesis of dibenzocrown ethers by cyclotrimerization of α,ω-diynes with monoalkynes.

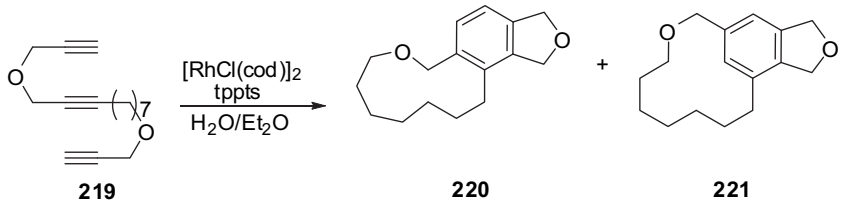


3.2.20.2. Benzofuro-macrocycles. Cyclotrimerization of 4,15-dioxaoctadeca-1,6,17-triyne (**219**) in the presence of a water-soluble rhodium catalyst (prepared *in situ* from $[RhCl(cod)]_2$ and the trisodium salt of tris(*m*-sulfonatophenyl)phosphine (tppts) in water at 75 °C) furnished the 12-membered methacyclophane **221** in 32% yield along with the normal 11-membered cyclized product **220** (57%) (Scheme 94).[118]

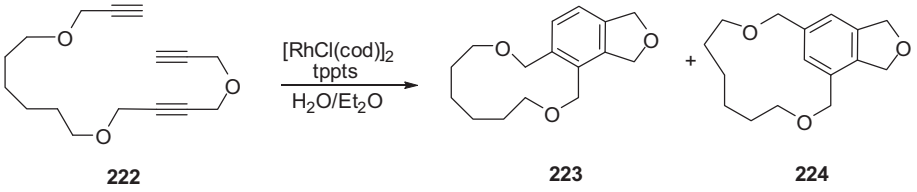
Table 45

Entry	α,ω-Diyne	**12** $R^1=R^2$	Rx. atm	Products	Yield[a] % (*o*:*m*:*p* ratio)
1	**209**	Pr	Ar	**212**	23 (0:0:100)
2	**209**	Pr	CO	**211**+**212**	29 (1:0:2)[b]
3	**209**	COOMe	Ar	**213**	33 (100:0:0)[c]
4	**209**	COOMe	CO	**213**+**214**	36 (11:1:0)[b]
5	**208**	COOMe	Ar	**215**	12[d]
6	**210**	COOMe	Ar	**216**	31, 27[e]

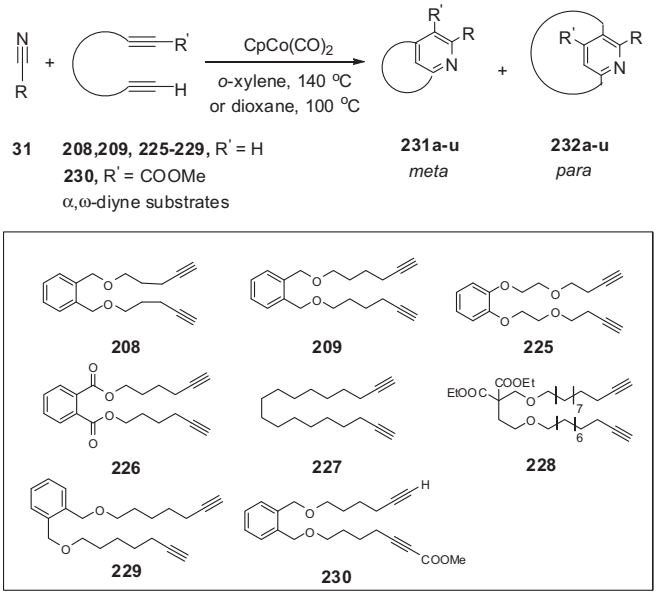
[a] Ratios determined from isolated isomeric products.
[b] A 9% yield of **217** was also isolated.
[c] A 7% yield of **217** was also isolated.
[d] A 11% yield of **218** was also isolated.
[e] A 27% yield of **216** was obtained when 1,4-dioxane was used as a solvent.



Scheme 94. Synthesis of benzofuro-macrocycles by intramolecular cyclotrimerization of triyne.



Scheme 95. Synthesis of 12- and 13-membered macrocycles by intramolecular cyclotrimerization of triyne.



Scheme 96. Synthesis of pyridino-macrocycles by cyclotrimerization of α,ω-diynes with nitriles.

In contrast to the reaction of diynes with 4-methylbenzonitrile, the reaction of alkynenitrile **233** with *p*-tolylacetylene furnished a 25% combined yield of a macrocycle bearing a 2,4,6-substituted pyridine **234** along with two macrocycles bearing the 2,3,6-substituted pyridines **235** and **236** in a 3:1:3 regioisomeric ratio. It is interesting that the regioisomeric *para* cycloadduct was not observed. Similarly, cyclotrimerization of **233** with 1-ethynyl-4-methoxybenzene provided a 1:1:1 ratio of three isomers of similar substitution pattern **234**, **235**, and **236** (Scheme 97). Despite the α,ω-alkynylnitrile/alkyne cycloaddition being nonselective, compared with the α,ω-diyne/nitrile cycloaddition, it offers access to other isomeric products that are not obtainable *via* the original route.[44,130]

3.3. Fused tetracyclic systems

3.3.1. Fused [5–5–6–5] systems: three heteroatoms [1:1:1].

3.3.1.1. Dipyrrolo[3,4-e:3′,4′-g]isoindole. Nitrogen-containing 15-membered triacetylenic macrocycles **237** underwent cyclotrimerization into the corresponding 2,5,8-tris[(4-arylsulfonyl)]-2,5,8-triazatriindane **238a–e**, when treated with the appropriate catalyst. Although different transition metals were tested in the cyclotrimerization, the $RhCl(CO)(PPh_3)_2$ complex was found to give the desired products in high yields (Scheme 98, Table 47).[131–133]

Roglans et al. reported that the cyclotrimerization of **237** in molten *n*-Bu_4NBr using either Wilkinson's catalyst $RhCl(PPh_3)_3$, or $PdCl_2$ leads to good yields (up to 86%) of the corresponding cyclotrimerized product. When $PdCl_2$/TBAB was used, transmission electron microscopy (TEM) analysis has shown the formation of nanoparticles, which, presumably, are the active catalytic species.[132]

Roglans et al. also studied the cyclotrimerization of the 15-membered macrocycle **239**, in which a methyl group is incorporated at the propargylic position, under similar conditions to those used with the nonmethyl-containing macrocycles.[134] The cycloaddition reaction did not seem to be affected by the steric hindrance introduced in the propargylic position. The cyclotrimerized product **240** could be obtained in 99% yield (Scheme 99).[134]

Table 46

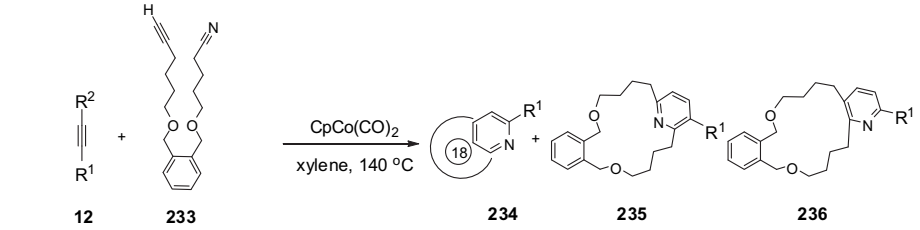
Entry	**31**	α,ω-Diyne	R′	**231/232**	Yield %	Ratio[c] **231:232**
	R			Products		
1	*p*-Me-C_6H_4	**208**	H	**231a/232a**	61,[a] 87[b]	1:5 (1:7)
2	*p*-Me-C_6H_4	**209**	H	**231b/232b**	57,[a] 58[b]	1:1
3	*p*-Me-C_6H_4	**225**	H	**231c/232c**	55,[a] 80[b]	1:5
4	*p*-Me-C_6H_4	**226**	H	**231d/232d**	34,[a] 30[b]	1:7
5	*p*-Me-C_6H_4	**227**	H	**231e/232e**	42[a]	1:1
6	*p*-Me-C_6H_4	**228**	H	**231f/232f**	49[a]	3:4
7	*p*-Me-C_6H_4	**230**	COOMe	**231g/232g**	22[a]	3:1
8	*p*-OMe-C_6H_4	**209**	H	**231h/232h**	38[a]	1:1
9	*p*-Br-C_6H_4	**209**	H	**231i/232i**	35,[a] 25[b]	1:1
10	*p*-MeOOC-C_6H_4	**209**	H	**231j/232j**	46[a]	2:1
11	2-Furyl	**209**	H	**231k/232k**	38[a]	1:3
12	2-Pyridyl	**209**	H	**231l/232l**	33[a]	1:1
13	3-Cyclohexenyl	**209**	H	**231m/232m**	30[a]	2:1
14	β-Styryl	**209**	H	**231n/232n**	43[a]	1:2
15	Adamantyl	**209**	H	**231o/232o**	11,[a] 9[b]	50:1
16	1-Pyrrolidinyl	**209**	H	**231p/232p**	64[b]	1:1
17	1-Pyrrolidinyl	**225**	H	**231q/232q**	50[b]	1:50
18	4-Morpholinyl	**208**	H	**231s/232s**	54[a]	1:50
19	Me_2N	**226**	H	**231r/232r**	32[a]	1:50
20	5-Dibenzo[*b*,*f*] azepinyl	**225**	H	**231t/232t**	80[a]	1:6
21	*p*-Me-C_6H_4	**229**	H	**231u/232u**	4[a]	1:1

[a] Reactions were carried out in refluxing xylene.
[b] The reaction was carried out in refluxing dioxane.
[c] Regioisomeric ratio is based on isolated yields.

Table 47

Entry	**237**, **238**	Product[a]	Yield (%)	Ref.
	Ar^1, Ar^2, Ar^3			
1	Ar^1=Ar^2=Ar^3=4-MeC_6H_4–	**238a**	54[b]	131,133
2	Ar^1=Ar^2=4-MeC_6H_4–Ar^3=Ferrocenyl	**238b**	54[b]	131
3	Ar^1=Ar^2=Ar^3=Ferrocenyl	**238c**	65b	131
4	Ar^1=Ar^2=Ar^3=2,4,6-$^iPrC_6H_2$–	**238d**	54[b]	131
5	Ar^1=4-MeC_6H_4–, Ar^2=Ferrocenyl, Ar^3=4-CH_2=CHC_6H_4	**238e**	45[b]	131
6	Ar^1=Ar^2=Ar^3=2,4,6-$^iPrC_6H_2$–	**238d**	44[c]	131
7	Ar^1=Ar^2=Ar^3=2,4,6-$^iPrC_6H_2$–	**238d**	88[d]	131
8	Ar^1=Ar^2=4-MeC_6H_4–, Ar^3=Ferrocenyl	**238b**	42[e]	131
9	Ar^1=Ar^2=Ar^3=2,4,6-$^iPrC_6H_2$–	**238d**	36[e]	131
10	Ar^1=Ar^2=Ar^3=2,4,6-$^iPrC_6H_2$–	**238d**	36[f]	131
11	Ar^1=Ar^2=4-MeC_6H_4–, Ar^3=Ferrocenyl	**238b**	88[g]	131
12	Ar^1=Ar^2=Ar^3=4-MeC_6H_4–	**238a**	89[g]	131
13	Ar^1=Ar^2=Ar^3=2,4,6-$^iPrC_6H_2$–	**238d**	96[g]	131
14	Ar^1=Ar^2=Ar^3=2,4,6-$^iPrC_6H_2$–	**238d**	80[h]	131
15	Ar^1=Ar^2=Ar^3=2,4,6-$^iPrC_6H_2$–	**238d**	88–96[i]	132
16	Ar^1=Ar^2=Ar^3=2,4,6-$^iPrC_6H_2$–	**238d**	45–65[j]	132

[a] Catalyst: A:$Pd_2(dba)_3$, B: $RhCl(CO)(PPh_3)_2$, C: $Pd(PPh_3)_4$ D: $CpCo(CO)_2$.
[b] 1.1 equiv Cat. C/toluene/Δ.
[c] 5% M Cat. D/*n*-decane/140 °C.
[d] 1 equiv Cat. D/*n*-decane/140 °C.
[e] 7% M Cat. A/toluene/Δ.
[f] 20% M Cat. A/toluene/A.
[g] 5% M Cat. B/toluene/65 °C.
[h] 1% M Cat. B/toluene/65 °C.
[i] 0.05 equiv Cat. B/toluene/90 °C/*n*-Bu_4NBr.
[j] 1.1 equiv Cat. C/toluene/90 °C/*n*-Bu_4NBr.

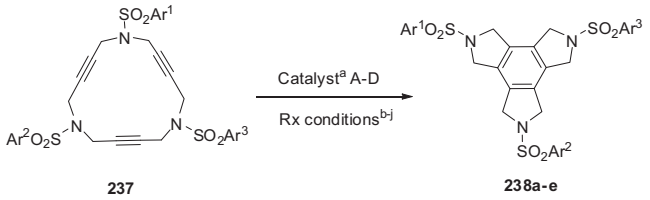


12 **233** **234** **235** **236**

R^1 = C_6H_4-Me-*p* or C_6H_4-OMe-*p*, R^2 = H

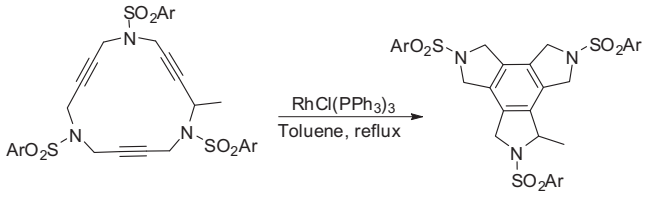
R^1 = C_6H_4-Me-*p*, yield = 25% **234**:**235**:**236** (3:1:3)
R^1 = C_6H_4-OMe-*p*, yield = 28% **234**:**235**:**236** (1:1:1)

Scheme 97. Synthesis of pyridino-macrocycles by cocyclization of α,ω-alkynenitrile with monoalkynes.



237 **238a-e**

Scheme 98. Synthesis of dipyrroloisoindoles by intramolecular cyclotrimerization of 15-membered macrocyclic triynes.



239 Ar = 4-MeC_6H_4- **240**

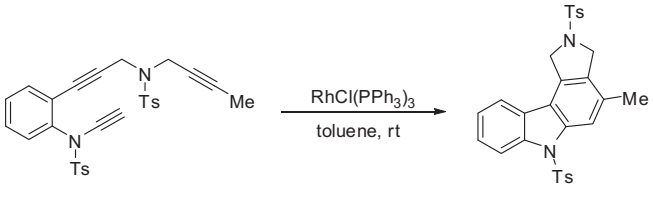
Scheme 99. Synthesis of 1-methyldipyrroloisoindole by intramolecular cyclotrimerization of methyl-substituted 15-membered macrocyclic triyne.

3.3.2. *Fused [5–6–6–5] systems: two heteroatoms [1:1].*

3.3.2.1. Pyrrolocarbazole. A triyne bearing an aniline tether **241** quantitatively underwent intramolecular cyclotrimerization in the presence of Wilkinson's catalyst to give pyrrolocarbazole **242** in 99% yield (Scheme 100).[122]

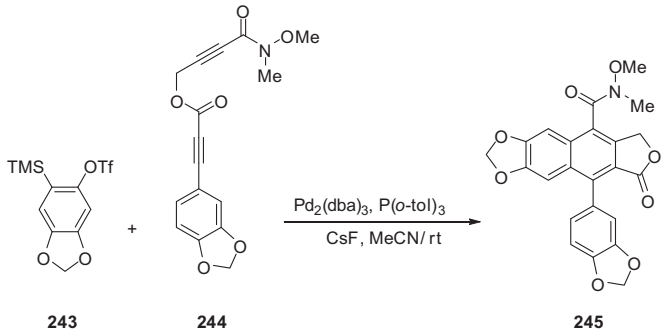
3.3.3. *Fused [5–6–6–5] systems: three heteroatoms [1:2].*

3.3.3.1. Furo[3′,4′:6,7]naphtho[2,3-d][1,3]dioxole. Sato and Mori have recently employed a cyclotrimerization reaction between diyne **244** and an aryne (generated in situ from aryl triflate **243** bearing an *o*-trimethylsilyl group) to give a 61% yield of **245** as a key step in the synthesis of taiwanins C and E (Scheme 101).[135]



241 **242**

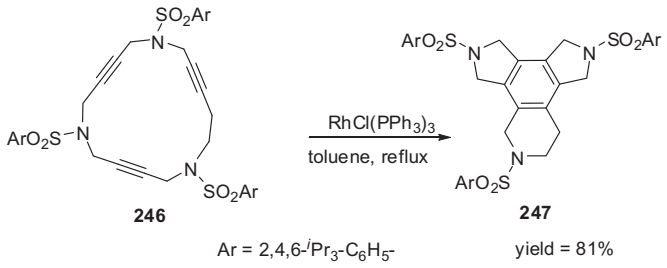
Scheme 100. Synthesis of pyrrolocarbazole by intramolecular cyclotrimerization of triyne.



Scheme 101. Synthesis of furonaphthodioxole by cocyclization of benzyne with diyne.

3.3.4. Fused [5–5–6–6] systems: three heteroatoms [1:1:1].

3.3.4.1. Dipyrrolo[3,4-f:3′,4′-h]isoquinoline. A fused tetracycle **247** was satisfactorily prepared in 81% yield by intramolecular [2+2+2] cycloadditions of the 16-membered triynic macrocycle **246** under $RhCl(PPh_3)_3$ catalysis (Scheme 102).[134]

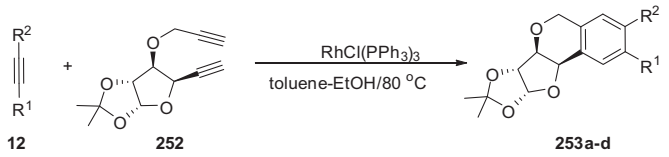


Scheme 102. Synthesis of dipyrroloisoquinoline by intramolecular cyclotrimerization of a 16-membered macrocyclic triyne.

Solà and Roglans et al. reported that the 25-membered azamacrocycle **248** chemoselectively afforded the cyclotrimerized compound **249** resulting from the reaction of three adjacent alkynes instead of the cyclotrimerization between non-adjacent triple bonds. On the other hand, the 20-membered macrocycle **250**, which is characterized by lack of reactivity, did not lead to the expected cyclotrimerized compound **251** (Scheme 103). The difference in reactivity of the 15-, 20-, and 25-membered macrocycles has been rationalized using density functional theory calculations.[136]

3.3.5. Fused [5–5–6–6] systems: four heteroatoms [2:1:1].

3.3.5.1. 6,7,9,10-Tetraoxapentaleno[2,1-a]naphthalene. Cyclotrimerization of diyne **252** with symmetrical monoyne **12** in the presence of Wilkinson's catalyst afforded tetraoxapentalenonaphthalenes **253a–d** in 45–65% yield (Scheme 104, Table 48).[137,138]



Scheme 104. Synthesis of chiral trioxapentalenonaphthalenes by cocyclization of chiral diyne with symmetrical monoalkynes.

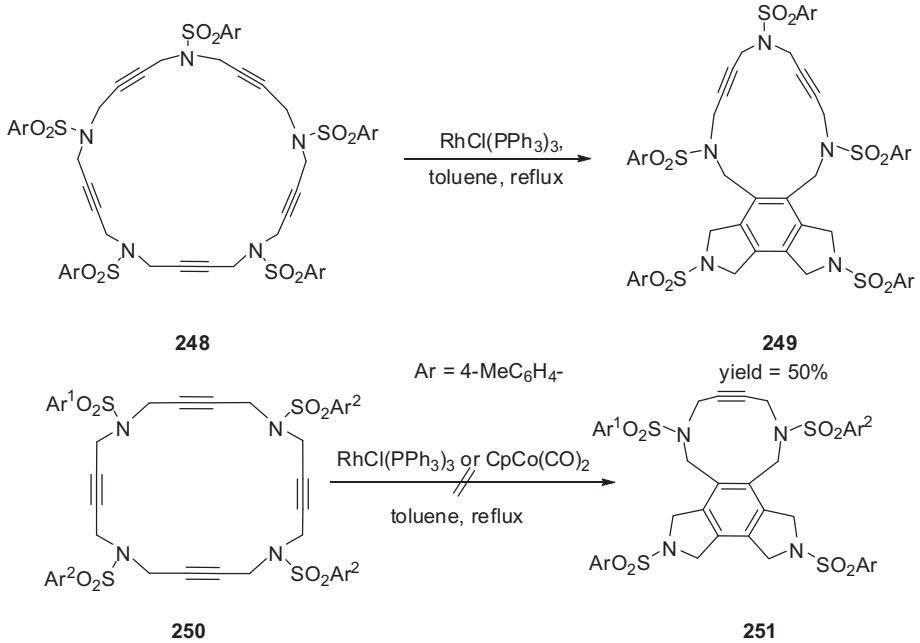
Table 48

Entry	**12** $R^1=R^2$	Product	Yield (%)
1	CH_2OH	**253a**	61
2	H	**253b**	65
3	CH_2OAc	**253c**	57
4	COOMe	**253d**	45

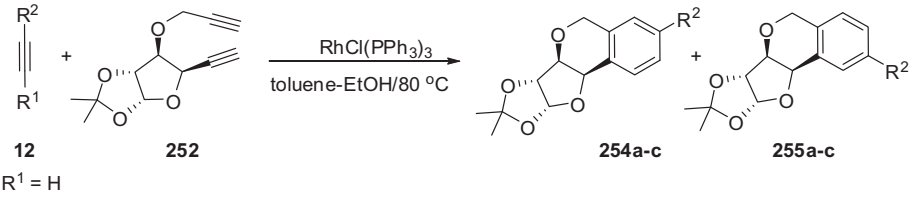
Under similar conditions, cyclotrimerization of **252** with unsymmetrical alkynes **12** (R^1=H) gave inseparable regiomeric mixtures of the tetracyclic products **254a–c** and **255a–c** in moderate-to-good yields (Scheme 105, Table 49).[137,138]

3.3.6. Fused [6–5–6–6] systems: one bridgehead heteroatom.

3.3.6.1. Isoindolo[1,2-a]isoquinoline. In the presence of 1 mol % Cp*RuCl(cod), 1,6-diyne **256** reacted with acetylene (**12**, $R^1=R^2$=H) (1 atm) at rt for 30 min to give the isoindoloisoquinoline **257** in 82% yield (Scheme 106).[96]

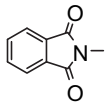


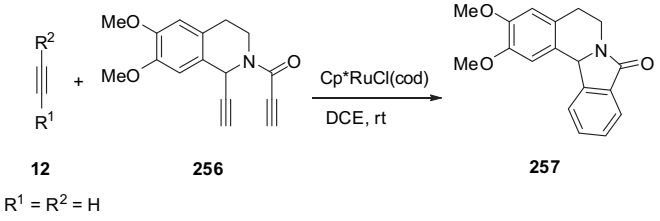
Scheme 103. Attempted intramolecular cyclotrimerization of 20- and 25-membered macrocyclic triynes.



Scheme 105. Synthesis of chiral trioxapentalenonaphthalene regioisomers by cocyclization of chiral diyne with unsymmetrical monoalkynes.

Table 49

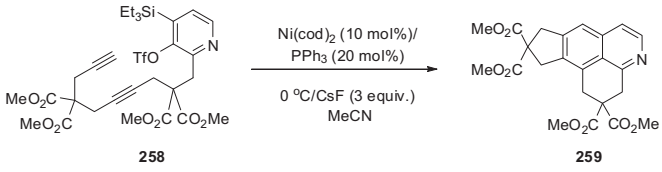
Entry	12	254/255	Yield (%) (254:255)
	R^2	Products	
1	Ph	**254a**/**255a**	72 (1:3)
2		**254b**/**255b**	67 (1:3)
3	n-$C_{14}H_{29}$	**254c**/**255c**	49 (1:1)



Scheme 106. Synthesis of isoindoloisoquinoline by cocyclization of 1,6-diyne with acetylene.

3.3.7. ortho- and peri Fused [5–6–6–6] systems: one heteroatom.

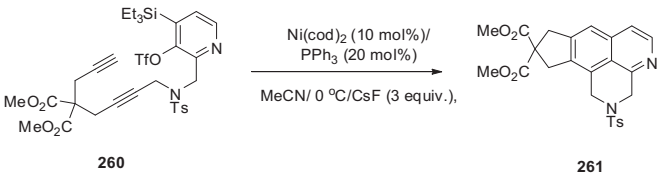
3.3.7.1. Hexahydroindeno[6,5,4-de]quinoline. Iwayama and Sato reported on a metal-catalyzed intramolecular [2+2+2] cycloaddition of a diyne and 3,4-pyridyne, generated *in situ* from silyl-triflate precursor of substrate **258**, providing quinoline derivative **259**. The reaction proceeded by the addition of a solution of diyne **258** to a mixture of $Ni(cod)_2$ (10 mol %), PPh_3 (20 mol %), and CsF (3 equiv) in MeCN. After the usual work up, the quinoline derivative **259** was obtained in 75% yield (Scheme 107).[124]



Scheme 107. Synthesis of indeno[6,5,4-*de*]quinoline by Ni-catalyzed intramolecular cyclotrimerization of triyne.

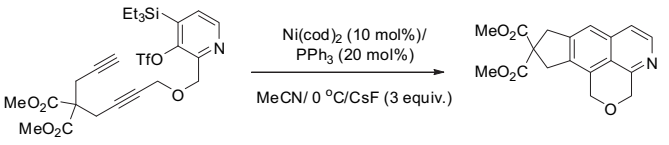
3.3.8. ortho- and peri Fused [5–6–6–6] systems: two heteroatoms [1:1]. 3.3.8.1. Hexahydroindeno[6,5,4-de][1,7]naphthyridine. Iwayama and Sato succeeded in synthesizing various polycyclic skeletons containing an isoquinoline subunit in good yields utilizing the intramolecular [2+2+2] cycloaddition of substrates **260** having a diyne and a 3,4-pyridyne in a tether by using a nickel(0) catalyst.

In the intramolecular reaction, synchronous coordination of the diyne part and the pyridyne part to the nickel complex would be important. The existence of a protected nitrogen, such as a tosyl amide in the tether did not affect the reaction, producing the polycyclic isoquinoline derivative **261** in 69% yield (Scheme 108).[124]



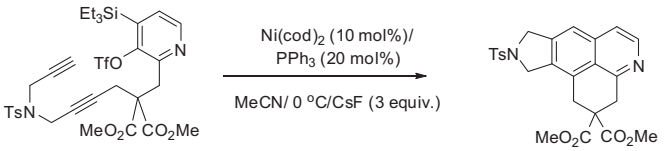
Scheme 108. Synthesis of indeno[6,5,4-*de*][1,7]naphthyridine by Ni-catalyzed intramolecular cyclotrimerization of triyne.

3.3.8.2. Tetrahydro-1H-cyclopenta[g]pyrano[3,4,5-ij]isoquinoline. The reaction of the substrate **262**, having an oxygen in the tether, under the above-mentioned optimized conditions gave the corresponding product **263** in 41% yield (Scheme 109). It was speculated that coordination of an oxygen atom to the nickel catalyst retarded the reaction, resulting in a lower yield.[124]



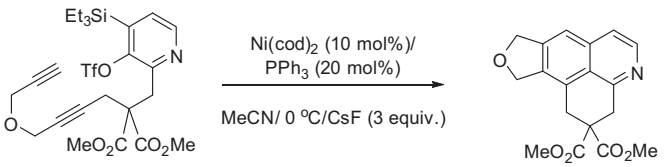
Scheme 109. Synthesis of cyclopenta[*g*]pyrano[3,4,5-*ij*]isoquinoline by Ni-catalyzed intramolecular cyclotrimerization of triyne.

3.3.9. ortho- and peri Fused [6–5–6–6] systems: two heteroatoms [1:1]. 3.3.9.1. Hexahydroisoindolo[6,5,4-de]quinoline. Iwayama and Sato reported the synthesis of hexahydroisoindolo[6,5,4-*de*]quinoline **264** in 62% yield by Ni-catalyzed intramolecular cyclotrimerization of triyne **265** (Scheme 110).[124]



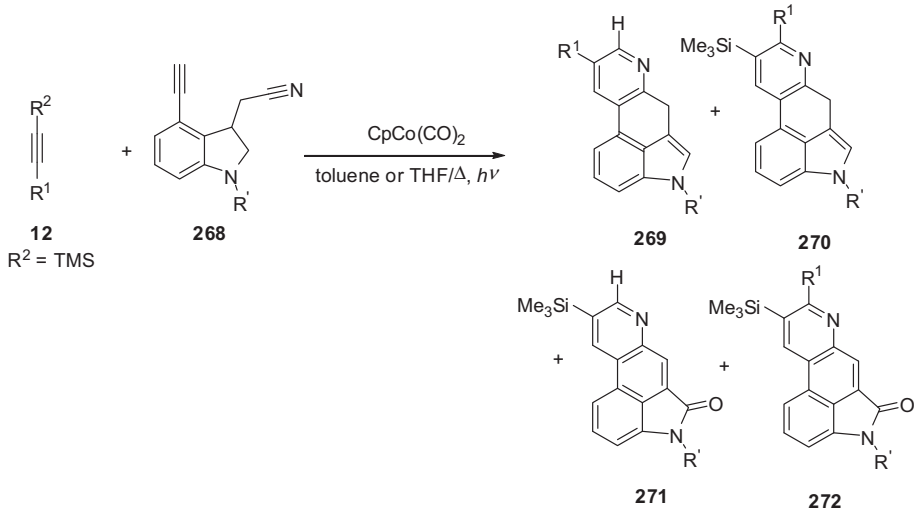
Scheme 110. Synthesis of isoindolo[6,5,4-*de*]quinoline by Ni-catalyzed intramolecular cyclotrimerization of triyne.

3.3.9.2. Tetrahydro-1H-isobenzofuro[6,5,4-de]quinoline. Cyclotrimerization of the substrate **266** using a nickel(0) catalyst gave a 43% yield of the corresponding isobenzofuro[6,5,4-*de*]quinoline derivative **267** (Scheme 111).[124]



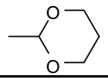
Scheme 111. Synthesis of isobenzofuro[6,5,4-*de*]quinoline by Ni-catalyzed intramolecular cyclotrimerization of triyne.

3.3.9.3. Indolo[4,3-fg]quinoline. Vollhardt et al. reported that the cocyclization of 4-ethynyl-3-indoloacetonitriles **268** with alkynes **12** in the presence of $CpCo(CO)_2$ led to the formation of ergoline derivatives **269**–**272**. The co-oligomerization reaction exhibited only modest regioselectivity when the trimethylsilyl group on **12** is paired with a substituent endowed with electron-withdrawing qualities (Scheme 112, Table 50).[60]

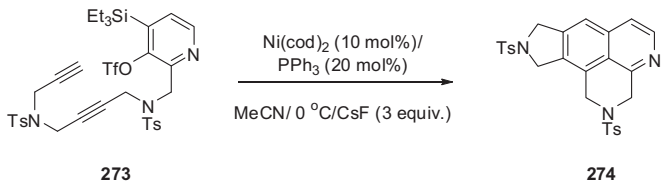


Scheme 112. Synthesis of indoloquinolines by cocyclization of alkynenitriles with monoalkynes.

Table 50

Entry	12	268	Yield (%)			
	R^1	R′	269	270	271	272
1	$SiMe_3$	Me	6	0	33	Trace
2	Me	Me	6	0	12	0
3	$CONEt_2$	Me	0	13	9	Trace
4	H	H	17	33	Trace	Trace
5	CH_2OH	H	38	11	0	0
6		H	10	41	Trace	Trace

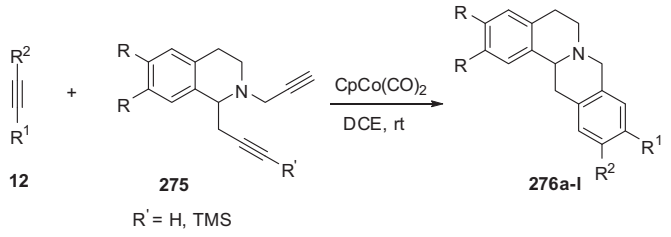
3.3.10. ortho- and peri Fused [6–5–6–6] systems: three heteroatoms [1:1:1]. 3.3.10.1. Hexahydroisoindolo[6,5,4-de][1,7]naphthyridine. Hexahydroisoindolo[6,5,4-*de*][1,7]naphthyridine **274** was obtained in 59% yield by Ni-catalyzed intramolecular [2+2+2] cycloaddition of substrate **273** having a diyne and 3,4-pyridyne, generated *in situ* from silyl-triflate precursor, in a tether (Scheme 113).[124] The reaction proceeded in acetonitrile at 0 °C in the presence of $Ni(cod)_2$ (10 mol %), PPh_3 (20 mol %), and CsF (3 equiv).



Scheme 113. Synthesis of isoindolo[6,5,4-*de*][1,7]naphthyridine by Ni-catalyzed intramolecular cyclotrimerization of triyne.

3.3.11. Fused [6–6–6–6] systems: one bridgehead heteroatom.

3.3.11.1. Isoquinolino[3,2-a]isoquinoline. Vollhardt et al. reported that $CpCo(CO)_2$ catalyzed the cocyclization of l,2-bis(propargyl)-l,2,3,4-tetrahydroisoquinolines **275** with alkynes **12** to give isoquinolino[3,2-*a*]isoquinolines **276a**–**l** in 2.5–100% isolated yield (Scheme 114, Table 51).[139]



Scheme 114. Synthesis of isoquinolinoisoquinolines by cocyclization of dialkynes with monoalkynes.

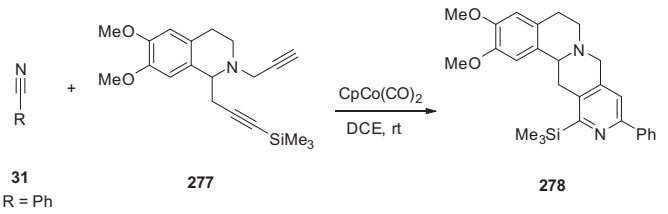
Table 51

Entry	12		275	Product	Yield (%)
	R^1	R^2	R		
1	MeO	MeO	MeO	**276a**	58
2	H	MeO	MeO	**276b**	75
3	TMS	Me_3CCH_2O	MeO	**276c**	61
4	H	Me_3CCH_2O	MeO	**276d**	99
5	^{n}Bu	H	MeO	**276e**	2.5
6	H	^{n}Bu	MeO	**276f**	2.5
7	TMS	TMS	H	**276g**	87
8	TMS	TMS	MeO	**276h**	93
9	H	H	MeO	**276i**	—
10	MeO	TMS	MeO	**276j**	34
11	TMS	MeO	MeO	**276k**	34
12	MeO	H	MeO	**276l**	100

3.3.12. Fused [6–6–6–6] systems: one bridgehead heteroatom with one extra heteroatom.

3.3.12.1. Isoquinolino[2,1-b][2,6]naphthyridine. Diyne **277** cyclotrimerizes regioselectively with benzonitrile **31** (R=Ph) in the

presence of $CpCo(CO)_2$ to give isoquinolino[2,1-*b*][2,6]naphthyridine **278** in 74% yield (Scheme 115).[139]



Scheme 115. Synthesis of isoquinolinonaphthyridine by cocyclization of diyne with benzonitrile.

4. Conclusions

Heterocyclic systems are of immense importance biologically and industrially, and are essential to life in various ways. They can be synthesized by a variety of synthetic approaches, among which the transition-metal-catalyzed concerted cycloaddition reactions seem to be the most attractive methodologies.

We have presented in this review the main strategies for the synthesis of many kinds of fused heterocycles by metal-mediated [2+2+2] cyclotrimerization of alkynes and/or nitriles as well as their specific syntheses. Late transition metals, such as Co, Ni, Rh, Ru, Pd, Ir, are commonly utilized in the synthesis of these systems. The reactions generally proceed *via* the formation of a metallacyclopentadiene intermediate followed by insertion of another unsaturated bond. The reactions described in this review clearly demonstrate the high ability of the transition-metal catalysts to carry out the regioselective preparation of fused heterocycles. The highly regioselective formation of these compounds has been mainly achieved in intramolecular reactions, but has also been observed in some intermolecular reactions. The fused heterocycles mentioned in this review are arranged in an organized manner with respect to the type of heterocyclic systems.

We hope that this review will be useful not only for organic synthetic and organometallic chemists, but also for heterocyclic and natural product synthetic chemists.

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