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Efficient Generation of Pyridines by Ruthenium Carbene Mediated [2 + 2 + 2] Cyclotrimerization

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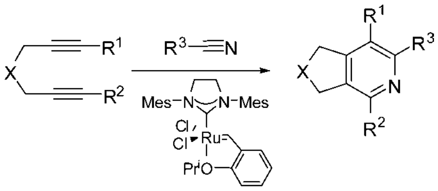
ABSTRACT



Ru-[III]

Hoveyda–Grubbs' catalyst is able to catalyze crossed [2 + 2 + 2] cyclotrimerizations of diynes with nitriles. Pyridines are obtained with excellent yields when using activated nitriles and low to moderate yields with nonactivated nitriles which are unreactive under previously described ruthenium catalyzed reaction conditions. Both terminal and internal alkynes give the reaction using this experimental procedure.

Metal catalyzed [2 + 2 + 2] cycloadditions allow the synthesis of carbo- and heterocycles, involving the formation of several C–C bonds in a single step. This elegant, atom-efficient, and group tolerant process is catalyzed by complexes of more than 17 metals.[1] The transition-metal-mediated cyclocotrimerization of alkynes with cyano groups was first pioneered by Wakatsuki and Yamazaki followed by Bönnemann.[2] Afterward Vollhardt's group reported cycloadditions of diynes and alkynenitriles leading to pyridines, mediated by cobalt. Later, other groups developed mild and catalytic reaction conditions using other metals and asymmetric reactions mainly en route to axially chiral products. De novo construction of pyridine ring systems is achieved now by reaction of diynes and oligoynes with nitriles, by completely intermolecular reactions between acetylenes and nitriles, or by reactions of alkynenitriles with alkynes. The reaction tolerates a wide variety of functional groups in the substrates, giving access to densely functionalized pyridinic products.[3]

With regard to the catalysts generally used for pyridine asembly through [2 + 2 + 2] cyclizations, Co complexes of the type [CpCoL$_2$] (L = CO, PR$_3$, olefin) have been extensively studied[4] as well as Rh,[5] Fe,[6] and Ni[7] catalysts.

Ruthenium catalysts such as [CpRuCl(cod)] are able to catalyze trimerization of alkynes[8] and are useful in the [2 + 2 + 2] cycloaddition of 1,6-diynes with nitriles, isocyanates,

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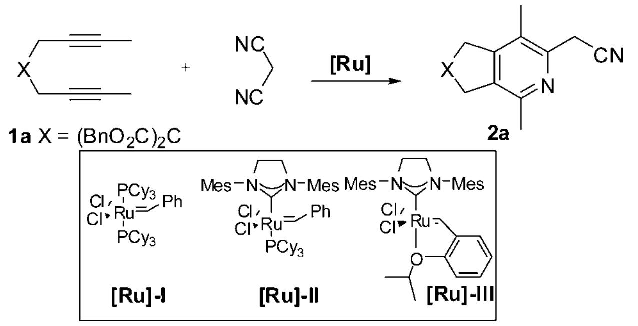
and isothiocyanates to afford pyridines, bicyclic pyridones, and thiopyridones in good yields.[9] In particular, dicyanides, cyanamides, and halonitriles exhibited exceptionally high reactivity toward the [Cp*RuCl(cod)] catalyzed cycloaddition with 1,6-diynes leading to bicyclic pyridines under mild conditions.[10]

There are a few precedents in using Grubbs' first generation catalysts **[Ru]-I** to mediate in cyclotrimerization [2 + 2 + 2] reactions for the synthesis of benzene rings.[11] Blechert et al. reported for the first time that **[Ru]-I** is an efficient catalyst for the intramolecular cyclotrimerization of alkynes. A cascade metathetic mechanism was postulated in these examples where vinyl carbene complexes would be the reactive intermediates.[12] We have recently published the use of second generation Grubbs' catalysts **[Ru]-II** and reusable Hoveyda–Grubbs' complex **[Ru]-III** for the synthesis of fused benzenes.[13]

We present here the synthesis of a wide variety of highly functionalized pyridines, obtained for the first time through an easy experimental procedure based on ruthenium carbene catalysts.

Table 1. Selection of Reaction Conditions for the Crossed Cyclotrimerization Reaction of **1a** with Malononitrile



entry	solvent	temp (°C)	time	cat. (mol %)	yield (%)[a] 1a	yield (%)[a] 2a
1	DCE	rt	48 h	5	70	30
2	DCE	80	16 h	5	–	78
3	DCE	90	16 h	5	–	92
4	acetone	75	16 h	5	–	85
5	MeCN	90	16 h	5	80	–
6	EtOAc	90	16 h	5	–	85
7	dioxane	90	16 h	5	–	47
8	DCE	90	1 h	5	–	95
9	DCE	90	15 min	5	–	99
10	DCE	90	15 min	2	27	73
11	DCE	90	15 min	5[b]	55	15
12	DCE	90	15 min	5[c]	–	80
13	DCE	90, rt	10 min, 48 h[d]	5	18	78
14	DCE	90, rt	10 min, 16 h[e]	5	80	–

[a] Reactions were conducted in a sealed tube except entries 1–2 (entry 2 under reflux), at 66.6 mM concentration of diyne with 5 equiv of nitrile. [b] With **[Ru]-I** as the catalyst. [c] With **[Ru]-II** as the catalyst. [d] Catalyst is dissolved and heated at 90 °C in a sealed tube for 10 min and then cooled to rt, and reagents were added and then stirred at rt for 48 h. [e] Catalyst and nitrile are dissolved and heated at 90 °C in a sealed tube for 10 min and then cooled to rt, and diyne was added and then stirred at rt for 16 h.

In order to optimize the reaction, diyne **1a** was reacted with malononitrile under a variety of reaction conditions (Table 1). The first tests were carried out in DCE with 5 mol % of catalyst **[Ru]-III** and 5 equivalents of nitrile. They showed the need for heating to achieve total conversion and reach good yields of product **2a** (entries 1 and 2, Table 1). The reaction was then performed in a sealed tube which increased the yield to 92% (entry 3). This improvement may be due to an increase in the population of the reactive conformation of the diyne under higher pressure. Next we check different solvents under these latter conditions (acetone, MeCN, EtOAc, dioxane, entries 4–7). We observed good results except for MeCN, possibly due to the poor solubility of the catalysts. However, DCE continued to be the best choice. Entries 8 and 9 show reactions in which reaction time was reduced to 1 h and 15 min respectively which allowed the best results (99%, entry 9). However when reducing the catalyst loading to 2 mol % the reaction was not complete (entry 10). Next, for comparison, we used our best conditions (5 equiv of nitrile, in DCE at 90 °C, sealed tube), using **[Ru]-I** and **[Ru]-II** as the catalysts (entries 11–12). The first generation Grubbs' catalyst proceeded with low yield while **[Ru]-II** gave a good result slightly below to that achieved with **[Ru]-III**. The ability of **[Ru]-III** to catalyze these cyclotrimerizations

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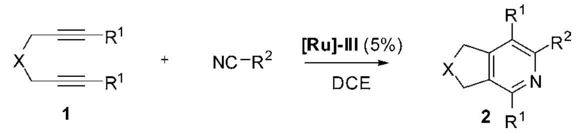
(14) **General procedure for synthesis of pyridines.** Over a solution of the diyne and the nitrile in 2 mL of 1,2-dichloroethane contained in a pressure flask, a solution of **[Ru]-III** in 2 mL of the same solvent was added. The flask was sealed and introduced in a 90 °C bath, and the resulting mixture was stirred until the reaction was completed (TLC). After cooling the flask to rt the reaction mixture was filtered through celite, the solvent was eliminated under reduced pressure, and the residue was purified by column chromatography. Preparation of **dibenzyl 3-(cyanomethyl)-1,4-dimethyl-5*H*-cyclopenta[*c*]pyridine-6,6(7*H*)-dicarboxylate, 2a.** From **1a** (0.100 g, 0.260 mmol), malononitrile (0.085 g, 1.290 mmol) and **[Ru]-III** (0.008 g, 0.013 mmol), following the general procedure for the synthesis of pyridines (reaction time: 15 min) and upon purification by column chromatography (Hex/EtOAc 4:1 to 2:1), 0.117 g (99%) of **2a** is obtained as a white solid (mp = 105–106 °C). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.33–7.31 (m, 6H, Ph), 7.24–7.21 (m, 4H, Ph), 5.14 (s, 4H, 2×CH_2O), 3.81 (s, 2H, CH_2CN), 3.56 (s, 2H, CH_2C), 3.55 (s, 2H CH_2C), 2.38 (s, 3H, CH_3), 2.22 (s, 3H, CH_3). ^{13}C NMR (75 MHz, CDCl$_3$) δ 170.8, 151.2, 149.7, 146.6, 135.1, 134.1, 128.6, 128.5, 128.1, 125.1, 116.9, 67.8, 59.7, 39.7, 38.9, 24.7, 21.6, 14.7. IR (KBr): 2240, 1732, 1586 cm^{-1}. Anal. Calcd for C$_{28}$H$_{26}$N$_2$O$_4$: C, 73.99; H, 5.77; N, 6.16. Found: C, 73.80; H, 5.83; N, 6.20.

possibly has to do with its transformation mediated by heat into a different species. Therefore we checked if, after the catalysts modification, the [2 + 2 + 2] reaction could proceed at rt. Thus, after heating the catalyst during 10 min at 90 °C in a sealed tube we added the reagents and stirred the mixture at rt (entry 13). After 48 h the reaction was not complete, and 78% of **2a** was isolated recovering 18% of the starting diyne. On the other hand, heating of the catalyst at high temperature with the nitrile and further addition of the diyne at rt precluded the reaction (entry 14). This result could be due to the formation of an inactive species upon reaction of the metal with the nitrile preventing its coordination with the diyne.

Once the best conditions for the cyclotrimerization of diynes with alkynes were selected, we studied the scope of the process reacting different diynes with nitriles.[14] Diynes **1a**–**e** were reacted with dinitriles, α-halonitriles, benzonitriles, cyanoformate, and benzoylcyanide (Table 2). The reactions with malononitrile (entries 1–5) gave good to excellent yields (71–99%). The exception was dipropargyl ether **1e** which gave 51% of pyridine **2e** along with 21% of the diyne dimer **3**. This diyne is very reactive and has a great tendency to oligomerize or polymerize as we observed in previous works.[13] Saa[10b] and Yamamoto's groups[9c,10a] have studied thoroughly the scope of the pyridine synthesis through CpRuCl-catalyzed [2 + 2 + 2] cyclotrimerization reactions. These groups described that only dinitriles (that could include further unsaturation, e.g. alkylidene, arene), nitriles which incorporate electron-deficient and -rich substituents, and α-halonitriles reacted with diynes. This especially good performance, in contrast with the behavior of benzonitriles or simple aliphatic nitriles, is thought to be due to an assisting effect of the additional functional group. These groups observed that in the cycloaddition reaction with dicyanides only one nitrile group reacted, leaving the other one unchanged, exactly what we have observed with **[Ru]-III**. Thus we reacted **1a** with benzodinitrile (entry 6) obtaining an excellent yield of **2f**. On the other hand, fumaronitrile (entries 7–9) and succinonitrile (entry 10) were less reactive giving moderate yields (43–64%) of the pyridines but with recovery of the starting material. In addition, we reacted chloro- and dichloroacetonitrile with **1a** and **1d** which gave the chloromethyl pyridines **2k**, **2l**, and dichloropyridine **2m** in moderate to good yields (entries 11–13), whereas diyne **1e** (entry 14) gave a poor yield of **2n**. Reactions of **1a** and **1d** with ethyl cyanoformate gave pyridines **2o** and **2p** with good yields (entries 15–16). Product **2q** was prepared with moderate yield using benzoylcyanide as a reagent (entry 17). Although previous reports in the literature[9,10] were discouraging in the consecution of Ru-catalyzed cyclotrimerizations of diynes with benzonitriles, we tried our conditions with diynes **1a**–**b** and benzonitrile or *p*-methylbenzonitrile. The results were poor with 5 mol % equiv of catalyst (entry 18) but could be increased up to a 22–30% yield of pyridine if the catalyst loading was doubled (entries 19–21). These results although not satisfactory have not been described previously in the literature with typical Ru catalysts and may imply a higher activity of the active species in our procedure.

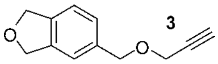
Table 2. Scope of the Crossed Cyclotrimerization Reaction



X = $(BnO_2C)_2C$, $(EtO_2C)_2C$, TsN, O,
R^1 = Me, H;
R^2 = CH_2CN, *p*-C_6H_4-CN, CH=CH-CN, CH_2Cl, $CHCl_2$, Ph, *p*-C_6H_4-CH_3, CO_2Et, COPh, $CH_2\underline{CH_2}CN$

entry	diyne	X	R^1	R^2	time (h)	prod.	yield (%)[a,b]
1	**1a**	$(BnO_2C)_2C$[c]	Me	CH_2CN	0.25	**2a**	99
2	**1b**	$(EtO_2C)_2C$	Me	CH_2CN	0.25	**2b**	99
3	**1c**	TsN	Me	CH_2CN	0.5	**2c**	83
4	**1d**	$(BnO_2C)_2C$[c]	H	CH_2CN	0.25	**2d**	71
5	**1e**	O	H	CH_2CN	0.5	**2e**	51[d]
6	**1a**	$(BnO_2C)_2C$[c]	Me	*p*-C_6H_4CN	19	**2f**	94
7	**1a**	$(BnO_2C)_2C$[c]	Me	CH=CHCN	1.5	**2g**	58 (40)[e]
8	**1c**	TsN	Me	CH=CHCN	0.5	**2h**	43 (47)[e]
9	**1d**	$(BnO_2C)_2C$[c]	H	CH=CHCN	1	**2i**	63 (18)[e]
10	**1a**	$(BnO_2C)_2C$[c]	Me	CH_2 CH_2CN	1	**2j**	64 (24)[e]
11	**1a**	$(BnO_2C)_2C$[c]	Me	CH_2Cl	1	**2k**	79
12	**1d**	$(BnO_2C)_2C$[c]	H	CH_2Cl	1	**2l**	46
13	**1d**	$(BnO_2C)_2C$[c]	H	$CHCl_2$	1	**2m**	63
14	**1e**	O	H	$CHCl_2$	0.5	**2n**	24
15	**1a**	$(BnO_2C)_2C$[c]	Me	CO_2Et	1	**2o**	68
16	**1d**	$(BnO_2C)_2C$[c]	H	CO_2Et	1	**2p**	74
17	**1a**	$(BnO_2C)_2C$[c]	Me	COPh	1	**2q**	49
18	**1b**	$(EtO_2C)_2C$	Me	Ph	16	**2r**	11
19	**1b**	$(EtO_2C)_2C$	Me	Ph	16	**2r**	22[f]
20	**1a**	$(BnO_2C)_2C$[c]	Me	Ph	16	**2s**	30[f]
21	**1a**	$(BnO_2C)_2C$[c]	Me	*p*-C_6H_4-CH_3	16	**2t**	25[f]

[a] Reactions were conducted in a sealed tube at 66.6 mM concentration of diyne with 5 equiv of nitrile and 5 mol % of **[Ru]-III**. [b] Yield (%) of pure product. [c] Bn = benzyl. [d] 21% of **3** was isolated. [e] Parentheses: yield of starting diyne recovered. [f] 10 mol % of catalyst was used.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The next step was the study of the regioselectivity of the pyridine synthesis with nonsymmetric diynes. Thus, we prepared diynes **1f**–**g** and reacted them with some of the above used nitriles (Scheme 1). The reactions proceeded with excellent yield with malononitrile (**2u**, **2x**) and moderate yields with fumaronitrile (**2v**). On the other hand benzonitrile and the α-halonitriles used produced the corresponding pyridines (**2w**, **2y**, **2z**, and **2α**) with lower yields. In all the examples the regioselectivity was complete

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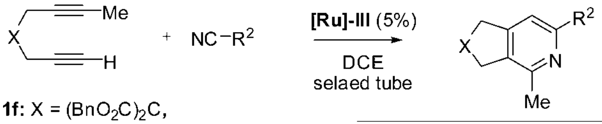
(15) Nonsymmetric diynes are known to give selectively the pyridine with the nitrogen adjacent to the more bulky substituent; see: (a) Zou, Y.; Liu, Q.; Deiters, A. *Org. Lett.* **2011**, *13*, 4352–4355. (b) Gray, B. L.; Wang, X.; Brown, W.; Kuai, C. L.; Schreiber, S. L. *Org. Lett.* **2008**, *10*, 2621–2624. (c) Garcia, P.; Evanno, Y.; George, P.; Sevrin, M.; Ricci, G.; Malacria, M.; Aubert, C.; Gandon, V. *Org. Lett.* **2011**, *13*, 2030–2033.

in favor of the less hindered product as observed in most studies with nonsymmetric diynes.[15]

Scheme 1. Crossed Cyclotrimerization of Nonsymmetric Diynes

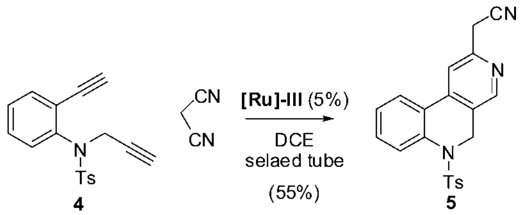


1f: X = $(BnO_2C)_2C$,
1g:X = TsN,

starting	R^2	yield (%)
1f	CH_2CN	**2u**: 93
1f	CH=CH-CN	**2v**: 67
1f	Ph	**2w**: 28
1g	CH_2CN	**2x**: 83
1g	CH_2Cl	**2y**: 23
1g	CH_2Br	**2z**:16
1g	$CHCl_2$	**2α**: 41

When using Ru catalysts in the [2 + 2 + 2] cyclotrimerization of diynes, we have found no precedents of the formation of fused six-membered rings upon reaction of 1,7-diynes. We envisioned the possibility of reacting a benzene-templated 1,7-diyne (**4**), under our conditions, and were pleased to obtain the benzonaphthyridine **5** in good yield. This product was obtained in a total regioselective manner as the isomer depicted in Scheme 2.

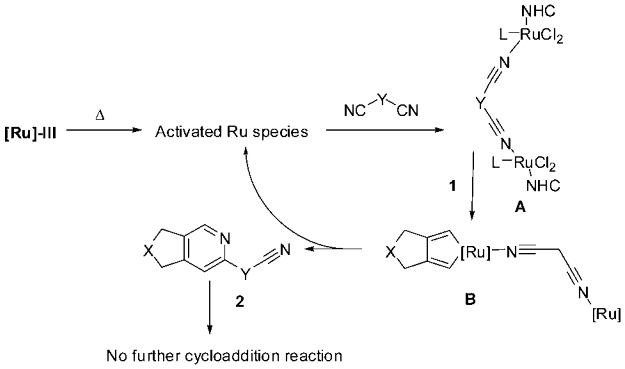
Scheme 2. Synthesis of Benzonaphthyridine **5**



4 **5**

With all these results in hand it is noteworthy the similar behavior that **[Ru]-III** catalysis has with regard to CpRuCl-based complexes. Provided that ruthenium carbene complexes have the tendency to be transformed in other species by loss of the phosphine and the benzylidene moieties, it is possible that, under our conditions, the carbene is transformed into a species structurally related with the aforementioned CpRuCl-based complexes. This would be in contrast with the mechanism assumed previously for [2 + 2 + 2] cyclotrimerizations of alkynes catalyzed by the **[Ru]-I** catalyst which was based on a cascade metathetic process.[12] Our results point to a possible different pathway that could be similar to the one depicted in Scheme 3 which was proposed by Varela and Saa for CpRuCl-type complexes.[16] Heating the initial **[Ru]-III** complex produces a new activated species as observed by us and other groups,[17] capable of coordination with dinitriles to give the dinuclear complex **A**. This complex allows formation of the intermediate ruthenacyclopentadiene **B** by reaction with diyne **1**. Pyridine **2** would be formed by insertion of the Ru-bound cyano group into the Ru−C bond.

Scheme 3. Possible Reaction Course for the Pyridine Formation



In conclusion, we have achieved a new protocol for crossed diyne−nitrile cyclotrimerizations mediated by Hoveyda−Grubbs' complex **[Ru]-III**. This catalytic protocol offers an efficient access to substituted pyridines.

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Supporting Information Available. Experimental procedures, spectroscopic data, and spectra for compounds **1**−**5**. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.