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RHODIUM-CATALYZED [2+2+2] CYCLOADDITION FOR THE SYNTHESIS OF SUBSTITUTED PYRIDINES, PYRIDONES, AND THIOPYRANIMINES

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Abstract – The transition-metal-catalyzed [2+2+2] cycloaddition of alkynes with nitriles is a useful and atom-economical method for the synthesis of substituted pyridines. The use of isocyanates and isothiocyanates in place of nitriles affords substituted pyridones and thiopyranimines, respectively. This review comprehensively covers the [2+2+2] cycloaddition reactions catalyzed by rhodium complexes for the synthesis of substituted pyridines, pyridones, and thiopyranimines. Asymmetric variants of these rhodium-catalyzed [2+2+2] cycloaddition reactions are also described.

CONTENTS

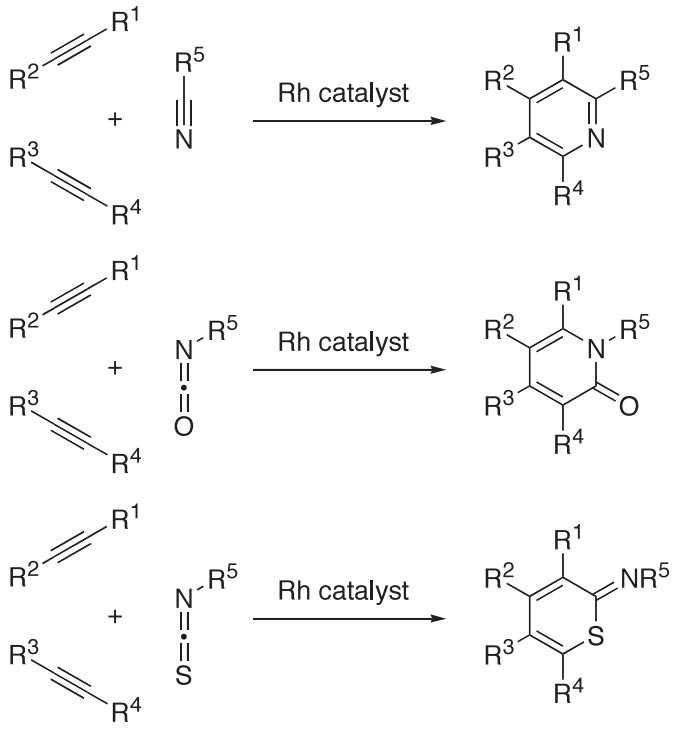
1. INTRODUCTION

The transition-metal-catalyzed [2+2+2] cycloaddition of alkynes with nitriles has been actively investigated to date for the synthesis of substituted pyridines.[1] Because different substituents can be introduced through the formation of the pyridine ring in the transition-metal-catalyzed [2+2+2] cycloaddition, this method is occasionally more advantageous than the conventional substitution or cross-coupling method for the synthesis of densely substituted pyridines. Since the pioneering works by Yamazaki and Wakatsuki,[2] Vollhardt,[3] and Bönnemann,[4] cobalt catalysts have been most widely used for this transformation and a number of useful synthetic applications, including the synthesis of natural products[5] and oligopyridines,[6] have been reported.[7] Not only cobalt complexes but also other transition-metal complexes have been employed. For example, ruthenium complexes are highly efficient catalysts for the reactions between tethered 1,6-diynes and activated nitriles under mild reaction conditions.[8] Nickel,[9] titanium,[10] and tantalum[11] complexes are also effective for this transformation, although stoichiometric amounts of metals are required. Recently, nickel/*N*-heterocyclic carbene complexes[12a,b] and a nickel/Xantphos complex[12c] are found to catalyze the [2+2+2] cycloaddition of internal alkynes with inactivated nitirles at room temperature.

Rhodium-based catalysts are known to be effective catalysts for the [2+2+2] cycloaddition.[13] In 1974, Müller reported the synthesis of substituted benzenes *via* the rhodium-mediated [2+2+2] cycloaddition of alkynes with rhodacyclopentadienes, which were prepared *via* the oxidative cyclization of tethered diynes with Wilkinson's complex [$RhCl(PPh_3)_3$].[14] After this pioneering work, in 1982, Grigg and co-workers reported a catalytic variant of this reaction using Wilkinson's complex as a catalyst.[15] The first example of the rhodium-catalyzed [2+2+2] cycloaddition of alkynes with nitriles was accomplished in 1987 by Ingrosso and co-workers using a cyclopentadienyl rhodium(I) complex as a catalyst.[16] In 2003, Tanaka and co-worker discovered that cationic rhodium(I)/biaryl bisphosphine complexes are highly active and selective catalysts for the [2+2+2] cycloaddition of alkynes.[17] After this discovery, in 2006, the cationic rhodium(I)/biaryl bisphosphine complexes were successfully applied to the [2+2+2] cycloaddition of alkynes with nitriles.[18]

Several reviews already summarized the pyridine synthesis *via* the transition-metal-catalyzed [2+2+2] cycloaddition,[1] while a review covering comprehensively the synthesis of pyridines *via* the rhodium-catalyzed [2+2+2] cycloaddition has not been appeared. Very recently, our research group comprehensively summarized the synthesis of substituted benzenes *via* the rhodium-catalyzed [2+2+2] cycloaddition of alkynes.[13a] In this review, the rhodium-catalyzed [2+2+2] cycloaddition of alkynes with nitriles for the synthesis of substituted pyridines is comprehensively summarized by classifying the reaction patterns (Scheme 1). In addition to the pyridine synthesis, the rhodium-catalyzed [2+2+2]

cycloaddition of alkynes with isocyanates and isothiocyanates for the synthesis of substituted pyridones and thiopyranimines, respectively, is also described (Scheme 1). Finally, asymmetric variants of these reactions catalyzed by the cationic rhodium(I)/axially chiral biaryl bisphosphine complexes are also presented.

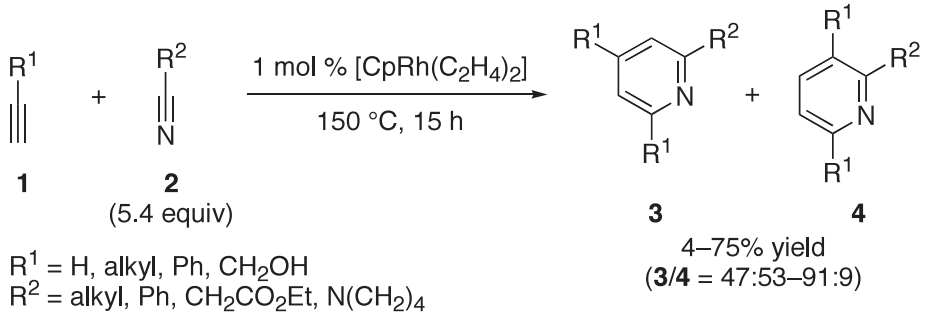


Scheme 1. Rhodium-Catalyzed [2+2+2] Cycloaddition of Alkynes with Nitriles, Isocyanates, and Isothiocyanates

2. SYNTHESIS OF SUBSTITUTED PYRIDINES

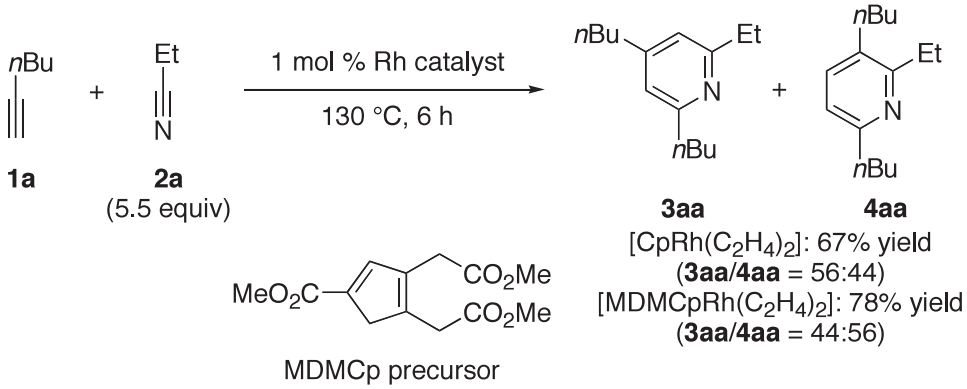
2-1. Intermolecular Reactions

The first report of the rhodium-catalyzed [2+2+2] cycloaddition of alkynes with nitriles is the intermolecular [2+2+2] cycloaddition of terminal alkynes **1** with nitriles **2** catalyzed by a cyclopentadienyl rhodium(I) ethylene complex, $[CpRh(C_2H_4)_2]$, which was reported by Ingrosso and co-workers in 1987 (Scheme 2).[16,19] In order to suppress the undesired formation of benzene derivatives through the homo-[2+2+2] cycloaddition of alkynes, nitrile to alkyne molar ratios higher than 5 were employed. This reaction was moderately regioselective and two regioisomers **3** and **4** were generated. Although this complex is long-lived catalyst, high reaction temperature (150 °C) was required to promote the desired cycloaddition. The use of polymer-anchored cyclopentadienyl rhodium(I) complexes was also reported by Ingrosso and co-workers.[20]



Scheme 2. Rhodium(I)/Cp Complex-Catalyzed [2+2+2] Cycloaddition of Terminal Alkynes with Nitriles

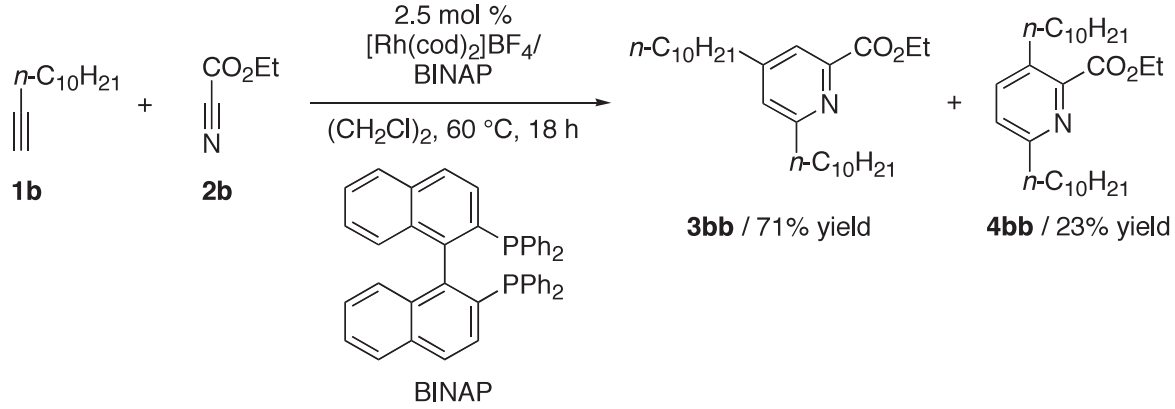
After this report, Costa and co-workers reported that the use of a [MDMCpRh(C_2H_4)$_2$] complex in place of the [CpRh(C_2H_4)$_2$] complex improved the yield of the intermolecular [2+2+2] cycloaddition products **3aa** and **4aa** from terminal alkyne **1a** and propionitrile (**2a**) (Scheme 3).[21]



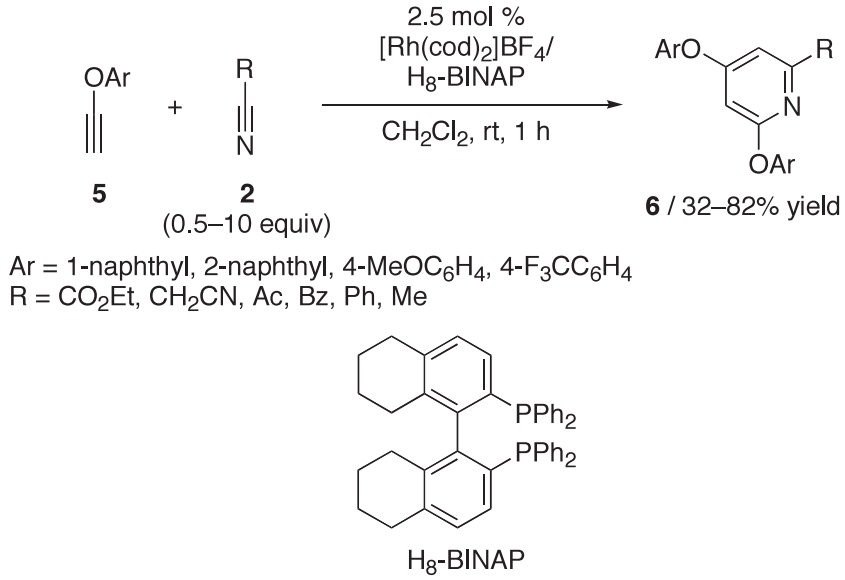
Scheme 3. Rhodium(I)/MDMCp Complex-Catalyzed [2+2+2] Cycloaddition of Terminal Alkyne with Nitrile

In 2006, Tanaka and co-workers reported that a cationic rhodium(I)/BINAP complex was found to be a highly active catalyst for the intermolecular [2+2+2] cycloaddition of alkynes with nitriles under mild reaction conditions.[18] The reaction of terminal alkyne **1b** with electron-deficient nitrile **2b** in the presence of [Rh(cod)$_2$]BF_4/BINAP (2.5 mol %) at 60 °C afforded the corresponding pyridines **3bb** and **4bb** in high yields, and **3bb** was obtained as a major regioisomer (Scheme 4).

As terminal alkyne substrates, aryl ethynyl ethers can also be employed. The intermolecular [2+2+2] cycloaddition of aryl ethynyl ethers **5** with both electron-deficient and electron-rich nitriles **2** in the presence of the cationic rhodium(I)/H_8-BINAP catalyst proceeded at room temperature to give 2,4-diaryloxypyridines **6** as a single regioisomer in good yields (Scheme 5).[22]



Scheme 4. Cationic Rhodium(I)/BINAP Complex-Catalyzed [2+2+2] Cycloaddition of Terminal Alkyne with Nitrile

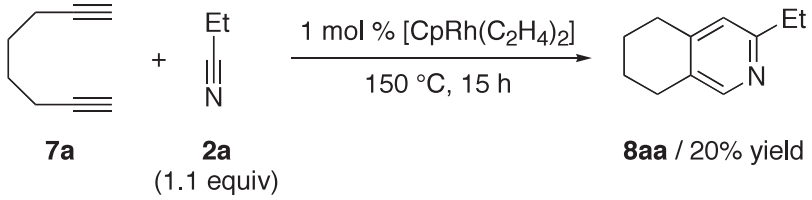


Scheme 5. Cationic Rhodium(I)/H_8-BINAP Complex-Catalyzed [2+2+2] Cycloaddition of Aryl Ethynyl Ethers with Nitriles

2-2. Partially Intramolecular Reactions

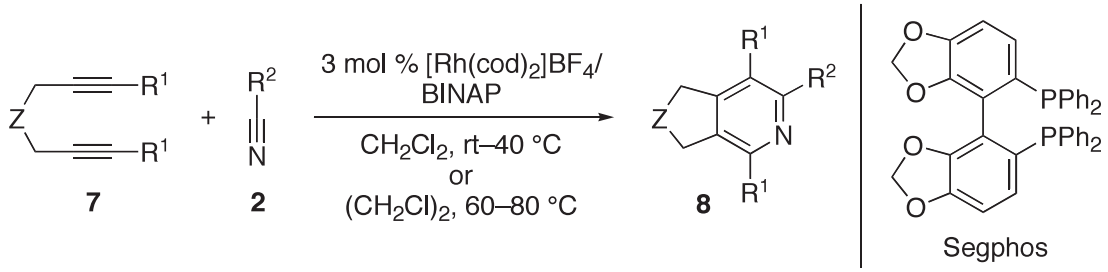
In 1987, Ingrosso and co-workers reported that the cyclopentadienyl rhodium(I) ethylene complex, [$CpRh(C_2H_4)_2$], is able to catalyze the partially intramolecular [2+2+2] cycloaddition of 1,7-diyne **7a** with propionitrile (**2a**) at 150 °C (Scheme 2).[16] However, the desired bicyclic pyridine **8aa** was obtained in low yield due to the formation of unidentified by-products.

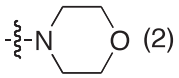
In 2006, Tanaka and co-workers successfully applied the cationic rhodium(I)/biaryl bisphosphine (BINAP, Segphos, and H_8-BINAP) catalysts to the partially intramolecular [2+2+2] cycloaddition of 1,6-diynes with nitriles under mild reaction conditions (Table 1).[18] The reactions of various internal and terminal 1,6-diynes **7b–f** with **2c** afforded the corresponding pyridines in excellent yields (entries 1–5).



Scheme 6. Rhodium(I)/Cp Complex-Catalyzed [2+2+2] Cycloaddition of 1,7-Diyne with Nitrile

Table 1. Cationic Rhodium(I)/biaryl bisphosphine Complex-Catalyzed [2+2+2] Cycloaddition of 1,6-Diynes with Nitriles



entry	**7** (R^1, Z)	**2** (R^2, equiv)	conditions	**8** (% yield[a])
1	**7b** [R^1 = Me, Z = $C(CO_2Me)_2$]	**2b** (CO_2Et, 1.1)	rt, 3 h	**8bb** (>99)
2	**7c** [R^1 = Me, Z = $C(CH_2OMe)_2$]	**2b** (CO_2Et, 1.1)	rt, 5 h	**8cb** (91)
3	**7d** (R^1 = Me, Z = NTs)	**2b** (CO_2Et, 1.1)	rt, 1 h	**8db** (>99)
4	**7e** (R^1 = Et, Z = O)	**2b** (CO_2Et, 1.1)	rt, 1 h	**8eb** (>99)
5	**7f** [R^1 = H, Z = $C(CO_2Me)_2$]	**2b** (CO_2Et, 1.1)	60 °C, 6 h	**8fb** (69)
6	**7b** [R^1 = Me, Z = $C(CO_2Me)_2$]	**2c** (Bz, 1.1)	60 °C, 16 h	**8bc** (>99)
7	**7b** [R^1 = Me, Z = $C(CO_2Me)_2$]	**2d** (Ac, 1.1)	80 °C, 40 h	**8bd** (98)
8[b]	**7f** [R^1 = H, Z = $C(CO_2Me)_2$]	**2e** (Ph, 5)	60 °C, 1 h	**8fe** (87)
9	**7f** [R^1 = H, Z = $C(CO_2Me)_2$]	**2f** (CH_3, solvent)	80 °C, 1 h	**8ff** (63)
10[b,c]	**7f** [R^1 = H, Z = $C(CO_2Me)_2$]	**2g** (Ts, 1.1)	80 °C, 16 h	**8fg** (60)
11[d]	**7f** [R^1 = H, Z = $C(CO_2Me)_2$]	**2h** (SMe, 2.0)	80 °C, 36 h	**8fh** (35)
12[e]	**7f** [R^1 = H, Z = $C(CO_2Me)_2$]	**2i**  (2)	40 °C, 5 h	**8fi** (47)
13[e,f]	**7b** [R^1 = Me, Z = $C(CO_2Me)_2$]	**2j** (CH_2CN, 1.1)	60 °C, 18 h	**8bj** (84)
14[e]	**7f** [R^1 = H, Z = $C(CO_2Me)_2$]	**2j** (CH_2CN, 1.1)	rt, 5 h	**8fj** (73)

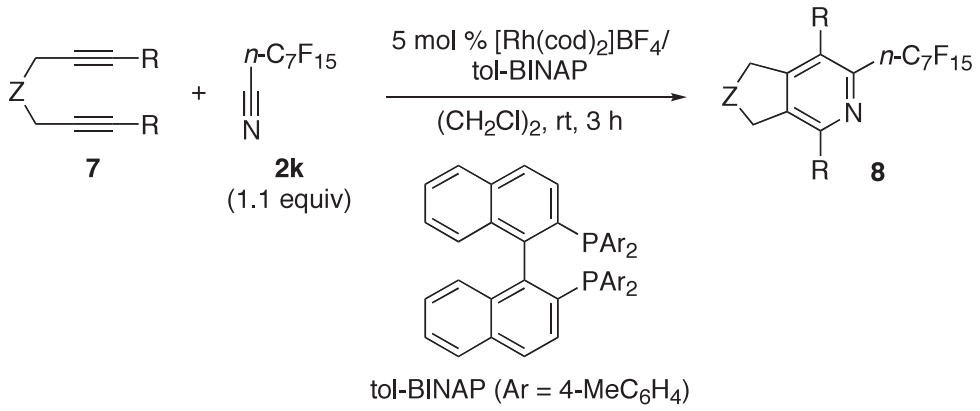
[a] Isolated yield. [b] Ligand: Segphos. [c] Catalyst: 10 mol %. [d] Catalyst: 20 mol %. [e] Ligand: H_8-BINAP. [f] Catalyst: 5 mol %.

With respect to nitriles, the reactions of electron-deficient nitriles **2b–d** with **7b** afforded the corresponding pyridines in almost quantitative yields (entries 1, 6, and 7). In the cases of electron-rich nitriles **2e**,**f**, the reactions proceeded in good yields using terminal diyne **7f** and excess nitriles **2e**,**f**

(entries 8 and 9). Sulphur contaning nitriles **2g** and **2h** could participate in this cycloaddition, although high catalyst loading and elevated temperature were required (entries 10 and 11). Cyanamide **2i** was more reactive than sulphur contaning nitriles to give the corresponding aminopyridine **8fi** at 40 °C (entry 12). The reactions of 1,6-diynes **7b**,**f** with malononitrile (**2j**) in the presence of the cationic rhodium(I)/H_8-BINAP catalyst selectively afforded the corresponding monopyridines **8bj** and **8fj**, respectively, without the formation of bipyridines (entries 13 and 14).

In the above cationic rhodium(I)/biaryl bisphosphine complex-catalyzed [2+2+2] cycloaddition of 1,6-diynes with nitriles, electron-deficient nitriles showed high reactivity. Commercially available electron-deficient perfluoroalkylnitrile **2k** was found to be a suitable cycloaddition partner with 1,6-diynes **7** to give the corresponding perfluoroalkylated pyridines **8** at room temperature in good yields (Table 2).[23]

Table 2. Cationic Rhodium(I)/tol-BINAP Complex-Catalyzed [2+2+2] Cycloaddition of 1,6-Diynes with Perfluoroalkylnitrile



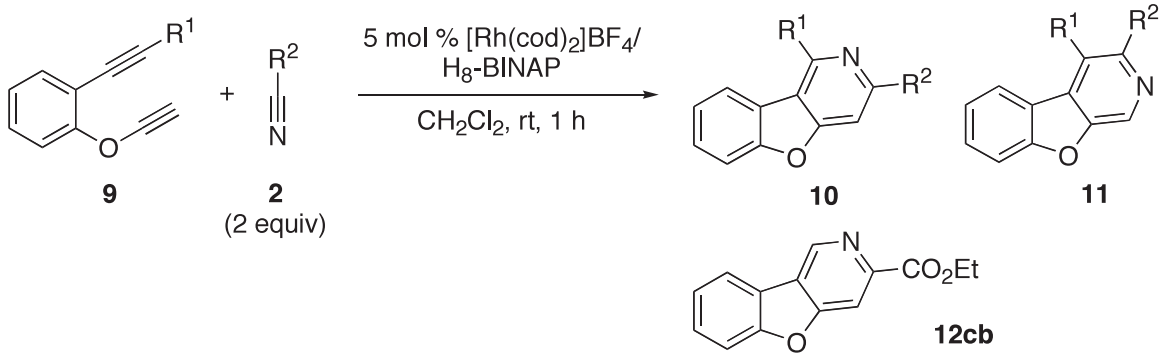
entry	**7**	Z	R	**8**	yield (%)[a]
1	**7b**	$C(CO_2Me)_2$	Me	**8bk**	85
2[b]	**7f**	$C(CO_2Me)_2$	H	**8fk**	62
3	**7g**	$C(CO_2Me)_2$	CO_2Et	**8gk**	55
4[c]	**7d**	NTs	Me	**8dk**	92
5	**7e**	O	Et	**8ek**	86
6	**7h**	CH_2	Et	**8hk**	85

[a] Isolated yield. [b] Reaction time: 2 h. [c] Reaction time: 1 h.

It was found that phenol-linked 1,6-diynes **9** smoothly react with monoynes in the presence of the cationic rhodium(I)/H_8-BINAP catalyst to give substituted dibenzofurans.[24] The use of nitriles **2** in place

of monoynes could furnish substituted azadibenzofurans at room temperature in good yields (Table 3).[24] These reactions were highly regioselective and the corresponding *meta*-disubstituted azadibenzofurans **10** were obtained in good yields with excellent regioselectivities (entries 1, 2, and 4–9). However, the reactions of trimethylsilyl-substituted 1,6-diyne **9c** with **2b** furnished desilylated product **12cb** along with *ortho*-disubstituted product **11cb** in moderate yield (entry 3).

Table 3. Cationic Rhodium(I)/H_8-BINAP Complex-Catalyzed [2+2+2] Cycloaddition of Phenol-Linked 1,6-Diynes with Nitriles

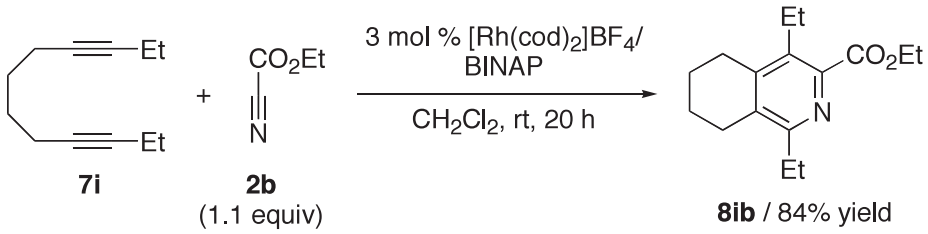


entry	**9** (R^1)	**2** (R^2, equiv)	**10–12** (% yield[a])
1	**9a** (*n*Bu)	**2b** (CO_2Et, 2)	**10ab** (67)
2	**9b** (Ph)	**2b** (CO_2Et, 2)	**10bb** (69)
3	**9c** ($SiMe_3$)	**2b** (CO_2Et, 2)	**12cb** (38) / **11cb** (21)
4	**9b** (Ph)	**2j** (CH_2CN, 2)	**10bj** (84)
5	**9b** (Ph)	**2c** (Bz, 2)	**10bc** (75)
6	**9b** (Ph)	**2d** (Ac, 2)	**10bd** (81)
7	**9b** (Ph)	**2e** (Ph, 5)	**10be** (77)
8	**9a** (*n*Bu)	**2e** (Ph, 5)	**10ae** (75)
9	**9b** (Ph)	**2f** (Me, 10)	**10bf** (46)

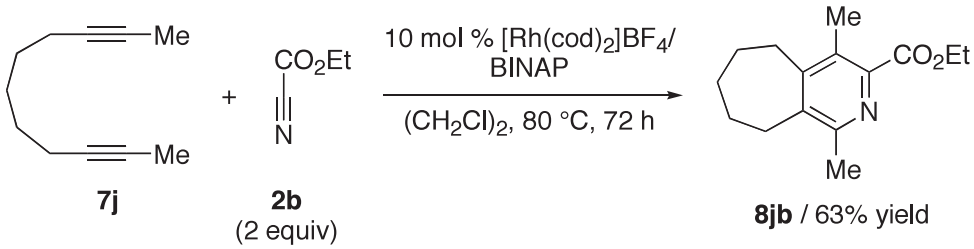
[a] Isolated yield.

The formation of not only a five-membered ring but also six- and seven-membered rings was possible using 1,7-diyne **7i** and 1,8-diyne **7j**, respectively (Schemes 7 and 8).[18] Importantly, these reactions smoothly proceed without Thorpe-Ingold effect.[25]

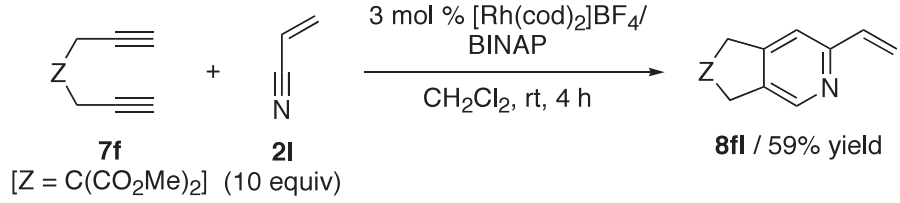
Grigg and co-workers reported that a 1,6-diyne selectively reacted with the double bond of acrylonitrile (**2l**) by using the $RhCl(PPh_3)_3$ catalyst.[26] On the contrary, 1,6-diyne **7f** selectively reacted with the cyano group of **2l** in the presence of the cationic rhodium(I)/BINAP catalyst to give vinylpyridine **8fl** in good yield (Scheme 9).[18]



Scheme 7. Cationic Rhodium(I)/BINAP Complex-Catalyzed [2+2+2] Cycloaddition of 1,7-Diyne with Nitrile

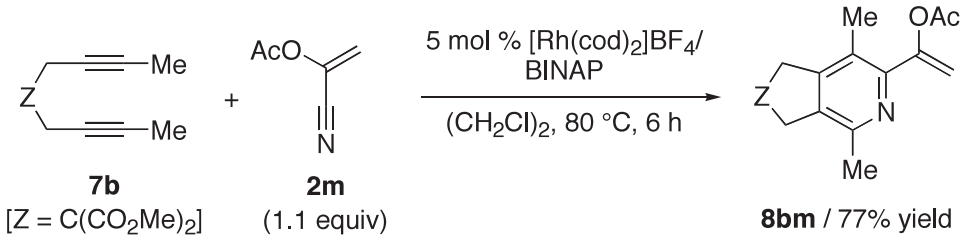


Scheme 8. Cationic Rhodium(I)/BINAP Complex-Catalyzed [2+2+2] Cycloaddition of 1,8-Diyne with Nitrile



Scheme 9. Cationic Rhodium(I)/BINAP Complex-Catalyzed Chemoselective [2+2+2] Cycloaddition of 1,6-Diyne with Acrylonitrile

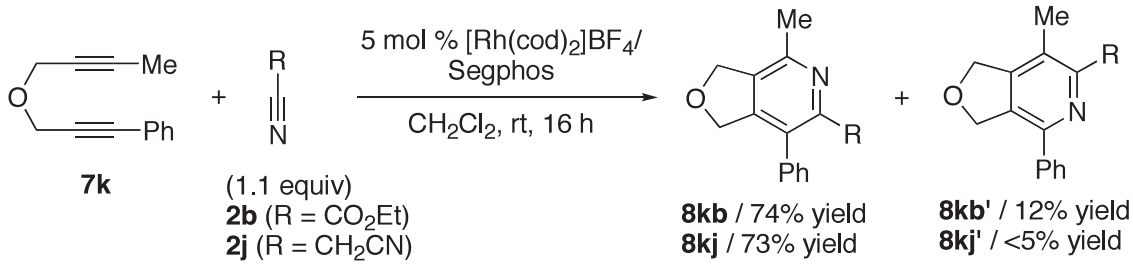
Like acrylonitrile, the cyano group of 1-cyanovinyl acetate (**2m**) selectively reacted with 1,6-diyne **7b** to give bicyclic 2-(1-acetoxyvinyl)pyridine **8bm** in high yield (Scheme 10).[27]



Scheme 10. Cationic Rhodium(I)/BINAP Complex-Catalyzed Chemoselective [2+2+2] Cycloaddition of 1,6-Diyne with 1-Cyanovinyl Acetate

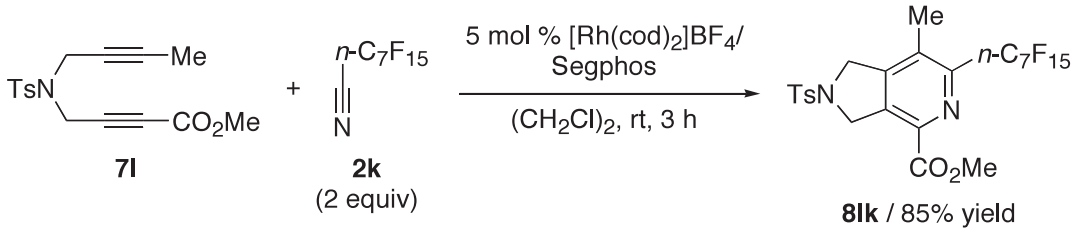
The cationic rhodium(I)/biaryl bisphosphine complex-catalyzed [2+2+2] cycloaddition of unsymmetrical 1,6-diyne **7k**, bearing the methyl and phenyl groups at each alkyne terminus, with ethyl cyanoformate

(**2b**) proceeded at room temperature to give the corresponding pyridines **8kb** and **8kb'** in good yield preferably **8kb** over **8kb'** by using Segphos as a ligand (Scheme 11).[18] Similarly, the reaction of **7k** with malononitrile (**2j**) afforded **8kj** as a predominant regioisomer (Scheme 11).[18]



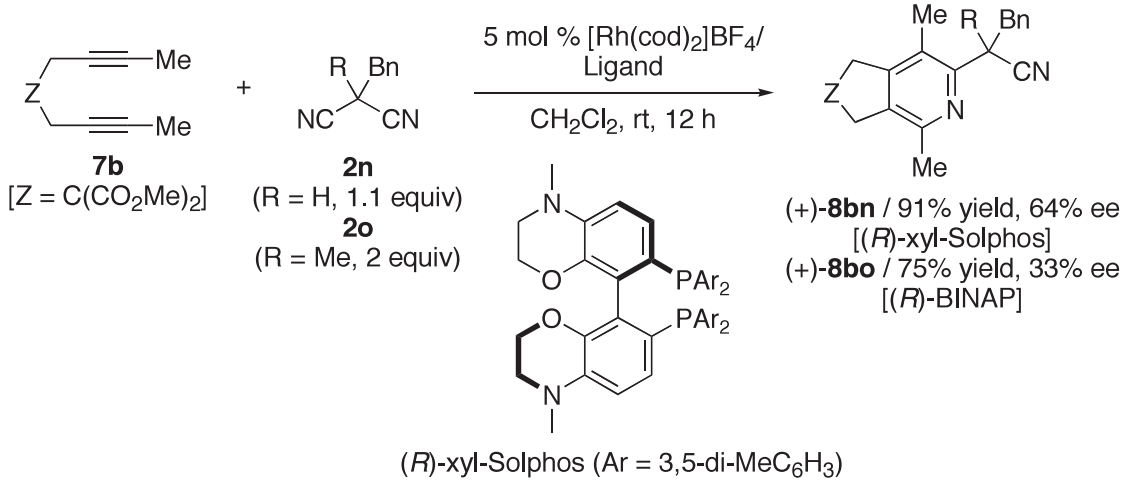
Scheme 11. Cationic Rhodium(I)/Segphos Complex-Catalyzed Regioselective [2+2+2] Cycloaddition of Unsymmetrical 1,6-Diyne with Nitriles

The cationic rhodium(I)/Segphos catalyst was also effective for the regioselective [2+2+2] cycloaddition of unsymmetrical 1,6-diyne **7l**, bearing the methyl and methoxycarbonyl groups at each alkyne terminus, with perfluoroalkylnitrile **2k** to give the corresponding pyridine **8lk** as a single regioisomer (Scheme 12).[23]



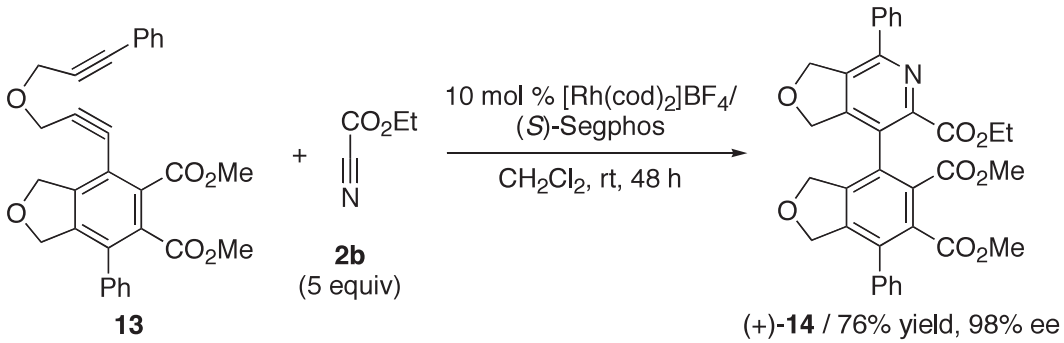
Scheme 12. Cationic Rhodium(I)/Segphos Complex-Catalyzed Regioselective [2+2+2] Cycloaddition of Unsymmetrical 1,6-Diyne with Perfluoroalkylnitrile

The use of the cationic rhodium(I)/axially chiral biaryl bisphosphine catalysts enabled asymmetric variants of the [2+2+2] cycloaddition of alkynes with nitriles. The enantioselective desymmetrization of monosubstituted malononitrile **2n** with 1,6-diyne **7b** proceeded at room temperature in the presence of a $[Rh(cod)_2]BF_4$/(*R*)-xyl-Solphos catalyst to give enantioenriched bicyclic pyridine (+)-**8bn**, possessing the tertiary stereocenter, in high yield with moderate ee value (Scheme 13).[18] The reaction of **7b** with sterically demanding disubstituted malononitrile **2o** also proceeded at room temperature in the presence of a $[Rh(cod)_2]BF_4$/(*R*)-BINAP catalyst to give enantioenriched bicyclic pyridine (+)-**8bo**, possessing the quarternary stereocenter, in good yield, although the product ee value was low (Scheme 13).[18]

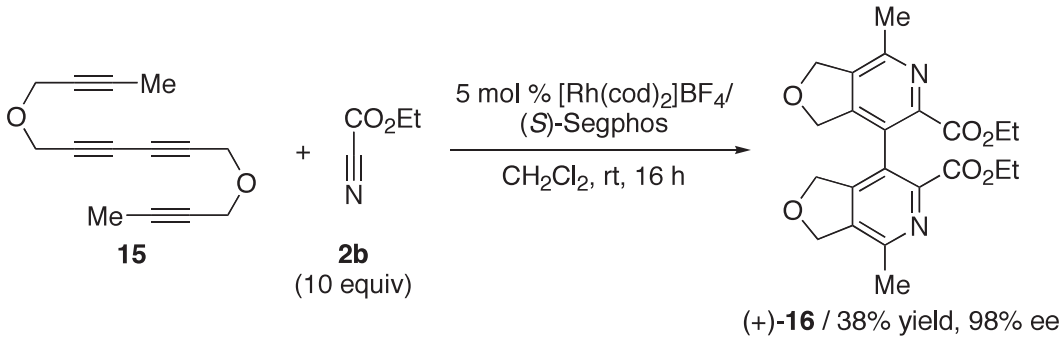


Scheme 13. Cationic Rhodium(I)/xyl-Solphos or BINAP Complex-Catalyzed Enantioselective [2+2+2] Cycloaddition of 1,6-Diyne with Nitriles

Subsequently, the atropselective arylpyridine synthesis were accomplished by using the cationic rhodium(I)/(*R*)-Segphos catalyst (Scheme 14).[28] The reaction of 1,6-diyne **13**, bearing the aryl groups at each alkyne terminus, with ethyl cyanoformate (**2b**) proceeded at room temperature to give axially chiral arylpyridine (+)-**14** in good yield with excellent ee value.



Scheme 14. Cationic Rhodium(I)/Segphos Complex-Catalyzed Atropselective [2+2+2] Cycloaddition of 1,6-Diyne with Nitrile



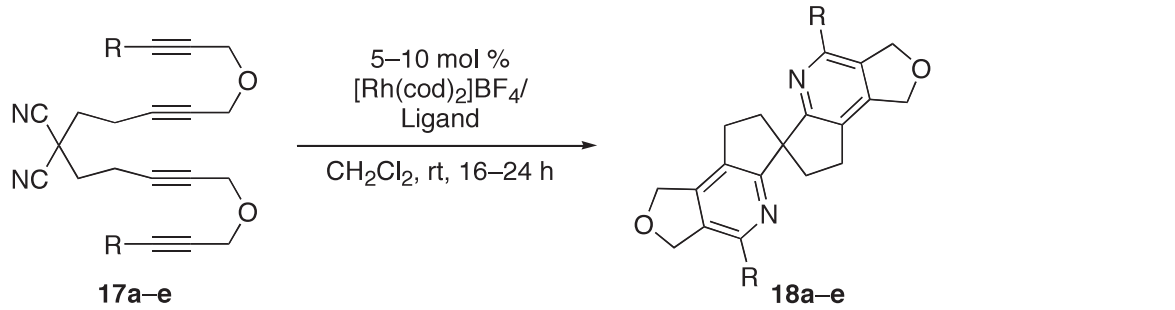
Scheme 15. Cationic Rhodium(I)/Segphos Complex-Catalyzed Atropselective Double [2+2+2] Cycloaddition of Tetrayne with Nitrile

The atropselective synthesis of a C_2-symmetric acxially chiral bipyridine *via* the double [2+2+2] cycloaddition was also accomplished by using the same rhodium catalyst (Scheme 15).[28] The reaction of tetrayne **15** with ethyl cyanoformate (**2b**) proceeded at room temperature to give axially chiral bipyridine (+)-**16** with excellent ee value, although the product yield was low due to the formation of achiral regioisomers as by-products.

2-3. Completely Intramolecular Reactions

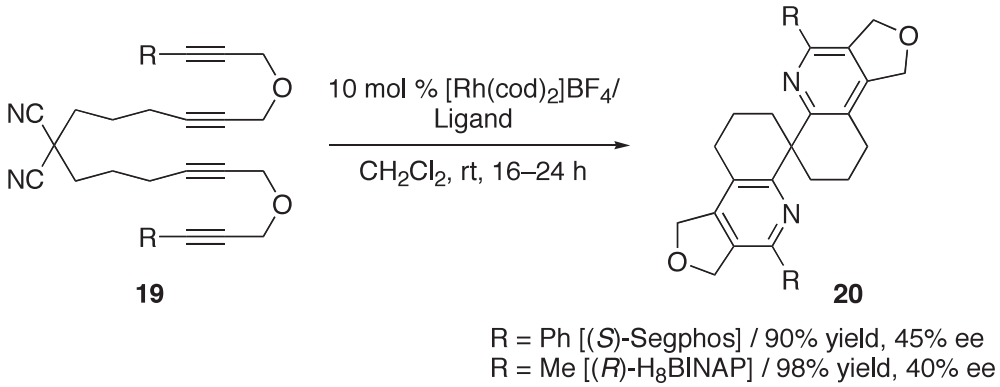
Heteroatom-containing C_2-symmetric axially chiral spiranes are valuable compounds for efficient chiral ligands.[29] However, their catalytic enantioselective synthesis is scarce.[30] In 1999, Saá and co-workers reported a novel approach to spirobipyridine ligands *via* the cobalt(I)-catalyzed double partially intramolecular [2+2+2] cycloaddition of bis-alkynenitriles with monoynes, although the synthesis afforded racemates and the product yields were low.[31]

In 2007, Tanaka and co-workers reported the enantioselective synthesis of C_2-symmetric spirobipyridines *via* the completely intramolecular double [2+2+2] cycloaddition of bis-diynenitriles by using the cationic rhodium(I)/axially chiral biaryl bisphosphine catalysts.[32] The [2+2+2] cycloaddition of various aryl-substituted bis-diynenitriles **17a–c** proceeded at room temperature to give the corresponding C_2-symmetric spirobipyridines **18a–c** in high yields with good ee values by using (*S*)-Segphos as a ligand (Scheme 16). Not only aryl-substituted bis-diynenitriles but methyl-substituted and terminal bis-diynenitriles **17d**,**e** could also participate in this process to give the corresponding C_2-symmetric spirobipyridines **18d**,**e** in high yields with moderate ee values by using (*R*)-H_8-BINAP as a ligand (Scheme 16).



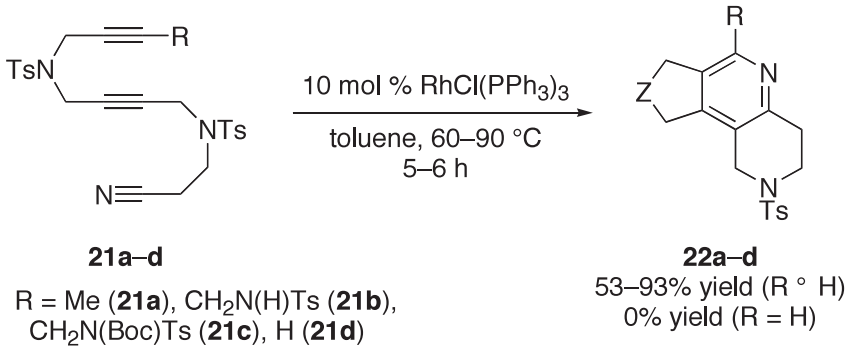
Scheme 16. Cationic Rhodium(I)/Segphos or H_8-BINAP Complex-Catalyzed Enantioselective Synthesis of C_2-symmetric Spirobipyridines, Possessing Five-Membered Spiro Skeletons

Furthermore, C_2-symmetric spirobipyridines **20**, possessing six-membered spiro skeletons, could be synthesized from bis-diynenitriles **19** in high yields by using (*S*)-Segphos or (*R*)-H_8-BINAP as a ligand, although lower enantioselectivities were observed (Scheme 17).[32]



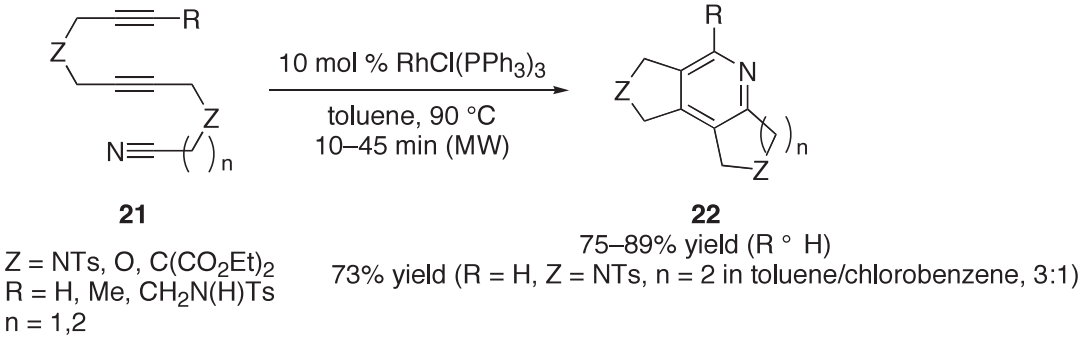
Scheme 17. Cationic Rhodium(I)/Segphos or H_8-BINAP Complex-Catalyzed Enantioselective Synthesis of C_2-symmetric Spirobipyridines, Possessing Six-Membered Spiro Skeletons

In 2010, Pla-Quintana, Roglans, and co-workers reported the synthesis of tricyclic pyridines *via* the completely intramolecular [2+2+2] cycloaddition of diynenitriles by using $RhCl(PPh_3)_3$ as a catalyst.[33] The [2+2+2] cycloaddition of tosylamide-linked internal diynenitriles **21a–c** proceeded at elevated temperature to give the corresponding tricyclic pyridines **22a–c** in moderate to high yields (Scheme 18). However, tosylamide-linked terminal diynenitrile **21d** did not afford the corresponding tricyclic pyridine **22d** at all (Scheme 18).



Scheme 18. $RhCl(PPh_3)_3$-Catalyzed [2+2+2] Cycloaddition of Diynenitriles

In these reactions, the microwave heating dramatically enhanced the catalytic efficiency and broadened the substrate scope.[33] Both internal and terminal diynenitriles **21**, possessing tosylamide, oxygen, and malonate linkages, smoothly cyclized in the presence of the $RhCl(PPh_3)_3$ catalyst to give the corresponding tricyclic pyridines **22** in high yields (Scheme 19).



Scheme 19. $RhCl(PPh_3)_3$-Catalyzed [2+2+2] Cycloaddition of Diynenitriles under Microwave Heating

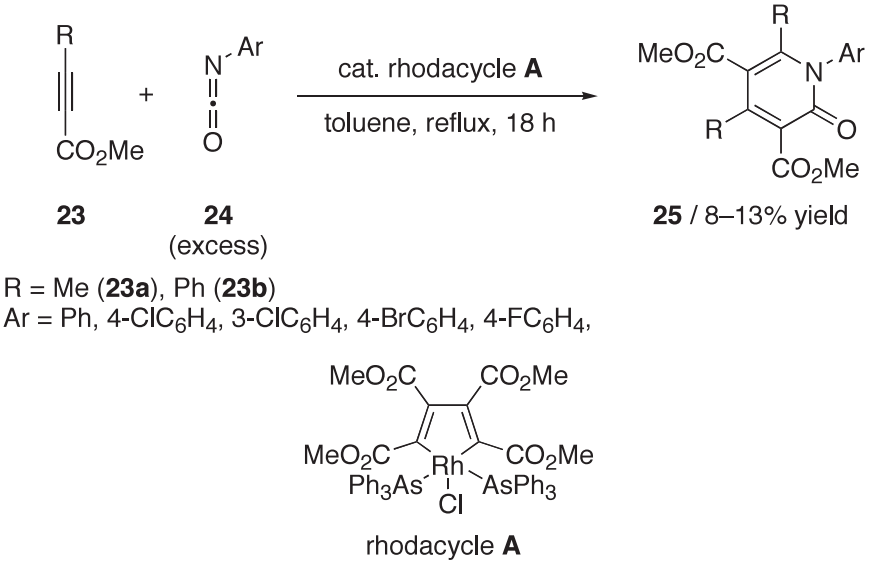
3. SYNTHESIS OF SUBSTITUTED PYRIDONES

3-1. Intermolecular Reactions

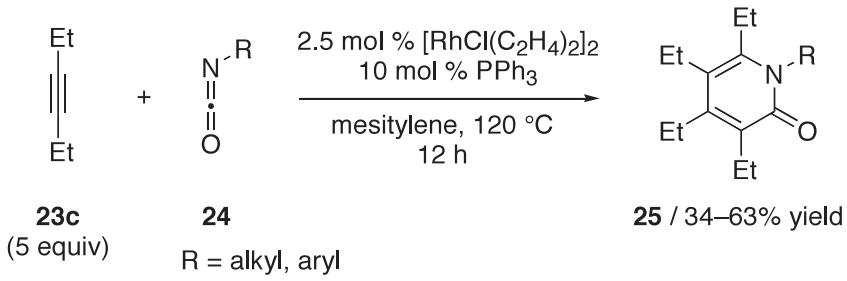
The transition-metal-catalyzed [2+2+2] cycloaddition of alkynes with isocyanates has also been actively investigated to date for the synthesis of substituted 2-pyridones.[1] The pioneering work for such a catalytic formation of 2-pyridones was first reported by Yamazaki using cobalt catalysts[34] and by Hoberg using nickel catalysts.[35] Subsequently, Vollhardt reported the cobalt-catalyzed partially intramolecular [2+2+2] cycloaddition of 5-isocyanatoalkynes.[36] Takahashi reported the selective preparation of 2-pyridones from two different internal alkynes and isocyanates *via* formation of azazirconacyclopentenones followed by transmetalation with $Ni(PPh_3)_2Cl_2$ using stoichiometric amounts of zirconiumu and nickel.[37] Yamamoto and Itoh reported the ruthenium-catalyzed [2+2+2] cycloaddition of 1,6-diynes with isocyanates under mild reaction conditions.[38] Recently, Louie demonstrated that a $Ni(cod)_2$/SIPr [1,3-bis-(2,6-diisopropylphenyl)imidazolin-2-ylidene] complex efficiently catalyzes the [2+2+2] cycloaddition of alkynes with isocyanates at room temperature.[39]

The first example of the rhodium-catalyzed [2+2+2] cycloaddition of alkynes with isocyanates was reported in 1985 by Flynn and co-workers.[40] They found that the intermolecular [2+2+2] cycloaddition of methyl 2-butynoate (**23a**) or 3-phenylpropiolate (**23b**) with aryl isocyanates **24** proceeds at elevated temperature to give the corresponding 2-pyridones **25** as a single regioisomer by using neutral rhodacycle **A** as a catalyst, while the product yields were low (Scheme 20).

In 2006, Kondo, Mitsudo, and co-workers reported a more efficient rhodium(I) catalyst for this transformation. They found that a neutral rhodium(I) complex, $[RhCl(C_2H_4)_2]_2/PPh_3$, is able to catalyze the intermolecular [2+2+2] cycloaddition of excess 3-hexyne (**23c**) with both alkyl and aryl isocyanates **24** at 120 °C to give the corresponding 2-pyridones **25** in moderate to good yields (Scheme 21).[41]

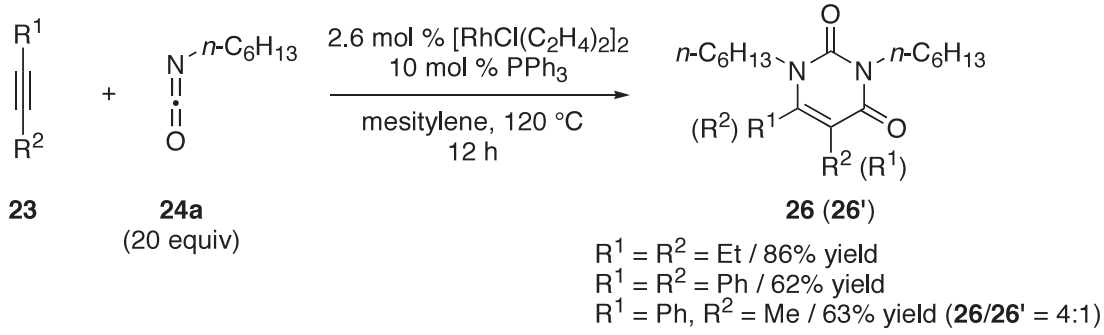


Scheme 20. Neutral Rhodallacycle **A**-Catalyzed [2+2+2] Cycloaddition of Internal Alkynes with Isocyanates



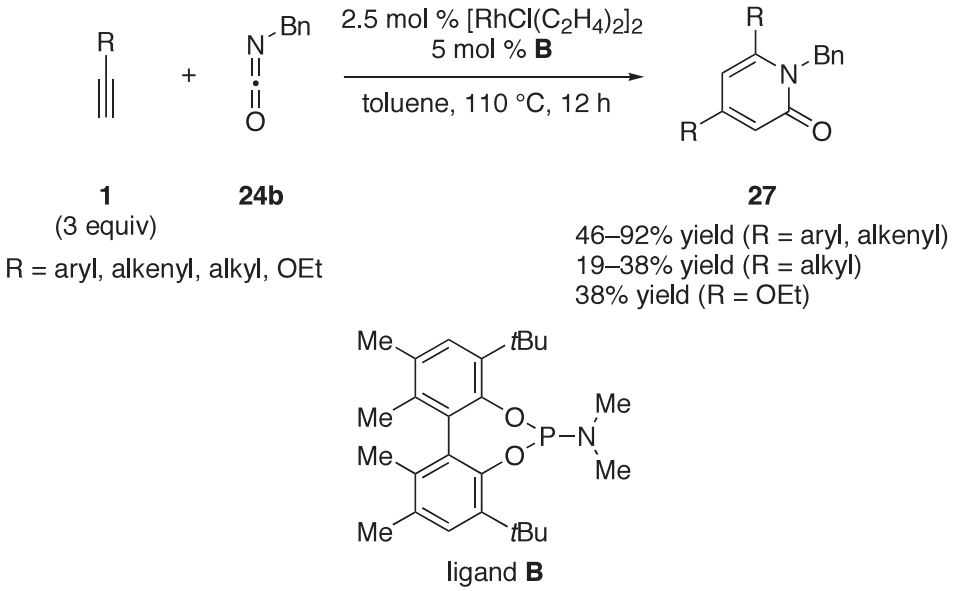
Scheme 21. $[RhCl(C_2H_4)_2]_2/PPh_3$-Catalyzed [2+2+2] Cycloaddition of Internal Alkynes with Isocyanates Leading to 2-Pyridones

Interestingly, the use of excess isocyanate **24a** afforded not the corresponding 2-pyridones **25** but the corresponding pyrimidine-2,4-diones **26** in good yields with good regioselectivity (Scheme 22).[41]



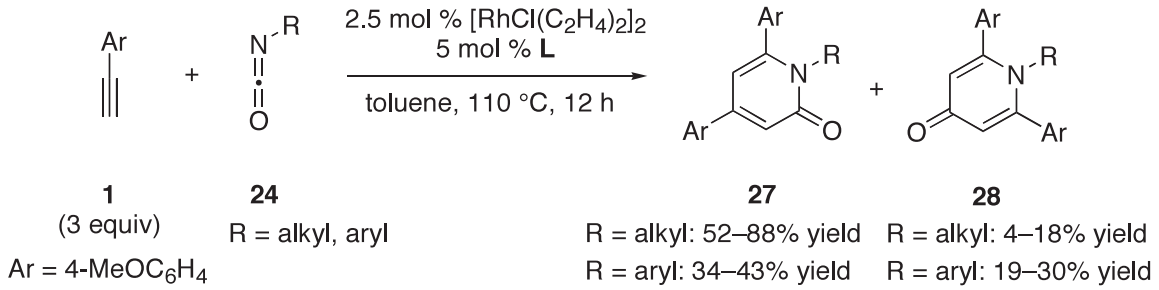
Scheme 22. $[RhCl(C_2H_4)_2]_2/PPh_3$-Catalyzed [2+2+2] Cycloaddition of Internal Alkynes with Isocyanates Leading to Pyrimidine-2,4-Diones

In 2009, Rovis and co-workers reported a highly regioselective catalyst for this transformation. They found that a neutral rhodium(I)/phosphoramidite (**B**) complex is an effective catalyst for the highly regioselective intermolecular [2+2+2] cycloaddition of terminal alkynes with isocyanates.[42] A wide variety of terminal alkynes **1** reacted with benzylisocyanate (**24b**) at 110 °C to give the corresponding 2-pyridones **27** in moderate to high yields with perfect regioselectivities (Scheme 23).



Scheme 23. Neutral Rhodium(I)/Phosphoramidite Complex-Catalyzed [2+2+2] Cycloaddition of Terminal Alkynes with Isocyanates: Alkyne Scope

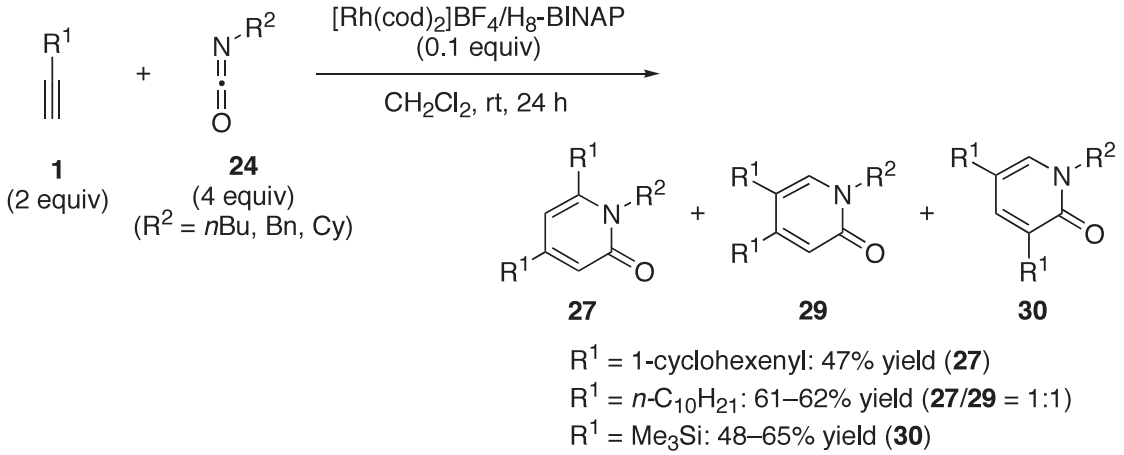
With respect to isocyanates, both alkyl and aryl isocyanates **24** could participate in this regioselective [2+2+2] cycloaddition.[42] Interestingly, 4-pyridones **28** were also generated in these reactions, especially in the cases of aryl isocyanates, through a CO migration in the rhodacycle intermediate (Scheme 24).[43]



Scheme 24. Neutral Rhodium(I)/Phosphoramidite Complex-Catalyzed [2+2+2] Cycloaddition of Terminal Alkynes with Isocyanates: Isocyanate Scope

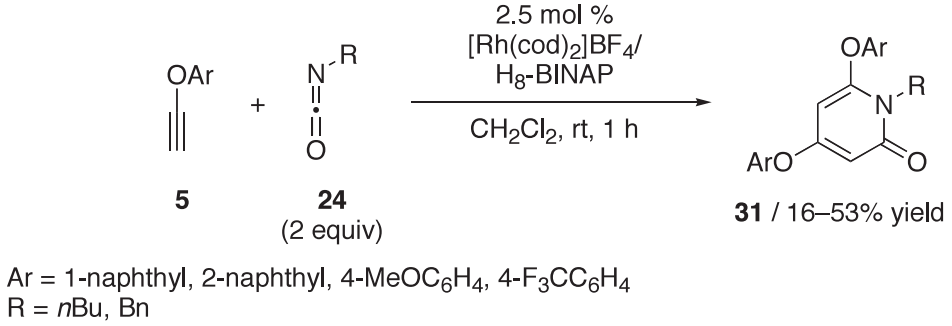
The above-mentioned catalysts required elevated temperature to promote the desired cycloaddition reactions. In 2005, Tanaka and co-workers reported that a cationic rhodium(I)/H_8-BINAP complex is able

to catalyze the intermolecular [2+2+2] cycloaddition of terminal alkynes with isocyanates at room temperature (Scheme 25).[44] Regioselectivities were highly dependent on the alkynes used. Although the reaction of conjugated alkyne (R^1 = 1-cyclohexenyl) furnished isomer **27** as a sole product, the reaction of nonconjugated alkyne (R^1 = *n*-$C_{10}H_{21}$) furnished a mixture of isomers **27** and **29**. On the other hand, the reaction of (trimethylsilyl)acetylene furnished isomer **30** as a sole product.



Scheme 25. Cationic Rhodium(I)/H_8-BINAP Complex-Catalyzed [2+2+2] Cycloaddition of Terminal Alkynes with Isocyanates

As shown in Scheme 5, aryl ethynyl ethers are reactive substrates in the cationic rhodium(I) complex-catalyzed [2+2+2] cycloaddition. The intermolecular [2+2+2] cycloaddition of aryl ethynyl ethers **5** with both electron-deficient and electron-rich nitriles **24** proceeded at room temperature in the presence of the cationic rhodium(I)/H_8-BINAP catalyst to give the corresponding 4,6-diaryloxy-2-pyridones **31** with perfect regioselectivity, although the product yields were low to moderate (Scheme 26).[22]

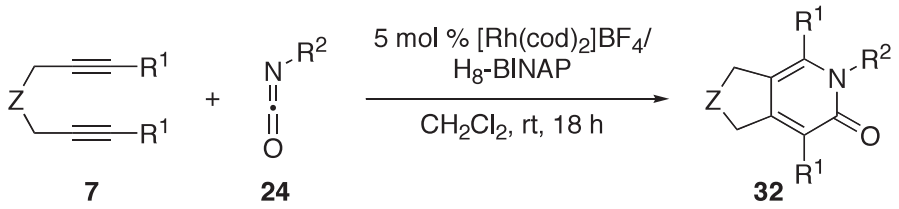


Scheme 26. Cationic Rhodium(I)/H_8-BINAP Complex-Catalyzed [2+2+2] Cycloaddition of Aryl Ethynyl Ethers with Isocyanates

3-2. Partially Intramolecular Reactions

The cationic rhodium(I)/H_8-BINAP complex is the highly effective catalyst for not only intermolecular [2+2+2] cycloaddition but also partially intramolecular one (Table 4).[44] The reactions of both internal 1,6-diynes **7b**,**d** (entries 1–3, 6, and 7) and terminal 1,6-diynes **7f**,**m** (entries 4, 5, and 8) with both alkyl isocyanates **24b**,**c**,**e** (entries 1, 2, and 4–8) and aryl isocyanate **24d** (entry 3) afforded the desired 2-pyridones **32** in good yields. In general, the reactions of internal 1,6-diynes **7b**,**d** proceeded in higher yields than those of terminal 1,6-diynes **7f**,**m**, due to the lower reactivity toward the homo-[2+2+2] cycloaddition.

Table 4. Cationic Rhodium(I)/H_8-BINAP Complex-Catalyzed [2+2+2] Cycloaddition of 1,6-Diynes with Isocyanates



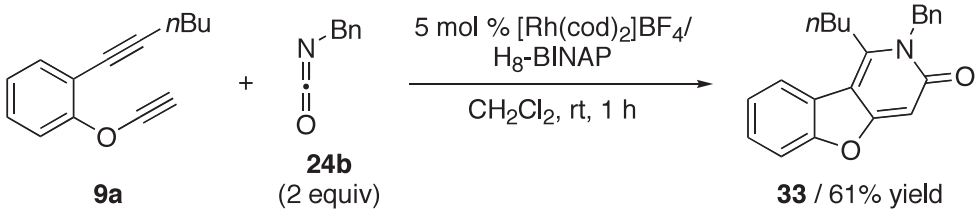
7 **24** **32**

entry	**7**	Z	R^1	**24** (equiv)	R^2	**32**	yield (%)[a]
1	**7b**	$C(CO_2Me)_2$	Me	**24b** (1.1)	Bn	**32bb**	99
2	**7b**	$C(CO_2Me)_2$	Me	**24c** (1.1)	*n*Bu	**32bc**	90
3	**7b**	$C(CO_2Me)_2$	Me	**24d** (1.1)	Ph	**32bd**	87
4	**7f**	$C(CO_2Me)_2$	H	**24b** (2)	Bn	**32fb**	84
5	**7f**	$C(CO_2Me)_2$	H	**24e** (2)	Cy	**32fe**	81
6	**7d**	NTs	Me	**24b** (1.1)	Bn	**32db**	93
7	**7d**	NTs	Me	**24c** (1.1)	*n*Bu	**32dc**	80
8[b]	**7m**	CH_2	H	**24b** (2)	Bn	**32mb**	64

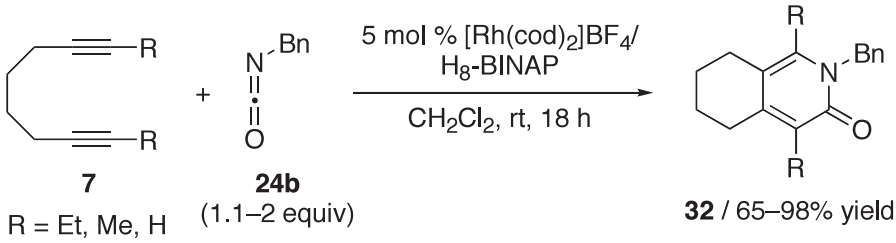
[a] Isolated yield. [b] Ligand: BINAP.

As shown in Table 3, phenol-linked 1,6-diynes can be employed in the cationic rhodium(I) complex-catalyzed [2+2+2] cycloaddition. The reaction of phenol-linked 1,6-diyne **9a** with isocyanate **24b** afforded the corresponding 2-pyridone-fused benzofuran **33** in good yield as a single regioisomer (Scheme 27).[24]

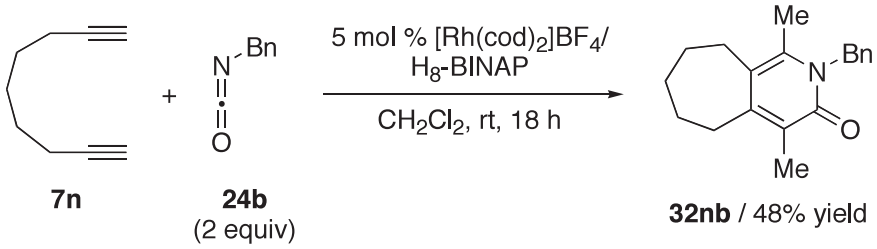
Not only 1,6-diynes but also 1,7- and 1,8-diynes **7** could be employed for this reaction to give six- or seven-membered ring fused 2-pyridones **32** in moderate to high yields (Schemes 28 and 29).[44] Like the pyridine synthesis, these reactions smoothly proceed without Thorpe-Ingold effect.[25]



Scheme 27. Cationic Rhodium(I)/H_8-BINAP Complex-Catalyzed [2+2+2] Cycloaddition of Phenol-Linked 1,6-Diyne with Isocyanate



Scheme 28. Cationic Rhodium(I)/H_8-BINAP Complex-Catalyzed [2+2+2] Cycloaddition of 1,7-Diynes with Isocyanate

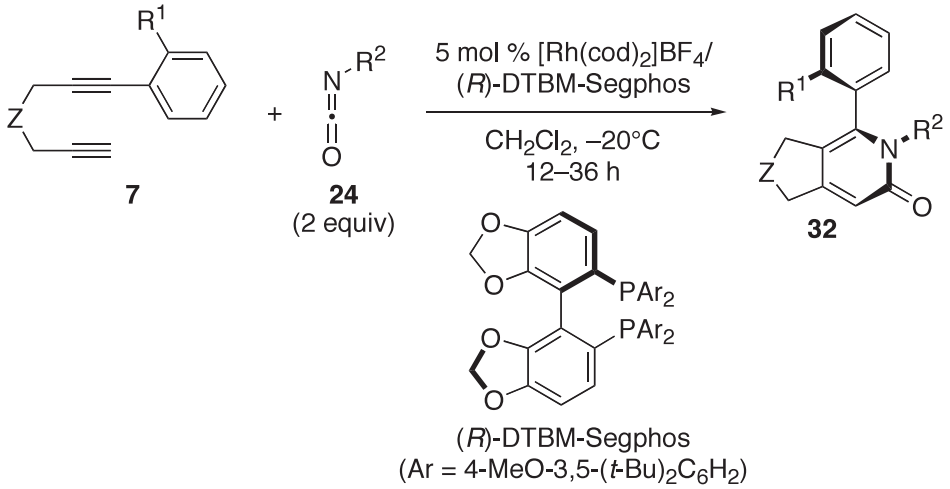


Scheme 29. Cationic Rhodium(I)/H_8-BINAP Complex-Catalyzed [2+2+2] Cycloaddition of 1,8-Diyne with Isocyanate

The use of the cationic rhodium(I)/axially chiral biaryl bisphosphine catalyst enabled the atropselective 2-pyridone synthesis (Table 5).[44] The reactions of 2-chlorophenyl (entries 1–3, 5, and 6) or 2-bromophenyl-substituted unsymmetrical 1,6-diynes **7** (entry 4) with alkyl isocyanates **24** in the presence of a cationic rhodium(I)/(*R*)-DTBM-Segphos catalyst proceeded at –20 °C to give sterically demanding and axially chiral regioisomers (+)-**32** with good yields and ee values.

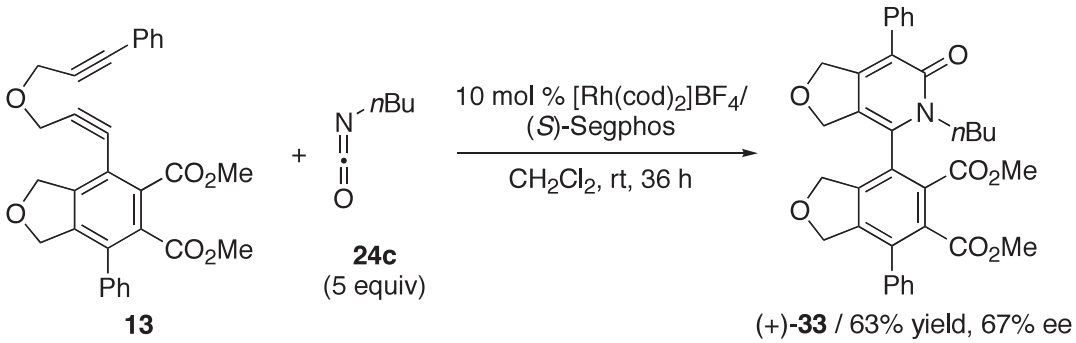
The high catalytic activity of the cationic rhodium(I)/axially chiral biaryl bisphosphine catalyst allowed the atropselective synthesis of a sterically more demanding tetra ortho-substituted 2-pyridone (Scheme 30).[28] The reaction of 1,6-diyne **13**, bearing the aryl groups at each alkyne terminus, with isocyanate **24c** proceeded at room temperature in the presence of the cationic rhodium(I)/(*S*)-Segphos catalyst to give axially chiral 2-pyridone (+)-**33** with moderate yield and ee value.

Table 5. Cationic Rhodium(I)/DTBM-Segphos Complex-Catalyzed Atropselective [2+2+2] Cycloaddition of 1,6-Diynes with Isocyanates



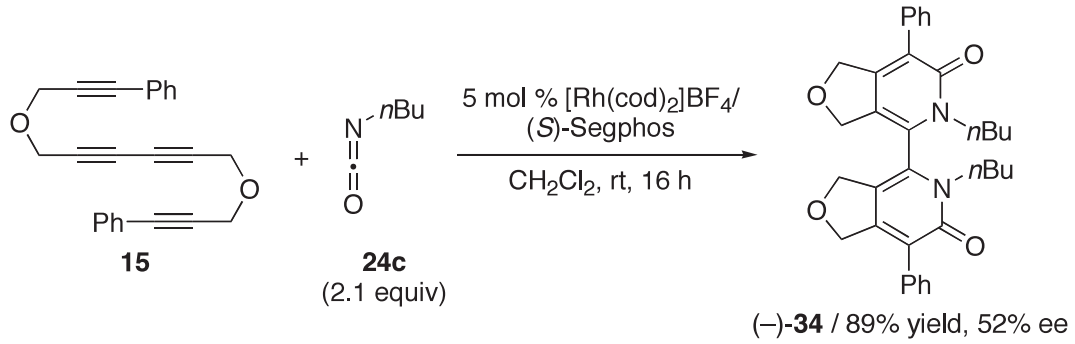
entry	7	Z	R^1	24	R^2	32	yield (%)[a]	ee (%)
1	**7o**	CH_2	Cl	**24b**	Bn	(+)-**32ob**	81	87
2	**7o**	CH_2	Cl	**24c**	*n*Bu	(*R*)-(+)-**32oc**	79	88
3	**7o**	CH_2	Cl	**24f**	*n*-C_8H_{17}	(+)-**32of**	75	90
4	**7p**	CH_2	Br	**24b**	Bn	(+)-**32pb**	83	85
5	**7q**	O	Cl	**24b**	Bn	(+)-**32qb**	58	91
6	**7r**	$C(CO_2Me)_2$	Cl	**24b**	Bn	(+)-**32rb**	89	92

[a] Isolated yield.



Scheme 30. Cationic Rhodium(I)/Segphos Complex-Catalyzed Atropselective [2+2+2] Cycloaddition of 1,6-Diyne with Isocyanate

The atropselective double [2+2+2] cycloaddition for the synthesis of a C_2-symmetric axially chiral bipyridone was also reported (Scheme 31).[28] The reaction of tetrayne **15** with isocyanate **24c** proceeded at room temperature in the presence of the cationic rhodium(I)/(*S*)-Segphos catalyst to give axially chiral bipyridone (–)-**34** in high yield, although the product ee value was moderate.



Scheme 31. Cationic Rhodium(I)/Segphos Complex-Catalyzed Atropselective Double [2+2+2] Cycloaddition of Tetrayne with Isocyanate

4. SYNTHESIS OF SUBSTITUTED THIOPYRANIMINES

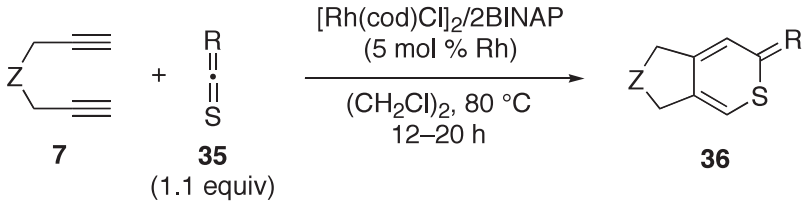
The transition-metal-catalyzed [2+2+2] cycloaddition of alkynes with isocyanates leading to substituted 2-pyridones has been developed using a number of transition-metal complexes.[1] In sharp contrast, only a few examples have been reported for the corresponding reaction with isothiocyanates in place of isocyanates to produce substituted thiopyranimines.[45,46] The pioneering work for such a transition-metal-catalyzed or mediated [2+2+2] cycloaddition of alkynes with isothiocyanates was first reported by Yamazaki using a stoichiometric amount of a cobaltacyclopentadiene.[45] Subsequently, Yamamoto and Itoh realized the catalytic version of this reaction using a Cp*Ru(cod)Cl complex as a catalyst.[46]

In 2006, Tanaka and co-workers reported that the neutral rhodium(I)/BINAP complex is a highly effective catalyst for the [2+2+2] cycloaddition of 1,6-diynes with isothiocyanates (Table 6).[47] Interestingly, the neutral rhodium(I)/BINAP complex showed higher catalytic activity than the cationic rhodium(I)/BINAP complex for this cycloaddition. Malonate-linked terminal 1,6-diyne **7f** reacted with a wide variety of isothiocyanates **35a–f** at 80 °C in the presence of a neutral rhodium(I)/BINAP catalyst to give the corresponding bicyclic thiopyranimines **36** in good yields (entries 1–6). With respect to 1,6-diynes, 1,3-diketone derivative **7s** and the 1,3-diol derivative **7t** gave the corresponding thiopyranimines **36sa** and **36ta** in high yields (entries 7 and 8). On the contrary, tosylamide- and ether-linked 1,6-diynes could not participate in this reaction. Thus, the aid of the Thorpe-Ingold effect[25] induced by the quaternary center at the 4-position of 1,6-diynes is necessary for this reaction. In addition to isothiocyanates, carbon disulfide **35g** could also be employed in this cycloaddition (entries 9–11).

An asymmetric variant of this reaction was also reported in the enantioselective desymmetrization of a 1,6-diyne (Scheme 32).[47] The reaction of phenylacetate-derived 1,6-diyne **7u** with phenyl isothiocyanate (**35a**) in the presence of the neutral rhodium(I)/(*R*)-BINAP catalyst proceeded at 60 °C to give

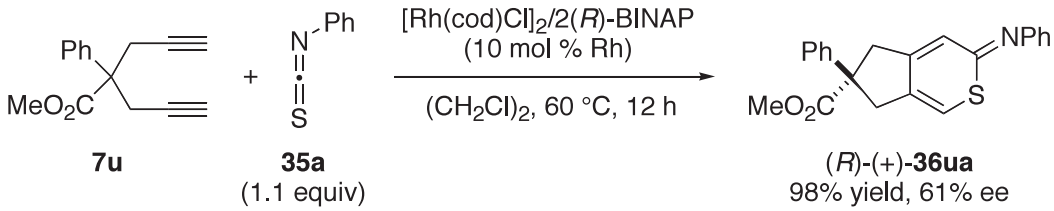
enantioenriched thiopyranimine (*R*)-(+)-**36ua** in excellent yield with moderate ee value (Scheme 32). However, Interestingly, the reactions using alkyl isothiocyanates gave the corresponding cycloaddition products with <10% ee values.

Table 6. Neutral Rhodium(I)/BINAP Complex-Catalyzed [2+2+2] Cycloaddition of 1,6-Diynes with Isothiocyanates and Carbon Disulfide



entry	**7** (Z)	**35** (R)	**36**	yield (%)[a]
1	**7f** [$C(CO_2Me)_2$]	**35a** (NPh)	**36fa**	88
2	**7f** [$C(CO_2Me)_2$]	**35b** [$N(2\text{-}MeC_6H_4)$]	**36fb**	74
3	**7f** [$C(CO_2Me)_2$]	**35c** [$N(4\text{-}MeOC_6H_4)$]	**36fc**	73
4[b]	**7f** [$C(CO_2Me)_2$]	**35d** [$N(4\text{-}ClC_6H_4)$]	**36fd**	89
5[b]	**7f** [$C(CO_2Me)_2$]	**35e** (NBn)	**36fe**	87
6	**7f** [$C(CO_2Me)_2$]]	**35f** (N*n*Bu)	**36ff**	59
7[b]	**7s** (CAc_2)	**35a** (NPh)	**36sa**	81
8	**7t** [$C(CH_2OMe)_2$]	**35a** (NPh)	**36ta**	87
9[c]	**7f** [$C(CO_2Me)_2$]	**35g** (S)	**36fg**	85
10[c]	**7s** (CAc_2)	**35g** (S)	**36sg**	74
11[c]	**7t** [$C(CH_2OMe)_2$]	**35g** (S)	**36tg**	75

[a] Isolated yield. [b] 10 mol % Rh was used. [c] CS_2 (5 equiv) was used.



Scheme 32. Neutral Rhodium(I)/BINAP Complex-Catalyzed Enantioselective [2+2+2] Cycloaddition of 1,6-Diyne with Isothiocyanate

5. CONCLUSION

As described in this review, several rhodium-based catalysts have been developed for the rhodium-catalyzed [2+2+2] cycloaddition reactions of alkynes with nitriles, isocyanates, and isothiocyanates. In the pyridines synthesis, the cyclopentadienyl rhodium(I) complexes are able to

catalyze the intermolecular [2+2+2] cycloaddition of terminal alkynes with nitriles at elevated temperature. Wilkinson's complex, $RhCl(PPh_3)_3$, is effective for the intramolecular [2+2+2] cycloaddition of diynenitriles under microwave heating. The cationic rhodium(I)/biaryl bisphosphine complexes are widely applicable catalysts for both intermolecular and intramolecular [2+2+2] cycloaddition of alkynes with nitriles under mild reaction conditions. In the pyridone synthesis, the neutral rhodium(I)/monophosphine complexes are effective for the regioselective intermolecular [2+2+2] cycloaddition of terminal alkynes with isocyanates at elevated temperature. The cationic rhodium(I)/biaryl bisphosphine complexes are widely applicable catalysts for both intermolecular and intramolecular [2+2+2] cycloaddition of alkynes with isocyanates under mild reaction conditions. Interestingly, not the cationic rhodium(I)/biaryl bisphosphine complex but the neutral rhodium(I)/biaryl bisphosphine complex is effective for the [2+2+2] cycloaddition of 1,6-diynes with isothiocyanates. Importantly, the use of the cationic or neutral rhodium(I)/axially chiral biaryl bisphosphine complexes as catalysts allowed developing asymmetric variants of these reactions. Although the rhodium-based catalysts are expensive, these are highly stable and readily handled by using conventional laboratory equipments. Therefore, I believe that the rhodium-catalyzed [2+2+2] cycloaddition will be one of the useful strategies for the synthesis of conjugated nitrogen heterocycles.

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