Cationic Rhodium(I)/BINAP-Type Bisphosphine Complexes: Versatile New Catalysts for Highly Chemo-, Regio-, and Enantioselective [2+2+2] Cycloadditions

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Abstract: Our research group was the first to discover that cationic rhodium(I)/BINAP-type bisphosphine complexes are versatile new catalysts for highly chemo-, regio-, and enantioselective [2+2+2] cycloadditions. The high chemo- and regioselectivity of these cycloadditions enabled efficient catalytic synthesis of substituted benzenes, cyclophanes, and nitrogen heterocycles. Furthermore, enantioselective variants of these cycloadditions were also developed that realized efficient catalytic constructions of axial, planar, central, and spiro chirality.

Key words: alkynes, asymmetric catalysis, BINAP, cycloadditions, rhodium

1 Introduction

Transition-metal-catalyzed enantioselective cycloadditions are powerful synthetic methods for the rapid construction of chiral cyclic frameworks.[1] Although a number of efficient enantioselective cycloadditions have been developed, only two examples of enantioselective [2+2+2] cycloadditions had been accomplished by the time we started this chemistry in 2002. The first example was reported in 1994 by Sato, Mori, and co-worker as an enantioselective desymmetrization of triynes leading to isoindoline and isoquinoline derivatives bearing a tertiary stereocenter using a nickel-catalyzed [2+2+2] cycloaddition.[2] The second example was reported in 1999 by Stará and co-workers as a nickel-catalyzed enantioselective [2+2+2] cycloaddition of triynes leading to a [6]helicene-like molecule.[3] These pioneering works clearly demonstrated the use of enantioselective [2+2+2] cycloadditions for the asymmetric synthesis of chiral aromatic compounds. However, I thought that the lack of highly active transition-metal/chiral bisphosphine complexes other than nickel complexes might strictly limit the further development of the enantioselective [2+2+2] cycloadditions.

During my organic process research at the Mitsubishi Chemical Corporation, I got the chance to work as a postdoctoral fellow at the Massachusetts Institute of Technology (MIT) under the supervision of Professor Gregory C. Fu. At MIT, I had been working on rhodium(I)-catalyzed enantioselective carbon–hydrogen and carbon–carbon bond forming reactions including the isomerization of allylic alcohols[4] and intramolecular hydroacylation of alk-4-ynals.[5] At the start of my independent work in academia at the Tokyo University of Agriculture and Technology, I imagined that rhodium(I)/chiral bisphosphine complexes, having a rigid chiral environment and multiple free coordination sites, would be potentially more suitable for enantioselective [2+2+2] cycloadditions than nickel(0) complexes.

Accordingly, I began to explore highly active and selective rhodium(I)/bisphosphine complexes for use in [2+2+2] cycloadditions. I summarize in this account our efforts at developing rhodium-catalyzed, highly chemo-, regio-, and enantioselective [2+2+2] cycloadditions over the past four years.

2 Chemo- and Regioselective [2+2+2] Cycloadditions

2.1 [2+2+2] Cycloaddition of Terminal Alkynes

The transition-metal-catalyzed [2+2+2] cycloaddition of alkynes has received much attention as a useful method for the construction of substituted benzenes.[6,7] Compared with conventional substitution methods of benzenes, the [2+2+2] cycloaddition strategy is considerably advantageous for the synthesis of substituted benzenes because of its high atom economy and convergent nature. Although various transition metals catalyze [2+2+2] cycloadditions, it has been difficult to carry out the intermolecular

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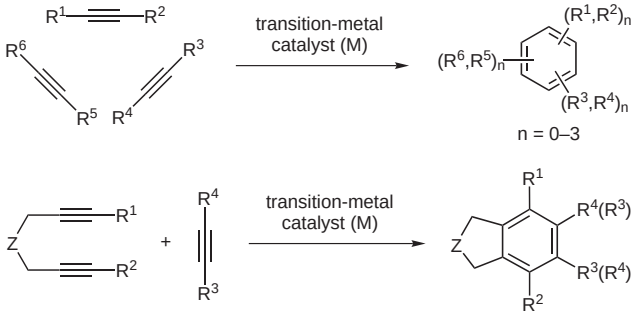
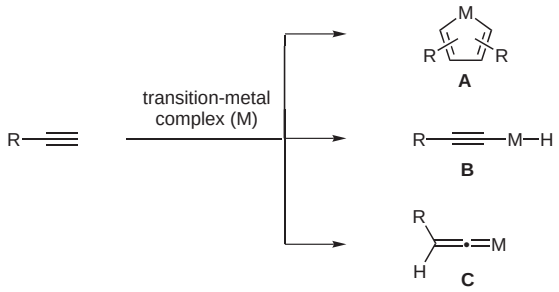
reactions in a highly regioselective manner.[8] In particular, an intermolecular cross-[2+2+2] cycloaddition of two or three different alkynes leads to a complex mixture of products which severely limits its application to organic synthesis (Scheme 1). Therefore, a partial intramolecular reaction between an α,ω-diyne and excess monoalkyne (Scheme 1) and a complete intramolecular reaction of a triyne have been employed to overcome this problem.[9]



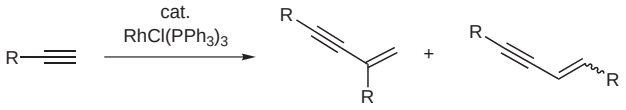
Scheme 1

In addition to the regioselectivity problem, selective [2+2+2] cycloadditions of terminal monoalkynes are difficult to achieve due to their various reactivities toward transition-metal complexes. The reaction of terminal alkynes with transition-metal complexes typically leads to three different intermediates including metallacyclopentadienes **A**, alkynylmetal hydrides **B**, and vinylidene complexes **C** (Scheme 2). To promote [2+2+2] cycloadditions, selective formation of complex **A** is required without formation of **B** and **C**. However, the selective formation of complex **A** from untethered monoalkynes is more difficult than that from tethered diynes.

Indeed, although a neutral rhodium(I) complex, such as $RhCl(PPh_3)_3$, can catalyze a partial or complete intramolecular [2+2+2] cycloaddition of diynes or triynes at



Scheme 2



Scheme 3

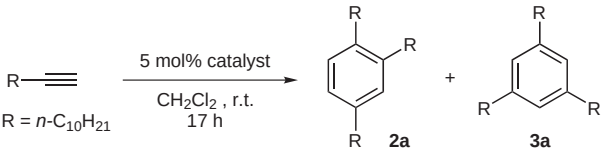
elevated temperatures,[10,11] it generally reacts with terminal monoalkynes to give linear dimers (Scheme 3).[12]

However, the application of a cationic rhodium(I) complex to [2+2+2] cycloadditions remained unexplored.[13,14] With this background information in mind, we began to explore the application of a cationic rhodium(I) complex to the [2+2+2] cycloaddition of terminal monoalkyne **1a**. After screening various rhodium(I) as well as iridium(I) complexes (Table 1),[15,16] we found dramatic enhancement of both catalytic activity and selectivity by using a cationic rhodium(I) complex with the Tol-BINAP ligand which gave [2+2+2] cycloaddition products **2a** and **3a** at room temperature in almost quantitative yield with moderate regioselectivity and without formation of linear oligomers (entry 6). The combination of the cationic rhodium(I) complex and the Tol-BINAP ligand is essential for this reaction. A neutral rhodium(I)/Tol-BINAP complex, and both cationic and neutral iridium(I)/Tol-BINAP complexes, did not show the same catalytic activity (entries 7–9).

Biographical Sketch

Ken Tanaka was born in Fukuoka, Japan, in 1967. He obtained his bachelors degree (1990) from the University of Tokyo under the supervision of Professor Atsushi Ishizu and his masters degree (1993) from the University of Tokyo under the supervision of Professor Koichi Narasaka. He joined the Mitsubishi Chemical Corporation in 1993. During his organic process research for manufacturing agrochemicals and pharmaceutical intermediates at Mitsubishi, he obtained his Ph.D. (1998) from the University of Tokyo under the supervision of Professor Takeshi Kitahara, and he worked as a post-doctoral fellow at Massachusetts Institute of Technology, USA, under the supervision of Professor Gregory C. Fu (November 1999–December 2001). After going back to Mitsubishi, he moved to Tokyo University of Agriculture and Technology as an associate professor in October 2002. His current research is focused on the use of cationic rhodium(I) complexes as catalytic reagents in organic synthesis. He is the recipient of the Synthetic Organic Chemistry Award, Japan (2001), the Banyu Award in Synthetic Organic Chemistry, Japan (2003), and the first prize of the Solvias Ligand Contest (2006).

Table 1 Screening of Catalysts for the Intermolecular Homo-[2+2+2] Cycloaddition of Dodec-1-yne (**1a**)



Entry[a]	Catalyst	Yield[b] (%) of **2a** + **3a**	Ratio of (**2a**/**3a**)[b]
1	$[Rh(cod)_2]BF_4$/2 Ph_3P	3	–
2	$[Rh(cod)_2]BF_4$/2 *n*-Bu_3P	5	–
3	$[Rh(cod)_2]BF_4$/dppe	<2	–
4	$[Rh(cod)_2]BF_4$/dcpe	3	–
5	$[Rh(cod)_2]BF_4$/dppf	<2	–
6	$[Rh(cod)_2]BF_4$/Tol-BINAP	>95	64:36
7	$[Rh(cod)Cl]_2$/2 Tol-BINAP	<2	–
8	$[Ir(cod)_2]BF_4$/Tol-BINAP	<2	–
9	$[Ir(cod)Cl]_2$/2 Tol-BINAP	0	–

[a] Catalyst (0.0050 mmol), **1a** (0.10 mmol), and CH_2Cl_2 (1.0 mL) were used.
[b] Determined by ^1H NMR spectroscopy.

In order to improve regioselectivity, a variety of cationic rhodium(I) complexes with BINAP-type bisphosphine ligands, possessing various dihedral angles, steric demands, and electronic nature, were screened (Figure 1).

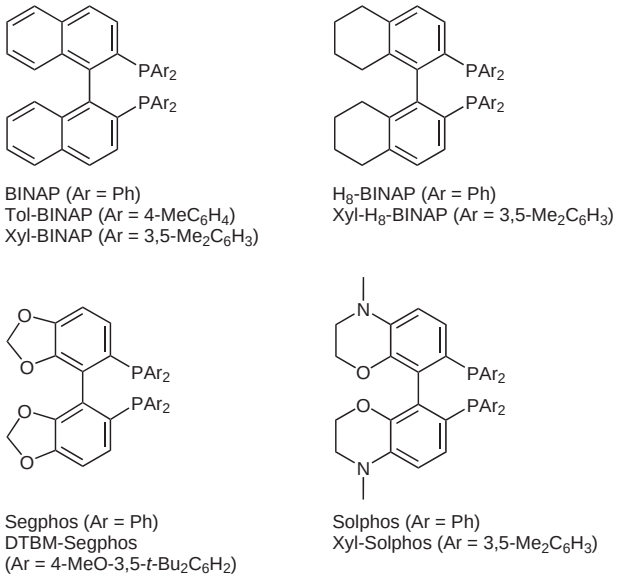
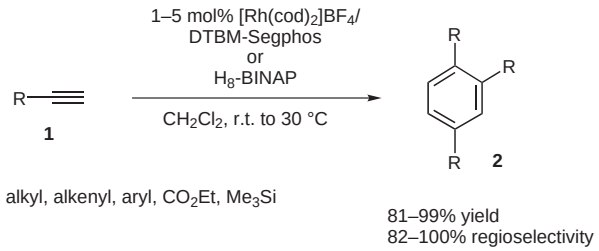


Figure 1

Both high catalytic activity and regioselectivity were achieved using a cationic rhodium(I)/DTBM-Segphos[17] or H_8-BINAP[18] complex. A series of terminal alkynes **1** were subjected to the above optimal reaction conditions, at room temperature or at 30 °C, to give 1,2,4-trisubstituted benzenes **2** in high yields and with high regioselectivity (Scheme 4).[15,16] To the best of our knowledge, these catalytic systems provide one of the most general methods for the regioselective [2+2+2] cycloaddition of terminal alkynes.[8]

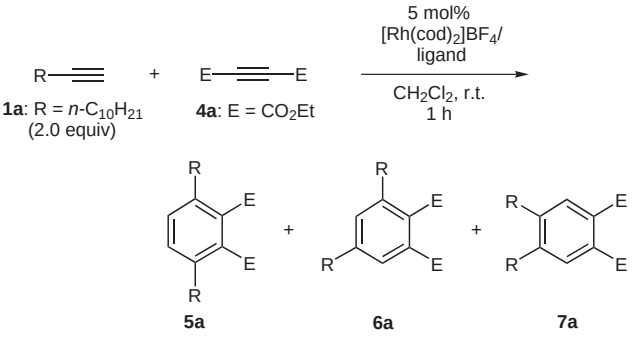


Scheme 4

2.2 [2+2+2] Cycloaddition of Two Different Alkynes

Encouraged by the above results, we subsequently investigated rhodium-catalyzed intermolecular cross-[2+2+2] cycloaddition of two different alkynes.[19] After screening combinations of dodec-1-yne (**1a**) and various terminal or internal alkynes in the presence of a cationic rhodium(I)/Tol-BINAP complex, we were pleased to discover that a chemoselective intermolecular cross-[2+2+2] cycloaddition of **1a** (2 equiv) and diethyl acetylenedicarboxylate (**4a**, 1 equiv) rapidly proceeded at room temperature to give a mixture of disubstituted phthalates **5a**, **6a**, and **7a**

Table 2 Screening of BINAP-Type Bisphosphine Ligands for Cross-[2+2+2] Cycloaddition of Dodec-1-yne (**1a**) and Diethyl Acetylenedicarboxylate (**4a**)

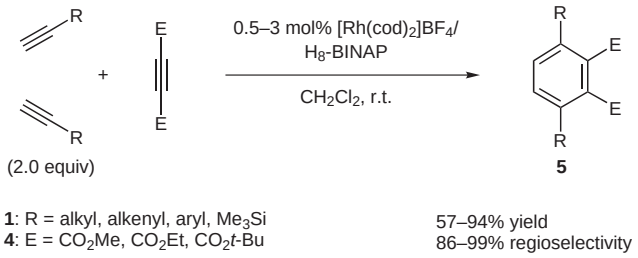


Entry[a]	Ligand	Yield[b] (%) of **5a** + **6a** + **7a**	Ratio of (**5a**/**6a**/**7a**)[b]
1	Tol-BINAP	82	46:22:32
2	BINAP	84	54:26:20
3	Xyl-BINAP	80	49:19:32
4	Segphos	82	81:17:2
5	DTBM-Segphos	69	32:62:6
6	H_8-BINAP	93	92:6:2

[a] $[Rh(cod)_2]BF_4$ (0.005 mmol), ligand (0.005 mmol), **1a** (0.2 mmol), **4a** (0.1 mmol), and CH_2Cl_2 (1.0 mL) were used.
[b] Determined by ^1H NMR spectroscopy.

with moderate regioselectivity (Table 2, entry 1). After screening various BINAP-type bisphosphine ligands, both high yield and regioselectivity were achieved using a cationic rhodium(I)/H_8-BINAP complex (entry 6).[15,16]

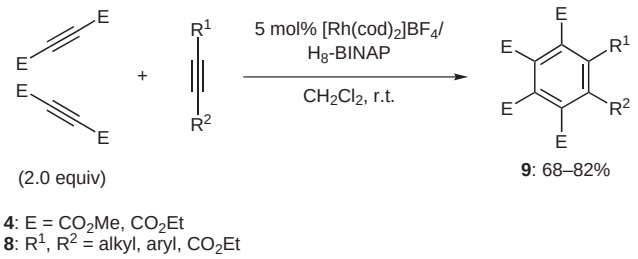
By employing a catalytic amount (0.5–3 mol%) of the cationic rhodium(I)/H_8-BINAP complex, two molecules of a wide variety of terminal alkynes **1** cleanly reacted with one molecule of a dialkyl acetylenedicarboxylate **4** to give 3,6-disubstituted dialkyl phthalates **5** in high yields and with high regioselectivity (Scheme 5).[15,16]



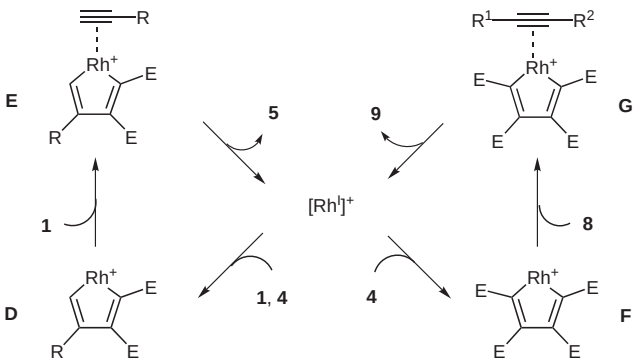
Scheme 5

The intermolecular cross-[2+2+2] cycloaddition of internal alkynes and dialkyl acetylenedicarboxylates **4** using a cationic rhodium(I)/H_8-BINAP complex as a catalyst was also investigated. Contrary to terminal alkynes, one molecule of various internal alkynes **8** cleanly reacted with two molecules of **4** to give hexasubstituted benzenes **9** in high yields (Scheme 6).[20]

Plausible mechanisms for the cationic rhodium(I)/H_8-BINAP complex catalyzed, intermolecular cross-[2+2+2] cycloadditions are illustrated in Scheme 7. Chemo- and regioselectivity is determined by the preferred formation of metallacycle **D** from terminal alkynes **1** and dialkyl acetylenedicarboxylates **4**, followed by the coordination of **1** to form complex **E**. Insertion of **1** followed by reductive elimination of rhodium gives **5** and regenerates the rhodium catalyst. Conversely, the reaction of **4** and internal alkynes **8** proceeds through the preferred formation of metallacycle **F**, followed by the coordination of **8** to form complex **G**.



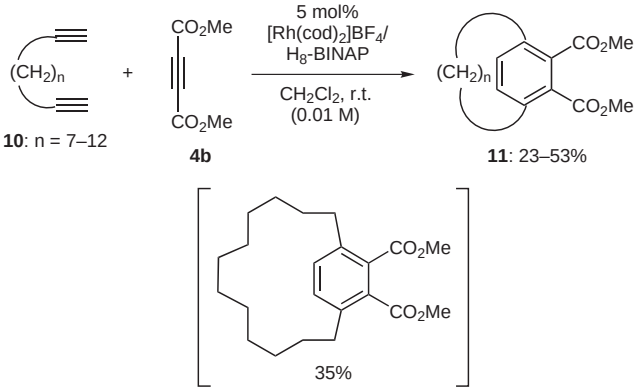
Scheme 6



Scheme 7

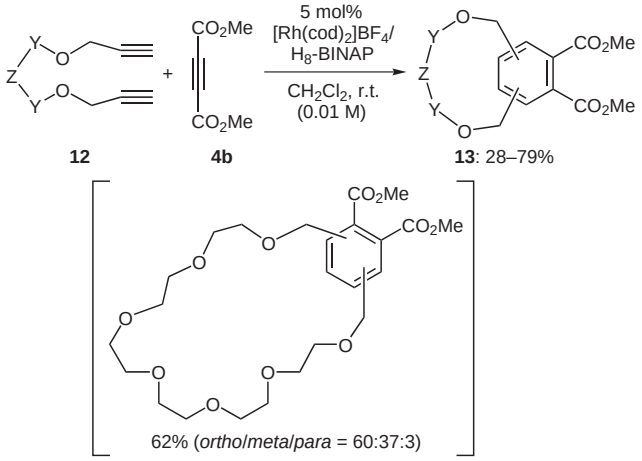
2.3 [2+2+2] Cycloaddition of α,ω-Diynes with Alkynes

The successful cross-[2+2+2] cycloaddition of two molecules of a terminal alkyne and one molecule of a dialkyl acetylenedicarboxylate to give a 3,6-disubstituted phthalate prompted us to investigate the synthesis of paracyclophanes using terminal α,ω-diynes instead of two molecules of a terminal alkyne.[20] Maryanoff and co-workers reported cobalt-catalyzed macrocyclizations to form pyridinophanes via [2+2+2] cycloaddition of α,ω-diynes with nitriles[21a,b,d] or isocyanates.[21c] However, formation of cyclophanes via [2+2+2] cycloaddition of α,ω-diynes with monoalkynes is inefficient using cobalt catalysts.[21a] As we expected, reactions of α,ω-diynes **10**, bearing different length carbon chains, and dimethyl acetylenedicarboxylate (**4b**) using the cationic rhodium(I)/H_8-BINAP complex as a catalyst gave the corresponding [7]–[12]paracyclophanes **11** in fair to good yields (Scheme 8). Importantly, the formation of the [8]–[12]paracyclophanes was predominant and the corresponding [8]–[12]meta- or [8]–[12]orthocyclophanes were generated in very low yield (<5%) or not at all; a mixture of meta- and paracyclophanes was obtained in the case of the highly strained [7]cyclophanes.[16]



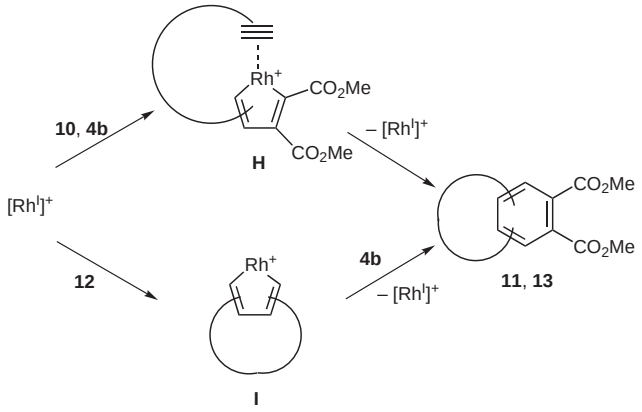
Scheme 8

The reactions of ether-linked α,ω-diynes **12** with **4b** were also investigated in the presence of 5 mol% [Rh(cod)$_2$]BF$_4$/H_8-BINAP at room temperature and they gave the desired polyether-containing cyclophanes **13** in good yields, including the crownlike [21]heptaoxacyclophanes (Scheme 9).[22]



Scheme 9

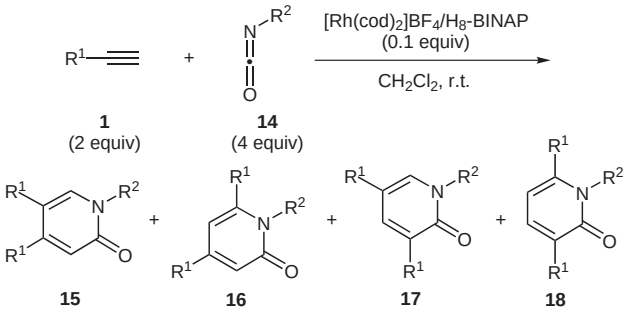
Scheme 10 depicts possible intermediates **H** and **I** generated from α,ω-diyne **10** or **12** and dimethyl acetylenedicarboxylate (**4b**) leading to cyclophanes **11** or **13**. Our mechanistic studies revealed that the syntheses of carbacyclophanes and polyether-containing cyclophanes proceed through different intermediates. In the case of [7]–[12]cyclophanes **11**, **H** is proposed as the predominant intermediate, which leads to a paracyclophane as the major product. On the other hand, in the case of α,ω-diynes **12** bearing an oxygen-containing linker, the formation of intermediate **I** would be rapid due to their high ability to coordinate to the cationic rhodium.



Scheme 10

2.4 [2+2+2] Cycloaddition of Alkynes with Isocyanates, Isothiocyanates, and Carbon Disulfide

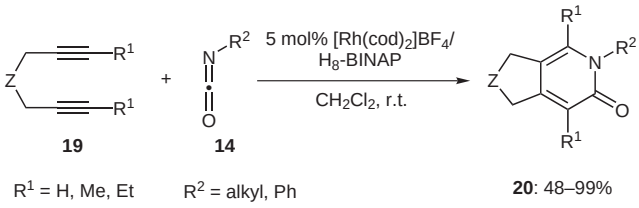
The above cross-[2+2+2] cycloaddition was then extended to the synthesis of nitrogen heterocycles[23–25] by the reaction of terminal monoalkynes **1** with isocyanates **14** instead of dialkyl acetylenedicarboxylates **4**.[15,16] Fortunately, the desired reactions proceeded in good yields using the [Rh(cod)$_2$]BF$_4$/H$_8$-BINAP catalyst at room temperature (Scheme 11).[26] In these reactions, regioselectivity is highly dependent on the alkynes used. Although the reaction of a conjugated alkyne gave isomer **15** as the major product, the reaction of a nonconjugated alkyne gave isomers **15** and **16** as major products, and in the reaction of (trimethylsilyl)acetylene, isomer **17** was formed as the sole product.



		Yield (%)			
R^1	R^2	**15**	**16**	**17**	**18**
cyclohex-1-enyl	Bn	47	1	0	0
n-C$_{10}$H$_{21}$	Bn	31	30	<5	0
Me$_3$Si	*n*-Bu	0	0	65	0

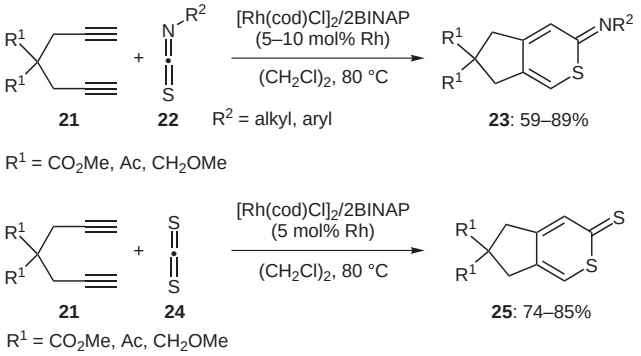
Scheme 11

The cycloaddition of both terminal and internal diynes **19** with isocyanates **14** was also investigated in the presence of 5 mol% [Rh(cod)$_2$]BF$_4$/H$_8$-BINAP at room temperature (Scheme 12).[26] The cycloaddition of a wide variety of 1,6-diynes **19** with isocyanates **14** afforded the expected 2-pyridones **20** in good yields. The formation of a fused six- or seven-membered ring (Z = CH_2CH_2 or $CH_2CH_2CH_2$) was also possible. In general, the reactions of internal diynes proceeded in higher yield than those of terminal diynes because of the latter's lower reactivity toward homo-[2+2+2] cycloadditions.



Scheme 12

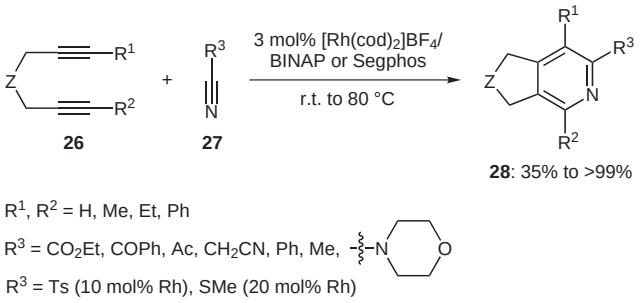
In the case of isothiocyanates **22**, a neutral rhodium(I)/BINAP complex effectively catalyzed a [2+2+2] cycloaddition with 1,6-diynes **21** to give bicyclic thiopyranimines **23** in high yields (Scheme 13).[27,28] However, the reactions cannot proceed without the aid of the Thorpe–Ingold effect induced by the tertiary center at the 4-position of the 1,6-diynes.[29] The reaction with carbon disulfide (**24**) also proceeded to give bicyclic dithiopyrones **25** in high yields (Scheme 13).[27]



Scheme 13

2.5 [2+2+2] Cycloaddition of Alkynes with Nitriles

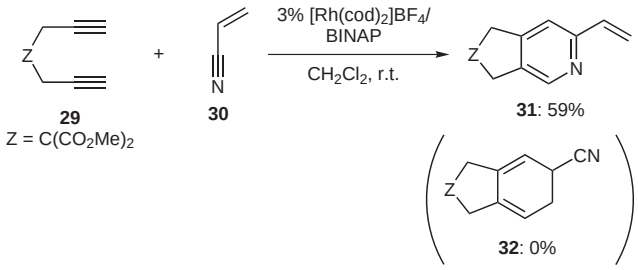
The cationic rhodium(I)/BINAP-type bisphosphine complexes are also effective for pyridine synthesis.[30–33] A cationic rhodium(I)/BINAP or Segphos[17] complex catalyzed [2+2+2] cycloadditions of a wide variety of 1,6-diynes **26** with both electron-deficient and electron-rich nitriles **27** leading to highly functionalized pyridines **28** under mild reaction conditions (Scheme 14).[34] Like the reactions with isocyanates, the formation of a fused six- or seven-membered ring (Z = CH_2CH_2 or $CH_2CH_2CH_2$) was also possible.



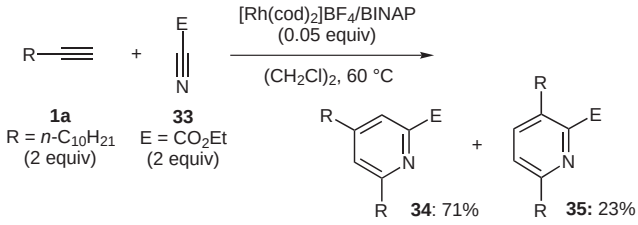
Scheme 14

Grigg and co-workers reported that a 1,6-diyne selectively reacted with the double bond of acrylonitrile (**30**) in the presence of 2 mol% $RhCl(PPh_3)_3$ at 82 °C to give a nitrile in 59% yield.[35] Conversely, 1,6-diyne **29** selectively reacted with the cyano group of **30** in the presence of 3 mol% $[Rh(cod)_2]BF_4$/BINAP at room temperature to give vinylpyridine **31** in good yield without the formation of nitrile **32** (Scheme 15).[34]

We also investigated pyridine synthesis through the cycloaddition of an untethered monoalkyne. The reaction of dodecyne (**1a**, 2 equiv) and substituted nitrile **33** (2 equiv) in the presence of $[Rh(cod)_2]BF_4$/BINAP (0.05 equiv) at 60 °C afforded the corresponding pyridines **34** and **35** in high total yield with **34** as the major isomer (Scheme 16).[34]



Scheme 15



Scheme 16

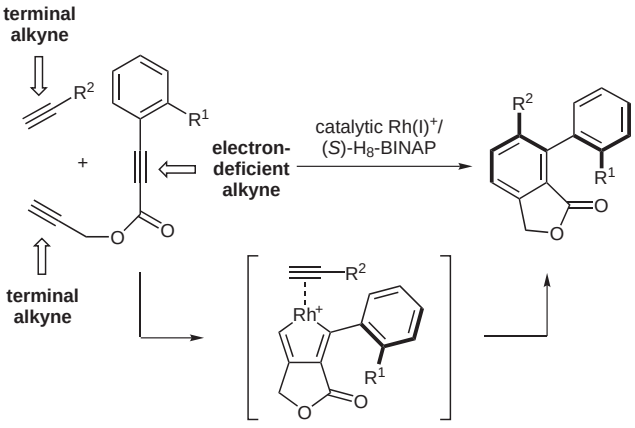
3 Enantioselective [2+2+2] Cycloadditions

3.1 Construction of Axial Chirality

Axially chiral biaryls are widely used as the key structure of effective chiral ligands and biologically active compounds. Therefore, a number of their catalytic asymmetric syntheses are reported to date.[36] However, an asymmetric aromatization approach has not been extensively studied.[37]

We anticipated that a cross-[2+2+2] cycloaddition of terminal alkynes and electron-deficient 1,6-diynes, possessing an *ortho*-substituted phenyl group and a hydrogen at each alkyne terminus, would construct axial chirality upon the formation of the benzene rings (Scheme 17).[38]

We were pleased to find that the reaction of electron-deficient 1,6-diynes **36**, possessing an *ortho*-substituted phenyl at an alkyne terminus, with propargyl acetate (**37**, R^2 = Ac) or propargyl alcohol (**37**, R^2 = H) in the presence of 5 mol% $[Rh(cod)_2]BF_4$/(*S*)-H_8-BINAP gave axially chiral

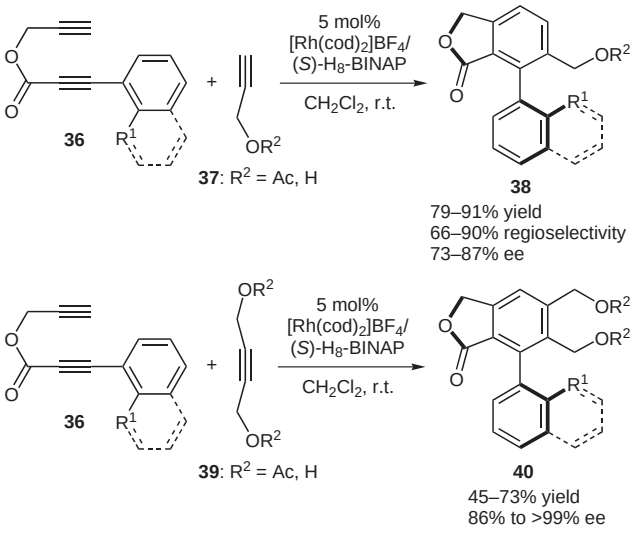


Scheme 17

phthalides **38** in high yields and with high enantioselectivity. Importantly, sterically demanding regioisomers were obtained with good regioselectivity (Scheme 18).[39]

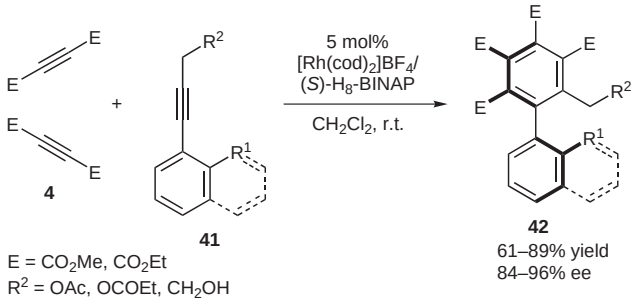
Interestingly, the use of a symmetrical internal monoalkyne, 1,4-diacetoxybut-2-yne (**39**, R^2 = Ac) or but-2-yne-1,4-diol (**39**, R^2 = H), enhanced the enantioselectivity giving axially chiral phthalides **40** in good yields and with excellent enantioselectivity (Scheme 18).[39]

During our preparation of the manuscript for the above work, two reports dealing with the same concept were published on the Web. Gutnov, Heller, and co-workers reported the synthesis of axially chiral 2-arylpyridines via a cobalt(I)/chiral cyclopentadiene complex catalyzed, asymmetric [2+2+2] cycloaddition of alkynes with nitriles.[40] Shibata and co-workers reported the synthesis of axially chiral 1,4-teraryls via a neutral iridium(I)/Me-Duphos complex catalyzed, asymmetric [2+2+2] cycloaddition of *symmetrical* α,ω-diynes and *symmetrical* monoalkynes.[41] Although our report is the third example of such work, a cationic rhodium(I)/BINAP-type bisphosphine complex realized a cross-[2+2+2] cycloaddition of *unsymmetrical* α,ω-diynes with both *unsymmetrical* and *symmetrical* monoalkynes. Furthermore, this type of rhodium catalyst showed remarkably wide applicability to various enantioselective [2+2+2] cycloadditions in addition to this axially chiral biaryl synthesis (Schemes 18– 48).



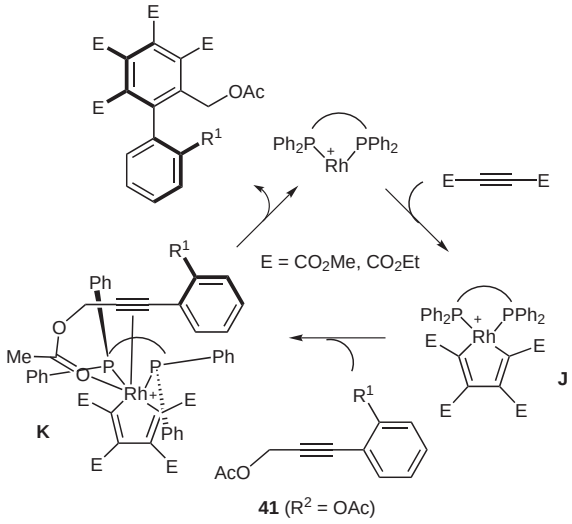
Scheme 18

By using the cationic rhodium(I)/H_8-BINAP complex, not only partial intramolecular reactions, but complete intermolecular asymmetric [2+2+2] cycloadditions could be accomplished. The reaction of internal alkynes **41**, bearing *ortho*-substituted phenyl and acetoxymethyl or hydroxyethyl groups at each terminus, with dialkyl acetylenedicarboxylates **4** at room temperature gave the corresponding axially chiral biaryls **42** in high yields and with high enantioselectivity (Scheme 19).[20]



Scheme 19

Chemo- and enantioselectivity may be determined by preferential formation of metallacycle **J** followed by the coordination of **41** to form complex **K**, resulting from avoidance of steric interaction between the *o*-alkyl group (R^1) of **41** and the diphenylphosphine (PPh_2) group of (*S*)-H_8-BINAP (Scheme 20).

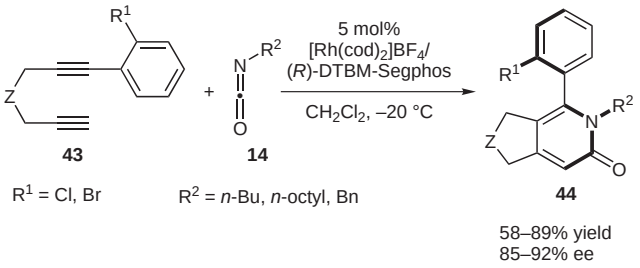


Scheme 20

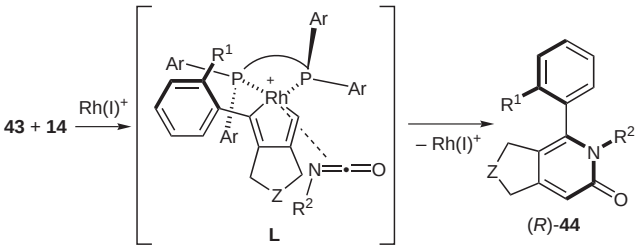
In the axially chiral biaryl synthesis through partial intramolecular reactions shown in Scheme 18, the use of isocyanates instead of monoalkynes would furnish axially chiral pyridones. The reaction of unsymmetrical 1,6-diynes **43**, possessing an *ortho*-substituted phenyl at an alkyne terminus, with isocyanates **14** in the presence of a cationic rhodium(I)/(*R*)-DTBM-Segphos complex at –20 °C gave sterically demanding and axially chiral regioisomers **44** as the sole products in high yields and with high enantioselectivity (Scheme 21).[26]

The observed high regio- and enantioselectivity may be explained by the selective formation of rhodium complex **L** from unsymmetrical 1,6-diynes **43**, which react with isocyanates **14** to give axially chiral regioisomers (*R*)-**44** (Scheme 22).

Tetra-*ortho*-substituted biaryls, having highly stable axial chirality, are valuable structures for chiral ligands used in a variety of asymmetric catalyses.[42] Therefore, various



Scheme 21

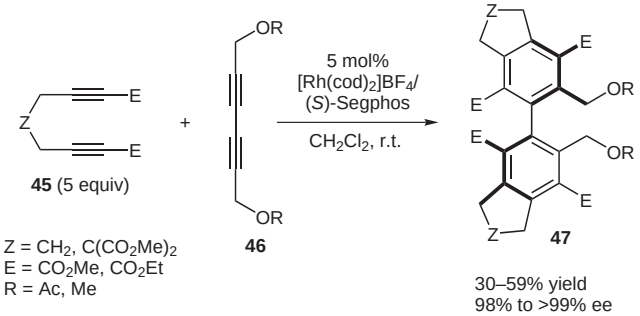


Scheme 22

enantioselective methods for their synthesis have been reported to date.[36] Although the enantioselective cross-coupling of sterically encumbered 2,6-disubstituted arenes to form tetra-*ortho*-substituted biaryls has been realized in several examples,[43] the efficient catalytic method, applicable to the enantioselective synthesis of *functionalized* axially chiral tetra-*ortho*-substituted biaryls, is scarce.[44]

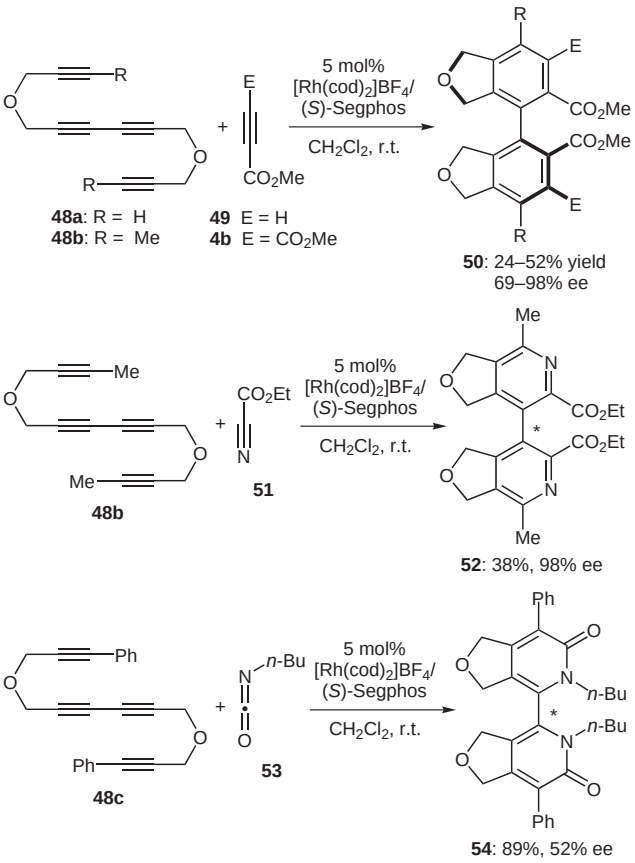
We anticipated that enantioselective synthesis of C_2 symmetric tetra-*ortho*-substituted axially chiral biaryls can be realized through a double [2+2+2] cycloaddition of electron-deficient 1,6-diynes with 1,3-diynes (Scheme 23), or tetraynes with electron-deficient monoalkynes (Scheme 24).

We first investigated the reaction of electron-deficient 1,6-diynes **45** and 1,3-diynes **46** in the presence of various cationic rhodium(I)/BINAP-type bisphosphine complexes. We were pleased to find that the use of 5 mol% [Rh(cod)$_2$]BF$_4$/(*S*)-Segphos gave the corresponding C_2-symmetric, tetra-*ortho*-substituted biaryls **47** in moderate yields and with excellent enantioselectivity (Scheme 23).[45]



Scheme 23

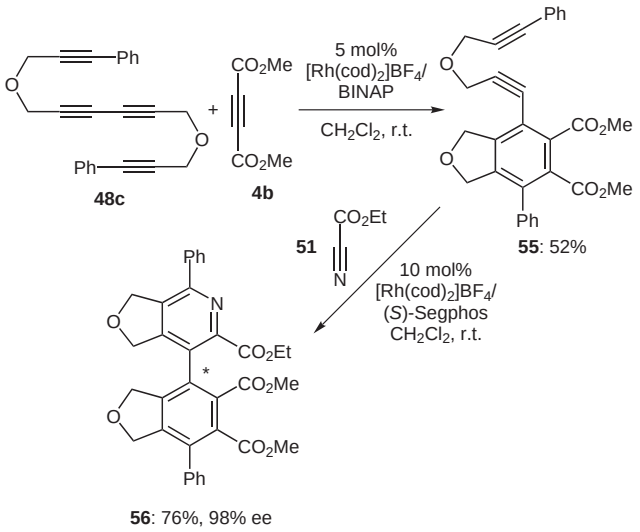
Next, the reaction of tetraynes **48** with electron-deficient monoalkynes **49** and **4b** was investigated. After screening various cationic rhodium(I)/BINAP-type bisphosphine complexes, we found that the use of 5 mol% [Rh(cod)$_2$]BF$_4$/(*S*)-Segphos gave the corresponding C_2-symmetric, axially chiral biaryls **50** with good to excellent enantioselectivity, although the yields were low to moderate (Scheme 24).[45] Importantly, this double [2+2+2] cycloaddition could be applied to the synthesis of axially chiral bipyridine **52** and bipyridone **54** using ethyl cyanoformate (**51**) and butyl isocyanate (**53**), respectively (Scheme 24).[45]



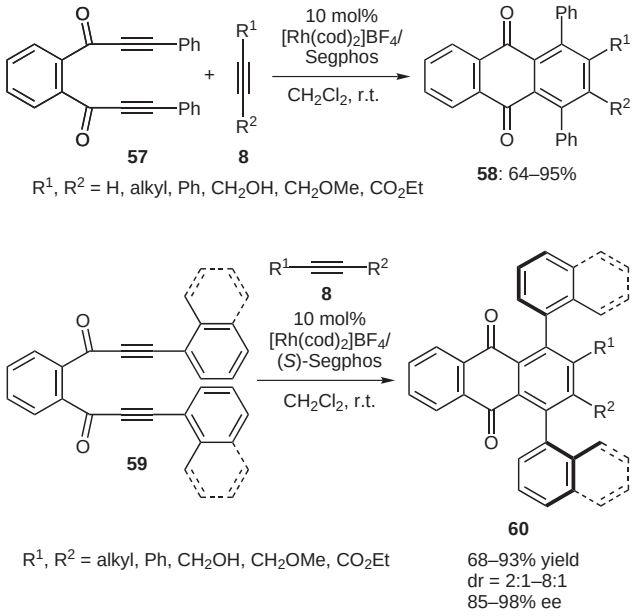
Scheme 24

Interestingly, the reaction of phenyl-substituted tetrayne **48c** with monoalkyne **4b** in the presence of 5 mol% [Rh(cod)$_2$]BF$_4$/BINAP gave the monoannulated product **55** in 52% yield and no corresponding biaryl was generated. The isolated monoannulated product **55** could be used for the enantioselective [2+2+2] cycloaddition with nitrile **51** in the presence of 5 mol% [Rh(cod)$_2$]BF$_4$/(*S*)-Segphos which gave axially chiral arylpyridine **56** in 76% yield and with 98% enantiomeric excess (ee) (Scheme 25).[45]

The cationic rhodium(I)/Segphos complex could be applied to the synthesis of 1,4-teraryls having anthraquinone structures.[46] We have determined that the reaction of 1,2-bis(3-phenylpropynoyl)benzene (**57**) with various monoalkynes **8** at room temperature gives 1,4-teraryls **58** in good yields (Scheme 26).[47] The use of 1,2-bis(3-aryl-



Scheme 25

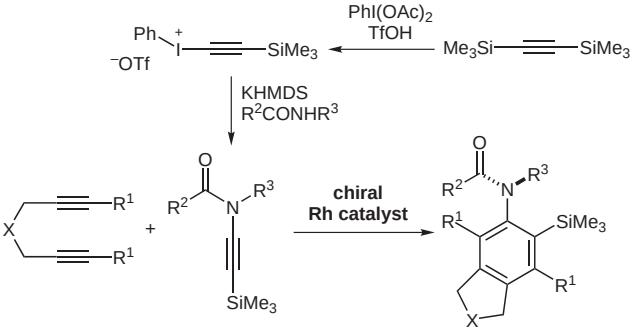


Scheme 26

propynoyl)benzenes **59**, possessing *ortho*-substituted phenyl at the alkyne termini, gave axially chiral 1,4-teraryls **60** in good yields and with good enantio- and diastereoselectivity (Scheme 26).[47]

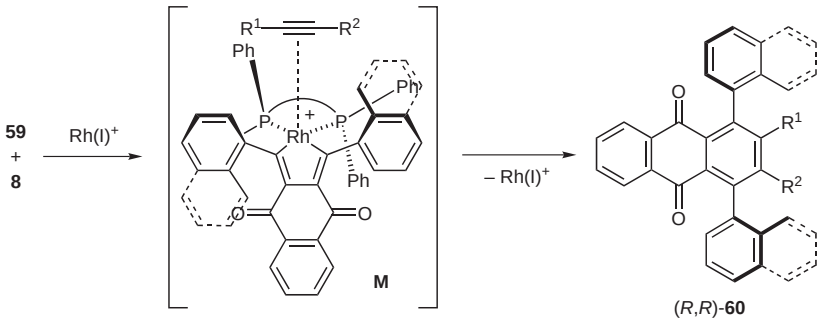
Both the enantio- and diastereoselectivities may be determined by the preferential formation of intermediate **M**, resulting from steric interaction between the *ortho*-substituents of **59** and the two axial PPh_2 groups of (*S*)-Segphos, and sterically less demanding coordination of monoalkyne **8** to rhodium. Reductive elimination of rhodium gives (*R*,*R*)-**60** and regenerates the rhodium catalyst (Scheme 27).

Construction of not only a chiral carbon–carbon axis, but also of a chiral carbon–nitrogen axis[48] is an interesting target of the cationic rhodium(I)/BINAP-type bisphosphine complex catalyzed, enantioselective [2+2+2] cycloaddition. We anticipated that a [2+2+2] cycloaddition of 1,6-diynes with *N*-[(trimethylsilyl)ethynyl]amides,[49] which can be readily prepared in two steps starting from commercially available bis(trimethysilyl)acetylene, would construct carbon–nitrogen axial chirality upon the formation of the benzene ring (Scheme 28).[50]

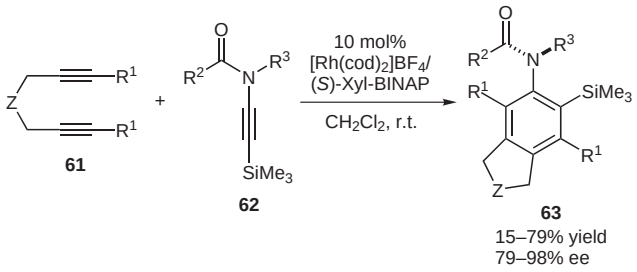


Scheme 28

Indeed, the reaction of 1,6-diynes **61** with *N*-[(trimethylsilyl)ethynyl]amides **62** in the presence of 10 mol% $[Rh(cod)_2]BF_4$/(*S*)-Xyl-BINAP gave axially chiral anilide derivatives **63** with good to excellent enantioselectivity (Scheme 29).[50] It should be noted that the trimethylsilyl group of product **63** is expected to be used for further functionalization.

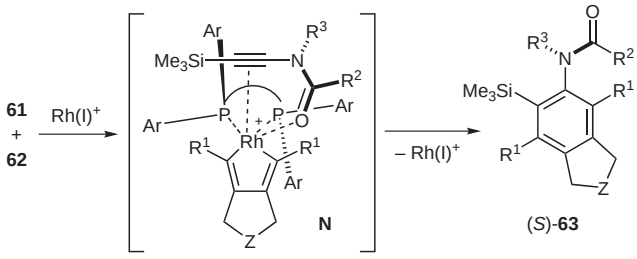


Scheme 27



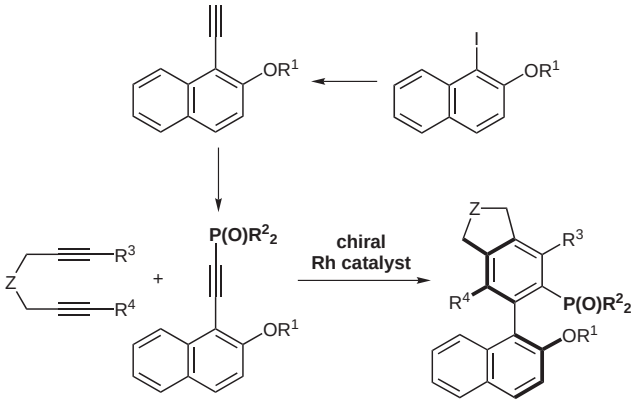
Scheme 29

The enantioselectivity of the above reaction may be determined by the preferential formation of intermediate **N**, resulting from coordination of the carbonyl group of **62** to rhodium, and the steric interaction between the *N*-alkyl group (R^3) of **62** and the diarylphosphine group (PAr_2) of (*S*)-Xyl-BINAP. Reductive elimination of rhodium gives (*S*)-**63** and regenerates the rhodium catalyst (Scheme 30).



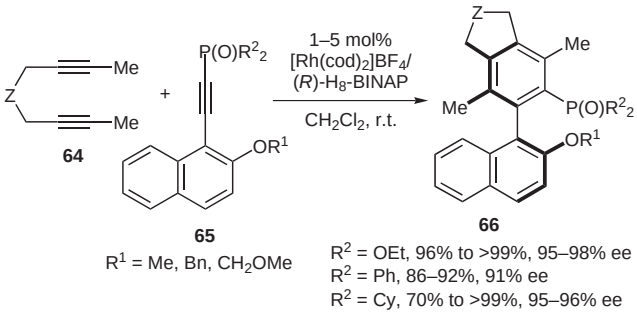
Scheme 30

In our enantioselective biaryl synthesis, the use of electron-deficient and coordinating alkynes possessing carbonyl groups was highly effective. However, although coordination of carbonyl groups to cationic rhodium enabled high enantioselectivity, high reactivity of alkynylcarbonyl compounds toward homo-[2+2+2] cycloaddition resulted in lowered yields of the desired cross-[2+2+2] cycloaddition products. To extend this methodology to the practical synthesis of axially chiral biaryl phosphorus compounds, the use of alkynylphosphonates instead of alkynylcarbonyl compounds was investigated (Scheme 31).[51–53] In this new approach, introduction of aromatic substituents including phosphorus, construction of a biaryl skeleton, and construction of axial chirality would be accomplished selectively in a single step. Furthermore, the reaction substrates, di-*ortho*-substituted (arylethynyl)phosphonates and phosphine oxides, are readily prepared through Sonogashira coupling of 2,6-disubstituted aryl halides with terminal alkynes followed by introduction of the phosphorus group at the resulting alkyne terminus. These two steps are not influenced by steric hindrance because of the sterically less demanding linear shape of alkynes. We envisaged that the electron-deficient and coordinating characteristics of the phosphorus moiety would enable high enantioselectivity, and its sterically demanding character would hinder homo-[2+2+2] cycloaddition.



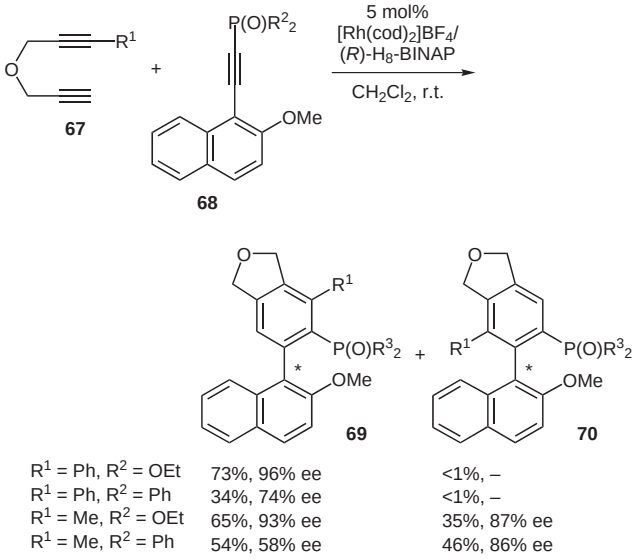
Scheme 31

Thus, we first investigated the asymmetric [2+2+2] cycloadditon of readily prepared 2-naphthol-derived alkynylphosphonates **65** with 1,6-diynes **64** in the presence of 5 mol% $[Rh(cod)_2]BF_4$/(*R*)-H_8-BINAP which successfully provided tetra-*ortho*-substituted, axially chiral biarylphosphonates **66** in excellent yields and with excellent enantioselectivity (Scheme 32).[53] Importantly, both high yields and enantioselectivity were achieved by employing sterically more demanding diphenylphosphine oxide and dicyclohexylphosphine oxide. Unreacted monoalkynes **65** could be recovered unchanged by silica gel chromatography. Furthermore, the catalytic activity of this rhodium complex is very high, so the reaction can be completed even in the presence of 1 mol% of the rhodium catalyst at room temperature and within one hour.



Scheme 32

The asymmetric [2+2+2] cycloaddition using unsymmetrical diynes was also examined (Scheme 33).[53] Diyne **67** possessing a phenyl group and a hydrogen at the alkyne termini reacted with **68** to give the corresponding biaryls **69** as single regioisomers with high enantioselectivity. On the other hand, diyne **67** possessing a methyl group and a hydrogen at the alkyne termini reacted with **68** to give the corresponding biaryls **69** and **70** as separable regioisomers in quantitative total yield and with good to high enantioselectivity.



Scheme 33

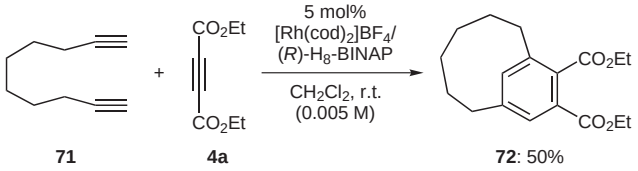
The above method allows the production of a range of new axially chiral biaryl phosphorus compounds containing polysubstituted top rings[54] which have not been readily accessible by conventional asymmetric aryl–aryl cross-coupling methods. Industrial application of this protocol is promising in view of the easy access to substrates, mild reaction conditions, simple operations, and high catalytic activity.

3.2 Construction of Planar Chirality

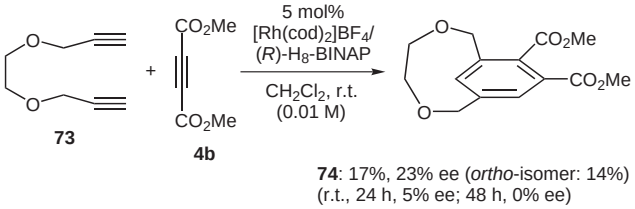
It is well-known that certain cyclophanes bearing short ansa chains exhibit planar chirality due to the restricted rotation of the aromatic ring.[55] Existing methods for their synthesis are based on the optical resolution of racemates, and straightforward enantioselective synthesis has not been realized to date.[56]

We found that the [2+2+2] cycloaddition of deca-1,9-diyne (**71**) and diethyl acetylenedicarboxylate (**4a**) gave [6]metacyclophane **72** in 50% yield (Scheme 34).[15] However, at room temperature, the ring flip of the hexamethylene chain of **72** was observed by ^{1}H NMR spectroscopy; therefore, cyclophane **72** cannot exhibit the planar chirality.[57]

Thus, the [2+2+2] cycloaddition of ether-linked terminal 1,9-diyne **73** and dimethyl acetylenedicarboxylate (**4b**) was investigated to increase the steric strain of the ansa chain. Although the reaction gave the desired ether-con-



Scheme 34

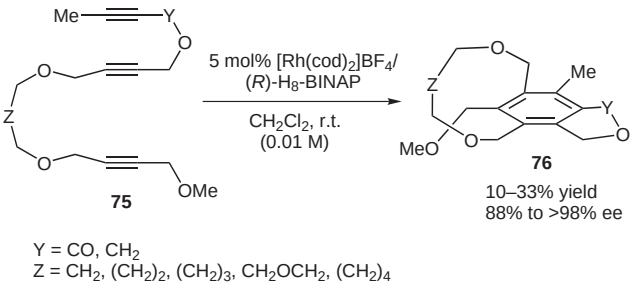


Scheme 35

taining [6]metacyclophane **74** with 23% ee, complete racemization of **74** proceeded at room temperature (Scheme 35).[58]

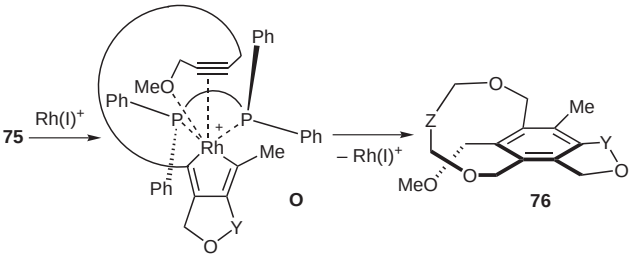
Consequently, we designed an intramolecular [2+2+2] cycloaddition of triynes, bearing substituents at two alkyne termini, which could form the corresponding ortho- or metacyclophanes.[59] These metacyclophanes would possess stable planar chirality because of no ring flip occurring.[60]

The reaction of methyl- and methoxymethyl-substituted triynes **75**, bearing ester or ether-linked 1,6-diyne moieties, in the presence of 5 mol% $[Rh(cod)_2]BF_4$/(*R*)-H_8-BINAP at room temperature gave the desired [7]–[10]metacyclophanes **76** with high enantioselectivity (88–>98% ee) (Scheme 36), although [7]–[10]orthocyclophanes were obtained as byproducts.[58]



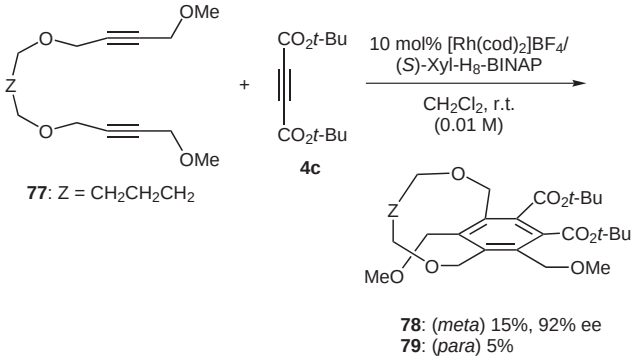
Scheme 36

The enantioselectivity would be determined by preferential formation of intermediate **O** resulting from the high reactivity of the 1,6-diyne moiety to the rhodium(I) complex, coordination of the terminal methoxy group to the cationic rhodium, and the steric interaction between the ansa chain of **75** and the PPh_2 groups of (*R*)-H_8-BINAP (Scheme 37).



Scheme 37

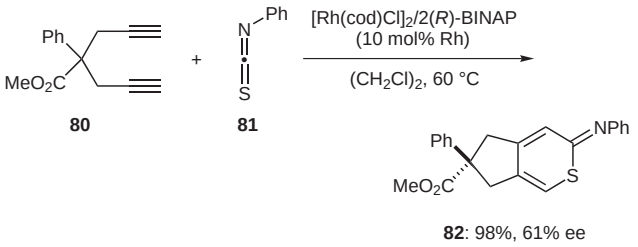
The intermolecular variant of this reaction was also investigated. The reaction of bis(methoxymethyl)-substituted diyne **77** with di-*tert*-butyl acetylenedicarboxylate (**4c**) in the presence of 10 mol% $[Rh(cod)_2]BF_4$/(*S*)-Xyl-H_8-BINAP at room temperature gave the desired [9]metacyclophane **78** in 15% yield and with 92% ee, along with [9]paracyclophane **79** in 5% yield (Scheme 38).[58] These intra- and intermolecular [2+2+2] cycloadditions represent a versatile new method for the synthesis of planar-chiral [7]–[10]metacyclophanes.



Scheme 38

3.3 Construction of Central Chirality

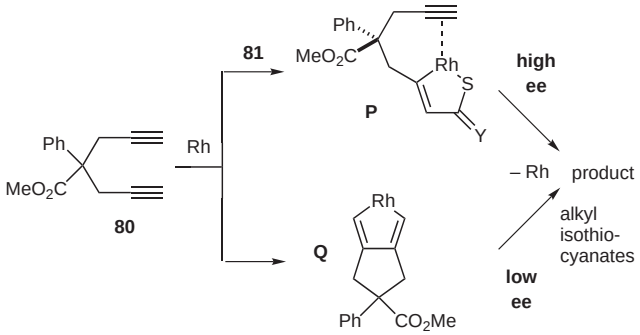
In order to construct central chirality using the rhodium-catalyzed [2+2+2] cycloaddition, an enantioselective desymmetrization of diynes was investigated. First we examined the desymmetrization of a symmetrical 1,6-diyne. When the reaction of phenylacetate-derived 1,6-diyne **80** with phenyl isothiocyanate (**81**) was conducted in the presence of $[Rh(cod)Cl]_2$/2 (*R*)-BINAP (10 mol% Rh) at 60 °C, enantioenriched bicyclic thiopyranimine **82** was obtained in 98% yield and with 61% ee (Scheme 39).[27] However, the reaction of **80** with alkyl isothiocyanates gave products with low ee.



Scheme 39

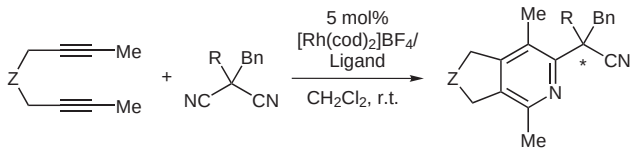
In the case of phenyl isothiocyanate (**81**), preferential formation of metallacycle **P** (Y = NPh) instead of **Q** may result in high enantioselectivity. On the other hand, preferential formation of metallacycle **Q** instead of **P** may result in low enantioselectivity, as observed in the case of alkyl isothiocyanates (Scheme 40).

The cationic rhodium(I)/BINAP-type bisphosphine complex catalyzed reaction of 1,6-diynes with malononitrile selectively afforded the corresponding monopyridines



Scheme 40

without formation of bipyridines.[34] Therefore, an enantioselective desymmetrization of substituted malononitriles was investigated. 1,6-Diyne **83** smoothly reacted with monosubstituted malononitrile **84a** in the presence of 5 mol% $[Rh(cod)_2]BF_4$/(*R*)-Xyl-Solphos[61] at room temperature to give enantioenriched bicyclic pyridine **85a**, containing a tertiary stereocenter, in 91% yield and with 64% ee (Scheme 41).[34] Furthermore, the reaction of **83** with sterically demanding disubstituted malononitrile **84b** proceeded in the presence of 5 mol% $[Rh(cod)_2]BF_4$/(*R*)-BINAP at room temperature to give enantioenriched bicyclic pyridine **85b**, containing a quarternary stereocenter, in 75% yield and with 33% ee.[34]

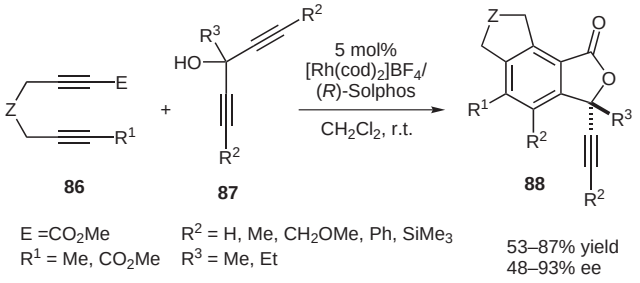


Scheme 41

Not only substituted malononitriles, but also 1,4-diynes could be employed for the rhodium-catalyzed enantioselective desymmetrization reactions. We anticipated that cationic rhodium(I)/BINAP-type bisphosphine complexes would catalyze the regio- and enantioselective formation of 3,3-disubstituted phthalides from diynes, possessing an alkoxycarbonyl group at an alkyne terminus, and tertiary propargylic alcohols through sequential one-pot transesterification and [2+2+2] cycloaddition because of the high Lewis acidity of cationic rhodium.[62,63]

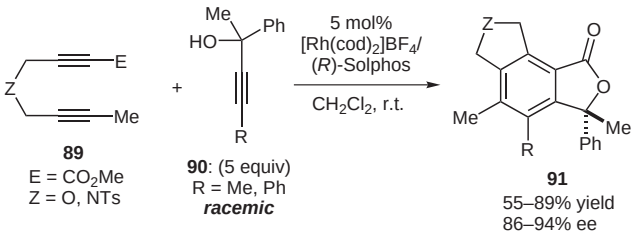
After screening various cationic rhodium(I)/BINAP-type bisphosphine complexes, we found that the reaction of symmetrical bispropargylic alcohols **87** and 1,6-diynes **86** in the presence of 5 mol% $[Rh(cod)_2]BF_4$/(*R*)-Solphos[61] at room temperature gave enantioenriched 3,3-disubstituted phthalides **88** in good yields and with good enantioselectivity without the formation of regioisomers (Scheme 42).[64,65]

The successful desymmetrization of symmetrical tertiary bispropargylic alcohols prompted our investigation into the kinetic resolution of racemic tertiary propargylic



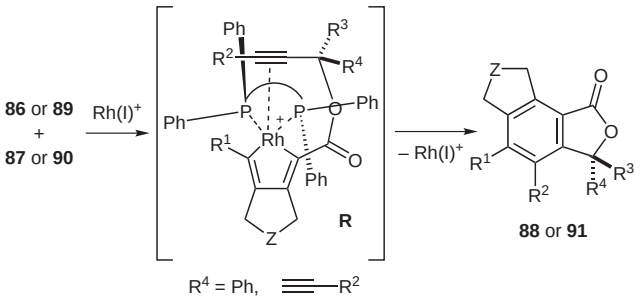
Scheme 42

alcohols. Although their reactivity is lower than that of tertiary bispropargylic alcohols, the reaction of racemic tertiary propargylic alcohols **90** (5 equiv), possessing phenyl or methyl groups at the alkyne terminus, with 1,6-diynes **89** proceeded to give the corresponding enantioenriched phthalides **91** in moderate to good yields and with high ee values (Scheme 43).[64]



Scheme 43

The observed high regio- and enantioselectivity may be explained by the selective formation of rhodium complex **R** obtained via oxidative coupling of the alkyne moieties of 1,6-diyne **86** or **89** and transesterification of the methoxycarbonyl group of **86** or **89**, activated by a cationic rhodium, with propargylic alcohol **87** or **90** (Scheme 44).

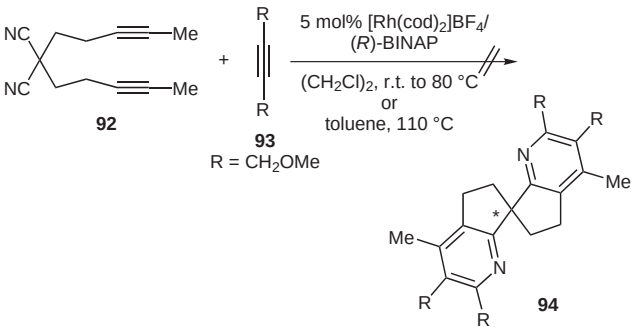


Scheme 44

3.4 Construction of Spiro Chirality

C_2-Symmetric spiranes with stable axial chirality are valuable structures for efficient chiral ligands because heteroatom-containing chiral spiranes easily form well-defined chelate complexes with many metals.[66] However, the catalytic enantioselective synthesis of C_2-symmetric spiranes is scarce.[67,68] A novel catalytic enantioselective synthesis of a C_2-symmetric spirane, 1,1′-spirobiindan-3,3′-dione, was developed by Hashimoto and co-workers through dirhodium(II)-catalyzed, double intramolecular carbon–hydrogen bond insertion.[67a] Saá and co-workers developed an elegant approach to spirobipyridine ligands that is based on a cobalt(I)-catalyzed, double [2+2+2] cycloaddition of bis-alkynenitriles with monoalkynes, although the synthesis provides racemates and the product yields are not sufficient (6–33% yield).[69]

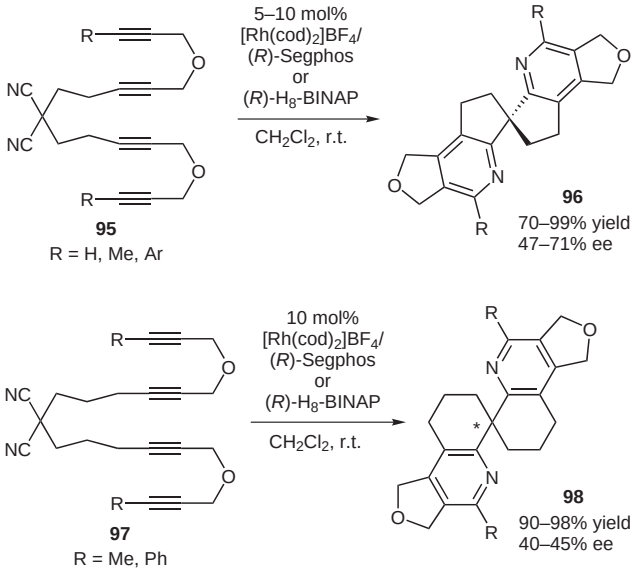
As described in the previous section, we have developed the enantioselective desymmetrization of substituted malononitrile with 1,6-diyne in the presence of 5 mol% $[Rh(cod)_2]BF_4$/(*R*)-BINAP yielding the corresponding enantioenriched monopyridine containing a quaternary stereocenter (Scheme 41). This successful enantioselective construction of a quaternary stereocenter prompted our investigation into a chiral spirobipyridine synthesis. First, we applied the abovementioned catalyst to the intermolecular double [2+2+2] cycloaddition of bis-alkynenitrile **92** with monoalkyne **93**, but spirobipyridine **94** was not obtained at all and **92** was recovered even at elevated temperatures (Scheme 45).[70]



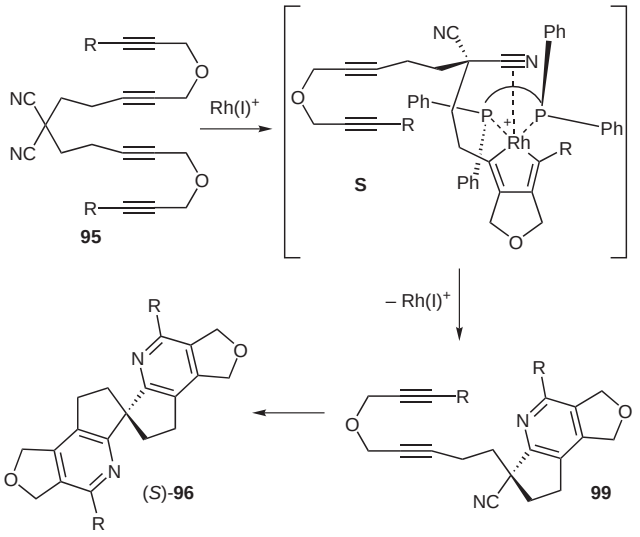
Scheme 45

Next, we attempted intramolecular double [2+2+2] cycloadditions of bis-diynenitriles **95**. Fortunately, these reactions proceeded in the presence of 5–10 mol% $[Rh(cod)_2]BF_4$/Segphos or H_8-BINAP to give the expected C_2-symmetric spirobipyridines **96** in 70–99% yield and with 47–71% ee values.[70] Although the reactions proceed intramolecularly, a diluted reaction condition or a slow addition was not necessary. Not only spirobipyridines **96** possessing a five-membered spiro skeleton, but also spirobipyridines **98** possessing a six-membered spiro skeleton could be synthesized; the latter were formed from bis-diynenitriles **97** (Scheme 46).

The enantioselectivity is determined by preferential formation of metallacycle **S** resulting from the avoidance of steric interaction between a cyano group of **95** and the PPh_2 groups of the *R*-ligand. Insertion of the cyano group followed by reductive elimination of rhodium gives the monoannulated product **99** and regenerates the rhodium catalyst. A subsequent intramolecular [2+2+2] cycloaddition of **99** provides the expected C_2-symmetric spirobipyridine (*S*)-**96** (Scheme 47).

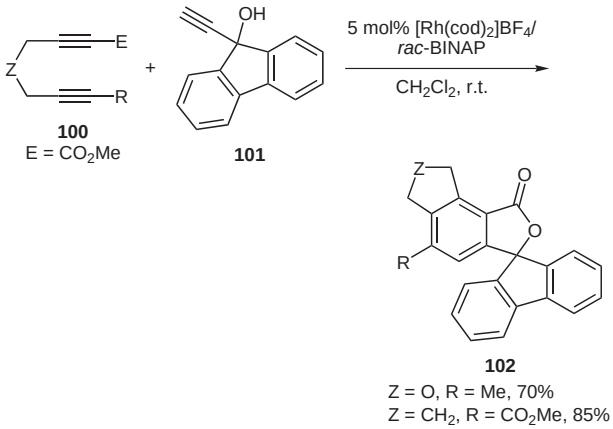


Scheme 46



Scheme 47

The rhodium-catalyzed sequential transesterification and [2+2+2] cycloaddition described in the previous section was successfully applied to the synthesis of spiro phthalides, which are key structures of functional dyes such as thermal recording materials.[71] Commercially available 9-ethynyl-9*H*-fluoren-9-ol (**101**) reacted with 1,6-diyne esters **100** in the presence of 5 mol% $[Rh(cod)_2]BF_4$/*rac*-BINAP to give spiro phthalides **102** in high yields (Scheme 48).[64]



Scheme 48

4 Summary

This account describes cationic rhodium(I)/BINAP-type bisphosphine complex catalyzed, highly chemo-, regio-, and enantioselective [2+2+2] cycloadditions. These reactions enabled the efficient catalytic synthesis of substituted benzenes, cyclophanes, and nitrogen heterocycles possessing axial, planar, central, and spiro chirality. We have demonstrated that the combination of a cationic rhodium(I) complex and a BINAP-type bisphosphine ligand exhibits dramatic enhancement of both catalytic activity and selectivity. Such a dramatic enhancement was also observed in the palladium-catalyzed cross-coupling reactions using a combination of specific palladium complexes and sterically demanding electron-rich monodentate phosphine ligands, such as tri-*tert*-butylphosphine. I believe that this account could demonstrate that not only new reagents, but also new combinations of known reagents sometimes can make a significant breakthrough in synthetic organic chemistry. Further development of highly selective [2+2+2] cycloadditions and applications of these procedures for the synthesis of valuable organic compounds including chiral reagents, functional organic materials, and biologically active compounds are in progress in our laboratory.[72] We would like to elucidate the mechanism for dramatic enhancement of catalytic activity and selectivity by the combination of cationic rhodium(I) complexes and BINAP-type bisphosphine ligands in due course.

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