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SYNTHESES OF HETEROCYCLES VIA ALKYNE CYCLOADDITIONS CATALYZED BY CYCLOPENTADIENYLRUTHENIUM-TYPE COMPLEXES

Yoshihiko Yamamoto*

Department of Basic Medicinal Sciences, Graduate School of Pharmaceutical Sciences, Nagoya University, Chikusa, Nagoya 464-8601, Japan

Abstract – Transition-metal catalysis not only simplifies molecular assemblies by reducing the synthetic steps but also decreases waste production, thus accomplishing an efficient and environmentally benign synthesis of heterocycles. Ruthenium catalysis has made significant progress in the past decades, and its application to heterocycle synthesis has become one of the major research topics. In particular, organoruthenium complexes with a cyclopentadienyl-type ligand have been successfully utilized in various carbon-carbon and carbon-heteroatom bond formations. This review extensively surveys the synthetic methods of five- and six-membered heterocycles via the ruthenium-catalyzed cycloadditions of alkynes with other unsaturated compounds. The applications of the ruthenium-catalyzed heterocycle synthesis are also briefly outlined.

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INTRODUCTION

Heterocyclic compounds are ubiquitous in natural products, pharmaceuticals, and advanced functional materials. Therefore, their efficient synthesis is one of the main research topics of organic chemistry. The conventional methods for heterocycle synthesis have relied on traditional condensation reactions under acidic or basic conditions; however, these methods lead to excessive waste production.[1] In order to make heterocycle synthesis an environmentally benign process, transition-metal (TM)-catalyzed reactions have been developed because TM catalysts, in general, work under mild and/or neutral conditions, thus decreasing the waste production.[2] Furthermore, TM catalysts enable the multicomponent assembly of heterocyclic structures from simple unsaturated precursors, thus simplifying the synthetic procedures. In this context, ruthenium catalysts have proved to be particularly versatile;[3] e.g., ruthenium-based metathesis catalysts have become extremely popular in heterocycle synthesis via carbon-carbon bond formations.[4] Apart from the metathesis chemistry, various types of ruthenium-catalyzed reactions can be employed for the fabrication of heterocyclic compounds via carbon-carbon and carbon-heteroatom bond formations.[5] This review surveys the syntheses of heterocycles via the ruthenium-catalyzed cycloadditions of alkynes because their reactive carbon-carbon triple bonds enable multiple carbon-carbon and carbon-heteroatom bond formations,[6] with particular attention to the ruthenium catalysts containing cyclopentadienyl (Cp)-type ligands. This is because the steric shielding by the Cp-type ligands plays a critical role not only in stabilizing the active ruthenium catalysts but also in controlling the product selectivity.[3,7] This review reports the examples involving carbon-heteroatom bond formations, and therefore, heterocycle syntheses via only carbon-carbon bond formations have not been discussed here. The applications of the ruthenium-catalyzed heterocycle synthesis will also be briefly outlined.

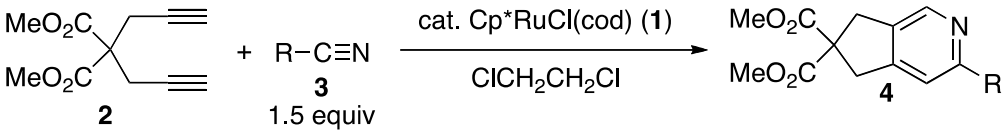
2. SYNTHESIS OF SIX-MEMBERED HETEROCYCLES

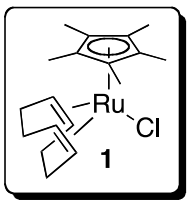
2-1. [2 + 2 + 2] CYCLOADDITIONS WITH NITRILES

Since the pioneering studies of stoichiometric reactions of cobaltacyclopentadienes by Wakatsuki and Yamazaki,[8] the TM-catalyzed [2 + 2 + 2] cycloadditions of two molecules of alkynes with nitriles or heterocumulenes have emerged as powerful tools for the synthesis of six-membered heterocycles such as pyridines and pyridones. Later, various TM complexes have been investigated to identify efficient catalysts for these useful synthetic processes.[9] The earliest examples of cobalt-catalyzed intermolecular [2 + 2 + 2] cycloadditions of alkynes with nitriles affording pyridines were independently reported by the Yamazaki and Bönneman groups.[10] The Vollhardt group reported the intramolecular variants using the cobalt catalyst.[11] In contrast, ruthenium catalysts had not been much explored until recently. Early

attempts of the ruthenium-catalyzed intermolecular [2 + 2 + 2] cycloaddition of alkynes with nitriles were not successful; the desired pyridines were not obtained with acceptable yield and selectivity.[12] In 2001, Itoh and coworkers reported that electron-deficient nitriles underwent partially intramolecular [2 + 2 + 2] cycloaddition with 1,6-diynes to selectively afford bicyclic pyridines.[13] The cycloaddition of malonate-derived 1,6-diyne **2** with nitriles **3**, which have an acyl group such as R = CO_2Et and COPh, in the presence of 2 mol% ruthenium catalyst **1**, which has a pentamethylcyclopentadienyl (Cp*) ligand, proceeded smoothly at 60 ˚C for 0.5 h to afford bicyclic pyridines **4** in high yields (Scheme 1). In contrast, simple nitriles such as acetonitrile and benzonitrile failed to undergo cycloddition with **2** under the same conditions.

Similarly, nitriles with 2-furoyl or acetyl groups were employed to afford the corresponding pyridines in good yields, although increased catalyst loadings and a higher reaction temperature of 80 ˚C were required. In contrast, tosyl cyanide (R = Ts), trichloroacetonitrile (R = CCl_3), and pentafluorobenzonitrile (R = C_6F_5) proved to be less efficient, affording moderate yields of pyridine derivatives (31%, 44%, and 67%, respectively). Increased loadings of these nitriles (3 equiv.) improved the product yields to 53%, 50%, and 80%, respectively. Various 1,6-diynes have been explored in this study, as shown in Figure 1, although lower yields were observed for diynes with a heteroatom tether.





R	**1**/mol%	Conditions	**4** yield/%
CO_2Et	2	60 ˚C, 0.5 h	83
COPh	2	60 ˚C, 0.5 h	84
CO(2-furyl)	5	60 ˚C, 5 h	79
COMe	10	80 ˚C, 1 h	90
Ts	10	80 ˚C, 24 h	31
CCl_3	10	60 ˚C, 24 h	44
C_6F_5	5	60 ˚C, 1 h	67

Scheme 1. [2 + 2 + 2] Cycloaddition of 1,6-diynes with electron-deficient nitriles

The cycloaddition of unsymmetrical ether-tethered diyne **5** with cyanoformate **3** furnished pyridine regioisomers **6** and **7** in 83% combined yield with the ratio of 88:12 (Scheme 2a);[14] thus, the cyanide was inserted in such a way that the steric repulsion between the terminal methyl substituent and the ethoxycarbonyl group was avoided. Interestingly, ester-tethered diyne **8** also exhibited a similar

regioselectivity, affording pyridine regioisomers **9** and **10** in 83% combined yield with the ratio of 82:18 (Scheme 2b). In this case, the regioselectivity was electronically controlled by the internal carbonyl group, and the ethoxycarbonyl group was oriented *para* to the carbonyl group in the major regioisomer. Moreover, the steric and electronic effects cooperatively improved the regioselectivity for the cycloaddition of diyne **11**, resulting in the formation of **12** and **13** in 84% combined yield with the ratio of 98:2 (Scheme 2c).

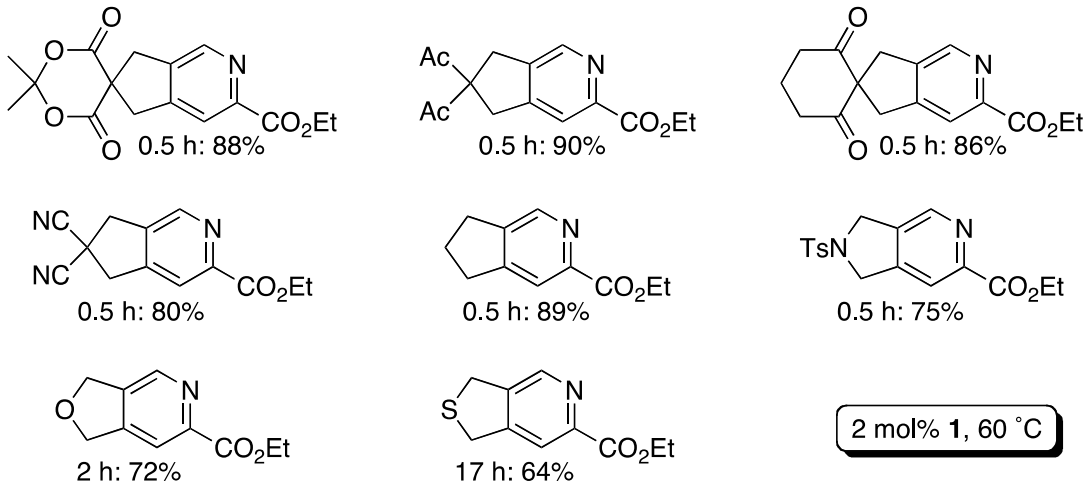
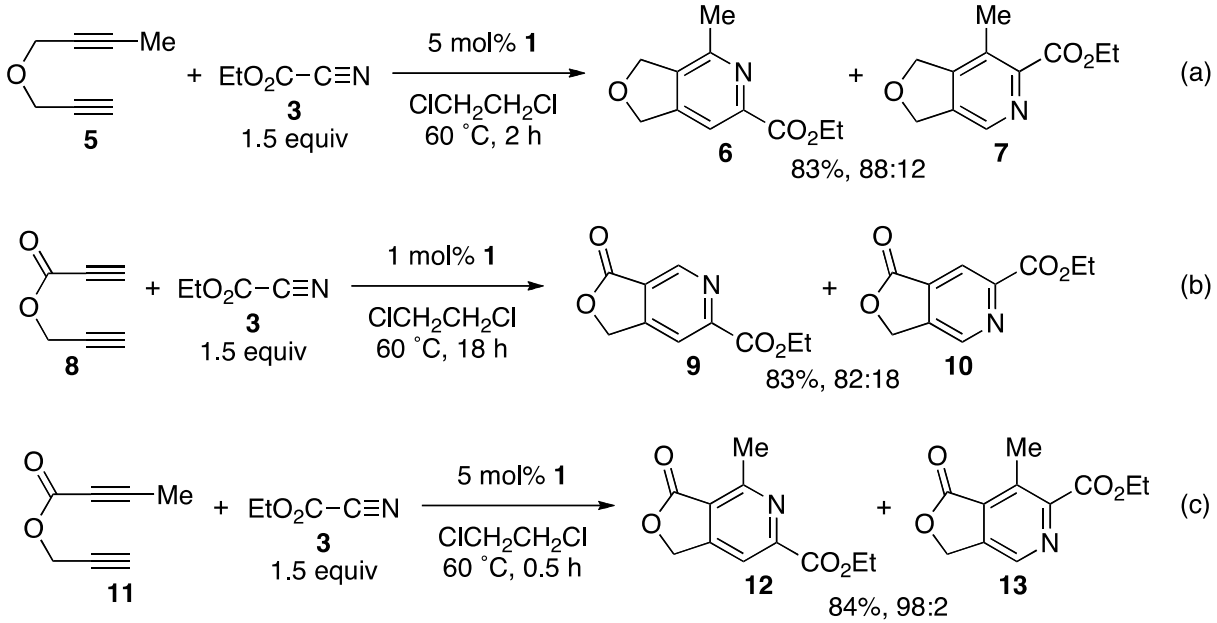
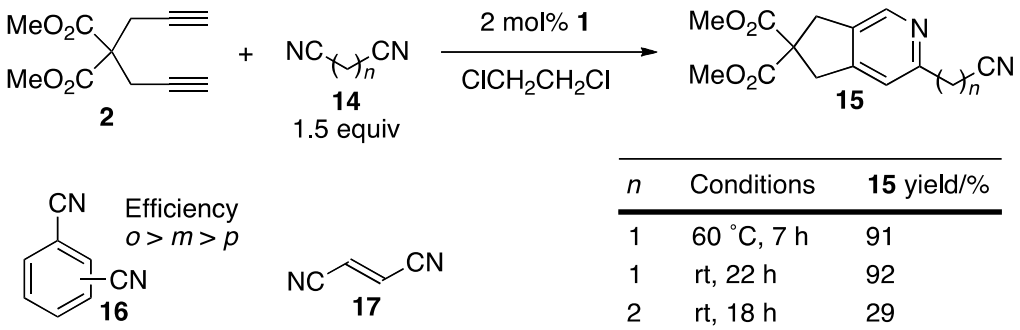


Figure 1. Scope of 1,6-diyne substrates in [2 + 2 + 2] cycloaddition with electron-deficient nitriles



Scheme 2. [2 + 2 + 2] Cycloaddition of unsymmetrical diynes with ethyl cyanoformate

Moreover, Itoh and coworkers also reported exceptional reactivity of dicyanides toward the ruthenium-catalyzed [2 + 2 + 2] cycloaddition with 1,6-diynes.[16] Diyne **2** and malononitrile (**14**, n = 1) underwent cycloaddition in the presence of 2 mol% catalyst **1** at 60 ˚C for 7 h to afford bicyclic pyridine **15** (n = 1) in 91% yield (Scheme 3). Furthermore, the above reaction proceeded even at room temperature; however, a prolonged reaction time (22 h) was required to afford **15** (n = 1) in 92% yield. Notably, one of the two cyano groups remained intact after the reaction, indicating that one cyano group coordinates to the catalyst, thus facilitating the incorporation of the other cyano group in the pyridine product. In good agreement with this observation, the distance between the two cyano groups was found to be critical. In fact, the reaction of homologous succinonitrile (**14**, n = 2) was found to be sluggish under similar conditions, affording the corresponding pyridine **15** (n = 2) in low yield (29%) because of the competitive [2 + 2 + 2] dimerization of the diyne. A similar effect of the distance between the cyano groups was observed for dicyanobenzenes **16**; the reactivity decreased in the following order: *o*- > *m*- > *p*-isomers. In contrast, the reactivity of fumaronitrile (**17**) was comparable to that of malononitrile, even though **17** has a two-carbon tether similar to succinonitrile. This may be attributed to the rigidity of the ethylene tether.

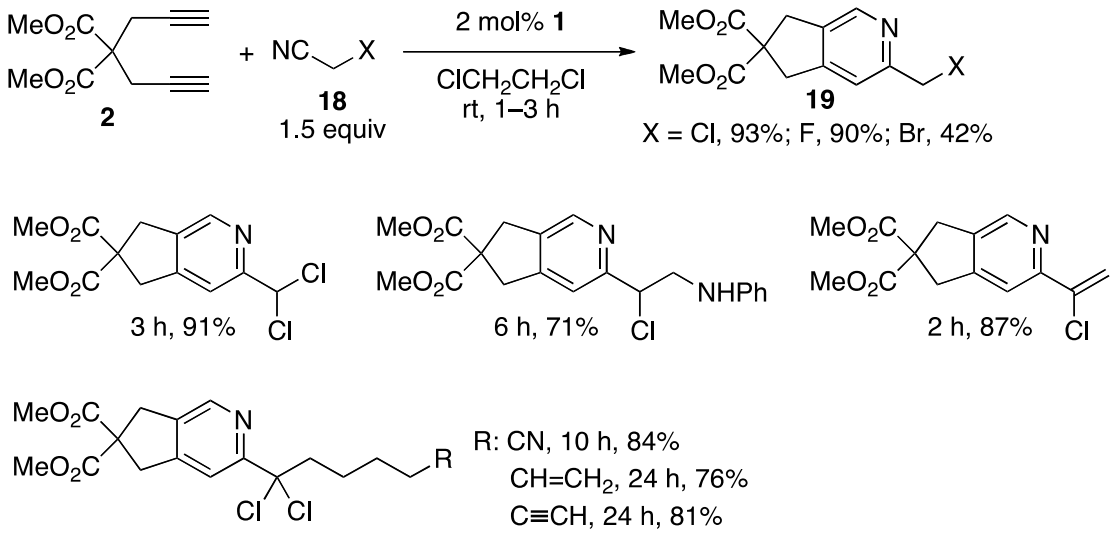


n	Conditions	**15** yield/%
1	60 ˚C, 7 h	91
1	rt, 22 h	92
2	rt, 18 h	29

Scheme 3. [2 + 2 + 2] Cycloaddition of 1,6-diyne with dicyanides

Similar to cyano groups, halogens were also found to act as a coordinating group in the ruthenium-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diynes and nitriles.[17] Acetonitrile derivatives **18** with a halogen atom α to the cyano group were allowed to react with diyne **2** in the presence of 2 mol% **1** at room temperature to afford bicyclic pyridines **19** (Scheme 4). The chloro- and fluoro-substituted nitriles furnished **19** (X = Cl or F) in excellent isolated yields (90–93%). However, for bromoacetonitrile, **19** (X = Br) was obtained in a low yield (42%), probably because of the instability of the bromomethyl-substituted product **19**. Various α-chloro nitriles furnished the corresponding pyridines in good yields (71–91%) as shown in Scheme 4. The functional moieties such as an aniline, alkenes, and even an alkyne, which is generally reactive toward the ruthenium-catalyzed cyclotrimerization, were tolerated in these reactions.

When a dichlorodicyanide was used, the cyano group in the close proximity of the chlorine atoms selectively underwent cycloaddition.

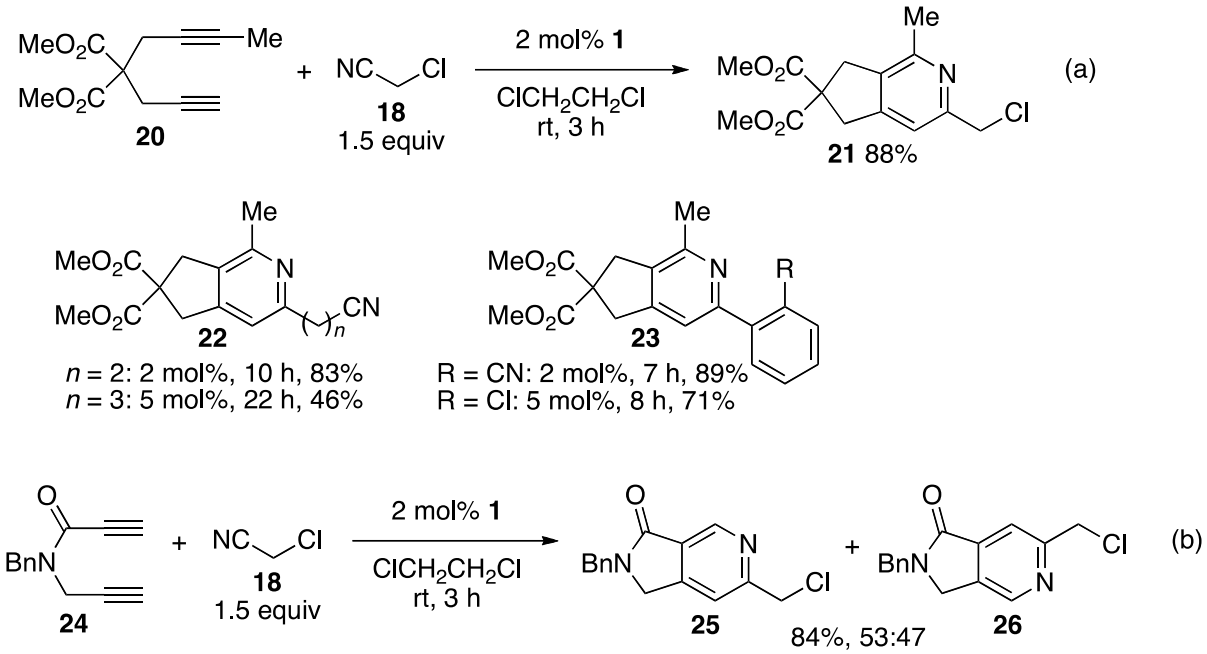


Scheme 4. [2 + 2 + 2] Cycloaddition of 1,6-diyne with α-haloacetonitriles

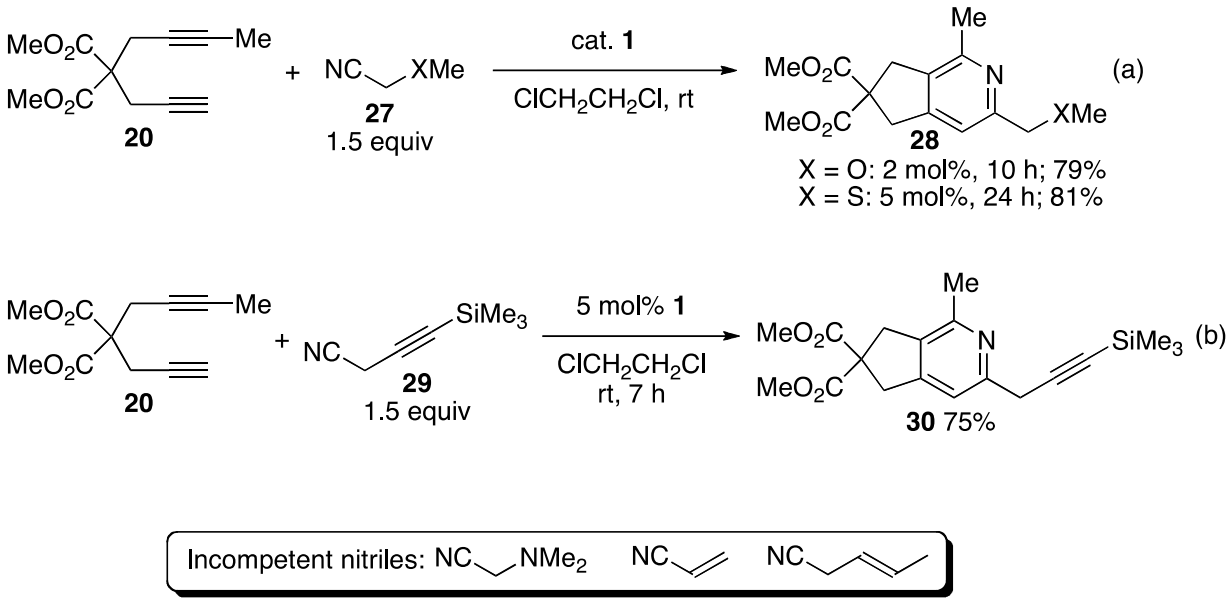
The steric and electronic effects on regioselectivity were investigated (Scheme 5).[18] The cycloaddition of unsymmetrical diyne **20**, which has a terminal methyl group, with chloroacetonitrile (**18**) proceeded at room temperature for 3 h to afford bicyclic pyridine **21** as the exclusive product in 88% yield (Scheme 5a). The introduction of a terminal methyl substituent on **20** demonstrated a favorable effect not only on the regioselectivity but also on the chemoselectivity for the desired pyridine by preventing the dimerization of **20**. In fact, the cycloaddition of **20** with less efficient dicyanides such as succinonitrile or glutaronitrile furnished the corresponding pyridines **22** in moderate-to-high yields (46–83%), and the use of phthalonitrile and *o*-chlorobenzonitrile furnished the desired biaryl products **23** in high yields (71–89%). In contrast, the cycloaddition of amide-tethered diyne **24** with **18** under the same conditions furnished regioisomeric pyridines **25** and **26** in an approximately 1:1 ratio, with almost complete loss of regioselectivity (Scheme 5b). Similar results were also obtained when malononitrile was used as the nitrile component. Thus, almost complete loss of the electronic directing effect in the halogen or cyano group-assisted [2 + 2 + 2] cycloadditions indicates that the reactions proceed by a different mechanism compared to the similar [2 + 2 + 2] cycloadditions using electron-deficient nitriles.

Other coordinating groups that assist [2 + 2 + 2] cycloaddition were also explored to expand the scope of nitrile components;[18] e.g., methoxy- or methylthio-substituted acetonitrile derivatives **27** underwent cycloaddition with diyne **20** to afford bicyclic pyridines **28** in ca. 80% yields (Scheme 6a). Moreover, the cycloaddition of diyne **20** with propargylnitrile **29** afforded the corresponding pyridine **30** in 75% yield,

indicating that the alkyne can work as a coordinating group (Scheme 6b). In contrast, dimethylaminoacetonitrile, acrylonitrile, and 3-pentenenitrile failed to undergo [2 + 2 + 2] cycloaddition. From these results, it was concluded that at least two lone pairs or π-bonds are necessary for the coordinating groups to be effective.

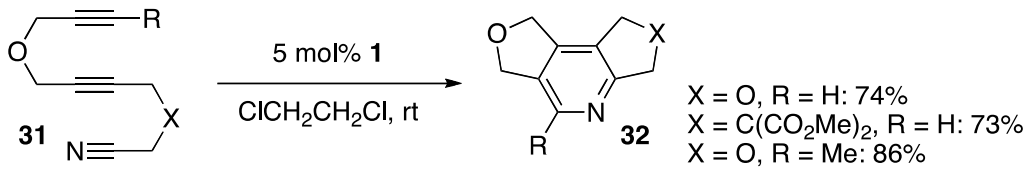


Scheme 5. [2 + 2 + 2] Cycloaddition of unsymmetrical diynes with chloronitriles and dicyanides



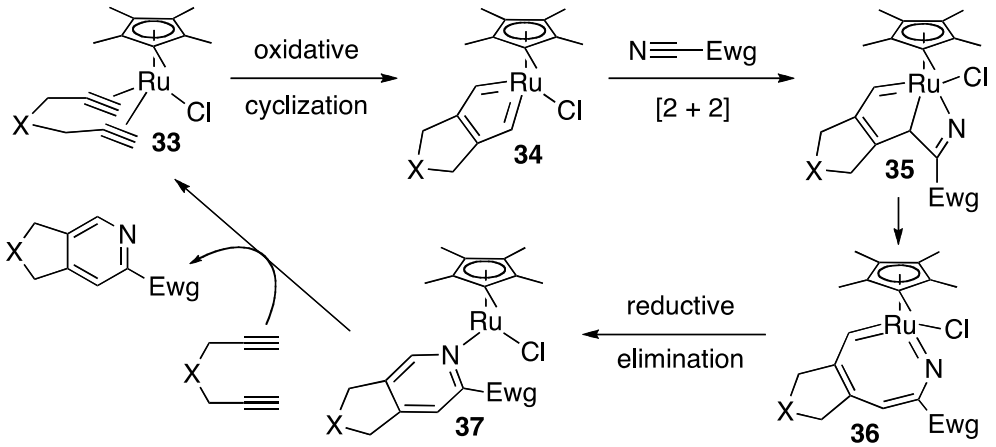
Scheme 6. [2 + 2 + 2] Cycloaddition of unsymmetrical diynes with various nitriles

Besides the above partially intramolecular [2 + 2 + 2] cycloadditions, a fully intramolecular cycloaddition was achieved using cyanodiynes **31** as shown in Scheme 7.[18] The desired tricyclic pyridines **32** were obtained in good yields (73–86%), although syringe pump addition was required to avoid intermolecular side reactions in the case of cyanodiynes with a terminal alkyne moiety (**31**, R = H).



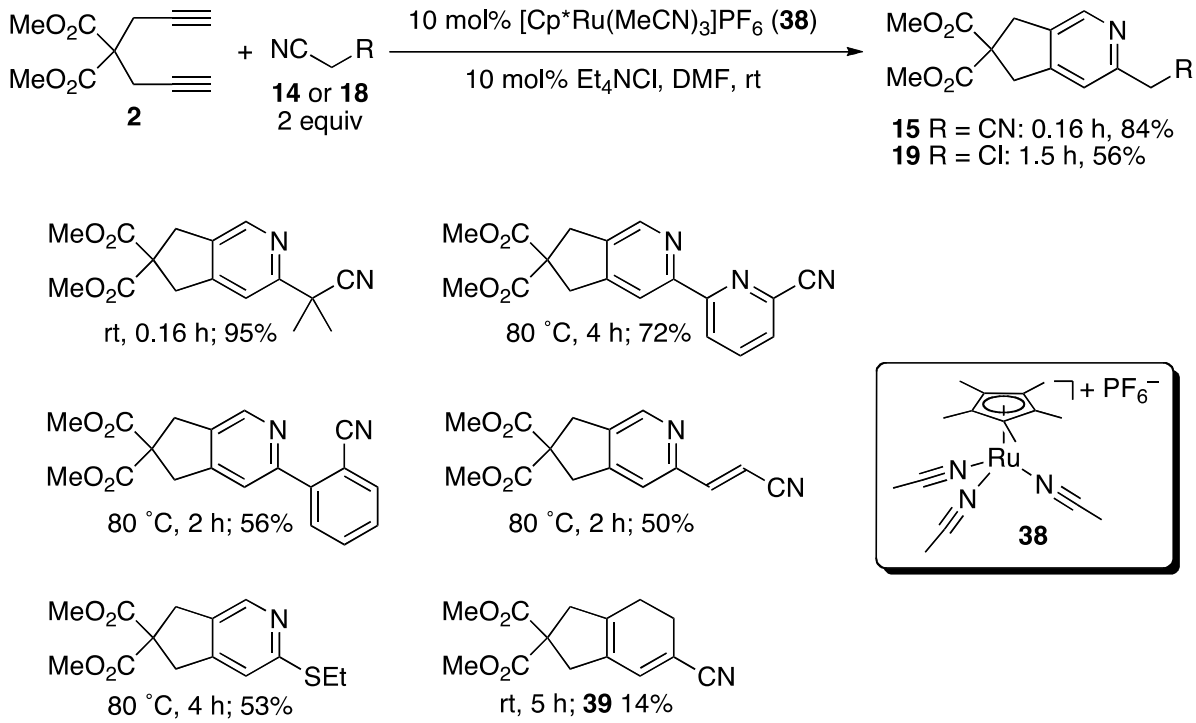
Scheme 7. Intramolecular [2 + 2 + 2] cycloaddition of cyanodiynes

A plausible mechanism for the ruthenium-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diynes with electron-deficient nitriles has been suggested based on the density functional theory (DFT) calculations (Scheme 8).[14,19] According to this mechanism, the cycloaddition starts with the oxidative cyclization of diyne complex **33** to produce ruthenacycle **34**, which, because of the metal-carbon double bonds, undergoes the [2 + 2] cycloaddition with an electron-deficient nitrile to produce azatricycle complex **35**. The DFT analysis showed that the electron-withdrawing group facilitates the [2 + 2] cycloaddition. The isomerization of **35** to **36** followed by reductive elimination produces η^1-pyridine complex **37**. Finally, the ligand exchange regenerates the initial diyne complex **33** and affords the cycloadduct, thus completing the catalytic cycle. On the other hand, the mechanism for the coordination-assisted [2 + 2 + 2] cycloaddition is unclear, even though a dinuclear pathway has been proposed to explain the role of the coordinating group.[18]

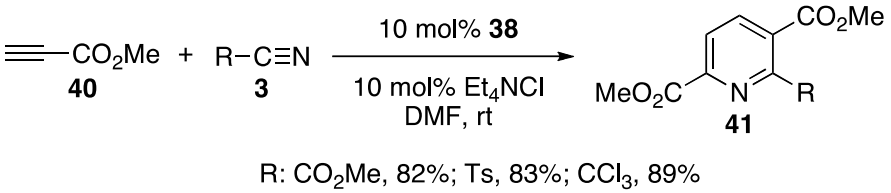


Scheme 8. Plausible mechanism for [2 + 2 + 2] cycloaddition of diynes with electron-deficient nitriles

The ruthenium-catalyzed [2 + 2 + 2] cycloadditions of alkynes with nitriles affording pyridines have also been achieved using different catalyst systems. Saá and coworkers used cationic complex **38** in the presence of a chloride anion source, Et_4NCl, in DMF.[20] The cycloaddition of diyne **2** with malononitrile (**14**) or chloroacetonitrile (**18**) in the presence of 10 mol% catalyst proceeded at room temperature to successfully afford bicyclic pyridines **15** and **19** in 84% and 56% yields, respectively (Scheme 9). This catalyst system exhibited a similar reactivity profile as that of catalyst **1** for the cycloaddition of alkynes with nitriles with a coordinating group. When dicyanides were used as the nitrile component, one of the two cyano groups remained intact. Interestingly, ethylthiocyanide was allowed to react with diyne **2** at 80 ˚C to afford the corresponding pyridine in a moderate yield (53%). On the other hand, acrylonitrile was shown to be an incompetent nitrile component, affording cyclohexadiene **39** in a low yield (14%) because of the competing cycloaddition of the activated alkene moiety of acrylonitrile. Cationic catalyst **38** in the presence of Et_4NCl was also effective for the intermolecular cyclocotrimerization of methyl propiolate (**40**) with electron-deficient nitriles **3** to exclusively afford 2,3,6-trisubstituted pyridines **41** in high yields of 82–89% (Scheme 10). In contrast, the same group reported that the attempted cycloaddition of malononitrile (**14**) with propiolate **40** failed to afford the corresponding pyridine, furnishing a regioisomer mixture of benzene triesters because of competitive cyclotrimerization of propiolate **40**.

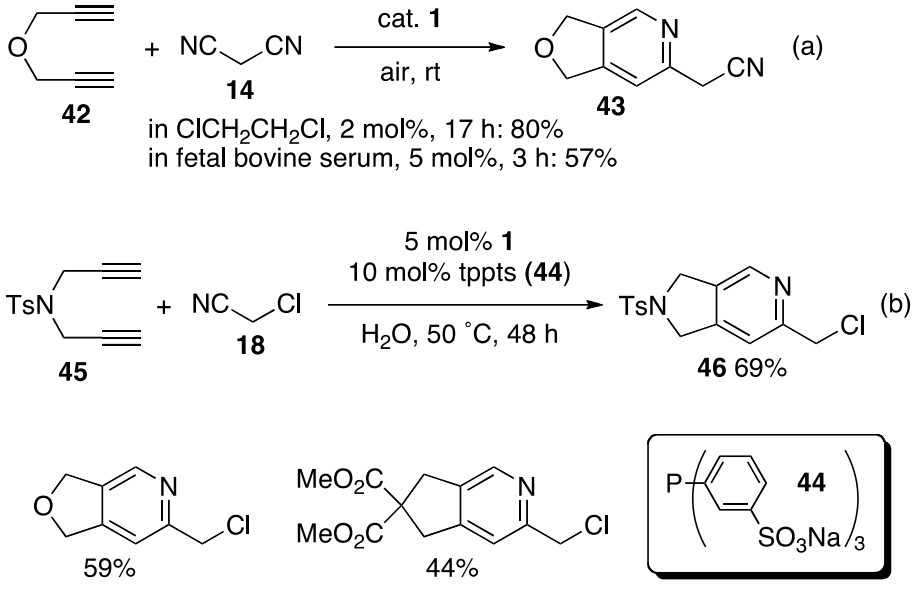


Scheme 9. [2 + 2 + 2] Cycloaddition of 1,6-diyne with nitriles using cationic catalyst



Scheme 10. [2 + 2 + 2] Cyclocotrimerization of propiolate with electron-deficient nitriles

The Teplý group demonstrated the robustness of ruthenium complex **1** in the presence of air for a series of catalytic reactions.[21] Thus, the [2 + 2 + 2] cycloaddition of diyne **42** with malononitrile (**14**) in the presence of air in 1,2-dichloroethane for 17 h furnished the desired bicyclic pyridine **43** in 80% yield, which was only slightly lower than that originally reported for the reaction under the argon atmosphere (Scheme 11a). The same reaction carried out in fetal bovine serum as the solvent with an increased catalyst loading furnished **43** in a moderate yield (57%), indicating the tolerance of catalyst **1** under biological conditions.[22] When a water-soluble phosphine ligand, trisodium tris(3-sulfonatophenyl)-phosphine (tppts, **44**) was employed, the [2 + 2 + 2] cycloaddition of tosylamide-tethered diyne **45** with chloroacetonitrile (**18**) in water at 50 ˚C for 48 h furnished bicyclic pyridine **46** in 69% yield (Scheme 11b).[23] However, the use of ether or malonate derivatives as the diyne substrates lowered the yields (44–59%). The coordination-assisted [2 + 2 + 2] cycloaddition of 1,6- and 1,7-diynes with dicyanides and halo nitriles were also carried out using Hoveyda-Grubbs catalyst.[24]

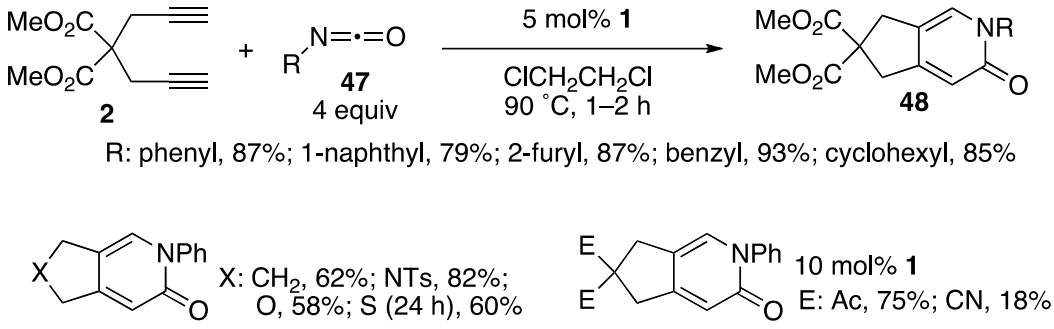


Scheme 11. [2 + 2 + 2] Pyridine formations under various conditions

2-2. [2 + 2 + 2] CYCLOADDITIONS WITH HETEROCUMULENES

The TM-catalyzed [2 + 2 + 2] cycloaddition of two molecules of alkynes with isocyanates has been studied as a powerful method for synthesizing pyridones. Hong and Yamazaki, and Hoberg and Oster independently reported an intermolecular reaction, i.e, cyclocotrimerization of alkynes with isocyanates.[25] Later, Vollhardt and Earl developed partially intramolecular versions using diynes and isocyanatoalkynes.[26] In particular, the cycloaddition of isocyanatoalkynes with alkynes affording 2,3-dihydro-5(1*H*)-indolizinones was successfully applied to the total synthesis of antitumor agent camptothecin.[26] Although the [2 + 2 + 2] cycloadditions of heterocumulenes have been less investigated than those of nitriles, several TM complexes have been identified as the catalysts for this reaction.[9]

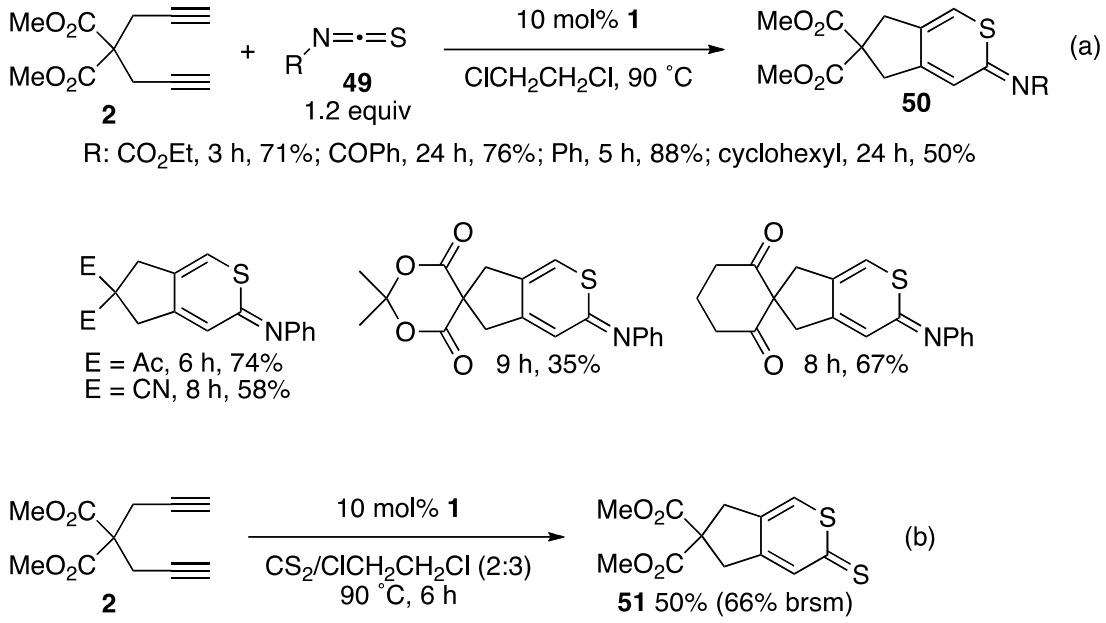
In 2001, Itoh and coworkers reported the ruthenium-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diynes with isocyanates to afford bicyclic pyridones.[27] Because of the electron-deficient carbon-nitrogen double bonds in isocyanates, they exhibit similar reactivity as electron-deficient nitriles. Diyne **2** and *N*-aryl and *N*-alkyl isocyanates **47** underwent cycloaddition in the presence of 5 mol% of **1** in refluxing 1,2-dichloroethane for 1–2 h to afford the expected bicyclic pyridones **48** in 79–93% yields (Scheme 12). Four equivalents of isocyanates **47** were required to ensure complete conversion of **2** because they tend to decompose under the reaction conditions. Besides the malonate derivative **2**, various 1,6-diynes were used for the pyridone synthesis except for the malononitrile-derived diyne, which furnished the product in a low yield (18%).



Scheme 12. [2 + 2 + 2] Cycloaddition of 1,6-diynes with isocyanates

Isothiocyanates were also investigated as heterocumulene components instead of isocyanates by Itoh and coworkers.[28] They reported that the carbon-sulfur double bond of isothiocyanates could be successfully incorporated in the [2 + 2 + 2] cycloaddition. Although 10 mol% of the catalyst was required, the reaction of diyne **2** with 1.2 equiv of isothiocyanates **49** in refluxing 1,2-dichloroethane furnished bicyclic thiopyranimines **50** in 50–88% yields (Scheme 13a). Isothiocyanates with *N*-substituents such as ester, ketone, phenyl, and cyclohexyl groups have also been used. The quaternary carbon center on the tether of

the diyne substrates is essential for the cycloaddition probably because isothiocyanates strongly coordinate to the ruthenium center as soft ligands. It is assumed that the Thorpe-Ingold effect of the quaternary centers plays an important role in facilitating the coordination of the diyne substrates and their oxidative cyclization leading to the ruthenacycle key intermediates.[29] In good agreement with this assumption, the increased loading of *N*-ethoxycarbonyl isothiocyanate lowered the yield of the cycloadduct. Besides isothiocyanates, carbon disulfide also participated in the [2 + 2 + 2] cycloaddition with a 1,6-diyne.[28] Diyne **2** was heated in a mixture of carbon disulfide/1,2-dichloroethane (2:3 v/v) in the presence of 10 mol% **1** at 90 ˚C for 6 h to afford the desired bicyclic dithiopyran **51** in 50% yield along with 24% recovery of diyne **2** (Scheme 13b).

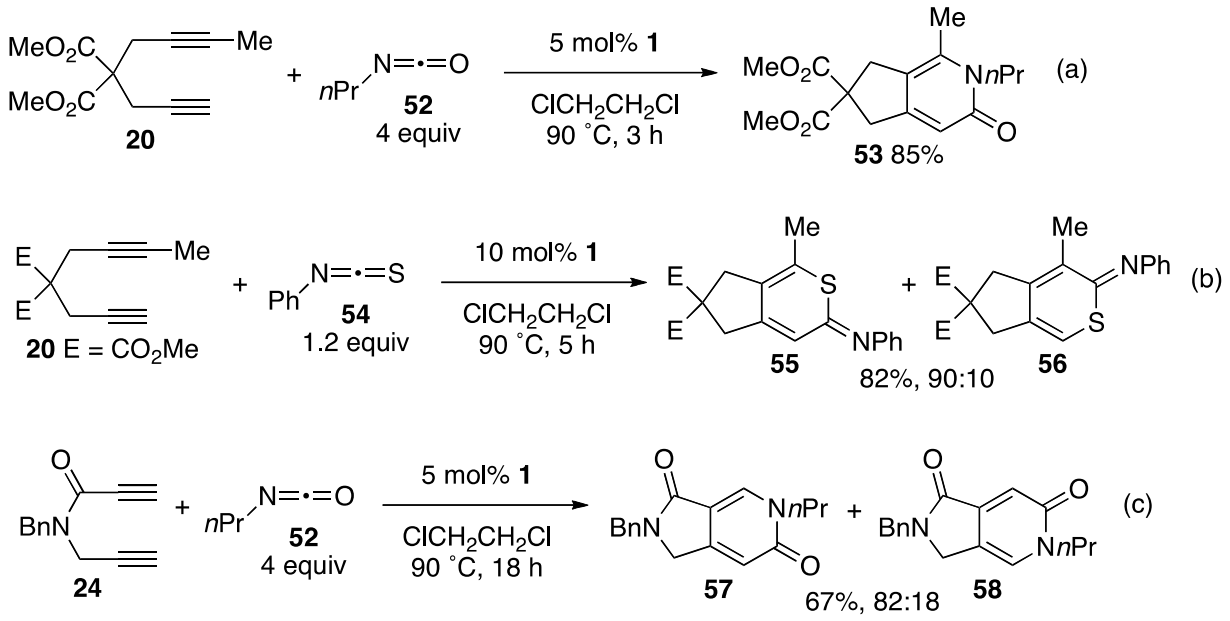


Scheme 13. [2 + 2 + 2] Cycloaddition of 1,6-diynes with isothiocyanates and carbon disulfide

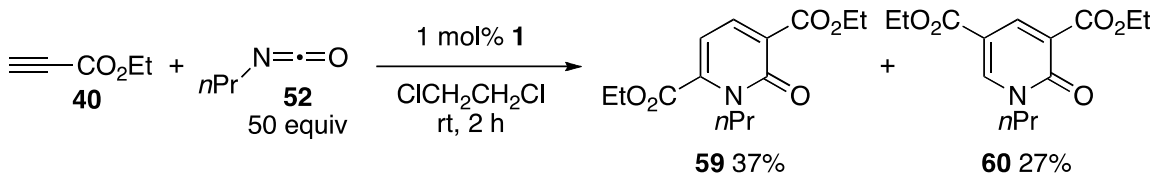
The regioselectivity of the [2 + 2 + 2] cycloadditions of *N*-propyl isocyanate (**52**) and *N*-phenyl isothiocyanate (**54**) has been investigated (Scheme 14).[14] The reaction of unsymmetrical diyne **20** and **52** in the presence of 5 mol% **1** exclusively furnished pyridone **53** in 85% yield (Scheme 14a). Similarly, the reaction of **20** with isothiocyanate **54** in the presence of 10 mol% **1** furnished a 9:1 regioisomer mixture of **55** and **56** in a high combined yield of 82% (Scheme 14b). Besides the steric effect, the electronic effect was also investigated by carrying out the reaction of amide **24** with isocyanate **52** for 18 h to afford **57** and **58** with a lower yield (67%) and a lower regioselectivity of 82:18 (Scheme 14c).

The cyclocotrimerization of ethyl propiolate (**40**) and isocyanate **52** furnished regioisomeric pyridones **59** and **60** in 37% and 27% yields, respectively (Scheme 15).[14] However, this fully intermolecular [2 + 2 + 2] cycloaddition was found to be less selective. Although a large excess of **52** (50 equiv) was used, the

pyridone formation was accompanied by the cyclotrimerization of **40**, leading to regioisomeric benzene triesters. Notably, two of the four possible regioisomers of the expected pyridones were selectively formed in the cyclocotrimerization of **40** with **52**.

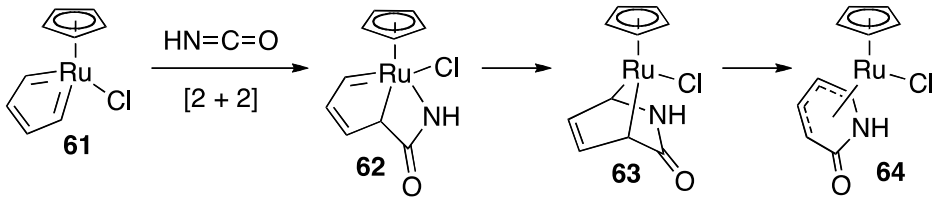


Scheme 14. [2 + 2 + 2] Cycloadditions of unsymmetrical diynes with heterocumulenes



Scheme 15. [2 + 2 + 2] Cyclocotrimerization of propiolate with isocyanate

The mechanism of [2 + 2 + 2] cycloadditions of heterocumulenes was proposed based on the DFT calculations by Kirchner and coworkers.[30] A model reaction of acetylene with isocyanic acid (HN=C=O) proceeds via ruthenacycle **61**, which undergoes [2 + 2] cycloaddition with the carbon-nitrogen double bond of isocyanic acid to produce ruthenabicycle **62** followed by the isomerization of **62** to **63** via a 1,2-nitrogen shift from the ruthenium center to the neighboring carbene carbon (Scheme 16). Finally, the reductive elimination of pyridone from **63** produces **64**. The transformation from **62** to **63** has the highest activation barrier. The reaction of isothiocyanic acid (HN=C=S) was also investigated to elucidate a similar mechanism.

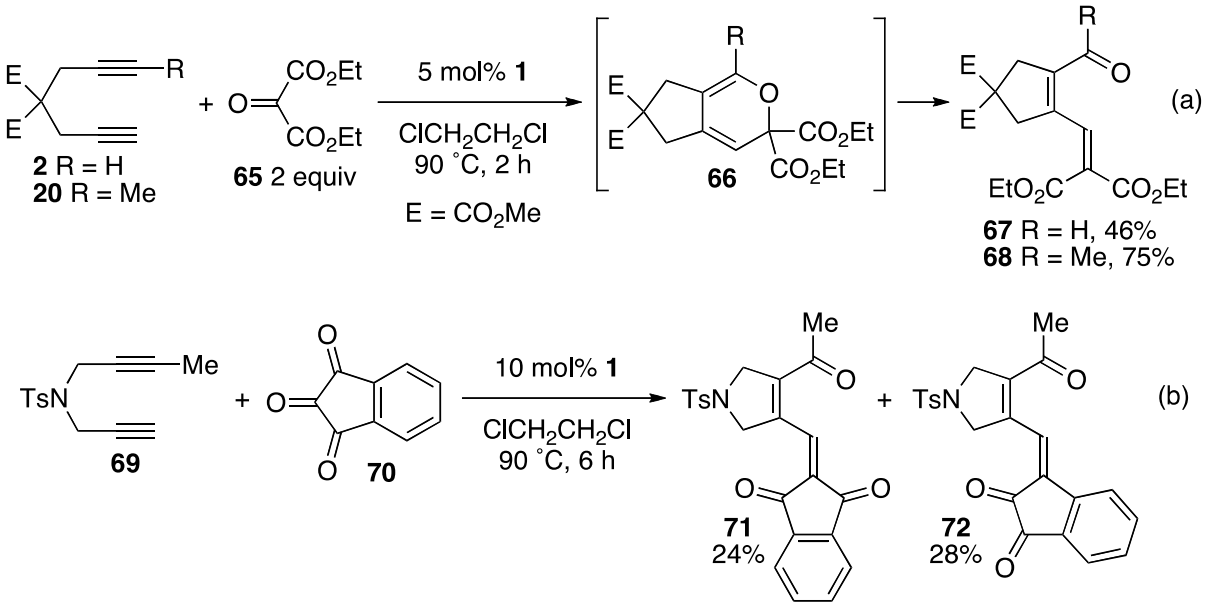


Scheme 16. Proposed mechanism of cyclocotrimerization of acetylene with isocyanic acid

The [2 + 2 + 2] cycloadditions of 1,6-diynes with isocyanates, isothiocyanate, and carbon disulfide were also carried out using Hoveyda-Grubbs catalyst.[31] Regioselectivities were similar to those observed for the above examples using catalyst **1**.

2-3. MISCELLANEOUS CYCLOADDITIONS WITH KETONES

As shown in the preceding sections, the ruthenium-catalyzed [2 + 2 + 2] cycloadditions involving the carbon-nitrogen triple bonds of nitriles and carbon-nitrogen and carbon-sulfur double bonds of heterocumulenes have been extensively explored. However, the catalytic cycloadditions involving the carbon-oxygen double bonds of ketones have attracted much less attention, probably because of the low coordinating ability of carbonyl groups to TM complexes. Stoichiometric and catalytic [2 + 2 + 2] cycloadditions of alkynes and ketones have been achieved using cobalt, zirconium, nickel, and rhodium complexes.[32–35] Itoh and coworkers also reported the ruthenium-catalyzed [2 + 2 + 2] cycloaddition of 1,6-diynes with tricarbonyl compounds.[36] The reaction of 1,6-diyne **2** with a highly electron-deficient ketone, ketomalonate **65**, in the presence of 5 mol% **1** at 90 ˚C did not afford the desired bicyclic pyran **66** (R = H); however, the corresponding elecrocyclic ring-opening product **67** was obtained in a moderate yield of 46% (Scheme 17a). When unsymmetrical diyne **20** with a terminal methyl group was used as the substrate, dienylketone **68** was obtained as a ring-opened product with an improved yield of 75%. The substrate scope of the diyne is shown in Figure 2. Similar dienyl ketones were obtained as single products in 42–71% yields from the reactions of various unsymmetrical 1,6-diynes with ketomalonate **65**. On the other hand, the reaction of diyne **69** with indanetrione **70** furnished two regioisomers **71** and **72** in 24% and 28% yields, respectively (Scheme 17b). Different carbonyl compounds such as ethyl pyruvate, diacetyl, and decafluorobenzophenone were also tested; however, none of them furnished the desired cycloaddition product. The mechanism of [2 + 2 + 2] cycloaddition of dipropargyl ether with ketomalonodialdehyde has been studied using the DFT calculations.[37]



Scheme 17. [2 + 2 + 2] Cycloaddition of 1,6-diynes with tricarbonyl compounds

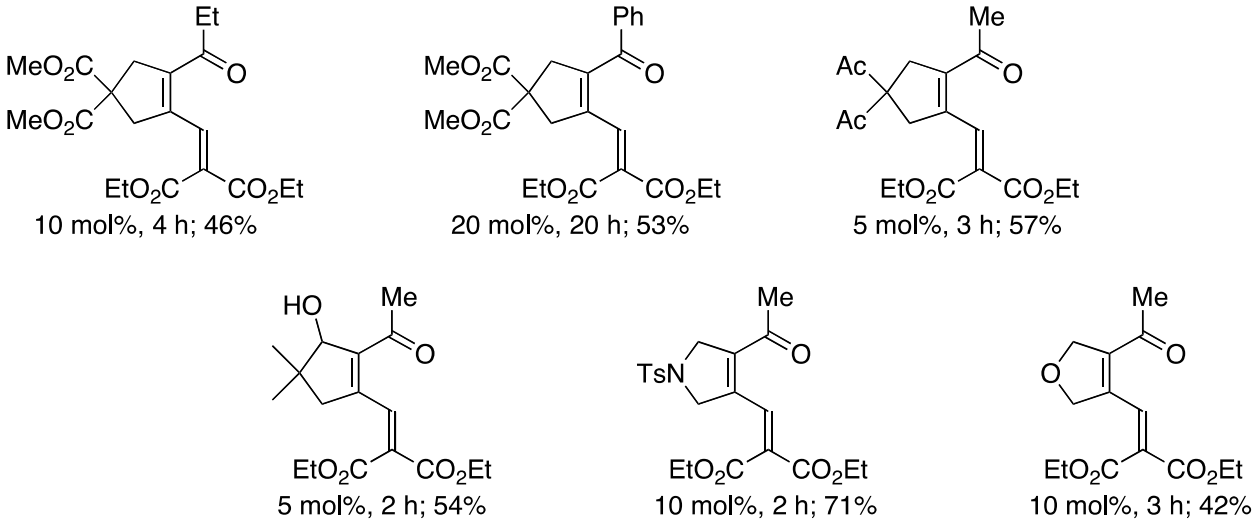
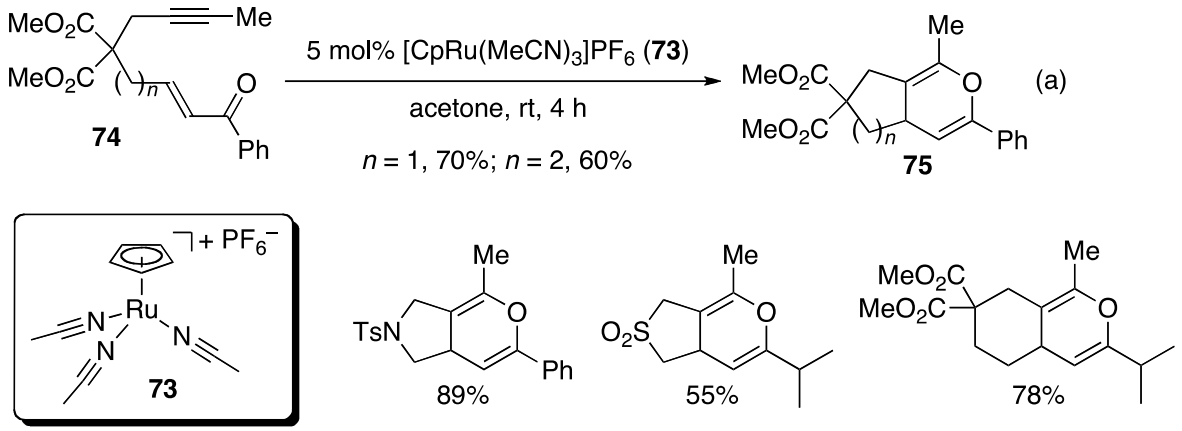


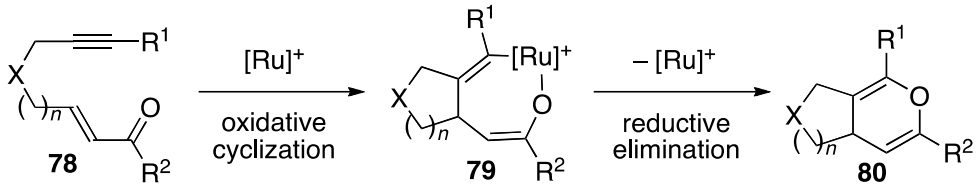
Figure 2. Scope of diyne substrates in [2 + 2 + 2] cycloaddition with ketomalonate

The bicyclic 2*H*-pyrans obtained by [2 + 2 + 2] cycloaddition readily underwent electrocyclic ring opening to afford dienyl carbonyl compounds as shown above.[34] In contrast, 4*H*-pyrans are stable at room temperature; thus, the ring opening reactions does not occur. Trost and co-workers reported interesting transformations of ω-alkynylenones using cationic ruthenium complex **73** as the catalyst.[38] ω-Alkynylenone **74** (n = 1) underwent intramolecular oxa Diles-Alder cycloaddition in the presence of 5 mol% **73** at room temperature to afford bicyclic 4*H*-pyran **75** (n = 1) in 70% yield (Scheme 18). This fascinating [4 + 2] cycloaddition also proceeded with homologous substrate **74** (n = 2), although the yield

of cyclohexane-fused product **75** (n = 2) decreased to 60%. This method tolerates sulfonamide, sulfone, and isopropyl ketones. However, a substrate with terminal alkyne moiety failed to afford the desired pyran. A plausible mechanism for this transformation was explained by the oxidative cyclization of ω-alkynylenone **78** leading to oxaruthenacycle **79** followed by reductive elimination to afford **80** (Scheme 19).



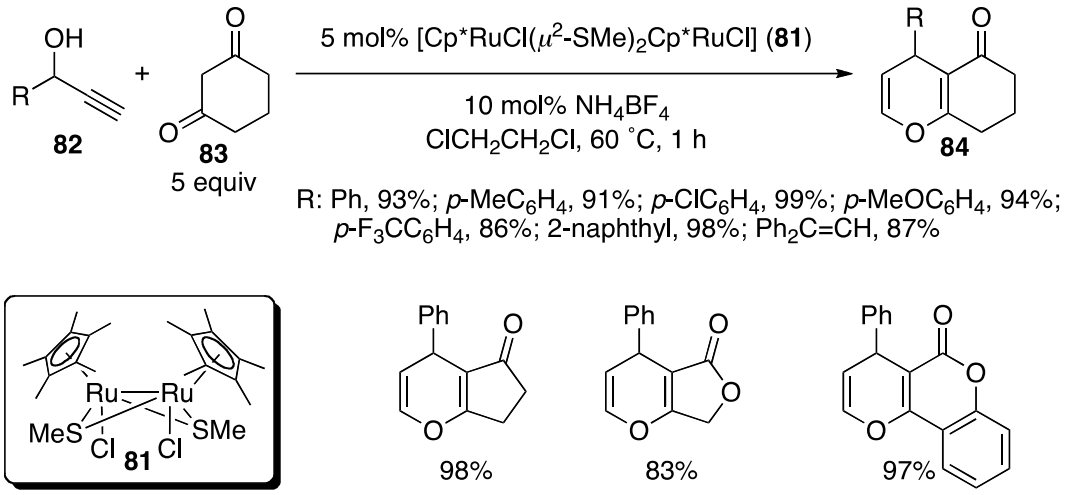
Scheme 18. Intramolecular [4 + 2] cycloaddition of ω-alkynylenones



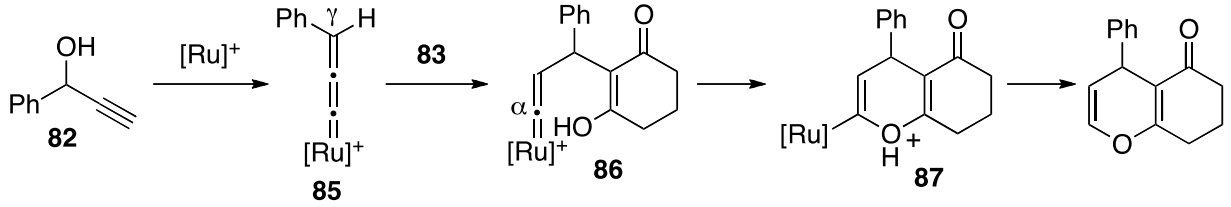
Scheme 19. Proposed mechanism for intramolecular [4 + 2] cycloaddition of ω-alkynylenones

A formal [3 + 3] cycloaddition route to bicyclic 4*H*-pyrans was also developed by Nishibayashi and coworkers.[39] They reported the ruthenium-catalyzed propargylic substitution of propargylic alcohols **82** with 1,3-cyclohexanedione **83** using a thiolate-bridged dinuclear complex **81** as the catalyst precursor (Scheme 20). The cycloaddition of **82** and 5 equiv of **83** in the presence of 5 mol% **81** and 10 mol% NH_4BF_4 at 60 ˚C for 1 h furnished cyclohexenone-fused pyrans **84** in high yields (86–99%). Electron-rich and electron-deficient aryl groups, 2-naphthyl group, and 2,2-diphenylvinyl group could be incorporated as the substituent R on the propargylic alcohol substrates **82**. Besides 1,3-diketones such as **83** and 1,3-cyclopentanedione, tetronic acid and 4-hydroxycoumarin also worked well as the 1,3-dicarbonyl components. However, 1,3-cycloheptanedione, acetylacetone, and methyl acetoacetate furnished simple propargylic substitution products rather than the corresponding pyrans. A cationic dinuclear ruthenium complex, which was produced from the reaction of **81** and NH_4BF_4, was proposed as the catalyst. This

cationic catalyst is presumed to convert propargylic alcohol **82** to allenylidene complex **85**, which would then react with 1,3-cyclohexanedione at the γ carbon to produce vinylidene complex **86** (Scheme 21). Because of the keto-enol equilibrium of the 1,3-diketone moiety of **86**, the hydroxyl group would attack the vinylidene α carbon to afford the final bicyclic pyrans via protonolysis of vinylruthenium **87**.



Scheme 20. Formal [3 + 3] cycloaddition of propargylic alcohols with 1,3-dicarbonyl compounds



Scheme 21. Proposed mechanism of formal [3 + 3] cyclocoupling leading to bicyclic pyran

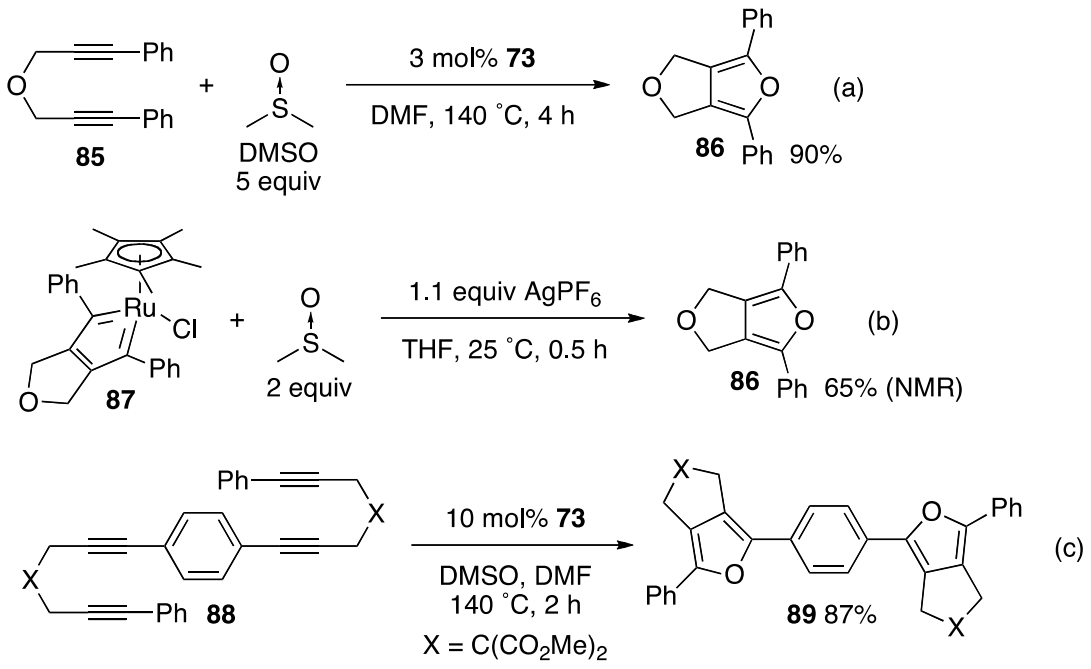
3. SYNTHESIS OF FIVE-MEMBERED HETEROCYCLES

3-1. [2 + 2 + 1] CYCLOADDITIONS

Furans are important oxygen heterocycles found in natural products, pharmaceuticals, and advanced functional materials.[1] Beller and co-workers have developed an efficient synthetic methodology to construct 2,5-diarylfurans form arylalkynes involving two TM-catalyzed reactions: (i) the ruthenium-catalyzed hydroalkoxylative dimerization of arylalkynes with alcohols, and (ii) the copper-catalyzed oxidative cyclization of the resulting dienyl ethers.[40] Although this two-step protocol

provides an efficient route to monocyclic furans, an alternative method involving the transformation of α,ω-diynes into bicyclic furans is also attractive. However, such a method has been confined to the stoichiometric oxidation via rhodacyclopentadienes and a single example of the palladium-catalyzed oxidative cyclization of 1,7-diphenyl-1,6-heptadiyne resulted in a low yield of the product.[41,42] Therefore, no general catalytic protocol for the synthesis of bicyclic furans from α,ω-diynes existed previously.

Yamamoto and coworkers developed a new method for the preparation of diverse furans via [2 + 2 + 1] cycloaddition.[43] The reaction of ether-tethered 1,6-diyne **85** and 5 equiv of dimethylsulfoxide (DMSO) in the presence of 3 mol% cationic ruthenium complex **73** in dimethylformamide (DMF) at 140 ˚C for 4 h furnished bicyclic furan **86** in 90% yield (Scheme 22a). In this novel [2 + 2 + 1] cycloaddition, the oxygen atom of the furan was derived from DMSO, as shown by the reaction of isolated ruthenacycle **87** with DMSO in the presence of $AgPF_6$ to afford **86** in 65% yield as estimated from the NMR spectrum (Scheme 22b). The wide scope of this novel transfer-oxygenative cyclization is shown in Figure 3. Various functional groups such as esters, ketones, nitriles, and a sulfonamide on the tether were shown to be well tolerated in the [2 + 2 + 1] cycloaddition. Interestingly, the oxygen-atom transfer did not take place from a sulfone. As a terminal aryl group, both electron-deficient and electron-rich phenyl groups, 2-thienyl, and ferrocenyl groups could be used. Besides 1,6-diynes, 1,7-diynes could be also used, even though increased catalyst loadings were required because of the slower reactions. Furthermore, the double transfer-oxygenative cyclization of *p*-phenylene-tethered tetrayne **88** furnished a fascinating pentaryl product **89** in 87% yield, even though 10 mol% loading of catalyst **73** was required (Scheme 22c).



Scheme 22. Transfer-oxygenative [2 + 2 + 1] cycloaddition of diynes with aryl terminal groups

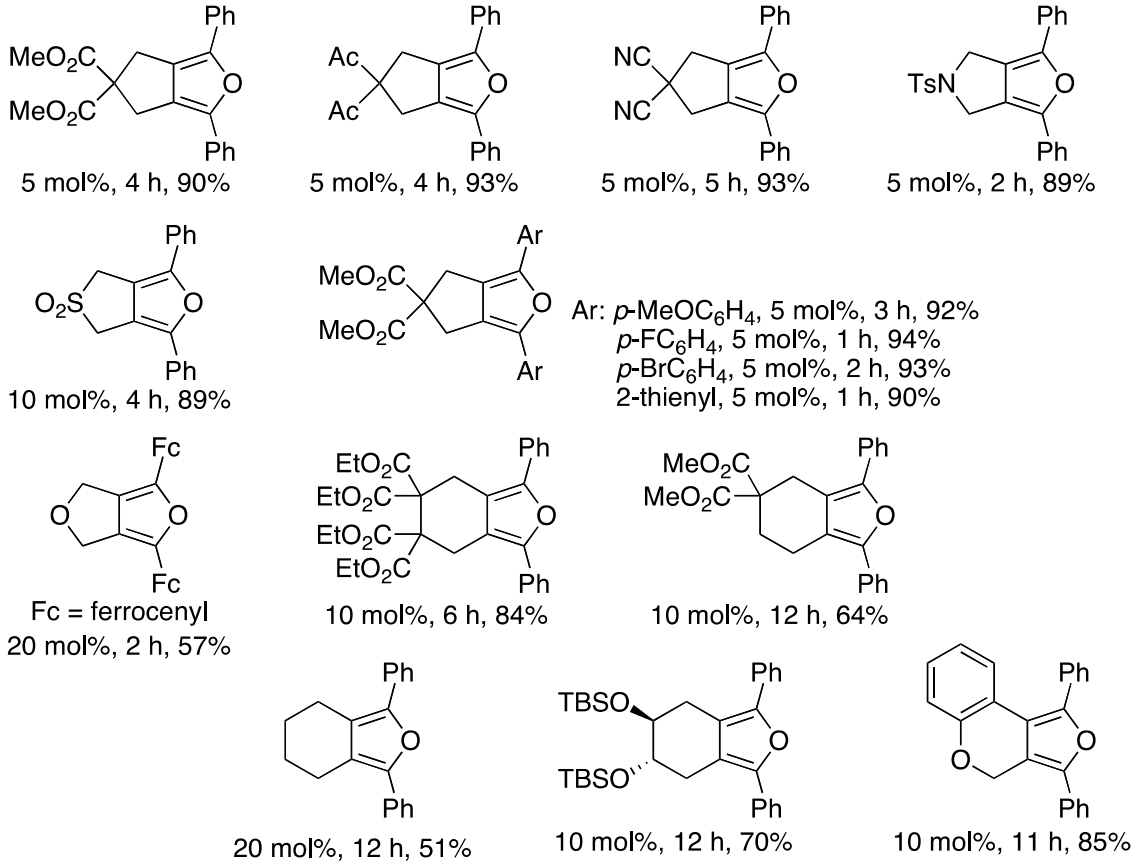
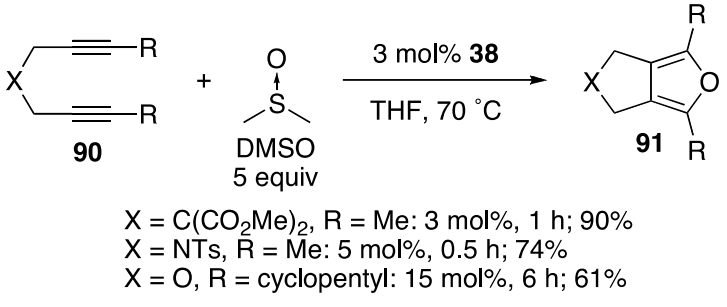


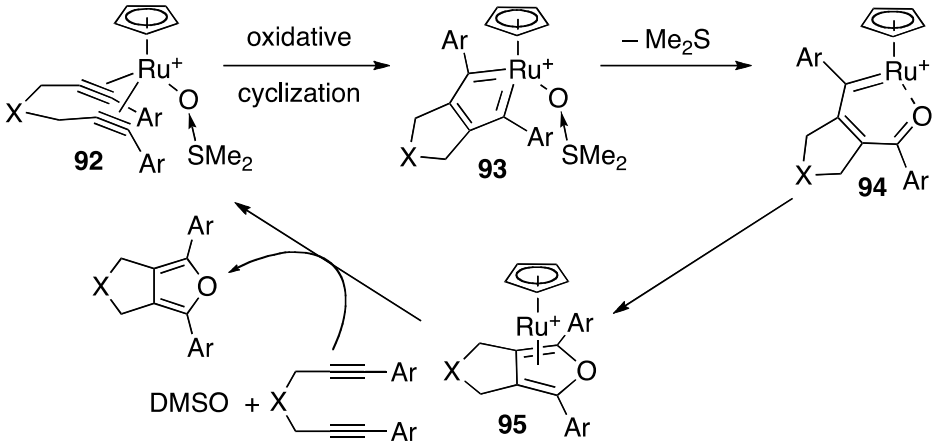
Figure 3. Scope of transfer-oxygenative [2 + 2 + 1] cycloaddition of diynes with aryl terminal groups

Besides diynes with terminal aryl groups, 1,6-diynes with terminal alkyl groups proved to be good substrates for the transfer-oxygenative cyclization.[43] However, catalyst **73** did not work for these substrates. Instead, pentamethylcyclopentadienyl ruthenium complex **38** was found to be the optimal catalyst. Thus, malonate- or tosylamide-derived 1,6-diynes **90** with a terminal methyl group were subjected to transfer-oxygenative cyclization using 3 or 5 mol% **38** in THF at 70 °C to afford the desired bicyclic furans **91** in 90% and 74% yields, respectively (Scheme 23). Similarly, an ether derivative with terminal cyclopentyl groups furnished the corresponding furan in 61%, even though 15 mol% catalyst loading was necessary.



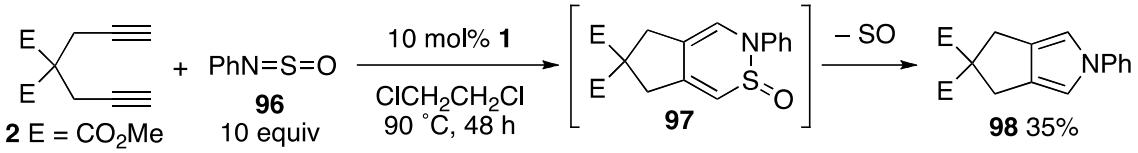
Scheme 23. Transfer-oxygenative [2 + 2 + 1] cycloaddition of diynes with alkyl terminal groups

Yamamoto and coworkers proposed a mechanism as outlined in Scheme 24 based on the DFT calculations of the model complexes.[43] The catalytic cycle involves the oxidative cyclization of DMSO-ligated diyne complex **92** to cationic ruthenacycle **93** followed by the concerted oxygen atom transfer from the DMSO ligand to one of the carbene carbons in **93** to generate ketocarbene complex **94**, which subsequently cyclized to afford η^4-furan complex **95**. Finally, ligand exchange regenerates the starting diyne complex **92** and affords the cycloadduct, thus completing the catalytic cycle.



Scheme 24. Proposed mechanism for transfer-oxygenative [2 + 2 + 1] cycloaddition of diynes

Wang and coworkers reported a similar [2 + 2 + 1] cycloaddition of α,ω-diynes affording bicyclic pyrroles using a palladium catalyst.[44] However, the diyne substrates were limited to 1,8-di(arylethynyl)naphthalenes. Thus, the substrate scope of the [2 + 2 + 1] pyrrole synthesis remained to be investigated. Yamamoto and coworkers reported an example of formal [2 + 2 + 1] cycloaddition catalyzed by a ruthenium complex, although the described method lacks generality.[14] They reported that the reaction of malonate-derived 1,6-diyne **2** with *N*-thionylaniline **96** might have formed [2 + 2 + 2] cycloadduct **97** (Scheme 25). However, the reaction of diyne **2** and large excess of **96** in the presence of 10 mol% **1** in 1,2-dichloroethane at 90 °C for 2 days furnished bicyclic pyrrole **98**, which was presumably formed by the extrusion of SO from **97**, albeit in a low yield (35%). The structure of **98** was unambiguously confirmed by X-ray crystallography.

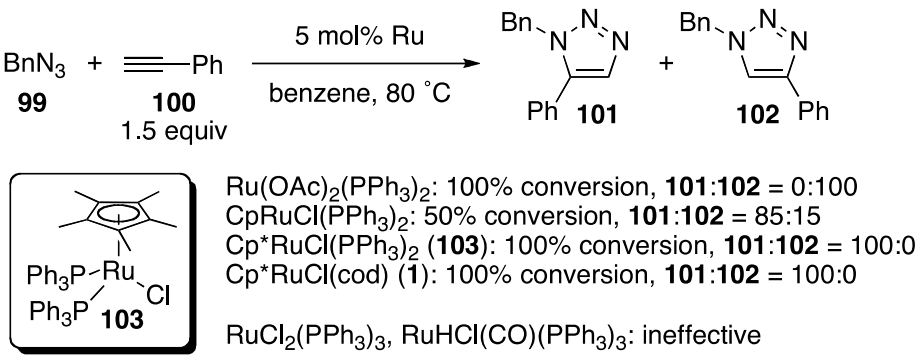


Scheme 25. Formal [2 + 2 + 1] cycloaddition of diyne leading to bicyclic pyrrole

3-2. [3 + 2] CYCLOADDITIONS WITH AZIDES

1,3-Dipolar cycloaddition of organic azides with alkynes, known as Huisgen cycloaddition, is a simple route to 1,2,3-triazoles.[45] However, relatively high reaction temperatures (80–120 °C) and the regioselectivity issue limit the immense synthetic potential of this fascinating [3 + 2] cycloaddition over three decades. In 2002, Sharpless and coworkers reported the copper-catalyzed azido-alkyne cycloaddition (CuAAC) that dramatically changed the course of the Huisgen cycloaddition, exclusively affording 1,4-disubstituted regioisomers of 1,2,3-triazoles.[46] Since 2002, the CuAAC have found diverse applications because the copper catalysis provides many synthetic advantages such as an impressive rate enhancement, a strict regiochemistry, diverse functional group compatibility, and a tolerance toward aqueous conditions.[47] Thus, an alternative catalyst that enables the synthesis of 1,5-disubstituted 1,2,3-triazoles was elusive. To address this issue, Fokin and coworkers investigated the cycloaddition of benzyl azide **99** with phenylacetylene **100** in the presence of $Ru(OAc)_2(PPh_3)_2$ in benzene at 80 °C for 4 h; the reaction exclusively furnished 1,4-disubstitued product **102** at 100% conversion of **99** (Scheme 26).[48] In contrast, $CpRuCl(PPh_3)_2$ favored 1,5-disubstituted regioisomer **101** over 1,4-disubstituted regioisomer **102** with a ratio of 85:15, albeit in a lower conversion. Further, a similar ruthenium complex, $Cp^*RuCl(PPh_3)_2$ (**103**), improved both the regioselectivity and conversion of **99**, resulting in the exclusive formation of 1,5-disubstituted product **101**. Other ruthenium complexes such as Cp*RuCl(cod) (**1**), Cp*RuCl(nbd) (nbd = norbornadiene), and $[Cp^*RuCl_2]_2$ gave similar results.

Among the ruthenium complexes explored, $Cp^*RuCl(PPh_3)_2$ (**103**) and Cp*RuCl(cod) (**1**) are particularly useful for the exclusive formation of 1,5-disubstituted 1,2,3-triazole regioisomers. Catalyst **103** is stable under air whereas catalyst **1** is more efficient because of the 1,5-cyclooctadiene ligand, which is more easily displaced than the triphenylphosphine ligand. The scope of the ruthenium-catalyzed azide-alkyne cycloaddition (RuAAC) using these representative catalysts is shown in Figure 4.[49] The 1,5-disubstituted 1,2,3-triazole derivatives containing amino acids, nucleosides, nitrogen heterocycles, terpenes, steroids, and even phenylboronate moieties were obtained in good yields.



Scheme 26. [3 + 2] Cycloaddition of benzyl azide with phenylacetylene

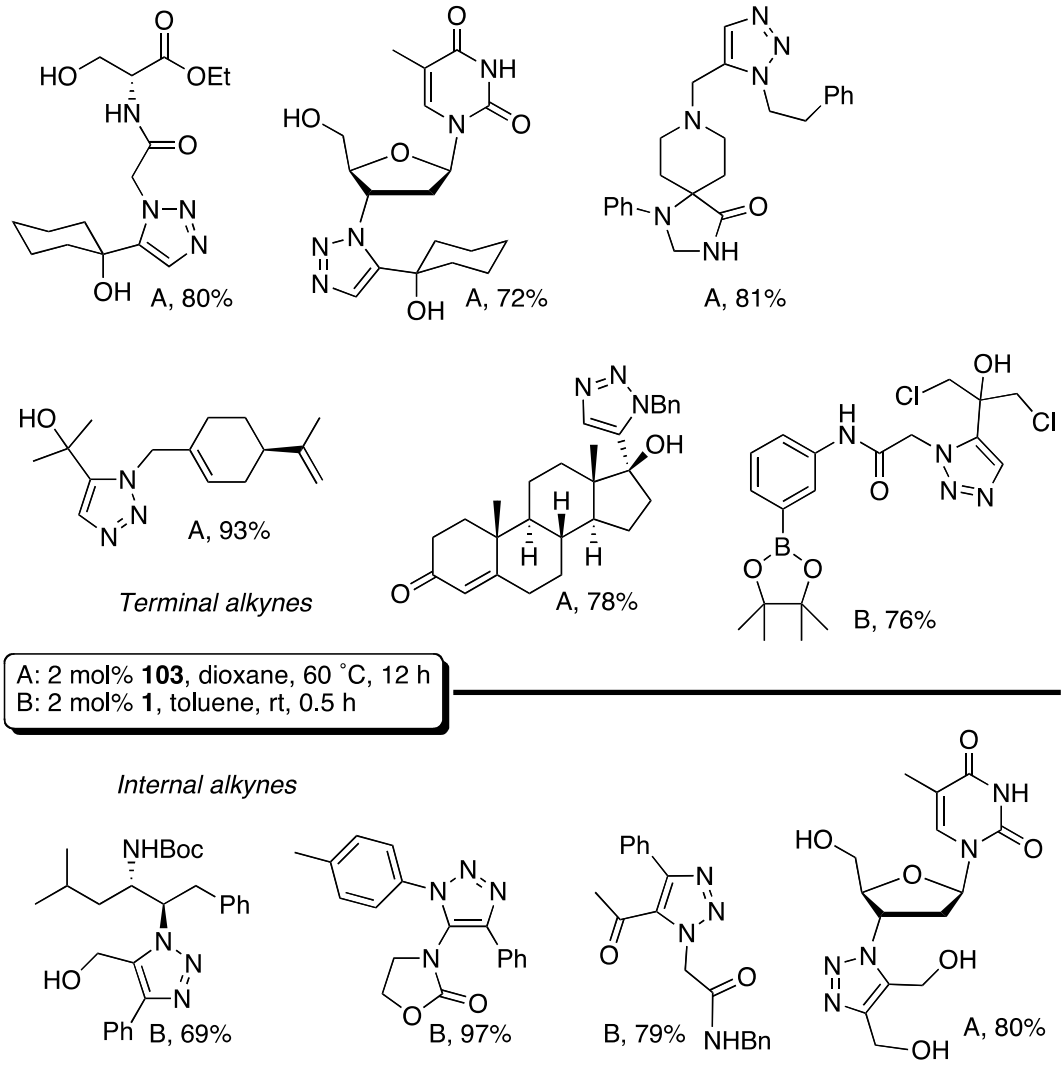
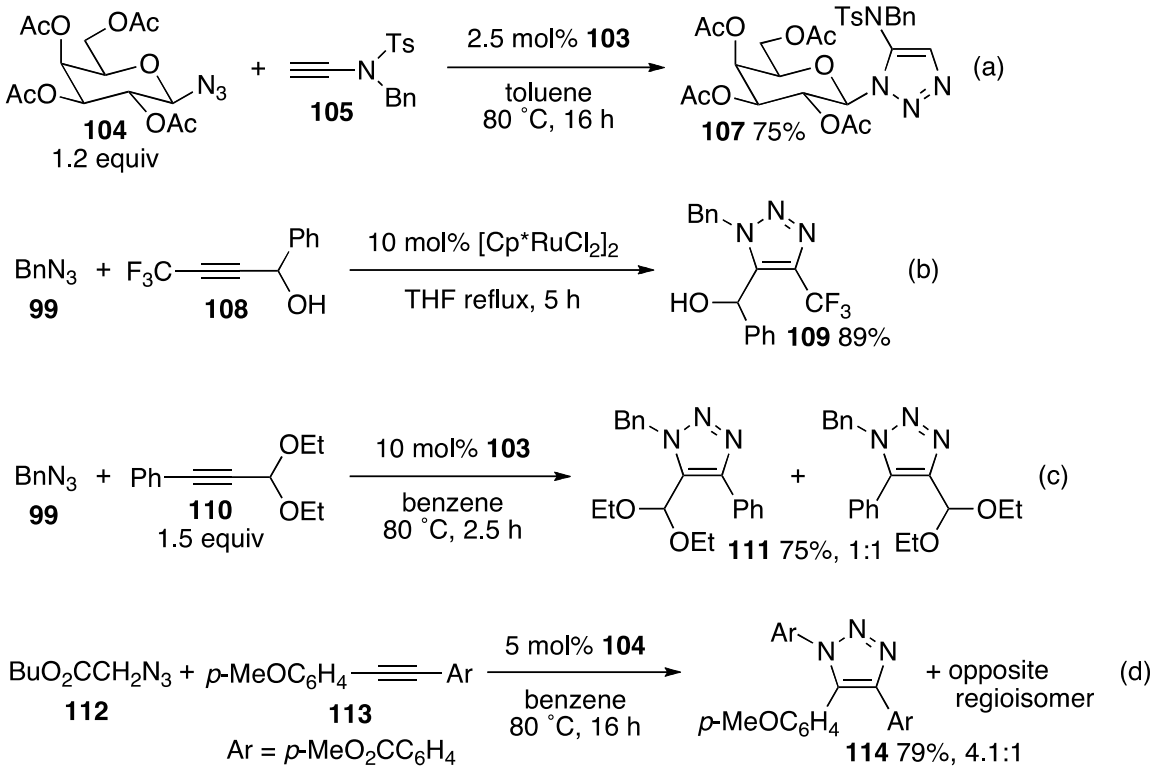


Figure 4. Scope of [3 + 2] cycloaddition of terminal and internal alkynes with azides

The main advantage of RuAAC over CuAAc is that internal alkynes can be used to obtain 1,4,5-trisubstituted triazoles. As shown in Figure 4, propargylic alcohols, an ynamide, and an alkynyl ketone were used as the internal alkyne components to afford highly functionalized triazoles in good yields.[49] Interestingly, in each case, one of the two possible regioisomers was selectively produced in such a way that hydroxymethyl or electron-withdrawing substituents are placed at the C5 position of the 1,2,3-triazole ring.

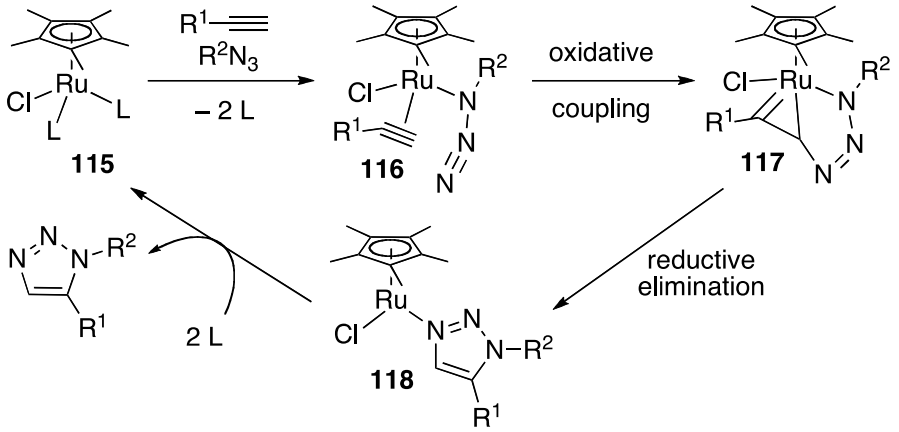
Other research groups have also explored the scope of RuAAC, e.g., the cycloaddition of pyranosyl azide **104** with ynamide **105** catalyzed by **103** exclusively furnished **107** in 75% yield (Scheme 27a).[50] Trifluoromethyl-substituted internal propargylic alcohol **108** also underwent cycloaddition with benzyl azide **99** to afford **109** in a high yield with 100% regioselectivity, thus orienting the hydroxymethyl group on the C5 of the triazole ring (Scheme 27b).[51] In contrast, Majireck and Weinreb reported the complete loss of regioselectivity in the formation of triazole **111** when alkynyl acetal **110** was used, indicating that

the electron-withdrawing or coordinating groups on the alkyne substrates are essential for the regioselective formation of triazoles (Scheme 27c).[52] Hou and coworkers demonstrated the electronic effect on the regiochemistry of RuAAC; they studied the cycloaddition of azide **112** with diarylacetylene **113**, which has both electron-rich and electron-deficient aryl groups (Scheme 27d).[53] A significant regioselectivity of 4.1:1 in favor of regioisomer **114** was observed, and this selectivity was attributed to a favorable transition state, in which a carbon-nitrogen bond was formed between the azide terminal nitrogen and the more electrophilic alkyne carbon.



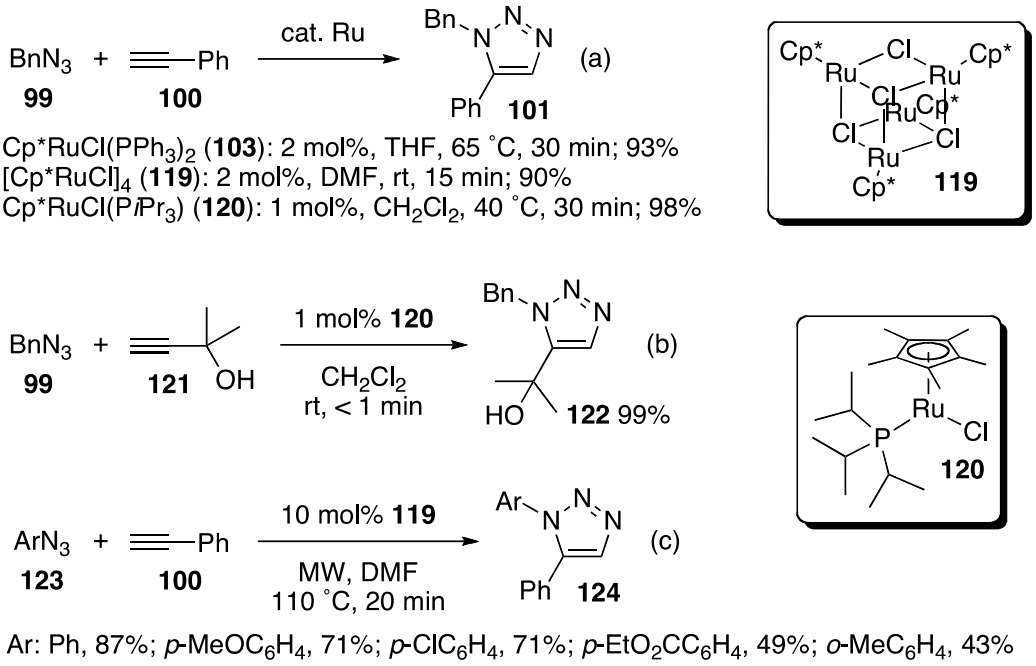
Scheme 27. Regioselectivity in [3 + 2] cycloaddition of azides and alkynes

DFT calculations have been carried out by several research groups to better understand the mechanism of the regioselective formation of 1,5-disubstituted 1,2,3-triazoles.[49,54,55] A simplified catalytic cycle proposed by Lin and coworkers is shown in Scheme 28.[49] The spectator ligands L are expected to be displaced by a terminal alkyne and an azide to produce intermediate **116**, where the alkyne ligates in a η^2 fashion and the azide coordinates at its nitrogen atom substituted by the R^2 group. The rate-determining oxidative coupling step in **116** produces bicyclic complex **117** via the carbon-nitrogen bond formation between the alkyne terminal carbon and the azide terminal nitrogen followed by reductive elimination to afford 16e triazole complex **118**. Finally, the triazole ligand is replaced by the spectator ligands to regenerate **115** and affords the cycloadduct, thus completing the catalytic cycle.



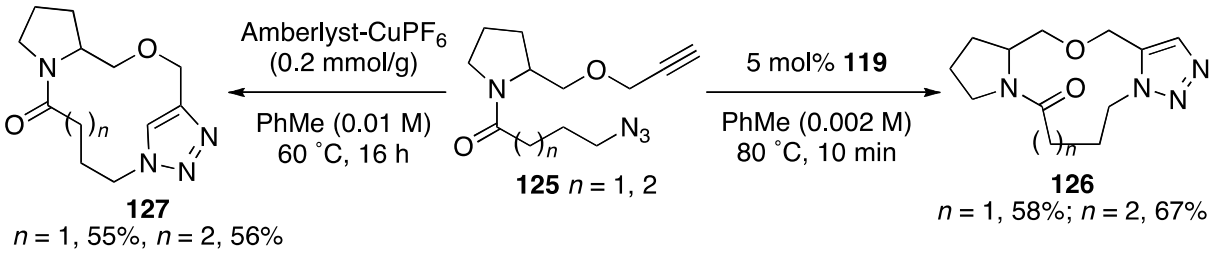
Scheme 28. Proposed catalytic cycle for alkyne-azide cycloaddition leading to 1,2,3-triazole

In the above mechanism, the spectator ligands L are not required for the [3 + 2] cycloaddition. Therefore, the more facile the displacement of the neutral ligand L, the more efficient the catalyst Cp*RuClL$_n$ is, indicating that the vacant coordination sites on the ruthenium center are important for RuAAC. In good agreement with this assumption, Fokin and coworkers confirmed that a tetranuclear complex without any spectator ligand, [Cp*RuCl]$_4$ (**119**), showed a better performance than the standard catalyst **103** in the diagnostic cycloaddition of benzyl azide **99** with phenylacetylene **100** (Scheme 29a).[56] On the other hand, Nolan and coworkers screened a series of bulky phosphines and *N*-heterocyclic carbenes to identify a superior coordinatively unsaturated 16-electron complex as the catalyst.[54] Thus, they reported that a monophosphine complex, Cp*RuCl(P*i*Pr$_3$) (**120**), exhibited a very high catalytic efficiency (Scheme 29a). The cycloaddition of **99** with propargylic alcohol **121** in the presence of 1 mol% **120** proceeded at room temperature within 1 min to quantitatively afford the desired triazole **122** (Scheme 29b). The cycloaddition of aryl azides is more challenging than that of alkyl azides such as **99**. The Fokin group reported that microwave (MW) irradiation facilitated the cycloaddition of aryl azides **123** with phenylacetylene **100** (Scheme 29c).[56] In fact, the reaction of phenyl azide **123** (Ar = Ph) and alkyne **100** under MW heating conditions (10 mol% **119**, DMF, 110 °C, 20 min) furnished **124** in 87% yield, while the reaction conducted using a conventional heating source under the same conditions resulted in a lower yield of 52%. In the same manner, *p*-anisyl and *p*-chlorophenyl derivatives were obtained in 71% yields, while *p*-ethoxycarbonylphenyl and *o*-tolyl derivatives gave lower yields. The MW heating conditions were also successfully applied to the one-pot sequential process assembling 1,2,3-triazoles from sodium azide, primary alkyl halides, and alkynes.[57] In this example, both the formation of alkyl azides and subsequent RuAAC were performed under MW irradiation.



Scheme 29. Superior ruthenium catalysts for RuAAC of terminal alkynes with azides

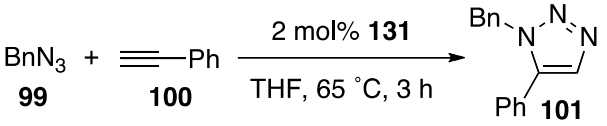
The catalyst **119** was also applied to the intramolecular RuAAC of ω-alkynyl azides, leading to macrocyclic triazoles (Scheme 30).[58] Although both higher dilution and temperature were required, the intramolecular RuAAC of **125** smoothly proceeded within 10 min to selectively afford 11- and 12-membered macrocycles **126** containing the 1,5-disubstituted triazoles in 58% and 67% yields, respectively. On the other hand, the intramolecular CuAAC of **125** furnished 12- and 13-membered macrocycles **127** in comparable yields owing to 1,4-disubstitued-triazole formation.



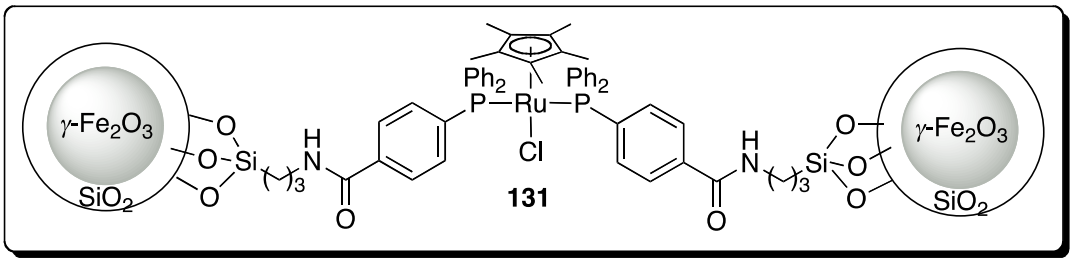
Scheme 30. Intramolecular [3 + 2] cycloadditions of ω-alkynyl azides

Fokin and coworkers further reported the implication of acetylide complexes in the RuAAC of terminal alkynes with azides.[59] Moreover, a recyclable ruthenium catalyst was developed by the Astruc group.[60] They prepared a magnetically separable ruthenium complex **131**, which was immobilized on iron oxide nanoparticles using a phosphine ligand (Scheme 31). Therefore, they successfully repeated the standard cycloaddition of benzyl azide **99** with phenylacetylene **100** using 2 mol% **131** in THF at 65 °C to afford

the desired triazole product **101** in good yields. The catalyst was recycled and found to be selective for at least five cycles.



Run	1	2	3	4	5
Yield/%	91	87	83	86	77
Selectivity/%	99.9	99.5	99.4	98.3	98.3



Scheme 31. Catalyst recycling experiment using immobilized ruthenium complex

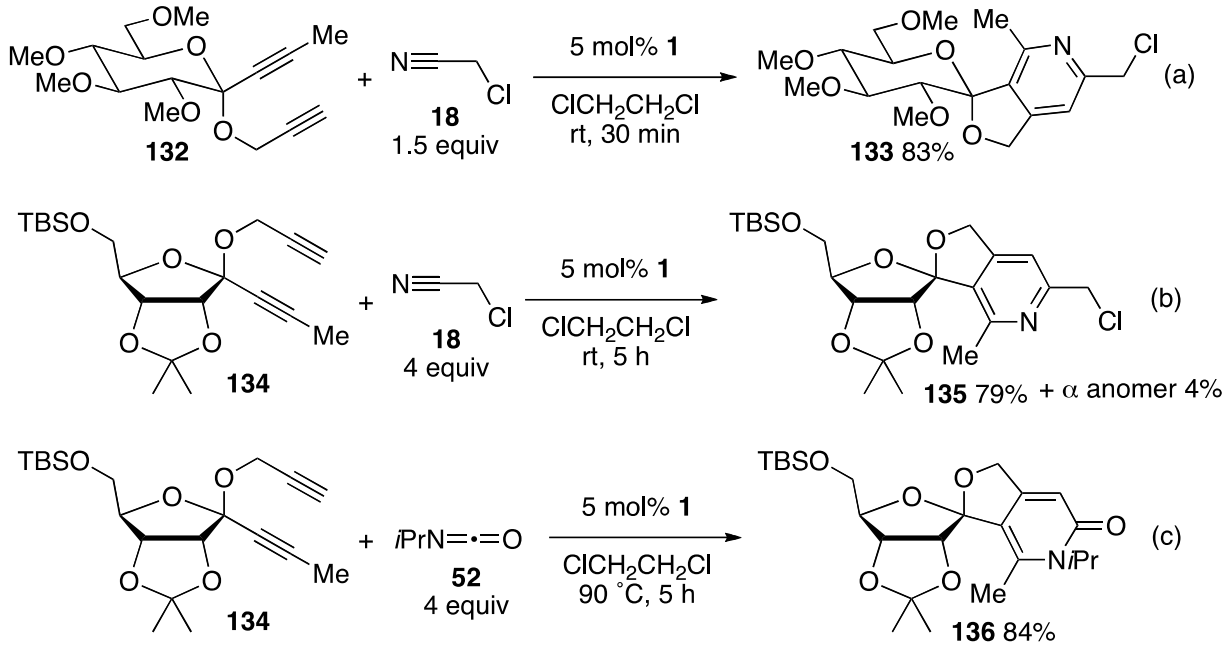
4. APPLICATIONS OF RUTHENIUM-CATALYZED SYNTHESIS OF HETEROCYCLES

This section deals with the synthesis of diverse heterocycles as well as natural products whose syntheses include some steps closely related to ruthenium-catalyzed alkyne cycloadditions. Several illustrative compounds prepared via ruthenium-catalyzed alkyne cycloadditions will be presented.

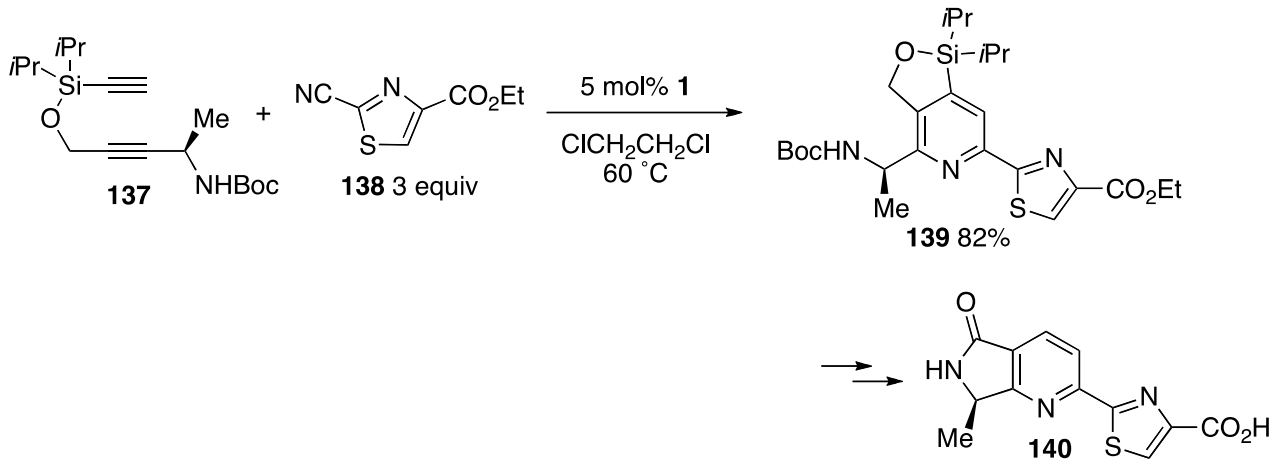
As discussed in the Sections 2-1 and 2-2, the ruthenium-catalyzed [2 + 2 + 2] cycloadditions of α,ω-diynes with nitriles and isocyanates are powerful methods to assemble diverse bicyclic heterocycles. Yamamoto and coworkers utilized their ruthenium-catalyzed alkyne [2 + 2 + 2] cycloaddition to the synthesis of the spirocyclic *C*-arylglycoside core motif of naturally occurring antibiotic papulacandins.[61] The synthesis of the heterocyclic analogs of this fascinating molecular target was attempted by the cycloaddition of glucose-derived unsymmetrical 1,6-diyne **132** with chloroacetonitrile **18** in the presence of 5 mol% **1** at room temperature to afford spirocyclic *C*-pyridylglycoside **133** in 83% yield as a single isomer (Scheme 32a). Moreover, *C*-heteroarylriboside analog **135** was also synthesized by the cycloaddition of ribose-derived unsymmetrical 1,6-diyne **134** with **18** (Scheme 32b). In this case, the expected β anomer **135** was obtained in 79% yield along with it's α anomer in 4% yield. In contrast, the reaction of **134** with isocyanate **52** exclusively furnished pyridone **136** in 84% yield (Scheme 32c).

Cyclothiazomycin is a member of the family of actinomycete thiopeptide antibiotics and features an interesting 2-thiazolylpyridine moiety. The Deiters group successfully synthesized 2-thiazolylpyridine building block **140** for the synthesis of cyclothiazomycin via temporary-tethered [2 + 2 + 2] cycloaddition (Scheme 33).[62] Enantiopure 1,6-diyne **137**, containing a C–Si–O tether, underwent cycloaddition with electron-deficient cyanothiazole **138** at 60 °C using catalyst **1** to afford pyridine cycloadduct **139** in 82%

yield. Notably, a similar cycloaddition of a model diyne substrate with nitrile **138** did not proceed using cobalt-based catalysts.



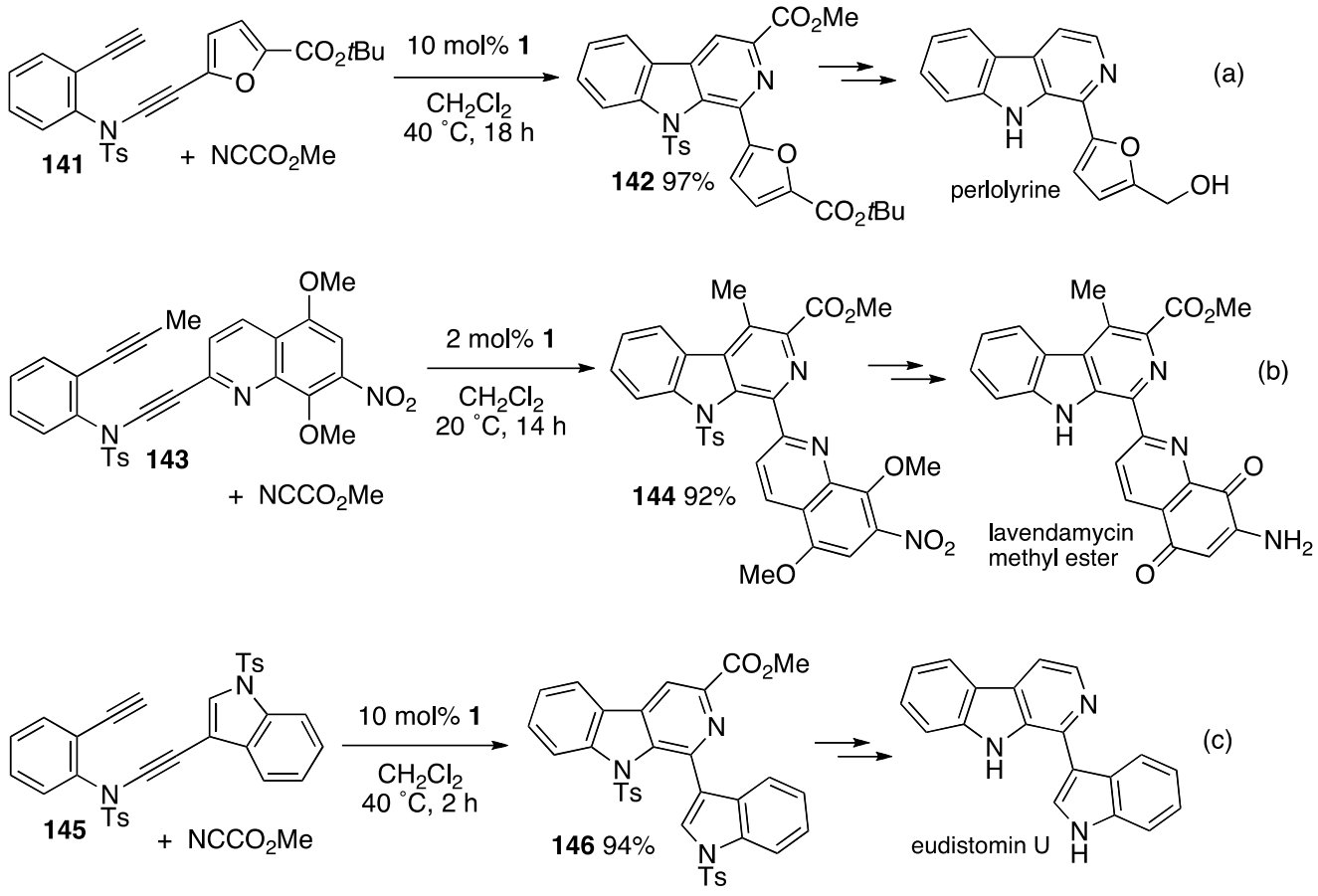
Scheme 32. Syntheses spirocyclic C-heteroarylglycosides via [2 + 2 + 2] cycloaddition



Scheme 33. Syntheses of spirocyclic *C*-heteroarylglycosides via [2 + 2 + 2] cycloaddition

The ruthenium-catalyzed [2 + 2 + 2] cycloaddition of diynes with electron-deficient nitriles selectively affords pyridines. Because the ester substituents on the resultant pyridine ring can be removed, cyanoformates can be used as the surrogates for hydrogen cyanide. Thus, Witulski, Nissen, Detert, and coworkers investigated the cycloadditions of yne-ynamides **141**, **143**, or **145**, which possess terminal

heterocyclic moieties, with methyl cyanoformate as an "HCN" surrogate to synthesize β-carboline structures (Scheme 34).[63] Although this key transformation can be catalyzed by $[Rh(cod)_2]BF_4$/BINAP, ruthenium catalyst **1** was found to be superior compared to the rhodium catalyst in terms of regioselectivity. The rhodium-catalyzed cycloaddition of **143** afforded an undesirable regioisomer as the major product along with **144**, whereas **1** exclusively furnished the desired regioisomer **144** in 92% yield (Scheme 34b). Similarly, cycloadducts **142** and **146** were obtained as the exclusive regioisomeric products in greater than 90% yields (Schemes 34a and 34c). The intermediates **142**, **144**, and **146** were ultimately transformed into the target natural products, i.e., perlolyrine, lavendamycin methyl ester, and eudistomin U, respectively.



Scheme 34. Total syntheses of β-carboline natural products via [2 + 2 + 2] cycloaddition

The copper- and ruthenium-catalyzed [3 + 2] alkyne-azide cycloadditions have found numerous applications such as the synthesis of bioactive molecules, advanced functional materials, and supramolecular structures.[47,64-75] Selected examples of the functional molecules synthesized using RuAAC are shown in Figure 5.

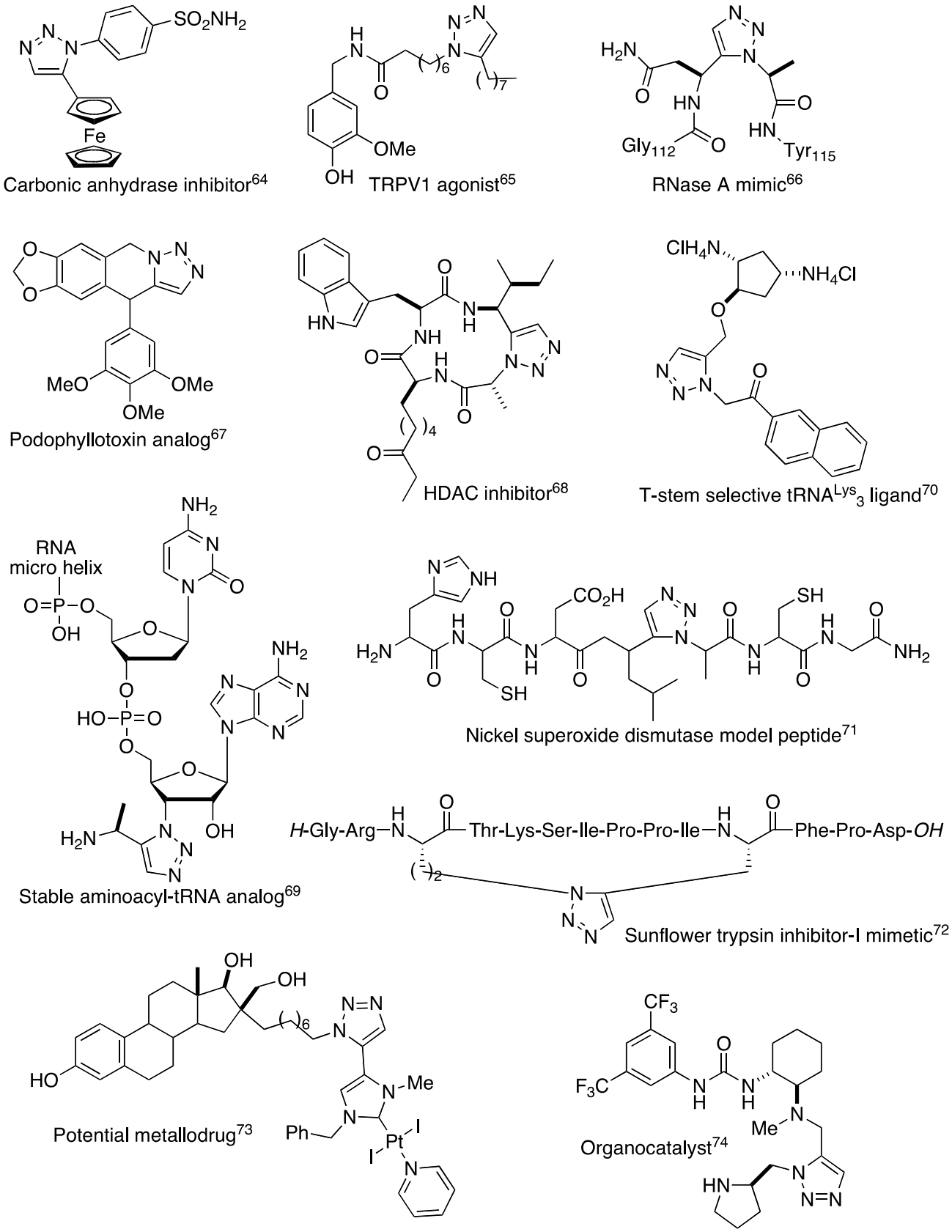


Figure 5. Functional molecules containing 1,5-disubstituted 1,2,3-triazoles synthesized using RuAAC

Two biologically significant molecules can be covalently attached using [3 + 2] cycloadditions, and several conjugate molecules with a triazole tether have been synthesized.[64,70,73,74] 1,2,3-Triazole rings are also considered as the bioisosteres of peptide bonds, esters, and olefins. In particular, 1,5-disubstituted 1,2,3-triazoles have been employed as stable *cis*-peptide bond surrogates.[66,68,71] Moreover, a 1,5-disubstituted 1,2,3-triazole has been successfully introduced as the surrogate of a disulfide bridge in a peptide.[72] RuAAC has also been used for the late-stage modification of reactive TM complexes.[73] The hybridization of a thiourea catalyst with a chiral pyrrolidine catalyst was accomplished using alkyne-azide couplings.[74] Among the prepared organocatalysts, those containing a 1,5-disubstituted triazole tether exhibited better yields and enantioselectivity compared to a 1,4-disubstituted triazole tether in an asymmetric Michael addition reaction. Hyperbranched polytriazoles have also been synthesized using the RuAAC polymerization.[75]

SUMMARY

Ruthenium catalysis has been extensively explored during the past decades. The newly developed ruthenium-catalyzed alkyne cycloadditions have significantly expanded the scope of heterocycle synthesis, e.g., the ruthenium-catalyzed [2 + 2 + 2] cycloadditions of α,ω-diynes with nitriles and heterocumulenes furnished bicyclic six-membered nitrogen or sulfur heterocycles with unprecedented efficiency and selectivity. The synthetic potential of these methods has also been demonstrated by the synthesis of natural products and biologically active molecules. Besides these [2 + 2 + 2] cycloadditions, the ruthenium-catalyzed [4 + 2] and [3 + 3] cycloadditions involving ketone derivatives provide important synthetic routes to six-membered oxygen heterocycles, such as 4*H*-pyran derivatives. Although it has not been much explored, the ruthenium-catalyzed [2 + 2 + 1] cycloaddition offer a powerful methodology for the synthesis of diverse five-membered heterocycles. Furthermore, the advances in the ruthenium-catalyzed [3 + 2] cycloaddition of alkynes with azides to afford 1,5-disubstituted 1,2,3-triazoles significantly progressed the application to chemical biology studies because of the diverse applicability of 1,2,3-triazole motif as an innocent tether connecting biologically active segments, bioisosteres of amides, esters, and olefins, and as the surrogates of *cis*-peptide bonds and disulfide bridges. In the future, further developments in the ruthenium catalysis will become significantly important in diverse fields such as natural product chemistry, chemical biology, pharmaceutical, and material sciences.

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Yoshihiko Yamamoto was born in Nagoya in 1968. He obtained his B.S. (1991), M.S. (1993), and Ph.D. (1996) degrees from Nagoya University, where he was appointed as an Assistant Professor in 1996 and promoted to an Associate Professor in 2003. In 2006, he moved to Tokyo Institute of Technology. After returning to Nagoya University in 2009, he was promoted to a Full Professor in 2012. He was awarded the Incentive Award in Synthetic Organic Chemistry, Japan (2003); the Japan Combinatorial Chemistry Focus Group Award in Synthetic Organic Chemistry, Japan (2004); and the Tokyo Tech Award for Challenging Research (2006). His research interests are focused on the development of organometallic reagents and catalysis and their application to the synthesis of biologically important molecules.