

Cp*RuCl-Catalyzed [2 + 2 + 2] Cycloadditions of α,ω -Diyne with Electron-Deficient Carbon–Heteroatom Multiple Bonds Leading to Heterocycles

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Abstract: In the presence of a catalytic amount of Cp*RuCl(cod), 1,6-diyne were allowed to react chemo- and regioselectively with electron-deficient nitriles and heterocumulenes at 60–90 °C to afford heterocyclic compounds. The mechanism of the ruthenium-catalyzed regioselective formations of bicyclic pyridines and pyridones were analyzed on the basis of density functional calculations. Cyclocotrimerizations of ethyl propiolate with ethyl cyanoformate or propyl isocyanate gave rise to two of the four possible pyridine or pyridone regioisomers.

Introduction

The occurrence of heterocyclic compounds in nature is widespread, and their applications to pharmaceuticals and functional materials are becoming more and more important.¹ The development of new efficient strategies to synthesize heterocycles with structural diversity is one major aim in modern synthetic organic chemistry. Heterocyclic compounds have generally been synthesized by means of condensation reactions under acidic or basic conditions, which produce salt waste. The formation of undesirable byproducts is also a problem to be avoided in the conventional methods that need stoichiometric reagents. In this respect, transition-metal catalysis is a powerful tool to construct heterocyclic frameworks under neutral and mild conditions.² In particular, the catalyzed cyclocotrimerizations of alkynes with carbon–heteroatom multiple bonds have received growing attention, since they can form multiple carbon–carbon and carbon–heteroatom bonds simultaneously without any reagents other than a catalyst.³ In other words, the catalytic [2 + 2 + 2] cycloaddition strategy is a highly convergent and atom-economical approach to heterocyclic compounds.

The transition-metal-mediated cyclocotrimerization of alkynes with carbon–heteroatom multiple bonds was first pioneered by Wakatsuki and Yamazaki in their work on the stoichiometric

reactions of cobaltacyclopentadienes with nitriles, carbon disulfide, or methyl isothiocyanate, leading respectively to pyridines, a dithiopyrone, and a thiopyridone.⁴ Since then, various stoichiometric and catalytic cyclocotrimerizations have been developed,³ but the control of chemo- and regioselectivity has been a crucial problem for the catalytic methods. In this context, the cobalt-catalyzed partially intramolecular cycloadditions of α,ω -diynes or ω -cyanoalkynes leading to bicyclic pyridines have been developed by Vollhardt and others,^{5,6} providing access to the syntheses of natural and artificial molecules.⁷ The catalytic pyridone formation, which was first accomplished independently by Yamazaki and Hoberg and their co-workers using Co or Ni

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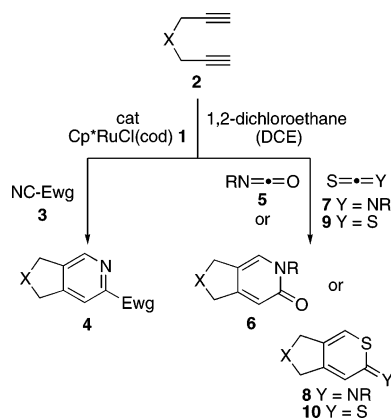
catalysts,⁸ has also been extended to partially intramolecular versions utilizing isocyanatopentynes or α,ω -diynes by Vollhardt and Earle.^{9,10}

As can be seen from these predecessors, the catalytic partially intramolecular cyclocotrimerizations have been almost confined to cobalt catalysis. In addition, the substrate scope, the efficiency, and the selectivity (especially regioselectivity) have remained to be greatly improved. Herein we report the Cp*RuCl-catalyzed cycloadditions of α,ω -diynes with electron-deficient carbon–heteroatom multiple bonds resulting in various heterocyclic compounds with significant chemo- and regioselectivity.

Results and Discussion

Scope and Limitations of Cp*RuCl-Catalyzed Cycloadditions of 1,6-Diynes with Electron-Deficient Nitriles and Heterocumulenes. We have previously reported that Cp*RuCl(cod) (**1**; Cp* = η^5 -C₅Me₅, cod = 1,5-cyclooctadiene) catalyzed the cycloaddition of 1,6-diynes **2** with electron-deficient nitriles **3**, which are inefficient nitrile components under the previous Co catalysis,⁵ to afford the desired bicyclic pyridines in moderate to high yields (Scheme 1 and Figure 1),^{11a} while simple nitriles

Scheme 1



such as acetonitrile or benzonitrile failed to undergo cycloaddition under the same reaction conditions. The scope of the ruthenium-catalyzed pyridine formation is broad with respect to the 1,6-diyne and the nitrile substrates as summarized in Table 1. Acyl, sulfonyl, and perhaloalkyl or aryl groups can be employed as an electron-withdrawing group on the nitrile component (runs 1–7), although the product yields were moderate for tosylcyanide **3e**, trichloroacetonitrile **3f**, and pentafluorobenzonitrile **3g** because of the competitive dimerization of **2a**. The yields of **4ae**, **4af**, and **4ag** were slightly improved by employing 3 equiv of these cyanides. The wide functional group compatibility is a significant advantage of the

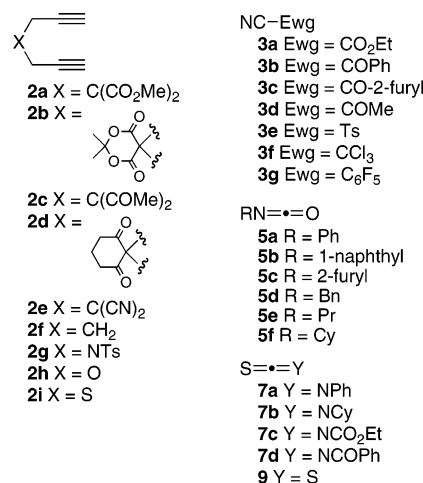


Figure 1.

Table 1. Cp*RuCl-Catalyzed Cycloaddition of **2** and **3a**

run	substrates	1/mol %, t/h	product, yield
1	2a/3a	2, 0.5	4aa , 83%
2	2a/3b	2, 0.5	4ab , 84%
3	2a/3c	5, 2	4ac , 79%
4	2a/3d	10, 1	4ad , 90%
5	2a/3e	10, 24	4ae , 31 (53) ^b %
6	2a/3f	10, 24	4af , 44 (50) ^b %
7	2a/3g	5, 1	4ag , 67 (80) ^b %
8	2b/3a	2, 0.5	4ba , 88%
9	2c/3a	2, 0.5	4ca , 90%
10	2d/3a	2, 0.5	4da , 86%
11	2e/3a	2, 0.5	4ea , 80%
12	2f/3a	2, 0.5	4fa , 89%
13	2g/3a	2, 0.5	4ga , 75%
14	2h/3a	2, 2	4ha , 72%
15	2i/3a	2, 17	4ia , 64%

^a All reactions were carried out with nitriles (1.5 equiv) at 60 °C (80 °C for runs 4 and 5) in DCE under Ar. ^b With 3 equiv of nitriles.

ruthenium catalysis. The 1,6-diynes **2b–e** bearing ester, ketone, and nitrile moieties gave rise to bicyclic pyridines **4ba–4ea** in high yields (runs 8–11). The parent 1,6-heptadiyne **2f** possessing no quaternary center afforded the desired pyridine **4fa** in 89% yield (run 12), indicative of the Thorpe–Ingold effect being less important.¹² Furthermore, pyridine-fused heterocycles **4ga**, **4ha**, and even sulfur-containing **4ia**, could be obtained in 75, 72, and 64% yields, respectively (runs 13–15).

In contrast to the cycloaddition of α,ω -diynes with nitriles, the relevant reaction with isocyanates has received less attention until recently we found the ruthenium-catalyzed protocol, because of the low efficiency of cobalt and nickel catalysts.^{9b} As previously reported,^{11b} adding a DCE solution of **2** and 2 equiv of isocyanates **5** into a refluxing DCE solution containing 5–10 mol % **1** and another 2 equiv of **5** furnished the desired bicyclic pyridones **6**, suppressing the competitive dimerization of **2** (Scheme 1, Figure 1, and Table 2). This procedure converted a variety of aryl or alkyl isocyanates to the corresponding pyridones **6aa–6af** in 79–93% yields (runs 1–6). Exceptionally, *tert*-butyl isocyanate gave no cycloadduct under the same reaction conditions. This is probably because the

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Table 2. Cp^{*}RuCl-Catalyzed Cycloaddition of **2** with **5**,^a **7**,^b or **9**^c

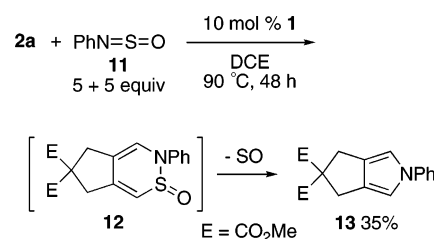
run	substrates	1/mol %, t/h	product, yield
1	2a/5a	5, 1	6aa , 87%
2	2a/5b	5, 1	6ab , 79%
3	2a/5c	5, 1	6ac , 87%
4	2a/5d	5, 1	6ad , 93%
5	2a/5e	5, 1	6ae , 89%
6	2a/5f	5, 1	6af , 85%
7	2b/5a	10, 1	6ba , 73%
8	2c/5a	10, 1	6ca , 75%
9	2d/5a	10, 1	6da , 58%
10	2e/5a	10, 1	6ea , 18%
11	2f/5a	5, 2	6fa , 62%
12	2g/5a	5, 1	6ga , 82%
13	2h/5a	5, 2	6ha , 58%
14	2i/5a	5, 24	6ia , 60%
15	2a/7a	10, 5	8aa , 88%
16	2a/7b	10, 24	8ab , 50%
17	2a/7c	10, 3	8ac , 71%
18	2a/7d	10, 24	8ad , 76%
19	2b/7a	10, 9	8ba , 35%
20	2c/7a	10, 6	8ca , 74%
21	2d/7a	10, 8	8da , 67%
22	2e/7a	10, 8	8ea , 58%
23	2a/9	10, 6	10 , 54%

^a To a refluxing solution of 5 mol % **1** and **5** (2 equiv) in DCE was added dropwise a solution of **2** and **5** (2 equiv) in DCE at 90 °C under Ar.

^b All reactions were carried out with **7** (1.2 equiv) at 90 °C in DCE under Ar. ^c The reaction was carried out in CS₂/DCE (2:3 v/v) at 90 °C under Ar.

coordination of its C=N bond to the ruthenium center was completely hampered by the sterically demanding *tert*-butyl group. In contrast to the malonate derivative **2a**, other diynes **2b–e** required increased catalyst loadings of 10 mol % (runs 7–10). The cycloaddition of these diynes bearing cyclic ester or ketone moieties gave rise to the desired pyridones **6ba–6da** in 58–75% yields, while the malononitrile derivative **2e** resulted in the low-yield formation of **6ea**. This is probably because of the competitive oligomerization of **2e** via diyne–dicyanide cycloaddition.¹³ The successful result with 1,6-heptadiyne **2f** (run 11) again shows that the Thorpe–Ingold effect is less influential.¹² Uneventfully, the pyridone-fused heterocyclic compounds **6ga–6ia** were obtained in 58–82% yields (runs 12–14).

Having examined the cycloaddition of the isocyanates, we turned our attention to isothiocyanates, because organosulfur compounds frequently behave as catalyst poisons.¹⁴ The cyclocotrimerization of two alkyne molecules with a thiocarbonyl compound is of synthetic significance, since two C–C bonds as well as a C–S bond are simultaneously formed by a single operation. To the best of our knowledge, there is only a few examples of such an interesting sulfur ring assembly,^{4,15} whereas thiocarbonyl compounds behave as more reactive dienophiles for Diels–Alder cycloaddition than the parent carbonyl compounds.¹⁶ Gratifyingly, we have found that in a refluxing DCE solution containing 10 mol % **1**, the cycloaddition of **2** and 1.2 equiv of isothiocyanates **7** took place on their C=S bond to afford thiopyranimines **8** (Scheme 1 and Figure 1).^{11c} The isothiocyanates **7a–d** bearing phenyl, cyclohexyl, ethoxycar-

Scheme 2

bonyl, and phenacyl groups on the nitrogen underwent cycloaddition with **2a** to give **8aa–8ad** in 50–88% yields (Table 2, runs 15–18). This novel sulfur–heterocycle formation requires the diyne substrates possessing a quaternary center at 4 position, which facilitates the oxidative cyclization of the diynes via the Thorpe–Ingold effect.¹² Indeed, the diynes bearing a quaternary center **2b–2e** gave rise to the corresponding thiopyranimines **8bc–8ec** in 35–74% yields (runs 19–22), while *N,N*-dipropargyl tosylamide **2g** and propargyl ether **2h** failed to undergo cycloaddition. Similar to the isothiocyanates, carbon disulfide **9** underwent the cycloaddition with **2a** in the presence of 10 mol % **1** in CS₂/DCE (2:3 v/v) at 90 °C for 6 h to furnish the expected bicyclic dithiopyrone **10** in 50% yield along with the recovered **2a** (24%) (Scheme 1 and Table 2, run 23). On the other hand, the use of commercially available diisopropyl or dicyclohexyl carbodiimides as heterocumulenes led to the formation of an intractable product mixture.

N-Thionylamines have been utilized as dienophiles for Diels–Alder reactions, in which the cycloaddition occurred on the S=N double bond to produce cyclic *N*-sulfinyl adducts.¹⁷ The reaction of **2a** with *N*-thionylaniline **11** was carried out by adding a solution of **2a** and 5 equiv of **11** into a refluxing solution containing the 10 mol % **1** and another 5 equiv of **11**. As a result, a bicyclic pyrrole **13** was obtained albeit in 35% yield instead of the expected cycloadduct **12** (Scheme 2). Although **2a** was completely consumed, its dimerization was more pronounced compared to the cycloaddition of the above heterocumulenes. The structure of **13** was unambiguously confirmed by X-ray analysis (see Supporting Information). The pyrrole ring of **13** might come from the *N*-sulfinyl ring of **12**, but the detailed mechanism of the S=O extrusion was not clear. The *N*-sulfinyl aniline proved essential for the pyrrole formation. Employing aniline or tosyl azide instead of **11** never gave the corresponding pyrrole.

Regiochemistry of Cp^{*}RuCl-Catalyzed Cycloaddition of Diynes. (a) **Steric Directing Effect.** Whereas partially intramolecular [2 + 2 + 2] cyclocotrimerizations of nitriles and heterocumulenes have been developed, the regioselective cycloadditions of unsymmetrical α,ω -diynes have attracted less attention. Vollhardt and Naiman have reported only one example of the Co(I)-catalyzed regioselective cycloaddition of unsymmetrical 1,7-decadiyne.^{5a} Quite recently, this regioselective pyridine formation was elegantly extended to its asymmetric versions by Gutnov and co-workers.⁶ⁱ To examine the regioselectivity of the Cp^{*}RuCl-catalyzed heterocycle formations, unsymmetrical 1,6-diynes **14a–d** having methyl or phenyl terminal groups were subjected to cycloaddition with ethyl cyanoformate **3a**, propyl isocyanate **5e**, or phenyl isothiocyanate **7a** (Scheme 3 and Table 3). In the presence of 5 mol % **1**, **14a**

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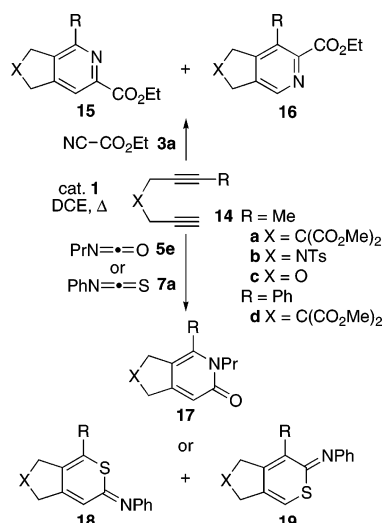
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(15) A noncatalyzed cyclocotrimerization involving a C=S double bond, see Bianchini, C.; Meli, A. *J. Organomet. Chem.* **1982**, *236*, C75–C77.

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Scheme 3

**Table 3.** Cp^{*}RuCl-Catalyzed Regioselective Cycloaddition of **14** with **3a**,^a **5e**,^b or **7a**^c

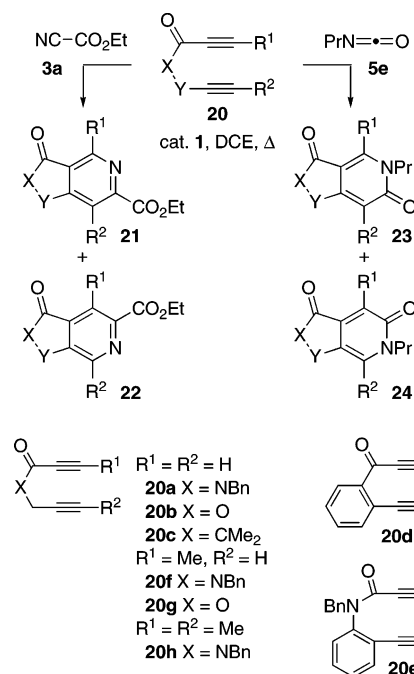
run	substrates	1/mol %, t/h	products, yield, ratio
1	14a/3a	5, 2	15aa/16aa , 87%, 88:12
2	14b/3a	5, 2	15ba/16ba , 86%, 89:11
3	14c/3a	5, 2	15ca/16ca , 83%, 88:12
4	14d/3a	20, 6	15da , 64%
5	14a/5e	5, 3	17ae , 85%
6	14b/5e	5, 6	17be , 80%
7	14c/5e	5, 15	17ce , 88%
8	14d/5e	10, 20	17de , 80% ^d
9	14a/7a	10, 5	18aa/19aa , 82%, 90:10

^a All reactions were carried out with **3a** (1.5 equiv) at 60 °C in DCE under Ar. ^b To a refluxing solution of **1** and **5e** (2 equiv) in DCE was added dropwise a solution of **14** and **5e** (2 equiv) in DCE at 90 °C under Ar. ^c All reactions were carried out with **7a** (1.2 equiv) at 90 °C in DCE under Ar. ^d A small amount of inseparable impurity was detected by ¹H NMR spectroscopy.

bearing a terminal methyl substituent was allowed to react with 1.5 equiv of **3a** at 60 °C for 2 h to afford a regioisomer mixture of the 2,3,4,6- and 2,3,4,5-substituted isomers **15aa** and **16aa** in 87% combined yield with the ratio of 88:12 (run 1). In the same manner, the tosylamide **14b** and the ether **14c** gave **15ba/16ba** and **15ca/16ca** with similar yields and regioselectivity (runs 2 and 3). On the other hand, a terminal phenyl group significantly improved the regioselectivity at the expense of the efficiency. In the presence of 20 mol % **1**, the reaction of **14d** at 60 °C for 6 h gave **15da** as a sole product in 64% yield (run 4). The reaction of **14a–c** with the isocyanate **5e** was carried out using 5 mol % **1** in refluxing DCE for 3–15 h. Interestingly, the pyridones **17ae–17ce** were exclusively obtained in 80–88% yields (runs 5–7). Although an increased catalyst loading of 10 mol % was required, **14d** also gave rise to **17de** as a single regioisomer (run 8). Similarly, the isothiocyanate **7a** underwent regioselective cycloaddition with **14a** upon refluxing in DCE containing 10 mol % **1** for 5 h to give rise to **18aa** and its regioisomer **19aa** in 82% combined yield with the ratio of 90:10 (run 9). The regiochemistry of the obtained products were determined on the basis of the ¹H NMR analysis (see Supporting Information). As shown in Figure S1, the diagnostic heterocyclic ring protons Ha α to the heteroatoms appeared in the lower magnetic field than Hb. The major isomer derived from **14a** and **7a** was also unambiguously assigned to **18aa** by X-ray crystallographic analysis (see Supporting Information).

(b) Electronic Directing Effect. In striking contrast to the previous regioselective cycloadditions utilizing the steric effect, an alternative mode of regiocontrol by taking advantage of an electronic influence of the internal substituent on the diyne substrate has been remained unexplored until we have reported the Ru-catalyzed regioselective cycloaddition of 1,6-diynes having a carbonyl group at the 3 position.¹⁸ The terminal substituent causes not only the regiocontrolling effect but also the deteriorative effect on the cycloaddition efficiency (Table 3, run 1 vs run 4). On the other hand, an electron-withdrawing carbonyl group introduced at the 3 position has a direct impact on the regiochemistry without causing such a negative steric influence. In this context, the Cp^{*}RuCl-catalyzed cycloadditions of the unsymmetrical diynes **20** possessing an internal carbonyl group conjugated with one of the two alkyne moieties was explored as outlined in Scheme 4 and Table 4.

Scheme 4



The reaction of amide-diyne **20a** with the cyanide **3a** was carried out in the presence of 1 mol % **1** at 60 °C for 18 h to afford a mixture of the expected pyridines in 77% combined yield (Table 4, run 1). The ¹H NMR analysis of the crude mixture revealed that the major regioisomer **21aa**, in which the ethoxycarbonyl group and the amide carbonyl moiety are in a *para* relationship, was formed preferentially with the ratio of 71:29. Similarly, the ester-diyne **20b** gave rise to the pyridine-fused lactones **21ba/22ba** in 83% combined yield with the ratio of 82:18 (run 2). As expected, the regioisomer ratio was improved for **20b**, indicative of the more electron-withdrawing carbonyl group favoring the formation of **21** over **22**. The regioselectivity was further increased up to around 90:10 for the ketodiyne **20c** and **20d** (runs 3 and 4). The cycloadditions of **20a–d** with the isocyanate **5e** were also carried out as summarized in Table 4. In the presence of 5 mol % **1**, the reaction completed for 18 h at 60 °C. The expected pyridones **23/24** were obtained in 66–77% combined yields (runs 9–12).

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Table 4. Cp*RuCl-Catalyzed Regioselective Cycloaddition of **20** with **3a**^a or **5e**^b

run	substrates	1/mol %, t/h	products, yield, ratio
1	20a/3a	1, 18	21aa/22aa , 77%, 71:29
2	20b/3a	1, 18	21ba/22ba , 83%, 82:18
3	20c/3a	1, 18	21ca/22ca , 64%, 89:11
4	20d/3a	1, 18	21da/22da , 89%, 91:9
5	20e/3a	20, 15	21ea , 64%
6	20f/3a	5, 0.5	21fa/22fa , 89%, 96:4
7	20g/3a	5, 0.5	21ga/22ga , 84%, 98:2
8	20h/3a	5, 6	21ha/22ha , 82%, 80:20
9	20a/5e	5, 18	23ae/24ae , 67%, 82:18
10	20b/5e	5, 18	23be/24be , 66%, 88:12
11	20c/5e	5, 18	23ce/24ce , 75%, 97:3
12	20d/5e	5, 18	23de/24de , 77%, 95:5
13	20e/5e	5, 18	23ee , 46%
14	20f/5e	5, 6	23fe , 82%
15	20g/5e	5, 6	23ge , 73%
16	20h/5e	5, 6	23he/24he , 77%, 83:17

^a All reactions were carried out with **3a** (1.5 equiv) at 60 °C in DCE under Ar. ^b To a refluxing solution of **1** and **5e** (2 equiv) in DCE was added dropwise a solution of **20** and **5e** (2 equiv) in DCE at 60 °C (90 °C for runs 14–16) under Ar.

The regioselectivity was higher than that observed for the corresponding pyridine **21/22** (runs 1–4) and increased from 82:18 for the amide **20a** to 97:3 for the ketone **20d**.

The regiochemistry of the obtained products were determined on the basis of the ¹H NMR analyses (see Supporting Information). As shown in Figure S2, the heterocyclic ring protons α to the nitrogen atom (Ha) appeared in the lower magnetic field than the β -protons (Hb). The Ha peaks of the major isomers were observed in the lower field than those of the corresponding minor isomers because of the deshielding effect of the adjacent carbonyl groups on the fused rings. Similarly, Hb of the minor isomers appeared in the lower field than those of the corresponding major isomers. This analysis can essentially be applied to all products except for the tricyclic pyridines **21da/22da**. The assigned regiochemistry was further confirmed by the X-ray analyses of the major regioisomers **21ca**, **21da**, and **23ae** (see Supporting Information).

In addition to these 1,6-diyne, the 1,7-diyne **20e** possessing an aniline tether proved to participate in the Cp*RuCl-catalyzed cycloadditions with **3a** or **5e**. In striking contrast to the corresponding 1,6-diyne, **20e** gave a tricyclic pyridine **21ea** as a sole product in 64% yield, although the increased catalyst loading of 20 mol % was required (Table 4, run 5). The reaction with **5e** proceeded with the lower catalyst loading of 5 mol % to afford the tricyclic pyridone **23ee** in 46% yield (run 13).

(c) Synergistic Effect of Steric and Electronic Directing Groups. To evaluate the cooperative effect of the steric and the electronic directing groups, the amide and ester diynes **20f–h** bearing both a terminal substituent and an internal carbonyl group were subjected to the cycloaddition with **3a** and **5e** (Scheme 4). In the presence of 5 mol % **1**, the reaction of the amide diyne **20f** with the cyanide **3a** completed within 0.5 h at 60 °C to furnish the expected pyridines **21fa/22fa** in 89% combined yield (Table 4, run 6). The regioselectivity of 96:4 was higher than those observed for **15aa/16aa** (88:12; Table 3, run 1) and **21aa/22aa** (71:29; Table 4, run 1). Similarly, **21ga/22ga** were obtained from the ester diyne **20g** in good combined yield and regioselectivity (Table 4, run 7). The cycloaddition of **20f,g** with the isocyanate **5e** gave the pyridones **23fe** and **23ge** in good yields as sole products (Table 4, runs 14 and 15).

Interestingly, the electron-deficient diyne **20h** was allowed to react with **3a** and **5e** to give rise to the four-substituted pyridines **21ha/22ha** or the fully substituted pyridones **23he/24he** with the 80:20 and 83:17 isomer ratios, respectively, whereas **20h** has a methyl substituent on both alkyne termini (Table 4, runs 8 and 16).

Mechanism of CpRuCl-Catalyzed Cyclocotrimerization. For the [2 + 2 + 2] alkyne cyclocotrimerizations, a general mechanism involving metallacyclopentadiene and metallacycloheptatriene intermediates has been proposed (the “common mechanism”).¹⁹ On the basis of density functional theory (DFT) calculations, we and others have reported the novel alkyne cyclocotrimerization mechanism, in which the intermediacy of an unprecedented ruthenabicyclo[3.2.0]heptatriene was proposed for the conversion of a ruthenacyclopentadiene–alkyne complex to a seven-membered ruthenacycle complex.^{20,21a} Soon after these reports, the relevant iridabicyclo[3.2.0]heptatriene was isolated and characterized by X-ray crystallography.²² Kirchner and co-workers also disclosed that the cyclocotrimerizations of acetylene with an isocyanate and an isothiocyanate proceed via similar mechanisms involving the corresponding ruthenabicyclo intermediates, and they reasonably explained the regioselectivity difference between these heterocumulenes.²¹ Thus, the new mechanism appears to be general for the CpRuCl-catalyzed cyclocotrimerizations, but the following two additional issues must be addressed with respect to the pyridine formations. First, the ruthenium catalysis prefers electron-deficient nitriles, and this is in striking contrast to the cobalt catalysis. Second, the oxidative cyclization between an alkyne and an electron-deficient nitrile might give rise to an elusive azaruthenacycle complex, which might be an alternative intermediate for the pyridine formation. The first issue is closely related with the second one, because the electron-accepting group facilitates the oxidative cyclization by lowering the LUMO of the C–N triple bond. With these points in mind, we carried out the DFT calculations of the CpRuCl-mediated cyclocotrimerization of acetylene with trifluoroacetonitrile as an electron-deficient nitrile as well as acetonitrile.

The oxidative cyclizations of two acetylene molecules or acetylene with trifluoroacetonitrile on the coordinatively unsaturated CpRuCl fragment were calculated by means of the Becke’s three-parameter hybrid density functional method (B3LYP)²³ with appropriate basis sets (for details, see Supporting Information). The results were outlined in Figure 2. As previously reported,^{20,21a} the oxidative cyclization of two acetylene molecules starts with the bis(acetylene) complex **I** to result in the ruthenacyclopentatriene **II**. The activation energy of this transformation is estimated as 14.8 kcal/mol.

The coordination modes of nitriles in mononuclear complexes can be divided into two categories: σ -bonding through the

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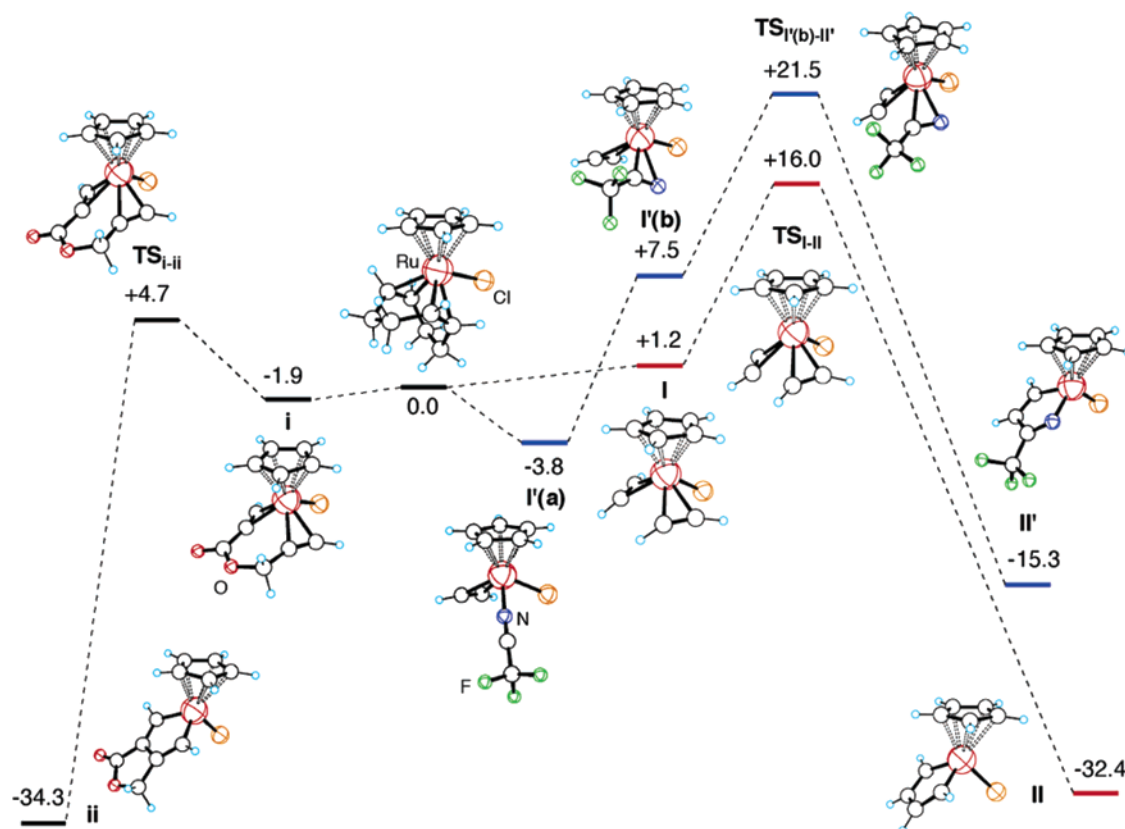


Figure 2. Oxidative cyclizations resulting in ruthenacycles **II**, **II'**, and **ii** (energies in kcal/mol).

nitrogen lone pair (end-on mode) and π -bonding with the nitrogen–carbon triple bond (side-on mode).²⁴ Although the former is the more common coordination mode, some η^2 side-bonded nitrile complexes have been isolated and unambiguously characterized by X-ray crystallography.²⁵ The η^1 -nitrile complex **I'(a)** was estimated to be 3.8 and 11.2 kcal/mol more stable than CpRuCl(cod) and the η^2 -nitrile complex **I'(b)**, respectively. The anticipated oxidative cyclization of **I'(b)** leading to the azaruthenacycle **II'** is expected to proceed with an activation barrier of 14.0 kcal/mol. The formation of **II'** from **I'(b)** is 10.8 kcal/mol less exothermic than that of **II** from **I**. This is because **II** is thermodynamically more stable than **II'** probably because of its aromatic character. The Ru–C1 distance of 1.952 Å in **II** shows a double-bond character, and the C1–C2 and C2–C3 bond lengths (1.395 and 1.404 Å, respectively) are very similar to that of benzene (1.40 Å) (see Figure S8 in Supporting Information). These features clearly show that **II** is a highly delocalized metallolene. On the other hand, **II'** has an azaruthenacyclopentadiene structure, in which the C2–C3 bond is

distinctly longer than the C1–C2 and C3–N bonds. The Ru–C1 bond length of 2.012 Å is close to typical Ru–C single-bond distances (Figure S8).

Although both oxidative cyclizations giving **II** or **II'** seem to be possible in terms of the activation barriers, the azaruthenacycle route is less attractive because of the following reasons. First, the η^2 -nitrile complex **I'(b)** is thermodynamically less favorable than both the bis(alkyne) complex **I** and the η^1 -nitrile complex **I'(a)**. Second, in the real catalytic system, an α,ω -diyne favors the oxidative cyclization leading to a bicyclic ruthenacyclopentatrienes, since intramolecular cyclizations are kinetically more favorable than the corresponding intermolecular ones. Therefore, we further explored only pathways involving the ruthenacycle **II**.

At the outset, the geometries of ruthenacycle complexes possessing a nitrile ligand were optimized at the same level of theory. Upon coordination of trifluoroacetonitrile to **II**, three ruthenacyclopentadiene–CF₃CN complexes **III(a)**–**III(c)** might be formed as shown in Figure 3. The η^1 -nitrile complex **III(a)** was 7.2 kcal/mol more stable than the η^2 -nitrile complex **III(b)**, which is, in turn, 5.8 kcal/mol more stable than the isomeric η^2 -nitrile complex **III(c)**. In these η^2 complexes, the C–N bond is elongated by 3.7 Å from that of the free CF₃CN because of the back-donation from the ruthenium center to the LUMO of the C–N triple bond (Figure S8). The C–C–N angles are 145.03° and 146.32° for **III(b)** and **III(c)**, respectively. In contrast, a smaller back-donation is expected for acetonitrile, which has a higher LUMO level. Indeed, the C–N distance (1.168 Å) and the C–C–N angle (179.23°) of the η^2 acetonitrile ligand in **III'(b)** is very similar to those of free CH₃CN. The

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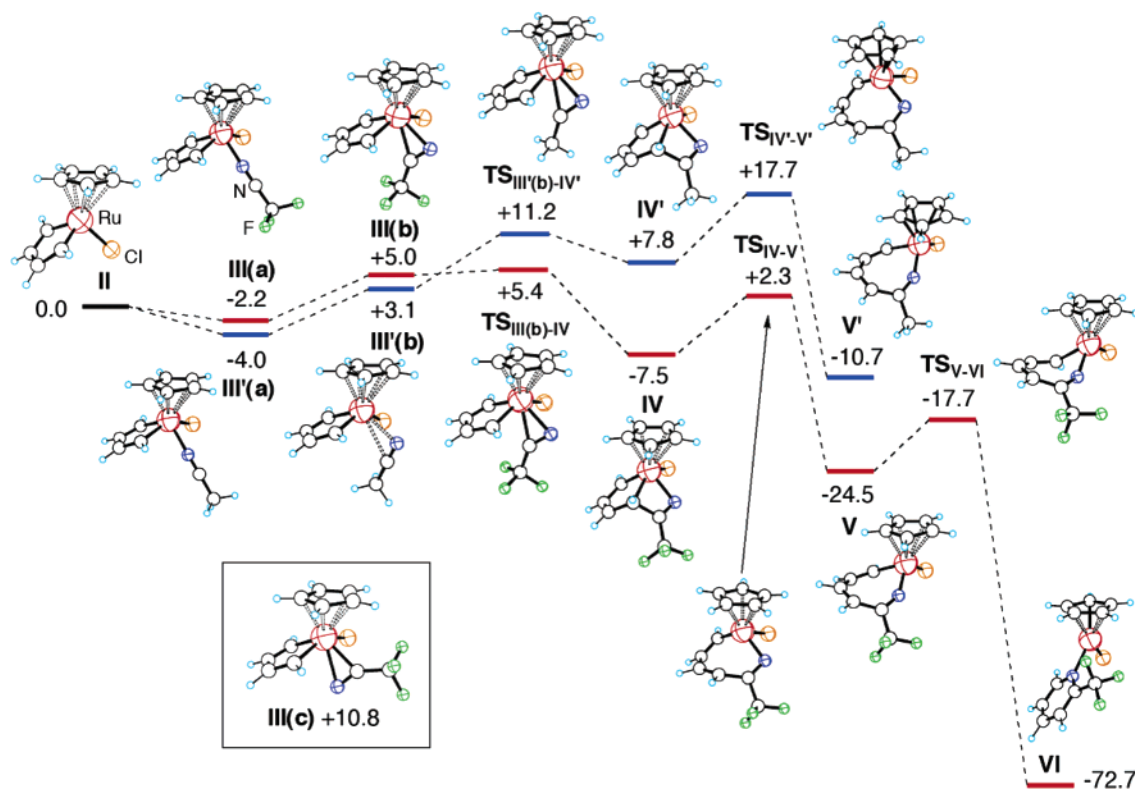


Figure 3. Reaction profile for for CpRuCl-catalyzed pyridine formation (energies in kcal/mol).

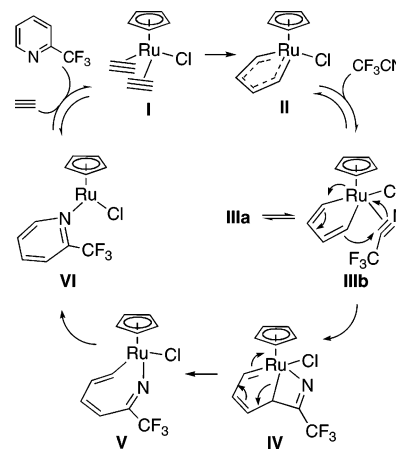
Ru–C(nitrile) and Ru–N distances in **III'(b)** are much longer than those in **III(b)**.

The nitrile insertion starts with the isomerization of the η^2 -nitrile complexes **III(b)** or **III'(b)** to the azaruthenabicyclo[3.2.0]-heptatrienes **IV** or **IV'**. The conversion of **III(b)** to **IV** occurs with a very small activation energy of 0.4 kcal/mol. This is due to the least geometry change upon progression to the transition state **TSIII(b)-IV** from **III(b)**. The formation of **IV** is thermodynamically favorable with an exothermicity of 12.5 kcal/mol. In striking contrast, the conversion of **III'(b)** to **IV'** turned out to be endothermic ($\Delta E = +4.7$ kcal/mol). In addition, the geometry change from **III'(b)** to **TSIII'(b)-IV'** is more pronounced, resulting in larger activation barrier of 8.1 kcal/mol. Consequently, the electron-withdrawing group on the nitrile ligand makes the formal [2 + 2] cycloaddition with the ruthenacyclopentatriene **II** both kinetically and thermodynamically favorable.

The subsequent conversion of **IV** to the azaruthenacycloheptatriene **V** proceeds with an exothermicity of 17.0 kcal/mol via the central Ru–C bond scission. The activation energy was estimated as 9.8 kcal/mol. The final ring closure of **V** is expected to be highly exothermic because of the formation of the aromatic pyridine ring. In fact, the exothermicity was estimated as 48.2 kcal/mol, and the η^1 -pyridine complex **VI** is the final product. The activation barrier of 6.8 kcal/mol is smaller than that for the ring opening of **IV**.

The overall mechanism of cyclocotrimerization of acetylene with trifluoroacetonitrile outlined in Scheme 5 is quite similar to that of the previously reported CpRuCl-mediated acetylene cyclotrimerization.^{20,21a} All elementary steps are exothermic, and the rate-determining step is the oxidative cyclization of two acetylene molecules to form the ruthenacyclopentatriene intermediate **II**. Thus, the 1,6-diyne, which make the oxidative

Scheme 5



cyclization more favorable, are excellent substrates for the present pyridine formation, in line with other CpRuCl-mediated [2 + 2 + 2] cyclotrimerizations.

Origin of Regioselectivity. On the basis of the theoretical calculations, the reaction pathways for the regioselective cycloaddition of the unsymmetrical diynes **14** were outlined in Scheme 6. The regiochemistry of the cycloadducts might be determined by the formal [2 + 2] cycloaddition of the unsymmetrical ruthenacycle intermediate **25** with **3a** or **5e**, leading to the intermediates **26** or **27**. If **3a** and **5e** attack the Ru–C α bond from the more substituted side, the diyne-derived substituent R comes close to the bulky Cp* ligand, imposing the severe steric repulsion on the unfavorable intermediates **26b** and **27b**. On the other hand, the access of **3a** and **5e** to **25** from the less substituted side leads to the major regioisomers **15** or **17**, respectively, avoiding such a deteriorative steric repulsion via the favorable intermediates **26a** and **27a**.

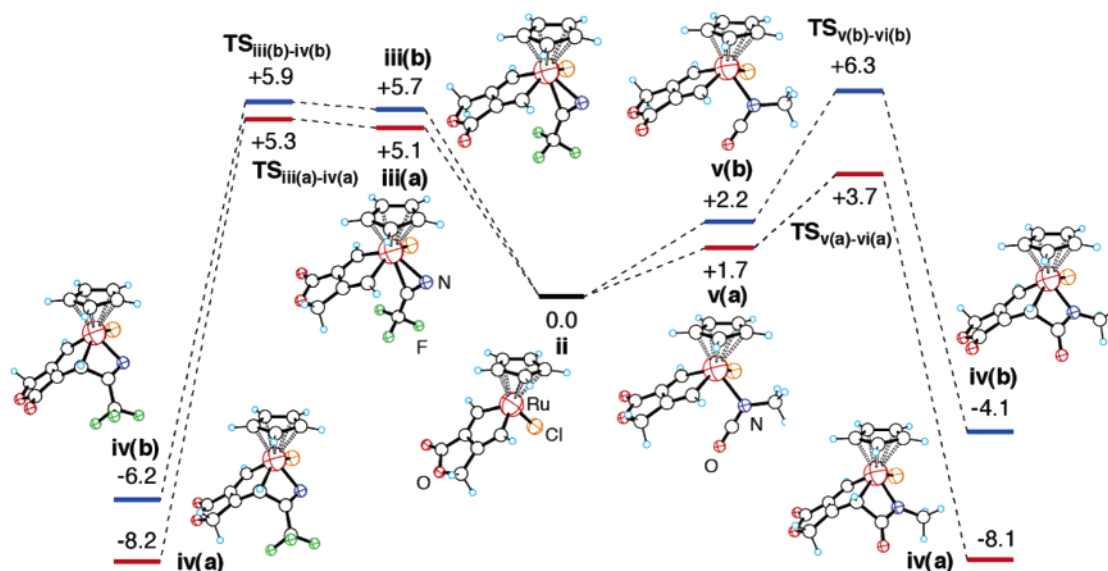


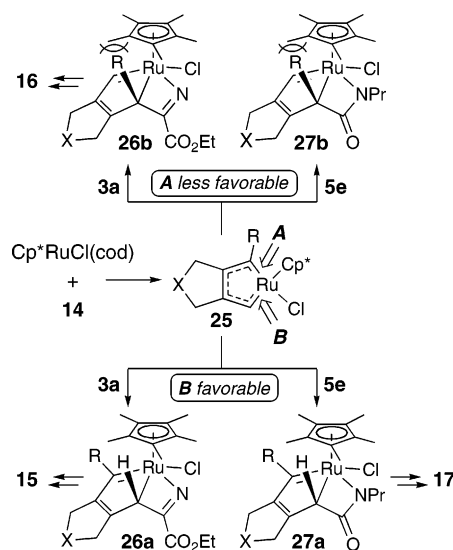
Figure 4. Reaction profile for for CpRuCl-catalyzed pyridine formation (energies in kcal/mol).

The electronic directing effect is somewhat complicated compared to the steric directing effect. As reported previously,¹⁸ the ruthenacyclopentatriene moieties in the model complexes, which were optimized at the B3LYP/LACVP* level of theory, are almost symmetrical, whereas the fused lactam, lactone, and cyclopentanone rings exhibited unsymmetrical geometries. Natural population analysis (NPA), however, revealed that these complexes are unsymmetrical in terms of the NPA charges (see Figure S9 in Supporting Information). With respect to the ruthenacycle carbons, the natural charges are increased for the α carbons anti to the carbonyl group. With these results, it is quite reasonable to assume that the [2 + 2] cycloaddition of these ruthenacycles with the electron-deficient nitriles and isocyanates might take place at the more negatively charged α carbons. To confirm this idea, we analyzed the formal [2 + 2] cycloaddition of the ester diyne **20b** with trifluoroacetonitrile and methyl isocyanate by means of the DFT calculations. The oxidative cyclization step was calculated and compared to that of acetylene. As outlined in Figure 2, the activation energy of 6.6 kcal/mol for the transformation of the diyne complex **i** into the bicyclic complex **ii** (**28b**) is about a half of that for **I** \rightarrow **II** (14.8 kcal/mol). Such a small barrier might be attributed not only to the intramolecular effect of the diyne substrate but also to the superior electron-accepting ability of the electron-deficient **20b**.

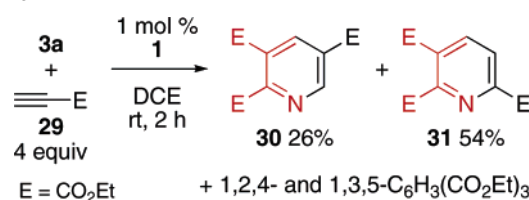
The coordination of **ii** to CF₃CN affords the two isomeric η^2 -nitrile complexes **iii(a)** and **iii(b)** (Figure 4). The nitrile ligand occupies the coordination site cis to the more electronegative α carbon in **iii(a)**, while it is accommodated in the cis site of the less negative carbon in **iii(b)**. The former is 0.6 kcal/mol more stable than the latter. The subsequent isomerization of these complexes occurs with the activation energy of 0.2 kcal/mol to produce the tricyclic intermediates **iv(a)** and **iv(b)**. The exothermicity of 13.3 and 11.9 kcal/mol were estimated for the formation of **iv(a)** and **iv(b)**, respectively. These results show that the [2 + 2] cycloaddition proceeds preferably on the more negative α carbon (**ii** \rightarrow **iii(a)** \rightarrow **iv(a)**).

Similarly, we also calculated the [2 + 2] cycloaddition of **ii** with methyl isocyanate. In contrast to the previous reports,²¹ we could locate the η^1 -isocyanate complexes **v(a)** and **v(b)** as

Scheme 6



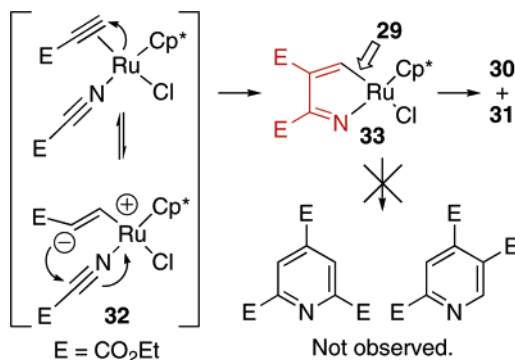
Scheme 7



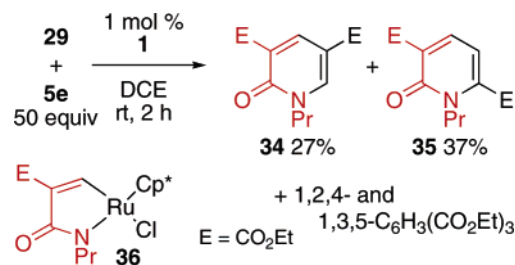
a local minimum. The former is 0.5 kcal/mol more stable than the latter. The activation barriers were estimated as 2.0 and 4.1 kcal/mol for TS_{v(a)-vi(a)} and TS_{v(b)-vi(b)}, respectively. The formation of **vi(a)** is 3.5 kcal/mol more exothermic than that of **vi(b)**. The difference in the activation energies for the [2 + 2] cycloaddition step turned out to be much more pronounced with the isocyanate than with CF₃CN. This is in accordance with the higher regioselectivity of the pyridone formations compared to the corresponding pyridine formations.

Intermolecular Cyclocotrimerization Using Electron-Deficient Monoalkyne. Previously, we have shown that electron-deficient monoalkynes underwent cyclocotrimerization at ambient

Scheme 8



Scheme 9



temperature under the ruthenium catalysis, while the reaction of electronically neutral ones were not efficient under the similar conditions.²⁰ These facts indicate that the electron deficiency facilitates the oxidative cyclization of the monoalkynes leading to ruthenacycle intermediates. Finally, we briefly examined the intermolecular cyclocotrimerization of ethyl propiolate with carbon–heteroatom multiple bonds.

In the presence of 1 mol % **1**, ethyl cyanofornate **3a** was treated with 4 equiv of ethyl propiolate **29** at ambient temperature for 2 h (Scheme 7). As a result, two unsymmetrical pyridine isomers **30** and **31** were obtained in 26 and 54% yields based on **3a**, respectively, along with 1,2,4- and 1,3,5-benzenetricarboxylic acid triethyl esters. The obtained products showed a couple of aromatic protons as doublets with coupling constants of 1.8 and 8.1 Hz, respectively, which allowed us to assign **30** and **31** to 2,3,5- and 2,3,6-substituted isomers, respectively. This interesting regioselectivity can be explained by assuming the selective formation of an azaruthenacycle intermediate. In the intermolecular reaction, the oxidative cyclization of a monoalkyne and an electron-deficient nitrile might be feasible as shown by the DFT calculations (Figure 2). Considering the polarization of the propiolate ligand in **32**, the cyclization might take place as outlined in Scheme 8 to give rise to an azaruthenacyclopentadiene **33** selectively. Subsequent reaction of **33** with **29** occurred with its Ru–C bond to furnish the only two pyridine isomers **30** and **31**.

In the same manner, phenyl isocyanate **5a** was treated with 4 equiv of **29** to give the benzenetricarboxylic acid esters almost exclusively. Thus, a large excess of an isocyanate was required to suppress the facile cyclotrimerization of **29**. In fact, employing 50 equiv of readily removable propyl isocyanate **5e** resulted in the formation of the desired pyridones **34** and **35** in 27 and 37% yields based on **29**, respectively (Scheme 9). Again, only two of the four possible regioisomers were formed, indicative of an azaruthenacyclopentenone **36** being an exclusive intermediate.

Conclusion

In conclusion, we successfully developed Cp^*RuCl -catalyzed cycloadditions of diynes with electron-deficient nitriles and heterocumulenes, leading to various heterobicyclic compounds. It was revealed that the regiochemistry of these cycloadditions was successfully controlled by the steric and electronic influence of the unsymmetrical diyne substrates. Density functional calculations of model reactions showed that the CpRuCl -catalyzed cyclocotrimerization of acetylene with CF_3CN starts with the oxidative cyclization of two acetylene molecules producing a ruthenacyclopentatriene intermediate. The formal [2 + 2] cycloaddition of the ruthenacycle intermediate with the $\text{C}\equiv\text{N}$ triple bond gives rise to the azaruthenabicyclo[3.2.0]-heptatriene and its transformation into the final η^1 -pyridine complex takes place via the azaruthenacycloheptatriene complex. The rate-determining step of the overall process was determined as the initial oxidative cyclization; therefore, the intramolecular system is suitable for the ruthenium catalysis. DFT calculations also suggested that the [2 + 2] cycloadditions of the ruthenabicyclo intermediate derived from the ester-tethered diyne with CF_3CN and methyl isocyanate take place at the more negatively charged α carbon of the ruthenacycle, in accordance with the observed regioselectivity.

Intermolecular cyclocotrimerizations of ethyl propiolate with ethyl cyanofornate or propyl isocyanate gave rise to two of the four possible regioisomers, indicative of azaruthenacycle intermediates playing an important role.

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Supporting Information Available: Experimental details, characterization data for the products, and the supplementary crystallographic data and X-ray crystallographic files (PDF, CIF). This material is available free of charge via the Internet at <http://pubs.acs.org>.

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