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Synthesis of benzo-fused lactams and lactones *via* Ru(II)-catalyzed cycloaddition of amide- and ester-tethered α,ω-diynes with terminal alkynes: electronic directing effect of internal conjugated carbonyl group

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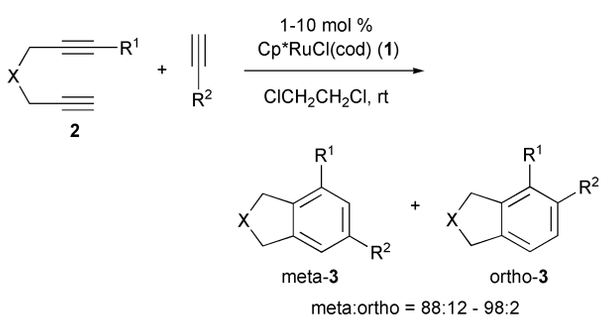
In the presence of a catalytic amount of Cp*RuCl(cod), 1,6- and 1,7-diynes connected by an amide or an ester tether underwent cycloaddition with terminal alkynes at room temperature to give rise to cycloadducts in 40–93% yields with 63 : 37–83 : 17 regioisomer ratios.

Introduction

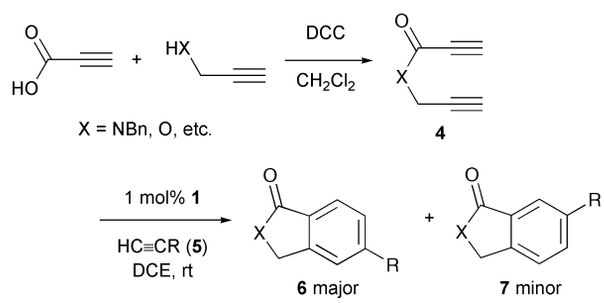
Transition-metal-catalyzed [2 + 2 + 2] cyclotrimerization of alkynes is straightforward and an atom-economical approach to substituted benzene derivatives.[1] One crucial disadvantage of this potentially useful method is the difficulty in controlling chemo- and regiochemistry.[2] In this context, we have developed the Ru(II)-catalyzed intramolecular alkyne cyclotrimerizations, in which we have found that the cycloaddition of unsymmetrical 1,6-diynes **2** with terminal alkynes proceeded in the presence of a ruthenium precatalyst, Cp*RuCl(cod) (**1**) (Cp* = η^5-C_5Me_5, cod = 1,5-cyclooctadiene), at room temperature to afford bicyclic benzenes **3** with good to excellent regioselectivity (*meta*/*ortho* = 88 : 12–98 : 2) (Scheme 1).[3]



Scheme 1

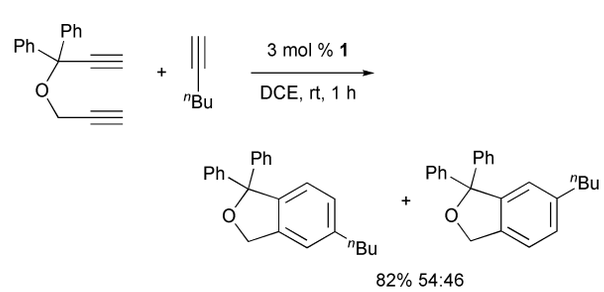
In order to extend the Ru(II)-catalyzed cycloaddition, we further explored the cycloaddition of amide- and ester-tethered α,ω-diynes **4**, which are readily prepared from propiolic acid and propargyl compounds (Scheme 2), because this strategy would provide an efficient entry into valuable heterocycles such as isoindolinones and phthalides. Isoindolinone ring systems have attracted considerable interest due to their biological activity, including anti-inflammatory (indoprofen), anxiolytic (pazinaclone), and protein kinase C inhibitor (staurosporine) activities.[4] The phthalide ring is also found in a biologically active natural product, mycophenolic acid.[5]

Unsymmetrical α,ω-diynes having no terminal substituent, however, might afford regioisomeric cycloadducts unselectively. In fact, an unsymmetrical propargyl ether derivative exhibited



Scheme 2

almost no regioselectivity, although it has a bulky diphenylmethylene moiety adjacent to one of the two terminal alkynes (Scheme 3). On the other hand, a carbonyl group directly connected to the alkyne terminal is expected to exert a direct electronic impact on the regioselectivity. To our surprise, such an *electronic effect* has remained unevaluated. With these facts in mind, we report herein the Ru(II)-catalyzed cycloaddition of unsymmetrical diynes bearing a conjugated carbonyl group in the tether with terminal alkynes (Fig. 1).



Scheme 3

Results and discussion

At the outset of this study, an amide-diyne **4a** (X = NBn) was reacted with 4 equiv. 1-hexyne **5a** in 1,2-dichloroethane (DCE) containing 1 mol% **1** at room temperature for 0.5 h to afford the expected isoindolinones **6aa** and **7aa** (Table 1, run 1). Interestingly, the ^{1}H NMR analysis of the crude product mixture

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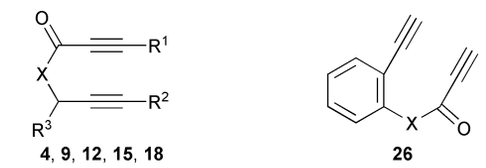
Table 1 Ru(II)-catalyzed cycloaddition of diynes **4** with alkynes **5**

Run	X	R	Time/h	Product (yield, %)[a]	**6/7**[b]
1	NBn	^{n}Bu	0.5	**6aa** (51), **7aa** (25)	63 : 37
2	NBn	^{t}Bu	2	**6ab** (31), **7ab** (9)	80 : 20
3	NBn	Ph	2	**6ac/7ac** (93)	80 : 20
4	NBn	CH_2OMe	1	**6ad/7ad** (90)	64 : 36
5	NBn	CH_2NMe_2	1	**6ae/7ae** (63)	64 : 36
6	O	^{n}Bu	2	**6ba/7ba** (93)	70 : 30
7	O	Ph	2	**6bc/7bc** (87)	75 : 25
8	CMe_2	^{n}Bu	0.5	**6ca/7ca** (70)	78 : 22

[a] Isolated yields. [b] Regioisomer ratio was determined by ^{1}H NMR analysis of crude products.



Diynes: series **a**, X = NBn; series **b**, X = O; series **c**, X = CMe_2

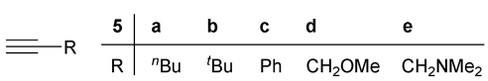


Fig. 1 Starting materials used in this study.

revealed that the cycloadduct **6aa**, in which the *n*-butyl substituent is placed in the *para*-position to the amide group, was found preferably over the other regioisomer **7aa** (**6aa** : **7aa** = 63 : 37). This observation is in sharp contrast to the previously repored Ni(0)-mediated cycloaddition of similar amide-diynes with methyl propargyl ether giving rise to 50 : 50 regioisomer mixtures.[6] Separation with silica gel chromatography yielded **6aa** and **7aa** in 51 and 25% yields, respectively.

The generality of the present regioselectivity was examined with respect to terminal alkynes as summarized in Table 1. In a similar manner, sterically demanding *tert*-butylacetylene **5b** was reacted with **4a** to afford **6ab** and **7ab** in 31 and 9% respective yields (run 2). Interestingly, the regioselectivity was improved up to 80 : 20, whereas the total yield was lower than that of **6aa/7aa**. Phenylacetylene **5c** gave an inseparable mixture of biphenyl analogues in excellent combined yield with the same regioisomeric ratio of **6ac** : **7ac** = 80 : 20 (run 3). Alkynes **5d** and **5e** bearing an ether or a tertiary amine functionality also underwent the cycloaddition to form the corresponding isoindolinones **6ad/7ad** and **6ae/7ae**, respectively, with the regioisomer ratio similar to that of **6aa/7aa** (runs 4 and 5).

The regiochemistry of the obtained products was determined on the basis of ^{1}H NMR (300 MHz, $CDCl_3$) analysis. As shown in Fig. 2, the diagnostic aromatic proton Ha appeared in a lower magnetic field than Hb-Hd, because of the deshielding effect of the adjacent carbonyl group. The Ha signals of the major isomers **6** were observed as doublet peaks with a coupling constant around 8 Hz, whereas those of the minor isomers **7** appeared as singlets. The major product derived from **4a** and **5c** was unambiguously assigned to **6ac** by X-ray crystallographic analysis (Fig. 3). †

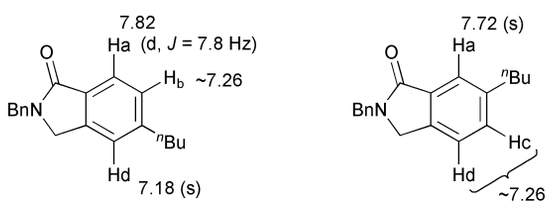


Fig. 2 ^{1}H NMR chemical shifts of **6aa** and **7aa**.

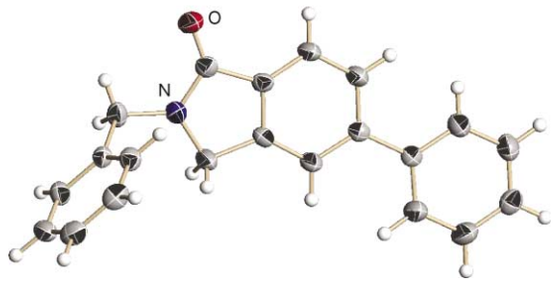


Fig. 3 ORTEP drawing of **6ac**.

Next we examined the influence of the electron-withdrawing ability of the carbonyl group. Toward this end, diynes **4b** and **4c** bearing an ester or a ketone carbonyl group were subjected to the cycloaddition with terminal alkynes. An ester-diyne **4b**[7] was reacted with 1-hexyne **5a** or phenylacetylene **5c** under similar reaction conditions to afford phthalides **6ba/7ba** and **6bc/7bc** in 93 and 87% combined yields (Table 1, runs 6 and 7). The observed regioselectivities are similar to those of corresponding isoindolinones. In contrast, the regioisomer ratio was slightly improved when a ketodiyne **4c** was employed (run 8). Indanones **6ca/7ca** were obtained in 70% combined yield with the ratio of **6ca** : **7ca** = 78 : 22. It is noteworthy that the present regioselectivity increased in the order of **4a** (X = NBn) ≅ **4b** (X = O) < **4c** (X = CMe_2), indicative of a carbonyl group with stronger electron-withdrawing ability favoring the formation of **6** over **7**.

In order to evaluate the cooperative effect of the terminal substituents and the internal carbonyl group, variously substituted amide- and ester-diynes were examined with respect to the cycloaddition with 1-hexyne **5a** (Scheme 4). Under the same reaction conditions with **4a**, an amide **9a** (X = NBn, R^1 = Me, R^2 = H) possessing a methyl substituent at the electron-deficient alkyne terminal furnished the expected regioisomer **10aa** in 81% yield as a sole product. Similarly, an ester analogue **9b** (X = O, R^1 = Me, R^2 = H) gave rise to **10ba** as a major product (**10ba** : **11ba** = 97 : 3). These results suggest that the *steric* directing effect of the terminal methyl substituent effectively suppressed the formation of the minor regioisomers, resulting in the selective formation of **10aa** and **10ba**. In striking contrast, the reaction of **12a** (X = NBn, R^1 = H, R^2 = Me) having a methyl substituent on the other alkyne moiety required increased catalyst loading (5 mol%) as well as a longer reaction time for completion of the reaction. In addition, **14aa** was obtained in 56% yield as a major product together with **13aa** (12%). Moreover, the regioselectivity was decreased from **13aa** : **14aa** = 18 : 82 to **13ba** : **14ba** = 21 : 79, when a more electron-deficient ester analogue **12b** (X = O, R^1 = H, R^2 = Me) was employed in place of **12a**. In these cases, the *electronic* directing effect was almost offset by the conflicting *steric* influence of the terminal

† *Crystallographic data*: A single crystal of **6ac** (0.2 × 0.4 × 0.8 mm^3) suitable for X-ray analysis was obtained by recrystallization from $CHCl_3$–ether. The single crystal was mounted on a quartz fiber, and diffraction data were collected in the θ range of 2.43–29.14° at 173 K on a Brucker SMART APEX CCD diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). An absorption correction was made using SADABS. The structure was solved by direct methods and refined by full-matrix least squares on F^2 by using SHELXTL. All non-hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were placed in calculated positions. Final refinement details of **6ac** [$C_{21}H_{17}NO$, Mw = 299.36]; space group *P*2(1), monoclinic; unit-cell dimensions a = 8.3987(6) Å, b = 5.7449(4) Å, c = 15.9653(12) Å, β = 90.7740(10)°, V = 770.25(10) Å^3; Z = 2, D_{calc} = 1.291 Mg m^{-3}; Total 5753 reflections were measured and 3608 were independent [R(int) = 0.0236]. Final R_1 = 0.0493, wR_2 = 0.1318 [$I > 2\sigma(I)$], and GOF = 0.719 (for all data, R_1 = 0.0506, wR_2 = 0.1349).

CCDC reference numbers 224127. See http://www.rsc.org/suppdata/ob/b4/b402649g/ for crystallographic data in.cif or other electronic format.

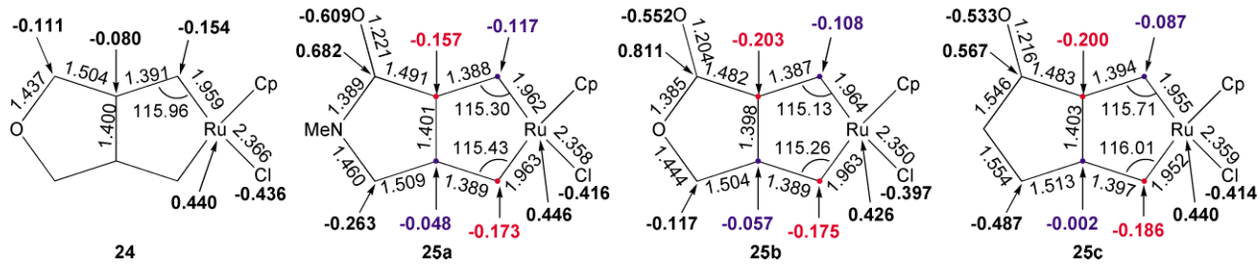
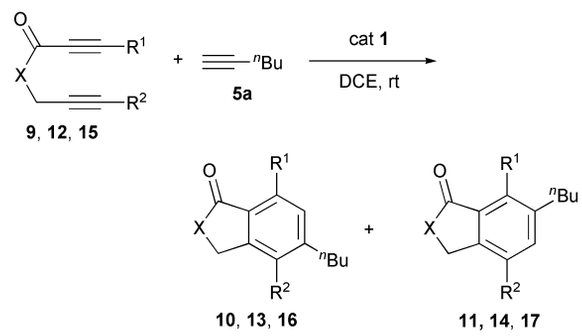


Fig. 4 DFT-optimized geometries of model ruthenacycles **24** and **25a**–**c** at the B3LYP/LACVP* level. Typical bond lengths (Å), angles (°) were shown with natural charges (bold).



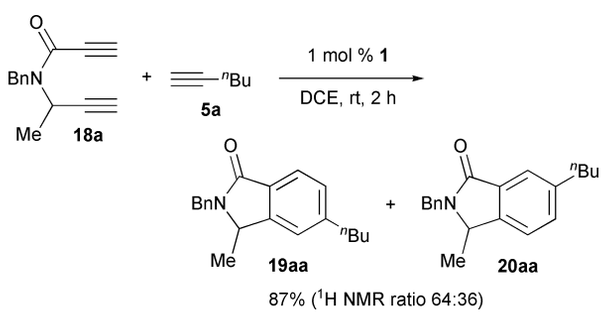
R^1	R^2	X	**1**, mol %	time, h	products (yield, %)	ratio[a]
Me	H	NBn	1	0.5	**10aa** (81)	100:0
Me	H	O	1	0.5	**10ba/11ba** (88)	97:3
H	Me	NBn	5	2	**13aa** (12), **14aa** (56)	18:82
H	Me	O	5	2	**13ba/14ba** (78)	21:79
Me	Me	NBn	5	1	**16aa** (80), **17aa** (13)	83:17
Me	Me	O	5	1	**16ba/17ba** (94)	90:10

[a] Determined by ^{1}H NMR analysis of crude products.

Scheme 4

methyl substituent. As a consequence, both the reaction rate and regioselectivity were decreased to give rise to both regioisomers. Interestingly, an amide-diyne **15a** (X = NBn, $R^1 = R^2$ = Me) and an ester-diyne **15b** (X = O, $R^1 = R^2$ = Me) reacted with **5a** at room temperature for 1 h in the presence of 5 mol% **1** to give rise to 83 : 17 and 90 : 10 regioisomer mixtures,[8] whereas they have methyl substituents on both alkyne termini.

The steric influence of an internal methyl substituent on the regiochemistry was again not observed for the reaction of **18a** (Scheme 5). Isoindolinones **19aa/20aa** were obtained with almost the same isomer ratio to that observed for **5a**.



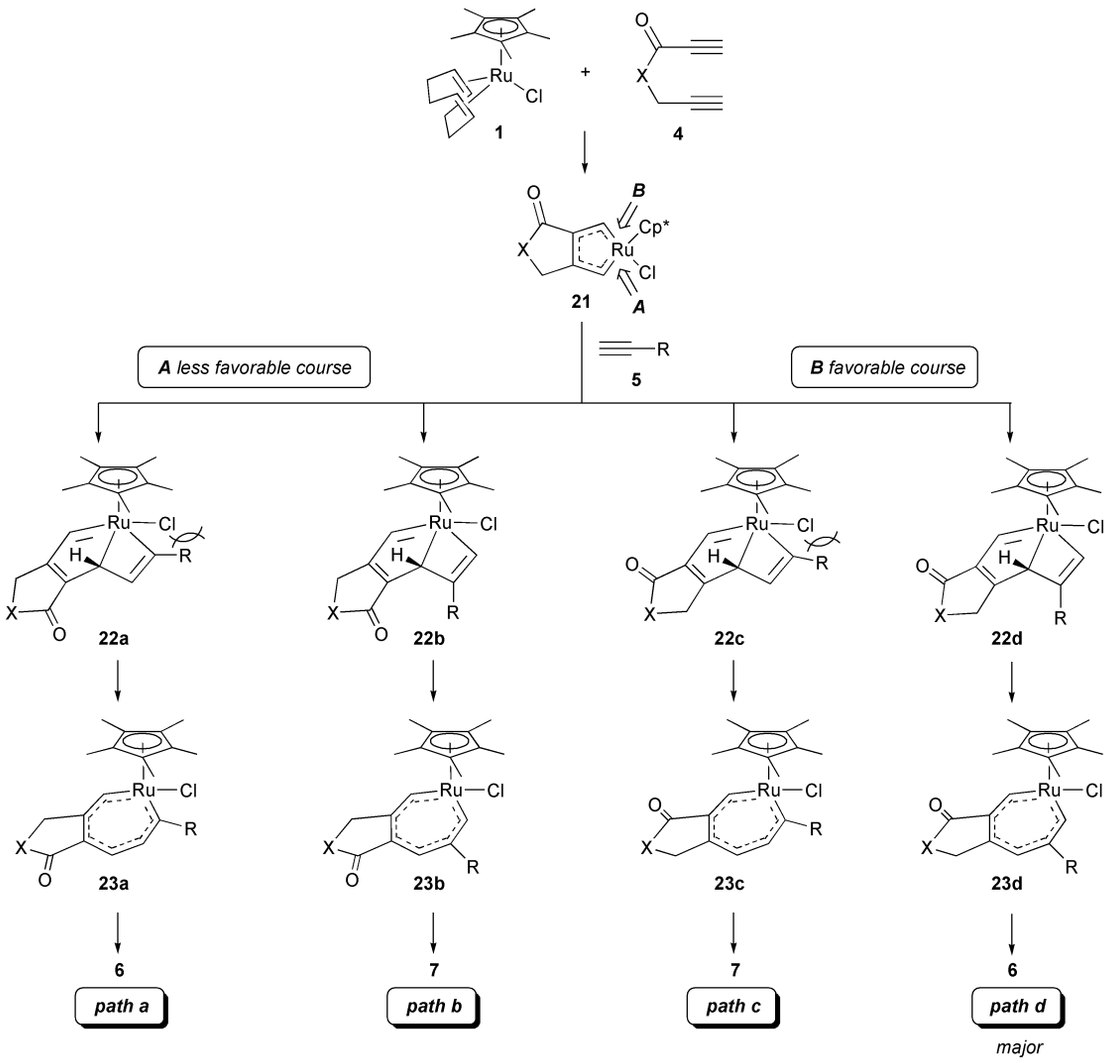
Scheme 5

Scheme 6 outlines the reaction mechanism of the cycloaddition of **4**, which reasonably explains the observed regioselectivity. The cycloaddition might start with the formation of a ruthenabicycle intermediate **21** from **1** and **4**. As previously proposed on the basis of the theoretical calculations,[3,9] the [2 + 2] cycloaddition of the ruthenacycle intermediate **21** with a terminal alkyne **5** might afford ruthenacycle intermediates **22a**–**d**, which subsequently undergo ring opening to result in seven-membered ruthenacycles **23a**–**d**.[10] The final reductive elimination affords the benzene regioisomers **6** and **7**, and the catalytically active species, Cp*RuCl, is restored. The regiochemistry of the cycloadducts might be determined by the [2 + 2] cycloaddition step. The access of the terminal alkyne to the Ru–Cα bond on the same side with the carbonyl group gives rise to **22a** or **22b**. On the other hand, **22c** or **22d** are produced, when the terminal alkyne comes close to the ruthenacycle from the other direction. The latter course seems favorable over the former, because the methyl substituent on the electronically neutral alkyne terminus in the diynes **12a**,**b** had a deleterious effect on both the reaction rate and the regioselectivity, although the methyl substituent on the electron-deficient alkyne terminal in **9a**,**b** improved the regioselectivity (Scheme 4). In addition, the repulsive interaction between the substituent R and the chlorine ligand makes **22a** and **22c** less favorable than **22b** or **22d**, respectively. According to these analyses, path d (**21** ⟶ **22d** ⟶ **23d** ⟶ **6**) is considered to be the major course of the present cycloaddition.

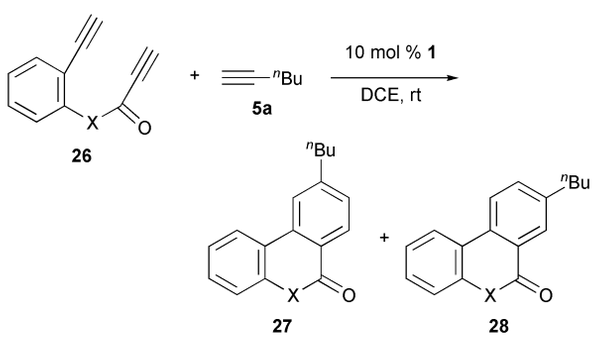
In order to obtain further information on the regioselection mechanism, we carried out the density functional study of the ruthenacycle key intermediate. To this aim, the geometries of model ruthenacycle complexes **25a**–**c** bearing a cyclopentadienyl ligand were optimized at the B3LYP/LACVP* level of theory. The obtained geometries are outlined with those for previously reported **24**[3] in Fig. 4. Surprisingly, the ruthenacyclopentatriene moieties are almost symmetrical, although the fused lactam, lactone, or cyclopentenone rings exhibited clearly unsymmetrical geometries. Further calculations of natural charges, however, uncovered the electronically unsymmetrical environment of these ruthenacycles. With respect to the ruthenacycle carbons, the natural charges are increased for the red-colored carbons and decreased for the blue-colored ones. With these results, we assumed that more negatively charged α carbons are favorable for the [2 + 2] cycloaddition with terminal alkynes.

The present regioselective cycloaddition was further extended to 1,7-diynes **26a** and **26b** derived from ethynylaniline and ethynylphenol, respectively (Scheme 7). In the presence of 10 mol% **1**, **26a** underwent cycloaddition with **5a** at room temperature for 1 h to afford the desired benzoquinolones **27aa**/**28aa**. To our delight, the ^{1}H NMR analysis of the crude mixture revealed that the regioselectivity of **27aa** : **28aa** = 83 : 17 was higher than that of the corresponding products from the 1,6-diyne **4a** (Table 1, run 1). The chromatographic purification gave **27aa** and **28aa** in 56 and 14% respective yields. With the decreased catalyst loadings of 1–5 mol%, the reaction did not complete within 15 h at room temperature. Analogously, **26b** reacted with **5a** for 2 h to furnish inseparable coumarin regioisomers **27ba** and **28ba** in 41% combined yield. The crude regioisomer ratio of **27ba** : **28ba** = 82 : 18 was again higher than that of the corresponding products from the ester-diyne **4b** (Table 1, run 6).

Apart from the regioselectivity issue, the ruthenium(II)-catalyzed cycloadditions of the amide-diynes are highly



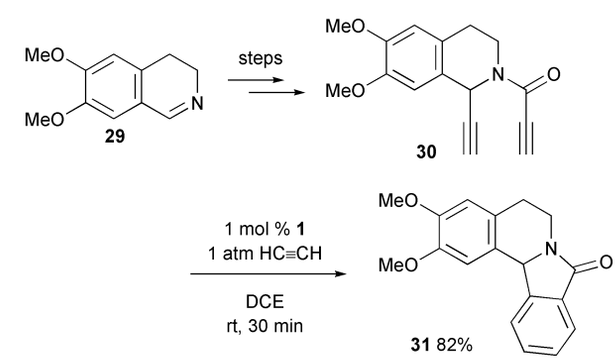
Scheme 6



X	time, h	products (yield, %)	ratio[a]
NBn	1	**27aa** (56), **28aa** (14)	83:17
O	2	**27ba**/**28ba** (41)	82:18

[a] Determined by ^{1}H NMR analysis of crude products.

Scheme 7



Scheme 8

valuable, because they provide an efficient access to isoindolinone frameworks. In order to demonstrate its synthetic potential, the present method was applied to the construction of an isoindoloisoquinoline skeleton, which is found in neuvamine, an alkaloide stemming from Berberis darwinii, and its derivatives (Scheme 8).[11,12] The desired precursor, 1,6-diyne **30** was prepared from a readily available dihydroisoquinoline **29**.[13] In the presence of 1 mol% **1**, **30** was reacted with acetylene (1 atm) at room temperature for 30 min to give rise to the expected isoindoloisoquinoline **31** in 82% yield. The analytical data of **31** were in good agreement with those reported in the literature.[12]

Conclusions

In conclusion, we successfully developed the mild and selective synthesis of isoindolinone and phthalide derivatives by means of the Ru(II)-catalyzed cycloaddition of the 1,6-diynes bearing amide and ester tethers, and uncovered the unprecedented regioselectivity. The ^{1}H NMR and X-ray crystallographic analyses revealed that the cycloadducts, in which the substituent derived from the terminal alkynes is placed in the *para*-position to the carbonyl group, were formed preferentially. The regioselectivity

varied depending on the tether group as well as substituents on terminal alkynes. The carbonyl group with stronger electron-withdrawing ability gave higher selectivity. Quinolone and coumarin frameworks were also assembled successfully from aniline- and phenol-derived 1,7-diynes. The synthetic potential of the ruthenium catalysis was also demonstrated by the construction of an isoindoloisoquinoline framework, which was found in a naturally occurring alkaloid, neuvamine.

Experimental

Flash chromatography was performed with a silica gel column (Merck Silica gel 60) eluted with mixed solvents [hexane–AcOEt]. ^{1}H and ^{13}C NMR spectra were obtained for samples in $CDCl_3$ solution at 25 °C on a Varian Mercury 300 spectrometer. ^{1}H NMR chemical shifts (δ) are reported in ppm relative to the singlet at 7.26 ppm for chloroform. Coupling constants (J) are reported in Hz. Infrared spectra were recorded for $CHCl_3$ sample solutions in 0.2 mm path length sodium chloride cavity cells on a JASCO FT/IR-230 spectrometer. Mass spectra were recorded on a JEOL JMS700 mass spectrometer. Elemental analyses were performed by the Microanalytical Center of Kyoto University and Instrumental Analysis Facility of Nagoya University. Melting points were obtained on a Büchi B-540 apparatus. CH_2Cl_2 and 1,2-dichloroethane was dried over CaH_2 and distilled. Cp*RuCl(cod) was prepared according to the reported method.[14]

Representative procedure for preparation of diynes: Synthesis of amide-diyne 9a

To a solution of *N*-benzylpropargylamine (1.54 g, 10.6 mmol), DCC (2.48 g, 12 mmol), and DMAP (147 mg, 1.2 mmol) in dry CH_2Cl_2 (20 cm^3) was added a solution of 2-butynoic acid (965 mg, 11.5 mmol) in dry CH_2Cl_2 (10 cm^3) at 0 °C. The reaction mixture was stirred overnight. The resultant precipitates were removed by filtration through a Celite pad, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel chromatography (hexane–AcOEt 6 : 1–3 : 1) to give **9a** (1.98 g, 88%) as pale yellow oil (Found: C, 79.51; H, 6.33; N, 6.58. $C_{14}H_{13}NO$ requires C, 79.59; H, 6.20; N, 6.63%); ν_{max}/cm^{-1} 3306, 2250, 2198, 1621 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (*syn*/*anti* isomer mixture with *ca.* 3 : 2 ratio) 2.01 and 2.04 (3 H, s), 2.21 and 2.32 (1 H, t, *J* 2.4), 4.11 and 4.25 (2 H, d, *J* 2.4), 4.73 and 4.91 (2 H, s), 7.27–7.40 (5 H, m); δ_C (75 MHz; $CDCl_3$) 4.03, 32.13 and 37.33, 46.23 and 51.19, 72.21 and 72.52, 72.80 and 72.96, 77.61, 89.88 and 90.19, 127.47 and 127.75, 128.16, 128.38 and 128.53, 135.31 and 135.49, 153.91; *m*/*z* (FAB) 212 (MH$^+$, 100), 144 (28).

Other diynes were prepared in a similar manner.

9b. (Found: C, 68.77; H, 4.83. $C_7H_6O_2$ requires C, 68.85; H, 4.95%); ν_{max}/cm^{-1} 3305, 2244, 2198, 1715 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.99 (3 H, d, *J* 0.3), 2.51 (1 H, t, *J* 2.4), 4.72 (2 H, dd, *J* 2.4, 0.9); δ_C (75 MHz; $CDCl_3$) 3.94, 52.95, 71.54, 75.57, 76.62, 87.06, 152.49; *m*/*z* (EI) no molecular ion peak 101 (M$^+$ − $CH_3C{\equiv}CCO$ − 2H, 93), 69 (100).

12a. (Found: C, 79.63; H, 6.20; N, 6.60. $C_{14}H_{13}NO$ requires C, 79.59; H, 6.20; N, 6.63%); ν_{max}/cm^{-1} 3299, 2112, 1629 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (*syn*/*anti* isomer mixture with *ca.* 3 : 2 ratio) 1.80 and 1.83 (3 H, t, *J* = 2.4), 3.15 and 3.17 (1 H, s), 4.06 and 4.21 (2 H, q, *J* 2.4), 4.72 and 4.91 (2 H, s), 7.27–7.40 (5 H, m); δ_C (75 MHz; $CDCl_3$) 3.44, 32.81 and 37.93, 46.41 and 51.19, 72.44 and 72.55, 75.13 and 75.44, 79.38 and 79.60, 80.27 and 81.09, 127.46 and 127.50, 127.78 and 128.23, 128.38 and 128.52, 135.21 and 135.46, 152.62 and 152.70; *m*/*z* (FAB) 212 (MH$^+$, 100), 143 (28).

12b. (Found: C, 68.68; H, 5.12. $C_7H_6O_2$ requires C, 68.85; H, 4.95%); ν_{max}/cm^{-1} 3298, 2123, 1719 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.86 (3 H, t, *J* = 2.4), 2.92 (1 H, s), 4.74 (2 H, q, *J* 2.4); δ_C (75 MHz; $CDCl_3$) 3.77, 54.45, 71.86, 74.09, 75.46, 84.45, 151.87; *m*/*z* (EI) no molecular ion peak 101 (M$^+$ − $CH_3C{\equiv}CCO$ − 2H, 53), 69 (100).

15a. (Found: C, 79.99; H, 6.72; N, 6.21. $C_{15}H_{15}NO$ requires C, 79.97; H, 6.71; N, 6.22%); ν_{max}/cm^{-1} 2247, 1621 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (*syn*/*anti* isomer mixture with *ca.* 55 : 45 ratio) 1.79 and 1.83 (3 H, t, *J* = 2.4), 2.00 and 2.03 (3 H, s), 4.05 and 4.20 (2 H, q, *J* 2.4), 4.71 and 4.88 (2 H, s), 7.27–7.40 (5 H, m); δ_C (75 MHz; $CDCl_3$) 3.48, 4.06 and 4.09, 32.72 and 37.90, 46.21 and 51.24, 72.72 and 72.82, 72.94 and 73.03, 79.92 and 80.78, 89.56 and 89.92, 127.35 and 127.64, 127.46, 128.19 and 128.33, 128.48, 135.75 and 135.88, 154.01; *m*/*z* (EI) 225 (M$^+$, 16), 172 (100), 149 (36).

15b. (Found: C, 70.39; H, 6.10. $C_8H_8O_2$ requires C, 70.57; H, 5.92%); ν_{max}/cm^{-1} 2242, 1712 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 1.85 (3 H, t, *J* = 2.4), 1.98 (3 H, s), 4.70 (2 H, q, *J* 2.4); δ_C (75 MHz; $CDCl_3$) 3.68, 3.85, 53.88, 71.80, 72.21, 83.90, 86.43, 152.74; *m*/*z* (EI) 137 (MH$^+$, 25), 121 (17), 69 (100).

18a. (Found: C, 73.51; H, 6.20; N, 6.32. $C_{14}H_{13}NO{\cdot}H_2O$ requires C, 73.34; H, 6.59; N, 6.11%); ν_{max}/cm^{-1} 3302, 2111, 1631 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (*syn*/*anti* isomer mixture with *ca.* 55 : 45 ratio) 1.16 and 1.33 (3 H, t, *J* = 7.2), 2.33 and 2.42 (1 H, d, *J* 2.4), 3.06 and 3.21 (1 H, s), 4.50 and 4.83 (1 H, d, *J* 16), 5.02 and 5.13 (1 H, d, *J* 16), 5.45 and 5.46 (1 H, q, *J* 7.2), 7.27–7.40 (5 H, m); δ_C (75 MHz; $CDCl_3$) 20.72 and 22.23, 42.30 and 45.57, 47.44 and 49.79, 73.40 and 73.90, 75.16 and 75.89, 79.16 and 79.97, 81.22 and 81.52, 127.06 and 127.17, 127.48 and 127.51, 128.23 and 128.38, 137.33 and 137.58, 152.94 and 153.18; *m*/*z* (EI) 212 (MH$^+$, 81), 184 (100), 158 (31).

26a. (Found: C, 83.28; H, 5.25; N, 5.28. $C_{18}H_{13}NO$ requires C, 83.37; H, 5.05; N, 5.40%); ν_{max}/cm^{-1} 3301, 2112, 1640 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 2.75 (1 H, s), 3.29 (1 H, s), 4.37 (1 H, d, *J* 14.4), 5.54 (1 H, d, *J* 14.4), 6.83–6.86 (1 H, m), 7.18–7.34 (7 H, m), 7.54–7.59 (1 H, m); δ_C (75 MHz; $CDCl_3$) 51.34, 76.13, 79.14, 79.27, 82.89, 122.19, 127.60, 128.29, 128.45, 129.14, 129.20 130.11, 133.50, 135.86, 142.36, 152.99; *m*/*z* (EI) 212 (M$^+$ − H, 42), 230 (68), 206 (100).

26b. (Found: C, 77.28; H, 3.91. $C_{11}H_6O_2$ requires C, 77.64; H, 3.55%); ν_{max}/cm^{-1} 3300, 2128, 1737 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 3.09 (1 H, s), 3.31 (1 H, s), 7.15 (1 H, dd, *J* 8.1 and 1), 7.26 (1 H, dt, *J* 7.8 and 1.2), 7.40 (1 H, dt, *J* 8.1 and 1.8), 7.56 (1 H, dd, *J* 7.5 and 1.8); δ_C (75 MHz; $CDCl_3$) 73.88, 77.16, 77.78, 82.97, 116.05, 121.87, 126.54, 130.02, 133.63, 150.06, 150.70; *m*/*z* (FAB) 171 (MH$^+$, 100), 142 (29).

Cp*RuCl(cod)-catalyzed cycloaddition of 3,3-diphenyl-4-oxahept-1,6-diyne with 1-hexyne

To a degassed solution of Cp*RuCl(cod) **1** (5.7 mg, 0.015 mmol) and 1-hexyne **5a** (175.1 mg, 2.1 mmol) in dry 1,2-dichloroethane (1 cm^3) was added a degassed solution of 3,3-diphenyl-4-oxahept-1,6-diyne (130.6 mg, 0.53 mmol) in dry 1,2-dichloroethane (2 cm^3) by syringe over 10 min under Ar at room temperature. The reaction mixture was stirred for 1 h. The solvent was evaporated, and the crude products were purified by silica gel chromatography (hexane–AcOEt 20 : 1) to give a regioisomer mixture of cycloadducts (142 mg, 82%) as colorless oil (Found: C, 87.70; H, 7.43. $C_{24}H_{24}O$ requires C, 87.76; H, 7.37%); δ_H (300 MHz; $CDCl_3$) 0.92 and 0.93 (3 H, t, *J* 7.2), 1.30–1.43 (2 H, m), 1.52–1.65 (2 H, m), 2.58–2.65 (2 H, m), 5.15 and 5.16 (2 H, s), 7.04–7.18 (3 H, m), 7.25–7.32 (10 H, m); *m*/*z* (FAB) 327 (M$^+$-H, 35), 251 (100), 194 (57).

Representative procedure for Cp*RuCl(cod)-catalyzed cycloaddition of electron-deficient diynes with terminal alkynes: synthesis of isoindolinones 7aa/8aa

To a degassed solution of Cp*RuCl(cod) **1** (1.9 mg, 0.005 mmol) and 1-hexyne **5a** (164.3 mg, 2 mmol) in dry 1,2-dichloroethane (2 cm^3) was added a degassed solution of **4a** (98.6 mg, 0.5 mmol) in dry 1,2-dichloroethane (3 cm^3) by syringe over 15 min under Ar at room temperature. The reaction mixture was stirred for 0.5 h. The solvent was evaporated, and the crude products were purified by silica gel chromatography (hexane–AcOEt 10 : 1) to give **7aa** (34.7 mg, 25%) as a colorless solid (mp. 61.1–61.8 °C). Further elution afforded **6aa** (70.7 mg, 51%) as a colorless solid (mp. 59.5–60.2 °C; Found: C, 81.68; H, 7.73; N, 4.87. $C_{19}H_{21}NO$ requires C, 81.68; H, 7.58; N, 5.01%); ν_{max}/cm^{-1} 1679, 1624 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**6aa**) 0.92 (3 H, t, *J* 7.2), 1.26–1.42 (2 H, m), 1.55–1.66 (2 H, m), 2.68 (2 H, t, *J* 7.5), 4.23 (2 H, s), 4.80 (2 H, s), 7.18 (1 H, s), 7.29–7.32 (6 H, m), 7.82 (1 H, d, *J* 7.8 Hz); (**7aa**) 0.92 (3 H, t, *J* 7.2), 1.29–1.41 (2 H, m), 1.58–1.68 (2 H, m), 2.70 (2 H, t, *J* 7.5), 4.22 (2 H, s), 4.80 (2 H, s), 7.28–7.35 (7 H, m), 7.72 (1 H, s); δ_C (75 MHz; $CDCl_3$) (**6aa**) 13.96, 22.35, 33.66, 35.97, 46.38, 49.35, 122.47, 123.55, 127.45, 127.98, 128.35, 128.60, 130.11, 137.01, 141.43, 146.88, 168.40; (**7aa**) 13.98, 22.26, 33.70, 35.48, 46.46, 49.30, 122.34, 123.38, 127.48, 128.00, 128.62, 131.72, 132.58, 136.98, 138.49, 143.02, 168.51; *m*/*z* (FAB) 280 (MH^+, 100), 202 (14).

6ab/7ab. (Found: C, 81.91; H, 7.47; N, 4.89. $C_{19}H_{21}NO$ requires C, 81.68; H, 7.58; N, 5.01%); ν_{max}/cm^{-1} 1679, 1626 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**6ab**) 1.34 (9 H, s), 4.25 (2 H, s), 4.80 (2 H, s), 7.27–7.36 (5 H, m), 7.39 (1 H, s), 7.51 (1 H, d, *J* = 8.1), 7.82 (1 H, d, *J* = 8.1); (**7ab**) 1.37 (9 H, s), 4.25 (2 H, s), 4.82 (2 H, s), 7.27–7.36 (6 H, m), 7.57 (1 H, d, *J* 7.5), 7.94 (1 H, s)]; δ_C (75 MHz; $CDCl_3$) 13.96, 22.35, 33.66, 35.97, 46.38, 49.35, 122.47, 123.55, 127.45, 127.98, 128.35, 128.60, 130.11, 137.01, 141.43, 146.88, 168.40; *m*/*z* (FAB) 280 (MH^+, 100), 249 (19).

6ac/7ac. (Found: C, 84.34; H, 5.83; N, 4.55. $C_{21}H_{17}NO$ requires C, 84.25; H, 5.72; N, 7.68%); ν_{max}/cm^{-1} 1681, 1672 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**6ac**) 4.33 (2 H, s), 4.83 (2 H, s), 7.27–7.49 (8 H, m), 7.56–7.61 (3 H, m), 7.69 (1 H, dd, *J* = 8.1 and 1.2), 7.96 (1 H, d, *J* = 8.1); (**7ac**) 4.31 (2 H, s), 4.84 (2 H, s), 7.28–7.50 (9 H, m), 7.63–7.66 (2 H, m), 7.76 (1 H, dd, *J* = 7.1 and 1.5), 8.13 (1 H, d, *J* 1.5); δ_C (75 MHz; $CDCl_3$) (**6ac**) 46.40, 49.45, 121.29, 123.97, 127.16, 127.19, 127.48, 127.79, 127.94, 128.60, 128.73, 131.28, 136.79, 140.17, 141.73, 144.47, 168.06; *m*/*z* (FAB) 280 (MH^+, 100), 249 (19).

6ad/7ad. (Found: C, 76.50; H, 6.40; N, 5.13. $C_{17}H_{17}NO_2$ requires C, 76.38; H, 6.41; N, 5.24%); ν_{max}/cm^{-1} 1682 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**6ad**) 3.41 (3 H, s), 4.26 (2 H, s), 4.53 (2 H, s), 4.80 (2 H, s), 7.27–7.43 (7 H, m), 7.82 (1 H, d, *J* = 7.8); (**7ad**) 3.40 (3 H, s), 4.26 (2 H, s), 4.54 (2 H, s), 4.80 (2 H, s), 7.27–7.43 (6 H, m), 7.52 (1 H, d, *J* 8.1), 7.85 (1 H, s); δ_C (75 MHz; $CDCl_3$) (**6ad**) 46.33, 49.32, 58.32, 74.16, 121.49, 123.62, 127.12, 127.45, 127.88, 128.57, 130.65, 136.77, 141.40, 141.98, 168.04; (**7ad**) 46.36, 49.27, 58.10, 74.06, 122.64, 122.79, 127.45, 127.91, 128.57, 131.78, 132.57, 136.77, 138.41, 140.43, 168.04; *m*/*z* (EI) 267 (M^+, 100), 236 (10), 190 (17), 176 (30), 163 (79).

6ae/7ae. (Found: C, 77.04; H, 7.58; N, 9.67. $C_{18}H_{20}N_2O$ requires C, 77.11; H, 7.19; N, 9.99%); ν_{max}/cm^{-1} 1682 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**6ae**) 2.39 (6 H, s), 3.69 (2 H, s), 4.27 (2 H, s), 4.79 (2 H, s), 7.27–7.37 (6 H, m), 7.42 (1 H, d, *J* = 7.6), 7.85 (1 H, d, *J* = 7.6); (**7ae**) 2.45 (6 H, s), 3.81 (2 H, s), 4.27 (2 H, s), 4.80 (2 H, s), 7.27–7.37 (6 H, m), 7.56 (1 H, s), 7.80 (1 H, s); δ_C (75 MHz; $CDCl_3$) (**6ae**) 45.21, 46.30, 49.27, 74.16, 63.96, 123.11, 123.44, 127.41, 127.88, 128.54, 128.80, 132.31, 136.81, 141.35, 142.27, 168.04; (**7ae**) 44.99, 46.33, 49.27, 74.06, 63.59, 122.62, 124.24, 127.42, 127.90, 128.54, 131.51, 132.45, 136.77, 138.24, 140.16, 168.04; *m*/*z* (EI) 280 (M^+, 100), 237 (25).

6ba/7ba. (Found: C, 75.63; H, 7.55. $C_{12}H_{14}O_2$ requires C, 75.76; H, 7.42%); ν_{max}/cm^{-1} 1760, 1619 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**6ba**) 0.94 (3 H, t, *J* 7.2), 1.30–1.42 (2 H, m), 1.58–1.67 (2 H, m), 2.74 (2 H, t, *J* 7.5), 5.28 (2 H, s), 7.58 (1 H, s), 7.34 (1 H, d, *J* = 7.8), 7.82 (1 H, d, *J* = 7.8); (**7ba**) 0.93 (3 H, t, *J* 7.2), 1.30–1.42 (2 H, m), 1.58–1.67 (2 H, m), 2.73 (2 H, t, *J* 7.5), 5.28 (2 H, s), 7.39 (1 H, d, *J* = 8.4), 7.50 (1 H, dd, *J* = 8.4 and 1.8), 7.73 (1 H, s); δ_C (75 MHz; $CDCl_3$) (**6ba**) 13.88, 22.29, 33.40, 36.02, 69.42, 121.58, 125.31, 129.46, 146.90, 150.03, 170.92; (**7ae**) 13.88, 22.16, 33.45, 35.25, 69.55, 121.68, 123.17, 124.86, 134.52, 143.89, 144.13, 170.92; *m*/*z* (FAB) 191 (MH^+, 100), 147 (7).

6bc/7bc. (Found: C, 79.82; H, 4.96. $C_{12}H_{14}O_2$ requires C, 79.98; H, 4.79%); ν_{max}/cm^{-1} 1762 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**6ba**) 5.38 (2 H, s), 7.41–7.53 (3 H, m), 7.59–7.64 (2 H, m), 7.67–7.68 (1 H, m), 7.73–7.77 (1 H, m), 7.98 (1 H, d, *J* = 8.1); (**7bc**) 5.38 (2 H, s), 7.38–7.53 (3 H, m), 7.57 (1 H, dd, *J* = 8.1, 0.8), 7.60–7.67 (2 H, m), 7.92 (1 H, dd, *J* = 8.1. 2.0), 8.14 (1 H, d, *J* = 1.2); δ_C (75 MHz; $CDCl_3$) (**6ba**) 69.56, 120.42, 124.23, 125.81, 127.31, 128.21, 128.44, 128.90, 139.39, 147.15, 170.72; *m*/*z* (EI) 210 (M^+, 100), 181 (52), 153 (35).

6ca/7ca. (Found: C, 83.20; H, 9.40. $C_{15}H_{20}O$ requires C, 83.28; H, 9.32%); ν_{max}/cm^{-1} 1704, 1609 cm^{-1}; δ_H (300 MHz; $CDCl_3$); (**6ca**) 0.94 (3 H, t, *J* 7.2), 1.23 (6 H, s), 1.31–1.44 (2 H, m), 1.56–1.68 (2 H, m), 2.68 (2 H, t, *J* 7.5), 2.96 (2 H, s), 7.19 (1 H, d, *J* 7.8), 7.22 (1 H, s), 7.67 (1 H, d, *J* = 7.8); (**7ca**) 0.92 (3 H, t, *J* 7.2), 1.23 (6 H, s), 1.31–1.44 (2 H, m), 1.56–1.68 (2 H, m), 2.66 (2 H, t, *J* 7.5), 2.96 (2 H, s), 7.32 (1 H, d, *J* 7.8), 7.42 (1 H, dd, *J* = 7.8, 0.9), 7.57 (1 H, s); δ_C (75 MHz; $CDCl_3$) (**6ca**) 13.98, 22.44, 25.40, 33.46, 36.19, 42.83, 45.61, 124.17, 126.15, 127.99, 135.43, 150.76, 152.49, 210.65; (**7ca**) 13.98, 22.28, 25.40, 33.59, 35.25, 42.59, 45.82, 123.59, 126.18, 133.10, 135.32, 142.26, 149.60, 210.65; *m*/*z* (FAB) 217 (MH^+, 100), 147 (22).

10aa. (Found: C, 81.87; H, 8.03; N, 4.64. $C_{20}H_{23}NO$ requires C, 81.87; H, 7.90; N, 4.77%); ν_{max}/cm^{-1} 1671 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 0.92 (3 H, t, *J* 7.2), 1.28–1.41 (2 H, m), 1.53–1.64 (2 H, m), 2.62 (2 H, t, *J* 7.5), 2.73 (3 H, s), 4.17 (2 H, s), 4.76 (2 H, s), 6.98 (1 H, s), 7.01 (1 H, s), 7.27–7.32 (5 H, m); δ_C (75 MHz; $CDCl_3$) 13.96, 17.29, 22.37, 33.62, 35.76, 46.11, 48.79, 119.88, 127.22, 127.31, 127.94, 128.52, 130.22, 137.18, 137.21, 141.95, 146.29, 169.06; *m*/*z* (FAB) 294 (MH^+, 100), 251 (16), 216 (70).

10ba/11ba. (Found: C, 76.39; H, 7.96. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90%); ν_{max}/cm^{-1} 1751 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**10ba**) 0.93 (3 H, t, *J* 7.2), 1.29–1.42 (2 H, m), 1.56–1.66 (2 H, m), 2.66 (3 H, s), 2.67 (2 H, t, *J* 7.8), 5.21 (2 H, s), 7.06 (1 H, s), 7.07 (1 H, s); (**11ba**) 0.94 (3 H, t, *J* 7.2), 1.29–1.42 (2 H, m), 1.56–1.66 (2 H, m), 2.66 (3 H, s), 2.67 (2 H, t, *J* 7.8), 5.19 (2 H, s), 7.19 (1 H, d, *J* = 7.8), 7.41 (1 H, d, *J* = 7.8); δ_C (75 MHz; $CDCl_3$) (**10ba**) 13.93, 17.32, 22.34, 33.41, 35.87, 68.66, 118.93, 120.70, 130.91, 139.07, 147.38, 149.69, 171.09; *m*/*z* (EI) 204 (M^+, 20), 187 (100).

13aa/14aa. (Found: C, 81.83; H, 7.93; N, 4.74. $C_{20}H_{23}NO$ requires C, 81.87; H, 7.90; N, 4.77%); ν_{max}/cm^{-1} 1679 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**13aa**) 0.94 (3 H, t, *J* 7.2), 1.33–1.45 (2 H, m), 1.50–1.59 (2 H, m), 2.19 (3 H, s), 2.67 (2 H, t, *J* 7.5), 4.16 (2 H, s), 4.81 (2 H, s), 7.26 (1 H, d, *J* 8.1), 7.29–7.35 (5 H, m), 7.67 (1 H, d, *J* 8.1 Hz); (**14aa**) 0.92 (3 H, t, *J* 7.2), 1.28–1.41 (2 H, m), 1.56–1.67 (2 H, m), 2.24 (3 H, s), 2.67 (2 H, t, *J* 7.5), 4.13 (2 H, s), 4.81 (2 H, s), 7.13 (1 H, s), 7.26–7.35 (5 H, m), 7.55 (1 H, s); δ_C (75 MHz; $CDCl_3$) (**13aa**) 14.05, 14.32, 22.75, 32.77, 33.11, 46.43, 49.04, 122.47, 123.55, 127.45, 127.98, 128.35,

128.60, 130.11, 137.01, 141.43, 146.88, 168.40; (**7aa**) 14.00, 17.56, 22.30, 33.77, 35.44, 46.44, 48.54, 120.89, 127.45, 127.97, 128.61, 131.94, 132.25, 132.69, 137.07, 137.44, 143.30, 168.88; *m*/*z* (FAB) 294 (MH^+, 100), 216 (13).

13ba/14ba. (Found: C, 76.25; H, 7.93. $C_{13}H_{16}O_2$ requires C, 76.44; H, 7.90%); ν_{max}/cm^{-1} 1760 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**13ba**) 0.92 (3 H, t, *J* 7.2), 1.28–1.40 (2 H, m), 1.53–1.66 (2 H, m), 2.32 (3 H, s), 2.67 (2 H, t, *J* 7.8), 5.20 (2 H, s), 7.27 (1 H, s), 7.54 (1 H, s); (**14ba**) 0.95 (3 H, t, *J* 7.2), 1.36–1.46 (2 H, m), 1.51–1.62 (2 H, m), 2.25 (3 H, s), 2.71 (2 H, t, *J* 7.8), 5.22 (2 H, s), 7.30 (1 H, d, *J* = 7.8), 7.66 (1 H, d, *J* = 7.8); δ_C (75 MHz; $CDCl_3$) (**13ba**) 13.95, 17.50, 22.24, 33.58, 35.26, 69.02, 122.34, 125.42, 130.25, 135.29, 142.95, 144.45, 171.53; *m*/*z* (EI) 204 (M^+, 100), 175 (96), 161 (91).

16aa/17aa. (Found: C, 82.26; H, 7.91; N, 4.63. $C_{21}H_{25}NO$ requires C, 82.04; H, 8.20; N, 4.56%); ν_{max}/cm^{-1} 1675 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**16aa**) 0.94 (3 H, t, *J* 7.2), 1.32–1.59 (4 H, m), 2.13 (3 H, s), 2.62 (2 H, t, *J* 7.8), 2.70 (3 H, s), 4.11 (2 H, s), 4.78 (2 H, s), 6.99 (1 H, s), 7.29–7.37 (5 H, m); (**17aa**) 0.95 (3 H, t, *J* 7.2), 1.32–1.59 (2 H, m), 2.19 (3 H, s), 2.65 (2 H, t, *J* 7.8), 2.73 (3 H, s), 4.06 (2 H, s), 4.78 (2 H, s), 7.06 (1 H, s), 7.29–7.37 (5 H, m), 7.55 (1 H, s); δ_C (75 MHz; $CDCl_3$) (**16aa**) 13.73, 14.03, 16.93, 22.76, 32.83, 32.95, 46.13, 48.52, 126.95, 127.15, 127.32, 127.99, 128.55, 131.04, 134.49, 137.27, 141.11, 144.24, 169.61; *m*/*z* (EI) 307 (M^+, 100), 250 (14), 216 (28).

16ba/17ba. (Found: C, 76.92; H, 8.49. $C_{14}H_{18}O_2$ requires C, 77.03; H, 8.31%); ν_{max}/cm^{-1} 1751 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**16ba**) 0.96 (3 H, t, *J* 7.2), 1.34–1.61 (4 H, m), 2.19 (3 H, s), 2.61 (3 H, m), 2.66 (2 H, t, *J* 7.5), 5.16 (2 H, s), 7.05 (1 H, s); (**17ba**) 0.95 (3 H, t, *J* 7.2), 1.34–1.61 (4 H, m), 2.26 (3 H, s), 2.66 (2 H, t, *J* 7.5), 5.12 (2 H, s), 7.20 (1 H, s); δ_C (75 MHz; $CDCl_3$) (**16ba**) 13.65, 13.92, 16.81, 22.66, 32.52, 32.81, 68.36, 120.39, 126.76, 131.58, 136.15, 146.45, 147.40, 171.49; *m*/*z* (EI) 218 (M^+, 100), 203 (22), 189 (100).

19aa/20aa. (Found: C, 82.15; H, 8.02; N, 4.49. $C_{20}H_{23}NO$ requires C, 81.87; H, 7.90; N, 4.77%); ν_{max}/cm^{-1} 1678 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**19aa**) 0.92 (3 H, t, *J* 7.2), 1.29–1.42 (2 H, m), 1.42 (3 H, d, *J* 6.6), 1.56–1.66 (2 H, m), 2.69 (2 H, t, *J* 7.8), 4.24 (1 H, d, *J* 15), 4.33 (1 H, q, *J* 6.6), 5.33 (1 H, d, *J* 15), 7.15 (1 H, s), 7.24–7.34 (6 H, m), 7.79 (1 H, d, *J* 7.8); (**20aa**) 0.93 (3 H, t, *J* 7.2), 1.29–1.43 (2 H, m), 1.41 (3 H, d, *J* 6.9), 1.58–1.68 (2 H, m), 2.70 (2 H, t, *J* 7.5), 4.25 (1 H, d, *J* 15.3), 4.34 (1 H, q, *J* 6.9), 5.33 (1 H, d, *J* 15.3), 7.24–7.32 (6 H, m), 7.34 (1 H, dd, *J* 7.8, 1.5), 7.71 (1 H, d, *J* 0.6); δ_C (75 MHz; $CDCl_3$) (**19aa**) 13.94, 18.08, 22.36, 33.66, 36.02, 43.62, 54.77, 121.63, 123.41, 127.28, 127.84, 128.34, 128.50, 129.11, 137.22, 147.01, 147.15, 167.92; *m*/*z* (EI) 293 (M^+, 100), 278 (44), 216 (25), 189 (24).

27aa/28aa. (Found: C, 84.23; H, 7.06; N, 4.02. $C_{24}H_{23}NO$ requires C, 84.42; H, 6.79; N, 4.10%); ν_{max}/cm^{-1} 1643 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**27aa**) 0.98 (3 H, t, *J* 7.2), 1.37–1.50 (2 H, m), 1.68–1.78 (2 H, m), 2.84 (2 H, t, *J* 7.8), 5.67 (2 H, s), 7.21–7.31 (7 H, m), 7.36–7.47 (1 H, m), 7.46 (1 H, dd, *J* 8.1, 1.5), 8.10 (1 H, s), 8.31 (1 H, d, *J* 8.1), 8.53 (1 H, d, *J* 7.8); (**28aa**) 0.96 (3 H, t, *J* 7.2), 1.34–1.47 (2 H, m), 1.66–1.74 (2 H, m), 2.81 (2 H, t, *J* 7.8), 5.68 (2 H, s), 7.20–7.33 (7 H, m), 7.34–7.40 (1 H, m), 7.63 (1 H, dd, *J* 8.1, 1.8), 8.23 (1 H, d, *J* 8.7), 8.27 (1 H, dd, *J* 8.1, 1.5), 8.43 (1 H, d, *J* 1.8); δ_C (75 MHz; $CDCl_3$) (**27aa**) 14.03, 22.46, 33.49, 36.26, 46.33, 115.86, 119.44, 120.99, 122.24, 123.06, 123.19, 126.36, 126.96, 128.60, 128.66, 129.04, 129.20, 133.64, 136.55, 137.27, 147.93, 161.68; *m*/*z* (EI) 341 (M^+, 100), 264 (7), 235 (43).

27ba/28ba. (Found: C, 80.98; H, 6.34. $C_{17}H_{16}O_2$ requires C, 80.93; H, 6.39%); ν_{max}/cm^{-1} 1726 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (**27ba**) 0.97 (3 H, t, *J* 7.2), 1.32–1.48 (2 H, m), 1.65–1.76 (2 H, m), 2.81 (2 H, t, *J* 7.5), 7.30–7.51 (3 H, m), 7.91 (1 H, s), 8.05 (1 H, d, *J* 8.1), 8.09 (1 H, dd, *J* 7.8, 1.5), 8.32 (1 H, d, *J* 8.1); (**28ba**) 0.95 (3 H, t, *J* 7.2), 1.32–1.48 (2 H, m), 1.65–1.76 (2 H, m), 2.76 (2 H, t, *J* 7.5), 7.30–7.51 (5 H, m), 7.66 (1 H, dd, *J* 8.4, 1.8), 8.22 (1 H, d, *J* 1.8); δ_C (75 MHz; $CDCl_3$) (**27ba**) 13.96, 22.41, 33.22, 36.26, 117.55, 118.00, 121.04, 122.54, 124.21, 129.32, 130.04, 130.37, 134.52, 135.27, 150.57, 151.18, 161.02; *m*/*z* (EI) 252 (M^+, 100), 210 (78), 181 (57).

Synthesis of isoindoloisoquinoline 31

Synthesis of diyne 30. To a solution of trimethylsilylacetylene (1.96 g, 20 mmol) in dry THF (39 cm^3) was added a 1.6 M hexane solution of *n*BuLi (12.8 cm^3, 20 mmol) by a syringe under Ar at −78 °C, and the solution was stirred for 30 min. To this solution, $BF_3{\cdot}OEt_2$ (2.84 g, 20 mmol) was added at −78 °C, and the solution was stirred for 10 min. To this solution was added a solution of dihydroisoquinoline **29** (1.91 g, 10 mmol) in dry THF (6 cm^3) at −78 °C, and the solution was stirred for 1 h at this temperature, and for another 1 h at rt. The reaction was quenched with 10% aqueous NaOH (30 cm^3), and THF was evaporated. The residue was then extracted with ether (20 cm^3 × 3). The combined organic layer was dried with K_2CO_3, and concentrated *in vacuo*. The crude product was purified by silica gel chromatography (hexane–AcOEt–MeOH 4 : 4 : 1) to give trimethylsilylethynyltetrahydroisoquinoline (1.06 g, 40%) as dark brown oil.

The above obtained tetrahydroisoquinoline (950 mg, 3.5 mmol) was dissolved in MeOH (12 cm^3) at room temperature, and the solution was treated with KF (610 mg, 10.5 mmol) for 16 h. The reaction was quenched with aqueous $NaHCO_3$ (15 cm^3), and insoluble materials were removed by filtration through a pad of Celite. After evaporation of MeOH, the residue was extracted with AcOH (20 cm^3 × 3), and the organic layer was dried with K_2CO_3, and concentrated *in vacuo*. The crude ethynyltetrahydroisoquinoline (626 mg, 82%) was submitted to the condensation with propiolic acid.

To a solution of the above prepared ethynyltetrahydroisoquinoline (626 mg, 2.88 mmol), DCC (619 mg, 3.0 mmol), and DMAP (36.7 mg, 0.3 mmol) in dry CH_2Cl_2 (5 cm^3) was added propiolic acid (210 mg, 3.0 mmol) at 0 °C. The reaction mixture was stirred for 15 h at rt. After filtration of insoluble materials, the solution was washed with aqueous $NaHCO_3$ (20 cm^3) and the aqueous layer was extracted with $CHCl_3$ (20 cm^3 × 3). The combined organic layer was dried with K_2CO_3, and concentrated in vacuo. The crude product was purified by silica gel chromatography (hexane–AcOEt 4 : 1–2 : 1) to give diyne **30** (228 mg, 30%) as a pale yellow solid (mp. 150.6–151.7 °C; Found: C, 66.94; H, 5.83; N, 4.96. $C_{16}H_{15}NO_3{\cdot}H_2O$ requires C, 66.89; H, 5.96; N, 4.88%); ν_{max}/cm^{-1} 3301, 2112, 1635 cm^{-1}; δ_H (300 MHz; $CDCl_3$) (*syn*/*anti* isomer mixture with *ca.* 3 : 2 ratio) 2.36 and 2.47(1 H, d, *J* 2.4), 2.70–3.05 (2 H, m), 3.16 and 3.25 (1 H, s), 3.27–3.37 and 3.69–3.79 (1 H, m), 3.56 and 3.87 (3 H, s), 3.87 and 3.90 (3 H, s), 4.44–4.54 and 4.57–4.66 (1 H, m), 6.09 and 6.21 (1 H, br s), 6.59 and 6.62 (1 H, s), 6.76 and 6.77 (1 H, s); δ_C (75 MHz; $CDCl_3$) 27.24 and 28.35, 36.48 and 41.70, 43.50 and 49.08, 55.79, 55.87 and 55.91, 71.55, 72.72 and 74.97, 79.32 and 80.19, 81.55 and 81.64, 109.25 and 109.52, 111.05 and 111.23, 123.96 and 124.08, 124.57 and 125.39, 147.79 and 147.93, 148.32 and 148.46, 151.39 and 151.48; *m*/*z* (EI) 269 (M^+, 100), 240 (50), 226 (25).

Cp*RuCl(cod)-catalyzed reaction of 30 with acetylene. To a degassed solution of Cp*RuCl(cod) **1** (1.1 mg, 0.003 mmol) in dry 1,2-dichloroethane (1 cm^3) was added a degassed solution of **30** (88.6 mg, 0.3 mmol) in dry 1,2-dichloroethane (2 cm^3) by a syringe over 15 min under acetylene atmosphere at room temperature. The reaction mixture was stirred for 0.5 h. The solvent was evaporated, and the crude products were purified by silica gel chromatography (hexane/AcOEt 1:1) to give **31** (71.9 mg,

82%) as pink solids (mp. 172.6–173.4 °C, lit[12] mp. 173 °C); ν_{max}/cm^{-1} 1683 cm^{-1}; δ_H (300 MHz; $CDCl_3$) 2.77 (1 H, dt, *J* 15.6, 3.9), 2.96–3.07 (1 H, m), 3.42 (1 H, ddd, *J* 13.2, 10.2, 4.5), 3.85 (3 H, s), 3.94 (3 H, s), 4.51 (1 H, ddd, *J* 12.9, 6, 3.6), 5.63 (1 H, s), 6.67 (1 H, s), 7.12 (1 H, s), 7.50 (1 H, t, *J* 7.5 Hz), 7.61 (1 H, dt, *J* 7.5, 1), 7.83 (1 H, dd, *J* 7.5, 0.6), 7.89 (1 H, dd, *J* 7.5, 1); δ_C (75 MHz; $CDCl_3$) 29.02, 38.13, 55.85, 56.13, 58.88, 108.50, 111.77, 122.84, 123.70, 125.79, 126.69, 128.23, 131.34, 132.51, 144.40, 147.60, 148.08, 167.60.

Computational methods

The Q-chem 2.0 program[15] in Spartan '02 software package[16] was used for geometry optimizations, and the NBO calculations for the obtained geometries were performed with the Gaussian 98 program package.[17] All geometries of ruthenacycles were fully optimized by the Becke's three-parameter hybrid density functional method (B3LYP)[18] with the LACVP* basis set. The LACVP* basis set uses a double-ζ basis set with the relativistic effective core potential of Hay and Wadt (LanL2 ECP)[19] for Ru and the 6-31G(d) basis sets[20] for other elements. The NBO calculations[21] were performed at the same level of theory.

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