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# Ruthenium(II)-catalyzed homo-Diels–Alder reactions of disubstituted alkynes and norbornadiene

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**Abstract**—The homo-Diels–Alder (HDA) reaction of norbornadiene (NBD) and internal functionalized alkynes leading to 8,9-disubstituted deltacyclenes using readily available electron-rich phosphine–ruthenium(II) catalysts is described.
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Cycloaddition reactions are among the most prominent methods for the construction of cyclic compounds with increased structural and functional complexity.[1] Typical promoters include heat, light, and Lewis acids. Due to the unique reactivity patterns imparted by the metal and its ligands, transition metal complexes provide another powerful tool for carrying out cycloaddition reactions, particularly when unactivated substrates are involved.[2] The transition metal acts as the template bringing the unsaturated substrates together and offers new opportunities to promote the cycloaddition reaction. The designs of catalysts able to promote cycloadditions vary over a wide range, from simple inorganic complexes to more sophisticated organometallics. Furthermore, the mildness of the reaction conditions offers opportunities to investigate enantioselective versions by the use of chiral ligands associated with the metal species. Among these, the well-known [2+2+2] cycloaddition of norbornadiene (NBD) **1** with alkynes **2**, the so-called homo-Diels–Alder (HDA) reaction,[3] gives rise to tetracyclic structures named deltacyclenes **3** with the formation of three new C–C bonds and up to six stereogenic centers.

Various catalyst systems appear to be effective only with terminal alkynes, and reactions with internal alkynes are less common. For instance, Schrauzer showed that $Ni(CN)_2(PPh_3)_2$ was able to catalyze the cycloaddition of electron-deficient alkynes such as DMAD **2a** ($R^1 = R^2 = CO_2Me$) to give **3a** (50%) while diphenylacetylene **2b** ($R^1 = R^2 = Ph$) was converted to the [2+2] cycloadduct **4b** (Scheme 1).[4] Later a catalyst system consisting of $Co(acac)_2/dppe/Et_2AlCl$ was developed by Lyons and promoted the [2+2+2] cycloaddition of **2b** ($R^1 = R^2 = Ph$) to give deltacyclene **3b** (41%) along with two homocoupled dimers of NBD as major products (54% combined yield).[5] The enhancement of catalyst activity with azeotropically dried $Co(acac)_3$ observed by Lautens allowed the formation of **3b** and **3c** ($R^1 = R^2 = Et$) in 58% and 65% yields, respectively.[6]
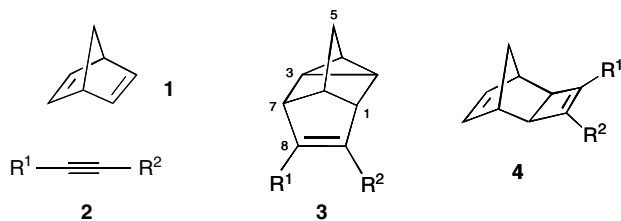


| | |
|---|---|
| **a** $R^1 = R^2 = CO_2Me$ | **i** $R^1 = CO_2Me$, $R^2 = Me$ |
| **b** $R^1 = R^2 = Ph$ | **j** $R^1 = CO_2Me$, $R^2 = Bu$ |
| **c** $R^1 = R^2 = Et$ | **k** $R^1 = CO_2Me$, $R^2 = Ph$ |
| **d** $R^1 = Pr$, $R^2 = Me$ | **l** $R^1 = CH_2OH$, $R^2 = CH_2OBn$ |
| **e** $R^1 = R^2 = CH_2OH$ | **m** $R^1 = CH_2OAc$, $R^2 = CH_2OBn$ |
| **f** $R^1 = R^2 = CH_2OAc$ | **n** $R^1 = CH_2OAc$, $R^2 = CH_2SO_2Ph$ |
| **g** $R^1 = R^2 = CH_2OCO_2Me$ | **o** $R^1 = R^2 = CH_2Cl$ |
| **h** $R^1 = R^2 = CH_2OBn$ | |

**Scheme 1.**

To date, the Cheng catalyst system consisting of mono-dentate phosphine complex $CoI_2(PPh_3)_2$ and Zn (1/10 molar ratio) proved superior and was effective for internal unfunctionalized alkynes (**3c**: 87%; **3d**: 84%).[7] Since very little was reported on the HDA reaction with disubtituted alkynes, especially with functionalized ones, a search for new catalysts able to promote the HDA reaction was addressed. The ability of ruthenium complexes to catalyze multiple array cycloadditions is well established.[8] Phosphine-free and half-sandwich $\eta^5$-ring derivatives of ruthenium(II) complexes containing labile ligands have attracted preferential attention in order to generate active catalytic species. For instance, an unusual [2+2+2] cycloaddition of 1,5-cyclooctadiene with alkynes to yield a novel class of tricyclo[4.2.0$^{2,5}$]dec-7-enes was reported by Trost et al.[9] with in situ generated cationic ruthenium species CpRu(cod)$^+$ from CpRu-(cod)Cl in protic solvents. In contrast, no cycloadduct was observed when norbornadiene was reacted with 1,6-heptadiynes using $(\eta^5-C_9H_7)Ru(PPh_3)_2Cl$.[10] We became interested in the HDA reaction of **1** and terminal alkynes using cobalt catalysts[11] and in the stereoselective functionalization of the deltacyclenes with oxygen nucleophiles through the use of NBS.[12] In this letter, we report that the HDA reaction involving various functionalized disubstituted alkynes can be achieved with readily available phosphine–ruthenium(II) complexes as catalysts.

As a model, we first investigated the HDA reaction of 2-butyne-1,4-diol **2e** and NBD **1** (3 equiv) using 5 mol % of CpRuCl(PPh$_3$)$_2$ in dioxane at 90 °C.[13] Although the reaction proceeded sluggishly (6 d), the deltacyclene **3e** was observed along with the cyclobutene **4e** (1:1 ratio) in 52% isolated yield. The concomitant formation of the [2+2+2] and [2+2] cycloadducts using this catalyst was intriguing insofar as Mitsudo showed that CpRuCl(PPh$_3$)$_2$ displayed no catalytic activity for the cycloaddition.[14] Encouraged by this result, various ruthenium(II) complexes were tested to promote selectively the [2+2+2] pathway. We anticipated that diene–ruthenium complexes able to coordinate NBD prior to the alkyne should favor this pathway. The screening results, using 5 mol % of ruthenium complexes in dioxane at 90 °C for 10 h, are summarized in Table 1.

No reaction was observed with the low-valent ruthenium complex Ru(cot)(cod)[15] or with [Ru(*p*-cymene)I$_2$]$_2$ with or without PPh$_3$ (Table 1, entries 1–4). Phosphine-free ruthenium(II) complexes were inefficient (entries 5 and 12) but proved operative when associated with PPh$_3$ yielding a single [2+2+2] cycloadduct **3e**[16] in excellent

**Table 1.** Ruthenium catalysts for the [2+2+2] cycloaddition of norbornadiene **1** with 2-butyn-1,4-diol **2e** to give **3e**[a]

| Entry | Catalyst (ratio) | Yield (%)[b] |
|---|---|---|
| 1 | Ru(cod)(cot) | 0 |
| 2 | Ru(cod)(cot)/PPh$_3$ (1/1) | 0 |
| 3 | [RuI$_2$(*p*-MeC$_6$H$_4$CHMe$_2$)]$_2$ | 0 |
| 4 | [RuI$_2$(*p*-MeC$_6$H$_4$CHMe$_2$)]$_2$/PPh$_3$ (1/2) | 0 |
| 5 | [RuCl$_2$(CO)(NBD)]$_2$ | 0 |
| 6 | [RuCl$_2$(CO)(NBD)]$_2$/PPh$_3$ (1/1) | 0 |
| 7 | [RuCl$_2$(CO)(NBD)]$_2$/PPh$_3$ (1/2) | 92 |
| 8 | [RuCl$_2$(CO)(NBD)]$_2$/dppe (1/1) | 0 |
| 9 | ($\eta^5$-C$_9$H$_7$)RuCl(PPh$_3$)$_2$ | 80 |
| 10 | RuCl$_2$(PPh$_3$)$_3$ | 89 |
| 11 | RuCl$_2$(PPh$_3$)$_2$(NBD) | 94 |
| 12 | [Ru(cod)Cl$_2$]$_n$ | 0 |
| 13 | [Ru(cod)Cl$_2$]$_n$/PPh$_3$ (1/1) | 94 |
| 14 | [Ru(cod)Cl$_2$]$_n$/dppe (1/1) | 0 |

[a] All reactions carried out with NBD/**2e**/Ru catalyst: 1.5/1/0.05 mmol, 0.125 M in **2e** at 90 °C for 10 h in dioxane.
[b] Isolated yields.

yields (entries 7 and 13). Other phosphine–Ru(II) complexes also gave **3e** in satisfactory yields (entries 9 and 11). A catalyst system with bisphosphine ligands such as [RuCl$_2$(CO)(NBD)]$_2$ or [RuCl$_2$(cod)]$_n$ and dppe in a 1/1 molar ratio could not be employed since bidentate phosphine shut down the cycloaddition (entries 8 and 14). Therefore, loss of one phosphine ligand, which is inhibited by the bidentate coordination, must occur during the process to generate a coordinatively unsaturated active species. This assumption finds support in the results observed with catalyst systems Ru/PPh$_3$ in a 1/1 molar ratio (entries 7 and 13). Finally, the best results were achieved with RuCl$_2$(PPh$_3$)$_2$(NBD), [Ru(cod)Cl$_2$]$_n$/PPh$_3$ (1/1), [RuCl$_2$(CO)(NBD)]$_2$/PPh$_3$ (1/2) or RuCl$_2$(PPh$_3$)$_3$. For the latter, it is worth noting that dissociation of PPh$_3$ and coordination to norbornadiene generates RuCl$_2$(PPh$_3$)$_2$(NBD) in situ (entry 10).[17] One important feature of the reaction was observed when using RuCl$_2$(PPh$_3$)$_2$(NBD) (entry 11). During the reaction, the medium remains heterogeneous. On cooling, the recovered suspension was characterized as the initial complex (70% recovery of the loaded catalyst) and proved active without loss of efficiency.

Having established the feasibility of the desired cycloaddition, we then examined disubstituted alkynes **2f**–**o** in order to expand its applicability. Under the established protocol and with RuCl$_2$(PPh$_3$)$_2$(NBD) as catalyst, alkynes **2f**–**o**[18] were converted to the expected [2+2+2]
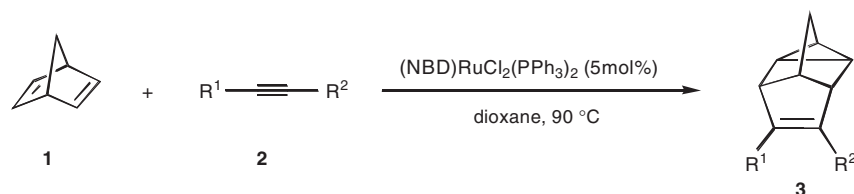


**Scheme 2.**

**Table 2.** Ruthenium-catalyzed [2+2+2] cycloaddition of NBD **1** and disubstituted alkynes **2**[a]

| Entry | Alkyne | $t$ (h) | Cycloadduct | Yield (%)[b] |
|---|---|---|---|---|
| 1 | **2c**[c] | 24 | **3c**[d] | 21 |
| 2 | **2f** | 14 | **3f** | 77 |
| 3 | **2g** | 16 | **3g** | 76 |
| 4 | **2h** | 22 | **3h** | 83 |
| 5 | **2i** | 36 | **3i** | 45 |
| 6 | **2j** | 24 | **3j** | 63 |
| 7 | **2k** | 60 | **3k** | 31 |
| 8 | **2l** | 18 | **3l** | 92 |
| 9 | **2m** | 15 | **3m** | 96 |
| 10 | **2n** | 50 | **3n** | 30 |
| 11 | **2o** | 5 | **3o** | 86 |

[a] All reactions were carried out in dioxane with NBD/**2**/RuCl$_2$(PPh$_3$)$_2$(NBD): 1.5/1/0.05 mmol, 0.05 M in **2** at 90 °C.

[b] Isolated yield.

[c] Molar ratio **1**/**2c**: 1/10.

[d] Cycloadduct **3c** contaminated with NBD oligomers (5–10%).
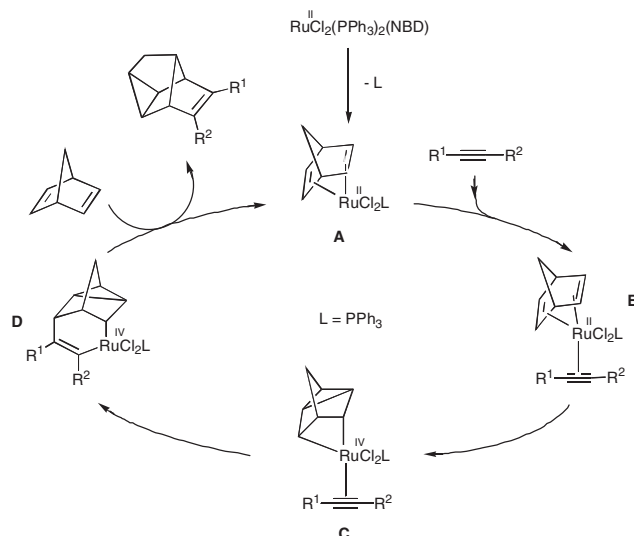
cycloadducts **3f**–**o** in fairly good yields (Scheme 2, Table 2).[19] No other codimers were detected by proton NMR spectroscopy of the crude reaction mixture. High yields were observed with symmetrical (entries 2 and 4) and unsymmetrical (entries 8 and 9) alkynes derived from 2-butyn-1,4-diol **2e**. Even dibenzyl ether **2h** reacted normally, a result in contrast with that observed with the ruthenium-catalyzed codimerization of 1,5-cyclooctadiene and alkynes.[9] Cycloaddition was also observed with electron-deficient alkynes (entries 5–7) and with alkynes featuring a polar propargylic withdrawing group such as **2n** although in lower yields. More noteworthy, propargyl dichloride **2o** can be used without complications to afford **3o**[20] in a satisfactory 86% yield. In this case, the careful control of the reaction time was necessary to avoid formation of by-products. These conditions were unsuitable for unfunctionalized alkynes such as hex-3-yne **2c** giving rise to deltacyclene **3c** in only 21% yield by the use of a 10-fold molar excess of **2c** with respect to norbornadiene (entry 1).

Although different mechanism pathways may account for the HDA reaction, a mechanistic rationale based on the results observed, involving Ru(II) and Ru(IV) species is depicted in Scheme 3. The dissociation of PPh$_3$ from RuCl$_2$(PPh$_3$)$_2$(NBD) generates the 16-electron complex (**A**), which is able to coordinate the alkyne partner to give (**B**). The oxidative coupling of NBD to the ruthenium allows the formation of the ruthenacyclobutane as part of tetracyclic framework (**C**). Insertion of the alkyne to form the ruthenacyclohexene (**D**) followed by reductive elimination of the ruthenium species accounts for the formation of the deltacyclene and the regeneration of intermediate (**A**) by coordination of NBD.

In summary, we have developed the homo-Diels–Alder reaction of norbornadiene with various internal alkynes to afford functionalized deltacyclenes with readily available electron-rich phosphine–ruthenium(II) catalysts. Catalysts such as RuCl$_2$(PPh$_3$)$_2$(NBD), featuring the coordination of one of the partners of the cycload-



**Scheme 3.**

dition to the metal center, favored the [2+2+2] over the [2+2] pathway.

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13. Dioxane gave the best results. Solvents such as toluene (87%), DCE (75%), THF (43%) or *i*-PrOH (50%) are suitable but not MeCN, DMF or MeOH.

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16. Tetracyclo[4.3.0.0$^{2,4}$.0$^{3,7}$]non-8-ene-8,9-diyldimethanol **3e**. White solid; $R_f$ (CH$_2$Cl$_2$/MeOH: 9/1) 0.71; mp 86–88 °C; IR (KBr) $v$ 3237, 2977, 2955, 1652, 1011 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.33 (d, $J = 4.8$ Hz, 2H), 1.47 (m, 2H), 1.66 (dt, $J = 4.8$, 1.2 Hz, 1H), 1.92 (m, 1H), 2.58 (m, 2H), 3.60 (m, 2H, OH), 4.20 (s, 4H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 22.9 (d), 25.1 (d), 32.4 (t), 51.0 (d), 55.7 (d), 58.5 (t), 142.7 (s). Anal. Calcd for C$_{11}$H$_{14}$O$_2$: C, 74.13; H, 7.92. Found: C, 74.02; H, 7.77.

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18. Terminal alkynes such as propargyl acetate **2p** (R$^1$ = CH$_2$OAc, R$^2$ = H) and NBD **1** resulted in extensive polymerization and only 9% yield of the expected [2+2+2] cycloadduct **3p**.

19. Typical procedure: To a suspension of RuCl$_2$(PPh$_3$)$_2$(NBD) (39.4 mg, 0.05 mmol) and dioxane (2 mL) in a 10 mL Schlenk tube under an Ar atmosphere, was added NBD (138 mg, 1.5 mmol), the alkyne (1 mmol), and dioxane (6 mL). The mixture was heated at 90 °C until completion (TLC monitoring). Dioxane was evaporated in vacuo and the crude product was purified by SiO$_2$ column chromatography.

20. The highly sensitive 8,9-bis(chloromethyl)tetracyclo [4.3.0.0$^{2,4}$.0$^{3,7}$]non-8-ene **3o** was obtained as a colorless oil after addition of petroleum ether to the crude reaction mixture, filtration of the solid residues over Celite, and evaporation of the solvents. $R_f$ (PE) 0.56; IR (neat) $v$ 3059, 2955, 1638, 904, 728 cm$^{-1}$; $^1$H NMR (CDCl$_3$, 200 MHz) $\delta$ 1.46 (d, $J = 4.8$ Hz, 2H), 1.52 (m, 2H), 1.66 (dt, $J = 4.8$, 1.3 Hz, 1H), 2.02 (m, 1H), 2.69 (m, 2H), 4.19 (m, 4H); $^{13}$C NMR (CDCl$_3$, 50 MHz) $\delta$ 23.1 (d), 24.9 (d), 32.3 (t), 39.4 (t), 51.5 (d), 55.6 (d), 142.2 (s).