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Ruthenium-Catalyzed [2 + 2] Cycloadditions of Bicyclic Alkenes with Alkynyl Phosphonates

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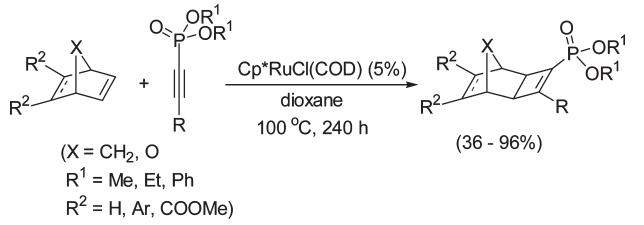

Ruthenium-catalyzed [2 + 2] cycloadditions of bicyclic alkenes with alkynyl phosphonates were investigated. The phosphonate moieties were found to be compatible with the Ru-catalyzed cycloadditions giving the corresponding cyclobutene cycloadducts in low to excellent yield (up to 96%). Alkynyl phosphonates showed lower reactivity than other heteroatom-substituted alkynes such as alkynyl halides, ynamides, alkynyl sulfides, and alkynyl sulfones and required a higher reaction temperature and much longer reaction time.

While cycloaddition reactions can be carried out by using heat, light, or Lewis acids,[1] these promoters usually require the presence of polar functional groups in the substrates. Unactivated substrates require extreme conditions (high temperature and high pressure) to promote reaction. Transition-metal catalysts provide a new opportunity to promote cycloadditions of unactivated substrates and cycloadditions that are theoretically forbidden or difficult to achieve. In this way, transition-metal catalysts have shown themselves to be a powerful method for the synthesis of rings and complex molecular stuctures.[2] Unlike many other metal-catalyzed cycloadditions for the formation of 5- to 8-membered rings (via [2 + 2 + 1], [4 + 2], [5 + 2], [6 + 2], and [4 + 4] cycloadditions) that have been studied extensively,[3−7] there are relatively few studies on metal-catalyzed [2 + 2] cycloadditions for the formation of 4-membered rings. Recently, various aspects of transition-metal-catalyzed [2 + 2] cycloadditions of an alkene and an alkyne for the synthesis of cyclobutenes have been studied by us and others, including development of novel catalysts, study of the intramolecular variant of the reaction, investigation of the chemo- and regioselectivity of unsymmetrical substrates, and asymmetric induction studies with chiral auxiliaries on the alkyne component.[8−13]

We have previously investigated the Ru-catalyzed [2 + 2] cycloaddition of bicyclic alkenes with various heteroatom functionalities (ynamide **2**,[8h,8n] halide **3**,[8g,8r] sulfide **4**,[8k] sulfone **5**[8k]) in the acetylenic position (Scheme 1). Alkynyl halides **3** (X = Cl, Br, I) were found to be the most reactive, proceeding at room temperature. Ynamides **2** (X = N-(CO_2Me)R′), alkynyl sulfides **4** (X = SAr, SR′), and sulfones **5** (*X* = SO_2Ar, SO_2R′) were less reactive than alkynyl halides and required longer reaction time and higher temperature.

To the best of our knowledge, no examples of Ru-catalyzed [2+2] cycloaddition of alkynyl phosphonates are reported in the literature. The electron-deficient phosphonate

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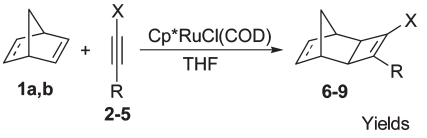
SCHEME 1. Previous Studies on Heteroatom-Substituted Alkynes in the Ru-Catalyzed [2 + 2]



		Yields
2, **6**: X = $N(CO_2Me)R'$	60 °C, 72 h	25-97%
3, **7**: X = Cl, Br, I	25 °C, 72 h	32-90%
4, **8**: X = SAr, SR'	90 °C, 168 h	23-80%
5, **9**: X = SO_2Ar, SO_2R'	90 °C, 72 h	55-84%

group allows for the scope of the reaction to be expanded to a new category of heteroatom substituents with phosphorus functionality that is stable toward further oxidation.

Formation of 1-cyclobutenyl phosphonates has previously been reported in the literature; however, these synthetic methods have limited scope and cannot be applied with our substrates.[14] Ruder and Norwood observed thermal [2 + 2] cycloaddition between an alkynyl phosphonate and enamine, though the temperatures necessary to promote the cycloaddition caused spontaneous electrocyclic ring-opening of the adduct, and no cyclobutene was isolated.[14d] In this paper, we report the first example of Ru-catalyzed [2 + 2] cycloadditions of alkynyl phosphonates with bicyclic alkenes to form 1-cyclobutnenyl phosphonates.

Vinyl phosphonates have been found to be important biomolecules in metabolic processes, as anticancer and antiviral drugs, as well as antibacterial and antifungal compounds.[15] The phosphonate group can also be modified by established procedures to a wide variety of other phosphorus groups including phosphines.[16,17] The possible phosphine derivatives of the cycloadduct products could find application in the growing field of phosphine−olefin ligands.[18]

To begin this study, the alkynyl phosphonates had to be synthesized. There are various methods in the literature for the formation of alkynyl phosphonates.[19] It was found that the procedure developed by Oh and co-workers was the simplest and most applicable.[19c] The original procedure involved deprotonating various terminal alkynes **10** with *n*-BuLi and subsequent trapping of the anion formed with chlorophosphates **11** to generate the desired alkynyl phosphonates **12**. However, it was found that unreacted *n*-BuLi was adding to **11** to form butyl phosphonate **13**, which had an R_f value very similar to that of **12** and was difficult to remove by flash chromatography. Therefore, the procedure was modified, and LDA was employed in place of *n*-BuLi to eliminate any nucleophilic addition side reactions (Scheme 2).

SCHEME 2. Synthesis of Alkynyl Phosphonates from Terminal Alkynes

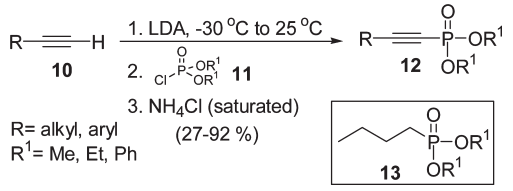
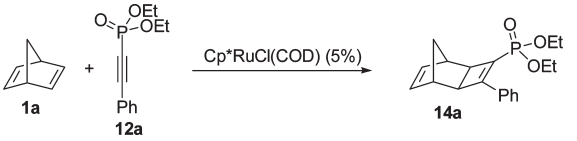


TABLE 1. Optimization of Ru-Catalyzed [2 + 2] Cycloadditions of Norbornadiene 1a with 1-Phenylethynyl phosphonate 12a



entry	solvent	*T* (°C)	time (h)	yield[a] (%)
1	THF	60	24	0[b]
2	THF	80	144	27[c]
3	THF	100	240	66
4	Et_3N	100	240	0[b]
5	dioxane	100	240	60
6	neat	100	240	71

[a]The yield of the isolated cycloadducts after column chromatography. [b]Only the starting alkyne was recovered. [c]The reaction did not go to completion, and some starting alkyne was recovered.

The reaction conditions of the Ru-catalyzed [2 + 2] cycloadditions were first optimized with alkynyl phosphonate **12a** and norbornadiene **1a** as the model reaction (Table 1). It was found that the alkynyl phosphonate **12a** was compatible with ruthenium-catalyzed [2 + 2] cycloaddition to produce the expected cyclobutene adduct **14a**. While the reaction did proceed, higher temperatures and longer reaction times were needed relative to the other alkyne substrates previously studied in this mode of reaction.[8] No reaction was observed when the reaction was carried out in THF at 60 °C, and the reaction did not go to completion at 80 °C for 144 h (entries 1 and 2). When the reaction was carried out in THF at 100 °C for 240 h, the desired cyclobutene cycloadduct **14a** was obtained in 66% yield (entry 3).

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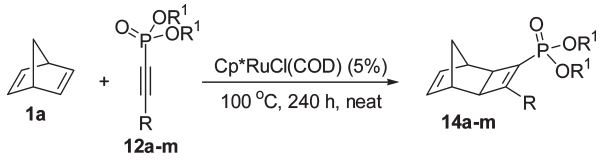
TABLE 2. Ru-Catalyzed [2 + 2] Cycloadditions of Norbornadiene with Alkynyl Phosphonates 3b−l



entry	alkyne	R^1	R	yield[a] (%)
1	**12a**	Et	Ph	71
2	**12b**	Me	Ph	44
3	**12c**	Ph	Ph	97
4	**12d**	Et	*n*-Bu	68
5	**12e**	Et	Cy	0[b]
6	**12f**	Et	CH_2OH	69
7	**12g**	Et	CH_2OTBS	67
8	**12h**	Et	*o*-Tol	8[c]
9	**12i**	Et	*p*-Tol	83
10	**12j**	Et	*p*-MeO-C_6H_4	80
11	**12k**	Et	*m*-NH_2-C_6H_4	78
12	**12l**	Et	*m*-F-C_6H_4	89
13	**12m**	Et	3-thiophene	65

[a]The yield of the isolated cycloadducts after column chromatography. [b]Only the starting alkyne was recovered. [c]The reaction did not go to completion, and some starting alkyne was recovered.

Unlike our previous studies with other alkynes in which Et_3N was shown to be a good solvent in the ruthenium-catalyzed [2+2] cycloadditions, no reaction was observed when Et_3N was used as solvent in the reactions with alkynyl phosphonate **12a** (entry 4). The best yield was observed when the reaction was carried out using 5 mol % of catalyst, Cp*RuCl(COD) (COD = 1,5-cyclooctadiene, Cp* = 1,2,3,-4,5-pentamethylcyclopentadiene), at 100 °C over 240 h in excess norbornadiene as solvent. The *exo* [2 + 2] cycloadduct **14a** was formed as the only stereoisomer.[20]

After the optimal conditions were determined, the effect of the alkynyl phosphonate on the cycloaddition was studied, and the results are given in Table 2. First, different groups on the phosphonate moiety, R^1 (**12a−c**, entries 1−3), were investigated. While dimethyl phosphonate (R^1 = Me, entry 2) gave the lowest yield (44%) in the cycloaddition, diphenyl phosphonate (R^1 = Ph, entry 3) was found to give the highest yield (97%) among the three phenylethynyl phosphonates (**12a−c**) tested. The effect of different groups (R) at the acetylenic position was studied (alkynes **12d−m**), and the results are shown in Table 2, entries 4−13.

In general, the reaction was found to proceed slower with aliphatic groups compared to aromatic groups with little exception. As with previous studies, the primary alkyl group (R = *n*-Bu, entry 4) produced a higher yield than the sterically hindered secondary alkyl group (R = Cy, entry 5), which produced no adduct. Interestingly, while previous studies demonstrated that propargylic alcohols stabilize coordination to the catalyst through hydrogen bonding to the chlorine ligand of the active catalyst, [Cp*RuCl],[8o] such increased reactivity was not observed in the reaction of **12f** (entry 6) as compared to its TBS-protected analogue **12g** (entry 7). Both substrates demonstrated similar reactivity to an unsubstituted alkyl chain (entry 4) and differed by only 2% in yield between the bare and protected alcohol groups.

Examining the reactions with aromatic substrates (**12h−m**, entries 8−13) illustrates similar trends as observed in previous studies. Again, steric hindrance reduced reactivity of the alkyne when comparing the substitution of a methyl group in either the *ortho* or *para* positions on the ring (entries 8 and 9). With the methyl group far from the reaction site in the *para* position, an 83% yield was achieved, whereas the methyl group *ortho* to the reaction site reduced the yield to a mere 8%. Substrates with electron-donating groups on the benzene ring (R = *p*-MeO-C_6H_4, *m*-NH_2-C_6H_4, entries 10 and 11) did not work as well as those with an electron-withdrawing group (R = *m*-F-C_6H_4, entry 12). Though all three moieties produced the desired cycloadducts in good yields, substrates with an electron-withdrawing group gave better yields. This is especially evident when considering the electron-rich 3-thiophene moiety **12m** (entry 13) which had a reduced yield of only 65%.

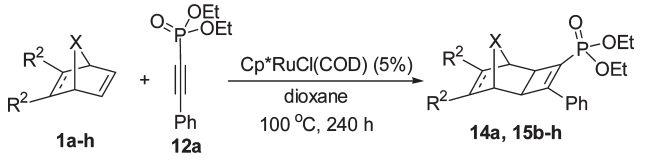
In order to investigate the scope of the Ru-catalyzed [2 + 2] cycloaddition of alkynyl phosphonates, cycloadditions of alkynyl phosphonate **12a** with various bicyclic alkenes were carried out, and the results are shown in Table 3. Though higher yields were observed with THF as solvent (Table 1, entry 3) compared to dioxane (entry 5), solvent loss of THF was experienced due to the elevated reaction temperatures. Therefore, dioxane was employed for this series of reactions. With the exception of **1h** (entry 8), all alkenes studied (**1b−g**, entries 1−7) underwent Ru-catalyzed [2 + 2] cycloaddition to produce, in a stereoselective manner, only the *exo* cycloadduct. In addition, when one of the homoconjugated olefins was substituted with methyl esters (**1c** and **d**, entries 3 and 4) the reaction was chemoselective, with cycloaddition occurring only on the less substituted double bonds.

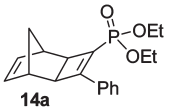
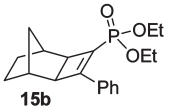
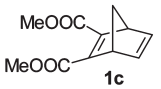
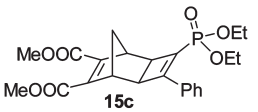
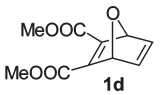
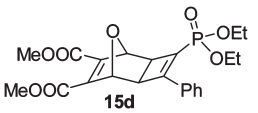
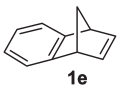
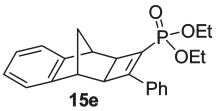
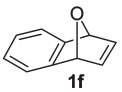
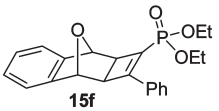
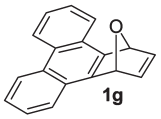
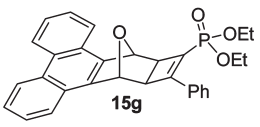
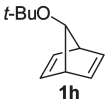
Considering the reactivity of different alkenes toward alkynyl phosphonates in the ruthenium-catalyzed [2 + 2] cycloaddition reaction, similar trends are observed as with previous reports. The loss of homoconjugation in comparing norbornadiene **1a** (entry 1) and norbornene **1b** (entry 2) did not greatly affect the yield of the reaction, though the yield was moderately improved as was observed with alkynyl sulfones.[8k] The addition of two methyl ester groups on norbornadiene (entry 3) increased the yield of the reaction, while replacing the one carbon bridge with an oxygen (entry 4) in that same molecule greatly reduced the yield. The large decrease in yields is attributed to the decomposition of the alkene reaction partner which was not stable at the elevated temperatures required to promote reaction. As previously observed,[8p] addition of a benzene ring to the bicyclic structure (entry 5) reduced the reactivity substantially. In contrast to **1d**, however, the substitution of an oxygen into the bridge greatly improved the yield of the reaction (entry 6). Investigations into the enhanced reactivity of oxabenzonorbornene **1f** in various reactions are currently underway in our laboratory. Extending the aromatic system (entry 7) reduced the yield of the reaction as did adding a *t*-BuO group on the bridge (entry 8), which can be attributed to decomposition of the alkene component as was observed with **1d**. 7-*t*-BuO-norbornadiene **1h** was also found to be inert in the Ru-catalyzed [2 + 2] cycloadditions with alkynyl sulfides.[8k]

In conclusion, we have demonstrated the first examples of ruthenium-catalyzed [2 + 2] cycloadditions between bicyclic

(20) For the determination of the *exo* and *endo* stereochemistry of [2 + 2] cycloadducts, see our previous work in ref 8. Also, no cycloaddition with the COD ligand was observed, as this type of Ru-catalyzed [2 + 2] cycloaddition was known to occur only on strained bicyclic alkenes; see refs 8 and 10.

TABLE 3. Ru-Catalyzed [2 + 2] Cycoladditions of Various Bicyclic Alkenes 1b−h and Alkynyl Phosphonate 12a



entry	Bicyclic alkene	Cycloadduct	yield (%)[a]
1	 1a	 14a	60
2	 1b	 15b	73
3	 1c	 15c	88
4	 1d	 15d	36[b]
5	 1e	 15e	46
6	 1f	 15f	96
7	 1g	 15g	39[b]
8	 1h	-	0[b,c]

[a]The yield of the isolated cycloadducts after column chromatography. [b]Decomposition of the alkene was evident by TLC of the crude mixture. [c]Only the starting alkyne was recovered

alkenes and alkynyl phosphonates. We found the alkynyl phosphonate moiety bearing diethyl, dimethyl and diphenyl groups to be compatible with Ru-catalyzed [2 + 2] cycloadditions, though with lower reactivity than other heteroatom functionalities previously reported.[8] Finally, it was found that Ru-catalyzed [2 + 2] cycloaddition of alkynyl phosphonates with various bicyclic alkenes proceeds in a chemo- and stereoselective manner, producing the desired cyclobutene adducts in moderate to good yields. Further investigation into the use of other phosphorus-containing alkynes (phosphonite, phosphine oxide, chiral alkynyl phosphonates) in Ru-catalyzed [2 + 2] cycloadditions, along with the functionalization and application of the cycloadduct as an olefin−phosphorus ligand are currently in progress in our laboratory.

Experimental Section

A representative procedure of the ruthenium-catalyzed [2 + 2] cycloaddition and characterization of a cycloadduct is described here. For the synthesis of alkynyl phosphonates and details of other adducts, see the Supporting Information.

General Procedure for Ruthenium-Catalyzed [2 + 2] Cycloadditions with Norbornadiene. A mixture of norbornadiene (0.4 mL, 3.94 mmol) and alkynyl phosphonate (1 equiv) was prepared in an oven-dried screw-cap vial. The vial was purged with nitrogen and taken into the drybox where 5−10 mol % of Cp*RuCl(COD) was weighed out and added and the vial sealed. The reaction mixture was stirred outside the glovebox at 100 °C for 10 days. The crude product was purified by flash chromatography to yield the corresponding cycloadduct (ethyl acetate/hexanes mixture).

Cycloadduct 14a (Table 1, Entry 6). The above general procedure was followed using alkynyl phosphonate **12a** (39.8 mg, 0.167 mmol) and Cp*RuCl(COD) (7.5 mg, 0.02 mmol). The crude product was purified by column chromatography (EtOAc/hexanes 6:4) to provide cycloadduct **14a** (39.3 mg, 0.119 mmol, 71%) as a yellow oil: R_f 0.34 (EtOAc/hexanes 1:1); IR (CH_2Cl_2, NaCl) 3058 (m), 2977 (s), 2939 (s), 1491 (m), 1447 (m), 1390 (w), 1243 (s), 1024 (s), 962 (s), 779 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 7.90 (dd, 2H, J = 7.9, 1.6 Hz), 7.41−7.35 (m, 3H), 6.19 (br s, 2H), 4.19−4.06 (m, 4H), 2.78 (t, 1H, J = 4.6 Hz), 2.71 (s, 2H), 2.52 (d, 1H, J = 3.5 Hz), 1.47 (d, 1H, J = 9.2 Hz), 1.36 (d, 1H, J = 9.2 Hz), 1.32 (td, 6H, J = 7.0, 1.0 Hz) ; ^{13}C NMR (APT, $CDCl_3$, 100 MHz) δ 161.3 (d, J = 8.4 Hz), 136.1, 135.3, 132.5 (d, J = 1.1 Hz), 129.7, 128.51 (d, J = 180.5 Hz), 128.46, 127.9, 61.55 (d, J = 3.4 Hz), 61.50 (d, J = 3.4 Hz), 45.2, 44.9, 43.3, 39.6, 39.2, 38.9, 16.4 (d, J = 3.8 Hz), 16.3 (d, J = 3.8 Hz); ^{31}P NMR ($CDCl_3$, 160 MHz) δ 10.74; HRMS (CI) calcd for $C_{19}H_{23}O_3P$ m/z 330.1385, found m/z 330.1389.

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Supporting Information Available: Detailed experimental procedures and compound characterization data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.