Synthetic Methods

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$PtCl_2$-Catalyzed Hydrative Cyclization of Trialkyne Functionalities to Form Bicyclic Spiro Ketones**

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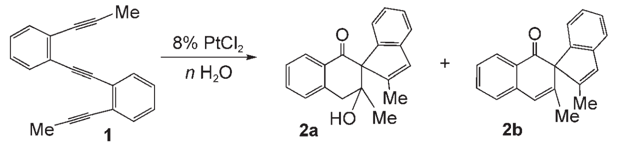
The metal-catalyzed coupling of multifunctional groups[1–4] is synthetically useful because two or more carbon–carbon and carbon–heteroatom bonds can be formed simultaneously in a one-pot operation. Regiocontrolled hydrative cyclization of an alkyne with another functional group is particularly notable, as this procedure provides complex oxygenated carbocyclic molecules from readily available alkynes.[2–4] The reported examples are restricted to two-component cyclizations, including hydrative cyclization of 1,n-diynes ($n = 5, 6$),[2] 1-yne-5-enones,[3] and 1-en-5-ynes.[4] Nucleophilic hydration of internal alkynes is seldom used in such cyclizations[2c] because the resulting ketones are generally inactive in the subsequent coupling with unactivated alkynes and alkenes.[5] Herein we report a new cyclization of triynes initiated by a $PtCl_2$-catalyzed nucleophilic hydration of internal alkynes. This coupling reaction yields bicyclic spiro ketones with remarkable regioselectivity, even for triynes with three inequivalent internal alkynes.

We previously reported the catalytic cyclization of enediynes with water and other nucleophiles in the presence of $[TpRuPPh_3(CH_3CN)_2]PF_6$ (Tp = tris(1-pyrazolyl)borate) to produce functionalized benzene derivatives regioselectively.[2c] Hydrative cyclization of triyne **1** with this ruthenium species (8 mol%) in hot, wet 1,4-dioxane ($6\,H_2O$, 100°C, 24 h) gave a complex mixture of products, from which spiro ketone **2b** was isolated in 3% yield (Table 1, entry 1). After screening the catalytic activity of common π-Lewis acids,[6] we found that only $PtCl_2$[7] (8 mol%) showed reasonable activity to give a 56% yield of spiro ketone **2b** (entry 2); the yield was further increased to 78% in the presence of CO (1 atm).[7] After a brief reaction (5 h, entry 4), we isolated π-ketonyl alcohol **2a** (14:1 d.r.) in 28% yield as well as the desired ketone **2b** (54%). Alcohol **2a** was verified to be the precursor of spiro ketone **2b** because it underwent facile dehydration when catalyzed by $PtCl_2$/CO in the presence or absence of water (entry 5). In contrast, ketone **2b** was recovered in hot, wet 1,4-dioxane (entry 6). Spiro ketone **2b** was characterized through an X-ray diffraction analysis,[8] while alcohol **2a** was identified according to the crystal structure of its analogue **28a**.[8]

Table 1: Hydrative cyclization of triyne species **1** with $PtCl_2$.

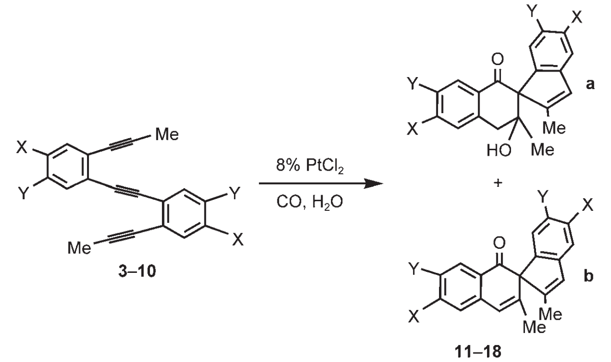


Entry	Substrate[a]	Catalyst	n	t	Product (yield [%])[b]
1	**1**	[TpRu][a]	6	24 h	**2b** (3)
2	**1**	$PtCl_2$	6	24 h	**2b** (56)
3	**1**	$PtCl_2$/CO	6	24 h	**2b** (78)
4	**1**	$PtCl_2$/CO	6	5 h	**2a** (28), **2b** (54)[c]
5	**2a**	$PtCl_2$/CO	0.6	20 h	**2b** (88, 76[d])
6	**2b**	$PtCl_2$/CO	6	24 h	**2b** (78)

[a] [TpRu] = $[TpRuPPh_3(CH_3CN)_2]PF_6$, 100°C, 1,4-dioxane, [triyne] = 0.2 M. [b] Yields are given after purification by column chromatography on silica gel. [c] The d.r. ratio for **2a** is 14:1. [d] This 76% yield corresponds to 6 equiv of water.

We extended this hydrative cyclization to symmetric triynes **3–10** containing two inequivalent internal alkynes (Table 2). Entries 1–4 show the results of the reaction when the Y substituents, which are in the *para* position to the prop-

Table 2: $PtCl_2$-catalyzed hydrative cyclization of symmetric triynes.



Entry	Triyne[a]	Product	Yield [%][b]
1	X = H, Y = OMe (**3**)	**11b**	35
2	X = H, Y = Me (**4**)	**12b**	62
3	X = H, Y = F (**5**)	**13b**	65
4	X = H, Y = CF_3 (**6**)	**14a**[c]	53
		14b	12
5	X = OMe, Y = H (**7**)	**15b**	81
6	X = Me, Y = H (**8**)	**16b**	70
7	X = F, Y = H (**9**)	**17b**	35
8	X = Y = $-OCH_2O-$ (**10**)	**18b**	69

[a] 100°C, 1,4-dioxane, [triyne] = 0.20 M, 24 h. [b] Yields are given after purification by column chromatography on silica gel. [c] The d.r. ratio for **14a** is 10:1.

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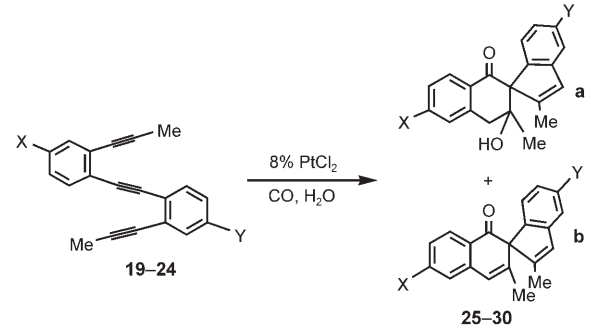
1-ynyl group, were varied; the methoxy substituent **3** is less efficient in the cyclization compared to its methyl-, fluoro-, and trifluoromethyl analogues **4–6**. The alcohol **14a** was obtained as the major product (in entry 4) because of its relative stability in aqueous 1,4-dioxane. Entries 5–7 show the results when the X substituents, which lie *para* to the inner alkyne, were varied. In these cases, this hydrative cyclization was found to be unfavorable for fluoro derivative **9**, relative to its methoxy and methyl analogues **7** and **8**. When triyne **10**, which contains a methylenedioxy group, was used, its corresponding cyclized ketone **18b** was obtained in 69 % yield (entry 8).

The value of this hydrative cyclization is reflected by its applicability to unsymmetric triynes **19–24**, which contain three inequivalent internal alkynes; the cyclization proceeded highly regioselectively to yield bicyclic spiro products of only one family (Table 3). The duration of the reactions in entries 1–5 and 7 (7–24 h) indicates the complete consumption of triynes **19–24**.[9] The ^{1}H NOE spectra of species **25a** and **26a**[8] reveal that the tertiary alcohol is situated on the cyclohexanone ring rather than the cyclopentane ring. This structural assignment was confirmed by an X-ray diffraction study of alcohol **28a**, of which the major diastereomer has the 2*R**,3*S** configuration.[8] In the cyclized products **25–30**, the more electron-rich C_6H_4X ring forms a spiro cyclohexanone ring whereas the remaining electron-deficient C_6H_4Y ring generates a spiro indene ring. Transformation of alcohols **25a–28a** into their spiro ketones **25b–28b** proceeded efficiently (83–89 % yields) in hot and anhydrous 1,4-dioxane in the presence of a $PtCl_2$/CO catalyst (8 mol %).

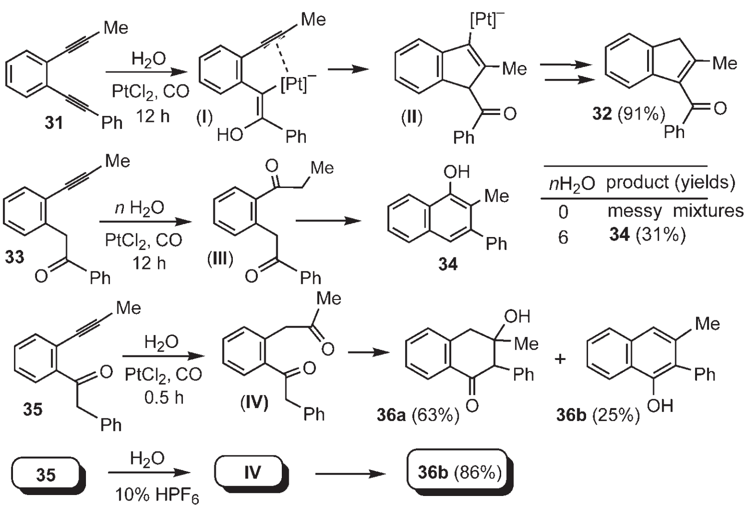
Table 3: $PtCl_2$-catalyzed hydrative cyclization of unsymmetric triynes.



Entry	Triyne[a]	t	Product	Yield [%][b]
1	X = OMe, Y = CF_3 (**19**)	12 h	**25a** (9.0:1 d.r.) **25b**	54 17
2	X = Me, Y = CF_3 (**20**)	24 h	**26a** (11:1 d.r.) **26b**	44 36
3	X = H, Y = CF_3 (**21**)	24 h	**27a** (12.9:1 d.r.) **27b**	23 38
4	X = Me, Y = F (**22**)	18 h	**28a** (7.3:1 d.r.) **28b**	47 26
5	X = Me, Y = H (**23**)	7 h	**29a** (> 20 d.r.) **29b**	51 26
6	X = Me, Y = H (**23**)	36 h	**29b**	76
7	X = OMe, Y = F (**24**)	8 h	**30b**	61

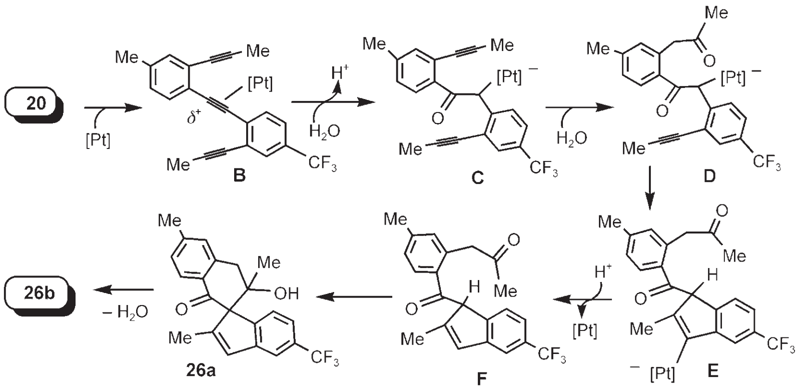
[a] 100 °C, 1,4-dioxane, [triyne] = 0.20 M. [b] Yields are given after purification by column chromatography on silica gel.

Scheme 1 shows the model reactions carried out to simulate the mechanism of cyclization. $PtCl_2$-catalyzed hydration of alkyne species **31** in hot, wet 1,4-dioxane (6 H_2O, 100 °C, 12 h) produced cyclized indene species **32** in a yield of up to 91 %. We also prepared ketone species **33**, which was shown to be unrelated to the formation of indene compound **32** because it gave a mixture of products in dry 1,4-dioxane, and gave 1-naphthol **34** in 31 % yield in wet conditions. These observations suggest that indene **32** is derived from an alkyne insertion in to intermediate **I**, followed by hydrodemetalation of intermediate **II**. Catalytic hydration of alkyne species **35** by $PtCl_2$ is rapid and complete in a short time (1,4-dioxane, 100 °C, 30 min) to give α-tetralone **36a** and 1-naphthol **36b** in yields of 63 % and 25 %, respectively; the common intermediate is thought to be diketone **IV**. The hydration selectivity occurs at the C≡*C*Me carbon atom rather than the expected Ph*C*≡C carbon atom.[10,11] Transformation of species **35** into 1-naphthol **36b** was also conducted effectively by wet HPF_6 (10 mol %) in hot 1,4-dioxane (100 °C, 2 h; Scheme 1).



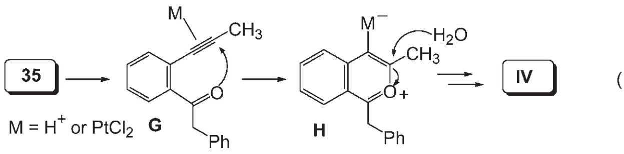
Scheme 1. Model reactions to simulate the cyclization mechanism.

The fact that alcohol species **26a** was verified as the primary product strongly indicates the participation of intermediate **E** in the cyclization mechanism (Scheme 2). According to the model reactions in Scheme 1, we envisage that hydration of triyne **20** occurs more readily at the inner diphenyl alkyne to give α-ketonyl platinum species **C**, of which the ketone group facilitates the second catalytic hydration at its *ortho*-alkynyl C(2′) carbon atom to produce diketone species **D**. This species undergoes a subsequent alkyne insertion and hydrodemetalation to form indene compound **F**, of which the C*H*CO hydrogen atom is highly acidic and activates aldol condensation to give the observed bicyclic alcohol **26a**.



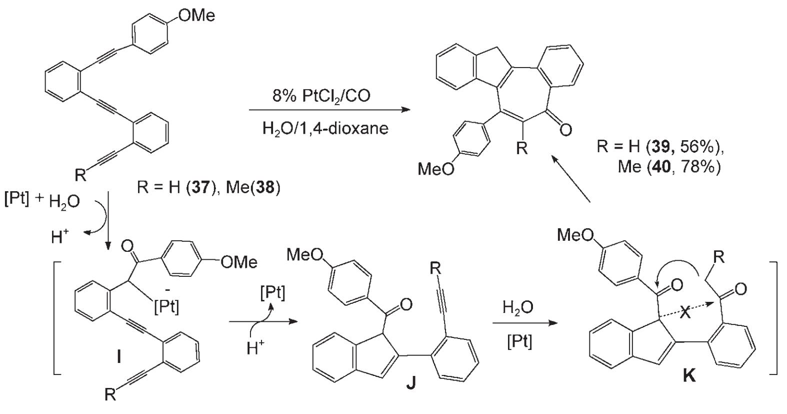
Scheme 2. A proposed mechanism for the formation of spiro ketones.

The selective hydrations of alkyne **35** to diketone **IV** and of **C** to **D** are crucial for the formation of the observed spiro ketones. The observed selectivity is contrary to literature reports[10] and our separate experiments[11] that π-Lewis acids prefer to add water at the Ph*C*≡CR carbon atom (R = alkyl). The C(2)-selectivity for the hydration of alkyne **35** is attributed to an initial $PtCl_2$- or proton-catalyzed *6-endo*-cyclization of π-alkyne species **G**[12] to form benzo[*c*]pyrylium **H**, which produces diketone **IV** upon hydrolysis of this intermediate [Eq. (1)].



(1)

The preceding proposed mechanism also rationalizes the effects of X and Y substituents in Table 2. A low yield was obtained with Y = OMe (Table 2, entry 1) because it favors the second hydration at the *C*≡CMe carbon atom rather than the desired C≡*C*Me carbon atom. A similarly low yield with X = F (Table 2, entry 7) arises from its slow hydration at the inner alkyne carbon atom because of its high electronegativity.



Scheme 3. One-pot synthesis of new bicyclic [5.3.0]ketones.

The understanding of the preceding cyclization mechanism is very helpful for the design of new hydrative cyclizations of triynes; one example is shown in Scheme 3. The $PtCl_2$/CO-catalyzed hydrative cyclization of triynes **37** and **38** provided a one-pot synthesis of new bicyclic ketones **39** and **40** in yields of 56 % and 78 %, respectively; the structure of compound **40** has been characterized by an X-ray diffraction study.[8] In this catalysis, H_2O initially attacks at the outer $MeOC_6H_4$*C*≡C carbon atom to form acylplatinum species **I**, which then undergoes alkyne insertion and hydrodemetalation to form indene species **J**. After a second hydration at the remaining alkyne of **J**, the resulting diketone species **K** undergoes a subsequent aldol condensation to initially form the [5.3.0]octenol species rather than the strained [3.3.0]octenol product.

In summary, we have reported a regioselective hydrative cyclization of triynes[13,14] to give bicyclic spiro ketones in good yields. According to our model reactions, this cyclization is proposed to proceed by two initial selective hydrations, followed by an alkyne insertion and aldol condensation. Further application of this catalysis to the synthesis of bioactive molecules is under investigation.

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Keywords: alkynes · cyclization · homogeneous catalysis · platinum · spiroketones

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[1] For selected examples, see a) A. de Meijere, P. von Zezschwitz, S. Bräse, *Acc. Chem. Res.* **2005**, *38*, 413; b) S. Kamijo, T. Jin, Z. Huo, Y. Yamamoto, *J. Am. Chem. Soc.* **2003**, *125*, 7786; c) S. J. Patel, T. F. Jamison, *Angew. Chem.* **2003**, *115*, 1402–1405; *Angew. Chem. Int. Ed.* **2003**, *42*, 1364–1367; d) H. Yoshida, H. Fukushima, J. Ohshita, A. Kunai, *Angew. Chem.* **2004**, *116*, 4025–4028; *Angew. Chem. Int. Ed.* **2004**, *43*, 3935–3938; e) Y. Tamaru, K. Yasui, H. Takanabe, S. Tanaka, K. Fugami, *Angew. Chem.* **1992**, *104*, 662–664; *Angew. Chem. Int. Ed. Engl.* **1992**, *31*, 645–646.

[2] For selected examples of the hydrative cyclization of 1,*n*-diynes, see a) B. M. Trost, M. T. Rudd, *J. Am. Chem. Soc.* **2003**, *125*, 11516; b) B. M. Trost, M. T. Rudd, *J. Am. Chem. Soc.* **2005**, *127*, 4763; c) A. Odedra, C.-J. Wu, T. B. Pratap, C.-W. Huang, Y. F. Ran, R.-S. Liu, *J. Am. Chem. Soc.* **2005**, *127*, 3406.

[3] For yne-enones, see B. M. Trost, R. E. Brown, F. D. Toste, *J. Am. Chem. Soc.* **2000**, *122*, 5877.

[4] For 1,5-enynes, see Y. Chen, D. M. Ho, C. Lee, *J. Am. Chem. Soc.* **2005**, *127*, 12184.

[5] Only highly enolizable ketones can be cyclized onto alkynes[5a] and alkenes[5b] by using suitable catalysts, see, for example a) J. J. Kennedy-Smith, S. T. Staben, F. D. Toste, *J. Am. Chem. Soc.* **2004**, *126*, 4526; b) H. Qian, R. A. Widenhoefer, *J. Am. Chem. Soc.* **2003**, *125*, 2056.

[6] The data obtained with catalyst screening, additives, effect of water and time-dependent product

distribution are provided in Table S1 and Figure S1 of the Supporting Information.

[7] This system is proposed to form $PtCl_2(CO)_n$; see a) A. Fürstner, P. W. Davies, T. Gress, *J. Am. Chem. Soc.* **2005**, *127*, 8244; b) A. Fürstner, C. Aïssa, *J. Am. Chem. Soc.* **2006**, *128*, 6306; c) A. Fürstner, P. W. Davies, *J. Am. Chem. Soc.* **2005**, *127*, 15024.

[8] CCDC-631140 (**2b**), CCDC-631139 (**28a**), and CCDC-632066 (**40**) contain the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Center via www.ccdc.cam.ac.uk/data request/cif.

[9] Triynes **19**–**22** gave the following products (and yields) after a reaction period of 36 h: **25a** (28 %)/**25b** (39 %) for entry 1; **26a** (31 %)/**26b** (42 %) for entry 2; **27a** (11 %)/**27b** (46 %) for entry 3; **28a** (21 %)/**28b** (45 %) for entry 4.

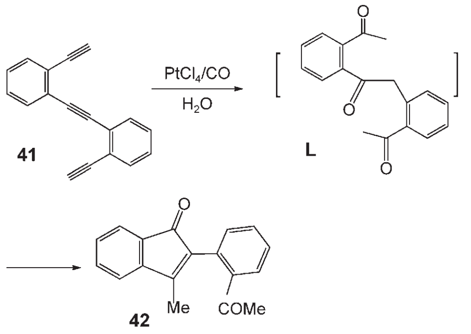
[10] For selected examples of metal-catalyzed hydration of alkynes, see a) W. Hiscox, P. W. Jennings, *Organometallics* **1990**, *9*, 1997; b) W. Baidossi, M. Lahav, J. Blum, *J. Org. Chem.* **1997**, *62*, 669; c) Y. Fukuda, K. Utimoto, *J. Org. Chem.* **1991**, *56*, 3729; d) E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem.* **2002**, *114*, 4745–4747; *Angew. Chem. Int. Ed.* **2002**, *41*, 4563–4565.

[11] Treatment of prop-1-ynylbenzene with $PtCl_2$/CO (10 mol %) and water (25 equiv) in hot 1,4-dioxone gave a mixture of phenyl ethyl ketone **a** and benzyl methyl ketone **b** (**a**/**b** 1.8).

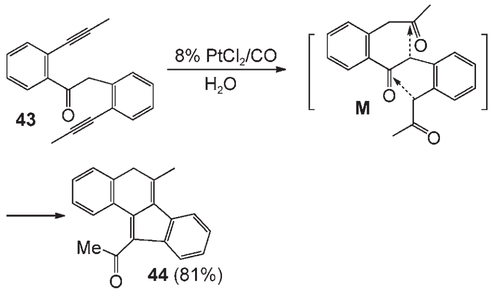
$$\mathrm{PhC{\equiv}CMe} \xrightarrow[H_2O]{PtCl_2/CO} \underset{(a)}{\mathrm{PhCOEt}} + \underset{(b)}{\mathrm{PhCH_2COMe}}\ (97\%)$$

[12] For this *6-endo-dig* cyclization, see a) N. Asao, K. Takahashi, S. Lee, T. Kasahara, Y. Yamamoto, *J. Am. Chem. Soc.* **2002**, *124*, 12650; b) N. Asao, H. Aikawa, Y. Yamamoto, *J. Am. Chem. Soc.* **2004**, *126*, 7458.

[13] Blum and co-workers[10b] used $PtCl_4$/CO (200 psi) to catalyze the hydrative cyclization of triyne **41** in wet THF (5 % water) to obtain indenone **42** (91 % yield) by a two-component coupling, and this ketone product is obtained from aldol condensation of the tris-ketone intermediate **L**. The active catalytic intermediate is proposed to be $HPtCl(CO)_2$.



[14] $PtCl_2$-catalyzed hydration of ketone species **43** gave bicyclic compound **44** (81 %) rather than the desired spiro ketone **2b**. Both species **43** and its tris-ketone intermediate **M** can be excluded from being the reaction intermediate in this spiro ketone synthesis. Spectra data of compounds **43** and **44** are provided in the Supporting Information.



[15] This new cyclization can be extended to triyne **45** bearing a bridging alkene group; the yield of spiro ketone **46** was 41 % using $PtCl_2$/CO and HPF_6 as an additive. Spectroscopic data of compounds **45**–**46** are provided in the Supporting Information.