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Diversity in Platinum-Catalyzed Hydrative Cyclization of Trialkyne Substrates To Form Tetracyclic Ketones

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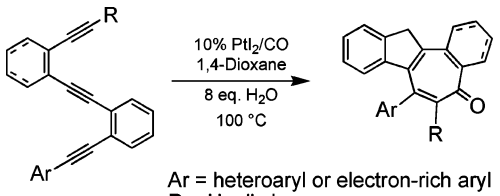
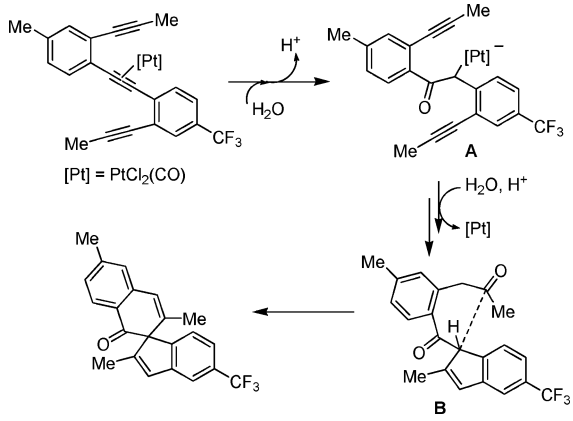


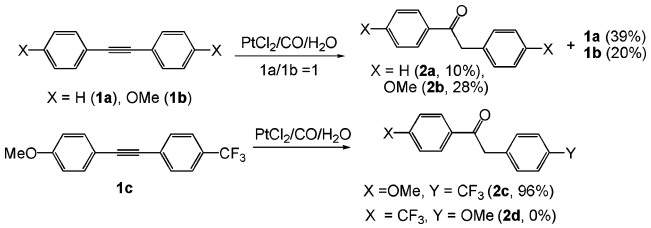
We report a one-pot synthesis of tetracyclic ketones via PtI_2-catalyzed hydrative cyclization of trialkyne functionalities. These triyne substrates bear an electron-rich aryl group at the outer alkyne to direct the initial hydration occurring at the adjacent alkynyl carbon. This tandem catalysis is proposed to comprise two alkyne hydrations, an alkyne insertion and an intramolecular aldol condensation.

The synthesis of complex polycarbocyclic molecules from metal-catalyzed multicomponent coupling reactions[1−2] is fascinating because multiple carbon−carbon bonds can be formed simultaneously. Regiocontrolled hydrative cyclization of an alkyne with another functionality is particularly notable as this approach provides complex oxygenated carbocyclic molecules from readily available alkynes. Most of the reported examples are restricted to two-component couplings that yield only monocyclic ring products.[3−5] To achieve a more complex framework, we recently reported[6] hydrative cyclization of trialkyne functionalities to produce bicyclic spiroketones using $PtCl_2$/CO as the catalyst; the protocol appears in Scheme 1. The design of this cyclization is based on kinetic differentiation such that diphenyl acetylene undergoes $PtCl_2$-catalyzed hydration much more rapidly than 1-propynylbenzene.[7] In this spiroketone synthesis, the initial hydration occurs exclusively at the central diphenyl alkynes to form α-ketonyl platinum species **A**, which subsequently forms intermediate **B** via an alkyne insertion and the second alkyne hydration.[6] To demonstrate the diversity of this tandem cyclization, we report here a remarkable hydrative cyclization of trialkyne substrates via an initial hydration at the outer alkyne, which ultimately gives varied tertacyclic ketones efficiently.

SCHEME 1



SCHEME 2



Scheme 2 shows the relative rates in the $PtCl_2$/CO[8]-catalyzed hydrations of the two diphenyl acetylenes **1a** and **1b** in a 1:1 reaction mixture; ketone products **2a** and **2b** were obtained in a molar ratio of 1:2.9 at 60% conversion relative to species **1b**. This information is indicative of the hydration preference for **1b,** likely due to platinum stabilizing the vinyl cationic character in the π-alkyne bonding.[9] To verify this hypothesis, an experiment with catalytic hydration of unsymmetric internal alkyne **1c** gave ketone **2c**[10] exclusively via selective hydration at the $MeOC_6H_4C\equiv$ carbon.

Accordingly, we prepared triyne **3** bearing a 4-methoxyphenyl group at the outer alkyne to facilitate hydration at the adjacent alkynyl carbon. Table 1 shows the hydrative cyclization of triyne

(1) For general reviews, see: (a) Ho, T.-L. *Tactics of Organic Synthesis*; Wiley-Interscience: New York, 1994: p 79. (b) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (c) Winkler, J. D. *Chem. Rev.* **1996**, *96*, 167. (d) Denmark, S. E.; Thorarensen, A. *Chem. Rev.* **1996**, *96*, 137.

(2) (a) Hegedus, L. S. In *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, California, 1999. (b) Patel, S. J.; Jamison, T. F. *Angew. Chem., Int. Ed.* **2003**, *42*, 1364. (c) de Meijere, A.; von Zezschwitz, P.; Bräse, S. *Acc. Chem. Res.* **2005**, *38*, 413.

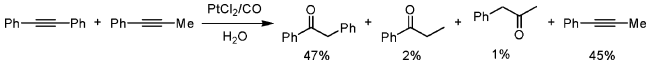
(3) For hydrative cyclization of 1,*n*-diynes, see selected examples: (a) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2003**, *125*, 11516. (b) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763. (c) Odedra, A.; Wu, C.-J.; Pratap, T. B.; Huang, C.-W.; Ran, Y.-F.; Liu, R.-S. *J. Am.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

(4) For yne−enone, see: Trost, B. M.; Brown, R. E.; Toste, F. D. *J. Am. Chem. Soc.* **2000**, *122*, 5877.

(5) For 1,5-enynes, see: Chen, Y.; Ho, D. M.; Lee, C. *J. Am. Chem. Soc.* **2005**, *127*, 12184.

(6) Chang, H.-K.; Datta, S.; Das, A.; Odedra, A.; Liu, R.-S. *Angew. Chem., Int. Ed.* **2007**, *46*, 4744.

(7) Treatment of a 1:1 mixture of diphenyl acetylene and 1-propynylbenzene with $PtCl_2$/CO (10 mol%) and water (1 equiv) in hot 1,4-dioxone (100 C, 12 h) gave a mixture of phenyl benzyl ketone (47%), phenyl ethyl ketone (2%), benzyl methyl ketone (1%), and recovered 1-propynylbenzene (45%).



(8) This catalytic system is proposed to form $PtCl_2(CO)_n$; see (a) Fürstner, A.; Davies, P. W.; Gress, T. *J. Am. Chem. Soc.* **2005**, *127*, 8244. (b) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306. (c) Fürstner, A.; Davies, P. W. *J. Am. Chem. Soc.* **2005**, *127*, 15024. (d) Taduri, B. P.; Ran, Y.-F.; Huang, C.-W.; Liu, R.-S. *Org. Lett.* **2006**, *8*, 883. (e) Lo, C.-Y.; Lin, C.-C.; Cheng, H.-M.; Liu, R.-S. *Org. Lett.* **2006**, *8*, 3153.

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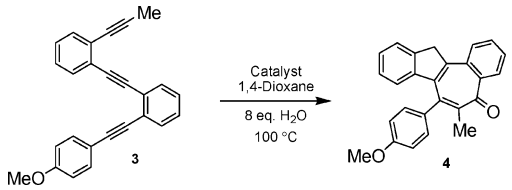
TABLE 1. Hydrative Cyclization of Triyne Species 3 over Various Catalysts



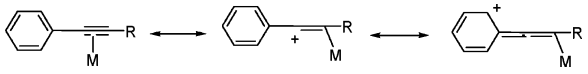
entry	catalyst	time (h)	yield (%)[a] 3	yield (%)[a] 4
1	10% $PtCl_2$/CO	6	–	76[b]
2	10% PtI_2/CO	3.5	–	83[b]
3	5% PtI_2/CO	18	–	62[b]
4	10% HPF_6	18	92	–
5	10% AuCl	18	88	trace[c]
6	10% $AuCl_3$	18	87	trace[c]
7	5% $AuClPPh_3$/5% AgOTf	12	91	–

[a] Yields were reported after separation from silica column. [b] 1,4-dioxane, [triyne] = 0.15 M. [c] [Triyne] = 0.075 M.

3 catalyzed with $PtCl_2$/CO (10 mol %) in wet 1,4-dioxane (100 °C, 6 h) (Table 1, entry 1), giving in 76% yield tetracyclic ketone **4** that was characterized by an X-ray diffraction study.[11] Among common π-Lewis acids, we found that PtI_2 (10 mol %) exhibited the best cyclization activity at a brief period to increase the yield of ketone **4** to 83% (entry 2). A low loading of PtI_2 (5 mol %) attained a decreased yield (62%, entry 3). The same reactions using HPF_6, AuCl, $AuCl_3$, and $AuPPh_3OTf$ only led to exclusive recovery of starting triyne **3** (entries 4−7).

Table 2 summarizes the results of the extension of this hydrative cyclization to various triynes **5**−**16** bearing three inequivalent internal alkynes. These triynes include an electron-rich aryl group to enhance the hydration at the ≡*C*Ar carbon. The catalytic reactions were performed by using 10 mol % PtI_2 in wet 1,4-dioxane at 100 °C; the duration of the reaction (1−6 h) enables the complete consumption of triynes **5**−**16**. Entries 1−4 show the variation of the aryl substituents; triyne **8** bearing a phenyl group is much less efficient for the cyclization than other triynes **5**−**7** containing an electron-rich phenyl substituent such as methyl, 3,4-dimethoxy, and methylenedioxy, which gave desired tetracyclic ketones **17**−**19** with 74−85% yields. In the case of phenyl substrate **8**, a mixture of products were obtained, from which desired tetracyclic ketone **20** was obtained in only 12% yield; the poor performance with species **8** demonstrates the importance of an electron-rich aryl substituent for the cyclization. The 2-thiophene and 2-furan derivatives **9** and **10** also exhibited reasonable activity; their corresponding tetracyclic ketones **21** and **22** were obtained in 62% and 57% yield, respectively (entry 5−6). Entries 7−10 show the applicability of this cyclization to triynes **11**−**14** bearing a terminal alkyne (R = H); the corresponding ketone products **23**−**26** were obtained in 61−72% yields. This hydrative cyclization worked satisfactory with triynes **15** and **16** bearing an R = *n*-butyl group, affording cyclized ketones **27**−**28** in 43−62% yields.

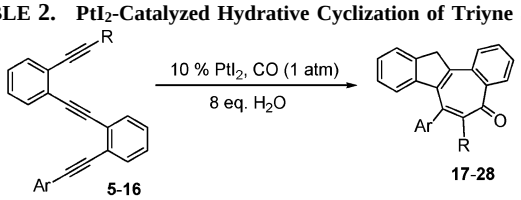
(9) In a π-alkyne moiety, the phenyl group is expected to stabilize the adjacent vinyl cation via extensive resonance forms.



(10) Spectra data of compound **2c** was identical to those reported in literature; see: Wang, D.; Zhang, Z. *Org. Lett.* **2003**, *5*, 4645.

(11) The X-ray crystallographic data of compound **4** are provided in the Supporting Information.

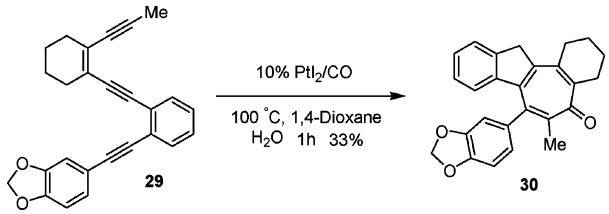
TABLE 2. PtI_2-Catalyzed Hydrative Cyclization of Triyne Species



entry	Triynes[a] Ar	R	time (h)	product (yield)[b]
1	*p*-MeC_6H_4,	Me (**5**)	4	**17** (74%)
2	3,4-$(MeO)_2C_6H_3$,	Me (**6**)	1.5	**18** (76%)
3	3,4-(OCH_2O)-C_6H_3,	Me (**7**)	1.5	**19** (85%)
4	C_6H_5,	Me (**8**)[c]	6	**20** (12%)
5		Me (**9**)	4	**21** (62%)
6		Me (**10**)	6	**22** (57%)
7	*p*-$MeOC_6H_4$,	H (**11**)[c]	1	**23** (67%)
8	*p*-MeC_6H_4,	H (**12**)	4	**24** (65%)
9	3,4-$MeOC_6H_3$,	H (**13**)	2	**25** (61%)
10	3,4-OCH_2O-C_6H_3,	H (**14**)	3	**26** (72%)
11	*p*-$MeOC_6H_4$,	^{n}Bu (**15**)	3	**27** (43%)
12	3,4-OCH_2O-C_6H_3,	^{n}Bu (**16**)	2	**28** (62%)

[a] 100 °C, 1,4-dioxane, [triyne] = 0.075 M. [b] Yields were reported after separation from silica column. [c] [Triyne] = 0.15 M.

SCHEME 3



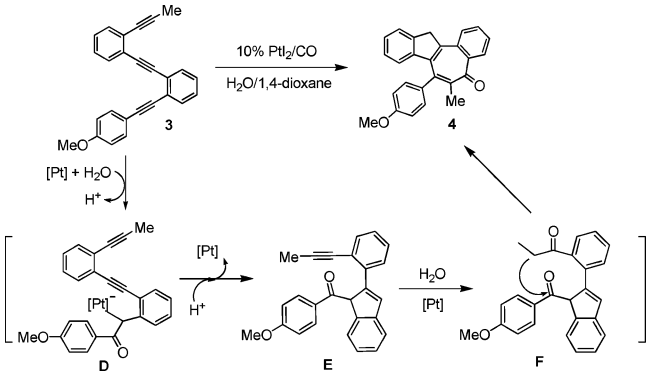
As depicted in Scheme 3, this cyclization is extensible to triyne **29** bearing a bridging cyclohexenyl group, giving tetracyclic ketone **30** in 33% yield using the PtI_2/CO/H_2O system; ^{1}H NOE effects confirmed its structure.[12] This case shows the applicability of this cyclization to construction of a complex carbocyclic framework.

This work demonstrates the diversity of hydrative cyclization of trialkyne substrates, which might provide tetracyclic ketones or bicyclic spiroketones (Scheme 1). For starting triyne **3**, the outer $MeOC_6H_4$***C***≡ carbon appears to be more active for hydrolysis based on our observations in Scheme 2. We propose a mechanism involving an initial attack of H_2O at the $MeOC_6H_4$***C***≡ carbon of triyne **3** to form α-carbonyl platinum species **D** (Scheme 4), which then undergoes alkyne insertion and hydrodemetalation to form indene species **E**. After a second hydration at the remaining alkyne of species **E**, the resulting diketone species **F** undergoes a subsequent aldol condensation to form an initial product bearing a central [5.3.0]decenol core rather than a strained [3.3.0]octenol structure.

In summary, we report a new regioselective hydrative cyclization of triynes to give tetracyclic ketones with satisfactory yields. The cyclization is proposed[13] to proceed via an initial attack of H_2O at the outer alkyne, followed by an alkyne insertion, a second hydration, and an ultimate aldol condensation. This work demonstrates the diversity of hydrative cyclization of trialkynes[14] bearing a suitable directing group.

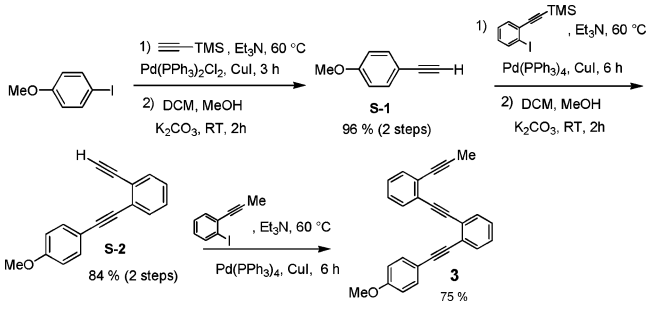
(12) ^{1}H NOE map of key compounds is provided in Supporting Information.

SCHEME 4



Experimental Section

General Procedures for the Synthesis of 1-[(4-Methoxyphenyl)ethynyl]-2-[(2-(1-propynyl)phenyl)ethynyl]benzene (3). (a) Synthesis of 4-Methoxyphenylacetylene (S-1).



Into a two-necked flask was placed $Pd(PPh_3)_2Cl_2$ (180 mg, 0.26 mmol), CuI (100.0 mg, 0.52 mmol), and degassed triethylamine under a nitrogen atmosphere; to this mixture were added 4-iodoanisole (3.0 g, 12.8 mmol) and trimethylsilylacetylene (2.2 mL, 15.4 mmol) under nitrogen. The reaction mixture was stirred at 60 °C for 3 h; triethylamine was removed under reduced pressure, and the residues were partitioned between ethyl acetate and water. The solution was extracted with ethyl acetate (30 mL × 2), washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel with hexane afforded (4-methoxyphenyl)ethynyltrimethylsilane as yellow oil. This silyl compound was then dissolved in dichloromethane (100 mL) and methanol (50 mL), added with K_2CO_3 (3.54 g, 25.6 mmol); the mixture was stirred at 23 °C for 2 h before the addition of water (100 mL). The solution was extracted with ethyl acetate (30 mL × 2), washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel with hexane afforded **S-1** (1.63 g, 12.3 mmol, 96%, two steps) as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, J = 8.0 Hz, 2 H), 6.78 (d, J = 8.0 Hz, 2 H), 3.71 (s, 3 H), 3.01 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 133.3 (2 × CH), 114.0, 113.7 (2 × CH), 83.5, 77.3, 54.8; HRMS calcd for C_9H_8O: 132.0575, found: 132.0571.

(b) Synthesis of 1-Ethynyl-2-[(4-methoxyphenyl)ethynyl]benzene (S-2). Into a two-necked flask was placed $Pd(PPh_3)_4$ (260 mg, 0.22 mmol), CuI (85.7 mg, 0.45 mmol), and degassed triethylamine under nitrogen atmosphere; to this mixture were added (2-iodophenyl)ethynyl]trimethylsilane (3.37 g, 11.2 mmol) and species **S-1** (1.63 g, 12.3 mmol) under nitrogen. The reaction mixture was stirred at 60 °C for 6 h. Triethylamine was removed under reduced pressure, and the residues were partitioned between ethyl acetate and water. The solution was extracted with ethyl acetate (30 mL × 2), washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel with hexane afforded a yellow oil, which further afforded **S-2** (yellow oil, 2.19 g, 9.43 mmol) following the desilylation procedure as described in preceding section. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.55−7.52 (m, 4 H), 7.30 (td, J = 8.0, 1.6 Hz, 1 H), 7.25 (td, J = 8.0, 1.6 Hz, 1 H), 6.87 (d, J = 8.0 Hz, 2 H), 3.78 (s, 3 H), 3.41 (s, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 133.1 (2 × CH), 132.4, 131.4, 128.4, 127.5, 126.5, 124.2, 115.1, 113.9 (2 × CH), 93.7, 86.6, 82.3, 81.0, 55.1; HRMS calcd for $C_{17}H_{12}O$: 232.0888, found: 232.0884.

(c) Synthesis of 1-[(4-methoxyphenyl)ethynyl]-2−[(2-(1-propynyl)phenyl) ethynyl]benzene (3). Into a two-necked flask was placed $Pd(PPh_3)_4$ (218 mg, 0.19 mmol), CuI (71.8 mg, 0.38 mmol), and degassed triethylamine under nitrogen atmosphere, and to this reaction mixture was added 1-iodo-2-(1-propynyl)benzene (2.51 g, 10.4 mmol) and compound **S-2** (2.19 g, 9.43 mmol) under nitrogen. The reaction mixture was stirred at 60 °C for 6 h, and triethylamine was removed under reduce pressure; the residues were partitioned between ethyl acetate and water. The solution was extracted with ethyl acetate (30 mL × 2), washed with saturated aqueous NaCl, dried over $MgSO_4$, and concentrated under reduced pressure. Column chromatography on silica gel with hexane afforded compound **3** as a yellow oil (2.45 g, 7.07 mmol, 75%). IR (neat, cm^{-1}): 3100 (s), 2115 (m), 1600 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57−7.50 (m, 5 H), 7.43−7.41 (m, 1 H), 7.30−7.22 (m, 4 H), 6.85 (d, J = 8.0 Hz, 2 H), 3.81 (s, 3 H), 1.97 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 159.7, 133.2 (2 × CH), 132.1, 131.9, 131.8, 131.5, 128.0 (2 × CH), 127.5, 127.2, 126.5, 126.0, 125.7, 125.5, 115.3, 113.9 (2 × CH), 93.6, 92.3, 91.7, 90.6, 87.1, 78.4, 55.3, 4.4; HRMS calcd for $C_{26}H_{18}O$: 346.1358, found: 346.1355.

General Procedures for Catalytic Reaction. A long tube containing PtI_2 (13 mg, 0.03 mmol) was dried in vacuo for 1 h; vacuum was released with CO gas using a CO balloon before the tube was charged with triyne **3** (100 mg, 0.3 mmol), water (41.6 μL, 2.3 mmol), and 1,4-dioxane (2.0 mL, 0.15 M). The mixture was stirred at 23 °C for 30 min and heated at 100 °C for 3.5 h. The solution was concentrated and eluted through a silica column (hexane/ethyl acetate) to afford compound **4** (87.0 mg, 0.24 mmol, 83%) as a yellow solid; mp 172.8−173.4 °C; IR (neat, cm^{-1}): 3075 (s), 1670 (s), 1630 (m), 1600 (w); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85−7.80 (m, 2 H), 7.66 (t, J = 8.0 Hz, 1 H), 7.54 (t, J = 8.0 Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2 H), 7.08 (t, J = 8.0 Hz, 1 H), 6.94−6.89 (m, 3 H), 6.22 (d, J = 8.0 Hz, 1 H), 4.10 (s, 2 H), 3.85 (s, 3 H), 2.20 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 198.7, 159.2, 145.0, 142.9, 141.8, 139.7, 138.7, 138.1, 137.7, 133.5, 132.2, 131.3, 131.1 (2 × CH), 128.9, 128.4, 127.1, 126.2, 125.2, 123.5, 123.4, 113.8 (2 × CH), 55.2, 41.0, 18.7; HRMS calcd for $C_{26}H_{20}O_2$: 364.1463, found: 364.1459.

Acknowledgment. We thank the National Science Council, Taiwan, for supporting this work.

Supporting Information Available: Spectra data and NMR spectra for compounds **3**−**30**; ^{1}H NOE map of key compounds; X-ray data for compound **4**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(13) The proposed mechanism in Scheme 4 suggests that this catalytic sequence is accomplished by both PtX_2 (X = Cl, I) and H^+. We propose that the superior activity of PtI_2 versus $PtCl_2$ is attributed to its easy hydrolysis to release more protons. In the presence of 2,6-lutidine, treatment of triyne **3** with PtI_2 (10 mol %) in wet and hot dioxane (100 °C, 3 h) only led to exclusive recovery of starting **3**. The role of H^+ is evident here.

(14) In Tables 1 and 2, we did not observe isomeric products because our substrates were designed for initial hydration at the outer diphenyl alkyne, which is more active than the remaining two internal alkynes in the alkyne hydration (see Scheme 2 and reference 4).