ORGANIC LETTERS

2006
Vol. 8, No. 21
4907−4910

Metal-Catalyzed Regioselective Oxy-Functionalization of Internal Alkynes: An Entry into Ketones, Acetals, and Spiroketals

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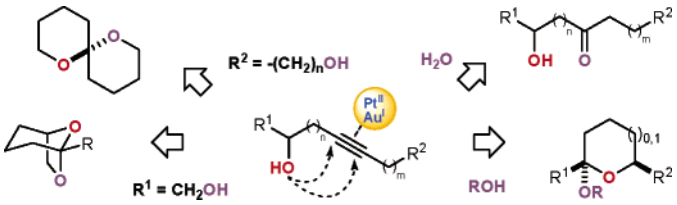
Received August 9, 2006

ABSTRACT



Platinum(II) and an unusual cationic gold(I) complex were identified as mild catalysts for the room temperature cycloisomerization or tandem hydroalkoxylation/acetal formation of unactivated internal alkynols. Under the appropriate conditions, 5-*endo*, 5-*exo*, 6-*endo*, and 6-*exo* cycloisomerization modes are all available.

The oxy-functionalization of internal alkynes (hydration, hydroalkoxylation)[1] represents a potentially attractive strategy for constructing ketone, acetal, or spiroketal substructures found in many natural products (Figure 1). Alkynes are

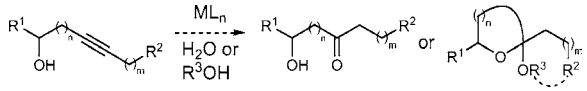


Figure 1. Oxy-functionalization of internal alkynes.

relatively inert toward many reaction conditions, a characteristic that can be leveraged to delay installation of valuable but rather sensitive δ-hydroxyketone or acetal functionality to later stages of the synthesis via C−O bond formation. Herein, we report efficient Pt^{II}- and Au^{I}-catalyzed regioselective oxy-functionalizations of unactivated internal alkynols.[2,3]

In contrast to the situation with terminal alkynes,[1] the addition of water or methanol to nonactivated and unbiased internal alkynes suffers from low regioselectivity.[4,5] A potential solution to this problem emerged from pioneering studies by Utimoto showing that Pd^{II}-catalyzed intramolecular hydroalkoxylation of internal alkynols provided cycloisomerization products with high regioselectivity.[6,7] The same

(1) For selected reviews, see: (a) Alonso, F.; Beletskaya, I. P.; Yus, M. *Chem. Rev.* **2004**, *104*, 3079. (b) Weyershausen, B.; Dötz, K. H. *Eur. J. Inorg. Chem.* **1999**, 1057. (c) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368.

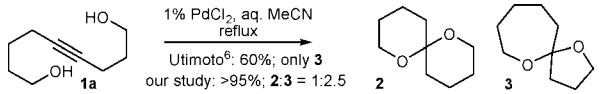
(2) For recent examples of intramolecular hydroalkoxylations with terminal alkynols, see: (a) Barluenga, J.; Diéguez, A.; Fernández, A.; Rodríguez, F.; Fañanás, F. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 2091. (b) Genin, E.; Antoniotti, S.; Michelet, V.; Genêt, J.-P. *Angew. Chem., Int. Ed.* **2005**, *44*, 4949. (c) Antoniotti, S.; Genin, E.; Michelet, V.; Genêt, J.-P. *J. Am. Chem. Soc.* **2005**, *127*, 9976. (d) Elgafi, S.; Field, L. D.; Messerle, B. A. *J. Organomet. Chem.* **2000**, *607*, 97. With electronically biased aryl alkynols: (e) Li, X.; Chianese, A. R.; Vogel, T.; Crabtree, R. H. *Org. Lett.* **2005**, *7*, 5437. (f) Messerle, B. A.; Vuong, K. Q. *Pure Appl. Chem.* **2006**, *78*, 385. (g) Hashmi, A. S. K.; Schwartz, L.; Choi, J.-H.; Frost, T. M. *Angew. Chem., Int. Ed.* **2000**, *39*, 2285. (h) Liu, Y.; Song, F.; Song, Z.; Liu, M.; Yan, B. *Org. Lett.* **2005**, *7*, 5409.

(3) For an attractive alkyne activation approach to the acetal/spiroketal framework via a gold(I)-catalyzed tandem propargyl Claisen rearrangement/heterocyclization, see: Sherry, B. D.; Maus, L.; Laforteza, B. N.; Toste, D. F. *J. Am. Chem. Soc.* **2006**, *128*, 8132.

10.1021/ol0619819 CCC: $33.50
Published on Web 09/20/2006

report also discloses the $PdCl_2$-catalyzed cycloisomerization of 4-nonyne-1,9-diol (**1a**) to yield selectively [4.6] spiroketal **3** in 60% yield (Scheme 1).[8] In our hands, however, a 2.5:1

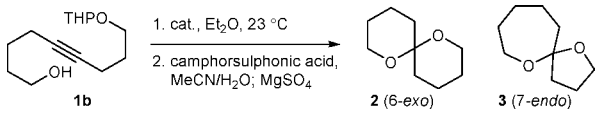
Scheme 1



mixture of [4.6] and [5.5] spiroketals **3** and **2** was consistently obtained.[9] We did not find this surprising considering that reduced selectivity could stem from the fact that both primary alcohols could react at comparable rates (i.e., a chemoselectivity issue) and with their own inherent *endo*-dig or *exo*-dig preference (i.e., a regioselectivity issue). We therefore decided to use mono-hydroxyalkynes as substrates in a screen to identify regioselective hydroalkoxylation catalysts.

In Table 1, we present our results with alkynol **1b**.[10] Contrary to expectation, we found that most catalysts delivered

Table 1. Catalyst Screening for the Hydroalkoxylation of **1b**



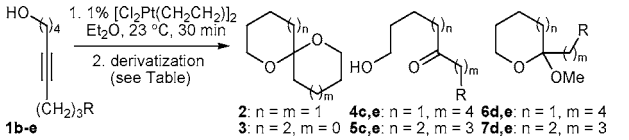
entry	mol % catalyst	time (h)	yield[a] (%)	ratio[a]
1[b]	1% $PdCl_2$	1.5	52	2:1
2	1% $MeAuPPh_3$, 10% TfOH	0.5	40	1.3:1
3	5% $ClAuPPh_3$/AgOTf (1:1)	0.5	36	2:1
4	5% $AuCl_3$	0.5	41	2.2:1
5	2% $PtCl_2$	24[c]	64	116:1
6	1% $[Cl_2Pt(CH_2{=}CH_2)]_2$	0.5	75	30:1

[a] Yields (at >95% conversion) and ratios (6-*exo*:7-*endo*) determined by GC with an external standard. [b] MeCN was used instead of Et_2O. [c] <5% conversion at 30 min.

mixtures resulting from 6-*exo*-dig and 7-*endo*-dig cyclization. Thus, $PdCl_2$ (entry 1), cationic gold(I) (entries 2 and 3) and $AuCl_3$ (entry 4) afforded rather low yields of *endo*/*exo* mixtures in ratios ranging from 1.3:1 to 2.2:1.[11] Gratifyingly, we found that Pt^{II} salts were effective and 6-*exo* selective hydroalkoxylation catalysts (entries 5 and 6). Although Zeise's dimer was slightly less selective than $PtCl_2$ (30:1 vs 116:1), it was a more efficient catalyst consuming starting material in less than 30 min at room temperature and 1 mol % catalyst loading.

Compared to substrate **1b**, TBS-protected variant **1c** yielded spiroketal **2**[10] with only a slight reduction in selectivity (20:1 vs 30:1, entries 1 and 2, Table 2) but higher

Table 2. Pt(II)-Catalyzed 6-*exo* Selective Hydroalkoxylation



entry	R	derivatization[a]	product (ratio)[b]	yield (%)[b]
1	OTHP (**1b**)	CSA, MeCN/H_2O; $MgSO_4$	**2**:**3** (30:1)	75
2	OTBS (**1c**)	CSA, MeCN/H_2O; $MgSO_4$	**2**:**3** (20:1)	83
3	OTBS (**1c**)	THF/H_2O, 23 °C, 5 min	**4c**:**5c** (30:1)	84
4	OAc (**1d**)	PPTS, MeOH, $HC(OMe)_3$	**6d**:**7d** (13:1)	94
5	*n*-Pr (**1e**)	PPTS, MeOH, $HC(OMe)_3$	**6e**:**7e** (7:1)	92
6	*n*-Pr (**1e**)	THF/H_2O, 23 °C, 5 min	**4e**:**5e** (7:1)	87

[a] See the Supporting Information for details. [b] Total yield and *endo*:*exo* ratio (**2**:**3**, **4**:**5**, or **6**:**7**) determined by GC with an external standard (entries 1 and 2), NMR (entries 4−6), or isolated yield (entry 3).

overall yield (83% vs 75%). Alternatively, the addition of moist THF upon completion of the Pt^{II}-catalyzed cycloisomerization of **1c** yielded δ-hydroxyketone **4c** in 84% yield (30:1; entry 3), demonstrating the stability of the TBS-protecting group to the reaction conditions. Similar conditions yielded δ-hydroxyketone **4e** from 4-dodecynol (**1e**) (entry 6). Entries 4 and 5 show that methylacetals are also accessible in high yields by the addition of an acidic MeOH/$HC(OMe)_3$ solution after completion of the cycloisomerization.

Having found a solution for the 6-*exo* selective hydroalkoxylation, we next examined the more intricate 5-*exo*/6-*endo* problem associated with the hydroalkoxylation of 4-alkynols. As shown in Table 3, Pt^{II}-catalyzed hydroalkoxylation of **8b**−**g** followed by derivatization as before[10] furnished the corresponding spiroketals **2**, **3** and methylacetals **6d**−**g**, **9d**−**g** favoring the 6-*endo* derived products (entries 1−7). Interestingly, δ-tetrahydropyranyloxy substitution has a beneficial impact on *endo*-selectivity (9−11:1; entries 1 and 2), followed to a lesser extent by silyloxy substitution (entry 3, 3.7:1). Acetoxy, methoxy, and (meth-

(4) For examples catalyzed by gold(I): (a) Teles, J. H.; Brode, S.; Chabanas, M. *Angew. Chem., Int. Ed.* **1998**, *37*, 1415. (b) Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 4563. (c) Roembke, P.; Schmidbaur, H.; Cronje, S.; Raubenheimer, H. *J. Mol. Catal.* **2004**, *212*, 35. By gold(III): (d) Fukuda, Y.; Utimoto, K. *J. Org. Chem.* **1991**, *56*, 3729. By platinum(II): (e) Jennings, P. W.; Hartman, J. W.; Hiscox, W. C. *Inorg. Chim. Acta* **1994**, *222*, 317. (f) Kataoka, Y.; Matsumoto, O.; Tani, K. *Organometallics* **1996**, *15*, 5246. (g) Hartman, J. W.; Sperry, L. *Tetrahedron Lett.* **2004**, *45*, 3787. By palladium(II): (h) Imi, K.; Imai, K.; Utimoto, K. *Tetrahedron Lett.* **1987**, *28*, 3127.

(5) For regioselective hydration controlled by participation of keto or ether neighboring groups, see ref 4e,h.

(6) Utimoto, K. *Pure Appl. Chem.* **1983**, *55*, 1845.

(7) For a Pt^{II}-catalyzed hydration of 3- and 4-pentyn-1-ol, see: Lucey, D. W.; Atwood, J. D. *Organometallics* **2002**, *21*, 2481.

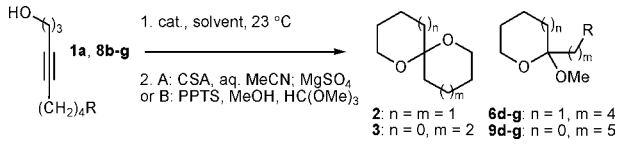
(8) For a nice application in total synthesis, see: Trost, B. M.; Horne, D. B.; Woltering, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5987.

(9) No experimental details regarding isolation, purification, and determination of selectivity were provided in the Utimoto paper.[6] We added camphorsulphonic acid and $MgSO_4$ at the end of the reaction to ensure complete conversion to the spiroketals (>95%) for GC analysis.

(10) All reactions documented in Tables 1−3 (aprotic solvents) yielded mixtures of cycloisomerization products (*endo*-enol and *E*/*Z*-mixtures of *exo*-enol ethers). These were derivatized after completion of the reaction to spiroketals (Tables 1−3) or acetals (Tables 2 and 3) to facilitate GC and NMR analyses.

(11) Triflic acid, AgOTf, $ClAuPPh_3$, and $PdCl_2(PhCN)_2$ were all incompetent catalysts for the cycloisomerization of **1b**.

Table 3. Metal-Catalyzed Hydroalkoxylation of 4-Alkynols[a,b]



entry	R	catalyst[c]	deriv[d]	product (ratio)[e]	yield (%)[e]
1	OTHP (**8b**)	$[Cl_2Pt(CH_2CH_2)]_2$	A	**3**:**2** (1:11)	70
2	OTHP (**8b**)	$[Cl_2Pt(CH_2CH_2)]_2$	A	**3**:**2** (1:9)	60
3	OTBS (**8c**)	$[Cl_2Pt(CH_2CH_2)]_2$	A	**3**:**2** (1:3.7)	58
4	OAc (**8d**)	$[Cl_2Pt(CH_2CH_2)]_2$	B	**9d**:**6d** (1:2.3)	93
5	Et (**8e**)	$[Cl_2Pt(CH_2CH_2)]_2$	B	**9e**:**6e** (1:2.3)	85
6	OMOM (**8f**)	$[Cl_2Pt(CH_2CH_2)]_2$	B	**9f**:**6f** (1:2.5)	90
7	OMe (**8g**)	$[Cl_2Pt(CH_2CH_2)]_2$	B	**9g**:**6g** (1:1.7)	88
8	Et (**8e**)	$PdCl_2$	B	**9e**:**6e** (2.6:1)	87
9	OH (**1a**)	$PdCl_2(PhCN)_2$	A	**3**:**2** (2:1)	>95
10	Et (**8e**)	$PdCl_2(PhCN)_2$	B	**9e**:**6e** (1:1.3)	90
11	OH (**1a**)	$MeAuPPh_3/AgPF_6$	A	**3**:**2** (3.7:1)	92
12	OTBS (**8c**)	$MeAuPPh_3/AgPF_6$	A	**3**:**2** (6.6:1)	73
13	Et (**8e**)	$MeAuPPh_3/AgPF_6$	B	**9e**:**6e** (6:1)	90
14	OMOM (**8f**)	$MeAuPPh_3/AgPF_6$	B	**9f**:**6f** (4:1)	94

[a] Reactions at 23 °C in Et_2O (entries 2−7, 9, 10), dioxane (entry 1), $^iPr_2O$ (entries 11−14), or refluxing aq MeCN (entry 8). [b] Reaction time was 30 min (entries 1−8, 11), 13 h (entries 12−14), or 3 h (entries 9, 10). [c] Catalyst loading: 1% (entries 1−7, 11), 5% (entries 8, 12−14), and 3% (entries 9, 10). [d] Derivatization method A: CSA, aq MeCN; then $MgSO_4$. Method B: PPTS, MeOH, $HC(OMe)_3$. [e] Determined by GC (entries 1−3, 9, 11, 12) or by NMR (entries 4−8, 10, 13, 14).

Table 4. Tandem Cycloisomerization/Acetal Formation[a]

entry	substrate	major product	ratio[b]	yield (%)[c]
1	R = OTHP; R' = H	6-*exo*	11:1	92 (86)[d]
2	R = OTBS; R' = H		14:1	90 (88)[d]
3	R = OMe; R' = H		12:1	93
4	R = OAc; R' = H		21:1	90
5	R = *n*-Pr; R' = H		11:1	96
6	R = OTBS; R' = Me		>20:1	82 (78)[d]
7	R = *n*-Pr; R' = *i*-Pr		>20:1	96
8[e]	R = Et; R' = CH_2OH		>100:1	99 (92)[d]
9	R = Hex	5-*endo*	>100:1	95
10	R = OTBS	5-*exo*	1.5:1[f]	98
11	R = OAc		1.7:1[f]	94
12	R = Et		1.4:1[f]	99
13[g]	R = Et		4.3:1	90

[a] Reaction conditions: alkynol (1.0 equiv), MeOH (5.0 equiv), $[Cl_2Pt(CH_2CH_2)]_2$ (1.0 mol %), THF:$HC(OMe)_3$ (10:1, 0.2 M), 23 °C, 10−30 min. [b] Ratio (NMR) of 6-*exo* vs 7-*endo* products (entries 1−7), and 5-*exo* vs 6-*endo* products (entries 10−13). [c] Determined by NMR. [d] Isolated yield. [e] Reaction in THF only. [f] The 6-*endo* products included 5−18% of the corresponding dihydropyrans. [g] Reaction run with 5% $MeAuPPh_3/AgPF_6$ (1:1) in Et_2O:$HC(OMe)_3$ (10:1) for 40.5 h.

oxymethyl)oxy substituents did not improve selectivity (1.7−2.5:1, entries 4, 6, and 7) versus the alkyl control (2.3:1, entry 5). It is of interest to note that Pd^{II}-catalyzed cycloisomerization of 4-undecynol (**8e**) was only marginally 5-*exo* selective with $PdCl_2$ (entry 8) and nonselective with $PdCl_2(PhCN)_2$ (entry 10), contrasting with reported results.[6,12]

After an extensive screen, we found that a $MeAuPPh_3/AgPF_6$ combination functions as an effective catalyst for the cycloisomerization of 4-alkynols with 5-*exo* selectivities ranging from 4:1 to 6−6.6:1 (Table 3, entries 12−14).[13] This catalyst combination also provided better 5-*exo* selectivity than Pd^{II} for the cycloisomerization of 4-nonyne-1,9-diol (compare entries 9 and 11).[6,9]

Having identified conditions for efficient 6-*exo*, 5-*exo*, and 6-*endo* selective cycloisomerizations of internal alkynols, we became interested in the possibility to effect a tandem cycloisomerization/acetal formation to obtain acetals directly.[10,14] To this end, various methylacetals were generated with good 6-*exo* selectivity upon reaction of 5-alkynols with 5 equiv of MeOH in the presence of 1% $[Cl_2Pt(CH_2{=}CH_2)]_2$ in a THF:$HC(OMe)_3$ (10:1) solvent mixture (Table 4, entries 1−7). This reaction is very fast and no dihydropyran products could be detected. Entries 1−4 demonstrate that various alcohol protecting groups, including the labile THP-ether, were stable to the reaction conditions. Furthermore, secondary alcohols were excellent substrates for this reaction and provided products resulting from excellent 6-*exo* selectivity and anomeric stabilization (entries 6 and 7). Entry 8 demonstrates the possibility of obtaining bicycloketals when cyclized intermediates can be trapped intramolecularly. Not surprisingly, 3-decynol provided 2-hexyl-2-methoxytetrahydrofuran via a 5-*endo* pathway (entry 9).

Finally, reaction of 4-alkynols was nonselective to mildly 5-*exo*-selective (Table 4, entries 10−12), whereas the corresponding cyclizations in anhydrous diethyl ether displayed modest to good 6-*endo* selectivity (Table 3, entries 1−7). Changing to a $MeAuPPh_3/AgPF_6$ catalyst system did improve somewhat the 5-*exo*-selectivity for this tandem cyclization/methoxylation of 4-alkynols (compare entries 12 and 13). Nevertheless, the highest 5-*exo* selectivities are achieved according to the conditions in Table 3, entries 11−14.

A mechanistic hypothesis consistent with the available data is depicted in Figure 2. Initial coordination of the alkynol to Pt^{II} (**A** → **B**) activates it for intramolecular attack by the alcohol to yield *endo*-**C** or *exo*-**C** adducts.

Deprotonation followed by reprotonation at carbon would then deliver the transient platinated oxocarbenium species

(12) With the same substrate and reaction conditions that we used in this study, Utimoto[6] reports 95% 6-*endo* selectivity with $PdCl_2(PhCN)_2$, and 95% 5-*exo* selectivity with $PdCl_2$.

(13) To the best of our knowledge, this catalyst combination has not been reported. The optimal solvent is $^iPr_2O$, yielding a 10−20% increase in selectivity versus Et_2O. Upon mixing $MeAuPPh_3$ and $AgPF_6$, a black precipitate forms that can be filtered. The remaining solution retains full catalytic activity with similar selectivity. Other Ag^I salts gave lower yields and selectivities and $MeAuPPh_3$ or $AgPF_6$ alone were catalytically incompetent. Cationic gold(I) complexes generated from halide abstraction of $ClAuPPh_3$ with various Ag^I salts gave lower yields and selectivities.

(14) ^1H NMR analysis of the cycloisomerization of 5-dodecyn-1-ol (**1e**) in THF-d_8 at low conversion revealed the presence of detectable levels of 2-heptyl-2-dodec-5-ynyloxy tetrahydropyran, indicating that acetals could be formed directly under the reaction conditions.

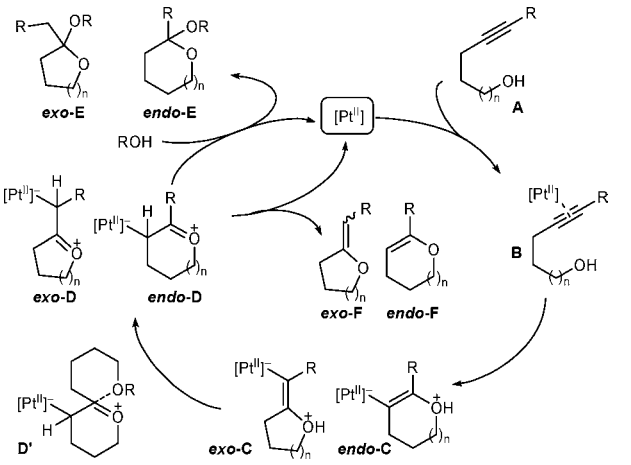
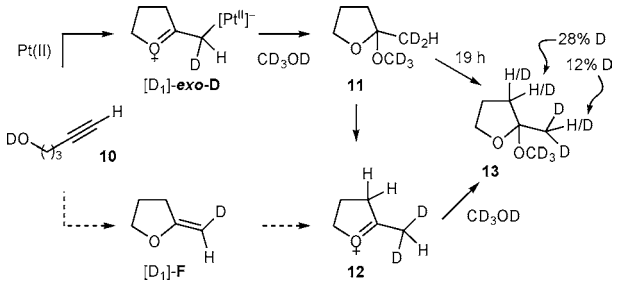


Figure 2. A mechanistic hypothesis.

exo-**D** and *endo*-**D**. In the absence of MeOH, we propose this proton transfer to be the rate-limiting and selectivity-determining step (i.e. *exo*-**C** and *endo*-**C** can establish a preequilibrium via **B**), favoring the formation of the 6-*endo*-isomer (*endo*-**D**, $n = 1$) to the extent of 2.3:1 (Table 3, entry 5). Deplatination leads to the cycloisomerization products *exo*-**F** and *endo*-**F**. Certain alkoxy-functionality can further enhance 6-*endo*-selectivity (up to 9:1; Table 3, entry 2), perhaps via stabilization of charge build-up in the transition state leading to *endo*-**D** (see **D′**).[15,16] In the presence of MeOH, proton transfer is fast and cyclization to **C** becomes rate limiting: 5-*exo* addition is favored slightly over 6-*endo* addition and independent of alkoxy functionality (Table 4, entries 10−12). Now, methoxylation precedes deplatination to yield methylacetals *exo*-**E** and *endo*-**E**, completing the catalytic cycle.[17]

Additional evidence indicates that enol ethers (**F**) are not intermediates en route to acetals **E**.[18] First, 6-heptyl-3,4-dihydro-2*H*-pyran (*endo*-**F**, $n = 1$, R = heptyl) was recovered unchanged when subjected to the same reaction conditions that gave a 96% yield of 2-heptyl-2-methoxy-tetrahydro-2*H*-pyran from alkynol **1e** (Table 4, entry 5). Moreover, the Pt^{II}-catalyzed tandem cycloisomerization/hydromethoxylation of 4-pentyn-1-ol (**10**) in CD_3OD afforded uniquely [D_5]-2-MeO-2-Me-tetrahydrofuran (**11**) after 3 min at room temperature (Scheme 2). Stirring the reaction mixture for an additional 19 h gave **13** with additional deuterium incorporation at the methyl carbon (12% D) and at the C_3-methylene carbon (28% D). These results rule out the intermediacy of enol ether [D_1]-**F** for the fast formation of **11**, as this would lead to H/D scrambling via oxocarbenium **12** as observed for the slower formation of **13** from **11**.

Scheme 2. Deuterium Labeling Experiment



In conclusion, we have developed efficient protocols for the Pt^{II}- and Au^{I}-catalyzed oxy-functionalization of unactivated internal alkynes. Zeise's dimer ($[Cl_2Pt(CH_2{=}CH_2)]_2$) was identified as an efficient and selective catalyst for the intramolecular hydroalkoxylation of 5-alkynols and 3-alkynols. For the 5-*exo* selective cycloisomerization of 4-alkynols, we identified a new catalyst combination obtained by premixing $MeAuPPh_3$ and $AgPF_6$. The studies reported herein also have led to an efficient tandem hydroalkoxylation/acetal formation and include experiments that provided initial mechanistic insight into this process. Additional mechanistic studies and applications of this methodology to natural product synthesis will be reported in the future.

Acknowledgment. Financial support was provided by the Robert A. Welch Foundation and Merck Research Laboratories.

Supporting Information Available: Experimental procedures, characterization data, GC chromatograms, and copies of NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(15) At this moment, we speculate that OTHP is better at stabilizing developing positive charge. For the proton transfer leading to *exo*-**D** ($n = 1$), stabilization of charge build-up through a seven-membered interaction would be less efficient.

(16) In agreement with this analysis, the 6-*endo* selectivity observed for the Pt^{II}-catalyzed cyclization of **8b** in Et_2O (9:1, Table 3, entry 2) eroded to 2.7:1 when performed in THF, i.e., the level of that observed for cyclization of **8e** (2.3:1, Table 3, entry 5).

(17) A bifurcation between acetal formation (→ **E**) and direct deplatination (→ **F**) is supported by the following observation: reaction of **1e** with 1% $[Cl_2Pt(CH_2{=}CH_2)]_2$ in THF with the more hindered 2-propanol (5 equiv) yielded a 1:1 mixture of 6-heptyl-3,4-dihydro-2*H*-pyran and 2-heptyl-2-isopropoxytetrahydro-2*H*-pyran, whereas no dihydropyran product was observed with methanol as the trapping nucleophile under otherwise identical conditions.

(18) Others have suggested that addition of the second alcohol could occur on metal-bound intermediates, see refs 2b, 2f, and 4g. For the cationic gold(I)-catalyzed double hydromethoxylation of alkynes, ab initio calculations located an aurated species similar to platinated oxocarbenium intermediate **D**, see ref 4a.