DOI: 10.1002/adsc.201200825

Intermolecular Gold(I)-Catalyzed Alkyne Carboalkoxylation Reactions for the Multicomponent Assembly of β-Alkoxy Ketones

Danielle M. Schultz,[a,*] Nicholas R. Babij,[a] and John P. Wolfe[a,*]

[a] Department of Chemistry, University of Michigan, 930 N. University Ave., Ann Arbor, MI 48109-1055, USA
E-mail: danims@umich.edu or jpwolfe@umich.edu

Received: September 12, 2012; Published online: December 4, 2012

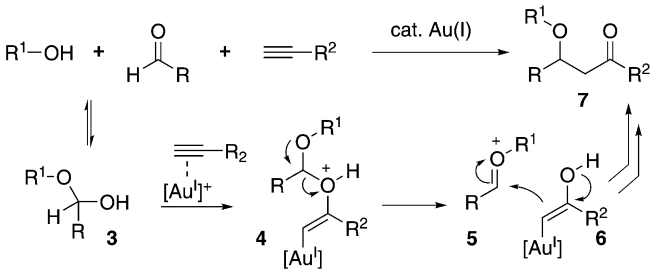
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200825.

Abstract: A new gold(I)-catalyzed multicomponent synthesis of β-alkoxy ketones from aldehydes, alcohols, and alkynes is described. This atom economical synthesis was achieved through the use of the gold complex (SPhos)AuNTf$_2$ as a catalyst, and allows for the preparation of a diverse array of β-alkoxy ketone products. Mechanistic studies illustrate that these reactions proceed *via* gold(I)-catalyzed hydrolysis of the alkyne to an aryl ketone, which then undergoes an aldol reaction with an oxocarbenium ion generated *in situ* from the aldehyde and alcohol components.

Keywords: aldehydes; alkynes; carbocations; gold; multicomponent reactions

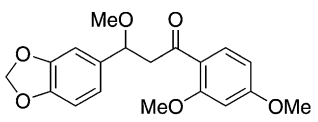
β-Alkoxy ketones are valuable building blocks in organic synthesis, and are also displayed in biologically active compounds and natural products such as dihydromilletonone methyl ether (**1**) and ovalitnin B (**2**).[1,2] We sought to develop a convenient new approach to the generation of these compounds *via* an Au(I)-catalyzed multicomponent coupling of readily available aldehydes, alcohols, and alkynes.[3,4] In this communication we describe our preliminary results in this area, and our initial investigations into the mechanism of this transformation.

Recently several groups have illustrated that acetals, hemiacetals, and hemiaminals can participate in intramolecular oxyauration reactions with alkynes to generate oxocarbenium or iminium ions and gold(I) enols or enol ethers.[5] These reactive species can then undergo further transformation *via* capture of the cationic electrophile with the gold(I) enol intermediate to generate heterocyclic products. Given this precedent, we reasoned that an *intermolecular* oxyauration reaction of an alkyne with hemiacetal **3** could provide **4**, which may fragment to gold(I) enol **6** and oxocarbenium ion **5** (Scheme 1). The oxocarbenium ion and the gold(I) enol intermediate could then undergo intermolecular addition to furnish β-alkoxy ketone product **7**.[6] In principle, we felt that the requisite hemiacetal could be generated *in situ* by the reaction of the aldehyde with one equivalent of the alcohol.

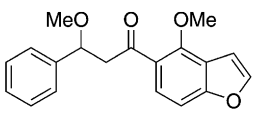


Scheme 1. Postulated mechanism for Au(I)-catalyzed synthesis of β-alkoxy ketones *via* oxyauration of hemiacetals.

In our preliminary experiments we elected to examine the coupling of 4-bromobenzaldehyde (**8**) and methanol with phenylacetylene (**9**). We reasoned that the aromatic aldehyde should stabilize the requisite oxocarbenium ion **5**, and thereby facilitate fragmentation of **4**. Moreover, phenylacetylene has proven to be a viable substrate in several Au-catalyzed reactions that involve oxyauration.[7] To optimize catalyst structure, a range of air-stable phosphine and NHC Au(I) bis(trifluoromethanesulfonyl)imidate catalysts[8,9] that have been shown to promote other oxyauration pro-

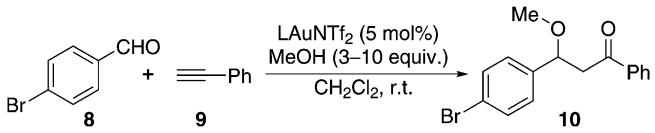


1
Dihydromilletenone methyl ether

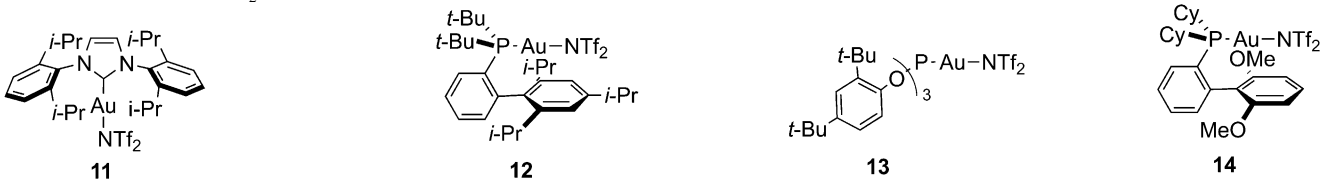


2
Ovalitnin B

Table 1. Optimization of reaction conditions.[a]



Entry	$LAuNTf_2$	Equiv. MeOH	Conv. [%][b]	Yield **10** [%][c]
1	$IPrAuNTf_2$ (**11**)	10	0	0
2	$Ph_3PAuNTf_2$	10	26	18
3	*t*-BuXPhosAuNTf_2 (**12**)	10	0	0
4	$(ArO)_3PAuNTf_2$ (**13**)	10	0	0
5	SPhosAuNTf_2 (**14**)	10	16	11
6	**11**	3	74	53
7	$Ph_3PAuNTf_2$	3	63	54
8	**12**	3	78	56
9	**13**	3	88	63
10	**14**	3	90	66 (59)[d]
11	$AgNTf_2$	3	0	0
12	$HNTf_2$	3	0	0



[a] *Reaction conditions:* all reactions were run in vials for 12 h using 1.0 equiv. of 4-bromobenzaldehyde, 1.5 equiv. phenylacetylene, 3–10 equiv. MeOH, 5 mol% catalyst, CH_2Cl_2 (0.1 M).
[b] The reaction conversion is based on the amount of aldehyde consumed in the transformation.
[c] Yields were determined by ^{1}H NMR analysis of crude reaction mixtures that contained phenanthrene as an internal standard.
[d] Isolated yield of product judged to be $\geq$95% pure by ^{1}H NMR analysis.

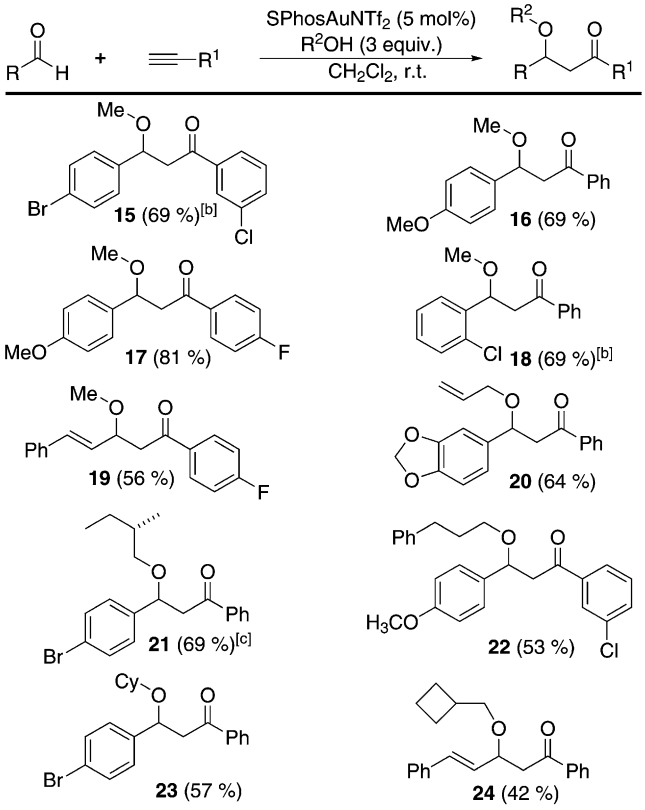
cesses were examined.[10] In our initial experiments we elected to use a ten-fold excess of methanol to facilitate hemiacetal formation. Under these conditions the NHC-ligated catalyst $IPrAuNTf_2$ (**11**) (Table 1, entry 1) showed no reactivity and use of the phosphine-derived catalysts PPh_3AuNTf_2 (entry 2) and SPhosAuNTf_2 (**14**) (entry 5) led to low conversion and formation of β-alkoxy ketone product **10** in only modest yield. However, when the amount of methanol present in the reaction mixture was decreased from ten equivalents to three equivalents the reactivity improved significantly. Nearly complete conversion was observed in 12 h with catalyst **14**, and the desired product was obtained in 59% isolated yield (entry 10). Control experiments using $AgNTf_2$ or $HNTf_2$ as catalysts did not afford the β-alkoxy ketone **10** (entries 11 and 12), which indicates the observed reactivity is due to the Au(I) catalyst rather than adventitious protic acid or silver triflimide (used for catalyst preparation).

With optimized conditions in hand we explored the scope of this transformation by varying the aldehyde, alkyne, and alcohol reaction partners. Both electron-withdrawing and electron-donating substituents on the aryl aldehyde were well tolerated, and β-alkoxy ketones **15**–**18** and **20**–**23** were formed in moderate to good yield (Table 2). The main side products observed in these reactions were aryl ketones resulting from hydration of the alkyne and acetals derived from the starting aldehyde and alcohol. In some instances the formation of 3-aryl-1,5-diketone side products was also observed. These presumably result from ionization of the β-alkoxy ketone products followed by capture of the resulting carbocation with a second equivalent of the enol nucleophile. In addition to aromatic aldehydes, *trans*-cinnamaldehyde also proved to be a viable substrate, affording **19** and **24** in 56% and 42% yield, respectively. In contrast, when aliphatic aldehydes were employed only the corresponding acetals were formed.

A wide variety of alcohol reaction partners can be successfully employed in these reactions including (*S*)-2-methylbutan-1-ol (**21**), cyclobutanemethanol (**24**), and allyl alcohol (**20**). The secondary alcohol cyclohexanol was also a viable reaction partner, leading to the formation of **23** in 57% yield. However, attempts to employ tertiary alcohols or phenols led to no conversion of the starting materials.

The transformations were effective with several different arylalkynes as coupling partners including 3-

Table 2. Scope of the Au(I)-catalyzed carboalkoxylation reactions.[a]

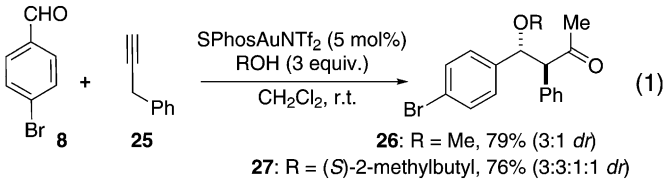


[a] *Reaction conditions:* all reactions were run in vials using 1.0 equiv. of aldehyde, 1.5 equiv. alkyne, 3 equiv. MeOH, 5 mol% $SPhosAuNTf_2$, CH_2Cl_2 (0.1 M). Reaction times were not minimized, but complete consumption of starting material was typically observed in <24 h. All yields are isolated yields of products judged to be $\geq 95\%$ pure by ^1H NMR analysis.

[b] The reaction was conducted with 5 mol% JohnPhosAuNTf$_2$ in place of $SPhosAuNTf_2$.

[c] The product was generated as a 1:1 mixture of diastereomers.

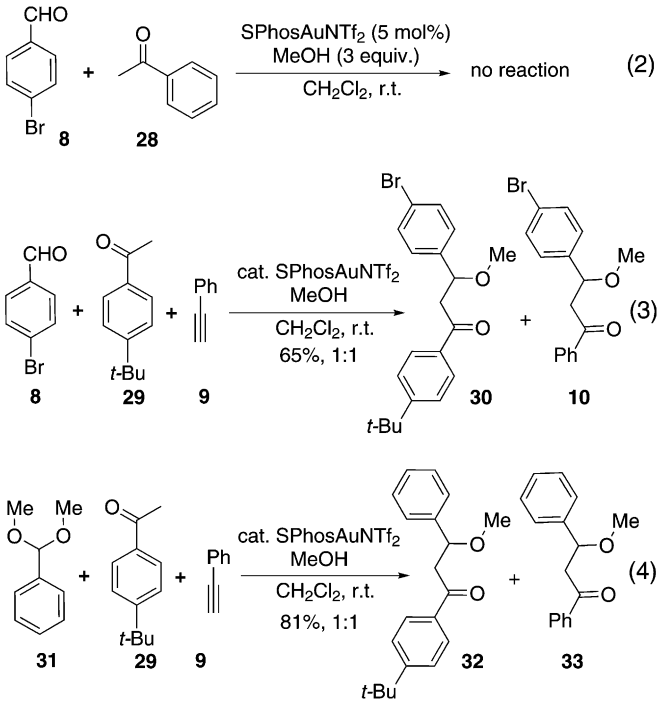
chlorophenylacetylene (**15**, **22**) and 1-ethynyl-4-fluorobenzene (**17**, **19**). Unfortunately, efforts to employ internal alkynes have thus far been unsuccessful. Interestingly, use of the alkyl-substituted alkyne 3-phenyl-1-propyne (**25**) as a coupling partner failed to generate the expected β-alkoxy ketone products. Instead, the reactions between 4-bromobenzaldehyde (**8**), **25**, and either methanol or (*S*)-2-methylbutan-1-ol led to the formation of α-phenyl-β-alkoxy ketones **26** and **27**, respectively [Eq. (1)].



(1)

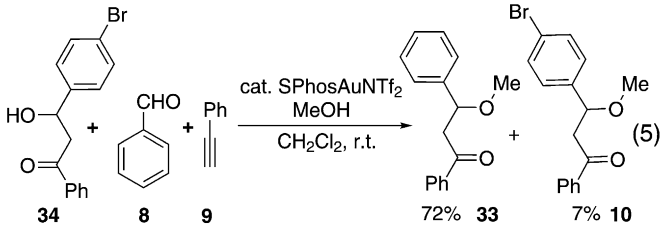
As described above in Scheme 1, we had initially envisioned a mechanism for β-alkoxy ketone formation that proceeds *via* intermolecular oxyauration of the alkyne with a hemiacetal followed by generation and intermolecular trapping of an oxocarbenium ion. However, the products formed in reactions of **25** led us to question this mechanism. In addition, since formation of acetals and aryl ketones was observed, we wondered if these species may in fact be the reactive participants that lead to the β-alkoxy ketone products.

As such, we conducted a series of control experiments to probe the possibility of product formation *via* Au(I)-catalyzed hydration of the alkyne followed by Au(I)-catalyzed reaction of the resulting aryl ketone with either the aldehyde or the corresponding acetal. As shown in Eq. (2), treatment of **8** and **28** with $SPhosAuNTf_2$ led to no reaction.[11] In contrast, a competition experiment in which 1.5 equiv. of **29** were added to a "standard" reaction of **8** and **9** led to the formation of a 1:1 mixture of **30** and **10** in 65% NMR yield [Eq. (3)]. In a similar manner, use of dimethyl acetal **31** in place of **8** also provided a 1:1 mixture of **32** and **33** in high yield [Eq. (4)]. Finally, the



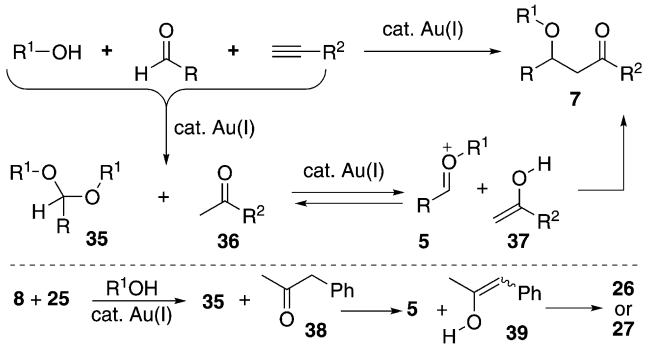
reaction of **8** and **9** was monitored by ^1H NMR spectroscopy. During the first hour of this experiment no formation of product **10** was observed. Instead, **8** was transformed to the corresponding dimethyl acetal and **9** was hydrolyzed to acetophenone (**28**), and after additional reaction time the formation of product **10** was then observed.[12]

To examine the possible intermediacy of β-hydroxy ketone **34**, which could be generated by Au(I)-catalyzed aldol reaction between **8** and **28**,[13] **34** was prepared by independent synthesis and added to the Au(I)-catalyzed reaction of **8** and **9**. This experiment provided predominantly **33**, with only a small amount of **10** observed [Eq. (5)]. Thus, the conversion of **34**



to **10** appears to be slow relative to the formation of **33** from the reaction between **8** and **9** (presumably by way of ketone **28**). This observation indicates that an Au(I)-catalyzed aldol reaction followed by substitution of methoxide for hydroxide is not the predominant pathway for product formation.[14]

Taken together, these experiments suggest the most plausible mechanism for our multicomponent coupling of alcohols, alkynes, and aldehydes involves relatively rapid Au(I)-catalyzed hydration[15,16] of the alkyne to **36** and conversion of aldehyde to acetal **35** (Scheme 2). The Au(I)-catalyzed ionization of acetal



Scheme 2. Mechanism for β-alkoxy ketone formation.

35 would then provide oxocarbenium ion **5**, which is then captured by the enol tautomer (**37**) of ketone **36**.[17] This mechanism also accounts for the formation of **26** or **27** in reactions of **25**. The Au(I)-catalyzed hydrolysis of **25** would afford unsymmetrical ketone **38**, which would be in equilibrium with its most stable internal alkene enol tautomer **39**. Nucleophilic addition of **39** to **5** would then afford the α-phenyl-β-alkoxy ketone products **26** and **27**.

In conclusion, we have developed a new Au(I)-catalyzed multicomponent coupling of an alkyne, an aldehyde, and an alcohol to generate a β-alkoxy ketone product. These Au(I)-catalyzed transformations provide a new method for the construction of β-alkoxy ketones, from readily available precursors. In addition, this approach alleviates the need to use preformed acetals as the electrophilic component in Au(I)-catalyzed aldol-type reactions of alkynes. Further studies on expanding the scope of this method are currently underway.

Experimental Section

General Procedure for the Au(I)-Catalyzed Coupling of Alkynes, Aldehydes, and Alcohols

An oven-dried test tube was equipped with a magnetic stir bar and cooled under a stream of N_2 before being charged with $SPhosAuNTf_2$ (5 mol%). The tube was then charged with a 0.1 M CH_2Cl_2 solution of aldehyde (1 equiv.), alkyne (1.5 equiv.) and alcohol (3 equiv.) before being sealed with a septum. The resulting mixture was stirred at room temperature and monitored by TLC analysis. After the starting material had been consumed, the mixture was concentrated under vacuum and purified by flash chromatography on silica gel using hexanes/ethyl acetate as the eluent.

Acknowledgements

The authors thank the NSF (CHE-1111218) for financial support of this work. Additional support was provided by Amgen and GlaxoSmithKline.

References

[1] a) A. Phrutivorapongkul, V. Lipipun, N. Ruangrungsi, K. Kirtikara, K. Nishikawa, S. Maruyama, T. Watanabe, T. Ishikawa, *Chem. Pharm. Bull.* **2003**, *51*, 187; b) T. Tanaka, M. Iinuma, K. Yuki, Y. Fujii, M. Mizuno, *Phytochemistry* **1992**, *31*, 993.

[2] M. M. Faul, B. E. Huff, *Chem. Rev.* **2000**, *100*, 2407.

[3] For recent reviews on Au-catalyzed reactions, see: a) A. S. K. Hashmi, *Chem. Rev.* **2007**, *107*, 3180; b) D. J. Gorin, F. D. Toste, *Nature* **2007**, *446*, 395; c) Z. G. Li, C. Brouwer, C. He, *Chem. Rev.* **2008**, *108*, 3239; d) A. Corma, A. Leyva-Perez, M. J. Sabater, *Chem. Rev.* **2011**, *111*, 1657.

[4] For other recent approaches to the synthesis of β-alkoxy ketones involving transition metal catalysis or organocatalysis, see: a) D. B. Ramachary, R. Mondal, *Tetrahedron Lett.* **2006**, *47*, 7689; b) E. M. Phillips, M. Riedrich, K. A. Scheidt, *J. Am. Chem. Soc.* **2010**, *132*, 13179; c) D. Yang, J. Huang, B. Liu, *Eur. J. Org. Chem.* **2010**, 4185; d) G. T. Hoang, V. J. Reddy, H. H. K. Nguyen, C. J. Douglas, *Angew. Chem.* **2011**, *123*, 1922; *Angew. Chem. Int. Ed.* **2011**, *50*, 1882.

[5] a) G. Zhang, L. Zhang, *J. Am. Chem. Soc.* **2008**, *130*, 12598; b) L. Liu, L. Zhang *Angew. Chem.* **2012**, *124*,

7413; *Angew. Chem. Int. Ed.* **2012**, *51*, 7301; c) C. Kim, H. J. Bae, J. H. Lee, W. Jeong, H. Kim, V. Sampath, Y. H. Rhee, *J. Am. Chem. Soc.* **2009**, *131*, 14660; d) H. Kim, Y. H. Rhee, *J. Am. Chem. Soc.* **2012**, *134*, 4011; e) H. J. Bae, W. Jeong, J. H. Lee, Y. H. Rhee, *Chem. Eur. J.* **2011**, *17*, 1433; f) E. M. L. Sze, W. Rao, M. J. Koh, P. W. H. Chan, *Chem. Eur. J.* **2011**, *17*, 1437; g) B. Alcaide, P. Almendros, R. Carracscosa, M. R. Torres, *Adv. Synth. Catal.* **2010**, *352*, 1277.

[6] For a related synthesis of β-alkoxy ketones *via* Au-catalyzed reactions of acetals with alkynes, which was published during the course of these studies, see: M. Zhang, Y. Wang, Y. Yang, X. Hu, *Adv. Synth. Catal.* **2012**, *354*, 981–985.

[7] a) E. Mizushima, K. Sato, T. Hayashi, M. Tanaka, *Angew. Chem.* **2002**, *114*, 4745; *Angew. Chem. Int. Ed. Engl.* **2002**, *41*, 4563; b) P. Roembke, H. Schmidbaur, S. Cronje, H. Raubenheimer, *J. Mol. Catal. A.* **2004**, *212*, 35; c) S. Sanz, L. A. Jones, F. Mohr, M. Laguna, *Organometallics* **2007**, *26*, 952.

[8] a) N. Mezailles, L. Ricard, F. Gagosz, *Org. Lett.* **2005**, *7*, 4133; b) L. Ricard, F. Gagosz, *Organometallics* **2007**, *26*, 4704.

[9] The reactions described in this paper do not appear to be air-sensitive, and use of rigorously anhydrous conditions is not required. All alcohols and alkynes were used as obtained from commercial sources, without drying, distillation, or purification by other means.

[10] W. Wang, G. B. Hammond, B. Xu, *J. Am. Chem. Soc.* **2012**, *134*, 5697.

[11] Addition of 10 mol% **9** to this reaction mixture also led to no observed reactivity.

[12] At no time was the formation of the corresponding β-hydroxy ketone product **34** observed.

[13] For a recent review on Au-catalyzed aldol reactions, see: A. Yanagisawa, in: *Modern Aldol Reactions,* Vol. 2, (Ed.: R. Mahrwald), Wiley-VCH, Weinheim, Germany, **2004**, pp 1–23.

[14] Treatment of **34** with SPhosAuNTf$_2$, phenylacetylene, and MeOH in CH_2Cl_2 for 16 h led to *ca.* 45% conversion to **10**, whereas the catalytic reaction between **8** and **9** to yield **10** was complete in 8 h.

[15] A. Levya, A. Corma, *J. Org. Chem.* **2009**, *74*, 2067–2074.

[16] We cannot rule out the possibility that the nucleophilic species in these reactions are enol ethers (derived from hydroalkoxylation of the alkyne) rather than enols. However, we have not directly observed the formation of these species.

[17] The lack of reactivity in the absence of the alkyne [Eq (2)] suggests that the alkyne may serve as a ligand for Au during one or more of the steps in this process. It is unclear why addition of 10 mol% alkyne failed to facilitate the Au-catalyzed reaction of **8** with **28**. However, it is possible that at this low alkyne concentration the binding of alcohol or aldehyde to the Au-complex outcompetes alkyne coordination (which is consistent with the observed poor reactivity when 10 equiv. of alcohol were employed in catalytic reactions). Under conditions of the catalytic reaction between **8** and **9** both the aldehyde and alcohol are consumed as the acetal intermediate is generated, which may minimize catalyst inhibition through this pathway.

