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Developing Pd(II) Catalyzed Double sp^3 C−H Alkoxylation for Synthesis of Symmetric and Unsymmetric Acetals

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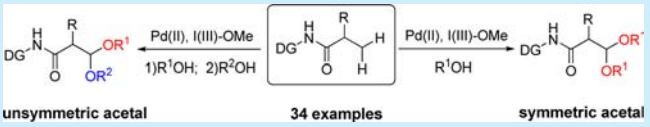
Supporting Information

ABSTRACT: An effective Pd(II) catalyzed double unactivated C(sp^3)−H alkoxylation has been developed to prepare both symmetric and unsymmetric acetals. This new reaction demonstrates good functional group tolerance, excellent reactivity, and high yields. A variety of novel acetals can be readily accessed via this new method.



Acetals are an important class of chemicals, which not only can be employed as protecting groups for carbonyl groups in organic synthesis,[1] but also serve as essential skeleton motifs in natural products such as saccharides, marasmene, xylomollin, sarracenin, etc. Traditional approaches to prepare acetals usually involve acetalization of aldehydes with alcohols[2] or diols,[3] transacetalization[4] or crossacetalization, or synthesis from vinyl and allyl ethers.[5] These methods either rely on the availability of aldehyde or need tedious steps to access desired products (Figure 1). Although a number of new protocols have been developed in recent years,[6] new methods for acetal synthesis are still in great demand. We are particularly interested in the development of an alternative approach toward acetal synthesis via transition-metal catalysis, which can serve as a practical and complementary protocol to prevalent strategies. Direct transformation of realily available alkanes into valuable complex acetals via transition-metal-catalyzed unactivated methyl and methylene C(sp^3)−H activation is arguably a highly atom-economic and efficient strategy toward these compounds.[7,8]

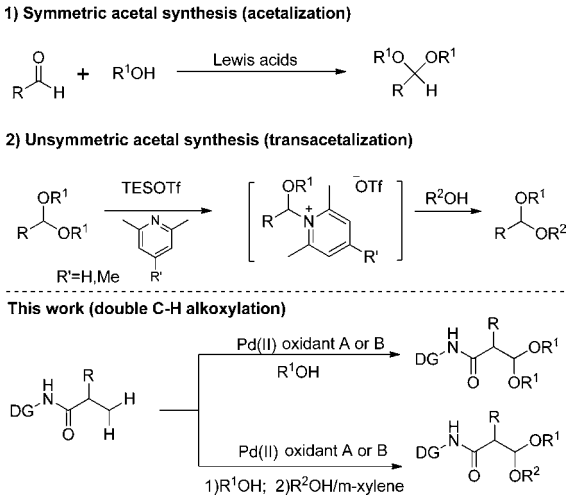


Figure 1. General synthetic approaches toward acetals.

Recently we developed a C(sp^3)−H alkoxylation of unactivated methylene via Pd(II) catalysis to prepare alkyl ethers.[9a] In our group's continued studies of the preparation of a functionalized alkane through transtion-metal catalysis, we envisioned that certain fine-tuned oxidative conditions with a proper combination of varied alcohols may promote a sequential dual Pd(II)-catalyzed C(sp^3)−H bond alkoxylation with different alcohol partners to afford corresponding acetal products. Herein, we report the first example of the synthesis of both symmetrical and unsymmetrical acetals via palladium catalyzed double sp^3 C−H alkoxylation (Figure 1).

To test our hypothesis, a model investigation was initiated with a 2,3-dimethylbutanamide derivative **1**, which contained the 8-aminoquinoline-derived auxiliary (Q)[10] as a directing group for the activation of C(sp^3)−H bonds. At the beginning of our studies, a variety of hypervalent iodine oxidants, such as PhI(OAc)$_2$, PhI(TFA)$_2$, DMP, I-OMe, I-OAc, NaIO$_4$, NaIO$_3$, etc., were examined in the presence of Pd(OAc)$_2$ in methanol (Table 1). Among them, only cyclic hypervalent iodine oxidants, such as 1-methoxy-1,2-benziodoxole-3(1*H*)-one (**A**), can provide desired product dimethoxy acetal **2** in a small amount at 80 °C (entry 2), and the major product is the monoalkoxylation product (the ratio of the monoalkoxylation to the dialkoxylation was about 2 to 1). Pleasingly, the following investigations discovered that a proper combination of temperature and the amount of oxidant could result in a significant improvement in yields. For example, we found that the elevated tempearture (such as 100 °C) and 3.50 equiv of oxidants can provide product in 54% yield (entry 3). Further optimization revealed that a cosolvent system (methanol/*m*-xylene 1:1) is superior to methanol in terms of efficiency. A variety of additives including ligands and inorganic salts were also examined. Among them, the addition of 1 equiv of Ag$_2$CO$_3$

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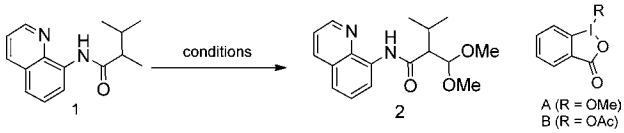
Table 1. Optimization of Reaction Conditions



entry	catalyst[a]	oxidant[b]	additive[c]	conditions	yield[d]
1	$Pd(OAc)_2$	$PhI(OAc)_2$		MeOH, 80 °C, 9 h	NR
2	$Pd(OAc)_2$	**A**[e]		MeOH, 80 °C, 9 h	27
3	$Pd(OAc)_2$	**A**		MeOH, 100 °C, 9 h	54
4	$Pd(OAc)_2$	**B**[f]		MeOH, 100 °C, 9 h	53
5	none[g]	**A**		MeOH, 100 °C, 9 h	NR
6	$Pd(OAc)_2$	DMP[h]		MeOH, 100 °C, 9 h	52
7	$Pd(OAc)_2$	**A**		MeOH, 130 °C, 9 h	43
8	$PdCl_2$	**A**		MeOH, 130 °C, 9 h	38
9	$PdCl_2(PPh_3)_2$	**A**		MeOH, 130 °C, 9 h	40
10	$Pd(OAc)_2$	**A**	AgOAc	MeOH, 130 °C, 9 h	38
11	$Pd(OAc)_2$	**A**	Na_2CO_3	MeOH, 130 °C, 9 h	10
12	$Pd(OAc)_2$[i]	**A**	Ag_2CO_3	MeOH, 80 °C, 3 h, 120 °C, 3 h	75 (65)[j]
13	$Pd(OAc)_2$	**A**	Ag_2CO_3	MeOH/*m*-xylene (1:1), 80 °C, 3 h, 120 °C, 3 h	64

[a]10 mol % catalyst. [b]3.5 equiv. [c]1.0 equiv. [d]Yield of conversion ratio. [e]**A**: 1-methoxy-1,2-benziodoxole-3(1*H*)-one. [f]**B**: 1-acetoxy-1,2-benziodoxole-3(1*H*)-one. [g]No $Pd(OAc)_2$. [h]DMP = Dess-Martin periodinane. [i]15 mol % catalyst. [j]Isolated yield.

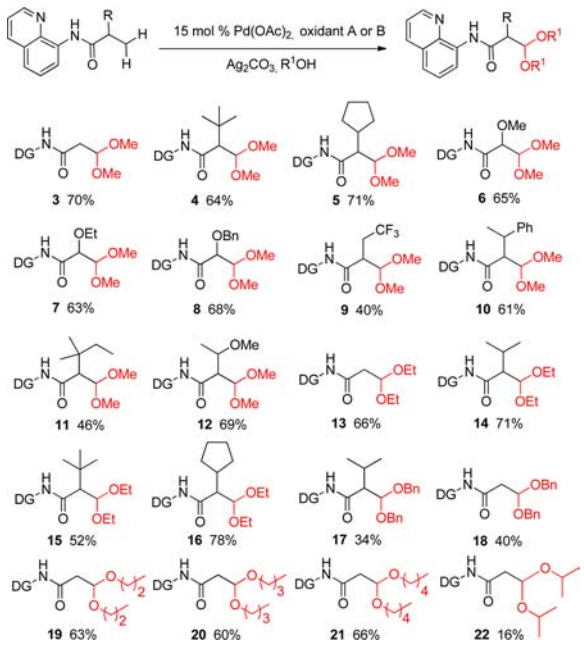


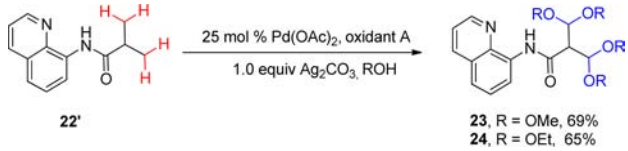
Figure 2. Synthesis of symmetrical acetals. Reaction conditions: 1.0 equiv of substrate, 15 mol % $Pd(OAc)_2$, 3.5−4.0 equiv of oxidant **A** or **B**, 1.0 equiv of Ag_2CO_3, R^1OH; temperature depends on different substrates. See Supporting Information for details.

was found to be able to improve the reaction (entry 12). Some other Pd(II) catalysts were tested in the reaction as well, such as $PdCl_2$, $PdCl_2(PPh_3)_2$, and $Pd(acac)_2$, which could give similar results as $Pd(OAc)_2$. In constrast, Ru(II) and Rh(II) catalysts cannot promote the reaction under the same conditions. A control reaction showed that omission of the palladium catalyst would result in a complete reaction failure (entry 5). In general, 0.125 equiv of $Pd(OAc)_2$ was enough to efficiently catalyze the reaction. Typically the reaction can proceed to completion within 6 h with 3.5 equiv of cyclic hypervalent iodine oxidant **A** at 120 °C.[11]

Having identified the optimal conditions, we next set out to explore the scope for this new double C(sp^3)−H alkoxylation reaction. As displayed in Figure 2, a variety of carboxylic acid derivatives were smoothly transformed into the corresponding acetal products in moderate to good yields (**3**−**22**). The scope of the substituents was found to be very broad. The alkyl, alkoxyl, and aryl groups, as well as the electron-withdrawing and -donating functional groups were well tolerated. For example, when substrates containing easily oxidizable α-protons were examined, it was discovered that these molecules can be efficiently transformed into acetal products (**7**−**9**) with remarkable chemoselectivity. Compounds having sterically hindered substituents, such as *tert*-butyl, cyclopentyl, isopropyl, etc., can be converted into products (**4**, **5**, **10**, **11**, **14**) as well with high efficiency. To our delight, not only methanol but also other alcohols such as ethanol, *n*-propanol, *n*-butanol, 1-pentanol, and phenylmethanol can be effectively employed to give corresponding acetal products (**13**, **14**, **18**, **19**−**21**). Interestingly, sterically hindered isopropanol can be directly used to furnish a diisopropoxyl acetal derivative **22**, albeit in a low yield.

To further explore the effectiveness of this protocol, an isobutyric acid substrate was tested (Scheme 1). Gratifyingly,

Scheme 1. Tetra C(sp^3)−H Alkoxylation for Synthesis of Symmetrical Acetals



we found that both methyl groups of compound **22′** can undergo dual C(sp^3)−H alkoxylation to give the symmetric diacetals **23** and **24** in good yields under optimal conditions. It is remarkable because four C(sp^3)−H bonds can be simultaneously transformed into alkoxyl groups in a one-step reaction.

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To expand the scope of this new reaction, next, we examined the efficiency of our method in the synthesis of unsymmetric acetals. However, directly applying previous optimum condtions was not successful. It was found that two different alcohols that were premixed would always give the symmetric acetal of the more reactive alcohol, but not the desired unsymmetric acetal, as the major product. After further condition optimization, a modified protocol was established. Instead of using a premixture of two alcohol substrates as in in the previous operation, the second alcohol will be charged to the reaction after a certain period of time in the new procedure. For instance, the first monoalkoxylation with R^1OH can be completed at 80 °C within 2−6 h. Then, after removal of R^1OH, R^2OH and the oxidant will be added. The following alkoxylation will be conducted at 120 °C for 2−6 h to give products (for more details, please see Supporting Information). As demonstrated in Figure 3, delightfully, the optimized

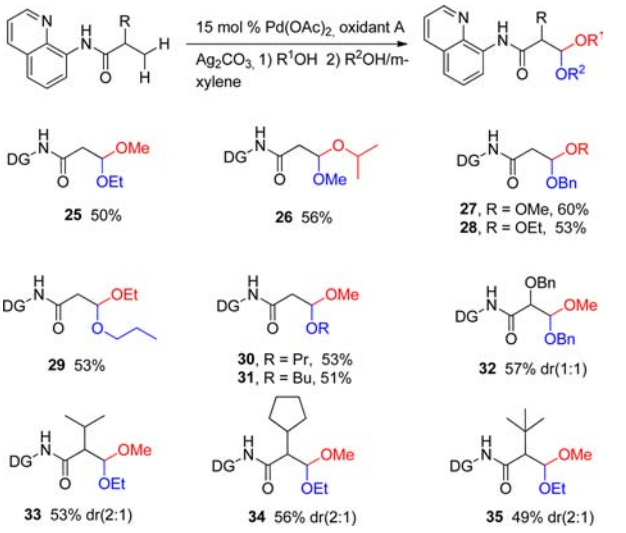
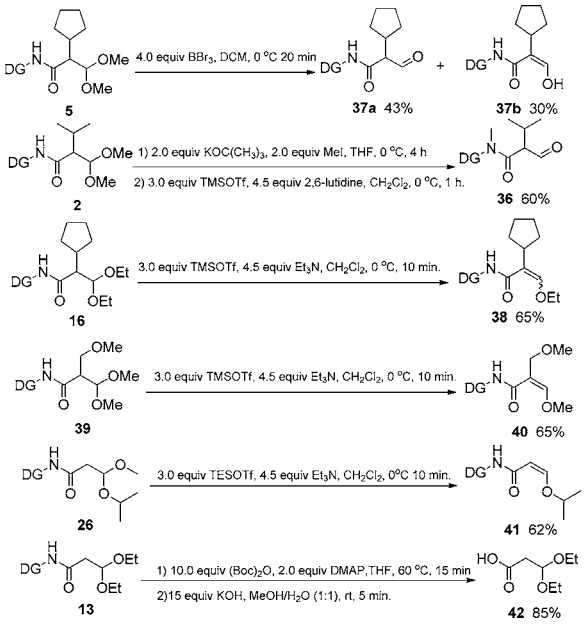


Figure 3. Synthesis of unsymmetric acetals. Reaction conditions: substrate (1.0 equiv), oxidant (**A** or **B**) (1.5−2.0 equiv), $Pd(OAc)_2$ (0.075 equiv), Ag_2CO_3 (0.5 equiv), R^1OH (2 mL), 70 to 80 °C for 2−6 h. Then R^1OH was replaced by 2 mL of R^2OH/*m*-xylene (1:1), oxidant (**A** or **B**) (2.0−2.5 equiv), $Pd(OAc)_2$ (0.075 equiv), Ag_2CO_3 (0.5 equiv), 120−130 °C for 2−6 h. See Supporting Information for details.

conditions were found to be effective to provide unsymmetric acetals (**25**−**35**) with varied alcohols in satisfactory yields. For instance, methanol can be combined with ethanol, isopropanol, and phenylmethanol to give products **25**, **26**, and **27** respectively. Unsymmetric acetal derivatives **28**, **29** can be readily obtained with ethanol and propanol or phenylmethanol as well. In the case of substrates containing chiral centers, two diastereoisomers with varied ratios can be observed (**32**−**35**). It is noteworthy to point out that these unsymmetric acetals either are difficult or need extra and tedious steps to prepare via traditional synthetic strategies.

Additionally, the synthetic utility of this new reaction was exemplified by further chemical transformation/manipulations (Scheme 2). We were pleased to find that the acetals **16**, **26**, and **39** can be smoothly converted into vinyl ethers **38**, **40**, and **41**. The acetals **2** and **5** can be hydrolyzed to provide corresponding aldehyde products **36** and **37**. Meanwhile, a sequential two-step deprotection procedure can readily cleave the 8-aminoquinoline-derived auxiliary (Q) from **13** to obtain

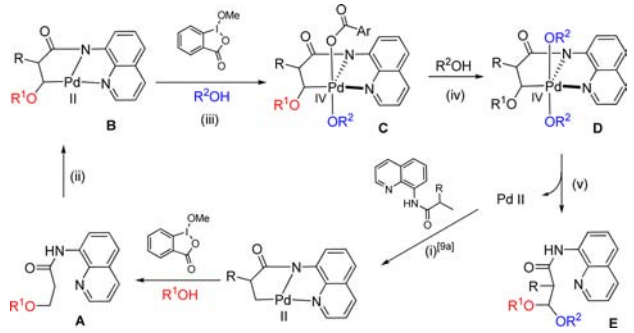
Scheme 2. Synthetic Applications and Removal of Directing Group



acetal product **42** containing a free carboxylic acid in a good yield of 85%.

Although the mechanism details remain to be ascertained, a possible mechanism for this reaction can be depicted (Scheme 3). The first $C(sp^3)$−H alkoxylation of the substrate will afford

Scheme 3. Plausible Mechanism



an ether intermediate **A**, which undergoes the following chelate-directed $C(sp^3)$−H activation to give a five-membered cyclopalladium(II) intermediate **B**. In the third step, Pd(II) was oxidized into plausible Pd(IV) intermediate[12] **C** by cyclic hypervalent iodine oxidants. In the presence of alcohols, the $ArCO_2$ ligands of **C** could be displaced by R^2OH to form Pd(IV) intermediate **D**. The final step involves C−O bond-forming reductive elimination to afford acetal products **E** which turned Pd(IV) back into Pd(II).

In conclusion, we have developed an efficient protocol to access both symmetric and unsymmetric acetals through Pd(II) catalyzed sequential double C−H alkoxylation of unactivated methyl $C(sp^3)$−H bonds.[13] This new reaction demonstrates good functional group tolerance, excellent reactivity, and high yields. A variety of acetals can be readily prepared via this method. It was found that both oxidants and Ag_2CO_3 serve as critical factors for this one-step dual C−H activation reaction.

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Further studies into the synthetic application of this reaction are in progress in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(13) The submission of the purified symmetrical acetals (Figure 2) to conditions described for the formation of unsymmetrical acetals only results in a small amount of unsymmetrical acetals (for more details, please see SI). This observation supports our proposed mechanism that the reaction does favor a sequential double C−H alkoxylation procedure, but not another pathway such as potential acetal exchange.