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O-Substituted Alkyl Aldehydes for Rhodium-Catalyzed Intermolecular Alkyne Hydroacylation: The Utility of Methylthiomethyl Ethers

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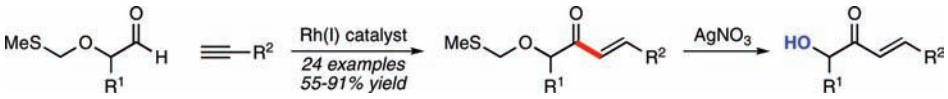
ABSTRACT



Combining α-methylthiomethyl (MTM) ether substituted aldehydes and 1-alkynes in the presence of [Rh(dppe)]ClO_4 results in efficient intermolecular alkyne hydroacylation to deliver α-O-MTM-substituted enone products. The product MTM ethers can be converted to the free hydroxyl group either in situ, by the addition of water to the completed reaction, or in a separate operation, by the action of silver nitrate.

The transition-metal-catalyzed addition of aldehydes across alkenes or alkynes—alkene and alkyne hydroacylation, respectively—are effective processes for the atom economic preparation of ketone containing molecules.[1] Intermolecular versions of these reactions are often plagued by competing decarbonylation processes. Despite significant recent advances, in particular from the groups of Brookhart[2] and Krische,[3] a general intermolecular reaction has yet to be described.[4] One approach to achieve efficient intermolecular reactions has been to stabilize the key acyl-metal intermediates through chelation control. For example, the temporary formation of picolylimines[5] and the use of salicylaldehydes[6] or acrylamides[7] have all delivered effective reactions.[8] Our laboratory has investigated the use of alkyl aldehydes in intermolecular hydroacylation chemistry, and we have found that *β*-*S*-substituted aldehydes work well in rhodium-catalyzed alkene and alkyne hydroacylation reactions.[9] Although chelation control has provided a number of very useful solutions for hydroacylation chemistry, the strategy has an inherent limitation in that the chelating group present in the starting materials will also be present in the products. The *β*-*S*-substituted ketone products, generated from the corresponding *β*-*S*-substituted aldehyde substrates, offer a number of opportunities for derivatization of the *S*-based functional group.[10] However, if the focus is to employ a chelating group more likely to be required in the final product, then *O*-based functionality becomes appealing

(1) (a) Willis, M. C. *Chem. Rev.* **2010**, *110*, 725. (b) Jun, C.-H.; Jo, E.-A.; Park, J.-W. *Eur. J. Org. Chem.* **2007**, 1869.

(2) (a) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965. (b) Roy, A. H.; Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 2082.

(3) (a) Shibahara, F.; Bower, J. F.; Krische, M. J. *J. Am. Chem. Soc.* **2008**, *130*, 14120. (b) Williams, V. M.; Leung, J. C.; Patman, R. L.; Krische, M. J. *Tetrahedron* **2009**, *65*, 5024.

(4) Other nonchelating examples: (a) Schwartz, J.; Cannon, J. B. *J. Am. Chem. Soc.* **1974**, *96*, 4721. (b) Vora, K. P.; Lochow, C. F.; Miller, R. G. *J. Organomet. Chem.* **1980**, *192*, 257. (c) Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451. (d) Kondo, T.; Tsuji, Y.; Watanabe, Y. *Tetrahedron Lett.* **1987**, *28*, 6229. (e) Omura, S.; Fukuyama, T.; Horiguchi, J.; Murakami, Y.; Ryu, I. *J. Am. Chem. Soc.* **2008**, *130*, 14094.

(5) (a) Jun, C.-H.; Lee, D.-Y.; Lee, H.; Hong, J.-B. *Angew. Chem., Int. Ed.* **2000**, *39*, 3070. (b) Park, Y. J.; Park, J.-W.; Jun, C.-H. *Acc. Chem. Res.* **2008**, *41*, 222.

(6) (a) Kokubo, K.; Matsumasa, K.; Nishinaka, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 303. (b) Imai, M.; Tanaka, M.; Tanaka, K.; Yamamoto, Y.; Imai-Ogata, N.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem.* **2004**, *69*, 1144. (c) Tanaka, T.; Tanaka, M.; Suemune, H. *Tetrahedron Lett.* **2005**, *46*, 6053. (d) Stemmler, R. T.; Bolm, C. *Adv. Synth. Catal.* **2007**, *349*, 1185. (f) Coulter, M. M.; Kou, K. G. M.; Galligan, B.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16330. (g) Phan, D. H. T.; Kou, K. G. M.; Dong, V. M. *J. Am. Chem. Soc.* **2010**, *132*, 16354.

(7) (a) Tanaka, K.; Shibata, Y.; Suda, T.; Hagiwara, Y.; Hirano, M. *Org. Lett.* **2007**, *9*, 1215. (b) Shibata, Y.; Tanaka, K. *J. Am. Chem. Soc.* **2009**, *131*, 12552.

(8) (a) Suggs, J. W. *J. Am. Chem. Soc.* **1978**, *100*, 640.

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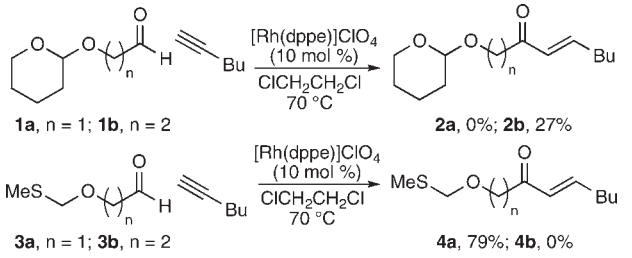
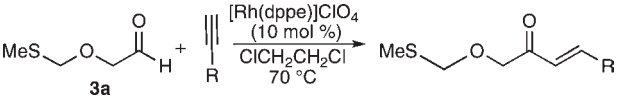
and should allow ready access to hydroxyl- and carbonyl-based functional groups. Although salicylaldehydes (and derivatives) have been employed successfully as hydroacylation substrates,[6,11] there are no examples of *O*-substituted alkyl aldehydes being used in these reactions.

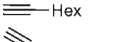
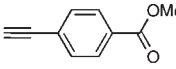
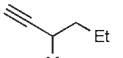
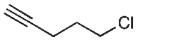
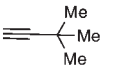
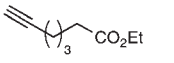
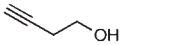
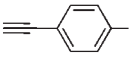
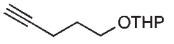
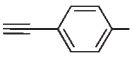
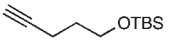
Scheme 1. *O*,*O*- and *O*,*S*-Acetals in Alkyne Hydroacylation



As we had previously shown that a simple β-methyl ether substituted aldehyde was a poor substrate in Rh-catalyzed intermolecular hydroacylation reactions,[9a] we were interested in evaluating alternative *O*-substituents. In particular, we speculated that the extra oxygen atom of an acetal or ketal group might be beneficial for reactivity. Accordingly, α- and β-*O*-THP-substituted aldehydes **1a** and **1b** were evaluated in intermolecular hydroacylation reactions with hexyne using a dppe-derived Rh-catalyst (Scheme 1).[12] Although β-substituted aldehyde **1b** provided a modest amount of the hydroacylation adduct we were unable to further optimize the reaction. Given our previous success with *S*-chelating aldehydes we reasoned that *O*-methylthiomethyl (MTM) ethers **3a** and **3b**, featuring *O*,*S*-acetal groups, would offer advantages over the simple *O*,*O*-acetals. Pleasingly, the reaction between α-*O*-MTM aldehyde **3a** and hexyne delivered the hydroacylation adduct in good yield after a 2 h reaction.

Table 1. Scope of Alkyne Variation using Aldehyde **3a**[a]



entry	alkyne	yield (%)[b]	entry	alkyne	yield (%)[b]
1		69	8		80
2		89	9		79
3		71	10		65
4		76	11		72
5		91	12		71
6		86	13		80
7		83	14		80

[a] Reaction conditions: aldehyde **3a** (1.0 equiv), alkyne (2.0 equiv), [Rh(dppe)]ClO_4 (10 mol %), $ClCH_2CH_2Cl$, 70 °C. Catalyst generated in situ from [Rh(dppe)(nbd)]ClO_4 and H_2. [b] Isolated yields.

α-*O*-MTM aldehyde **3a** could be combined with a broad range of terminal alkynes (Table 1): simple and branched alkyl (entries 1−4), as well as electronically varied aryl alkynes (entries 5−8), all provided the expected enone products in high yields. A variety of functional groups were also tolerated, including trimethylsilyl, chloro, ester, and free- and protected-hydroxyl groups (entries 9−14). Although 10 mol % of catalyst was routinely employed in these reactions, lower loadings were also possible; for example, repetition of entry 5 employing 5 mol % catalyst resulted in a 90% yield after a 2 h reaction. However, performing the same transformation with 2.5 mol % of catalyst delivered only 53% product after 24 h. In all cases, single regio- and geometrical isomers were isolated. Unfortunately, internal alkynes were unreactive under these conditions.

Variation of the aldehyde to include either a methyl or phenyl α-substituent was also possible. Table 2 documents the reactions of aldehydes **3c** and **3d** with a number of representative alkynes. In all cases good yields of the hydroacylation products were returned.

One of the motivations for exploring the use of alkyl *O*-substituted chelating aldehydes was the desire to access the corresponding alcohols. Although a number of MTM ether cleavage conditions have been described,[13] we established that treatment of MTM ether **7** with $AgNO_3$, while excluding light,[14] effected smooth deprotection (Scheme 2). Alternatively, we found that simply introducing a small amount of water (0.1 mL to a 2.0 mL reaction) into the reaction flask when the hydroacylation reaction had

(9) (a) Willis, M. C.; McNally, J. S.; Beswick, P. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 340. (b) Willis, M. C.; Randell-Sly, H. E.; Woodward, R. L.; Currie, G. S. *Org. Lett.* **2005**, *7*, 2249. (c) Willis, M. C.; Woodward, R. L. *J. Am. Chem. Soc.* **2005**, *127*, 18012. (d) Willis, M. C.; Randell-Sly, H. E.; Woodward, R. L.; McNally, S. J.; Currie, G. S. *J. Org. Chem.* **2006**, *71*, 5291. (e) Moxham, G. L.; Randell-Sly, H. E.; Brayshaw, S. K.; Woodward, R. L.; Weller, A. S.; Willis, M. C. *Angew. Chem., Int. Ed.* **2006**, *45*, 7618. (f) Moxham, G. L.; Randell-Sly, H. E.; Brayshaw, S. K.; Weller, A. S.; Willis, M. C. *Chem.—Eur. J.* **2008**, *14*, 8383. (g) Osborne, J. D.; Willis, M. C. *Chem. Commun.* **2008**, 5025. (h) Osborne, J. D.; Randell-Sly, H. E.; Currie, G. S.; Cowley, A. R.; Willis, M. C. *J. Am. Chem. Soc.* **2008**, *130*, 17232. (i) Randell-Sly, H. E.; Osborne, J. D.; Woodward, R. L.; Currie, G. S.; Willis, M. C. *Tetrahedron* **2009**, *65*, 5110. (j) Pawley, R. J.; Moxham, G. L.; Dallanegra, R.; Chaplin, A. B.; Brayshaw, S. K.; Weller, A. S.; Willis, M. C. *Organometallics* **2010**, *29*, 1717. (k) González-Rodríguez, C.; Parsons, S. R.; Thompson, A. L.; Willis, M. C. *Chem.—Eur. J.* **2010**, *16*, 10950. For an example of *S*-chelation used in an intramolecular reaction, see: (e) Bendorf, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matukonis, A. N.; Musselman, J. D.; Tiley, T. A. *Tetrahedron Lett.* **2002**, *43*, 7031.

(10) For example, β-thioethers can be eliminated to generate enones, while thioacetals can either be hydrolysed to the corresponding carbonyl, or reduced to deliver a methylene unit (see ref 9d).

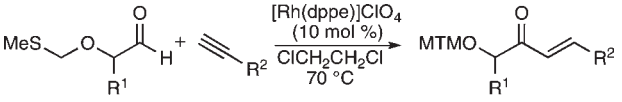
(11) For examples of salicylaldehydes used in intramolecular hydroacylation reactions, see: Coulter, M. M.; Dornan, P. K.; Dong, V. M. *J. Am. Chem. Soc.* **2009**, *131*, 6932.

(12) A dppe-derived catalyst was selected as being the most general from our own β-*S*-aldehyde examples (see refs 9).

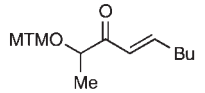
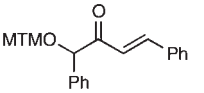
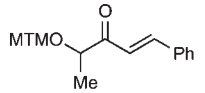
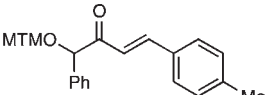
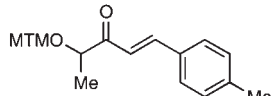
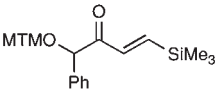
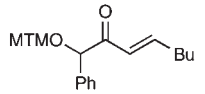
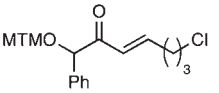
(13) Wuts, P. G. M.; Greene, T. W. *Greene's Protective Groups in Organic Synthesis*, 4th ed.; Wiley: NJ, 2007.

(14) Corey, E. J.; Bock, M. G. *Tetrahedron Lett.* **1975**, *16*, 3269.

Table 2. Me- and Ph-Substituted Aldehydes **3c** and **3d** in Intermolecular Alkyne Hydroacylation Reactions[a]



3c, R^1 = Me; **3d**, R^1 = Ph **5**

entry	product	entry	product
1	 **5a**, 82%	5	 **5e**, 78%
2	 **5b**, 79%	6	 **5f**, 89%
3	 **5c**, 89%	7	 **5g**, 75%
4	 **5d**, 78%	8	 **5h**, 89%

[a] Reaction conditions: aldehyde (1.0 equiv), alkyne (2.0 equiv), [Rh(dppe)]ClO_4 (10 mol %), $ClCH_2CH_2Cl$, 70 °C. Catalyst generated in situ from [Rh(dppe)(nbd)]ClO_4 and H_2. Isolated yields.

reached completion allowed the hydroxy-enone product (**8**) to be isolated directly, albeit in a reduced yield.

Having established α-*O*-MTM aldehydes as viable substrates for intermolecular alkyne hydroacylation reactions we wanted to explore the origin of their favorable reactivity. With the *β*-*S*-aldehyde series we had been able to use X-ray diffraction studies to establish the formation of 5-membered *S*-chelated intermediates.[9e,f] Unfortunately, with the *O*-MTM aldehydes we were unable to isolate suitable crystalline material. We therefore resorted to studying the reactivity of a series of of aldehydes designed

Scheme 2. Deprotection of *O*-MTM-Hydroacylation Adducts

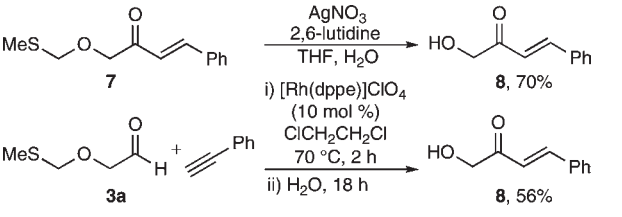
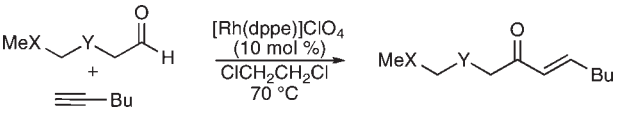
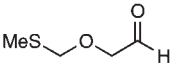
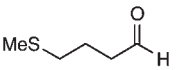
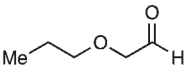
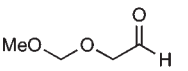


Table 3. Probing the Reactivity of *O*- and *S*-Substituted Aldehydes in Alkyne Hydroacylation Reactions[a]



entry	product	entry	product
1	 **3a**, 79%	3	 **3f**, 14%
2	 **3e**, 0%	4	 **3g**, 0%

[a] Reaction conditions: aldehyde (1.0 equiv), alkyne (2.0 equiv), [Rh(dppe)]ClO_4 (10 mol %), $ClCH_2CH_2Cl$, 70 °C. Catalyst generated in situ from [Rh(dppe)(nbd)]ClO_4 and H_2. Isolated yields.

to probe the importance of each heteroatom of the *O*-MTM functional group (Table 3). Reactions with aldehyde **3e**, corresponding to deletion of the MTM *S*-atom, did not deliver any hydroacylation products. The corresponding *O*-deleted aldehyde, **3f**, provided the enone in 14% yield. Finally, and as expected from the earlier experiments using the *O*-THP aldehydes, the *O*-MOM aldehyde, **3g**, was also ineffective. These data indicate that both the *S*- and *O*-atoms of the *O*-MTM group are needed for reactivity. The requirement for a free coordination site on the Rh-center to allow for alkyne binding suggests that *O*,*S*-bidentate coordination does not take place; one possible explanation is that the presence of the *O*-atom acts to make 6-membered *S*-chelation more favorable via an electronic bias for a gauche conformation.[15]

In conclusion, we have shown for the first time that *O*-substituted alkyl aldehydes can be employed in rhodium-catalyzed intermolecular alkyne hydroacylation reactions. α-*O*-MTM-substituted aldehydes are effective substrates in combination with a broad range of functionalized alkynes, delivering linear enone products with good selectivities and in high yields.

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Supporting Information Available. Experimental procedures and full characterization for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

(15) *The Anomeric Effect and Associated Stereoelectronic Effects*; Thatcher, G. R. J., Ed.; ACS Symposium Series; American Chemical Society: Washington, DC, 1993.