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Chelation-Controlled Intermolecular Alkene and Alkyne Hydroacylation: The Utility of β-Thioacetal Aldehydes

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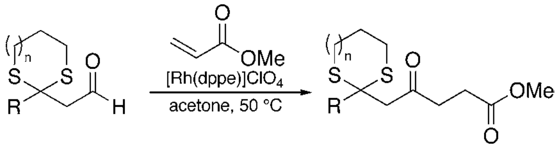
ABSTRACT



β-Thioacetal-substituted aldehydes, which are conveniently prepared from the corresponding ynals, can be combined with a range of alkynes or electron-poor alkenes to deliver intermolecular hydroacylation adducts. The reactions employ [Rh(dppe)]ClO$_4$ as a catalyst and are proposed to proceed via a chelated rhodium acyl intermediate. The thioacetal-containing products can be deprotected to the corresponding ketones or reduced to alkanes in good yields.

Transition metal-catalyzed hydroacylation reactions, in which an aldehyde is added across a C−C multiple bond, have the potential to be useful methods for the synthesis of ketone-containing products. Although intramolecular versions of the reaction have been employed successfully for the synthesis of a range of cyclopentanone systems,[1,2] the synthesis of larger ring systems[3] and intermolecular reactions remain significantly more challenging.[4] The main obstacle with these systems is the instability of the metal−acyl intermediates, which preferentially undergo decarbonylation processes. Stabilization of these intermediates by chelation has emerged as a potential solution;[5] in efforts to develop a synthetically useful chelation-controlled intermolecular hydroacylation system, we recently reported that β-methyl sulfide-substituted aldehydes were efficient substrates for combination with a range of electron-poor alkenes under the action of Rh(I) catalysis (Scheme 1).[6] Although the methyl sulfide group functions as a coordinating substituent, the opportunities for modification of the group after the hydroacylation reaction were relatively limited.[7] To expand the synthetic utility of

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(1) For an example of stoichiometric cyclopentanone synthesis, see: Sakai, K.; Ide, J.; Oda, O.; Nakamura, N. *Tetrahedron Lett.* **1972**, 1287−1290.

(2) For selected recent examples of catalytic cyclopentanone synthesis, see: (a) Gable, K. P.; Benz, G. A. *Tetrahedron Lett.* **1991**, *32*, 3473−3476. (b) Fairlie, D. P.; Bosnich, B. *Organometallics* **1988**, *7*, 936−945. (c) Sattelkau, T.; Eilbracht, P. *Tetrahedron Lett.* **1998**, *39*, 9647−9648. For examples of enantioselective cyclisations, see: (d) Ducray, P.; Rousseau, B.; Mioskowski, C. *J. Org. Chem.* **1999**, *64*, 3800−3801. (e) Bosnich, B. *Acc. Chem. Res.* **1998**, *31*, 667−674 and references therein. (f) Tanaka, M.; Imai, M.; Fujio, M.; Sakamoto, E.; Takahashi, M.; Eto-Kato, Y.; Wu, X. M.; Funakoshi, K.; Sakai, K.; Suemune, H. *J. Org. Chem.* **2000**, *65*, 5806−5816 and references therein.

(3) (a) Aloise, A. D.; Layton, M. E.; Shair, M. D. *J. Am. Chem. Soc.* **2000**, *122*, 12610−12611. (b) Sato, Y.; Oonishi, Y.; Mori, M. *Angew. Chem., Int. Ed.* **2002**, *41*, 1218−1221.

(4) For Rh-based systems used in combination with CO or ethylene atmopspheres, see: (a) Schwartz, J.; Cannon, J. B. *J. Am. Chem. Soc.* **1974**, *96*, 4721−4723. (b) Vora, K. P.; Lochow, C. F.; Miller, R. G. *J. Organomet. Chem.* **1980**, *192*, 257−264. (c) Isnard, P.; Denise, B.; Sneeden, R. P. A.; Cognio, J. M.; Dural, P. *J. Organomet. Chem.* **1982**, *240*, 285−288. (d) Vora, K. P. *Synth. Commun.* **1983**, *13*, 99−102. (e) Marder, T. B.; Roe, D. C.; Milstein, D. *Organometallics* **1988**, *7*, 1451−1453. For Ru-based systems, see: (f) Kondo, T.; Tsuji, Y.; Watanabe, Y. *Tetrahedron Lett.* **1987**, *28*, 6229−6230. (g) Kondo, T.; Akazome, M.; Tsuji, Y.; Watanabe, Y. *J. Org. Chem.* **1990**, *55*, 1286−1291. (h) Kondo, T.; Hiraishi, N.; Morisaki, Y.; Wada, K.; Watanabe, Y.; Mitsudo, T.-A. *Organometallics* **1998**, *17*, 2131−2134. For a Co-based method, see: (i) Lenges, C. P.; Brookhart, M. *J. Am. Chem. Soc.* **1997**, *119*, 3165−3166. (j) Lenges, C. P.; White, P. S.; Brookhart, M. *J. Am. Chem. Soc.* **1998**, *120*, 6965−6979. Also see ref 4a.

10.1021/ol050638l CCC: $30.25

Scheme 1. *S*-Chelate-Controlled Alkene Hydoacylation

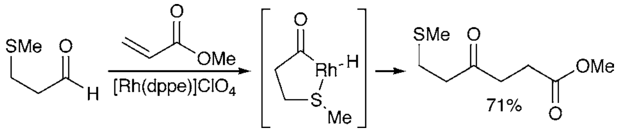
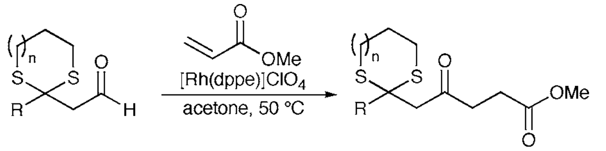
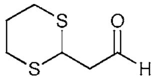
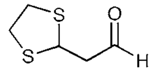
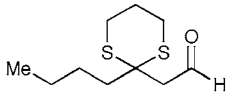
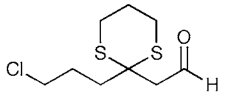
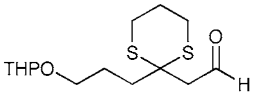
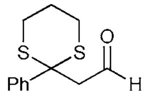
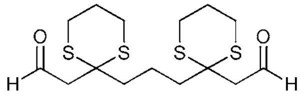


Table 1. Intermolecular Hydroacylation: Scope of the Thioacetal-Substituted Aldehyde[a,b]



Entry	Aldehyde	Time (h)	Yield[c,d] (%)
1		2	74
2		4	71
3		18	77
4		18	72
5		18	70
6		18	0
7		8	84

[a] Reaction conditions: aldehyde (1.0 equiv), methyl acrylate (5.0 equiv), [Rh(dppe)]ClO$_4$ (10 mol %), acetone, 50 °C. [b] Catalyst generated in situ from [Rh(dppe)(nbd)]ClO$_4$ and H$_2$. [c] Isolated yields. [d] Only linear isomers observed.

the process, we wished to design a series of aldehyde substrates that maintained the same stabilizing five-membered *S*-chelate yet offered more flexibility for synthetic elaboration. In this Letter, we document that *β*-thioacetal-substituted aldehydes fulfill these requirements.

The synthetic utility of thioacetals is well established; in particular, they are regularly employed as carbonyl surrogates, with a variety of hydrolysis methods available.[8] In addition, conditions to convert thioacetals directly to alcohols, carboxylic acids, and alkanes are well-known. *β*-Thioacetal-substituted aldehydes were thus attractive compounds to investigate as hydoacylation substrates. The required aldehydes were readily available from a double conjugate addition of a dithiol to the corresponding ynal or indirectly via addition to an ynoate followed by reduction.[9,10]

Reaction of the simple dithiane- and dithiolane-substituted propanals with methyl acrylate under the same mild conditions ([Rh(dppe)]ClO$_4$, DCE, 50 °C)[11] employed for the methyl sulfide-substituted aldehydes delivered the required hydroacylation adducts as single regioisomers in good yield (Table 1, entries 1 and 2). It is interesting to note that methyl sulfide-substituted propanal delivered the corresponding methyl acrylate adduct as a 5:1 mixture of linear and branched regioisomers.[6] We attribute the greater selectivity observed with the thioacetal-substituted aldehydes to the increased steric demands around the chelating *S*-atom. Having established that *β*-thioacetals serve as suitable chelating groups, we explored the range of additional functionality that could be tolerated in the aldehyde. Simple alkyl substituents, chloro-alkyl and acetal-protected alcohols were all tolerated well, delivering linear adducts in good yields (entries 3−5). Reactions employing substituted aldehydes required longer reaction times to reach completion, and the aldehyde bearing a phenyl substituent provided too significant a steric barrier, with no reaction being observed (entry 6). Finally, the use of a bis-aldehyde allowed a double hydroacylation to provide the corresponding diketone in excellent yield (entry 7).

We next explored the scope of the process with respect to the alkene component; the simple alkyl-substituted aldehyde was employed as a standard (Table 2). In analogy to the methyl sulfide-aldehydes, simple acrylates and amides were accommodated well (entries 1−3). A lower reactivity toward electronically neutral alkenes such as octene was observed, with only trace amounts of product being isolated (entry 4). However, the process was far more tolerant of electronically varied alkynes,[12] with both electron-poor (entry 5) and -neutral systems delivering the required adducts in good yields (entry 6). Significant variation in alkyne structure was possible, with chloro- and cyano-substituted examples performing well (entries 7 and 8). Interestingly, the cyano-substituted alkyne delivers exclusively the branched hydroacylation adduct, possibly resulting from interaction of the

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(5) (a) Suggs, J. W. *J. Am. Chem. Soc.* **1978**, *100*, 640−641. (b) Bendorf, H. D.; Colella, C. M.; Dixon, E. C.; Marchetti, M.; Matukonis, A. N.; Musselman, J. D.; Tiley, T. A. *Tetrahedron Lett.* **2002**, *43*, 7031−7034. (c) Jun, C.-H.; Moon, C. W.; Lee, D.-Y. *Chem. Eur. J.* **2002**, *8*, 2423−2428. (d) Jun, C. H.; Lee, J. H. *Pure Appl. Chem*. **2004**, *76*, 577−587 and references therein. (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*, 7031−7034. (f) Tanaka, M.; Imai, M.; Yamamoto, Y.; Tanaka, K.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *Org. Lett*. **2003**, *5*, 1365−1367. (g) Imai, M.; Tanaka, M.; Tanaka, K.; Yamamoto, Y.; Imai-Ogata, N.; Shimowatari, M.; Nagumo, S.; Kawahara, N.; Suemune, H. *J. Org. Chem*. **2004**, *69*, 1144−1150.

(6) Willis, M. C.; McNally, J. S.; Beswick, P. J. *Angew. Chem., Int. Ed.* **2004**, *43*, 340−343.

(7) Elimination of the methyl sulfide group was possible by simple treatment with MeOTf and KHCO$_3$.

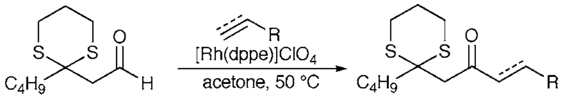
(8) For a review on the applications of 1,3-dithianes in synthesis, see: Yus, M.; Najera, C.; Foubelo, F. *Tetrahedron* **2003**, *59*, 6147−6212.

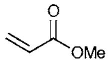
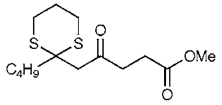
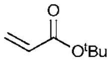
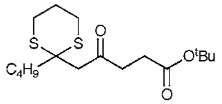
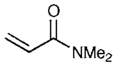
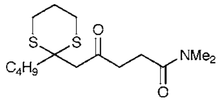
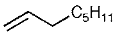
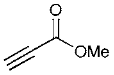
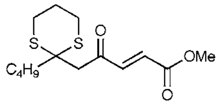
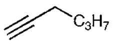
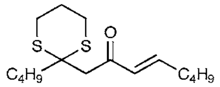
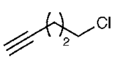
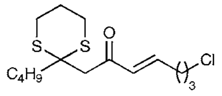
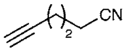
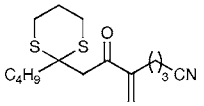
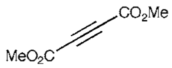
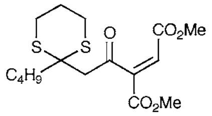
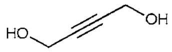
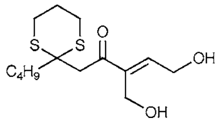
(9) (a) Gaunt, M. J.; Sneddon, H. F.; Hewitt, P. R.; Orsini, P.; Hook, D. F.; Ley, S. V. *Org. Biomol. Chem*. **2003**, *1*, 15−16. (b) Sneddon, H. F.; Gaunt, M. J.; Ley, S. V. *Org. Lett*. **2003**, *5*, 1147−1150. (c) Kuroda, H.; Tomita, I.; Endo, T. *Synth. Commun*. **1996**, *26*, 1539−1543. (d) Ranu, B. C.; Bhar, S.; Chakraborti, R. *J. Org. Chem*. **1992**, *57*, 7349−7352.

(10) See Supporting Information for details.

(11) See ref 6 for evaluation of various catalysts and reaction conditions using the MeS-substituted aldehyde.

Table 2. Intermolecular Hydroacylation: Scope of Alkene or Alkyne Component[a,b]



Entry	Alkene/ alkyne	Product	Yield[c,d] (%)
1			77
2			70
3			68
4		no reaction	0
5[e]			75[f]
6[e]			75
7[e]			73
8[e]			68
9[e]			71[g]
10[e]			83

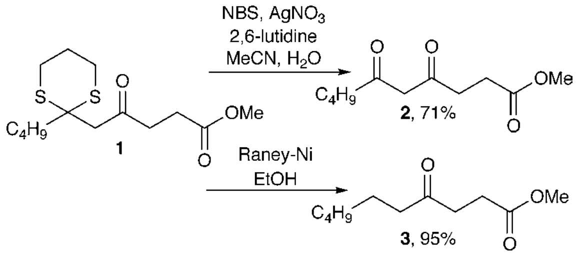
[a] Reaction conditions: aldehyde (1.0 equiv), alkene or alkyne (5.0 equiv), $[Rh(dppe)]ClO_4$ (10 mol %), acetone, 50 °C. [b] Catalyst generated in situ from $[Rh(dppe)(nbd)]ClO_4$ and H_2. [c] Isolated yields. [d] Only linear isomers observed. [e] Performed with 5.0 mol % catalyst. [f] Isolated as a 4:1 mix of *E*:*Z* isomers (major isomer shown). [g] Isolated as a 3:1 mix of *Z*:*E* isomers.

cyano group with the rhodium center. The final two examples demonstrate that internal alkynes are also excellent hydroacylation substrates, with the final entry also illustrating the tolerance of the process toward hydroxyl functionality.

To achieve convenient reaction times, all of the examples described involving alkene substrates employed 10 mol % catalyst, while alkyne substrates used 5 mol % catalyst, however, lower loadings are possible. For example, the reaction between dithiane-substituted propanal and methyl acrylate (Table 1, entry 1) using 2.5 mol % catalyst delivers 78% product after 24 h at 50 °C. The same reaction employing 1.0 mol % catalyst provides 70% product after 48 h.

Finally, to demonstrate the potential synthetic utility of the hydroacylation adducts, thioacetal **1** was treated with $NBS/AgNO_3$ to deliver diketone **2** or alternatively reduced with Raney nickel to generate ketone **3** (Scheme 2).

Scheme 2. Modification of Thioacetal **1**



In conclusion, we have demonstrated that synthetically flexible β-thioacetal-substituted aldehydes are efficient substrates for intermolecular rhodium-catalyzed hydroacylation of alkenes and alkynes. Reactions are conducted under mild conditions, can tolerate a variety of reactive functionality and deliver highly functionalized products. The adducts are obtained in good yields and in general with high levels of regioselectivity. The greater reactivity of alkynes allows disubstituted (internal) examples to be employed.

Acknowledgment. This work was supported by the EPSRC and AstraZeneca. The EPSRC Mass Spectrometry Service at the University of Wales Swansea is also thanked for their assistance.

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.

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(12) For an example of intramolecular alkyne hydroacylation, see: (a) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 11492−11493. Intramolecular enantioselective alkyne hydroacylation: (b) Tanaka, K.; Fu, G. C. *J. Am. Chem. Soc.* **2002**, *124*, 10296−10297. For intermolecular alkyne hydroacylation, see: (c) Tsuda, T.; Kiyoi, T.; Saegusa, T. *J. Org. Chem.* **1990**, *55*, 2554−2558. (d) Kokubo, K.; Matsumasa, K.; Nishinaka, Y.; Miura, M.; Nomura, M. *Bull. Chem. Soc. Jpn*. **1999**, *72*, 303−311. (e) Lee, D.-Y.; Hong, B.-S.; Cho, E.-G.; Lee, H.; Jun, C.-H. *J. Am. Chem. Soc.* **2003**, *125*, 6372.