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Tandem Molybdenum Catalyzed Hydrosilylations: An Expedient Synthesis of β-Aryl Aldehydes

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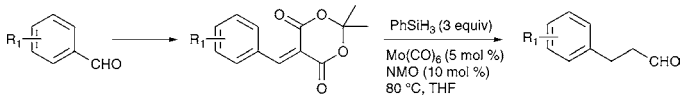
ABSTRACT

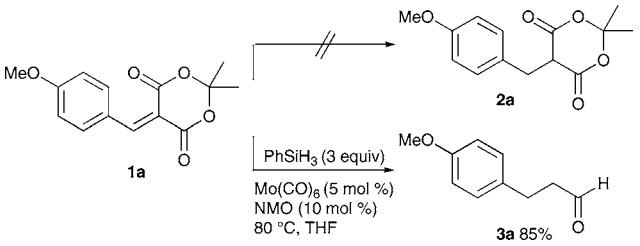


The synthesis of β-aryl aldehydes utilizing a tandem molybdenum catalyzed hydrosilylation is described. This new functional group interconversion provides an efficient method for the two-carbon homologation of aryl aldehydes.

The transition-metal-catalyzed hydrosilylation of α,β-unsaturated esters is a well-developed and important method in organic synthesis.[1] Of notable interest is the subsequent functionalization of the derived silylketene acetal in tandem processes.[2] Of the various transition metal reagents known to promote this type of transformation, the air-stable, commercially available, and inexpensive complex $Mo(CO)_6$ is appealing yet surprisingly rarely used. Keinan and Perez first reported the application of phenylsilane and catalytic amounts of $Mo(CO)_6$ in the hydrosilylation of a wide-range of Michael acceptors including α,β-unsaturated ketones, carboxylic acids, carboxylic esters, amides, and nitriles.[3]

During a recent study into the activation of $Mo(CO)_6$ by the oxidative removal of carbonyl ligands, we attempted the catalytic hydrosilylation of the α,β-unsaturated Meldrum's acid derivative **1a** in the presence of *N*-methylmorpholine-*N*-oxide (NMO). After quenching with water, none of the expected product **2a** was observed. Interestingly, we isolated the β-aryl aldehyde **3a** as the sole product of the reaction in excellent yield (Scheme 1). Given the ready availability of the substrates, the broad utility of the product β-aryl aldehydes and the lack of precedent for this functional group interconversion, we decided to investigate further. In this

Scheme 1. The Catalytic Synthesis of β-Aryl Aldehydes



(1) For leading references, see: (a) Keinan, E.; Greenspoon, N. *J. Am. Chem. Soc.* **1986**, *108*, 7314. (b) Takeshita, K.; Seki, Y.; Kawamoto, K.; Murai, S.; Sonoda, N. *J. Org. Chem.* **1987**, *52*, 4864. (c) Doyle, M. P.; Devora, G. A.; Nefedov, A. O.; High, K. G. *Organometallics* **1992**, *11*, 549. (d) Zheng, G. Z.; Chan, T. H. *Organometallics* **1995**, *14*, 70. (e) Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. *Tetrahedron Lett.* **1997**, *38*, 8887. (f) Lipshutz, B. H.; Keith, J.; Papa, P.; Vivian, R. *Tetrahedron Lett.* **1998**, *39*, 4627. (g) Appella, D. H.; Moritani, Y.; Shintani, R.; Ferreira, E. M.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9473.

(2) (a) Revis, A.; Hilty, T. K. *Tetrahedron Lett.* **1987**, *28*, 4809. (b) Kiyooka, S.; Shimizu, A. *Tetrahedron Lett.* **1998**, *39*, 5237. (c) Isayama, S.; Mukaiyama, T. *Chem. Lett.* **1989**, 2005. (d) Taylor, S. J.; Morken, J. P. *J. Am. Chem. Soc.* **1999**, *121*, 12202. (e) Taylor, S. J.; Duffey, M. O.; Morken, J. P. *J. Am. Chem. Soc.* **2000**, *122*, 4528. (f) Lipshutz, B. H; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J. A.; Vivian, R. W.; Keith, J. M. *Tetrahedron* **2000**, *56*, 2779. (g) Zhao, C. X.; Duffey, M. O.; Taylor, S. J.; Morken, J. P. *Org. Lett.* **2001**, *3*, 1829. (h) Baik, T.-G.; Luis, A. L.; Wang, L.-C.; Krische, M. J. *J. Am. Chem. Soc.* **2001**, *123*, 5112. (i) Wang, L.-C.; Jang, H.-Y.; Roh, Y.; Lynch, V.; Schultz, A. J.; Wang, X.; Krische, M. J. *J. Am. Chem. Soc.* **2002**, *124*, 9448. (j) For a review and further leading references, see: Huddleston, R. R.; Krische, M. J. *Synlett* **2003**, 12. (k) Fuller, N. O.; Morken, J. P. *Synlett* **2005**, 1459. (l) Nishiyama, H.; Siomi, T.; Tsuchiya, Y.; Matsuda, I. *J. Am. Chem. Soc.* **2005**, *127*, 6972. (m) Lam, H.-W.; Joensuu, P. M. *Org. Lett.* **2005**, *7*, 4225. (n) Lam, H.-W.; Murray, G. J.; Firth, J. D. *Org. Lett.* **2005**, *7*, 5743.

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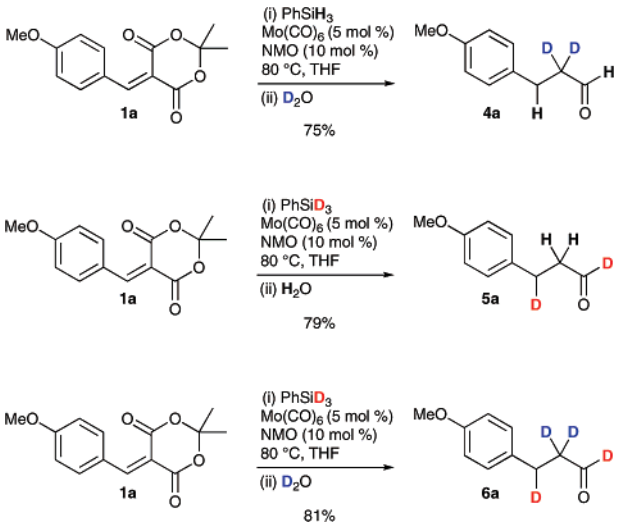
communication, we present a mechanistic rationale for the observed products and demonstrate the scope of this potentially useful transformation.

To learn more about the sequence of events in the reaction, the incorporation of deuterium as both nucleophile and electrophile was investigated. The molybdenum catalyzed hydrosilylation of α,β-unsaturated Meldrum's acid derivative **1a** with phenylsilane followed by quenching with deuterium oxide afforded the α,α′-dideuterated product **4a** (Scheme 2).

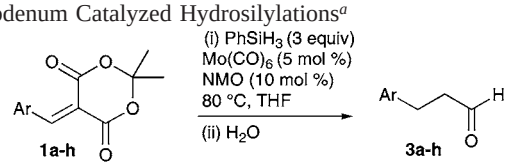
Scheme 2. Regioselective Incorporation of Deuterium



The use of trideuteriophenylsilane in the reduction followed by treatment with water led to the formation of deuterioaldehyde **5a** with the expected deuterium atom at the β-carbon.[4] The combination of trideuteriophenylsilane and quenching with deuterium oxide yielded **6a** with four deuterium atoms being incorporated in a manner consistent with the previous experiments. While these experiments were carried out to elucidate a mechanism for the formation of the aldehyde products, the highly regioselective incorporation of deuterium to organic molecules (as in **4a** and **5a**) is also of considerable value for biosynthesis and pharmacology research and could be exploited further.[5]

A mechanism consistent with the deuterium labeling studies is shown in Figure 1 (for the preparation of **5a**). The deuteriosilylation of α,β-unsaturated Meldrum's acid derivative **1a** with trideuteriophenylsilane would be expected to furnish the β-deuterated dioxinone **7**. On heating, rapid cycloreversion occurs to reveal the ketene **8** which is susceptible to attack by nucleophiles.[6] It is proposed that the ketene undergoes deuteriosilylation to afford enol silane **9**. On quenching, a double protonation (or deuteration in the case of **4a** and **6a**) occurs with concomitant evolution of carbon dioxide (confirmed by limewater test) to release the aldehyde product **5a**.

Table 1. Synthesis of β-Aryl Aldehydes by Tandem Molybdenum Catalyzed Hydrosilylations[a]



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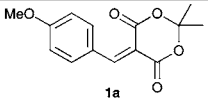
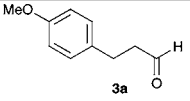
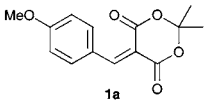
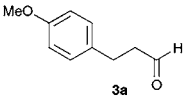
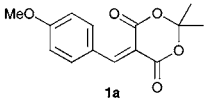
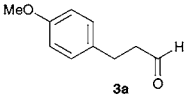
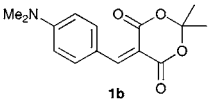
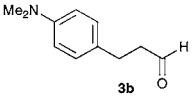
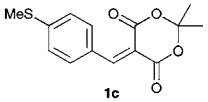
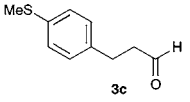
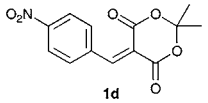
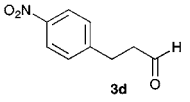
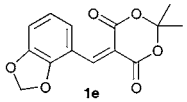
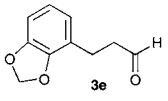
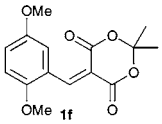
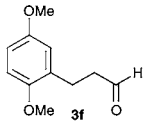
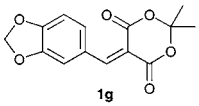
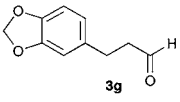
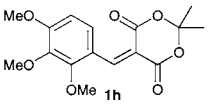
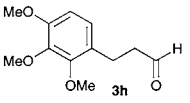
1			85
2			49[c]
3			43[d]
4			81
5			66
6			37
7			78
8			76
9			65
10			45

[a] Reaction conditions: **1** (1.0 equiv), phenylsilane (3.0 equiv), $Mo(CO)_6$ (5 mol %), *N*-methylmorpholine-*N*-oxide (10 mol %), THF, 80 °C, 16 h. [b] Isolated yields. [c] With 2.0 equiv of phenylsilane. [d] No added *N*-methylmorpholine-*N*-oxide.

The established conditions did not yield to further optimization. Other silanes (Ph_2SiH_2, Et_3SiH, and PMHS) were significantly less reactive, and reducing the number of

(4) (a) Ojima, I.; Kogure, T. *Organometallics* **1982**, *1*, 1390. (b) Keinan, E.; Greenspoon, N. *Tetrahedron Lett.* **1985**, *26*, 1353. (c) Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* **1999**, *55*, 4573. (d) Otsuka, H.; Shirakawa, E.; Hayashi, T. *Chem. Commun.* **2007**, 1819.

(5) (a) Fate, G. D.; Benner, C. P.; Grode, S. H.; Gilbertson, T. J. *J. Am. Chem. Soc.* **1996**, *118*, 1163. (b) Sack, I.; Balazs, Y. S.; Rahimipour, S.; Vega, S. *J. Am. Chem. Soc.* **2000**, *122*, 12263.

(6) (a) Sato, M.; Ogasawara, H.; Sekiguchi, K.; Kaneko, C. *Heterocycles* **1984**, *22*, 2563. (b) Sato, M.; Ogasawara, H.; Kato, T. *Chem. Pharm. Bull.* **1984**, *32*, 2602. (c) Sato, M.; Yoneda, N.; Katagiri, N.; Watanabe, H.; Kaneko, C. *Synthesis* **1986**, 672. (d) Sato, M.; Ban, H.; Kaneko, C. *Tetrahedron Lett.* **1997**, *38*, 6689.

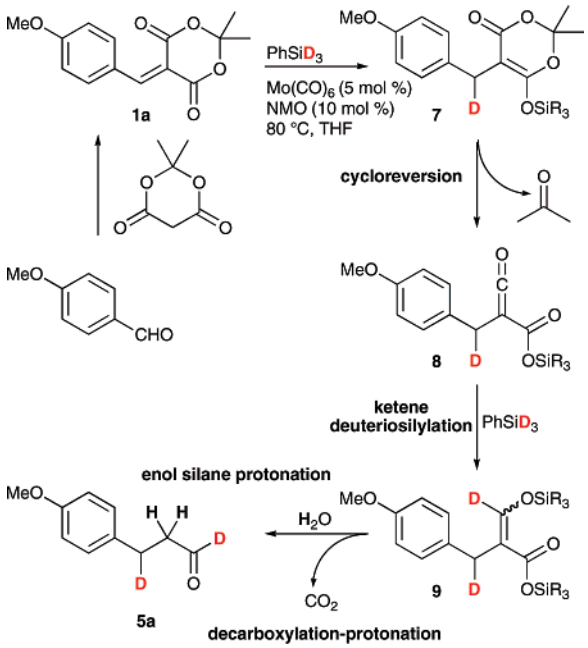


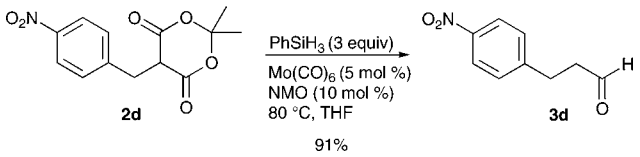
Figure 1. Proposed mechanism of aldehyde formation.

equivalents of silane led to lower yields (Table 1, entry 1). The omission of *N*-methylmorpholine-*N*-oxide was detrimental to the reaction (Table 1, entry 2), which corresponds to the assumption that the active catalyst is a coordinatively unsaturated $Mo(THF)_n(CO)_{6-n}$ complex. Having established the basis for a useful new functional group transformation, we next explored the scope of the process with respect to aryl substitution (Table 1). The required α,β-unsaturated Meldrum's acid derivatives (**1a**−**h**) were easily prepared by a Knoevenagel condensation of an aryl aldehyde and Meldrum's acid in water.[7] The yields were consistently good for a range of substrates that possess electron-donating substituents on the aryl ring. Of particular note is the successful tandem catalytic synthesis of β-aryl aldehydes containing thiomethyl, dimethylamino, and trimethoxy functional groups on the aryl ring (Table 1, entries 4, 5, and 10).

(7) (a) Bigi, F.; Carloni, S.; Ferrari, L.; Maggi, R.; Mazzacani, A.; Sartori, G. *Tetrahedron Lett.* **2001**, *42*, 5203. (b) Maggi, R.; Bigi, F.; Carloni, S.; Mazzacani, A.; Sartori, G. *Green Chem.* **2001**, *3*, 173. (c) Frost, C. G.; Penrose, S. D.; Lambshead, K.; Raithby, P. R.; Warren, J. E.; Gleave, R. *Org. Lett.* **2007**, *9*, 2119.

In contrast, α,β-unsaturated Meldrum's acid derivative **1d** with the *p*-NO_2 group on the aryl ring was significantly less reactive under the standard reaction conditions (Table 1, entry 6). This observation can be rationalized by the inductive deactivation of the α,β-unsaturated Meldrum's acid derivative to the initial hydrosilylation by the electron-withdrawing *p*-NO_2 group. However, if **1d** is reduced to **2d** using sodium borohydride and then **2d** is subjected to the hydrosilylation conditions, the β-aryl aldehyde **3d** is obtained in excellent yield (Scheme 3). Under the described reaction conditions,

Scheme 3. Reduction of 5-Monosubstituted Meldrum's Acid Derivative **2d**



silylation of **2d** would be expected to occur followed by cycloreversion and ketene hydrosilylation. The direct reduction of 5-monosubstituted Meldrum's acid derivatives to β-aryl aldehydes via hydrosilylation is of significant value in addition to the presented tandem catalytic method.

In conclusion, we have developed an efficient synthesis of β-aryl aldehydes from α,β-unsaturated Meldrum's acid derivatives (prepared from aryl aldehydes) employing a tandem molybdenum catalyzed hydrosilylation reaction. A plausible mechanism is proposed that suggests the reaction proceeds via the hydrosilylation of a key ketene intermediate. The tandem reaction can tolerate a broad range of functional groups on the aryl ring to deliver elaborated products in good yields. Overall, this is practical method for the two-carbon homologation of aryl aldehydes.

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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.

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