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A New Method for the Preparation of Silyl Enol Ethers from Carbonyl Compounds and (Trimethylsilyl)diazomethane in a Regiospecific and Highly Stereoselective Manner

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Silyl enol ethers are fundamental building blocks in organic synthesis,[1] but their synthesis in a regio- and especially stereo-defined manner can be problematic.[2] In the case of unsymmetrical ketones bearing similar groups it is difficult to control the regioselectivity in enolization, and therefore alternative strategies have to be employed. In this communication we describe a new method for converting aldehydes into silyl enol ethers in a regiospecific and highly stereoselective manner.[3]

We considered the reaction of lithium(trimethylsilyl)diazomethane (LTMSD) **1** with an aldehyde, a reaction which normally furnishes alkynes **4**.[4] We reasoned that if the initial alkoxide addition product **2** could be captured by a transition metal catalyst either before or after a protonation event to give **6**, subsequent 1,2-hydride migration[5] would then furnish the silyl enol ether **7** (Scheme 1).

To achieve our synthesis of silyl enol ethers we required a Brook rearrangement[6] to intervene prior to the protonation/metal carbene 1,2-hydride migration event. However, literature precedent was not encouraging as it had been reported that quenching adduct **2** with AcOH led to the silyl diazo compound **5**.[7] Furthermore, the product of Brook rearrangement **6** was required not to eliminate $LiOSiMe_3$, otherwise alkyne formation would result via **3**. Both of these processes were unprecedented.

In the event, when cyclohexane carboxaldehyde was reacted with LTMSD at −78 °C followed by addition of *MeOH* and $Rh_2(OAc)_4$ and then slow warming to 0 °C, the terminal silyl enol ether was obtained as the sole product. The reaction was found to be general for a range of aliphatic aldehydes (Table 1) and could even be used with base-sensitive aldehydes (entry 6) without racemization. Aldehydes prone to enolization (e.g., phenylacetaldehyde (entry 7)) could also be employed and furnished the terminal silyl enol ether in high yield. Despite a number of attempts, it has proved impossible to generate this silyl enol ether regioselectively by deprotonation of the corresponding ketone,[2c,8] thus demonstrating the unique advantage of the current methodology. Aromatic aldehydes (entry 8) were also suitable substrates, although unexpectedly, phenyl migration competed with and dominated hydride migration.[5a,b,9] In addition, the methodology could be extended to include aromatic ketones (entry 9). In this case, exclusive migration of the phenyl group was observed, leading to the silyl enol ether in good yield and with very high stereoselectivity (vide infra).

Quenching the reaction with CD_3OD instead of MeOH gave the mono-deuterated silyl enol ether **8** with essentially complete stereoselectivity in favor of the *Z*-isomer (Scheme 2). The corresponding *E*-isomer could be obtained, again with very high stereoselectivity (96:4) and in high yield (82%) by reacting deuteriocyclohexane carboxaldehyde under the same conditions, but quenching with MeOH.

These experiments provide not only a unique synthetic method for the stereo-controlled synthesis of labeled silyl enol ethers which would otherwise be extremely difficult to prepare but also useful insights into the mechanism of the process. The two experiments unequivocally show that one of the two protons of the terminal silyl enol ether originate from the quench and the other from the aldehyde C−H. Furthermore, they illustrate that the 1,2-hydride/deuteride migration occurs with very high stereoselectivity.

Scheme 1. Pathways in the Reaction of LTMSD with RCHO

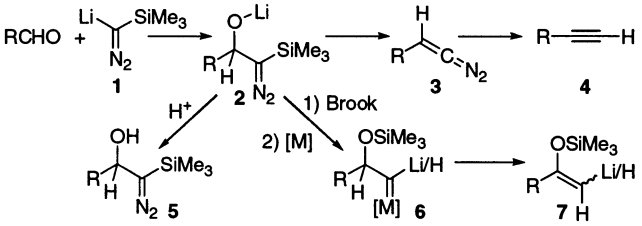
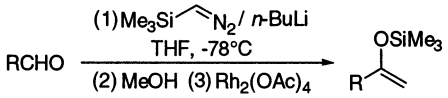


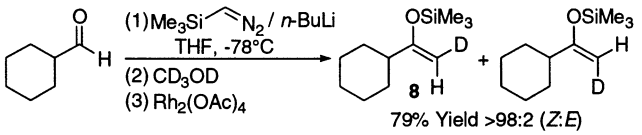
Table 1. Formation of Silyl Enol Ethers from Carbonyl Compounds



entry	substrate	product yield (%)[a]
1	cyclohexane carboxaldehyde	84
2	octaldehyde	81
3	valeraldehyde	71
4	3-phenylpropanol	74
5	pivaldehyde	77
6	*N*-(BOC)-D-prolinal	70
7	phenylacetaldehyde	83
8	benzaldehyde	74[b]
9	acetophenone	75[c]

[a] Isolated yield after Kugelrohr distillation. [b] 92:1:7 mixture of *E*- and *Z*-1-phenyl-2-(trimethylsiloxy)ethene, and 1-phenyl-1-(trimethylsiloxy) ethene. [c] 96:4 mixture of *E*- and *Z*-1-phenyl-2-(trimethylsiloxy)propene.

Scheme 2. Synthesis of Labeled Silyl Enol Ethers



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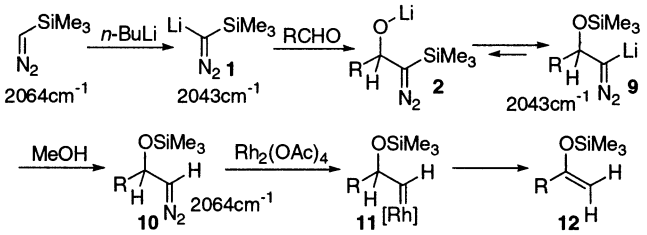
Scheme 3. Mechanism Determined by ReactIR



Having established a novel transformation which converted aldehydes into silyl enol ethers we wished to determine the mechanism and the precise order of events of this process. ReactIR was employed to unravel the sequence of events as shifts in the diazo stretching frequency provide characteristic information on the reaction intermediates (see Supporting Information). From this analysis we concluded that the mechanism shown in Scheme 3 was operative. Following addition of LTMSD to the aldehyde, a Brook rearrangement occurred to give **9**. This species was in equilibrium with **2** as quenching with AcOH at low temperature, as described by Schöllkopf,[7] gave the alcohol derived from **2**, whereas quenching with MeOH gave **10**. Neither **9** nor **10** reacted with $Rh_2(OAc)_4$ at low temperature. Upon warming **10** in the presence of $Rh_2(OAc)_4$, N_2 was evolved, and the silyl enol ether **12** was formed presumably via the metal carbene **11**. Intermediate **10** was isolated, where R = *t*-Bu and Ph, and subjected to $Rh_2(OAc)_4$, and the same silyl enol ether products were obtained as in entries 5 and 8 (Table 1), proving the intermediacy of this species.

The *E*/*Z* selectivity of the silyl enol ethers originates from the 1,2-hydride migration step and can be rationalized by considering the possible stereoelectronically required conformations **A** and **B** (Figure 1) which place the migrating group parallel with the empty p orbital on carbon.[9a,b,10] Of the two conformations, **B** is likely to be disfavored because of electronic repulsions between the acetate ligands attached to rhodium and the oxygen of the silyl ether. Thus, rearrangement is proposed to occur via transition state **A** which leads to the observed *Z*-isomer.

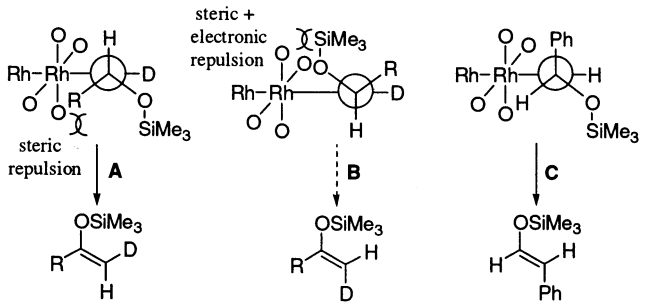
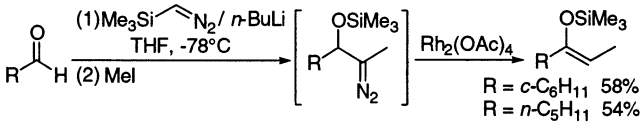


Figure 1. Model for stereoselectivity.

This model accounts not only for the deuterium experiments above but also for the *E*/*Z* selectivities observed in entries 8 and 9. Furthermore, it also accounts for the preferred migration of the phenyl group over hydride migration (entry 8). In this case, as H and Ph can both migrate with almost equal ease, conformers **A** and **C** need to be considered, and **C** suffers less steric hindrance than **A**, thus leading to the unusual preference for phenyl migration.

A corollary of the above model is that the electronic repulsion shown in transition state **B** must be very severe as transition state **A** suffers from a significant steric hindrance between the wall of ligands around rhodium and the cyclohexyl group and yet **A** is strongly preferred over **B**. If the above model is indeed correct, it should be possible to destabilize transition state **A** by using an even bulkier R group. To test this proposition, the deuterium-labeling experiment shown in Scheme 2 was repeated with pivaldehyde, and this time a 68:32 ratio of silyl enol ethers was obtained with the *E*-isomer dominating. Thus when R = *t*-Bu, transition state **A** is destabilized due to very severe steric hindrance, and the reaction preferentially occurs via transition state **B**. The strength of the electronic repulsion is still evident though, as over 30% of the reaction occurs via the severely sterically hindered transition state **A**.

Scheme 4. Formation of Substituted Silyl Enol Ethers



Having established the mechanism of this novel process we sought to exploit this chemistry further by preparing more substituted silyl enol ethers in a regio- and stereo-defined manner. This was achieved by quenching the reaction with MeI instead of MeOH. To our delight, the corresponding silyl enol ethers were produced with complete regio- and stereoselectivity (Scheme 4).

In conclusion we have discovered a new synthesis of terminal and substituted silyl enol ethers with complete control over regio- and stereochemistry. The mechanism of this novel process has been mapped out through a combination of deuterium labeling, ReactIR, and isolation of reaction intermediates.

Acknowledgment. We gratefully thank the EPSRC and Glaxo-SmithKline for a CASE Award to C.G.S.

Supporting Information Available: Experimental procedures, compound characterization data, and ReactIR data (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) (a) Brownbridge, P. *Synthesis* **1983**, 1. (b) Brownbridge, P. *Synthesis* **1983**, 85.

(2) For notable contributions see: (a) Nakamura, E.; Hashimoto, K.; Kuwajima, I. *Tetrahedron Lett.* **1978**, *19*, 2079. (b) Reich, H. J.; Rusek, J. J.; Olson, R. E. *J. Am. Chem. Soc.* **1979**, *101*, 2225. (c) Corey, E. J.; Gross, A. W. *Tetrahedron Lett.* **1984**, *25*, 495. (d) Cahiez, G.; Figadère, B.; Cléry, P. *Tetrahedron Lett.* **1994**, *35*, 6295.

(3) Brookhart recently described the one carbon homologation of aromatic aldehydes to silyl enol ethers with TMSD using a Rh(I) complex, but the process was limited to aromatic aldehydes, and low *Z*-selectivity was observed (2.1−8.8:1). Dias, E. L.; Brookhart, M.; White, P. S. *J. Am. Chem. Soc.* **2001**, *123*, 2442.

(4) Miwa, K.; Aoyama, T.; Shioiri, T. *Synlett* **1994**, 107.

(5) For examples of 1,2-hydride migration reactions of metal carbenes to give enols, see: (a) Pellicciari, R.; Fringuelli, R.; Ceccherelli, P.; Sisani, E. *J. Chem. Soc., Chem. Commun.* **1979**, 959. (b) Hudlicky, T.; Olivio, H. F.; Natchus, M. G.; *J. Org. Chem.* **1990**, *55*, 4767. (c) Ye, T.; McKervey, A. *Tetrahedron* **1992**, *48*, 8007.

(6) For a review see: Moser, W. H. *Tetrahedron* **2001**, *57*, 2065.

(7) Schöllkopf, U.; Scholz, H.-U. *Synthesis* **1976**, 271.

(8) Gaudemar, M.; Bellassoued, M. *Tetrahedron Lett.* **1989**, *30*, 2779.

(9) In this type of rearrangement, hydrogen usually migrates more readily than a phenyl group: (a) Ikota, N.; Takamura, N.; Young, S. D.; Ganem, B. *Tetrahedron Lett.* **1981**, *22*, 4163. (b) Taber, D. F.; Herr, R. J.; Pack, S. K.; Geremia, J. M. *J. Org. Chem.* **1996**, *61*, 2908. For a discussion see: (c) Nickon, A. *Acc. Chem. Res.* **1993**, *26*, 84. However, an exception to this has recently been reported: (d) Jiang, N.; Qu, Z.; Wang, J. *Org. Lett.* **2001**, *3*, 2989.

(10) (a) Nickon, A.; Huang, F.; Weglein, R.; Matsuo, K.; Yagi, H. *J. Am. Chem. Soc.* **1974**, *96*, 5264. (b) Nickon, A.; Bronfenbrenner, J. K. *J. Am. Chem. Soc.* **1982**, *104*, 2022.

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